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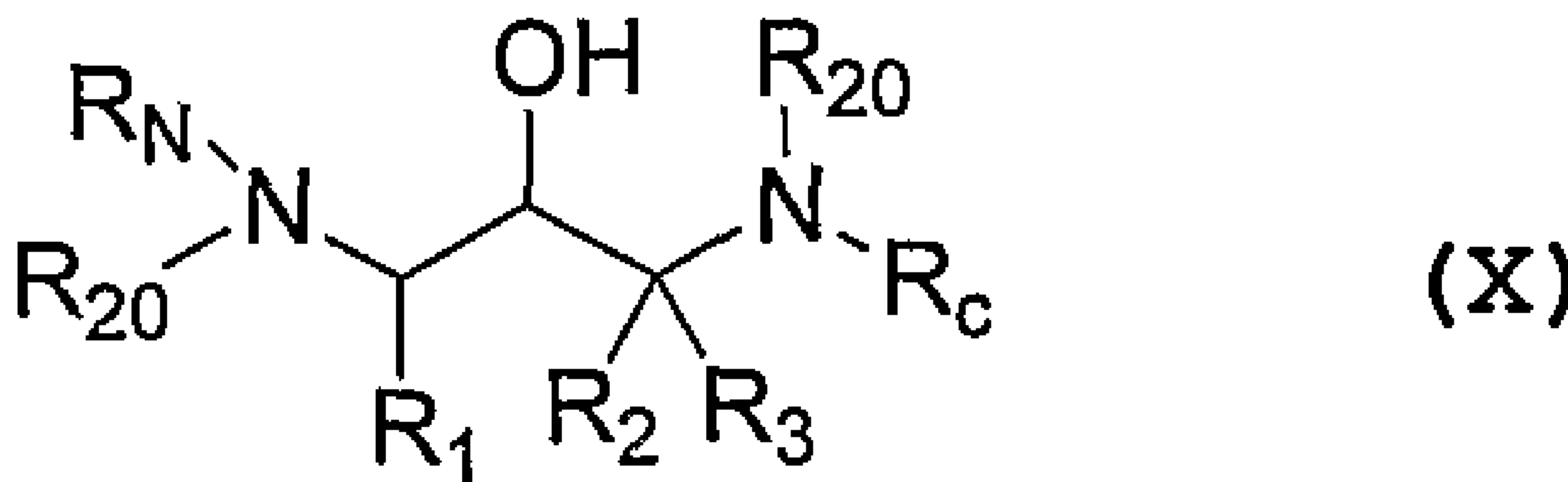
(71) Demandeurs/Applicants:  
 ELAN PHARMACEUTICALS, INC., US;  
 PHARMACIA & UPJOHN COMPANY, US

(72) Inventeurs/Inventors:  
 FRESKOS, JOHN N., US;  
 BROWN, DAVID L., US;  
 FANG, LARRY, US;  
 FOBIAN, YVETTE M., US;  
 VARGHESE, JOHN, US;  
 ROMERO, ARTHUR GLENN, US

(74) Agent: OSLER, HOSKIN & HARCOURT LLP

(54) Titre : HYDROXYALKYLAMINES

(54) Title: HYDROXY ALKYL AMINE DERIVATIVES AS BETA-SECRETASE INHIBITORS AND THEIR USE FOR THE TREATMENT OF ALZHEIMER'S DISEASE AND SIMILAR DISEASES



(57) Abrégé/Abstract:

Disclosed are compounds of formula X, where R<sub>n</sub>, R<sub>20</sub>, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>c</sub> are defined herein. These compounds are useful in treating Alzheimer's disease and other similar diseases. Pharmaceutical compositions comprising compounds of formula X and methods of preparing the compounds of formula X are also disclosed.

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Arthur, Glenn [US/US]; 6629 Morningstar Way, Kalamazoo, MI 49009 (US).

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(74) Agent: SARUSSI, Steven, J.; McDonnell Boehnen Hulbert &amp; Berghoff, 300 South Wacker Drive, Chicago, IL 60606 (US).

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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): FRESKOS, John [US/US]; 7572 York Drive, Clayton, MO 63105 (US). BROWN, David, L. [US/US]; 15504 Twingate, Chesterfield, MO 63017 (US). FANG, Larry [US/US]; 1193 Beach Park Blvd., Foster City, CA 94404 (US). FOBIAN, Yvette, M. [US/US]; 580 Eagles Nest Court, Wildwood, MI 63011 (US). VARGHESE, John [US/US]; 1722 18th Avenue, San Francisco, CA 94122 (US). ROMERO,

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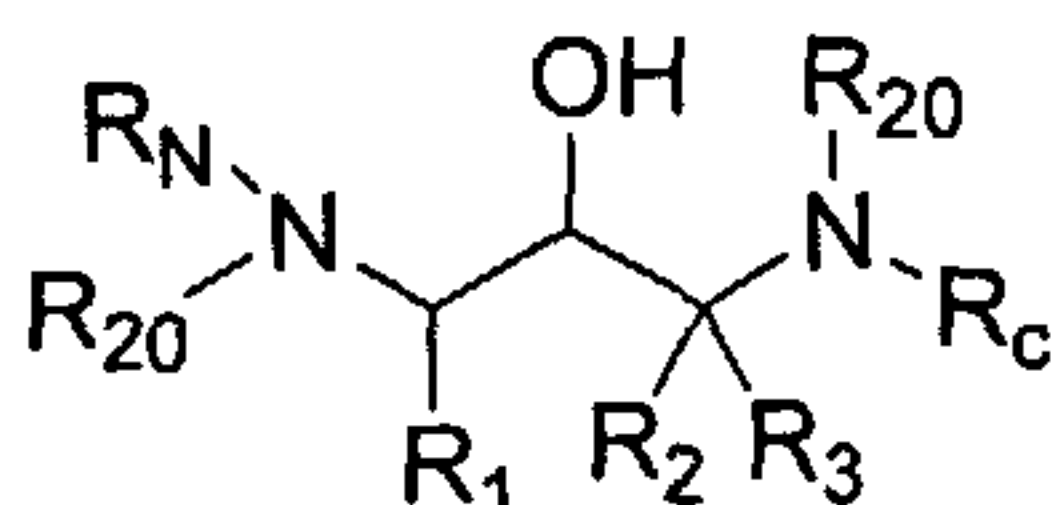
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(54) Title: HYDROXY ALKYL AMINE DERIVATIVES AS BETA-SECRETASE INHIBITORS AND THEIR USE FOR THE TREATMENT OF ALZHEIMER'S DISEASE AND SIMILAR DISEASES



(X)

(57) Abstract: Disclosed are compounds of formula X, where R<sub>i</sub>n?, R<sub>i</sub>20?, R<sub>i</sub>1?, R<sub>i</sub>2?, R<sub>i</sub>3?, and R<sub>i</sub>c? are defined herein. These compounds are useful in treating Alzheimer's disease and other similar diseases. Pharmaceutical compositions comprising compounds of formula X and methods of preparing the compounds of formula X are also disclosed.

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**HYDROXY ALKYL AMINES****BACKGROUND OF THE INVENTION**

5           This application claims priority from U.S. Provisional Application Serial No. 60/343,772, filed December 28, 2001, U.S. Provisional Application Serial No. 60/332,639, filed November 19, 2001, and U.S. Provisional Application Serial No. 60/295,332, filed June 1, 2001.

10   **Field of the Invention**

          The invention relates to hydroxy alkylamine derivatives and to such compounds that are useful in the treatment of Alzheimer's disease and similar diseases. More specifically the invention is directed to such compounds that are capable of  
15   inhibiting beta-secretase, an enzyme that cleaves amyloid precursor protein to produce amyloid beta peptide (A-beta), a major component of the amyloid plaques found in the brains of Alzheimer's sufferers.

20   **Description of the Related Art**

          Alzheimer's disease (AD) is a progressive degenerative disease of the brain primarily associated with aging. Clinical presentation of AD is characterized by loss of memory, cognition, reasoning, judgment, and orientation. As the  
25   disease progresses, motor, sensory, and linguistic abilities are also affected until there is global impairment of multiple cognitive functions. These cognitive losses occur gradually, but typically lead to severe impairment and eventual death in the range of four to twelve years.

30           Alzheimer's disease is characterized by two major pathologic observations in the brain: neurofibrillary tangles and beta amyloid (or neuritic) plaques, comprised predominantly of an aggregate of a peptide fragment know as A-beta. Individuals with AD exhibit characteristic beta-amyloid

deposits in the brain (beta amyloid plaques) and in cerebral blood vessels (beta amyloid angiopathy) as as neurofibrillary tangles. Neurofibrillary tangles occur not only in Alzheimer's disease but also in other dementia-inducing disorders. On  
5 autopsy, large numbers of these lesions are generally found in areas of the human brain important for memory and cognition.

Smaller numbers of these lesions in a more restricted anatomical distribution are found in the brains of most aged humans who do not have clinical AD. Amyloidogenic plaques and  
10 vascular amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D), and other neurogenerative disorders. Beta-amyloid is a defining feature of AD, now believed to be a causative  
15 precursor or factor in the development of disease. Deposition of A-beta in areas of the brain responsible for cognitive activities is a major factor in the development of AD. Beta-amyloid plaques are predominantly composed of amyloid beta peptide (A-beta, also sometimes designated betaA4). A-beta  
20 peptide is derived by proteolysis of the amyloid precursor protein (APP) and is comprised of 39-42 amino acids. Several proteases called secretases are involved in the processing of APP.

Cleavage of APP at the N-terminus of the A-beta peptide by  
25 beta-secretase and at the C-terminus by one or more gamma-secretases constitutes the beta-amyloidogenic pathway, i.e. the pathway by which A-beta is formed. Cleavage of APP by alpha-secretase and the same or a different gamma-secretase produces alpha-sAPP, a secreted form of APP that does not result in  
30 beta-amyloid plaque formation. This alternate pathway precludes the formation of A-beta peptide. A description of the proteolytic processing fragments of APP is found, for example, in U.S. Patent Nos. 5,441,870; 5,721,130; and 5,942,400.

An aspartyl protease has been identified as the enzyme responsible for processing of APP at the beta-secretase cleavage site. The beta-secretase enzyme has been disclosed using varied nomenclature, including BACE, Asp, and Mamepsin. See, for example, Sindha et.al., 1999, *Nature* 402:537-554 (p501) and published PCT application WO00/17369.

Several lines of evidence indicate that progressive cerebral deposition of beta-amyloid peptide (A-beta) plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe, 1991, *Neuron* 6:487. Release of A-beta from neuronal cells grown in culture and the presence of A-beta in cerebrospinal fluid (CSF) of both normal individuals and AD patients has been demonstrated. See, for example, Seubert et al., 1992, *Nature* 359:325-327.

It has been proposed that A-beta peptide accumulates as a result of APP processing by beta-secretase, thus inhibition of this enzyme's activity is desirable for the treatment of AD. *In vivo* processing of APP at the beta-secretase cleavage site is thought to be a rate-limiting step in A-beta production, and is thus a therapeutic target for the treatment of AD. See for example, Sabbagh, M., et al., 1997, *Alz. Dis. Rev.* 3, 1-19.

BACE1 knockout mice fail to produce A-beta, and present a normal phenotype. When crossed with transgenic mice that over express APP, the progeny show reduced amounts of A-beta in brain extracts as compared with control animals (Luo et.al., 2001 *Nature Neuroscience* 4:231-232). This evidence further supports the proposal that inhibition of beta-secretase activity and reduction of A-beta in the brain provides a therapeutic method for the treatment of AD and other beta amyloid disorders.

At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. Therefore, there is an urgent need for pharmaceutical

agents capable of slowing the progression of Alzheimer's disease and/or preventing it in the first place.

Compounds that are effective inhibitors of beta-secretase, that inhibit beta-secretase-mediated cleavage of APP, that are  
5 effective inhibitors of A-beta production, and/or are effective to reduce amyloid beta deposits or plaques, are needed for the treatment and prevention of disease characterized by amyloid beta deposits or plaques, such as AD.

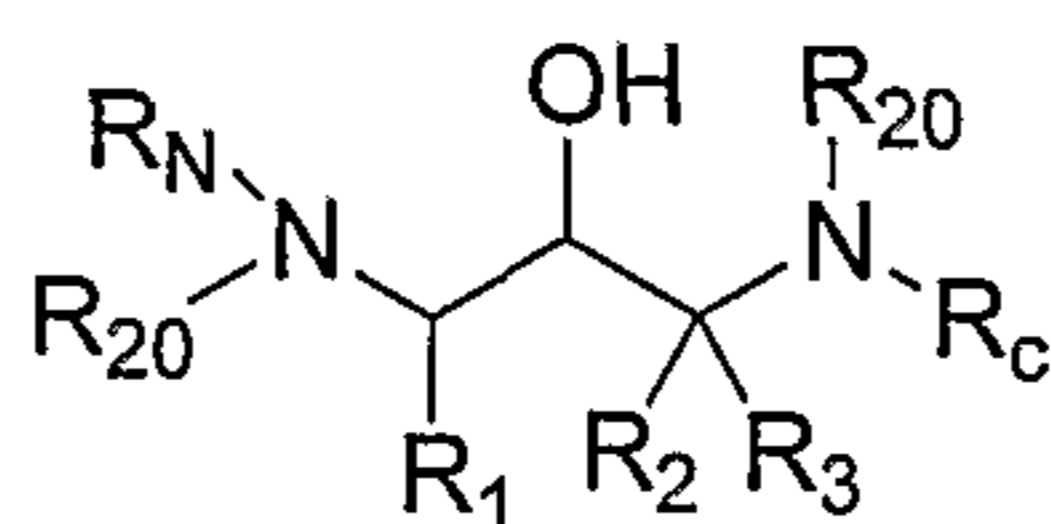
Various pharmaceutical agents have been proposed for the  
10 treatment of Alzheimer's disease but without any real success.

Compounds that are effective inhibitors of beta-secretase activity, that inhibit beta-secretase-mediated cleavage of APP, or that are effective inhibitors of A-beta production or deposition are needed for the treatment and prevention of  
15 disease characterized by beta-amyloid deposits or plaques, including AD.

At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. There is an urgent need for compounds capable of  
20 slowing A-beta peptide production and/or deposition in the brain, which presents a therapeutic approach to treatment of Alzheimer's disease.

Summary of the Invention

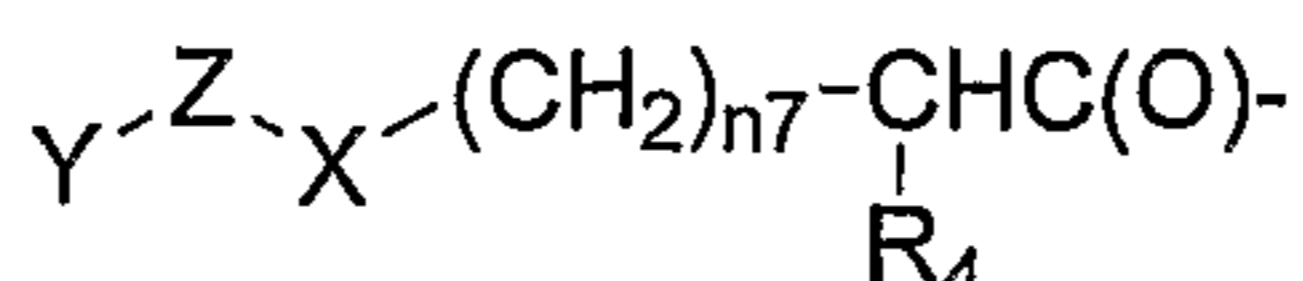
In a broad aspect, the invention provides compounds of the formula X



X

5

and the pharmaceutically acceptable salts thereof, wherein  $R_N$  is:



wherein

10  $R_4$  is selected from the group consisting of H;  $\text{NH}_2$ ;  $-\text{NH}-(\text{CH}_2)_{n_6}-$   
 $\text{R}_{4-1}$ ;  $-\text{NHR}_8$ ;  $-\text{NR}_{50}\text{C(O)R}_5$ ;  $\text{C}_1\text{-C}_4$  alkyl-NHC(O) $\text{R}_5$ ;  $-(\text{CH}_2)_{0-4}\text{R}_8$ ;  $-$   
 $\text{O-C}_1\text{-C}_4$  alkanoyl; OH;  $\text{C}_6\text{-C}_{10}$  aryloxy optionally substituted  
with 1, 2, or 3 groups that are independently halogen,  $\text{C}_1\text{-C}_4$   
 $\text{C}_4$  alkyl,  $-\text{CO}_2\text{H}$ ,  $-\text{C(O)-C}_1\text{-C}_4$  alkoxy, or  $\text{C}_1\text{-C}_4$  alkoxy;  $\text{C}_1\text{-C}_6$   
15 alkoxy; aryl  $\text{C}_1\text{-C}_4$  alkoxy;  $-\text{NR}_{50}\text{CO}_2\text{R}_{51}$ ;  $-\text{C}_1\text{-C}_4$  alkyl-  
 $\text{NR}_{50}\text{CO}_2\text{R}_{51}$ ;  $-\text{C}\equiv\text{N}$ ;  $-\text{CF}_3$ ;  $-\text{CF}_2\text{-CF}_3$ ;  $-\text{C}\equiv\text{CH}$ ;  $-\text{CH}_2\text{-CH=CH}_2$ ;  $-(\text{CH}_2)_{1-}$   
 $4\text{-R}_{4-1}$ ;  $-(\text{CH}_2)_{1-4}\text{-NH-R}_{4-1}$ ;  $-\text{O}-(\text{CH}_2)_{n_6}\text{-R}_{4-1}$ ;  $-\text{S}-(\text{CH}_2)_{n_6}\text{-R}_{4-1}$ ;  $-$   
 $(\text{CH}_2)_{0-4}\text{-NHC(O)-}(\text{CH}_2)_{0-6}\text{-R}_{52}$ ;  $-(\text{CH}_2)_{0-4}\text{-R}_{53}\text{-}(\text{CH}_2)_{0-4}\text{-R}_{54}$ ;

wherein

20  $n_6$  is 0, 1, 2, or 3;

$n_7$  is 0, 1, 2, or 3;

$\text{R}_{4-1}$  is selected from the group consisting of  $-\text{SO}_2\text{-(C}_1\text{-C}_8$   
alkyl),  $-\text{SO-(C}_1\text{-C}_8$  alkyl),  $-\text{S-(C}_1\text{-C}_8$  alkyl),  $-\text{S-CO-}$   
 $(\text{C}_1\text{-C}_6$  alkyl),  $-\text{SO}_2\text{-NR}_{4-2}\text{R}_{4-3}$ ;  $-\text{CO-C}_1\text{-C}_2$  alkyl;  $-\text{CO-NR}_{4-}$   
25  $3\text{R}_{4-4}$ ;

$\text{R}_{4-2}$  and  $\text{R}_{4-3}$  are independently H,  $\text{C}_1\text{-C}_3$  alkyl, or  $\text{C}_3\text{-C}_6$   
cycloalkyl;

$\text{R}_{4-4}$  is alkyl, arylalkyl, alkanoyl, or arylalkanoyl;

$\text{R}_{4-6}$  is H or  $\text{C}_1\text{-C}_6$  alkyl;

30  $\text{R}_5$  is selected from the group consisting of  $\text{C}_3\text{-C}_7$   
cycloalkyl;  $\text{C}_1\text{-C}_6$  alkyl optionally substituted with

1, 2, or 3 groups that are independently halogen, -NR<sub>6</sub>R<sub>7</sub>, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl, C<sub>5</sub>-C<sub>6</sub> heteroaryl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl, -S-C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>7</sub>, -CO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>6</sub>-C<sub>10</sub> aryloxy; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or OH; heterocycloalkyl optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or C<sub>2</sub>-C<sub>4</sub> alkanoyl; aryl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkyl; and -NR<sub>6</sub>R<sub>7</sub>; wherein

R<sub>6</sub> and R<sub>7</sub> are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>8</sub> is selected from the group consisting of -SO<sub>2</sub>-heteroaryl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heterocycloalkyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>10</sub> alkyl, -C(O)NHR<sub>9</sub>, heterocycloalkyl, -S-C<sub>1</sub>-C<sub>6</sub> alkyl, -S-C<sub>2</sub>-C<sub>4</sub> alkanoyl, wherein R<sub>9</sub> is aryl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, or H;

R<sub>50</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>51</sub> is selected from the group consisting of aryl C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, heteroaryl, -NR<sub>6</sub>R<sub>7</sub>, -C(O)NR<sub>6</sub>R<sub>7</sub>, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, or -C<sub>1</sub>-C<sub>4</sub> alkoxy; heterocycloalkyl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, aryl C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; alkenyl; alkynyl; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub>



alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); heteroarylalkyl optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); aryl; heterocycloalkyl; C<sub>3</sub>-C<sub>8</sub> cycloalkyl; and cycloalkylalkyl; wherein the aryl; heterocycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and cycloalkylalkyl groups are optionally substituted with 1, 2, 3, 4 or 5 groups that are independently halogen, CN, NO<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, hydroxy, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> thioalkoxy, C<sub>1</sub>-C<sub>6</sub> thioalkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkoxy;

R<sub>52</sub> is heterocycloalkyl, heteroaryl, aryl, cycloalkyl, -S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -CO<sub>2</sub>-alkyl, -NHS(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(alkyl)S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -S(O)<sub>0-2</sub>-heteroaryl, -S(O)<sub>0-2</sub>-aryl, -NH(arylalkyl), -N(alkyl)(arylalkyl), thioalkoxy, or alkoxy, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, thioalkoxy, halogen, haloalkyl, haloalkoxy, alkanoyl, NO<sub>2</sub>, CN, alkoxy carbonyl, or aminocarbonyl;

R<sub>53</sub> is absent, -O-, -C(O)-, -NH-, -N(alkyl)-, -NH-S(O)<sub>0-2</sub>-, -N(alkyl)-S(O)<sub>0-2</sub>-, -S(O)<sub>0-2</sub>-NH-, -S(O)<sub>0-2</sub>-N(alkyl)-, -NH-C(S)-, or -N(alkyl)-C(S)-;

R<sub>54</sub> is heteroaryl, aryl, arylalkyl, heterocycloalkyl, CO<sub>2</sub>H, -CO<sub>2</sub>-alkyl, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -C(O)NH<sub>2</sub>, C<sub>1</sub>-C<sub>8</sub> alkyl, OH, aryloxy, alkoxy, arylalkoxy, NH<sub>2</sub>, NH(alkyl), N(alkyl)(alkyl), or -C<sub>1</sub>-C<sub>6</sub> alkyl-CO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, CO<sub>2</sub>H, -CO<sub>2</sub>-alkyl, thioalkoxy, halogen, haloalkyl, haloalkoxy,

hydroxyalkyl, alkanoyl, NO<sub>2</sub>, CN, alkoxy carbonyl, or aminocarbonyl;

X is selected from the group consisting of -C<sub>1</sub>-C<sub>6</sub> alkylidanyl optionally optionally substituted with 1, 2, or 3 methyl groups; and -NR<sub>4-6</sub>-; or

R<sub>4</sub> and R<sub>4-6</sub> combine to form -(CH<sub>2</sub>)<sub>n<sub>10</sub></sub>-, wherein n<sub>10</sub> is 1, 2, 3, or 4;

Z is selected from the group consisting of a bond; SO<sub>2</sub>; SO; S; and C(O);

Y is selected from the group consisting of H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl; C<sub>6</sub>-C<sub>10</sub> aryl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from the group consisting of halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C<sub>3</sub>-C<sub>8</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, and halogen; alkoxy; aryl optionally substituted with halogen, alkyl, alkoxy, CN or NO<sub>2</sub>; arylalkyl optionally substituted with halogen, alkyl, alkoxy, CN or NO<sub>2</sub>; wherein

Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or

Y<sub>1</sub>, Y<sub>2</sub> and the nitrogen to which they are attached form a ring selected from the group consisting of piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen;

R<sub>20</sub> at each occurrence is independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkanoyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups independently selected from halogen, alkyl, hydroxy, alkoxy, and NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>, wherein

R<sub>26</sub> is selected from the group consisting of -C(O)-, -SO<sub>2</sub>-, -CO<sub>2</sub>-, -C(O)NH-, and -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-;

R<sub>27</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, heterocycloalkyl, and heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, haloalkyl, hydroxyalkyl, -C(O)NH<sub>2</sub>, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);

R<sub>1</sub> is -(CH<sub>2</sub>)<sub>1-2</sub>-S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), or

C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, OH, =O, -SH, -C≡N, -CF<sub>3</sub>, -C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R'-, -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or

C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino, or

aryl, heteroaryl, heterocyclyl, -C<sub>1</sub>-C<sub>6</sub> alkyl-aryl, -C<sub>1</sub>-C<sub>6</sub> alkyl-heteroaryl, or -C<sub>1</sub>-C<sub>6</sub> alkyl-heterocyclyl, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NR<sub>105</sub>R'<sub>105</sub>, -CO<sub>2</sub>R, -N(R)COR', or -N(R)SO<sub>2</sub>R', -C(=O)-(C<sub>1</sub>-C<sub>4</sub>) alkyl, -SO<sub>2</sub>-amino, -SO<sub>2</sub>-

- mono or dialkylamino, -C(=O)-amino, -C(=O)-mono or dialkylamino, -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub>) alkyl, or -C<sub>1</sub>-C<sub>6</sub> alkoxy optionally substituted with 1, 2, or 3 groups which are independently a halogen, or
- 5 C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, -C<sub>1</sub>-C<sub>6</sub> alkyl and mono- or dialkylamino, or
- 10 C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, -C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, mono- or dialkylamino and -C<sub>1</sub>-C<sub>3</sub> alkyl, or
- 15 C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>10</sub> alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, C<sub>1</sub>-C<sub>6</sub> alkyl and mono- or dialkylamino; and
- the heterocyclyl group is optionally further substituted with oxo;
- 20 R and R' independently are hydrogen or C<sub>1</sub>-C<sub>10</sub> alkyl;
- R<sub>2</sub> is selected from the group consisting of H; C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with 1, 2, or 3 substituents that are independently selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy,
- 25 and -NR<sub>1-a</sub>R<sub>1-b</sub>; wherein
- R<sub>1-a</sub> and R<sub>1-b</sub> are -H or C<sub>1</sub>-C<sub>6</sub> alkyl; -(CH<sub>2</sub>)<sub>0-4</sub>-aryl; -(CH<sub>2</sub>)<sub>0-4</sub>-heteroaryl; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkynyl; -CONR<sub>N-2</sub>R<sub>N-3</sub>; -SO<sub>2</sub>NR<sub>N-2</sub>R<sub>N-3</sub>; -CO<sub>2</sub>H; and -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl);
- 30 R<sub>3</sub> is selected from the group consisting of H; C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -

NR<sub>1-a</sub>R<sub>1-b</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-aryl; -(CH<sub>2</sub>)<sub>0-4</sub>-heteroaryl; C<sub>2</sub>-C<sub>6</sub> alkenyl;  
 C<sub>2</sub>-C<sub>6</sub> alkynyl; -CO-NR<sub>N-2</sub>R<sub>N-3</sub>; -SO<sub>2</sub>-NR<sub>N-2</sub>R<sub>N-3</sub>; -CO<sub>2</sub>H; and -CO-  
 O-(C<sub>1</sub>-C<sub>4</sub> alkyl);

or

5 R<sub>2</sub>, R<sub>3</sub> and the carbon to which they are attached form a  
 carbocycle of three thru seven carbon atoms, wherein one  
 carbon atom is optionally replaced by a group selected  
 from-O-, -S-, -SO<sub>2</sub>-, or -NR<sub>N-2</sub>-;

R<sub>C</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>10</sub> alkyl  
 10 optionally substituted with 1, 2, or 3 groups  
 independently selected from the group consisting of R<sub>205</sub>,  
 -OC=ONR<sub>235</sub>R<sub>240</sub>, -S(=O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), -SH, -NR<sub>235</sub>C=ONR<sub>235</sub>R<sub>240</sub>,  
 -C=ONR<sub>235</sub>R<sub>240</sub>, and -S(=O)<sub>2</sub>NR<sub>235</sub>R<sub>240</sub>; -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>8</sub>)  
 cycloalkyl wherein the cycloalkyl is optionally  
 15 substituted with 1, 2, or 3 groups independently selected  
 from the group consisting of R<sub>205</sub>, -CO<sub>2</sub>H, and -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub>  
 alkyl); -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl; -  
 (CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocycloalkyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl-  
 heteroaryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl-heterocycloalkyl;  
 20 -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl-aryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl-aryl; -  
 (CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl-heterocycloalkyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-  
 heteroaryl-heteroaryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocycloalkyl-  
 heteroaryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocycloalkyl-  
 heterocycloalkyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocycloalkyl-aryl;  
 25 -[C(R<sub>255</sub>)(R<sub>260</sub>)]<sub>1-3</sub>-CO-N-(R<sub>255</sub>)<sub>2</sub>; -CH(aryl)<sub>2</sub>; -CH(heteroaryl)<sub>2</sub>;  
 -CH(heterocycloalkyl)<sub>2</sub>; -CH(aryl)(heteroaryl);  
 cyclopentyl, cyclohexyl, or cycloheptyl ring fused to  
 aryl, heteroaryl, or heterocycloalkyl wherein one carbon  
 of the cyclopentyl, cyclohexyl, or cycloheptyl is  
 30 optionally replaced with NH, NR<sub>215</sub>, O, or S(=O)<sub>0-2</sub>, and  
 wherein the cyclopentyl, cyclohexyl, or cycloheptyl group  
 can be optionally substituted with 1 or 2 groups that are  
 independently R<sub>205</sub> or =O; -CO-NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 C<sub>2</sub>-C<sub>10</sub> alkenyl optionally substituted with 1, 2, or 3 R<sub>205</sub>

groups; C<sub>2</sub>-C<sub>10</sub> alkynyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -(CH<sub>2</sub>)<sub>0-1</sub>-CH((CH<sub>2</sub>)<sub>0-6</sub>-OH)-(CH<sub>2</sub>)<sub>0-1</sub>-aryl; -(CH<sub>2</sub>)<sub>0-1</sub>-CHR<sub>C-6</sub>-(CH<sub>2</sub>)<sub>0-1</sub>-heteroaryl; -CH(-aryl or -heteroaryl)-CO-O(C<sub>1</sub>-C<sub>4</sub> alkyl); -CH(-CH<sub>2</sub>-OH)-CH(OH)-phenyl-NO<sub>2</sub>; (C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-OH; -CH<sub>2</sub>-NH-CH<sub>2</sub>-CH(-O-CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>; -H; and -(CH<sub>2</sub>)<sub>0-6</sub>-C(=NR<sub>235</sub>)(NR<sub>235</sub>R<sub>240</sub>); wherein each aryl is optionally substituted with 1, 2, or 3 R<sub>200</sub>; each heteroaryl is optionally substituted with 1, 2, 3, or 4 R<sub>200</sub>;

each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R<sub>210</sub>;

R<sub>200</sub> at each occurrence is independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; OH; -NO<sub>2</sub>; halogen; -CO<sub>2</sub>H; C≡N; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>220</sub>R<sub>225</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>1</sub>-C<sub>12</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub> alkenyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub> alkynyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO-aryl; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-heteroaryl; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-heterocycloalkyl; -(CH<sub>2</sub>)<sub>0-4</sub>-CO<sub>2</sub>R<sub>215</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-NR<sub>220</sub>R<sub>225</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-SO-(C<sub>1</sub>-C<sub>8</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>12</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>215</sub>)-CO<sub>2</sub>R<sub>215</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>215</sub>)-CO-N(R<sub>215</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-N-CS-N(R<sub>215</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-N(-H or R<sub>215</sub>)-CO-R<sub>220</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-NR<sub>220</sub>R<sub>225</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-O-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-O-P(O)-(OR<sub>240</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-O-CO-N(R<sub>215</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-O-CS-N(R<sub>215</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-O-(R<sub>215</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-O-(R<sub>215</sub>)<sub>2</sub>-COOH; -(CH<sub>2</sub>)<sub>0-4</sub>-S-(R<sub>215</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-O-(C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, or 5 -F); C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>2</sub>-C<sub>6</sub> alkenyl optionally substituted with 1 or 2 R<sub>205</sub> groups; C<sub>2</sub>-C<sub>6</sub> alkynyl optionally substituted with 1 or 2 R<sub>205</sub> groups; -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>215</sub>)-SO<sub>2</sub>-R<sub>220</sub>; and -(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>7</sub> cycloalkyl;

wherein each aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups

that are independently  $R_{205}$ ,  $R_{210}$  or  $C_1-C_6$  alkyl substituted with 1, 2, or 3 groups that are independently  $R_{205}$  or  $R_{210}$ ;

wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently  $R_{210}$ ;

wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently  $R_{205}$ ,  $R_{210}$ , or  $C_1-C_6$  alkyl substituted with 1, 2, or 3 groups that are independently  $R_{205}$  or  $R_{210}$ ;

$R_{205}$  at each occurrence is independently selected from the group consisting of  $C_1-C_6$  alkyl, halogen, -OH, -O-phenyl, -SH,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_6$  alkoxy,  $NH_2$ ,  $NH(C_1-C_6$  alkyl), and  $N-(C_1-C_6$  alkyl)( $C_1-C_6$  alkyl);

$R_{210}$  at each occurrence is independently selected from the group consisting of  $C_1-C_6$  alkyl optionally substituted with 1, 2, or 3  $R_{205}$  groups;  $C_2-C_6$  alkenyl optionally substituted with 1, 2, or 3  $R_{205}$  groups;  $C_2-C_6$  alkynyl optionally substituted with 1, 2, or 3  $R_{205}$  groups; halogen;  $C_1-C_6$  alkoxy;  $C_1-C_6$  haloalkoxy;  $-NR_{220}R_{225}$ ; OH;  $C\equiv N$ ;  $C_3-C_7$  cycloalkyl optionally substituted with 1, 2, or 3  $R_{205}$  groups;  $-CO-(C_1-C_4$  alkyl);  $-SO_2-NR_{235}R_{240}$ ;  $-CO-NR_{235}R_{240}$ ;  $-SO_2-(C_1-C_4$  alkyl); and =O; wherein

$R_{215}$  at each occurrence is independently selected from the group consisting of  $C_1-C_6$  alkyl,  $-(CH_2)_{0-2}-(aryl)$ ,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl,  $C_3-C_7$  cycloalkyl, and  $-(CH_2)_{0-2}-(heteroaryl)$ ,  $-(CH_2)_{0-2}-(heterocycloalkyl)$ ;

wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently  $R_{205}$  or  $R_{210}$ ; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3  $R_{210}$ ; wherein

each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>;

R<sub>220</sub> and R<sub>225</sub> at each occurrence are independently selected from the group consisting of -H, -C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, amino C<sub>1</sub>-C<sub>6</sub> alkyl; halo C<sub>1</sub>-C<sub>6</sub> alkyl; -C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>2</sub> alkyl)-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), -C<sub>2</sub>-C<sub>6</sub> alkenyl, -C<sub>2</sub>-C<sub>6</sub> alkynyl, -C<sub>1</sub>-C<sub>6</sub> alkyl chain with one double bond and one triple bond, -aryl, -heteroaryl, and -heterocycloalkyl; wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>270</sub> groups, wherein

R<sub>270</sub> at each occurrence is independently R<sub>205</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; C<sub>2</sub>-C<sub>6</sub> alkenyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; C<sub>2</sub>-C<sub>6</sub> alkynyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; halogen; C<sub>1</sub>-C<sub>6</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkoxy; NR<sub>235</sub>R<sub>240</sub>; OH; C≡N; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); -SO<sub>2</sub>-NR<sub>235</sub>R<sub>240</sub>; -CO-NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); and =O; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>205</sub> groups;

R<sub>235</sub> and R<sub>240</sub> at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, -(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, aryl C<sub>1</sub>-C<sub>4</sub> alkyl, heteroaryl C<sub>1</sub>-C<sub>4</sub> alkyl, and phenyl; or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6,



or 7 carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-, -SO<sub>2</sub>-, and -NR<sub>220</sub>-;

R<sub>255</sub> and R<sub>260</sub> at each occurrence are independently selected from the group consisting of H; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; C<sub>2</sub>-C<sub>6</sub> alkenyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; C<sub>2</sub>-C<sub>6</sub> alkynyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -(CH<sub>2</sub>)<sub>1-2</sub>-S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -(C<sub>1</sub>-C<sub>4</sub> alkyl)-aryl; -(C<sub>1</sub>-C<sub>4</sub> alkyl)-heteroaryl; -(C<sub>1</sub>-C<sub>4</sub> alkyl)-heterocycloalkyl; -aryl; -heteroaryl; -heterocycloalkyl; -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>265</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-aryl; -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>265</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-heteroaryl; and; -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>265</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-heterocycloalkyl; wherein R<sub>265</sub> at each occurrence is independently -O-, -S- or -N(C<sub>1</sub>-C<sub>6</sub> alkyl)-;

each aryl or phenyl is optionally substituted with 1, 2, or 3 groups that are independently R<sub>205</sub>, R<sub>210</sub>, or C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 1, 2, or 3 groups that are independently R<sub>205</sub> or R<sub>210</sub>;

each heteroaryl is optionally substituted with 1, 2, 3, or 4 R<sub>200</sub>, each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R<sub>210</sub>.

The invention also encompasses methods for the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease comprising

administration of a therapeutically effective amount of a compound or salt of formula X, to a patient in need thereof.

Preferably, the patient is a human.

More preferably, the disease is Alzheimer's disease.

5 More preferably, the disease is dementia.

The invention also provides pharmaceutical compositions comprising a compound or salt of formula X and at least one pharmaceutically acceptable carrier, solvent, adjuvant or  
10 diluent.

The invention also provides the use of a compound or salt according to formula X for the manufacture of a medicament.

The invention also provides the use of a compound or salt of formula X for the treatment or prevention of Alzheimer's  
15 disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with  
20 progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease.

The invention also provides compounds, pharmaceutical  
25 compositions, kits, and methods for inhibiting beta-secretase-mediated cleavage of amyloid precursor protein (APP). More particularly, the compounds, compositions, and methods of the invention are effective to inhibit the production of A-beta peptide and to treat or prevent any human or veterinary disease  
30 or condition associated with a pathological form of A-beta peptide.

The compounds, compositions, and methods of the invention are useful for treating humans who have Alzheimer's Disease (AD), for helping prevent or delay the onset of AD, for

treating patients with mild cognitive impairment (MCI), and preventing or delaying the onset of AD in those patients who would otherwise be expected to progress from MCI to AD, for treating Down's syndrome, for treating Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type, for treating cerebral beta-amyloid angiopathy and preventing its potential consequences such as single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, for treating dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type AD, and for treating frontotemporal dementias with parkinsonism (FTDP).

15 The compounds of the invention possess beta-secretase inhibitory activity. The inhibitory activities of the compounds of the invention is readily demonstrated, for example, using one or more of the assays described herein or known in the art.

20 Unless the substituents for a particular formula are expressly defined for that formula, they are understood to carry the definitions set forth in connection with the preceding formula to which the particular formula makes reference.

25 The invention also provides methods of preparing the compounds of the invention and the intermediates used in those methods.

**Detailed Description of the Invention**

As noted above, the invention provides compound of Formula X.

In alternate aspects of the invention, R<sub>5</sub> is is a C<sub>3</sub>-C<sub>8</sub> cycloalkyl optionally substituted with one or two groups that are C<sub>1</sub>-C<sub>6</sub> alkyl, more preferably C<sub>1</sub>-C<sub>2</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, more preferably C<sub>1</sub>-C<sub>2</sub> alkoxy, CF<sub>3</sub>, OH, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), halogen, CN, or NO<sub>2</sub>.

In this aspect, preferred R<sub>5</sub> groups are C<sub>3</sub>-C<sub>6</sub> cycloalkyl groups optionally substituted with 2, more preferably 1 group selected from methyl, ethyl, OH, halogen, preferably F or Cl, methoxy or ethoxy. Other preferred R<sub>5</sub> groups within this aspect are C<sub>3</sub>-C<sub>6</sub> cycloalkyl groups substituted with 1 or 2 groups that are independently CF<sub>3</sub>, Cl, F, methyl, ethyl or cyano.

Preferred compounds of formula X include those of formula X-I, i.e., compounds of formula X wherein

R<sub>1</sub> is (CH<sub>2</sub>)<sub>n1</sub>-(R<sub>1-aryl</sub>) where n<sub>1</sub> is zero or one and R<sub>1-aryl</sub> is phenyl optionally substituted with 1, 2, 3, or 4 groups independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -NR<sub>1-a</sub>R<sub>1-b</sub>, -C≡N, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>3</sub> alkoxy; halogen; C<sub>1</sub>-C<sub>6</sub> alkoxy; -NR<sub>N-2</sub>R<sub>N-3</sub>; and OH; wherein

R<sub>N-2</sub> and R<sub>N-3</sub> at each occurrence are independently selected from the group consisting of -C<sub>1</sub>-C<sub>8</sub> alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of -OH, -NH<sub>2</sub>, phenyl and halogen; -C<sub>3</sub>-C<sub>8</sub> cycloalkyl; -(C<sub>1</sub>-C<sub>2</sub> alkyl)-(C<sub>3</sub>-C<sub>8</sub> cycloalkyl); -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl); -C<sub>2</sub>-C<sub>6</sub> alkenyl; -C<sub>2</sub>-C<sub>6</sub> alkynyl; -C<sub>1</sub>-C<sub>6</sub> alkyl chain with one double bond and one triple bond; aryl; heteroaryl; heterocycloalkyl;

or

$R_{N-2}$ ,  $R_{N-3}$  and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or heteroaryl group, wherein said heterocycloalkyl or heteroaryl group is optionally fused to a benzene, pyridine, or pyrimidine ring, and said groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that at each occurrence are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -OH, -C(O)NH<sub>2</sub>, -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> thioalkoxy, and C<sub>1</sub>-C<sub>6</sub> thioalkoxy C<sub>1</sub>-C<sub>6</sub> alkyl.

More preferred compounds of formula X-I include those of formula X-II, i.e., compounds of formula X-I wherein  $R_2$  and  $R_3$  are independently selected from H or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>.

Preferred compounds of formula X-II include those wherein  $R_C$  is selected from the group consisting of C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of  $R_{205}$ , -OC=ONR<sub>235</sub>R<sub>240</sub>, -S(=O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), -SH, -NR<sub>235</sub>C=ONR<sub>235</sub>R<sub>240</sub>, -C=ONR<sub>235</sub>R<sub>240</sub>, and -S(=O)<sub>2</sub>NR<sub>235</sub>R<sub>240</sub>; -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>8</sub>) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of  $R_{205}$ , -CO<sub>2</sub>H, and -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocycloalkyl; -[C(R<sub>255</sub>)(R<sub>260</sub>)]<sub>1-3</sub>-CO-N-(R<sub>255</sub>)<sub>2</sub>; -CH(aryl)<sub>2</sub>; -CH(heteroaryl)<sub>2</sub>; -CH(heterocycloalkyl)<sub>2</sub>; -CH(aryl)(heteroaryl); -CO-

NR<sub>235</sub>R<sub>240</sub>; -(CH<sub>2</sub>)<sub>0-1</sub>-CH((CH<sub>2</sub>)<sub>0-6</sub>-OH)-(CH<sub>2</sub>)<sub>0-1</sub>-aryl; -(CH<sub>2</sub>)<sub>0-1</sub>-  
 CHR<sub>C-6</sub>-(CH<sub>2</sub>)<sub>0-1</sub>-heteroaryl; -CH(-aryl or -heteroaryl)-CO-  
 O(C<sub>1</sub>-C<sub>4</sub> alkyl); -CH(-CH<sub>2</sub>-OH)-CH(OH)-phenyl-NO<sub>2</sub>; (C<sub>1</sub>-C<sub>6</sub>  
 alkyl)-O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-OH; -CH<sub>2</sub>-NH-CH<sub>2</sub>-CH(-O-CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>; -H;  
 5 and -(CH<sub>2</sub>)<sub>0-6</sub>-C(=NR<sub>235</sub>)(NR<sub>235</sub>R<sub>240</sub>); wherein

each aryl is optionally substituted with 1, 2, or 3 R<sub>200</sub>;  
 each heteroaryl is optionally substituted with 1, 2, 3, or

4 R<sub>200</sub>;

each heterocycloalkyl is optionally substituted with 1, 2,  
 10 3, or 4 R<sub>210</sub>;

R<sub>200</sub> at each occurrence is independently selected from the  
 group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl optionally  
 substituted with 1, 2, or 3 R<sub>205</sub> groups; OH; -NO<sub>2</sub>;  
 halogen; -CO<sub>2</sub>H; C≡N; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>220</sub>R<sub>225</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-  
 15 (C<sub>1</sub>-C<sub>12</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO<sub>2</sub>R<sub>215</sub>; and -(CH<sub>2</sub>)<sub>0-4</sub>-O-(C<sub>1</sub>-C<sub>6</sub>  
 alkyl optionally substituted with 1, 2, 3, or 5 -F);

wherein each aryl group at each occurrence is  
 optionally substituted with 1, 2, or 3 groups  
 that are independently R<sub>205</sub>, R<sub>210</sub> or C<sub>1</sub>-C<sub>6</sub> alkyl  
 20 substituted with 1, 2, or 3 groups that are  
 independently R<sub>205</sub> or R<sub>210</sub>;

wherein each heterocycloalkyl group at each  
 occurrence is optionally substituted with 1, 2,  
 or 3 groups that are independently R<sub>210</sub>;

25 wherein each heteroaryl group at each occurrence is  
 optionally substituted with 1, 2, or 3 groups  
 that are independently R<sub>205</sub>, R<sub>210</sub>, or C<sub>1</sub>-C<sub>6</sub> alkyl  
 substituted with 1, 2, or 3 groups that are  
 independently R<sub>205</sub> or R<sub>210</sub>;

30 R<sub>205</sub> at each occurrence is independently selected from the  
 group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, -OH, -O-  
 phenyl, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub>  
 alkyl), and N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);

- R<sub>210</sub> at each occurrence is independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; halogen; C<sub>1</sub>-C<sub>6</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkoxy; -NR<sub>220</sub>R<sub>225</sub>; OH; C≡N; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); -SO<sub>2</sub>-NR<sub>235</sub>R<sub>240</sub>; -CO-NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); and =O; wherein
- R<sub>215</sub> at each occurrence is independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(aryl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and -(CH<sub>2</sub>)<sub>0-2</sub>-(heteroaryl), -(CH<sub>2</sub>)<sub>0-2</sub>-(heterocycloalkyl); wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R<sub>205</sub> or R<sub>210</sub>; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>;
- R<sub>220</sub> and R<sub>225</sub> at each occurrence are independently selected from the group consisting of -H, -C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, amino C<sub>1</sub>-C<sub>6</sub> alkyl; halo C<sub>1</sub>-C<sub>6</sub> alkyl; -C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), -aryl, -heteroaryl, and -heterocycloalkyl; wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>270</sub> groups, each heteroaryl is optionally substituted with 1, 2, 3, or 4 R<sub>200</sub>, each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R<sub>210</sub> wherein
- R<sub>270</sub> at each occurrence is independently R<sub>205</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; halogen; C<sub>1</sub>-C<sub>6</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkoxy; NR<sub>235</sub>R<sub>240</sub>; OH; C≡N; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); and =O; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>205</sub> groups;

wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; R<sub>235</sub> and R<sub>240</sub> at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;

5 R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, or

10 R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6, or 7 carbon atoms, wherein the carbocycle is optionally substituted with 1 or 2 groups that are independently OH, methyl, Cl, F, OCH<sub>3</sub>, CF<sub>3</sub>, NO<sub>2</sub>, or CN;

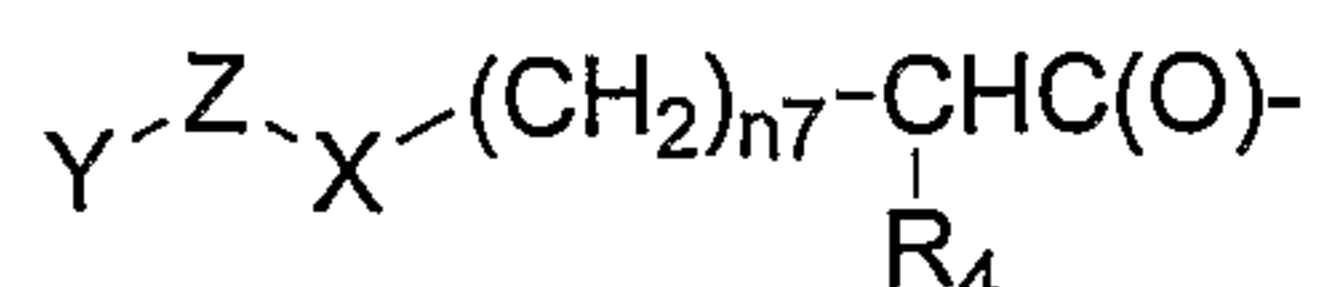
15 R<sub>255</sub> and R<sub>260</sub> at each occurrence are independently selected from the group consisting of H; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -(C<sub>1</sub>-C<sub>4</sub> alkyl)-aryl; -(C<sub>1</sub>-C<sub>4</sub> alkyl)-heteroaryl; -(C<sub>1</sub>-C<sub>4</sub> alkyl)-heterocycloalkyl; 20 aryl; heteroaryl; heterocycloalkyl; -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>265</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-aryl; -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>265</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-heteroaryl; and; -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>265</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-heterocycloalkyl; wherein R<sub>265</sub> at each occurrence is independently -O-, -S- or -N(C<sub>1</sub>-C<sub>6</sub> alkyl)-;

25 each aryl or phenyl is optionally substituted with 1, 2, or 3 groups that are independently R<sub>205</sub>, R<sub>210</sub>, or C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 1, 2, or 3 groups that are independently R<sub>205</sub> or R<sub>210</sub>.

30 Other preferred compounds of formulas X-I and X-II include compounds of formula X-III, i.e., those of formulas X-I or X-II wherein

R<sub>N</sub> is:





wherein

R<sub>4</sub> is NH<sub>2</sub>; -NH-(CH<sub>2</sub>)<sub>n<sub>6</sub></sub>-R<sub>4-1</sub>; -NHR<sub>8</sub>; -NR<sub>50</sub>C(O)R<sub>5</sub>; or -NR<sub>50</sub>CO<sub>2</sub>R<sub>51</sub>;

wherein

5 n<sub>6</sub> is 0, 1, 2, or 3;

n<sub>7</sub> is 0, 1, 2, or 3;

R<sub>4-1</sub> is selected from the group consisting of -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub> alkyl), -SO-(C<sub>1</sub>-C<sub>8</sub> alkyl), -S-(C<sub>1</sub>-C<sub>8</sub> alkyl), -S-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl), -SO<sub>2</sub>-NR<sub>4-2</sub>R<sub>4-3</sub>; -CO-C<sub>1</sub>-C<sub>2</sub> alkyl; -CO-NR<sub>4-</sub>  
10 <sub>3</sub>R<sub>4-4</sub>;

R<sub>4-2</sub> and R<sub>4-3</sub> are independently H, C<sub>1</sub>-C<sub>3</sub> alkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

R<sub>4-4</sub> is alkyl, phenylalkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, or phenylalkanoyl;

15 R<sub>5</sub> is cyclopropyl; cyclobutyl; cyclopentyl; and cyclohexyl;

wherein each cycloalkyl group is optionally substituted with one or two groups that are C<sub>1</sub>-C<sub>6</sub> alkyl, more preferably C<sub>1</sub>-C<sub>2</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, more preferably C<sub>1</sub>-C<sub>2</sub> alkoxy, CF<sub>3</sub>, OH, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), halogen, CN, or NO<sub>2</sub>; or the cycloalkyl group is substituted with 1 or 2 groups that are independently CF<sub>3</sub>, Cl, F, methyl, ethyl or cyano; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, -NR<sub>6</sub>R<sub>7</sub>, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl, C<sub>5</sub>-C<sub>6</sub> heteroaryl, phenyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -S-C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>7</sub>, -CO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, or phenyloxy; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or OH; heterocycloalkyl optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or C<sub>2</sub>-C<sub>4</sub> alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4

groups that are independently halogen, OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkyl; and -NR<sub>6</sub>R<sub>7</sub>; wherein

R<sub>6</sub> and R<sub>7</sub> are independently selected from the group

consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, and phenyl C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>8</sub> is selected from the group consisting of -SO<sub>2</sub>-

heteroaryl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl or halogen;, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heterocycloalkyl, -C(O)NHR<sub>9</sub>,

heterocycloalkyl, -S-C<sub>2</sub>-C<sub>4</sub> alkanoyl, wherein

R<sub>9</sub> is phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, or H;

R<sub>50</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>51</sub> is selected from the group consisting of phenyl C<sub>1</sub>-C<sub>4</sub>

alkyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR<sub>6</sub>R<sub>7</sub>, -C(O)NR<sub>6</sub>R<sub>7</sub>, C<sub>3</sub>-C<sub>7</sub> or -C<sub>1</sub>-C<sub>4</sub> alkoxy;

heterocycloalkyl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub>

alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl,

and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; heterocycloalkylalkyl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl,

phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; alkenyl;

alkynyl; heteroaryl optionally substituted with 1, 2,

or 3 groups that are independently OH, C<sub>1</sub>-C<sub>4</sub> alkyl,

C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); heteroarylalkyl optionally

substituted with 1, 2, or 3 groups that are

independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>,

NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); phenyl;

C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and cycloalkylalkyl, wherein the

phenyl; C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and cycloalkylalkyl groups

are optionally substituted with 1, 2, 3, 4 or 5

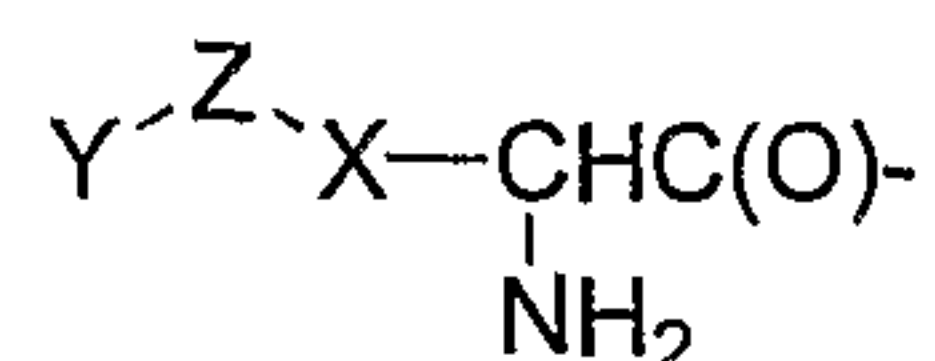
groups that are independently halogen, CN, NO<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>

alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, hydroxy, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> thioalkoxy, C<sub>1</sub>-C<sub>6</sub> thioalkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkoxy.

5

Preferred compounds of formula X-III include compounds wherein

R<sub>N</sub> is



10 wherein

X is C<sub>1</sub>-C<sub>4</sub> alkylidenyl optionally optionally substituted with 1, 2, or 3 methyl groups; or -NR<sub>4-6</sub>-; or

R<sub>4</sub> and R<sub>4-6</sub> combine to form -(CH<sub>2</sub>)<sub>n<sub>10</sub></sub>-, wherein

n<sub>10</sub> is 1, 2, 3, or 4;

15 Z is selected from a bond; SO<sub>2</sub>; SO; S; and C(O);

Y is selected from H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl containing at least one N, O, or S; phenyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C<sub>3</sub>-C<sub>8</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, and halogen; alkoxy; phenyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

25

Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; and C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or

30

-N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl,  
 piperidinyl, morpholinyl, and pyrrolidinyl, wherein  
 each ring is optionally substituted with 1, 2, 3, or  
 4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
 5 alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen; and  
 R<sub>20</sub> at each occurrence is independently selected from hydrogen,  
 C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-  
 C<sub>6</sub> alkanoyl, each of which is unsubstituted or substituted  
 with 1, or 2 groups independently selected from halogen,  
 10 C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>,  
 wherein  
 R<sub>26</sub> is selected from -C(O)-, -SO<sub>2</sub>-, -CO<sub>2</sub>-, -C(O)NH-, and  
 -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-; and  
 R<sub>27</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl,  
 15 C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, heterocycloalkyl, and  
 heteroaryl, wherein each of the above is  
 unsubstituted or substituted with 1, 2, 3, 4, or 5  
 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub>  
 alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub>  
 20 alkyl, -C(O)NH<sub>2</sub>, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub>  
 alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -  
 C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl).

More preferred compounds of formula X-III include  
 25 compounds wherein  
 X is C<sub>1</sub>-C<sub>4</sub> alkylidenyl optionally optionally substituted with  
 1, 2, or 3 methyl groups;  
 Z is selected from SO<sub>2</sub>; SO; S; and C(O);  
 Y is selected from H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl  
 30 containing at least one N, O, or S; phenyl; OH; -  
 N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 thru  
 3 substituents which can be the same or different and are  
 selected from the group consisting of halogen, hydroxy,  
 alkoxy, thioalkoxy, and haloalkoxy; C<sub>3</sub>-C<sub>8</sub> cycloalkyl

optionally substituted with 1, 2, or 3 groups  
independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, and halogen;  
alkoxy; phenyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub>  
alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl  
5 optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub>  
alkoxy, CN or NO<sub>2</sub>; wherein

Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>6</sub> alkyl  
optionally substituted with 1, 2, or 3 substituents  
selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub>  
10 alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub>  
alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub>  
alkyl; or C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or  
-N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl,  
piperidinyl, morpholinyl, and pyrrolidinyl, wherein  
15 each ring is optionally substituted with 1, 2, 3, or  
4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen;

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl,  
C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl,  
20 each of which is unsubstituted or substituted with 1 or 2  
groups independently selected from halogen, hydroxy, C<sub>1</sub>-C<sub>6</sub>  
alkoxy, and NH<sub>2</sub>.

Even more preferred compounds of formula X-III include  
25 compounds wherein

R<sub>C</sub> is C<sub>1</sub>-C<sub>8</sub> alkyl optionally substituted with 1, 2, or 3 groups  
independently selected from the group consisting of R<sub>205</sub>,  
-OC=ONR<sub>235</sub>R<sub>240</sub>, -S(=O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), -SH, -C=ONR<sub>235</sub>R<sub>240</sub>, and  
-S(=O)<sub>2</sub>NR<sub>235</sub>R<sub>240</sub>; -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>8</sub>) cycloalkyl wherein the  
30 cycloalkyl is optionally substituted with 1, 2, or 3  
groups independently selected from the group consisting of  
R<sub>205</sub>, -CO<sub>2</sub>H, and -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-phenyl;  
-(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocycloalkyl;  
-(CH<sub>2</sub>)<sub>0-1</sub>-CH((CH<sub>2</sub>)<sub>0-4</sub>-OH)-(CH<sub>2</sub>)<sub>0-1</sub>-phenyl; -(CH<sub>2</sub>)<sub>0-1</sub>-CHR<sub>C-6</sub>-

(CH<sub>2</sub>)<sub>0-1</sub>-heteroaryl; -CH(-CH<sub>2</sub>-OH)-CH(OH)-phenyl-NO<sub>2</sub>; (C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-OH; or -(CH<sub>2</sub>)<sub>0-6</sub>-C(=NR<sub>235</sub>)(NR<sub>235</sub>R<sub>240</sub>); wherein

each aryl is optionally substituted with 1, 2, or 3 R<sub>200</sub>;

5 each heteroaryl is optionally substituted with 1, 2, 3, or 4 R<sub>200</sub>;

each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R<sub>210</sub>;

10 R<sub>200</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; OH; -NO<sub>2</sub>; halogen; -CO<sub>2</sub>H; C≡N; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>220</sub>R<sub>225</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>1</sub>-C<sub>12</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO<sub>2</sub>R<sub>215</sub>; or -(CH<sub>2</sub>)<sub>0-4</sub>-O-(C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, or 5 -F);

15 R<sub>205</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, -OH, -O-phenyl, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);

20 R<sub>210</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; halogen; C<sub>1</sub>-C<sub>6</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkoxy; -NR<sub>220</sub>R<sub>225</sub>; OH; C≡N; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); -SO<sub>2</sub>-NR<sub>235</sub>R<sub>240</sub>; -CO-NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); and =O; wherein

25 R<sub>215</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(phenyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and -(CH<sub>2</sub>)<sub>0-2</sub>-(heteroaryl), -(CH<sub>2</sub>)<sub>0-2</sub>-(heterocycloalkyl); wherein the phenyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are

30 independently R<sub>205</sub> or R<sub>210</sub>; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>;

R<sub>220</sub> and R<sub>225</sub> at each occurrence are independently -H, -C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl; -C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl);

R<sub>235</sub> and R<sub>240</sub> at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6, or 7 carbon atoms.

Still yet even more preferred compounds of formula X-III include compounds wherein

R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, hydroxy, and C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, or 3 substituents halogen, OH, SH, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), C≡N, CF<sub>3</sub>;

R<sub>2</sub> and R<sub>3</sub> are independently selected from H or C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1 substituent selected from halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), and NH(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> alkoxy C<sub>1</sub>-C<sub>4</sub> alkyl, halo C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, each of which is unsubstituted or substituted with 1 or 2 groups independently selected from halogen, hydroxy, and NH<sub>2</sub>;

R<sub>c</sub> is C<sub>1</sub>-C<sub>8</sub> alkyl optionally substituted with 1, 2, or 3 groups independently selected from R<sub>205</sub>, -SH, -C=ONR<sub>235</sub>R<sub>240</sub>, and -S(=O)<sub>2</sub>NR<sub>235</sub>R<sub>240</sub>; -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>6</sub>) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from R<sub>205</sub>, -CO<sub>2</sub>H, and -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-phenyl optionally substituted

with 1, 2, or 3 R<sub>200</sub>; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyridyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
 pyridazinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrimidinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
 pyrazinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-furyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-indolyl;  
 -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-thienyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrrolyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
 5 pyrazolyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-benzoxazolyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
 imidazolyl; each of the above heteroaryl groups is  
 optionally substituted with 1, 2, 3, or 4 R<sub>200</sub>; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
 3-imidazolidinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-tetrahydrofuryl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
 3-tetrahydropyranyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-piperazinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
 10 pyrrolidinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-piperidinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
 indolyl; each of the above heterocycloalkyl groups is  
 optionally substituted with 1, 2, 3, or 4 R<sub>210</sub>; (CH<sub>2</sub>)<sub>0-1</sub>-  
 CH((CH<sub>2</sub>)<sub>0-4</sub>-OH)-(CH<sub>2</sub>)<sub>0-1</sub>-phenyl; -(CH<sub>2</sub>)<sub>0-1</sub>-CH(C<sub>1</sub>-C<sub>4</sub>  
 hydroxyalkyl)-(CH<sub>2</sub>)<sub>0-1</sub>-pyridyl;  
 15 R<sub>200</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl  
 optionally substituted with 1, 2, or 3 R<sub>205</sub> groups;  
 OH; -NO<sub>2</sub>; halogen; -CO<sub>2</sub>H; C≡N; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>220</sub>R<sub>225</sub>;  
 -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>1</sub>-C<sub>8</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO<sub>2</sub>R<sub>215</sub>; and -  
 (CH<sub>2</sub>)<sub>0-4</sub>-O-(C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1,  
 20 2, 3, or 5 -F);  
 R<sub>205</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl,  
 halogen, -OH, -O-phenyl, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>  
 alkoxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), and N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub>  
 alkyl);  
 25 R<sub>210</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl  
 optionally substituted with 1 or 2 R<sub>205</sub> groups;  
 halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> haloalkoxy; -NR<sub>220</sub>R<sub>225</sub>; OH;  
 C≡N; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1  
 or 2 R<sub>205</sub> groups; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); -SO<sub>2</sub>-NR<sub>235</sub>R<sub>240</sub>; -CO-  
 30 NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); and =O; wherein  
 R<sub>215</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl,  
 -(CH<sub>2</sub>)<sub>0-2</sub>-(phenyl), C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-  
 (pyridyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(pyrrolyl), -(CH<sub>2</sub>)<sub>0-2</sub>-  
 (imidazolyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(pyrimidyl), -(CH<sub>2</sub>)<sub>0-2</sub>-



- (pyrrolidinyl),  $-(\text{CH}_2)_{0-2}$ -(imidazolidinyl)  $-(\text{CH}_2)_{0-2}$ -(piperazinyl),  $-(\text{CH}_2)_{0-2}$ -(piperidinyl), and  $-(\text{CH}_2)_{0-2}$ -(morpholinyl); wherein the phenyl group at each occurrence is optionally substituted with 1 or 2 groups that are independently  $\text{R}_{205}$  or  $\text{R}_{210}$ ; wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1 or 2  $\text{R}_{210}$ ; wherein each heteroaryl group at each occurrence is optionally substituted with 1 or 2  $\text{R}_{210}$ ;
- 5  $\text{R}_{220}$  and  $\text{R}_{225}$  at each occurrence are independently  $-\text{H}$ ,  $-\text{C}_1-\text{C}_4$  alkyl, hydroxy  $\text{C}_1-\text{C}_4$  alkyl, halo  $\text{C}_1-\text{C}_4$  alkyl;  $-\text{C}_3-\text{C}_6$  cycloalkyl, and  $-(\text{C}_1-\text{C}_4 \text{ alkyl})-\text{O}-(\text{C}_1-\text{C}_2 \text{ alkyl})$ ;
- $\text{R}_{235}$  and  $\text{R}_{240}$  at each occurrence are independently  $\text{H}$ , or  $\text{C}_1-\text{C}_6$  alkyl;
- 15  $\text{R}_{245}$  and  $\text{R}_{250}$  at each occurrence are independently  $\text{H}$ ,  $\text{C}_1-\text{C}_4$  alkyl,  $\text{C}_1-\text{C}_4$  hydroxyalkyl,  $\text{C}_1-\text{C}_4$  alkoxy,  $\text{C}_1-\text{C}_4$  haloalkoxy, or
- $\text{R}_{245}$  and  $\text{R}_{250}$  are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, or
- 20 6 carbon atoms.

Other more preferred compounds of formula X-III include compounds wherein

- 25 X is  $-\text{C}_1-\text{C}_3$  alkylidenyl optionally optionally substituted with 1 or 2 methyl groups;
- Z is  $\text{SO}_2$ ;  $\text{SO}$ ;  $\text{S}$ ; or  $\text{C}(\text{O})$ ;
- Y is  $\text{C}_1-\text{C}_4$  haloalkyl;  $\text{OH}$ ;  $-\text{N}(\text{Y}_1)(\text{Y}_2)$ ;  $\text{C}_1-\text{C}_{10}$  alkyl optionally substituted with 1 or 2 substituents which can be the same or different and are selected from halogen, hydroxy,  $\text{C}_1-\text{C}_4$  alkoxy,  $\text{C}_1-\text{C}_4$  thioalkoxy, and  $\text{C}_1-\text{C}_4$  haloalkoxy;  $\text{C}_1-\text{C}_4$  alkoxy; phenyl optionally substituted with halogen,  $\text{C}_1-\text{C}_4$  alkyl,  $\text{C}_1-\text{C}_4$  alkoxy,  $\text{CN}$  or  $\text{NO}_2$ ; and benzyl optionally substituted with halogen,  $\text{C}_1-\text{C}_4$  alkyl,  $\text{C}_1-\text{C}_4$  alkoxy,  $\text{CN}$  or  $\text{NO}_2$ ; wherein
- 30

Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>6</sub> alkyl  
 optionally substituted with 1, 2, or 3 substituents  
 selected from halogen, C<sub>1</sub>-C<sub>2</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
 and OH; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl;  
 5        benzyl; and C<sub>3</sub>-C<sub>6</sub> cycloalkyl C<sub>1</sub>-C<sub>2</sub> alkyl; or  
 -N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl,  
 piperidinyl, morpholinyl, and pyrrolidinyl, wherein  
 each ring is optionally substituted with 1, 2, 3, or  
 4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
 10        alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen.

Other even more preferred compounds of formula X-III  
 include those of formula X-IV, i.e., compounds of formula X-III  
 wherein

- 15        X is -C<sub>1</sub>-C<sub>3</sub> alkylidenyl optionally optionally substituted with 1  
           methyl group;  
           Z is SO<sub>2</sub>; SO; S; or C(O);  
           Y is OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); phenyl; benzyl; or C<sub>1</sub>-C<sub>10</sub> alkyl optionally  
 20        substituted with 1 or 2 substituents which can be the same  
           or different and are selected from halogen, hydroxy,  
           methoxy, ethoxy, thiomethoxy, thioethoxy, and CF<sub>3</sub>; wherein  
           Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>4</sub> alkyl  
           optionally substituted with 1 or 2 substituents  
           selected from halogen, methoxy, ethoxy, cyclopropyl,  
 25        and OH; or  
           -N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl,  
           piperidinyl, morpholinyl, and pyrrolidinyl, wherein  
           each ring is optionally substituted with 1 or 2  
           groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub>  
 30        alkoxy, or halogen;  
           R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, or 3  
           groups independently selected from methyl, ethyl, n-  
           propyl, isopropyl, hydroxymethyl, monohalomethyl,  
           dihalomethyl, trihalomethyl, -CH<sub>2</sub>CF<sub>3</sub>, methoxymethyl,

halogen, methoxy, ethoxy, n-propyloxy, isopropyloxy, and  
OH;

R<sub>2</sub> and R<sub>3</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl,

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl,  
5 or C<sub>2</sub>-C<sub>4</sub> alkanoyl;

R<sub>C</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub>  
groups; cyclopropyl, cyclopropylmethyl, cyclopentyl,  
cyclopentylmethyl, cyclohexyl, cyclohexylmethyl;

10 -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-phenyl optionally substituted with 1 or 2 R<sub>200</sub>  
groups; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyridyl optionally substituted with 1  
or 2 R<sub>200</sub>; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-piperazinyll; or (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
pyrrolidinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-piperidinyl; each of the above  
heterocycloalkyl groups is optionally substituted with 1  
or 2 R<sub>210</sub> groups;

15 R<sub>200</sub> at each occurrence is independently selected from C<sub>1</sub>-  
C<sub>4</sub> alkyl optionally substituted with 1 or 2 R<sub>205</sub>  
groups; OH; and halogen;

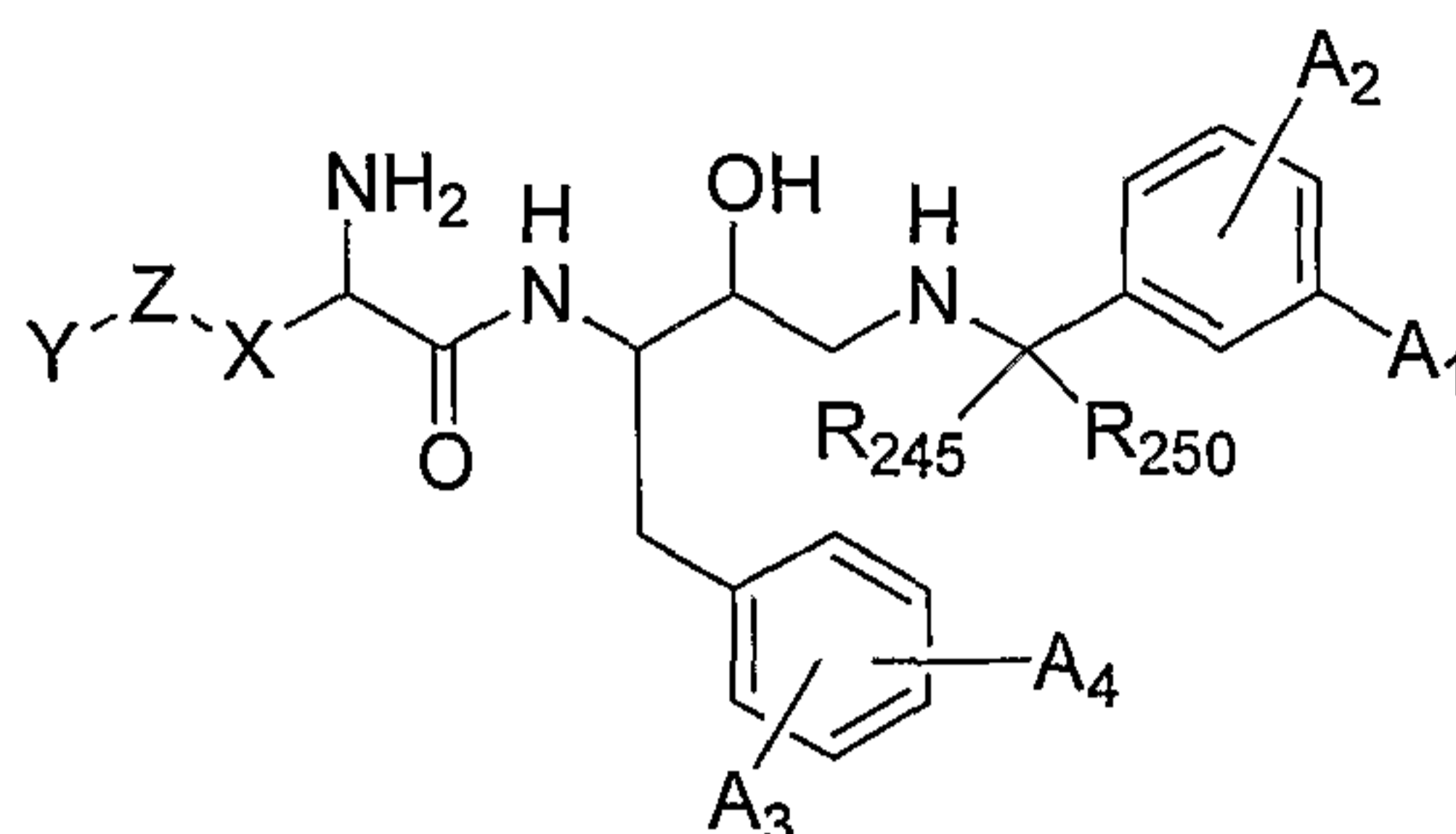
R<sub>205</sub> at each occurrence is independently selected from C<sub>1</sub>-  
C<sub>4</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>4</sub>  
20 alkoxy;

R<sub>210</sub> at each occurrence is independently selected from C<sub>1</sub>-  
C<sub>4</sub> alkyl optionally substituted with 1 or 2 R<sub>205</sub>  
groups; halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; OCF<sub>3</sub>; NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub>  
alkyl); N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); OH; and -CO-(C<sub>1</sub>-C<sub>4</sub>  
25 alkyl); wherein

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently selected  
from H, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which  
they are attached to form a carbocycle of 3, 5, or 6  
30 carbon atoms.

Preferred compounds of formula X-IV include those of  
formula X-IV-a:



X-IV-a

wherein X, Y, Z, R<sub>245</sub>, and R<sub>250</sub> are as defined for formula X-IV;  
 A<sub>1</sub> and A<sub>2</sub> are independently H, methyl, ethyl, propyl, methoxy,  
 5 F, Cl, Br, I, or CF<sub>3</sub>;

A<sub>3</sub> and A<sub>4</sub> are independently F, Cl, Br, I, methyl, methoxy, or  
 H;

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they  
 are attached to form a carbocycle of 3, 5, or 6 carbon  
 10 atoms.

More preferred compounds of formula X-IV-a include those  
 wherein

A<sub>2</sub> is H;

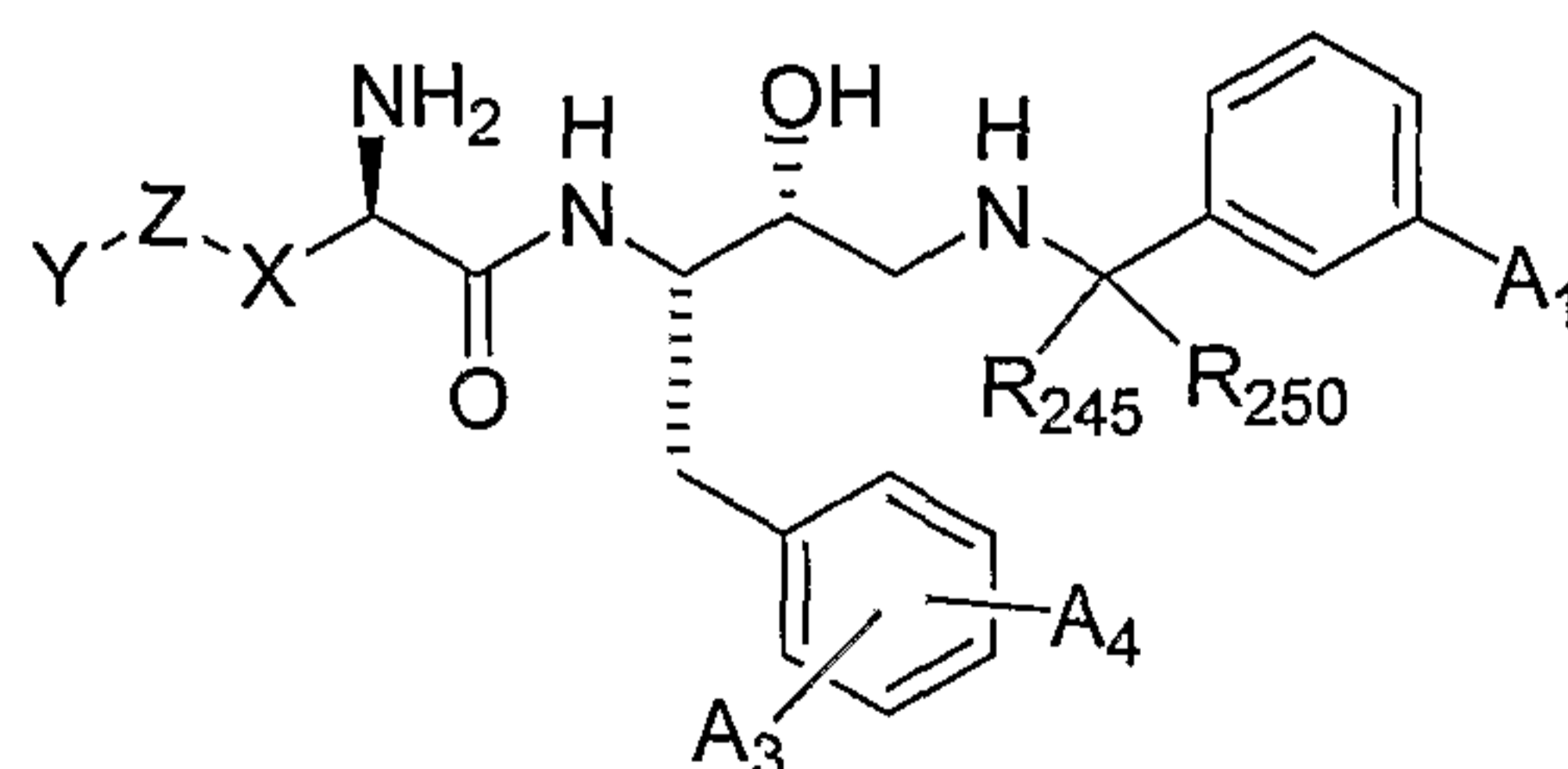
15 A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, Br, or I;

X is C<sub>1</sub> or C<sub>2</sub> alkylidenyl;

Z is SO<sub>2</sub>; SO; or S; and

Y is phenyl, or C<sub>1</sub>-C<sub>11</sub> alkyl. More preferably, Y is methyl,  
 propyl, n-butyl, isobutyl, isopentyl, 4-heptyl, 3-heptyl,  
 20 3-pentyl, or 5-nonyl.

Even more preferred compounds of formula X-IV include  
 those of formula X-IV-b:



X-IV-b

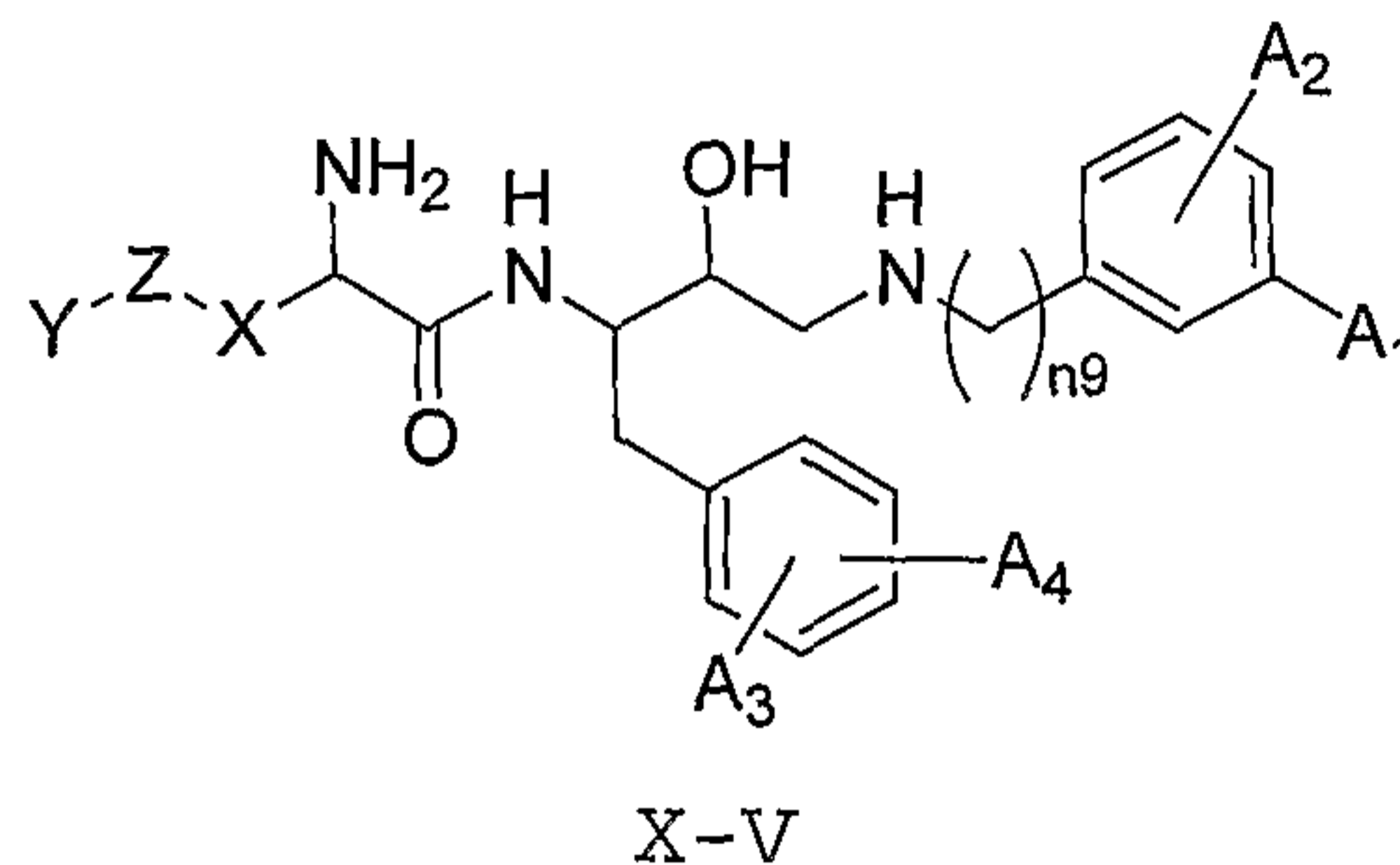
25

wherein  $A_1$ ,  $X$ ,  $Y$ ,  $Z$ ,  $R_{245}$ , and  $R_{250}$  are as defined for formula X-IV;

$A_3$  and  $A_4$  are independently H, F, Cl, methyl, ethyl, methoxy, ethoxy,  $CF_3$  or  $OCF_3$ .

5

Other preferred compounds of formula X-IV include those of formula X-V wherein



10 wherein

$n_9$  is 1 or 2;

$A_1$  and  $A_2$  are independently H, methyl, ethyl, propyl, methoxy, ethoxy, F, Cl, Br, I,  $CF_3$ ,  $OCF_3$ , or  $C_2-C_6$  alkynyl; and

$A_3$  and  $A_4$  are independently F, Cl, Br, I, methyl, methoxy, or

15 H.

Preferred compounds of formula X-V include those wherein  $A_1$  is  $C_1-C_2$  alkyl, preferably ethyl, or  $C_2-C_3$  alkynyl. More preferably  $A_1$  is ethyl, I, or  $C_2$  alkynyl;

20  $A_2$  is H;

$A_3$  and  $A_4$  are independently H, F, Cl, Br, or I;

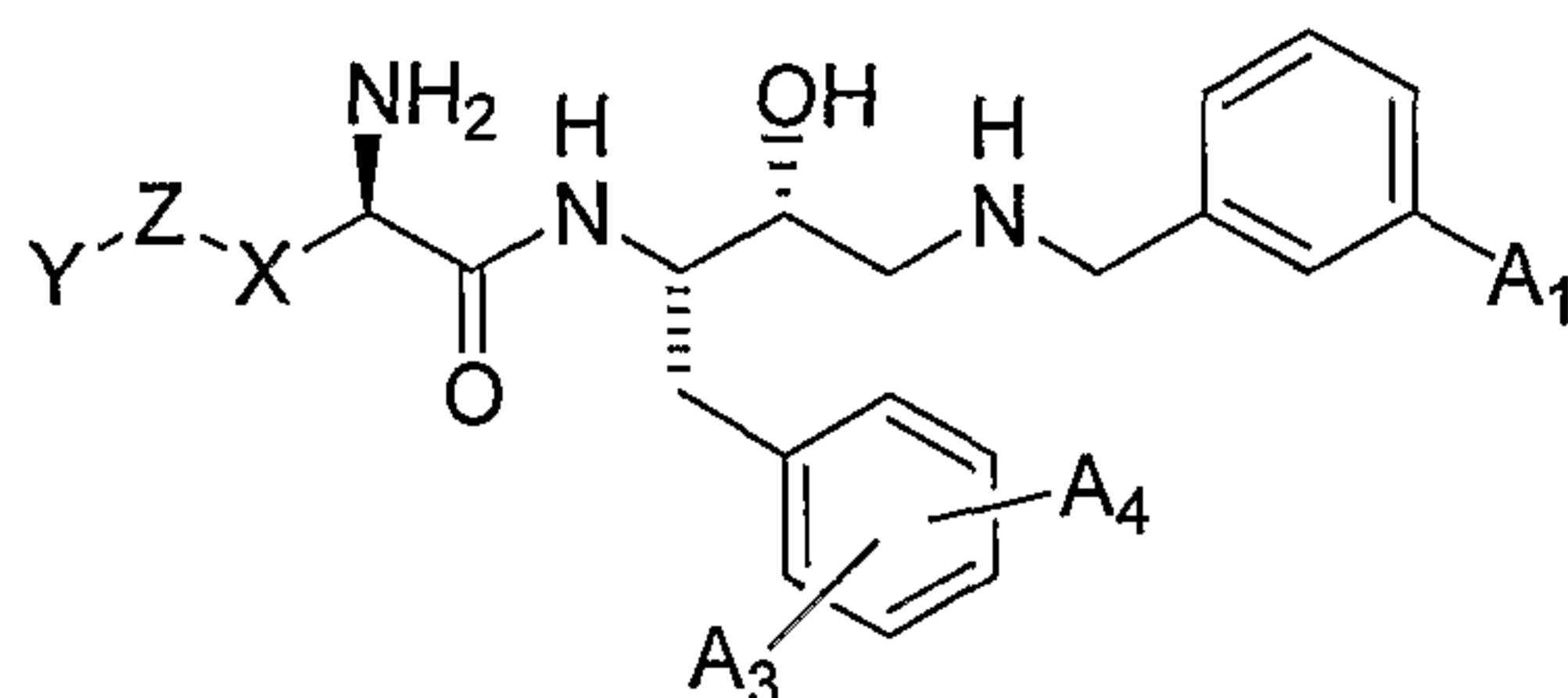
$X$  is  $C_1$  or  $C_2$  alkylidenyl;

$Z$  is  $SO_2$ ;  $SO$ ; or  $S$ ; and

$Y$  is phenyl, methyl, propyl, n-butyl, isobutyl, isopentyl, 4-heptyl, 3-heptyl, 3-pentyl, or 5-nonyl.

25

More preferred compounds of formula X-V include those of formula X-V-a



formula X-V-a

wherein

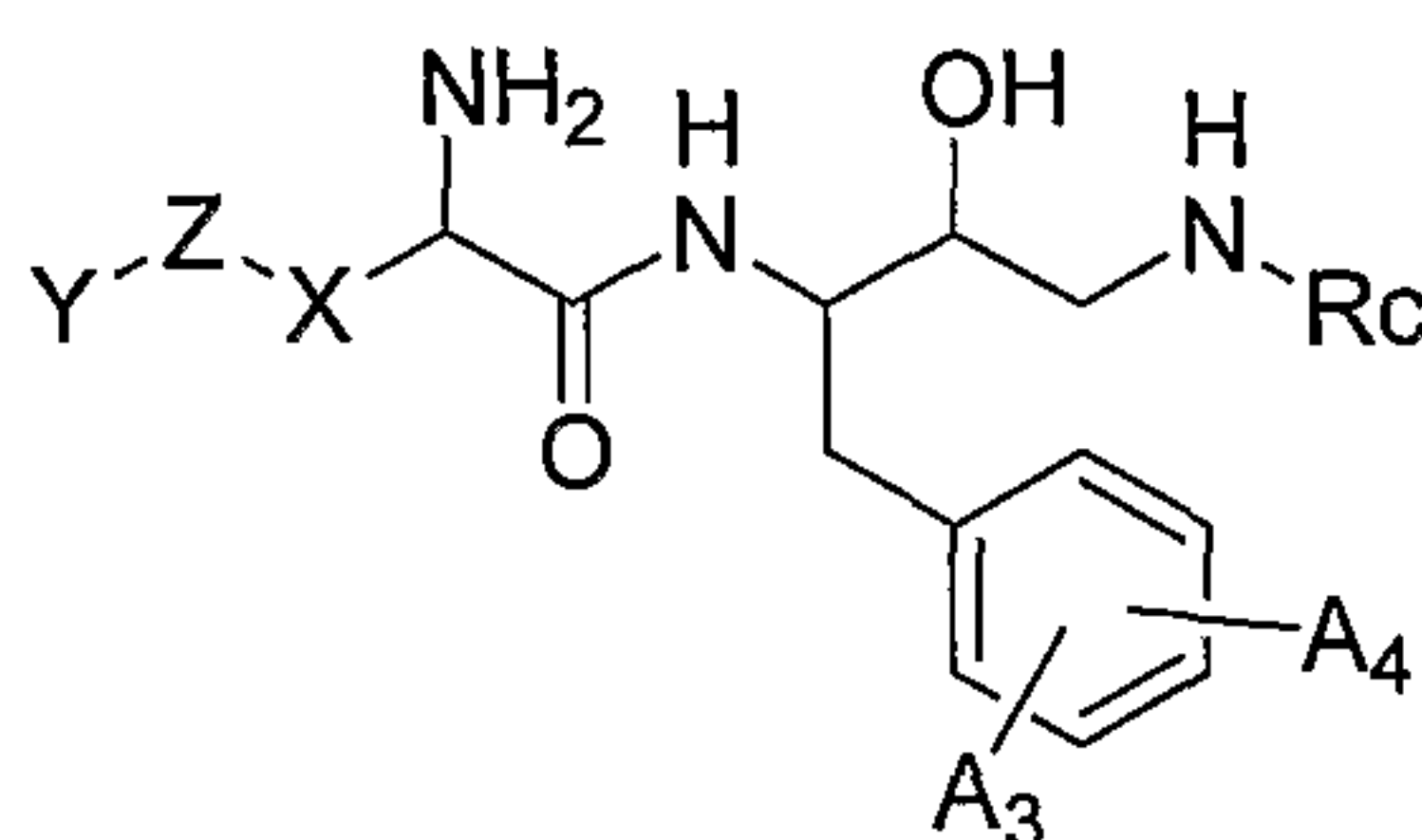
A<sub>3</sub> and A<sub>4</sub> are independently H, F, or Cl.

5

Other preferred compounds of formula X-IV include those of formula X-VI, i.e., compounds of formula X-IV wherein R<sub>c</sub> is C<sub>3</sub>-C<sub>8</sub> alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or -(C<sub>1</sub>-C<sub>4</sub> alkyl)-cyclopropyl. Even more preferred R<sub>c</sub> is n-butyl, isobutyl, n-pentyl, isopentyl, n-hexyl, isohexyl, cyclopropyl, or cyclopropylmethyl.

10

Preferred compounds of formula X-VI include those of formula X-VI-a:



X-VI-a

wherein

A<sub>3</sub> and A<sub>4</sub> are independently halogen, methyl, ethyl, n-propyl, iso-propyl, methoxy, ethoxy, n-propoxy, iso-propoxy, or H;

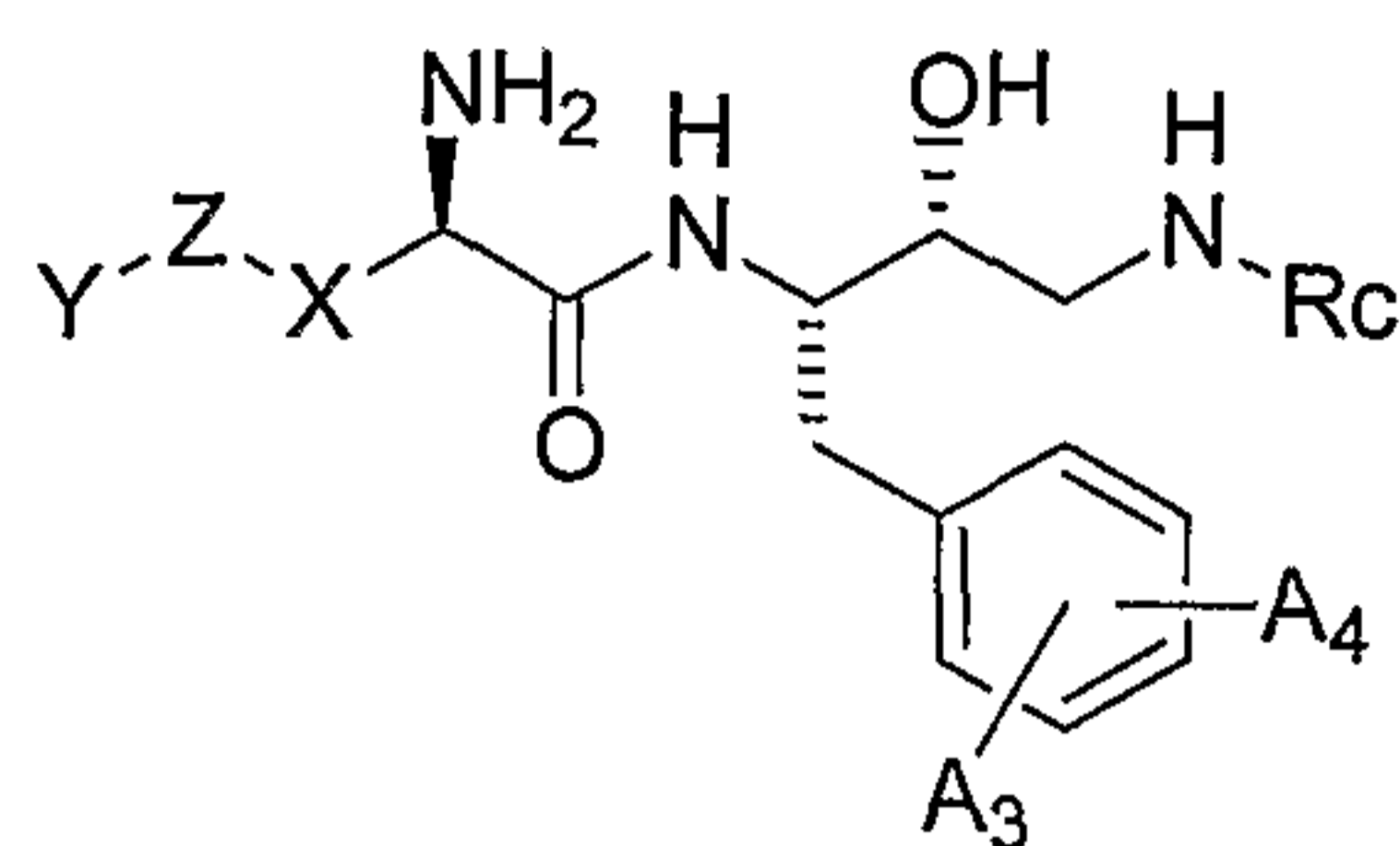
20 X is C<sub>1</sub> or C<sub>2</sub> alkylidenyl;

Z is SO<sub>2</sub>; SO; or S; and

Y is phenyl, or C<sub>1</sub>-C<sub>10</sub> alkyl. Even more preferred is when Y is methyl, propyl, n-butyl, isobutyl, isopentyl, 4-heptyl, 3-heptyl, 3-pentyl, or 5-nonyl.

25

More preferred compounds of formula X-VI include those of formula X-VI-b:



X-VI-b

wherein

A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, methyl, or methoxy.

5

Representative compounds of formula X-III wherein R<sub>4</sub> is NH<sub>2</sub> are

S-butyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-cysteinamide;

3-(butylsulfinyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-L-alaninamide;

3-(butylsulfonyl)-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-L-alaninamide;

N~1~-[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxypropyl-3-(isopentylamino)]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

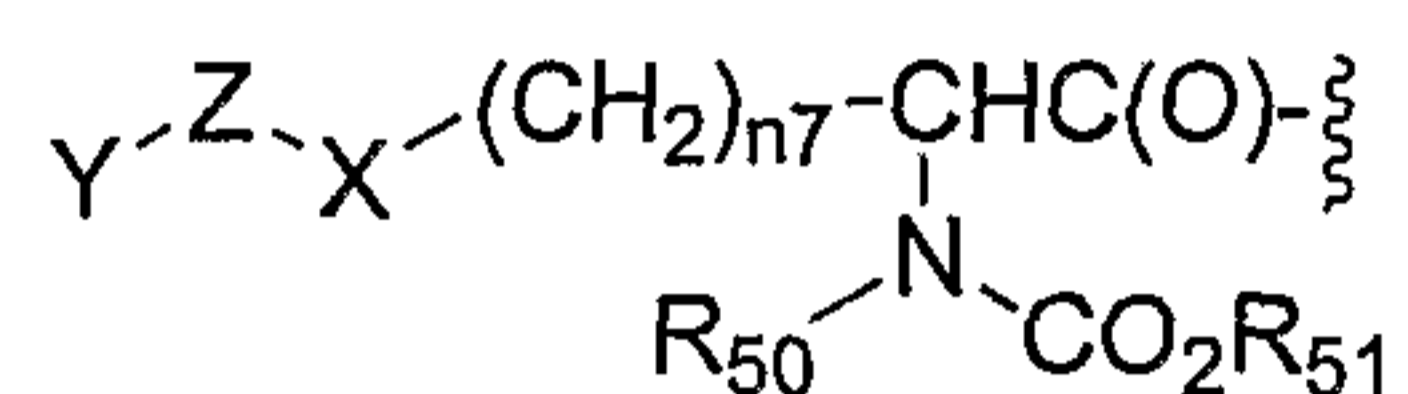
N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide;

(2S)-2-amino-N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-oxo-5-piperidin-1-ylpentanamide; and  
 (2R)-2-amino-N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-oxo-5-piperidin-1-ylpentanamide and  
 pharmaceutically acceptable salts thereof.

Other preferred compounds of formula X-II include those of  
 formula X-VII, i.e., compounds of formula X-II wherein

5  $R_N$  is:



$n_7$  is 0, 1, 2, or 3;

$R_{50}$  is H or  $C_1-C_6$  alkyl;

10  $R_{51}$  is phenyl  $C_1-C_4$  alkyl;  $C_1-C_6$  alkyl optionally substituted  
 with 1, 2, or 3 groups that are independently halogen,  
 cyano,  $-NR_6R_7$ ,  $-C(O)NR_6R_7$ , or  $-C_1-C_4$  alkoxy;  
 heterocycloalkyl optionally substituted with 1 or 2 groups  
 that are independently  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, halogen,  
 $C_2-C_4$  alkanoyl, phenyl  $C_1-C_4$  alkyl, and  $-SO_2$   $C_1-C_4$  alkyl;  
 15 heterocycloalkylalkyl optionally substituted with 1 or 2  
 groups that are independently  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,  
 halogen,  $C_2-C_4$  alkanoyl, phenyl  $C_1-C_4$  alkyl, and  $-SO_2$   $C_1-C_4$   
 alkyl; alkenyl; alkynyl; heteroaryl optionally substituted  
 with 1, 2, or 3 groups that are independently OH,  $C_1-C_4$   
 20 alkyl,  $C_1-C_4$  alkoxy, halogen,  $NH_2$ ,  $NH(C_1-C_6$  alkyl) or  $N(C_1-$   
 $C_6$  alkyl)( $C_1-C_6$  alkyl); heteroarylalkyl optionally  
 substituted with 1, 2, or 3 groups that are independently  
 $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, halogen,  $NH_2$ ,  $NH(C_1-C_6$  alkyl) or  
 $N(C_1-C_6$  alkyl)( $C_1-C_6$  alkyl); phenyl;  $C_3-C_8$  cycloalkyl; or  
 25 cycloalkylalkyl; wherein the phenyl,  $C_3-C_8$  cycloalkyl, and  
 cycloalkylalkyl groups are optionally substituted with 1,  
 2, 3, 4 or 5 groups that are independently halogen, CN,  
 $NO_2$ ,  $C_1-C_6$  alkyl,  $C_1-C_6$  alkoxy,  $C_2-C_6$  alkanoyl,  $C_1-C_6$



haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, hydroxy, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> thioalkoxy, C<sub>1</sub>-C<sub>6</sub> thioalkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkoxy;

R<sub>6</sub> and R<sub>7</sub> are independently H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub>

5 alkanoyl, phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, or phenyl C<sub>1</sub>-C<sub>4</sub> alkyl;

X is C<sub>1</sub>-C<sub>4</sub> alkylidenyl optionally optionally substituted with 1, 2, or 3 methyl groups; or -NR<sub>4-6</sub>-; or

R<sub>4</sub> and R<sub>4-6</sub> combine to form -(CH<sub>2</sub>)<sub>n<sub>10</sub></sub>-, wherein

10 n<sub>10</sub> is 1, 2, 3, or 4;

Z is a bond; SO<sub>2</sub>; SO; S; or C(O);

Y is H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl containing at least one N, O, or S; phenyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 thru 3 substituents which

15 can be the same or different and are selected from halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C<sub>3</sub>-C<sub>8</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, and halogen; alkoxy; phenyl optionally substituted with

20 halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; or phenyl C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 substituents

25 selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or

-N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl,

30 piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen;

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkanoyl, each of which is unsubstituted or substituted with 1, or 2 groups independently selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>,  
 5 wherein

R<sub>26</sub> is -C(O)-, -SO<sub>2</sub>-, -CO<sub>2</sub>-, -C(O)NH-, or -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-;

R<sub>27</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl C<sub>1</sub>-C<sub>6</sub> alkyl,  
 10 heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NH<sub>2</sub>, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -  
 15 C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl).

Preferred compounds of formula X-VII include those wherein:

20 R<sub>2</sub> and R<sub>3</sub> are independently H or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, or 2 substituents selected from halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>3</sub> alkoxy;

n<sub>7</sub> is 0, 1, or 2;

R<sub>50</sub> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

25 R<sub>51</sub> is selected from benzyl; phenethyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR<sub>6</sub>R<sub>7</sub>, -C(O)NR<sub>6</sub>R<sub>7</sub>, or -C<sub>1</sub>-C<sub>4</sub> alkoxy; heterocycloalkyl containing at least one N, O, or S and optionally substituted with 1 or 2 groups that are  
 30 independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; heterocycloalkylalkyl containing at least one N, O, or S and optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub>

5 alkanoyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>2</sub>-C<sub>6</sub>  
 alkenyl; C<sub>2</sub>-C<sub>6</sub> alkynyl; heteroaryl optionally substituted  
 with 1, 2, or 3 groups that are independently OH, C<sub>1</sub>-C<sub>4</sub>  
 alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-  
 10 C<sub>6</sub> alkyl) (C<sub>1</sub>-C<sub>6</sub> alkyl); heteroarylalkyl containing at least  
 one N, O, or S and optionally substituted with 1, 2, or 3  
 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy,  
 halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl) (C<sub>1</sub>-C<sub>6</sub>  
 alkyl); phenyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub>  
 15 alkyl, wherein the phenyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub>  
 cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl groups are optionally substituted  
 with 1, 2, or 3 groups that are independently halogen, CN,  
 NO<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>4</sub>  
 haloalkyl, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, hydroxy, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl,  
 20 C<sub>1</sub>-C<sub>4</sub> thioalkoxy;

R<sub>6</sub> and R<sub>7</sub> are independently H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl,  
 phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl or phenethyl;

X is -C<sub>1</sub>-C<sub>4</sub> alkylidanyl optionally optionally substituted with  
 1 or 2 methyl groups;

25 Z is SO<sub>2</sub>; SO; S; or C(O);

Y is H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl containing at  
 least one N, O, or S; phenyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl  
 optionally substituted with 1 thru 3 substituents which  
 can be the same or different and are selected from the  
 30 group consisting of halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub>  
 thioalkoxy, and C<sub>1</sub>-C<sub>4</sub> haloalkoxy; C<sub>3</sub>-C<sub>6</sub> cycloalkyl  
 optionally substituted with 1 group selected from C<sub>1</sub>-C<sub>3</sub>  
 alkyl, and halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; phenyl optionally  
 substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or  
 NO<sub>2</sub>; or phenyl C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with  
 halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein  
 Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>10</sub> alkyl  
 optionally substituted with 1, or 2 substituents  
 selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,

and OH; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl;  
 phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or  
 -N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl,  
 piperidinyl, morpholinyl, and pyrrolidinyl, wherein  
 5 each ring is optionally substituted with 1, 2, or 3  
 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub>  
 alkoxy, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>4</sub> alkyl, or halogen;

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl,  
 halo C<sub>1</sub>-C<sub>4</sub> alkyl, or C<sub>2</sub>-C<sub>4</sub> alkanoyl, each of which is  
 10 unsubstituted or substituted with 1, or 2 groups  
 independently selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, hydroxy,  
 C<sub>1</sub>-C<sub>4</sub> alkoxy, NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>; wherein  
 R<sub>26</sub> is -C(O)-, -SO<sub>2</sub>-, or -CO<sub>2</sub>-;  
 R<sub>27</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl, or phenethyl, wherein each of  
 15 the above is unsubstituted or substituted with 1, 2,  
 or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub>  
 alkoxy, halogen, CF<sub>3</sub>, or hydroxy C<sub>1</sub>-C<sub>4</sub> alkyl.

More preferred compounds of formula X-VII include those  
 20 wherein:

R<sub>C</sub> is C<sub>1</sub>-C<sub>8</sub> alkyl optionally substituted with 1, 2, or 3 groups  
 independently selected from the group consisting of R<sub>205</sub>,  
 -OC=ONR<sub>235</sub>R<sub>240</sub>, -S(=O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), -SH, -C=ONR<sub>235</sub>R<sub>240</sub>, and  
 -S(=O)<sub>2</sub>NR<sub>235</sub>R<sub>240</sub>; -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>8</sub>) cycloalkyl wherein the  
 25 cycloalkyl is optionally substituted with 1, 2, or 3  
 groups independently selected from the group consisting of  
 R<sub>205</sub>, -CO<sub>2</sub>H, and -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-phenyl;  
 -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocycloalkyl; or  
 -(CH<sub>2</sub>)<sub>0-1</sub>-CH(C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl)-(CH<sub>2</sub>)<sub>0-1</sub>-heteroaryl; wherein  
 30 each aryl is optionally substituted with 1, 2, or 3 R<sub>200</sub>;  
 each heteroaryl is optionally substituted with 1, 2, 3, or  
 4 R<sub>200</sub>;  
 each heterocycloalkyl is optionally substituted with 1, 2,  
 3, or 4 R<sub>210</sub>;

- R<sub>200</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; OH; -NO<sub>2</sub>; halogen; -CO<sub>2</sub>H; C≡N; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>220</sub>R<sub>225</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>1</sub>-C<sub>12</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO<sub>2</sub>R<sub>215</sub>; or -(CH<sub>2</sub>)<sub>0-4</sub>-O-(C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, or 5 -F);
- R<sub>205</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, -OH, -O-phenyl, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);
- R<sub>210</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; halogen; C<sub>1</sub>-C<sub>6</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkoxy; -NR<sub>220</sub>R<sub>225</sub>; OH; C≡N; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); -SO<sub>2</sub>-NR<sub>235</sub>R<sub>240</sub>; -CO-NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); or =O; wherein
- R<sub>215</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(phenyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and -(CH<sub>2</sub>)<sub>0-2</sub>-(heteroaryl), or -(CH<sub>2</sub>)<sub>0-2</sub>-(heterocycloalkyl); wherein the phenyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R<sub>205</sub> or R<sub>210</sub>; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>;
- R<sub>220</sub> and R<sub>225</sub> at each occurrence are independently -H, -C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkyl, halo C<sub>1</sub>-C<sub>4</sub> alkyl; -C<sub>3</sub>-C<sub>7</sub> cycloalkyl, or -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl);
- R<sub>235</sub> and R<sub>240</sub> at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;
- R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkoxy, or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, or 6 carbon atoms.

5 Even more preferred compounds of formula X-VII include those wherein:

R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1, or 2 substituents selected from  
 10 halogen, -OH, -SH, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C≡N, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>3</sub> alkoxy; halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; and OH;

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> alkoxy C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, each of which is  
 15 unsubstituted or substituted with 1 or 2 groups independently selected from halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, and NH<sub>2</sub>;

R<sub>C</sub> is C<sub>1</sub>-C<sub>8</sub> alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R<sub>205</sub>, -  
 20 SH, -C=ONR<sub>235</sub>R<sub>240</sub>, and -S(=O)<sub>2</sub>NR<sub>235</sub>R<sub>240</sub>; -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>6</sub>) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R<sub>205</sub>, -CO<sub>2</sub>H, and -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-phenyl optionally substituted with 1,  
 25 2, or 3 R<sub>200</sub>; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyridyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyridazinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrimidinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrazinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-furyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-indolyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-thienyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrrolyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrazolyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-benzoxazolyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
 30 imidazolyl; each of the above heteroaryl groups is optionally substituted with 1, 2, 3, or 4 R<sub>200</sub>; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-imidazolidinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-tetrahydrofuryl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-tetrahydropyranyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-piperazinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrrolidinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-piperidinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-

indolinyl; each of the above heterocycloalkyl groups is optionally substituted with 1, 2, 3, or 4  $R_{210}$ ;  $(CH_2)_{0-1}-CH((CH_2)_{0-4}-OH)-(CH_2)_{0-1}-phenyl$ ; or  $-(CH_2)_{0-1}-CH(C_1-C_4 hydroxyalkyl)-(CH_2)_{0-1}-pyridyl$ ;

5  $R_{200}$  at each occurrence is independently  $C_1-C_6$  alkyl optionally substituted with 1, 2, or 3  $R_{205}$  groups; OH;  $-NO_2$ ; halogen;  $-CO_2H$ ;  $C\equiv N$ ;  $-(CH_2)_{0-4}-CO-NR_{220}R_{225}$ ;  $-(CH_2)_{0-4}-CO-(C_1-C_8 alkyl)$ ;  $-(CH_2)_{0-4}-CO_2R_{215}$ ; or  $-(CH_2)_{0-4}-O-(C_1-C_6 alkyl$  optionally substituted with 1, 2, 3, or 5  $-F$ );

10  $R_{205}$  at each occurrence is independently  $C_1-C_6$  alkyl, halogen,  $-OH$ ,  $-O-phenyl$ ,  $-SH$ ,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_6$  alkoxy,  $NH_2$ ,  $NH(C_1-C_6 alkyl)$ , or  $N-(C_1-C_6 alkyl)(C_1-C_6 alkyl)$ ;

15  $R_{210}$  at each occurrence is independently  $C_1-C_6$  alkyl optionally substituted with 1 or 2  $R_{205}$  groups; halogen;  $C_1-C_4$  alkoxy;  $C_1-C_4$  haloalkoxy;  $-NR_{220}R_{225}$ ; OH;  $C\equiv N$ ;  $C_3-C_7$  cycloalkyl optionally substituted with 1 or 2  $R_{205}$  groups;  $-CO-(C_1-C_4 alkyl)$ ;  $-SO_2-NR_{235}R_{240}$ ;  $-CO-NR_{235}R_{240}$ ;  $-SO_2-(C_1-C_4 alkyl)$ ; or  $=O$ ; wherein

20  $R_{215}$  at each occurrence is independently  $C_1-C_6$  alkyl,  $-(CH_2)_{0-2}-(phenyl)$ ,  $C_3-C_6$  cycloalkyl,  $-(CH_2)_{0-2}-(pyridyl)$ ,  $-(CH_2)_{0-2}-(pyrrolyl)$ ,  $-(CH_2)_{0-2}-(imidazolyl)$ ,  $-(CH_2)_{0-2}-(pyrimidyl)$ ,  $-(CH_2)_{0-2}-(pyrrolidinylyl)$ ,  $-(CH_2)_{0-2}-(imidazolidinylyl)$ ,  $-(CH_2)_{0-2}-(piperazinylyl)$ ,  $-(CH_2)_{0-2}-(piperidinylyl)$ , or  $-(CH_2)_{0-2}-(morpholinyl)$ ; wherein the phenyl group at each occurrence is optionally substituted with 1 or 2 groups that are independently  $R_{205}$  or  $R_{210}$ ; wherein

25 each heterocycloalkyl group at each occurrence is optionally substituted with 1 or 2  $R_{210}$ ; wherein each heteroaryl group at each occurrence is optionally substituted with 1 or 2  $R_{210}$ ;

30

R<sub>220</sub> and R<sub>225</sub> at each occurrence are independently -H, -C<sub>1</sub>-C<sub>4</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkyl, halo C<sub>1</sub>-C<sub>4</sub> alkyl; -C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-(C<sub>1</sub>-C<sub>2</sub> alkyl);

R<sub>235</sub> and R<sub>240</sub> at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkoxy, or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms.

Even more preferred compounds of formula X-VII include those wherein:

R<sub>51</sub> is benzyl; phenethyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR<sub>6</sub>R<sub>7</sub>, -C(O)NR<sub>6</sub>R<sub>7</sub>, or -C<sub>1</sub>-C<sub>4</sub> alkoxy; pyrrolidinyl, tetrahydrofuryl, tetrahydro-thienyl 1,1-dioxide, tetrahydrothienyl, pyranyl, piperidinyl, pyrrolidinonyl, dihydropyridazinonyl, 2-thioxo-thiazolidin-4-one, each of which is optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, benzyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; pyrrolidinonyl C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>2</sub>-C<sub>4</sub> alkenyl; C<sub>2</sub>-C<sub>4</sub> alkynyl; pyrazolyl, imidazolyl, pyrazinyl, pyridyl, isoxazolyl, thiazolyl, indolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); pyridinyl C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); phenyl;



cyclopropyl; cyclopentyl; cyclohexyl; cyclopropylmethyl;  
wherein the phenyl; cycloalkyl, and cycloalkylalkyl groups  
are optionally substituted with 1, 2, or 3 groups that are  
independently halogen, CN, NO<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy,  
5 C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, hydroxy,  
C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, or C<sub>1</sub>-C<sub>4</sub> thioalkoxy;

R<sub>6</sub> and R<sub>7</sub> are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl,  
or benzyl;

X is-C<sub>1</sub>-C<sub>3</sub> alkylidenyl optionally optionally substituted with 1  
10 or 2 methyl groups;

Z is SO<sub>2</sub>; SO; S; or C(O);

Y is C<sub>1</sub>-C<sub>4</sub> haloalkyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl optionally  
substituted with 1 or 2 substituents which can be the same  
or different and are selected from the group consisting of  
15 halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> thioalkoxy, and C<sub>1</sub>-C<sub>4</sub>  
haloalkoxy; C<sub>1</sub>-C<sub>4</sub> alkoxy; phenyl optionally substituted  
with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; or  
benzyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl,  
C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

20 Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>6</sub> alkyl  
optionally substituted with 1, 2, or 3 substituents  
selected from halogen, C<sub>1</sub>-C<sub>2</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
and OH; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl;  
benzyl; and C<sub>3</sub>-C<sub>6</sub> cycloalkyl C<sub>1</sub>-C<sub>2</sub> alkyl; or

25 -N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl,  
piperidinyl, morpholinyl, and pyrrolidinyl, wherein  
each ring is optionally substituted with 1, 2, 3, or  
4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen.

30 Other even more preferred compounds of formula X-VII  
include those wherein:

X is-C<sub>1</sub>-C<sub>3</sub> alkylidenyl;

Z is SO<sub>2</sub>; SO; S; or C(O);

Y is OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); phenyl; benzyl; or C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 or 2 substituents which can be the same or different and are selected from halogen, hydroxy, methoxy, ethoxy, thiomethoxy, thioethoxy, and CF<sub>3</sub>; wherein  
 5 Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1 or 2 substituents selected from halogen, methoxy, ethoxy, cyclopropyl, and OH; or

-N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein  
 10 each ring is optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or halogen;

R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, or 3  
 15 groups independently selected from methyl, ethyl, n-propyl, isopropyl, hydroxymethyl, monohalomethyl, dihalomethyl, trihalomethyl, -CH<sub>2</sub>CF<sub>3</sub>, methoxymethyl, halogen, methoxy, ethoxy, n-propyloxy, isopropyloxy, and OH;

20 R<sub>2</sub> and R<sub>3</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl;  
 R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, or C<sub>2</sub>-C<sub>4</sub> alkanoyl;

R<sub>C</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub>  
 25 groups; cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl;  
 -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-phenyl optionally substituted with 1 or 2 R<sub>200</sub> groups; or -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyridyl optionally substituted with 1 or 2 R<sub>200</sub>;

R<sub>200</sub> at each occurrence is independently C<sub>1</sub>-C<sub>4</sub> alkyl  
 30 optionally substituted with 1 or 2 R<sub>205</sub> groups; OH; or halogen;

R<sub>205</sub> at each occurrence is independently C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, or C<sub>1</sub>-C<sub>4</sub> alkoxy;

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently H, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, or C<sub>1</sub>-C<sub>4</sub> alkoxy, or  
R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3 carbon atoms.

Additional more preferred compounds of formula X-VII include those wherein:

R<sub>51</sub> is benzyl; phenethyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR<sub>6</sub>R<sub>7</sub>, -C(O)NR<sub>6</sub>R<sub>7</sub>, or -C<sub>1</sub>-C<sub>4</sub> alkoxy; pyrrolidinyl, tetrahydrofuryl, tetrahydro-thienyl 1,1-dioxide, tetrahydrothienyl, pyranyl, piperidinyl, pyrrolidinonyl, each of which is optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, benzyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; pyrrolidinonyl C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>2</sub>-C<sub>4</sub> alkenyl; C<sub>2</sub>-C<sub>4</sub> alkynyl; pyridinyl C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1, or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); cyclopentyl; cyclohexyl; or cyclopropylmethyl; wherein the cycloalkyl, and cycloalkylalkyl groups are optionally substituted with 1, or 2 groups that are independently halogen, CN, NO<sub>2</sub>, methyl, ethyl, methoxy, ethoxy, C<sub>2</sub>-C<sub>4</sub> alkanoyl, CF<sub>3</sub>, OCF<sub>3</sub>, or hydroxy;

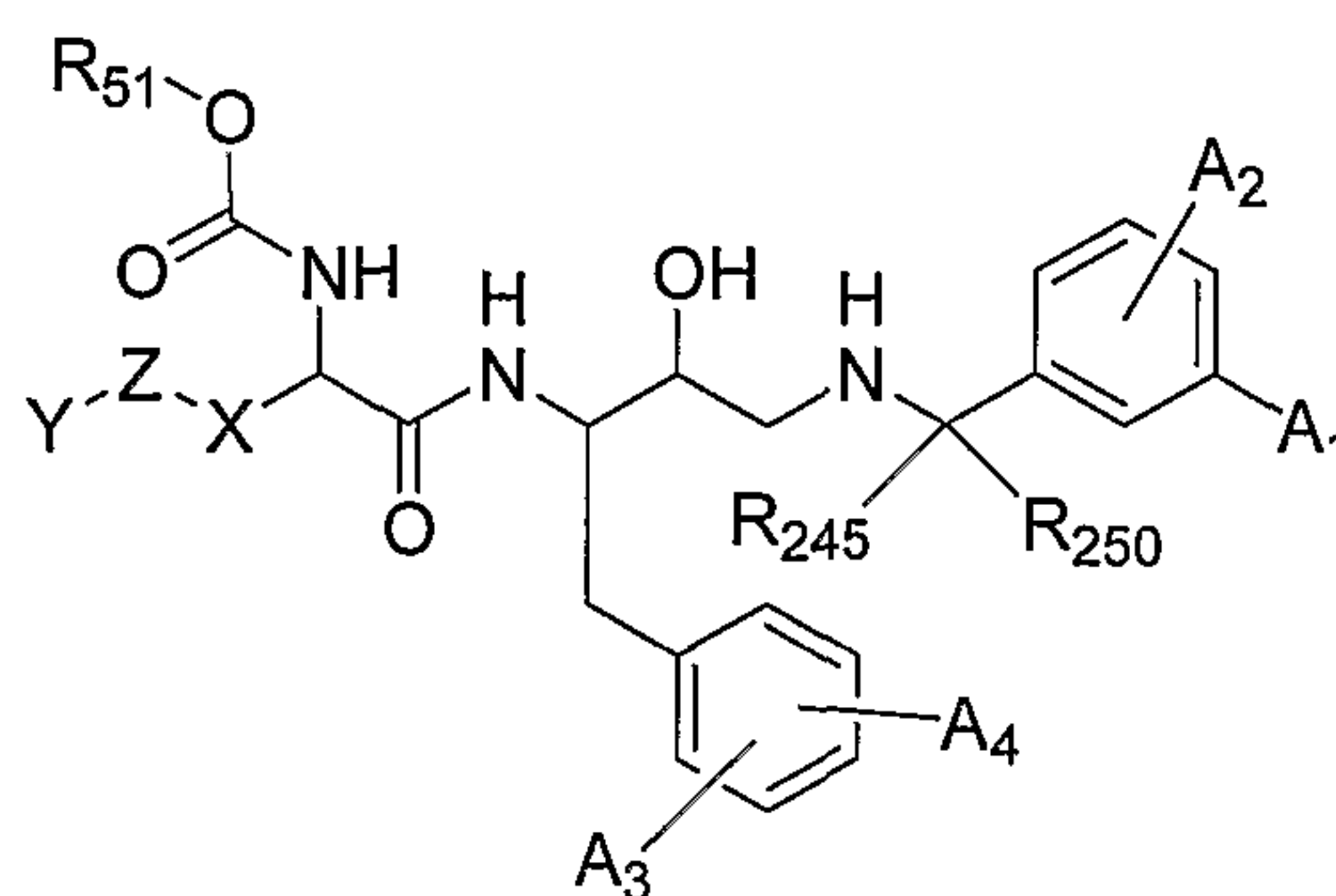
R<sub>6</sub> and R<sub>7</sub> are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, or benzyl;

Y is OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); phenyl; benzyl; or C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 or 2 substituents which can be the same or different and are selected from halogen, hydroxy, methoxy, ethoxy, thiomethoxy, thioethoxy, and CF<sub>3</sub>; wherein

$Y_1$  and  $Y_2$  are the same or different and are H or  $C_1-C_4$  alkyl optionally substituted with 1 or 2 substituents selected from halogen, methoxy, ethoxy, cyclopropyl, and OH.

5

Even more preferred compounds of formula X-VII include those of formula X-VIII:



X-VIII

10 wherein

$A_1$  and  $A_2$  are independently H, methyl, ethyl, propyl, methoxy, F, Cl, Br, I,  $CF_3$  or  $C_2-C_6$  alkynyl; and  
 $A_3$  and  $A_4$  are independently F, Cl, Br, I, methyl, ethyl, methoxy, ethoxy, or H.

15

Preferred compounds of formulae X-VII and X-VIII include those wherein:

$A_1$  is methyl, ethyl, methoxy,  $C_2$  alkynyl, or I;

$A_3$  and  $A_4$  are independently H, F, Cl, Br, or I;

20 X is  $C_1$  or  $C_2$  alkylidenyl;

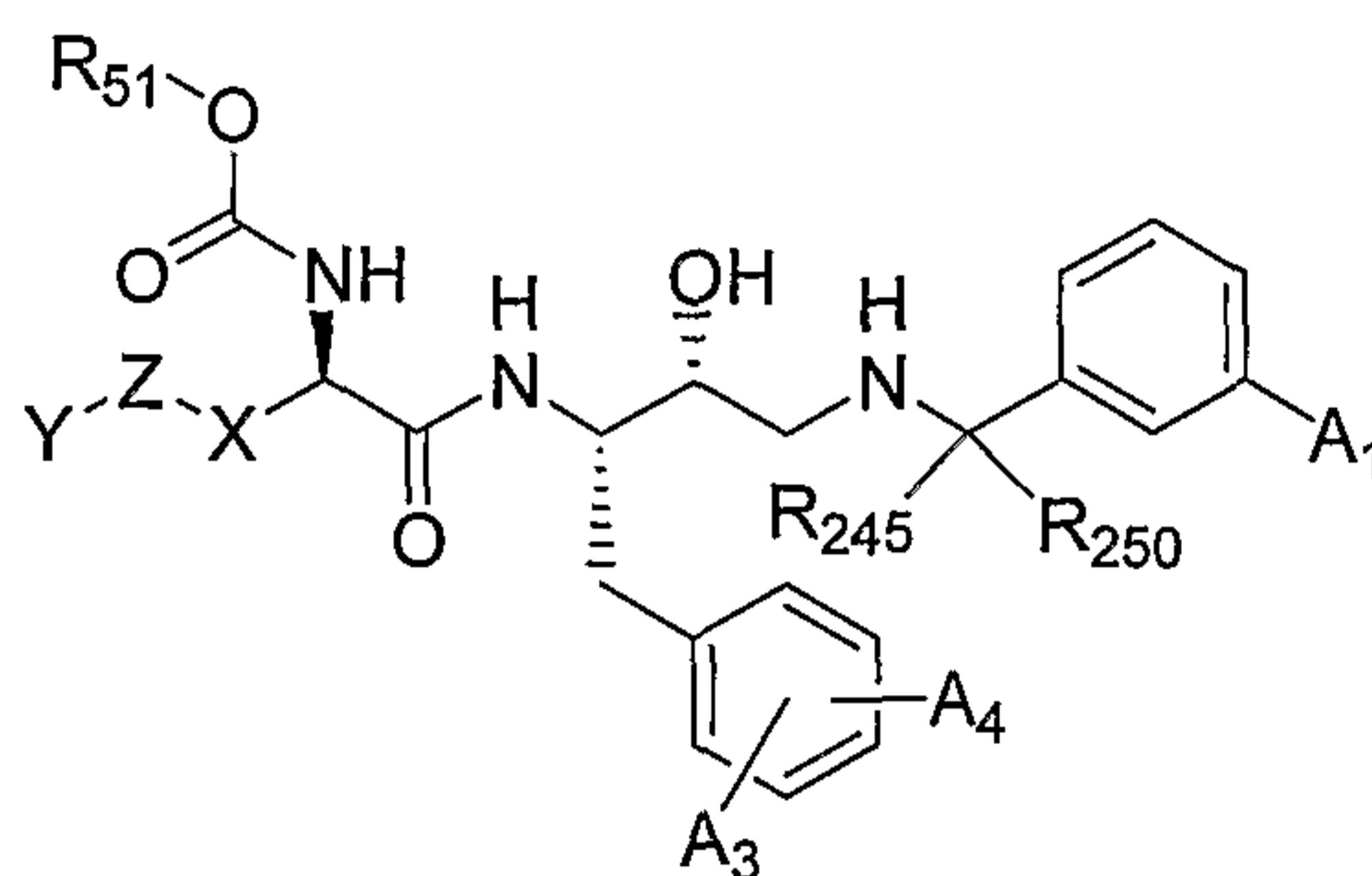
Z is  $SO_2$ ; SO; S; or C(O); and

Y is phenyl, methyl, propyl, n-butyl, isobutyl, isopentyl, 4-heptyl, 3-heptyl, 3-pentyl, or 5-nonyl; or

Y is  $-N(Y_1)(Y_2)$ ; wherein

25  $Y_1$  and  $Y_2$  are independently H or  $C_1-C_4$  alkyl.

Preferred compounds of formula X-VIII include those of formula X-VIII-a



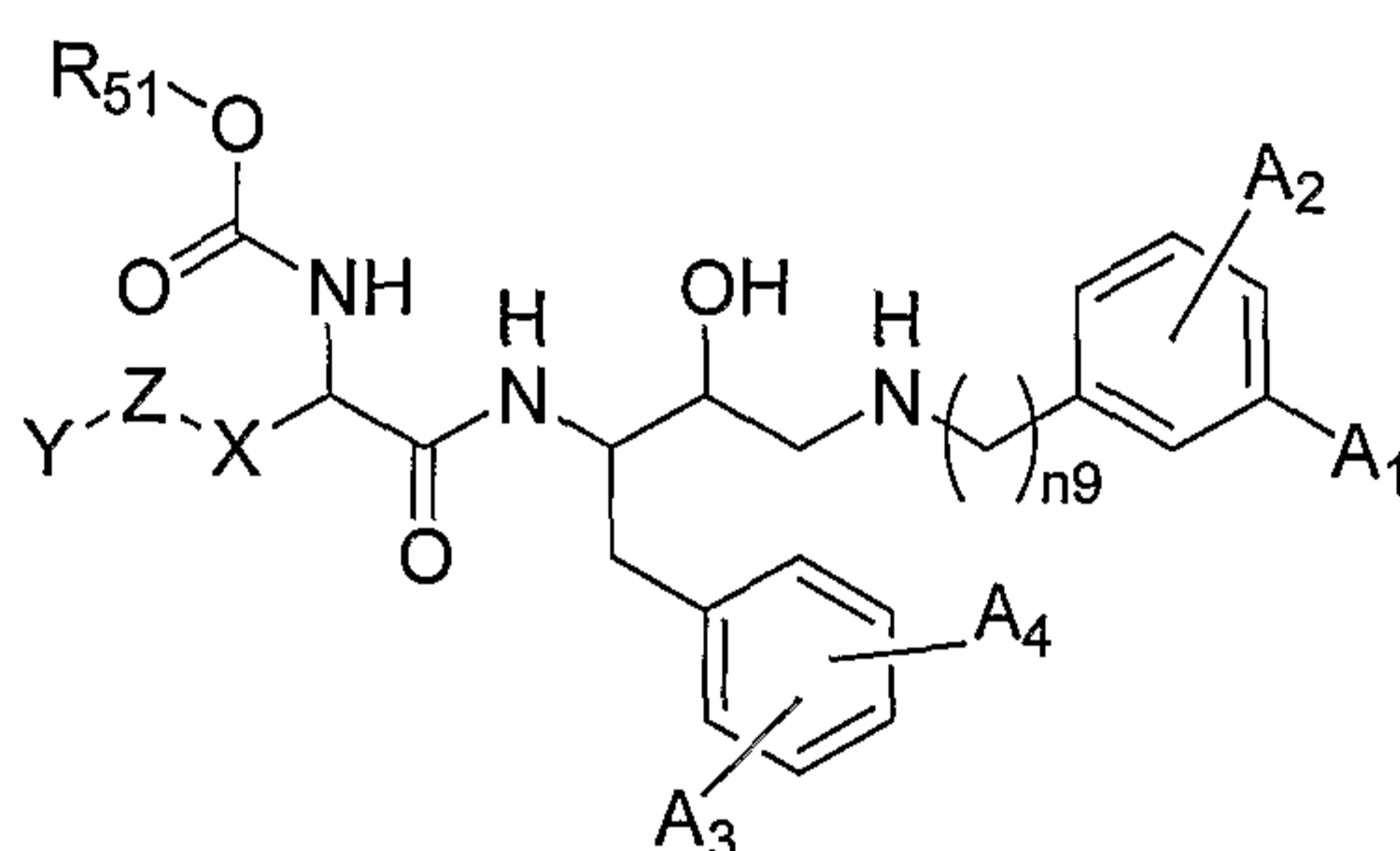
X-VIII-a

wherein

A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, methyl or methoxy; and

5 R<sub>51</sub> is benzyl; phenethyl; CH<sub>3</sub>; CH<sub>2</sub>CF<sub>3</sub>; CH<sub>2</sub>CH<sub>2</sub>CN; CH<sub>2</sub>CH<sub>2</sub>NHC(O)CH<sub>3</sub>; CH<sub>2</sub>C(O)N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>; isopropyl; CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>; pyrrolidinyl, tetrahydrofuryl, tetrahydro-thienyl 1,1-dioxide, tetrahydrothienyl, pyranyl, piperidinyl, pyrrolidinonyl, each of which is optionally substituted with 1 or 2 groups that are independently methyl, ethyl, methoxy, ethoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, benzyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; 10 pyrrolidinonyl C<sub>1</sub>-C<sub>4</sub> alkyl; allyl; propargyl; pyridinyl C<sub>1</sub>-C<sub>4</sub> alkyl; cyclopentyl; cyclohexyl; or cyclopropylmethyl.

15 Other preferred compounds of formula X-VII include those of formula X-IX



X-IX

wherein

20 n<sub>9</sub> is 1 or 2;

A<sub>1</sub> and A<sub>2</sub> are independently H, methyl, ethyl, propyl, methoxy, F, Cl, Br, I, CF<sub>3</sub> or C<sub>2</sub>-C<sub>6</sub> alkynyl; and

A<sub>3</sub> and A<sub>4</sub> are independently F, Cl, Br, I, methyl, methoxy, or H.

Preferred compounds of formula X-IX include those wherein  
 $A_1$  is methyl, ethyl, I, or  $C_2$  alkynyl;

$A_3$  and  $A_4$  are independently H, F, Cl, Br, or I;

5 X is  $C_1$  or  $C_2$  alkylidenyl;

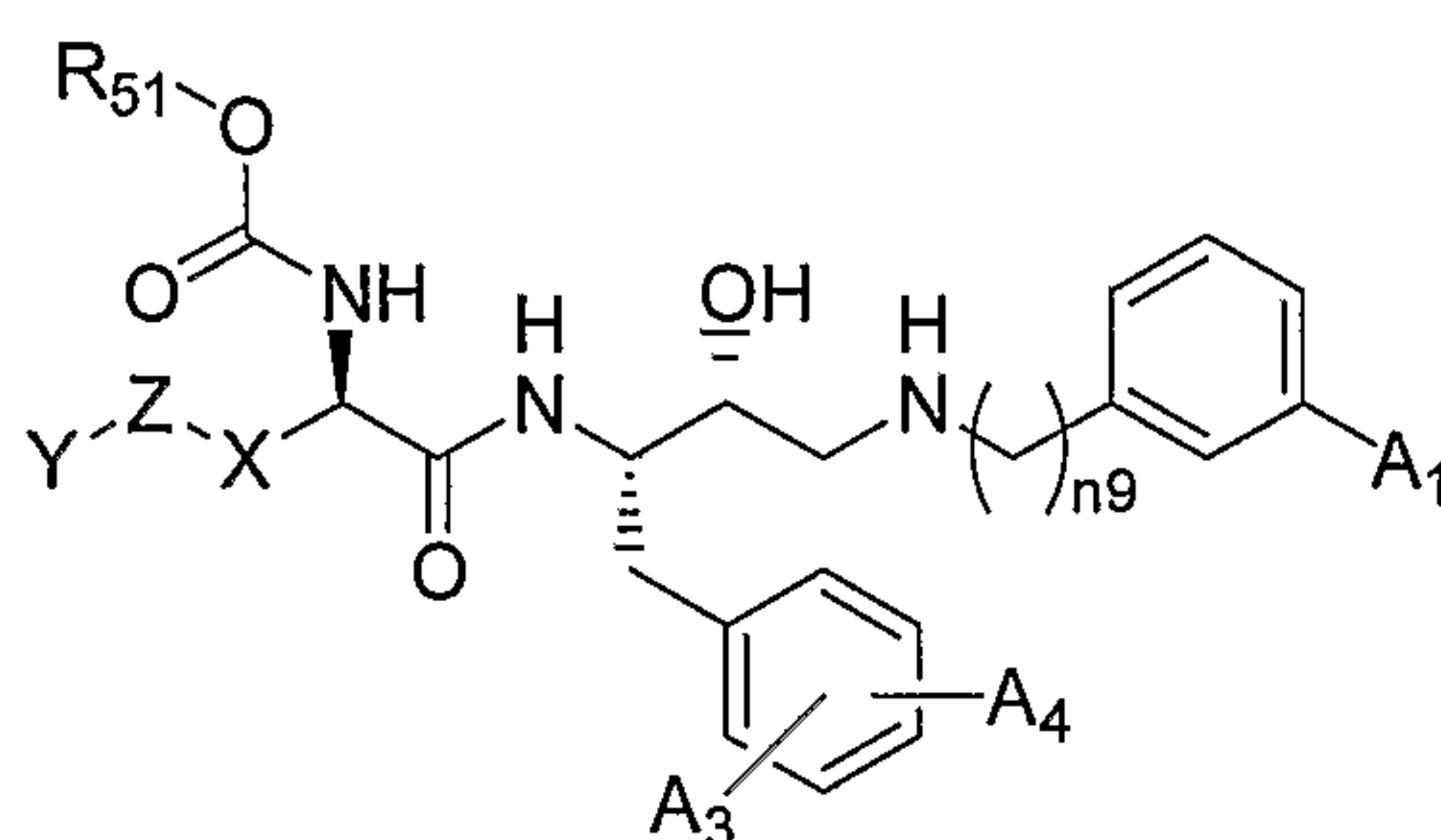
Z is  $SO_2$ ; SO; S; or C(O); and

Y is phenyl, methyl, propyl, n-butyl, isobutyl, isopentyl, 4-heptyl, 3-heptyl, 3-pentyl, or 5-nonyl; or

Y is  $-N(Y_1)(Y_2)$ ; wherein

10  $Y_1$  and  $Y_2$  are independently H or  $C_1$ - $C_4$  alkyl.

More preferred compounds of formula X-IX include those of  
 formula X-IX-a



X-IX-a

15

wherein

$A_3$  and  $A_4$  are both H or both F; and

$R_{51}$  is benzyl; phenethyl;  $CH_3$ ;  $CH_2CF_3$ ;  $CH_2CH_2CN$ ;  $CH_2CH_2NHC(O)CH_3$ ;  
 $CH_2C(O)N(CH_2CH_3)_2$ ; isopropyl;  $CH_2CH_2OCH_3$ ; pyrrolidinyl;

20

tetrahydrofuryl; tetrahydro-thienyl 1,1-dioxide;

tetrahydrothienyl; pyranyl; piperidinyl; pyrrolidinonyl;

each of which is optionally substituted with 1 or 2 groups  
 that are independently methyl, ethyl, methoxy, ethoxy,  
 halogen,  $C_2$ - $C_4$  alkanoyl, benzyl, and  $-SO_2$   $C_1$ - $C_4$  alkyl;

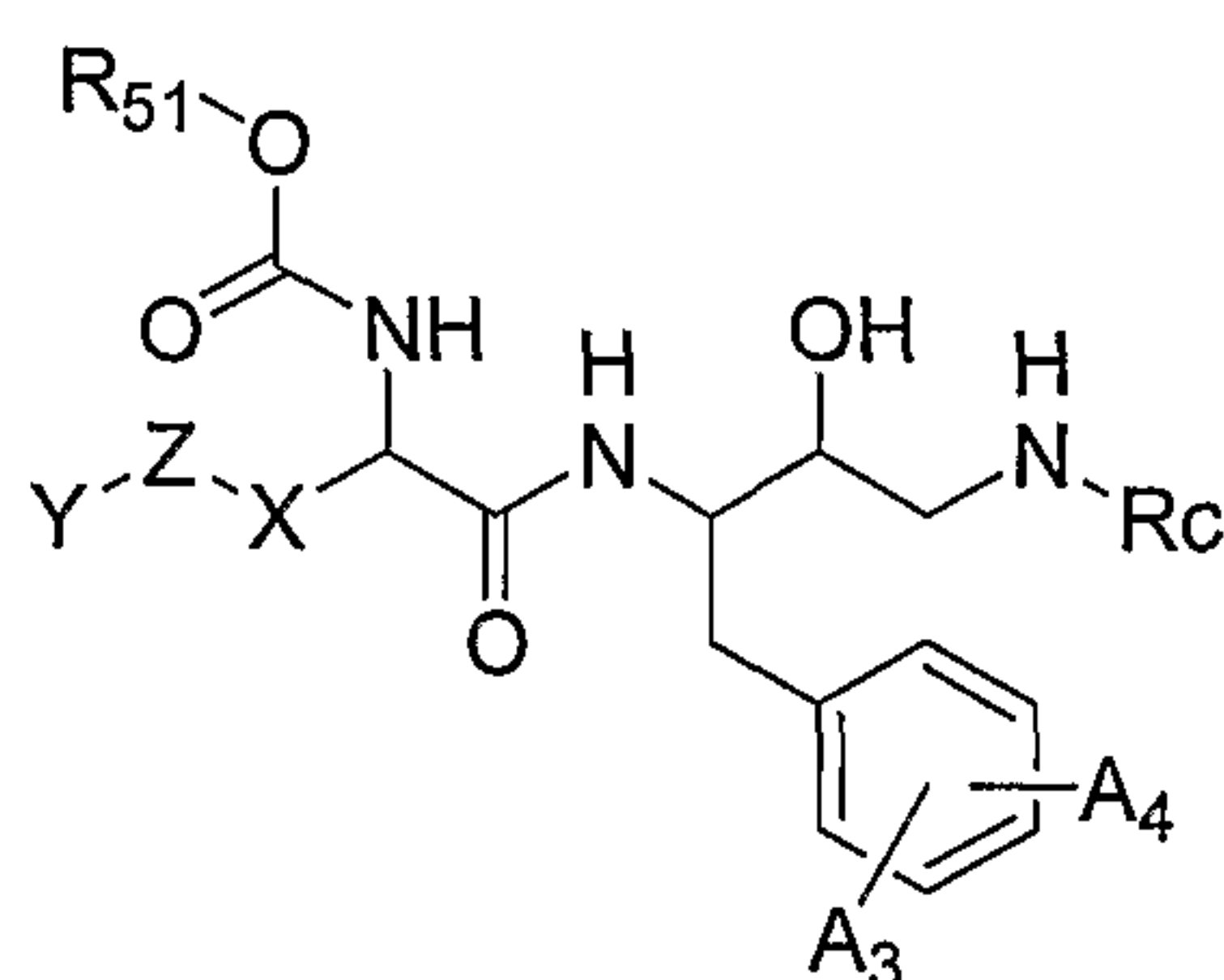
25

pyrrolidinonyl  $C_1$ - $C_4$  alkyl; allyl; propargyl; pyridinyl  $C_1$ - $C_4$  alkyl; cyclopentyl; cyclohexyl; or  $-(C_1-C_4)$ alkyl-cyclopropyl.

Preferred compounds of formula X-VII include those of formula X-X, i.e. compounds of formula X-VII wherein  $R_C$  is  $C_3$ - $C_8$  alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or - $(C_1$ - $C_4)$ alkyl-cyclopropyl.

5

Preferred compounds of formula X-X include those of formula X-X-a:



X-X-a

10 wherein

$A_3$  and  $A_4$  are independently F, Cl, Br, I, methyl, ethyl, methoxy, ethoxy, or H;

X is  $C_1$  or  $C_2$  alkylidenyl;

Z is  $SO_2$ ; SO; S; or C(O); and

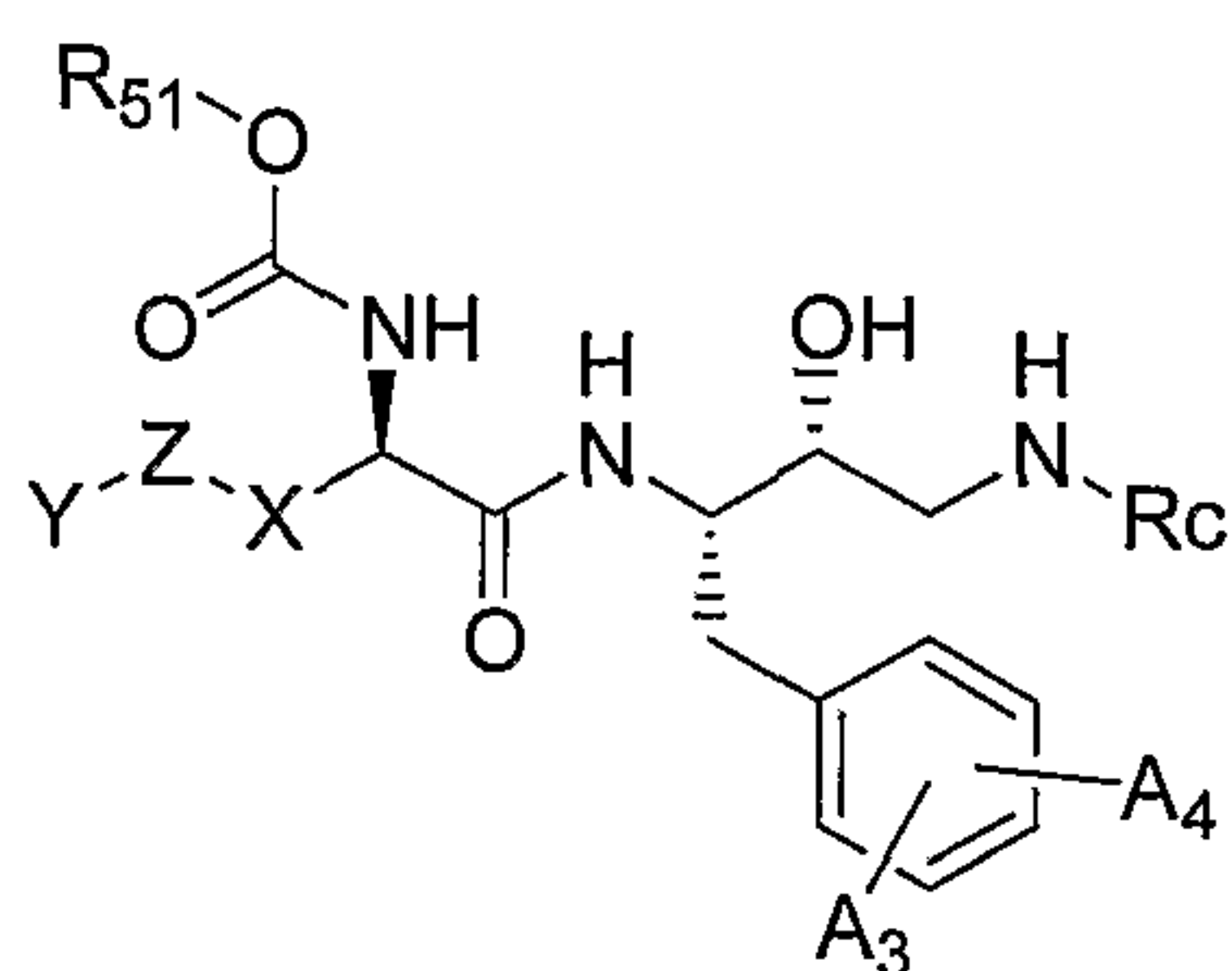
15 Y is phenyl,  $C_1$ - $C_{10}$  alkyl. More preferably, Y is methyl, propyl, n-butyl, isobutyl, isopentyl, 4-heptyl, 3-heptyl, 3-pentyl, or 5-nonyl. Or,

Y is  $-N(Y_1)(Y_2)$ ; wherein

$Y_1$  and  $Y_2$  are independently H or  $C_1$ - $C_4$  alkyl.

20

More preferred compounds of formula X-X include those of formula X-X-b:



X-X-b

wherein

A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, methyl, ethyl, methoxy, ethoxy, CF<sub>3</sub> or OCF<sub>3</sub>; and

R<sub>51</sub> is benzyl; phenethyl; CH<sub>3</sub>; CH<sub>2</sub>CF<sub>3</sub>; -CH<sub>2</sub>CH<sub>2</sub>CN; CH<sub>2</sub>CH<sub>2</sub>NHC(O)CH<sub>3</sub>; -CH<sub>2</sub>C(O)N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>; isopropyl; CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>; pyrrolidinyl, tetrahydrofuryl, tetrahydro-thienyl 1,1-dioxide, tetrahydrothienyl, pyranyl, piperidinyl, pyrrolidinonyl, each of which is optionally substituted with 1 or 2 groups that are independently methyl, ethyl, methoxy, ethoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, benzyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; pyrrolidinonyl C<sub>1</sub>-C<sub>4</sub> alkyl; allyl; propargyl; pyridinyl C<sub>1</sub>-C<sub>4</sub> alkyl; cyclopentyl; cyclohexyl; or cyclopropylmethyl.

Representative compounds of formula X-VII are

3-(butylsulfinyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-D-alaninamide;

S-butyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-D-cysteinamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(4,4,4-trifluorobutyl)sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(4,4,4-trifluorobutyl)sulfinyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-S-(4,4,4-trifluorobutyl)-D-cysteinamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(2,2,2-



trifluoroethoxy) carbonyl]-D-alaninamide;

N~2~- [(2-cyanoethoxy) carbonyl]-N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-(butylsulfonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[(3R)-pyrrolidin-3-yl] carbonyl}-D, L-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy] carbonyl}-D-alaninamide;

N~2~-{[2-(acetylamino) ethoxy] carbonyl}-3-(butylsulfonyl)-N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[(pyridin-3-yl)methyl] oxy] carbonyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[(pyridin-4-yl)methyl] oxy] carbonyl}-D-alaninamide;

3-(butylsulfonyl)-N~2~-[(methoxy) carbonyl]-N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~2~-[(2-cyanoethoxy) carbonyl]-N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-D-alaninamide;

N~2~-[(benzyloxy) carbonyl]-3-(butylsulfonyl)-N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-methylbutyl) amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-methylbutyl) amino]-2-hydroxypropyl}-N~2~-[(methoxy) carbonyl]-D-alaninamide;

N~2~-[(2-cyanoethoxy) carbonyl]-N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-{ [2-(acetylamino)ethoxy] carbonyl }-N~1~-{ (1S, 2R)-1-(3, 5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{ (1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-methylbutyl) amino]-2-hydroxypropyl }-N~2~-[(methoxy) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{ (1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-methylbutyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-{ [2-(diethylamino)-2-oxoethoxy] carbonyl }-N~1~-{ (1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{ (1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-N~2~-[(methoxy) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{ (1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-N~2~-[(isopropoxy) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[(cyclopropylmethoxy) carbonyl]-N~1~-{ (1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[(allyloxy) carbonyl]-N~1~-{ (1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[(2-cyanoethoxy) carbonyl]-N~1~-{ (1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-{ [2-(acetylamino)ethoxy] carbonyl }-N~1~-{ (1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{ (1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-N~2~-{ [(pyridin-3-

yl)methyl]oxy]carbonyl}-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{[(pyridin-4-yl)methyl]oxy]carbonyl}-D-alaninamide;

benzyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]-3-(methylsulfonyl)propylcarbamate;

N~2~-[(benzyloxy)carbonyl]-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide trifluoroacetate;

N~2~-[(benzyloxy)carbonyl]-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-L-alaninamide trifluoroacetate;

N~2~-[(benzyloxy)carbonyl]-N~1~-((1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-2-hydroxy-1-phenylethyl]amino)propyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-((1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]amino)propyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-((1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1S)-2-methoxy-1-phenylethyl]amino)propyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{[(prop-2-ynyl)oxy]carbonyl}-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (2-methoxyethylcarbonyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-{[(3R)-1-acetylpyrrolidin-3-yl] carbonyl}-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy] carbonyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy] carbonyl}-3-[(1-propylbutyl) sulfonyl]-L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl) cyclopropyl] amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(cyclopropylmethyl) amino]-2-hydroxypropyl}-

3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylphenyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)propyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{[(pyridin-3-yl)methyloxy]carbonyl}-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3R)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~-{[(3R)-1-acetylpyrrolidin-3-yl]carbonyl}-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{[(3R)-pyrrolidin-3-yl]carbonyl}-D,L-alaninamide;

N~2~-{[(3R)-1-benzylpyrrolidin-3-yl]carbonyl}-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{ [(3S)-1,1-dioxidotetrahydrothien-3-yloxy] carbonyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{ [(3S)-tetrahydrothiophen-3-yloxy] carbonyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-{(cyclopentylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-{(cyclohexylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-{ [tetrahydropyran-4-yloxy] carbonyl}-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-{ [tetrahydropyran-4-yloxy] carbonyl}-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{ [1-(methylsulfonyl)piperidin-4-yloxy] carbonyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-{ [1-acetylpiperidin-4-yloxy] carbonyl}-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{ [[[(3S)-5-oxopyrrolidin-3-yl]methyl]oxy] carbonyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{ [[[(3R)-5-oxopyrrolidin-3-yl]methyl]oxy] carbonyl}-3-[(1-

propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[[2-methoxyethyl]oxy] carbonyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-3-[(3-methoxybenzyl) amino]-2-hydroxypropyl}-N~2~-[(benzyloxy) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[2-(3-methoxyphenyl) ethyl] amino]propyl)-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~5~,N~5~-dipropyl-L-glutamamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~5~,N~5~-dipropyl-D-glutamamide;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl) amino) carbonyl]-3-oxoheptylcarbamate;

4-butyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (methoxycarbonyl)-D-homoserinamide;

3-(2-butyl-1,3-dioxolan-2-yl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (methoxycarbonyl)-D-alaninamide;

3-(2-butyl-1,3-dioxan-2-yl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (methoxycarbonyl)-D-alaninamide;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl) amino]-2-hydroxypropyl} amino) carbonyl]-3,3-difluoroheptylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl} amino) carbonyl]-3-fluoroheptylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl} amino) carbonyl]-4-oxooctylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl} amino) carbonyl]-4-hydroxyoctylcarbamate;

methyl (1R)-3-(2-butyl-1,3-dioxolan-2-yl)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl} amino) carbonyl]propylcarbamate;

methyl (1R)-3-(2-butyl-1,3-dioxan-2-yl)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl} amino) carbonyl]propylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl} amino) carbonyl]-4-fluorooctylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl} amino) carbonyl]-4,4-difluorooctylcarbamate;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl) amino]-2-hydroxypropyl}-N~2~(methoxycarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl] amino}propyl)-N~2~(methoxycarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl) cyclopropyl] amino}-2-hydroxypropyl)-N~2~(methoxycarbonyl)-D-alaninamide;

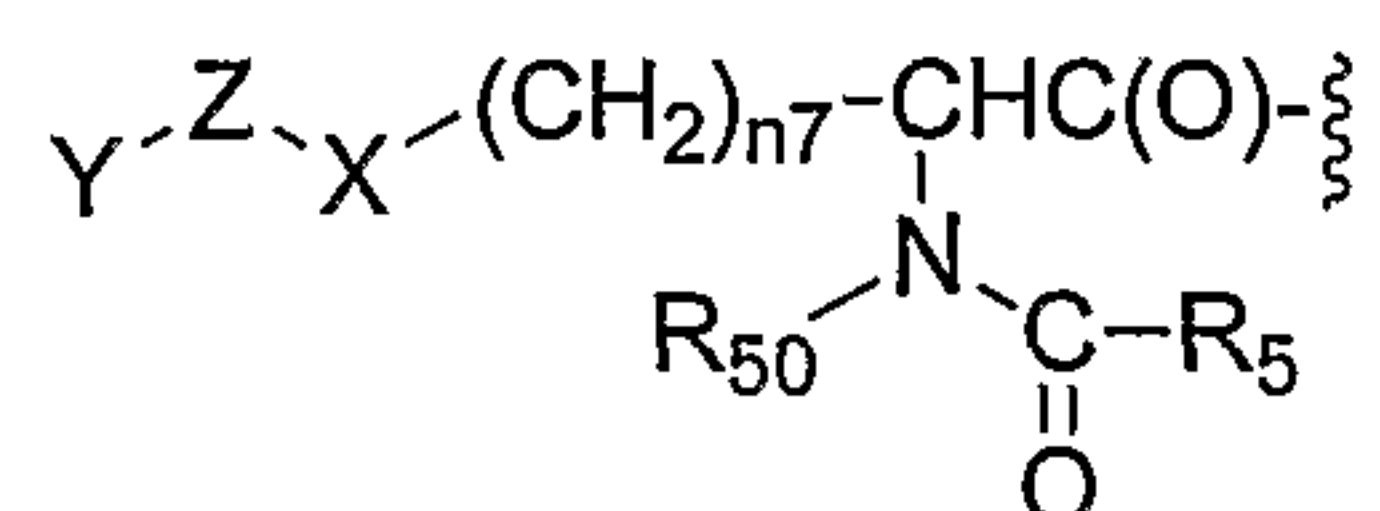
3-(butylsulfonyl)-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl) cyclopropyl] amino}-2-hydroxypropyl)-



N~2~(methoxycarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3-(trifluoromethyl)phenyl]cyclopropyl}amino)propyl]-N~2~(methoxycarbonyl)-D-alaninamide; and pharmaceutically acceptable salts thereof.

Other preferred compounds of the invention include those of formula X-XI, i.e., compounds of formula X-II wherein  $R_N$  is:



5

wherein

$n_7$  is 0, 1, 2, or 3;

$R_{50}$  is H or  $C_1$ - $C_6$  alkyl;

$R_5$  is selected from the group consisting of cyclopropyl;

10

cyclopentyl; cyclohexyl;  $C_1$ - $C_6$  alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen,  $-NR_6R_7$ ,  $C_1$ - $C_4$  alkoxy,  $C_5$ - $C_6$  heterocycloalkyl,  $C_5$ - $C_6$  heteroaryl, phenyl,  $C_3$ - $C_7$  cycloalkyl,  $-S-C_1$ - $C_4$  alkyl,  $-SO_2-C_1$ - $C_4$  alkyl,  $-CO_2H$ ,  $-CONR_6R_7$ ,  $-CO_2-C_1$ - $C_4$  alkyl, or

15

phenyloxy; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, halogen,  $C_1$ - $C_4$  haloalkyl, or OH; heterocycloalkyl optionally substituted with 1, 2, or 3 groups that are independently  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, halogen, or  $C_2$ - $C_4$

20

alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, or  $C_1$ - $C_4$  haloalkyl; and  $-NR_6R_7$ ; wherein

$R_6$  and  $R_7$  are independently selected from the group

consisting of H,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkanoyl, phenyl,

25

$-SO_2-C_1$ - $C_4$  alkyl, and phenyl  $C_1$ - $C_4$  alkyl;

X is C<sub>1</sub>-C<sub>4</sub> alkylidenyl optionally optionally substituted with  
1, 2, or 3 methyl groups; or -NR<sub>4-6</sub>-; or

R<sub>4</sub> and R<sub>4-6</sub> combine to form -(CH<sub>2</sub>)<sub>n<sub>10</sub></sub>-, wherein  
n<sub>10</sub> is 1, 2, 3, or 4;

5 Z is a bond; SO<sub>2</sub>; SO; S; or C(O);

Y is H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl containing at  
least one N, O, or S; phenyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl  
optionally substituted with 1 thru 3 substituents which  
can be the same or different and are selected from

10 halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C<sub>3</sub>-  
C<sub>8</sub> cycloalkyl optionally substituted with 1, 2, or 3  
groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, and  
halogen; alkoxy; phenyl optionally substituted with  
halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; or phenyl C<sub>1</sub>-  
15 C<sub>4</sub> alkyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl,  
C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>10</sub> alkyl  
optionally substituted with 1, 2, or 3 substituents  
selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl,  
20 and OH; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-  
C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub>  
alkyl; or

-N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl,  
piperidinyl, morpholinyl, and pyrrolidinyl, wherein  
25 each ring is optionally substituted with 1, 2, 3, or  
4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen; and

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl,  
C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub>  
30 alkanoyl, each of which is unsubstituted or substituted  
with 1, or 2 groups independently selected from halogen,  
C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>,  
wherein

R<sub>26</sub> is -C(O)-, -SO<sub>2</sub>-, -CO<sub>2</sub>-, -C(O)NH-, or -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-;

R<sub>27</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NH<sub>2</sub>, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl).

Preferred compounds of formula X-XI include those of formula X-XI-a, i.e., formula X-XI wherein

R<sub>2</sub> and R<sub>3</sub> are independently H or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, or 2 substituents selected from halogen, OH, SH, C≡N, CF<sub>3</sub>, and C<sub>1</sub>-C<sub>3</sub> alkoxy; and

R<sub>c</sub> is C<sub>1</sub>-C<sub>8</sub> alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R<sub>205</sub>, -OC=ONR<sub>235</sub>R<sub>240</sub>, -S(=O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), -SH, -C=ONR<sub>235</sub>R<sub>240</sub>, and -S(=O)<sub>2</sub>NR<sub>235</sub>R<sub>240</sub>; -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>8</sub>) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R<sub>205</sub>, -CO<sub>2</sub>H, and -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-phenyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocycloalkyl; or -(CH<sub>2</sub>)<sub>0-1</sub>-CH(C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl)-(CH<sub>2</sub>)<sub>0-1</sub>-heteroaryl; wherein each aryl is optionally substituted with 1, 2, or 3 R<sub>200</sub>; each heteroaryl is optionally substituted with 1, 2, 3, or 4 R<sub>200</sub>;

each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R<sub>210</sub>;

R<sub>200</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; OH; -NO<sub>2</sub>; halogen; -CO<sub>2</sub>H; C≡N; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>220</sub>R<sub>225</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>1</sub>-C<sub>12</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO<sub>2</sub>R<sub>215</sub>; or -(CH<sub>2</sub>)<sub>0-</sub>

$_4$ -O-(C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, or 5 -F);

R<sub>205</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, -OH, -O-phenyl, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);

R<sub>210</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; halogen; C<sub>1</sub>-C<sub>6</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkoxy; -NR<sub>220</sub>R<sub>225</sub>; OH; C≡N; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); -SO<sub>2</sub>-NR<sub>235</sub>R<sub>240</sub>; -CO-NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); or =O; wherein

R<sub>215</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(phenyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and -(CH<sub>2</sub>)<sub>0-2</sub>-(heteroaryl), or -(CH<sub>2</sub>)<sub>0-2</sub>-(heterocycloalkyl); wherein the phenyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R<sub>205</sub> or R<sub>210</sub>; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>;

R<sub>220</sub> and R<sub>225</sub> at each occurrence are independently -H, -C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkyl, halo C<sub>1</sub>-C<sub>4</sub> alkyl; -C<sub>3</sub>-C<sub>7</sub> cycloalkyl, or -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl);

R<sub>235</sub> and R<sub>240</sub> at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkoxy, or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, or 6 carbon atoms.

More preferred compounds of formula X-XI-a include those of formula X-XI-b, i.e. X-XI-a, wherein R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1, or 2 substituents selected from halogen, -OH, -SH, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C≡N, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>3</sub> alkoxy; halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; and OH.

Even more preferred compounds of formula X-XI-b include those of formula X-XI-c, i.e., X-XI-b wherein n<sub>7</sub> is 0, 1, or 2; R<sub>5</sub> is selected from the group consisting of cyclopropyl; cyclopentyl; cyclohexyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, -NR<sub>6</sub>R<sub>7</sub>, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl, C<sub>5</sub>-C<sub>6</sub> heteroaryl, phenyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -S-C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>7</sub>, -CO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, or phenyloxy; pyridyl, thiazolyl, pyrazolyl, pyrazinyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or OH; piperidinyl, dihydropyridazinonyl, pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl, imidazolyl, indolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or C<sub>2</sub>-C<sub>4</sub> alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkyl; and -NR<sub>6</sub>R<sub>7</sub>; wherein R<sub>6</sub> and R<sub>7</sub> are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl, and phenethyl.

More preferred compounds of formulae X-XI, X-XI-a, X-XI-b and X-XI-c include those wherein

$R_{20}$  at each occurrence is independently hydrogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_2$  alkoxy  $C_1$ - $C_4$  alkyl,  $C_2$ - $C_6$  alkanoyl, each of which is  
 5 unsubstituted or substituted with 1 or 2 groups independently selected from halogen, hydroxy,  $C_1$ - $C_4$  alkoxy, tertiary-butoxy carbonyl, benzyloxycarbonyl, and  $NH_2$ ;

$R_c$  is  $C_1$ - $C_8$  alkyl optionally substituted with 1, 2, or 3 groups  
 10 independently selected from the group consisting of  $R_{205}$ , -SH,  $-C=ONR_{235}R_{240}$ , and  $-S(=O)_2NR_{235}R_{240}$ ;  $-(CH_2)_{0-3}-(C_3-C_6)$  cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of  $R_{205}$ ,  $-CO_2H$ , and  $-CO_2-(C_1-C_4$   
 15 alkyl);  $-(CR_{245}R_{250})_{0-4}$ -phenyl optionally substituted with 1, 2, or 3  $R_{200}$ ;  $-(CR_{245}R_{250})_{0-3}$ -pyridyl;  $-(CR_{245}R_{250})_{0-3}$ -pyridazinyl;  $-(CR_{245}R_{250})_{0-3}$ -pyrimidinyl;  $-(CR_{245}R_{250})_{0-3}$ -pyrazinyl;  $-(CR_{245}R_{250})_{0-3}$ -furyl;  $-(CR_{245}R_{250})_{0-3}$ -indolyl;  $-(CR_{245}R_{250})_{0-3}$ -thienyl;  $-(CR_{245}R_{250})_{0-3}$ -pyrrolyl;  $-(CR_{245}R_{250})_{0-3}$ -  
 20 pyrazolyl;  $(CR_{245}R_{250})_{0-3}$ -benzoxazolyl;  $-(CR_{245}R_{250})_{0-3}$ -imidazolyl; each of the above heteroaryl groups is optionally substituted with 1, 2, 3, or 4  $R_{200}$ ;  $-(CR_{245}R_{250})_{0-3}$ -imidazolidinyl;  $(CR_{245}R_{250})_{0-3}$ -tetrahydrofuryl;  $(CR_{245}R_{250})_{0-3}$ -tetrahydropyranyl;  $(CR_{245}R_{250})_{0-3}$ -piperazinyl;  $(CR_{245}R_{250})_{0-3}$ -  
 25 pyrrolidinyl;  $(CR_{245}R_{250})_{0-3}$ -piperidinyl;  $(CR_{245}R_{250})_{0-3}$ -indolinyl; each of the above heterocycloalkyl groups is optionally substituted with 1, 2, 3, or 4  $R_{210}$ ;  $(CH_2)_{0-1}$ - $CH((CH_2)_{0-4}-OH)-(CH_2)_{0-1}$ -phenyl; or  $-(CH_2)_{0-1}$ - $CH(C_1-C_4$  hydroxyalkyl)- $(CH_2)_{0-1}$ -pyridyl;

$R_{200}$  at each occurrence is independently  $C_1$ - $C_6$  alkyl optionally substituted with 1, 2, or 3  $R_{205}$  groups; OH;  $-NO_2$ ; halogen;  $-CO_2H$ ;  $C\equiv N$ ;  $-(CH_2)_{0-4}-CO-NR_{220}R_{225}$ ;  $-(CH_2)_{0-4}-CO-(C_1-C_8$  alkyl);  $-(CH_2)_{0-4}-CO_2R_{215}$ ; or  $-(CH_2)_{0-}$

$_4$ -O-(C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, or 5 -F);

R<sub>205</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, -OH, -O-phenyl, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);

R<sub>210</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1 or 2 R<sub>205</sub> groups; halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> haloalkoxy; -NR<sub>220</sub>R<sub>225</sub>; OH; C≡N; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1 or 2 R<sub>205</sub> groups; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); -SO<sub>2</sub>-NR<sub>235</sub>R<sub>240</sub>; -CO-NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); or =O; wherein

R<sub>215</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(phenyl), C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(pyridyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(pyrrolyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(imidazolyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(pyrimidyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(pyrrolidinyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(imidazolidinyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(piperazinyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(piperidinyl), or -(CH<sub>2</sub>)<sub>0-2</sub>-(morpholinyl); wherein the phenyl group at each occurrence is optionally substituted with 1 or 2 groups that are independently R<sub>205</sub> or R<sub>210</sub>; wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1 or 2 R<sub>210</sub>; wherein each heteroaryl group at each occurrence is optionally substituted with 1 or 2 R<sub>210</sub>;

R<sub>220</sub> and R<sub>225</sub> at each occurrence are independently -H, -C<sub>1</sub>-C<sub>4</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkyl, halo C<sub>1</sub>-C<sub>4</sub> alkyl; -C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-(C<sub>1</sub>-C<sub>2</sub> alkyl);

R<sub>235</sub> and R<sub>240</sub> at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkoxy, or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms.

- 5 Still other more preferred compounds of formulae X-XI, X-XI-a, X-XI-b and X-XI-c include those wherein X is -C<sub>1</sub>-C<sub>3</sub> alkylidanyl optionally optionally substituted with 1 or 2 methyl groups;
- Z is SO<sub>2</sub>; SO; S; or C(O);
- 10 Y is H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; pyrrolidinyl; piperidinyl; imidazolidinyl; piperazinyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> thioalkoxy, and C<sub>1</sub>-C<sub>4</sub> haloalkoxy; C<sub>3</sub>-C<sub>6</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl and halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; phenyl, benzyl or phenethyl each of which is optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein
- 20 Y<sub>1</sub> and Y<sub>2</sub> are independently H; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or C<sub>3</sub>-C<sub>6</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or
- 25 -N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>4</sub> alkyl, or halogen; and
- 30 R<sub>2</sub> and R<sub>3</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl.

Still other even more preferred compounds of formula X-XI include those of formula X-XII, i.e., compounds of formula X-XI wherein



$n_7$  is 0, or 1;

$R_5$  is selected from the group consisting of cyclopropyl; cyclobutyl, cyclopentyl; cyclohexyl;  $C_1$ - $C_6$  alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen,  $-NR_6R_7$ ,  $C_1$ - $C_4$  alkoxy, piperidinyl, pyrrolidinyl, tetrahydrofuryl, tetrahydrothienyl dioxide, pyranyl, pyridyl, phenyl,  $C_3$ - $C_6$  cycloalkyl,  $S$ - $C_1$ - $C_4$  alkyl,  $SO_2$ - $C_1$ - $C_4$  alkyl,  $CO_2H$ ,  $CONR_6R_7$ ,  $CO_2$ - $C_1$ - $C_4$  alkyl, or phenyloxy; pyridyl, thiazolyl, pyrazolyl, pyrazinyl, optionally substituted with 1, 2, or 3 groups that are independently  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, halogen,  $C_1$ - $C_4$  haloalkyl, or OH; piperidinyl, dihydropyridazinonyl, pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl, imidazolyl, indolyl, optionally substituted with 1, 2, or 3 groups that are independently  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, halogen, or  $C_2$ - $C_4$  alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, or  $C_1$ - $C_2$  haloalkyl; and  $-NR_6R_7$ ; wherein

$R_6$  and  $R_7$  are independently selected from the group consisting of H,  $C_1$ - $C_4$  alkyl,  $C_2$ - $C_6$  alkanoyl, phenyl,  $-SO_2$ - $C_1$ - $C_4$  alkyl, and benzyl;

$R_{20}$  at each occurrence is independently hydrogen,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkanoyl, tertiary-butoxy carbonyl, and benzyloxycarbonyl;

$R_c$  is  $C_1$ - $C_8$  alkyl optionally substituted with 1 or 2 groups independently selected from  $R_{205}$ , and  $-SH$ ;  $-(CH_2)_{0-3}$ - $(C_3$ - $C_6)$  cycloalkyl wherein the cycloalkyl is optionally substituted with 1  $R_{205}$  group;  $-(CR_{245}R_{250})_{0-3}$ -phenyl optionally substituted with 1 or 2  $R_{200}$ ;  $-(CR_{245}R_{250})_{0-3}$ -pyridyl;  $-(CR_{245}R_{250})_{0-3}$ -pyrrolyl;  $(CR_{245}R_{250})_{0-3}$ -benzoxazolyl;  $-(CR_{245}R_{250})_{0-3}$ -imidazolyl; each of the above heteroaryl groups is optionally substituted with 1 or 2  $R_{200}$ ;  $-(CR_{245}R_{250})_{0-3}$ -imidazolidinyl;  $(CR_{245}R_{250})_{0-3}$ -tetrahydrofuryl;

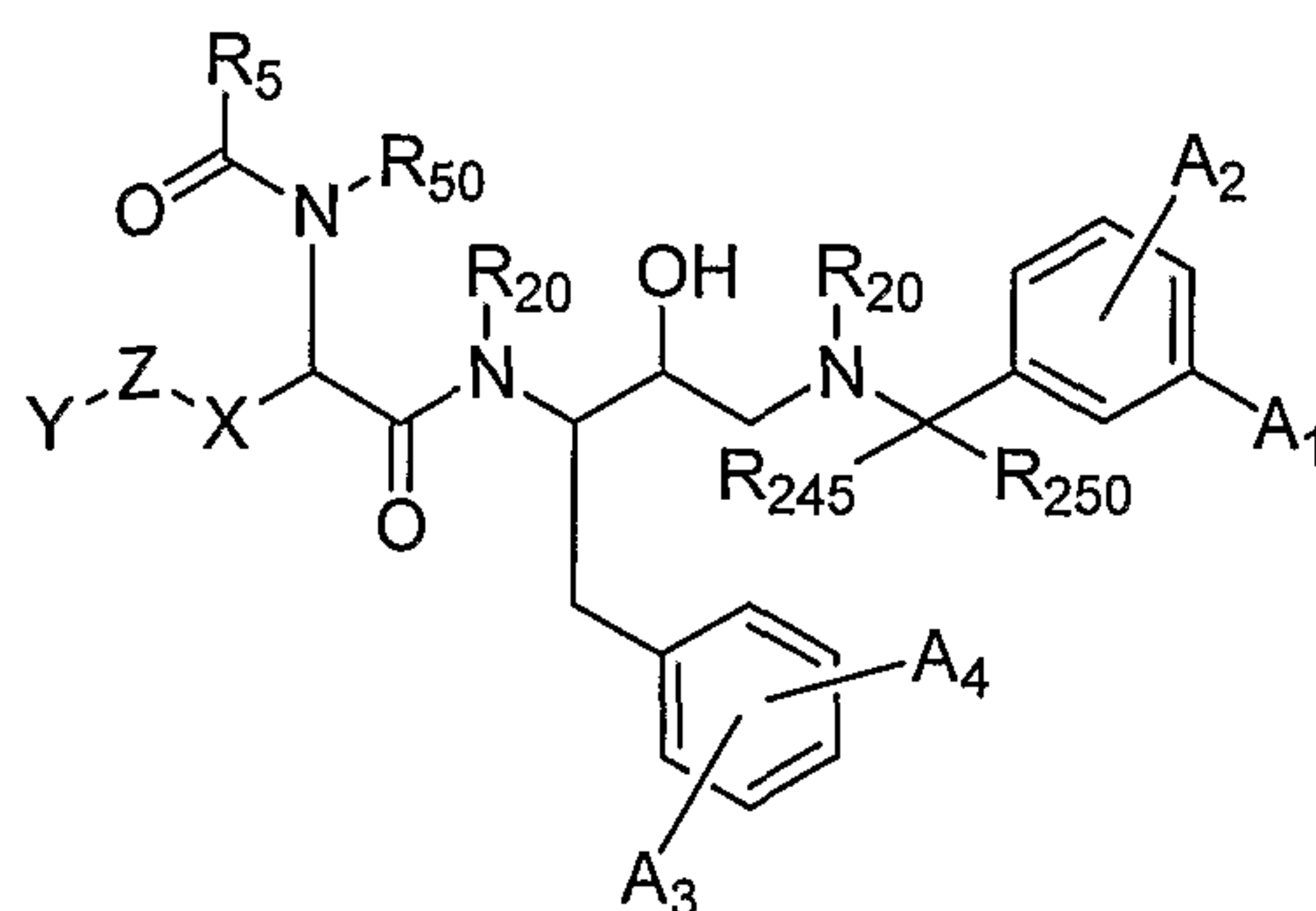
$(CR_{245}R_{250})_{0-3}$ -tetrahydropyranyl;  $(CR_{245}R_{250})_{0-3}$ -pyrrolidinyl;  
 $(CR_{245}R_{250})_{0-3}$ -piperidinyl; each of the above  
heterocycloalkyl groups is optionally substituted with 1  
or 2  $R_{210}$ ;  $(CH_2)_{0-1}$ -CH $(CH_2)_{0-4}$ -OH)- $(CH_2)_{0-1}$ -phenyl; or  $-(CH_2)_{0-1}$ -CH(C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl)- $(CH_2)_{0-1}$ -pyridyl;  
5  $R_{200}$  at each occurrence is independently C<sub>1</sub>-C<sub>4</sub> alkyl  
optionally substituted with 1, 2, or 3  $R_{205}$  groups;  
OH; NO<sub>2</sub>; halogen; CO<sub>2</sub>H; C≡N; or  $-(CH_2)_{0-4}$ -O-(C<sub>1</sub>-C<sub>6</sub>  
alkyl optionally substituted with 1, 2, 3, or 5 -F);  
10  $R_{205}$  at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl,  
halogen, OH, -O-phenyl, SH, C≡N, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy,  
NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);  
 $R_{210}$  at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl  
optionally substituted with 1  $R_{205}$  group; halogen; C<sub>1</sub>-  
15 C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> haloalkoxy; OH; C≡N; or =O; wherein  
 $R_{235}$  and  $R_{240}$  at each occurrence are independently H, or C<sub>1</sub>-  
C<sub>6</sub> alkyl;  
 $R_{245}$  and  $R_{250}$  at each occurrence are independently H, C<sub>1</sub>-C<sub>4</sub>  
alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or  
20  $R_{245}$  and  $R_{250}$  are taken together with the carbon to which  
they are attached to form a carbocycle of 3, 5, or 6  
carbon atoms;  
X is-C<sub>1</sub>-C<sub>3</sub> alkylidenyl;  
Z is SO<sub>2</sub>; SO; S; or C(O);  
25 Y is H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; pyrrolidinyl; piperidinyl;  
imidazolidinyl; piperazinyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl  
optionally substituted with 1 thru 3 substituents which  
can be the same or different and are selected from  
halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> thioalkoxy, and C<sub>1</sub>-C<sub>4</sub>  
30 haloalkoxy; C<sub>3</sub>-C<sub>6</sub> cycloalkyl optionally substituted with  
1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl  
and halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; phenyl, benzyl or phenethyl  
each of which is optionally substituted with halogen, C<sub>1</sub>-  
C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

Y<sub>1</sub> and Y<sub>2</sub> are independently H; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or C<sub>3</sub>-C<sub>6</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or  
 5 -N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl, piperidinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>4</sub> alkyl, or halogen;  
 10

R<sub>2</sub> and R<sub>3</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl; and

R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1 substituent selected from halogen, -OH, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>4</sub> alkyl), N-(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>1</sub>-C<sub>4</sub> alkyl), -C≡N, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>3</sub> alkoxy; halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; and OH.  
 15

More preferred compounds of formula X-XI and preferred compounds of formula X-XII include those of formula X-XIII  
 20 wherein



X-XIII

wherein

A<sub>1</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>2</sub>-C<sub>6</sub> alkynyl;

25 A<sub>2</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl or OH;

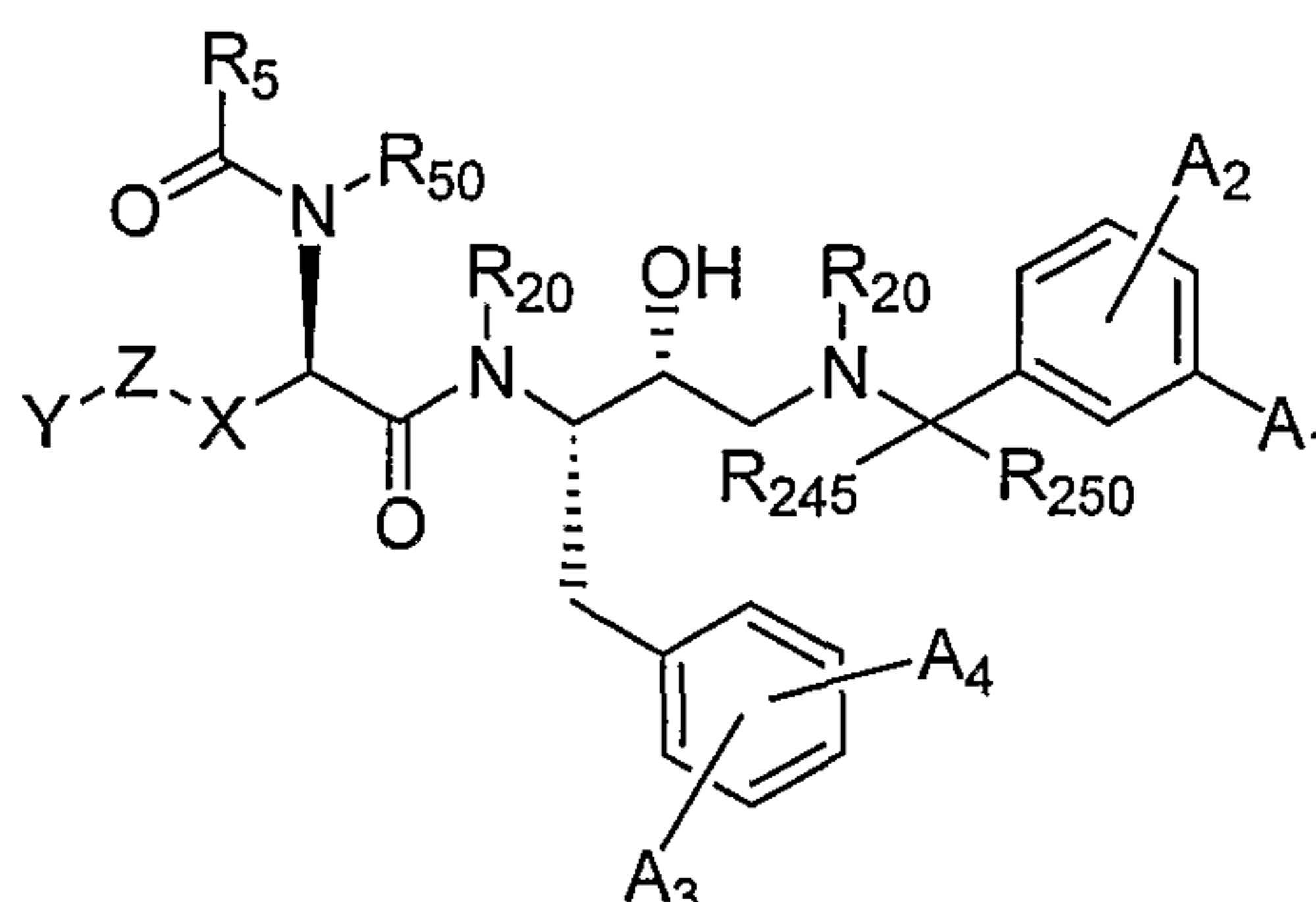
A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, Br, or I;

R<sub>5</sub> is selected from cyclopropyl; cyclobutyl, cyclopentyl;  
 cyclohexyl; pyridyl, thiazolyl, pyrazolyl, or pyrazinyl  
 each of which is optionally substituted with 1, 2, or 3  
 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy,  
 5 halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or OH; piperidinyl,  
 dihydropyridazinonyl, pyrrolidinonyl,  
 thioxothiazolidinonyl, isoxazolyl, imidazolyl, or indolyl  
 each of which is optionally substituted with 1, or 2  
 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy,  
 10 halogen, or C<sub>2</sub>-C<sub>4</sub> alkanoyl; phenyl optionally substituted  
 with 1, 2, 3, or 4 groups that are independently halogen,  
 OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>2</sub> haloalkyl; and  
 -NR<sub>6</sub>R<sub>7</sub>.

15 Preferred compounds of formula X-XIII include those  
 wherein

R<sub>20</sub> at each occurrence is independently H or C<sub>1</sub>-C<sub>4</sub> alkyl;  
 X is C<sub>1</sub> or C<sub>2</sub> alkylidenyl;  
 Z is SO<sub>2</sub>; SO; S; or C(O); and  
 20 Y is phenyl; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3  
 halogen; or OH; or  
 Y is -N(Y<sub>1</sub>)(Y<sub>2</sub>); wherein  
 Y<sub>1</sub> and Y<sub>2</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl.

25 More preferred compounds of formula X-XIII include those  
 of formula X-XIV:



X-XIV.

Preferred compounds of formulas X-XIII and X-XIV include those wherein

A<sub>1</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub> alkynyl, or I;

5 R<sub>50</sub> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

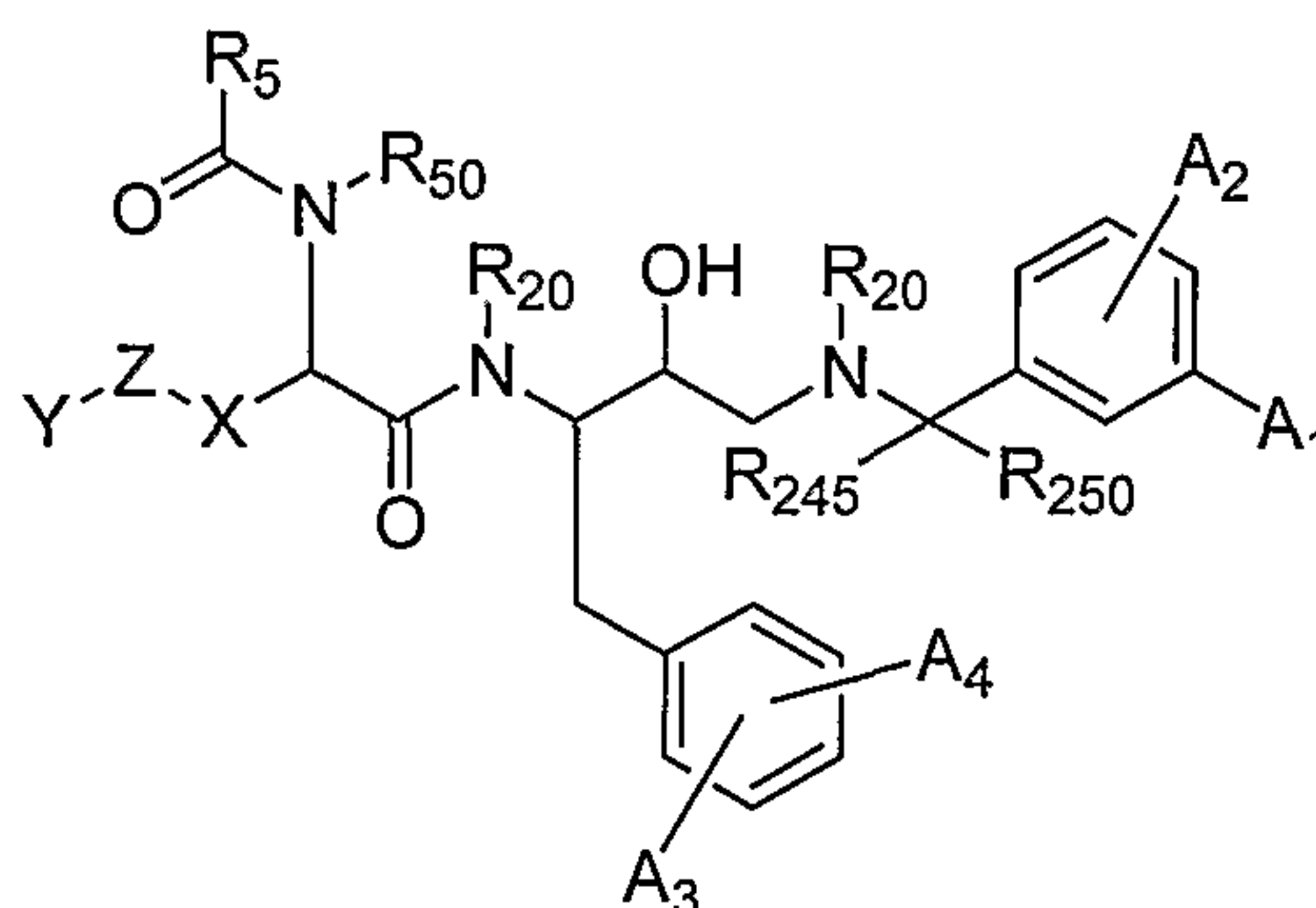
A<sub>2</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, OCF<sub>3</sub>, CF<sub>3</sub> or OH;

A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, Br, or I.

Even more preferred compounds of formulas X-XIII and X-XIV  
10 include those wherein

R<sub>245</sub> and R<sub>250</sub> are both hydrogen or R<sub>245</sub> and R<sub>250</sub> form a cyclopropyl group.

Other preferred compounds of formula X-XII include those  
15 of formula X-XV:



X-XV

wherein

A<sub>1</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>2</sub> alkynyl, or I;

20 A<sub>2</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl or OH;

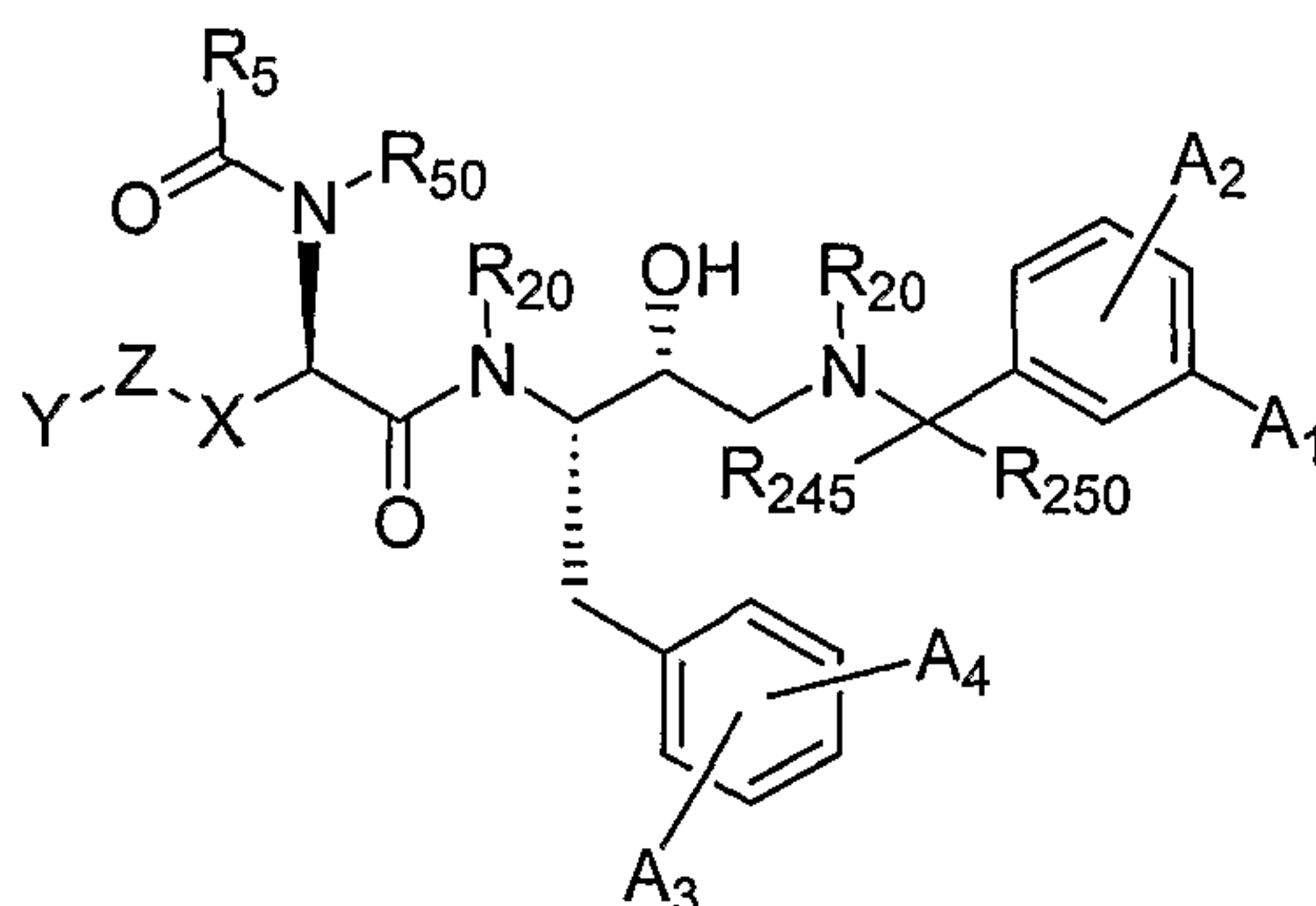
A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, Br, or I;

R<sub>5</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups  
25 that are independently halogen, -NR<sub>6</sub>R<sub>7</sub>, C<sub>1</sub>-C<sub>4</sub> alkoxy,  
piperidinyl, pyrrolidinyl, pyridyl, phenyl, C<sub>3</sub>-C<sub>6</sub>  
cycloalkyl, S-C<sub>1</sub>-C<sub>4</sub> alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, CO<sub>2</sub>H, CONR<sub>6</sub>R<sub>7</sub>,  
CO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, or phenyloxy; and -NR<sub>6</sub>R<sub>7</sub> wherein

R<sub>6</sub> and R<sub>7</sub> are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, phenyl, and -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl.

5 Preferred compounds of formula X-XV include those wherein R<sub>20</sub> at each occurrence is independently H or C<sub>1</sub>-C<sub>4</sub> alkyl; X is C<sub>1</sub> or C<sub>2</sub> alkylidenyl; Z is SO<sub>2</sub>; SO; S; or C(O); and Y is phenyl; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3  
10 halogen; or OH; or Y is -N(Y<sub>1</sub>)(Y<sub>2</sub>); wherein Y<sub>1</sub> and Y<sub>2</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl.

More preferred compounds of formula X-XV include those of  
15 formula X-XVI:



XVI.

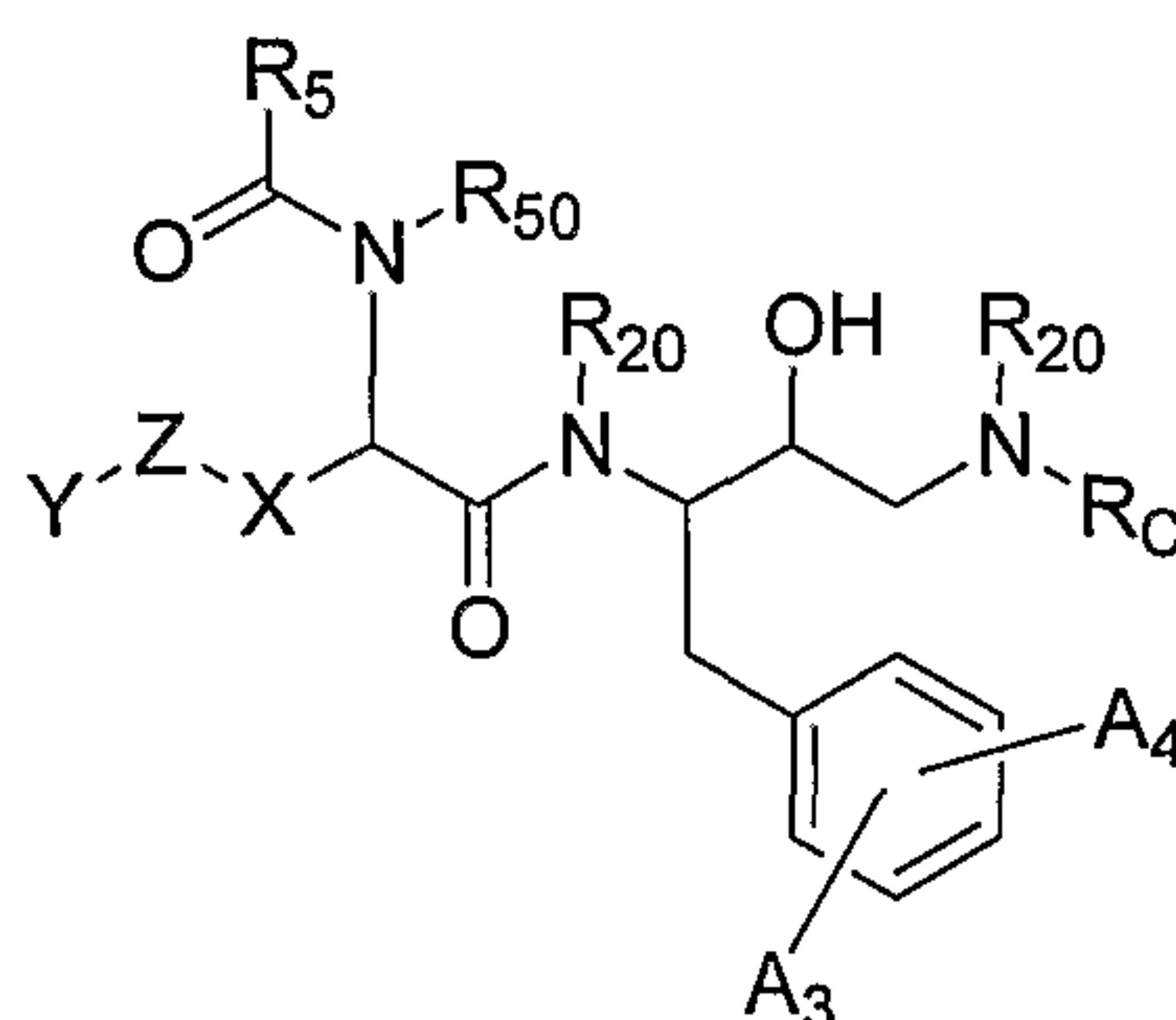
Preferred compounds of formulas X-XV and X-XVI include  
20 those wherein A<sub>1</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl; R<sub>50</sub> is H or C<sub>1</sub>-C<sub>4</sub> alkyl; A<sub>2</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, OCF<sub>3</sub>, CF<sub>3</sub> or OH; A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, Br, or I.

25

More preferred compounds of formulas X-XV and X-XVI include those wherein

R<sub>245</sub> and R<sub>250</sub> are both hydrogen or R<sub>245</sub> and R<sub>250</sub> form a cyclopropyl group.

Other preferred compounds of formula X-XII include those  
5 of formula X-XVII:



X-XVII

wherein

R<sub>C</sub> is C<sub>3</sub>-C<sub>8</sub> alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or -  
10 (C<sub>1</sub>-C<sub>4</sub>)alkyl-cyclopropyl;

A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, Br, or I;

R<sub>5</sub> is selected from cyclopropyl; cyclopentyl; cyclohexyl;  
pyridyl, thiazolyl, pyrazolyl, or pyrazinyl each of which  
is optionally substituted with 1, 2, or 3 groups that are  
15 independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>4</sub>  
haloalkyl, or OH; piperidinyl, dihydropyridazinonyl,  
pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl,  
imidazolyl, or indolyl each of which is optionally  
substituted with 1, or 2 groups that are independently C<sub>1</sub>-  
20 C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or C<sub>2</sub>-C<sub>4</sub> alkanoyl; phenyl  
optionally substituted with 1, 2, 3, or 4 groups that are  
independently halogen, OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or  
C<sub>1</sub>-C<sub>2</sub> haloalkyl; and -NR<sub>6</sub>R<sub>7</sub>.

25 Preferred compounds of formula X-XVII include those  
wherein

R<sub>20</sub> at each occurrence is independently H or C<sub>1</sub>-C<sub>4</sub> alkyl;

X is C<sub>1</sub> or C<sub>2</sub> alkylidenyl;

Z is SO<sub>2</sub>; SO; S; or C(O); and

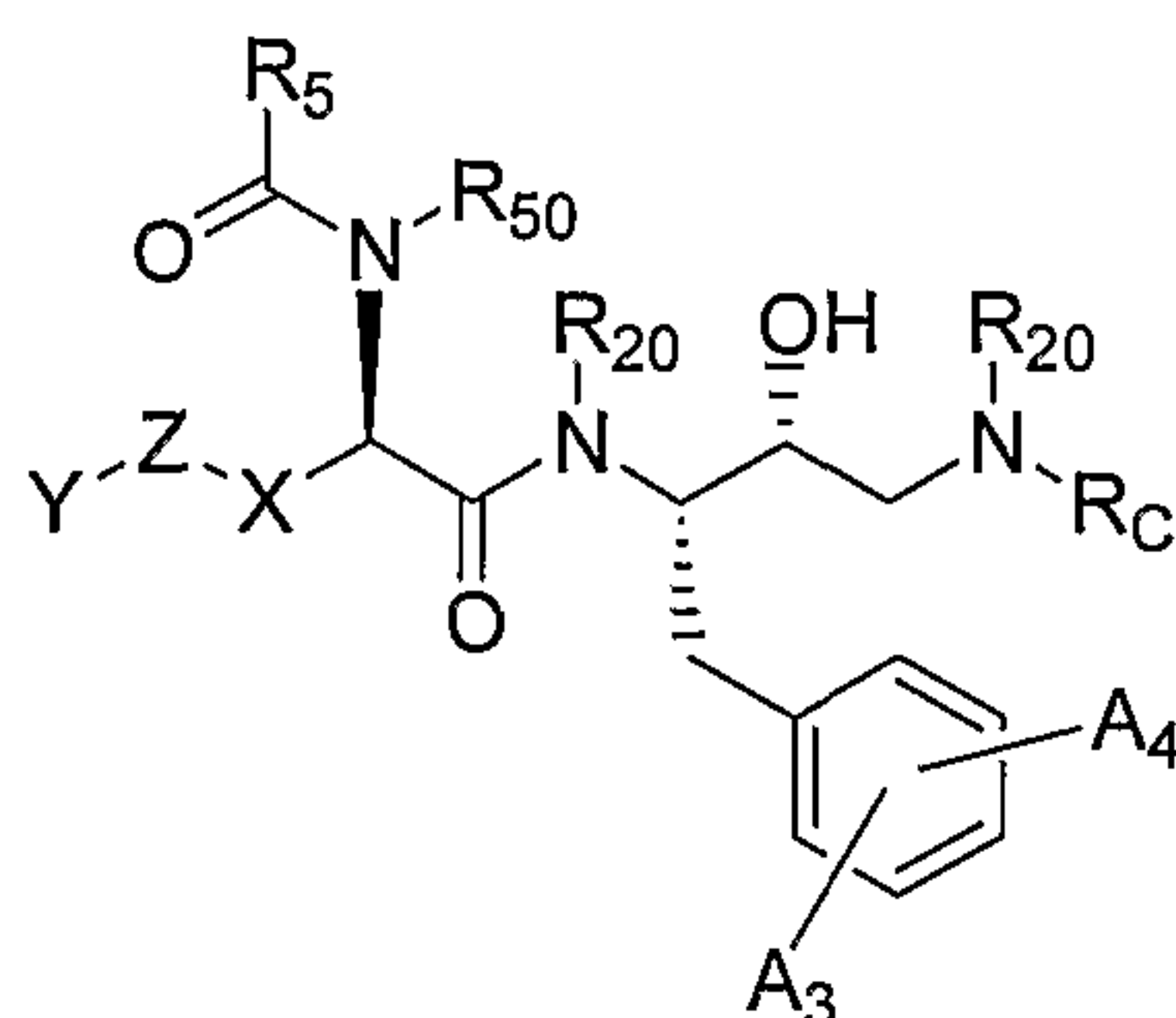
Y is phenyl; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 halogen; or OH; or

Y is -N(Y<sub>1</sub>)(Y<sub>2</sub>); wherein

Y<sub>1</sub> and Y<sub>2</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl.

5

More preferred compounds of formula X-XVII include those of formula X-XVIII:



X-XVIII.

10

Preferred compounds of formulas X-XVII and X-XVIII include those wherein

R<sub>50</sub> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, Br, or I.

15

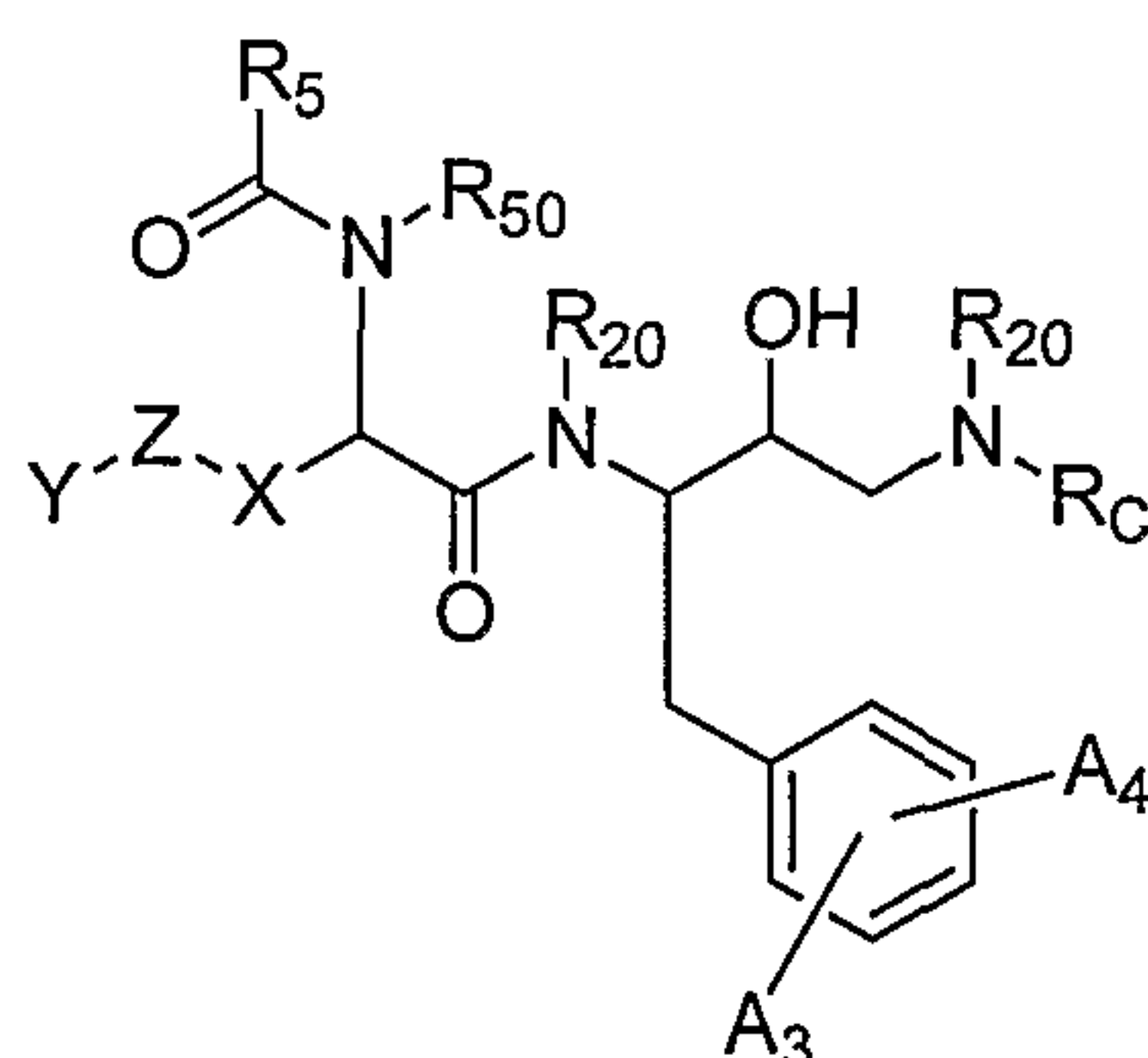
More preferred compounds of formulas X-XVII and X-XVIII include those wherein

R<sub>245</sub> and R<sub>250</sub> are both hydrogen or R<sub>245</sub> and R<sub>250</sub> form a cyclopropyl group.

20

Other preferred compounds of formula X-XII include those of formula X-XIX:





X-XIX

wherein

R<sub>c</sub> is C<sub>3</sub>-C<sub>8</sub> alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or -  
 5 (C<sub>1</sub>-C<sub>4</sub>)alkyl-cyclopropyl;

A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, Br, or I;

R<sub>5</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups  
 that are independently halogen, -NR<sub>6</sub>R<sub>7</sub>, C<sub>1</sub>-C<sub>4</sub> alkoxy,  
 piperidinyl, pyrrolidinyl, pyridyl, phenyl, C<sub>3</sub>-C<sub>6</sub>  
 10 cycloalkyl, S-C<sub>1</sub>-C<sub>4</sub> alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, CO<sub>2</sub>H, CONR<sub>6</sub>R<sub>7</sub>,  
 CO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, or phenyloxy; wherein

R<sub>6</sub> and R<sub>7</sub> are independently selected from the group  
 consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl,  
 phenyl, and -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl.

15

Preferred compounds of formula X-XIX include those wherein  
 R<sub>20</sub> at each occurrence is independently H or C<sub>1</sub>-C<sub>4</sub> alkyl;

X is C<sub>1</sub> or C<sub>2</sub> alkylidenyl;

Z is SO<sub>2</sub>; SO; S; or C(O); and

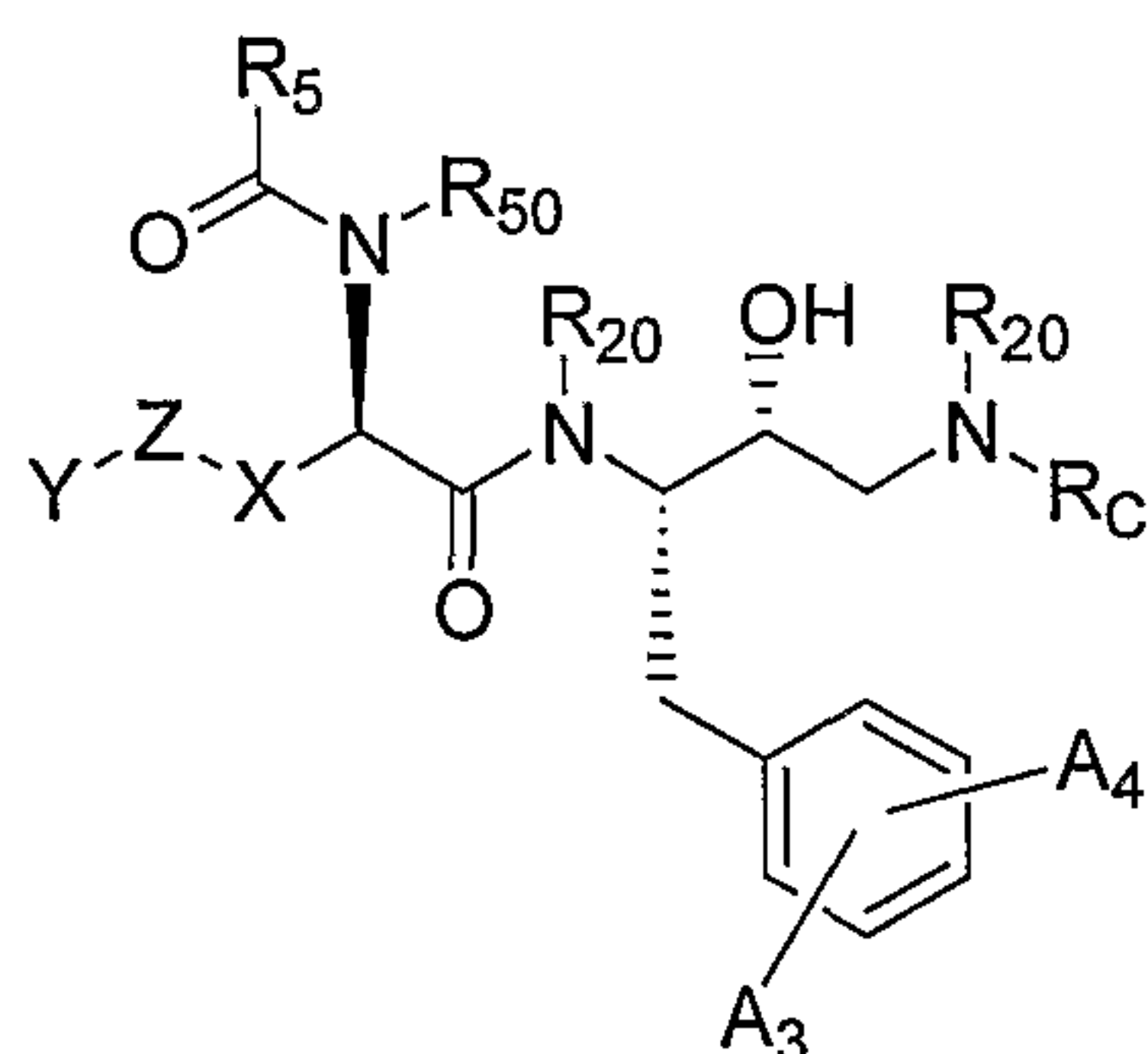
20 Y is phenyl; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3  
 halogen; or OH; or

Y is -N(Y<sub>1</sub>)(Y<sub>2</sub>); wherein

Y<sub>1</sub> and Y<sub>2</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl.

25

Preferred compounds of formula X-XIX include those of  
 formula X-XX:



X-XX.

Preferred compounds of formulas X-XIX and X-XX include  
5 those wherein

R<sub>50</sub> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, Br, or I.

More preferred compounds of formulas X-XIX and X-XX  
10 include those wherein

R<sub>245</sub> and R<sub>250</sub> are both hydrogen or R<sub>245</sub> and R<sub>250</sub> form a cyclopropyl group.

Representative compounds of formula X-XI are:

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-  
[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(3,3,3-  
trifluoropropanoyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-  
[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~- (trifluoroacetyl)-  
D-alaninamide;

N~2~-acetyl-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-  
difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-  
alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-  
[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~- (pyridin-4-  
ylcarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~2~- (cyclopropylcarbonyl)-N~1~-  
{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-

hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~(beta-alanyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~glycyl-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~(N,N-dimethylglycyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~(N,N-dimethyl-beta-alanyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~(methoxyacetyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~(pyridin-3-ylcarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(2,4-dimethyl-1,3-thiazol-5-yl)carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[3-(trifluoromethyl)-1H-pyrazol-4-yl]carbonyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(3-methyl-1H-pyrazol-5-yl)carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~(1H-imidazol-4-ylacetyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~(pyrazin-2-ylcarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[ (3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(6-hydroxypyridin-3-yl) carbonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-(pyridin-4-ylcarbonyl)-D-alaninamide;

N~2~-acetyl-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl) amino]-2-hydroxypropyl}-D-alaninamide;

N~1~-[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-N~2~-(cyclopropylcarbonyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-acetyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-(pyridin-4-ylcarbonyl)-D-alaninamide;

N~2~-[(5-bromopyridin-3-yl) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[(5-chloropyridin-3-yl) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-(3-fluorobenzoyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(5-methylpyridin-3-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-phenylglycyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-

propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-{[3-(trifluoromethyl)-1H-pyrazol-4-yl] carbonyl}-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(3-methyl-1H-pyrazol-5-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-(1,3-thiazol-4-yl carbonyl)-D-alaninamide;

N~2~-[(1-acetylpiperidin-4-yl) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[4-(acetylamino)butanoyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-acetyl-beta-alanyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-(chloroacetyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-(methoxyacetyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-(3-methoxypropanoyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-(2,2-dimethylpropanoyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-isobutyryl-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-butyryl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-acetyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl) cyclopropyl] amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-[(pyridin-3-yl) carbonyl]-D-alaninamide trifluoroacetate;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl) cyclopropyl] amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-[(pyridin-4-yl) carbonyl]-D-alaninamide trifluoroacetate;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl) cyclopropyl] amino]-2-hydroxypropyl)-N~2~-(3-hydroxybenzoyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide trifluoroacetate;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-[(pyridin-3-yl) carbonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-N~2~-(3-hydroxybenzoyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-cyclopropylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-N~2~-propionyl-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

3-[butylsulfonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-

[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(pyridin-3-yl) carbonyl]-D,L-alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl) cyclopropyl] amino}-2-hydroxypropyl)-N~2~- (3-hydroxybenzoyl)-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide trifluoracete;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl) cyclopropyl] amino}-2-hydroxypropyl)-3-[(1-propylbutyl) sulfonyl]-N~2~-[(pyridin-4-yl) carbonyl]-D-alaninamide trifluoracetate;

N~1~-((1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-N~2~-[(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]alaninamide hydrochloride;

5-oxo-D-prolyl-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-[(1-propylbutyl) sulfonyl]alaninamide;

5-oxo-L-prolyl-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-[(1-propylbutyl) sulfonyl]alaninamide;

N~1~-((1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-N~2~- [3-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl) propanoyl]-3-[(1-propylbutyl) sulfonyl]alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-N~2~-[(piperidin-4-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-N~2~-[(2,4-dimethyl-1,3-thiazol-5-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-N~2~-[(2-methyl-4-(trifluoromethyl)-1,3-thiazol-5-yl) carbonyl]-3-[(1-

propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(3,5-dimethylisoxazol-4-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(3-methyl-1H-pyrazol-5-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide trifluoroacetate;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(1H-pyrazol-4-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(1H-imidazol-5-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(1H-imidazol-4-yl) acetyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-[(pyrazin-2-yl) carbonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(3,5-dihydroxypyridin-4-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(6-hydroxypyridin-3-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(6-chloropyridin-3-yl) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-



propylbutyl) sulfonyl]-N~2~-[(pyridin-4-yl) carbonyl]-D, L-alaninamide;

N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(pyridin-3-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-[(pyridin-2-yl) carbonyl]-D, L-alaninamide;

N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(1H-indole-6-carbonyl)-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-(2, 3, 4-trimethoxybenzoyl)-D, L-alaninamide;

N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(pyridin-2-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-(3-hydroxybenzoyl)-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide

N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-(3-methylbenzoyl)-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-(3-ethylbenzoyl)-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N~2~-(3-chlorobenzoyl)-N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N~1~-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-(4-methylbenzoyl)-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(4-methoxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(4-trifluoromethylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~-(cyclohexylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~(benzoyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~(benzoyl)-N~1~-[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(phenylacetyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(3-phenylpropanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-(3-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)-3-oxo-2-((1-propylbutyl)sulfonyl)methyl)propyl)benzamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-(cyclopropylacetyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-[(methylsulfonyl)acetyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-[(methylthio)acetyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide

N~1~-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-(4-hydroxy-4-oxobutanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-[4-(methylamino)-4-oxobutanoyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-(4-methoxy-4-oxobutanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-(methylsulfonyl)glycyl-N~1~-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~-acetyl-N~1~-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(phenylsulfonyl)-D,L-alaninamide;

N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-(2S)-2-[(4-methoxy-4-oxobutanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide;

(2R)-2-[[benzyloxy]carbonyl]amino}-N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-oxo-5-piperidin-1-ylpentanamide;

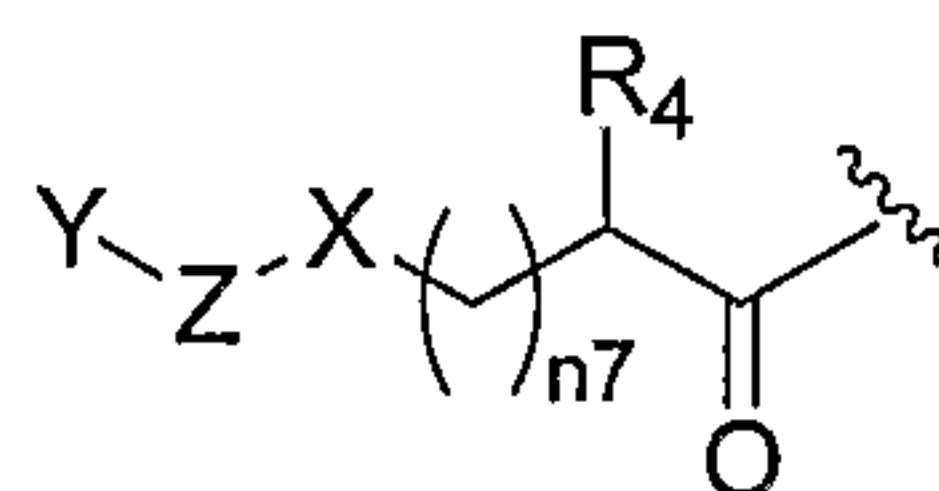
N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-(2R)-2-[(3-ethoxy-3-oxopropanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide;

N~1~-{(1S, 2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl}-N~2~-(4-methoxy-4-oxobutanoyl)-N~5~, N~5~-dipropyl-D-glutamamide;

N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-(2R)-2-[(4-methoxy-4-oxobutanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide; and

N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-(2R)-2-[(5-methoxy-5-oxopentanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide and pharmaceutically acceptable salts thereof.

Other preferred compounds of formula X-XII include those of formula X-XXI, i.e., compounds of formula X-XII wherein  $R_N$  is of the formula:



5 wherein

$n_7$  is 0, 1, or 2;

$R_4$  is  $-NHR_8$  or  $-NH(CH_2)_{n_6}-R_{4-1}$ ; wherein

$n_6$  is 0, 1, 2, or 3;

10  $R_{4-1}$  is selected from the group consisting of  $-SO_2-(C_1-C_8$  alkyl),  $-SO-(C_1-C_8$  alkyl),  $-S-(C_1-C_8$  alkyl),  $-S-CO-(C_1-C_6$  alkyl),  $-SO_2-NR_{4-2}R_{4-3}$ ;  $-CO-C_1-C_2$  alkyl;  $-CO-NR_{4-3}R_{4-4}$ ;

$R_{4-2}$  and  $R_{4-3}$  are independently H,  $C_1-C_3$  alkyl, or  $C_3-C_6$  cycloalkyl;

15  $R_{4-4}$  is  $C_1-C_4$  alkyl, phenyl  $C_1-C_4$  alkyl,  $C_2-C_4$  alkanoyl, or phenyl  $C_1-C_4$  alkanoyl;

$R_8$  is selected from the group consisting of  $-SO_2-$  heteroaryl optionally substituted with 1 or 2 groups that are independently  $C_1-C_4$  alkyl or halogen;  $-SO_2-$  phenyl;  $-SO_2-$  heterocycloalkyl;  $-C(O)NHR_9$ ; heterocycloalkyl;  $-S-C_2-C_4$  alkanoyl; wherein

$R_9$  is phenyl  $C_1-C_4$  alkyl,  $C_1-C_6$  alkyl, or H;

X is  $C_1-C_4$  alkylidenyl optionally optionally substituted with 1, 2, or 3 methyl groups; or  $-NR_{4-6}-$ ; or

25  $R_4$  and  $R_{4-6}$  combine to form  $-(CH_2)_{n_{10}}-$ , wherein

$n_{10}$  is 1, 2, 3, or 4;

Z is  $SO_2$ ; SO; S; or C(O);

30 Y is H;  $C_1-C_4$  haloalkyl;  $C_5-C_6$  heterocycloalkyl containing at least one N, O, or S; phenyl; OH;  $-N(Y_1)(Y_2)$ ;  $C_1-C_{10}$  alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy;  $C_3-$

C<sub>8</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, and halogen; alkoxy; phenyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; or phenyl C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or

-N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen; and

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkanoyl, each of which is unsubstituted or substituted with 1, or 2 groups independently selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>, wherein

R<sub>26</sub> is -C(O)-, -SO<sub>2</sub>-, -CO<sub>2</sub>-, -C(O)NH-, or -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-;

R<sub>27</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NH<sub>2</sub>, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl).

Preferred compounds of formula X-XXI include those wherein  $R_2$  and  $R_3$  are independently H or  $C_1$ - $C_6$  alkyl optionally substituted with 1, or 2 substituents selected from halogen, OH, SH,  $C\equiv N$ ,  $CF_3$ , and  $C_1$ - $C_3$  alkoxy; and

5  $R_C$  is  $C_1$ - $C_8$  alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of  $R_{205}$ ,  $-OC=ONR_{235}R_{240}$ ,  $-S(=O)_{0-2}(C_1-C_6 \text{ alkyl})$ ,  $-SH$ ,  $-C=ONR_{235}R_{240}$ , and  $-S(=O)_2NR_{235}R_{240}$ ;  $-(CH_2)_{0-3}-(C_3-C_8)$  cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3

10 groups independently selected from the group consisting of  $R_{205}$ ,  $-CO_2H$ , and  $-CO_2-(C_1-C_4 \text{ alkyl})$ ;  $-(CR_{245}R_{250})_{0-4}$ -phenyl;  $-(CR_{245}R_{250})_{0-4}$ -heteroaryl;  $-(CR_{245}R_{250})_{0-4}$ -heterocycloalkyl; or  $-(CH_2)_{0-1}-CH(C_1-C_4 \text{ hydroxyalkyl})-(CH_2)_{0-1}$ -heteroaryl; wherein each aryl is optionally substituted with 1, 2, or 3  $R_{200}$ ;

15 each heteroaryl is optionally substituted with 1, 2, 3, or 4  $R_{200}$ ;

each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4  $R_{210}$ ;

$R_{200}$  at each occurrence is independently  $C_1$ - $C_6$  alkyl

20 optionally substituted with 1, 2, or 3  $R_{205}$  groups; OH;  $-NO_2$ ; halogen;  $-CO_2H$ ;  $C\equiv N$ ;  $-(CH_2)_{0-4}-CO-NR_{220}R_{225}$ ;  $-(CH_2)_{0-4}-CO-(C_1-C_{12} \text{ alkyl})$ ;  $-(CH_2)_{0-4}-CO_2R_{215}$ ; or  $-(CH_2)_{0-4}-O-(C_1-C_6 \text{ alkyl optionally substituted with 1, 2, 3, or 5 } -F)$ ;

25  $R_{205}$  at each occurrence is independently  $C_1$ - $C_6$  alkyl, halogen,  $-OH$ ,  $-O$ -phenyl,  $-SH$ ,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1$ - $C_6$  alkoxy,  $NH_2$ ,  $NH(C_1-C_6 \text{ alkyl})$ , or  $N-(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ ;

$R_{210}$  at each occurrence is independently  $C_1$ - $C_6$  alkyl

30 optionally substituted with 1, 2, or 3  $R_{205}$  groups; halogen;  $C_1$ - $C_6$  alkoxy;  $C_1$ - $C_6$  haloalkoxy;  $-NR_{220}R_{225}$ ; OH;  $C\equiv N$ ;  $C_3$ - $C_7$  cycloalkyl optionally substituted with 1,

2, or 3 R<sub>205</sub> groups; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); -SO<sub>2</sub>-NR<sub>235</sub>R<sub>240</sub>; -CO-NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); or =O; wherein

R<sub>215</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(phenyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and -(CH<sub>2</sub>)<sub>0-2</sub>-(heteroaryl), or -(CH<sub>2</sub>)<sub>0-2</sub>-(heterocycloalkyl); wherein the phenyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R<sub>205</sub> or R<sub>210</sub>; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>;

R<sub>220</sub> and R<sub>225</sub> at each occurrence are independently -H, -C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkyl, halo C<sub>1</sub>-C<sub>4</sub> alkyl; -C<sub>3</sub>-C<sub>7</sub> cycloalkyl, or -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl);

R<sub>235</sub> and R<sub>240</sub> at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkoxy, or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, or 6 carbon atoms.

More preferred compounds of formula X-XXI include those wherein

R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1, or 2 substituents selected from halogen, -OH, -SH, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C≡N, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>3</sub> alkoxy; halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; and OH.

Other more preferred compounds of formula X-XXI include those wherein

$n_7$  is 0, 1, or 2;

$R_4$  is  $-NHR_8$  or  $-NH(CH_2)_{n_6}-R_{4-1}$ ; wherein

5  $N_6$  is 0, 1, or 2;

$R_{4-1}$  is selected from the group consisting of  $-SO_2-(C_1-C_8$  alkyl),  $-S-CO-(C_1-C_6$  alkyl),  $-SO_2-NR_{4-2}R_{4-3}$ ;  $-CO-C_1-C_2$  alkyl;  $-CO-NR_{4-3}R_{4-4}$ ;

$R_{4-2}$  and  $R_{4-3}$  are independently H, or  $C_1-C_3$  alkyl;

10  $R_{4-4}$  is  $C_1-C_4$  alkyl, phenyl  $C_1-C_4$  alkyl,  $C_2-C_4$  alkanoyl, or phenyl  $C_1-C_4$  alkanoyl;

$R_8$  is  $-SO_2$ -thienyl optionally substituted with 1 or 2 groups that are independently  $C_1-C_4$  alkyl or halogen;  $-SO_2$ -phenyl,  $-SO_2$ -piperidinyl,  $-SO_2$ -pyrrolidinyl,  $-C(O)NHR_9$ , morpholinyl, or  $-S-C_2-C_4$  alkanoyl, wherein

15  $R_9$  is phenyl  $C_1-C_4$  alkyl,  $C_1-C_6$  alkyl, or H.

Even more preferred compounds of formula X-XXI include those wherein

20  $R_{20}$  at each occurrence is independently hydrogen,  $C_1-C_6$  alkyl,  $C_1-C_2$  alkoxy  $C_1-C_4$  alkyl,  $C_2-C_6$  alkanoyl, each of which is unsubstituted or substituted with 1 or 2 groups independently selected from halogen, hydroxy,  $C_1-C_4$  alkoxy, tertiary-butoxy carbonyl, benzyloxycarbonyl, and

25  $NH_2$ ;

$R_C$  is  $C_1-C_8$  alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of  $R_{205}$ ,  $-SH$ ,  $-C=ONR_{235}R_{240}$ , and  $-S(=O)_2NR_{235}R_{240}$ ;  $-(CH_2)_{0-3}-(C_3-C_6)$  cycloalkyl wherein the cycloalkyl is optionally

30 substituted with 1, 2, or 3 groups independently selected from the group consisting of  $R_{205}$ ,  $-CO_2H$ , and  $-CO_2-(C_1-C_4$  alkyl);  $-(CR_{245}R_{250})_{0-4}$ -phenyl optionally substituted with 1, 2, or 3  $R_{200}$ ;  $-(CR_{245}R_{250})_{0-3}$ -pyridyl;  $-(CR_{245}R_{250})_{0-3}$ -pyridazinyl;  $-(CR_{245}R_{250})_{0-3}$ -pyrimidinyl;  $-(CR_{245}R_{250})_{0-3}$ -



pyrazinyl;  $-(\text{CR}_{245}\text{R}_{250})_{0-3}$ -furyl;  $-(\text{CR}_{245}\text{R}_{250})_{0-3}$ -indolyl;  
 $-(\text{CR}_{245}\text{R}_{250})_{0-3}$ -thienyl;  $-(\text{CR}_{245}\text{R}_{250})_{0-3}$ -pyrrolyl;  $-(\text{CR}_{245}\text{R}_{250})_{0-3}$ -  
 pyrazolyl;  $(\text{CR}_{245}\text{R}_{250})_{0-3}$ -benzoxazolyl;  $-(\text{CR}_{245}\text{R}_{250})_{0-3}$ -  
 imidazolyl; each of the above heteroaryl groups is  
 5 optionally substituted with 1, 2, 3, or 4  $\text{R}_{200}$ ;  $-(\text{CR}_{245}\text{R}_{250})_{0-3}$ -  
 imidazolidinyl;  $(\text{CR}_{245}\text{R}_{250})_{0-3}$ -tetrahydrofuryl;  $(\text{CR}_{245}\text{R}_{250})_{0-3}$ -  
 tetrahydropyranyl;  $(\text{CR}_{245}\text{R}_{250})_{0-3}$ -piperazinyl;  $(\text{CR}_{245}\text{R}_{250})_{0-3}$ -  
 pyrrolidinyl;  $(\text{CR}_{245}\text{R}_{250})_{0-3}$ -piperidinyl;  $(\text{CR}_{245}\text{R}_{250})_{0-3}$ -  
 indolinyl; each of the above heterocycloalkyl groups is  
 10 optionally substituted with 1, 2, 3, or 4  $\text{R}_{210}$ ;  $(\text{CH}_2)_{0-1}$ -  
 $\text{CH}((\text{CH}_2)_{0-4}\text{-OH})-(\text{CH}_2)_{0-1}$ -phenyl; or  $-(\text{CH}_2)_{0-1}$ - $\text{CH}(\text{C}_1\text{-C}_4$   
 hydroxyalkyl)- $(\text{CH}_2)_{0-1}$ -pyridyl;

$\text{R}_{200}$  at each occurrence is independently  $\text{C}_1\text{-C}_6$  alkyl  
 optionally substituted with 1, 2, or 3  $\text{R}_{205}$  groups;  
 15 OH;  $-\text{NO}_2$ ; halogen;  $-\text{CO}_2\text{H}$ ;  $\text{C}\equiv\text{N}$ ;  $-(\text{CH}_2)_{0-4}\text{-CO-NR}_{220}\text{R}_{225}$ ;  
 $-(\text{CH}_2)_{0-4}\text{-CO-(C}_1\text{-C}_8\text{ alkyl)}$ ;  $-(\text{CH}_2)_{0-4}\text{-CO}_2\text{R}_{215}$ ; or  $-(\text{CH}_2)_{0-4}$ -  
 $\text{O-(C}_1\text{-C}_6\text{ alkyl optionally substituted with 1, 2, 3,$   
 or 5  $-\text{F})$ ;

$\text{R}_{205}$  at each occurrence is independently  $\text{C}_1\text{-C}_6$  alkyl,  
 20 halogen,  $-\text{OH}$ ,  $-\text{O-phenyl}$ ,  $-\text{SH}$ ,  $-\text{C}\equiv\text{N}$ ,  $-\text{CF}_3$ ,  $\text{C}_1\text{-C}_6$   
 alkoxy,  $\text{NH}_2$ ,  $\text{NH(C}_1\text{-C}_6\text{ alkyl)}$ , or  $\text{N-(C}_1\text{-C}_6\text{ alkyl)(C}_1\text{-C}_6$   
 alkyl);

$\text{R}_{210}$  at each occurrence is independently  $\text{C}_1\text{-C}_6$  alkyl  
 optionally substituted with 1 or 2  $\text{R}_{205}$  groups;  
 25 halogen;  $\text{C}_1\text{-C}_4$  alkoxy;  $\text{C}_1\text{-C}_4$  haloalkoxy;  $-\text{NR}_{220}\text{R}_{225}$ ; OH;  
 $\text{C}\equiv\text{N}$ ;  $\text{C}_3\text{-C}_7$  cycloalkyl optionally substituted with 1  
 or 2  $\text{R}_{205}$  groups;  $-\text{CO-(C}_1\text{-C}_4\text{ alkyl)}$ ;  $-\text{SO}_2\text{-NR}_{235}\text{R}_{240}$ ;  $-\text{CO-}$   
 $\text{NR}_{235}\text{R}_{240}$ ;  $-\text{SO}_2\text{-(C}_1\text{-C}_4\text{ alkyl)}$ ; or  $=\text{O}$ ; wherein

$\text{R}_{215}$  at each occurrence is independently  $\text{C}_1\text{-C}_6$  alkyl,  
 30  $-(\text{CH}_2)_{0-2}$ -(phenyl),  $\text{C}_3\text{-C}_6$  cycloalkyl,  $-(\text{CH}_2)_{0-2}$ -  
 (pyridyl),  $-(\text{CH}_2)_{0-2}$ -(pyrrolyl),  $-(\text{CH}_2)_{0-2}$ -  
 (imidazolyl),  $-(\text{CH}_2)_{0-2}$ -(pyrimidyl),  $-(\text{CH}_2)_{0-2}$ -  
 (pyrrolidinyl),  $-(\text{CH}_2)_{0-2}$ -(imidazolidinyl)  $-(\text{CH}_2)_{0-2}$ -  
 (piperazinyl),  $-(\text{CH}_2)_{0-2}$ -(piperidinyl), or  $-(\text{CH}_2)_{0-2}$ -

(morpholinyl); wherein the phenyl group at each occurrence is optionally substituted with 1 or 2 groups that are independently  $R_{205}$  or  $R_{210}$ ; wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1 or 2  $R_{210}$ ; wherein each heteroaryl group at each occurrence is optionally substituted with 1 or 2  $R_{210}$ ;

$R_{220}$  and  $R_{225}$  at each occurrence are independently -H, -C<sub>1</sub>-C<sub>4</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkyl, halo C<sub>1</sub>-C<sub>4</sub> alkyl; -C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-(C<sub>1</sub>-C<sub>2</sub> alkyl);

$R_{235}$  and  $R_{240}$  at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;

$R_{245}$  and  $R_{250}$  at each occurrence are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkoxy, or

$R_{245}$  and  $R_{250}$  are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms.

Still other more preferred compounds of formula X-XXI include those wherein

X is -C<sub>1</sub>-C<sub>3</sub> alkylidenyl optionally optionally substituted with 1 or 2 methyl groups;

Z is SO<sub>2</sub>; SO; S; or C(O);

Y is H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; pyrrolidinyl; piperidinyl; imidazolidinyl; piperazinyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> thioalkoxy, and C<sub>1</sub>-C<sub>4</sub> haloalkoxy; C<sub>3</sub>-C<sub>6</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl and halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; phenyl, benzyl or phenethyl each of which is optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

Y<sub>1</sub> and Y<sub>2</sub> are independently H; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or C<sub>3</sub>-C<sub>6</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or  
 5 -N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>4</sub> alkyl, or halogen; and  
 10 R<sub>2</sub> and R<sub>3</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl.

Other more preferred compounds of formula X-XXI include those wherein

15 n<sub>7</sub> is 0, 1, or 2;

R<sub>4</sub> is -NHR<sub>8</sub> or -NH(CH<sub>2</sub>)<sub>n<sub>6</sub></sub>-R<sub>4-1</sub>; wherein

N<sub>6</sub> is 0, 1, or 2;

R<sub>4-1</sub> is selected from the group consisting of -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub> alkyl), -SO<sub>2</sub>-NR<sub>4-2</sub>R<sub>4-3</sub>; -CO-C<sub>1</sub>-C<sub>2</sub> alkyl; -CO-NR<sub>4-3</sub>R<sub>4-4</sub>;

20 R<sub>4-2</sub> and R<sub>4-3</sub> are independently H, or C<sub>1</sub>-C<sub>3</sub> alkyl;

R<sub>4-4</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, or phenyl C<sub>1</sub>-C<sub>4</sub> alkanoyl;

R<sub>8</sub> is -SO<sub>2</sub>-thienyl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl or halogen;

25 -SO<sub>2</sub>-phenyl, -SO<sub>2</sub>-piperidinyl, -SO<sub>2</sub>-pyrrolidinyl,

-C(O)NHR<sub>9</sub>, or -S-C<sub>2</sub>-C<sub>4</sub> alkanoyl, wherein

R<sub>9</sub> is phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, or H;

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, tertiary-butoxy carbonyl, and

30 benzyloxycarbonyl;

R<sub>c</sub> is C<sub>1</sub>-C<sub>8</sub> alkyl optionally substituted with 1 or 2 groups independently selected from R<sub>205</sub>, and -SH; -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>6</sub>) cycloalkyl wherein the cycloalkyl is optionally substituted with 1 R<sub>205</sub> group; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-phenyl

- optionally substituted with 1 or 2  $R_{200}$ ;  $-(CR_{245}R_{250})_{0-3}$ -pyridyl;  $-(CR_{245}R_{250})_{0-3}$ -pyrrolyl;  $(CR_{245}R_{250})_{0-3}$ -benzoxazolyl;  $-(CR_{245}R_{250})_{0-3}$ -imidazolyl; each of the above heteroaryl groups is optionally substituted with 1 or 2  $R_{200}$ ;
- 5  $(CR_{245}R_{250})_{0-3}$ -imidazolidinyl;  $(CR_{245}R_{250})_{0-3}$ -tetrahydrofuryl;  $(CR_{245}R_{250})_{0-3}$ -tetrahydropyranyl;  $(CR_{245}R_{250})_{0-3}$ -pyrrolidinyl;  $(CR_{245}R_{250})_{0-3}$ -piperidinyl; each of the above heterocycloalkyl groups is optionally substituted with 1 or 2  $R_{210}$ ;  $(CH_2)_{0-1}$ -CH $(CH_2)_{0-4}$ -OH)- $(CH_2)_{0-1}$ -phenyl; or  $-(CH_2)_{0-1}$ -CH(C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl)- $(CH_2)_{0-1}$ -pyridyl;
- 10  $R_{200}$  at each occurrence is independently C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, or 3  $R_{205}$  groups; OH; NO<sub>2</sub>; halogen; CO<sub>2</sub>H; C≡N; or  $-(CH_2)_{0-4}$ -O-(C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, or 5 -F);
- 15  $R_{205}$  at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, OH, -O-phenyl, SH, C≡N, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);
- $R_{210}$  at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1  $R_{205}$  group; halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> haloalkoxy; OH; C≡N; or =O; wherein
- 20  $R_{235}$  and  $R_{240}$  at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;
- $R_{245}$  and  $R_{250}$  at each occurrence are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or
- 25  $R_{245}$  and  $R_{250}$  are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms;
- X is C<sub>1</sub>-C<sub>3</sub> alkylidenyl;
- Z is SO<sub>2</sub>; SO; S; or C(O);
- 30 Y is H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; pyrrolidinyl; piperidinyl; imidazolidinyl; piperazinyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> thioalkoxy, and C<sub>1</sub>-C<sub>4</sub>

haloalkoxy; C<sub>3</sub>-C<sub>6</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl and halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; phenyl, benzyl or phenethyl each of which is optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

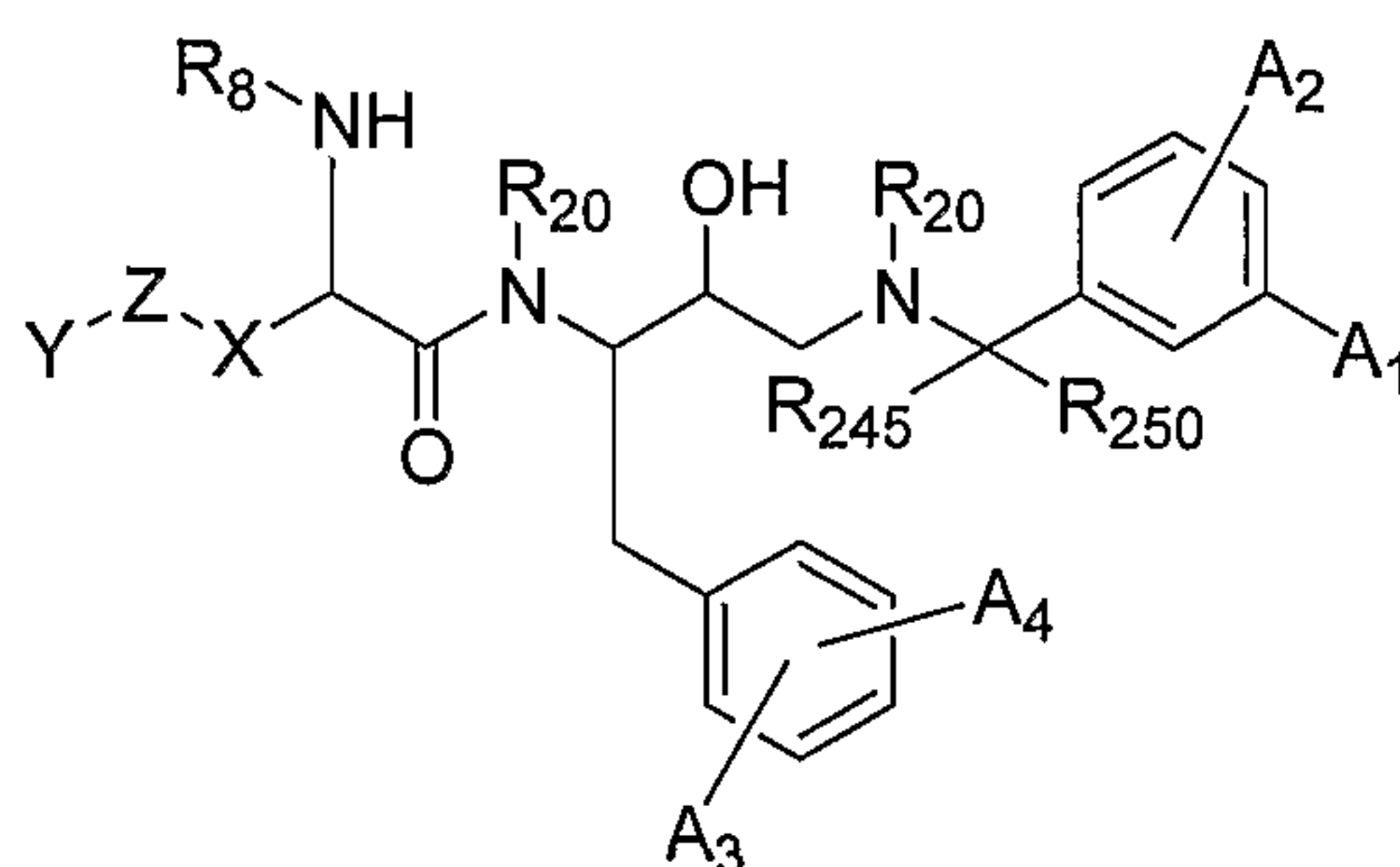
Y<sub>1</sub> and Y<sub>2</sub> are independently H; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or cyclopropyl C<sub>1</sub>-C<sub>4</sub> alkyl; or

-N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl, piperidinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or halogen;

R<sub>2</sub> and R<sub>3</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl; and

R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1 substituent selected from halogen, -OH, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>3</sub> alkoxy; halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; and OH.

Particularly preferred compounds of formula X-XXI include those of formula X-XXII:



X-XXII

wherein

A<sub>1</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkynyl, or halogen;

A<sub>2</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl or OH;

A<sub>3</sub> and A<sub>4</sub> are independently C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, or H;

R<sub>8</sub> is -SO<sub>2</sub>-thienyl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl or halogen; -SO<sub>2</sub>-phenyl, -SO<sub>2</sub>-piperidinyl, -SO<sub>2</sub>-pyrrolidinyl, -C(O)NHR<sub>9</sub>, or -S-C<sub>2</sub>-C<sub>4</sub> alkanoyl, wherein

5 R<sub>9</sub> is phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, or H.

Preferred compounds of formulas X-XXI and X-XXII include those wherein

R<sub>20</sub> at each occurrence is independently H or C<sub>1</sub>-C<sub>4</sub> alkyl;

10 X is C<sub>1</sub> or C<sub>2</sub> alkylidenyl;

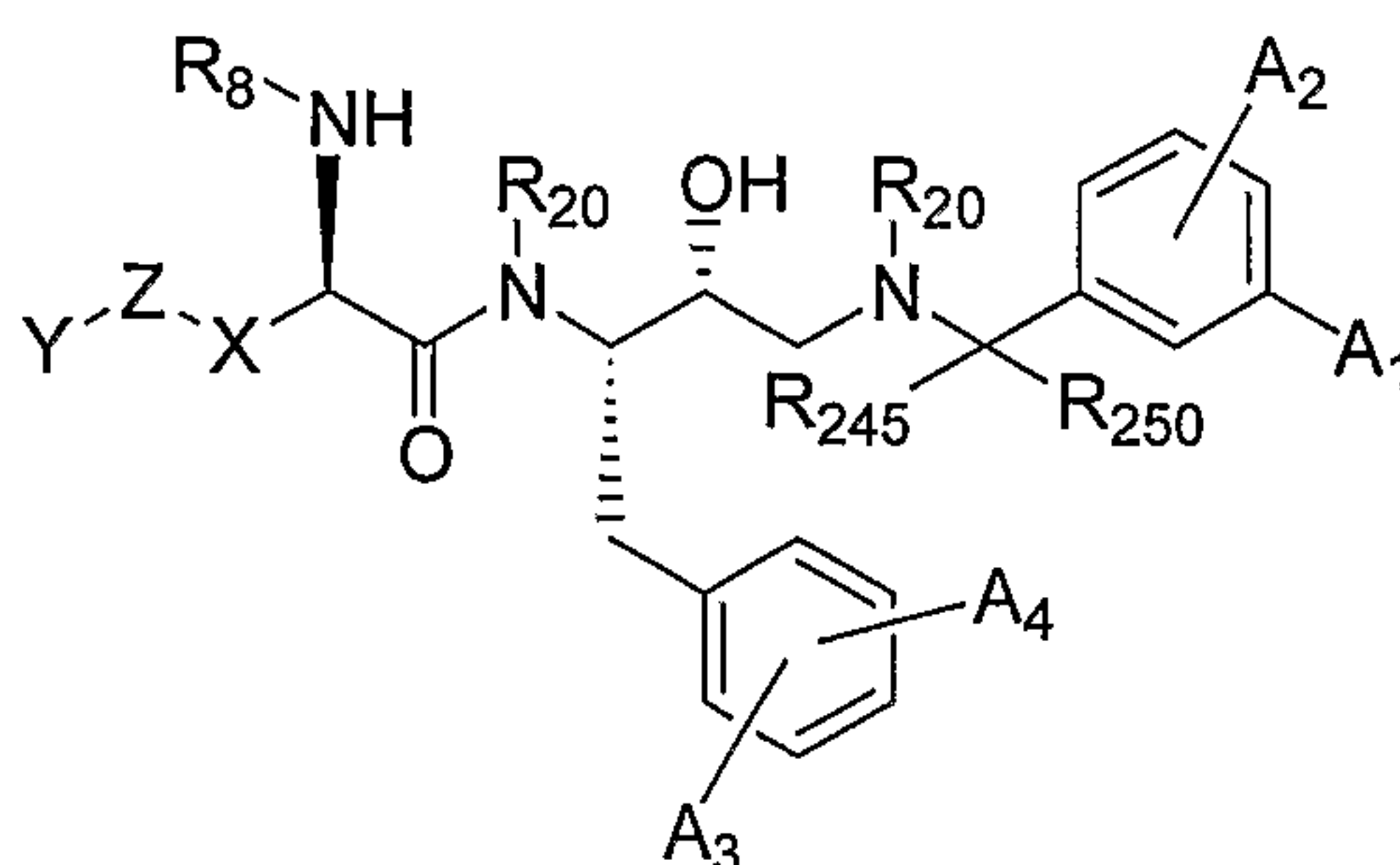
Z is SO<sub>2</sub>; SO; S; or C(O); and

Y is phenyl; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 halogen; or OH; or

Y is -N(Y<sub>1</sub>)(Y<sub>2</sub>); wherein

15 Y<sub>1</sub> and Y<sub>2</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl.

Preferred compounds of formula X-XXII include those of formula X-XXIII:



20

X-XXIII.

Preferred compounds of formulas X-XXII and X-XXIII include those wherein

A<sub>1</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub> alkynyl, or I;

25 A<sub>2</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, OCF<sub>3</sub>, CF<sub>3</sub> or OH;

A<sub>3</sub> and A<sub>4</sub> are independently H or halogen; and

R<sub>8</sub> is -SO<sub>2</sub>-thienyl optionally substituted with 1 or 2 groups

that are independently C<sub>1</sub>-C<sub>4</sub> alkyl or halogen; -SO<sub>2</sub>-phenyl; or -C(O)NHR<sub>9</sub>; wherein

R<sub>9</sub> is phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, or H.

Other preferred compounds of formulas X-XXII and X-XXIII include those wherein

- 5 R<sub>245</sub> and R<sub>250</sub> are both hydrogen or R<sub>245</sub> and R<sub>250</sub> form a cyclopropyl group.

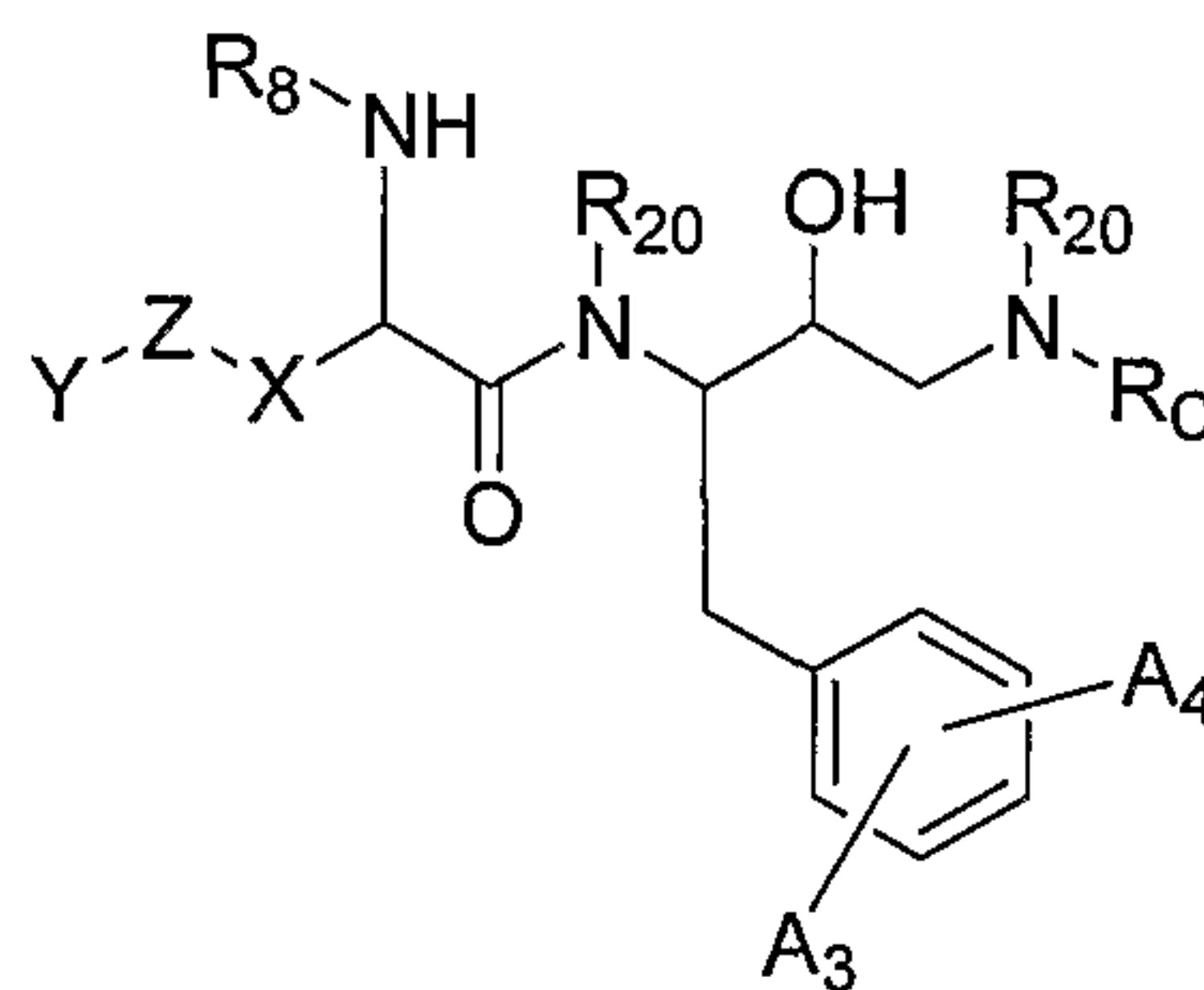
Other preferred compounds of formulas X-XXII and X-XXIII include those wherein

- 10 R<sub>20</sub> and A<sub>2</sub> are both hydrogen; and  
A<sub>3</sub> and A<sub>4</sub> are independently halogen.

Still other preferred compounds of formulas X-XXII and X-XXIII include those wherein

- 15 A<sub>3</sub> and A<sub>4</sub> are meta to each other.

Other preferred compounds of formula X-XXI include those of formula X-XXIV:



X-XXIV

20

wherein

R<sub>C</sub> is C<sub>3</sub>-C<sub>8</sub> alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or -  
(C<sub>1</sub>-C<sub>4</sub>)alkyl-(C<sub>3</sub>-C<sub>6</sub>) cycloalkyl.

- 25 Preferred compounds of formula X-XXIV include those wherein

R<sub>20</sub> at each occurrence is independently H or C<sub>1</sub>-C<sub>4</sub> alkyl;  
X is C<sub>1</sub> or C<sub>2</sub> alkylidenyl;  
Z is SO<sub>2</sub>; SO; S; or C(O); and

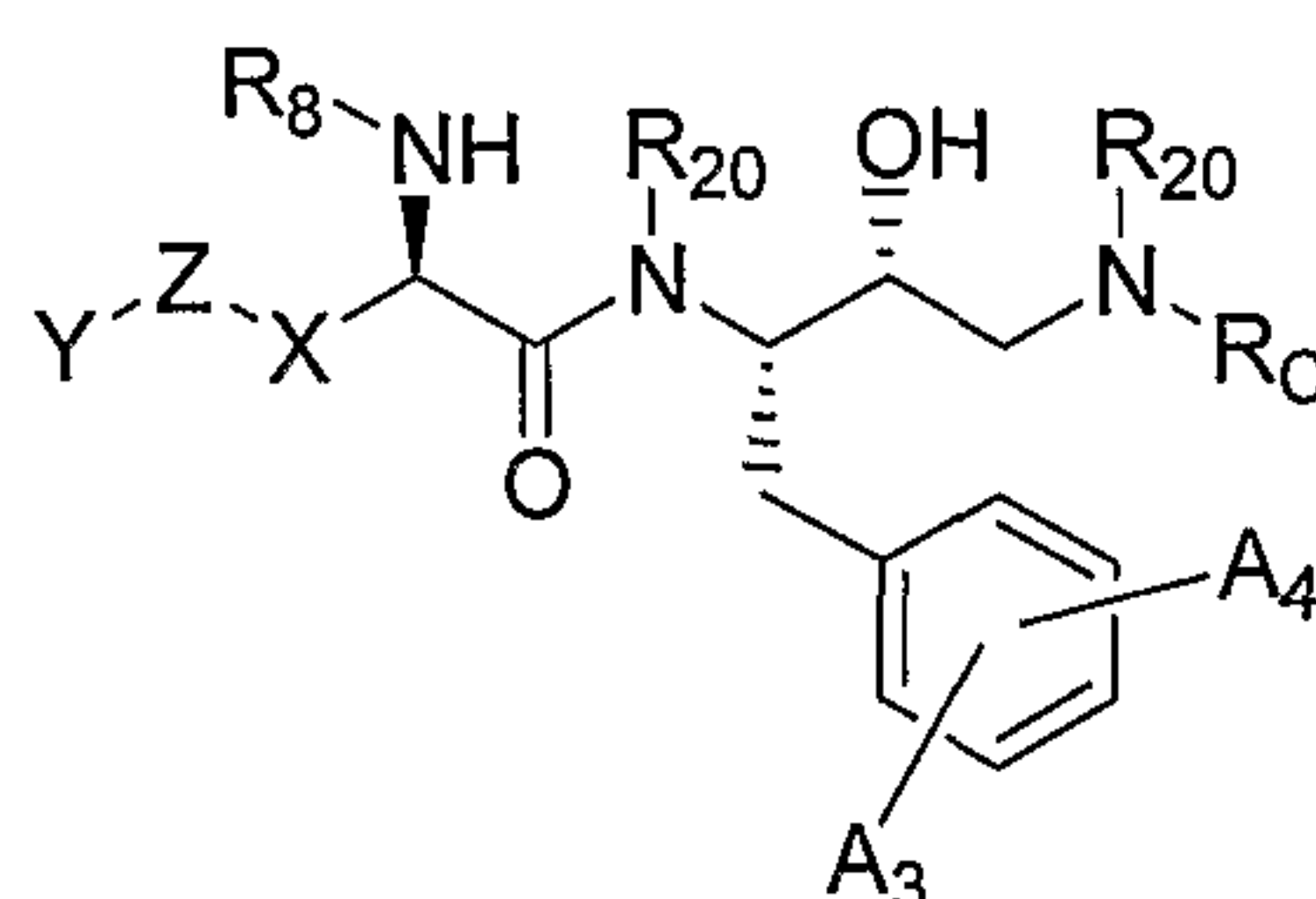
Y is phenyl; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 halogen; or OH; or

Y is -N(Y<sub>1</sub>)(Y<sub>2</sub>); wherein

Y<sub>1</sub> and Y<sub>2</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl.

5

More preferred compounds of formula X-XXIV include those of formula X-XXV:



X-XXV.

10

Preferred compounds of formulas X-XXIV and X-XXV include those wherein wherein

R<sub>8</sub> is -SO<sub>2</sub>-thienyl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl or halogen; -SO<sub>2</sub>-phenyl; or -C(O)NHR<sub>9</sub>; wherein

15

R<sub>9</sub> is phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, or H.

Other preferred compounds of formulas X-XXIV and X-XXV include those wherein

20

R<sub>20</sub> and A<sub>2</sub> are both hydrogen; and A<sub>3</sub> and A<sub>4</sub> are independently halogen.

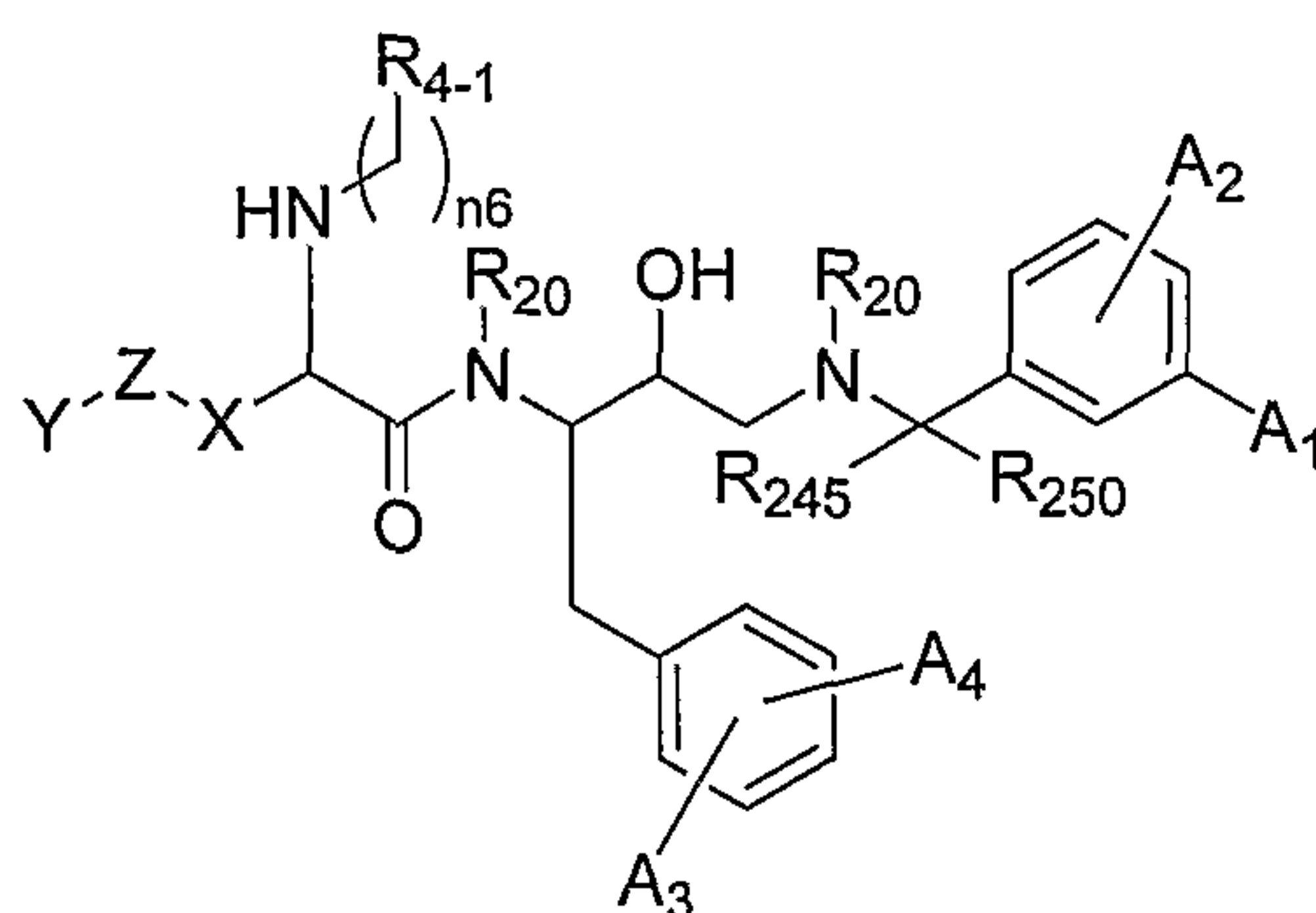
More preferred compounds of formulas X-XXIV and X-XXV include those wherein

25

A<sub>3</sub> and A<sub>4</sub> are meta to each other. Even more preferably, A<sub>3</sub> and A<sub>4</sub> are at the 3 and 5 positions of the benzene ring.

Other preferred compounds of formula X-XXI include those of formula X-XXVI:





X-XXVI

wherein

$N_6$  is 0, 1, or 2;

5  $R_{4-1}$  is selected from the group consisting of  $-SO_2-(C_1-C_8 \text{ alkyl})$ ,  $-SO_2-NR_{4-2}R_{4-3}$ ;  $-CO-C_1-C_2 \text{ alkyl}$ ;  $-CO-NR_{4-3}R_{4-4}$ ;

$R_{4-2}$  and  $R_{4-3}$  are independently H, or  $C_1-C_3 \text{ alkyl}$ ;

$R_{4-4}$  is  $C_1-C_4 \text{ alkyl}$ , phenyl  $C_1-C_4 \text{ alkyl}$ ,  $C_2-C_4 \text{ alkanoyl}$ , or phenyl  $C_1-C_4 \text{ alkanoyl}$ ;

10  $A_1$  is H,  $C_1-C_4 \text{ alkyl}$ ,  $C_1-C_4 \text{ alkoxy}$ , halogen or  $C_2-C_6 \text{ alkynyl}$ ;

$A_2$  is H,  $C_1-C_4 \text{ alkyl}$ ,  $C_1-C_4 \text{ alkoxy}$ ,  $C_1-C_4 \text{ haloalkoxy}$ ,  $C_1-C_4 \text{ haloalkyl}$  or OH;

$A_3$  and  $A_4$  are independently  $C_1-C_4 \text{ alkyl}$ , halogen, or H.

15 Preferred compounds of formula X-XXVI include those wherein

$R_{20}$  at each occurrence is independently H or  $C_1-C_4 \text{ alkyl}$ ;

X is  $C_1$  or  $C_2 \text{ alkylidenyl}$ ;

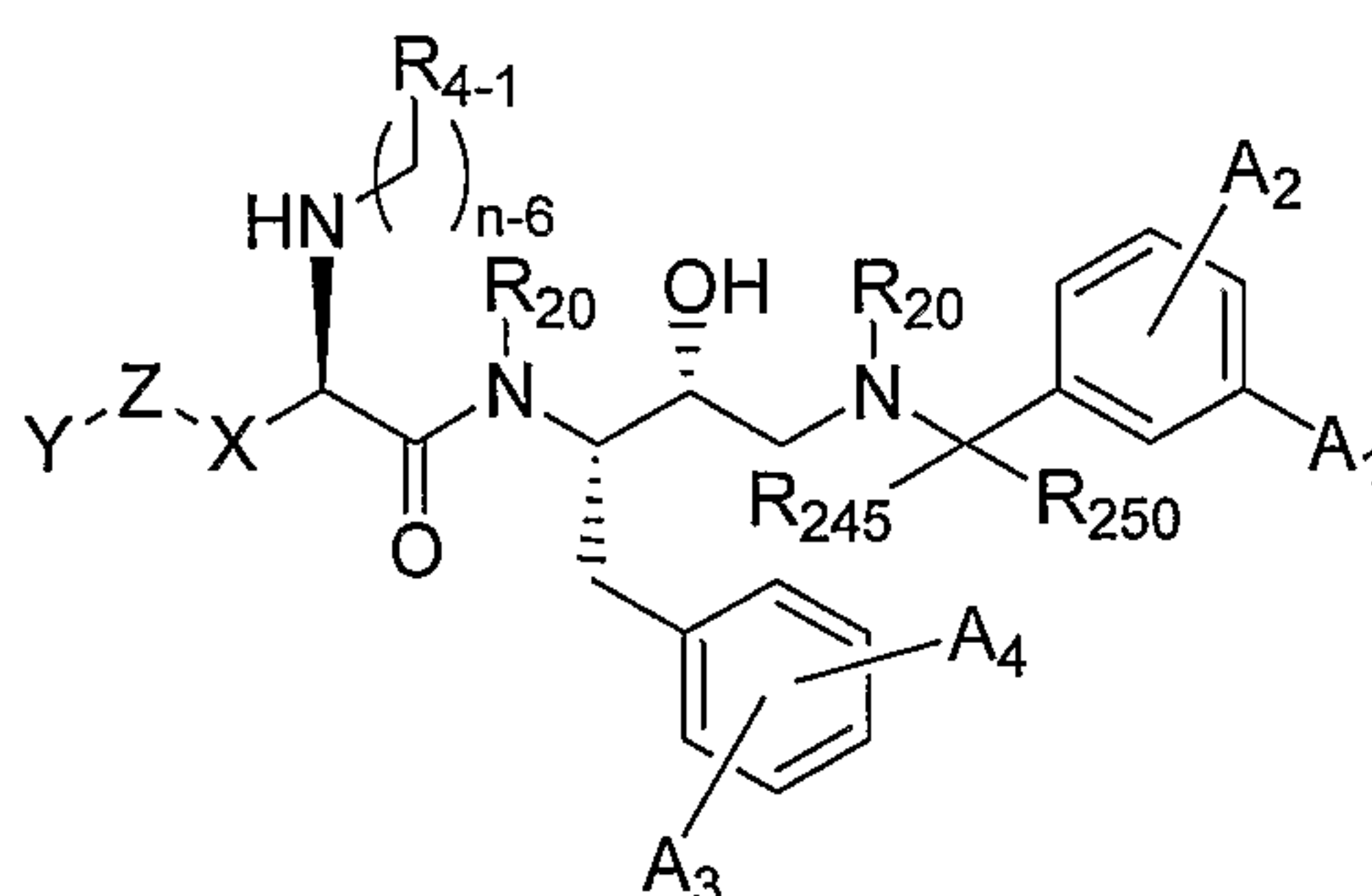
Z is  $SO_2$ ; SO; S; or C(O); and

20 Y is phenyl;  $C_1-C_{10} \text{ alkyl}$  optionally substituted with 1, 2, or 3 halogen; or OH; or

Y is  $-N(Y_1)(Y_2)$ ; wherein

$Y_1$  and  $Y_2$  are independently H or  $C_1-C_4 \text{ alkyl}$ .

25 More preferred compounds of formula X-XXVI include those of formula X-XXVII:



X-XXVII

wherein

A<sub>1</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub> alkynyl or I;

5 A<sub>2</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, OCF<sub>3</sub>, CF<sub>3</sub> or OH;

A<sub>3</sub> and A<sub>4</sub> are independently H or halogen; and

N<sub>6</sub> is 0, 1, or 2;

R<sub>4-1</sub> is selected from the group consisting of -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub> alkyl),  
-SO<sub>2</sub>-NR<sub>4-2</sub>R<sub>4-3</sub>; -CO-C<sub>1</sub>-C<sub>2</sub> alkyl; -CO-NR<sub>4-3</sub>R<sub>4-4</sub>;

10 R<sub>4-2</sub> and R<sub>4-3</sub> are independently H, or C<sub>1</sub>-C<sub>3</sub> alkyl;

R<sub>4-4</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, or  
phenyl C<sub>1</sub>-C<sub>4</sub> alkanoyl.

Preferred compounds of formulas X-XXVI and X-XXVII include  
15 those wherein

R<sub>245</sub> and R<sub>250</sub> are both hydrogen or R<sub>245</sub> and R<sub>250</sub> form a cyclopropyl  
group.

More preferred compounds of formulas X-XXVI and X-XXVII  
20 include those wherein

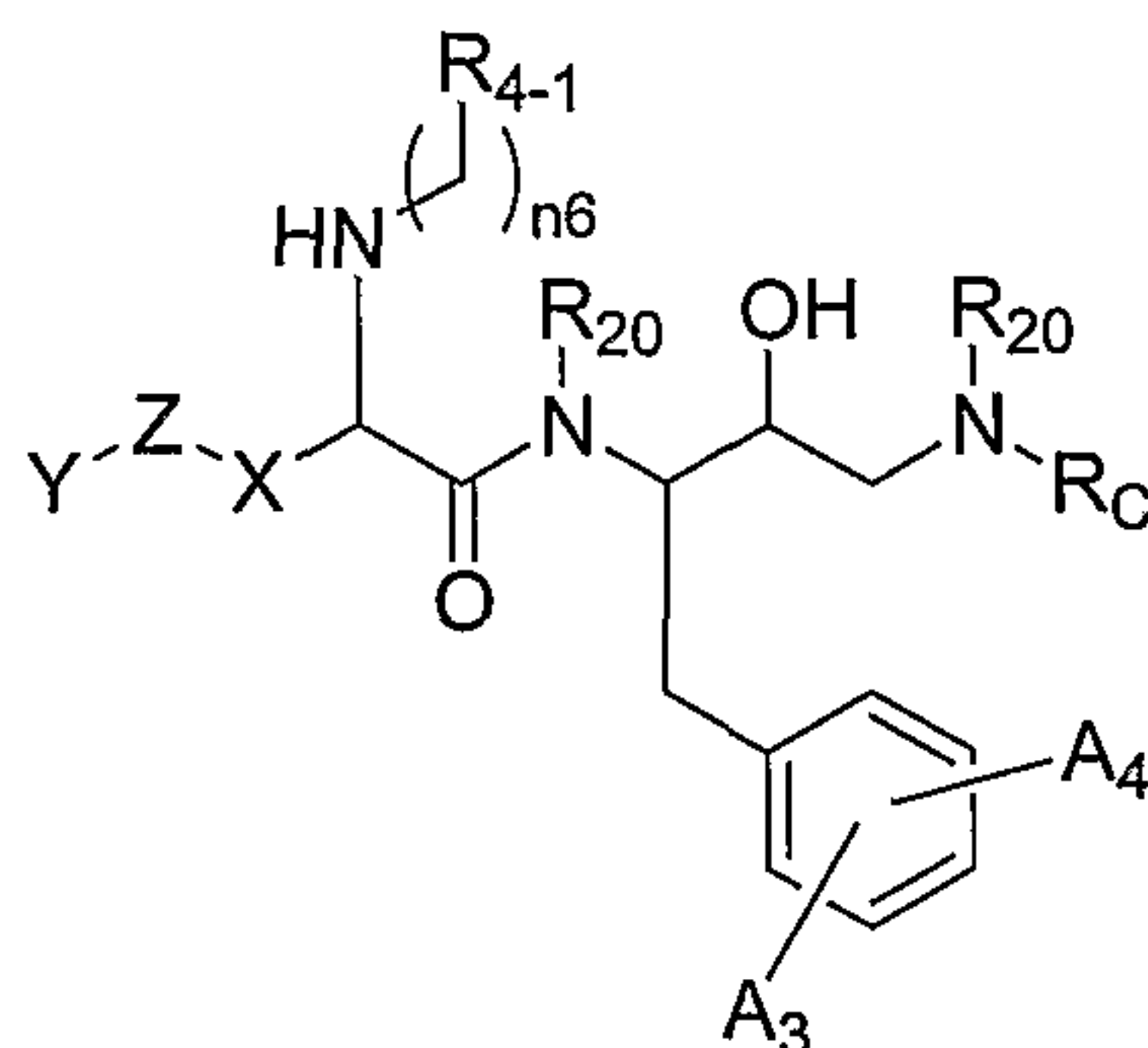
R<sub>20</sub> and A<sub>2</sub> are both hydrogen; and

A<sub>3</sub> and A<sub>4</sub> are independently halogen.

More preferred compounds of formulas X-XXVI and X-XXVII  
25 include those wherein

A<sub>3</sub> and A<sub>4</sub> are meta to each other. More preferably, A<sub>3</sub> and A<sub>4</sub>  
are at the 3 and 5 positions of the phenyl ring.

Other preferred compounds of formula X-XXI include those of formula X-XXVIII:



X-XXVIII

5 wherein

$R_C$  is  $C_3$ - $C_8$  alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or  $-(C_1-C_4)$ alkyl- $(C_3-C_6)$  cycloalkyl.

Preferred compounds of formula X-XXVIII include those

10 wherein

$R_{20}$  at each occurrence is independently H or  $C_1$ - $C_4$  alkyl;

X is  $C_1$  or  $C_2$  alkylidenyl;

Z is  $SO_2$ ; SO; S; or C(O); and

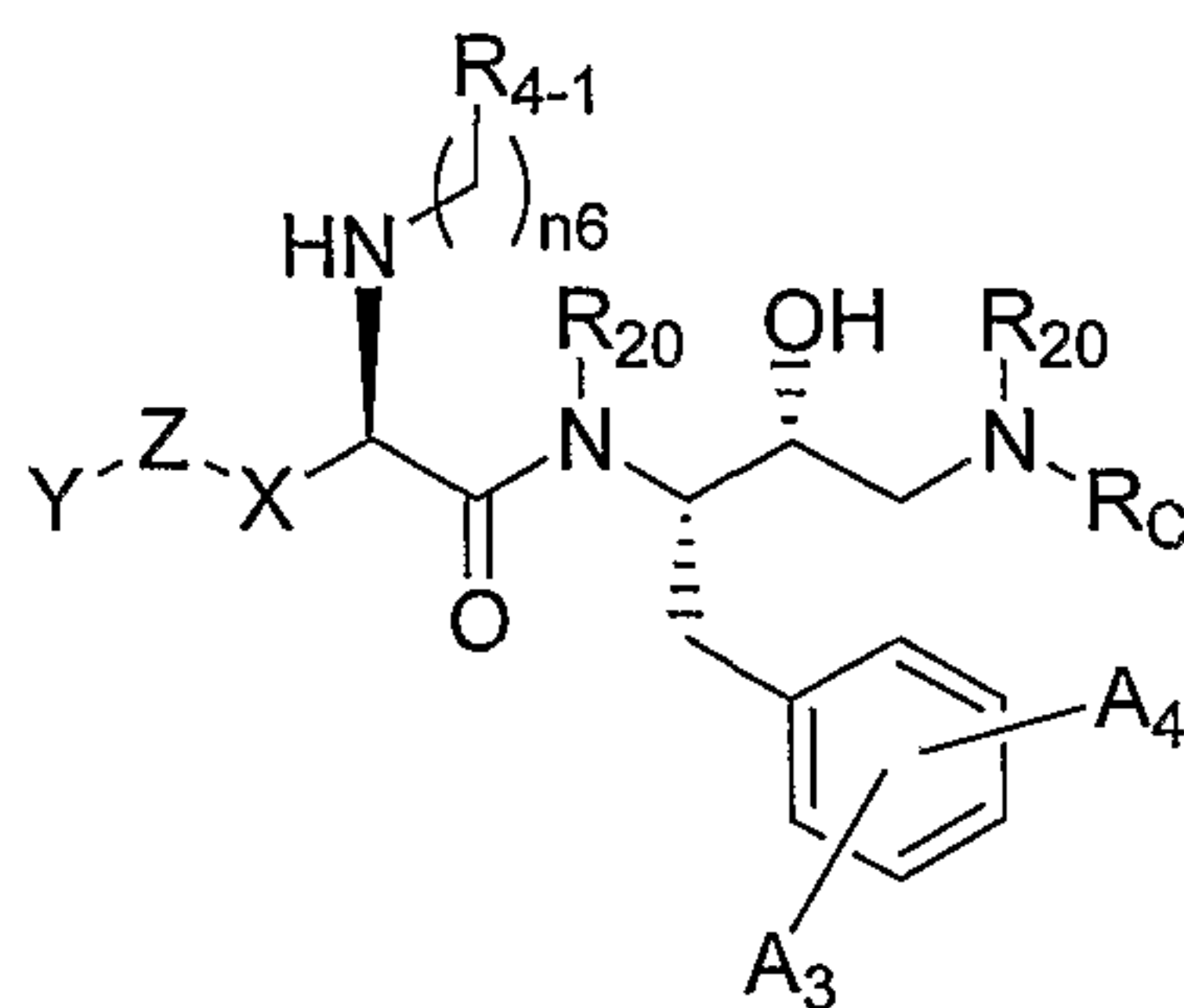
15 Y is phenyl;  $C_1$ - $C_{10}$  alkyl optionally substituted with 1, 2, or 3 halogen; or OH; or

Y is  $-N(Y_1)(Y_2)$ ; wherein

$Y_1$  and  $Y_2$  are independently H or  $C_1$ - $C_4$  alkyl.

More preferred compounds of formula X-XXVIII include those

20 of formula X-XXIX:



X-XXIX.

Preferred compounds of formulas X-XXVIII and X-XXIX include those wherein

$N_6$  is 0, 1, or 2;

$R_{4-1}$  is selected from the group consisting of  $-SO_2-(C_1-C_8 \text{ alkyl})$ ,  
5  $-SO_2-NR_{4-2}R_{4-3}$ ;  $-CO-NR_{4-3}R_{4-4}$ ;

$R_{4-2}$  and  $R_{4-3}$  are independently H, or  $C_1-C_3$  alkyl;

$R_{4-4}$  is  $C_1-C_4$  alkyl, phenyl  $C_1-C_4$  alkyl,  $C_2-C_4$  alkanoyl, or phenyl  $C_1-C_4$  alkanoyl;

10 Other preferred compounds of formulas X-XXVIII and X-XXIX include those wherein

$R_{20}$  and  $A_2$  are both hydrogen; and

$A_3$  and  $A_4$  are independently halogen.

15 More preferred compounds of formulas X-XXVIII and (X-XXVIX) include those wherein

$A_3$  and  $A_4$  are meta to each other. More preferably,  $A_3$  and  $A_4$  are at the 3 and 5 positions of the benzene ring.

20 Other preferred compounds of formula X include those of formula X-XXX, i.e., compounds of formula X wherein

$R_4$  is H;  $C_1-C_4$  alkyl-NHC(O) $R_5$ ;  $-(CH_2)_{0-4}R_8$ ;  $-O-C_1-C_4$  alkanoyl; OH;

$C_6-C_{10}$  aryloxy optionally substituted with 1, 2, or 3

groups that are independently halogen,  $C_1-C_4$  alkyl,  $CO_2H$ , -

25  $C(O)-C_1-C_4$  alkoxy, or  $C_1-C_4$  alkoxy;  $C_1-C_6$  alkoxy; aryl  $C_1-C_4$

alkoxy;  $-C_1-C_4$  alkyl- $NR_{50}CO_2R_{51}$ ;  $-C\equiv N$ ;  $-CF_3$ ;  $-CF_2-CF_3$ ;  $-C\equiv CH$ ;

$-CH_2-CH=CH_2$ ;  $-(CH_2)_{1-4}-R_{4-1}$ ;  $-(CH_2)_{1-4}-NH-R_{4-1}$ ;  $-O-(CH_2)_{n6}-R_{4-1}$ ; -

$S-(CH_2)_{n6}-R_{4-1}$ ;  $(CH_2)_{0-4}-NHC(O)-(CH_2)_{0-6}-R_{52}$ ; or  $-(CH_2)_{0-4}-R_{53}-$

$(CH_2)_{0-4}-R_{54}$ .

30

Preferred compounds of formula X-XXX include those wherein

$R_1$  is  $(CH_2)_{n1}-(R_{1-aryl})$  where  $n_1$  is zero or one and  $R_{1-aryl}$  is

phenyl optionally substituted with 1, 2, 3, or 4 groups

independently selected from  $C_1-C_6$  alkyl optionally

substituted with 1, 2, or 3 substituents selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -NR<sub>1-a</sub>R<sub>1-b</sub>, -C≡N, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>3</sub> alkoxy; halogen; C<sub>1</sub>-C<sub>6</sub> alkoxy; -NR<sub>N-2</sub>R<sub>N-3</sub>; and OH; wherein

5 R<sub>N-2</sub> and R<sub>N-3</sub> at each occurrence are independently selected from the group consisting of -C<sub>1</sub>-C<sub>8</sub> alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of -OH, -NH<sub>2</sub>, phenyl and halogen; -C<sub>3</sub>-C<sub>8</sub> cycloalkyl; -(C<sub>1</sub>-C<sub>2</sub> alkyl)-(C<sub>3</sub>-C<sub>8</sub> cycloalkyl); -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl); -10 C<sub>2</sub>-C<sub>6</sub> alkenyl; -C<sub>2</sub>-C<sub>6</sub> alkynyl; -C<sub>1</sub>-C<sub>6</sub> alkyl chain with one double bond and one triple bond; aryl; heteroaryl; heterocycloalkyl;

or

15 R<sub>N-2</sub>, R<sub>N-3</sub> and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or heteroaryl group, wherein said heterocycloalkyl or heteroaryl group is optionally fused to a benzene, pyridine, or pyrimidine ring, and said groups are unsubstituted or 20 substituted with 1, 2, 3, 4, or 5 groups that at each occurrence are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -OH, -C(O)NH<sub>2</sub>, -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), 25 -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> thioalkoxy, and C<sub>1</sub>-C<sub>6</sub> thioalkoxy C<sub>1</sub>-C<sub>6</sub> alkyl.

More preferred compounds of formula X-XXX include those 30 wherein

R<sub>2</sub> and R<sub>3</sub> are independently selected from H or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl,

halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>;  
and

R<sub>C</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>10</sub> alkyl  
optionally substituted with 1, 2, or 3 groups

5 independently selected from the group consisting of R<sub>205</sub>,  
-OC=ONR<sub>235</sub>R<sub>240</sub>, -S(=O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), -SH, -NR<sub>235</sub>C=ONR<sub>235</sub>R<sub>240</sub>,  
-C=ONR<sub>235</sub>R<sub>240</sub>, and -S(=O)<sub>2</sub>NR<sub>235</sub>R<sub>240</sub>; -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>8</sub>)

cycloalkyl wherein the cycloalkyl is optionally  
substituted with 1, 2, or 3 groups independently selected  
10 from the group consisting of R<sub>205</sub>, -CO<sub>2</sub>H, and -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub>  
alkyl); -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl; -  
(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocycloalkyl; -[C(R<sub>255</sub>)(R<sub>260</sub>)]<sub>1-3</sub>-CO-N-  
(R<sub>255</sub>)<sub>2</sub>; -CH(aryl)<sub>2</sub>; -CH(heteroaryl)<sub>2</sub>;

-CH(heterocycloalkyl)<sub>2</sub>; -CH(aryl)(heteroaryl); -CO-

15 NR<sub>235</sub>R<sub>240</sub>; -(CH<sub>2</sub>)<sub>0-1</sub>-CH((CH<sub>2</sub>)<sub>0-6</sub>-OH)-(CH<sub>2</sub>)<sub>0-1</sub>-aryl; -(CH<sub>2</sub>)<sub>0-1</sub>-  
CHR<sub>C-6</sub>-(CH<sub>2</sub>)<sub>0-1</sub>-heteroaryl; -CH(-aryl or -heteroaryl)-CO-  
O(C<sub>1</sub>-C<sub>4</sub> alkyl); -CH(-CH<sub>2</sub>-OH)-CH(OH)-phenyl-NO<sub>2</sub>; (C<sub>1</sub>-C<sub>6</sub>  
alkyl)-O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-OH; -CH<sub>2</sub>-NH-CH<sub>2</sub>-CH(-O-CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>; -H;  
and -(CH<sub>2</sub>)<sub>0-6</sub>-C(=NR<sub>235</sub>)(NR<sub>235</sub>R<sub>240</sub>); wherein

20 each aryl is optionally substituted with 1, 2, or 3 R<sub>200</sub>;  
each heteroaryl is optionally substituted with 1, 2, 3, or  
4 R<sub>200</sub>;

each heterocycloalkyl is optionally substituted with 1, 2,  
3, or 4 R<sub>210</sub>;

25 R<sub>200</sub> at each occurrence is independently selected from the  
group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl optionally  
substituted with 1, 2, or 3 R<sub>205</sub> groups; OH; -NO<sub>2</sub>;  
halogen; -CO<sub>2</sub>H; C≡N; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>220</sub>R<sub>225</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-  
(C<sub>1</sub>-C<sub>12</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO<sub>2</sub>R<sub>215</sub>; and -(CH<sub>2</sub>)<sub>0-4</sub>-O-(C<sub>1</sub>-C<sub>6</sub>  
30 alkyl optionally substituted with 1, 2, 3, or 5 -F);  
wherein each aryl group at each occurrence is  
optionally substituted with 1, 2, or 3 groups  
that are independently R<sub>205</sub>, R<sub>210</sub> or C<sub>1</sub>-C<sub>6</sub> alkyl

substituted with 1, 2, or 3 groups that are independently R<sub>205</sub> or R<sub>210</sub>;

wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R<sub>210</sub>;

wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R<sub>205</sub>, R<sub>210</sub>, or C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 1, 2, or 3 groups that are independently R<sub>205</sub> or R<sub>210</sub>;

R<sub>205</sub> at each occurrence is independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, -OH, -O-phenyl, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), and N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);

R<sub>210</sub> at each occurrence is independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; halogen; C<sub>1</sub>-C<sub>6</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkoxy; -NR<sub>220</sub>R<sub>225</sub>; OH; C≡N; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); -SO<sub>2</sub>-NR<sub>235</sub>R<sub>240</sub>; -CO-NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); and =O; wherein

R<sub>215</sub> at each occurrence is independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(aryl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and -(CH<sub>2</sub>)<sub>0-2</sub>-(heteroaryl), -(CH<sub>2</sub>)<sub>0-2</sub>-(heterocycloalkyl); wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R<sub>205</sub> or R<sub>210</sub>; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>;

R<sub>220</sub> and R<sub>225</sub> at each occurrence are independently selected from the group consisting of -H, -C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, amino C<sub>1</sub>-C<sub>6</sub> alkyl; halo C<sub>1</sub>-C<sub>6</sub>

alkyl; -C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), -aryl, -heteroaryl, and -heterocycloalkyl; wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>270</sub> groups, each heteroaryl is optionally substituted with 1, 2, 3, or 4 R<sub>200</sub>, each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R<sub>210</sub> wherein

R<sub>270</sub> at each occurrence is independently R<sub>205</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; halogen; C<sub>1</sub>-C<sub>6</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkoxy; NR<sub>235</sub>R<sub>240</sub>; OH; C≡N; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); and =O; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>205</sub> groups;

R<sub>235</sub> and R<sub>240</sub> at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6, or 7 carbon atoms,

R<sub>255</sub> and R<sub>260</sub> at each occurrence are independently selected from the group consisting of H; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -(C<sub>1</sub>-C<sub>4</sub> alkyl)-aryl; -(C<sub>1</sub>-C<sub>4</sub> alkyl)-heteroaryl; -(C<sub>1</sub>-C<sub>4</sub> alkyl)-heterocycloalkyl; -aryl; -heteroaryl; -heterocycloalkyl; -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>265</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-aryl; -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>265</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-heteroaryl; and; -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>265</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-heterocycloalkyl; wherein R<sub>265</sub> at each occurrence is independently -O-, -S- or -N(C<sub>1</sub>-C<sub>6</sub> alkyl)-;



each aryl or phenyl is optionally substituted with 1, 2, or 3 groups that are independently  $R_{205}$ ,  $R_{210}$ , or  $C_1$ - $C_6$  alkyl substituted with 1, 2, or 3 groups that are independently  $R_{205}$  or  $R_{210}$ .

5

Even more preferred compounds of formula X-XXX include those wherein

$R_{20}$  at each occurrence is independently selected from hydrogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_4$  alkoxy  $C_1$ - $C_4$  alkyl, halo  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_4$  alkanoyl, each of which is unsubstituted or substituted with 1, or 2 groups independently selected from halogen,  $C_1$ - $C_6$  alkyl, hydroxy,  $C_1$ - $C_6$  alkoxy,  $NH_2$ , and  $-R_{26}$ - $R_{27}$ , wherein

10

$R_{26}$  is selected from  $-C(O)-$ ,  $-SO_2-$ ,  $-CO_2-$ ;

15

$R_{27}$  is selected from  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, aryl  $C_1$ - $C_6$  alkyl, piperidyl, pyrrolyl, and pyridyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, halogen, halo  $C_1$ - $C_6$  alkyl, hydroxy  $C_1$ - $C_6$  alkyl,  $-C(O)NH_2$ ,  $NH_2$ ,  $NH(C_1$ - $C_6$  alkyl),  $N(C_1$ - $C_6$  alkyl) ( $C_1$ - $C_6$  alkyl),  $-C(O)NH(C_1$ - $C_6$  alkyl), or  $-C(O)N(C_1$ - $C_6$  alkyl) ( $C_1$ - $C_6$  alkyl).

20

Preferred compounds of formula X-XXX include those of formula X-XXXI, i.e., compounds of formula X-XXX wherein  $R_4$  is H;  $C_1$ - $C_4$  alkyl-NHC(O) $R_5$ ;  $-(CH_2)_{0-4}R_8$ ;  $-C_1$ - $C_4$  alkyl-NR<sub>50</sub>CO<sub>2</sub>R<sub>51</sub>;  $-C\equiv N$ ;  $-CF_3$ ;  $-CF_2-CF_3$ ;  $-C\equiv CH$ ;  $-CH_2-CH=CH_2$ ;  $-(CH_2)_{1-4}-R_{4-1}$ ;  $-(CH_2)_{1-4}-NH-R_{4-1}$ ;  $(CH_2)_{0-4}-NHC(O)-(CH_2)_{0-6}-R_{52}$ ; or  $-(CH_2)_{0-4}-R_{53}-(CH_2)_{0-4}-R_{54}$ .

30

Preferred compounds of formula X-XXXI include those wherein

X is  $C_1$ - $C_4$  alkylidenyl optionally optionally substituted with 1, 2, or 3 methyl groups; or  $-NR_{4-6}-$ ; or

R<sub>4</sub> and R<sub>4-6</sub> combine to form -(CH<sub>2</sub>)<sub>n<sub>10</sub></sub>-, wherein

n<sub>10</sub> is 1, 2, 3, or 4;

Z is selected from a bond; SO<sub>2</sub>; SO; S; and C(O);

Y is selected from H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl

5 containing at least one N, O, or S; phenyl; OH; -

N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 thru  
3 substituents which can be the same or different and are  
selected from halogen, hydroxy, alkoxy, thioalkoxy, and  
haloalkoxy; C<sub>3</sub>-C<sub>8</sub> cycloalkyl optionally substituted with  
10 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl,  
and halogen; alkoxy; phenyl optionally substituted with  
halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; phenyl C<sub>1</sub>-C<sub>4</sub>  
alkyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-  
C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

15 Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>10</sub> alkyl  
optionally substituted with 1, 2, or 3 substituents  
selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub>  
alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub>  
alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub>  
20 alkyl; and C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or  
-N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyll,  
piperidinyl, morpholinyl, and pyrrolidinyl, wherein  
each ring is optionally substituted with 1, 2, 3, or  
4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
25 alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen.

More preferred compounds of formula X-XXXI include those  
wherein

R<sub>20</sub> at each occurrence is independently selected from hydrogen,  
30 C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl,  
tertiary-butoxy carbonyl, and benzyloxycarbonyl;  
R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, 3, or 4  
groups independently selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy,  
hydroxy, and C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2,

or 3 substituents halogen, OH, SH, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl),  
N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), C≡N, CF<sub>3</sub>;

R<sub>2</sub> and R<sub>3</sub> are independently selected from H or C<sub>1</sub>-C<sub>4</sub> alkyl  
optionally substituted with 1 substituent selected from  
5 halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub>  
alkyl), and NH(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl,  
C<sub>1</sub>-C<sub>2</sub> alkoxy C<sub>1</sub>-C<sub>4</sub> alkyl, halo C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl,  
each of which is unsubstituted or substituted with 1 or 2  
10 groups independently selected from halogen, hydroxy, and  
NH<sub>2</sub>;

R<sub>C</sub> is C<sub>1</sub>-C<sub>8</sub> alkyl optionally substituted with 1, 2, or 3 groups  
independently selected from R<sub>205</sub>, -SH, -C=ONR<sub>235</sub>R<sub>240</sub>, and  
-S(=O)<sub>2</sub>NR<sub>235</sub>R<sub>240</sub>; -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>6</sub>) cycloalkyl wherein the  
15 cycloalkyl is optionally substituted with 1, 2, or 3  
groups independently selected from R<sub>205</sub>, -CO<sub>2</sub>H, and -CO<sub>2</sub>-  
(C<sub>1</sub>-C<sub>4</sub> alkyl); -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-phenyl optionally substituted  
with 1, 2, or 3 R<sub>200</sub>; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyridyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
pyridazinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrimidinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
20 pyrazinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-furyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-indolyl;  
-(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-thienyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrrolyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
pyrazolyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-benzoxazolyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
imidazolyl; each of the above heteroaryl groups is  
optionally substituted with 1, 2, 3, or 4 R<sub>200</sub>; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
25 3-imidazolidinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-tetrahydrofuryl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
tetrahydropyranyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-piperazinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
pyrrolidinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-piperidinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
indolinyl; each of the above heterocycloalkyl groups is  
optionally substituted with 1, 2, 3, or 4 R<sub>210</sub>; (CH<sub>2</sub>)<sub>0-1</sub>-  
30 CH((CH<sub>2</sub>)<sub>0-4</sub>-OH)-(CH<sub>2</sub>)<sub>0-1</sub>-phenyl; -(CH<sub>2</sub>)<sub>0-1</sub>-CH(C<sub>1</sub>-C<sub>4</sub>  
hydroxyalkyl)-(CH<sub>2</sub>)<sub>0-1</sub>-pyridyl;

R<sub>200</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl  
optionally substituted with 1, 2, or 3 R<sub>205</sub> groups;  
OH; -NO<sub>2</sub>; halogen; -CO<sub>2</sub>H; C≡N; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>220</sub>R<sub>225</sub>;

$-(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_1-\text{C}_8 \text{ alkyl})$ ;  $-(\text{CH}_2)_{0-4}-\text{CO}_2\text{R}_{215}$ ; and  $-(\text{CH}_2)_{0-4}-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl optionally substituted with 1, 2, 3, or 5 -F})$ ;

$\text{R}_{205}$  at each occurrence is independently  $\text{C}_1-\text{C}_6$  alkyl, halogen,  $-\text{OH}$ ,  $-\text{O-phenyl}$ ,  $-\text{SH}$ ,  $-\text{C}\equiv\text{N}$ ,  $-\text{CF}_3$ ,  $\text{C}_1-\text{C}_6$  alkoxy,  $\text{NH}_2$ ,  $\text{NH}(\text{C}_1-\text{C}_6 \text{ alkyl})$ , and  $\text{N}-(\text{C}_1-\text{C}_6 \text{ alkyl})(\text{C}_1-\text{C}_6 \text{ alkyl})$ ;

$\text{R}_{210}$  at each occurrence is independently  $\text{C}_1-\text{C}_6$  alkyl optionally substituted with 1 or 2  $\text{R}_{205}$  groups; halogen;  $\text{C}_1-\text{C}_4$  alkoxy;  $\text{C}_1-\text{C}_4$  haloalkoxy;  $-\text{NR}_{220}\text{R}_{225}$ ;  $\text{OH}$ ;  $\text{C}\equiv\text{N}$ ;  $\text{C}_3-\text{C}_7$  cycloalkyl optionally substituted with 1 or 2  $\text{R}_{205}$  groups;  $-\text{CO}-(\text{C}_1-\text{C}_4 \text{ alkyl})$ ;  $-\text{SO}_2-\text{NR}_{235}\text{R}_{240}$ ;  $-\text{CO}-\text{NR}_{235}\text{R}_{240}$ ;  $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkyl})$ ; and  $=\text{O}$ ; wherein

$\text{R}_{215}$  at each occurrence is independently  $\text{C}_1-\text{C}_6$  alkyl,  $-(\text{CH}_2)_{0-2}-(\text{phenyl})$ ,  $\text{C}_3-\text{C}_6$  cycloalkyl,  $-(\text{CH}_2)_{0-2}-(\text{pyridyl})$ ,  $-(\text{CH}_2)_{0-2}-(\text{pyrrolyl})$ ,  $-(\text{CH}_2)_{0-2}-(\text{imidazolyl})$ ,  $-(\text{CH}_2)_{0-2}-(\text{pyrimidyl})$ ,  $-(\text{CH}_2)_{0-2}-(\text{pyrrolidinyl})$ ,  $-(\text{CH}_2)_{0-2}-(\text{imidazolidinyl})$ ,  $-(\text{CH}_2)_{0-2}-(\text{piperazinyl})$ ,  $-(\text{CH}_2)_{0-2}-(\text{piperidinyl})$ , and  $-(\text{CH}_2)_{0-2}-(\text{morpholinyl})$ ; wherein the phenyl group at each occurrence is optionally substituted with 1 or 2 groups that are independently  $\text{R}_{205}$  or  $\text{R}_{210}$ ; wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1 or 2  $\text{R}_{210}$ ; wherein each heteroaryl group at each occurrence is optionally substituted with 1 or 2  $\text{R}_{210}$ ;

$\text{R}_{220}$  and  $\text{R}_{225}$  at each occurrence are independently  $-\text{H}$ ,  $\text{C}_1-\text{C}_4$  alkyl, hydroxy  $\text{C}_1-\text{C}_4$  alkyl, halo  $\text{C}_1-\text{C}_4$  alkyl;  $\text{C}_3-\text{C}_6$  cycloalkyl, and  $-(\text{C}_1-\text{C}_4 \text{ alkyl})-\text{O}-(\text{C}_1-\text{C}_2 \text{ alkyl})$ ;

$\text{R}_{235}$  and  $\text{R}_{240}$  at each occurrence are independently  $\text{H}$ , or  $\text{C}_1-\text{C}_6$  alkyl;

$\text{R}_{245}$  and  $\text{R}_{250}$  at each occurrence are independently  $\text{H}$ ,  $\text{C}_1-\text{C}_4$  alkyl,  $\text{C}_1-\text{C}_4$  hydroxyalkyl,  $\text{C}_1-\text{C}_4$  alkoxy,  $\text{C}_1-\text{C}_4$  haloalkoxy, or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms.

5 Even more preferred compounds of formula X-XXXI include those wherein

R<sub>4</sub> is H; C<sub>1</sub>-C<sub>4</sub> alkyl-NHC(O)R<sub>5</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>R<sub>8</sub>; -C<sub>1</sub>-C<sub>4</sub> alkyl-NR<sub>50</sub>CO<sub>2</sub>R<sub>51</sub>; -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>4-1</sub>; -(CH<sub>2</sub>)<sub>1-4</sub>-NH-R<sub>4-1</sub>; (CH<sub>2</sub>)<sub>1-4</sub>-NHC(O)-(CH<sub>2</sub>)<sub>0-6</sub>-R<sub>52</sub>; or -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>53</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>54</sub>; wherein

10 R<sub>4-1</sub> is -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub> alkyl), -SO<sub>2</sub>-NR<sub>4-2</sub>R<sub>4-3</sub>; or -CO-NR<sub>4-3</sub>R<sub>4-4</sub>; wherein

R<sub>4-2</sub> and R<sub>4-3</sub> are independently H, or C<sub>1</sub>-C<sub>3</sub> alkyl;

R<sub>4-4</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, or phenyl C<sub>1</sub>-C<sub>4</sub> alkanoyl;

15 R<sub>5</sub> is selected from the group consisting of cyclopropyl; cyclopentyl; cyclohexyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, -NR<sub>6</sub>R<sub>7</sub>, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl, C<sub>5</sub>-C<sub>6</sub> heteroaryl, phenyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -S-C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>7</sub>, -CO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, or phenyloxy; pyridyl, thiazolyl, pyrazolyl, pyrazinyl, optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or OH; piperidinyl, dihydropyridazinonyl, pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl, imidazolyl, indolyl, optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or C<sub>2</sub>-C<sub>4</sub> alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkyl; wherein

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R<sub>6</sub> and R<sub>7</sub> are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl, and phenethyl;

R<sub>8</sub> is -SO<sub>2</sub>-thienyl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl or halogen; -SO<sub>2</sub>-phenyl, -SO<sub>2</sub>-piperidinyl, -SO<sub>2</sub>-pyrrolidinyl, imidazolidinyyl dione, -C(O)NHR<sub>9</sub>, -S-C<sub>1</sub>-C<sub>6</sub> alkyl, or -S-C<sub>2</sub>-C<sub>4</sub> alkanoyl, wherein

R<sub>9</sub> is phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, or H;

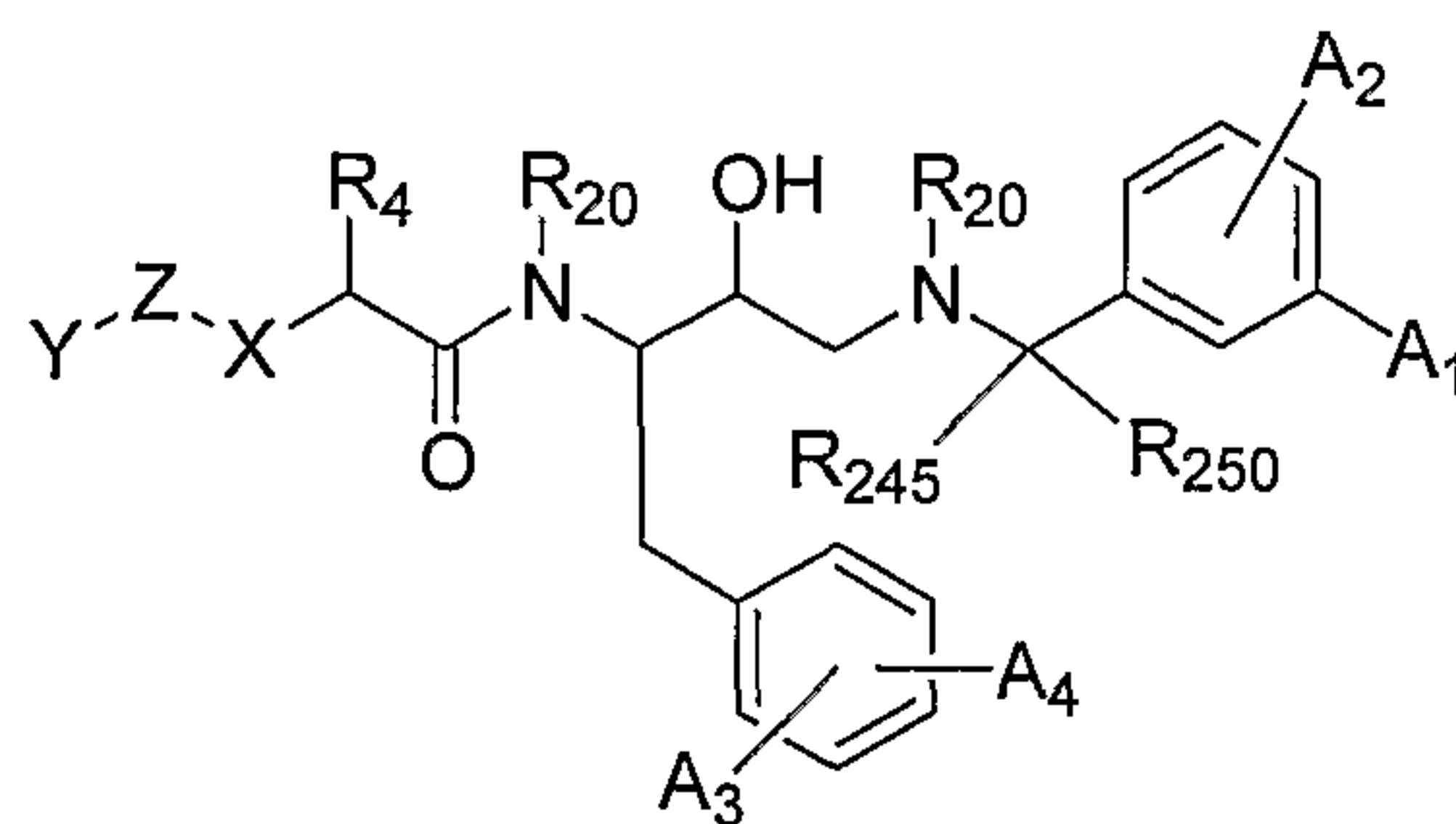
R<sub>50</sub> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>51</sub> is selected from benzyl; phenethyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR<sub>6</sub>R<sub>7</sub>, -C(O)NR<sub>6</sub>R<sub>7</sub>, or -C<sub>1</sub>-C<sub>4</sub> alkoxy; heterocycloalkyl containing at least one N, O, or S and optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; heterocycloalkylalkyl containing at least one N, O, or S and optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkynyl; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); heteroarylalkyl containing at least one N, O, or S and optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); phenyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl, wherein the phenyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl groups are optionally substituted with 1, 2, or 3 groups that are

independently halogen, CN, NO<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, hydroxy, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> thioalkoxy;

- 5 R<sub>52</sub> is heterocycloalkyl, heteroaryl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -CO<sub>2</sub>-alkyl, -NHS(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(alkyl)S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -S(O)<sub>0-2</sub>-heteroaryl, -S(O)<sub>0-2</sub>-aryl, -NH(arylalkyl),  
 10 -N(alkyl)(arylalkyl), thioalkoxy, or alkoxy, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> thioalkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, haloalkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, NO<sub>2</sub>, CN, C<sub>1</sub>-C<sub>4</sub>  
 15 alkoxy carbonyl, or aminocarbonyl;
- R<sub>53</sub> is absent, -O-, -C(O)-, -NH-, -N(alkyl)-, -NH-S(O)<sub>0-2</sub>-, -N(alkyl)-S(O)<sub>0-2</sub>-, -S(O)<sub>0-2</sub>-NH-, or -S(O)<sub>0-2</sub>-N(alkyl)-;
- R<sub>54</sub> is pyridyl, thienyl, imidazolyl, phenyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, piperidyl, pyrrolidinyl, imidazolidinyl dione,  
 20 CO<sub>2</sub>H, -CO<sub>2</sub>-alkyl, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -C(O)NH<sub>2</sub>, C<sub>1</sub>-C<sub>8</sub> alkyl, OH, phenyloxy, alkoxy, phenylalkoxy, NH<sub>2</sub>, NH(alkyl), N(alkyl)(alkyl), or -C<sub>1</sub>-C<sub>6</sub> alkyl-CO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, each of which is  
 25 optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, CO<sub>2</sub>H, -CO<sub>2</sub>-alkyl, thioalkoxy, halogen, haloalkyl, haloalkoxy, hydroxyalkyl, alkanoyl, NO<sub>2</sub>, CN, alkoxy carbonyl, or aminocarbonyl.

- 30 Even more preferred compounds of formula X-XXXI are those of formula X-XXXII:



X-XXXII

wherein

A<sub>1</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen or C<sub>2</sub>-C<sub>6</sub> alkynyl;

5 A<sub>2</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl or OH;

A<sub>3</sub> and A<sub>4</sub> are independently C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, or H.

Preferred compounds of formulas X-XXXI and X-XXXII include  
10 those wherein

R<sub>20</sub> at each occurrence is independently H or C<sub>1</sub>-C<sub>4</sub> alkyl;

X is C<sub>1</sub> or C<sub>2</sub> alkylidenyl;

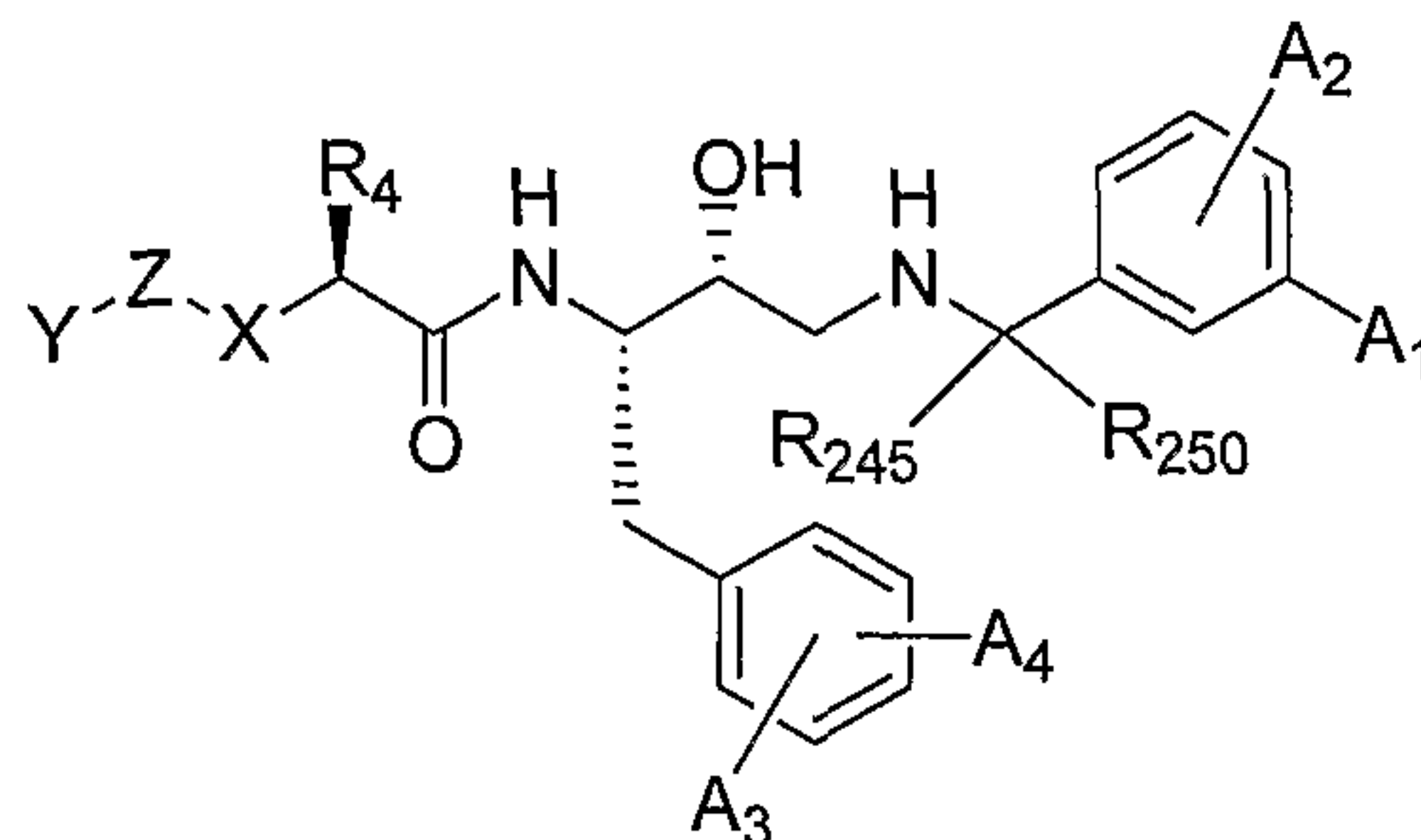
Z is SO<sub>2</sub>; SO; S; or C(O); and

Y is phenyl; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3  
15 halogen; or OH; or

Y is -N(Y<sub>1</sub>)(Y<sub>2</sub>); wherein

Y<sub>1</sub> and Y<sub>2</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl.

More preferred compounds of formula X-XXXII include those  
20 of formula X-XXXIII:



X-XXXIII.



Preferred compounds of formulas X-XXXII and X-XXXIII include those wherein

R<sub>4</sub> is H; or C<sub>1</sub>-C<sub>4</sub> alkyl-NHC(O)R<sub>5</sub>; wherein

R<sub>5</sub> is selected from the group consisting of cyclopropyl;

5 cyclopentyl; cyclohexyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, -NR<sub>6</sub>R<sub>7</sub>, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl, C<sub>5</sub>-C<sub>6</sub> heteroaryl, phenyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -S-C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>7</sub>, -CO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, or

10 phenyloxy; pyridyl, thiazolyl, pyrazolyl, pyrazinyl, optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or OH; piperidinyl, dihydropyridazinonyl, pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl,

15 imidazolyl, indolyl, optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or C<sub>2</sub>-C<sub>4</sub> alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkyl; wherein

20 R<sub>6</sub> and R<sub>7</sub> are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl, and phenethyl.

Other preferred compounds of formula X-XXXIII include  
25 those wherein

R<sub>4</sub> is -(CH<sub>2</sub>)<sub>0-4</sub>R<sub>8</sub>; wherein

R<sub>8</sub> is -SO<sub>2</sub>-thienyl optionally substituted with 1 or 2  
groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl or halogen;  
-SO<sub>2</sub>-phenyl, -SO<sub>2</sub>-piperidinyl, -SO<sub>2</sub>-pyrrolidinyl,  
30 imidazolidinyyl dione, -C(O)NHR<sub>9</sub>, -S-C<sub>1</sub>-C<sub>6</sub> alkyl, or -S-C<sub>2</sub>-C<sub>4</sub> alkanoyl, wherein

R<sub>9</sub> is phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, or H;

Other preferred compounds of formula X-XXXIII include those wherein

$R_4$  is  $-C_1-C_4$  alkyl- $NR_{50}CO_2R_{51}$ ;  $-(CH_2)_{1-4}-NH-R_{4-1}$ ; or  $(CH_2)_{1-4}-NHC(O)-(CH_2)_{0-6}-R_{52}$ ; wherein

5  $R_{50}$  is H or  $C_1-C_4$  alkyl;

$R_{51}$  is selected from benzyl; phenethyl;  $C_1-C_6$  alkyl

optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano,  $-NR_6R_7$ ,  $-C(O)NR_6R_7$ , or  $-C_1-C_4$  alkoxy; heterocycloalkyl containing at

10 least one N, O, or S and optionally substituted with 1 or 2 groups that are independently  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, halogen,  $C_2-C_4$  alkanoyl, phenyl  $C_1-C_4$  alkyl, and  $-SO_2$   $C_1-C_4$  alkyl; heterocycloalkylalkyl

containing at least one N, O, or S and optionally substituted with 1 or 2 groups that are independently  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, halogen,  $C_2-C_4$  alkanoyl, phenyl  $C_1-C_4$  alkyl, and  $-SO_2$   $C_1-C_4$  alkyl;  $C_2-C_6$

15 alkenyl;  $C_2-C_6$  alkynyl; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently OH,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, halogen,  $NH_2$ ,  $NH(C_1-C_6$  alkyl) or  $N(C_1-C_6$  alkyl)( $C_1-C_6$  alkyl); heteroarylalkyl containing at least one N, O, or S

20 and optionally substituted with 1, 2, or 3 groups that are independently  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, halogen,  $NH_2$ ,  $NH(C_1-C_6$  alkyl) or  $N(C_1-C_6$  alkyl)( $C_1-C_6$  alkyl); phenyl;  $C_3-C_6$  cycloalkyl, and  $C_3-C_6$  cycloalkyl

25  $C_1-C_4$  alkyl, wherein the phenyl;  $C_3-C_6$  cycloalkyl, and  $C_3-C_6$  cycloalkyl  $C_1-C_4$  alkyl groups are optionally substituted with 1, 2, or 3 groups that are

30 independently halogen, CN,  $NO_2$ ,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,  $C_2-C_6$  alkanoyl,  $C_1-C_4$  haloalkyl,  $C_1-C_4$  haloalkoxy, hydroxy,  $C_1-C_4$  hydroxyalkyl,  $C_1-C_4$  thioalkoxy;

R<sub>6</sub> and R<sub>7</sub> are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl, and phenethyl;

R<sub>52</sub> is heterocycloalkyl, heteroaryl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -CO<sub>2</sub>-alkyl, -NHS(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(alkyl)S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -S(O)<sub>0-2</sub>-heteroaryl, -S(O)<sub>0-2</sub>-aryl, -NH(arylalkyl), -N(alkyl)(arylalkyl), thioalkoxy, or alkoxy, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> thioalkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, haloalkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, NO<sub>2</sub>, CN, C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl, or aminocarbonyl.

Still other preferred compounds of formula X-XXXIII include those wherein

R<sub>4</sub> is -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>4-1</sub> or -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>53</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>54</sub>; wherein

R<sub>4-1</sub> is -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub> alkyl), -SO<sub>2</sub>-NR<sub>4-2</sub>R<sub>4-3</sub>; or -CO-NR<sub>4-3</sub>R<sub>4-4</sub>;

wherein

R<sub>4-2</sub> and R<sub>4-3</sub> are independently H, or C<sub>1</sub>-C<sub>3</sub> alkyl;

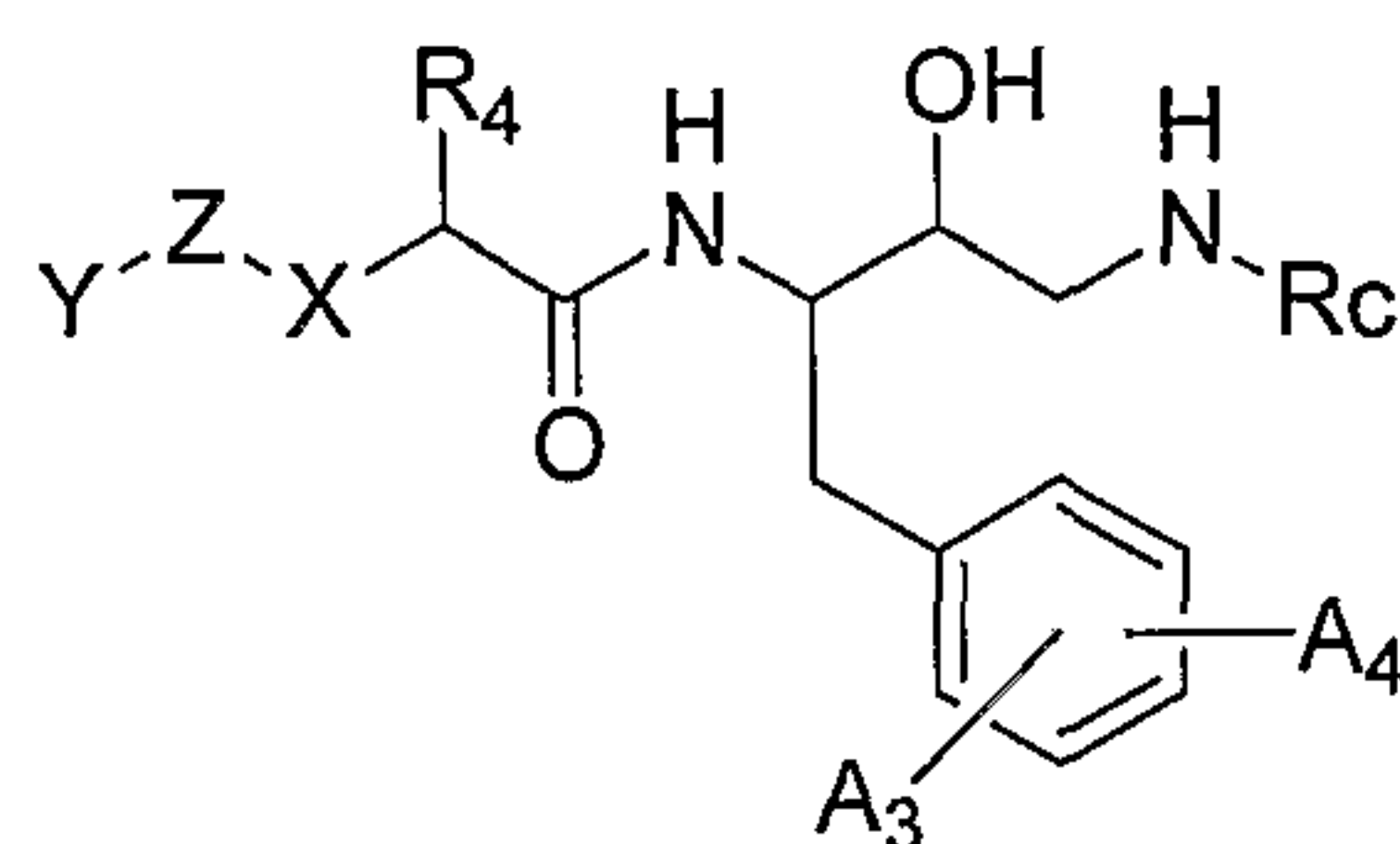
R<sub>4-4</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, or phenyl C<sub>1</sub>-C<sub>4</sub> alkanoyl;

R<sub>53</sub> is absent, -O-, -C(O)-, -NH-, -N(alkyl)-, -NH-S(O)<sub>0-2</sub>-, -N(alkyl)-S(O)<sub>0-2</sub>-, -S(O)<sub>0-2</sub>-NH-, or -S(O)<sub>0-2</sub>-N(alkyl)-;

R<sub>54</sub> is pyridyl, thienyl, imidazolyl, phenyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, piperidyl, pyrrolidinyl, imidazolidinyl dione, CO<sub>2</sub>H, -CO<sub>2</sub>-alkyl, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -C(O)NH<sub>2</sub>, C<sub>1</sub>-C<sub>8</sub> alkyl, OH, phenyloxy, alkoxy, phenylalkoxy, NH<sub>2</sub>, NH(alkyl), N(alkyl)(alkyl), or -C<sub>1</sub>-C<sub>6</sub> alkyl-CO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, CO<sub>2</sub>H, -CO<sub>2</sub>-alkyl, thioalkoxy, halogen, haloalkyl, haloalkoxy,

hydroxyalkyl, alkanoyl, NO<sub>2</sub>, CN, alkoxy carbonyl, or aminocarbonyl.

Other preferred compounds of formula X-XXXIII include  
5 those of formula X-XXXIV:



X-XXXIV

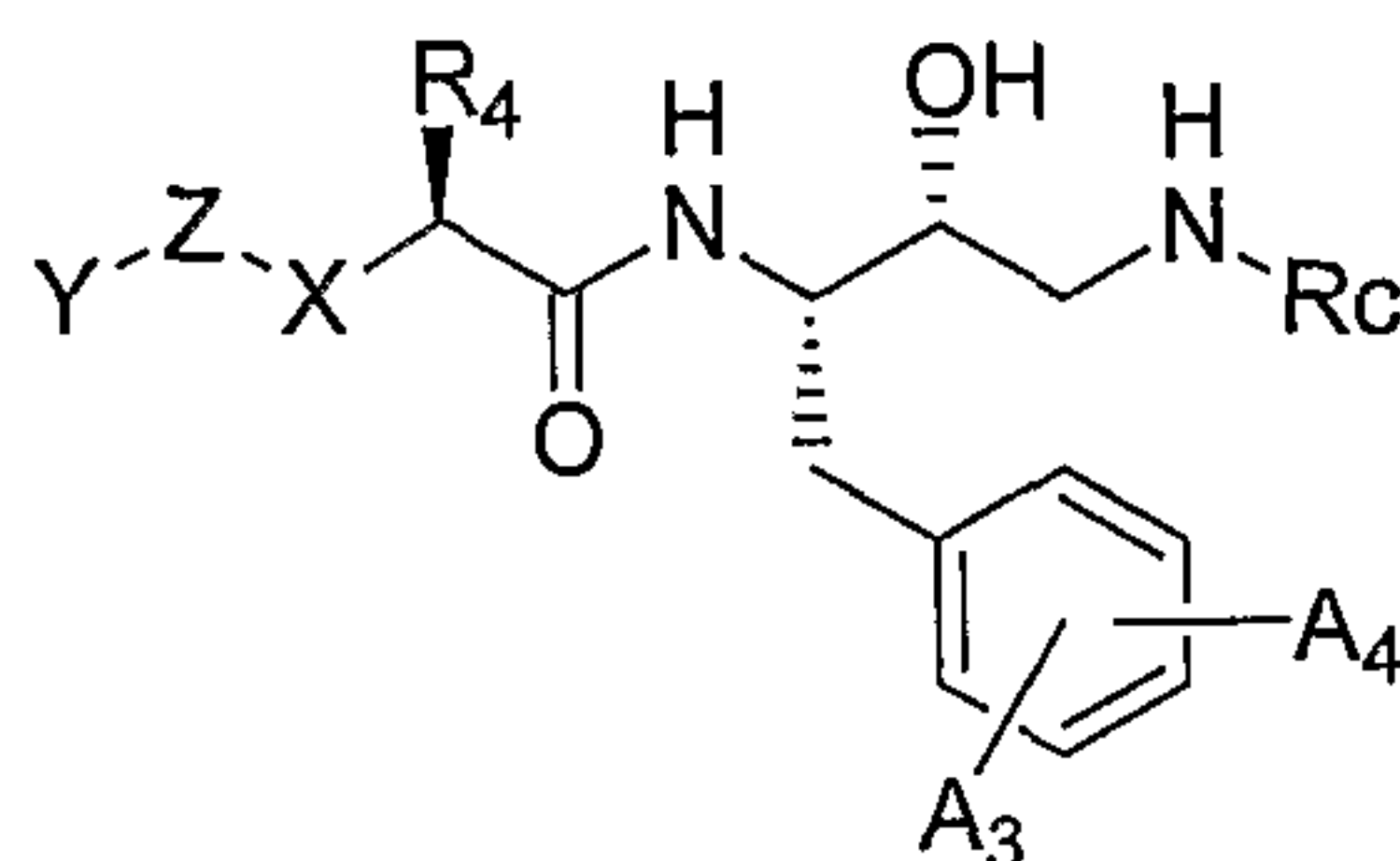
wherein

R<sub>c</sub> is C<sub>3</sub>-C<sub>8</sub> alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or -  
10 (C<sub>1</sub>-C<sub>4</sub>)alkyl-(C<sub>3</sub>-C<sub>6</sub>) cycloalkyl; and  
A<sub>3</sub> and A<sub>4</sub> are independently C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, or H.

Preferred compounds of formula X-XXXIV include

R<sub>20</sub> at each occurrence is independently H or C<sub>1</sub>-C<sub>4</sub> alkyl;  
15 X is C<sub>1</sub> or C<sub>2</sub> alkylidenyl;  
Z is SO<sub>2</sub>; SO; S; or C(O); and  
Y is phenyl; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3  
halogen; or OH; or  
Y is -N(Y<sub>1</sub>)(Y<sub>2</sub>); wherein  
20 Y<sub>1</sub> and Y<sub>2</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl.

More preferred compounds of formula X-XXXIV include those  
of formula X-XXXV:



X-XXXV.

25

Preferred compounds of formula X-XXXV include those wherein

$R_4$  is H; or  $C_1-C_4$  alkyl-NHC(O) $R_5$ ; wherein

$R_5$  is selected from the group consisting of cyclopropyl;

5 cyclopentyl; cyclohexyl;  $C_1-C_6$  alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen,  $-NR_6R_7$ ,  $C_1-C_4$  alkoxy,  $C_5-C_6$  heterocycloalkyl,  $C_5-C_6$  heteroaryl, phenyl,  $C_3-C_7$  cycloalkyl,  $-S-C_1-C_4$  alkyl,  $-SO_2-C_1-C_4$  alkyl,  $-CO_2H$ ,  $-CONR_6R_7$ ,  $-CO_2-C_1-C_4$  alkyl, or  
 10 phenyloxy; pyridyl, thiazolyl, pyrazolyl, pyrazinyl, optionally substituted with 1, 2, or 3 groups that are independently  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, halogen,  $C_1-C_4$  haloalkyl, or OH; piperidinyl, dihydropyridazinonyl, pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl,  
 15 imidazolyl, indolyl, optionally substituted with 1, 2, or 3 groups that are independently  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, halogen, or  $C_2-C_4$  alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, or  $C_1-C_4$  haloalkyl; and  $NR_6R_7$   
 20 wherein

$R_6$  and  $R_7$  are independently selected from the group

consisting of H,  $C_1-C_6$  alkyl,  $C_2-C_6$  alkanoyl, phenyl,  $-SO_2-C_1-C_4$  alkyl, benzyl, and phenethyl.

25 Other preferred compounds of formula X-XXXV include those wherein

$R_4$  is  $-(CH_2)_{0-4}R_8$ ; wherein

$R_8$  is  $-SO_2$ -thienyl optionally substituted with 1 or 2 groups that are independently  $C_1-C_4$  alkyl or halogen;  
 30  $-SO_2$ -phenyl,  $-SO_2$ -piperidinyl,  $-SO_2$ -pyrrolidinyl, imidazolidinyyl dione,  $-C(O)NHR_9$ ,  $-S-C_1-C_6$  alkyl, or  $-S-C_2-C_4$  alkanoyl, wherein

$R_9$  is phenyl  $C_1-C_4$  alkyl,  $C_1-C_4$  alkyl, or H;

Other preferred compounds of formula X-XXXV include those wherein

$R_4$  is  $-C_1-C_4$  alkyl- $NR_{50}CO_2R_{51}$ ;  $-(CH_2)_{1-4}-NH-R_{4-1}$ ; or  $(CH_2)_{1-4}-NHC(O)-(CH_2)_{0-6}-R_{52}$ ; wherein

5  $R_{50}$  is H or  $C_1-C_4$  alkyl;

$R_{51}$  is selected from benzyl; phenethyl;  $C_1-C_6$  alkyl

optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano,  $-NR_6R_7$ ,  $-C(O)NR_6R_7$ , or  $-C_1-C_4$  alkoxy; heterocycloalkyl containing at

10 least one N, O, or S and optionally substituted with 1 or 2 groups that are independently  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, halogen,  $C_2-C_4$  alkanoyl, phenyl  $C_1-C_4$  alkyl, and  $-SO_2$   $C_1-C_4$  alkyl; heterocycloalkylalkyl

containing at least one N, O, or S and optionally

15 substituted with 1 or 2 groups that are independently  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, halogen,  $C_2-C_4$  alkanoyl, phenyl  $C_1-C_4$  alkyl, and  $-SO_2$   $C_1-C_4$  alkyl;  $C_2-C_6$  alkenyl;  $C_2-C_6$  alkynyl; heteroaryl optionally

substituted with 1, 2, or 3 groups that are

20 independently OH,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, halogen,  $NH_2$ ,  $NH(C_1-C_6$  alkyl) or  $N(C_1-C_6$  alkyl)( $C_1-C_6$  alkyl);

heteroarylalkyl containing at least one N, O, or S and optionally substituted with 1, 2, or 3 groups

that are independently  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,

25 halogen,  $NH_2$ ,  $NH(C_1-C_6$  alkyl) or  $N(C_1-C_6$  alkyl)( $C_1-C_6$  alkyl); phenyl;  $C_3-C_6$  cycloalkyl, and  $C_3-C_6$  cycloalkyl

$C_1-C_4$  alkyl, wherein the phenyl;  $C_3-C_6$  cycloalkyl, and

$C_3-C_6$  cycloalkyl  $C_1-C_4$  alkyl groups are optionally substituted with 1, 2, or 3 groups that are

30 independently halogen, CN,  $NO_2$ ,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,  $C_2-C_6$  alkanoyl,  $C_1-C_4$  haloalkyl,  $C_1-C_4$

haloalkoxy, hydroxy,  $C_1-C_4$  hydroxyalkyl,  $C_1-C_4$  thioalkoxy;

R<sub>6</sub> and R<sub>7</sub> are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl, and phenethyl;

R<sub>52</sub> is heterocycloalkyl, heteroaryl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -CO<sub>2</sub>-alkyl, -NHS(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(alkyl)S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -S(O)<sub>0-2</sub>-heteroaryl, -S(O)<sub>0-2</sub>-aryl, -NH(arylalkyl), -N(alkyl)(arylalkyl), thioalkoxy, or alkoxy, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> thioalkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, haloalkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, NO<sub>2</sub>, CN, C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl, or aminocarbonyl.

Still other preferred compounds of formula X-XXXV include those wherein

R<sub>4</sub> is -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>4-1</sub> or -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>53</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>54</sub>; wherein

R<sub>4-1</sub> is -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub> alkyl), -SO<sub>2</sub>-NR<sub>4-2</sub>R<sub>4-3</sub>; or -CO-NR<sub>4-3</sub>R<sub>4-4</sub>;

wherein

R<sub>4-2</sub> and R<sub>4-3</sub> are independently H, or C<sub>1</sub>-C<sub>3</sub> alkyl;

R<sub>4-4</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl (preferably benzyl or phenethyl), C<sub>2</sub>-C<sub>4</sub> alkanoyl, or phenyl C<sub>1</sub>-C<sub>4</sub> alkanoyl (preferably benzoyl or C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>CO-);

R<sub>53</sub> is absent, -O-, -C(O)-, -NH-, -N(alkyl)-, -NH-S(O)<sub>0-2</sub>-, -N(alkyl)-S(O)<sub>0-2</sub>-, -S(O)<sub>0-2</sub>-NH-, or -S(O)<sub>0-2</sub>-N(alkyl)-;

R<sub>54</sub> is pyridyl, thienyl, imidazolyl, phenyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, piperidyl, pyrrolidinyl, imidazolidinyl dione, CO<sub>2</sub>H, -CO<sub>2</sub>-alkyl, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -C(O)NH<sub>2</sub>, C<sub>1</sub>-C<sub>8</sub> alkyl, OH, phenyloxy, alkoxy, phenylalkoxy, NH<sub>2</sub>, NH(alkyl), N(alkyl)(alkyl), or -C<sub>1</sub>-C<sub>6</sub> alkyl-CO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, CO<sub>2</sub>H, -CO<sub>2</sub>-

alkyl, thioalkoxy, halogen, haloalkyl, haloalkoxy, hydroxyalkyl, alkanoyl, NO<sub>2</sub>, CN, alkoxy-carbonyl, or aminocarbonyl.

5 Other preferred compounds of formula X-XXXII include those of formula X-XXXVI, i.e., compounds of formula X-XXXII wherein R<sub>4</sub> is -O-C<sub>1</sub>-C<sub>4</sub> alkanoyl; OH; C<sub>6</sub>-C<sub>10</sub> aryloxy optionally substituted with 1, 2, or 3 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, CO<sub>2</sub>H, -C(O)-C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> alkoxy; aryl C<sub>1</sub>-C<sub>4</sub> alkoxy; -O-(CH<sub>2</sub>)<sub>n6</sub>-R<sub>4-1</sub>; -S-(CH<sub>2</sub>)<sub>n6</sub>-R<sub>4-1</sub>.

Still other preferred compounds of formula X-XXXVI include those wherein

15 R<sub>4</sub> is -O-C<sub>1</sub>-C<sub>4</sub> alkanoyl; OH; phenyloxy or naphthyloxy, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, CO<sub>2</sub>H, -C(O)-C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> alkoxy; phenyl C<sub>1</sub>-C<sub>4</sub> alkoxy; -O-(CH<sub>2</sub>)<sub>n6</sub>-R<sub>4-1</sub>; or -S-(CH<sub>2</sub>)<sub>n6</sub>-R<sub>4-1</sub>

20 R<sub>4-1</sub> is -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub> alkyl), -SO<sub>2</sub>-NR<sub>4-2</sub>R<sub>4-3</sub>; or -CO-NR<sub>4-3</sub>R<sub>4-4</sub>; wherein R<sub>4-2</sub> and R<sub>4-3</sub> are independently H, or C<sub>1</sub>-C<sub>3</sub> alkyl; R<sub>4-4</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, or phenyl C<sub>1</sub>-C<sub>4</sub> alkanoyl;

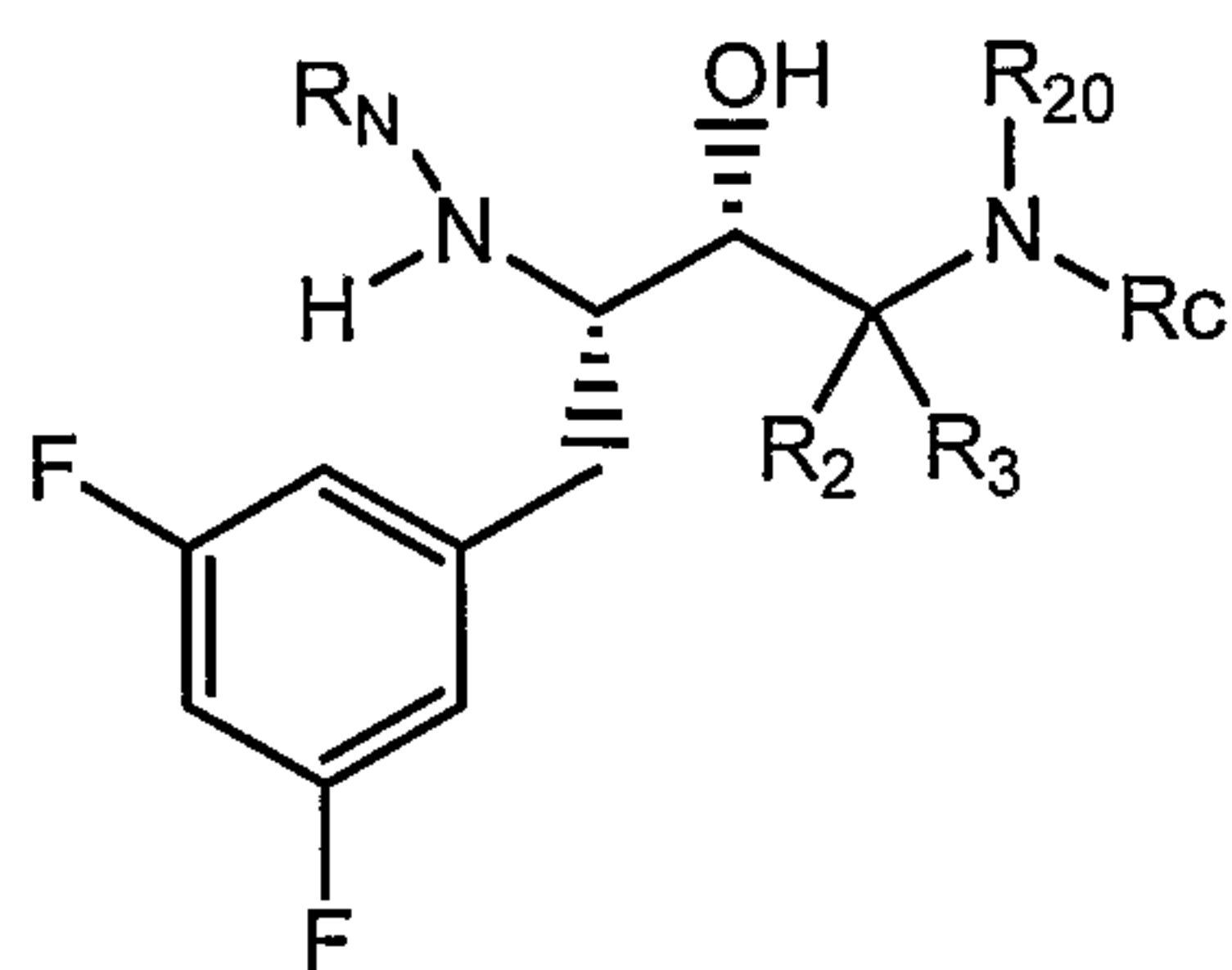
25 More preferred compounds of formula X-XXXVI include those wherein

R<sub>4</sub> is -O-C<sub>1</sub>-C<sub>4</sub> alkanoyl; OH; phenyloxy optionally substituted with 1, or 2 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, CO<sub>2</sub>H, -C(O)-C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> alkoxy; or phenyl C<sub>1</sub>-C<sub>4</sub> alkoxy.

30

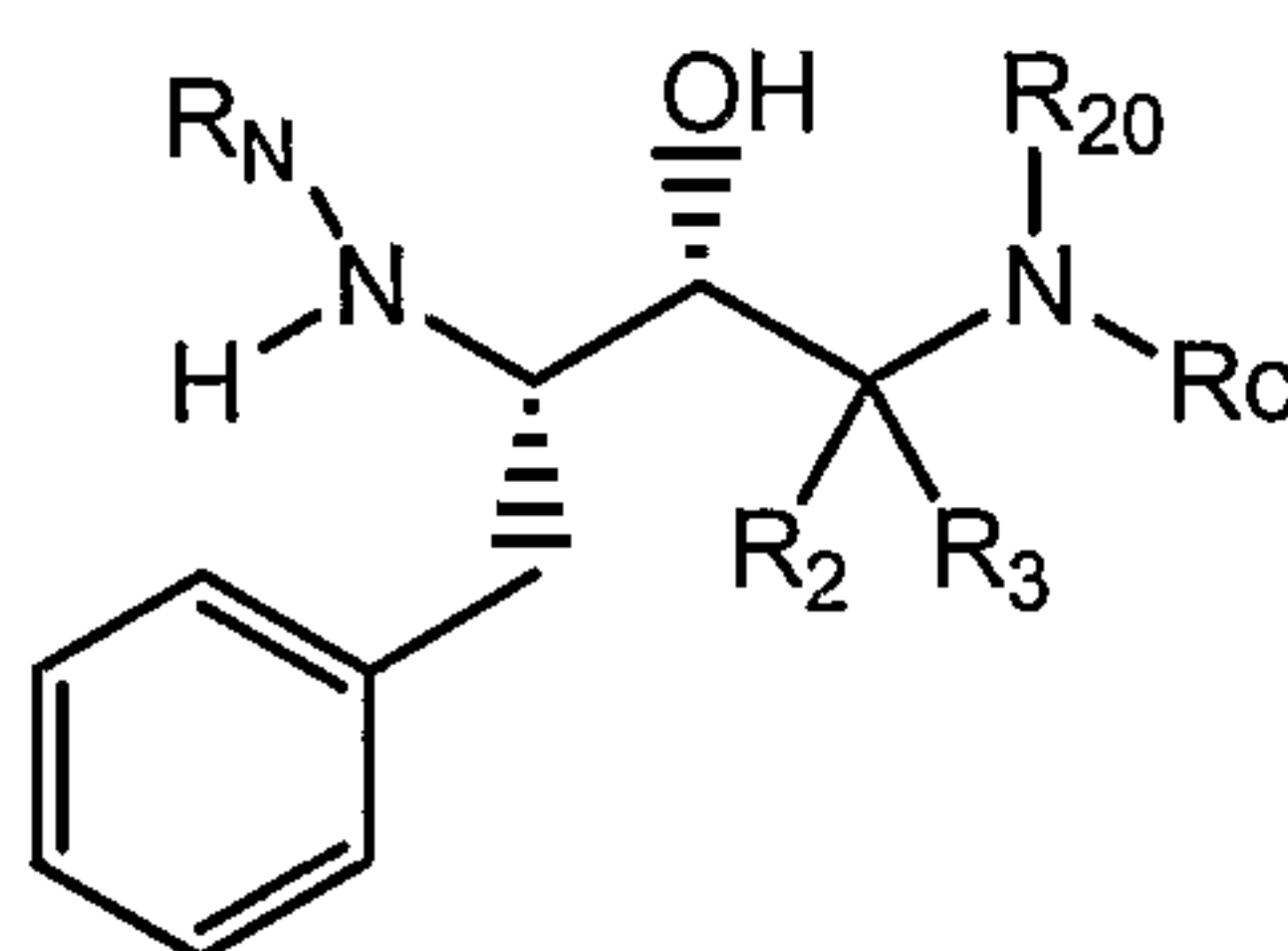
Other preferred compounds of the invention are those of formulae X-40 to X-47:





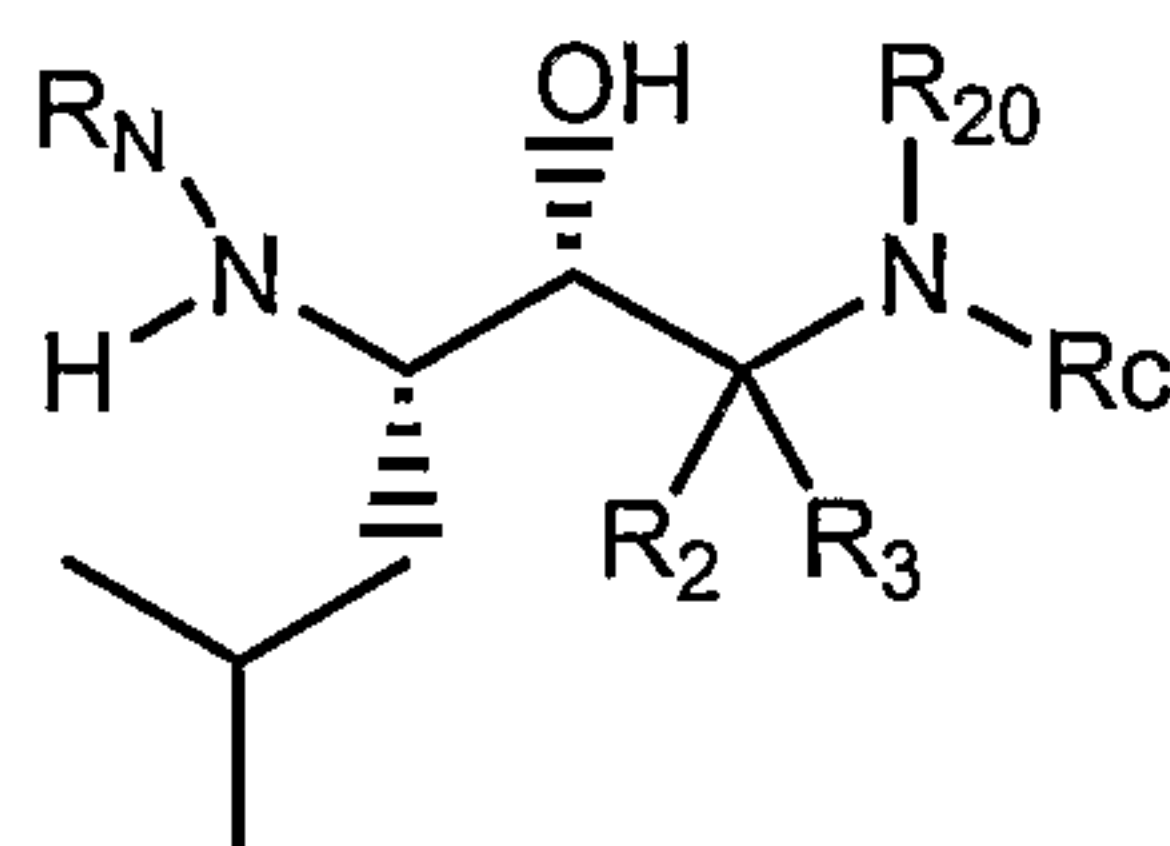
X-40

where  $R_N$ ,  $R_2$ ,  $R_3$ ,  $R_{20}$  and  $R_C$  are as defined above for structure X.



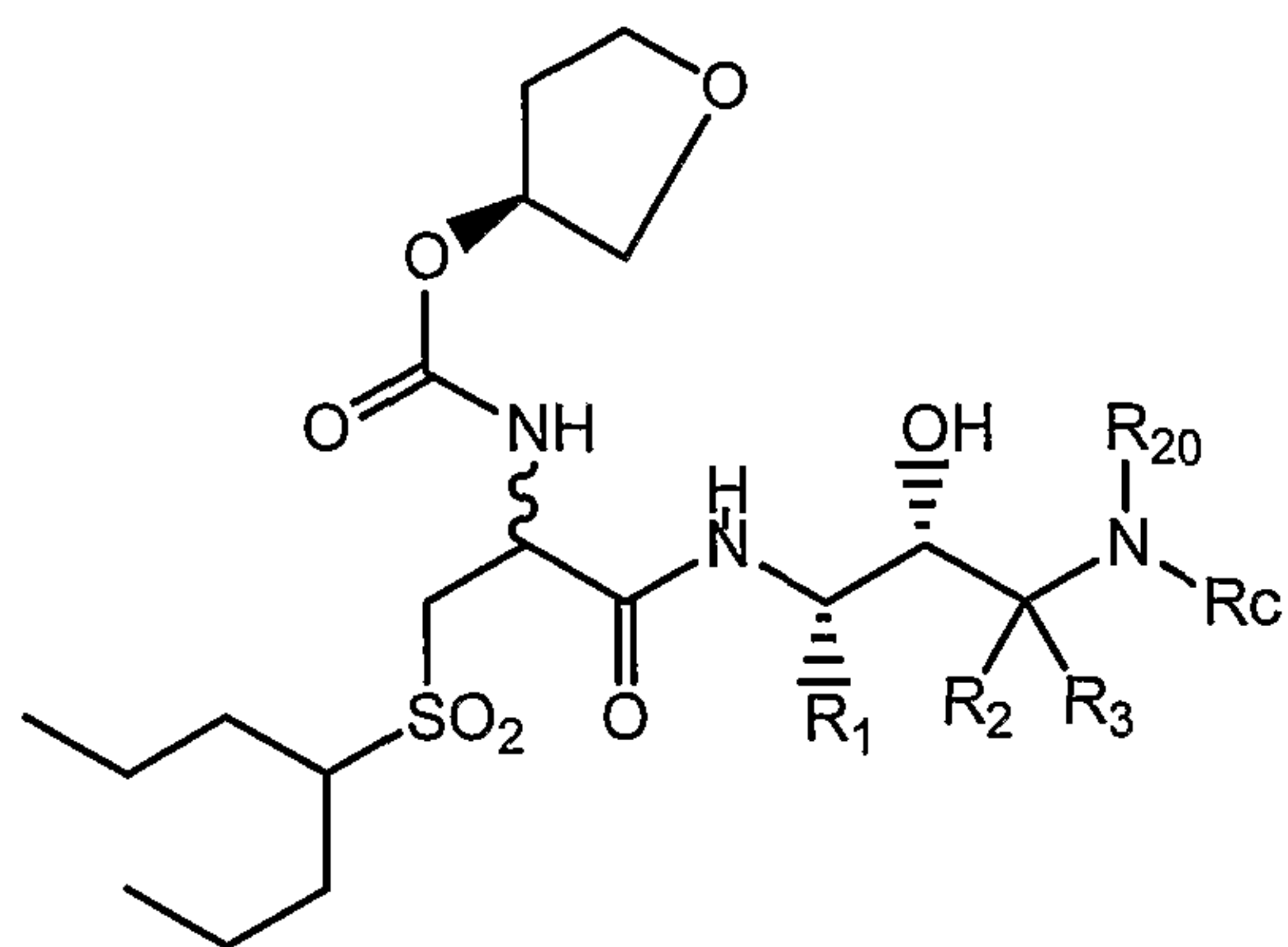
X-41

where  $R_N$ ,  $R_2$ ,  $R_3$ ,  $R_{20}$  and  $R_C$  are as defined above for structure X.



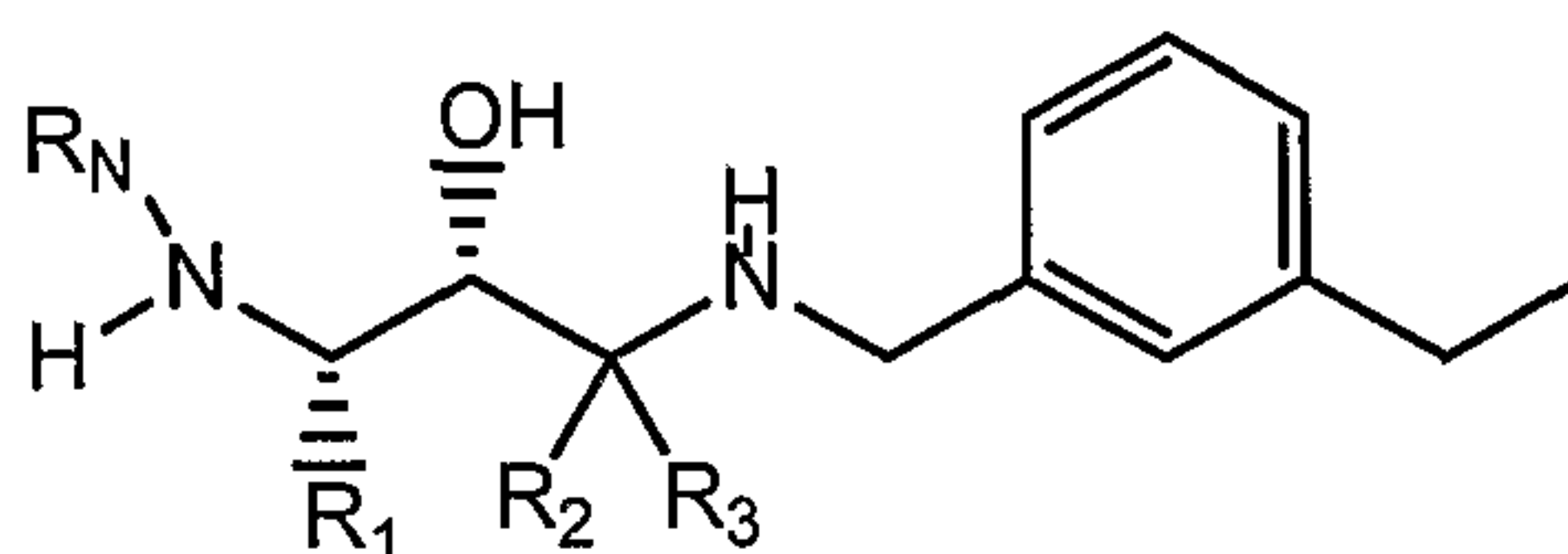
X-42

where  $R_N$ ,  $R_2$ ,  $R_3$ ,  $R_{20}$  and  $R_C$  are as defined above for structure X.



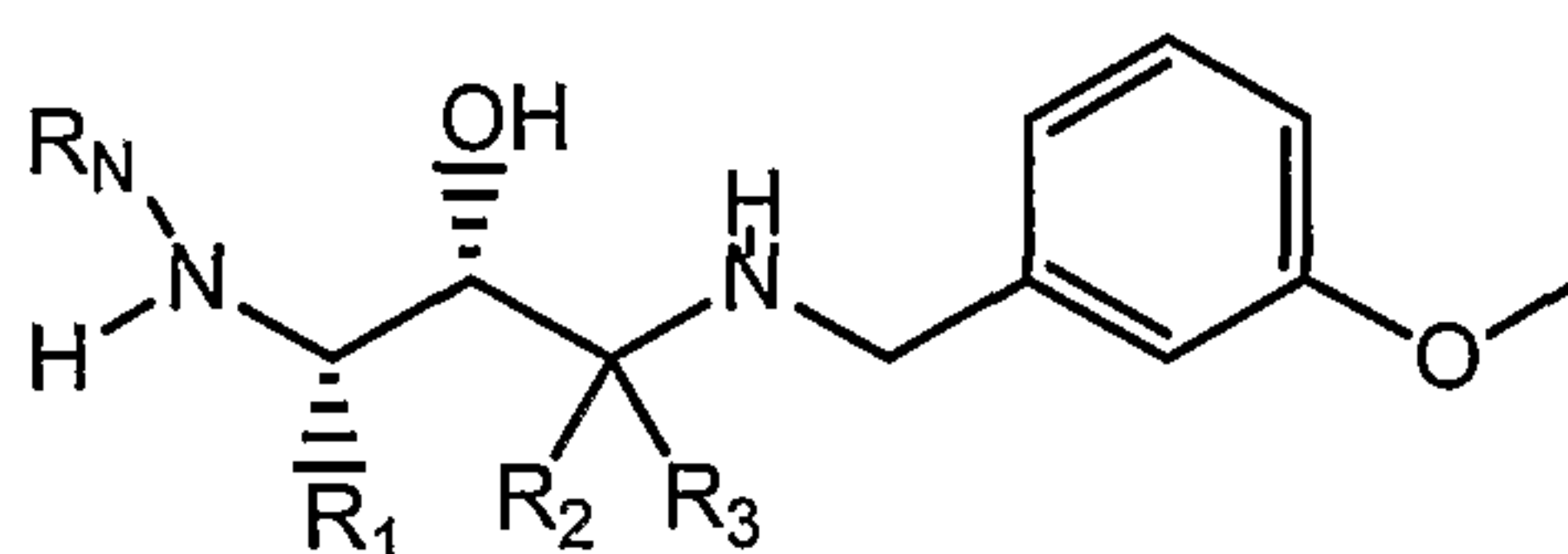
X-43

where  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{20}$  and  $R_c$  are as defined above for structure X.



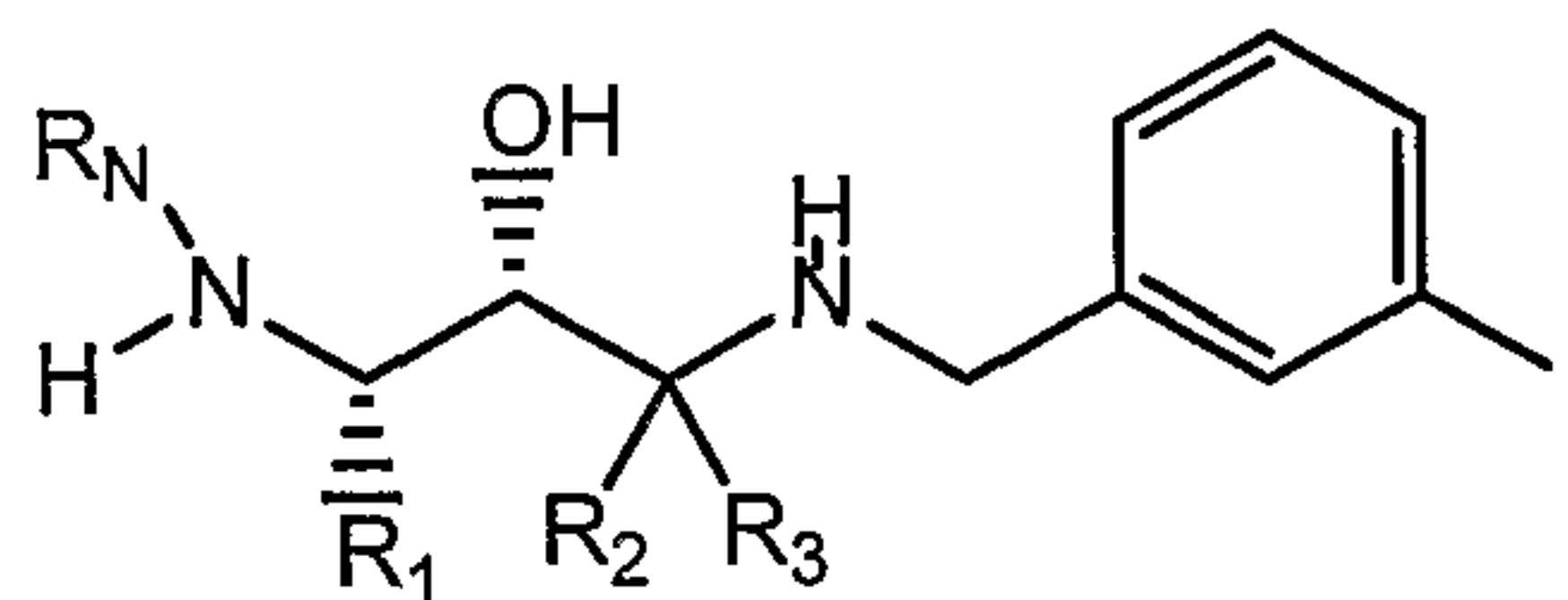
X-44

where  $R_N$ ,  $R_1$ ,  $R_2$ , and  $R_3$  are as defined above for structure X.



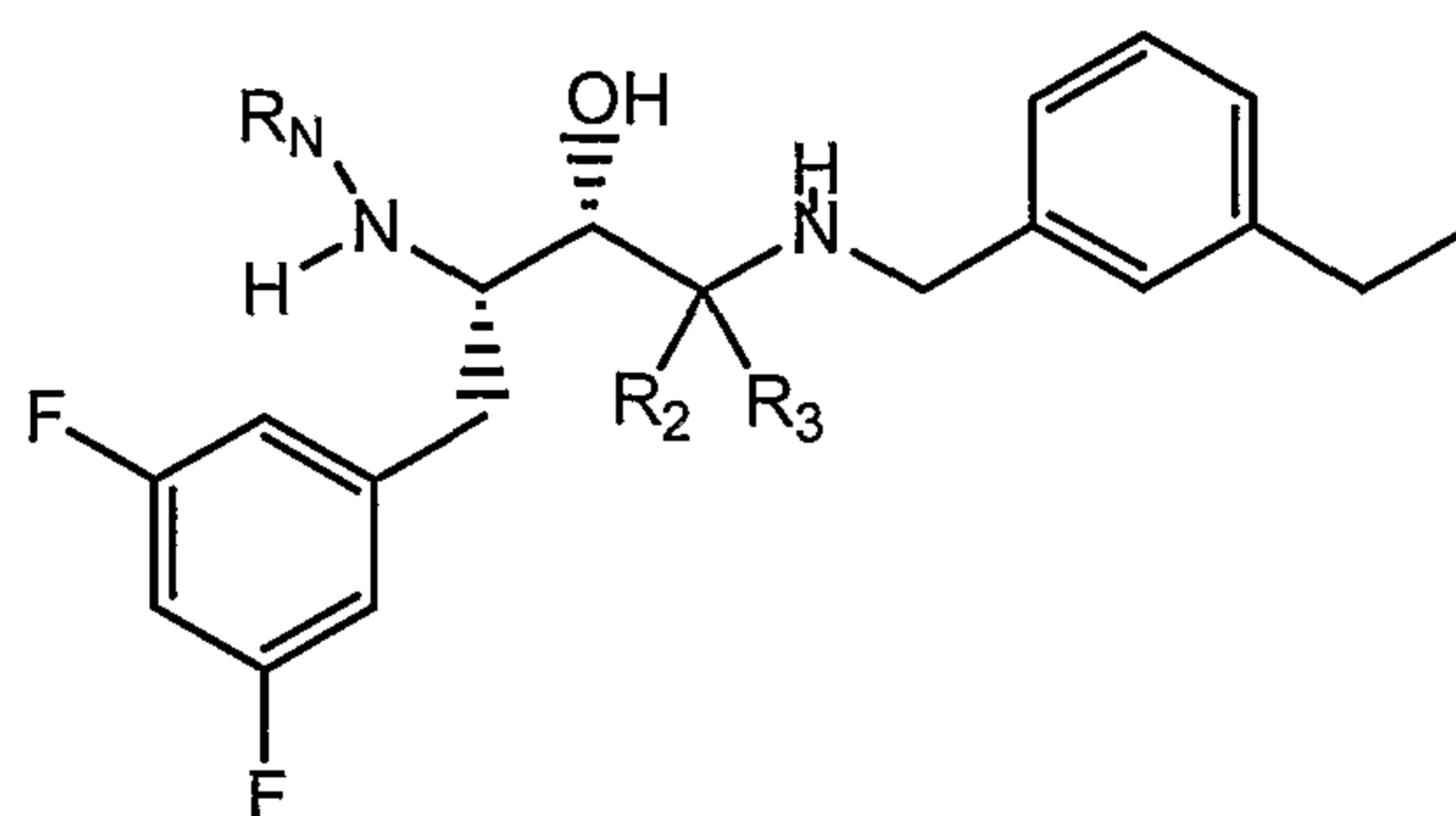
X-45

10 where  $R_N$ ,  $R_1$ ,  $R_2$ , and  $R_3$  are as defined above for structure X.



X-46

where  $R_N$ ,  $R_1$ ,  $R_2$ , and  $R_3$  are as defined above for structure X.



X-47

where  $R_N$ ,  $R_2$ , and  $R_3$  are as defined above for structure X.

- 5 Other representative compounds of the invention are
- N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(ethylthio)-2-[[isobutylsulfonyl]amino]methyl}propanamide;
- N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-(isopentylsulfonyl)-L-methioninamide;
- N~2~-[(5-chlorothiophen-2-yl)sulfonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;
- N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[[1-propylbutyl)sulfonyl]methyl}propanamide;
- N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[[1-propylbutyl)sulfonyl]methyl}propanamide;
- N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[[1-propylbutyl)sulfonyl]methyl}propanamide; and
- S-3-({(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}amino)-2-

[(isopentylsulfonyl)methyl]-3-oxopropyl} ethanethioate and the pharmaceutically acceptable salts thereof.

Still other representative compounds of the invention are selected from:

4-({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)-4-oxo-3-[(1-propylbutyl)sulfonyl]methyl}butanoic acid;

4-({(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}amino)-3-[(isopentylsulfonyl)methyl]-4-oxobutanoic acid;

methyl 4-({(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}amino)-3-[(isopentylsulfonyl)methyl]-4-oxobutanoate;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-[(isopentylsulfonyl)methyl]succinamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-[(isopentylsulfonyl)methyl]-N~4~-methylsuccinamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-[(isopentylsulfonyl)methyl]-N~4~,N~4~-dimethylsuccinamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(4,4-dimethyl-2,5-dioximidazolidin-1-yl)-2-[(1-propylbutyl)sulfonyl]methyl}propanamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(4,4-dimethyl-2,5-dioximidazolidin-1-yl)-2-[(1-propylbutyl)sulfonyl]methyl}propanamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(4,4-dimethyl-2,5-dioximidazolidin-1-yl)-2-[(1-

propylbutyl) sulfonyl]methyl}propanamide;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-3-(ethylsulfonyl)-2-[(isobutylsulfonyl) amino]methyl}propanamide; and

(2S)-N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-2-[(isopentylsulfonyl) amino]-4-(methylsulfonyl)butanamide and the pharmaceutically acceptable salts thereof.

Yet still other representative compounds of the invention are:

2-N-1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-1-[(butylsulfonyl) methyl]-2-oxoethyl acetate;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-2-hydroxy-3-[(1-propylbutyl) sulfonyl]propanamide;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-2-hydroxy-3-(isopentylsulfonyl)propanamide;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-2-hydroxy-3-[(3-methoxyphenyl) sulfonyl]propanamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-2-hydroxy-4-(phenylsulfonyl)butanamide;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-2-hydroxy-4-(isopentylsulfonyl)butanamide;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-4-(isopentylsulfonyl)-2-phenoxybutanamide;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-4-(isopentylsulfonyl)-2-(3-

methoxyphenoxy) butanamide;

3-[1-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]amino)carbonyl]-3-(isopentylsulfonyl)propoxy]benzoic acid;

methyl 3-[1-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]amino)carbonyl]-3-(isopentylsulfonyl)propoxy]benzoate;

N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-2-hydroxy-4-(phenylsulfonyl)butanamide;

N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-2-hydroxy-4-(phenylthio)butanamide;

N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-2-methoxy-4-(phenylsulfonyl)butanamide;

N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-2-methoxy-4-(phenylthio)butanamide;

N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-4-(phenylsulfonyl)-2-propoxybutanamide; and

N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-2-(benzyloxy)-4-(phenylsulfonyl)butanamide and pharmaceutically acceptable salts thereof.

Other preferred compounds of the invention are selected from:

N-[(1R)-3-(butylsulfonyl)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]propyl]-3-methyl-1H-pyrazole-5-carboxamide;

N-[(1R)-3-(butylsulfonyl)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-(trifluoromethyl)benzyl)amino]propyl]amino)carbonyl]propyl]-3-

methyl-1H-pyrazole-5-carboxamide;

N-((1R)-3-(butylsulfonyl)-1-[[[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl]amino]carbonyl]propyl)-3-methyl-1H-pyrazole-5-carboxamide;

N-((1R)-3-(butylsulfonyl)-1-[[[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl]amino]carbonyl]propyl)-3-methyl-1H-pyrazole-5-carboxamide;

N-[(1R)-3-(butylsulfonyl)-1-([[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([1-[3-(trifluoromethyl)phenyl]cyclopropyl]amino)propyl]amino]carbonyl)propyl]-3-methyl-1H-pyrazole-5-carboxamide;

(2R)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-[[methylamino]carbonyl]amino]-4-oxooctanamide;

4-butyl-N<sup>1</sup>-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N<sup>2</sup>-[[methylamino]carbonyl]-D-homoserinamide;

3-(2-butyl-1,3-dioxolan-2-yl)-N<sup>1</sup>-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N<sup>2</sup>-[[methylamino]carbonyl]-D-alaninamide;

3-(2-butyl-1,3-dioxan-2-yl)-N<sup>1</sup>-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N<sup>2</sup>-[[methylamino]carbonyl]-D-alaninamide

(2R)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4,4-difluoro-2-[[methylamino]carbonyl]amino]octanamide;

(2R)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-fluoro-2-[[methylamino]carbonyl]amino]octanamide;

(2R)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-[[methylamino]carbonyl]amino]-5-oxononanamide;

(2R)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-hydroxy-2-[[methylamino]carbonyl]aminononanamide;

(2R)-4-(2-butyl-1,3-dioxolan-2-yl)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-[[methylamino]carbonyl]aminobutanamide;

(2R)-4-(2-butyl-1,3-dioxan-2-yl)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-[[methylamino]carbonyl]aminobutanamide;

(2R)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-fluoro-2-[[methylamino]carbonyl]aminononanamide;

(2R)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5,5-difluoro-2-[[methylamino]carbonyl]aminononanamide;

3-(butylsulfonyl)-N<sup>1</sup>-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl]-N<sup>2</sup>-[[methylamino]carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N<sup>1</sup>-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl]-N<sup>2</sup>-[[methylamino]carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N<sup>1</sup>-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl]-N<sup>2</sup>-[[methylamino]carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N<sup>1</sup>-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl]-N<sup>2</sup>-[[methylamino]carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N<sup>1</sup>-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((1-[3-(trifluoromethyl)phenyl]cyclopropyl)amino)propyl]-N<sup>2</sup>-[[methylamino]carbonyl]-D-alaninamide;

4-Methyl-pyrazole-1-carboxylic acid {2-(butane-1-sulfonyl)-1-[1-(3,5-difluoro-benzyl)-3-(3-ethynyl-benzylamino)-2-hydroxy-propylcarbonyl]-ethyl}-amide;



4-Methyl-pyrazole-1-carboxylic acid {2-(butane-1-sulfonyl)-1-[1-(3,5-difluoro-benzyl)-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propylcarbamoyl]-ethyl}-amide;

4-Methyl-pyrazole-1-carboxylic acid (2-(butane-1-sulfonyl)-1-{1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propylcarbamoyl}-ethyl)-amide;

4-Methyl-pyrazole-1-carboxylic acid (2-(butane-1-sulfonyl)-1-{1-(3,5-difluoro-benzyl)-3-[1-(3-ethyny-1-phenyl)-cyclopropylamino]-2-hydroxy-propylcarbamoyl}-ethyl)-amide;

4-Methyl-pyrazole-1-carboxylic acid (2-(butane-1-sulfonyl)-1-{1-(3,5-difluoro-benzyl)-2-hydroxy-3-[1-(3-trifluoromethyl-phenyl)-cyclopropylamino]-propylcarbamoyl}-ethyl)-amide; and pharmaceutically acceptable salts thereof.

#### Definitions

All temperatures are in degrees Celsius.

TLC refers to thin-layer chromatography.

5 psi refers to pounds/in<sup>2</sup>.

HPLC refers to high pressure liquid chromatography.

THF refers to tetrahydrofuran.

DMF refers to dimethylformamide.

HOBt refers to 1-hydroxy bezotriazole hydrate.

10 NMM refers to N-methyl morpholine.

EDC refers to ethyl-1-(3-dimethylaminopropyl)carbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

NBS refers to N-bromosuccinimide.

TEA refers to triethylamine.

15 BOC refers to 1,1-dimethylethoxy carbonyl or *t*-butoxycarbonyl, -CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>.

CBZ refers to benzyloxycarbonyl, -CO<sub>2</sub>-CH<sub>2</sub>-phenyl.

TFA refers to trifluoroacetic acid, CF<sub>3</sub>COOH.

CDI refers to 1,1'-carbonyldiimidazole.

20 Saline refers to an aqueous saturated sodium chloride solution.

Chromatography (column and flash chromatography) refers to purification/separation of compounds expressed as (support, eluent). It is understood that the appropriate fractions are pooled and concentrated to give the desired compound(s).

5       CMR refers to C-13 magnetic resonance spectroscopy, chemical shifts are reported in ppm ( $\delta$ ) downfield from TMS.

NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm ( $\delta$ ) downfield from TMS.

10       - $\phi$  refers to phenyl ( $C_6H_5$ ).

MS refers to mass spectrometry expressed as m/e, m/z or mass/charge unit.  $MH^+$  refers to the positive ion of a parent plus a hydrogen atom. EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom bombardment.

15       HRMS refers to high resolution mass spectrometry.

Ether refers to diethyl ether.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

20       When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

TBDMSCl refers to *t*-butyldimethylsilyl chloride.

25       TBDMSOTf refers to *t*-butyldimethylsilyl trifluosulfonic acid ester.

Trisomy 21 refers to Down's Syndrome.

EDC refers to 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide.

30       DIPMAP refers to (*R,R*)-1,2-bis[(*o*-methoxyphenyl)-phenylphosphin]ethane.

MeDuPhos refers to 1,2-bis ((*2S,5S*)-2,5-dimethylphospholano)benzene.

EtDuPhos refers to 1,2-bis ((*2S,5S*)-2,5-diethylphospholano)benzene.

Binaphane refers to (S,S)-1,2-Bis{(S)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]phosphino}benzene.

f-Binaphane refers to (R,R)-1,1'-Bis{(R)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]phosphino}ferrocene.

5 Me-KetalPhos refers to 1,2-Bis-[(2S,3S,4S,5S)-3,4-O-isopropylidene-3,4-dihydroxy-2,5-dimethyl]benzene.

Me-f-KetalPhos refers to 1,1'-Bis-[(2S,3S,4S,5S)-2,5-dimethyl-3,4-O-isopropylidene-3,4-dihydroxyphospholanyl]ferrocene.

10 Et-f-KetalPhos refers to 1,1'-Bis-[(2S,3S,4S,5S)-2,5-diethyl-3,4-O-isopropylidene-3,4-dihydroxyphospholanyl]ferrocene

BINAP refers to R-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

15 DIOP refers to (R,R)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane.

BPPFA refers to R-1-[(S)-1'2-bisdiphenylphosphino]ferrocenyl]- ethyldimethylamine.

20 BPPM refers to (2S,4S)-1-tert-butoxycarbonyl-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine.

CHIRAPHOS refers to (S,S)-2,3-bis(diphenylphosphino)butane.

PROPHOS refers to (S)-1,2-bis(diphenylphosphino)propane.

25 NORPHOS refers to (R,R)-5,6-bis(diphenylphosphino)-2-norbornene.

CYCLOPHOS refers to R-1-cyclohexyl-1,2-bis(diphenylphosphino)ethane.

BDPP refers to (2S,4S)-bis(diphenylphosphine) pentane.

30 DEGPHOS refers to 1-substituted (S,S)-3,4-bis(diphenylphosphino)- pyrrolidine.

PNNP refers to N,N'-bis(diphenylphosphino)-N,N'-bis[(R)-1-phenyl]ethylenediamine.

LDA refers to lithium diisopropylamide.

LiHMDS refers to lithium hexamethyldisilazane.

KHMDS refers to potassium hexamethyldisilazane.

By the terms "alkyl" and "C<sub>1</sub>-C<sub>6</sub> alkyl" is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. It is understood that in cases where an alkyl chain of a substituent (e.g. of an alkyl, alkoxy or alkenyl group) is shorter or longer than 6 carbons, it will be so indicated in the second "C" as, for example, "C<sub>1</sub>-C<sub>10</sub>" indicates a maximum of 10 carbons.

By the terms "alkoxy" and "C<sub>1</sub>-C<sub>6</sub> alkoxy" is meant straight or branched chain alkyl groups having 1-6 carbon atoms, attached through at least one divalent oxygen atom, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, and 3-methylpentoxy.

By the term "halogen" is meant fluorine, bromine, chlorine, and/or iodine.

The terms "alkenyl" and "C<sub>2</sub>-C<sub>6</sub> alkenyl" refer to straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and from one to three double bonds and includes, for example, ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like.

The terms "alkynyl" and "C<sub>2</sub>-C<sub>6</sub> alkynyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and one or two triple bonds and includes ethynyl, propynyl, butynyl, pentyn-2-yl and the like.

As used herein, the term "cycloalkyl" refers to saturated carbocyclic radicals having three to twelve carbon atoms. The cycloalkyl can be monocyclic, or a polycyclic fused system. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl groups herein are unsubstituted or, as specified, substituted in one

or more substitutable positions with various groups. For example, such cycloalkyl groups may be optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl or di(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl.

By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl), which is optionally mono-, di-, or trisubstituted. Preferred aryl groups of the invention are phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, tetralinyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl. Even more preferred aryl groups are phenyl and naphthyl. The most preferred aryl group is phenyl.

The aryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such aryl groups may be optionally substituted with, for example, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, -COOH, -C(=O)O(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(=O)NH<sub>2</sub>, -C(=O)N(mono- or di-C<sub>1</sub>-C<sub>6</sub>alkyl), -S(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-C(=O)(C<sub>1</sub>-C<sub>6</sub>alkyl), -NH-C(=O)-(C<sub>1</sub>-C<sub>6</sub>alkyl), -N(C<sub>1</sub>-C<sub>6</sub>alkyl)-C(=O)-(C<sub>1</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -N(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -NH-C(=O)NH<sub>2</sub>, -NH-C(=O)N(mono- or di-C<sub>1</sub>-C<sub>6</sub>alkyl), -NH(C<sub>1</sub>-C<sub>6</sub>alkyl)-C(=O)-NH<sub>2</sub> or -NH(C<sub>1</sub>-C<sub>6</sub>alkyl)-C(=O)-N-(mono- or di-C<sub>1</sub>-C<sub>6</sub>alkyl).

By "heteroaryl" is meant one or more aromatic ring systems of 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four

heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heteroaryl groups of the invention include pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanlyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranlyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranlyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridinyl-N-oxide, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N-oxide, indazolyl N-oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide.

The heteroaryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions

with various groups. For example, such heteroaryl groups may be optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl or di(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, -COOH, -C(=O)O(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(=O)NH<sub>2</sub>, -C(=O)N(mono- or di-C<sub>1</sub>-C<sub>6</sub>alkyl), -S(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-C(=O)(C<sub>1</sub>-C<sub>6</sub>alkyl), -NH-C(=O)-(C<sub>1</sub>-C<sub>6</sub>alkyl), -N(C<sub>1</sub>-C<sub>6</sub>alkyl)-C(=O)-(C<sub>1</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -N(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -NH-C(=O)NH<sub>2</sub>, -NH-C(=O)N(mono- or di-C<sub>1</sub>-C<sub>6</sub>alkyl), -NH(C<sub>1</sub>-C<sub>6</sub>alkyl)-C(=O)-NH<sub>2</sub> or -NH(C<sub>1</sub>-C<sub>6</sub>alkyl)-C(=O)-N-(mono- or di-C<sub>1</sub>-C<sub>6</sub>alkyl).

By the terms "heterocycle", "heterocycloalkyl" and "heterocyclyl" is meant one or more carbocyclic ring systems of 4-, 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heterocycles of the invention include morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide.

The heterocycle groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such heterocycle groups may be optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl,

C<sub>1</sub>-C<sub>6</sub> haloalkoxy, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl or =O.

APP, amyloid precursor protein, is defined as any APP polypeptide, including APP variants, mutations, and isoforms, for example, as disclosed in U.S. Patent No. 5,766,846.

A-beta, amyloid beta peptide, is defined as any peptide resulting from beta-secretase mediated cleavage of APP, including peptides of 39, 40, 41, 42, and 43 amino acids, and extending from the beta-secretase cleavage site to amino acids 39, 40, 41, 42, or 43.

Beta-secretase (BACE1, Asp2, Memapsin 2) is an aspartyl protease that mediates cleavage of APP at the amino-terminal edge of A-beta. Human beta-secretase is described, for example, in W000/17369.

Pharmaceutically acceptable refers to those properties and/or substances that are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

A therapeutically effective amount is defined as an amount effective to reduce or lessen at least one symptom of the disease being treated or to reduce or delay onset of one or more clinical markers or symptoms of the disease.

### **Pharmaceutical Compositions**

Compositions containing therapeutically effective amounts of the compounds are provided of the invention. The compounds are preferably formulated into suitable pharmaceutical preparations such as tablets, capsules or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures known in the art.



A unit dose of about 0.1 to 1000 mg of a compound or mixture of compounds of the invention or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in those compositions or preparations is such that a suitable dosage in the range indicated is obtained. The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.1 to about 1000 mg the desired amount of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Preferably, the compound of the invention is employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

To prepare compositions, one or more compounds of the invention are mixed with a suitable pharmaceutically acceptable carrier. Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. Liposomal suspensions may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating at least one symptom of the disease, disorder, or condition treated and may be empirically determined.

Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action or have other action. The compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients.

In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as Tween®, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as salts of the compounds or prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

The concentration of the compounds in the composition is effective for delivery of an amount that, upon administration, ameliorates one or more symptoms of the disorder for which the compound is administered. Typically, the compositions are formulated for single dosage administration.

The compounds of the invention may be prepared with carriers that protect them against rapid elimination from the body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, microencapsulated delivery systems. The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration

may be determined empirically by testing the compounds in known *in vitro* and *in vivo* model systems for the treated disorder.

The compositions can be enclosed in ampoules, disposable syringes, or multiple or single dose vials made of glass, plastic, or other suitable material. Such enclosed compositions can be provided in kits.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the active compound, the dosage schedule, and amount administered, as well as other factors known to those of skill in the art.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens may be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

If oral administration is desired, the compound may be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

Oral compositions will generally include an inert diluent or an edible carrier and may be compressed into tablets or enclosed in gelatin capsules. For the purpose of oral therapeutic administration, the active compound or compounds  
5 can be incorporated with excipients and used in the form of tablets, capsules or troches. Pharmaceutically compatible binding agents and adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches, and the like can  
10 contain any of the following ingredients or compounds of a similar nature: a binder, such as, but not limited to, gum tragacanth, acacia, corn starch, or gelatin; an excipient such as microcrystalline cellulose, starch, or lactose; a disintegrating agent such as, but not limited to, alginic acid  
15 or corn starch; a lubricant such as, but not limited to, magnesium stearate; a gildant, such as, but not limited to, colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and a flavoring agent such as peppermint, methyl salicylate, or fruit flavoring.

20 When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials that modify the physical form of the dosage unit, for example, coatings of sugar or other enteric  
25 agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, chewing gum, or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent or certain preservatives, dyes and colorings, and flavors.

30 The active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the

following components: a sterile diluent, such as water for injection, saline solution, fixed oil, a naturally occurring vegetable oil such as sesame oil, coconut oil, peanut oil, cottonseed oil, and the like, or a synthetic fatty vehicle such as ethyl oleate or the like, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antimicrobial agents, such as benzyl alcohol or methyl parabens; antioxidants, such as ascorbic acid or sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates, or phosphates; and agents for the adjustment of tonicity, such as sodium chloride or dextrose. Parenteral preparations can be enclosed in ampoules, disposable syringes, or multiple dose vials made of glass, plastic, or other suitable material. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, polypropyleneglycol, and mixtures thereof. Liposomal suspensions, including tissue-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as described in U.S. Pat. No. 4,522,811.

The active compounds may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid, and others. Methods for

preparation of such formulations are known to those skilled in the art.

### **Methods of the Invention**

5           The compounds of the invention, and pharmaceutically acceptable salts thereof, are useful for treating humans or animals suffering from a condition characterized by a pathological form of beta-amyloid peptide, such as beta-amyloid plaques, and for helping to prevent or delay the onset of such  
10 a condition. For example, the compounds are useful for treating Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from  
15 MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative  
20 dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type Alzheimer's disease. The compounds and  
25 compositions of the invention are particularly useful for treating Alzheimer's disease. When treating these diseases, the compounds of the invention can either be used individually or in combination, as is best for the patient.

As used herein, the term "treating" means that the  
30 compounds of the invention can be used in humans with at least a tentative diagnosis of disease. The compounds of the invention will delay or slow the progression of the disease thereby giving the individual a longer and more useful life span.

The term "preventing" means that the compounds of the invention are useful when administered to a patient who has not been diagnosed as having or possibly having the disease at the time of administration, but who would normally be expected to  
5 develop the disease or be at increased risk for the disease. The compounds of the invention will slow the development of disease symptoms, delay the onset of the disease, or prevent the individual from developing the disease. Preventing thus includes administration of the compounds of the invention to  
10 those individuals thought to be predisposed to the disease due to age, familial history, genetic or chromosomal abnormalities, and/or due to the presence of one or more biological markers for the disease, such as a known genetic mutation of APP or APP cleavage products in brain tissues or fluids.

15 In treating or preventing the above diseases, the compounds of the invention are administered in a therapeutically effective amount. The therapeutically effective amount will vary depending on the particular compound used and the route of administration, as is known to those  
20 skilled in the art.

In treating a patient displaying any of the diagnosed above conditions a physician may administer a compound of the invention immediately and continue administration indefinitely, as needed. In treating patients who are not diagnosed as  
25 having Alzheimer's disease, but who are believed to be at substantial risk for Alzheimer's disease, the physician should preferably start treatment when the patient first experiences early pre-Alzheimer's symptoms such as, memory or cognitive problems associated with aging. In addition, there are some  
30 patients who may be determined to be at risk for developing Alzheimer's through the detection of a genetic marker such as APOE4 or other biological indicators that are predictive for Alzheimer's disease. In these situations, even though the patient does not have symptoms of the disease, administration

of the compounds of the invention may be started before symptoms appear, and treatment may be continued indefinitely to prevent or delay the outset of the disease.

#### 5 **Modes of Administration, Dosage Forms and Amounts**

The compounds of the invention can be administered orally, parenterally (IV, IM, depo-IM, SQ and depo-SQ), sublingually, intranasally (inhalation), intrathecally, topically and rectally. Dosage forms known to those skilled in the art are  
10 suitable for delivery of the novel substituted amines X of the invention.

Compositions are provided that contain therapeutically effective amounts of the compounds of the invention. The compounds are preferably formulated into suitable  
15 pharmaceutical preparations such as tablets, capsules, or elixirs for oral administration or in sterile solutions or suspensions for parenteral administration. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures known in the art.

20 About 1 to 500 mg of a compound or mixture of compounds of the invention or a physiologically acceptable salt or ester is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical  
25 practice. The amount of active substance in those compositions or preparations is such that a suitable dosage in the range indicated is obtained. The compositions are preferably formulated in a unit dosage form, each dosage containing from about 2 to about 100 mg, more preferably about 10 to about 30  
30 mg of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce



the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

To prepare compositions, one or more compounds of the invention are mixed with a suitable pharmaceutically acceptable carrier. Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion, or the like. Liposomal suspensions may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for lessening or ameliorating at least one symptom of the disease, disorder, or condition treated and may be empirically determined.

Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, or have another action. The compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients.

Where the compounds exhibit insufficient solubility, methods for solubilizing may be used. Such methods are known and include, but are not limited to, using cosolvents such as dimethylsulfoxide (DMSO), using surfactants such as Tween®, and dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as salts or prodrugs may also be used in formulating effective pharmaceutical compositions.

The concentration of the compound is effective for delivery of an amount upon administration that lessens or

ameliorates at least one symptom of the disorder for which the compound is administered. Typically, the compositions are formulated for single dosage administration.

5 The compounds of the invention may be prepared with carriers that protect them against rapid elimination from the body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, microencapsulated delivery systems. The active compound is included in the pharmaceutically acceptable carrier  
10 in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in known *in vitro* and *in vivo* model systems for the treated disorder.

15 The compounds and compositions of the invention can be enclosed in multiple or single dose containers. The enclosed compounds and compositions can be provided in kits, for example, including component parts that can be assembled for use. For example, a compound inhibitor in lyophilized form and  
20 a suitable diluent may be provided as separated components for combination prior to use. A kit may include a compound inhibitor and a second therapeutic agent for co-administration. The inhibitor and second therapeutic agent may be provided as separate component parts. A kit may include a plurality of  
25 containers, each container holding one or more unit dose of the compound of the invention. The containers are preferably adapted for the desired mode of administration, including, but not limited to tablets, gel capsules, sustained-release capsules, and the like for oral administration; depot  
30 products, pre-filled syringes, ampules, vials, and the like for parenteral administration; and patches, medipads, creams, and the like for topical administration.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and

excretion rates of the active compound, the dosage schedule, and amount administered as as other factors known to those of skill in the art.

The active ingredient may be administered at once, or may  
5 be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test  
10 data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional  
15 judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

If oral administration is desired, the compound should be  
20 provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in  
25 combination with an antacid or other such ingredient.

Oral compositions will generally include an inert diluent or an edible carrier and may be compressed into tablets or enclosed in gelatin capsules. For the purpose of oral  
therapeutic administration, the active compound or compounds  
30 can be incorporated with excipients and used in the form of tablets, capsules, or troches. Pharmaceutically compatible binding agents and adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches, and the like can contain any of the following ingredients or compounds of a similar nature: a binder such as, but not limited to, gum tragacanth, acacia, corn starch, or gelatin; an excipient such as microcrystalline cellulose, starch, or lactose; a disintegrating agent such as, but not limited to, alginic acid and corn starch; a lubricant such as, but not limited to, magnesium stearate; a gildant, such as, but not limited to, colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and a flavoring agent such as peppermint, methyl salicylate, or fruit flavoring.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials, which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings, and flavors.

The active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent such as water for injection, saline solution, fixed oil, a naturally occurring vegetable oil such as sesame oil, coconut oil, peanut oil, cottonseed oil, and the like, or a synthetic fatty vehicle such as ethyl oleate, and the like, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antimicrobial agents such as benzyl alcohol and methyl parabens; antioxidants such as ascorbic acid and sodium bisulfite; chelating agents

such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates, and phosphates; and agents for the adjustment of tonicity such as sodium chloride and dextrose. Parenteral preparations can be enclosed in ampoules, disposable  
5 syringes, or multiple dose vials made of glass, plastic, or other suitable material. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Where administered intravenously, suitable carriers include physiological saline, phosphate buffered saline (PBS),  
10 and solutions containing thickening and solubilizing agents such as glucose, polyethylene glycol, polypropyleneglycol, and mixtures thereof. Liposomal suspensions including tissue-targeted liposomes may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to  
15 methods known for example, as described in U.S. Patent No. 4,522,811.

The active compounds may be prepared with carriers that protect the compound against rapid elimination from the body, such as time-release formulations or coatings. Such carriers  
20 include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid, and the like. Methods for  
25 preparation of such formulations are known to those skilled in the art.

The compounds of the invention can be administered orally, parenterally (IV, IM, depo-IM, SQ, and depo-SQ), sublingually, intranasally (inhalation), intrathecally, topically, or  
30 rectally. Dosage forms known to those skilled in the art are suitable for delivery of the compounds of the invention.

Compounds of the invention may be administered enterally or parenterally. When administered orally, compounds of the invention can be administered in usual dosage forms for oral

administration as is known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions, and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so that the compounds of the invention need to be administered only once or twice daily.

The oral dosage forms are administered to the patient 1, 2, 3, or 4 times daily. It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily. Hence, it is preferred that the compounds of the invention be administered in oral dosage form. It is preferred that whatever oral dosage form is used, that it be designed so as to protect the compounds of the invention from the acidic environment of the stomach. Enteric coated tablets are known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also known to those skilled in the art.

When administered orally, an administered amount therapeutically effective to inhibit beta-secretase activity, to inhibit A-beta production, to inhibit A-beta deposition, or to treat or prevent AD is from about 0.1 mg/day to about 1,000 mg/day. It is preferred that the oral dosage is from about 1 mg/day to about 100 mg/day. It is more preferred that the oral dosage is from about 5 mg/day to about 50 mg/day. It is understood that while a patient may be started at one dose, that dose may be varied over time as the patient's condition changes.

Compounds of the invention may also be advantageously delivered in a nano crystal dispersion formulation. Preparation of such formulations is described, for example, in U.S. Patent 5,145,684. Nano crystalline dispersions of HIV protease inhibitors and their method of use are described in US

6,045,829. The nano crystalline formulations typically afford greater bioavailability of drug compounds.

The compounds of the invention can be administered parenterally, for example, by IV, IM, depo-IM, SC, or depo-SC. 5 When administered parenterally, a therapeutically effective amount of about 0.5 to about 100 mg/day, preferably from about 5 to about 50 mg daily should be delivered. When a depo formulation is used for injection once a month or once every two weeks, the dose should be about 0.5 mg/day to about 50 10 mg/day, or a monthly dose of from about 15 mg to about 1,500 mg. In part because of the forgetfulness of the patients with Alzheimer's disease, it is preferred that the parenteral dosage form be a depo formulation.

The compounds of the invention can be administered 15 sublingually. When given sublingually, the compounds of the invention should be given one to four times daily in the amounts described above for IM administration.

The compounds of the invention can be administered intranasally. When given by this route, the appropriate dosage 20 forms are a nasal spray or dry powder, as is known to those skilled in the art. The dosage of the compounds of the invention for intranasal administration is the amount described above for IM administration.

The compounds of the invention can be administered 25 intrathecally. When given by this route the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art. The dosage of the compounds of the invention for intrathecal administration is the amount described above for IM administration.

30 The compounds of the invention can be administered topically. When given by this route, the appropriate dosage form is a cream, ointment, or patch. Because of the amount of the compounds of the invention to be administered, the patch is preferred. When administered topically, the dosage is from

about 0.5 mg/day to about 200 mg/day. Because the amount that can be delivered by a patch is limited, two or more patches may be used. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the compounds of the invention be delivered as is known to those skilled in the art. The compounds of the invention can be administered rectally by suppository as is known to those skilled in the art. When administered by suppository, the therapeutically effective amount is from about 0.5 mg to about 500 mg.

The compounds of the invention can be administered by implants as is known to those skilled in the art. When administering a compound of the invention by implant, the therapeutically effective amount is the amount described above for depot administration.

The invention here is the new compounds of the invention and new methods of using the compounds of the invention. Given a particular compound of the invention and a desired dosage form, one skilled in the art would know how to prepare and administer the appropriate dosage form.

The compounds of the invention are used in the same manner, by the same routes of administration, using the same pharmaceutical dosage forms, and at the same dosing schedule as described above, for treating patients with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia



associated with cortical basal degeneration , diffuse Lewy body type of Alzheimer's disease.

The compounds of the invention can be used in combination, with each other or with other therapeutic agents or approaches used to treat or prevent the conditions listed above. Such agents or approaches include: acetylcholine esterase inhibitors such as tacrine (tetrahydroaminoacridine, marketed as COGNEX®), donepezil hydrochloride, (marketed as Aricept® and rivastigmine (marketed as Exelon®); gamma-secretase inhibitors; anti-inflammatory agents such as cyclooxygenase II inhibitors; anti-oxidants such as Vitamin E and ginkgolides; immunological approaches, such as, for example, immunization with A-beta peptide or administration of anti-A-beta peptide antibodies; statins; and direct or indirect neurotropic agents such as Cerebrolysin®, AIT-082 (Emilieu, 2000, *Arch. Neurol.* 57:454), and other neurotropic agents of the future.

In addition, the compounds of the invention can also be used with inhibitors of P-glycoprotein (P-gp). The use of P-gp inhibitors is known to those skilled in the art. See for example, *Cancer Research*, 53, 4595-4602 (1993), *Clin. Cancer Res.*, 2, 7-12 (1996), *Cancer Research*, 56, 4171-4179 (1996), International Publications WO99/64001 and WO01/10387. The important thing is that the blood level of the P-gp inhibitor be such that it exerts its effect in inhibiting P-gp from decreasing brain blood levels of the compounds of the invention. To that end the P-gp inhibitor and the compounds of the invention can be administered at the same time, by the same or different route of administration, or at different times. The important thing is not the time of administration but having an effective blood level of the P-gp inhibitor.

Suitable P-gp inhibitors include cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506,

VX-710, LY335979, PSC-833, GF-102,918 and other steroids. It is to be understood that additional agents will be found that do the same function and are also considered to be useful.

The P-gp inhibitors can be administered orally,  
5 parenterally, (IV, IM, IM-depo, SQ, SQ-depo), topically, sublingually, rectally, intranasally, intrathecally and by implant.

The therapeutically effective amount of the P-gp inhibitors is from about 0.1 to about 300 mg/kg/day, preferably  
10 about 0.1 to about 150 mg/kg daily. It is understood that while a patient may be started on one dose, that dose may have to be varied over time as the patient's condition changes.

When administered orally, the P-gp inhibitors can be administered in usual dosage forms for oral administration as  
15 is known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as as liquid dosage forms such as solutions, suspensions and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so  
20 that the P-gp inhibitors need to be administered only once or twice daily. The oral dosage forms are administered to the patient one thru four times daily. It is preferred that the P-gp inhibitors be administered either three or fewer times a day, more preferably once or twice daily. Hence, it is  
25 preferred that the P-gp inhibitors be administered in solid dosage form and further it is preferred that the solid dosage form be a sustained release form which permits once or twice daily dosing. It is preferred that what ever dosage form is used, that it be designed so as to protect the P-gp inhibitors  
30 from the acidic environment of the stomach. Enteric coated tablets are known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also known to those skilled in the art.

In addition, the P-gp inhibitors can be administered parenterally. When administered parenterally they can be administered IV, IM, depo-IM, SQ or depo-SQ.

5 The P-gp inhibitors can be given sublingually. When given sublingually, the P-gp inhibitors should be given one thru four times daily in the same amount as for IM administration.

10 The P-gp inhibitors can be given intranasally. When given by this route of administration, the appropriate dosage forms are a nasal spray or dry powder as is known to those skilled in the art. The dosage of the P-gp inhibitors for intranasal administration is the same as for IM administration.

15 The P-gp inhibitors can be given intrathecally. When given by this route of administration the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art.

20 The P-gp inhibitors can be given topically. When given by this route of administration, the appropriate dosage form is a cream, ointment or patch. Because of the amount of the P-gp inhibitors needed to be administered the patch is preferred. However, the amount that can be delivered by a patch is limited. Therefore, two or more patches may be required. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the P-gp inhibitors be delivered as is known to those skilled in the art.

The P-gp inhibitors can be administered rectally by suppository as is known to those skilled in the art.

The P-gp inhibitors can be administered by implants as is known to those skilled in the art.

30 There is nothing novel about the route of administration nor the dosage forms for administering the P-gp inhibitors. Given a particular P-gp inhibitor, and a desired dosage form, one skilled in the art would know how to prepare the appropriate dosage form for the P-gp inhibitor.

It should be apparent to one skilled in the art that the exact dosage and frequency of administration will depend on the particular compound administered, the particular condition being treated, the severity of the condition being treated, the  
5 age, weight, general physical condition of the particular patient, other medication the individual may be taking as is known to those skilled in the art.

The invention provides compounds, compositions, and methods for inhibiting beta-secretase enzyme activity and A-  
10 beta peptide production. Inhibition of beta-secretase enzyme activity halts or reduces the production of A-beta from APP and reduces or eliminates the formation of beta-amyloid deposits in the brain.

The invention provides compounds, compositions, kits, and  
15 methods for inhibiting beta-secretase enzyme activity and A-beta peptide production. Inhibition of beta-secretase enzyme activity halts or reduces the production of A-beta from APP and reduces or eliminates the formation of beta-amyloid deposits in the brain.

20 The invention provides compounds that are useful in treating and preventing Alzheimer's disease. The compounds of the invention are made by methods known to those skilled in the art from starting materials either known to those skilled in the art, commercially available and/or that can be prepared  
25 readily using literature methods. The process chemistry is known to those skilled in the art. A general process to prepare the compounds of formula X is set forth in SCHEME A. The chemistry is straight forward and in summary involves the steps of N-protecting the amino acid (I) starting material to  
30 produce the corresponding protected amino acid (II), reaction of the protected amino acid (II) with diazomethane followed by work-up as described below to add a carbon atom to produce the corresponding protected compound (III), reduction of the protected halide to the corresponding alcohol (IV), formation

of the corresponding epoxide (V), opening of the epoxide (V) with a C-terminal amine,  $R_C-NH_2$  (VI) to produce the corresponding protected alcohol (VII) which then has the nitrogen protecting group removed to produce the corresponding amine (VIII), which is then reacted with an amide forming agent such as, for example,  $(R_N-)_2O$  or  $R_N-X$  or  $R_N-OH$  (IX) to produce the compounds of formula X. One skilled in the art will appreciate that these are all known reactions in organic chemistry. A chemist skilled in the art, knowing the chemical structure of the biologically active substituted amine end product X of the invention would be able to prepare them by known methods from known starting materials without any additional information. The explanation below therefore is not necessary but is deemed helpful to those skilled in the art who desire to make the compounds of the invention.

The backbone of the compounds of the invention can be considered a hydroxyethylamine moiety,  $-NH-CH(R)-CH(OH)-$ . It can be prepared by methods disclosed in the literature and known to those skilled in the art. For example, *J. Med. Chem.*, 36, 288-291 (1993), *Tetrahedron Letters*, 28, 5569-5572 (1987), *J. Med. Chem.*, 38, 581-584 (1995) and *Tetrahedron Letters*, 38, 619-620 (1997) and WO 02/02506 all disclose processes to prepare hydroxyethylamine type compounds and/or their intermediates.

SCHEME A sets forth a general method used in the invention to prepare the appropriately substituted amines X. The compounds of the invention are prepared by starting with the corresponding amino acid (I). The amino acids (I) are known to those skilled in the art or can be readily prepared by methods known to those skilled in the art. The compounds of the invention have at least two chiral centers, which give 2 sets of diastereomers, each of which is racemic for a total of at least four stereoisomers. While biologically active end products result from all stereoisomers, the (S,R) configuration

is preferred. The first of these chiral centers (the carbon carrying  $R_1$ ) derives from the amino acid starting material (I). It is preferred to commercially obtain or produce the desired enantiomer rather than produce an enantiomerically impure mixture and then have to separate out the desired enantiomer. Thus it is preferred to start the process with enantiomerically pure (S)-amino acid (I) of the same configuration as that of the desired X product.

10 In Scheme A, the protection of free amine (I) to produce the (S)-protected amino acid (II) is depicted. Amino protecting groups are known to those skilled in the art. See for example, "Protecting Groups in Organic Synthesis", John Wiley and sons, New York, N.Y., 1981, Chapter 7; "Protecting Groups in Organic Chemistry", Plenum Press, New York, N.Y., 1973, Chapter 2. The function of the amino protecting group is to protect the free amino functionality ( $-NH_2$ ) during subsequent reactions on the (S)-amino acid (I) which would not proceed either because the amino group would react and be functionalized in a way that is inconsistent with its need to be free for subsequent reactions or the free amino group would interfere in the reaction. When the amino protecting group is no longer needed, it is removed by methods known to those skilled in the art. By definition the amino protecting group must be readily removable as is known to those skilled in the art by methods known to those skilled in the art. Suitable amino PROTECTING GROUPS include *t*-butoxycarbonyl, benzyloxycarbonyl, formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-ethoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl; 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-

nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-5 methylcycoopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycabonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl, fluorenylmethoxycarbonyl, 10 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, 15 isobronnyloxycarbonyl, 1-piperidyloxycarbonyl, 9-fluoroenylmethyl carbonate,  $-\text{CH}-\text{CH}=\text{CH}_2$  and phenyl-C(=N)-H.

It is preferred that the protecting group be *t*-butoxycarbonyl (BOC) and/or benzyloxycarbony (CBZ), it is more preferred that the protecting group be *t*-butoxycarbonyl. One 20 skilled in the art will understand the preferred methods of introducing a *t*-butoxycarbonyl or benzyloxycarbonyl protecting group and may additionally consult T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry, John Wiley and Sons, 1991 for guidance.

25 The (S)-protected amino acid (II) is transformed to the corresponding (S)-protected compound (III) by two different methods depending on nature of R<sub>2</sub> and R<sub>3</sub>.

R<sub>2</sub> and R<sub>3</sub> can be the same or different. It is preferred that R<sub>2</sub> and R<sub>3</sub> both be -H. If R<sub>2</sub> and R<sub>3</sub> are not the same, an 30 additional chiral or stereogenic center is added to the molecule. To produce compounds of formula (III) where R<sub>2</sub> and R<sub>3</sub> are both -H, the (S)-protected amino acid (II) is reacted with diazomethane, as is known to those skilled in the art, followed by reaction with a compound of the formula H-X<sub>1</sub> to

produce the (S)-protected compound (III).  $X_1$  includes -Cl, -Br, -I, -O-tosylate, -O-mesylate, -O-nosylate and -O-brosylate. It is preferred that  $-X_1$  be -Br or -Cl. Suitable reaction conditions include running the reaction in inert solvents, such as but not limited to ether, tetrahydrofuran and the like. The reactions from the (S)-protected amino acid (II) to the (S)-protected compound (III) are carried out for a period of time between 10 minutes and 1 day and at temperatures ranging from about  $-78^\circ$  to about  $20-25^\circ$ . It is preferred to conduct the reactions for a period of time between 1-4 hours and at temperatures between  $-30^\circ$  to  $-10^\circ$ . This process adds one methylene group.

Alternatively, the (S)-protected compounds of formula (III) can be prepared by first converting the (S)-protected amino acid (II) to a corresponding methyl or ethyl ester, according to methods established in the art, followed by treatment with a reagent of formula  $X_1-C(R_2)(R_3)-X_1$  and a strong metal base. The base serves to affect a halogen-metal exchange, where the  $-X_1$  undergoing exchange is a halogen selected from chlorine, bromine or iodine. The nucleophilic addition to the ester derivative gives directly the (S)-protected compound (III). Suitable bases include, but are not limited to the alkylolithiums including, for example, *sec*-butyllithium, *n*-butyllithium, and *t*-butyllithium. The reactions are preferably conducted at low temperature, such as  $-78^\circ$ . Suitable reaction conditions include running the reaction in inert solvents, such as but not limited to, ether, tetrahydrofuran and the like. Where  $R_2$  and  $R_3$  are both hydrogen, then examples of  $X_1-C(R_2)(R_3)-X_1$  include dibromomethane, diiodomethane, chloriodomethane, bromiodomethane and bromochloromethane. One skilled in the art knows the preferred conditions required to conduct this reaction. Furthermore, if  $R_2$  and/or  $R_3$  are not -H, then by the addition of  $-C(R_2)(R_3)-X_1$  to esters of the (S)-protected amino



acid (II) to produce the (S)-protected compound (III), an additional chiral center will be incorporated into the product, provided that R<sub>2</sub> and R<sub>3</sub> are not the same.

The (S)-protected compound (III) is then reduced by means known to those skilled in the art for reduction of a ketone to the corresponding secondary alcohol affording the corresponding alcohol (IV). The means and reaction conditions for reducing the (S)-protected compound (III) to the corresponding alcohol (IV) include, for example, sodium borohydride, lithium borohydride, borane, diisobutylaluminum hydride, and lithium aluminium hydride. Sodium borohydride is the preferred reducing agent. The reductions are carried out for a period of time between 1 hour and 3 days at temperatures ranging from -78° to elevated temperature up to the reflux point of the solvent employed. It is preferred to conduct the reduction between -78° and 0°. If borane is used, it may be employed as a complex, for example, borane-methyl sulfide complex, borane-piperidine complex, or borane-tetrahydrofuran complex. The preferred combination of reducing agents and reaction conditions needed are known to those skilled in the art, see for example, Larock, R.C. in Comprehensive Organic Transformations, VCH Publishers, 1989. The reduction of the (S)-protected compound (III) to the corresponding alcohol (IV) produces the second chiral center (third chiral center if R<sub>2</sub> and R<sub>3</sub> are not the same). The reduction of the (S)-protected compound (III) produces a mixture of enantiomers at the second center, (S, R/S)-alcohol (IV). This enantiomeric mixture is then separated by means known to those skilled in the art such as selective low-temperature recrystallization or chromatographic separation, for example by HPLC, employing commercially available chiral columns. The enantiomer that is used in the remainder of the process of SCHEME A is the (S,S)-alcohol (IV) since this enantiomer will give the desired biologically active anti-Alzheimer (S,R)-substituted amine X.

The (S, S)-alcohol (IV) is transformed to the corresponding epoxide (V) by means known to those skilled in the art. The stereochemistry of the (S)-(IV) center is maintained in forming the epoxide (V). A preferred means is by  
5 reaction with base, for example, but not limited to, hydroxide ion generated from sodium hydroxide, potassium hydroxide, lithium hydroxide and the like. Reaction conditions include the use of C<sub>1</sub>-C<sub>6</sub> alcohol solvents; ethanol is preferred. A  
10 common co-solvent, such as for example, ethyl acetate may also be employed. Reactions are conducted at temperatures ranging from -45° up to the reflux temperature of the alcohol employed; preferred temperature ranges are between -20° and 40°.

An alternative, and preferable process for preparing the epoxide (V) when R<sub>1</sub> is 3,5-difluorobenzyl, is set forth in  
15 SCHEME E. The first step of the process is to protect the free amino group of the (S)-amino acid (I) with an amino protecting group, PROTECTING GROUP, as previously discussed to produce the (S)-protected amino acid (II).

In the alternative process, the (S)-protected amino acid  
20 (I) is transformed to the corresponding (S)-protected ester (XVII) in one of a number of ways. One method involves the use of lithium hydroxide. Using lithium hydroxide, the (S)-protected amino acid (I) and the lithium hydroxide are mixed and cooled to from about -20° to about 10°. Next a methylating  
25 agent, selected from the group consisting of dimethylsulfate, methyl iodide and methyl triflate, is added. It is more preferred that the methylating agent is dimethylsulfate. This is followed by heating to from about 20° to about 50°.

Alternatively, the (S)-protected amino acid (I) is  
30 contacted with a weak base such as bicarbonate or preferably carbonate. This is followed by addition of the methylating agent. Heat is not necessary but can be used to facilitate the reaction. The carbonate method is known to those skilled in

the art. For those (S)-protected esters (XVII) where Z<sub>1</sub> is not methyl, one skilled in the art knowing the chemical structure would know how to prepare the desired compounds from known starting materials. In one known method the (S)-protected amino acid (I) is contacted with an activating agent, such as DCC, followed addition of the appropriate alcohol, Z<sub>1</sub>-OH. This method is operable when Z<sub>1</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl (optionally substituted), -CH<sub>2</sub>-CH=CH<sub>2</sub> or phenyl (optionally substituted).

SCHEME F and PREPARATIONS 10 and 11 set forth an alternative process for the preparation of the ester (II). In the process of SCHEME F, the aldehyde (XX), which is known to those skilled in the art, is reacted with the phosphorous compound (XXI), where X<sub>3</sub> is a good leaving group, to produce the olefin (XXI). The phosphorous compounds (XXI) are known to those skilled in the art. It is preferred that X<sub>3</sub> is C<sub>1</sub>-C<sub>3</sub> alkyl; it is more preferred that X<sub>3</sub> is C<sub>1</sub> alkyl. The aldehyde (XX) and the phosphate (XXI) are combined in an organic solvent then cooled to about 0°. A base such as DBU or TMG is added and the contents of the reaction mixture are warmed to about 20-25° and stirred until the reaction is complete. Once the reaction is complete, it is preferred to separate the E- and Z-olefin isomers (XXII). The separation is done by methods known to those skilled in the art, such as by silica gel chromatography. Next the olefin (XXII) is hydrogenated with a suitable hydrogenation catalyst to obtain the desired ester (II). Some hydrogenation reactions will give racemic ester (II). The desired stereochemistry of the ester (II) is (S)-, and therefore it is preferable to use the Z-olefin (XXII) with a hydrogenation catalyst. It is preferred that the hydrogenation catalyst is a compound of the formula

$$[\text{Rh}(\text{diene})\text{L}]^+\text{X}^-$$

where Rh is rhodium;

where diene is cyclooctadiene and nonbornadiene;

where L is DIPMAP, MeDuPhos, EtDuPhos, Binaphane, f-Binaphane, Me-KetalPhos, Me-f-KetalPhos, BINAP, DIOP, BPPFA, BPPM, CHIRAPHOS, PROPHOS, NORPHOS, CYCLOPHOS, BDPP, DEGPHOS, PNNP and where X<sup>-</sup> is ClO<sub>4</sub><sup>-</sup>, BF<sub>4</sub><sup>-</sup>, CF<sub>3</sub>-SO<sub>3</sub><sup>-</sup>, Cl<sup>-</sup>, Br<sup>-</sup>, PF<sub>6</sub><sup>-</sup> and  
5 SbF<sub>6</sub><sup>-</sup>. It is preferred that the hydrogenation catalyst be either DIPMAP or EtDuPhos. Suitable solvents include polar solvents such as alcohols, preferably C<sub>1</sub>-C<sub>5</sub> alcohols and THF, more preferably methanol, ethanol, isopropanol and THF. The chiral hydrogenation is performed in a temperature range of  
10 from about -20° to about reflux. It is preferred that the reaction be performed in the temperature range from about 0° to about room temperature (25°). The chiral hydrogenation is performed under a pressure of from about one atmosphere to about 100 psig; it is more preferred that the chiral  
15 hydrogenation be performed under a pressure of from about 10 psig to about 40 psig.

The (S)-protected ester (II) is then transformed to the corresponding (S)-protected ketone (III) by reaction with a slight excess of a compound of the formula CH<sub>2</sub>ClX<sup>2</sup> where X<sup>2</sup> is -  
20 Br and -I in one of two different ways. In one process, no exogenous nucleophile is used. That process requires (1) the presence of three or more equivalents of strong base which has a pK<sub>b</sub> of greater than about 30 followed by (2) adding acid. The other process requires (1) the presence of about 2 to about  
25 2.5 equivalents of strong base which has a pK<sub>b</sub> of greater than about 30, (2) contacting the mixture of step (1) with about 1 to about 1.5 equivalents of an exogenous nucleophile and (3) adding acid. Suitable strong bases are those which has a pK<sub>b</sub> of greater than about 30. It is preferred that the strong base  
30 be selected from the group consisting of LDA, LiHMDS and KHMDS; it is more preferred that the strong base be LDA. Suitable acids are those, which have a pK<sub>a</sub> of less than about 10. It is preferred the acid be selected from the group consisting of acetic, sulfuric, hydrochloric, citric, phosphoric and benzoic

acids; it is more preferred that the acid be acetic acid. The preferred solvent for the process is THF. The reaction can be performed in the temperature range from about  $-80^{\circ}$  to about  $-50^{\circ}$ ; it is preferred to perform the reaction in the temperature  
5 range of from about  $-75^{\circ}$  to about  $-65^{\circ}$ . Suitable nucleophiles include alkyl lithium, aryl lithium, alkyl-Grignard and aryl-Grignard reagents. It is preferred that the nucleophile be selected from the group consisting of phenyl lithium, n-butyl lithium, methyl magnesium bromide, methyl magnesium chloride,  
10 phenyl magnesium bromide, phenyl magnesium chloride; it is more preferred that the nucleophile be n-butyl lithium. PREPARATION 2 discloses the process with no nucleophile and PREPARATION 16 discloses the process with an exogenous nucleophile.

The (S)-protected ketone (III) is then reduced to the  
15 corresponding (S)-alcohol (IV) by means known to those skilled in the art for reduction of a ketone to the corresponding secondary alcohol. The means and reaction conditions for reducing the (S)-protected compound (III) to the corresponding alcohol (IV) include, for example, sodium borohydride, lithium  
20 borohydride, borane, diisobutylaluminum hydride, zinc borohydride and lithium aluminium hydride. Sodium borohydride is the preferred reducing agent. The reductions are carried out for a period of time between about 1 hour and about 3 days at temperatures ranging from about  $-78^{\circ}$  to elevated temperature  
25 up to the reflux point of the solvent employed. It is preferred to conduct the reduction between about  $-78^{\circ}$  and about  $0^{\circ}$ . If borane is used, it may be employed as a complex, for example, borane-methyl sulfide complex, borane-piperidine complex, or borane-tetrahydrofuran complex. The preferred  
30 combination of reducing agents and reaction conditions needed are known to those skilled in the art, see for example, Larock, R.C. in Comprehensive Organic Transformations, VCH Publishers, 1989. The reduction of the (S)-protected compound (III) to the

corresponding alcohol (IV) produces a second chiral center. The reduction of the (S)-protected compound (III) produces a mixture of diastereomers at the second center, (S, R/S)-alcohol (IV). This diastereomeric mixture is then separated by means  
5 known to those skilled in the art such as selective low-temperature recrystallization or chromatographic separation, most preferably by recrystallization or by employing commercially available chiral columns. The diastereomer that is used in the remainder of the process of SCHEME A is the  
10 (S,S)-alcohol (IV) since this stereochemistry will give the desired epoxide (V).

The alcohol (IV) is transformed to the corresponding epoxide (V) by means known to those skilled in the art. The stereochemistry of the (S)-(IV) center is maintained in forming  
15 the epoxide (V). A preferred means is by reaction with base, for example, but not limited to, hydroxide ion generated from sodium hydroxide, potassium hydroxide, lithium hydroxide and the like. Reaction conditions include the use of C<sub>1</sub>-C<sub>6</sub> alcohol solvents; ethanol is preferred. A common co-solvent, such as  
20 for example, ethyl acetate may also be employed. Reactions are conducted at temperatures ranging from about -45° up to the reflux temperature of the alcohol employed; preferred temperature ranges are between about -20° and about 40°. The epoxide (V) is then reacted with the appropriately  
25 substituted C-terminal amine, R<sub>C</sub>-NH<sub>2</sub> (VI) by means known to those skilled in the art which opens the epoxide to produce the desired corresponding enantiomerically pure (S,R)-protected alcohol (VII). The substituted C-terminal amines, R<sub>C</sub>-NH<sub>2</sub> (VI) of this invention are commercially available or are known to  
30 those skilled in the art and can be readily prepared from known compounds. It is preferred that when R<sub>C</sub> is phenyl, it is substituted in the 3-position or 3,5-positions.

Suitable reaction conditions for opening the epoxide (V) include running the reaction in a wide range of common and

inert solvents. C<sub>1</sub>-C<sub>6</sub> alcohol solvents are preferred and isopropyl alcohol most preferred. The reactions can be run at temperatures ranging from 20-25° up to the reflux temperature of the alcohol employed. The preferred temperature range for conducting the reaction is between 50° up to the reflux temperature of the alcohol employed. When the substituted C-terminal amine (VI) is a 1-amino-3,5-cis-dimethyl cyclohexyldicarboxylate it is preferably prepared as follows. To dimethyl-5-isophthalate in acetic acid and methanol, is added rhodium in alumina in a high-pressure bottle. The bottle is saturated with hydrogen at 55 psi and shaken for one week of time. The mixture is then filtered through a thick layer of celite cake and rinsed with methanol three times, the solvents are removed under reduced pressure (with heat) to give a concentrate. The concentrate is triturated with ether and filtered again to give the desired C-terminal amine (VI). When the substituted C-terminal amine (VI) is 1-amino-3,5-cis-dimethoxy cyclohexane it is preferably following the general procedure above and making non-critical variations but starting with 3,5-dimethoxyaniline.

When the substituted C-terminal amine (VI) is an aminomethyl group where the substituent on the methyl group is an aryl group, for example NH<sub>2</sub>-CH<sub>2</sub>-aryl, is not commercially available it is preferably prepared as follows. A suitable starting material is the (appropriately substituted) aralkyl compound. The first step is bromination of the alkyl substituent via methods known to those skilled in the art, see for example R.C. Larock in Comprehensive Organic Transformations, VCH Publishers, 1989, p. 313. Next the alkyl halide is reacted with azide to produce the aryl-(alkyl)-azide. Last the azide is reduced to the corresponding amine by hydrogen/catalyst to give the C-terminal amine (VI) of formula NH<sub>2</sub>-CH<sub>2</sub>-R<sub>C</sub>-aryl.

SCHEME B discloses an alternative process for production of the enantiomerically pure (S,R)-protected alcohol (VII) from the (S)-protected compound (III). In the alternative process, the (S)-protected compound (III) is first reacted with the  
5 appropriately substituted C-terminal amine  $R_C-NH_2$  (VI) using the preferred conditions described above to produce the corresponding (S)-protected ketone (XI) which is then reduced using the preferred conditions described above to produce the corresponding (S,R)-protected alcohol (VII).

10 SCHEME C discloses another alternative process for production of enantiomerically pure (S,R)-protected alcohol (VII) but this time from the epoxide (V). In the process of SCHEME C, the epoxide (V) is reacted with azide to produce the corresponding enantiomerically pure (S,R)-protected azide  
15 (XII). Conditions to conduct the azide mediated epoxide opening are known to those skilled in the art, see for example, J. March, Advanced Organic Chemistry, 3<sup>rd</sup> Edition, John Wiley & Sons Publishers, 1985, p. 380. Next, the (S,R)-protected azide (XII) is reduced to the corresponding protected amine (XIII) by  
20 methods known to those skilled in the art. Preferred reducing conditions to reduce the (S,R)-protected azide (XII) in the presence of a *t*-butoxycarbonyl N-protecting group include catalytic hydrogenation, the conditions for which are known to those skilled in the art. Alternative reducing conditions  
25 which may be used to avoid N-deprotection with protecting groups other than *t*-butoxycarbonyl are known to those skilled in the art, see for example, R.C. Larock in Comprehensive Organic Transformations, VCH Publishers, 1989, p. 409.

The (S,R)-protected alcohol (VII) is deprotected to the  
30 corresponding (S,R)-amine (VIII) by means known to those skilled in the art for removal of amine protecting group. Suitable means for removal of the amine protecting group depends on the nature of the protecting group. Those skilled in the art, knowing the nature of a specific protecting group,



know which reagent is preferable for its removal. For example, it is preferred to remove the preferred protecting group, BOC, by dissolving the (S,R)-protected alcohol (VII) in a trifluoroacetic acid/dichloromethane (1/1) mixture. When  
5 complete, the solvents are removed under reduced pressure to give the corresponding (S,R)-amine (as the corresponding salt, i.e. trifluoroacetic acid salt) which is used without further purification. However, if desired, the (S,R)-amine can be purified further by means known to those skilled in the art,  
10 such as for example, recrystallization. Further, if the non-salt form is desired that also can be obtained by means known to those skilled in the art, such as for example, preparing the free base amine via treatment of the salt with mild basic conditions. Additional BOC deprotection conditions and  
15 deprotection conditions for other protecting groups can be found in T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry, John Wiley and Sons, 1991, p. 309. Suitable chemically suitable salts include trifluoroacetate, and the anion of mineral acids such as chloride, sulfate, phosphate;  
20 preferred is trifluoroacetate.

The (S,R)-amine (VIII) is then reacted with an appropriately substituted amide forming agent (IX) such as, for example, an anhydride, acyl halide, or acid of the formulas  $(R_N)_2O$  or  $R_NX$  or  $R_NOH$  (IX) respectively, by means known to those  
25 skilled in the art to produce the corresponding (S,R)-substituted amine X. Nitrogen acylation conditions for reaction of the (S,R)-amine (VIII) with an amide forming agent (IX) to produce the corresponding (S,R)-substituted amine X are known to those skilled in the art and can be found in R.C.  
30 Larock in Comprehensive Organic Transformations, VCH Publishers, 1989, p. 981, 979, and 972.

The nitrogen-acylation of primary amines to produce secondary amides is a known reaction. Amide forming agents,

(R<sub>N</sub>)<sub>2</sub>O, R<sub>N</sub>X, and R<sub>N</sub>OH (IX) (which are acid anhydrides, acid halides and acids respectively) are known to those skilled in the art and are commercially available or can be readily prepared from known starting materials by methods known in the literature.

SCHEME D sets forth an alternative processes for production of the (S,R)-substituted amine X from the (S,R)-protected azide (XII), which is produced from the corresponding epoxide (V) in SCHEME C. The amino protecting group is removed to produce the corresponding unprotected azide (XIV) by methods previously described in SCHEME A for the conversion of (S,R)-protected alcohol (VII) to the corresponding (S,R)-amine (VIII). The (S,R)-unprotected azide (XIV) is then acylated on nitrogen to produce the corresponding (S,R)-azide (XV). Next, the azide functionality is reduced as previously discussed for the conversion of the (S,R)-protected azide (XII) to the corresponding (S,R)-protected amine (XIII) to give the (S,R)-free amine (XVI). Last, the (S,R)-free amine (XVI) is transformed to the corresponding (S,R)-substituted amine X by nitrogen alkylation with a compound of the formula R<sub>C</sub>-X<sub>3</sub> to give the corresponding (S,R)-substituted amine X. X<sub>3</sub> is an appropriate leaving group, such as but not limited to, -Cl, -Br, -I, -O-mesylate, -O-tosylate, O-triflate, etc. X<sub>3</sub> may also be an aldehyde; the corresponding coupling with (XVI) via the known reductive amination procedure gives the (S,R)-substituted amine X.

SCHEME G discloses an alternative, and preferable, process for preparing the substituted amines X from the corresponding protected alcohol (VII). The corresponding protected alcohol (VII) which then has the unprotected amino group protected with an amino PROTECTING GROUP, as previously discussed, to form the diprotected diamine (XXXIV). The diprotected diamine (XXXIV) has the protecting group at the N-terminal end then removed, as previously discussed, to form the monoprotected diamine (XXXV)

which is then reacted with an amide forming agent (IX), as discussed above to produce the coupled product (XXXVI). Upon removal of the remaining protecting group from the coupled product (XXXVI), the desired (S,R)-substituted amine X is  
5 produced.

SCHEME H discloses a process for the preparation of a racemic amide forming agent (IX-XLI) where for  $R_N$ ,  $R_4$  is  $-NH-R_{4-1}$ ,  $n_7$  is 0; X is  $-CH_2-$ ; Z is either  $-SO-$  or  $-SO_2-$  and ultimately  
10 the substituted amines (X-XLV) and (X-XLVI). The process of SCHEME H begins with the alcohol (XXXVII) where  $X_4$  is  $C_1-C_4$  alkyl or phenyl. The alcohol (XXXVII) has the alcohol group converted to a good LEAVING GROUP which includes tosylate, mesylate, nosylate and other groups known to those skilled in  
15 the art as "leaving groups" to produce the LEAVING GROUP-alcohol compound (XXXVIII). The LEAVING GROUP is replaced by the group Y-S- by reaction with a mercaptan to prepare the thiol ether (XXXIX) by means known to those skilled in the art. The thiol ether (XXXIX) is then converted to the corresponding  
20 sulfone acid (XL) by hydrolysis of the ester group. The thiol acid is then oxidized to the corresponding sulfone acid (XLI). Should it be desired that Z be  $-SO-$  rather than  $-SO_2-$ , only one equivalent of oxidizing agent, rather than two equivalents, is used to produce the sulfoxide ( $-SO-$ ) rather than the sulfone  
25 ( $-SO_2-$ ) as is known to those skilled in the art. Since the remainder of the process chemistry for SCHEME H is the same regardless of whether Z is  $-SO-$  or  $-SO_2-$  for simplicity, only  $-SO_2-$  will be illustrated and referred to. However, the explanation is equally relevant for  $-SO-$  as is apparent to one  
30 skilled in the art. Next, the sulfone acid (XLI) is reacted with the monoprotected diamine (XXXV of SCHEME G) to produce the diprotected coupled intermediate (XLII). The diprotected coupled product (XLII) then has the PROTECTING GROUP on the  $R_N$  group (preferably BOC) selectively removed to give the

monoprotected compound (XLIII). This selective removal of a PROTECTING GROUP is known to those skilled in the art and is referred to as "orthonigally protected". The monoprotected compound (XLIII) then can be selectively deprotected to give the  
5 corresponding  $-NH-R_{4-1}$ . To give the corresponding amine substituted intermediate (XLIV). The amine substituted intermediate (XLIV) is then has the remaining PROTECTING GROUP (preferably CBZ) removed by hydrogenation to give the substituted amine (X-XLV). Alternatively, the diprotected  
10 coupled intermediate (XLII) can have both PROTECTING GROUPS removed to produce the corresponding sulfone substituted amine (X-XLVI) by heating in a strong acid such as hydrochloric acid.

SCHEME I discloses a process for the preparation of  
15 enantiomerically pure thiol acid (XLIX) whereas SCHEME H disclosed a process to produce racemic thiol acid (XL). The stereoselective process of SCHEME I begins with the optically pure acid (XLVII) which is converted to the lactone (XLVIII) by Mitsunobu dehydration. The lactone (XLVIII) is converted to the  
20 corresponding optically pure thiol (XLIX) by reaction of the thiol with sodium hydride in THF. The optically pure thiol (XLIX) is then oxidized as explained in SCHEME H to produce the corresponding sulfoxide ( $-SO-$ ) or sulfone ( $-SO_2-$ ). As with SCHEME H, only the sulfone has been carried thru by  
25 exemplification. However, the exact same process chemistry would be used to prepare the corresponding sulfoxide substituted amines (X-LIV) as was explained with regards to SCHEME H.

SCHEME J discloses a process for the preparation of  
30 substituted amines X where in the variable substituent  $R_N$ ,  $R_4$  is (III),  $-(CH_2)_{1-4}-R_{4-1}$ , where only one methylene group is present and  $R_4$  is (G) giving for  $R_4$ ,  $-CH_2-CO-NR_{4-3}R_{4-4}$  or (M)  $-CH_2-CO-OH$ . The process of SCHEME J begins with the cyclic compound (LV) which is opened by the appropriate alcohol, as is

known to those skilled in the art, to give the olefin acid (LVI) where X<sub>4</sub> is as defined above. The olefin acid (LVI) is then transformed to the corresponding diester, preferably the activated ester (LVII) by means known to those skilled in the art. Next the Y-S- group is added to the double bond producing the thiol ester (LVIII) by Michael reaction with the appropriate thiol in methanol with triethylamine. The thiol ester (LVIII) is then converted to the corresponding acid and then reacted with the appropriate amine (VIII) to produce the protected thiol (LIX) as previously explained. This diester (LVIII) can be selectively coupled with the amine to give the protected sulfide ester (LIX). This sulfide ester (LIX) can be hydrolyzed under standard conditions (lithium hydroxide/THF/water) to give the sulfide acid (LX). Oxidation of the sulfide acid (LX) to the sulfoxide or sulfone is performed as previously stated to give the protected sulfone acid (LXI). If desired, the protected sulfone acid (LXI) can be converted to an amide by simple peptide coupling with the desired amine to give the sulfone amide (LXII). The sulfone amide (LXII) illustrates the methylamine. Simple deprotection of the R<sub>c</sub> protecting group with an appropriate deprotecting agent is known by one skilled in the art and gives the sulfone-amide substituted amine (X-LXIII).

SCHEME K discloses an alternative and preferred process to transform the cyclic compound (LV) to the corresponding protected sulfone acid (LXI). The process of SCHEME K replaces the X<sub>4</sub> protecting group with a specific protecting group *p*-methoxybenzyl. The advantage of this group is that it, as the PROTECTING GROUP on the amine nitrogen, both can be removed in one step, by hydrogenation, when the PROTECTING GROUP is CBZ.

Scheme L discloses a process to prepare aminomethylene derivatives. The allylic halide (LXXI), preferably bromide, is reacted with a protected amine like phthalimide to give the N-

protected amino acrylate (LXXII). The acrylate (LXXII) is reacted with the appropriate thiol, as previously described, to give the Michael product (LXXIII). Base hydrolysis of the sulfide ester (LXXIII) gives the acid (LXXIV) which is reacted  
5 with the amine (IX) as previously described to give the orthogonally protected compound (LXXV). The protecting group is removed from the protected compound (LXXV) with hydrazine to give the free amine (LXXVI) which is either acylated, X is -C(O)R to give an amide, or reacted with a mixed carbonate, X is  
10 -C(O)OR to give a carbamate (LXXVII). The sulfide (LXXVII) is oxidized as previously described to give the protected sulfone (LXXVIII). Simple de-protection of the protected sulfone (LXXVIII), as previously described, gives the target sulfone substituted amine (X-LXXIX).

15 Scheme M discloses the preparation of a series of racemic substituted alpha amino sulfones while Scheme N discloses the preparation of the active enantiomer. In SCHEME M, the first step discloses the Michael reaction of an appropriate thiol with a protected dehydroalanine methyl ester (LXXX) to give the  
20 thio compound (LXXXI). Oxidation as previously described gives the corresponding sulfone (LXXXII). Hydrolysis of the ester group and amino protecting group, such as acetate (-CO-CH<sub>3</sub>) can be accomplished with strong acid, such as 6N hydrochloric acid - acetic acid at elevated temperature, to  
25 give the free amino acid hydrochloride salt (LXXXIII). Amino acid (LXXXIII) is reacted, as the free amine or salt, with the appropriate protecting group (preferably either CBZ or BOC) to give the protected amine (IX-LXXXIV). Standard peptide coupling of the protected amine (IX-LXXXIV) preferentially  
30 gives the protected sulfone (LXXXV) which is orthogonally protected to give the diprotected sulfone (LXXXVI). Selective removal of the R<sub>N</sub> protecting group gives the monoprotected sulfone (LXXXVII). This monoprotected sulfone (LXXXVII) can be converted as previously described, into amides, carbamates and

also into ureas (by reaction of the amine with the appropriate isocyanide) and into sulfonamides by reaction with the appropriate sulfonyl chlorides. The final step is removal of the R<sub>c</sub> protecting group to give the corresponding desired amide (X-LXXXIX). SCHEME N is identical to SCHEME M except it discloses that one can separate the isomers of (IX-LXXXIV) either by chemical, enzymatic or by chiral chromatography to yield the single isomer acid (XC) which is transformed to final product (X-XCV) as described above.

10 Scheme O illustrates several alcohols that can be used to prepare the carbamates of the instant invention.

Scheme P illustrates one method for preparing the compounds of the invention, starting with an enantiomerically enriched amino acid. One of ordinary skill in the art will readily recognize that the method described in Scheme P is equally as useful for preparing compounds with the opposite stereochemistry or for preparing racemic compounds.

In Scheme P, cysteine is alkylated using a base and an alkylating agent. One of ordinary skill in the art will readily recognize that other amino acids and other methods for generating the thioether can be used. The free amine is then converted into a carbamate using a chloroformate. One of skill in the art will readily recognize that the free amine may be converted into an amide, alkylated, sulfonylated, or protected rather than being converted into an carbamate. The carbamate nitrogen can optionally be alkylated using a base and an alkylating agent to generate a tertiary nitrogen. In Scheme P, the carbamate nitrogen is alkylated with a base and an alkyl halide.

30 The carboxyl moiety of the starting amino acid is then reacted with an amino compound to generate the coupled compound. The amino compound can be achiral, a single enantiomer, racemic or a mixture of diastereomers. The coupled product may be further manipulated to convert the thiol

into a sulfoxide, which can then be converted into a sulfone or the thiol can be directly converted into a sulfone. Other groups in the coupled product can, if desired, be manipulated using methods known in the art of organic synthesis. For  
5 example, nitrogens can be alkylated, acylated or sulfonylated. Alcohols can be converted into esters or oxidized into aldehydes or acids. Aryl groups can be acylated and halides can be coupled.

One skilled in the art will appreciate that these are all  
10 known reactions in organic chemistry. A chemist skilled in the art, knowing the chemical structure of the biologically active end product X of the invention would be able to prepare them by known methods from known starting materials without any additional information. The explanation below therefore is not  
15 necessary but is deemed helpful to those skilled in the art who desire to make the compounds of the invention.

The backbone of the compounds of the invention is a hydroxyethylamine moiety,  $-\text{NH}-\text{CH}(\text{R}_1)-\text{CH}(\text{OH})-$ . It can be readily prepared by methods disclosed in the literature and  
20 known to those skilled in the art. For example, *J. Med. Chem.*, 36, 288-291 (1993), *Tetrahedron Letters*, 28, 5569-5572 (1987), *J. Med. Chem.*, 38, 581-584 (1995) and *Tetrahedron Letters*, 38, 619-620 (1997), and WO 02/02506 all disclose processes to prepare hydroxyethylamine type compounds and/or their  
25 intermediates.

The compounds of the invention may contain geometric or optical isomers as as tautomers. Thus, the invention includes all tautomers and pure geometric isomers, such as the *E* and *Z* geometric isomers, as as mixtures thereof. Further, the  
30 invention includes pure enantiomers and diastereomers as as mixtures thereof, including racemic mixtures. The individual geometric isomers, enantiomers or diastereomers may be prepared or isolated by methods known to those skilled in the art, including but not limited to chiral chromatography; preparing



diastereomers, separating the diastereomers and converting the diastereomers into enantiomers through the use of a chiral resolving agent.

Compounds of the invention with the stereochemistry designated in formula X can be included in mixtures, including racemic mixtures, with other enantiomers, diastereomers, geometric isomers or tautomers. Compounds of the invention with the (S,R) stereochemistry are typically present in these mixtures in excess of 50 percent. Preferably, compounds of the invention with the stereochemistry designated in formula X are present in these mixtures in excess of 80 percent. More preferably, compounds of the invention with the stereochemistry designated in formula X are present in these mixtures in excess of 90 percent. Even more preferably, compounds of the invention with the stereochemistry designated in formula X are present in these mixtures in excess of 99 percent.

Where the compounds of formula X are amines, they form salts when reacted with acids. Pharmaceutically acceptable salts are preferred over the corresponding free amines since they produce compounds which are generally more water soluble, stable and/or more crystalline. Pharmaceutically acceptable salts are any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The preferred pharmaceutically acceptable salts include salts of the following acids acetic, aspartic, benzenesulfonic, benzoic, bicarbonic, bisulfuric, bitartaric, butyric, calcium edetate, camsylic, carbonic, chlorobenzoic, citric, edetic, edisylic, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycollylarsanilic, hexamic, hexylresorcinoic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic,

maleic, malic, malonic, mandelic, methanesulfonic,  
methylnitric, methylsulfuric, mucic, muconic, napsylic, nitric,  
oxalic, p-nitromethanesulfonic, pamoic, pantothenic,  
phosphoric, monohydrogen phosphoric, dihydrogen phosphoric,  
5 phthalic, polygalactouronic, propionic, salicylic, stearic,  
succinic, succinic, sulfamic, sulfanilic, sulfonic, sulfuric,  
tannic, tartaric, teoclic and toluenesulfonic. For other  
acceptable salts, see *Int. J. Pharm.*, 33, 201-217 (1986) and  
*J.Pharm.Sci.*, 66(1), 1, (1977).

10

#### **Inhibition of APP Cleavage**

The compounds of the invention are believed to inhibit  
cleavage of APP between Met595 and Asp596 numbered for the  
APP695 isoform, or a mutant thereof, or at a corresponding site  
15 of a different isoform, such as APP751 or APP770, or a mutant  
thereof (sometimes referred to as the "beta secretase site".  
While not wishing to be bound by a particular theory,  
inhibition of beta-secretase activity is thought to inhibit  
production of beta amyloid peptide (A-beta). Inhibitory  
20 activity is demonstrated in one of a variety of inhibition  
assays, whereby cleavage of an APP substrate in the presence of  
a beta-secretase enzyme is analyzed in the presence of the  
inhibitory compound, under conditions normally sufficient to  
result in cleavage at the beta-secretase cleavage site.  
25 Reduction of APP cleavage at the beta-secretase cleavage site  
compared with an untreated or inactive control is correlated  
with inhibitory activity. Assay systems that can be used to  
demonstrate efficacy of the compound inhibitors of the  
invention are known. Representative assay systems are  
30 described, for example, in U.S. Patents No. 5,942,400,  
5,744,346, as as in the Examples below.

The enzymatic activity of beta-secretase and the  
production of A-beta can be analyzed *in vitro* or *in vivo*, using  
natural, mutated, and/or synthetic APP substrates, natural,

mutated, and/or synthetic enzyme, and the test compound. The analysis may involve primary or secondary cells expressing native, mutant, and/or synthetic APP and enzyme, or may utilize transgenic animal models expressing the substrate and enzyme.

5 Detection of enzymatic activity can be by analysis of one or more of the cleavage products, for example, by immunoassay, flurometric or chromogenic assay, HPLC, or other means of detection. Inhibitory compounds are determined as those having the ability to decrease the amount of beta-secretase cleavage  
10 product produced in comparison to a control, where beta-secretase mediated cleavage in the reaction system is observed and measured in the absence of inhibitory compounds.

#### **Beta-secretase**

15 Various forms of beta-secretase enzyme are known, and are available and useful for assay of enzyme activity and inhibition of enzyme activity. These include native, recombinant, and synthetic forms of the enzyme. Human beta-secretase is known as Beta Site APP Cleaving Enzyme (BACE),  
20 Asp2, and memapsin 2, and has been characterized, for example, in U.S. Patent No. 5,744,346 and published PCT patent applications WO98/22597, WO00/03819, WO01/23533, and WO00/17369, as as in literature publications (Hussain et.al., 1999, *Mol.Cell.Neurosci.* 14:419-427; Vassar et.al., 1999,  
25 *Science* 286:735-741; Yan et.al., 1999, *Nature* 402:533-537; Sinha et.al., 1999, *Nature* 40:537-540; and Lin et.al., 2000, *PNAS USA* 97:1456-1460). Synthetic forms of the enzyme have also been described (WO98/22597 and WO00/17369). Beta-secretase can be extracted and purified from human brain tissue  
30 and can be produced in cells, for example mammalian cells expressing recombinant enzyme.

Preferred compounds are effective to inhibit 50% of beta-secretase enzymatic activity at a concentration of less than about 50 micromolar, preferably at a concentration of less than

about 10 micromolar, more preferably less than about 1 micromolar, and most preferably less than about 10 nanomolar.

### **APP Substrate**

5 Assays that demonstrate inhibition of beta-secretase-mediated cleavage of APP can utilize any of the known forms of APP, including the 695 amino acid "normal" isotype described by Kang et.al., 1987, *Nature* 325:733-6, the 770 amino acid isotype described by Kitaguchi et. al., 1981, *Nature* 331:530-532, and  
10 variants such as the Swedish Mutation (KM670-1NL) (APP-SW), the London Mutation (V7176F), and others. See, for example, U.S. Patent No. 5,766,846 and also Hardy, 1992, *Nature Genet.* 1:233-234, for a review of known variant mutations. Additional useful substrates include the dibasic amino acid modification,  
15 APP-KK disclosed, for example, in WO 00/17369, fragments of APP, and synthetic peptides containing the  $\vartheta$ -secretase cleavage site, wild type (WT) or mutated form, e.g., SW, as described, for example, in U.S. Patent No 5,942,400 and WO00/03819.

The APP substrate contains the beta-secretase cleavage  
20 site of APP (KM-DA or NL-DA) for example, a complete APP peptide or variant, an APP fragment, a recombinant or synthetic APP, or a fusion peptide. Preferably, the fusion peptide includes the beta-secretase cleavage site fused to a peptide having a moiety useful for enzymatic assay, for example, having  
25 isolation and/or detection properties. A useful moiety may be an antigenic epitope for antibody binding, a label or other detection moiety, a binding substrate, and the like.

### **Antibodies**

30 Products characteristic of APP cleavage can be measured by immunoassay using various antibodies, as described, for example, in Pirttila et.al., 1999, *Neuro.Lett.* 249:21-4, and in U.S. Patent No. 5,612,486. Useful antibodies to detect A-beta include, for example, the monoclonal antibody 6E10 (Senetek,

St. Louis, MO) that specifically recognizes an epitope on amino acids 1-16 of the A-beta peptide; antibodies 162 and 164 (New York State Institute for Basic Research, Staten Island, NY) that are specific for human A-beta 1-40 and 1-42, respectively; 5 and antibodies that recognize the junction region of beta-amyloid peptide, the site between residues 16 and 17, as described in U.S. Patent No. 5,593,846. Antibodies raised against a synthetic peptide of residues 591 to 596 of APP and SW192 antibody raised against 590-596 of the Swedish mutation 10 are also useful in immunoassay of APP and its cleavage products, as described in U.S. Patent Nos. 5,604,102 and 5,721,130.

### **Assay Systems**

15 Assays for determining APP cleavage at the beta-secretase cleavage site are known in the art. Exemplary assays, are described, for example, in U.S. Patent Nos. 5,744,346 and 5,942,400, and described in the Examples below.

### **20 Cell Free Assays**

Exemplary assays that can be used to demonstrate the inhibitory activity of the compounds of the invention are described, for example, in WO00/17369, WO 00/03819, and U.S. Patents No. 5,942,400 and 5,744,346. Such assays can be 25 performed in cell-free incubations or in cellular incubations using cells expressing a beta-secretase and an APP substrate having a beta-secretase cleavage site.

An APP substrate containing the beta-secretase cleavage site of APP, for example, a complete APP or variant, an APP 30 fragment, or a recombinant or synthetic APP substrate containing the amino acid sequence: KM-DA or NL-DA, is incubated in the presence of beta-secretase enzyme, a fragment thereof, or a synthetic or recombinant polypeptide variant having beta-secretase activity and effective to cleave the

beta-secretase cleavage site of APP, under incubation conditions suitable for the cleavage activity of the enzyme. Suitable substrates optionally include derivatives that may be fusion proteins or peptides that contain the substrate peptide and a modification useful to facilitate the purification or detection of the peptide or its beta-secretase cleavage products. Useful modifications include the insertion of a known antigenic epitope for antibody binding; the linking of a label or detectable moiety, the linking of a binding substrate, and the like.

Suitable incubation conditions for a cell-free *in vitro* assay include, for example: approximately 200 nanomolar to 10 micromolar substrate, approximately 10 to 200 picomolar enzyme, and approximately 0.1 nanomolar to 10 micromolar inhibitor compound, in aqueous solution, at an approximate pH of 4 -7, at approximately 37 degrees C, for a time period of approximately 10 minutes to 3 hours. These incubation conditions are exemplary only, and can be varied as required for the particular assay components and/or desired measurement system. Optimization of the incubation conditions for the particular assay components should account for the specific beta-secretase enzyme used and its pH optimum, any additional enzymes and/or markers that might be used in the assay, and the like. Such optimization is routine and will not require undue experimentation.

One useful assay utilizes a fusion peptide having maltose binding protein (MBP) fused to the C-terminal 125 amino acids of APP-SW. The MBP portion is captured on an assay substrate by anti-MBP capture antibody. Incubation of the captured fusion protein in the presence of beta-secretase results in cleavage of the substrate at the beta-secretase cleavage site. Analysis of the cleavage activity can be, for example, by immunoassay of cleavage products. One such immunoassay detects a unique epitope exposed at the carboxy terminus of the cleaved

fusion protein, for example, using the antibody SW192. This assay is described, for example, in U.S. Patent No 5,942,400.

### **Cellular Assay**

5 Numerous cell-based assays can be used to analyze beta-secretase activity and/or processing of APP to release A-beta. Contact of an APP substrate with a beta-secretase enzyme within the cell and in the presence or absence of a compound inhibitor of the invention can be used to demonstrate beta-secretase  
10 inhibitory activity of the compound. Preferably, assay in the presence of a useful inhibitory compound provides at least about 30%, most preferably at least about 50% inhibition of the enzymatic activity, as compared with a non-inhibited control.

In one embodiment, cells that naturally express beta-secretase are used. Alternatively, cells are modified to  
15 express a recombinant beta-secretase or synthetic variant enzyme as discussed above. The APP substrate may be added to the culture medium is preferably expressed in the cells. Cells that naturally express APP, variant or mutant forms of APP, or  
20 cells transformed to express an isoform of APP, mutant or variant APP, recombinant or synthetic APP, APP fragment, or synthetic APP peptide or fusion protein containing the beta-secretase APP cleavage site can be used, provided that the expressed APP is permitted to contact the enzyme and enzymatic  
25 cleavage activity can be analyzed.

Human cell lines that normally process A-beta from APP provide a useful means to assay inhibitory activities of the compounds of the invention. Production and release of A-beta and/or other cleavage products into the culture medium can be  
30 measured, for example by immunoassay, such as Western blot or enzyme-linked immunoassay (EIA) such as by ELISA.

Cells expressing an APP substrate and an active beta-secretase can be incubated in the presence of a compound inhibitor to demonstrate inhibition of enzymatic activity as

compared with a control. Activity of beta-secretase can be measured by analysis of one or more cleavage products of the APP substrate. For example, inhibition of beta-secretase activity against the substrate APP would be expected to  
5 decrease release of specific beta-secretase induced APP cleavage products such as A-beta.

Although both neural and non-neural cells process and release A-beta, levels of endogenous beta-secretase activity are low and often difficult to detect by EIA. The use of cell  
10 types known to have enhanced beta-secretase activity, enhanced processing of APP to A-beta, and/or enhanced production of A-beta are therefore preferred. For example, transfection of cells with the Swedish Mutant form of APP (APP-SW); with APP-KK; or with APP-SW-KK provides cells having enhanced  $\beta$ -  
15 secretase activity and producing amounts of A-beta that can be readily measured.

In such assays, for example, the cells expressing APP and beta-secretase are incubated in a culture medium under conditions suitable for beta-secretase enzymatic activity at  
20 its cleavage site on the APP substrate. On exposure of the cells to the compound inhibitor, the amount of A-beta released into the medium and/or the amount of CTF99 fragments of APP in the cell lysates is reduced as compared with the control. The cleavage products of APP can be analyzed, for example, by  
25 immune reactions with specific antibodies, as discussed above.

Preferred cells for analysis of beta-secretase activity include primary human neuronal cells, primary transgenic animal neuronal cells where the transgene is APP, and other cells such as those of a stable 293 cell line expressing APP, for example,  
30 APP-SW.

#### **In vivo Assays: Animal Models**

Various animal models can be used to analyze beta-secretase activity and /or processing of APP to release A-beta,



as described above. For example, transgenic animals expressing APP substrate and beta-secretase enzyme can be used to demonstrate inhibitory activity of the compounds of the invention. Certain transgenic animal models have been  
5 described, for example, in U.S. Patent Nos: 5,877,399; 5,612,486; 5,387,742; 5,720,936; 5,850,003; 5,877,015,, and 5,811,633, and in Ganes et.al., 1995, *Nature* 373:523. Preferred are animals that exhibit characteristics associated with the pathophysiology of AD. Administration of the compound  
10 inhibitors of the invention to the transgenic mice described herein provides an alternative method for demonstrating the inhibitory activity of the compounds. Administration of the compounds in a pharmaceutically effective carrier and via an administrative route that reaches the target tissue in an  
15 appropriate therapeutic amount is also preferred.

Inhibition of beta-secretase mediated cleavage of APP at the beta-secretase cleavage site and of A-beta release can be analyzed in these animals by measure of cleavage fragments in the animal's body fluids such as cerebral fluid or tissues.  
20 Analysis of brain tissues for A-beta deposits or plaques is preferred.

On contacting an APP substrate with a beta-secretase enzyme in the presence of an inhibitory compound of the invention and under conditions sufficient to permit enzymatic  
25 mediated cleavage of APP and/or release of A-beta from the substrate, the compounds of the invention are effective to reduce  $\beta$ -secretase-mediated cleavage of APP at the beta-secretase cleavage site and/or effective to reduce released amounts of A-beta. Where such contacting is the administration  
30 of the inhibitory compounds of the invention to an animal model, for example, as described above, the compounds are effective to reduce A-beta deposition in brain tissues of the animal, and to reduce the number and/or size of beta amyloid plaques. Where such administration is to a human subject, the

compounds are effective to inhibit or slow the progression of disease characterized by enhanced amounts of A-beta, to slow the progression of AD in the, and/or to prevent onset or development of AD in a patient at risk for the disease.

5 Unless defined otherwise, all scientific and technical terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are hereby incorporated by reference for all purposes.

10

### **Biology Examples**

#### **Example A**

##### **Enzyme inhibition assay**

The compounds of the invention are analyzed for inhibitory activity by use of the MBP-C125 assay. This assay determines the relative inhibition of beta-secretase cleavage of a model APP substrate, MBP-C125SW, by the compounds assayed as compared with an untreated control. A detailed description of the assay parameters can be found, for example, in U.S. Patent No. 15 5,942,400. Briefly, the substrate is a fusion peptide formed of maltose binding protein (MBP) and the carboxy terminal 125 amino acids of APP-SW, the Swedish mutation. The beta-secretase enzyme is derived from human brain tissue as described in Sinha et.al, 1999, *Nature* 40:537-540) or 20 recombinantly produced as the full-length enzyme (amino acids 1-501), and can be prepared, for example, from 293 cells expressing the recombinant cDNA, as described in W000/47618.

Inhibition of the enzyme is analyzed, for example, by immunoassay of the enzyme's cleavage products. One exemplary 30 ELISA uses an anti-MBP capture antibody that is deposited on precoated and blocked 96- high binding plates, followed by incubation with diluted enzyme reaction supernatant, incubation with a specific reporter antibody, for example, biotinylated anti-SW192 reporter antibody, and further incubation with

streptavidin/alkaline phosphatase. In the assay, cleavage of the intact MBP-C125SW fusion protein results in the generation of a truncated amino-terminal fragment, exposing a new SW-192 antibody-positive epitope at the carboxy terminus. Detection is effected by a fluorescent substrate signal on cleavage by the phosphatase. ELISA only detects cleavage following Leu 596 at the substrate's APP-SW 751 mutation site.

#### **Specific Assay Procedure**

Compounds are diluted in a 1:1 dilution series to a six-point concentration curve (two wells per concentration) in one 96-plate row per compound tested. Each of the test compounds is prepared in DMSO to make up a 10 millimolar stock solution. The stock solution is serially diluted in DMSO to obtain a final compound concentration of 200 micromolar at the high point of a 6-point dilution curve. Ten (10) microliters of each dilution is added to each of two wells on row C of a corresponding V-bottom plate to which 190 microliters of 52 millimolar NaOAc, 7.9% DMSO, pH 4.5 are pre-added. The NaOAc diluted compound plate is spun down to pellet precipitant and 20 microliters/well is transferred to a corresponding flat-bottom plate to which 30 microliters of ice-cold enzyme-substrate mixture (2.5 microliters MBP-C125SW substrate, 0.03 microliters enzyme and 24.5 microliters ice cold 0.09% TX100 per 30 microliters) is added. The final reaction mixture of 200 micromolar compound at the highest curve point is in 5% DMSO, 20 millimolar NaAc, 0.06% TX100, at pH 4.5.

Warming the plates to 37 degrees C starts the enzyme reaction. After 90 minutes at 37 degrees C, 200 microliters/cold specimen diluent is added to stop the reaction and 20 microliters/ was transferred to a corresponding anti-MBP antibody coated ELISA plate for capture, containing 80 microliters/ specimen diluent. This reaction is incubated overnight at 4 degrees C and the ELISA is developed the next day after a 2 hour incubation with anti-192SW antibody,

followed by Streptavidin-AP conjugate and fluorescent substrate. The signal is read on a fluorescent plate reader.

Relative compound inhibition potency is determined by calculating the concentration of compound that showed a fifty-  
5 percent reduction in detected signal (IC<sub>50</sub>) compared to the enzyme reaction signal in the control s with no added compound. In this assay, the compounds of the invention exhibited an IC<sub>50</sub> of less than 50 micromolar.

10 **Example B**

**Cell free inhibition assay utilizing a synthetic APP substrate**

A synthetic APP substrate that can be cleaved by beta-secretase and having N-terminal biotin and made fluorescent by  
15 the covalent attachment of oregon green at the Cys residue is used to assay beta-secretase activity in the presence or absence of the inhibitory compounds of the invention. Useful substrates include the following:

- 20 Biotin-SEVNL-DAEFRC[oregon green]KK [SEQ ID NO: 1]  
 Biotin-SEVKM-DAEFRC[oregon green]KK [SEQ ID NO: 2]  
 Biotin-GLNIKTEEISEISY-EVEFRC[oregon green]KK [SEQ ID NO: 3]  
 Biotin-ADRGLTTRPGSGLTNIKTEEISEVNL-DAEFRC[oregon green]KK [SEQ  
 ID NO:4]  
 25 Biotin-FVNQHLCoxGSHLVEALY-LVCoxGERGFFYTPKAC[oregon green]KK  
 [SEQ ID NO: 5]

The enzyme (0.1 nanomolar) and test compounds (0.001 - 100 micromolar) are incubated in pre-blocked, low affinity, black plates (384 ) at 37 degrees for 30 minutes. The reaction is  
30 initiated by addition of 150 millimolar substrate to a final volume of 30 microliter per . The final assay conditions are: 0.001 - 100 micromolar compound inhibitor; 0.1 molar sodium acetate (pH 4.5); 150 nanomolar substrate; 0.1 nanomolar soluble beta-secretase; 0.001% Tween 20, and 2% DMSO. The

assay mixture is incubated for 3 hours at 37 ° C, and the reaction is terminated by the addition of a saturating concentration of immunopure streptavidin. After incubation with streptavidin at room temperature for 15 minutes, 5 fluorescence polarization is measured, for example, using a LJL Acquest (Ex485 nm/ Em530 nm). The activity of the beta-secretase enzyme is detected by changes in the fluorescence polarization that occur when the substrate is cleaved by the enzyme. Incubation in the presence or absence of compound 10 inhibitor demonstrates specific inhibition of beta-secretase enzymatic cleavage of its synthetic APP substrate. In this assay, compounds of the invention exhibited an IC50 of less than 50 micromolar.

15

**Example C****Beta-secretase inhibition: P26-P4'SW assay**

Synthetic substrates containing the  $\theta$ -secretase cleavage site of APP are used to assay beta-secretase activity, using  
5 the methods described, for example, in published PCT application WO00/47618. The P26-P4'SW substrate is a peptide of the sequence: (biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNLDAEF

[SEQ ID NO: 6]

The P26-P1 standard has the sequence:

10 (biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNL [SEQ ID NO: 7]

Briefly, the biotin-coupled synthetic substrates are incubated at a concentration of from about 0 to about 200 micromolar in this assay. When testing inhibitory compounds, a substrate concentration of about 1.0 micromolar is preferred.  
15 Test compounds diluted in DMSO are added to the reaction mixture, with a final DMSO concentration of 5%. Controls also contain a final DMSO concentration of 5%. The concentration of beta secretase enzyme in the reaction is varied, to give product concentrations with the linear range of the ELISA  
20 assay, about 125 to 2000 picomolar, after dilution.

The reaction mixture also includes 20 millimolar sodium acetate, pH 4.5, 0.06% Triton X100, and is incubated at 37 degrees C for about 1 to 3 hours. Samples are then diluted in assay buffer (for example, 145.4 nanomolar sodium chloride,  
25 9.51 millimolar sodium phosphate, 7.7 millimolar sodium azide, 0.05% Triton X405, 6g/liter bovine serum albumin, pH 7.4) to quench the reaction, then diluted further for immunoassay of the cleavage products.

Cleavage products can be assayed by ELISA. Diluted  
30 samples and standards are incubated in assay plates coated with capture antibody, for example, SW192, for about 24 hours at 4 degrees C. After washing in TTBS buffer (150 millimolar sodium chloride, 25 millimolar Tris, 0.05% Tween 20, pH 7.5), the samples are incubated with strepavidin-AP according to the

manufacturer's instructions. After a one hour incubation at room temperature, the samples are washed in TTBS and incubated with fluorescent substrate solution A (31.2 g/liter 2-amino-2-methyl-1-propanol, 30 mg/liter, pH 9.5). Reaction with  
5 streptavidin-alkaline phosphate permits detection by fluorescence. Compounds that are effective inhibitors of  $\theta$ -secretase activity demonstrate reduced cleavage of the substrate as compared to a control.

#### 10 **Example D**

##### **Assays using synthetic oligopeptide-substrates**

Synthetic oligopeptides are prepared that incorporate the known cleavage site of beta-secretase, and optionally detectable tags, such as fluorescent or chromogenic moieties.  
15 Examples of such peptides, as well as their production and detection methods are described in U.S. Patent No: 5,942,400, herein incorporated by reference. Cleavage products can be detected using high performance liquid chromatography, or fluorescent or chromogenic detection methods appropriate to the  
20 peptide to be detected, according to methods known in the art.

By way of example, one such peptide has the sequence SEVNL-DAEF [SEQ ID NO: 8], and the cleavage site is between residues 5 and 6. Another preferred substrate has the sequence  
25 ADRGLTTRPGSGLTNIKTEEISEVNL-DAEF [SEQ ID NO: 9], and the cleavage site is between residues 26 and 27.

These synthetic APP substrates are incubated in the presence of beta-secretase under conditions sufficient to result in beta-secretase mediated cleavage of the substrate. Comparison of the cleavage results in the presence of the  
30 compound inhibitor to control results provides a measure of the compound's inhibitory activity.

#### **Example E**

##### **Inhibition of beta-secretase activity-cellular assay**

An exemplary assay for the analysis of inhibition of beta-secretase activity utilizes the human embryonic kidney cell line HEKp293 (ATCC Accession No. CRL-1573) transfected with APP751 containing the naturally occurring double mutation Lys651Met52 to Asn651Leu652 (numbered for APP751), commonly called the Swedish mutation and shown to overproduce A-beta (Citron et.al., 1992, *Nature* 360:672-674), as described in USPN 5,604,102.

The cells are incubated in the presence/absence of the inhibitory compound (diluted in DMSO) at the desired concentration, generally up to 10 micrograms/ml. At the end of the treatment period, conditioned media is analyzed for beta-secretase activity, for example, by analysis of cleavage fragments. A-beta can be analyzed by immunoassay, using specific detection antibodies. The enzymatic activity is measured in the presence and absence of the compound inhibitors to demonstrate specific inhibition of beta-secretase mediated cleavage of APP substrate.

## 20 **Example F**

### **Inhibition of beta-secretase in animal models of AD**

Various animal models can be used to screen for inhibition of beta-secretase activity. Examples of animal models useful in the invention include, but are not limited to, mouse, guinea pig, dog, and the like. The animals used can be wild type, transgenic, or knockout models. In addition, mammalian models can express mutations in APP, such as APP695-SW and the like described herein. Examples of transgenic non-human mammalian models are described in U.S. Patent Nos. 5,604,102, 5,912,410 and 5,811,633.

PDAPP mice, prepared as described in Games et.al., 1995, *Nature* 373:523-527 are useful to analyze *in vivo* suppression of A-beta release in the presence of putative inhibitory compounds. As described in USPN 6,191,166, 4 month old PDAPP



mice are administered compound formulated in vehicle, such as corn oil. The mice are dosed with compound (1-30 mg/ml; preferably 1-10 mg/ml). After time, e.g., 3-10 hours, the animals are sacrificed, and brains removed for analysis.

5 Transgenic animals are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Control animals are untreated, treated with vehicle, or treated with an inactive compound. Administration can be acute, i.e., single dose or multiple  
10 doses in one day, or can be chronic, i.e., dosing is repeated daily for a period of days. Beginning at time 0, brain tissue or cerebral fluid is obtained from selected animals and analyzed for the presence of APP cleavage peptides, including A-beta, for example, by immunoassay using specific antibodies  
15 for A-beta detection. At the end of the test period, animals are sacrificed and brain tissue or cerebral fluid is analyzed for the presence of A-beta and/or beta-amyloid plaques. The tissue is also analyzed for necrosis.

Animals administered the compound inhibitors of the  
20 invention are expected to demonstrate reduced A-beta in brain tissues or cerebral fluids and reduced beta amyloid plaques in brain tissue, as compared with non-treated controls.

**Example G****Inhibition of A-beta production in human patients**

Patients suffering from Alzheimer's Disease (AD) demonstrate an increased amount of A-beta in the brain. AD patients are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

10 Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A-beta present in CSF or plasma; brain or hippocampal volume; A-beta deposits in the brain; amyloid  
15 plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

**Example H****Prevention of A-beta production in patients at risk for AD**

20 Patients predisposed or at risk for developing AD are identified either by recognition of a familial inheritance pattern, for example, presence of the Swedish Mutation, and/or by monitoring diagnostic parameters. Patients identified as predisposed or at risk for developing AD are administered an  
25 amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

30 Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A-beta present in CSF or plasma; brain or hippocampal volume; amyloid plaque in the brain; and scores

for cognitive and memory function, as compared with control, non-treated patients.

#### EXAMPLES

5 The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize  
10 appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

#### PREPARATION 1 tert-Butyl (1S)-3-bromo-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate (III)

15 N-methyl-morpholine (5.83 mL, 53 mmole, 1.05 eq.) is added to (2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,5-difluorophenyl)propanoic acid (II, 15 g, 50 mmole) in THF (100 mL) and the reaction is cooled to  $-78^{\circ}$ . Isobutyl chloroformate (6.87 mL, 53 mmole, 1.05 eq.) is added rapidly. The cold bath  
20 is then removed and the mixture stirred for 1 hr. The reaction was monitored by TLC to insure completion of the reaction and the mixture is then filtered and washed with dry THF (50 mL) and kept cold in the filtered flask at  $-20^{\circ}$ .

In a ice-salt bath is placed a 500 mL graduate cylinder  
25 containing ether (200 mL) and aqueous potassium hydroxide (40%, 60 mL). 1-methyl-3-nitro-1-nitrosoguanidine (5.6 g, 106 mmole, 2.1 eq.) is added slowly with stirring and temperature kept below zero degree. The mixture turned yellow and the bubbling lasted for 10 minutes. The stirring is stopped and without  
30 mixing the layers, the top diazomethane ethereal layer is transferred with non-ground tip pipette into the stirred mixed anhydride mixture at  $-20^{\circ}$ . The reaction is monitored by TLC (ethyl acetate/hexane, 50/50;  $R_f = 0.69$ ). After 1 hour nitrogen is then bubbled into the mixture. The solvent is

removed under reduced pressure (with heat) and the mixture is partitioned between ether and water. The phases are separated, the organic phase is washed with bicarbonate, saline, dried over anhydrous sodium sulfate, filtered, and solvent removed  
5 under reduced pressure (with heat). The residue is dissolved in ether (100 mL) and hydrobromous acid (48%, 15 mL, 135 mmole, 2.7 eq,) is added at  $-20^{\circ}$ , the cold bath is removed and the mixture is stirred for another half hour. The reaction is monitored by TLC (ethyl acetate/hexane, 50/50;  $R_f = 0.88$ ). The  
10 mixture is partitioned between ether and water, washed with bicarbonate, saline, dried over anhydrous sodium sulfate, filtered, and the solvent removed. The residue is recrystallized from ethanol to give the title compound, TLC (ethyl acetate/hexane, 50/50)  $R_f = 0.88$ ; MS ( $MH^+$ ) = 379.3

15

PREPARATION 2 tert-Butyl (1S, 2S)-3-bromo-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV)

Sodium borohydride (1.32 g, 34.9 mmole, 1.1 eq.) is added to tert-Butyl (1S)-3-bromo-1-(3,5-difluorobenzyl)-2-  
20 oxopropylcarbamate (III, PREPARATION 1, 12 g, 31.75 mmole) dissolved in absolute alcohol (500 mL)  $-78^{\circ}$ . The reaction mixture is stirred for 30 minutes and monitored by TLC (ethyl acetate/hexane, 20/80;  $R_f = 0.2$ ). The mixture is quenched with water (10 mL) and the solvent removed under reduced pressure  
25 with heat (not exceeding  $30^{\circ}$ ) to dryness. The solid is partitioned between dichloromethane and water, washed with saline, dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure to give the title compound, TLC (ethyl acetate/hexane, 20/80)  $R_f = 0.2$ ; MS ( $MH^+$ ) = 381.2

30

PREPARATION 3 tert-Butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V)

tert-Butyl (1S, 2S)-3-bromo-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV, PREPARATION 2) is dissolved in

absolute alcohol (150 mL) and ethyl acetate (100 mL) and potassium hydroxide (2.3 g, 34.9 mmole, 1.1eq.) in ethyl alcohol (85%, 5mL) is added at -20°. The cold bath is then removed and the mixture stirred for 30 minutes. The reaction  
5 is monitored by TLC (ethyl acetate/hexane, 20/80). When the reaction is complete, it is diluted with dichloromethane and extracted, washed with water, saline, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The crude material is purified by flash chromatography on  
10 silica gel to give the title compound, TLC (ethyl acetate/hexane, 20/80)  $R_f = 0.3$ ; MS ( $MH^+$ ) = 300.4.

PREPARATION 4 Benzyl (1S)-3-chloro-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate (III)

15 Following the general procedure of PREPARATION 1 and making non critical variations but starting with the CBZ protecting group and using hydrochloric acid, the title compound is obtained.

20 PREPARATION 5 Benzyl (1S, 2S)-3-chloro-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV)

Following the general procedure of PREPARATION 2 and making non critical variations but starting with benzyl (1S)-3-chloro-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate (III,  
25 PREPARATION 4), the title compound is obtained.

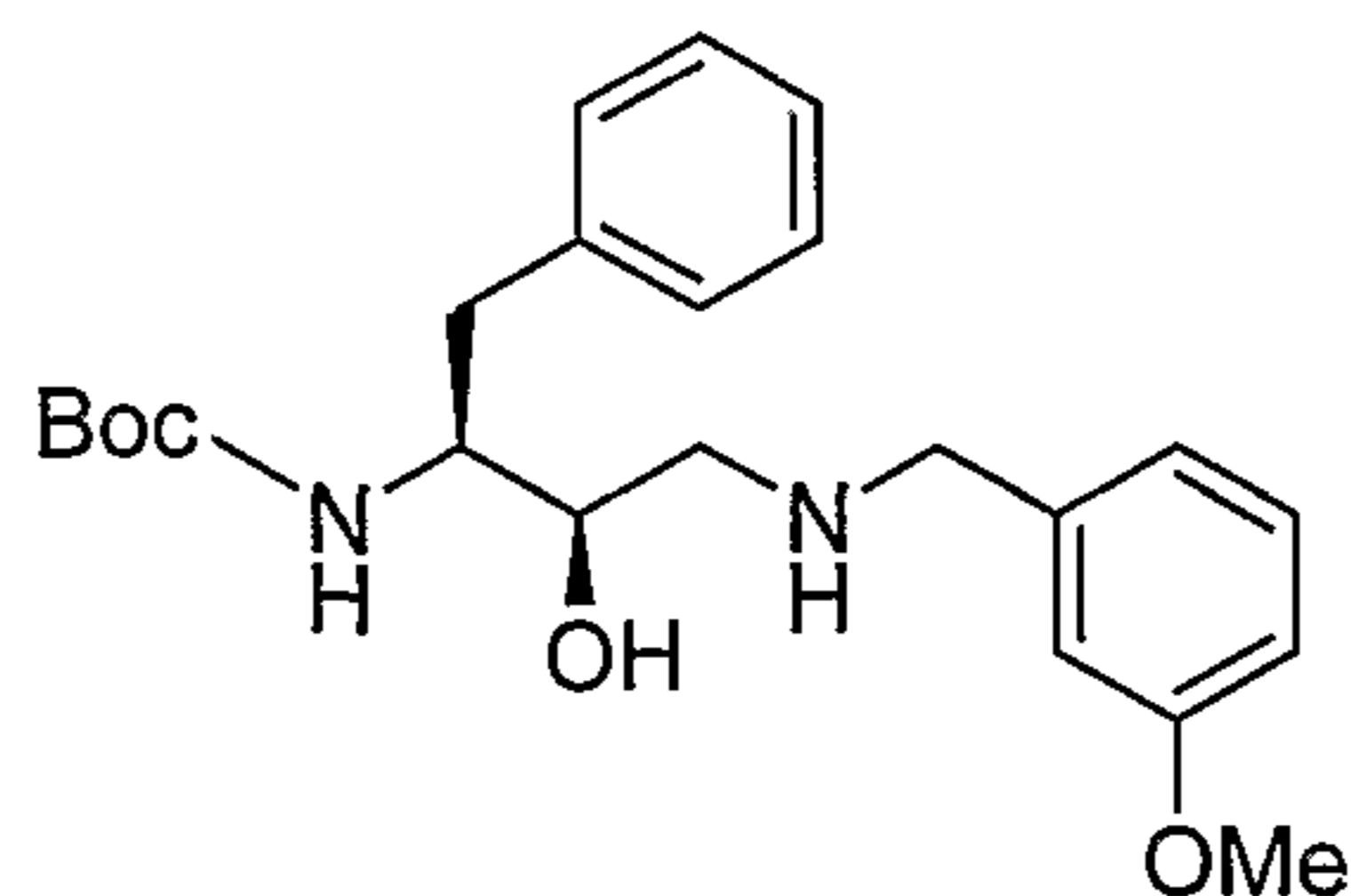
PREPARATION 6 Benzyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V)

30 Following the general procedure of PREPARATION 3 and making non critical variations but starting with benzyl (1S, 2S)-3-chloro-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV, PREPARATION 5), the title compound is obtained.

PREPARATION 7 tert-Butyl (1S, 2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (VII)

tert-Butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, PREPARATION 3, 245 mg, 0.82 mmol) is suspended in isopropyl alcohol (6 mL) and 3-methoxybenzylamine (160  $\mu$ L, 1.22 mmol) is added with stirring at 20-25°. This mixture is heated to gentle reflux (bath temp 85°) under nitrogen for 2 hr, whereupon the resulting mixture is concentrated under reduced pressure to give the title compound. The title compound is purified by flash chromatography (2-5% methanol/methylene chloride; gradient elution) to give purified title compound.

PREPARATION 8 tert-Butyl (1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (VII)



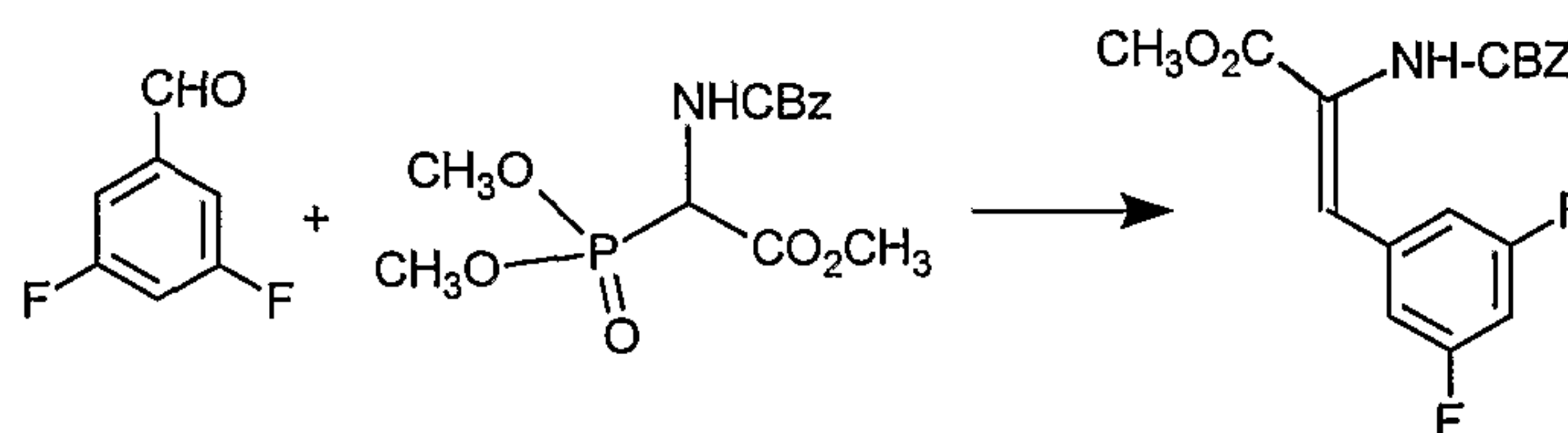
tert-Butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V, commercially available, 20 g, 76 mmole) is dissolved in *i*-propanol (380 ml). To this mixture is added 3-methoxybenzylamine (49 ml, 380 mmole). The reaction mixture is heated to reflux for 1 hr (when HPLC indicated complete reaction). The reaction mixture is concentrated under reduced pressure and the residue is treated with hexane (500 ml). The product is isolated by filtration. The mother liquors are concentrated under reduced pressure to give additional crude material which is partitioned between ethyl acetate (50 ml) and water (50 ml). The mixture is acidified with concentrated hydrochloric acid (to pH = 4), the organic phase is separated and washed with

water, saline, dried over sodium sulfate and then concentrated under reduced pressure to give additional title compound, M+H = 401.

5 PREPARATION 9 Benzyl (1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]ethyl carbamate (VII)

Following the general procedure of PREPARATION 7 and making non-critical variations but using benzyl 1-(2-oxiranyl)-2-phenyl carbamate (V), as the epoxide, the title compound is  
10 obtained.

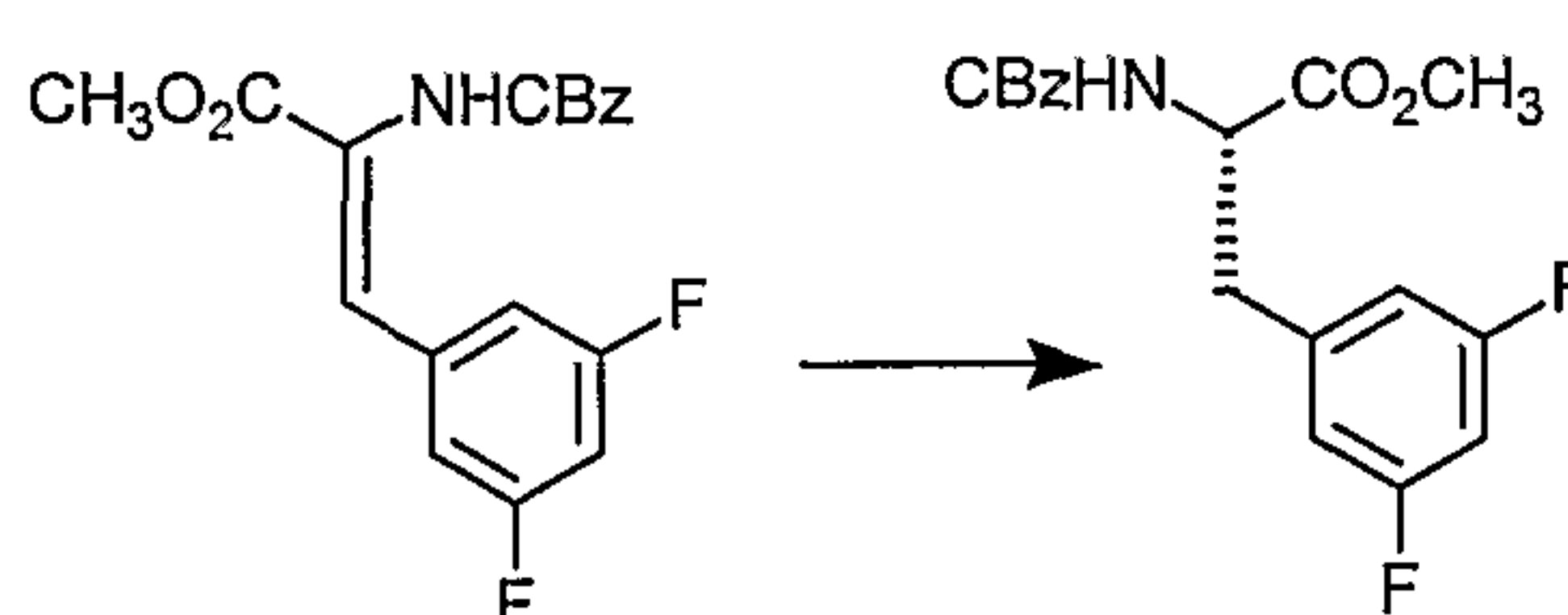
PREPARATION 10 Methyl (2Z)-2-[[ (benzyloxy) carbonyl]-3-(3,5-difluorophenyl)-2-propenonate (XXII)



15 3,5-Difluorobenzaldehyde (XX, 2.87 g, 0.02 moles, 1 eq) and THF (100 mL) are mixed and cooled to about 0°. N-(Benzyloxycarbonyl)phosphonyl-glycinetrimethylester (XXI, 8.7 g, 0.026 moles, 1.3 eq) is added to the 3,5-difluorobenzaldehyde (XX)/THF mixture. This is followed by  
20 1,1,3,3-tetramethyl guanidine (4.0 mL, 0.032 moles, 1.56 eq) added dropwise. The reaction is stirred for 5 min at 0° then allowed to warm to 20-25°. After 2 hr, the reaction is complete (by TLC analysis) at which time water (100 mL) and ethyl acetate (100 mL) are added. The phases are separated and  
25 the aqueous phase is extracted with ethyl acetate (100 mL) and the combined organic phases are washed with saline (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a crude solid. The solid is purified by silica gel chromatography (ethyl acetate/hexanes; 15/85) to  
30 give the title compound, mp = 112°; NMR (CDCl<sub>3</sub>) δ 7.19, 7.06,

6.86, 6.15, 6.43, 4.97 and 3.69; CMR (CDCl<sub>3</sub>)  $\delta$  165.56, 164.54, 164.41, 162.07, 137.39, 136.02, 128.97, 128.80, 128.62, 128.57, 128.47, 126.25, 112.57, 112.38, 105.22, 104.97, 104.72, 68.17 and 53.33. Additional material is recovered that is a mixture  
 5 of E and Z olefins.

PREPARATION 11 methyl (2S)-2-[[ (benzyloxy) carbonyl] amino]-3-(3,5-difluorophenyl)propanoate (II)

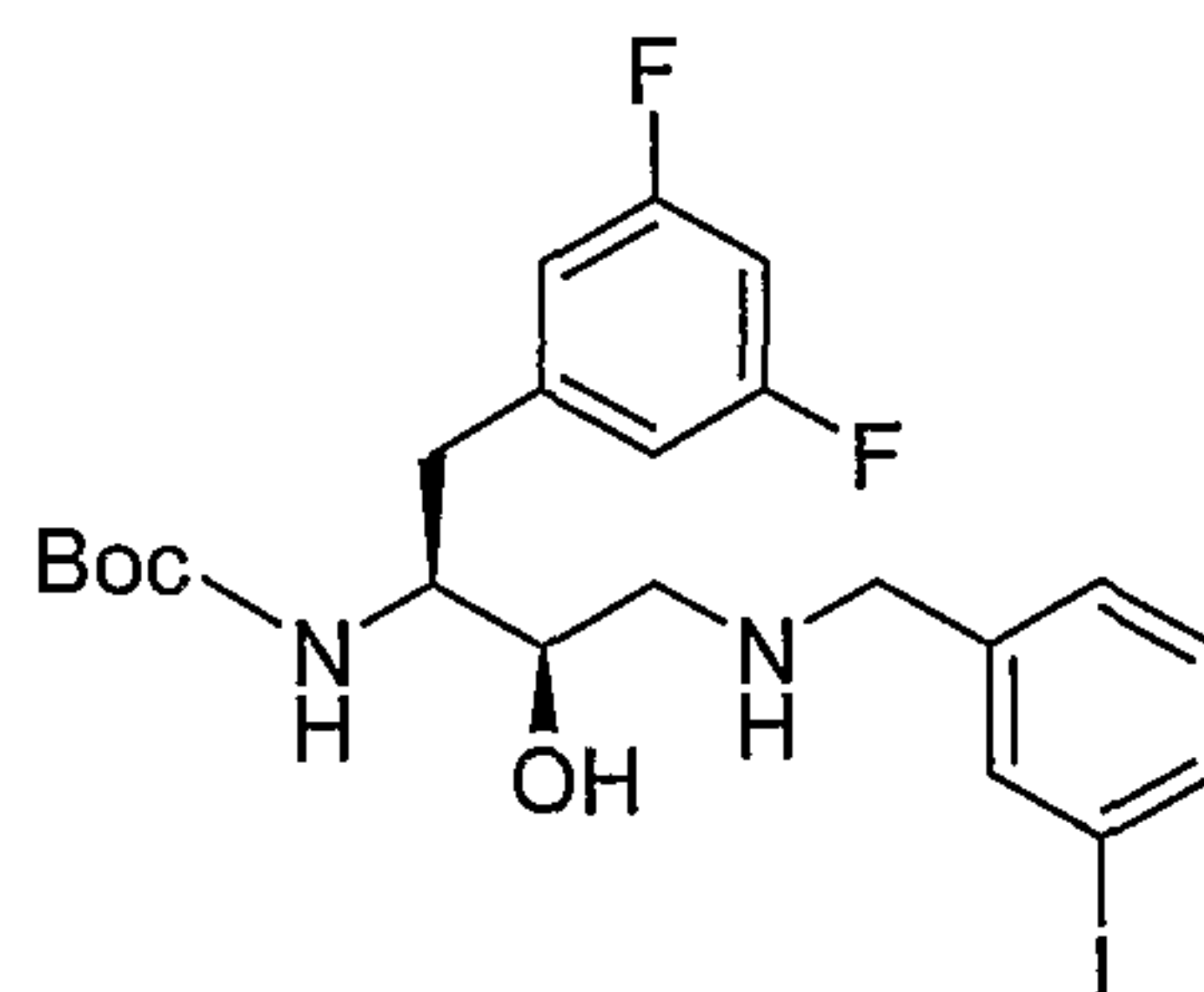


10

Methyl (2Z)-2-[[ (benzyloxy) carbonyl]-3-(3,5-difluorophenyl)-2-propenonate (XXII, PREPARATION 10, 0.100 g, 0.228 mmol) and degassed methanol (10 ml) are mixed in a 100 mL Hastelloy bomb. The reaction mixture is purged three times with  
 15 hydrogen (60 psig) and then stirred at 60 psig hydrogen for 60 min at 20-25°. Then (R,R)-DIPAP)Rh (5.2 mg, 3 mole%) is dissolved in methanol (1 mL, degassed) is added and the system purged with hydrogen (3 x 60 psig). The contents are then stirred at 20 psig hydrogen at 25° overnight at which time the  
 20 reaction is complete as determined by HPLC. The system is then purged and filtered to remove the catalyst and the solvent is removed under reduced pressure to give the title compound.

PREPARATION 12 1- tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl) amino]propylcarbamate (VII)  
 25

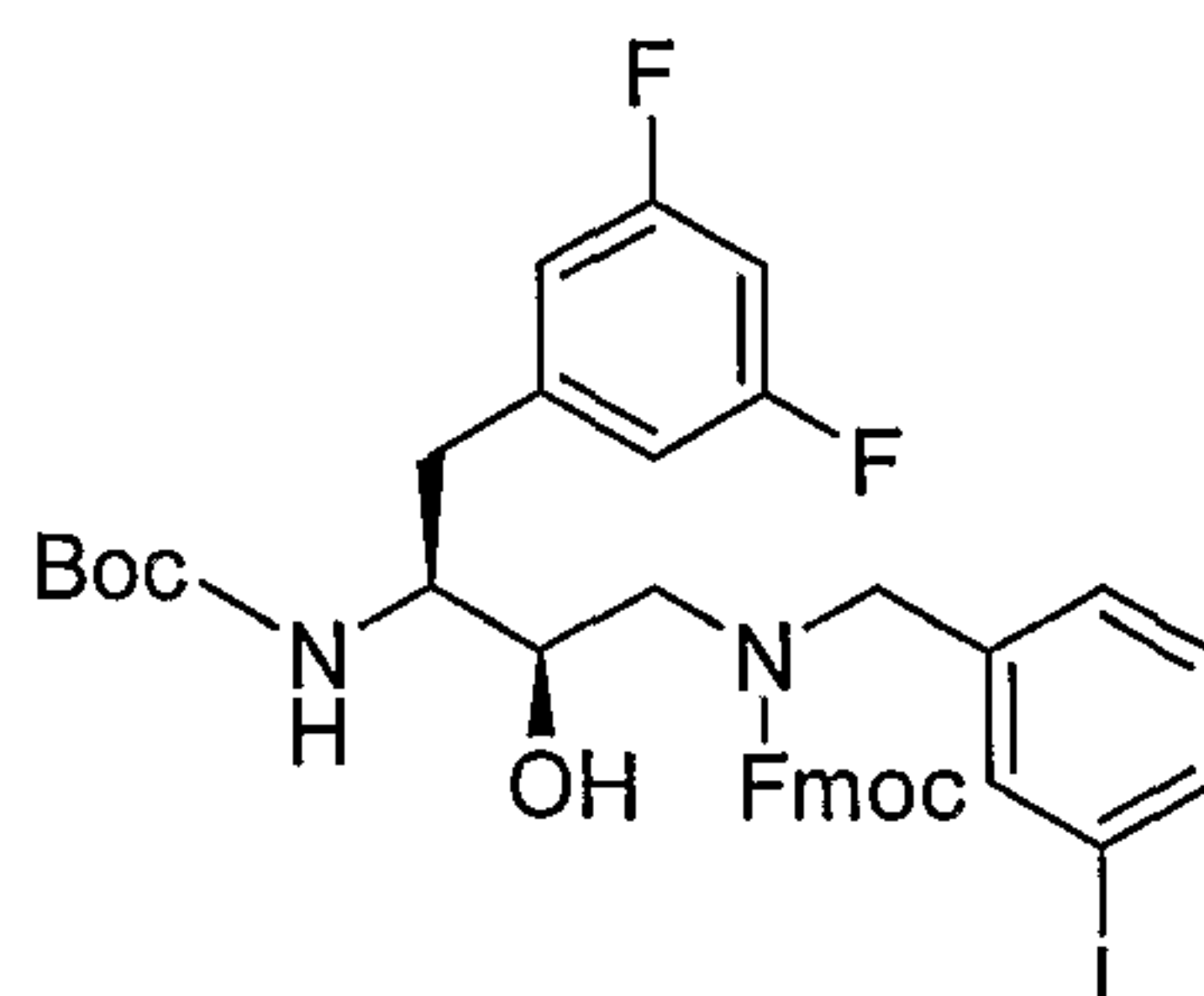




tert-Butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-  
 oxiranyl]ethylcarbamate (V, PREPARATION 3, 1.75 g, 5.8 mmole)  
 5 is mixed with isopropanol (30 ml). The reaction flask is  
 charged with 3-iodobenzylamine (VI). The reaction mixture is  
 heated to reflux for 45 minutes, HPLC analysis indicates  
 complete disappearance of the epoxide (V). The reaction  
 mixture is concentrated under reduced pressure and the residue  
 10 is partitioned between ethyl acetate (150 ml) and aqueous  
 hydrochloric acid (3%, 35 ml). The organic phase is separated  
 and washed with aqueous hydrochloric acid (3%, 20 ml),  
 bicarbonate, saline and dried over sodium sulfate.  
 Concentration under reduced pressure gives the title compound,  
 15 M + H = 535.

PREPARATION 13 1-9H-fluoren-9-ylmethyl (2R,3S)-3-(3-t-  
 butyloxycarbonyl)amino-4-(3,5-difluorophenyl)-2-  
 hydroxybutyl(3'-iodobenzyl)carbamate hydrochloride (XXXIV)

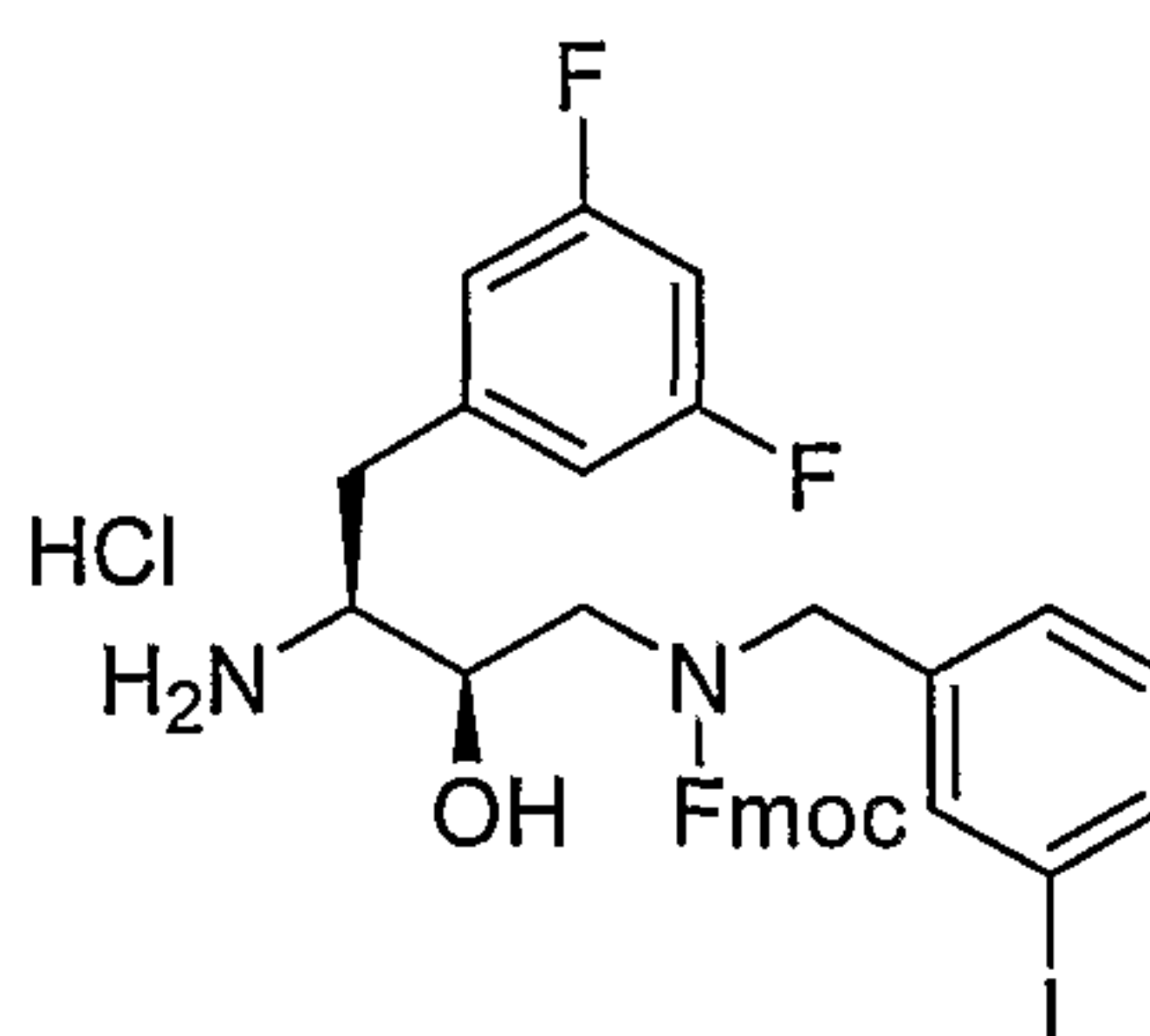
20



1- tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-  
 [(3-iodobenzyl)amino]propylcarbamate (VII, PREPARATION 12, 2.5

g, 4.7 mmole) and triethylamine (0.72 ml, 5.1 mmole) in THF (10 ml) are mixed. The reaction is cooled to 0° and treated with Fmoc (1.2 g, 4.7 mmole) in THF (2 ml) via addition funnel. After 15 minutes HPLC indicates complete  
 5 disappearance of starting material. The reaction is diluted with ethyl acetate and washed with aqueous potassium bisulfate, saturated aqueous bicarbonate, saline and dried over sodium sulfate. Concentration under reduced pressure gives crude product which is purified by flash chromatography,  
 10 eluting with ethyl acetate/hexane (20/80) followed by ethyl acetate to give the title compound, M + H = 757.

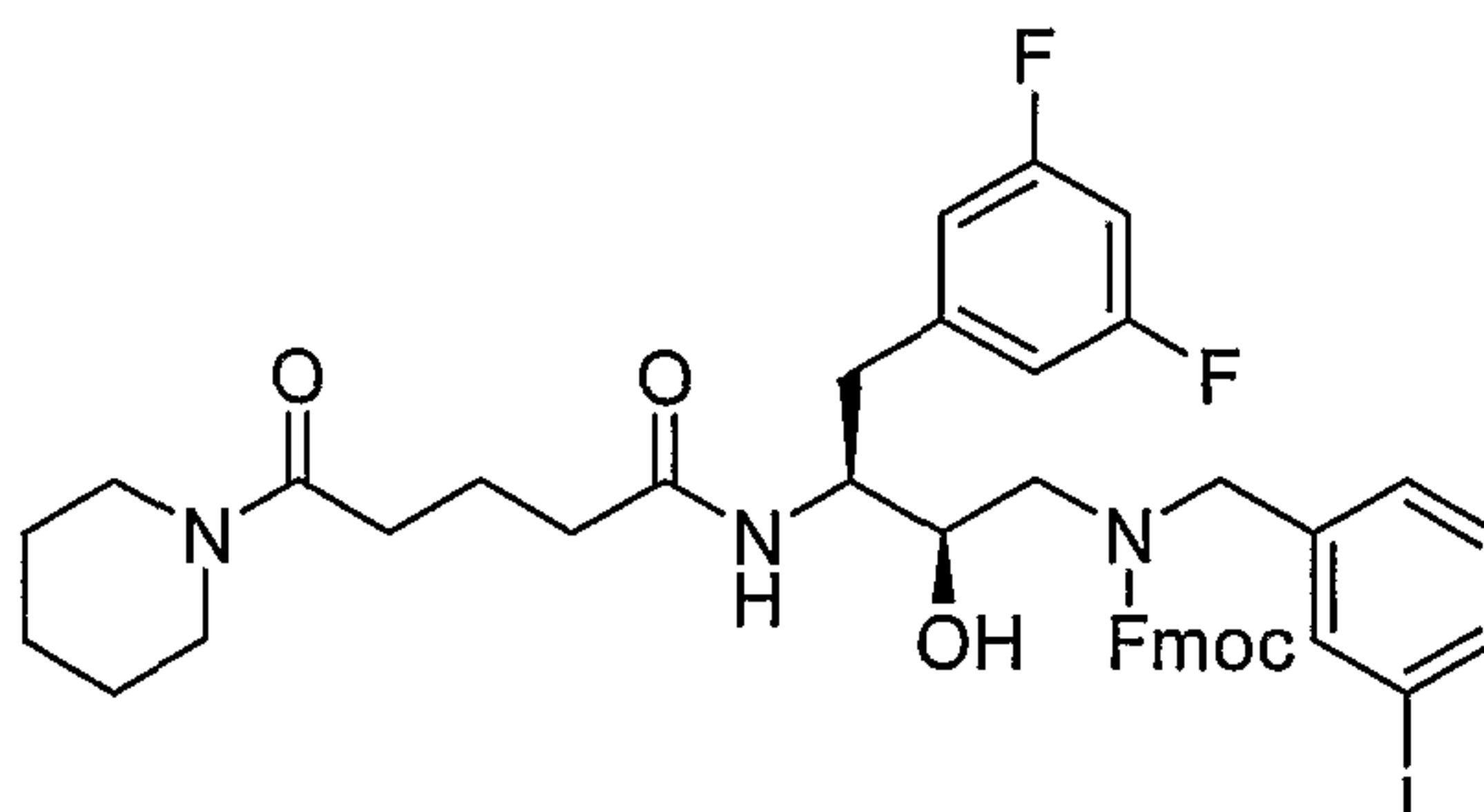
PREPARATION 14 1-9H-fluoren-9-ylmethyl (2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl (3-iodobenzyl) carbamate  
 15 hydrochloride (XXXV)



1-9H-fluoren-9-ylmethyl (2R,3S)-3-(3-t-  
 20 butyloxycarbonyl)amino-4-(3,5-difluorophenyl)-2-hydroxybutyl (3'-iodobenzyl) carbamate hydrochloride (XXXIV, PREPARATION 13, 2.9 g) in hydrochloric acid/dioxane (4N, 10 ml). The mixture is stirred 1 hour then slowly poured into rapidly stirring ether (200 ml). The product is filtered and  
 25 dried to give the title compound, M + H = 657.

PREPARATION 15 1-9H-fluoren-9-ylmethyl (2R,3S)-4-(3,5-difluorophenyl)-2-hydroxy-3-{[5-oxo-5-(1-

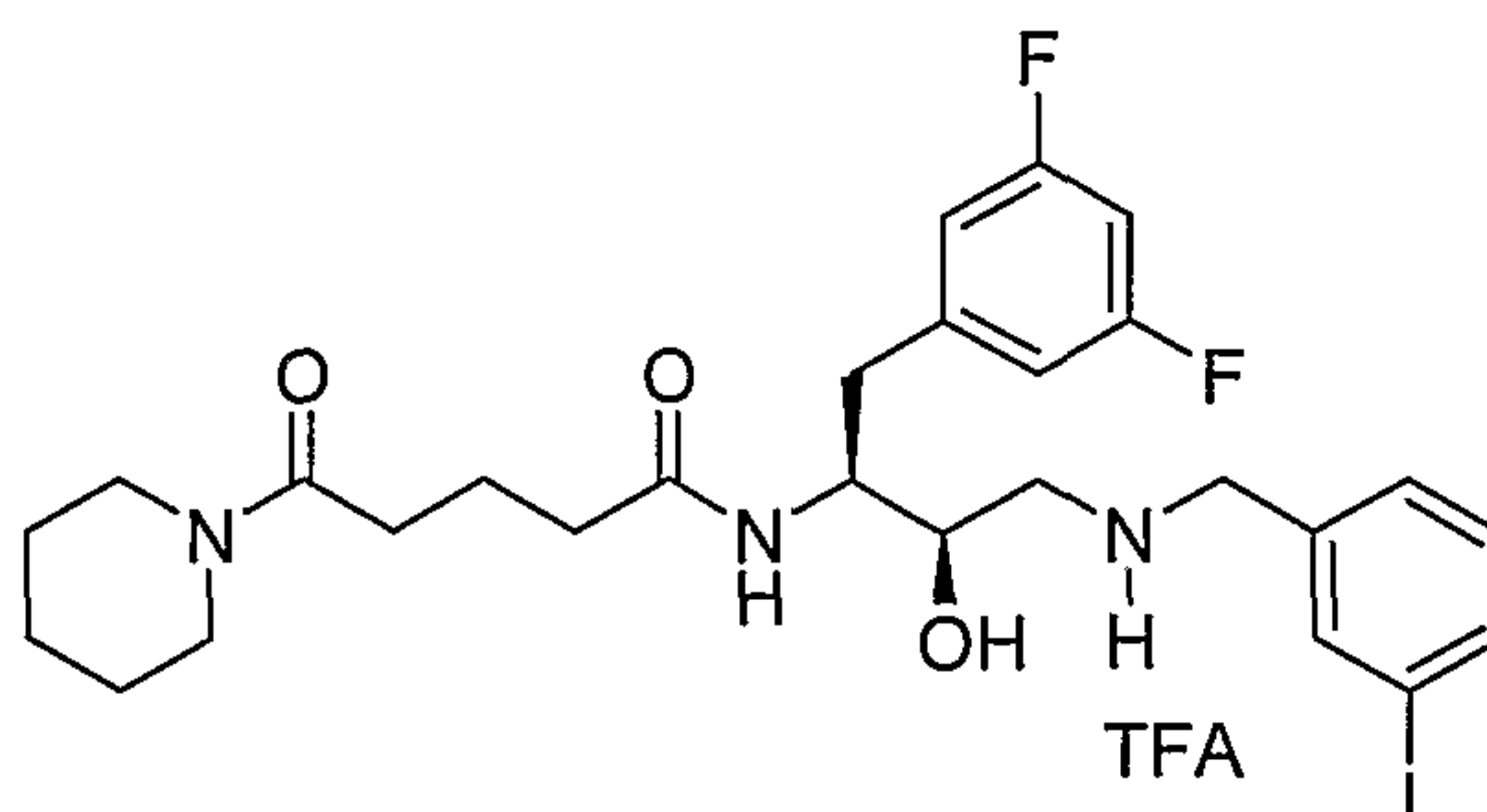
piperidinyl)pentanoyl]amino}butyl(3-iodobenzyl) carbamate  
(XXXVI)



5 HOBt (81 mg, 0.6 mmole) and EDC (105 mg, 0.55 mmole) are added to 1-carboxy-5-piperdinyglutaramide (IX, 100 mg, 0.5 mmole) in DMF (2 ml). The acid is activated 60 minutes then treated with 1-9H-fluoren-9-ylmethyl (2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl(3-iodobenzyl)carbamate  
10 hydrochloride (XXXV, PREPARATION 14, 300 mg, 0.43 mmole) and NMM (0.19 ml, 1.72 mmole). The reaction is stirred 3 hrs then concentrated under reduced pressure. The residue is partitioned between ethyl acetate and saturated aqueous bicarbonate. The organic phases are washed with aqueous  
15 potassium bisulfate, saline, dried over sodium sulfate and finally concentrated under reduced pressure to give crude product. Purification via flash chromatography with ethyl acetate/hexane (50/50) then methanol/ethyl acetate (10/90) gives the title compound, M + H = 838 g/m.

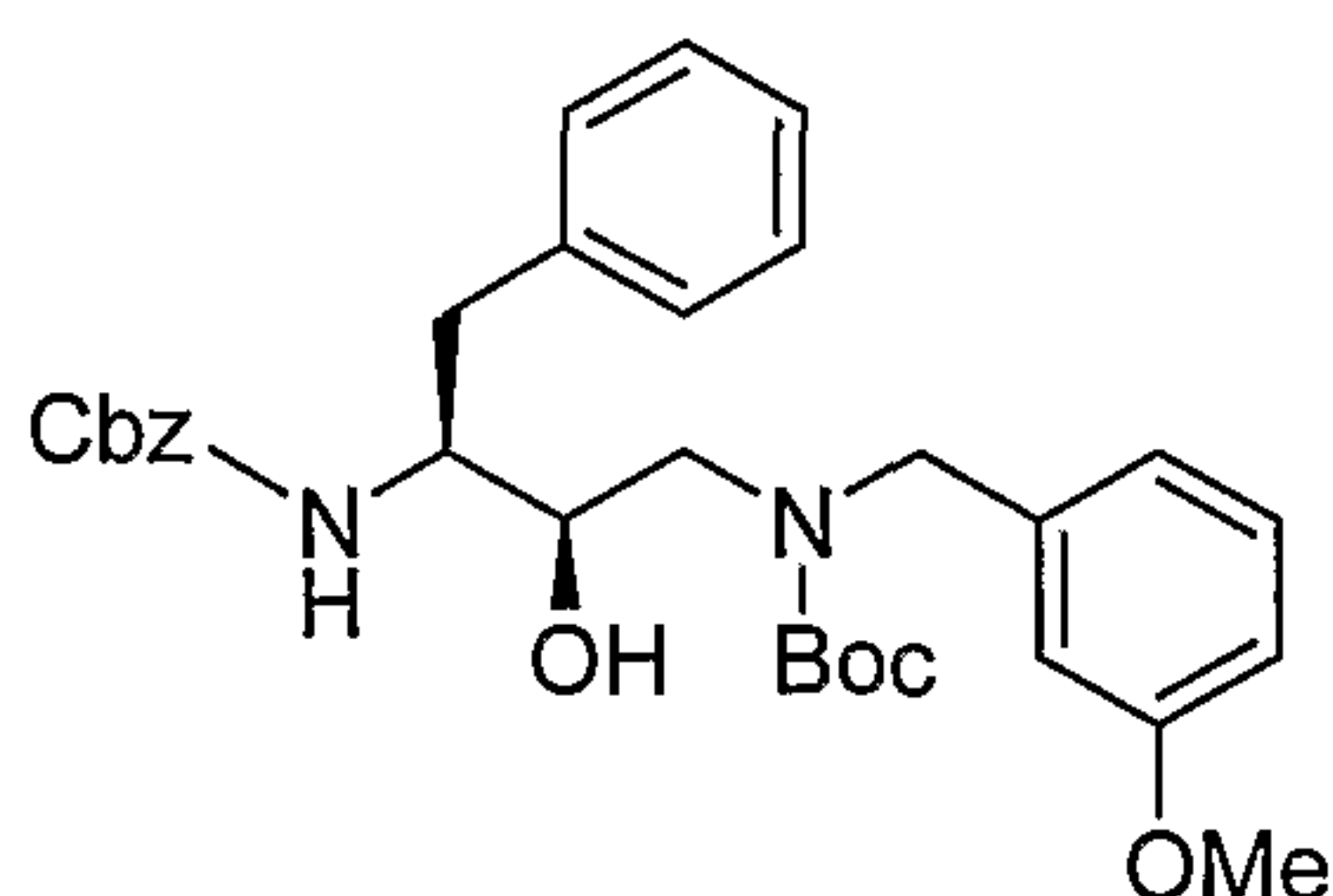
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PREPARATION 16 1- N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-5-oxo-5-(1-piperidinyl)pentanamide trifluoroacetate X



1- N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-5-oxo-5-(1-piperidinyl)pentanamide trifluoroacetate (XXXVI, PREPARATION 15, 240 mg, 0.29 mmole is dissolved in diethylamine (10%, 9 ml) in methylene chloride. The reaction is stirred at 20-25° overnight. Next morning the reaction is concentrated under reduced pressure and the residue is redissolved in methylene chloride and purified by preparative reverse phase HPLC. The appropriate fractions are pooled and concentrated under reduced pressure and partitioned between ethyl acetate and saline. The organic phase is separated and dried over sodium sulfate and concentrated to give the title compound, M + H = 614.

15 PREPARATION 17 1-tert-butyl (2R,3S)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutyl (3-methoxybenzyl) carbamate (XXXIV)



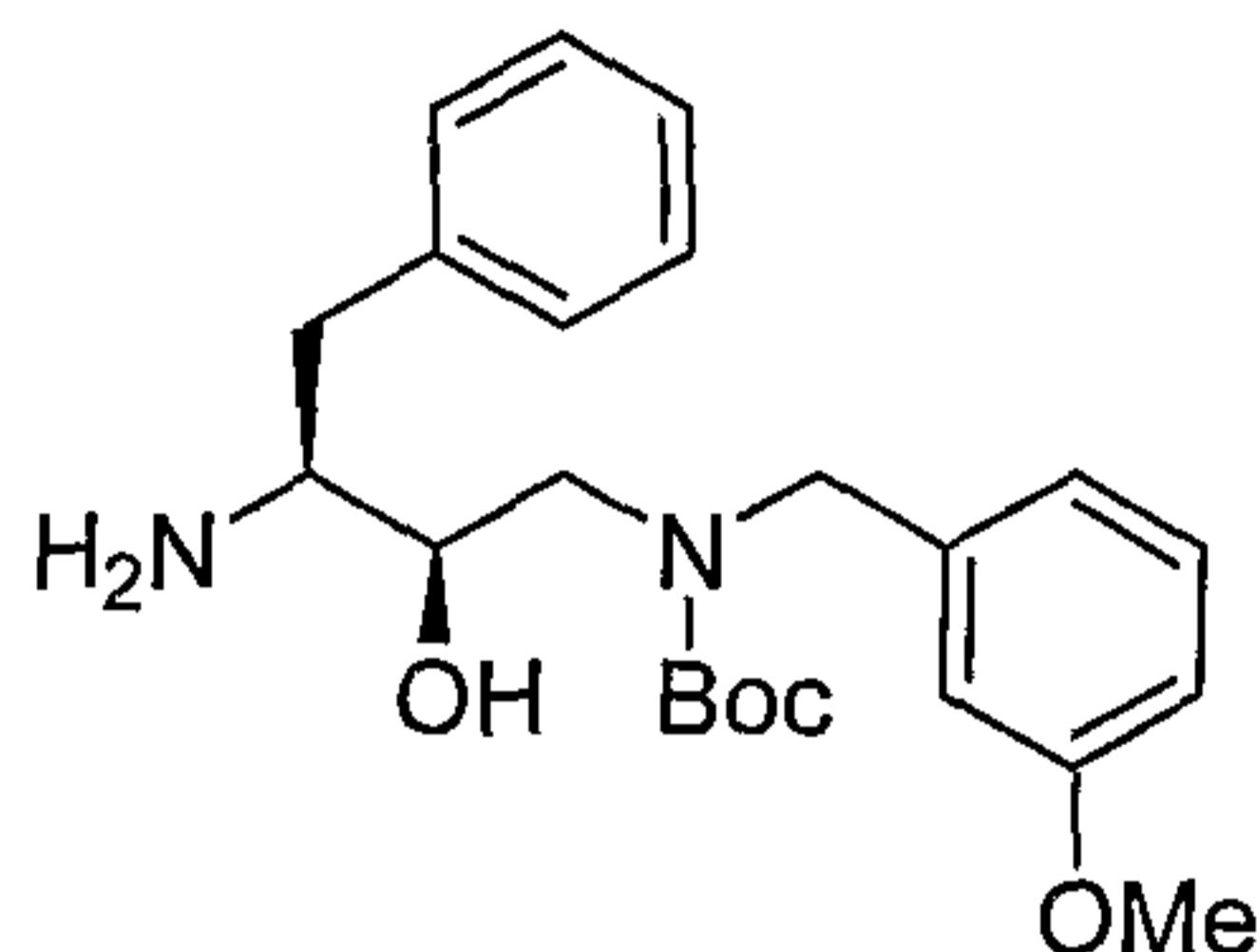
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1-benzyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate hydrochloride (VII, PREPARATION 9, 8.16 g, 18.8 mmole) is mixed with THF (150 ml). The reaction mixture is cooled to 0° and treated with triethylamine (2.9 ml, 20.6 mmole) and di-*t*-butyl pyrocarbonate (4.1 g, 18.8 mmole). The reaction mixture is stirred at 20-25° for 3 hours. The reaction mixture is concentrated under reduced pressure and the residue is partitioned between ethyl acetate and aqueous citric acid (5 %). The organic phase is separated and washed with saturated aqueous bicarbonate,

30

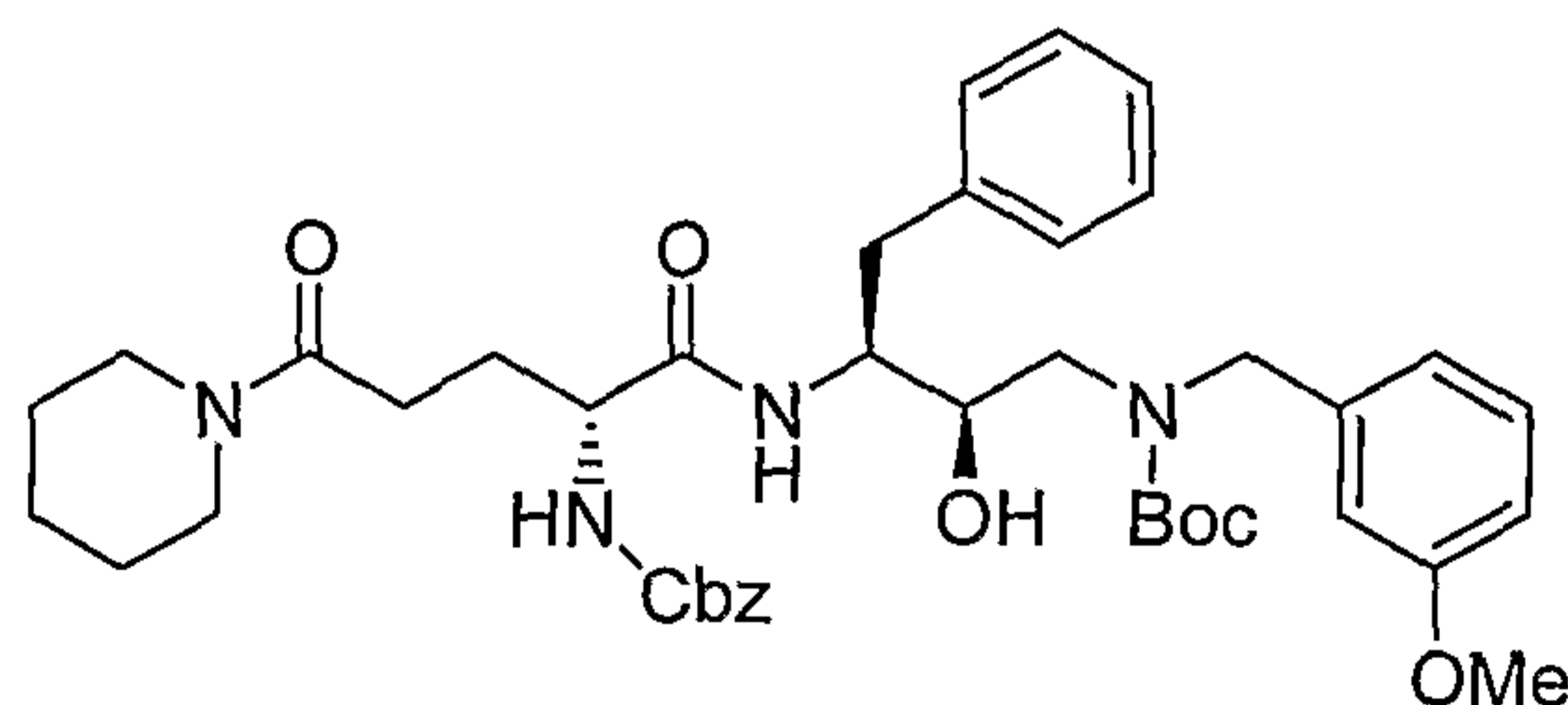
saline, dried over sodium sulfate and concentrated to give the title compound (96% purity by HPLC).

PREPARATION 18 1-tert-butyl (2R,3S)-3-amino-2-hydroxy-4-phenylbutyl(3-methoxybenzyl) carbamate (XXXV)



1-tert-butyl (2R,3S)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutyl(3-methoxybenzyl) carbamate (XXXIV, EXAMPLE 1, 9.47 g), palladium-on-carbon (wet, 5%, 1.9 g) and methanol (95 ml) are added to a 300 ml Fisher Porter bottle. The reaction mixture is charged with hydrogen (50 psi) and hydrogenated for 1.2 hours until gas uptake ceased. The reaction mixture is filtered thru celite and concentrated under reduced pressure to give the title compound, M+H = 401.

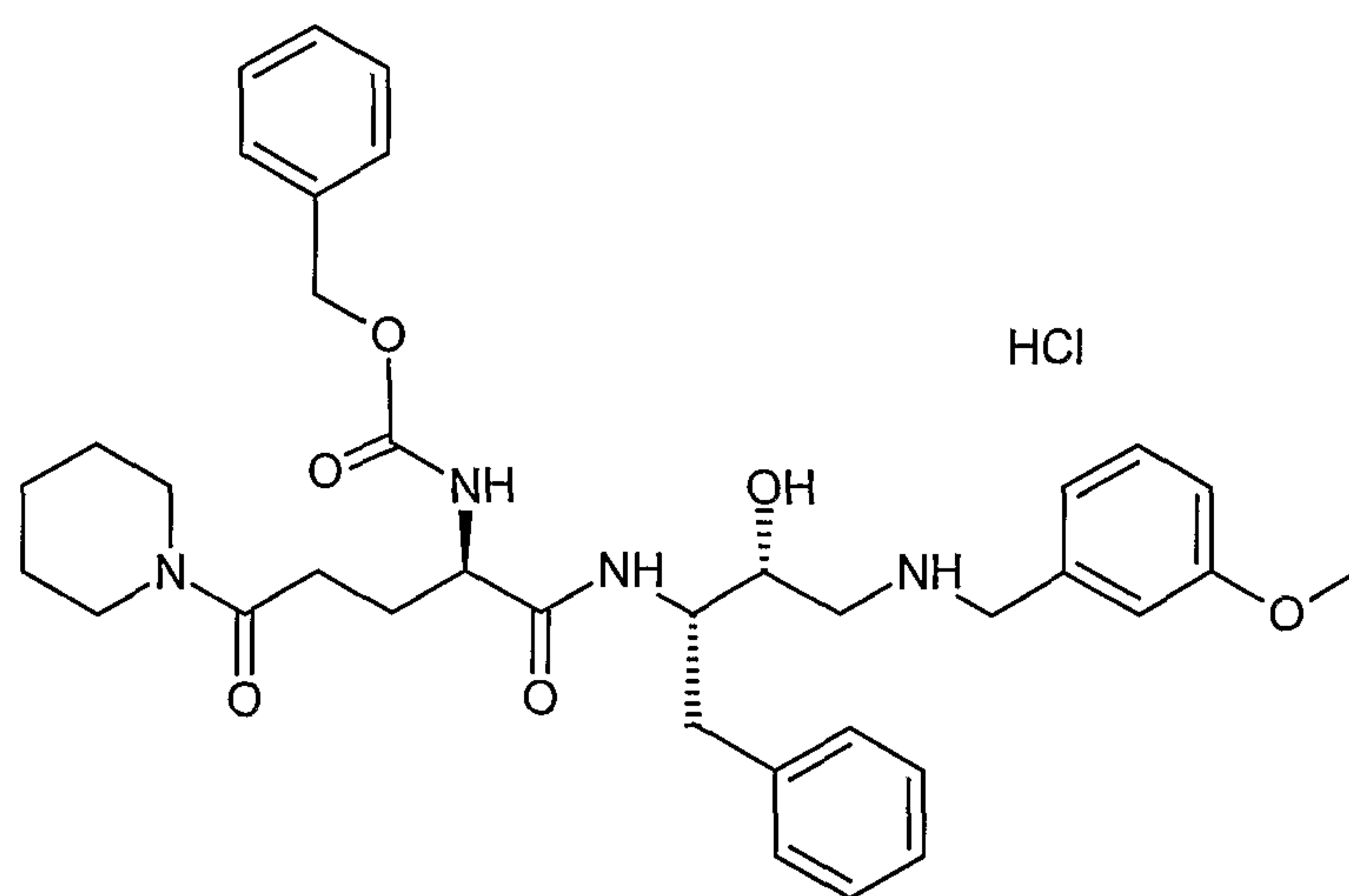
PREPARATION 19 1-Benzyl (1S)-1-[(1S,2R)-1-benzyl-3-[(tert-butoxycarbonyl)(3-methoxybenzyl)amino]-2-hydroxypropyl]amino) carbonyl]-4-oxo-4-(1-piperidinyl)butylcarbamate (XXXVI)



1- (2S)-2-{[(Benzyloxy) carbonyl]amino}-5-oxo-5-(1-piperidinyl)pentanoic (IX, 1.1 g), HOBT (0.64 g, 1.5 eq) and

EDC (700 mg, 1.15 eq) and DMF (4 ml) are mixed. The acid is activated for 20 minutes and then treated with 1-tert-butyl (2R,3S)-3-amino-2-hydroxy-4-phenylbutyl (3-methoxybenzyl) carbamate (XXXV, EXAMPLE 2, 1.3 g) and NMM (0.65 g, 2 eq) in DMF (4 ml). The reaction mixture is stirred 14 hours then concentrated under reduced pressure. The residue is partitioned between ethyl acetate and saturated aqueous bicarbonate. The organic phase is separated and washed with aqueous potassium bisulfate, saline, dried over sodium sulfate and concentrated under reduced pressure to give crude product. The crude product is purified via flash chromatography eluting with ethyl acetate (100 %) to give the title compound, M + H = 731.

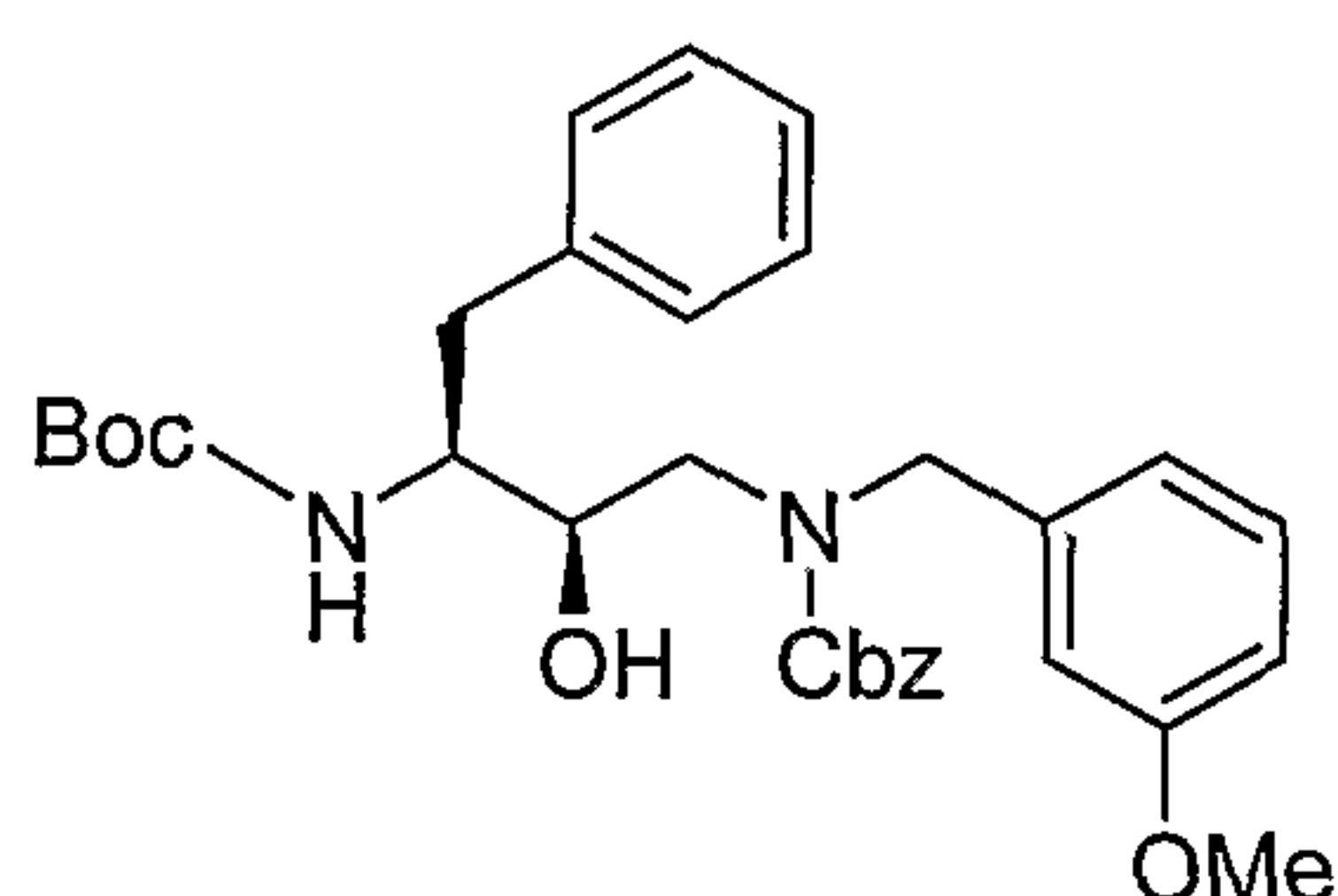
PREPARATION 20 (2R)-2-Carbobenzyloxyamino-N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-oxo-5-piperidin-1-ylpentanamide hydrochloride X



A 50 ml round bottom flask was charged with 1-benzyl (1S)-1-[(1S,2R)-1-benzyl-3-[(tert-butoxycarbonyl)(3-methoxybenzyl)amino]-2-hydroxypropyl]amino) carbonyl]-4-oxo-4-(1-piperidinyl)butylcarbamate (XXXVI, EXAMPLE 3, 100 mg) in dioxane/hydrochloric acid (4 N, 4 ml). The reaction is stirred 15 minutes when HPLC analysis indicates complete de-protection.

The reaction mixture is concentrated under reduced pressure. The crude product is chased with acetonitrile (5 ml) then methylene chloride (5 ml). The resulting hydrochloride salt is dried under reduced pressure, to give the title compound, M + H = 631.

PREPARATION 21 1-tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (XXXIV)

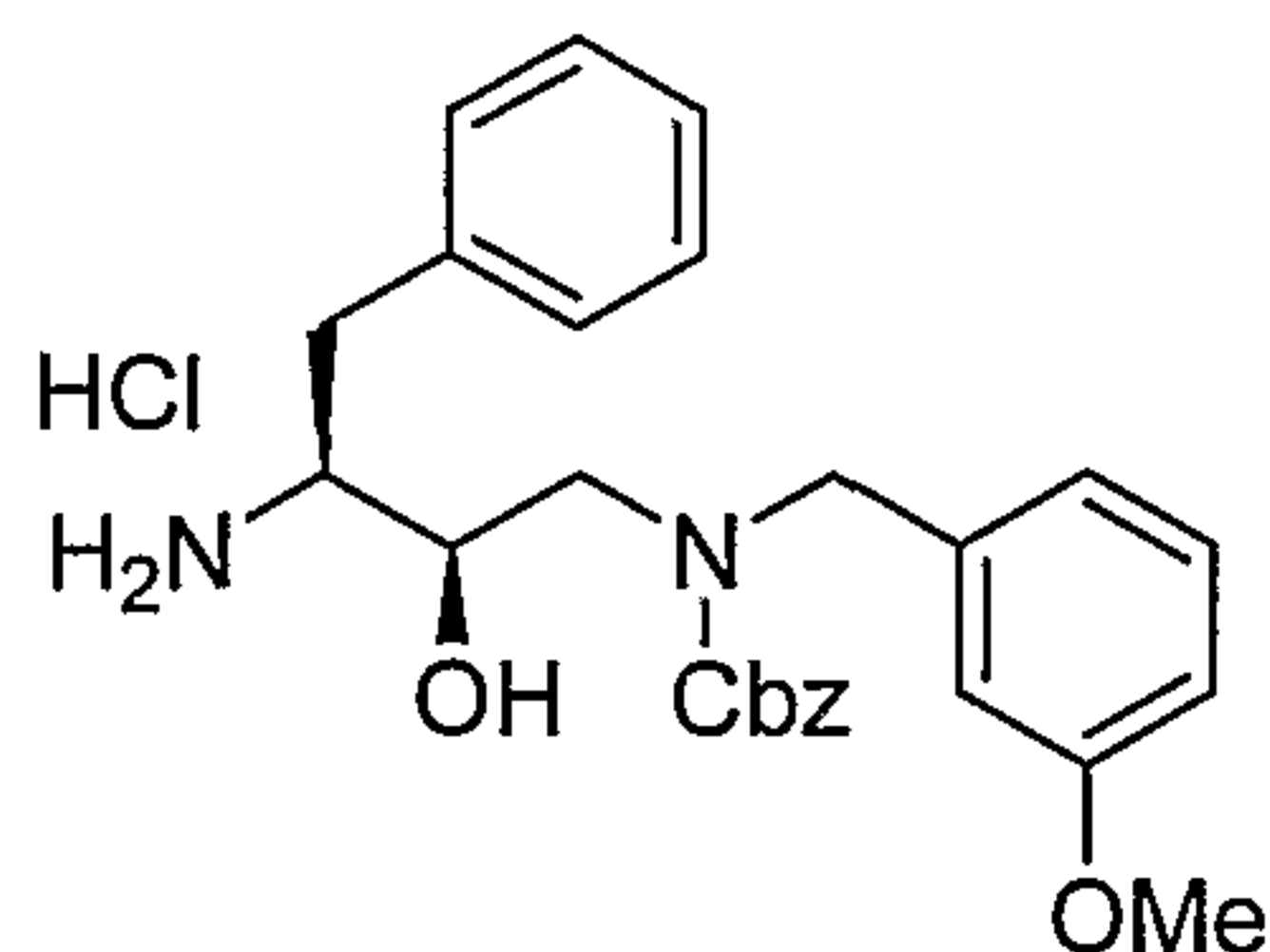


10

*tert*-Butyl (1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (VII, PREPARATION 8, 19.2 g, 48 mmole) in THF (100 ml). The reaction mixture is cooled to 0° and treated with N-benzyloxy carbonyloxysuccinamide (11.9 g, 48 mmole) while maintaining temperature < 5°. The reaction mixture is stirred overnight and in the morning is concentrated under reduced pressure. The residue is partitioned between ethyl acetate and saturated aqueous bicarbonate. The organic phase is separated and washed with citric acid (5%), saline, dried over sodium sulfate and concentrated. The crude product is purified by preparatory HPLC eluting with a gradient of from 20/80-50/50 ethyl acetate. To give the title compound, M + H = 534.

25

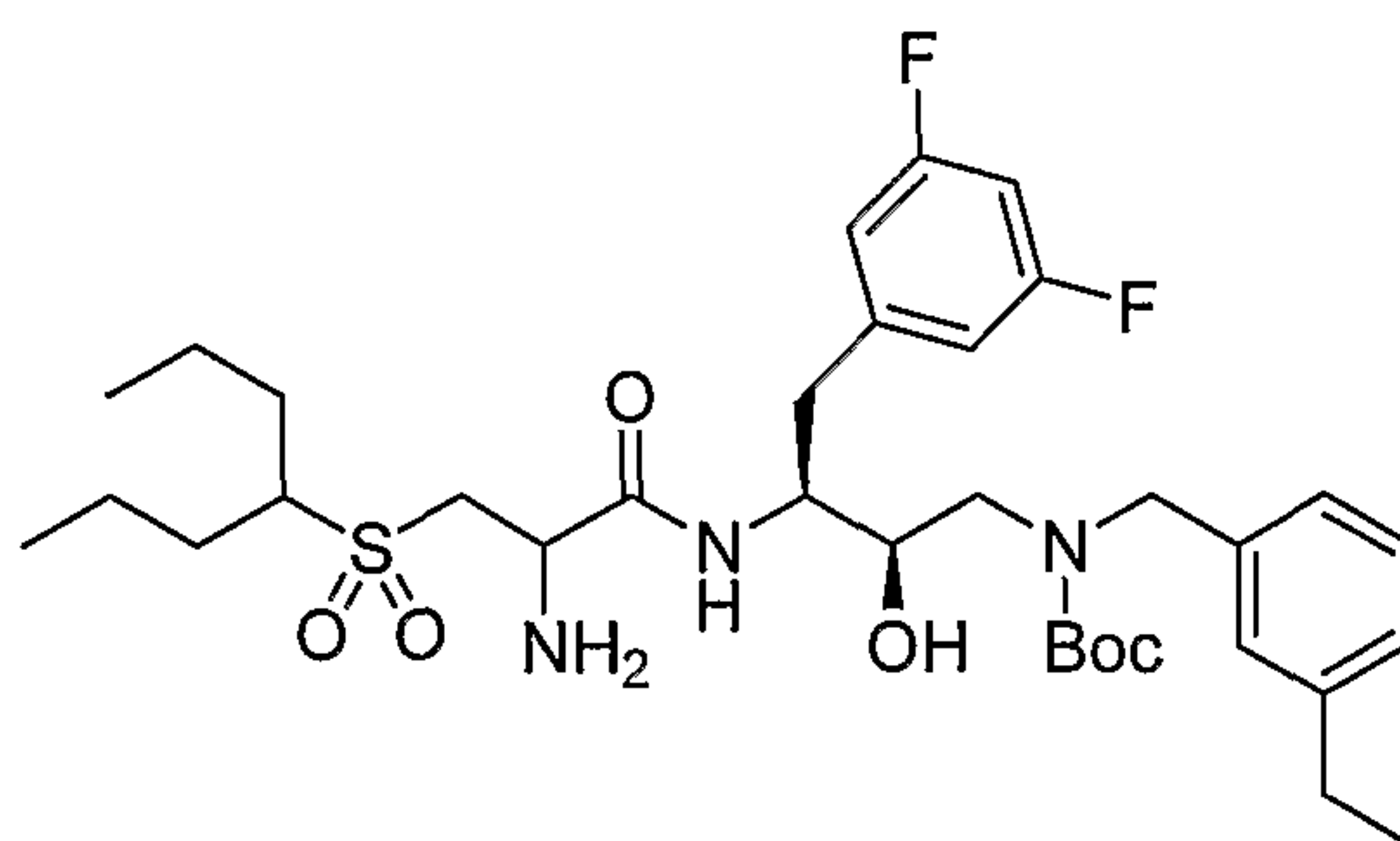
PREPARATION 22 (2R,3S)-3-amino-2-hydroxy-4-phenylbutyl (3-methoxybenzyl)carbamate hydrochloride. (XXXV)



1-tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (XXXIV, EXAMPLE 5, 5.4 g) and dioxane-hydrochloric acid (20 ml, 4 N) are mixed. The reaction mixture is stirred at 20-25° for 30 minutes then poured into stirred ether (300 ml). The product is filtered and dried under reduced pressure to give the title compound, M + H = 435.

10

PREPARATION 23 tert-butyl (2R,3S)-4-(3,5-difluorophenyl)-2-hydroxy-3-({3-[(1-propylbutyl)sulfonyl]alanyl}amino)butyl (3-ethylbenzyl)carbamate (LXXXVII)



15 Methyl 2-acetamidoacrylate (LXXX, 5.0 g, 34 mmole) and 4-mercaptoheptane (4.6 g, 34 mmole) in methanol (50 ml) are mixed. Triethylamine (3.6 g, 36 mmole) is added and the mixture is stirred at 20-25° for 45 minutes. The reaction vessel is then treated with oxone (47.2 g, 77 mmole). After 90  
20 minutes HPLC indicated complete oxidation to the desired sulfone (LXXXII). The reaction mixture is filtered and concentrated under reduced pressure. The residue is partitioned between ethyl acetate and water and the organic



phase is separate and is washed with saline, dried over sodium sulfate, and concentrated under reduced pressure to give methyl N-acetyl-3-[(1-propylbutyl)sulfonyl]alaninate (LXXXII),  
M + H = 308 g/m.

5 Methyl N-acetyl-3-[(1-propylbutyl)sulfonyl]alaninate (LXXXII, 9.2 g) in acetic acid (50 ml) and concentrated hydrochloric acid (50 ml). The mixture is refluxed for 4 hours then concentrated under reduced pressure. The residue is chased with toluene (2 x) then vacuum dried overnight to give  
10 3-[(1-propylbutyl)sulfonyl]alanine hydrochloride salt (LXXXIII).

3-[(1-Propylbutyl)sulfonyl]alanine (LXXXIII, 7.8 g, 27 mmole) and N-CBZ succinamide (7.4 g, 30 mmole) are mixed in methylene chloride (100 ml). The reaction is cooled to 0<sup>o</sup>, and  
15 NMM (6.9 g) is added dropwise. The reaction is allowed to warm to 20-25<sup>o</sup> and stirred for 4 hours at which point HPLC analysis indicated complete reaction. The reaction mixture is concentrated under reduced pressure and partitioned between ethyl acetate and hydrochloric acid (1 N). The organic phase  
20 is washed with water, saline, dried over sodium sulfate, and concentrated under reduced pressure to give N-[(benzyloxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]alanine (LXXXIV) that is used without further purification, M + H = 386.

25 N-[(benzyloxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]alanine (LXXXIV, 4.0 g, 10 mmole) and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (1.2 g, 12 mmole) are mixed in anhydrous methylene chloride (50 ml). To the reaction mixture is added  
30 NMM (5.6 ml, 51 mmole), hydroxybenzotriazole (1.7 g, 13 mmole) and lastly 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.1 g (16 mmole). After stirring at 20-25<sup>o</sup> for 3 hours, HPLC analysis indicates complete reaction. The reaction mixture is diluted with methylene chloride and washed

with saturated sodium bicarbonate solution, citric acid (0.5 M), and saline. The organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure to give N<sup>2</sup>-[(benzyloxy)carbonyl]-N<sup>1</sup>-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide (LXXXV).

N<sup>2</sup>-[(benzyloxy)carbonyl]-N<sup>1</sup>-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide (LXXXV) is dissolved in anhydrous methylene chloride. The mixture is cooled to 0° and di-*tert*-butyl dicarbonate (2.5 g, 12 mmole) and *N*-methyl morpholine (1.2 ml, 11 mmole) are added. The reaction mixture is allowed to warm to 20-25° and stirred for 18 hours at which point HPLC analysis indicates complete reaction. The reaction mixture is diluted with methylene chloride and washed with saturated sodium bicarbonate solution, and saline. The phases are separated and the organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate is purified on silica gel by flash chromatography using a gradient solvent of ethyl acetate/hexane (5/94 to 40/60) to give N<sup>2</sup>-[(benzyloxy-)carbonyl]-N<sup>1</sup>-{(1S,2R)-N-[(*t*-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide (LXXXVI), M + Na = 824.

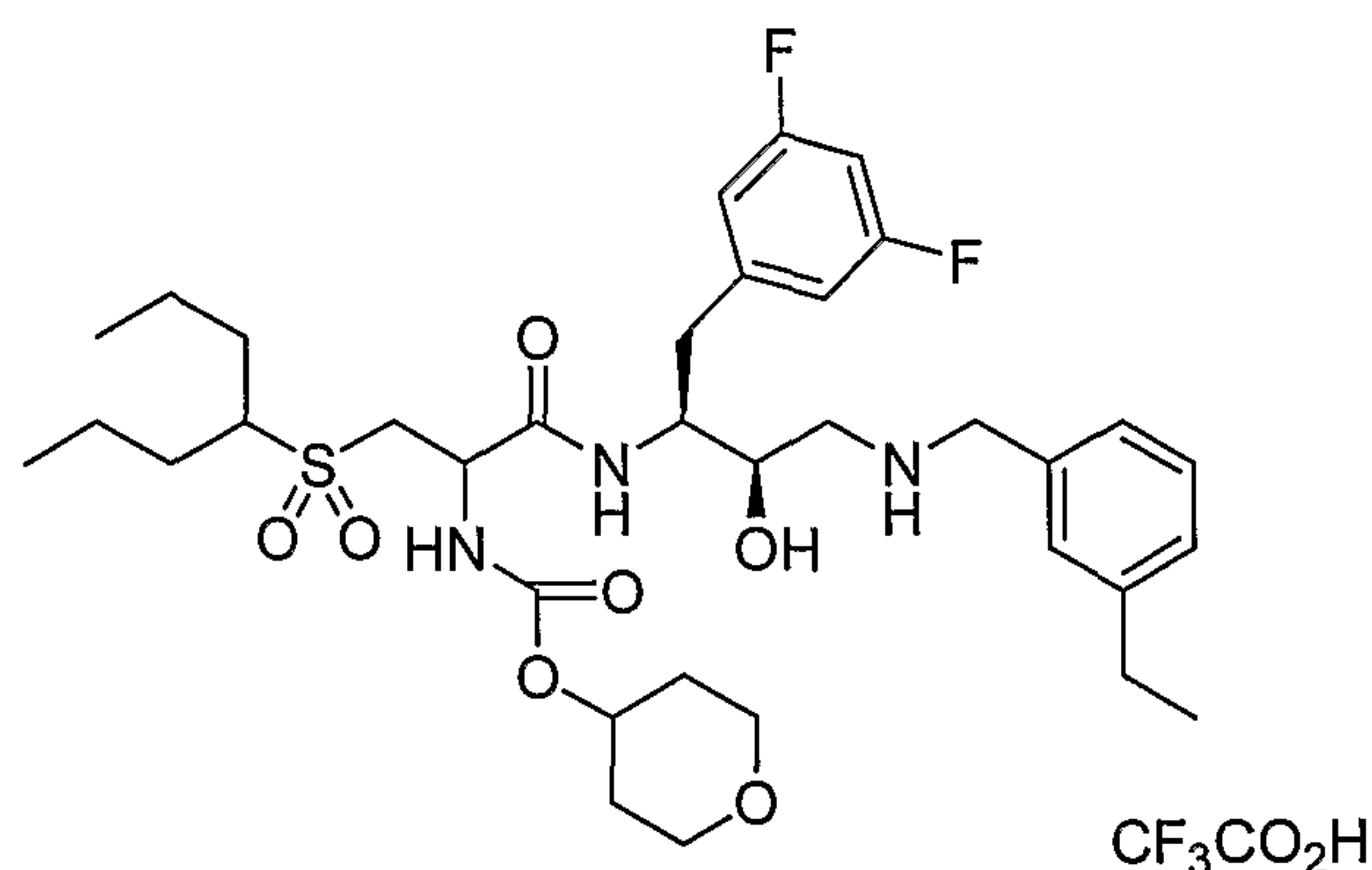
N<sup>2</sup>-[(benzyloxy-)carbonyl]-N<sup>1</sup>-{(1S,2R)-N-[(*t*-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide (LXXXVI, 3.4 g, 4.2 mmole) in methanol (50 ml) is added to a Fisher-Porter bottle. After degassing with nitrogen, palladium on carbon (5% Pd/C, 1.6 g, Degussa E101 50% water) is added. The reaction vessel is purged with nitrogen (40 psi, 4 x) then pressurized to 50 psi with hydrogen. After 15 minutes, HPLC analysis indicates complete reaction. The catalyst is removed by filtration

through celite, and the filtrate concentrated under reduced pressure to give  $N^1$ -{(1S,2R)-N-[(*t*-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alanine (LXXXVII),  $M+H = 668$ .

5

PREPARATION 24  $N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- $N^2$ -{[tetrahydropyran-4-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate (X-LXXXIX)

10



Tetrahydro-4H-pyran-4-ol (1.0 g, 9.8 mmole) is mixed with acetonitrile (50 ml). Di-(N-succinimidyl)carbonate (3.5 g, 13.5 mmole) is then added and stirred for 42 hours at 20-25°.

15 The reaction mixture is then concentrated under reduced pressure, redissolved in ethyl acetate, and washed with aqueous hydrochloric acid (1 N), saturated sodium bicarbonate solution, and saline. The phases are separated and the organic phase is dried over sodium sulfate, filtered, and concentrated under  
20 reduced pressure. The crude material is recrystallized from hot ethyl acetate and hexane to give 1-{[(tetrahydro-2H-pyran-4-yloxy)carbonyl]oxy}pyrrolidine-2,5-dione,  $M + Na = 266$ .

25  $N^1$ -{(1S,2R)-N-[(benzyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alanine (LXXXVII, EXAMPLE 101, 251 mg, 0.31 mmole) is mixed with 1-{[(tetrahydro-2H-pyran-4-yloxy)carbonyl]-oxy}pyrrolidine-2,5-dione (100 mg) in methylene

chloride (3 ml). Triethylamine (70  $\mu$ l, 0.51 mmole) is added and the mixture stirred at 20-25° overnight. The reaction mixture is diluted with ethyl acetate and washed with citric acid (5%), saturated sodium bicarbonate solution, and saline.

5 The phases are separated and the organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material is purified by reverse phase HPLC using a gradient solvent of acetonitrile in water with 0.5% trifluoroacetic acid to give of N<sup>1</sup>-{(1S,2R)-N-

10 [(benzyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N<sup>2</sup>-{[tetrahydropyran-4-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide (LXXXVIII, M + H = 830.

N<sup>1</sup>-{(1S,2R)-N-[(benzyloxy)carbonyl]-1-(3,5-

15 difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N<sup>2</sup>-{[tetrahydropyran-4-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide (LXXXVIII, 163 mg, 0.20 mmole) in methanol/tetrahydrofuran (1/1, 10 ml) is added to a Fisher-Porter bottle. After degassing with nitrogen, palladium

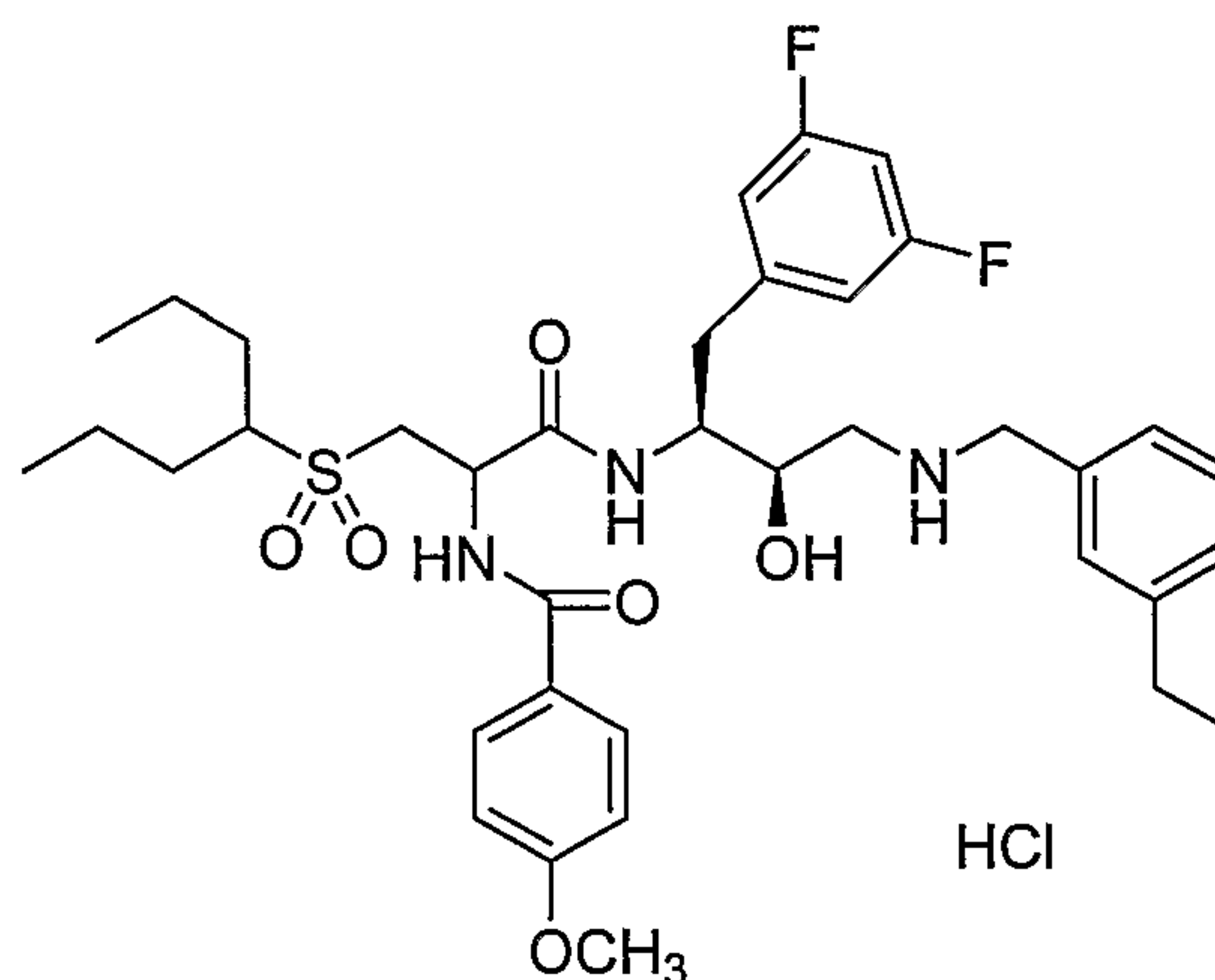
20 on carbon (5% Pd/C, 88 mg, Degussa E101 50% water) is added. The reaction vessel is purged with 40 psi nitrogen (4 x) then pressurized to 50 psi with hydrogen. After 25 minutes, HPLC analysis indicates the reaction is complete. The catalyst is removed by filtration through celite, and the filtrate

25 concentrated under reduced pressure. The crude material is purified by reverse phase HPLC using a gradient solvent of acetonitrile in water with 0.5% trifluoroacetic acid to give N<sup>1</sup>-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-

30 hydroxypropyl}-N<sup>2</sup>-{[tetrahydropyran-4-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate (X-LXXXIX), M+H = 696.

PREPARATION 25 N<sup>1</sup>-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N<sup>2</sup>-(4-methoxybenzoyl)-3-

[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride (X-LXXXIX)



5  $N^1$ -{(1S,2R)-N-[(*t*-benzyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alanine (LXXXVII, EXAMPLE 101, 150 mg, 0.22 mmole) in methylene chloride (1 ml). *p*-anisoyl chloride (32  $\mu$ l, 0.22 mmole) and 4-methylmorpholine (60  $\mu$ l, 10 0.55 mmole) are added. After stirring at 20-25° for 10 minutes, HPLC indicates the reaction is complete. The reaction mixture is diluted with ethyl acetate and washed with saturated sodium bicarbonate solution, citric acid (5%) and saline. The phases are separated and the organic phase is dried over sodium 15 sulfate, filtered, and concentrated under reduced pressure. The crude material is purified on silica gel using flash chromatography (ethyl acetate 20-50% in hexane as eluant to give  $N^1$ -{(1S,2R)-N-[(*t*-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)-amino]-2-hydroxypropyl}- $N^2$ - 20 (4-methoxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide, (LXXXVIII)  $M+H = 802$ .

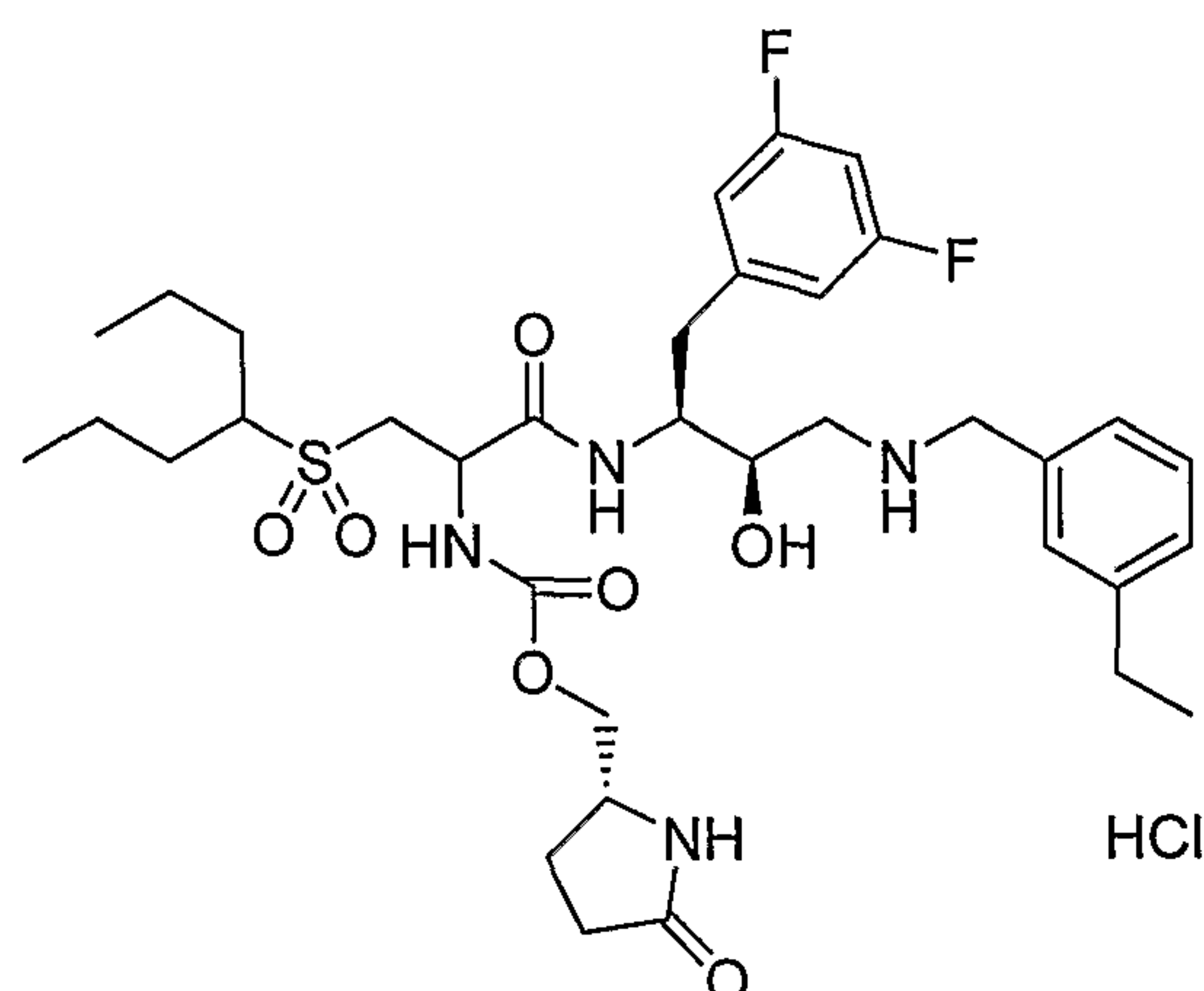
$N^1$ -{(1S,2R)-N-[(*t*-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)-amino]-2-hydroxypropyl}- $N^2$ - 25 (4-methoxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide, (LXXXVIII, 114 mg, 0.14 mmole) in hydrochloric acid (4 N, 1 ml) in dioxane. After stirring for 10 minutes at 20-25°, the

solvent is removed under reduced pressure to give N<sup>1</sup>-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N<sup>2</sup>-(4-methoxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride,

5

PREPARATION 26 N<sup>1</sup>-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N<sup>2</sup>-{[[[(3R)-5-oxopyrrolidin-3-yl]methyl]oxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride (X-LXXXIX)

10



Di-(N-succinimidyl)carbonate (3.1 g, 12.3 mmole) and  
 15 pyridine (1.7 ml, 21.1 mmole) pyridine is added to (R)-(-)-5-(hydroxymethyl)-2-pyrrolidinone (1.0 g, 8.8 mmole) in acetonitrile (50 ml). After stirring for 18 hours at 20-25°, the reaction mixture is concentrated under reduced pressure, redissolved in ethyl acetate, and washed with saturated sodium  
 20 bicarbonate solution and saline. The organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure to give 1-[[[(2S)-5-oxopyrrolidin-2-yl]methoxy]carbonyl]oxy]pyrrolidine-2,5-dione, M+H = 257.

The compound of example 101 (200 mg, 0.30 mmole) and 1-  
 25 [[[(2S)-5-oxopyrrolidin-2-yl]methoxy]carbonyl]oxy]pyrrolidine-2,5-dione (108 mg, 0.45 mmole) are mixed in methylene chloride

(5 ml). To the reaction mixture is added triethylamine (60  $\mu$ l, 0.45 mmole) and stirred at 20-25° overnight. The reaction mixture is diluted with ethyl acetate and washed with citric acid (5%), saturated sodium bicarbonate solution, and saline.

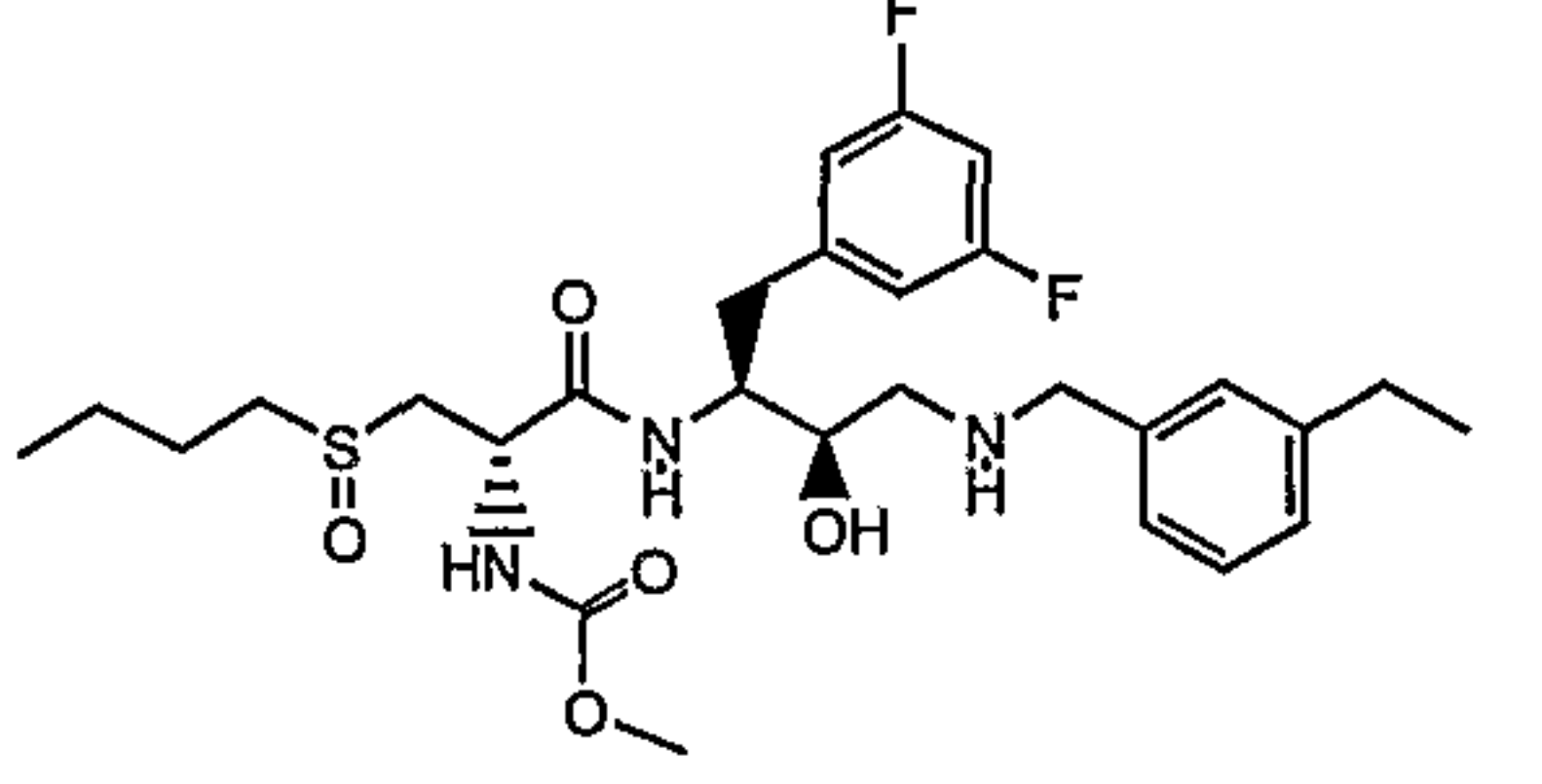
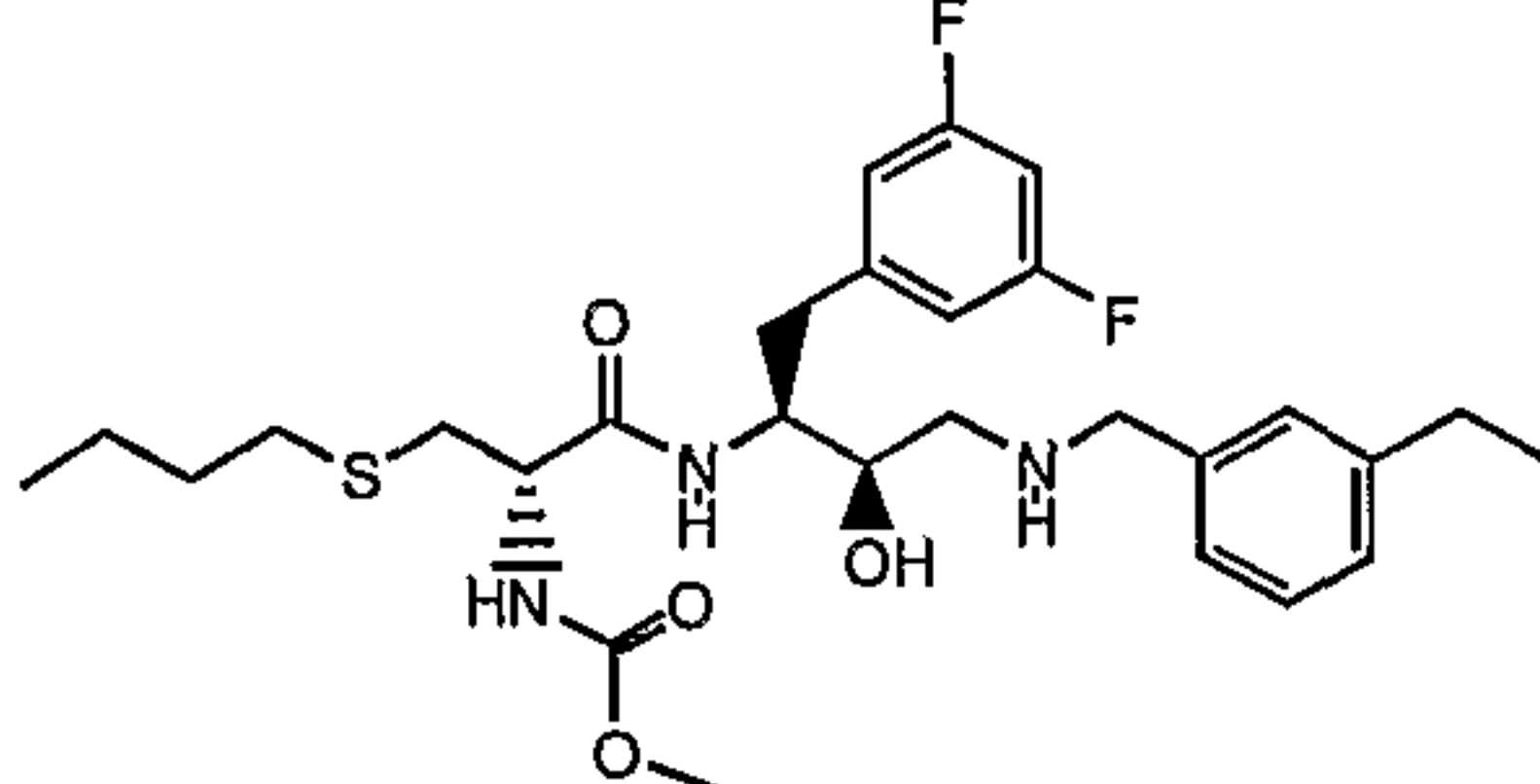
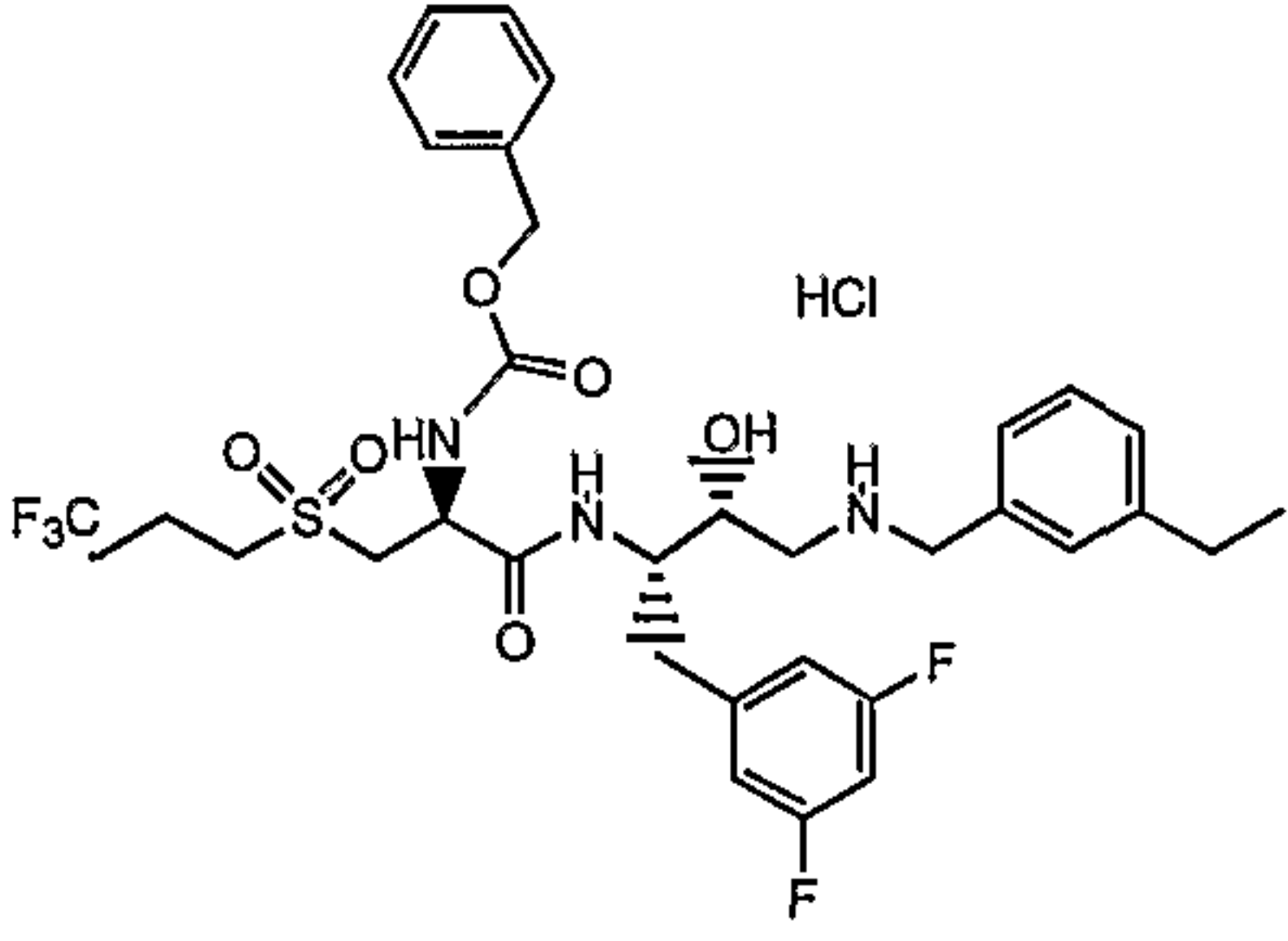
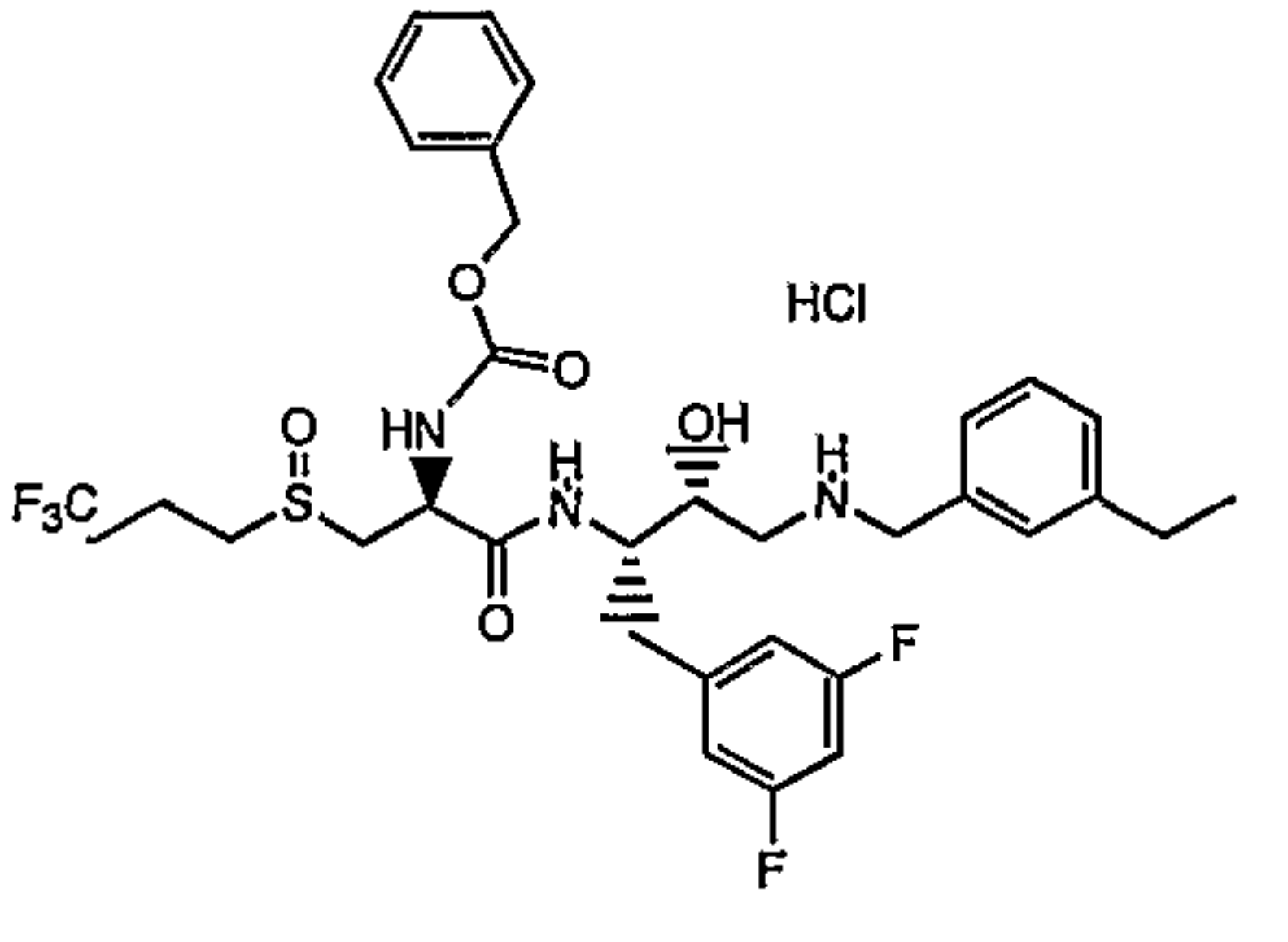
5 The organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by reverse phase HPLC using a gradient solvent of acetonitrile in water with 0.5% trifluoroacetic acid to give  
 10  $N^1$ -{(1S,2R)-[1-(3,5-difluorobenzyl)-3-[(N-[(t-butyloxy)carbonyl])-(3-ethylbenzyl)amino]-2-hydroxypropyl]- $N^2$ -{[[[(3R)-5-oxopyrrolidin-3-yl]methyl]oxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide, M+H = 809.

$N^1$ -{(1S,2R)-[1-(3,5-difluorobenzyl)-3-[(N-[(t-butyloxy)carbonyl])-(3-ethylbenzyl)amino]-2-hydroxypropyl]- $N^2$ -  
 15 {[[[(3R)-5-oxopyrrolidin-3-yl]methyl]-oxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide (247 mg, 0.31 mmole) is mixed with dioxane (2 ml, 4 N hydrochloric acid). After stirring for 10 minutes at 20-25°, the solvent was removed under reduced pressure to give the title compound, M+H = 709.

20

The following compounds in table 1 are prepared essentially according to the procedures described in the schemes, examples and preparations set forth herein. The names in table 1 were generated at least in part by using the  
 25 Advanced Chemistry Development Inc. (ACD) nomenclature program, IUPAC Name Batch Version 4, 4.5 or 5, or Chemdraw Ultra versions 6.0 or 6.02.

Table 1

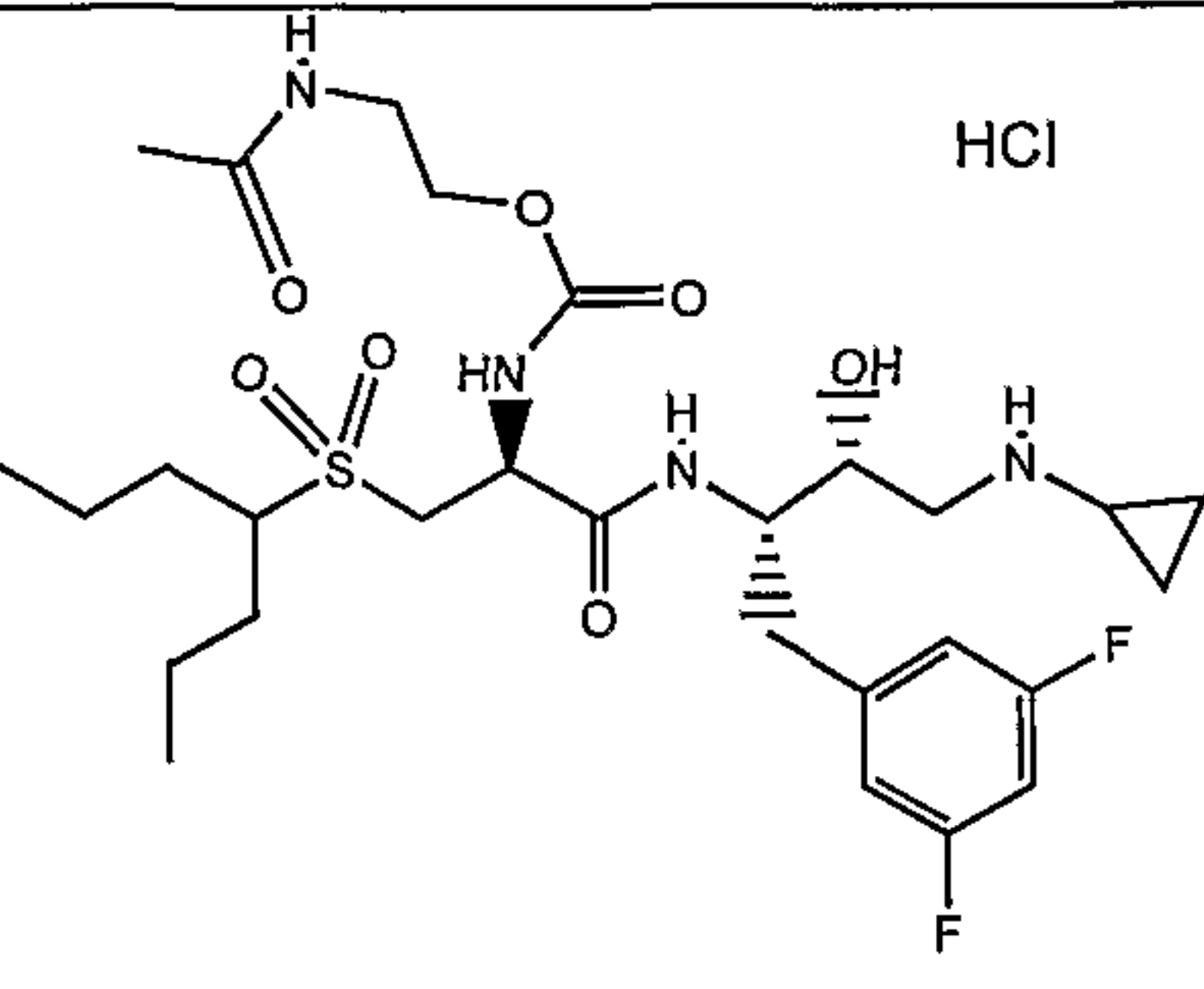
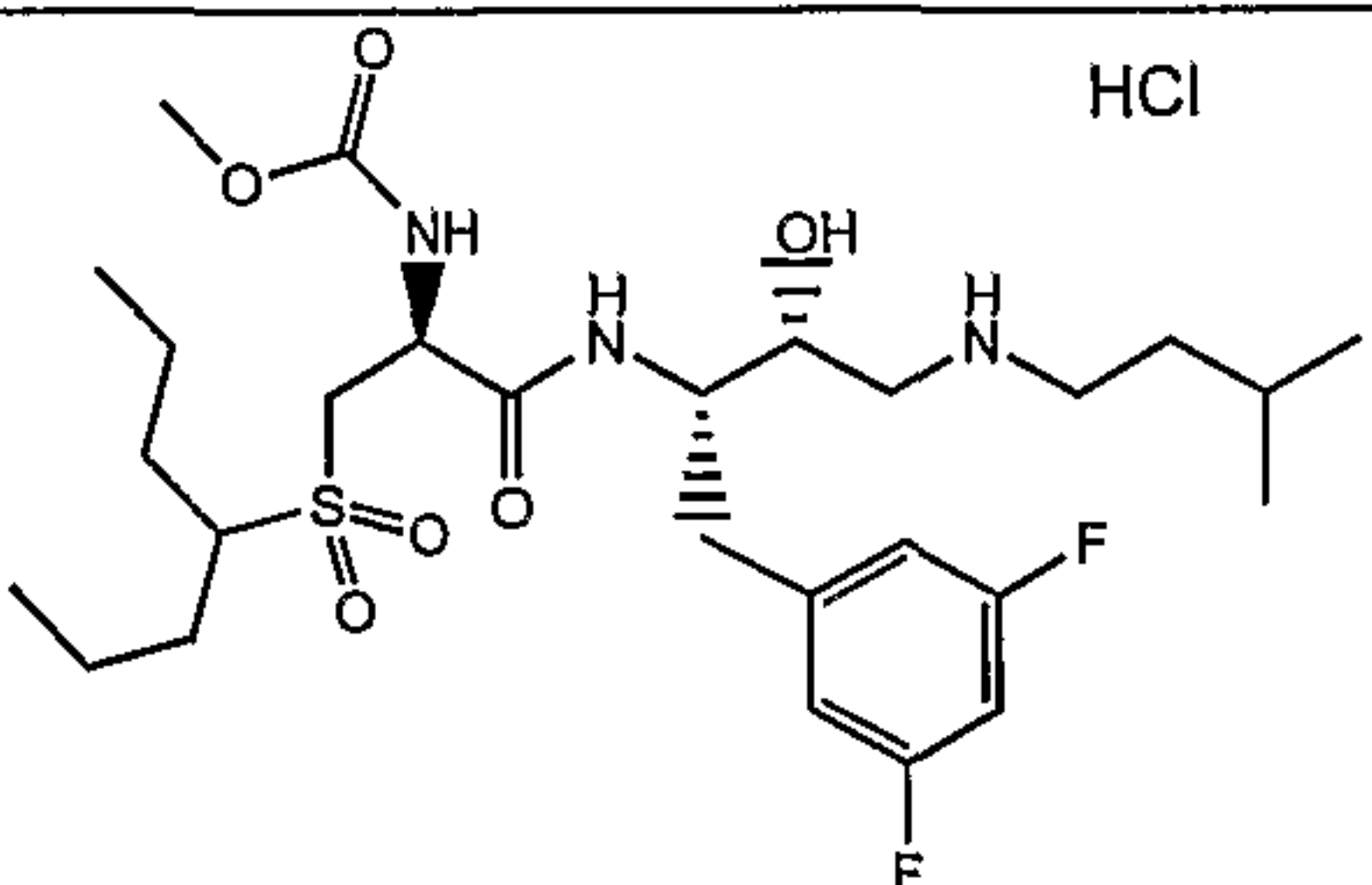
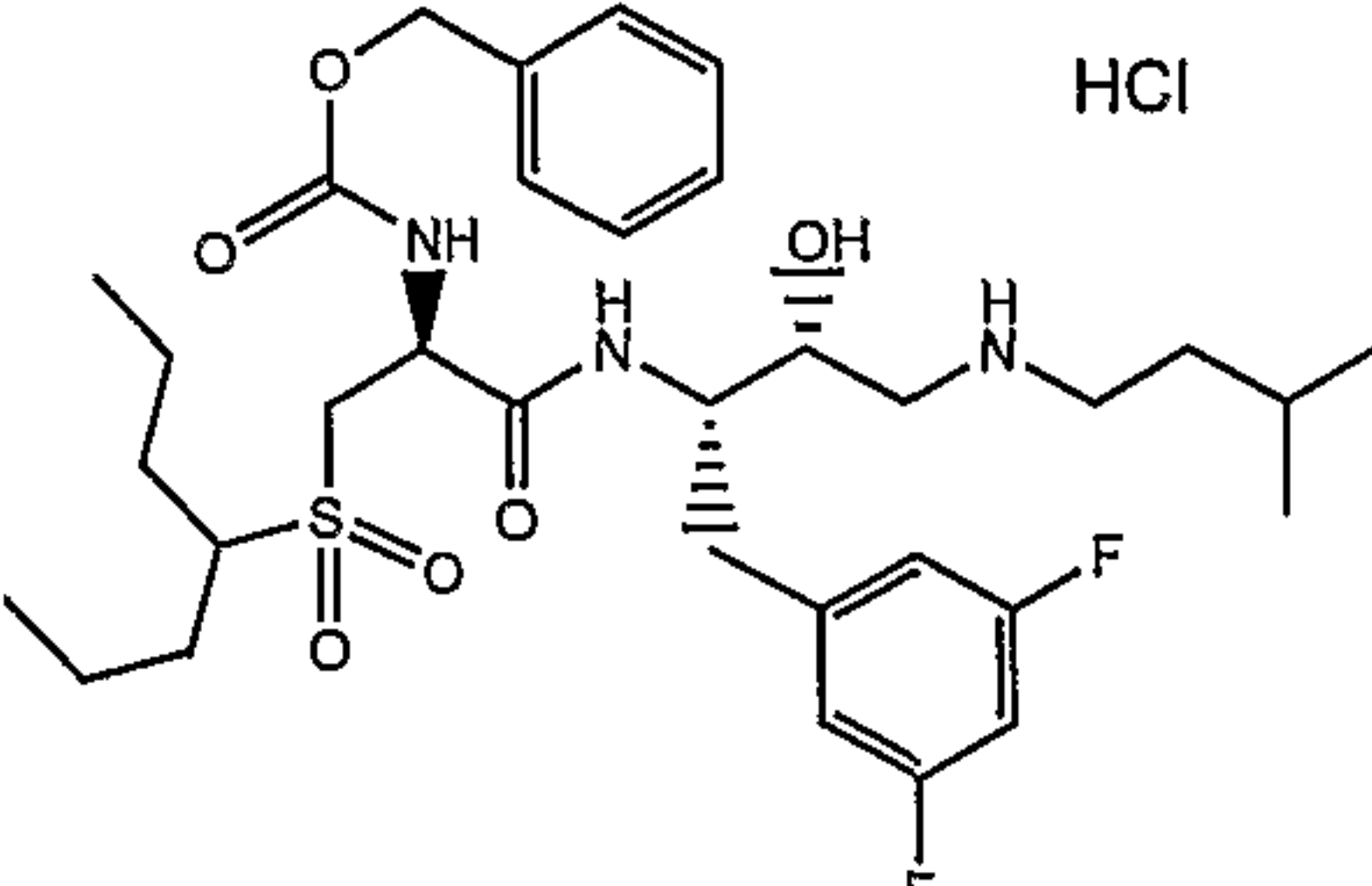
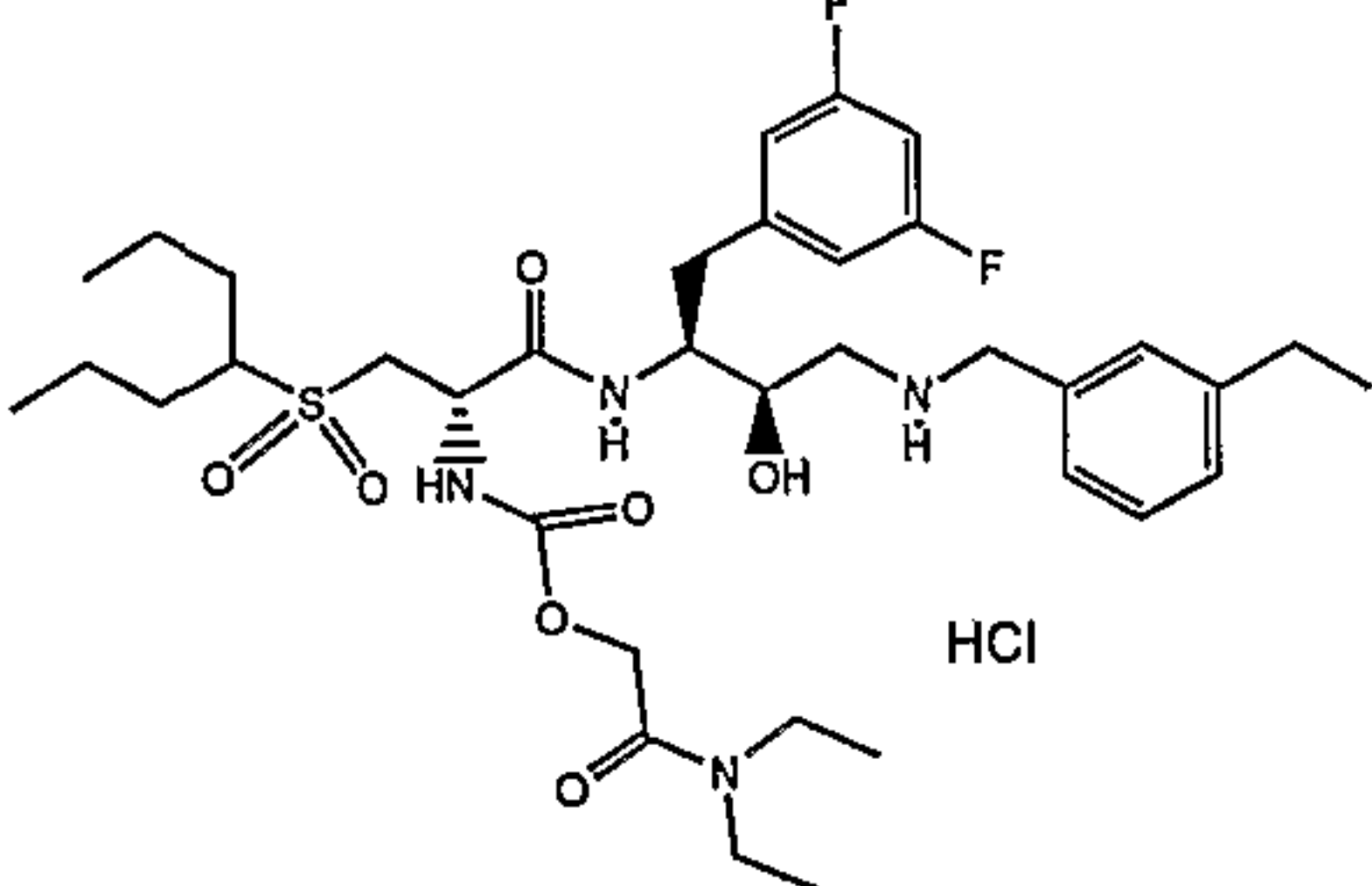
Structure	Compound Name(s)	Low Res Mass Spec M+H
	3-(butylsulfinyl)-N1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N2-[(methoxy)carbonyl]-D-alaninamide	568
	S-butyl-N1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N2-[(methoxy)carbonyl]-D-cysteinamide	552
	N2-[(benzyloxy)carbonyl]-N1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(4,4,4-trifluorobutyl)sulfonyl]-D-alaninamide hydrochloride	714
	N2-[(benzyloxy)carbonyl]-N1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(4,4,4-trifluorobutyl)sulfinyl]-D-alaninamide hydrochloride	698

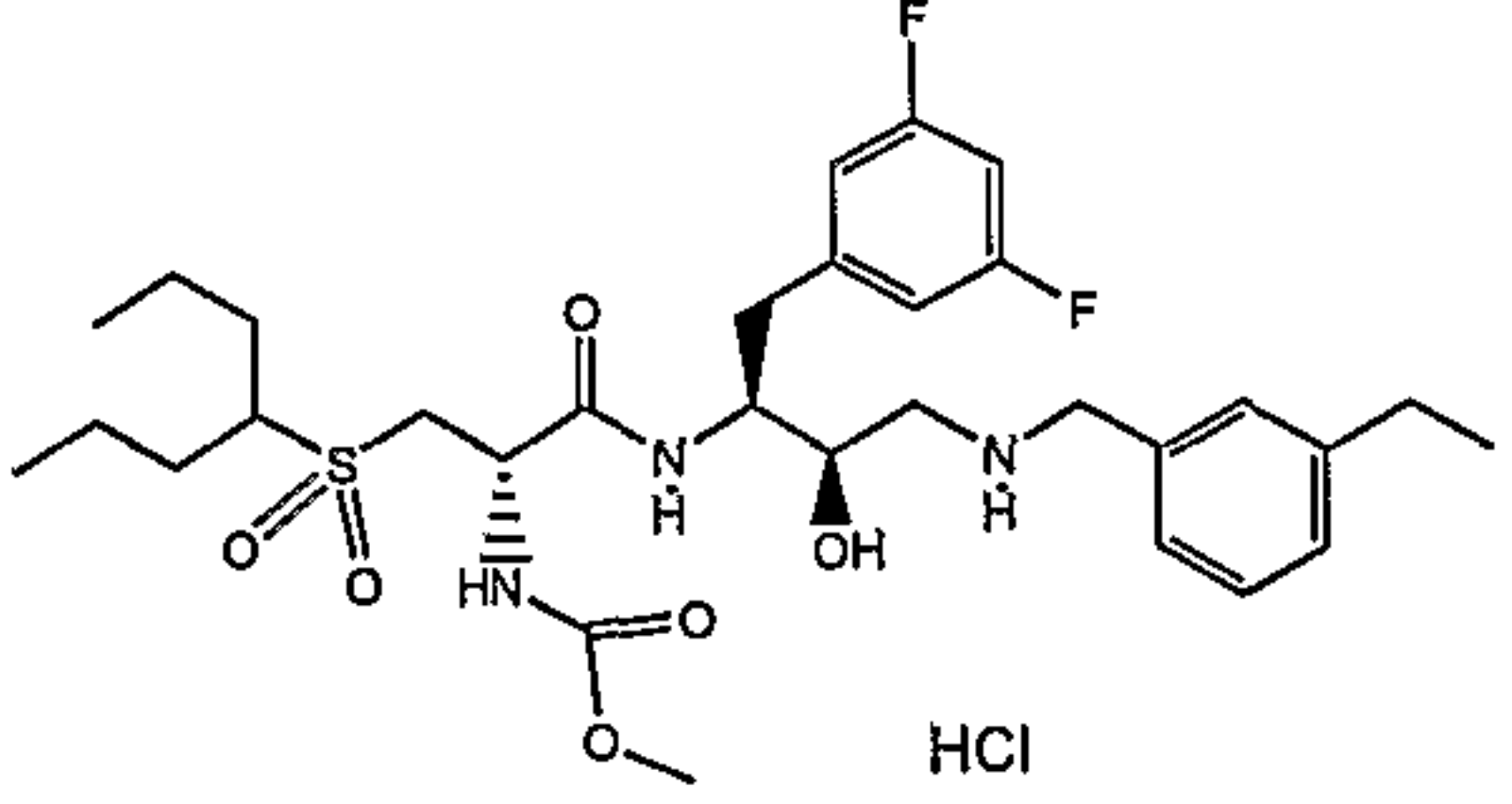
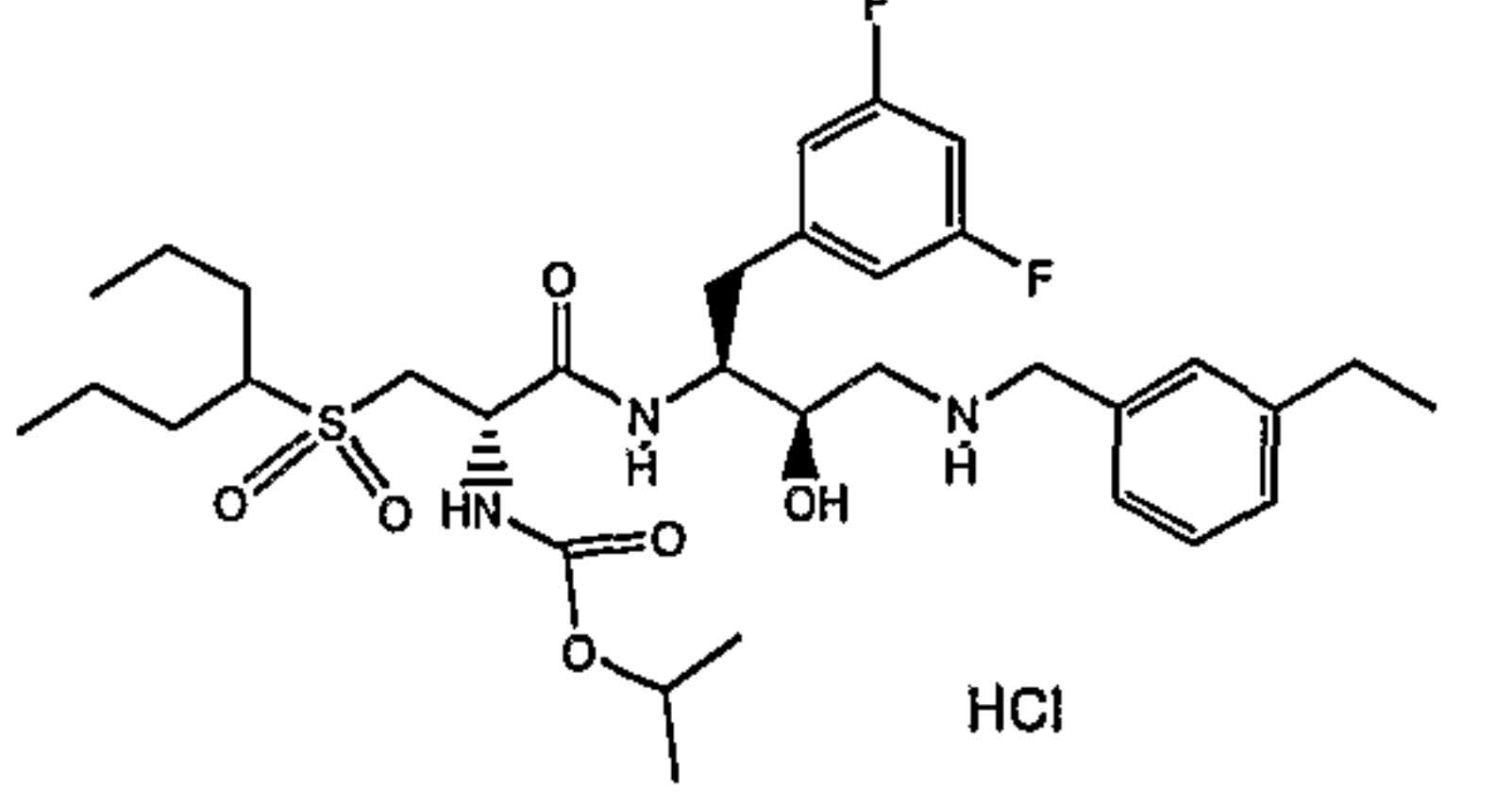
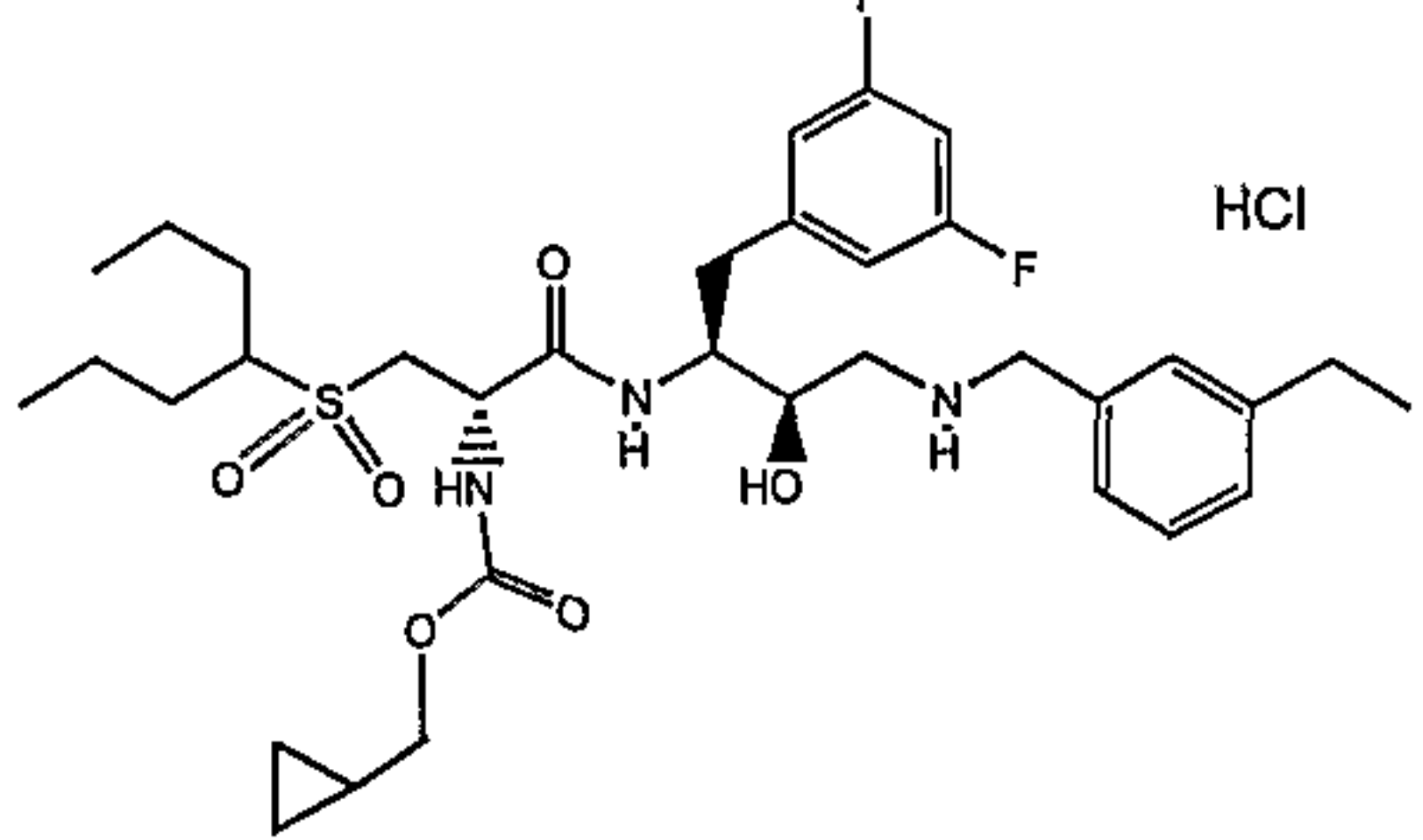
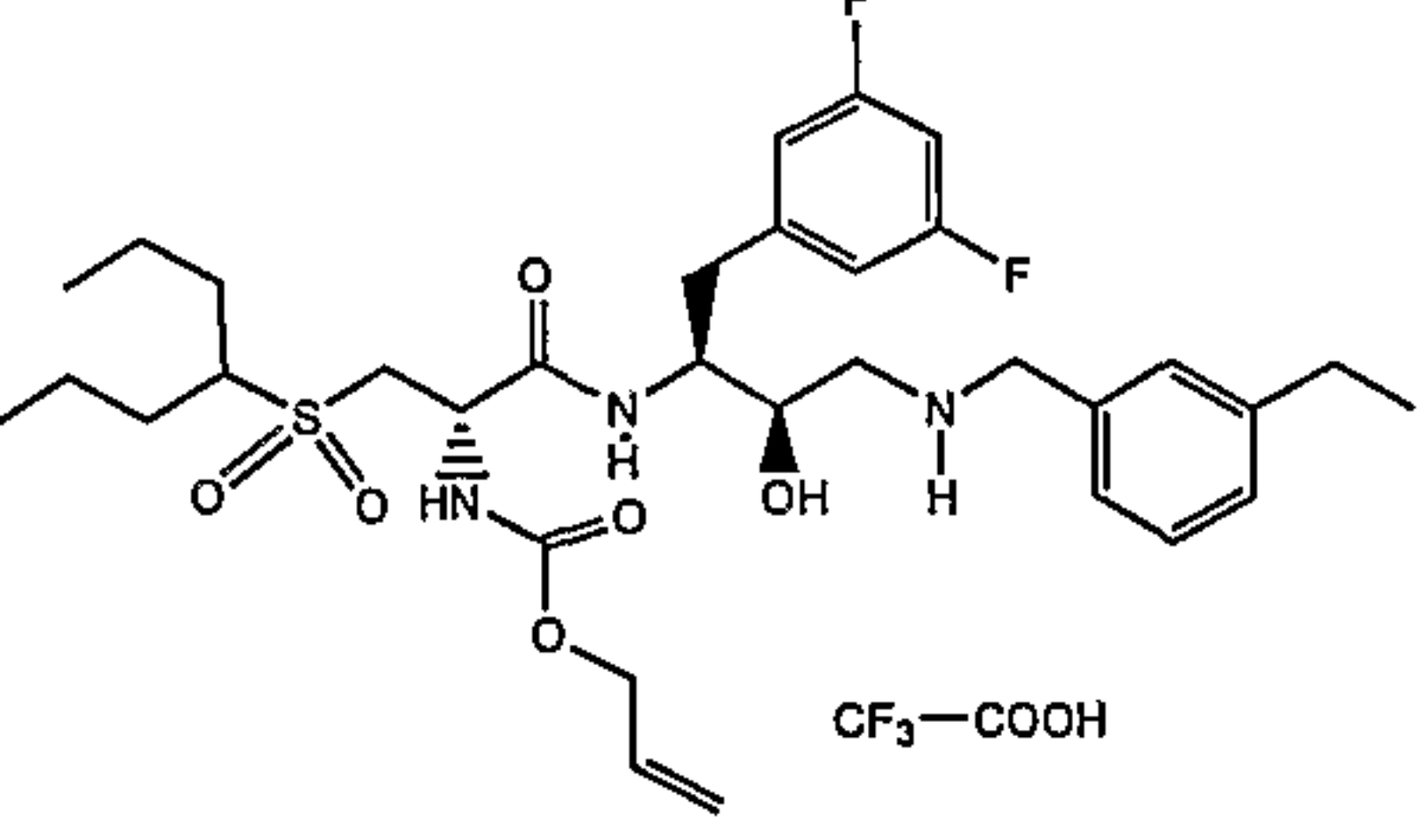


	<p>N~2~- [(benzyloxy) carbonyl] - N~1~- { (1S,2R) -1- (3,5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl } -S- (4,4,4- trifluorobutyl) -D-cysteinamide</p>	682
	<p>3- (butylsulfonyl) -N~1~- { (1S,2R) -1- (3,5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl } -N~2~- [ (methoxy) carbonyl] -D- alaninamide hydrochloride</p>	584
	<p>3- (butylsulfonyl) -N~1~- { (1S,2R) -1- (3,5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl } -N~2~- [ (2,2,2- trifluoroethoxy) carbonyl] -D- alaninamide hydrochloride</p>	652
	<p>N~2~- [ (2- cyanoethoxy) carbonyl] -N~1~- { (1S,2R) -1- (3,5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl } -3- (butylsulfonyl) -D-alaninamide hydrochloride</p>	623
	<p>3- (butylsulfonyl) -N~1~- { (1S,2R) -1- (3,5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl } -N~2~- { [ (3R) - pyrrolidin-3-yl] carbonyl } -D, L-</p>	639

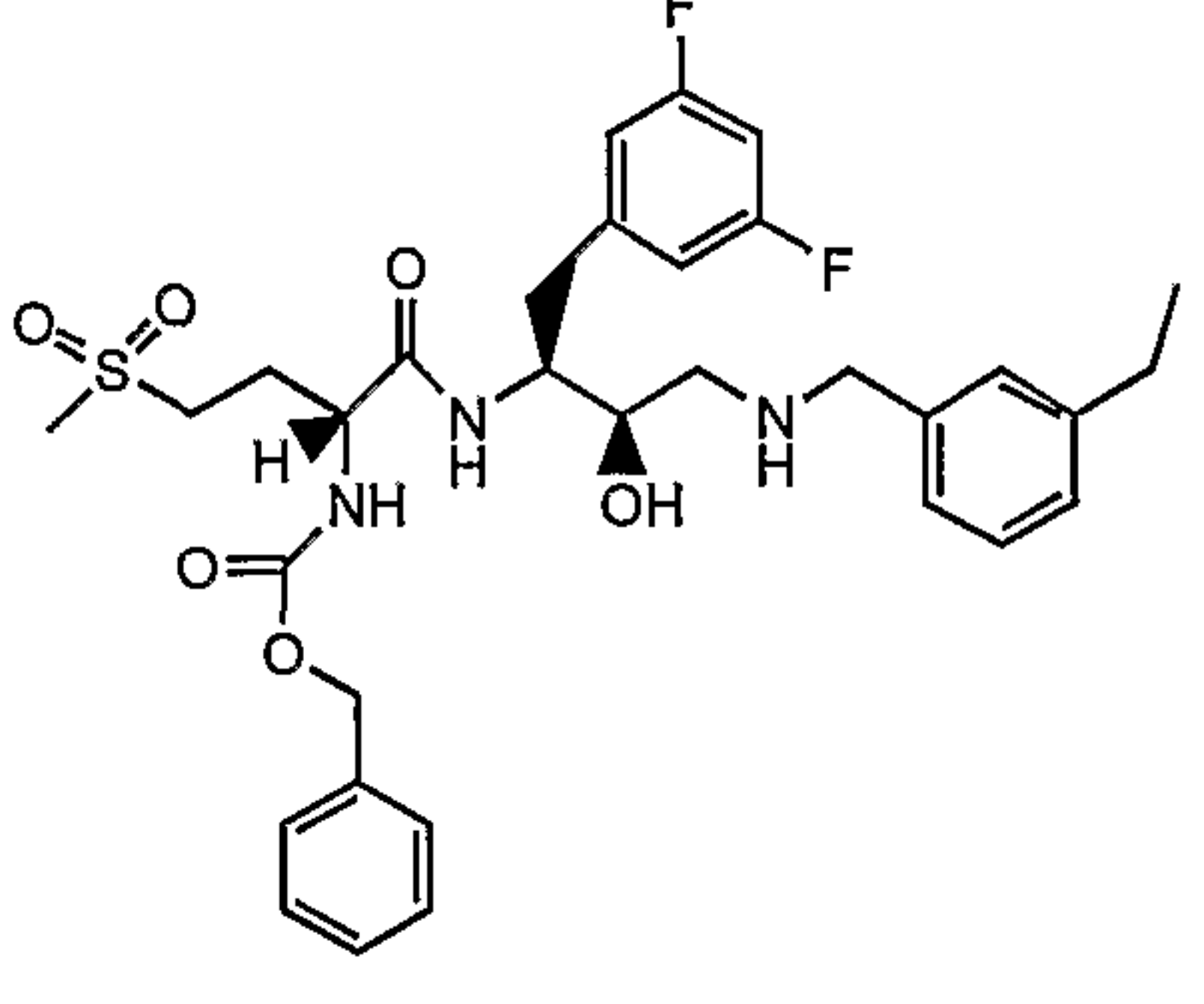
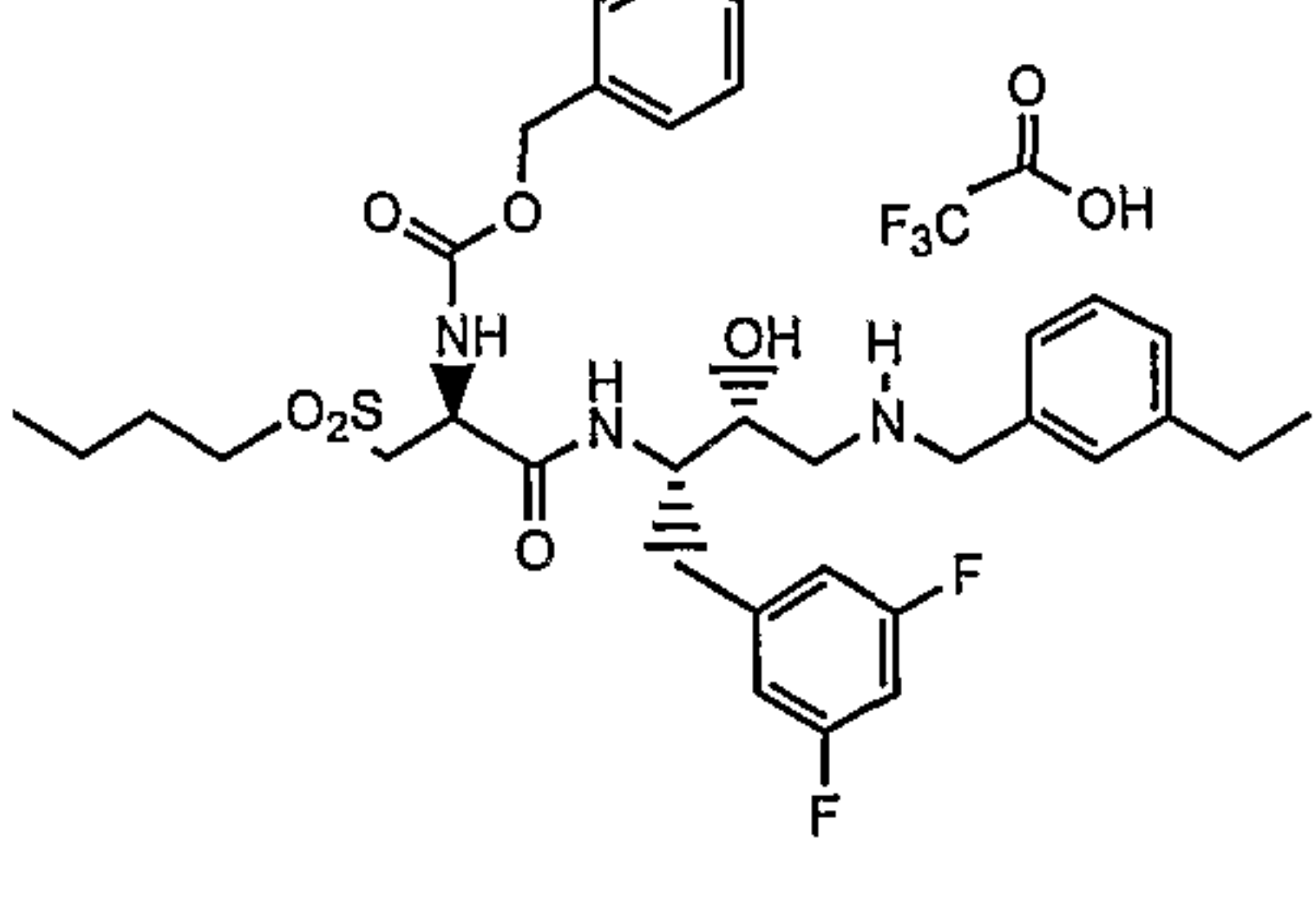
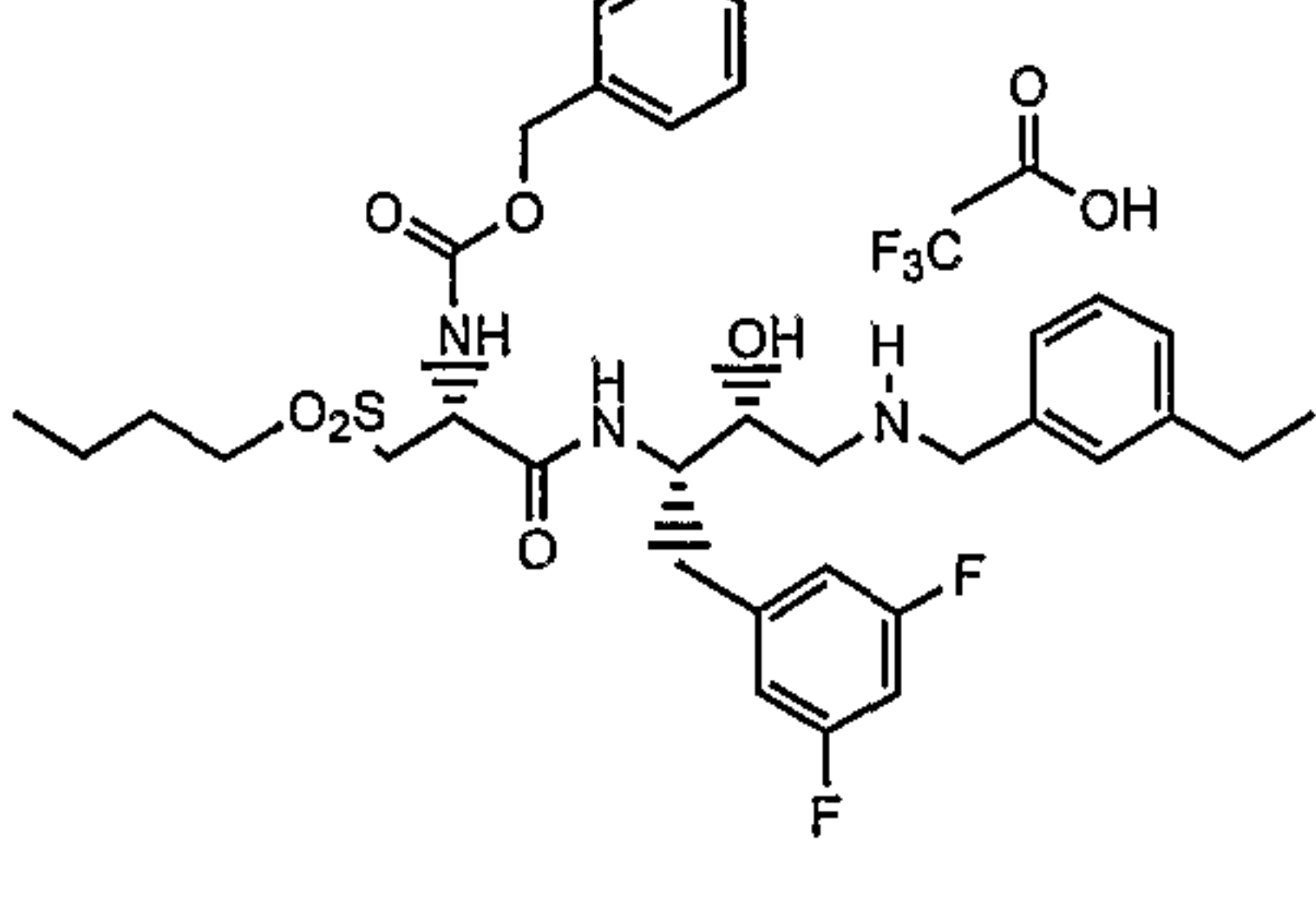
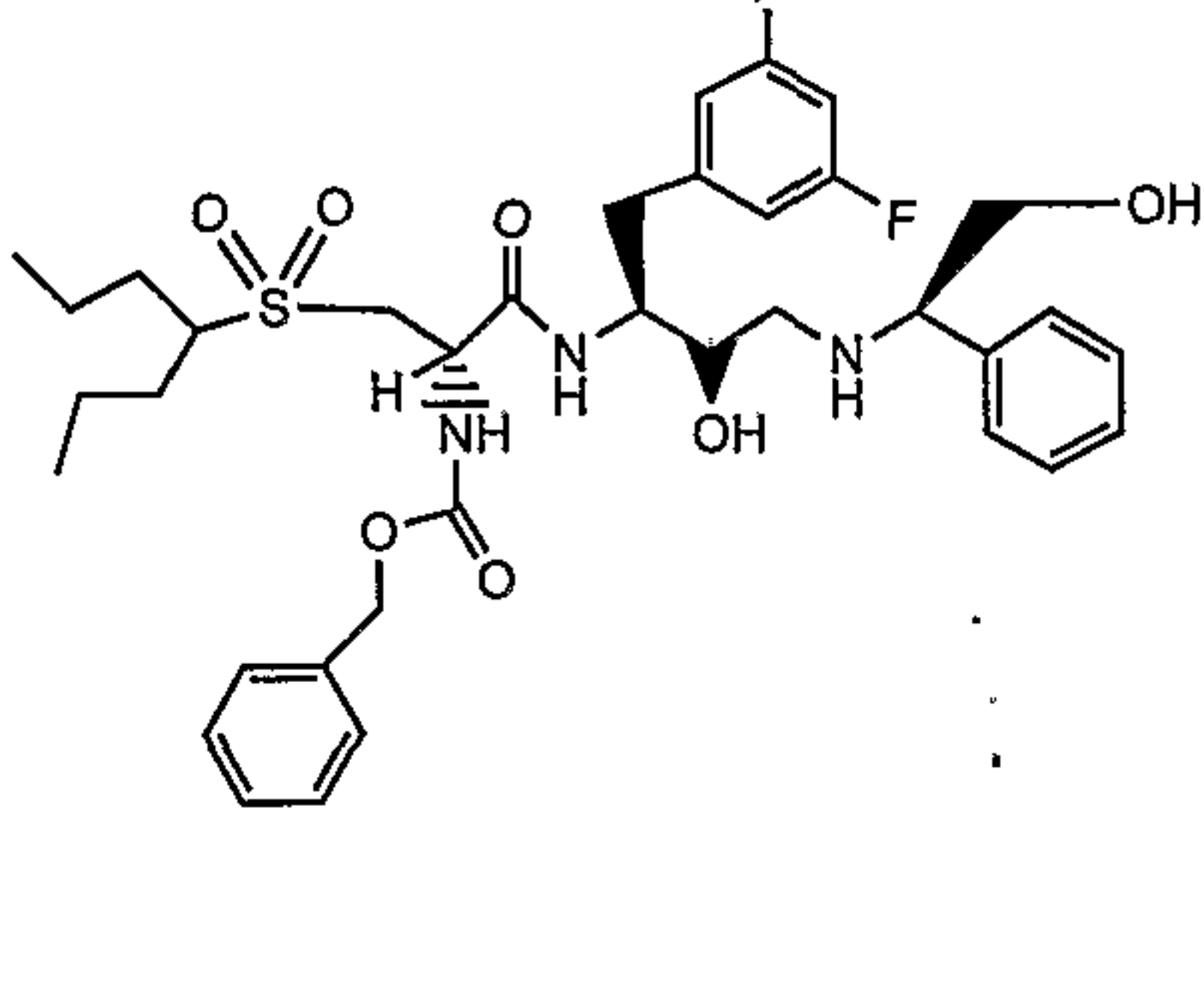
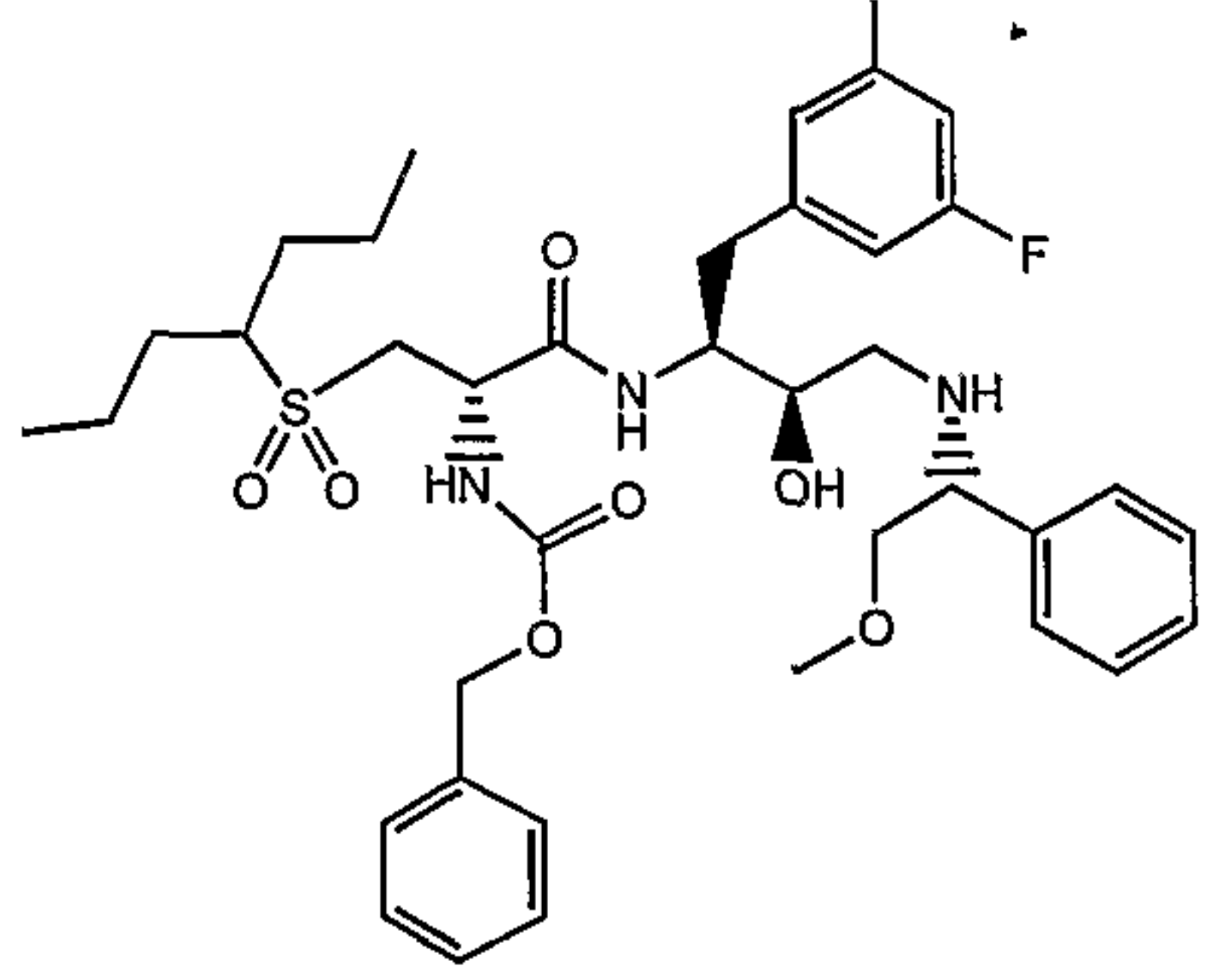
	<p>alaninamide dihydrochloride</p> <p>3-(butylsulfonyl)-N-1-          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2-          {[(3S)-          tetrahydrofuran-3-          yloxy]carbonyl}-D-alaninamide          hydrochloride</p>	640
	<p>N-2-          {[2-          (acetylamino)ethoxy]carbonyl}-          3-(butylsulfonyl)-N-1-          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-D-alaninamide          trifluoroacetate</p>	655
	<p>3-(butylsulfonyl)-N-1-          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2-          {[(pyridin-3-          yl)methyl]oxy]carbonyl}-D-          alaninamide hydrochloride</p>	661
	<p>3-(butylsulfonyl)-N-1-          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2-          {[(pyridin-4-          yl)methyl]oxy]carbonyl}-D-          alaninamide hydrochloride</p>	661

	<p>3-(butylsulfonyl)-N-2- [(methoxy)carbonyl]-N-1- {(1S,2R)-1-(3,5- difluorobenzyl)-3- (cyclopropylamino)-2- hydroxypropyl}-D-alaninamide hydrochloride</p>	506
	<p>3-(butylsulfonyl)-N-2- [(2-cyanoethoxy)carbonyl]-N-1- {(1S,2R)-1-(3,5- difluorobenzyl)-3- (cyclopropylamino)-2- hydroxypropyl}-D-alaninamide hydrochloride</p>	545
	<p>N-2- [(benzyloxy)carbonyl]-3- (butylsulfonyl)-N-1- {(1S,2R)- 1-(3,5-difluorobenzyl)-3- [(3-methylbutyl)amino]-2- hydroxypropyl}-D-alaninamide hydrochloride</p>	612
	<p>3-(butylsulfonyl)-N-1- {(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3-methylbutyl)amino]-2- hydroxypropyl}-N-2- [(methoxy)carbonyl]-D- alaninamide hydrochloride</p>	536
	<p>N-2- [(2-cyanoethoxy)carbonyl]-N-1- {(1S,2R)-1-(3,5- difluorobenzyl)-3- (cyclopropylamino)-2- hydroxypropyl}-3- [(1-propylbutyl)sulfonyl]-D- alaninamide hydrochloride</p>	587

	alaninamide hydrochloride	
	N~2~-{ [2-(acetylamino)ethoxy] carbonyl }-N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide hydrochloride	619
	N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl) amino]-2-hydroxypropyl }-N~2~-{ (methoxy) carbonyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide hydrochloride	578
	N~2~-{ (benzyloxy) carbonyl }-N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide hydrochloride	654
	N~2~-{ [2-(diethylamino)-2-oxoethoxy] carbonyl }-N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide hydrochloride	725

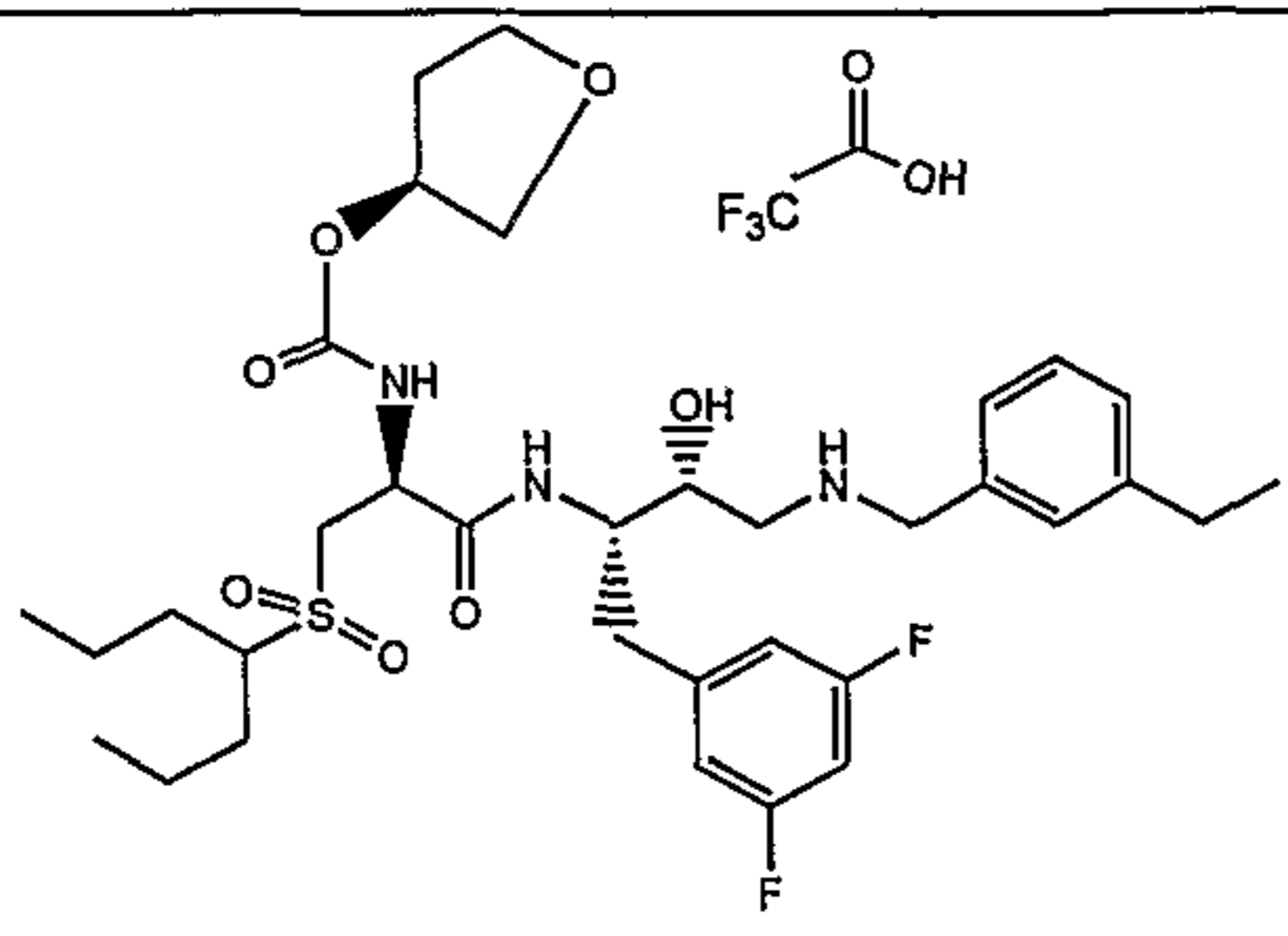
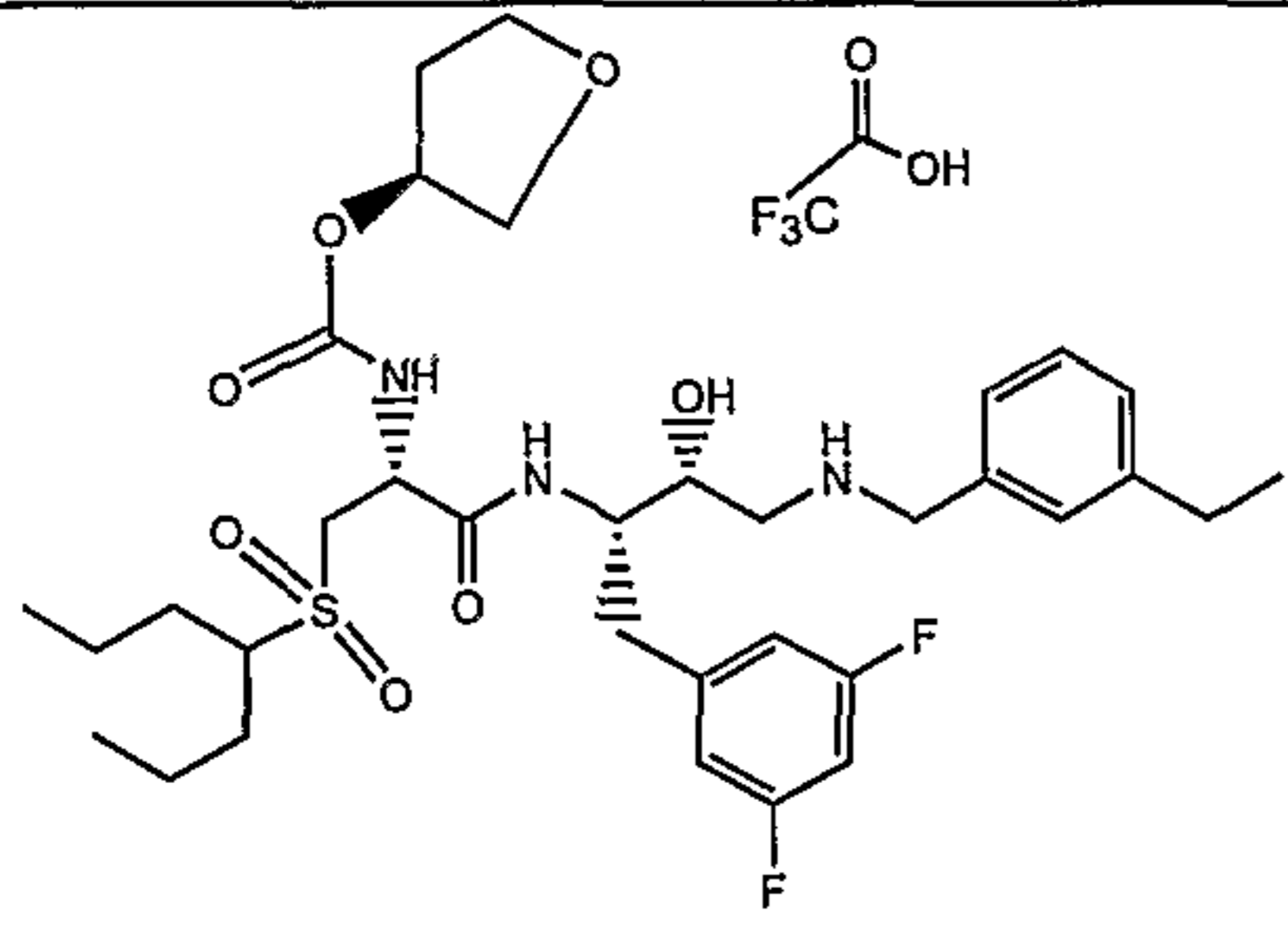
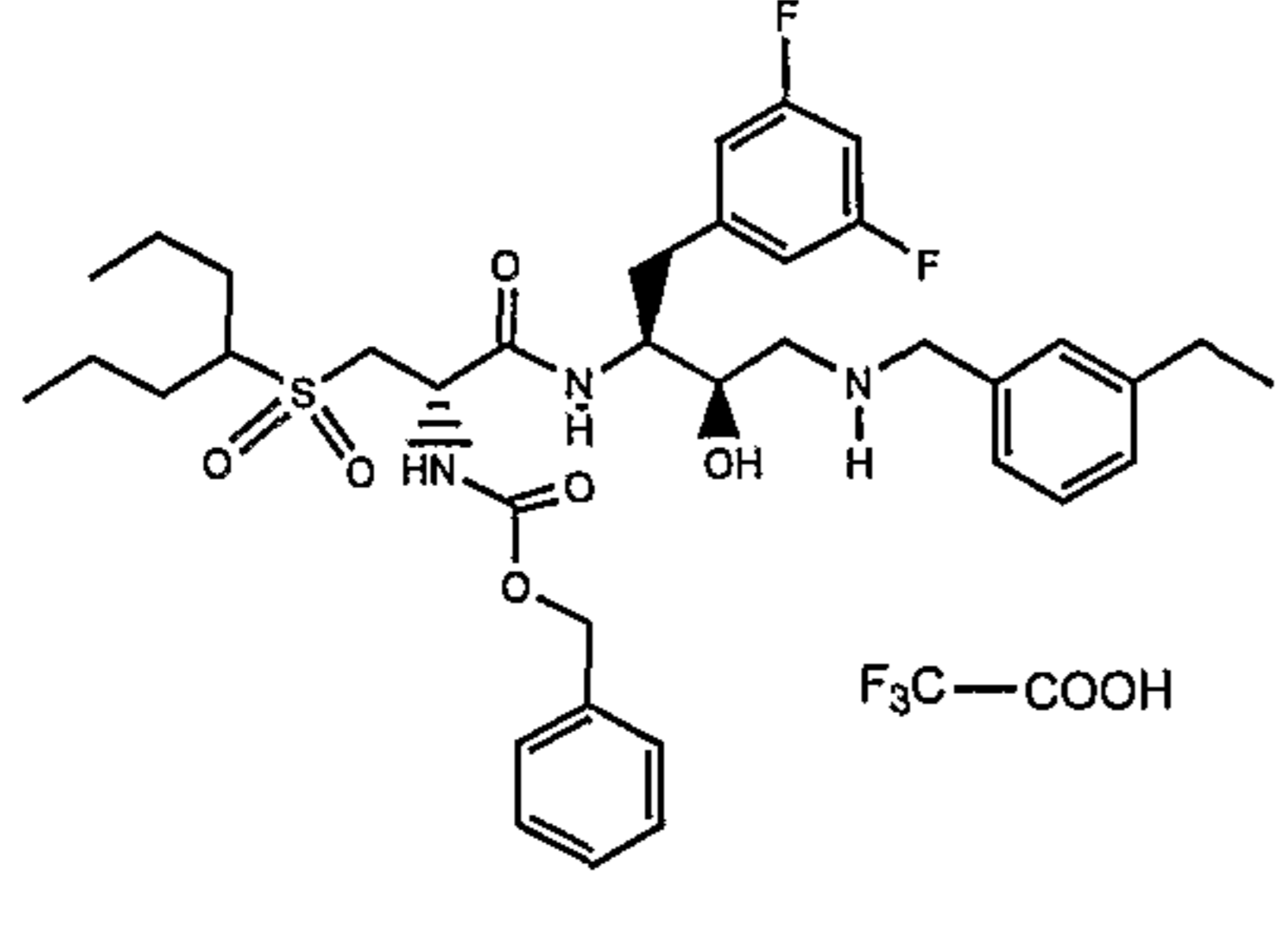
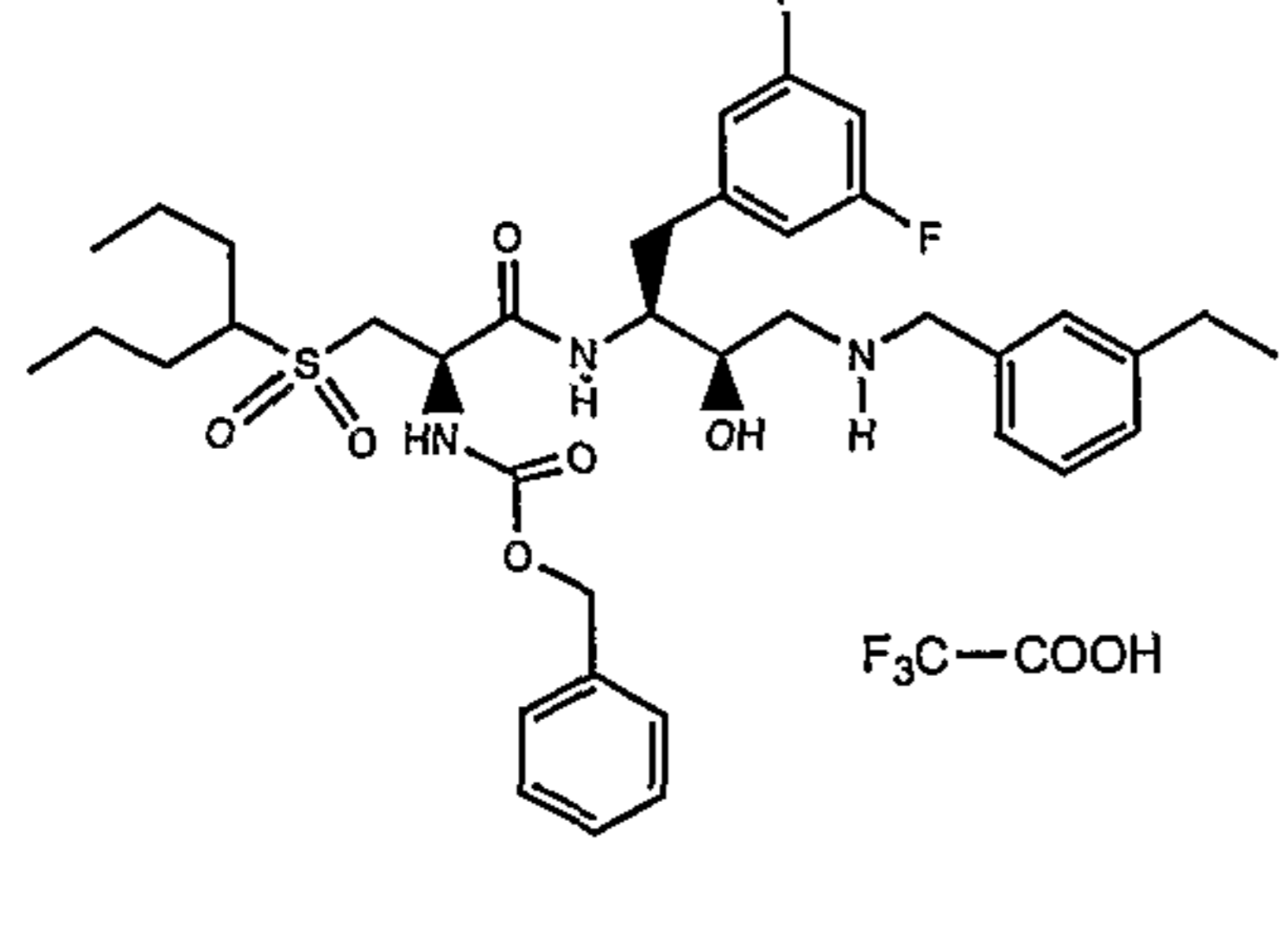
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	626
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(isopropoxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	654
	<p>N~2~-[(cyclopropylmethoxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	666
	<p>N~2~-[(allyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide trifluoroacetate</p>	652

	<p>N~2~-[(2-cyanoethoxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide trifluoroacetate</p>	665
	<p>N~2~-{(2-(acetylamino)ethoxy) carbonyl}-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide hydrochloride</p>	697
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-{[(pyridin-3-yl)methyl]oxy} carbonyl}-D-alaninamide hydrochloride</p>	703
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-{[(pyridin-4-yl)methyl]oxy} carbonyl}-D-alaninamide hydrochloride</p>	703

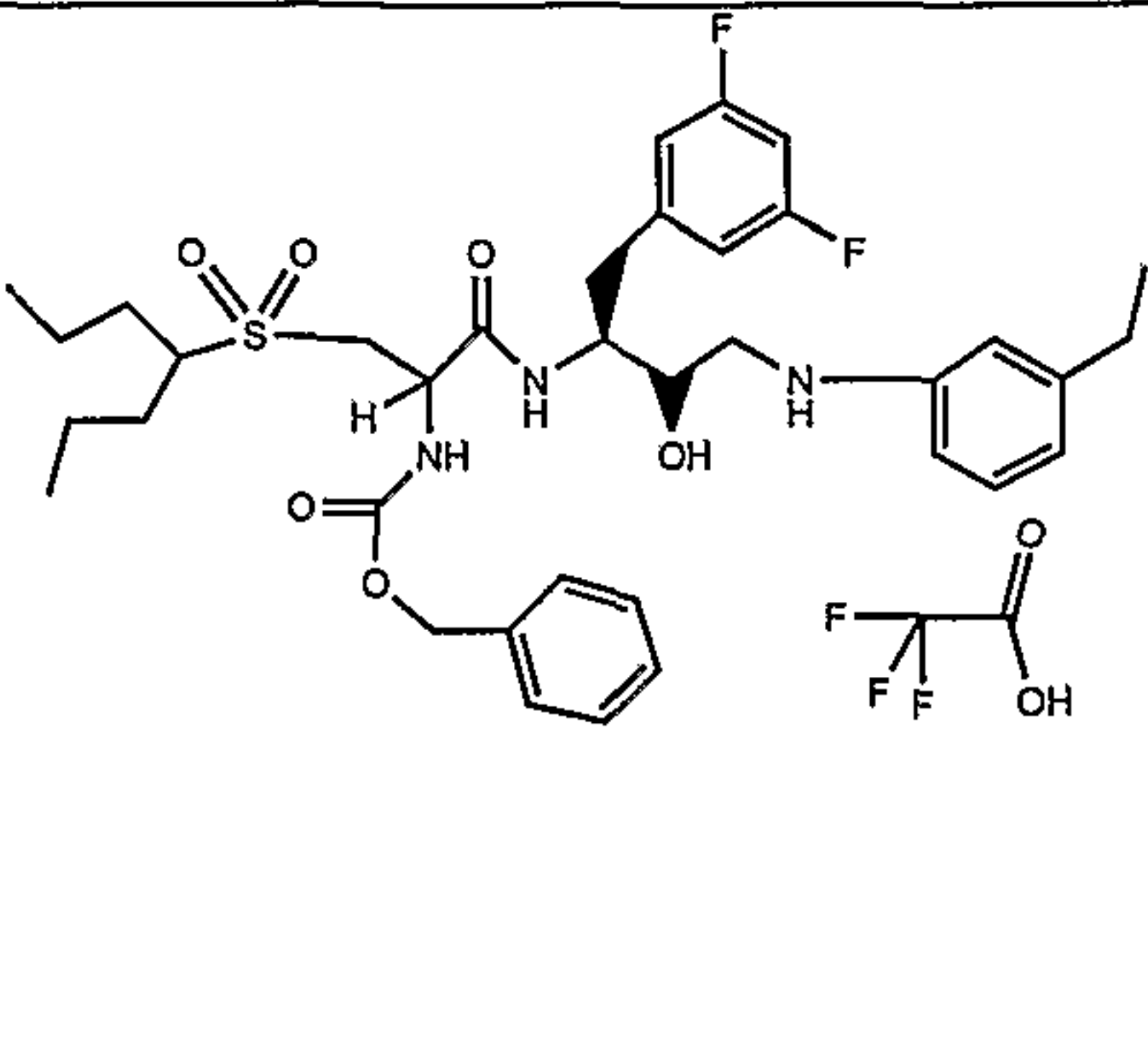
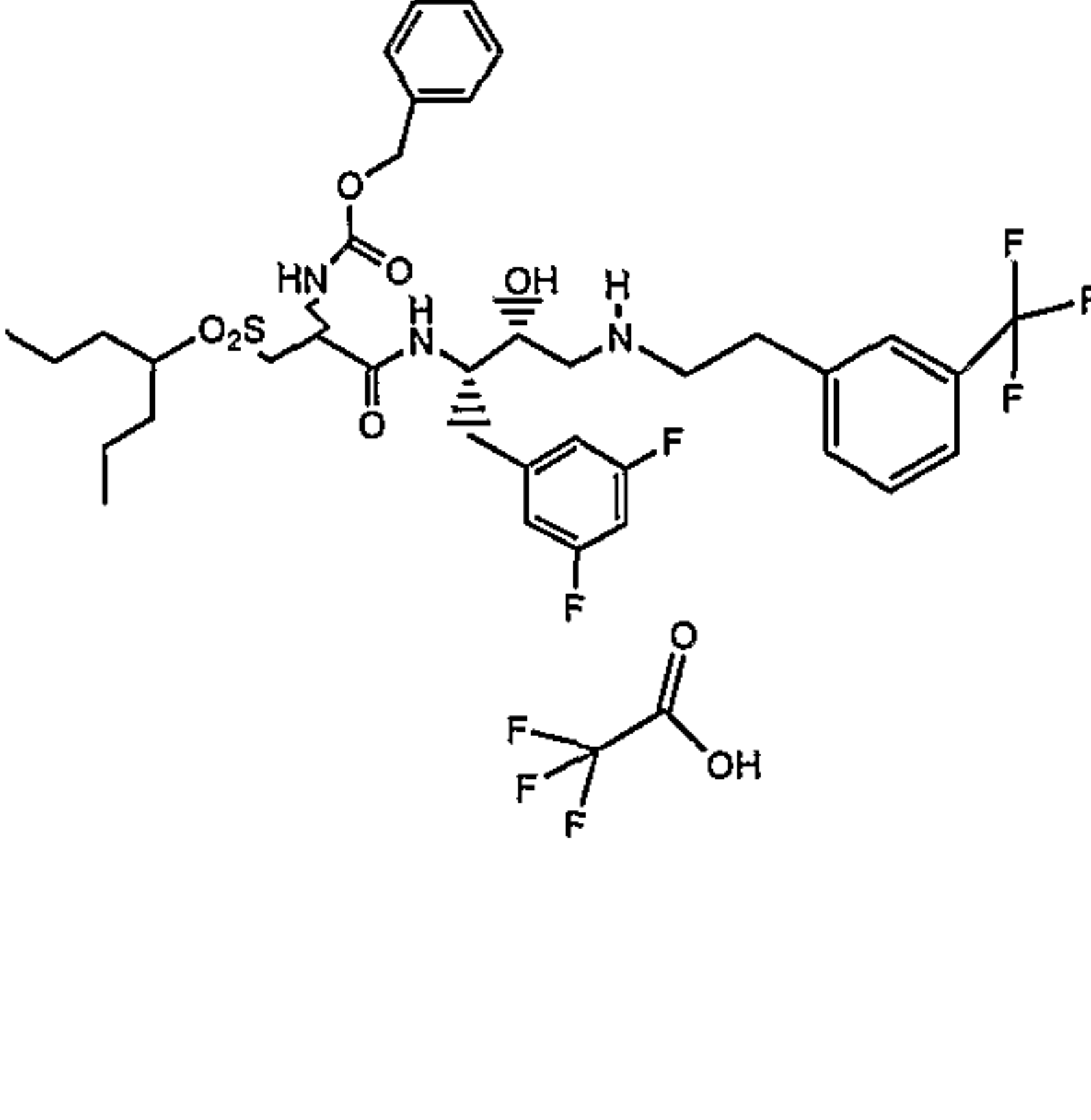
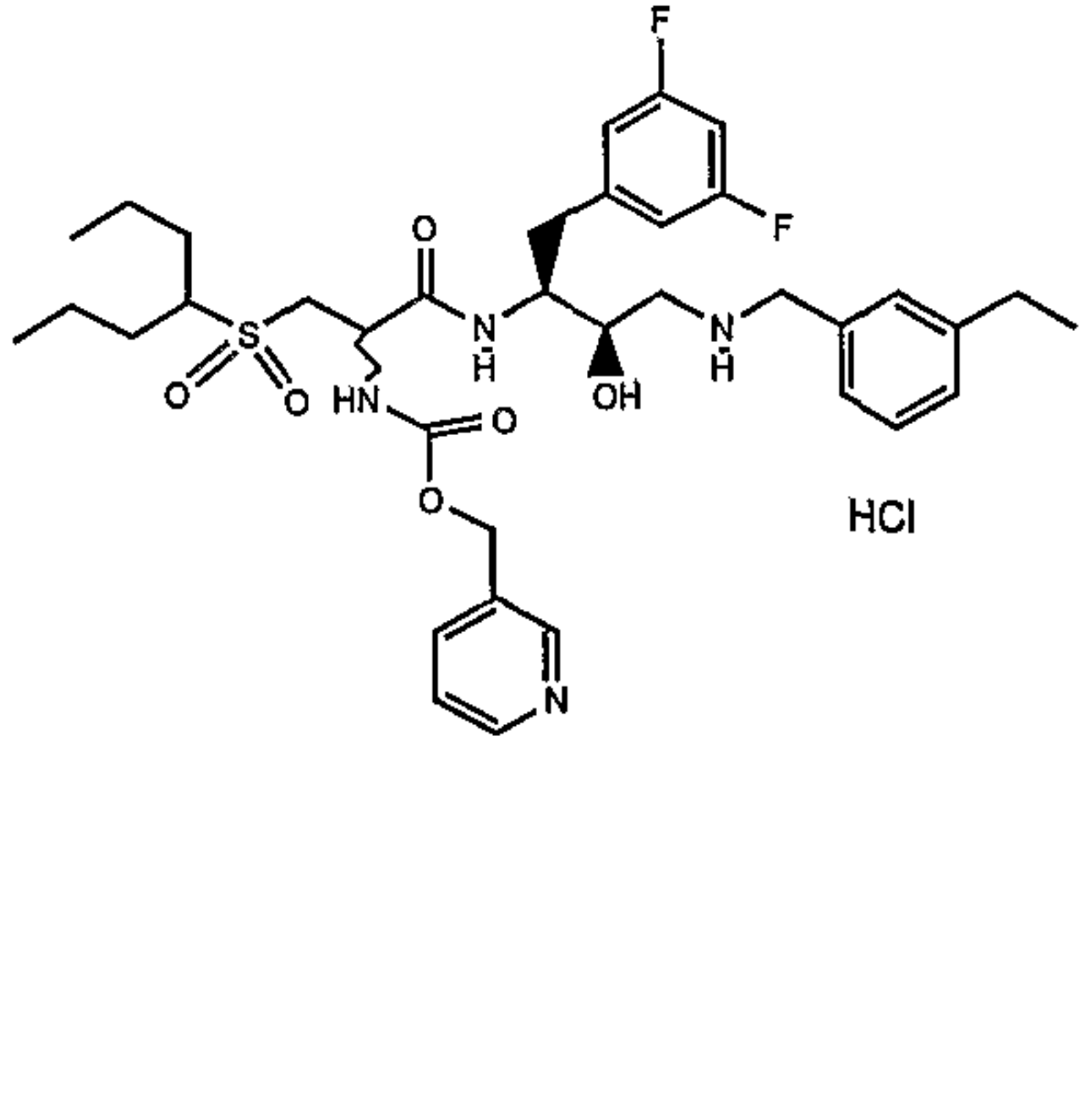
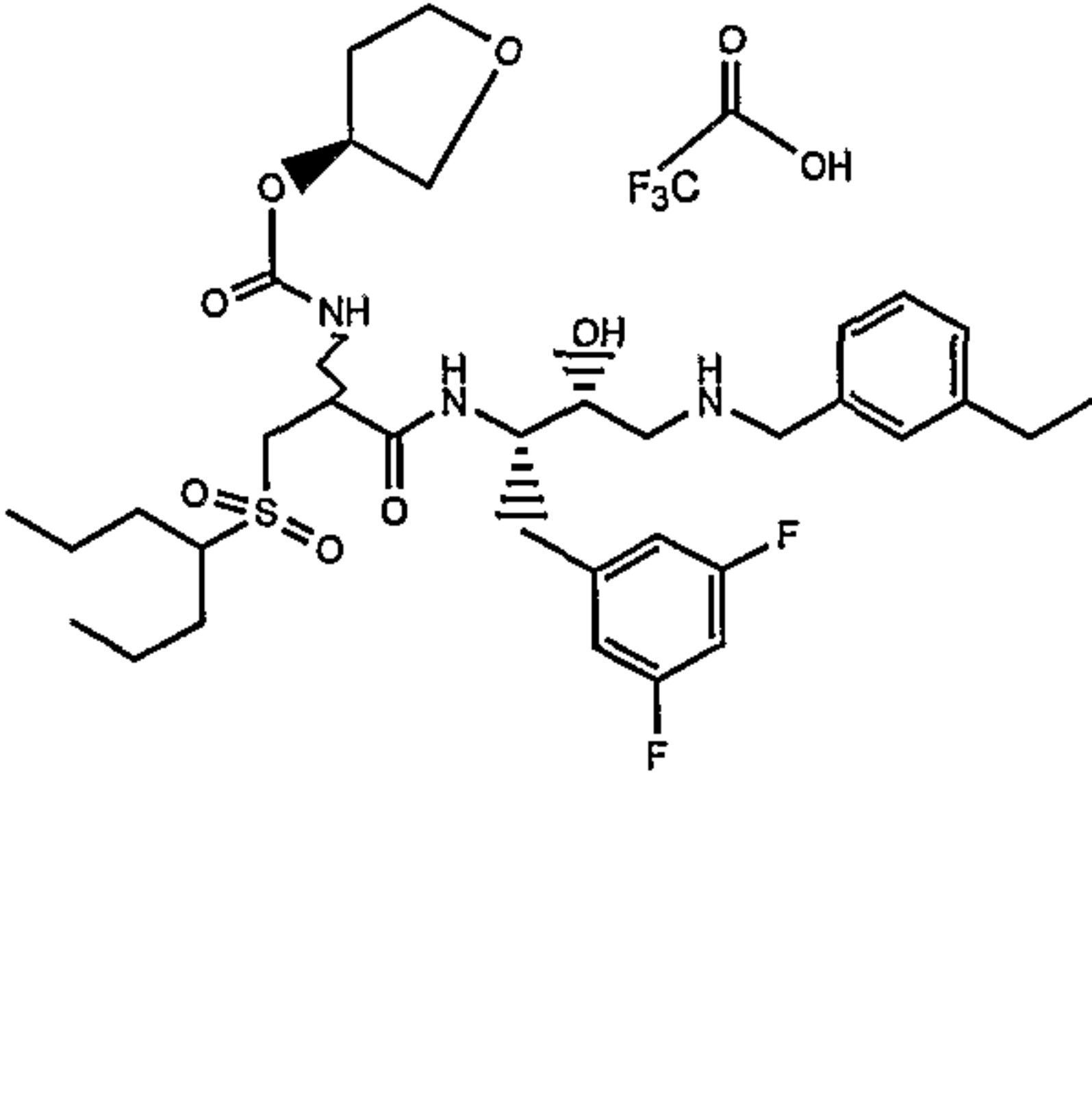
	benzyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino) carbonyl]-3-(methylsulfonyl)propylcarbamate	632
	N~2~-[(benzyloxy) carbonyl]-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide trifluoroacetate	660
	N~2~-[(benzyloxy) carbonyl]-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-L-alaninamide trifluoroacetate	660
	N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-2-hydroxy-1-phenylethyl]amino}propyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide	704
	N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]amino}propyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide	718

	<p>N~2~-[(benzyloxy) carbonyl]- N~1~-((1S,2S)-1-(3,5- difluorobenzyl)-2-hydroxy-3- {[(1S)-2-methoxy-1- phenylethyl] amino}propyl)-3- [(1-propylbutyl) sulfonyl]-D- alaninamide</p>	718
	<p>N~2~-[(benzyloxy) carbonyl]- N~1~-((1S,2R)-1-(3,5- difluorobenzyl)-3-[[1-(3- ethylphenyl) cyclopropyl] amino} -2-hydroxypropyl)-3-[(1- propylbutyl) sulfonyl]-D- alaninamide</p>	728
	<p>N~1~-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl)-3-[(1- propylbutyl) sulfonyl]-N~2~- {[(prop-2-ynyl) oxy] carbonyl}- D-alaninamide trifluoroacetate</p>	650
	<p>N~1~-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl)-N~2~-(2- methoxyethyl) carbonyl)-3-[(1- propylbutyl) sulfonyl]-D- alaninamide hydrochloride</p>	670
	<p>N~2~-{[(3R)-1- acetylpyrrolidin-3- yl] carbonyl}-N~1~-((1S,2R)-1- (3,5-difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl)-3-[(1-</p>	723



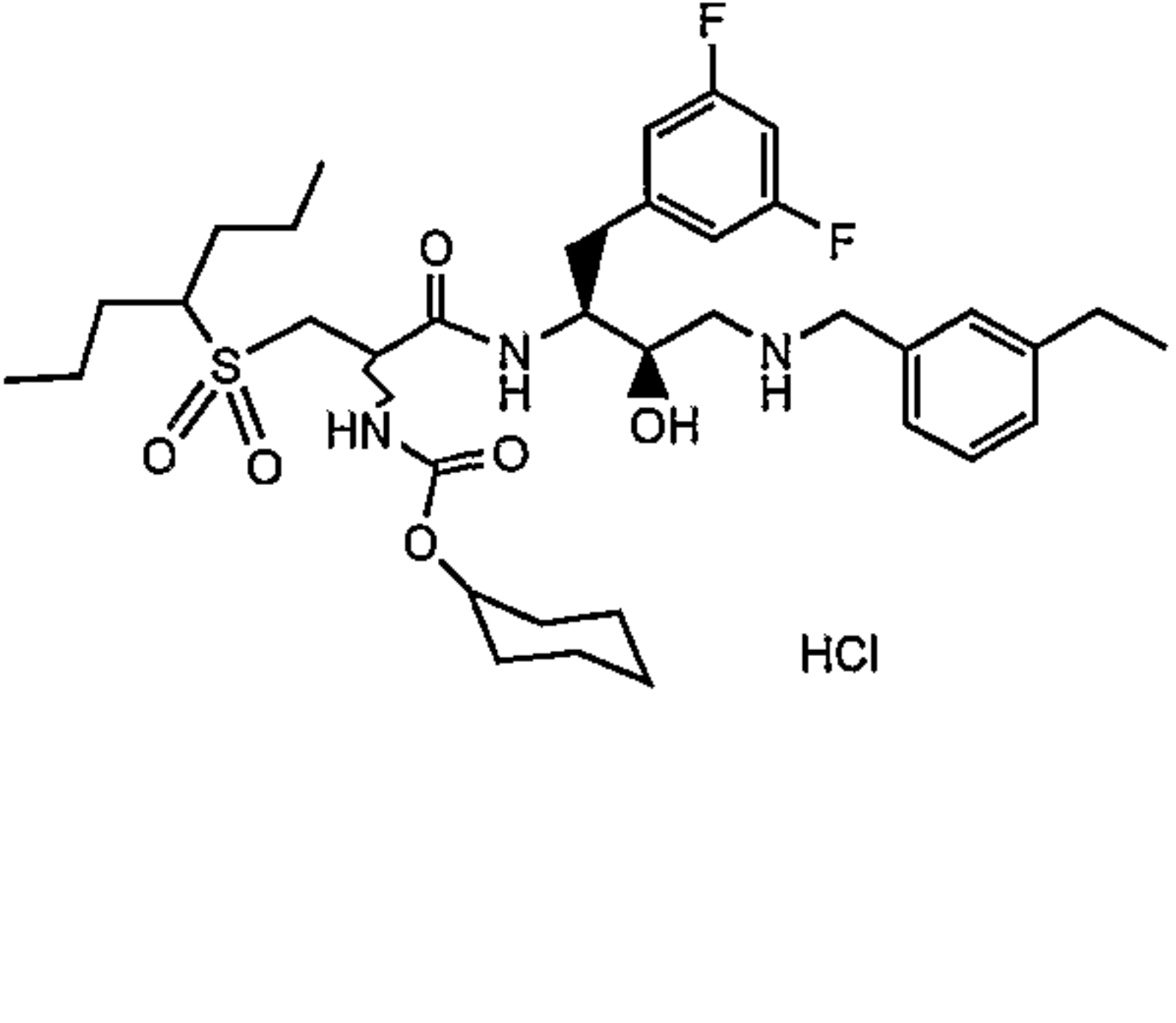
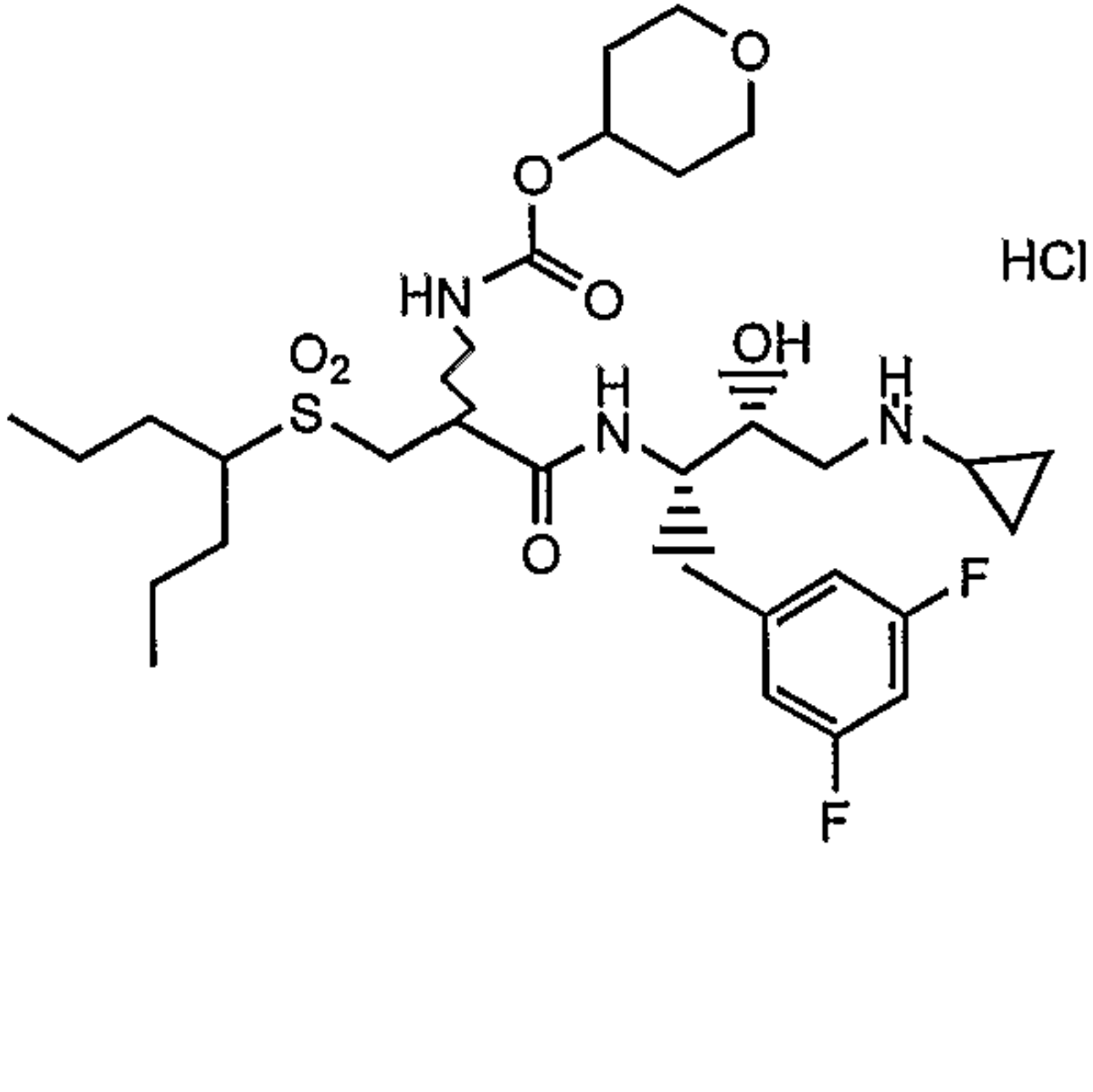
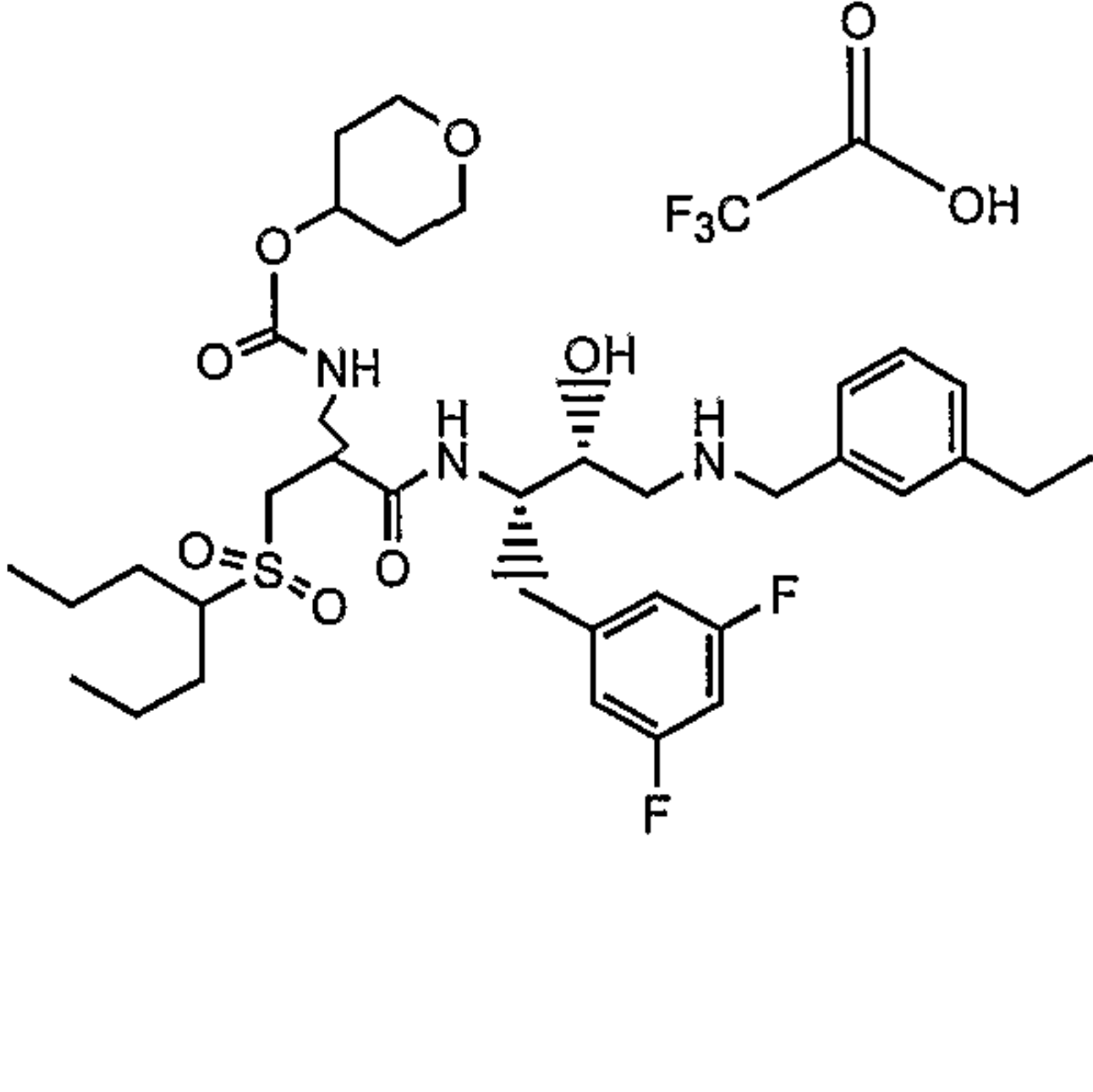
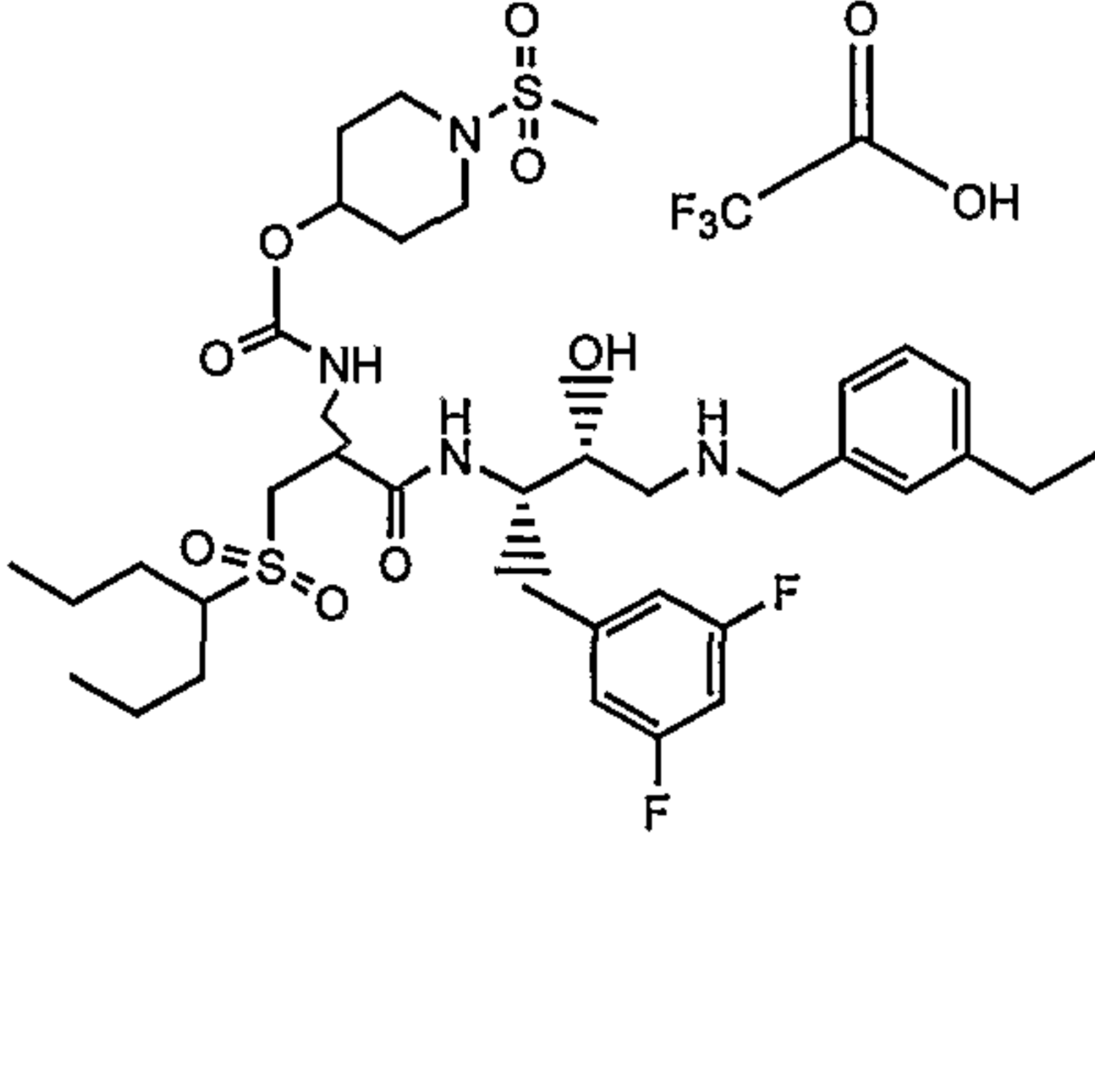
	propylbutyl) sulfonyl]-D-alaninamide hydrochloride	
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide trifluoroacetate	682
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-L-alaninamide trifluoroacetate	682
	N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide trifluoroacetate	702
	N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-L-alaninamide trifluoroacetate	702

	<p>N~2~-[(benzyloxy) carbonyl]- N~1~-((1S,2R)-1-(3,5- difluorobenzyl)-3-{[1-(3- ethylphenyl)cyclopropyl]amino} -2-hydroxypropyl)-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide trifluoroacetate</p>	728
	<p>N~2~-[(benzyloxy) carbonyl]- N~1~-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide trifluoroacetate</p>	702
	<p>N~2~-[(benzyloxy) carbonyl]- N~1~-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- methylbutyl)amino]-2- hydroxypropyl)-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide</p>	654
	<p>N~2~-[(benzyloxy) carbonyl]- N~1~-((1S,2R)-1-(3,5- difluorobenzyl)-3- (cyclopropylamino)-2- hydroxypropyl)-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide trifluoroacetate</p>	624
	<p>N~2~-[(benzyloxy) carbonyl]- N~1~-((1S,2R)-1-(3,5- difluorobenzyl)-3- [(cyclopropylmethyl)amino]-2- hydroxypropyl)-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide trifluoroacetate</p>	638

	propylbutyl) sulfonyl]-D,L-alaninamide trifluoroacetate	
	N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylphenyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide trifluoroacetate	688
	N~2~-[(benzyloxy) carbonyl]-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({2-[3-(trifluoromethyl)phenyl]ethyl} amino)propyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide trifluoroacetate	756
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-{[(pyridin-3-yl)methyl]oxy} carbonyl}-D,L-alaninamide hydrochloride	703
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy] carbonyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide trifluoroacetate	682

	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3R)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate</p>	682
	<p>N~1~-{(1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	648
	<p>N~2~-{[(3R)-1-acetylpyrrolidin-3-yl]carbonyl}-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate</p>	723
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{[(3R)-pyrrolidin-3-yl]carbonyl}-D,L-alaninamide dihydrochloride</p>	681

	<p>N~2~-{ [(3R)-1-benzylpyrrolidin-3-yl] carbonyl }-N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide hydrochloride</p>	771
	<p>N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-N~2~-{ [(3S)-1,1-dioxidotetrahydrothien-3-yloxy] carbonyl }-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide trifluoroacetate</p>	730
	<p>N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-N~2~-{ [(3S)-tetrahydrothiophen-3-yloxy] carbonyl }-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide trifluoroacetate</p>	698
	<p>N~2~- (cyclopentylcarbonyl) -N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide hydrochloride</p>	680

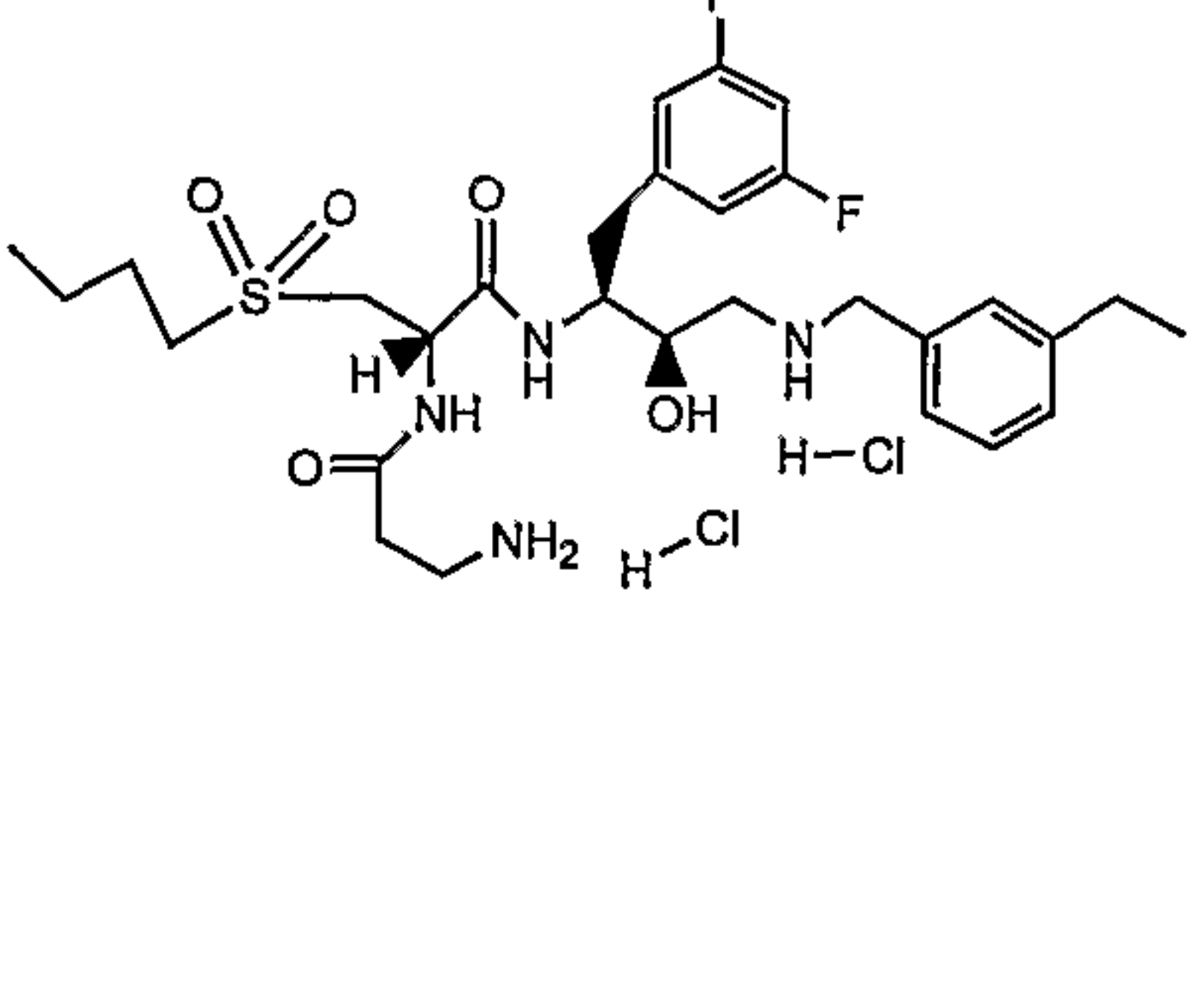
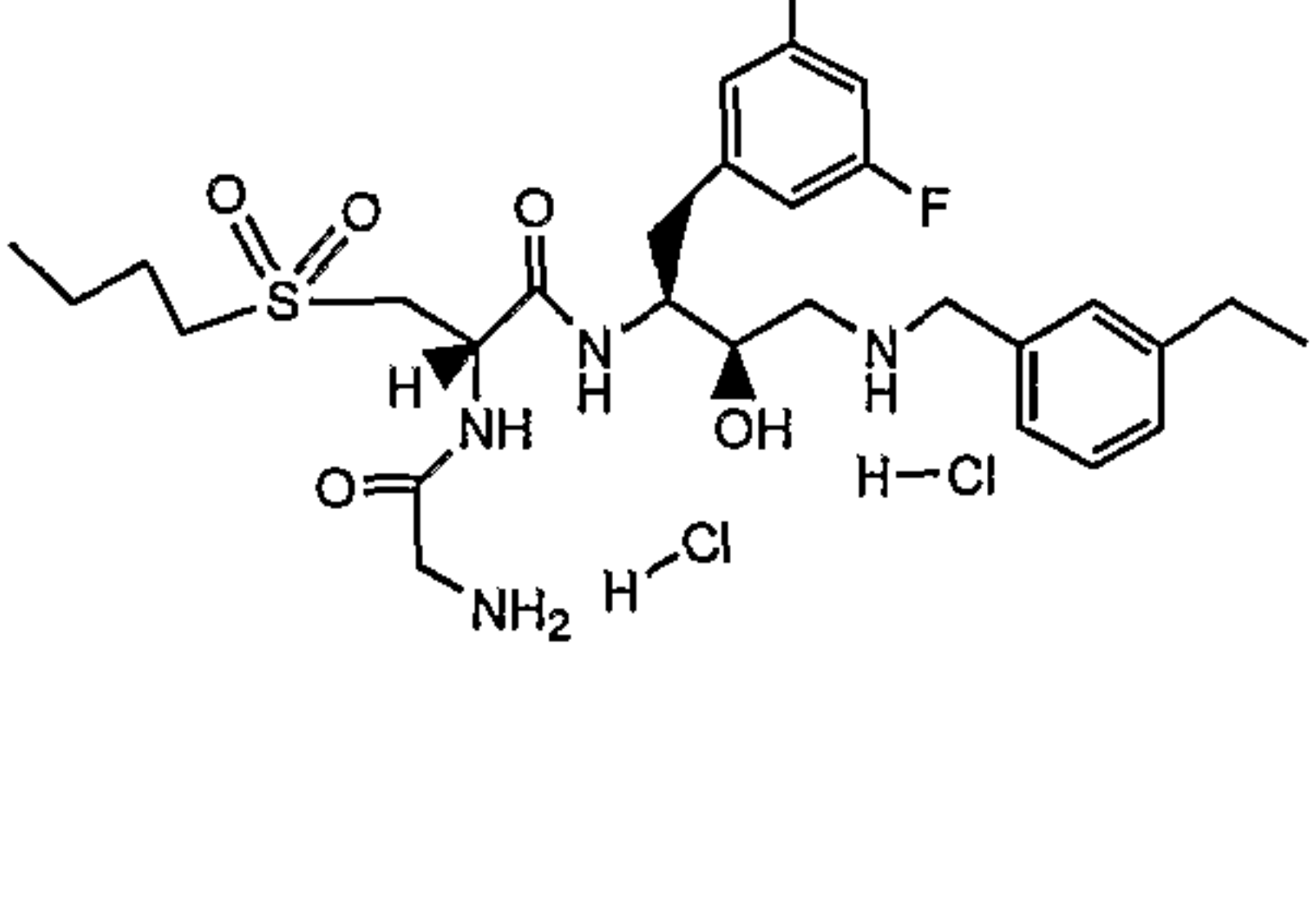
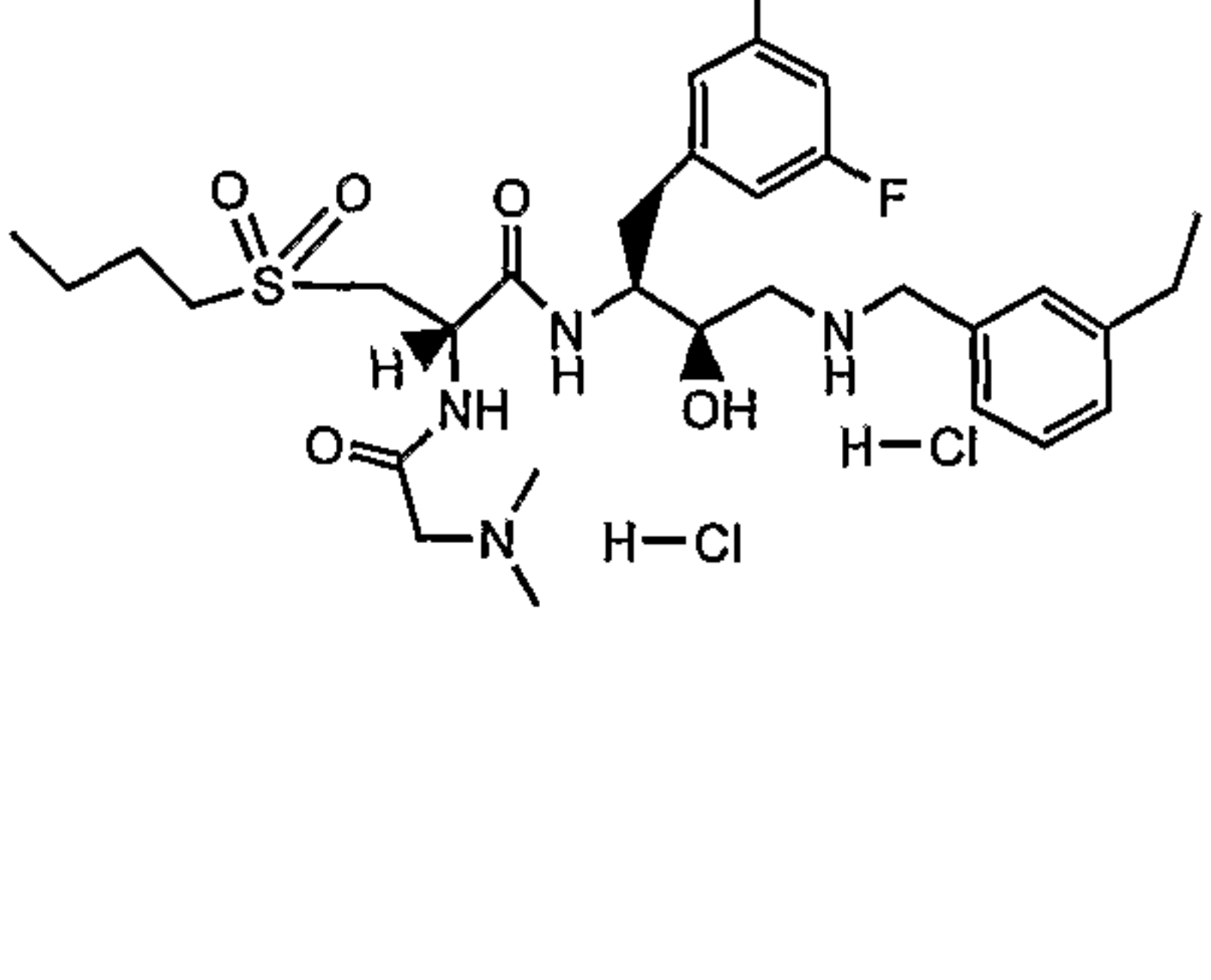
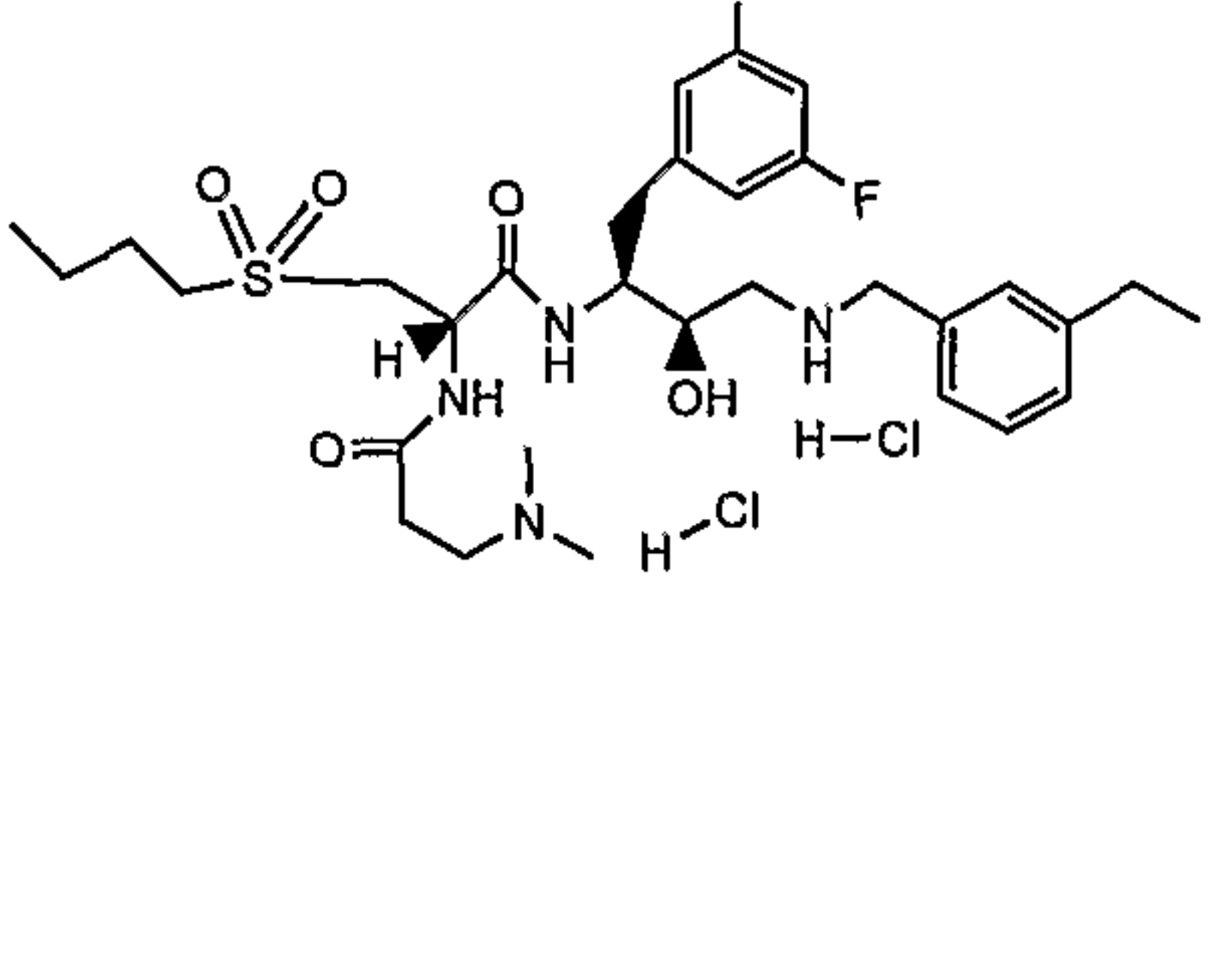
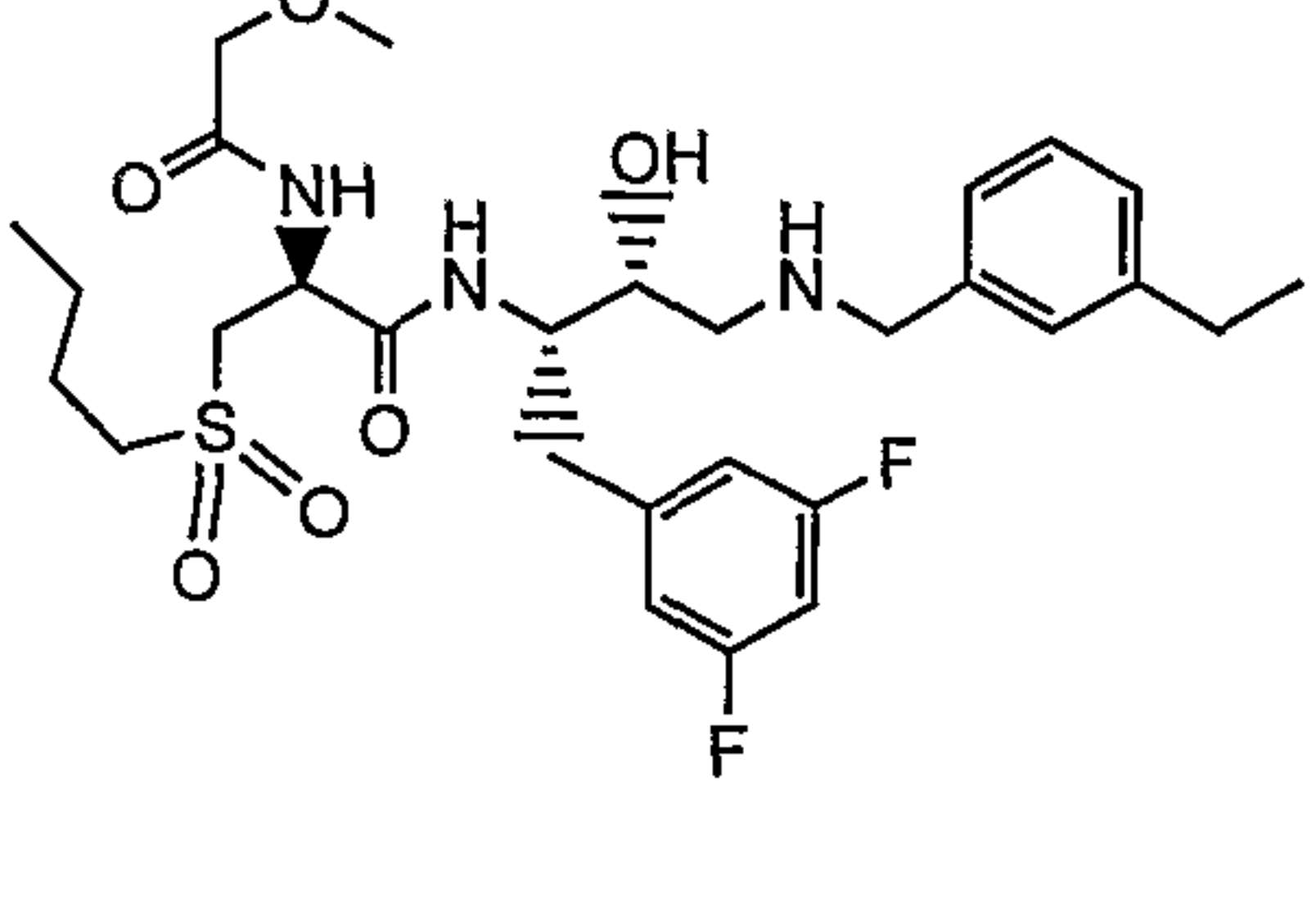
	<p>N~2~- (cyclohexylcarbonyl) - N~1~- { (1S, 2R) - 1 - (3, 5 - difluorobenzyl) - 3 - [ (3 - ethylbenzyl) amino] - 2 - hydroxypropyl } - 3 - [ (1 - propylbutyl) sulfonyl] - D, L - alaninamide hydrochloride</p>	694
	<p>N~1~- [ (1S, 2R) - 3 - (cyclopropylamino) - 1 - (3, 5 - difluorobenzyl) - 2 - hydroxypropyl ] - 3 - [ (1 - propylbutyl) sulfonyl] - N~2~- { [ tetrahydropyran - 4 - yloxy ] carbonyl } - D, L - alaninamide hydrochloride</p>	618
	<p>N~1~- { (1S, 2R) - 1 - (3, 5 - difluorobenzyl) - 3 - [ (3 - ethylbenzyl) amino] - 2 - hydroxypropyl } - 3 - [ (1 - propylbutyl) sulfonyl] - N~2~- { [ tetrahydropyran - 4 - yloxy ] carbonyl } - D, L - alaninamide trifluoroacetate</p>	696
	<p>N~1~- { (1S, 2R) - 1 - (3, 5 - diflourobenzyl) - 3 - [ (3 - ethylbenzyl) amino] - 2 - hydroxypropyl } - N~2~- { [ 1 - (methylsulfonyl) piperidin - 4 - yloxy ] carbonyl } - 3 - [ (1 - propylbutyl) sulfonyl] - D, L - alaninamide trifluoroacetate</p>	773

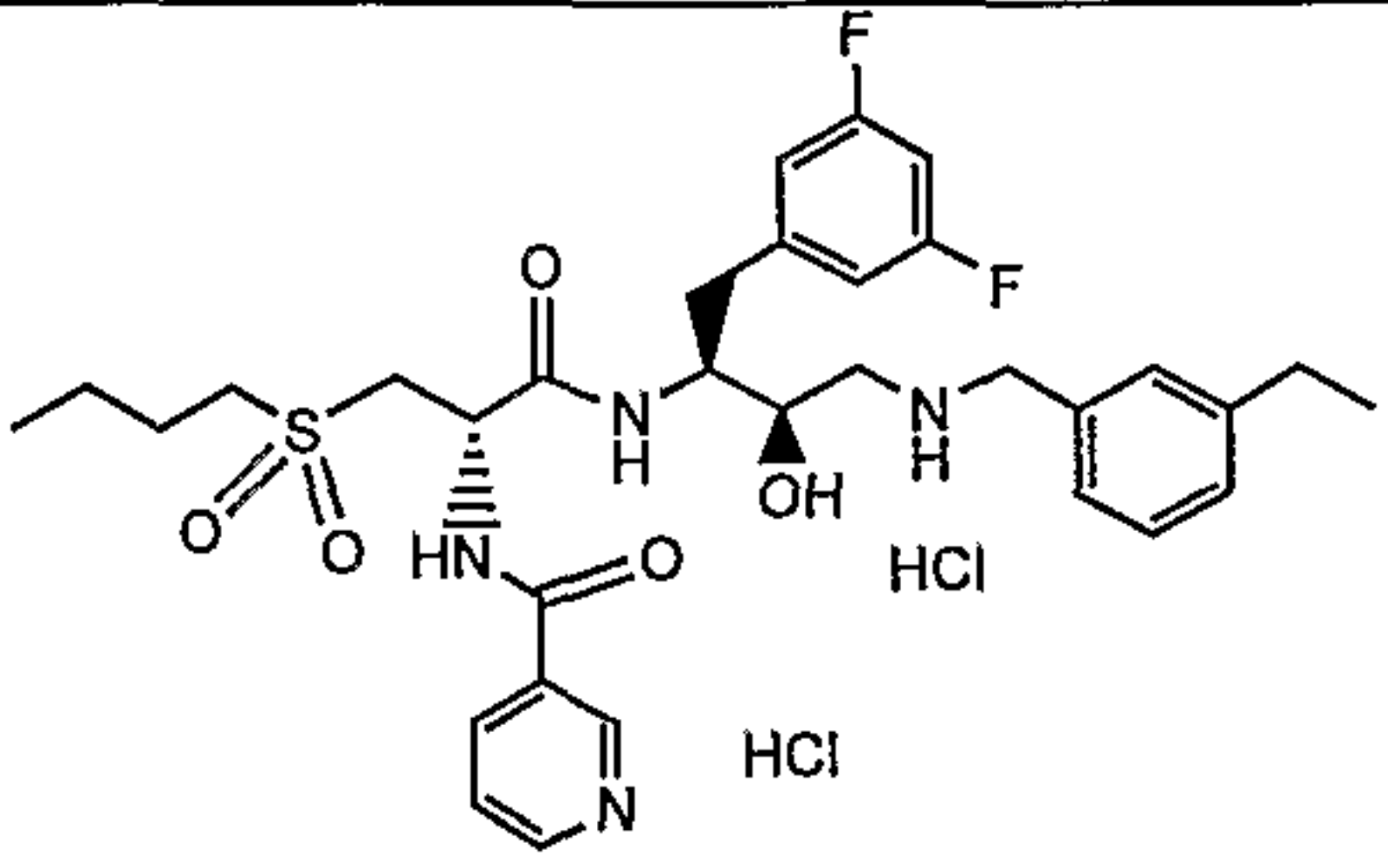
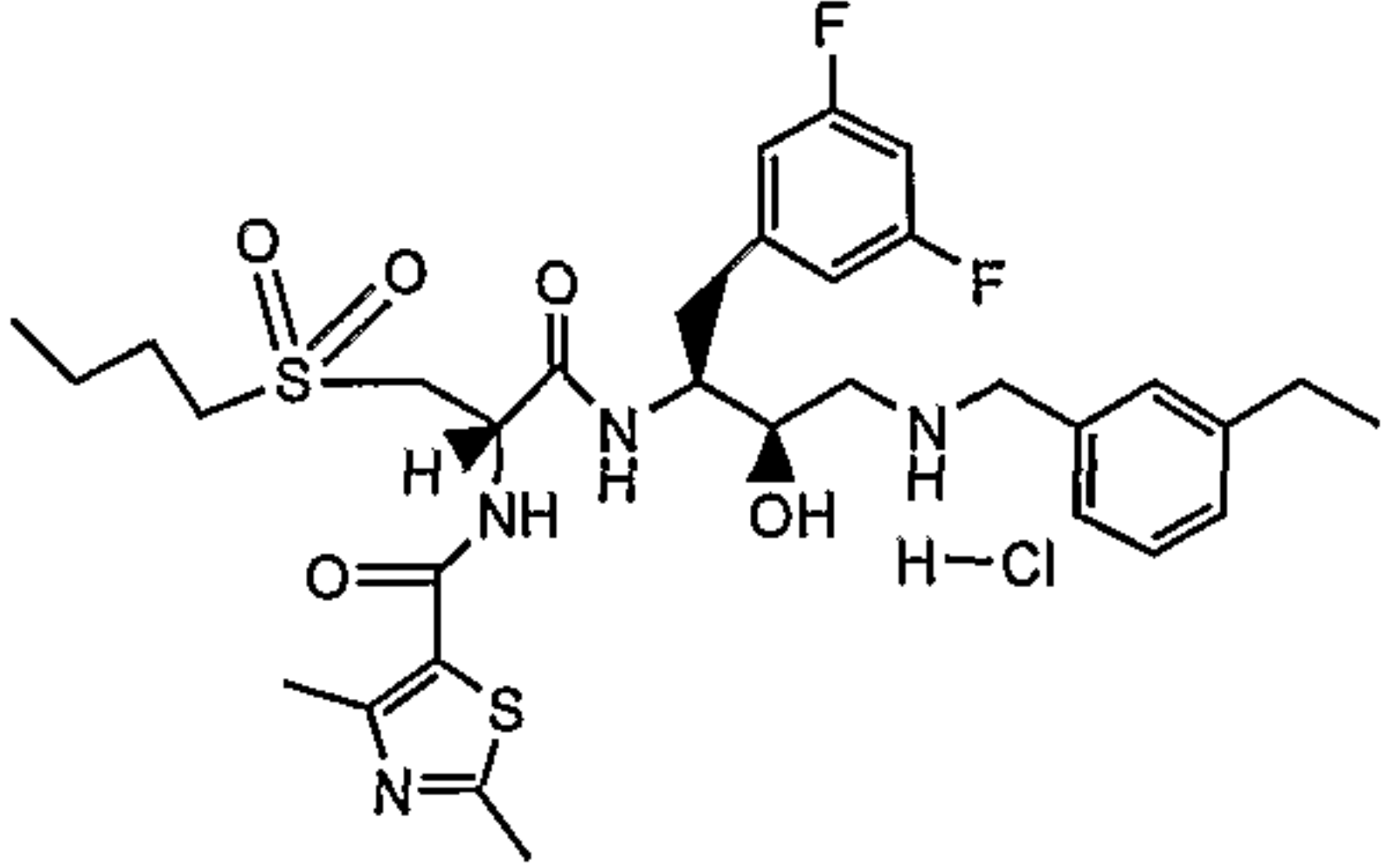
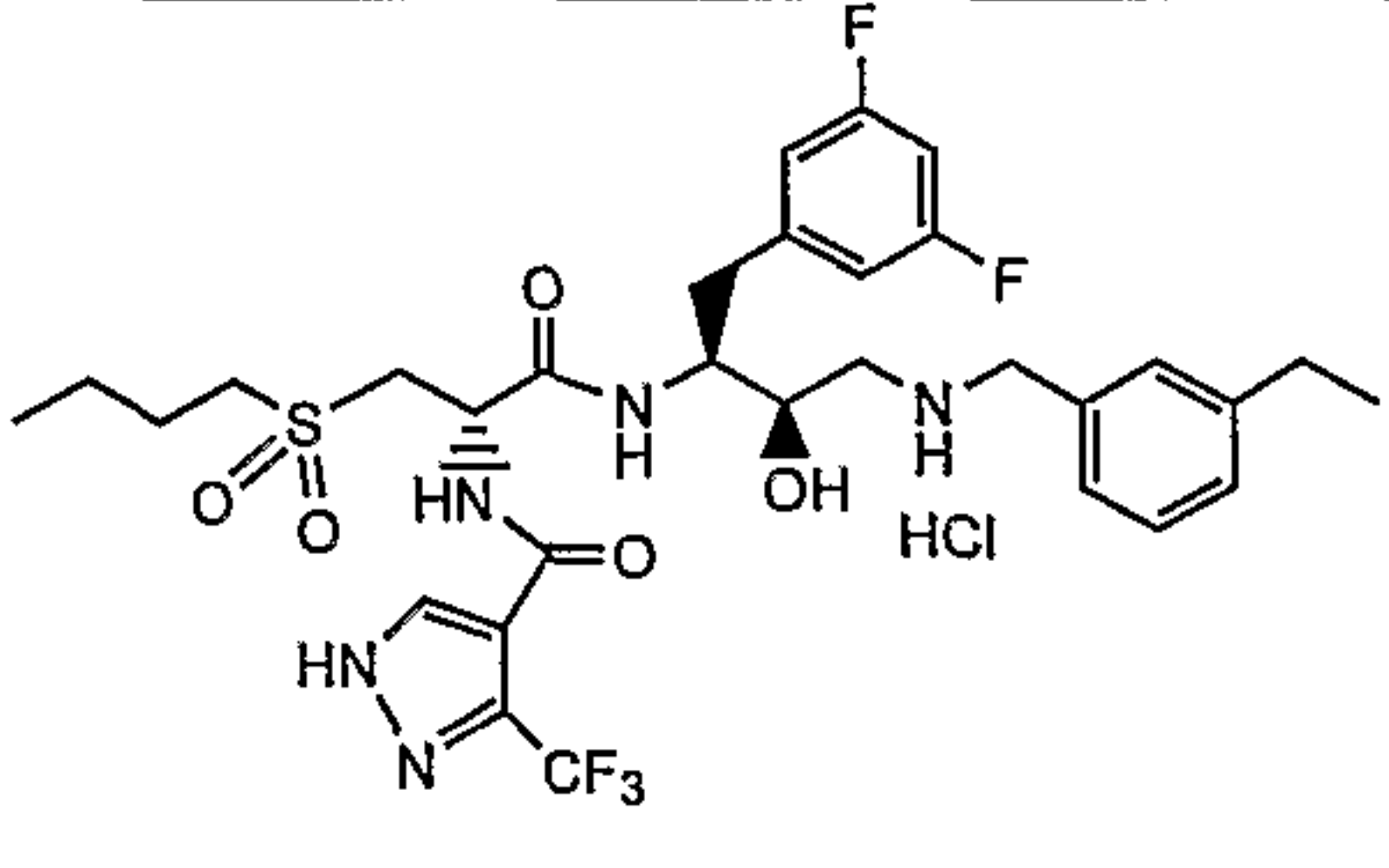
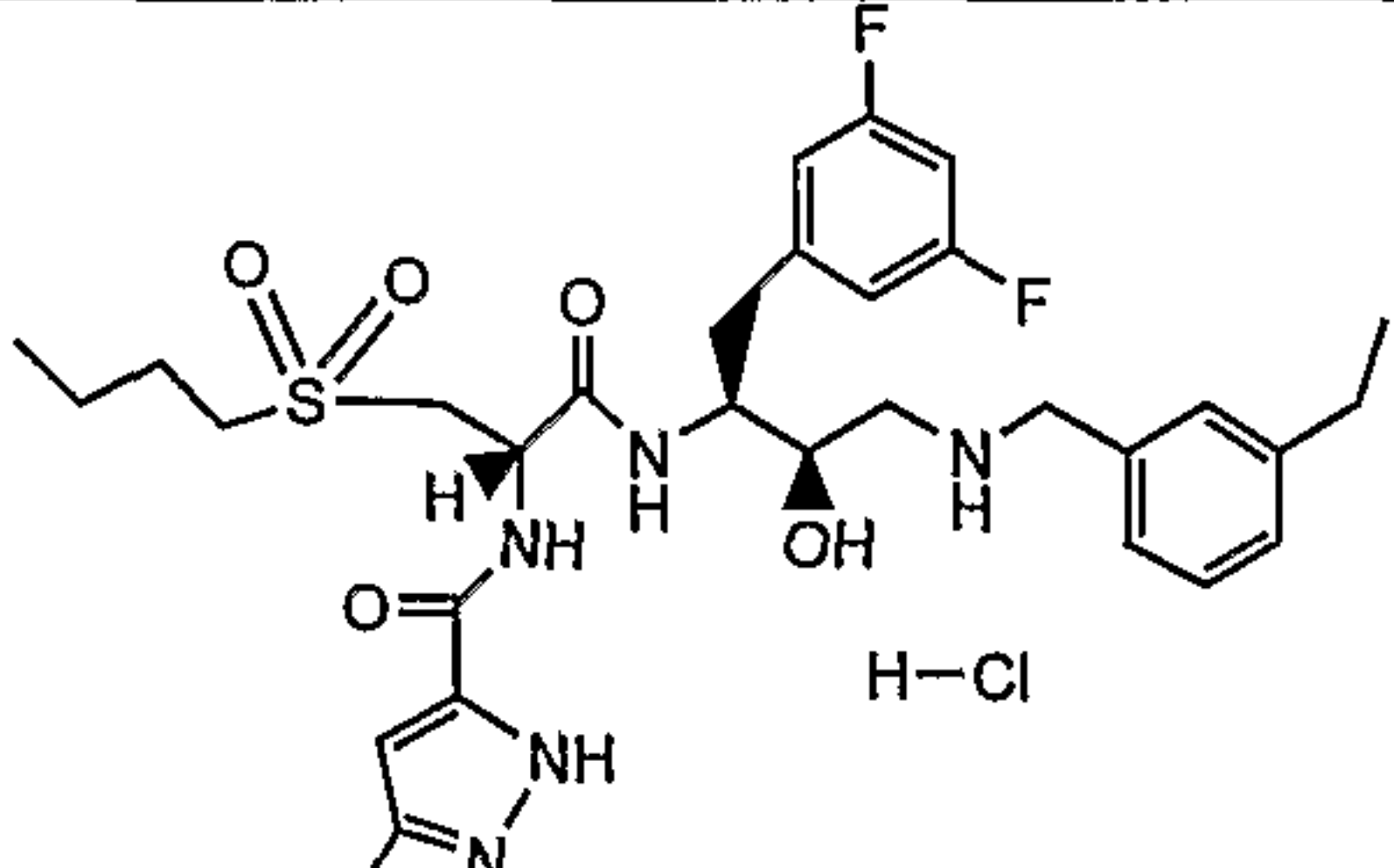
	<p>N~2~-{ [1-acetylpiperidin-4-yloxy] carbonyl }-N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide trifluoroacetate</p>	737
	<p>N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-N~2~-{ [[[(3S)-5-oxopyrrolidin-3-yl]methyl]oxy] carbonyl }-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide hydrochloride</p>	709
	<p>N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-N~2~-{ [[[(3R)-5-oxopyrrolidin-3-yl]methyl]oxy] carbonyl }-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide trifluoroacetate</p>	709
	<p>N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-N~2~-{ [[2-methoxyethyl]oxy] carbonyl }-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide hydrochloride</p>	670

	<p>N~2~- [(benzyloxy) carbonyl]-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-D,L-alaninamide</p>	660
	<p>N~1~-{(1S,2R)-1-benzyl-3-[(3-methoxybenzyl) amino]-2-hydroxypropyl}-N~2~-[(benzyloxy) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide hydrochloride</p>	668
	<p>N~2~- [(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[2-(3-methoxyphenyl) ethyl] amino]propyl)-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide trifluoroacetate</p>	718
	<p>N~2~- [(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~5~,N~5~-dipropyl-L-glutamamide trifluoroacetate</p>	681
	<p>N~2~- [(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~5~,N~5~-dipropyl-D-glutamamide</p>	681

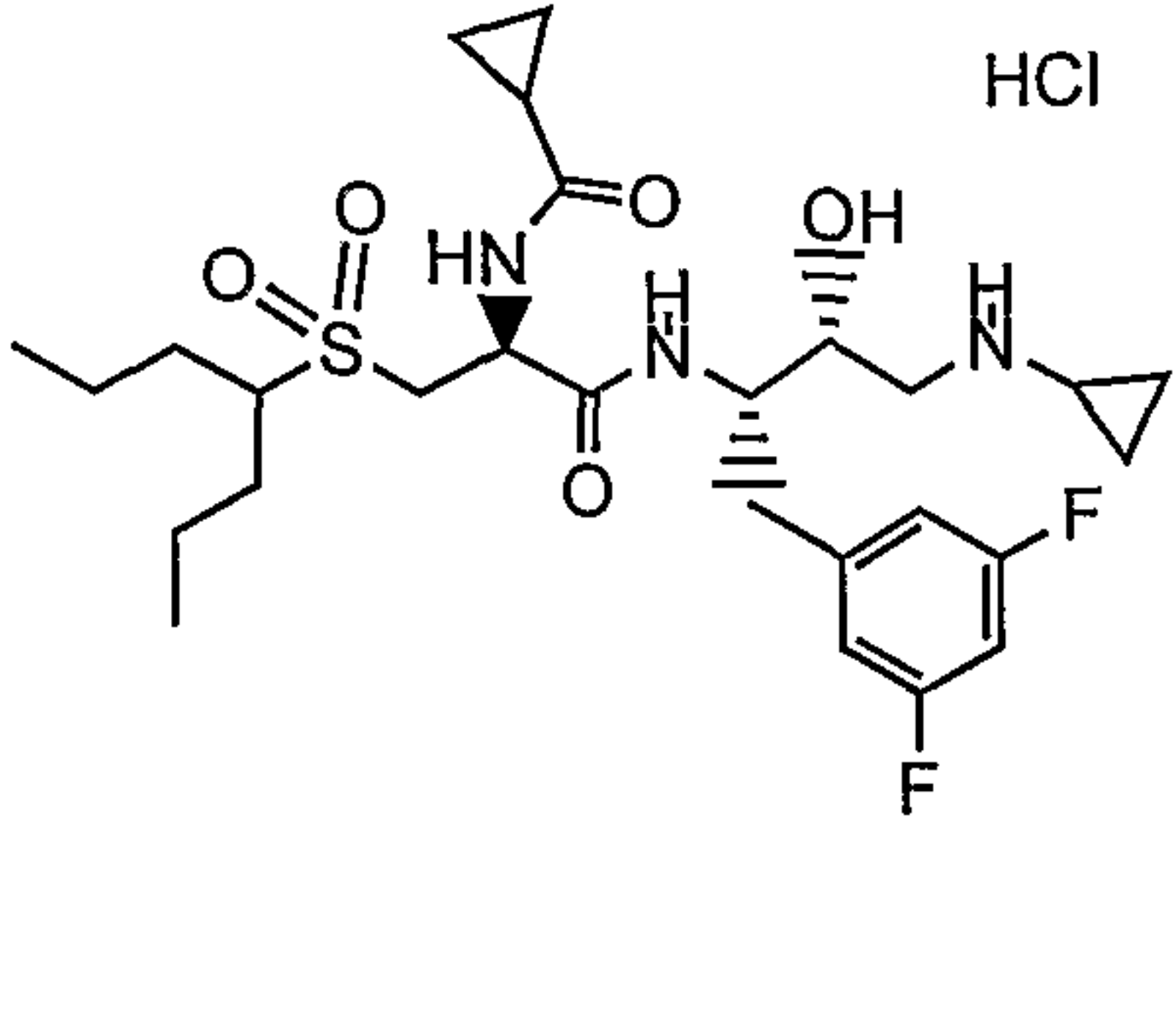
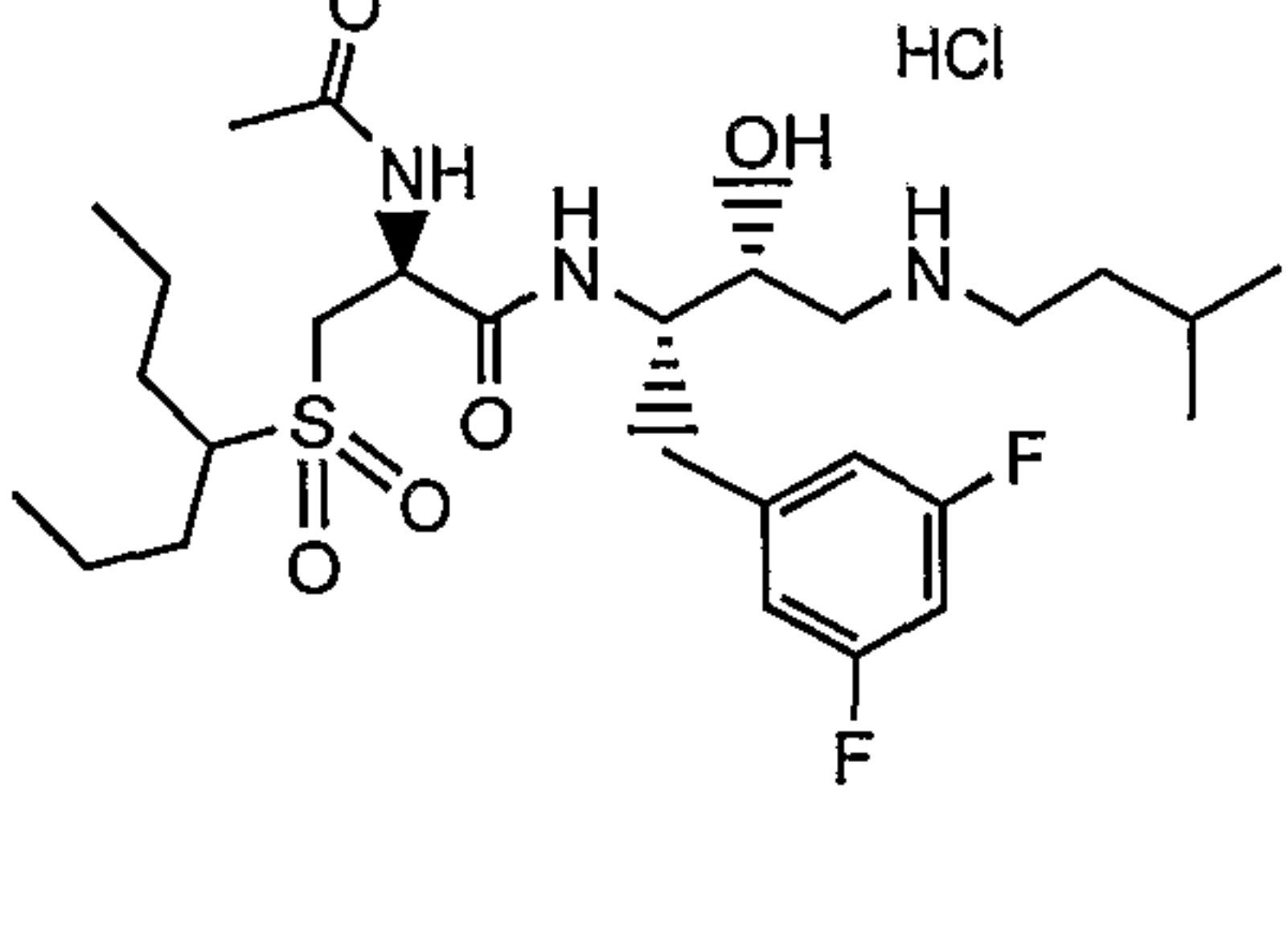
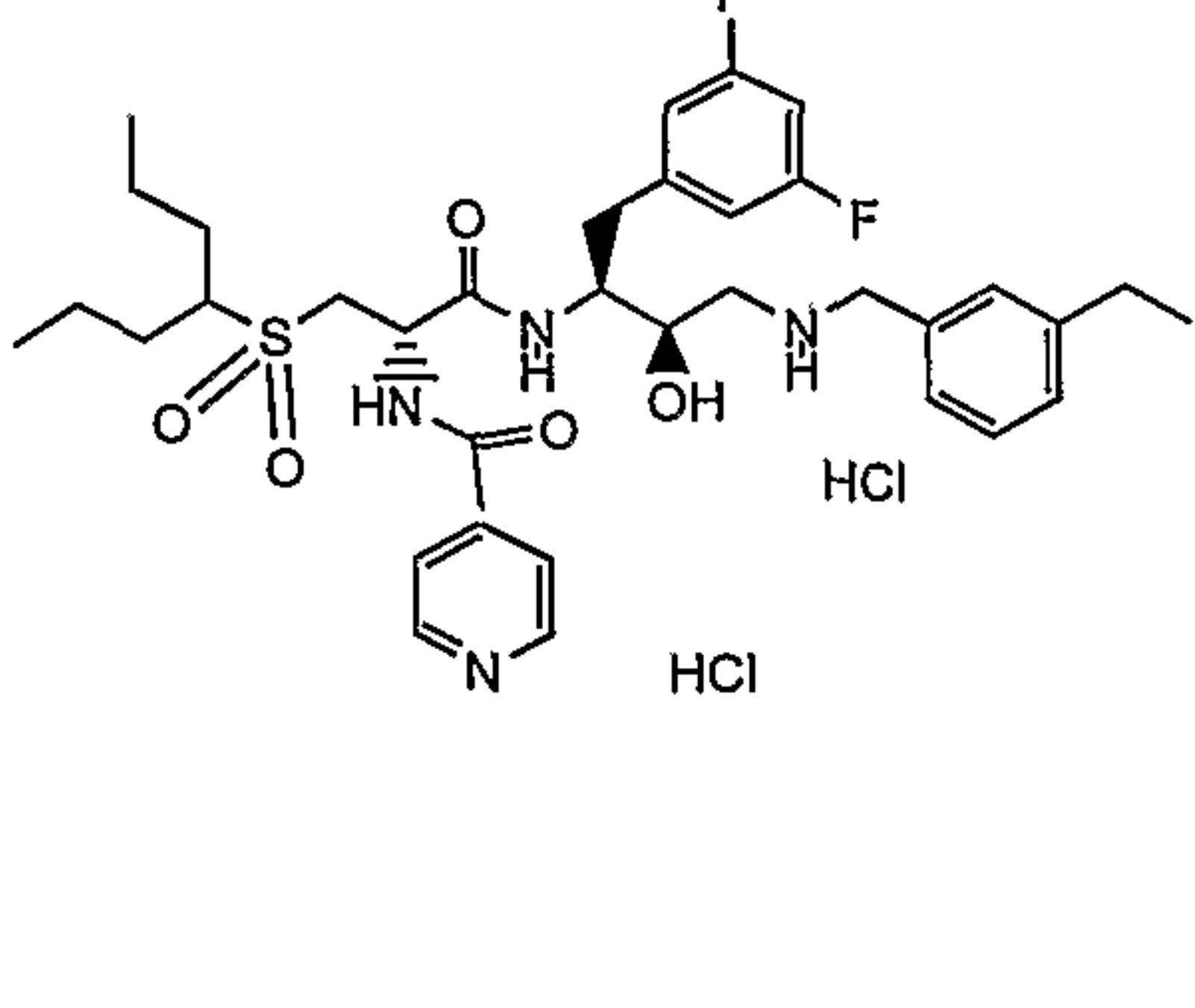
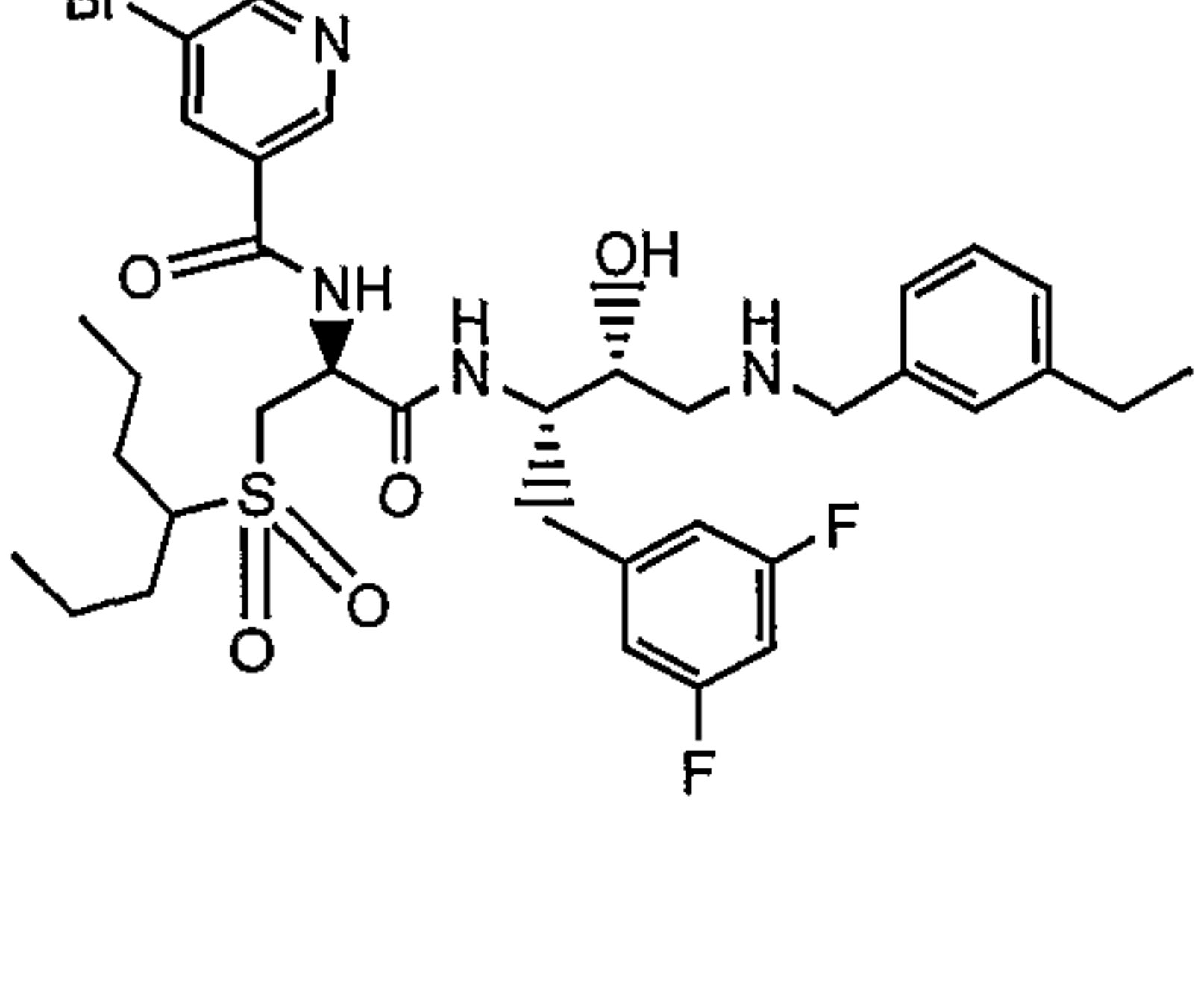
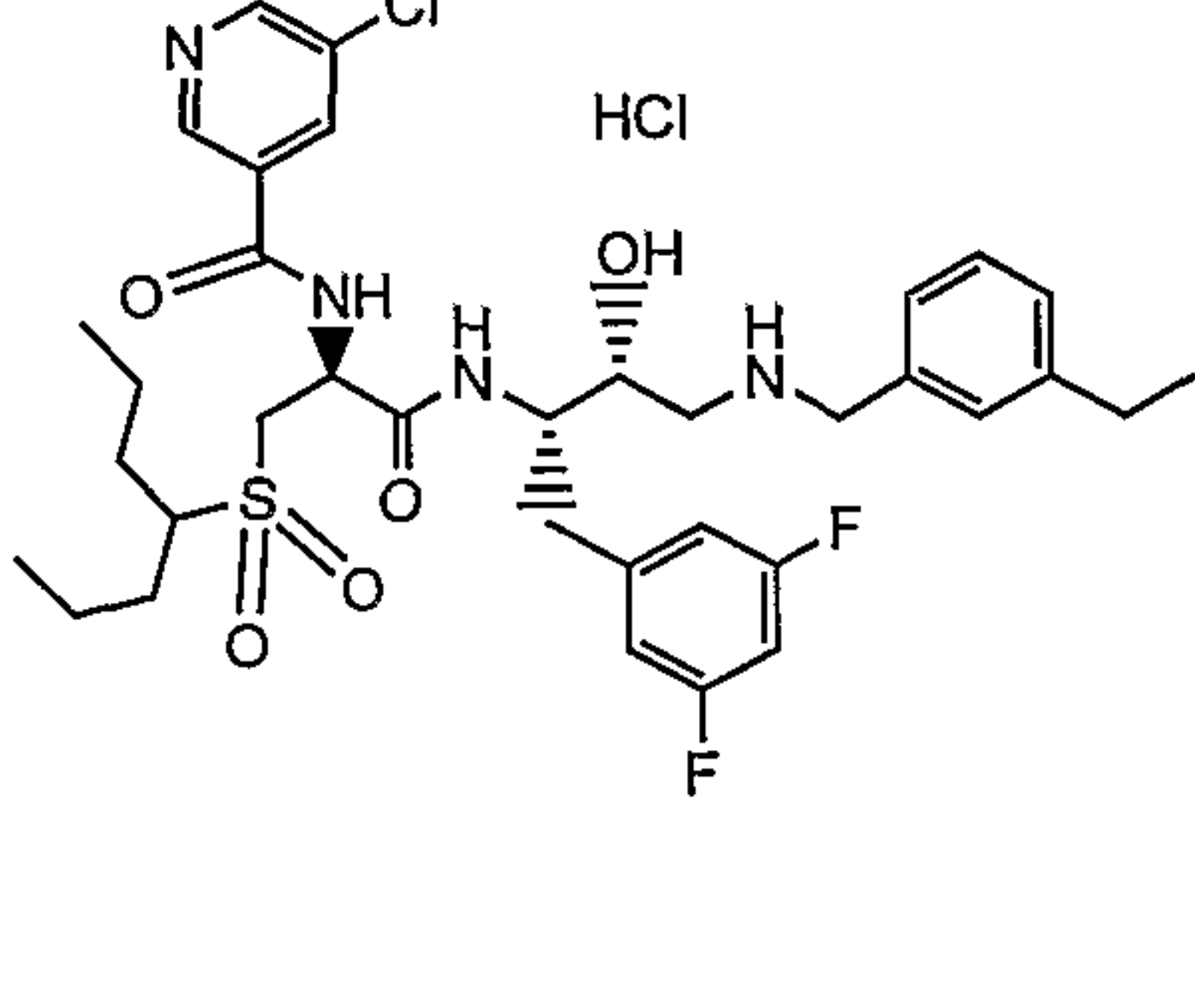


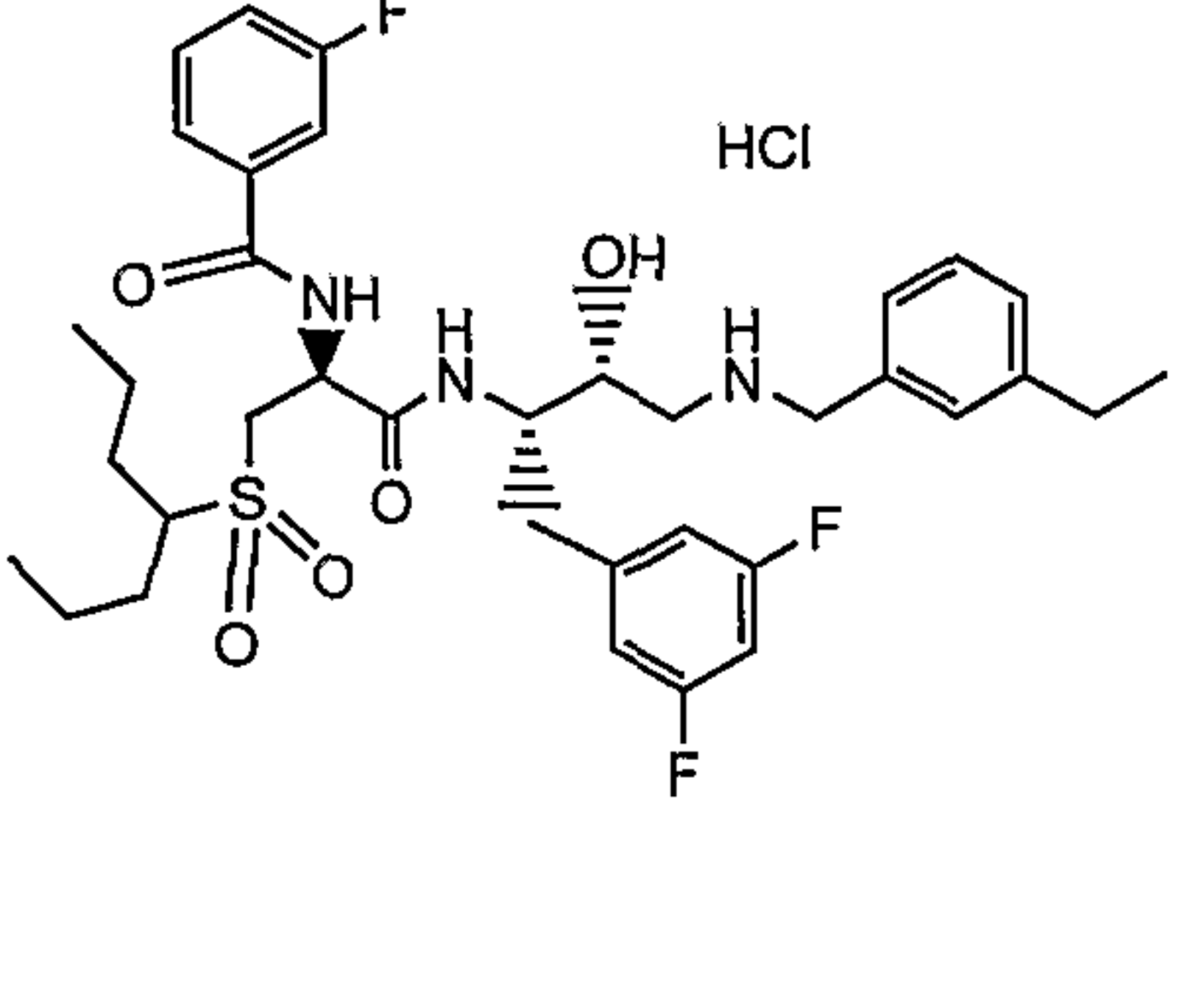
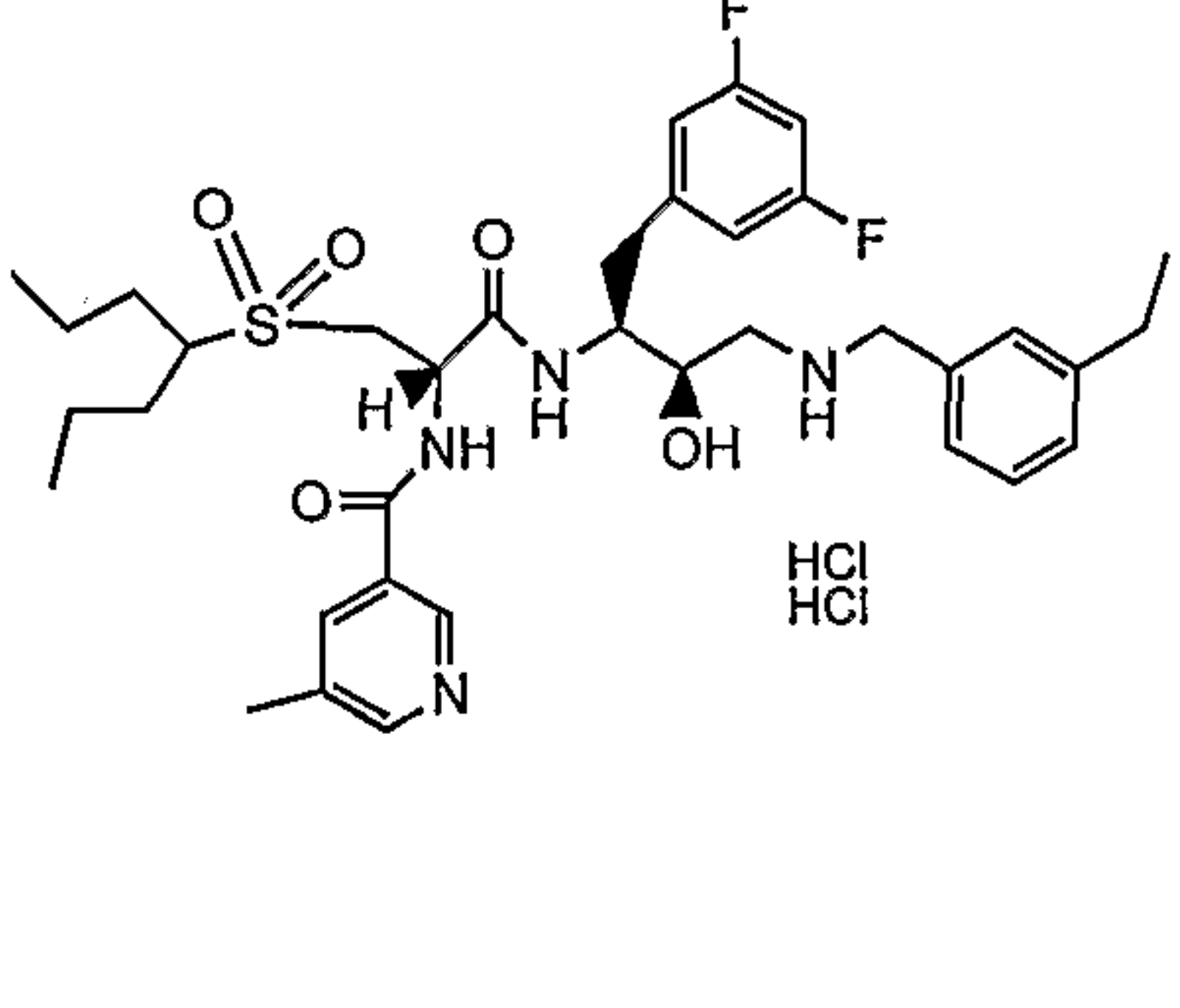
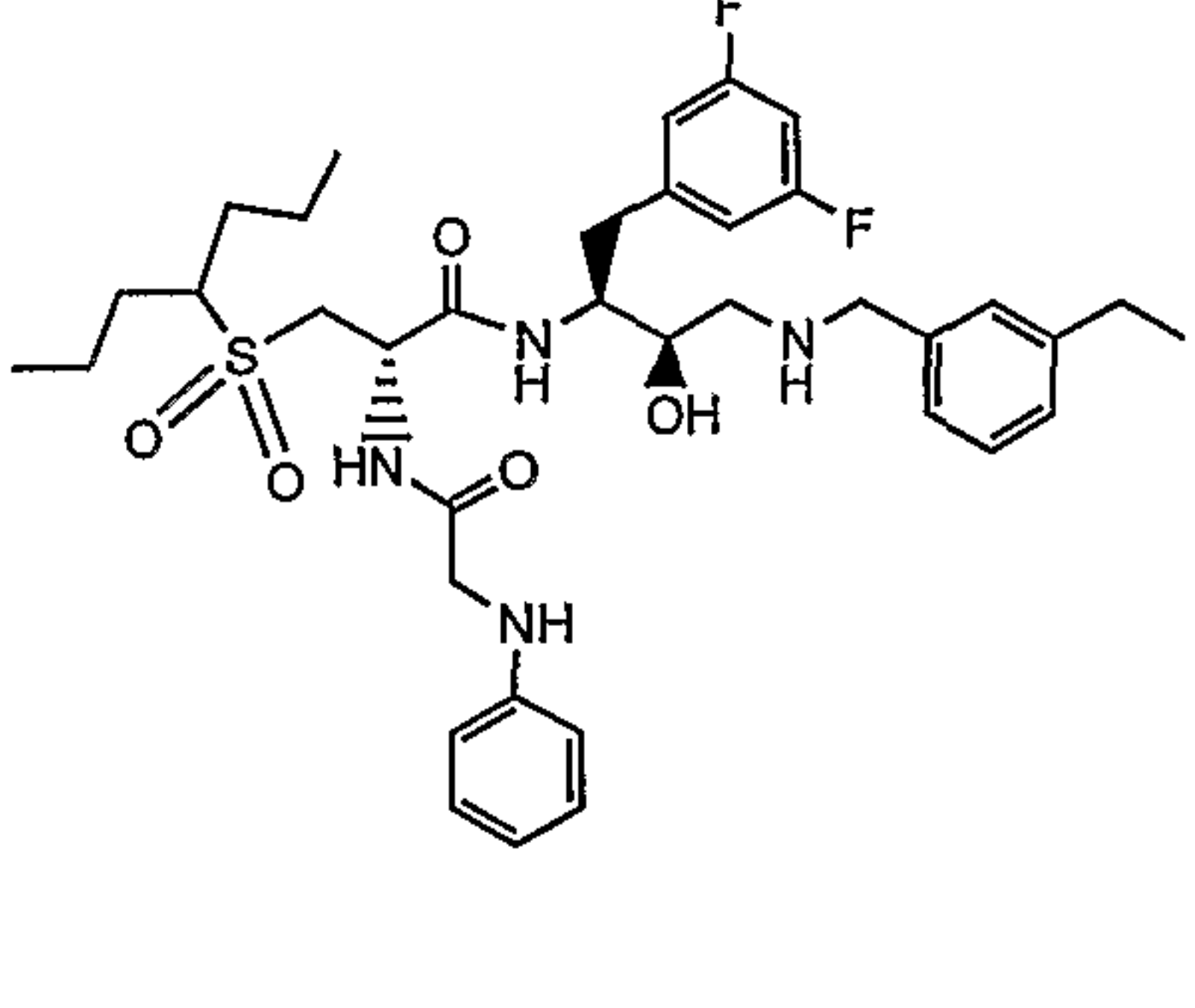
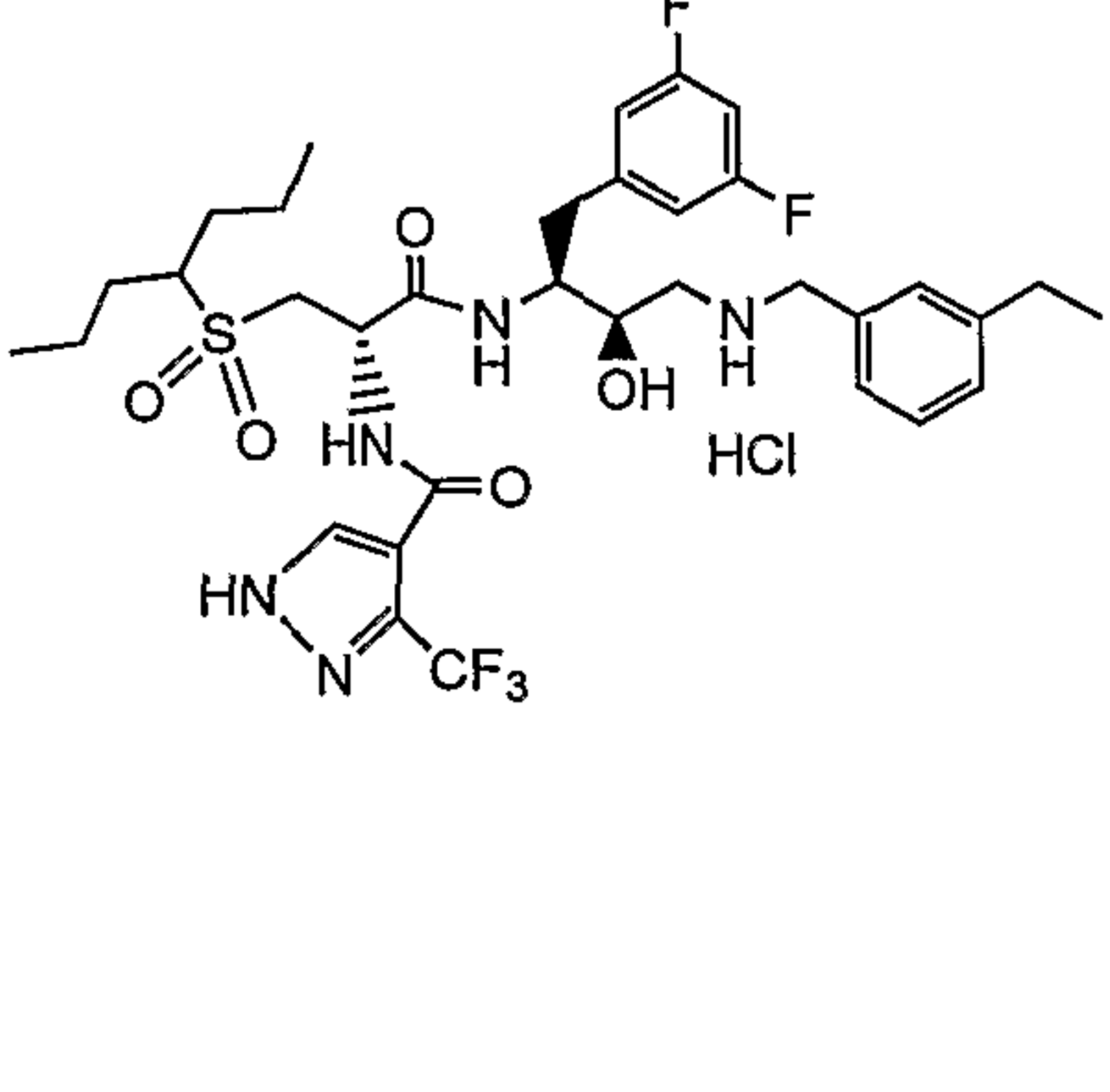
	<p>3-(butylsulfonyl)-N-1--          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2--(3,3,3-          trifluoropropanoyl)-D-          alaninamide hydrochloride</p>	636
	<p>3-(butylsulfonyl)-N-1--          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2--          (trifluoroacetyl)-D-          alaninamide hydrochloride</p>	622
	<p>N-2--acetyl-3-(butylsulfonyl)-          N-1--{(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-D-alaninamide          hydrochloride</p>	568
	<p>3-(butylsulfonyl)-N-1--          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2--(pyridin-          4-ylcarbonyl)-D-alaninamide          dihydrochloride</p>	631
	<p>3-(butylsulfonyl)-N-2--          (cyclopropylcarbonyl)-N-1--          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-D-alaninamide          hydrochloride</p>	594

	<p>3-(butylsulfonyl)-N-1-          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2-(beta-          alanyl)-D-alaninamide          dihydrochloride</p>	597
	<p>3-(butylsulfonyl)-N-1-          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2-glycyl-D-          alaninamide dihydrochloride</p>	583
	<p>3-(butylsulfonyl)-N-1-          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2-(N,N-          dimethylglycyl)-D-alaninamide          dihydrochloride</p>	611
	<p>3-(butylsulfonyl)-N-1-          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2-(N,N-          dimethyl-beta-alanyl)-D-          alaninamide dihydrochloride</p>	625
	<p>3-(butylsulfonyl)-N-1-          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2--          (methoxyacetyl)-D-alaninamide</p>	598

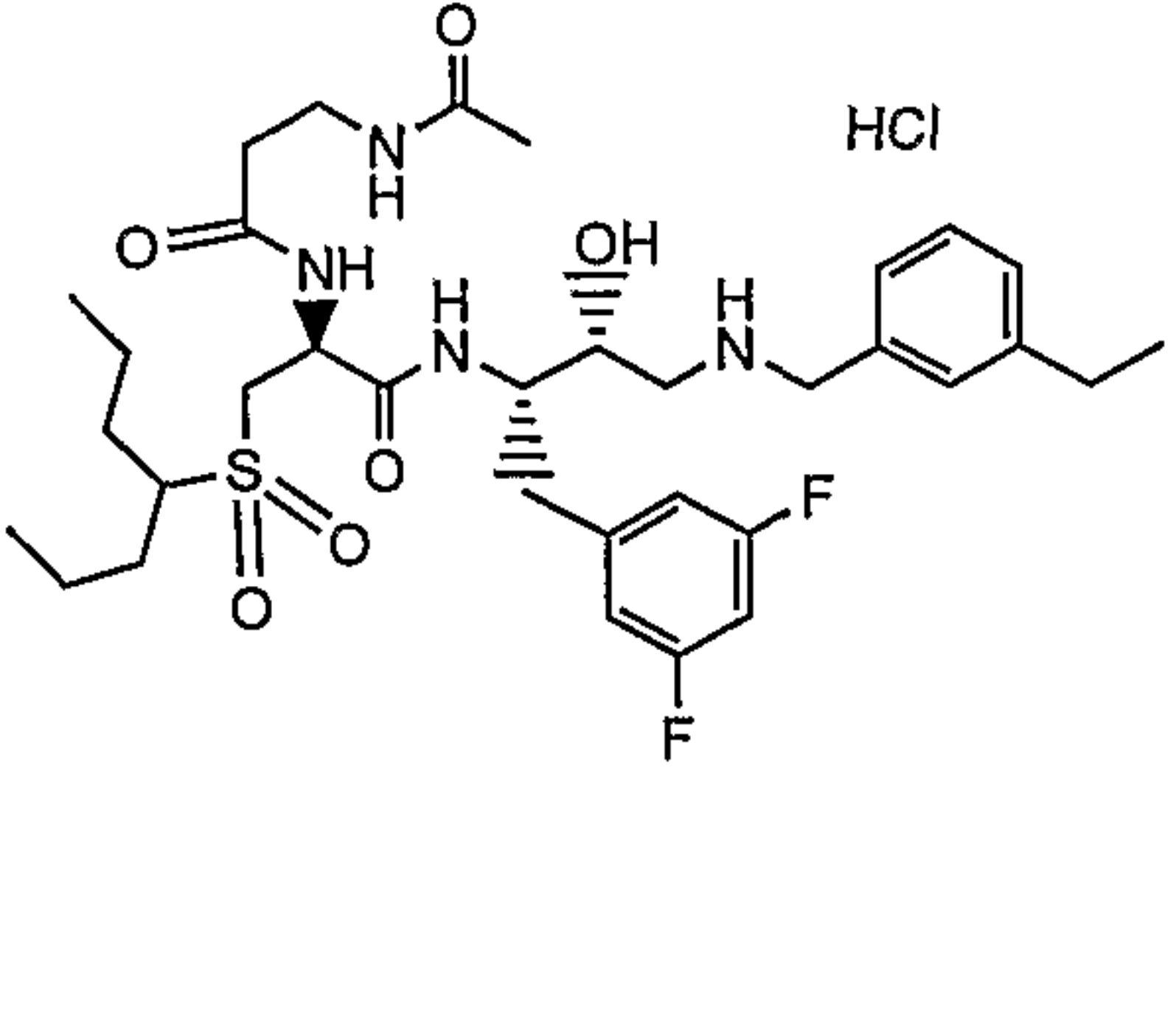
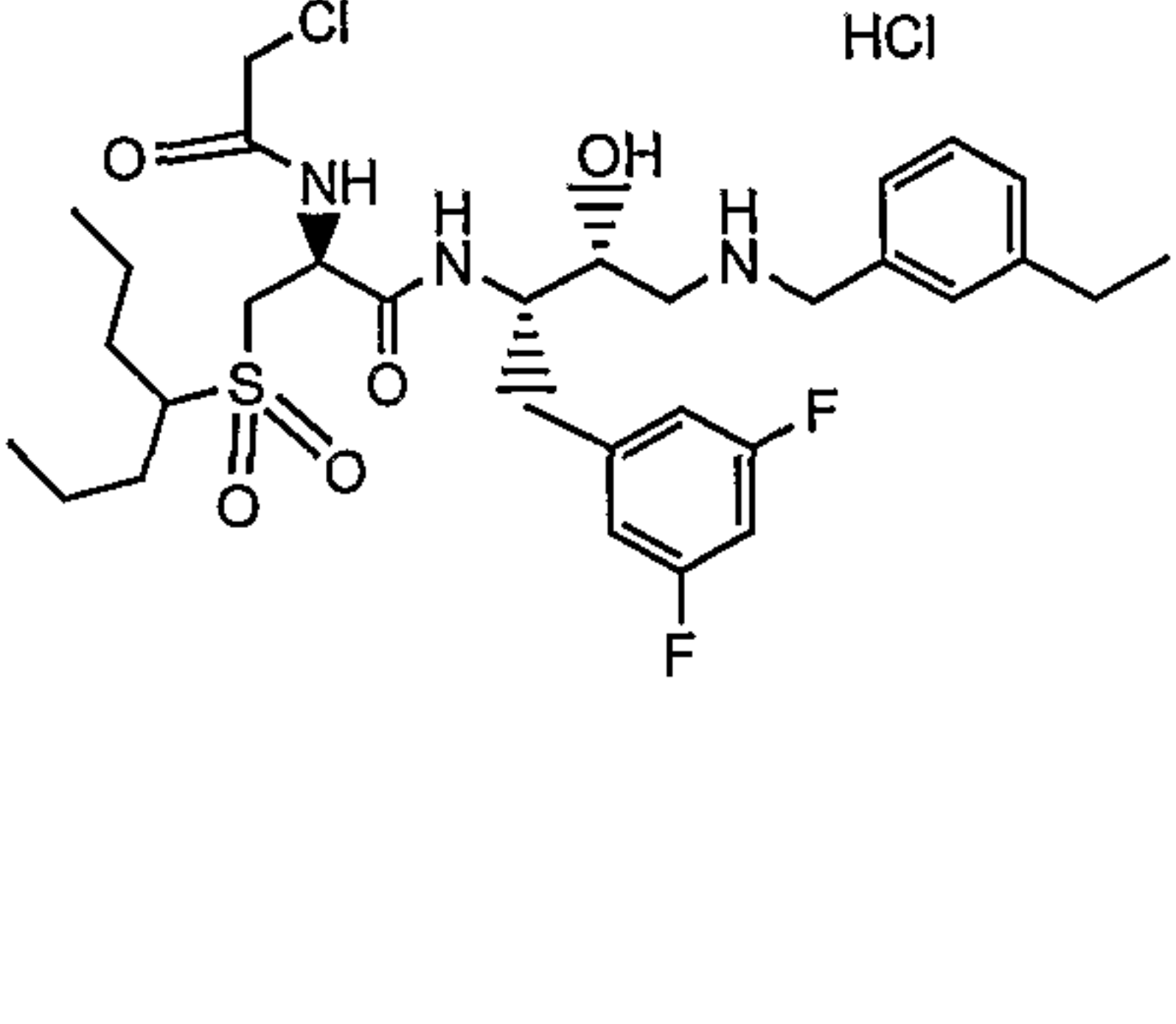
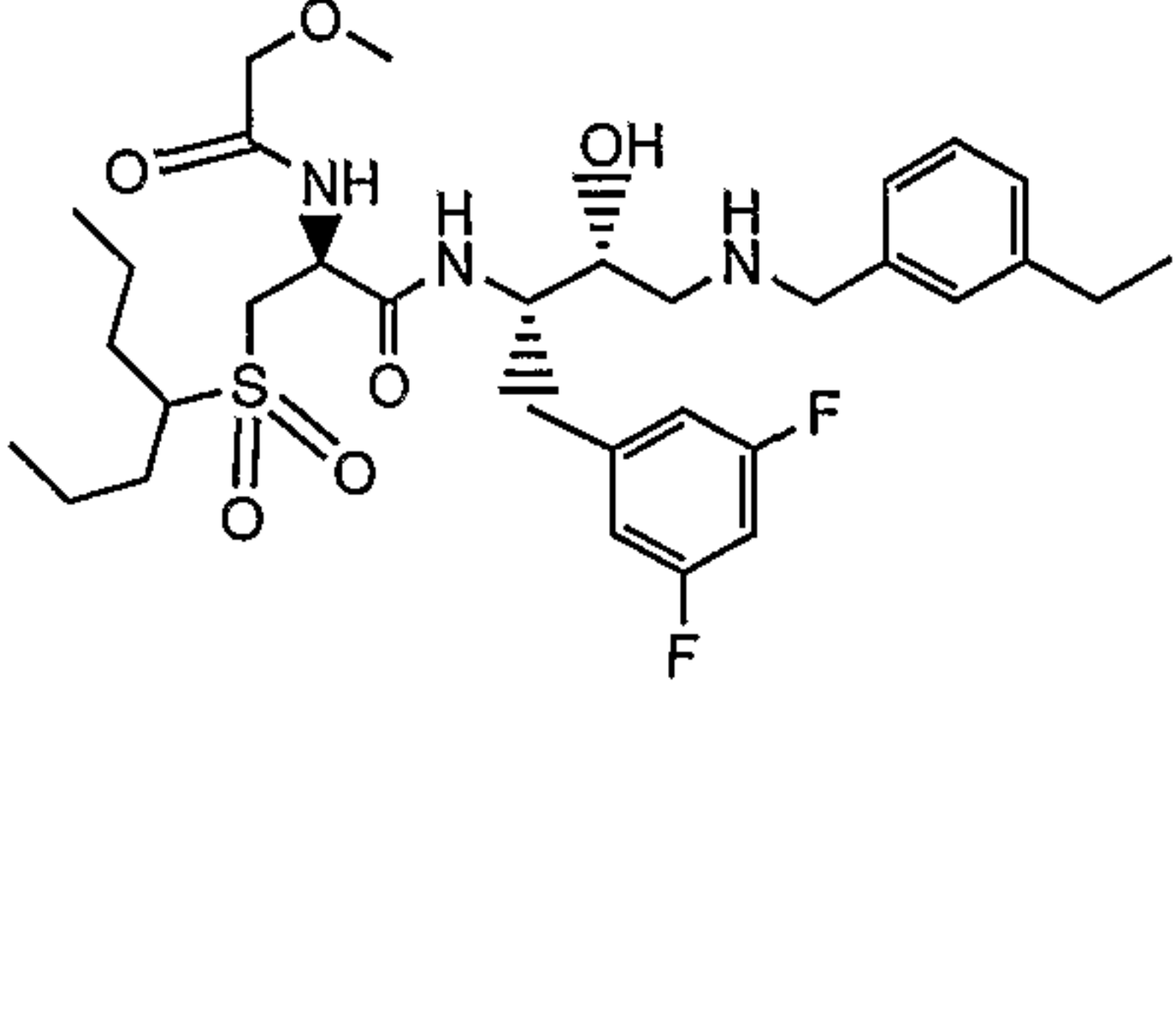
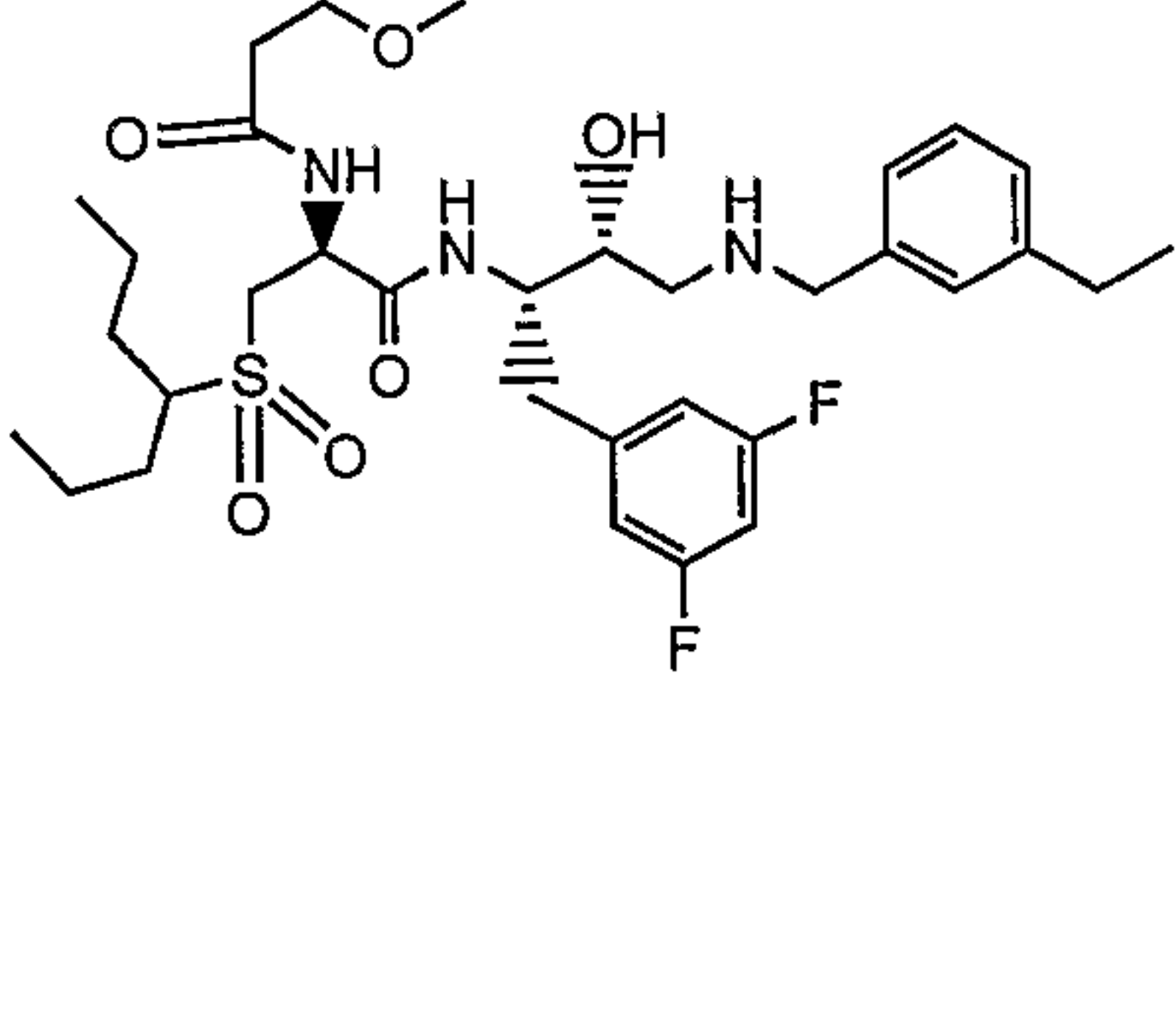
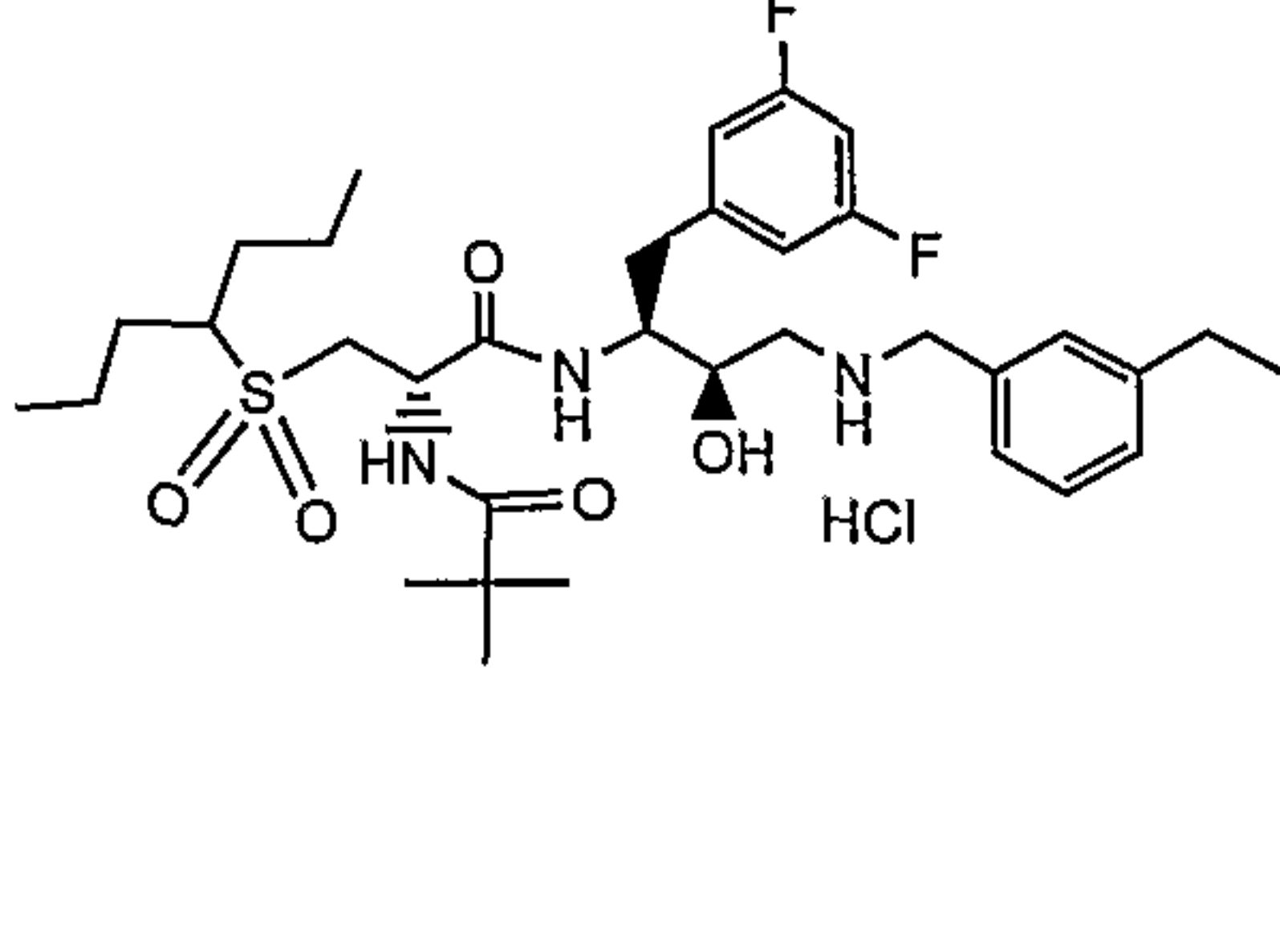
	<p>3-(butylsulfonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-(pyridin-3-ylcarbonyl)-D-alaninamide dihydrochloride</p>	631
	<p>3-(butylsulfonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-[(2,4-dimethyl-1,3-thiazol-5-yl)carbonyl]-D-alaninamide hydrochloride</p>	665
	<p>3-(butylsulfonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-[(3-(trifluoromethyl)-1H-pyrazol-4-yl)carbonyl]-D-alaninamide hydrochloride</p>	688
	<p>3-(butylsulfonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-[(3-methyl-1H-pyrazol-5-yl)carbonyl]-D-alaninamide hydrochloride</p>	634

	<p>3-(butylsulfonyl)-N-1--          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2--(1H-          imidazol-4-ylacetyl)-D-          alaninamide dihydrochloride</p>	620
	<p>3-(butylsulfonyl)-N-1--          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2--(pyrazin-          2-ylcarbonyl)-D-alaninamide          dihydrochloride</p>	632
	<p>3-(butylsulfonyl)-N-1--          {(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          ethylbenzyl)amino]-2-          hydroxypropyl}-N-2--[(6-          hydroxypyridin-3-yl)carbonyl]-          D-alaninamide dihydrochloride</p>	647
	<p>N-1--{(1S,2R)-1-(3,5-          difluorobenzyl)-3-          (cyclopropylamino)-2-          hydroxypropyl}-3-[(1-          propylbutyl)sulfonyl]-N-2--          (pyridin-4-ylcarbonyl)-D-          alaninamide dihydrochloride</p>	553
	<p>N-2--acetyl-3-(butylsulfonyl)-          N-1--{(1S,2R)-1-(3,5-          difluorobenzyl)-3-[(3-          methylbutyl)amino]-2-          hydroxypropyl}-D-alaninamide          hydrochloride</p>	520

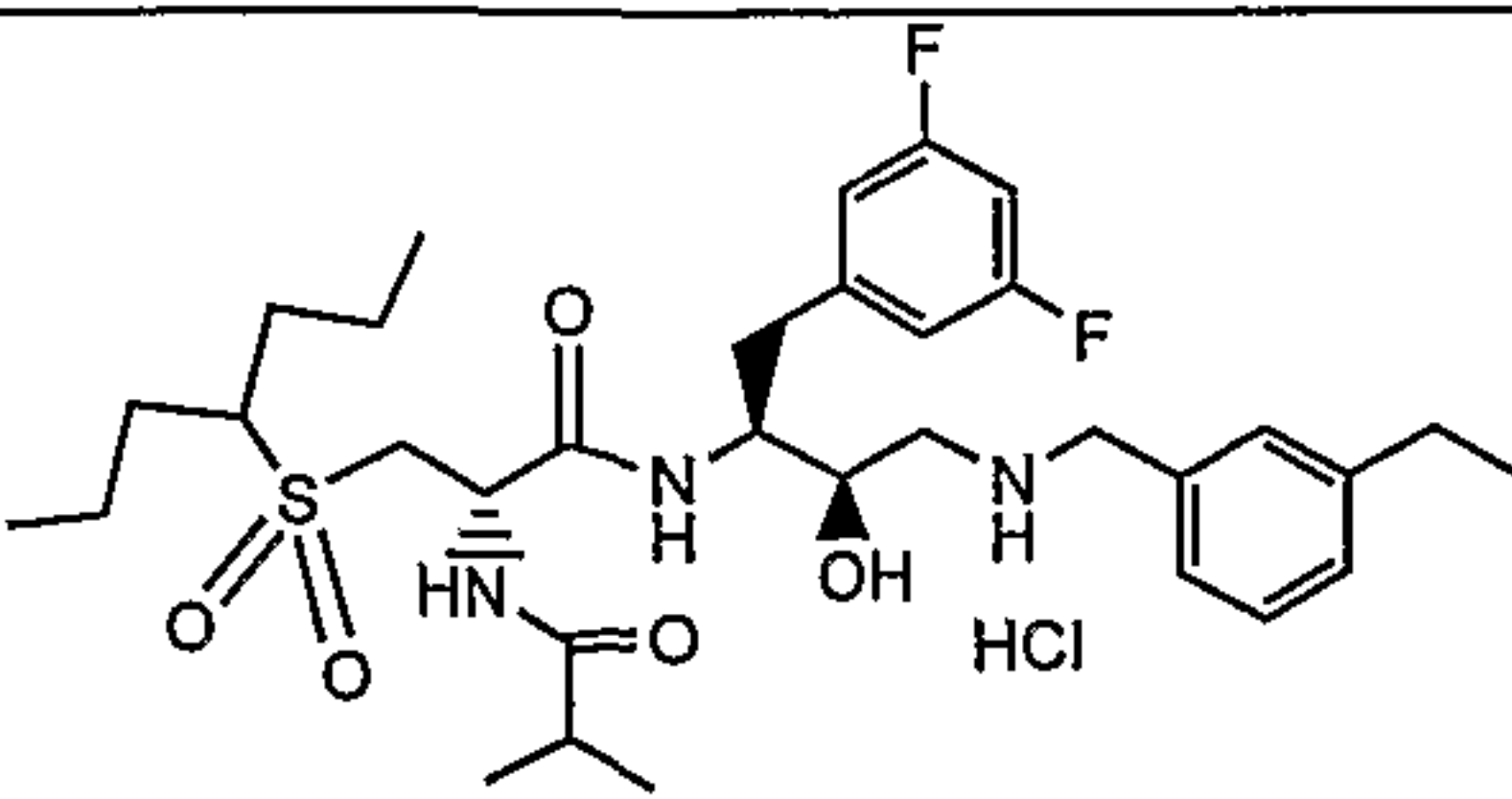
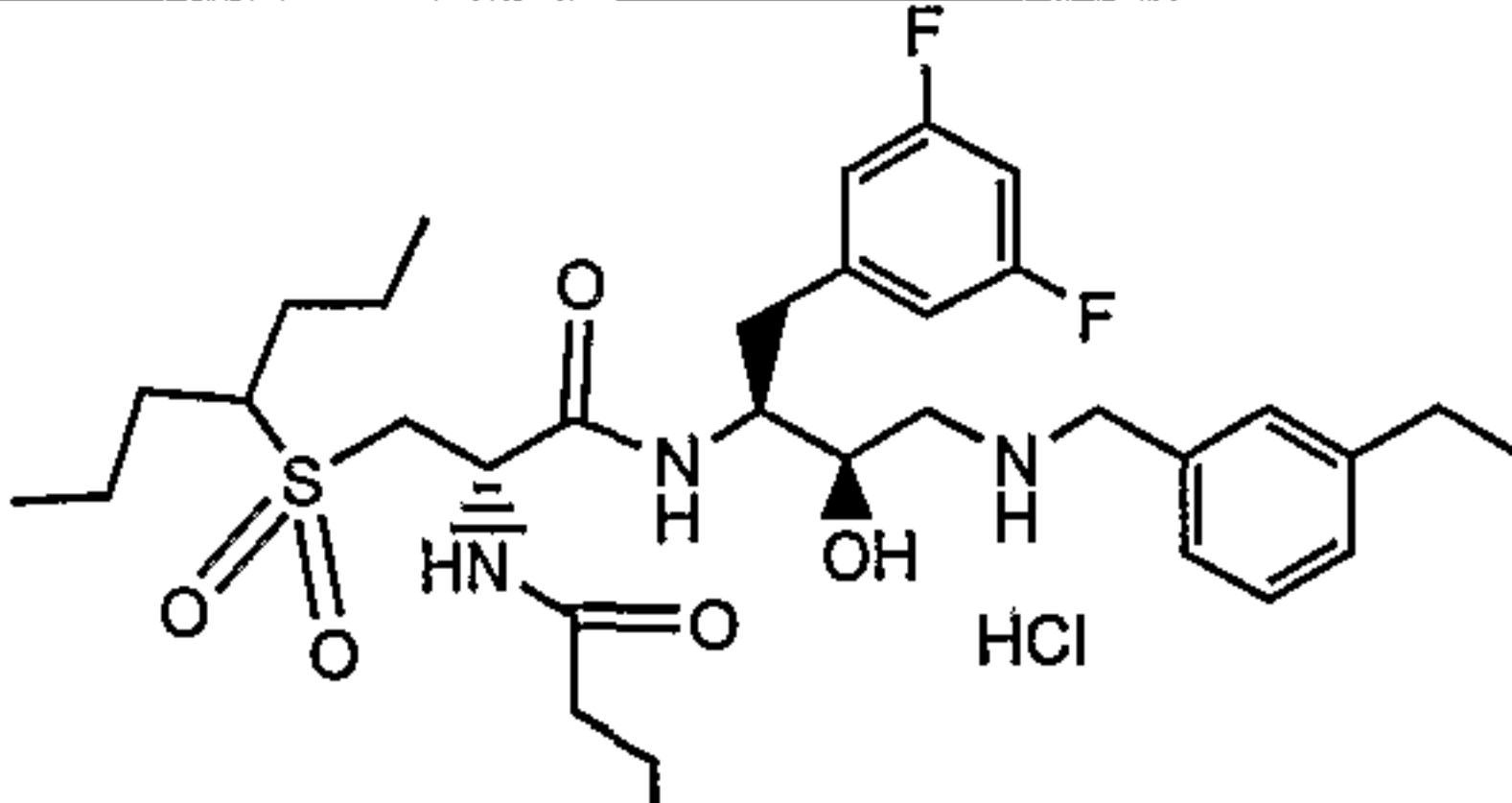
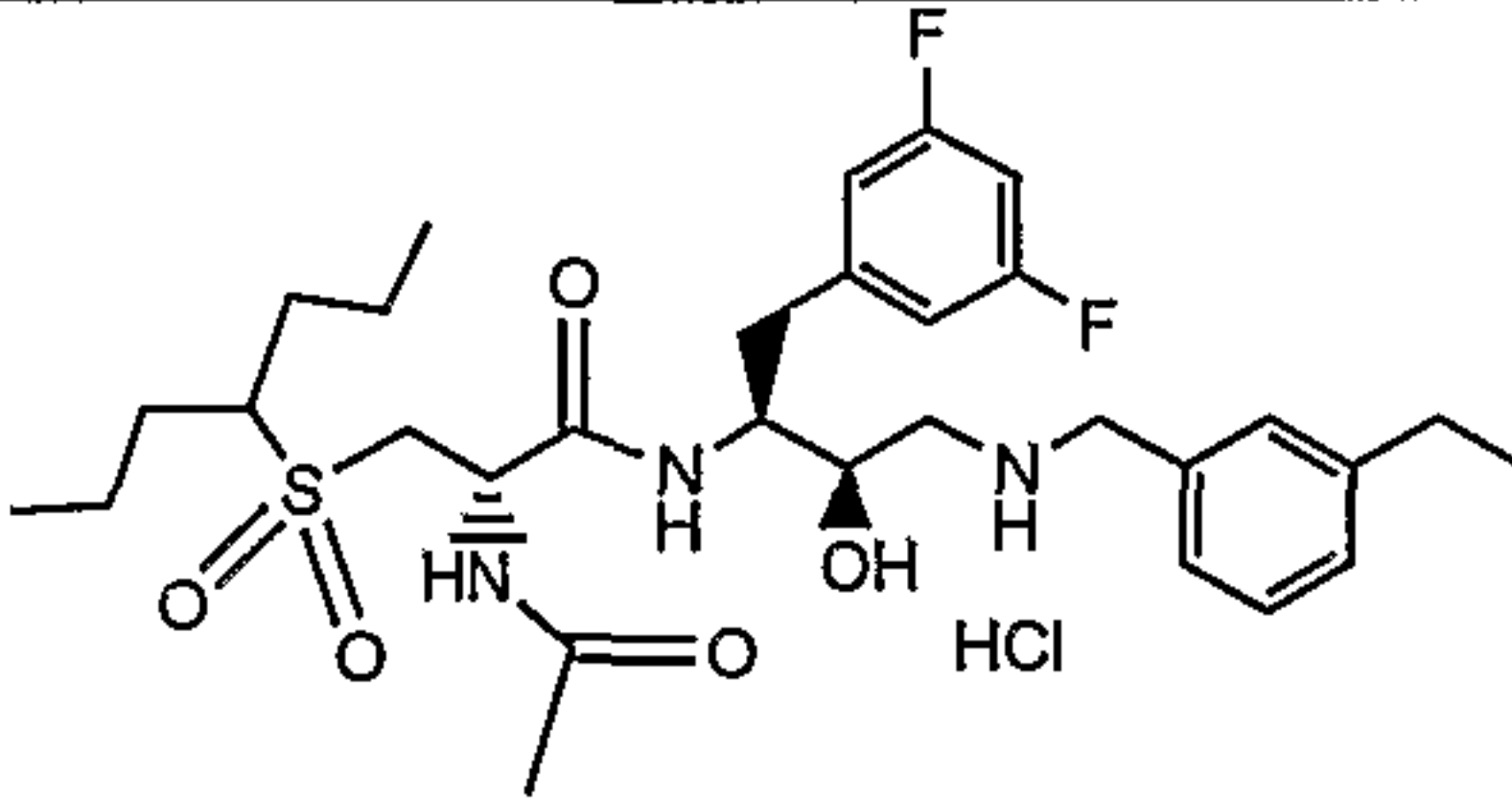
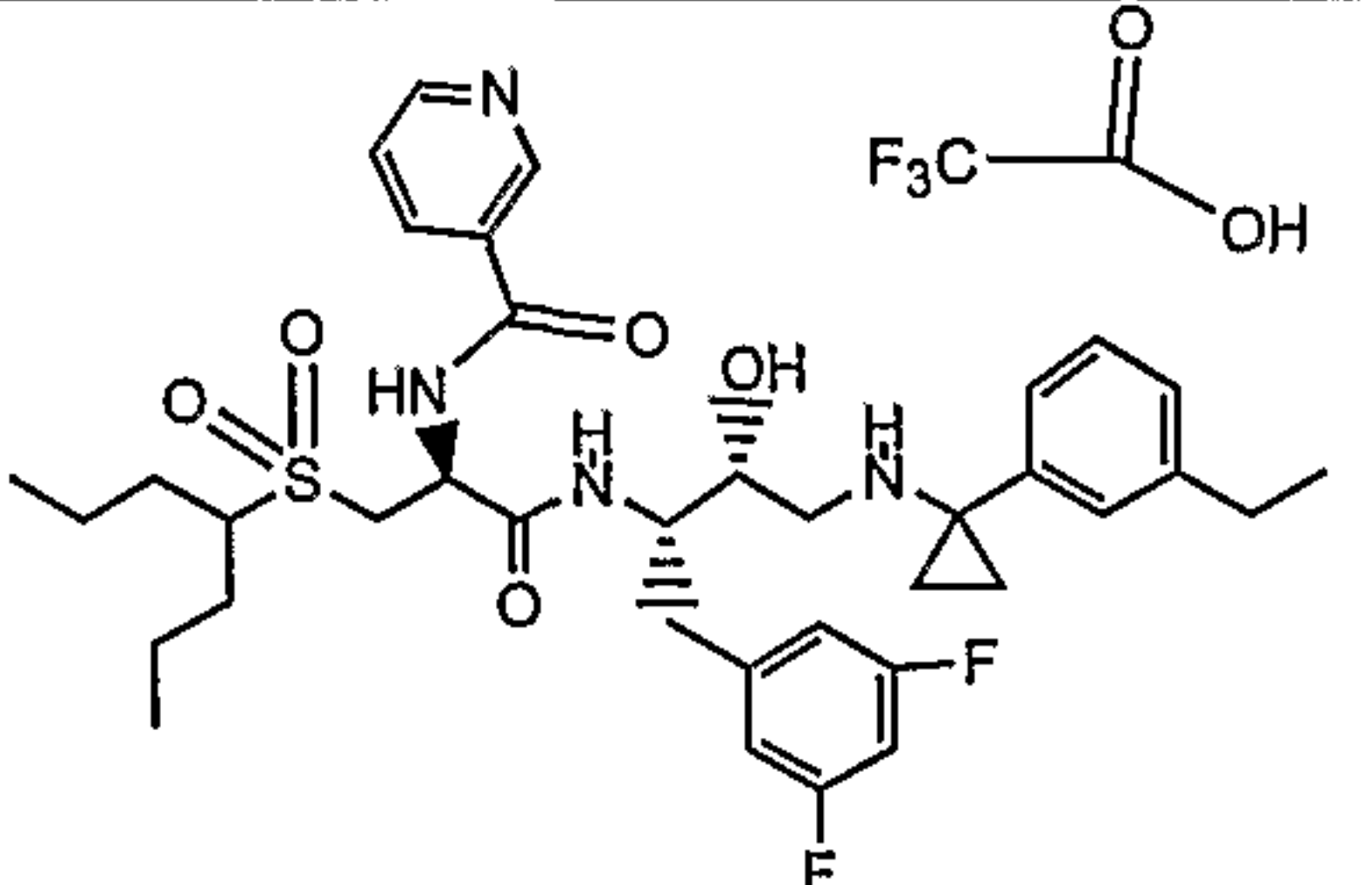
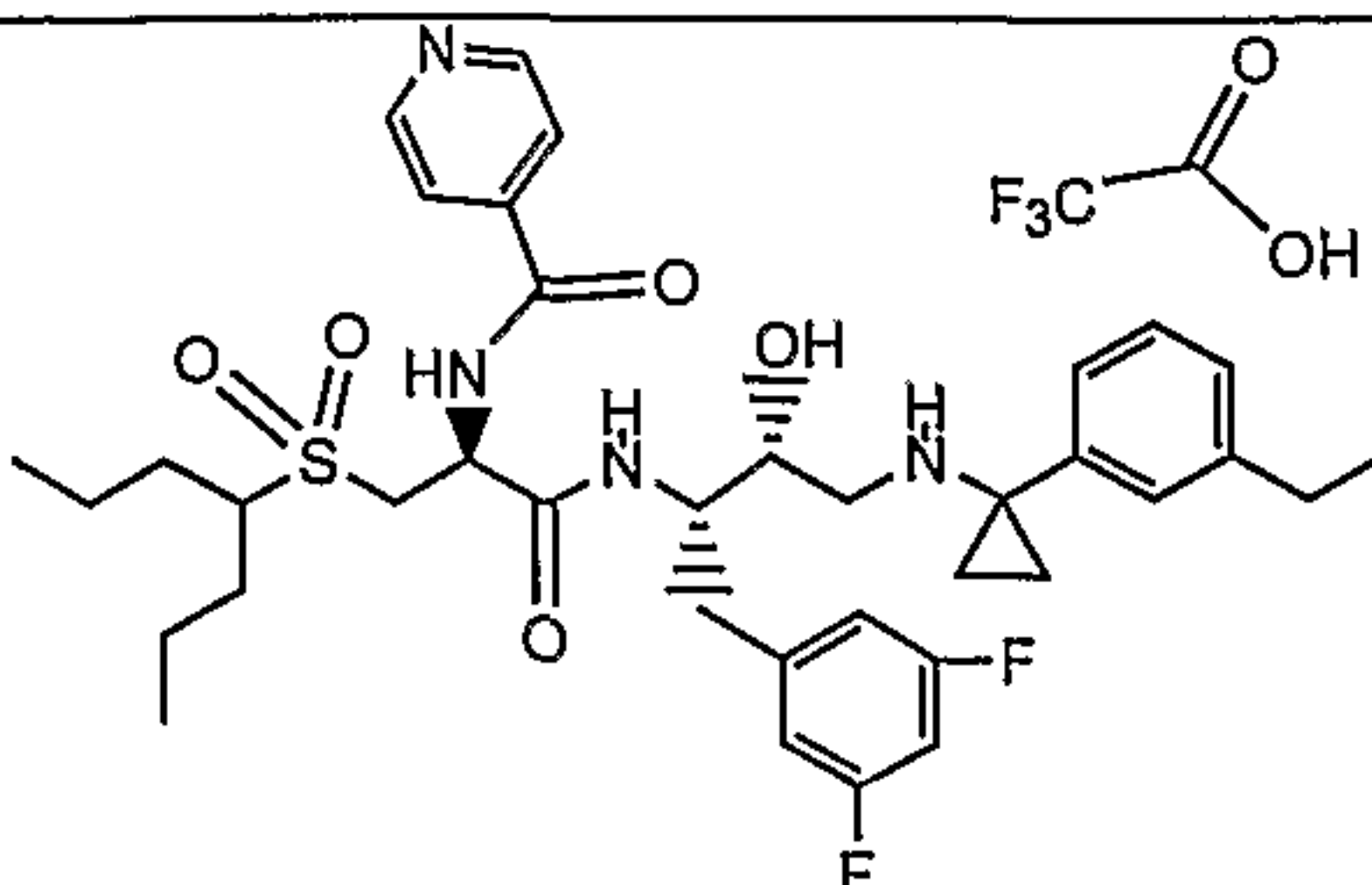
	<p>N~1~-[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-N~2~-[(cyclopropylcarbonyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	558
	<p>N~2~-acetyl-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	562
	<p>N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-N~2~-[(pyridin-4-ylcarbonyl)-D-alaninamide dihydrochloride</p>	673
	<p>N~2~-[(5-bromopyridin-3-yl)carbonyl]-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide</p>	751
	<p>N~2~-[(5-chloropyridin-3-yl)carbonyl]-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	707

	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(3-fluorobenzoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	690
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(5-methylpyridin-3-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide dihydrochloride</p>	687
	<p>N~2~-phenylglycyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide</p>	701
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-[[3-(trifluoromethyl)-1H-pyrazol-4-yl]carbonyl]-D-alaninamide hydrochloride</p>	730

	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(3-methyl-1H-pyrazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	676
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-[(1,3-thiazol-4-yl)carbonyl]-D-alaninamide hydrochloride</p>	679
	<p>N~2~-[(1-acetylpiperidin-4-yl)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	721
	<p>N~2~-[(4-(acetylamino)butanoyl)]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	695

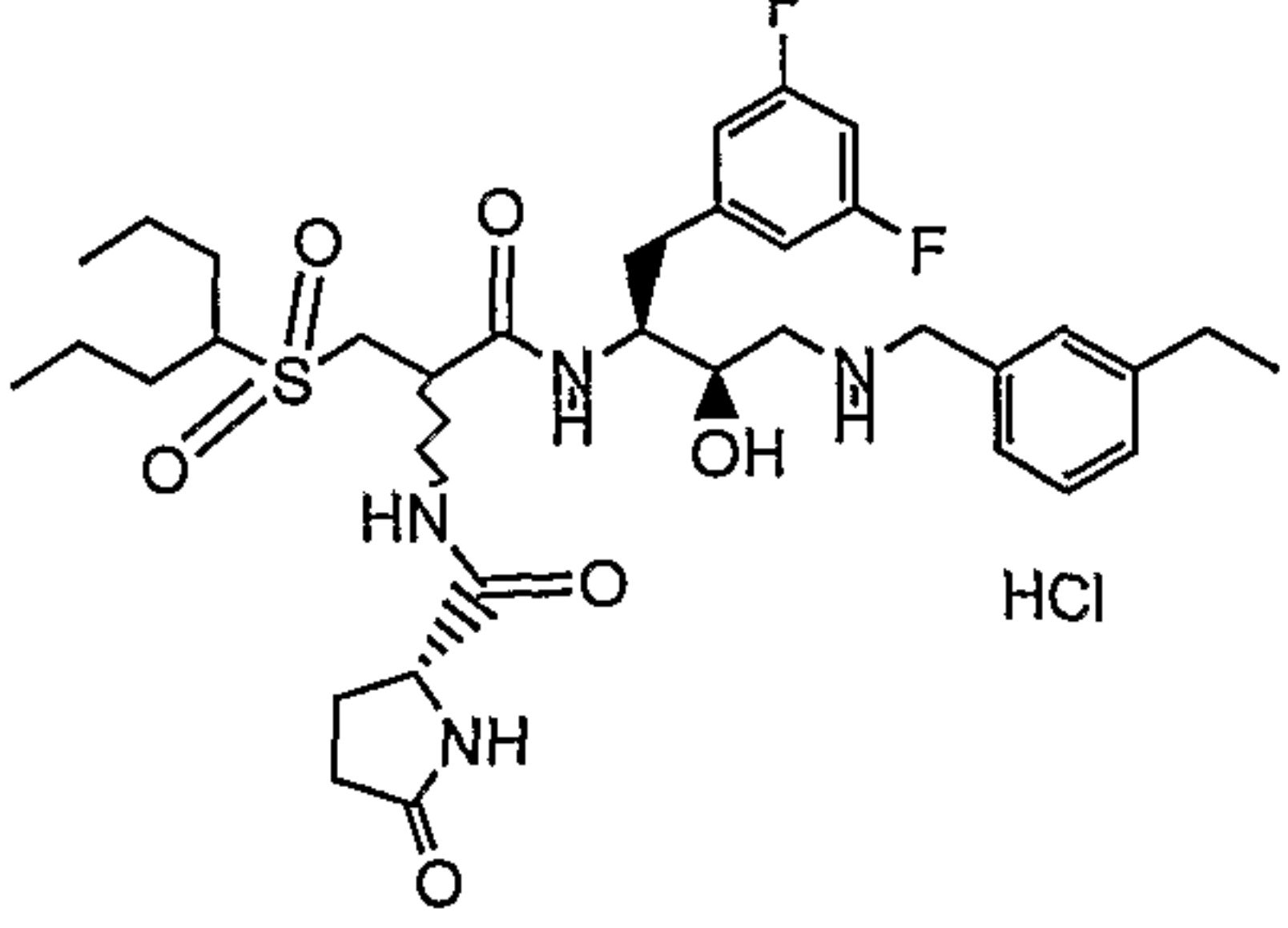
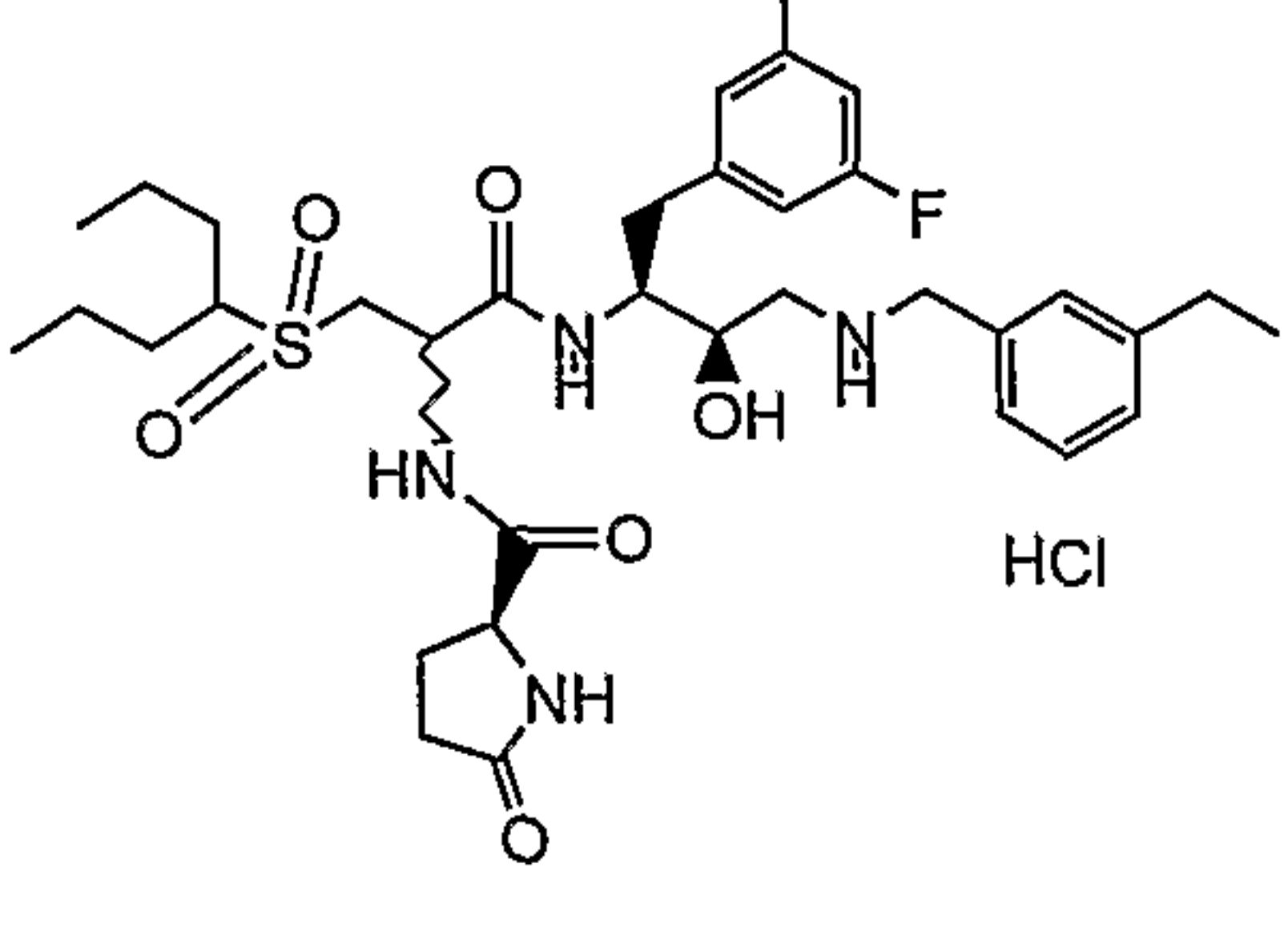
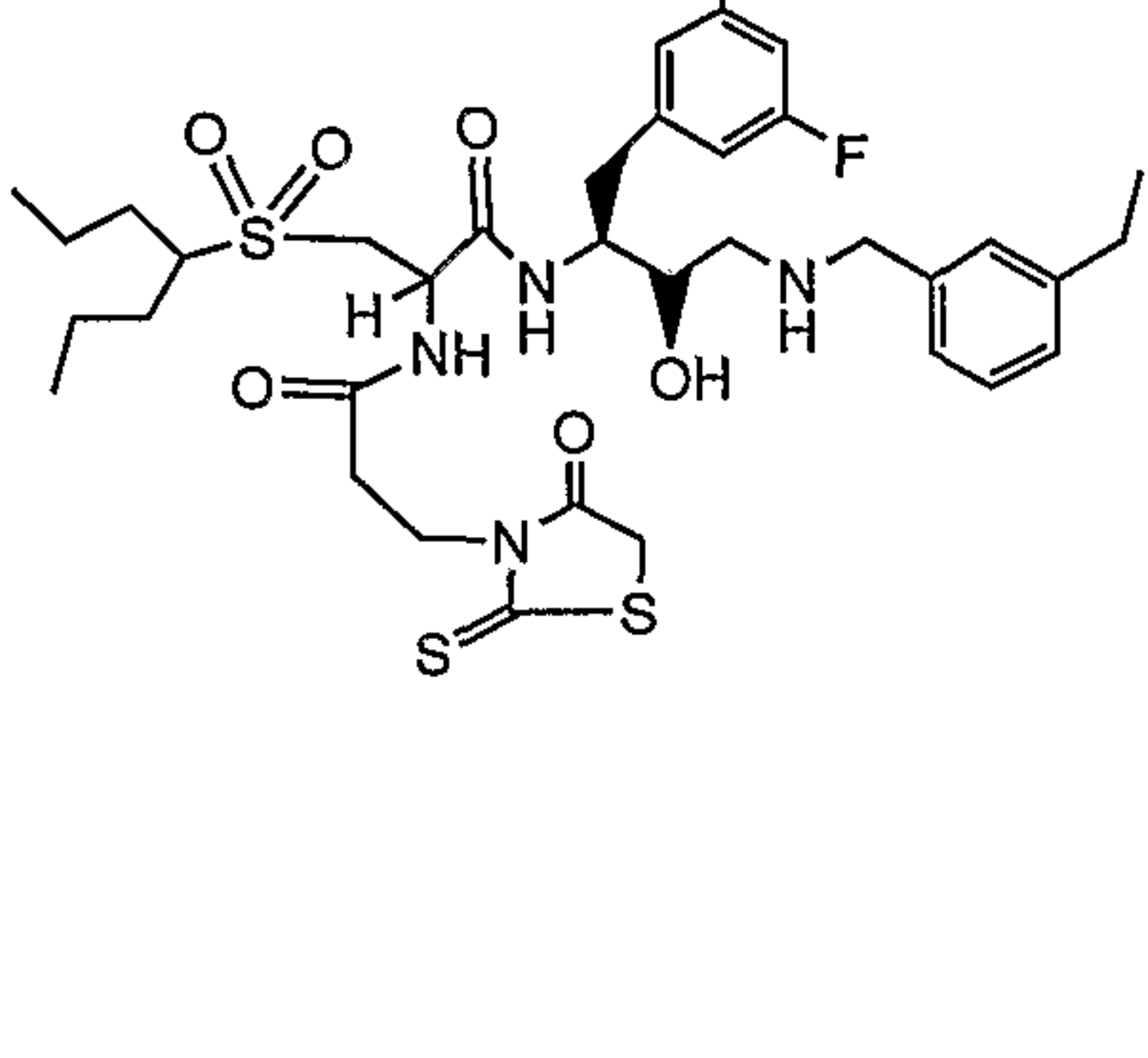
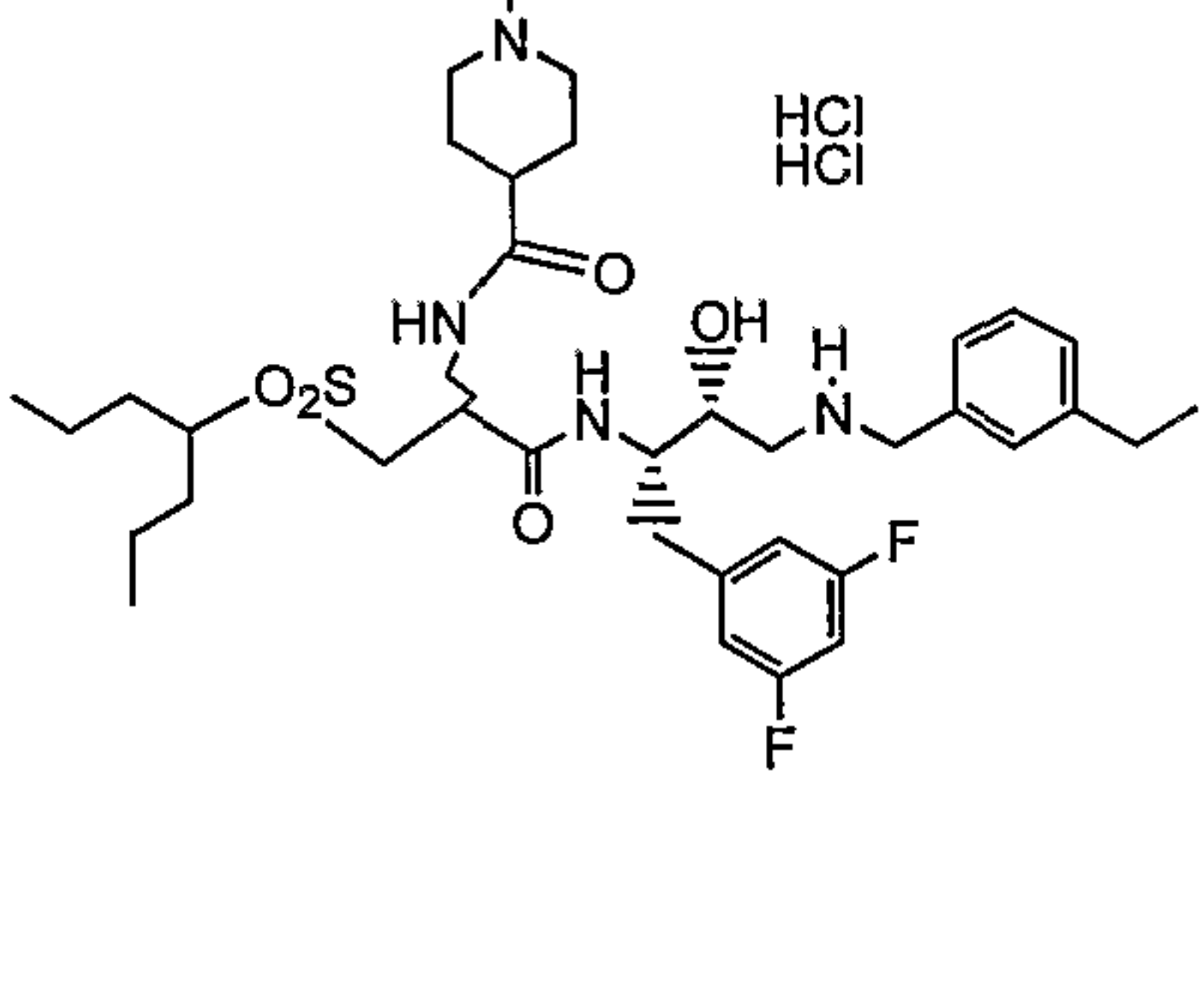
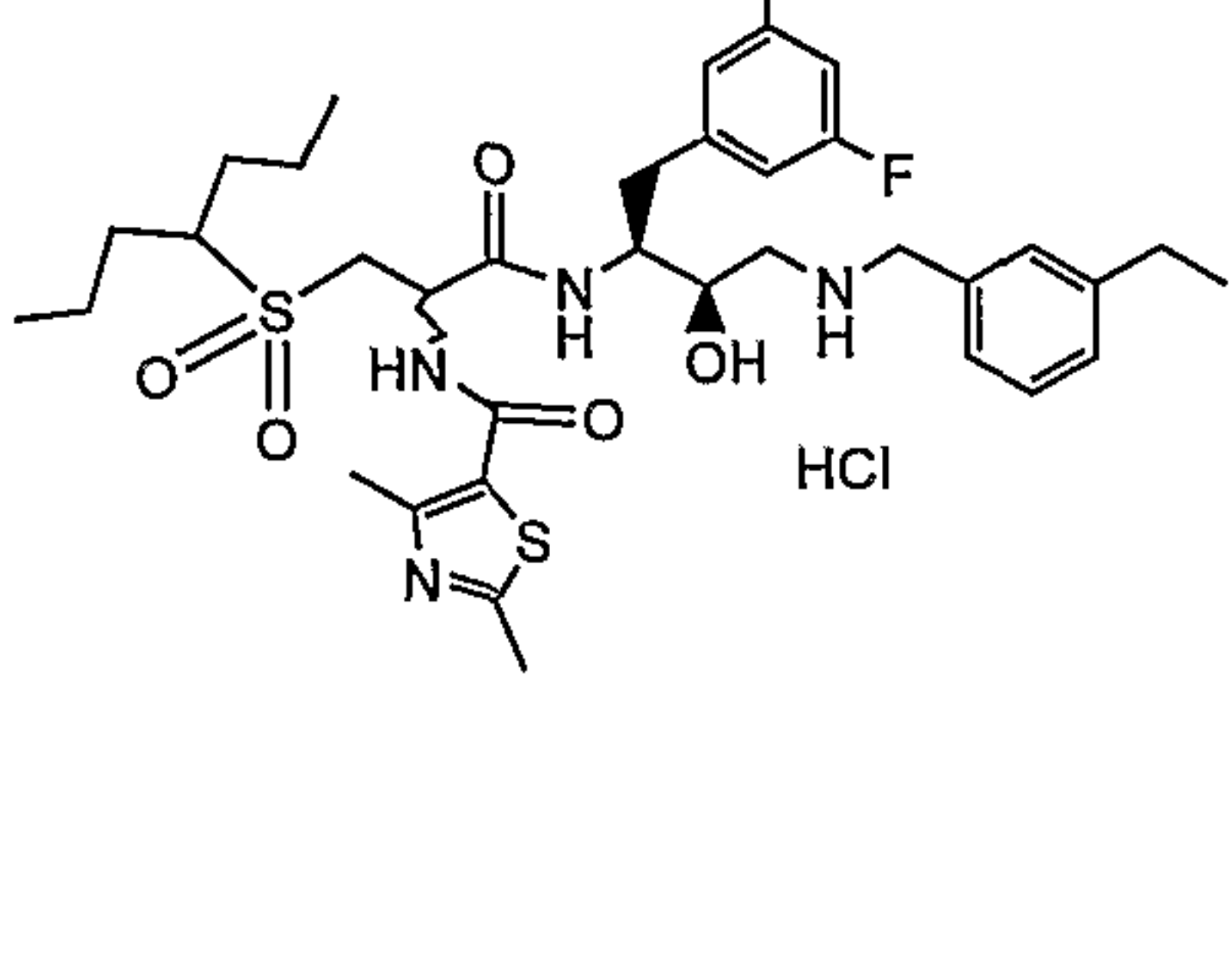
	<p>N-2--acetyl-beta-alanyl-N-1--  {(1S,2R)-1-(3,5-  difluorobenzyl)-3-[(3-  ethylbenzyl)amino]-2-  hydroxypropyl}-3-[(1-  propylbutyl)sulfonyl]-D-  alaninamide hydrochloride</p>	681
	<p>N-2--(chloroacetyl)-N-1--  {(1S,2R)-1-(3,5-  difluorobenzyl)-3-[(3-  ethylbenzyl)amino]-2-  hydroxypropyl}-3-[(1-  propylbutyl)sulfonyl]-D-  alaninamide hydrochloride</p>	644
	<p>N-1--{(1S,2R)-1-(3,5-  difluorobenzyl)-3-[(3-  ethylbenzyl)amino]-2-  hydroxypropyl}-N-2--  (methoxyacetyl)-3-[(1-  propylbutyl)sulfonyl]-D-  alaninamide</p>	640
	<p>N-1--{(1S,2R)-1-(3,5-  difluorobenzyl)-3-[(3-  ethylbenzyl)amino]-2-  hydroxypropyl}-N-2--(3-  methoxypropanoyl)-3-[(1-  propylbutyl)sulfonyl]-D-  alaninamide</p>	654
	<p>N-1--{(1S,2R)-1-(3,5-  difluorobenzyl)-3-[(3-  ethylbenzyl)amino]-2-  hydroxypropyl}-N-2--(2,2-  dimethylpropanoyl)-3-[(1-  propylbutyl)sulfonyl]-D-</p>	652

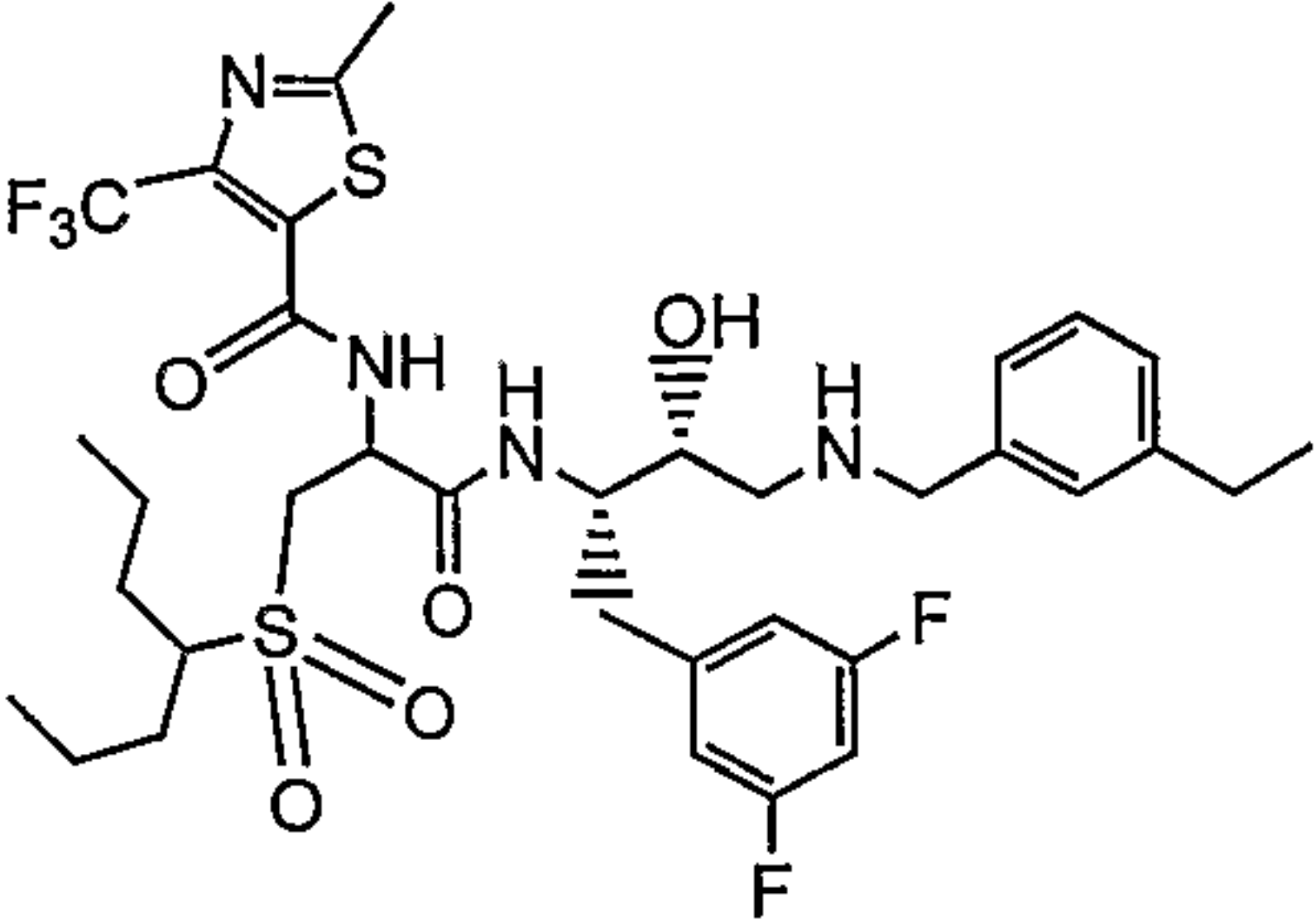
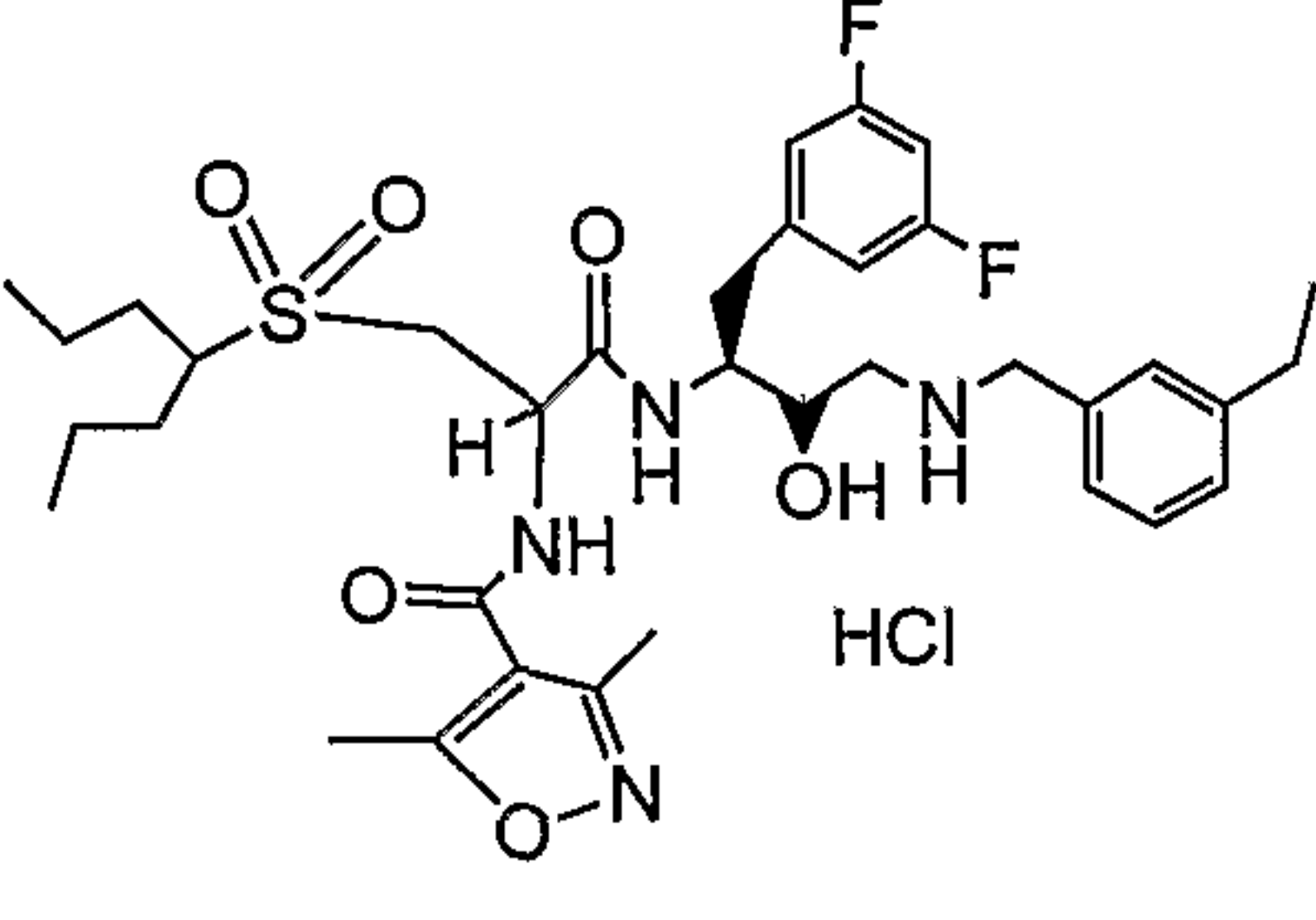
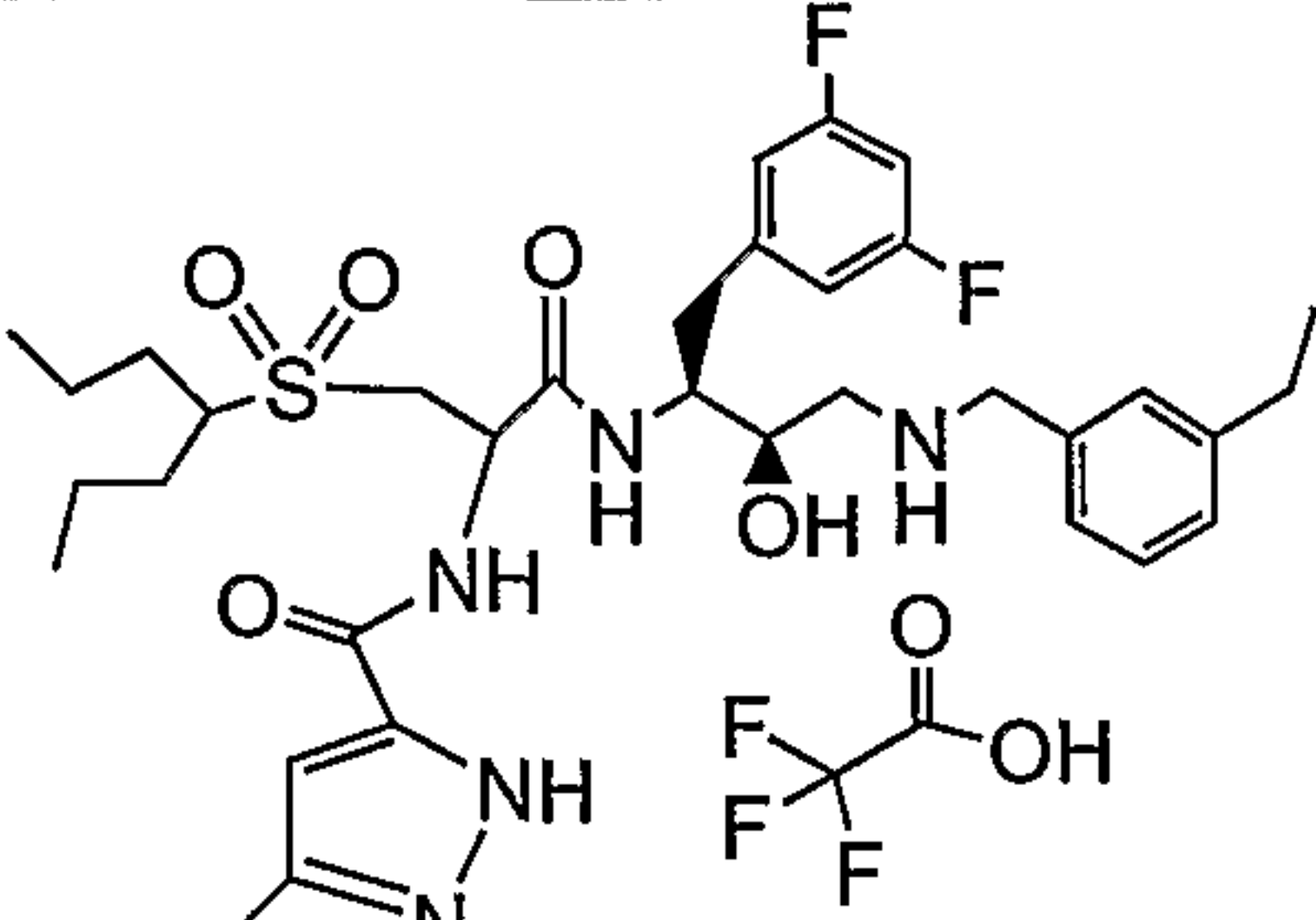
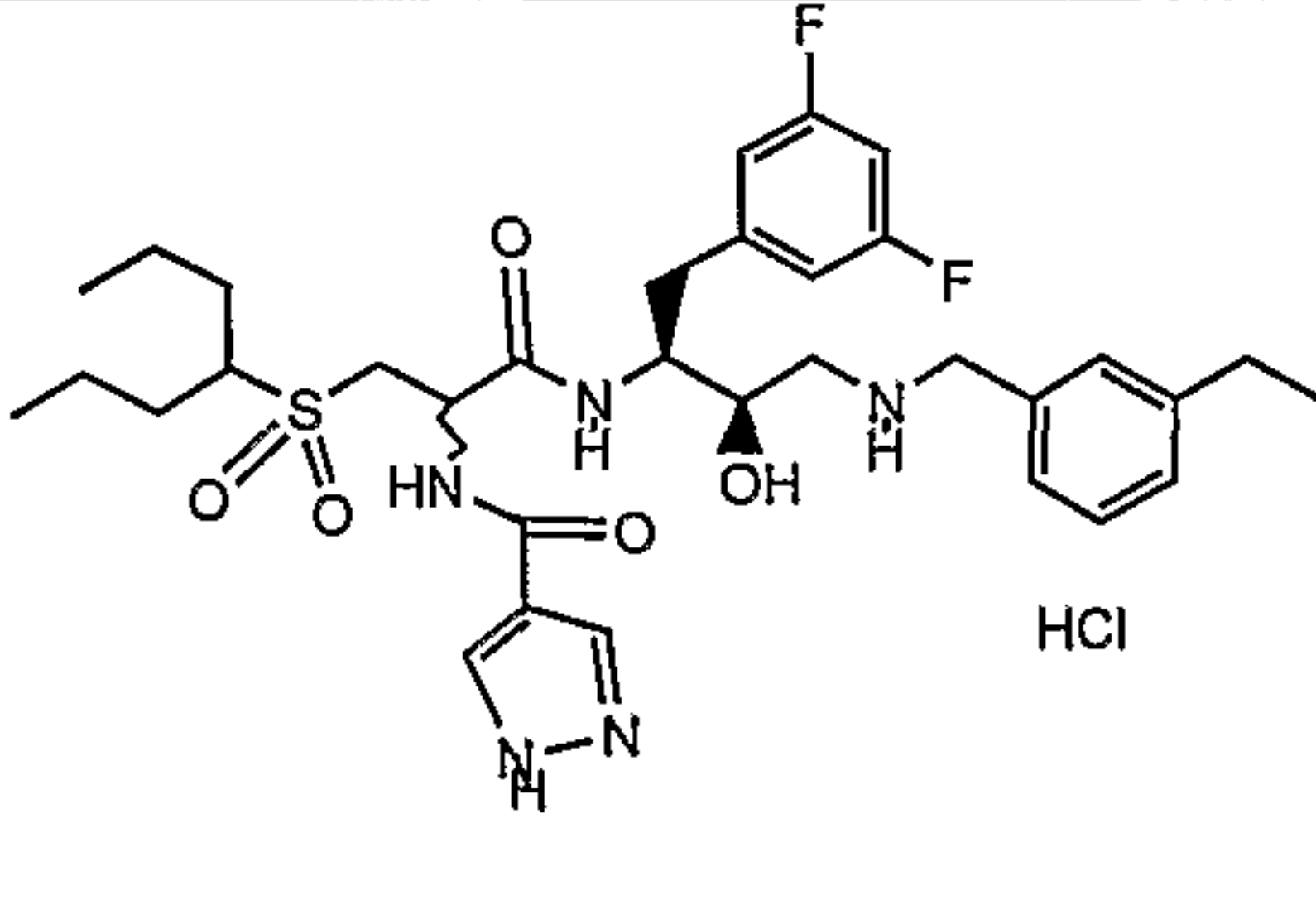


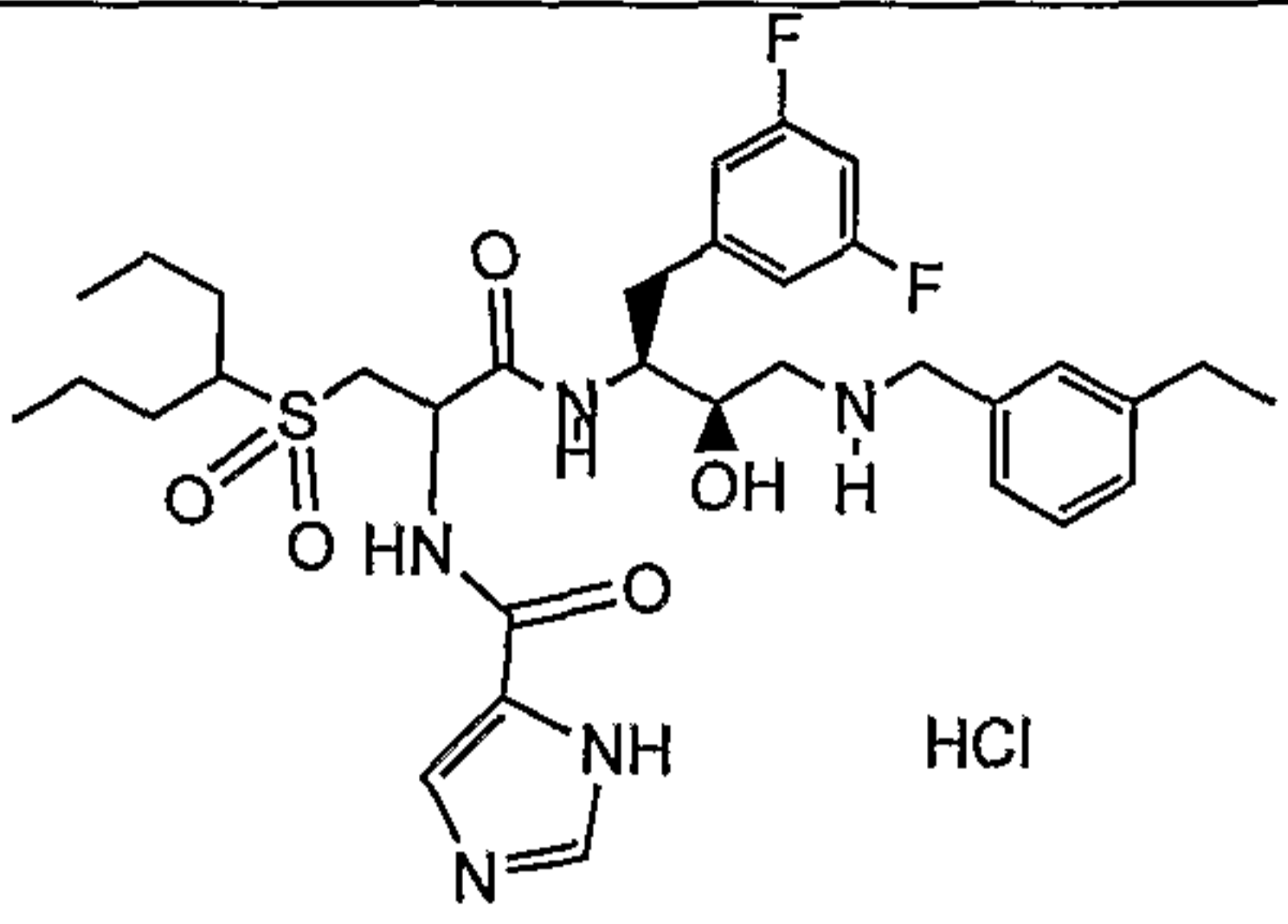
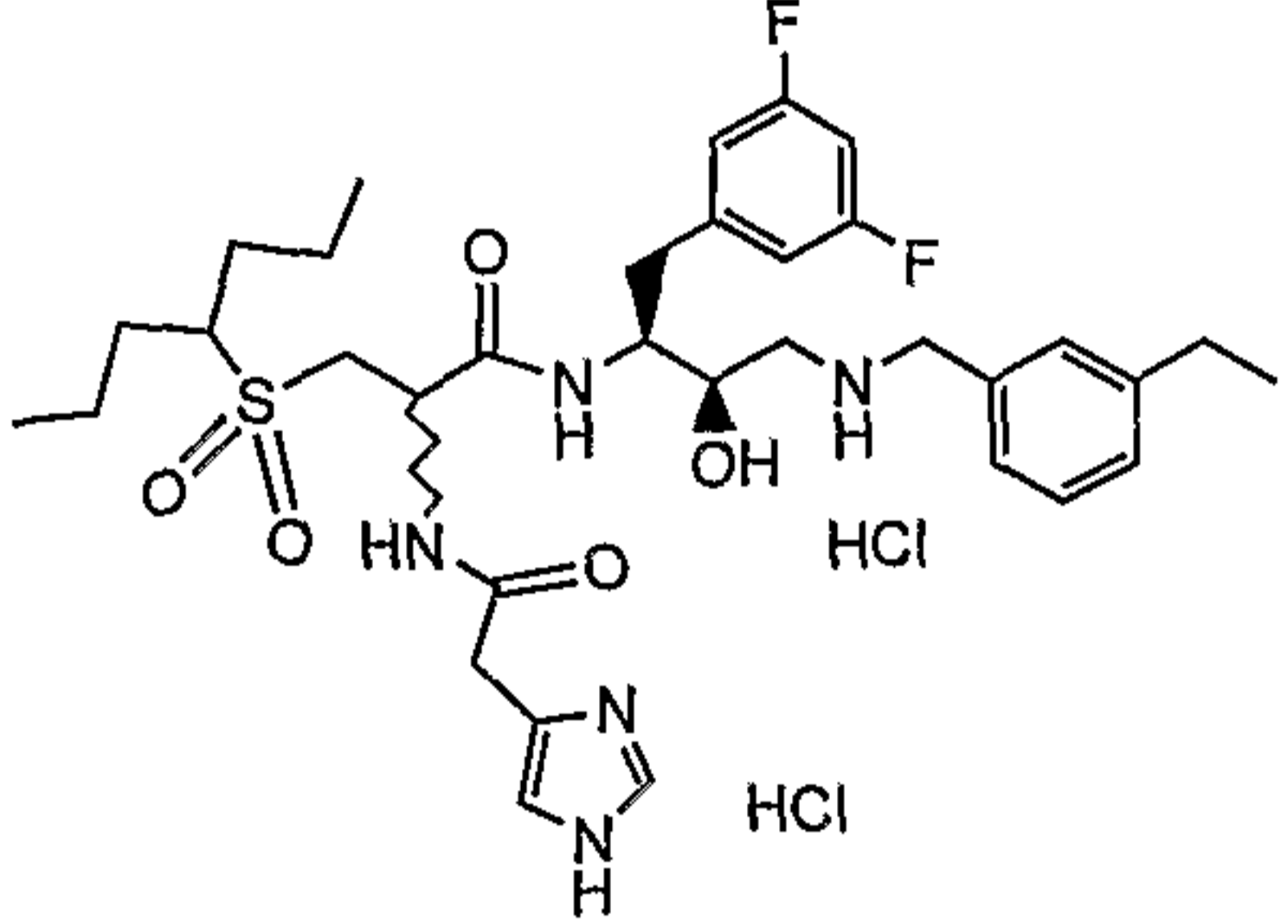
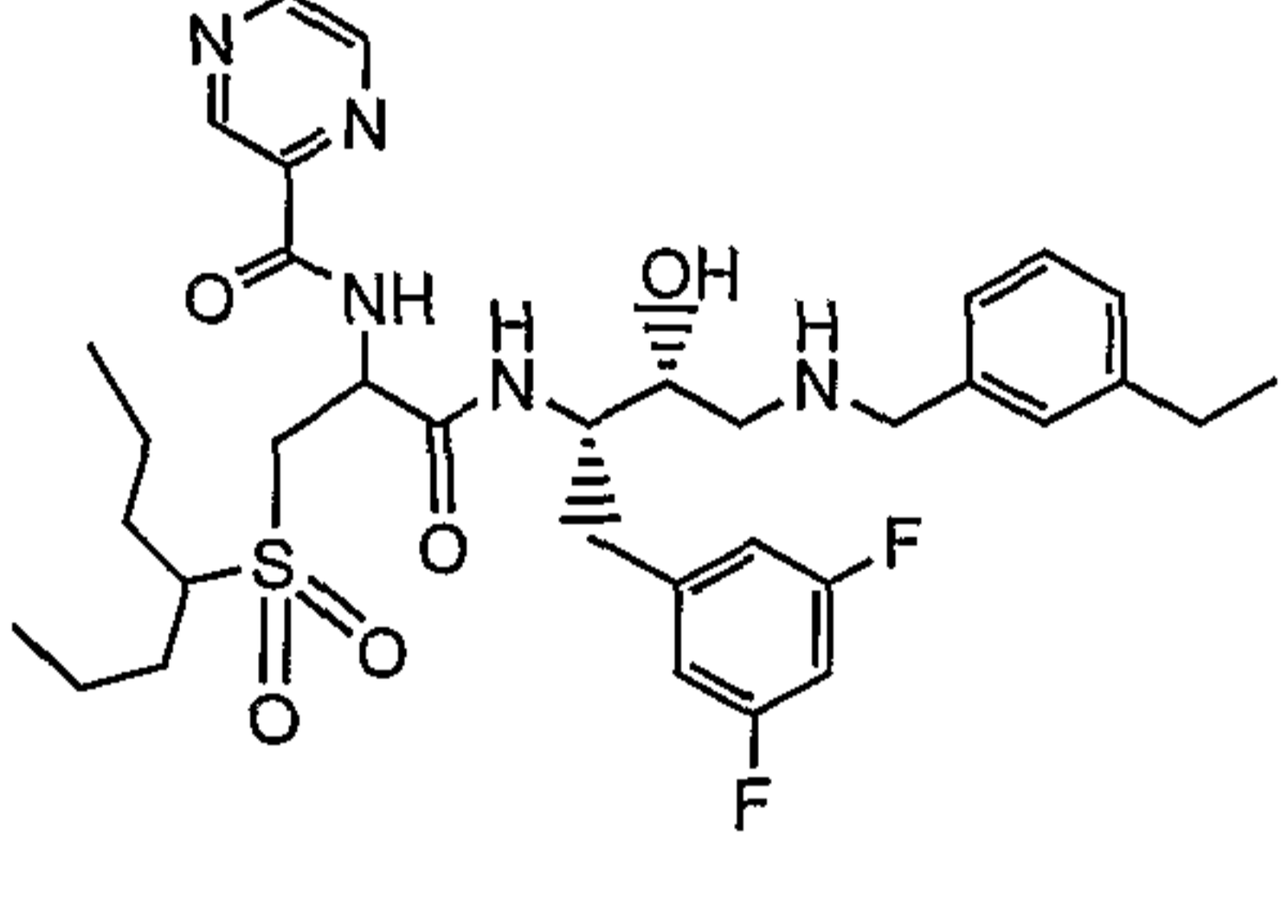
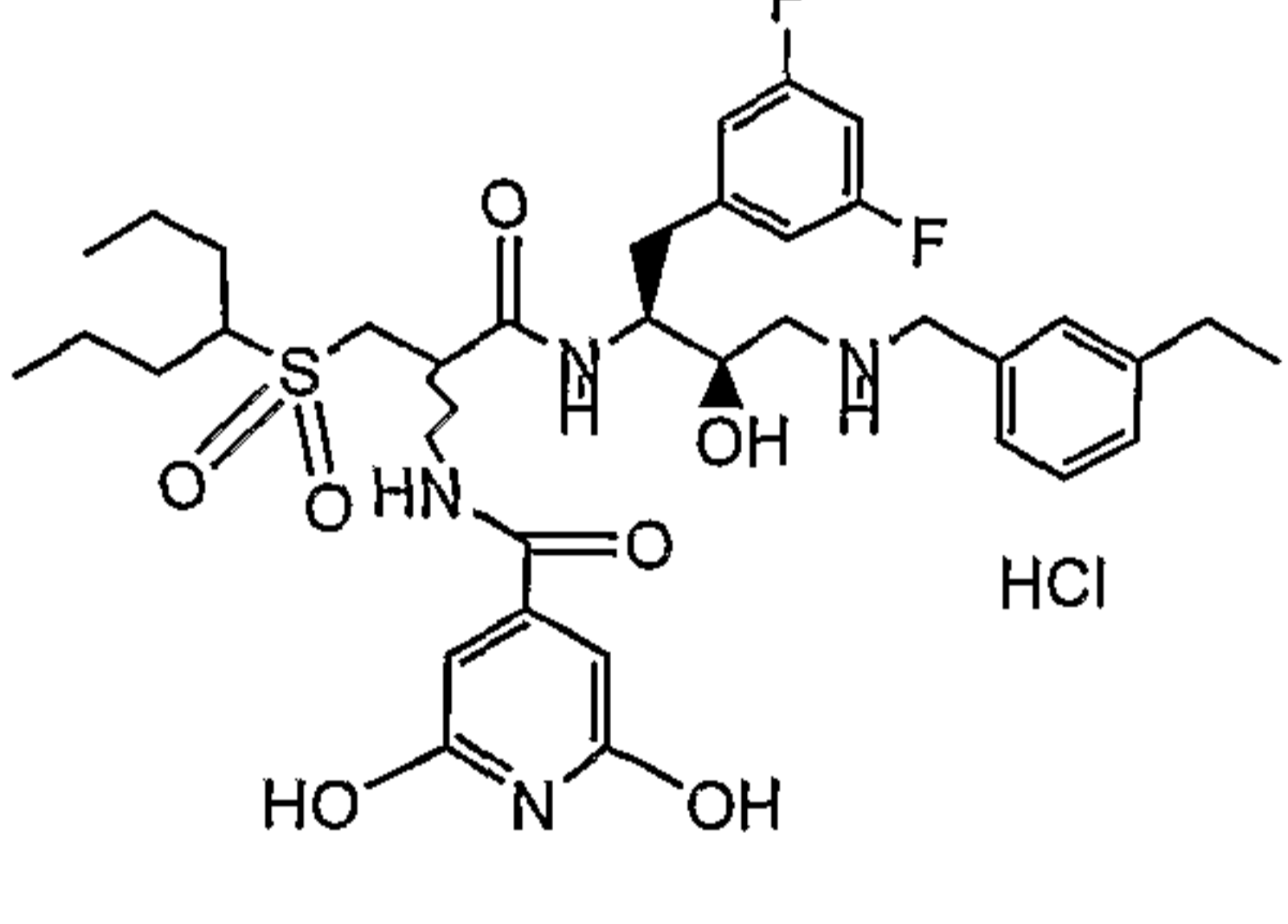
	alaninamide hydrochloride	
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2-isobutyryl-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	638
	N-2-butyl-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	638
	N-2-acetyl-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	610
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N-2-[(pyridin-3-yl)carbonyl]-D-alaninamide trifluoroacetate	699
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N-2-[(pyridin-4-yl)carbonyl]-D-alaninamide trifluoroacetate	699

	<p>N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-N~2~-(3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide trifluoroacetate</p>	714
	<p>N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N~2~-[(pyridin-3-yl)carbonyl]-D-alaninamide</p>	673
	<p>N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N~2~-(3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide</p>	688
	<p>N~2~-((cyclopropylcarbonyl)-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	636
	<p>N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N~2~-propionyl-3-[(1-propylbutyl)sulfonyl]-D-alaninamide</p>	624

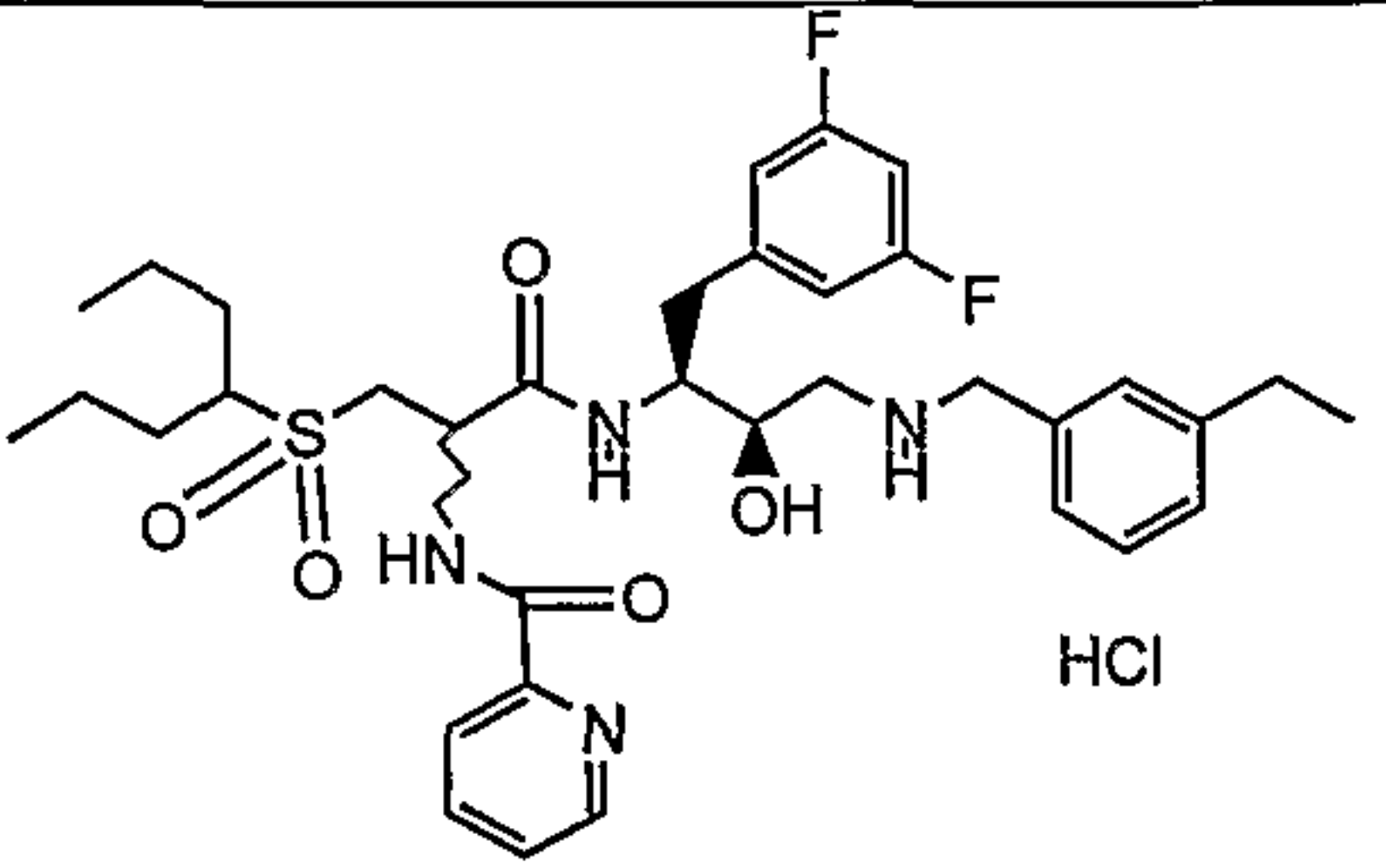
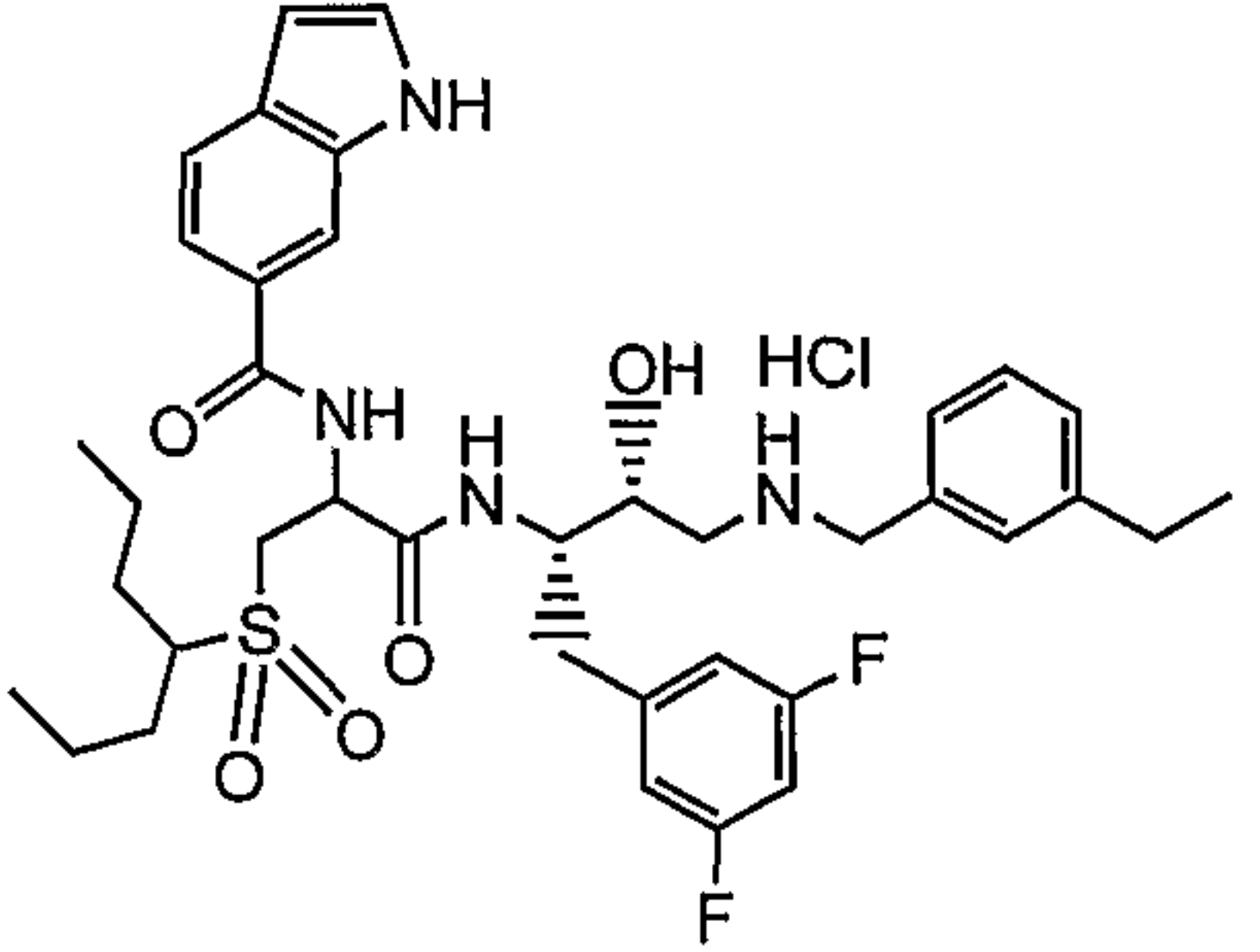
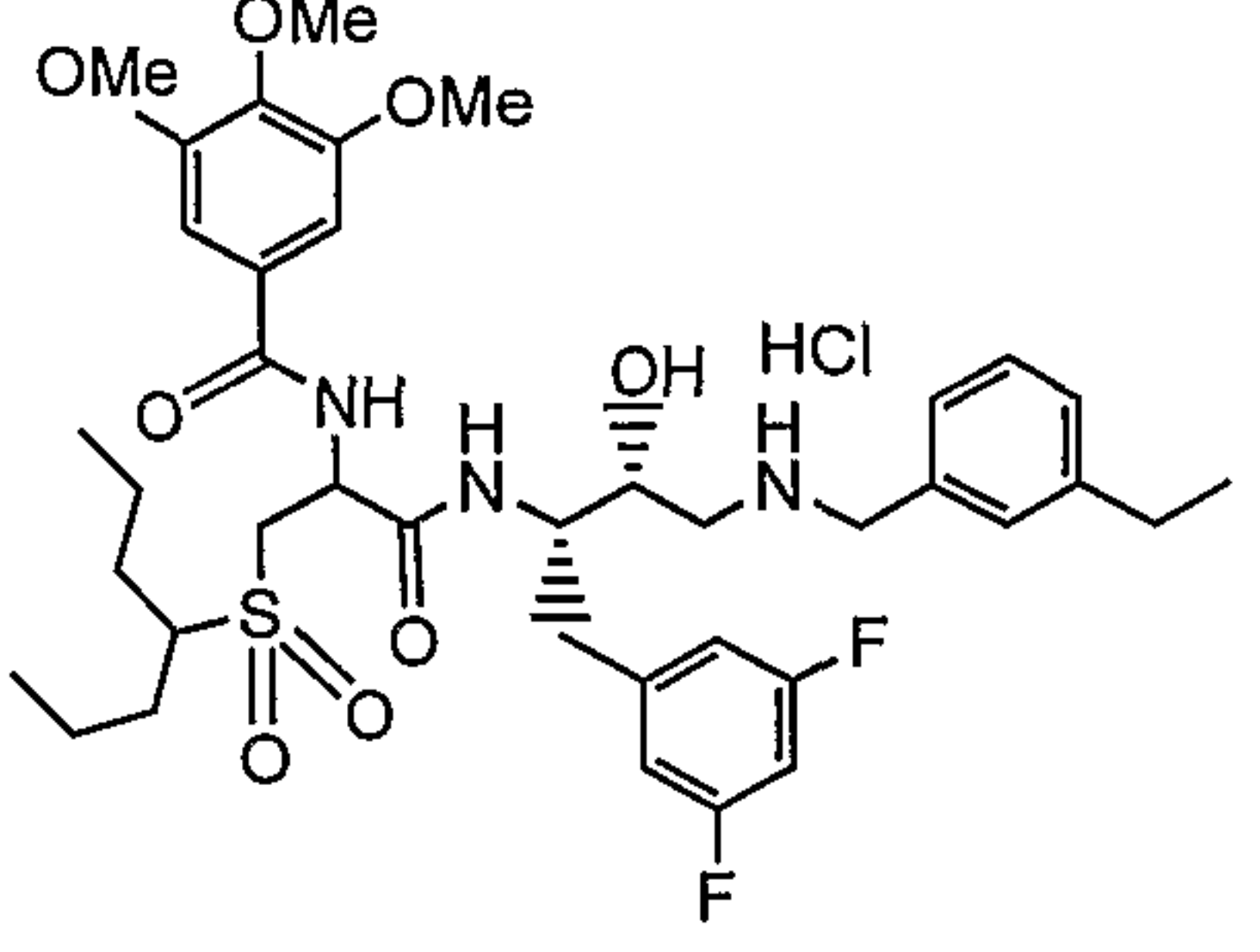
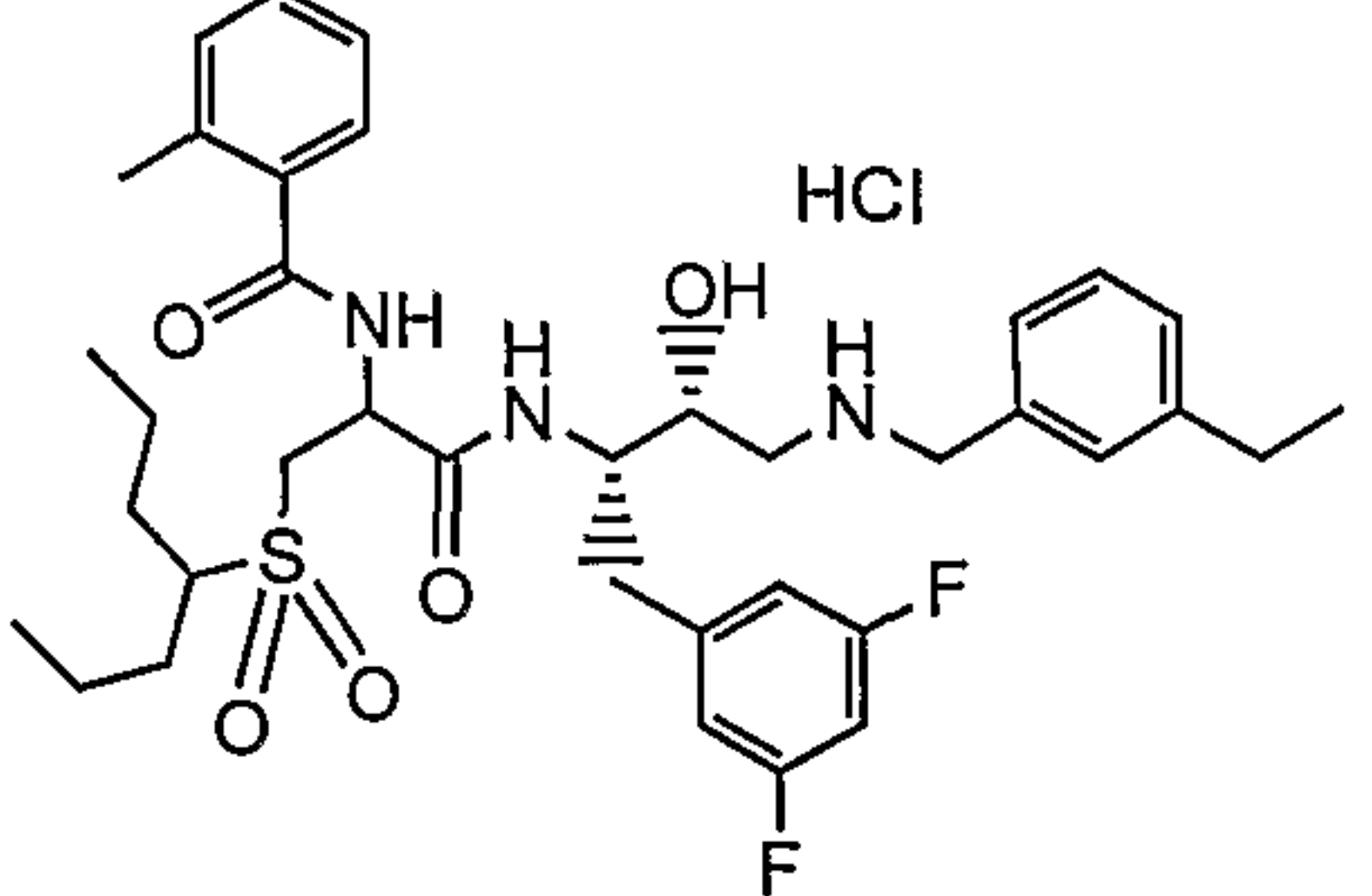
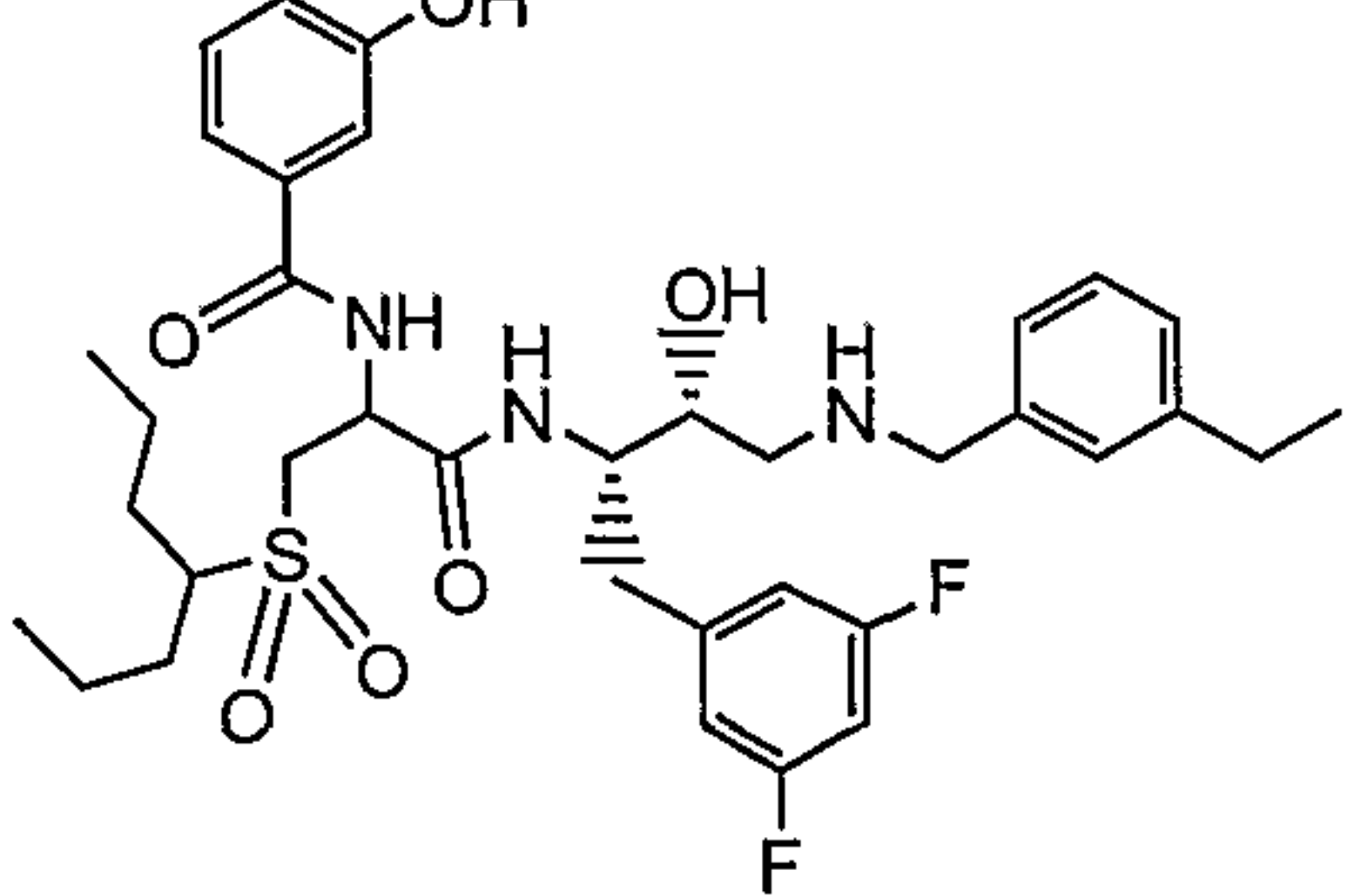
	<p>3-[butylsulfonyl]-N~1~-  { (1S,2R)-1-(3,5-  difluorobenzyl)-3-[(3-  ethylbenzyl)amino]-2-  hydroxypropyl}-N~2~-[(pyridin-  3-yl)carbonyl]-D,L-alaninamide  hydrochloride</p>	631
	<p>N~1~-((1S,2R)-1-(3,5-  difluorobenzyl)-3-[[1-(3-  ethylphenyl)cyclopropyl]amino}  -2-hydroxypropyl)-N~2~-((3-  hydroxybenzoyl)-3-[(1-  propylbutyl)sulfonyl])-D,L-  alaninamide trifluoroacete</p>	714
	<p>N~1~-((1S,2R)-1-(3,5-  difluorobenzyl)-3-[[1-(3-  ethylphenyl)cyclopropyl]amino}  -2-hydroxypropyl)-3-[(1-  propylbutyl)sulfonyl]-N~2~-  [(pyridin-4-yl)carbonyl]-D-  alaninamide trifluoroacetate</p>	699
	<p>N~1~-{(1S,2S)-1-(3,5-  difluorobenzyl)-3-[(3-  ethylbenzyl)amino]-2-  hydroxypropyl}-N~2~-[(6-oxo-  1,4,5,6-tetrahydropyridazin-3-  yl)carbonyl]-3-[(1-  propylbutyl)sulfonyl]alaninami  de hydrochloride</p>	692

	<p>5-oxo-D-prolyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide hydrochloride</p>	679
	<p>5-oxo-L-prolyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide hydrochloride</p>	679
	<p>N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[3-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoyl]-3-[(1-propylbutyl)sulfonyl]alaninamide</p>	755
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(piperidin-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide dihydrochloride</p>	679
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(2,4-dimethyl-1,3-thiazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-</p>	707

	alaninamide hydrochloride	
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(2-methyl-4-(trifluoromethyl)-1,3-thiazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide	761
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(3,5-dimethylisoxazol-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	691
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(3-methyl-1H-pyrazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	676
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(1H-pyrazol-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	662

	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(1H-imidazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	662
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(1H-imidazol-4-ylacetyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide dihydrochloride</p>	676
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-[(pyrazin-2-yl)carbonyl]-D,L-alaninamide</p>	674
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(3,5-dihydroxypyridin-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	705

	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(6-hydroxypyridin-3-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate</p>	689
	<p>N~2~-[(6-chloropyridin-3-yl)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	707
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-[(pyridin-4-yl)carbonyl]-D,L-alaninamide dihydrochloride</p>	673
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(pyridin-3-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide</p>	673

	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-[(pyridin-2-yl)carbonyl]-D,L-alaninamide hydrochloride</p>	673
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[1H-indole-6-carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	711
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-(2,3,4-trimethoxybenzoyl)-D,L-alaninamide hydrochloride</p>	762
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(pyridin-2-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	686
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-</p>	688



	alaninamide	
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(3-methylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	686
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(3-ethylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide	700
	N~2~-(3-chlorobenzoyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	706
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(4-methylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	686

	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(4-methoxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	702
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(4-trifluoromethylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	740
	<p>N~2~-(cyclohexylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	678
	<p>N~2~-(benzoyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide</p>	672
	<p>N~2~-(benzoyl)-N~1~-[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]alaninamide hydrochloride</p>	594

	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(phenylacetyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide</p>	686
	<p>N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(3-phenylpropanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate</p>	700
	<p>N-(3-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)-3-oxo-2-((1-propylbutyl)sulfonyl)methyl}propyl)benzamide</p>	686
	<p>N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-(cyclopropylacetyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	616
	<p>N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-[(methylsulfonyl)acetyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate</p>	654

	<p>N-1-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-N-2-((methylthio)acetyl)-3-((1-propylbutyl)sulfonyl)-D,L-alaninamide hydrochloride</p>	622
	<p>N-1-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-N-2-(4-hydroxy-4-oxobutanoyl)-3-((1-propylbutyl)sulfonyl)-D,L-alaninamide hydrochloride</p>	634
	<p>N-1-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-N-2-(4-(methylamino)-4-oxobutanoyl)-3-((1-propylbutyl)sulfonyl)-D,L-alaninamide hydrochloride</p>	647
	<p>N-1-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-N-2-(4-methoxy-4-oxobutanoyl)-3-((1-propylbutyl)sulfonyl)-D,L-alaninamide hydrochloride</p>	648
	<p>N-(methylsulfonyl)glycyl-N-1-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-3-((1-propylbutyl)sulfonyl)-D,L-alaninamide hydrochloride</p>	669

	<p>N-2--acetyl-N-1--{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(phenylsulfonyl)-D,L-alaninamide hydrochloride</p>	554
	<p>N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-(2S)-2-[(4-methoxy-4-oxobutanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide hydrochloride</p>	611
	<p>(2R)-2-[(benzyloxy)carbonyl]amino-N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-oxo-5-piperidin-1-ylpentanamide hydrochloride</p>	631
	<p>N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-(2R)-2-[(3-ethoxy-3-oxopropanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide hydrochloride</p>	611
	<p>N-1--{(1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl}-N-2--(4-methoxy-4-oxobutanoyl)-N-5~,N-5~-dipropyl-D-glutamamide hydrochloride</p>	627

	<p>N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-(2R)-2-((4-methoxy-4-oxobutanoyl)amino)-5-oxo-5-piperidin-1-ylpentanamide hydrochloride</p>	611
	<p>N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-(2R)-2-((5-methoxy-5-oxopentanoyl)amino)-5-oxo-5-piperidin-1-ylpentanamide hydrochloride</p>	625
	<p>2-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1-((butylsulfonyl)methyl)-2-oxoethyl acetate</p>	569
	<p>S-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-D-cysteinamide dihydrochloride</p>	494
	<p>3-(butylsulfinyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-D-alaninamide</p>	510

	<p>3-(butylsulfonyl)-N-1-  { (1S,2R)-1-(3,5-  difluorobenzyl)-3-[(3-  ethylbenzyl)amino]-2-  hydroxypropyl}-D-alaninamide  bis(trifluoroacetate)</p>	526
	<p>3-(butylsulfonyl)-N-1-  { (1S,2R)-1-(3,5-  difluorobenzyl)-3-[(3-  ethylbenzyl)amino]-2-  hydroxypropyl}-L-alaninamide  dihydrochloride</p>	526
	<p>3-(butylsulfonyl)-N-1-  [ (1S,2R)-1-(3,5-  difluorobenzyl)-2-hydroxy-3-  (isopentylamino)propyl]-D-  alaninamide dihydrochloride</p>	478
	<p>N-1-((1S,2R)-1-(3,5-  difluorobenzyl)-3-[[1-(3-  ethylphenyl)cyclopropyl]amino]-  2-hydroxypropyl)-3-[(1-  propylbutyl)sulfonyl]-D-  alaninamide  bis(trifluoroacetate)</p>	594
	<p>N-1-((1S,2R)-1-(3,5-  difluorobenzyl)-3-[(3-  ethylbenzyl)amino]-2-  hydroxypropyl)-3-[(1-  propylbutyl)sulfonyl]-L-  alaninamide dihydrochloride</p>	568

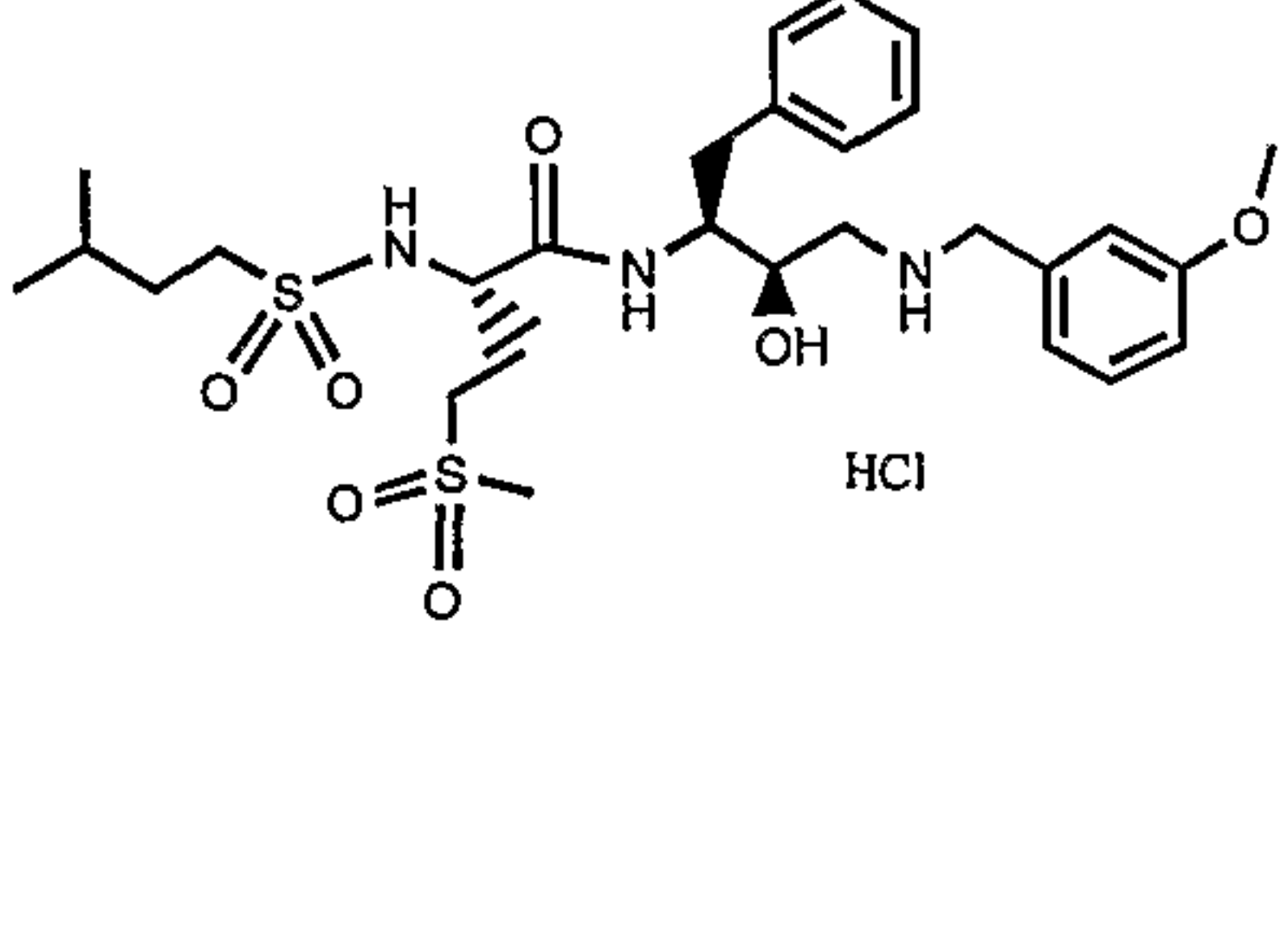
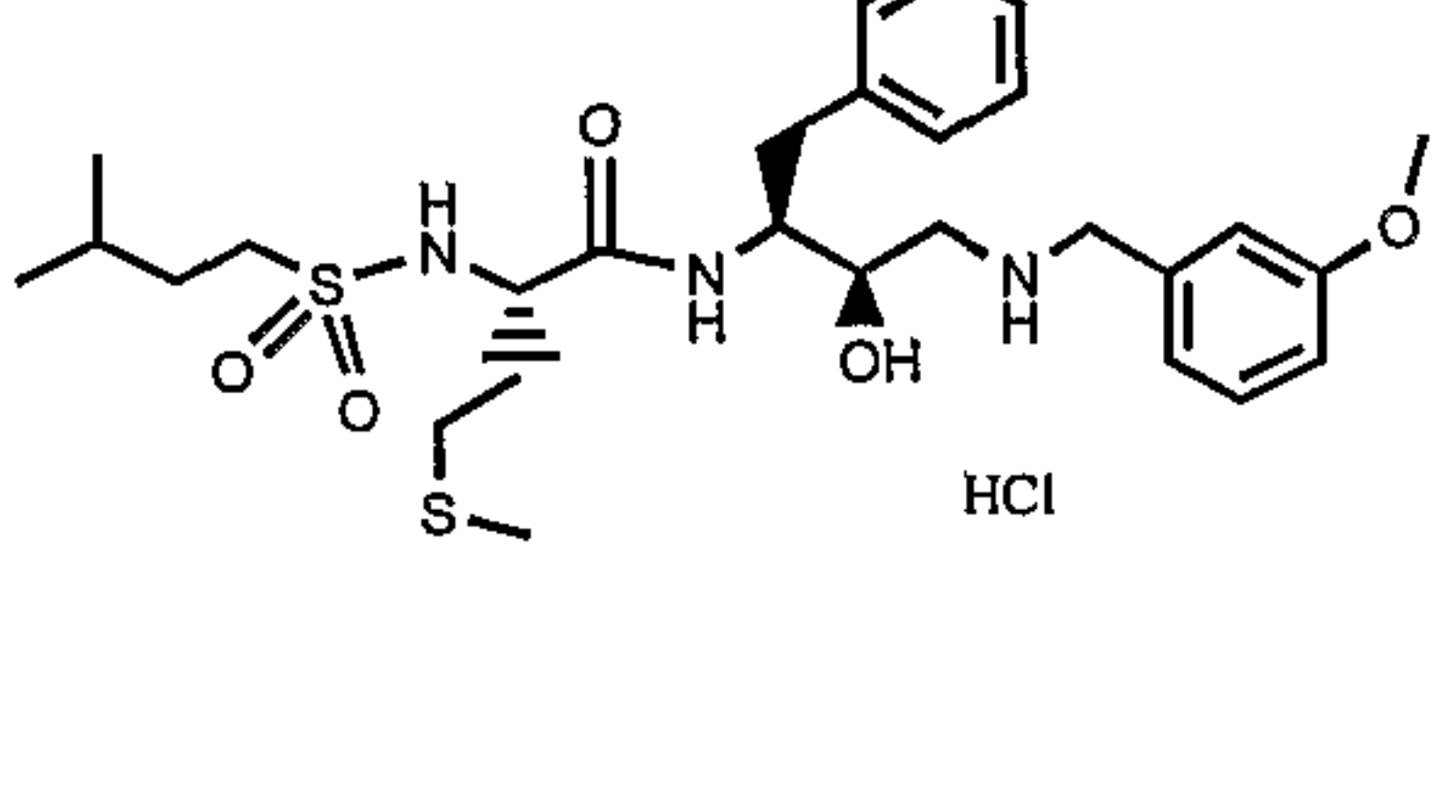
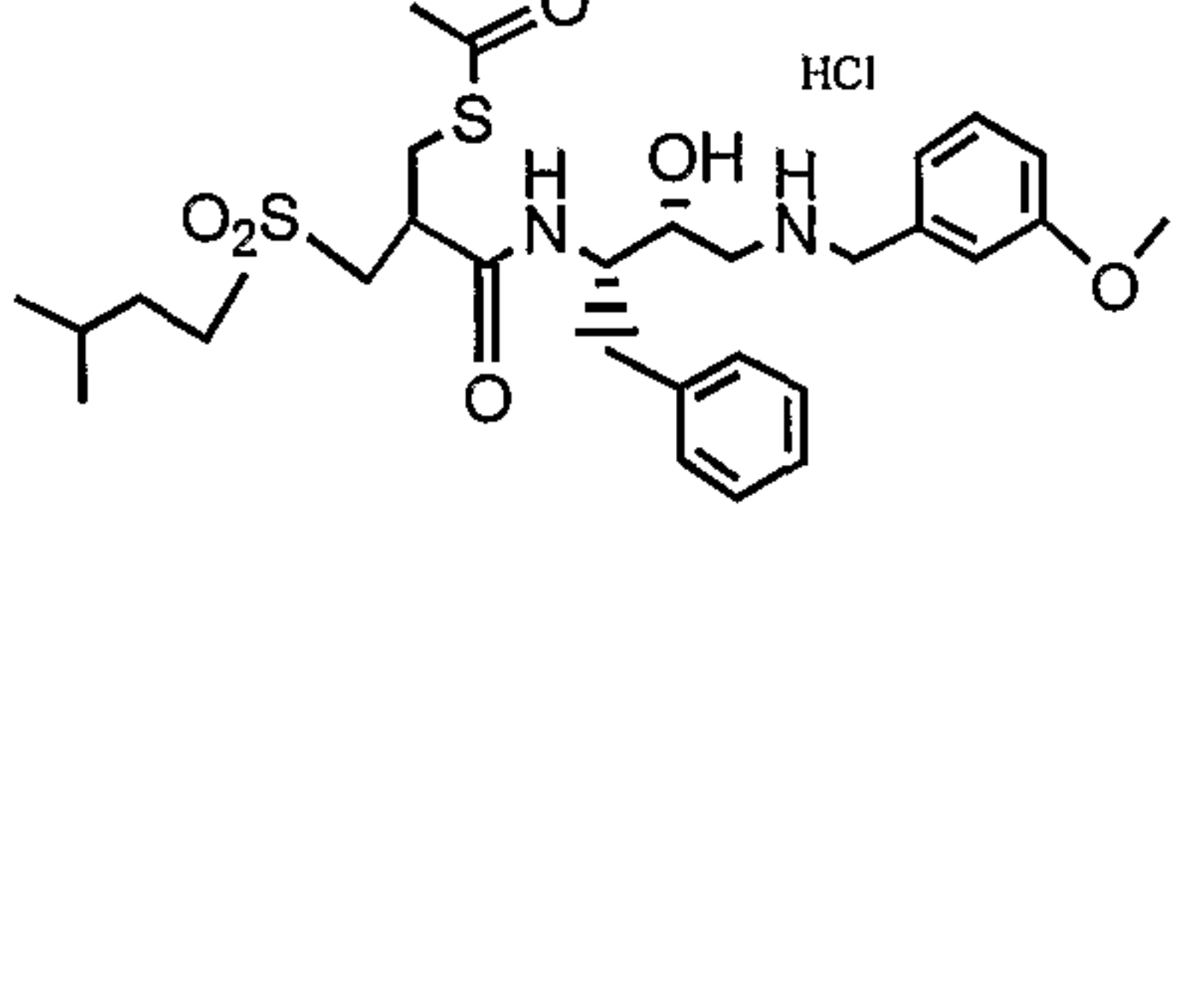
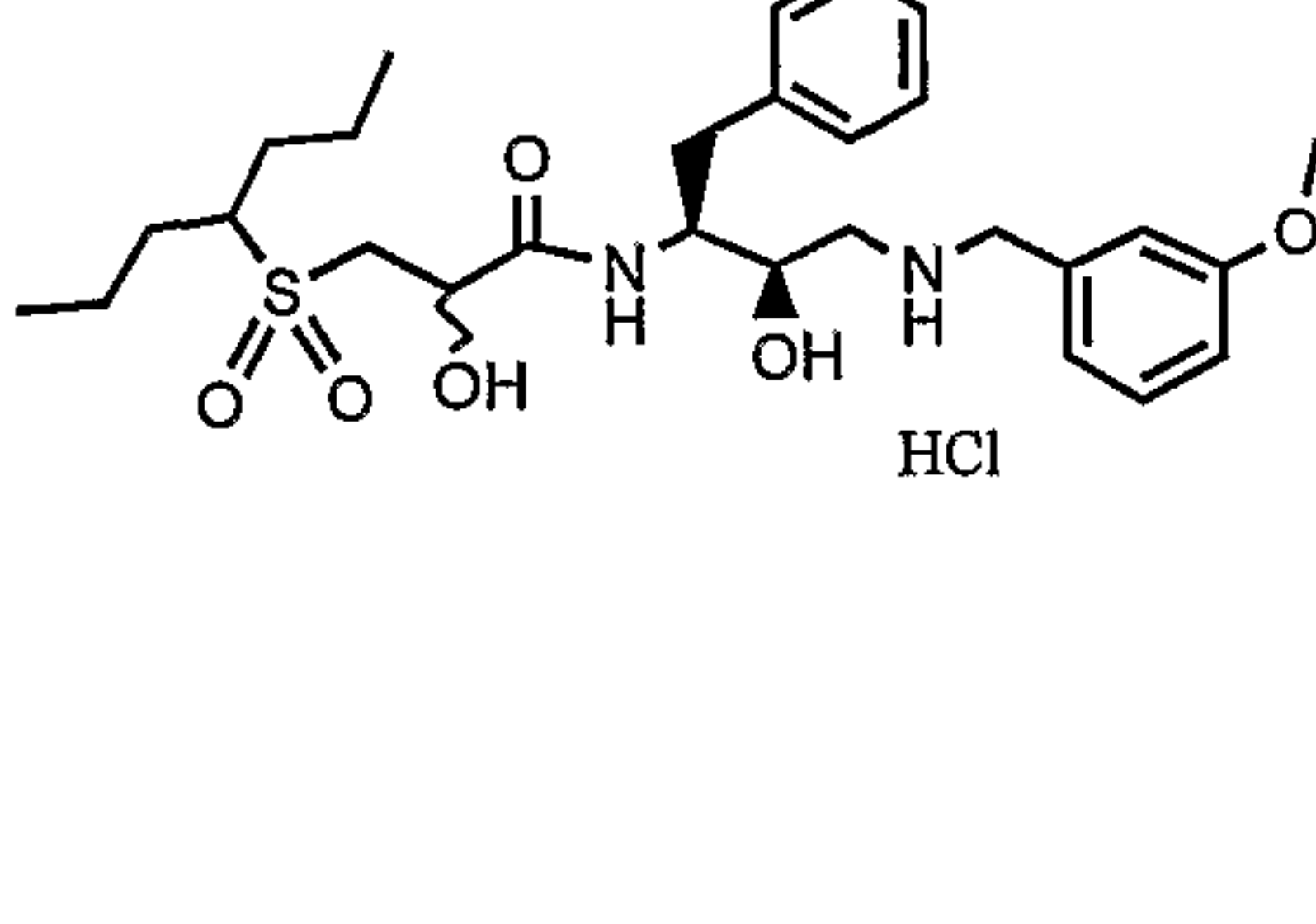
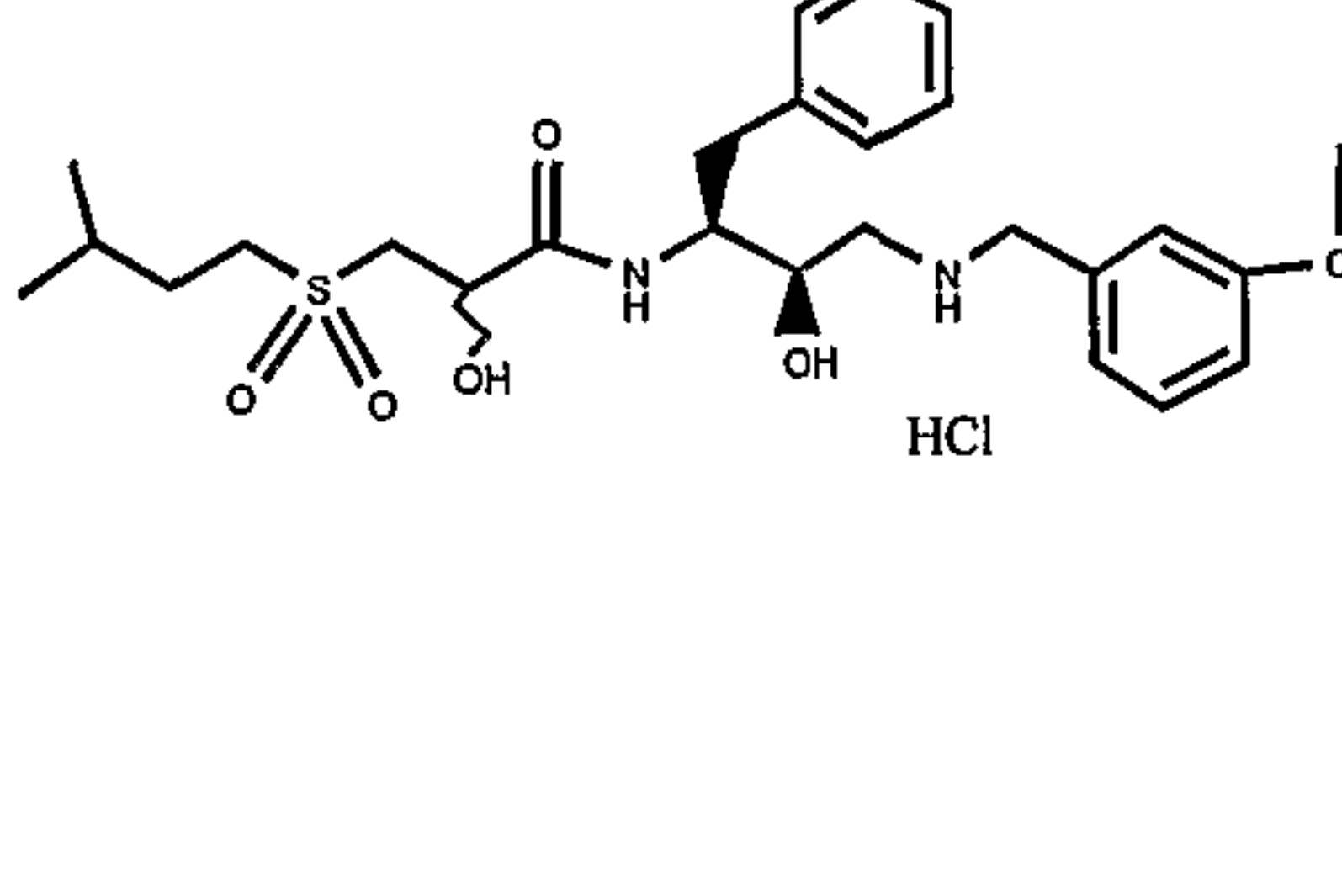
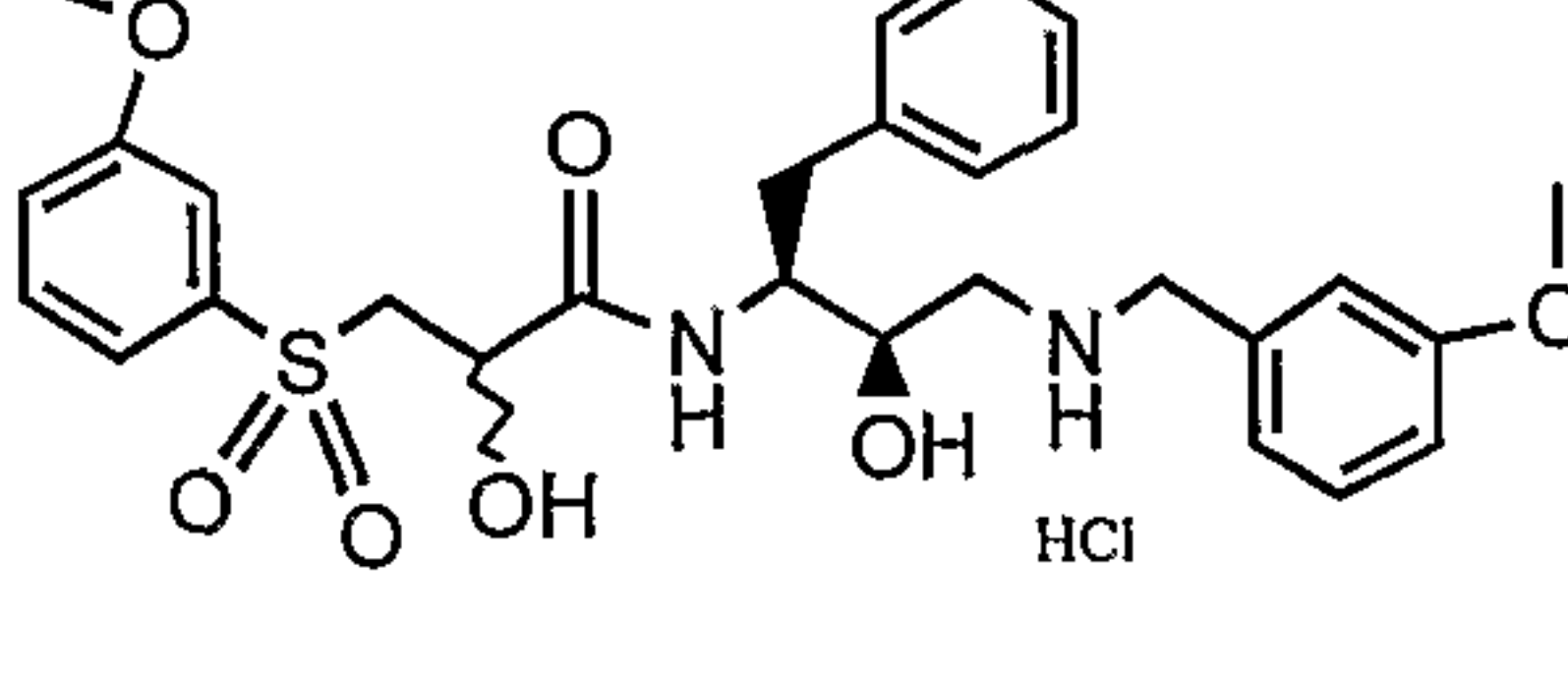
	<p>N~1~-[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide dihydrochloride</p>	490
	<p>N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-[(isopentylamino)]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide dihydrochloride</p>	520
	<p>N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide dihydrochloride</p>	568
	<p>N~1~-[(1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]alaninamide hydrochloride</p>	568
	<p>N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N~2~-[(phenoxyacetyl)-3-[(1-propylbutyl)sulfonyl]alaninamide hydrochloride</p>	702

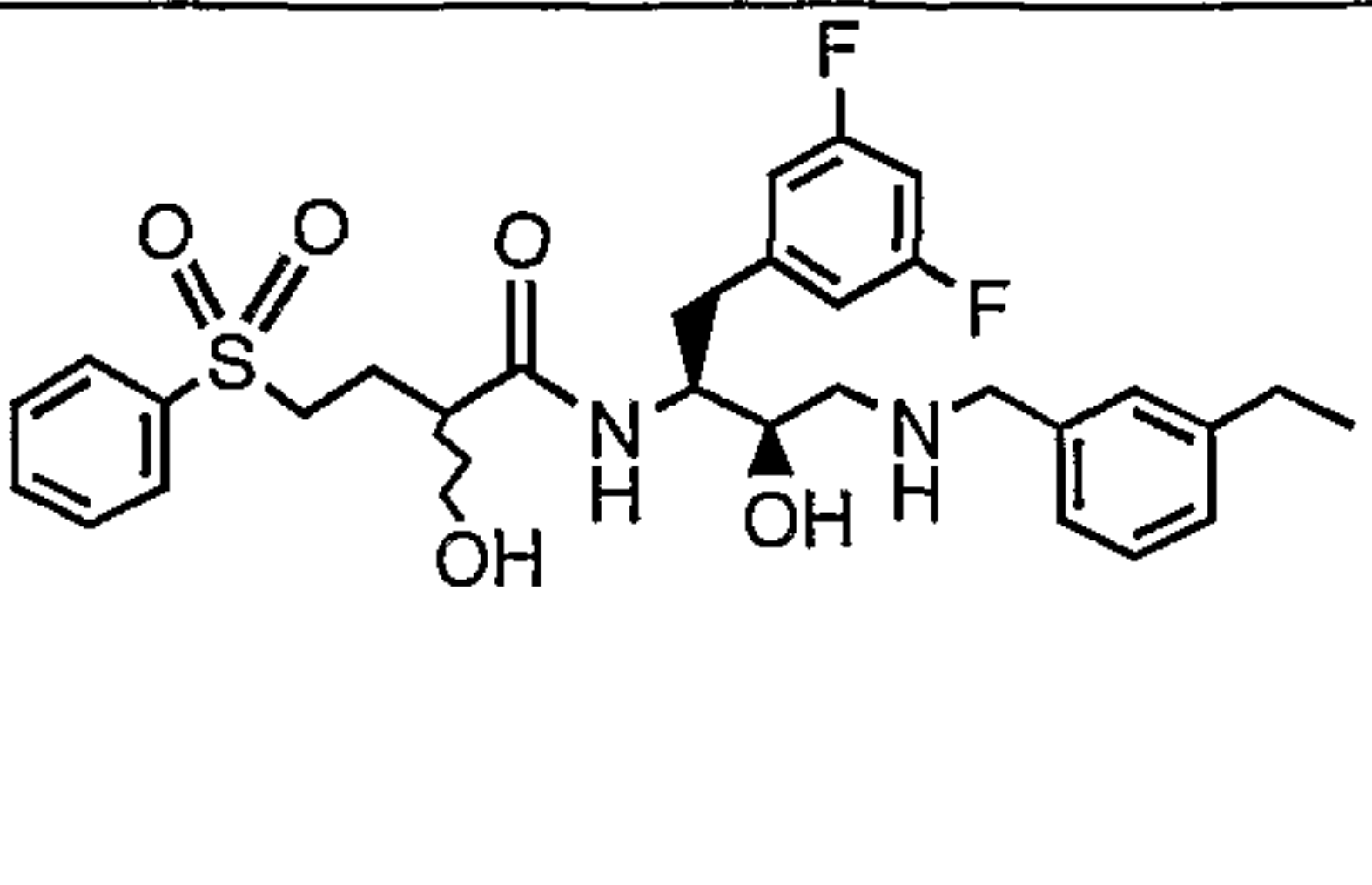
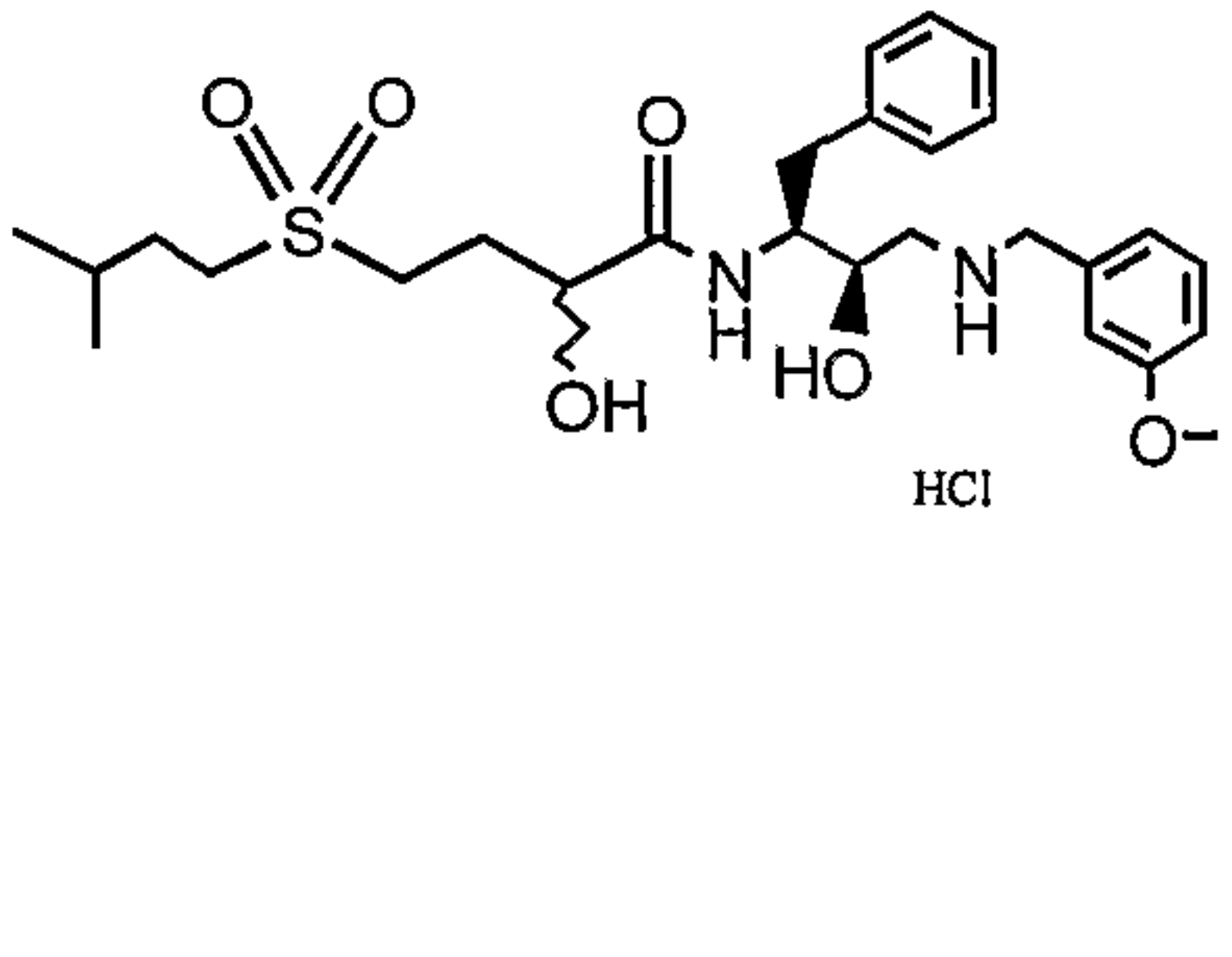
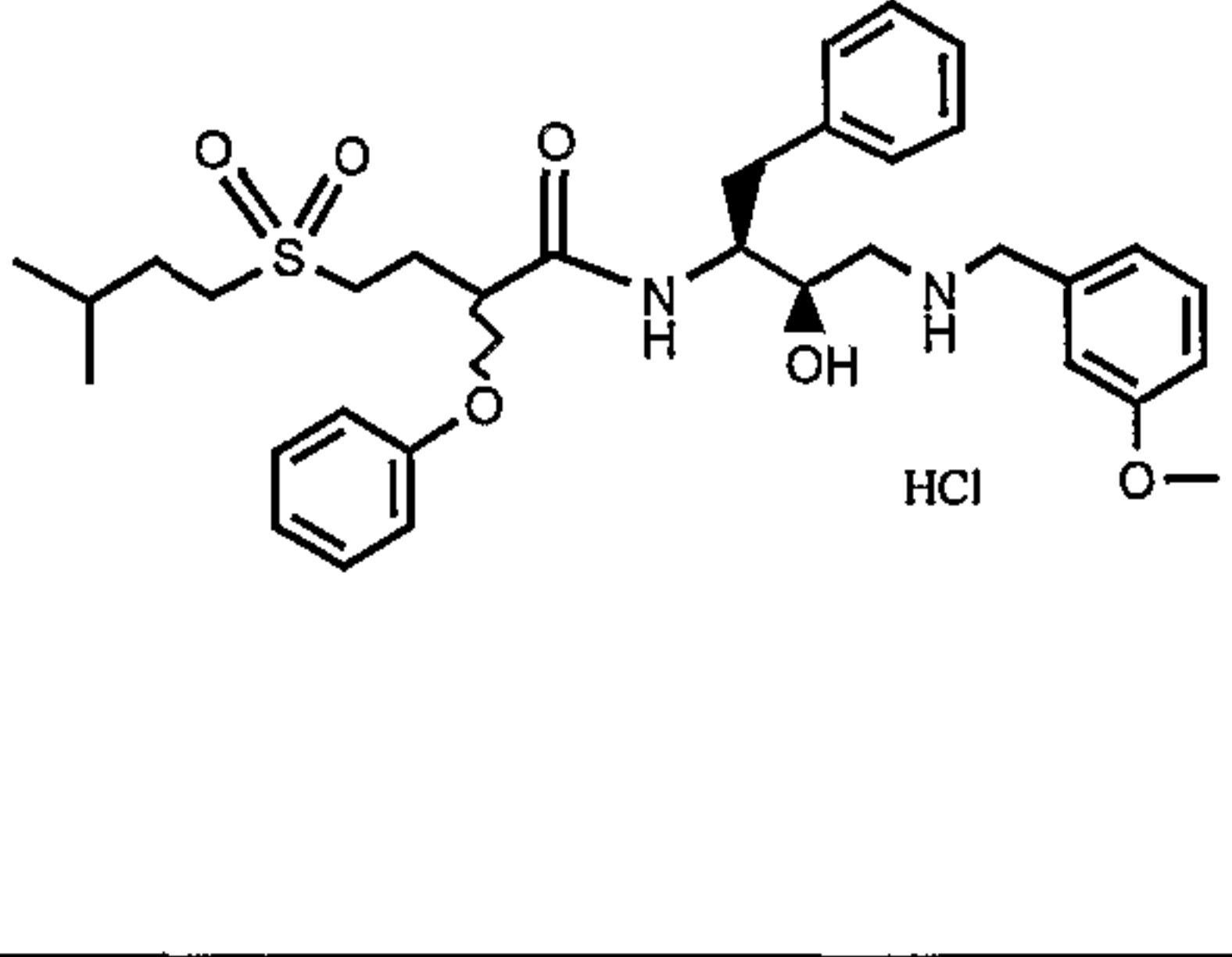
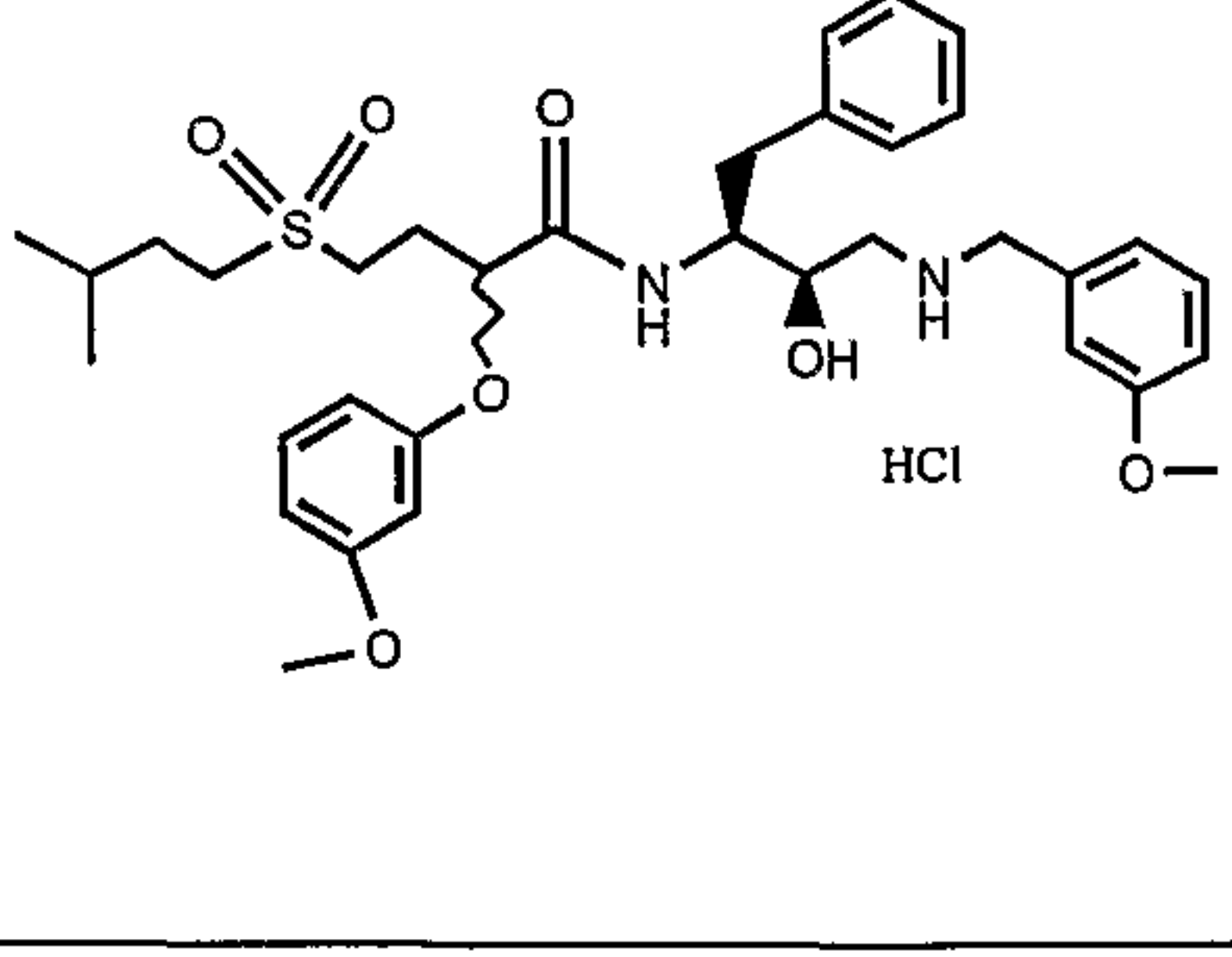
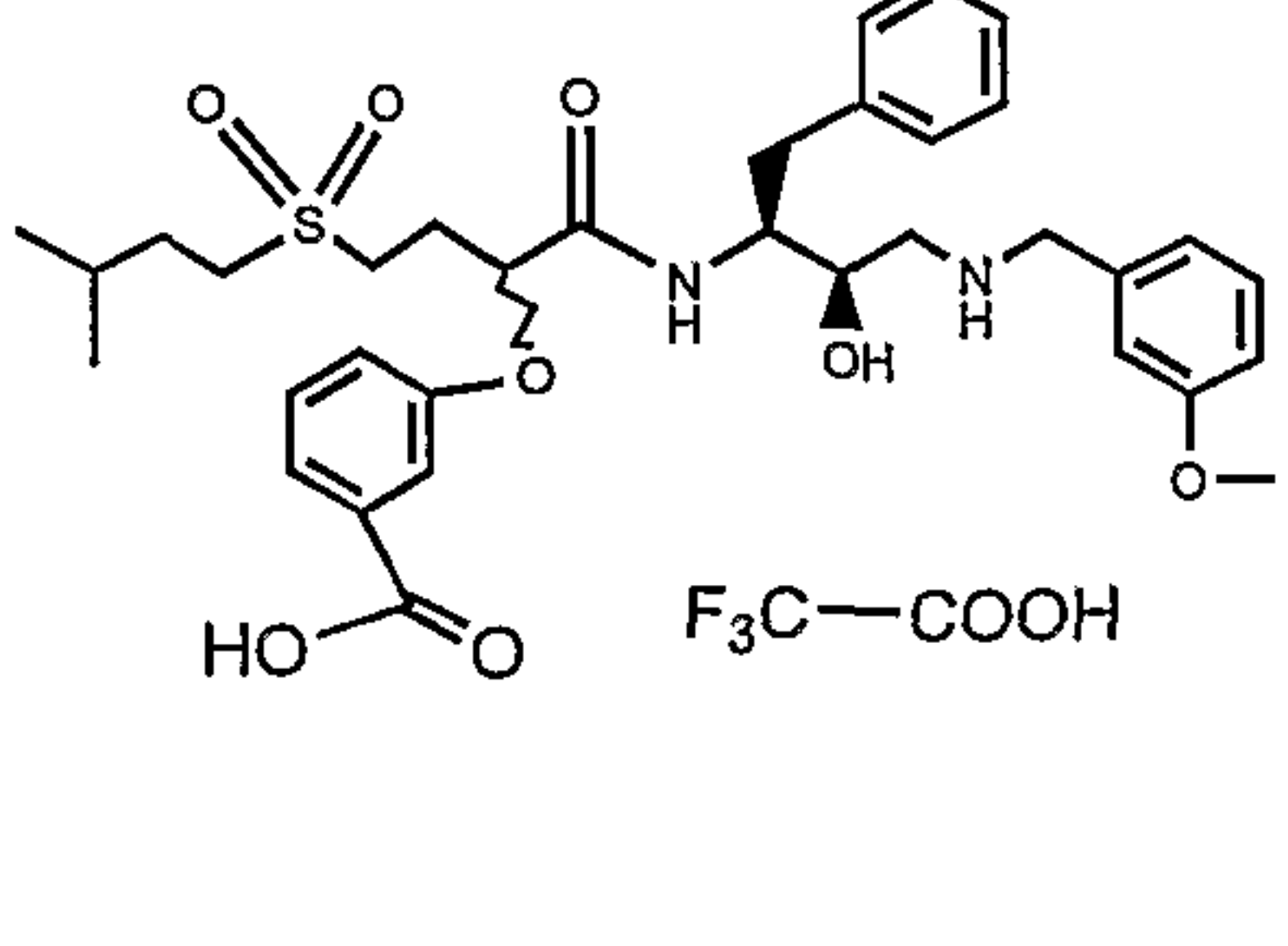


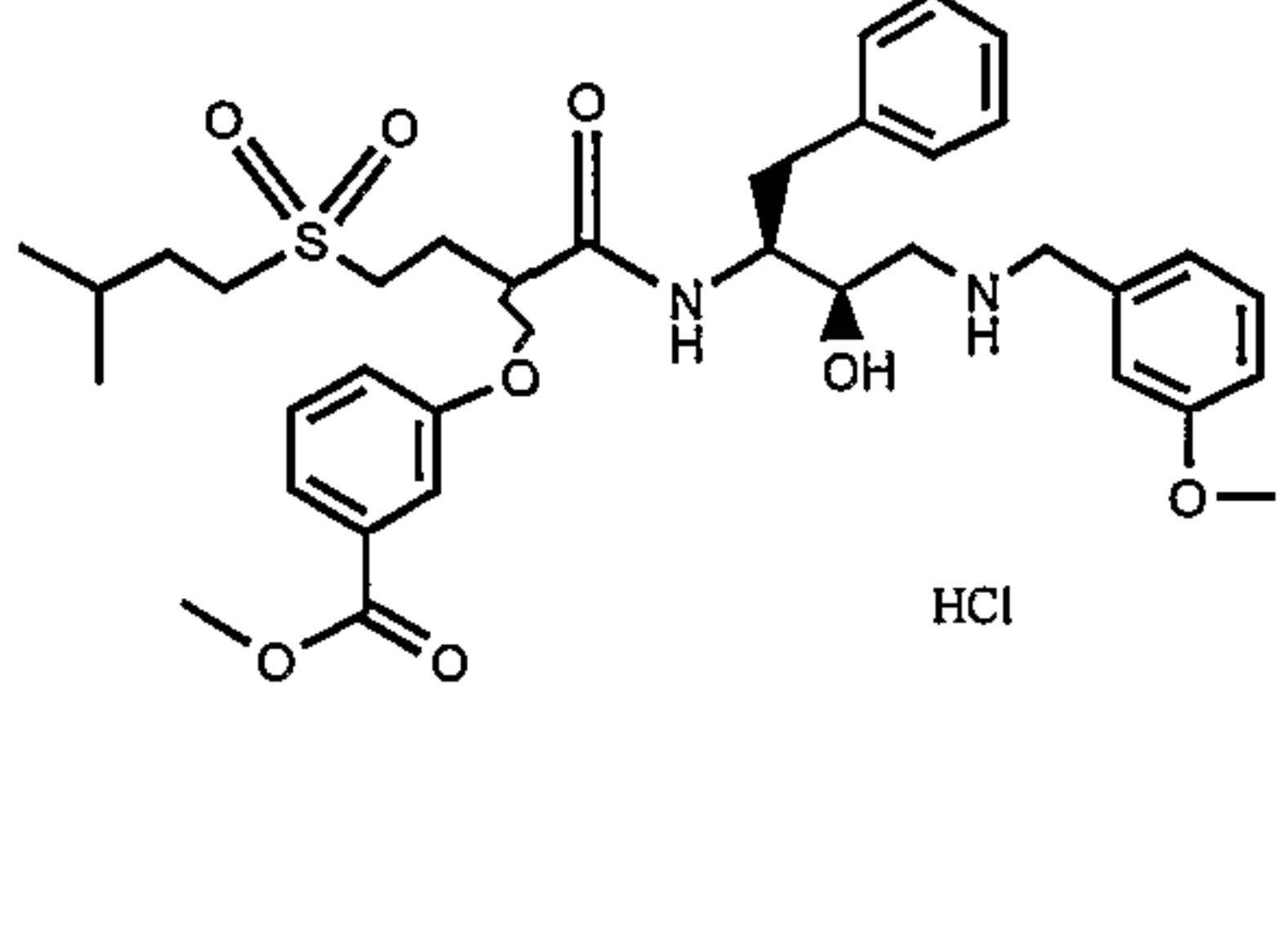
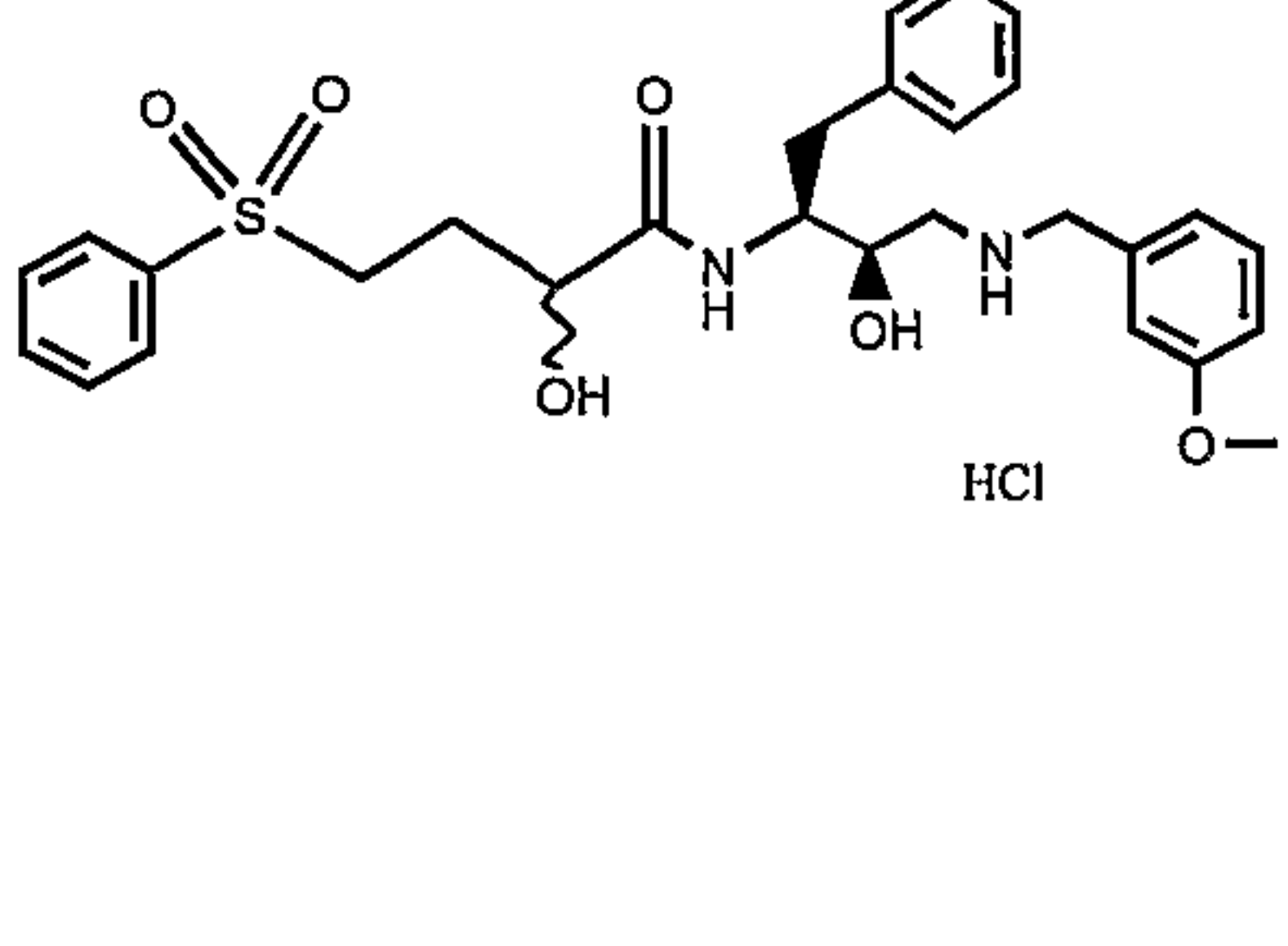
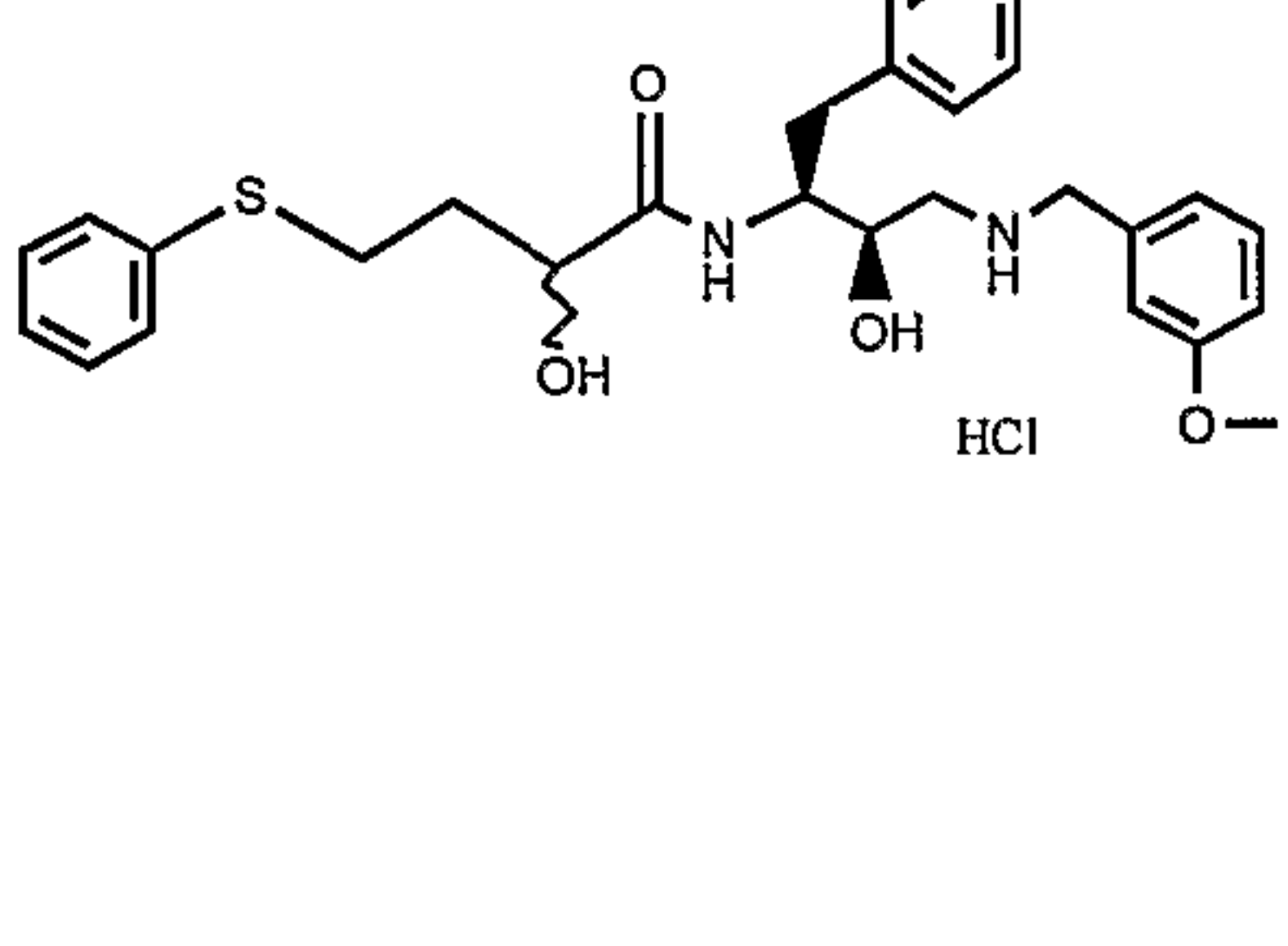
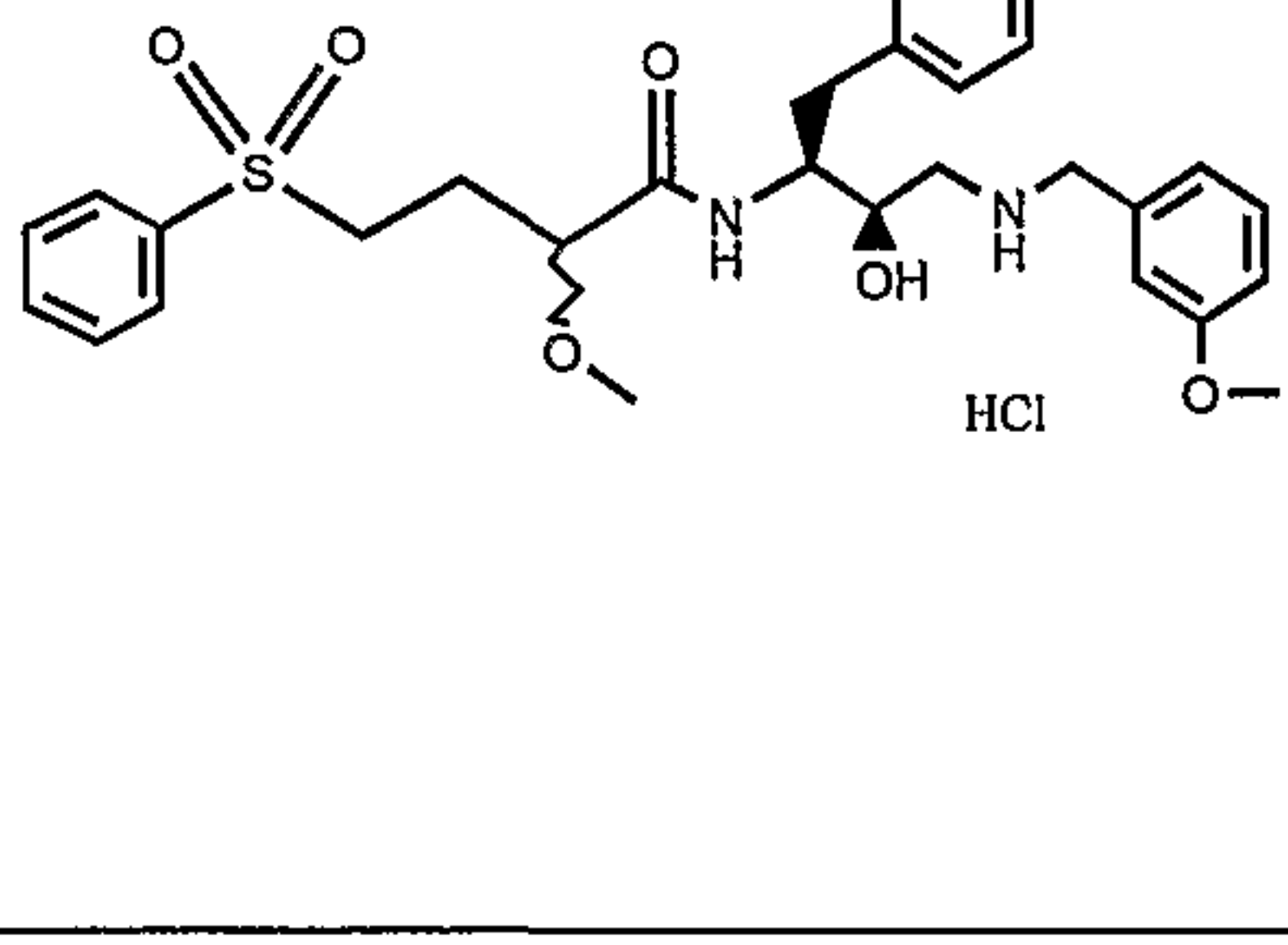
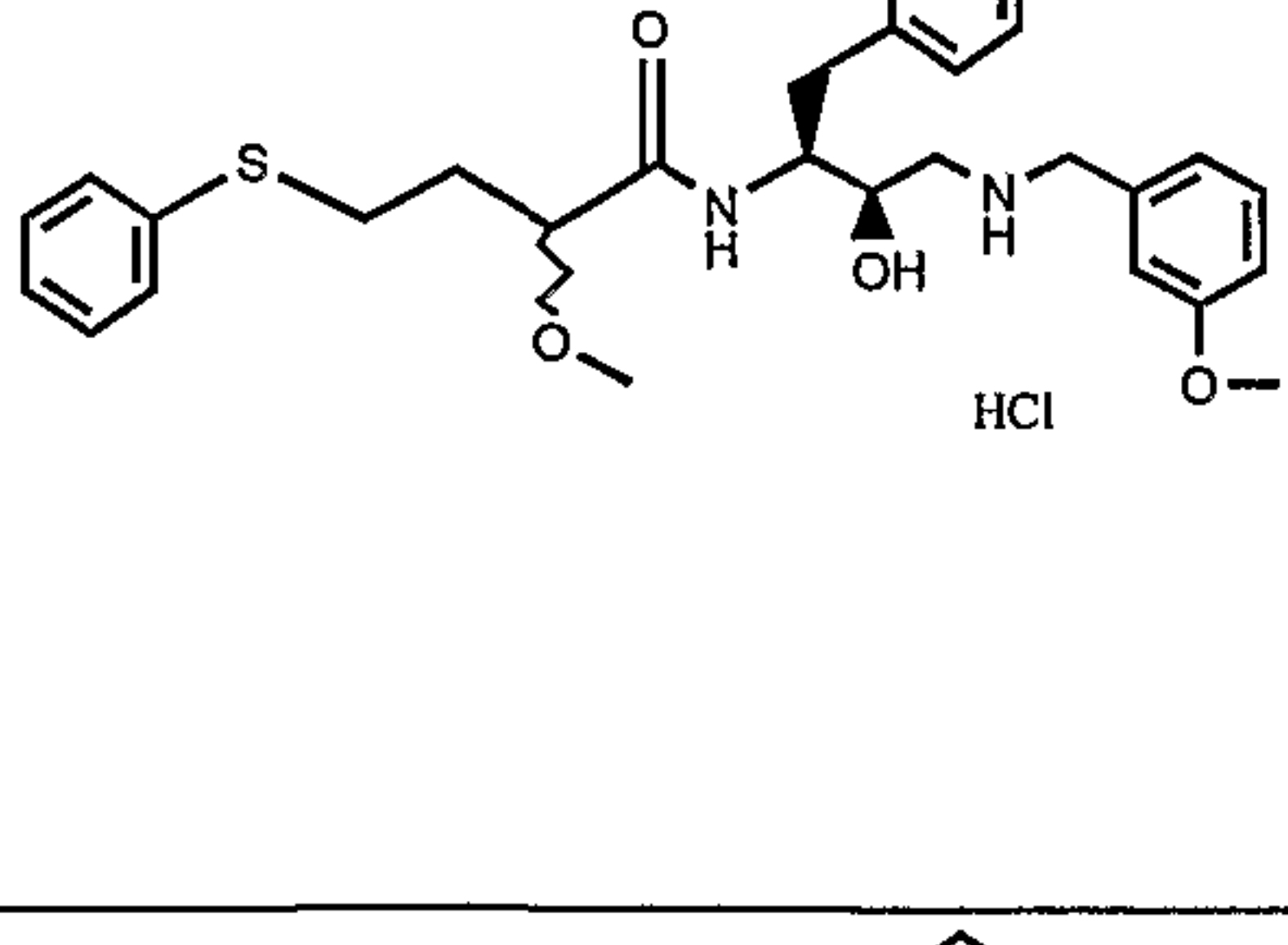
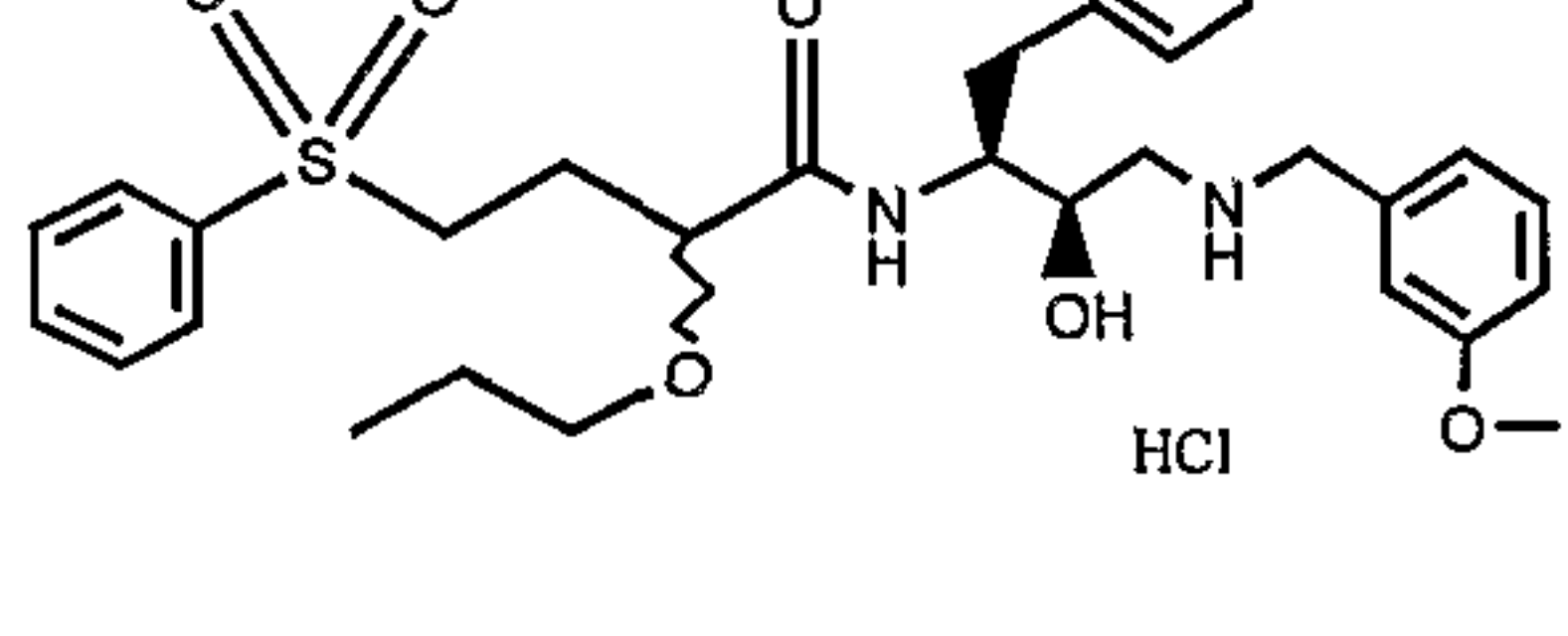
	<p>N-2-[(5-chlorothiophen-2-yl)sulfonyl]-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide</p>	748
	<p>N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N-2-[(phenylsulfonyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide</p>	708
	<p>N-2-[(benzylamino)carbonyl]-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide</p>	701
	<p>4-([(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)-4-oxo-3-([(1-propylbutyl)sulfonyl]methyl)butanoic acid trifluoroacetate</p>	611
	<p>4-([(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]amino)-3-[(isopentylsulfonyl)methyl]-4-oxo-3-([(1-propylbutyl)sulfonyl]methyl)butanoic acid trifluoroacetate</p>	549

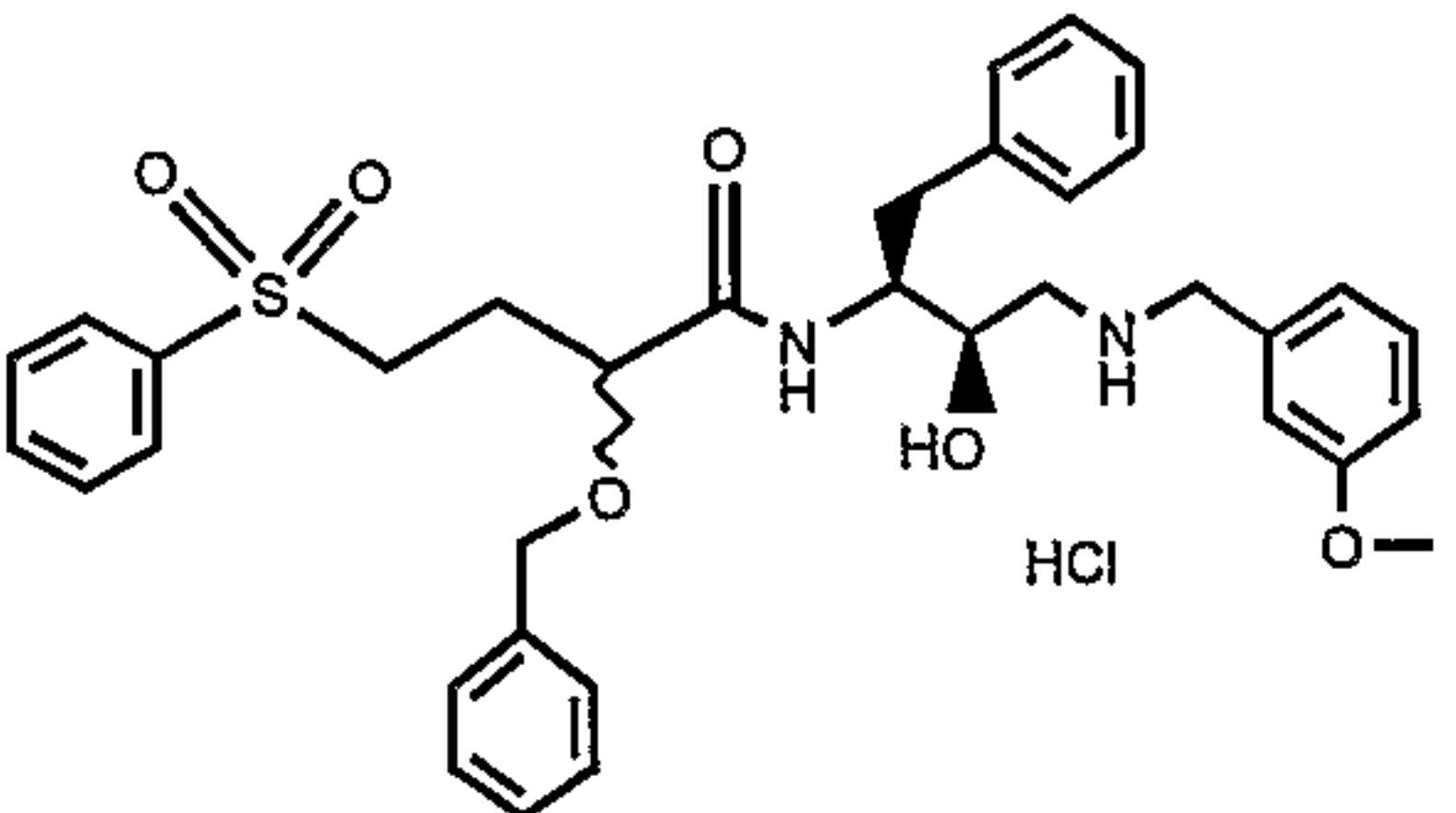
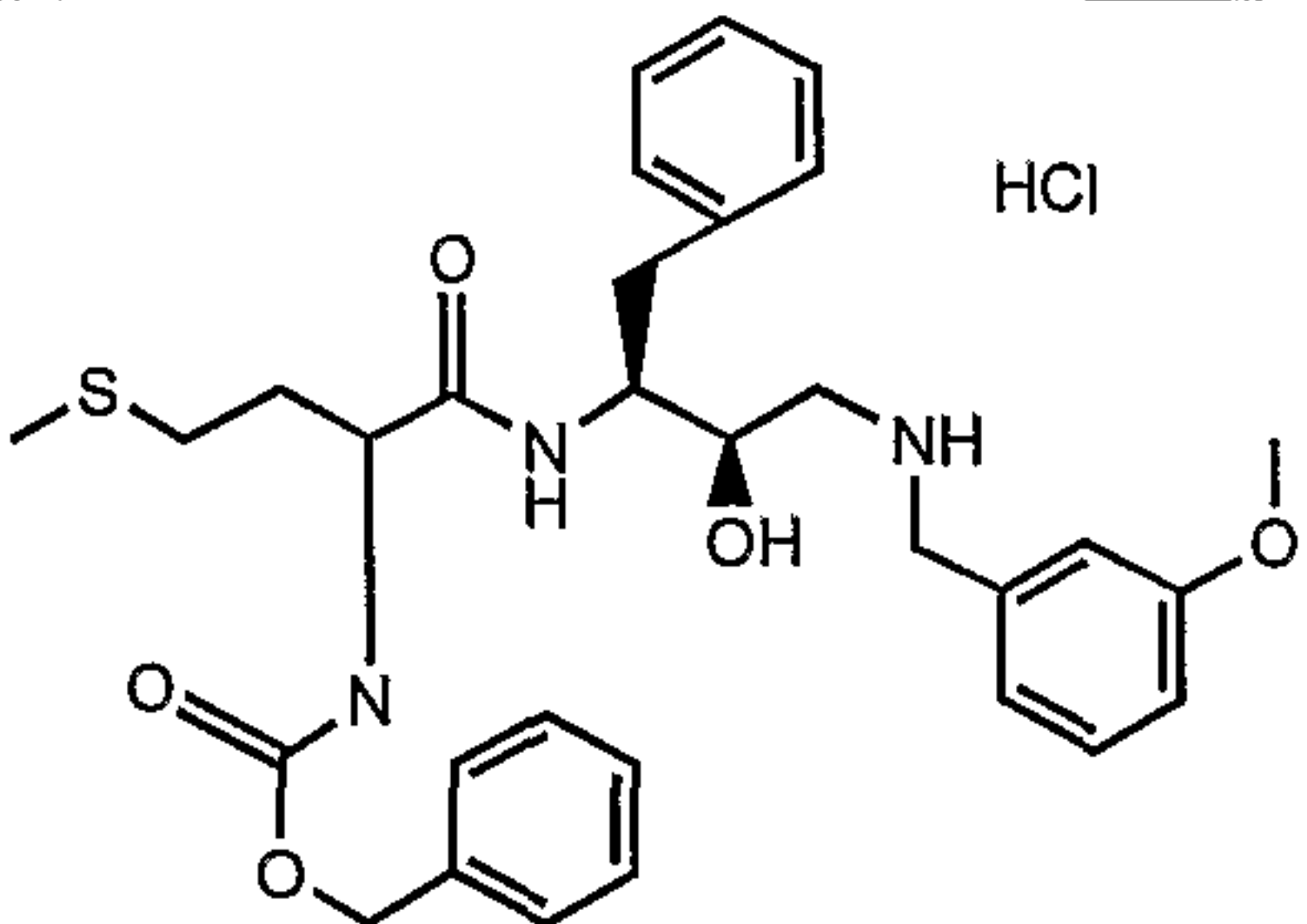
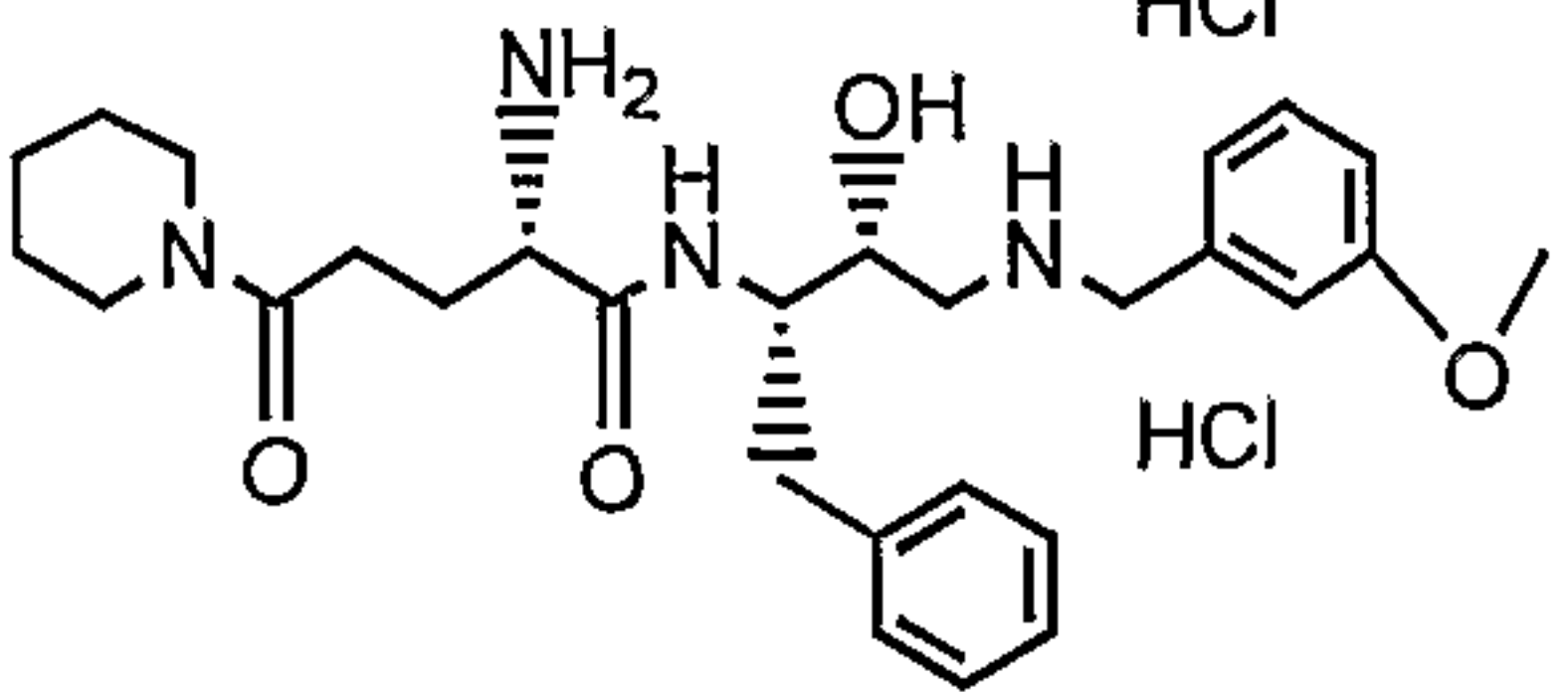
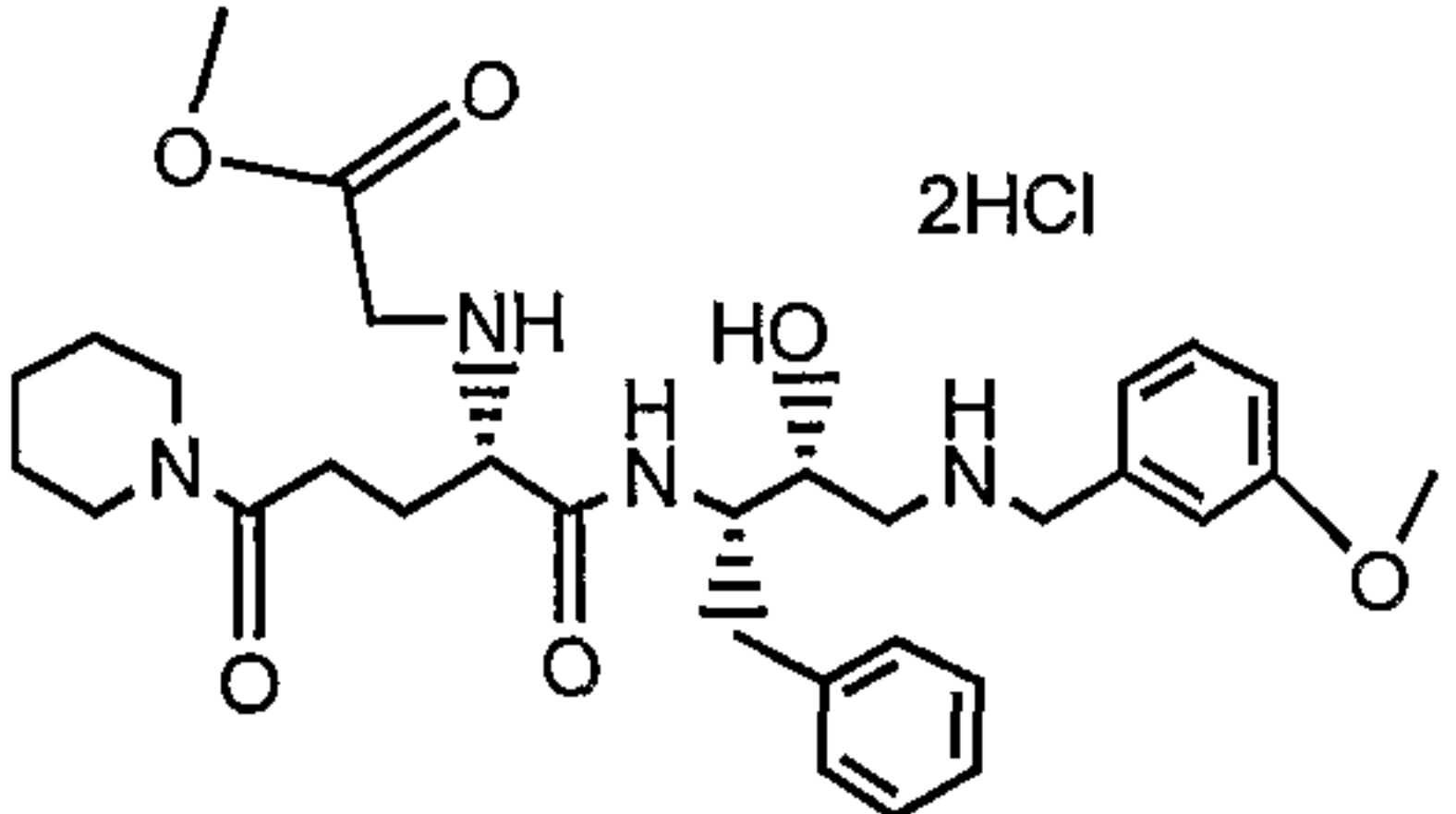
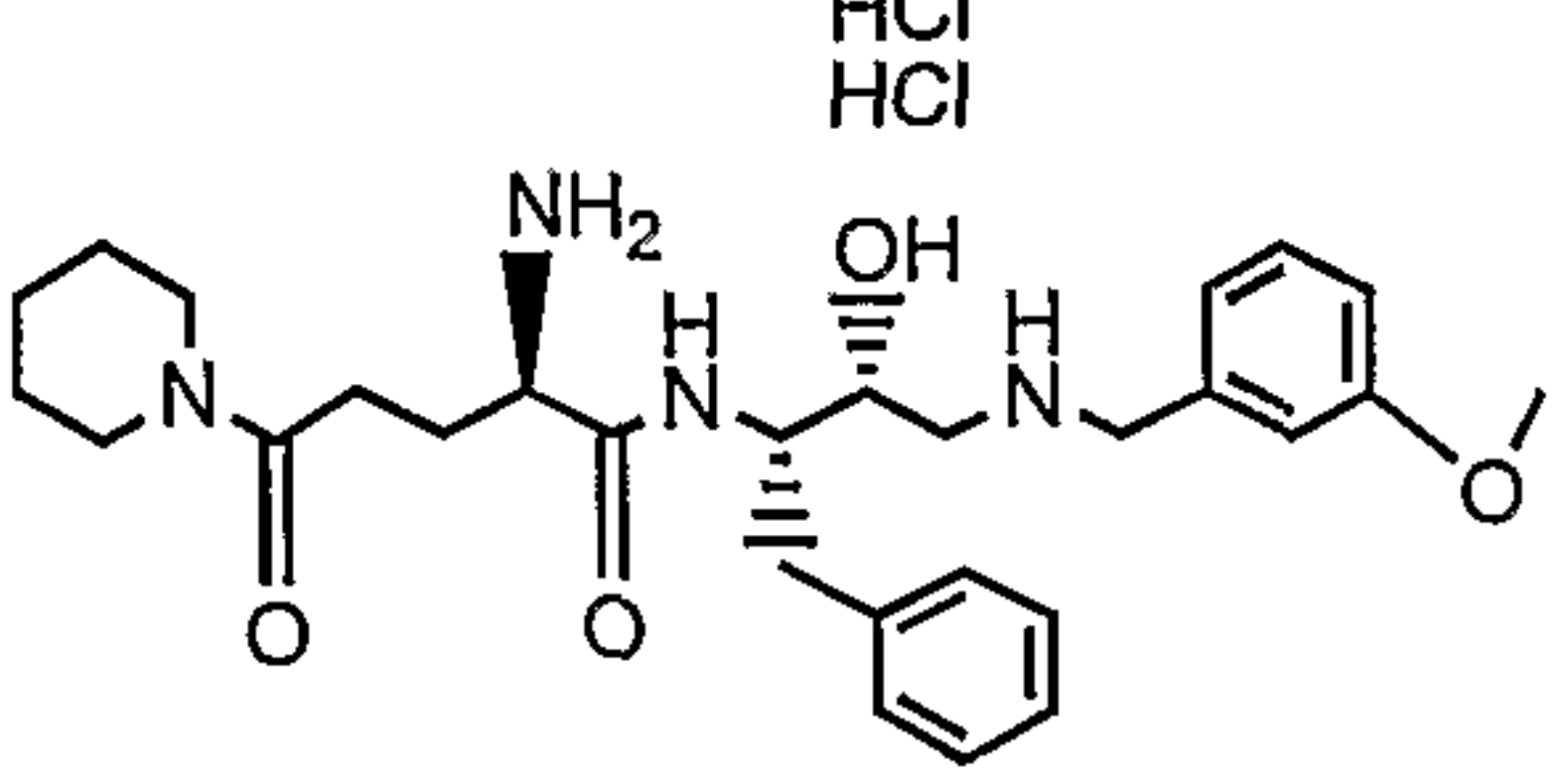
	oxobutanoic acid hydrochloride	
	methyl 4-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino)-3-[(isopentylsulfonyl)methyl]-4-oxobutanoate hydrochloride	563
	N-1-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-[(isopentylsulfonyl)methyl]succinamide hydrochloride	548
	N-1-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-[(isopentylsulfonyl)methyl]-N-4-methylsuccinamide hydrochloride	562
	N-1-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-[(isopentylsulfonyl)methyl]-N-4,N-4-dimethylsuccinamide hydrochloride	576
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[(1-propylbutyl)sulfonyl)methyl]propanamide	693

	<p>N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-((1-propylbutyl)sulfonyl)methyl}propanamide (first isomer)</p>	693
	<p>N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-((1-propylbutyl)sulfonyl)methyl}propanamide (second isomer)</p>	693
	<p>N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-3-(ethylsulfonyl)-2-((isobutylsulfonyl)amino)methyl}propanamide hydrochloride</p>	598
	<p>N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-3-(ethylthio)-2-((isobutylsulfonyl)amino)methyl}propanamide hydrochloride</p>	566

	<p>(2S)-N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-[(isopentylsulfonyl)amino]-4-(methylsulfonyl)butanamide hydrochloride</p>	598
	<p>N-1-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N-2-((isopentylsulfonyl)-L-methioninamide hydrochloride</p>	566
	<p>S-((3-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino)-2-((isopentylsulfonyl)methyl)-3-oxopropyl)ethanethioate hydrochloride</p>	579
	<p>N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-hydroxy-3-((1-propylbutyl)sulfonyl)propanamide</p>	535
	<p>N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-hydroxy-3-((isopentylsulfonyl)propanamide hydrochloride</p>	507
	<p>N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-hydroxy-3-((3-methoxybenzyl)sulfonyl)propanamide hydrochloride</p>	543

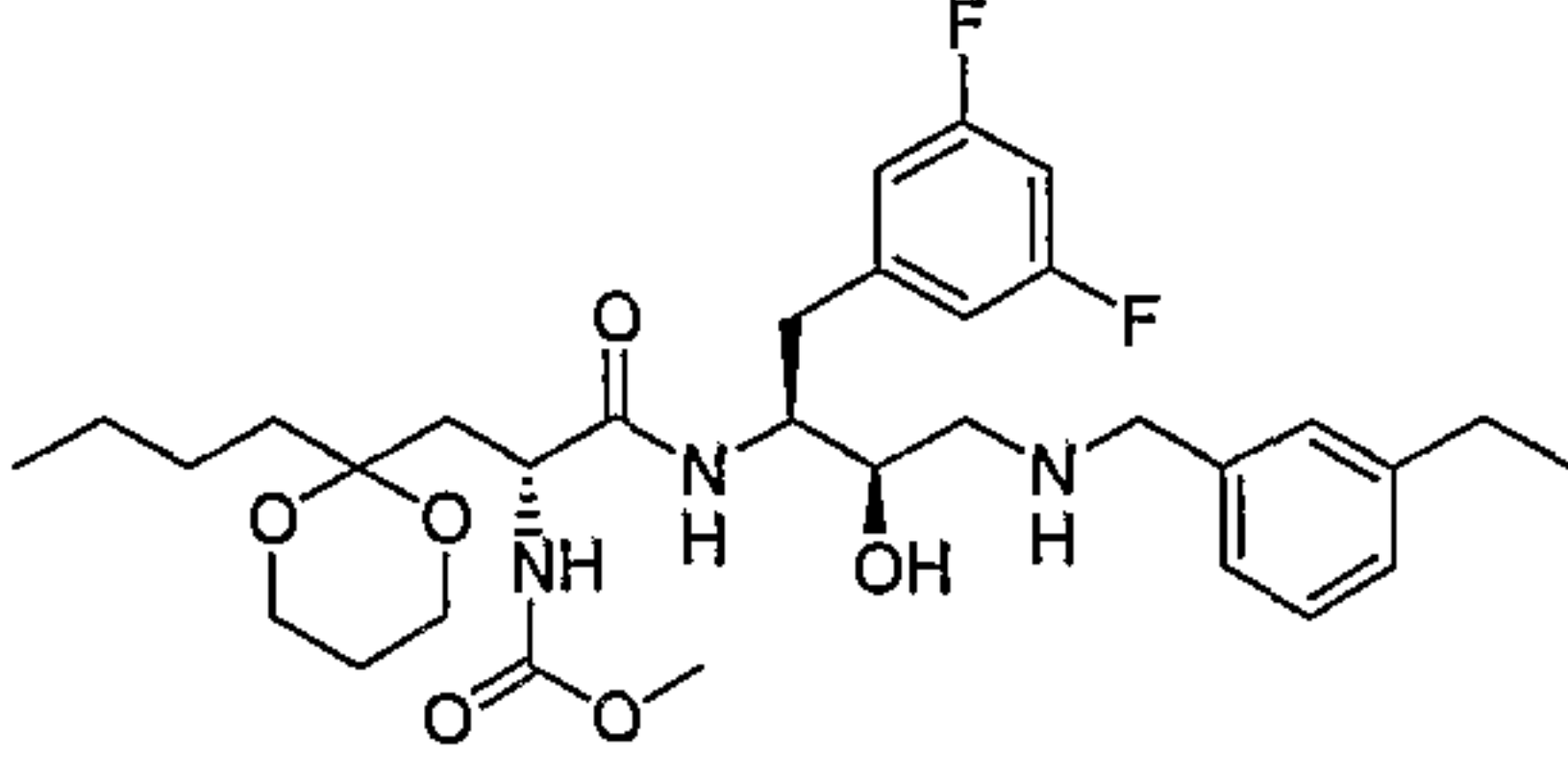
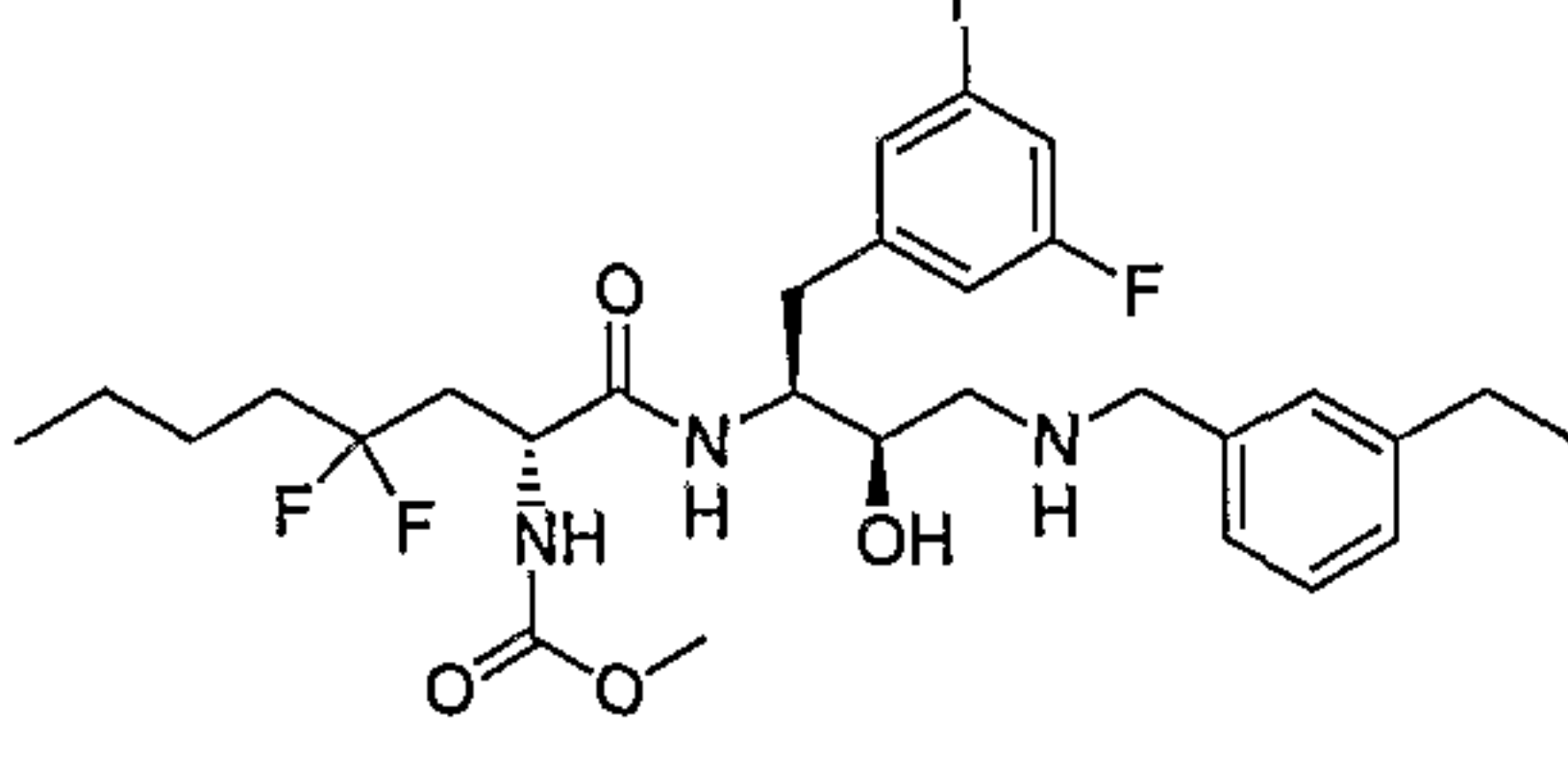
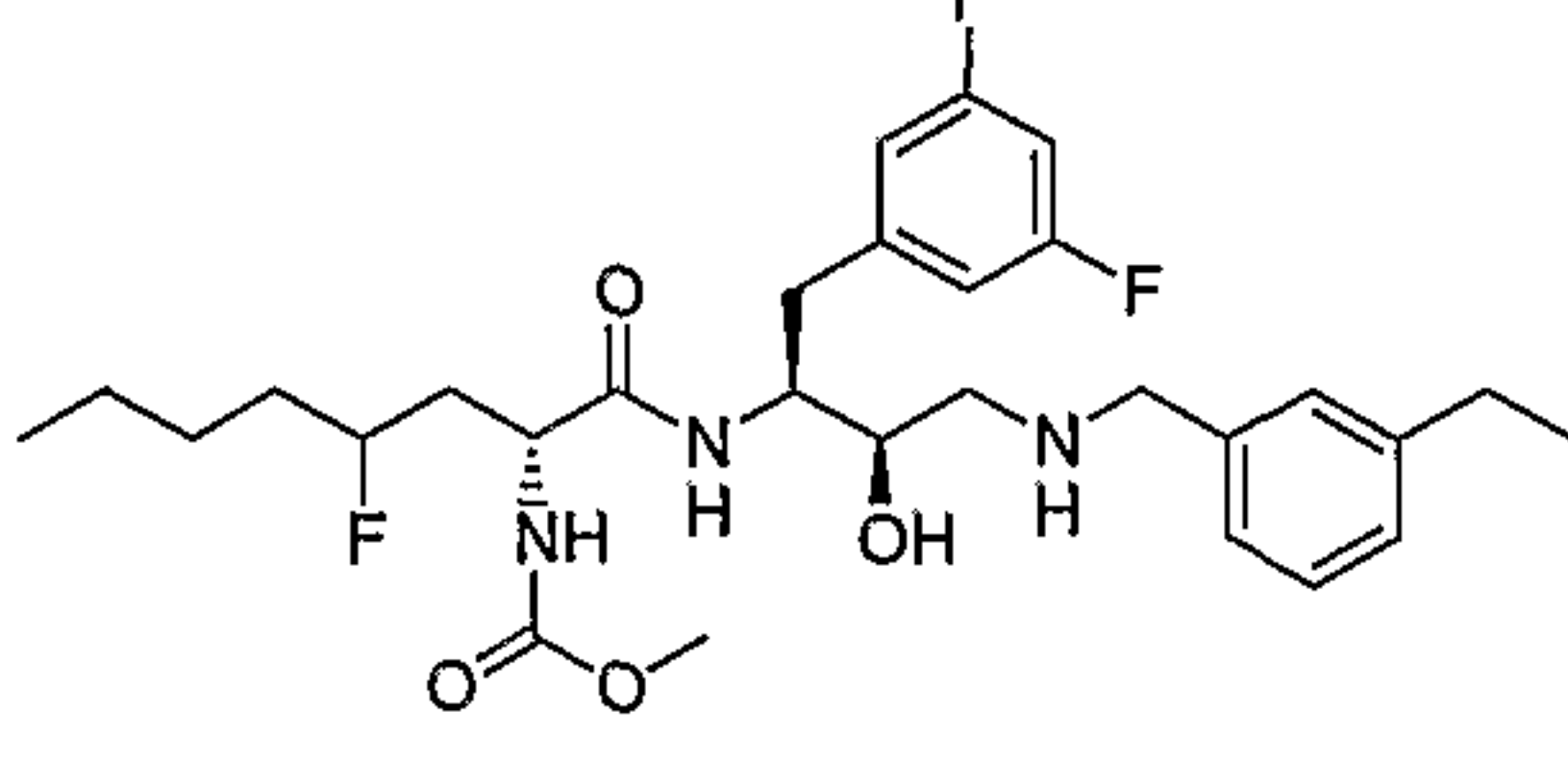
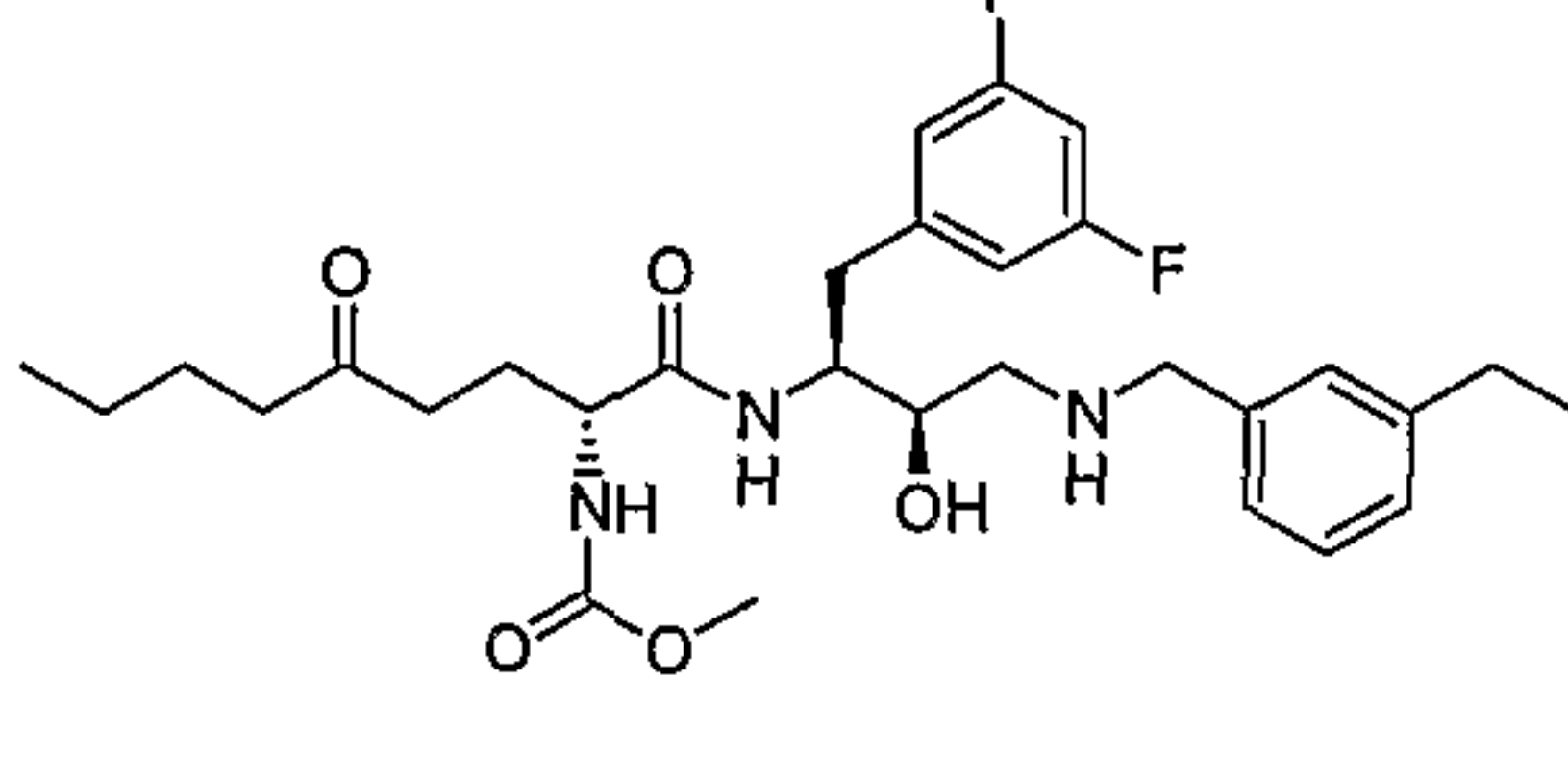
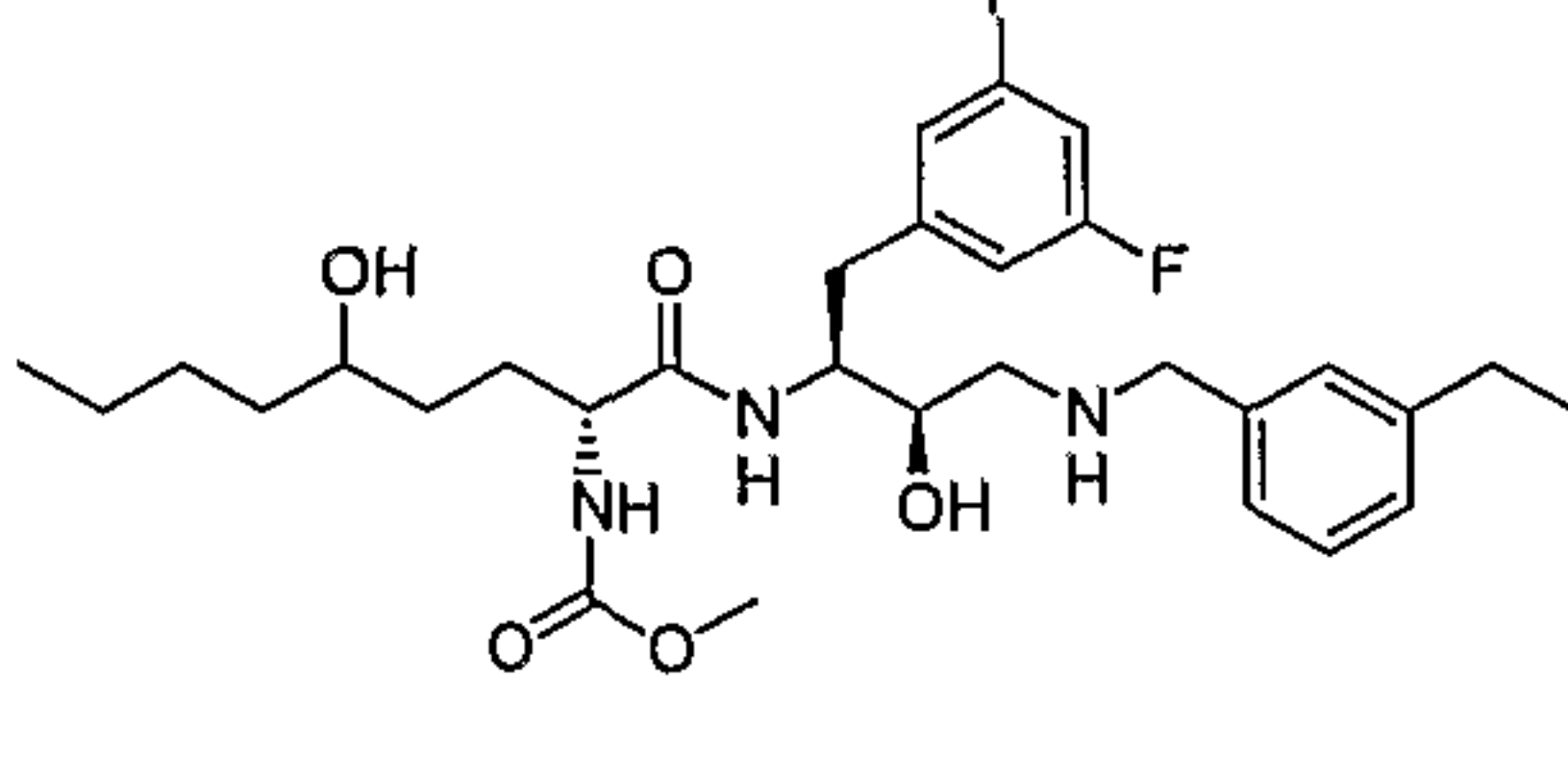
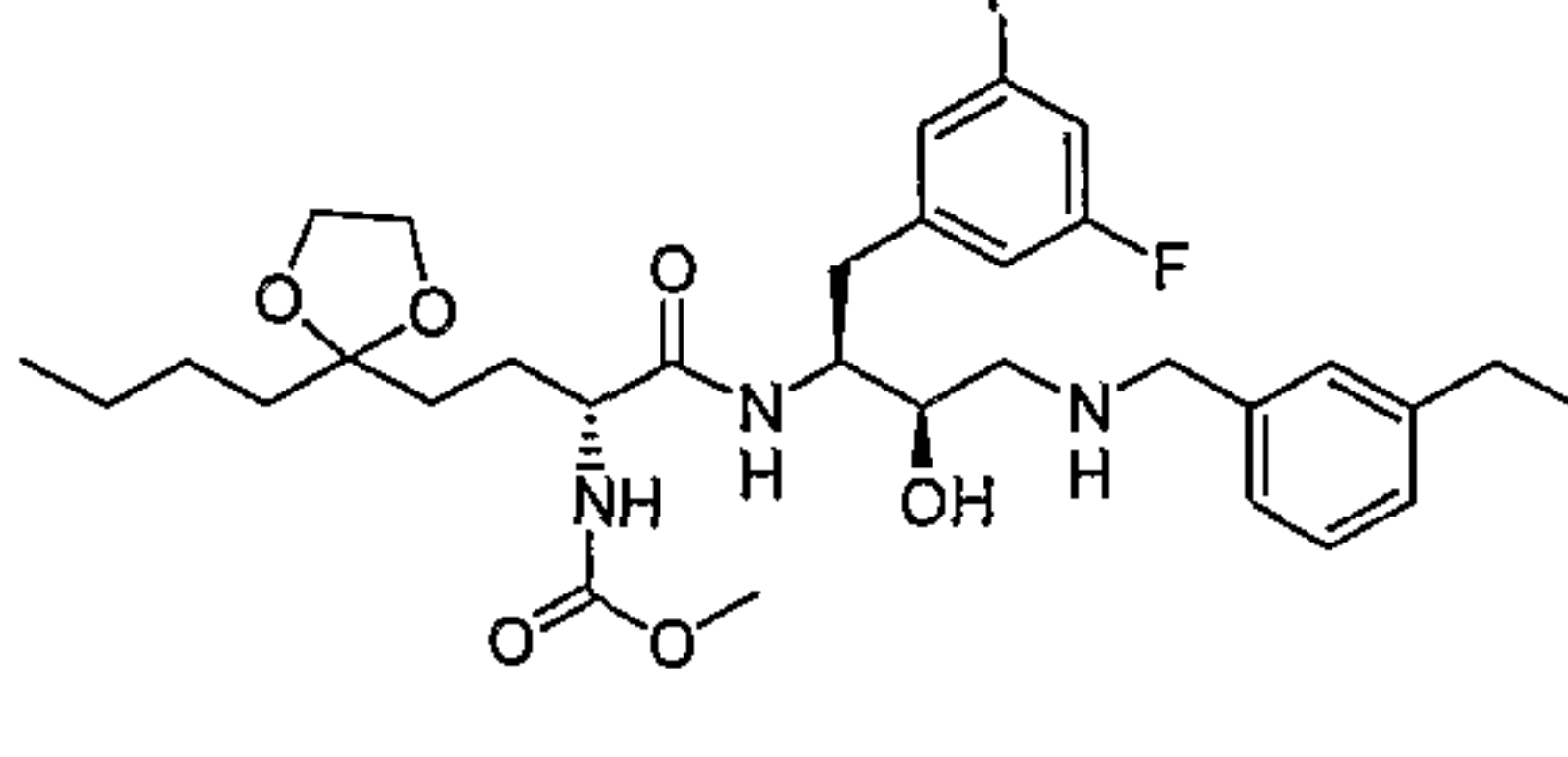
	methoxyphenyl) sulfonyl]propanamide hydrochloride	
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-hydroxy-4-(phenylsulfonyl)butanamide	561
	N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-2-hydroxy-4-(isopentylsulfonyl)butanamide hydrochloride	521
	N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-4-(isopentylsulfonyl)-2-phenoxybutanamide hydrochloride	597
	N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-4-(isopentylsulfonyl)-2-(3-methoxyphenoxy)butanamide hydrochloride	627
	3-(1-(((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)amino)carbonyl)-3-(isopentylsulfonyl)propoxy]benzoic acid trifluoroacetate	641

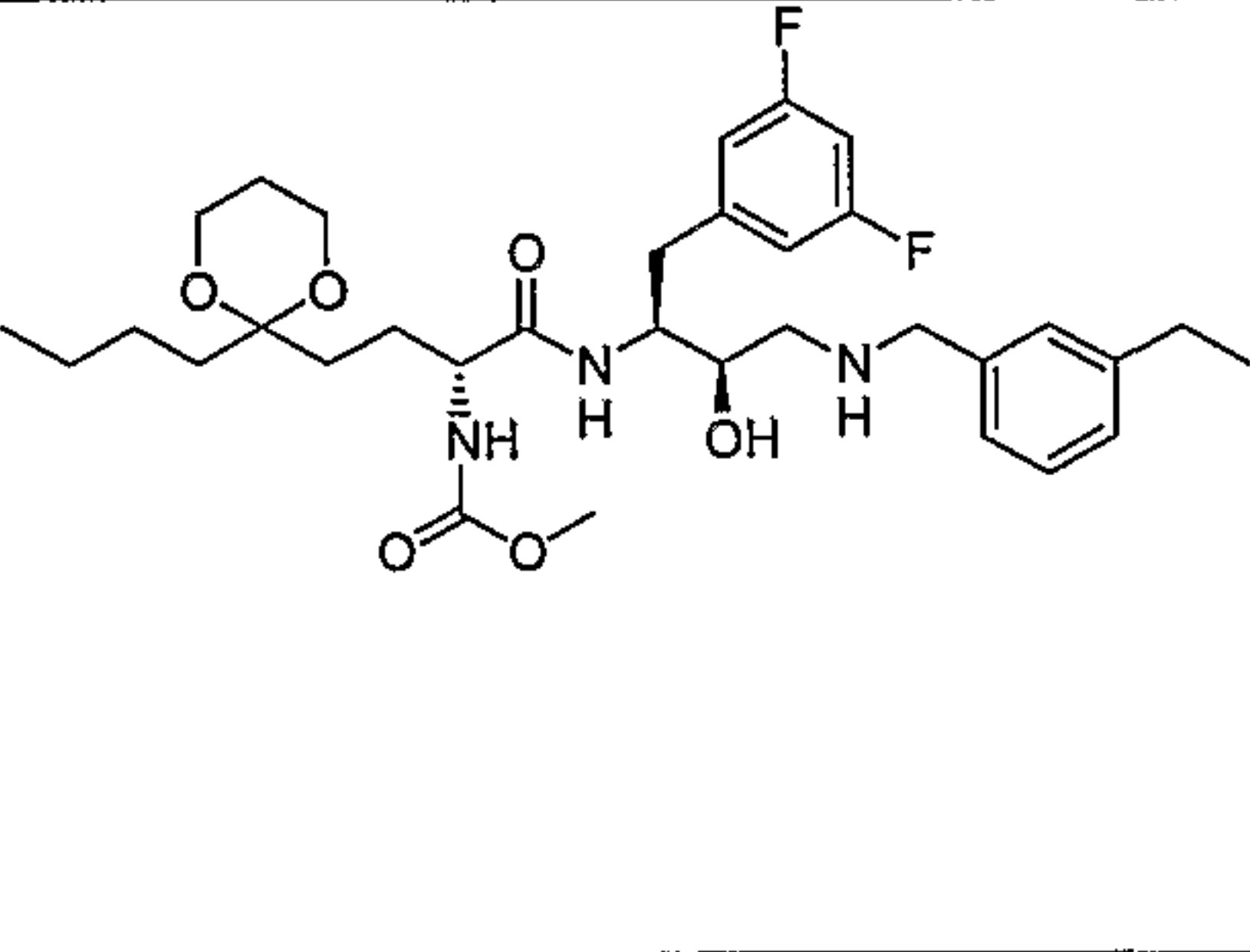
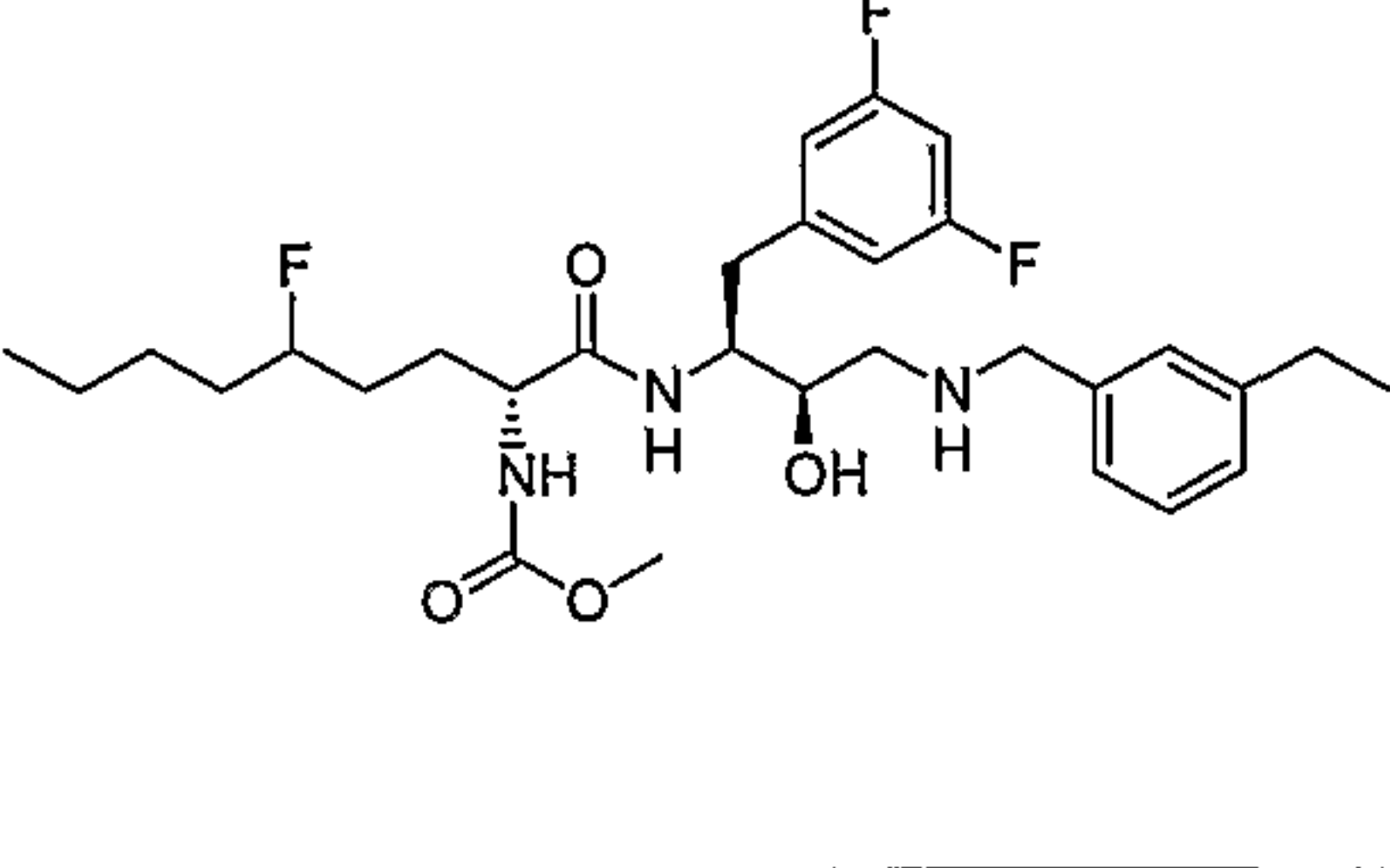
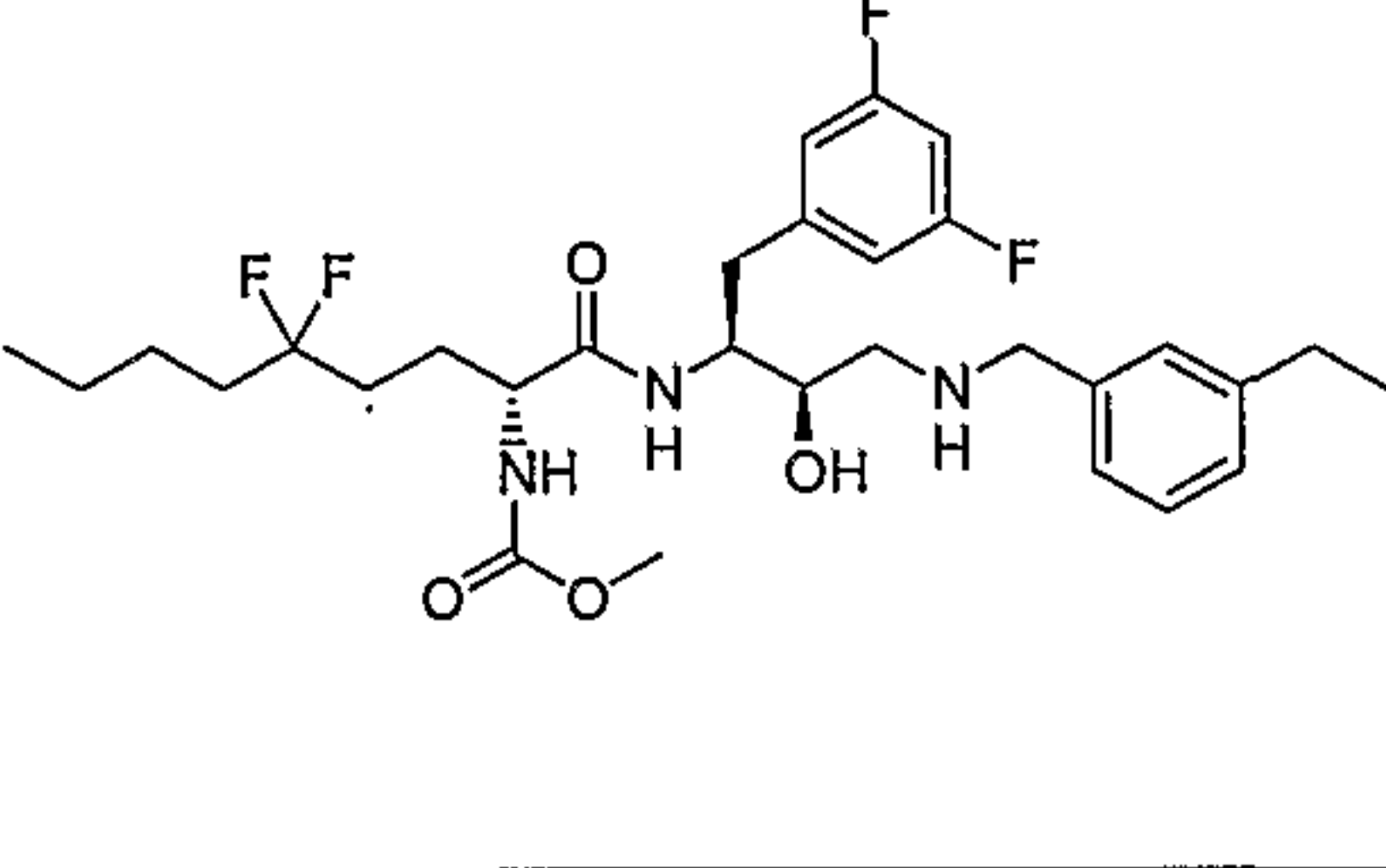
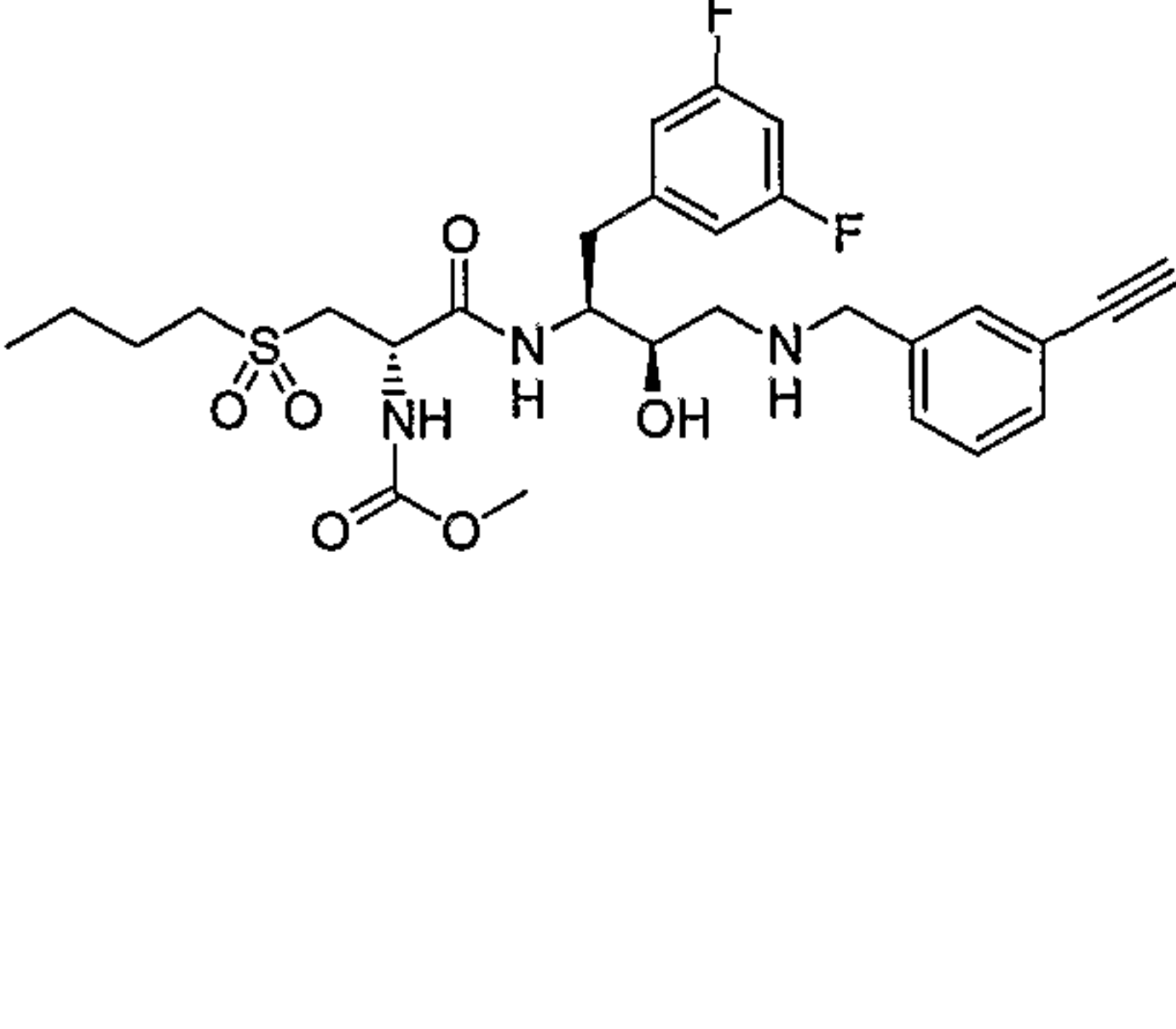
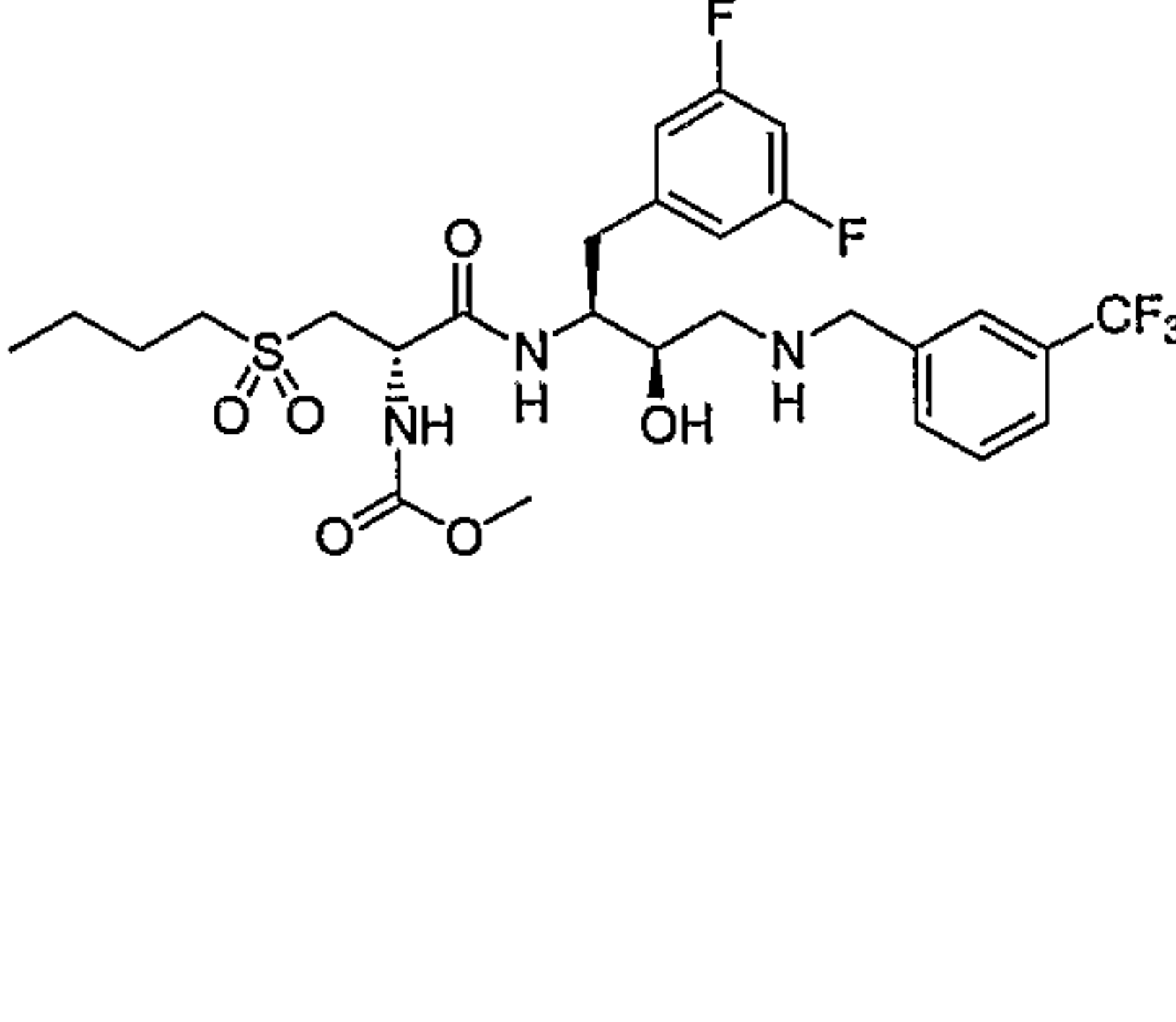
	methyl 3-[1-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]amino]carbonyl]-3-(isopentylsulfonyl)propoxy]benzoate hydrochloride	655
	N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-2-hydroxy-4-(phenylsulfonyl)butanamide hydrochloride	527
	N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-2-hydroxy-4-(phenylthio)butanamide hydrochloride	495
	N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-2-methoxy-4-(phenylsulfonyl)butanamide hydrochloride	541
	N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-2-methoxy-4-(phenylthio)butanamide hydrochloride	509
	N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-4-(phenylsulfonyl)-2-(propoxy)butanamide hydrochloride	569

	propoxybutanamide hydrochloride	
	N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-2-(benzyloxy)-4-(phenylsulfonyl)butanamide hydrochloride	617
	N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-N-(2-((benzyloxy)carbonyl)-D,L-methioninyl)butanamide hydrochloride	566
	(2S)-2-amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-5-oxo-5-piperidin-1-ylpentanamide dihydrochloride	497
	N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-(2S)-2-((2-ethoxy-2-oxoethyl)amino)-5-oxo-5-piperidin-1-ylpentanamide dihydrochloride	569
	(2R)-2-amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-5-oxo-5-piperidin-1-ylpentanamide dihydrochloride	497

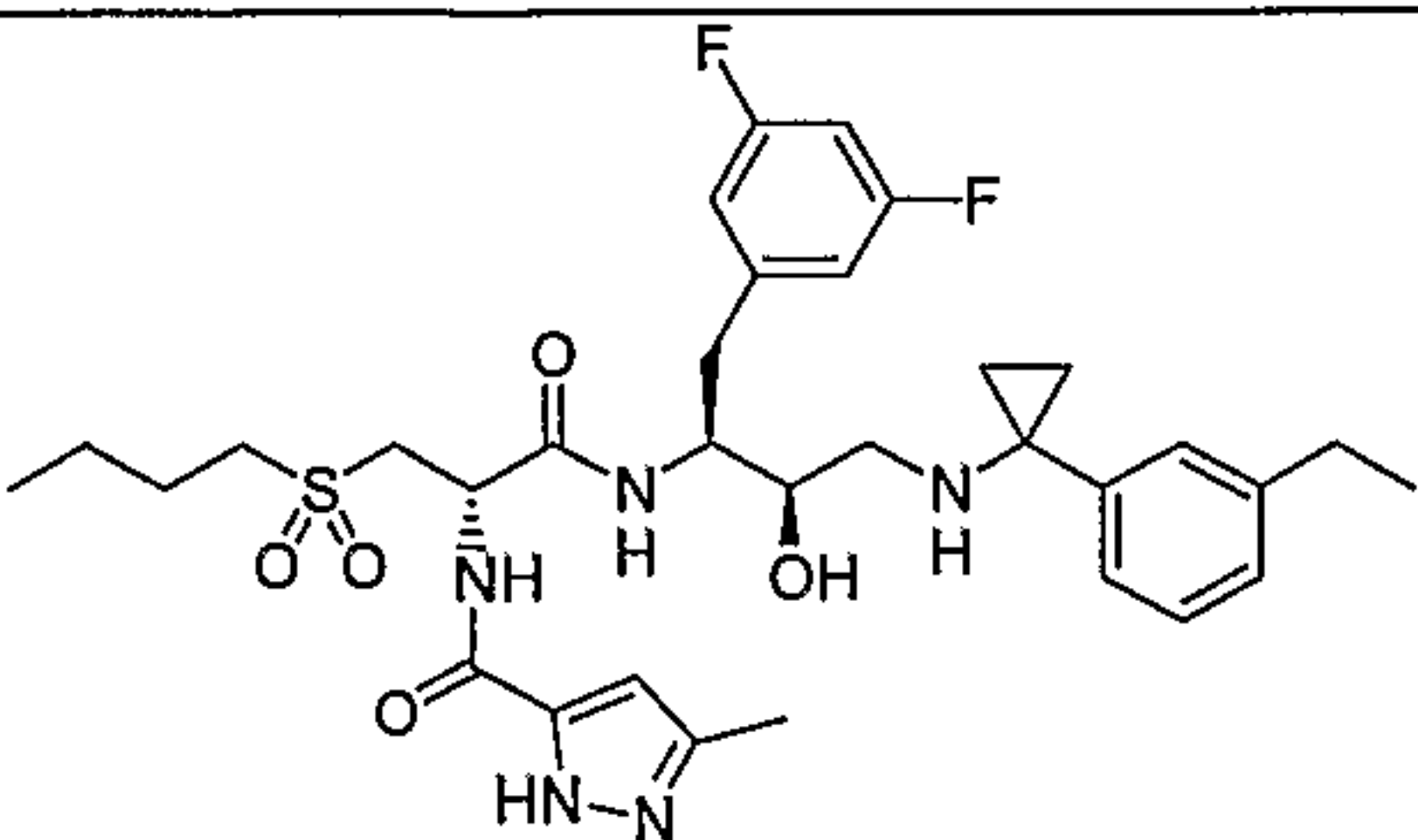
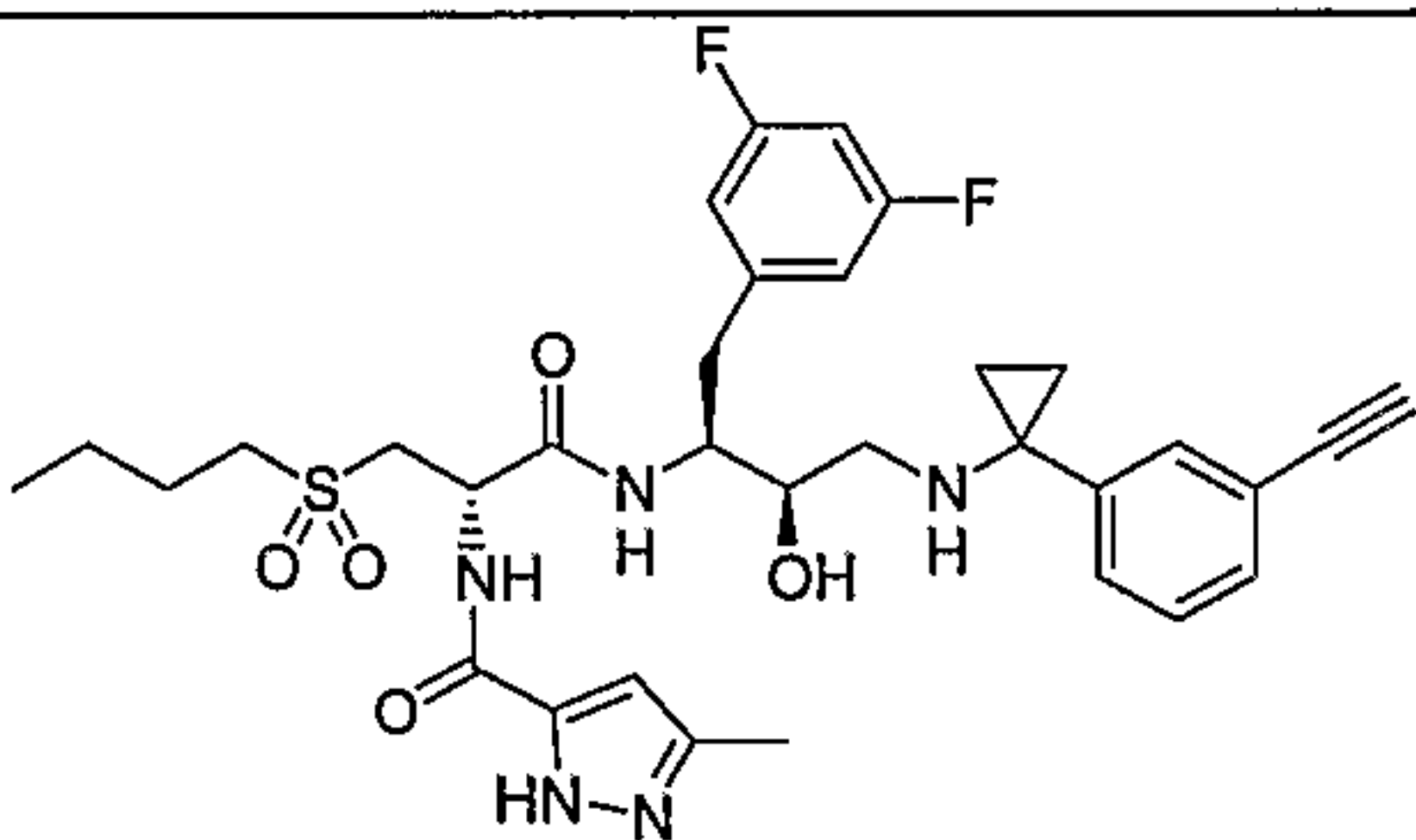
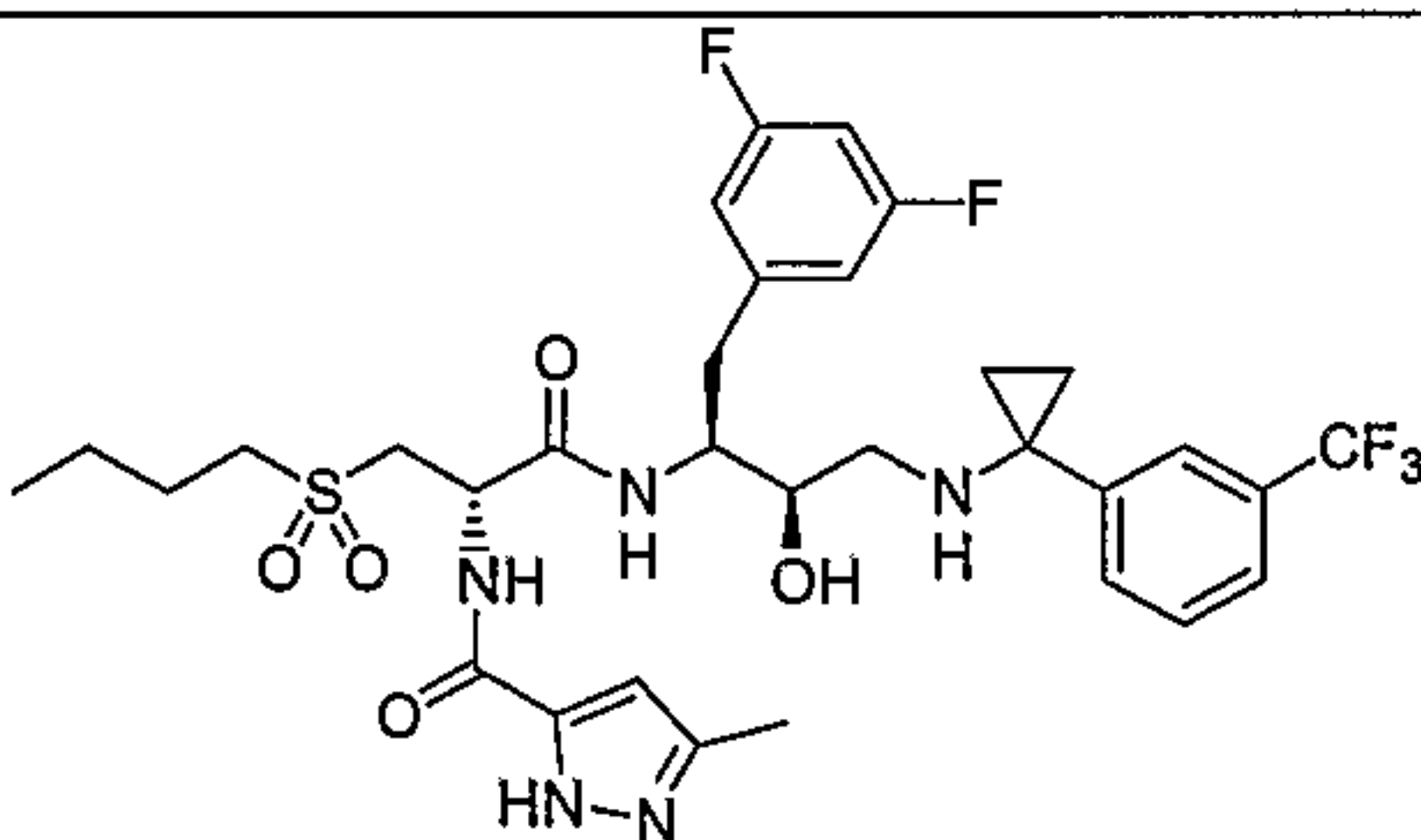
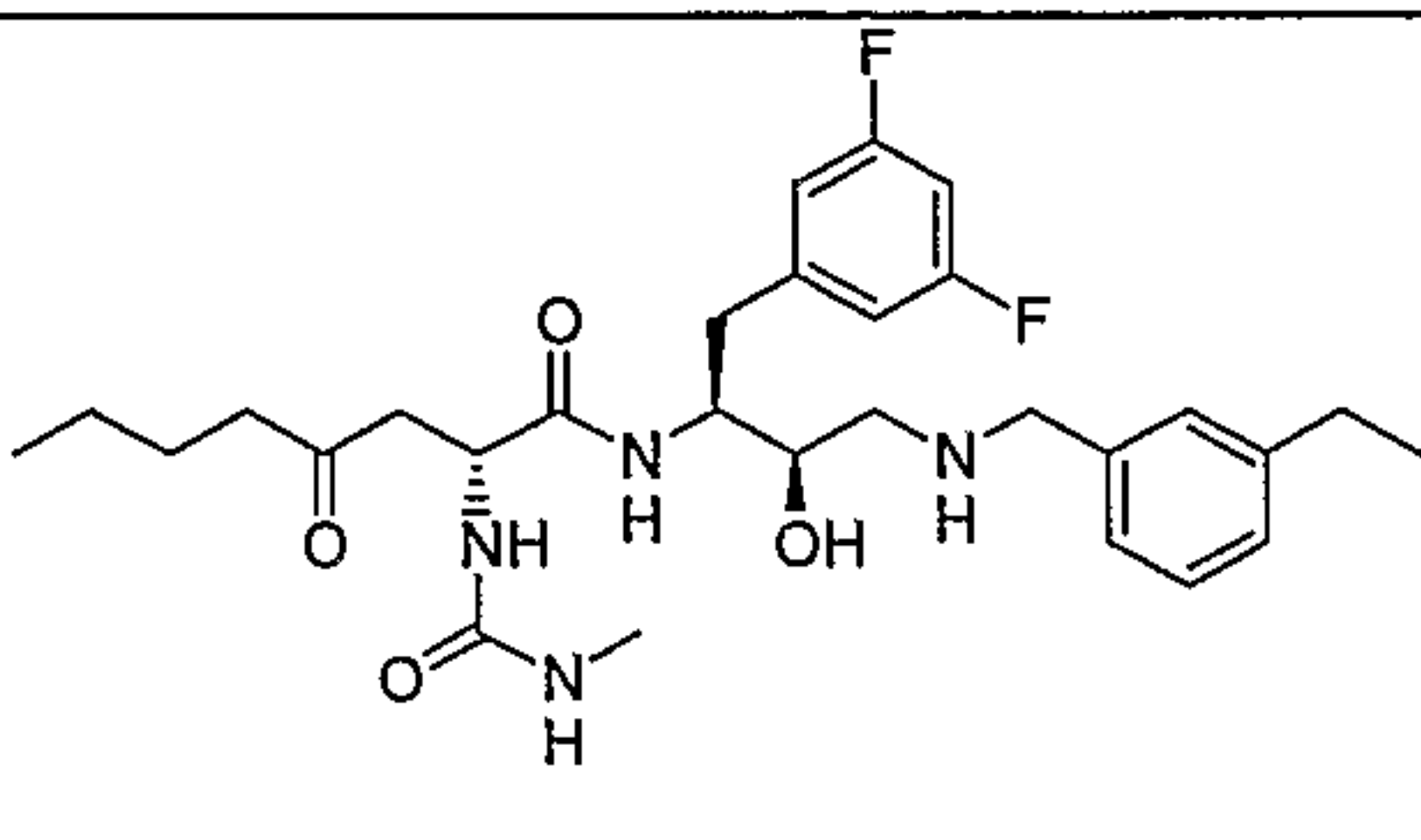
	<p>N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-(2R)-2-((2-ethoxy-2-oxoethyl)amino)-5-oxo-5-piperidin-1-ylpentanamide dihydrochloride</p>	583
	<p>N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-(2R)-2-((4-ethoxy-4-oxobutyl)amino)-5-oxo-5-piperidin-1-ylpentanamide ditrifluoroacetate</p>	611
	<p>methyl (1R)-1-(((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)amino)carbonyl]-3-oxoheptylcarbamate</p>	
	<p>4-butyl-N-1-(((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-(methoxycarbonyl)-D-homoserinamide</p>	
	<p>3-(2-butyl-1,3-dioxolan-2-yl)-N-1-(((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-(methoxycarbonyl)-D-alaninamide</p>	

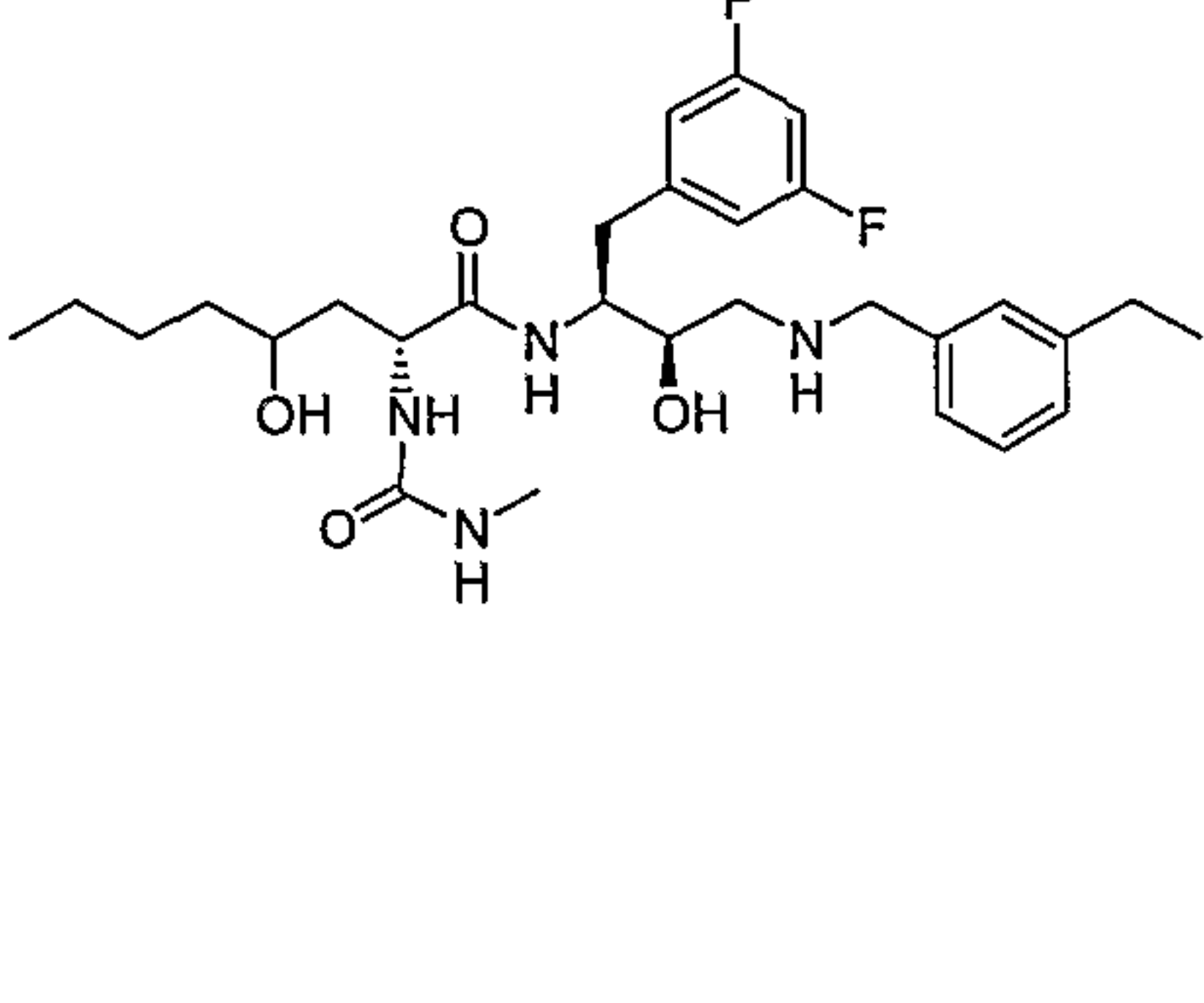
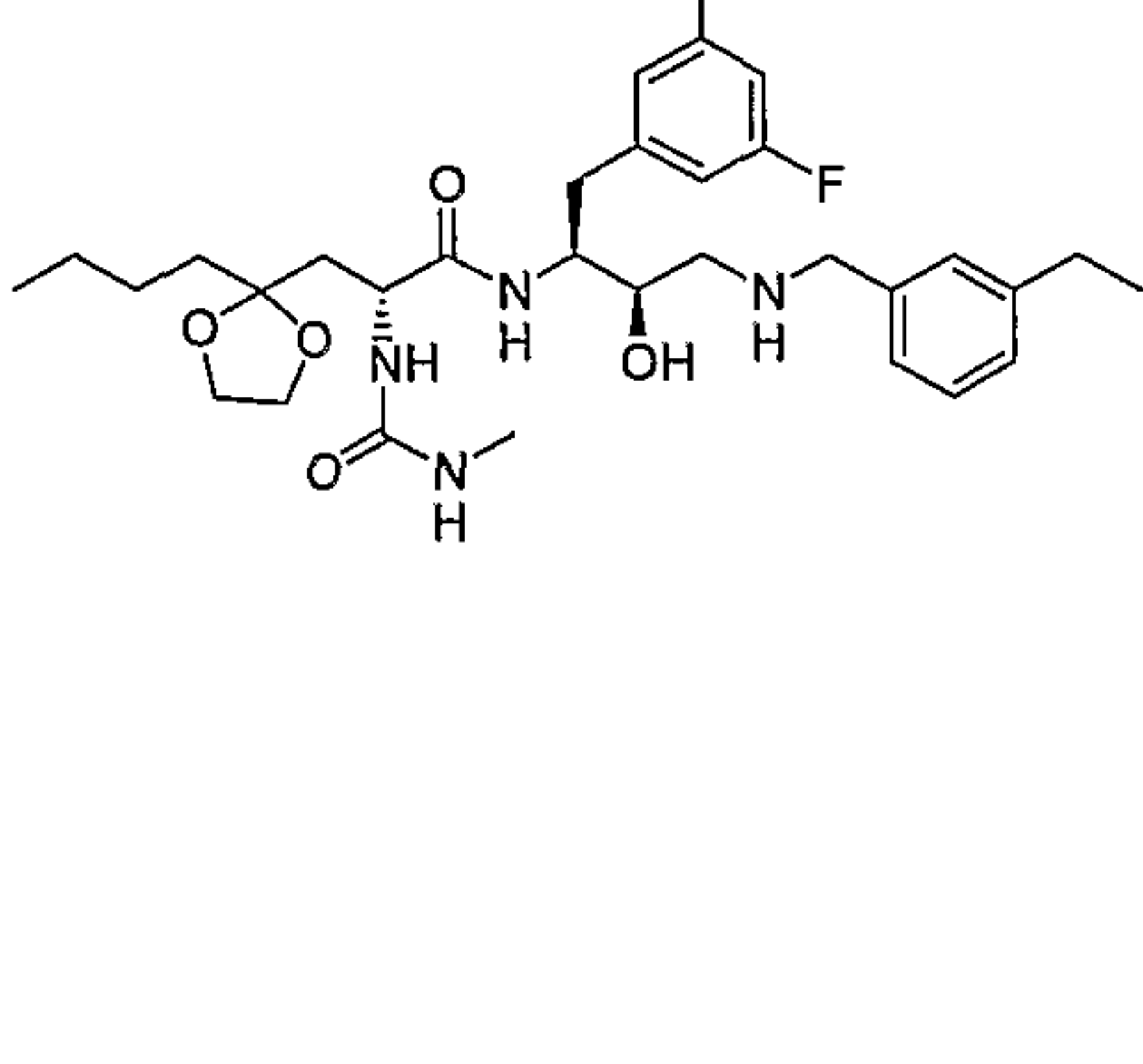
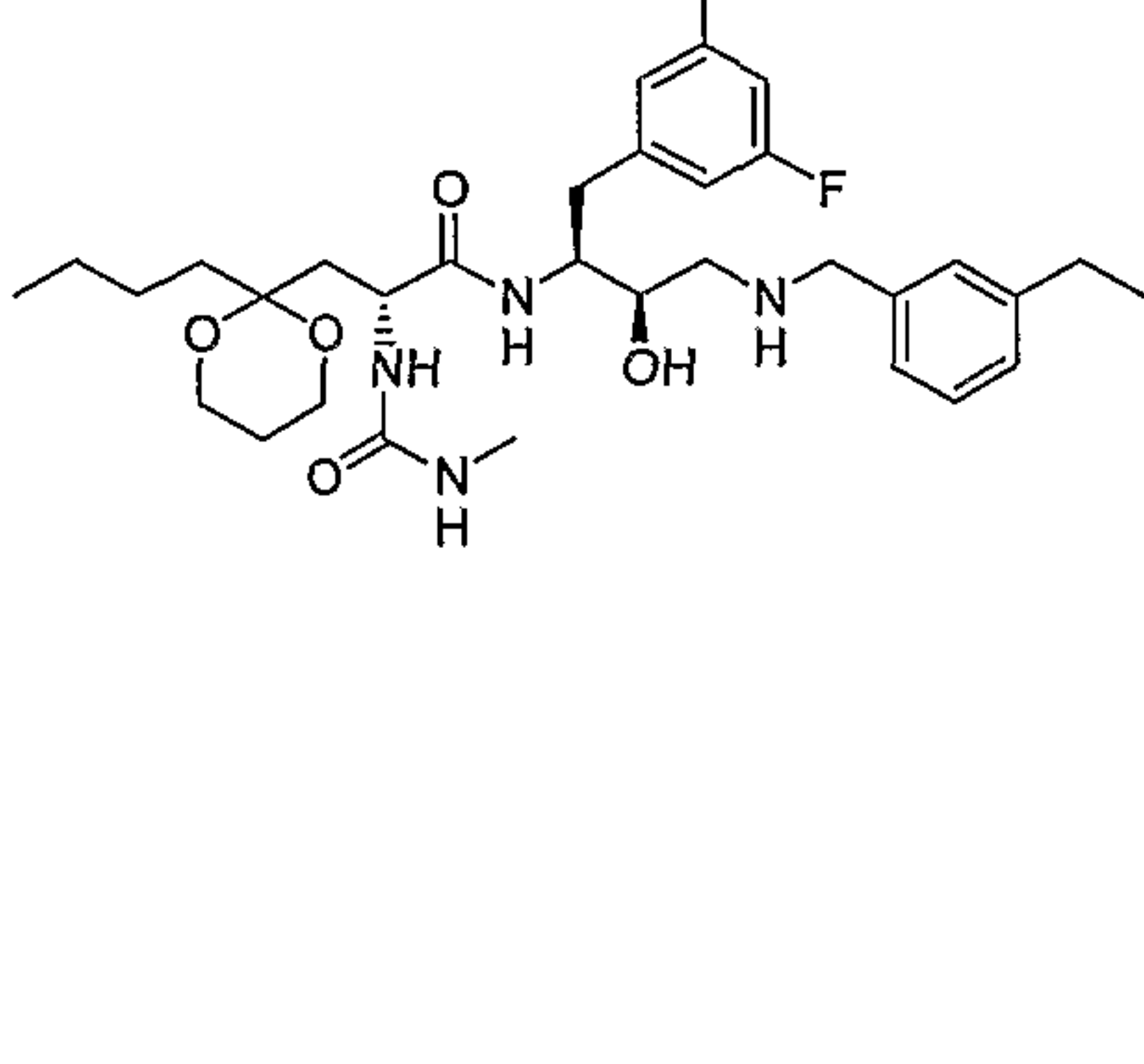
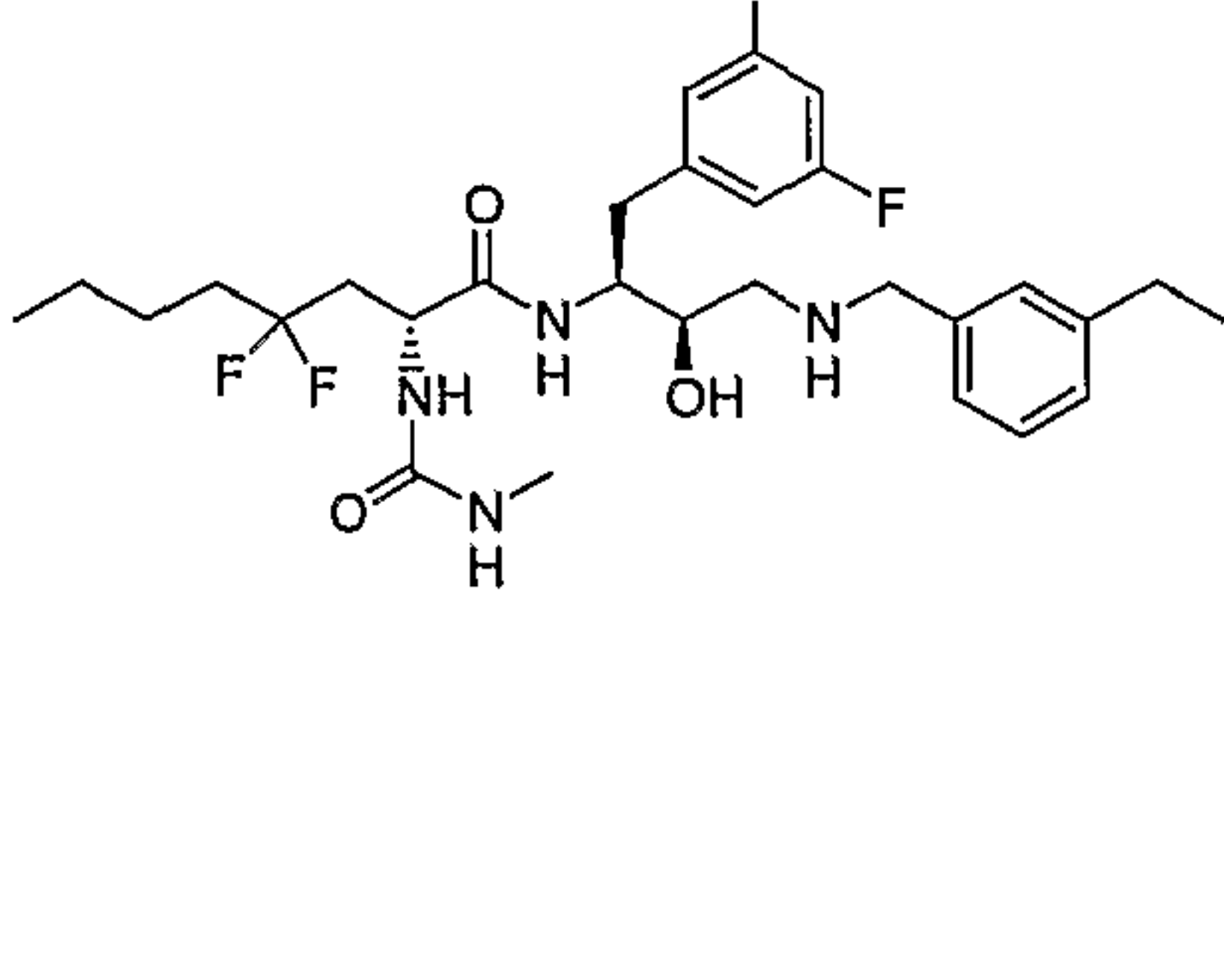


	<p>3-(2-butyl-1,3-dioxan-2-yl)- N~1~-{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N~2~- (methoxycarbonyl)-D- alaninamide</p>	
	<p>methyl (1R)-1-[(1S,2R)-1- (3,5-difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl]amino) carbonyl]- 3,3-difluoroheptylcarbamate</p>	
	<p>methyl (1R)-1-[(1S,2R)-1- (3,5-difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl]amino) carbonyl]- 3-fluoroheptylcarbamate</p>	
	<p>methyl (1R)-1-[(1S,2R)-1- (3,5-difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl]amino) carbonyl]- 4-oxooctylcarbamate</p>	
	<p>methyl (1R)-1-[(1S,2R)-1- (3,5-difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl]amino) carbonyl]- 4-hydroxyoctylcarbamate</p>	
	<p>methyl (1R)-3-(2-butyl-1,3- dioxolan-2-yl)-1-[(1S,2R)-1- (3,5-difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl]amino) carbonyl]p ropylcarbamate</p>	

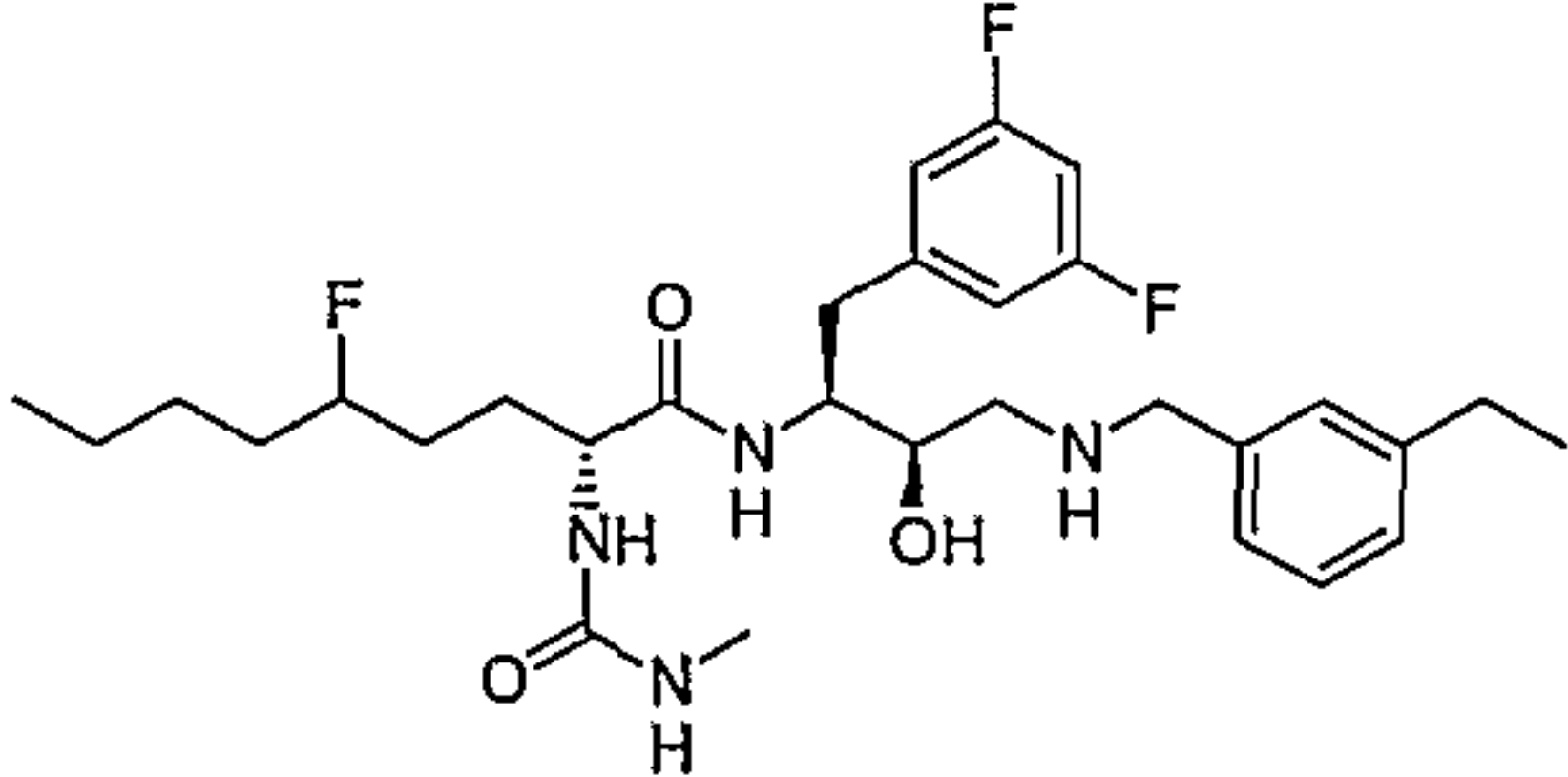
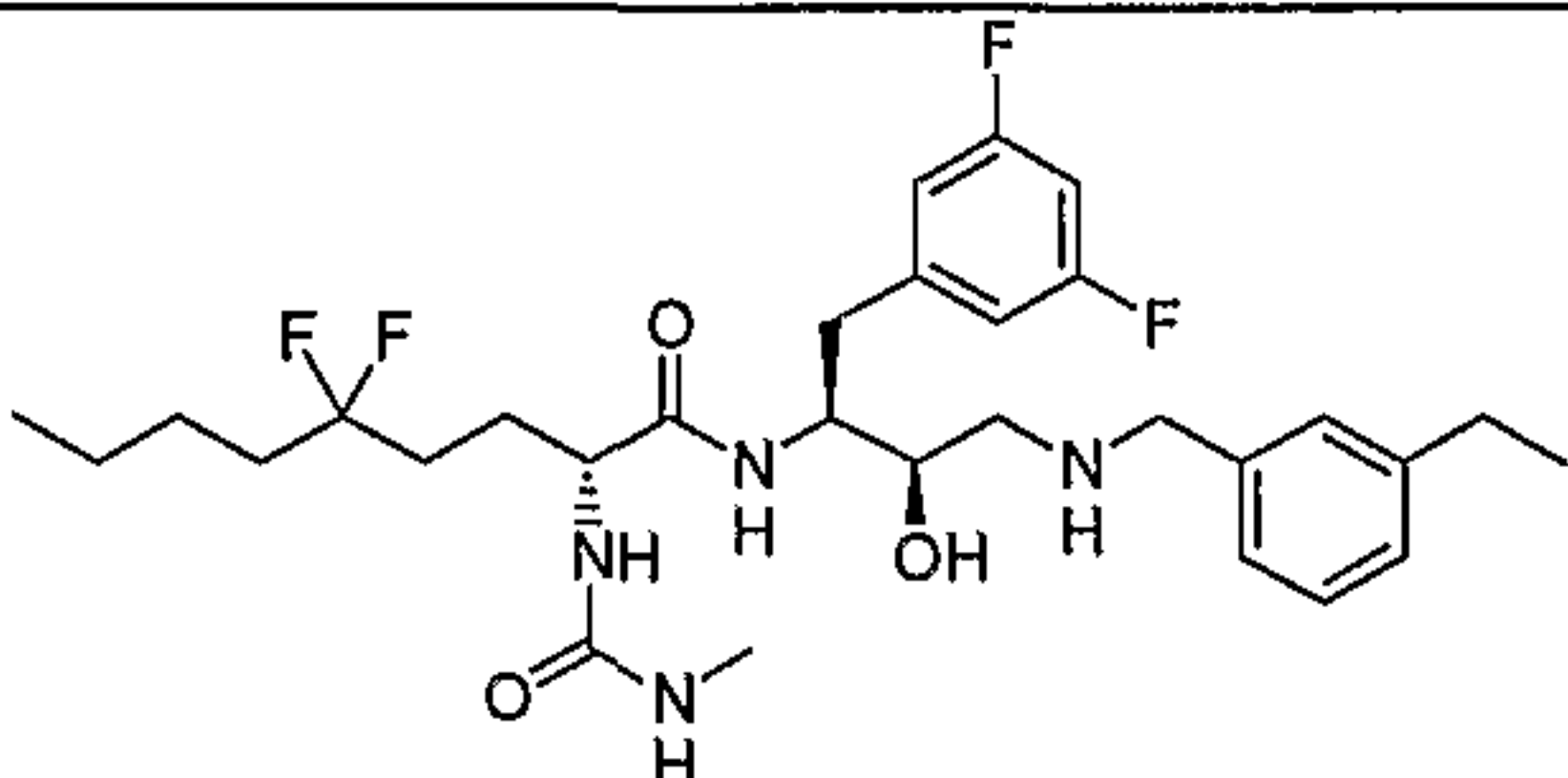
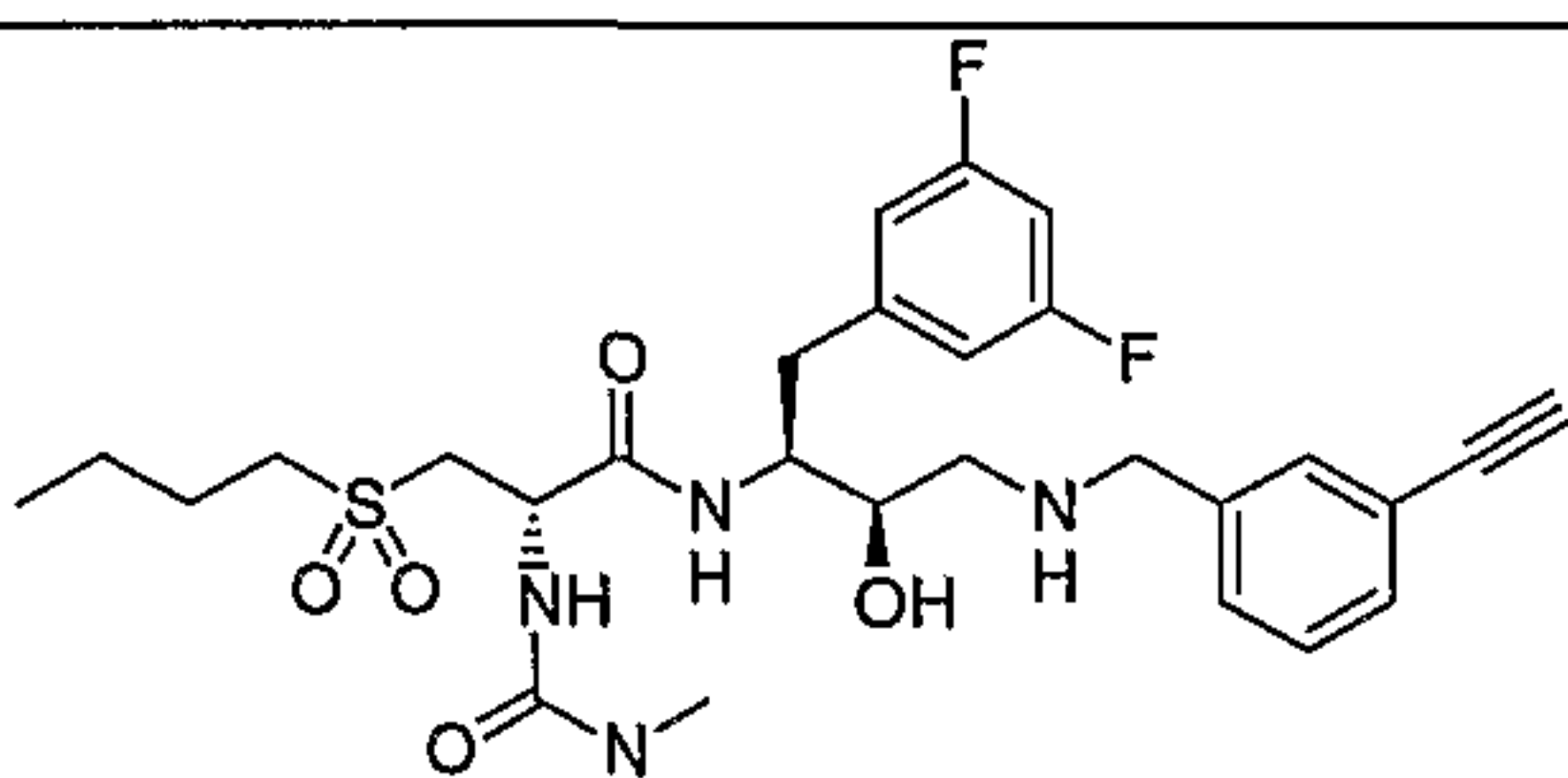
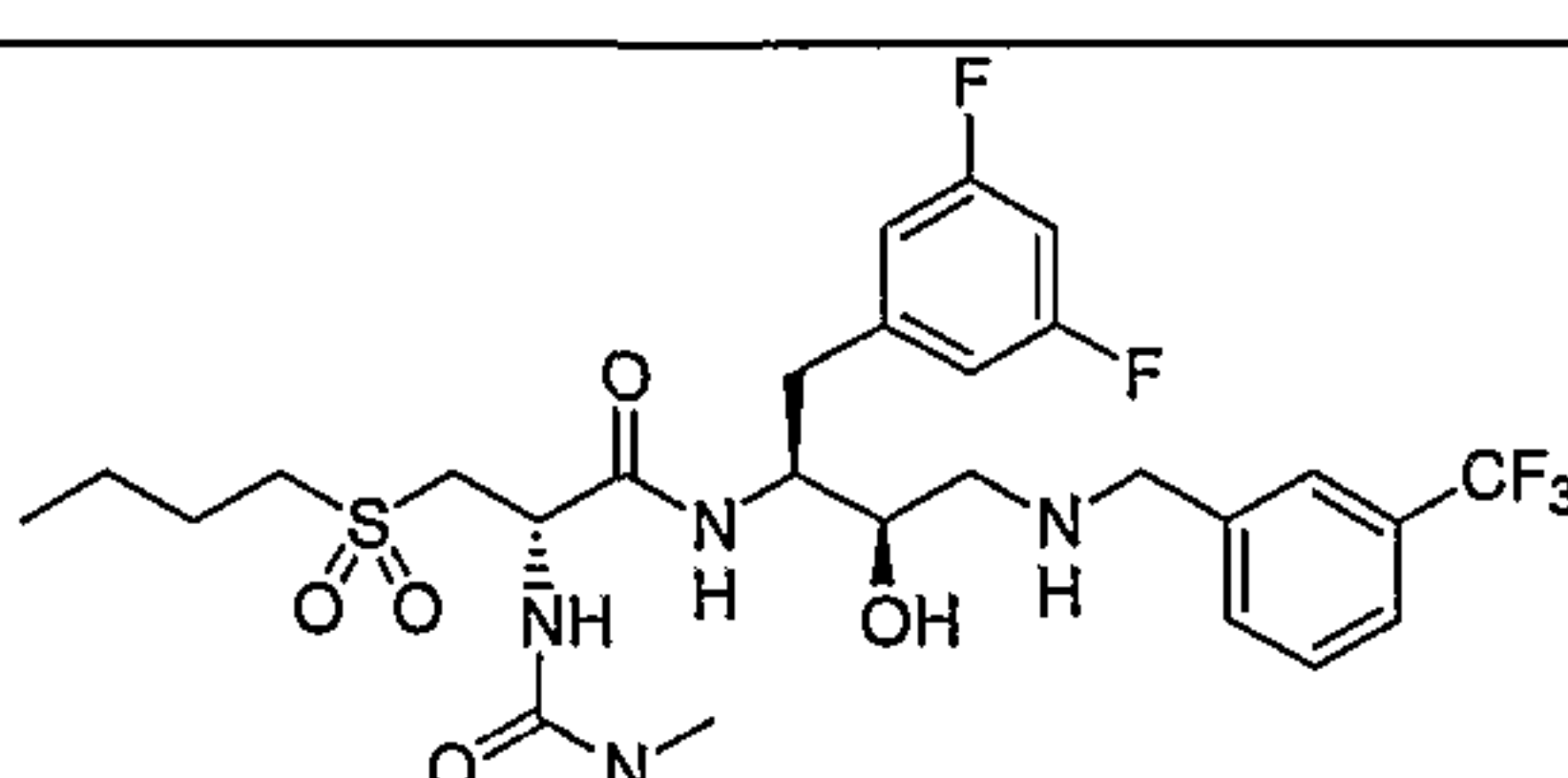
	<p>methyl (1R)-3-(2-butyl-1,3-dioxan-2-yl)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino) carbonyl]propylcarbamate</p>	
	<p>methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino) carbonyl]-4-fluorooctylcarbamate</p>	
	<p>methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino) carbonyl]-4,4-difluorooctylcarbamate</p>	
	<p>3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl]-N-2-(methoxycarbonyl)-D-alaninamide</p>	
	<p>3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-(trifluoromethyl)benzyl)amino]propyl]-N-2-(methoxycarbonyl)-D-alaninamide</p>	

	<p>3-(butylsulfonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-({1-(3-ethylphenyl)cyclopropyl}amino)-2-hydroxypropyl)-N-(methoxycarbonyl)-D-alaninamide</p>	
	<p>3-(butylsulfonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-({1-(3-ethynylphenyl)cyclopropyl}amino)-2-hydroxypropyl)-N-(methoxycarbonyl)-D-alaninamide</p>	
	<p>3-(butylsulfonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3-(trifluoromethyl)phenyl]cyclopropyl}amino)propyl)-N-(methoxycarbonyl)-D-alaninamide</p>	
	<p>N-((1R)-3-(butylsulfonyl)-1-(((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethynylbenzyl)amino)-2-hydroxypropyl)amino)carbonyl)propyl)-3-methyl-1H-pyrazole-5-carboxamide</p>	
	<p>N-((1R)-3-(butylsulfonyl)-1-(((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({3-(trifluoromethyl)benzyl}amino)propyl)amino)carbonyl)propyl)-3-methyl-1H-pyrazole-5-carboxamide</p>	

	propyl) amino] carbonyl} propyl) - 3-methyl-1H-pyrazole-5- carboxamide	
	N-((1R)-3-(butylsulfonyl)-1- {[(1S,2R)-1-(3,5- difluorobenzyl)-3-([1-(3- ethylphenyl)cyclopropyl]amino) -2- hydroxypropyl]amino]carbonyl}p ropyl)-3-methyl-1H-pyrazole-5- carboxamide	
	N-((1R)-3-(butylsulfonyl)-1- {[(1S,2R)-1-(3,5- difluorobenzyl)-3-([1-(3- ethynylphenyl)cyclopropyl]amin o)-2- hydroxypropyl]amino]carbonyl}p ropyl)-3-methyl-1H-pyrazole-5- carboxamide	
	N-[(1R)-3-(butylsulfonyl)-1- ([(1S,2R)-1-(3,5- difluorobenzyl)-2-hydroxy-3- ([1-[3- (trifluoromethyl)phenyl]cyclop ropyl]amino)propyl]amino)carbo nyl)propyl]-3-methyl-1H- pyrazole-5-carboxamide	
	(2R)-N-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-2- {[(methylamino)carbonyl]amino} -4-oxooctanamide	

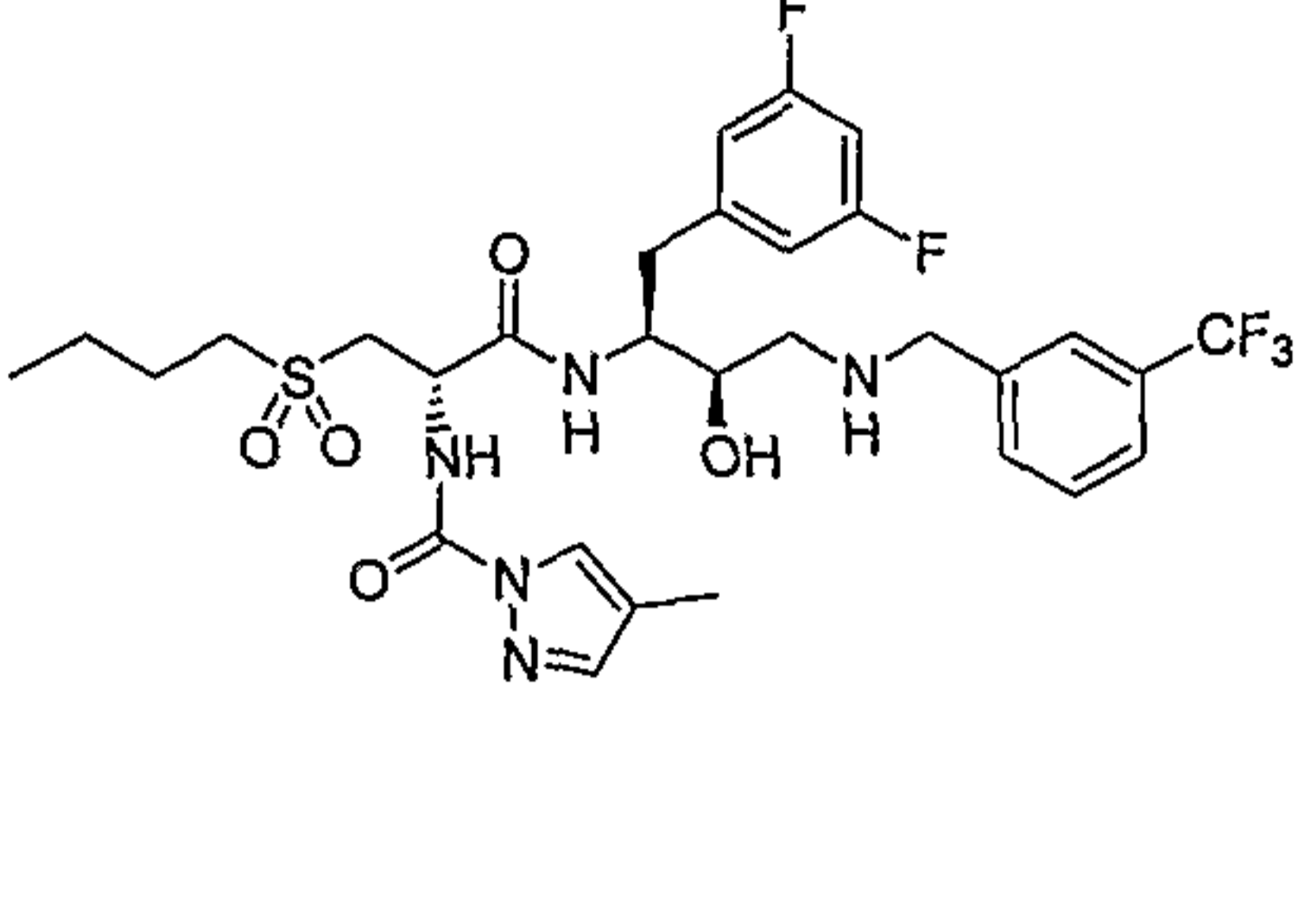
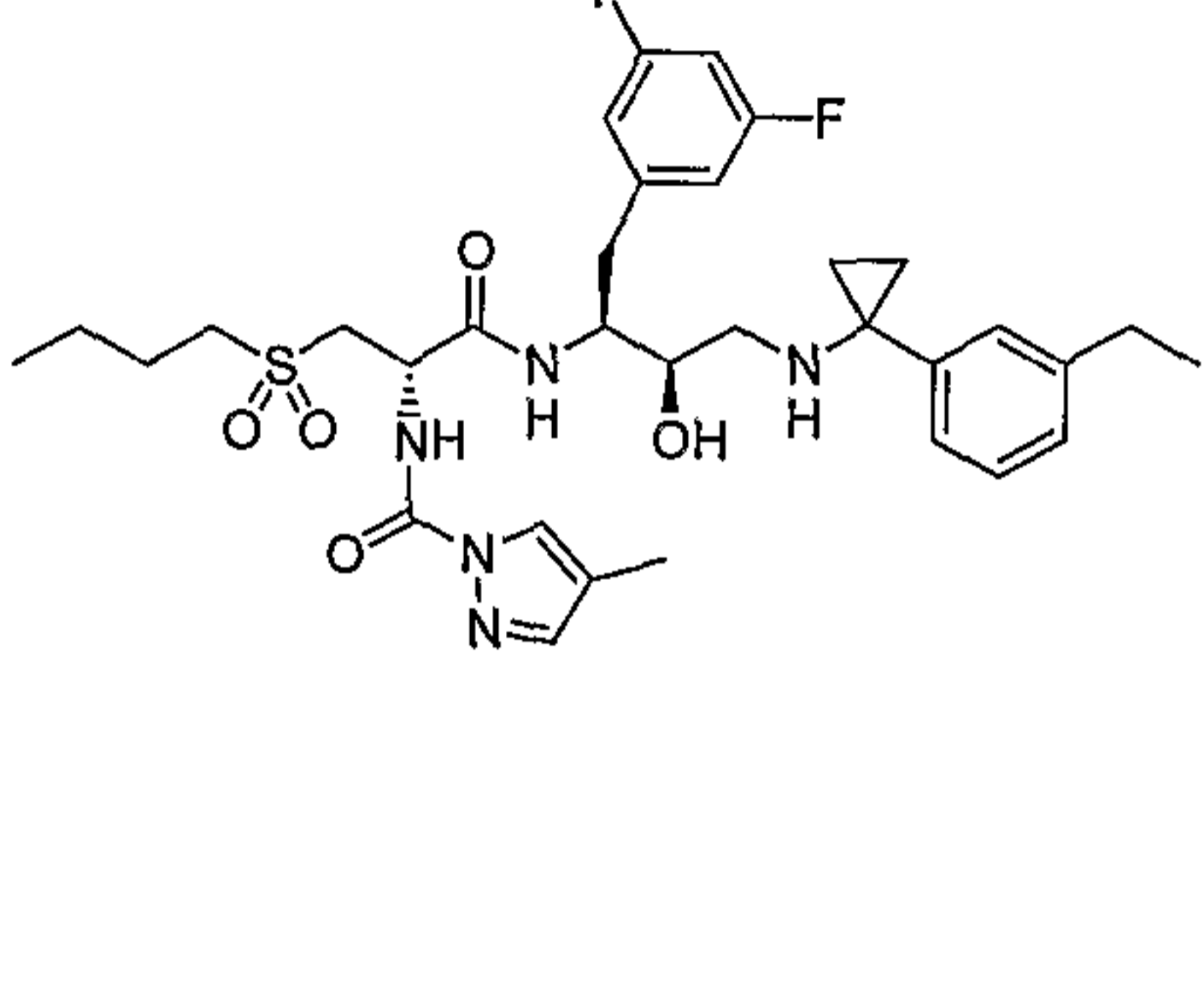
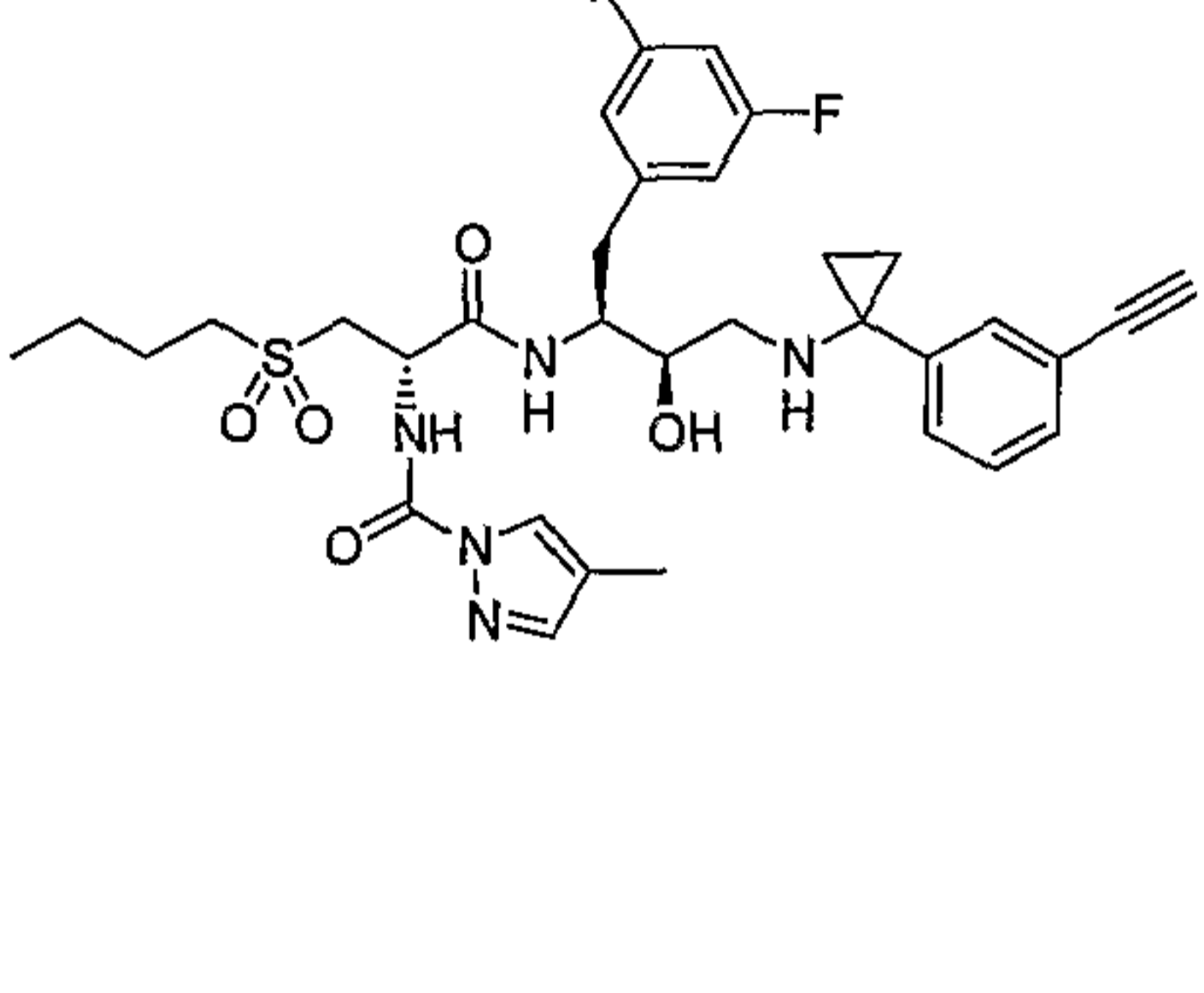
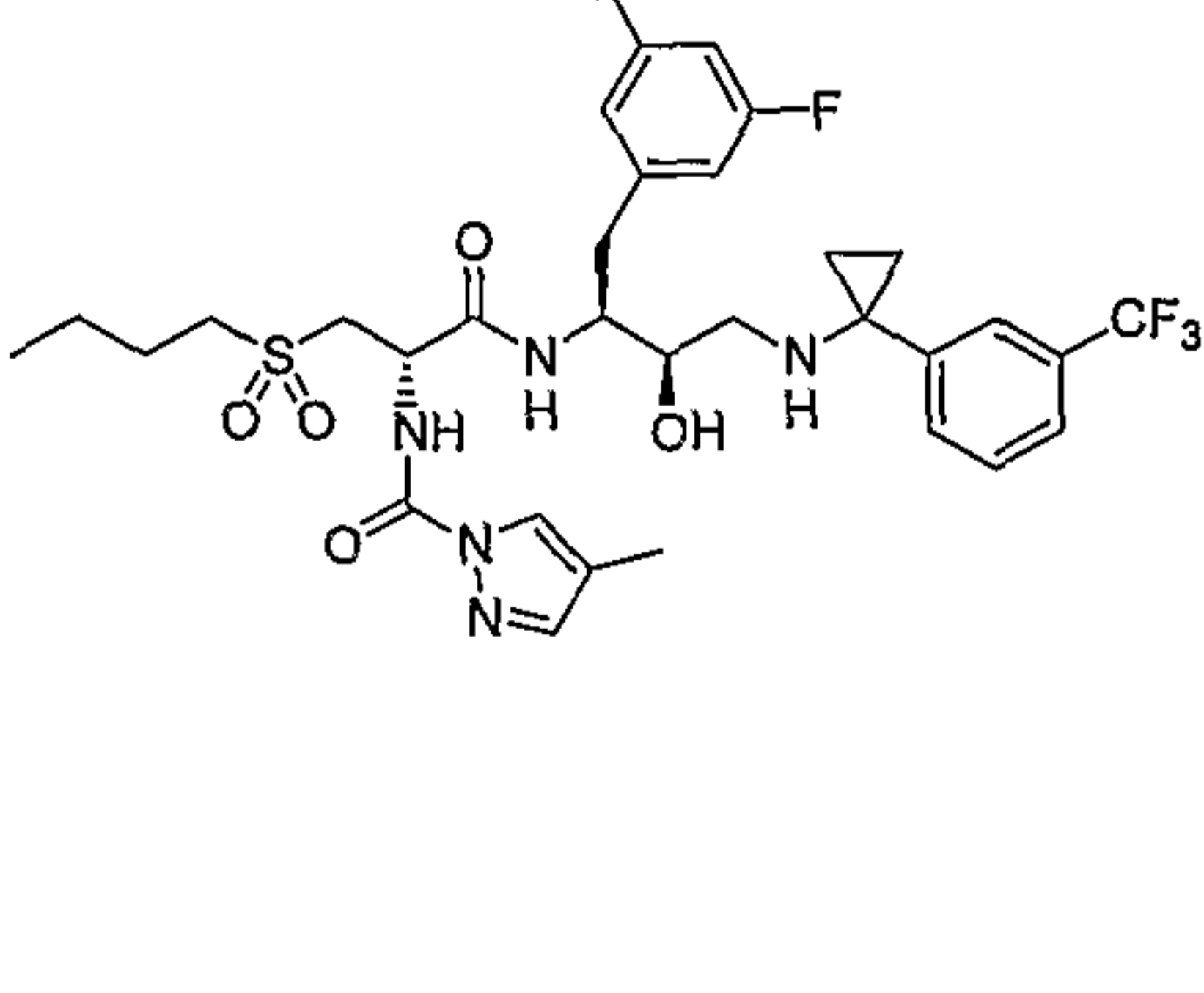
	<p>4-butyl-<math>N^1</math>-{(1<i>S</i>,2<i>R</i>)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-<math>N^2</math>-[(methylamino)carbonyl]-D-homoserinamide</p>	
	<p>3-(2-butyl-1,3-dioxolan-2-yl)-<math>N^1</math>-{(1<i>S</i>,2<i>R</i>)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-<math>N^2</math>-[(methylamino)carbonyl]-D-alaninamide</p>	
	<p>3-(2-butyl-1,3-dioxan-2-yl)-<math>N^1</math>-{(1<i>S</i>,2<i>R</i>)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-<math>N^2</math>-[(methylamino)carbonyl]-D-alaninamide</p>	
	<p>(2<i>R</i>)-<math>N</math>-{(1<i>S</i>,2<i>R</i>)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4,4-difluoro-2-[(methylamino)carbonyl]amino} octanamide</p>	

	<p>(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-fluoro-2-((methylamino)carbonyl)amino)octanamide</p>	
	<p>(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-((methylamino)carbonyl)-5-oxononanamide</p>	
	<p>(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-hydroxy-2-((methylamino)carbonyl)aminononanamide</p>	
	<p>(2R)-4-(2-butyl-1,3-dioxolan-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-((methylamino)carbonyl)aminobutanamide</p>	
	<p>(2R)-4-(2-butyl-1,3-dioxan-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-((methylamino)carbonyl)aminobutanamide</p>	

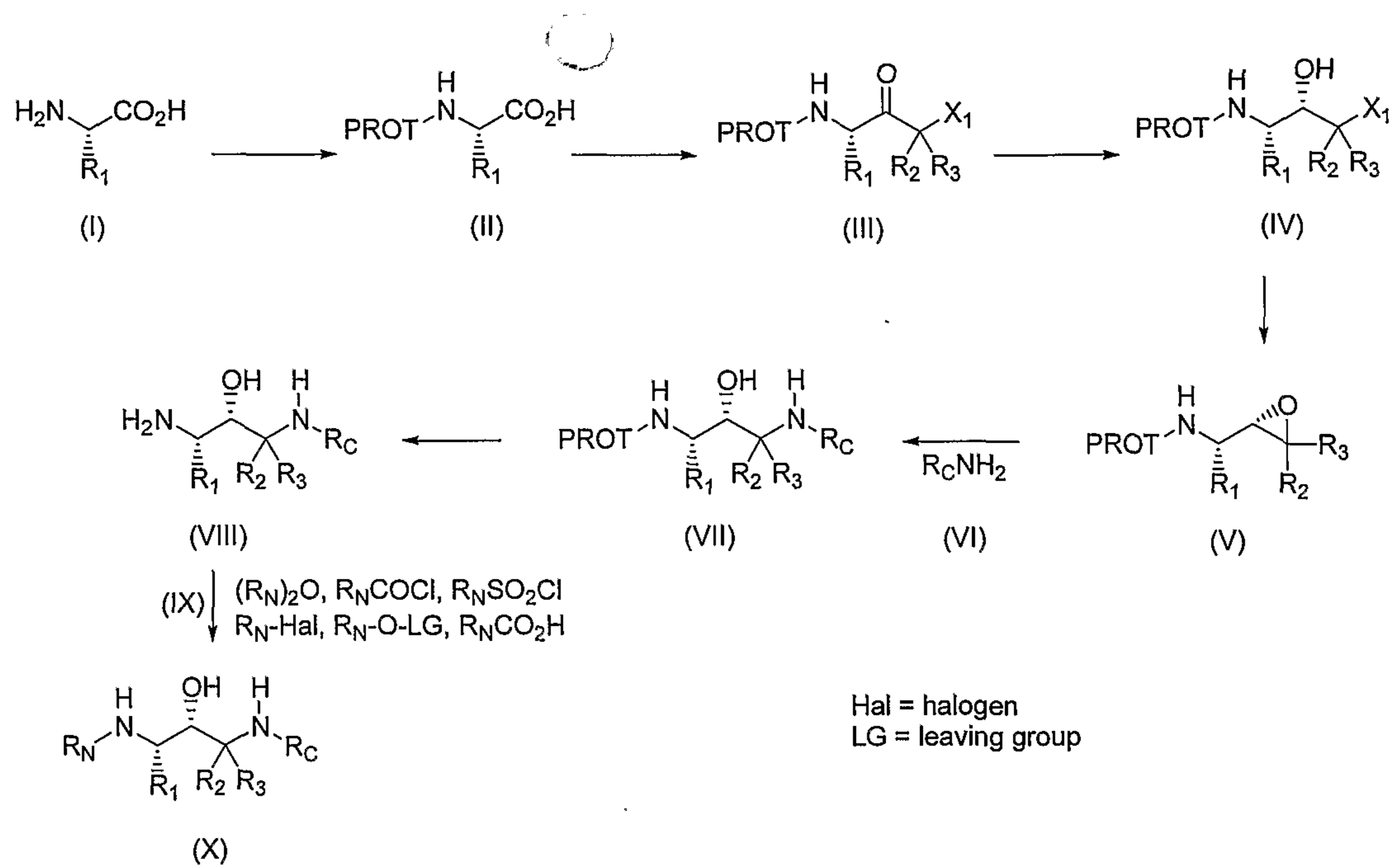
	{ [(methylamino) carbonyl] amino} butanamide	
	(2R)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-fluoro-2-[(methylamino) carbonyl] nonanamide	
	(2R)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5,5-difluoro-2-[(methylamino) carbonyl] nonanamide	
	3-(butylsulfonyl)-N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl]-N <sup>2</sup> -[(methylamino) carbonyl]-D-alaninamide	
	3-(butylsulfonyl)-N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-(trifluoromethyl)benzyl)amino]propyl]-N <sup>2</sup> -[(methylamino) carbonyl]-D-alaninamide	

	<p>3-(butylsulfonyl)-<math>N^1</math>-((1<i>S</i>,2<i>R</i>)-1-(3,5-difluorobenzyl)-3-{{1-(3-ethylphenyl)cyclopropyl}amino}-2-hydroxypropyl)-<math>N^2</math>-[(methylamino)carbonyl]-D-alaninamide</p>	
	<p>3-(butylsulfonyl)-<math>N^1</math>-((1<i>S</i>,2<i>R</i>)-1-(3,5-difluorobenzyl)-3-{{1-(3-ethynylphenyl)cyclopropyl}amino}-2-hydroxypropyl)-<math>N^2</math>-[(methylamino)carbonyl]-D-alaninamide</p>	
	<p>3-(butylsulfonyl)-<math>N^1</math>-[(1<i>S</i>,2<i>R</i>)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3-(trifluoromethyl)phenyl]cyclopropyl}amino)propyl]-<math>N^2</math>-[(methylamino)carbonyl]-D-alaninamide</p>	
	<p>4-Methyl-pyrazole-1-carboxylic acid {2-(butane-1-sulfonyl)-1-[1-(3,5-difluoro-benzyl)-3-(3-ethynyl-benzylamino)-2-hydroxy-propylcarbamoyl]-ethyl}-amide</p>	



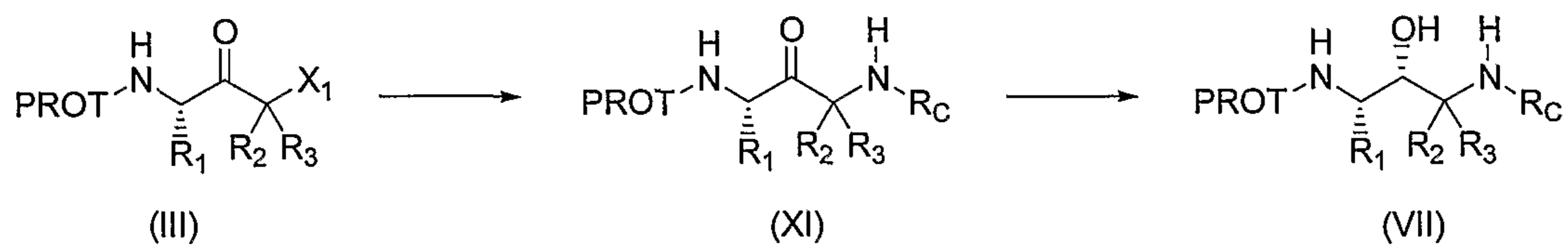
	<p>4-Methyl-pyrazole-1-carboxylic acid {2-(butane-1-sulfonyl)-1-[1-(3,5-difluoro-benzyl)-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propylcarbamoyl]-ethyl}-amide</p>	
	<p>4-Methyl-pyrazole-1-carboxylic acid (2-(butane-1-sulfonyl)-1-{1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propylcarbamoyl}-ethyl)-amide</p>	
	<p>4-Methyl-pyrazole-1-carboxylic acid (2-(butane-1-sulfonyl)-1-{1-(3,5-difluoro-benzyl)-3-[1-(3-ethynyl-1-phenyl)-cyclopropylamino]-2-hydroxy-propylcarbamoyl}-ethyl)-amide</p>	
	<p>4-Methyl-pyrazole-1-carboxylic acid (2-(butane-1-sulfonyl)-1-{1-(3,5-difluoro-benzyl)-2-hydroxy-3-[1-(3-trifluoromethyl-phenyl)-cyclopropylamino]-propylcarbamoyl}-ethyl)-amide</p>	

## SCHEME A

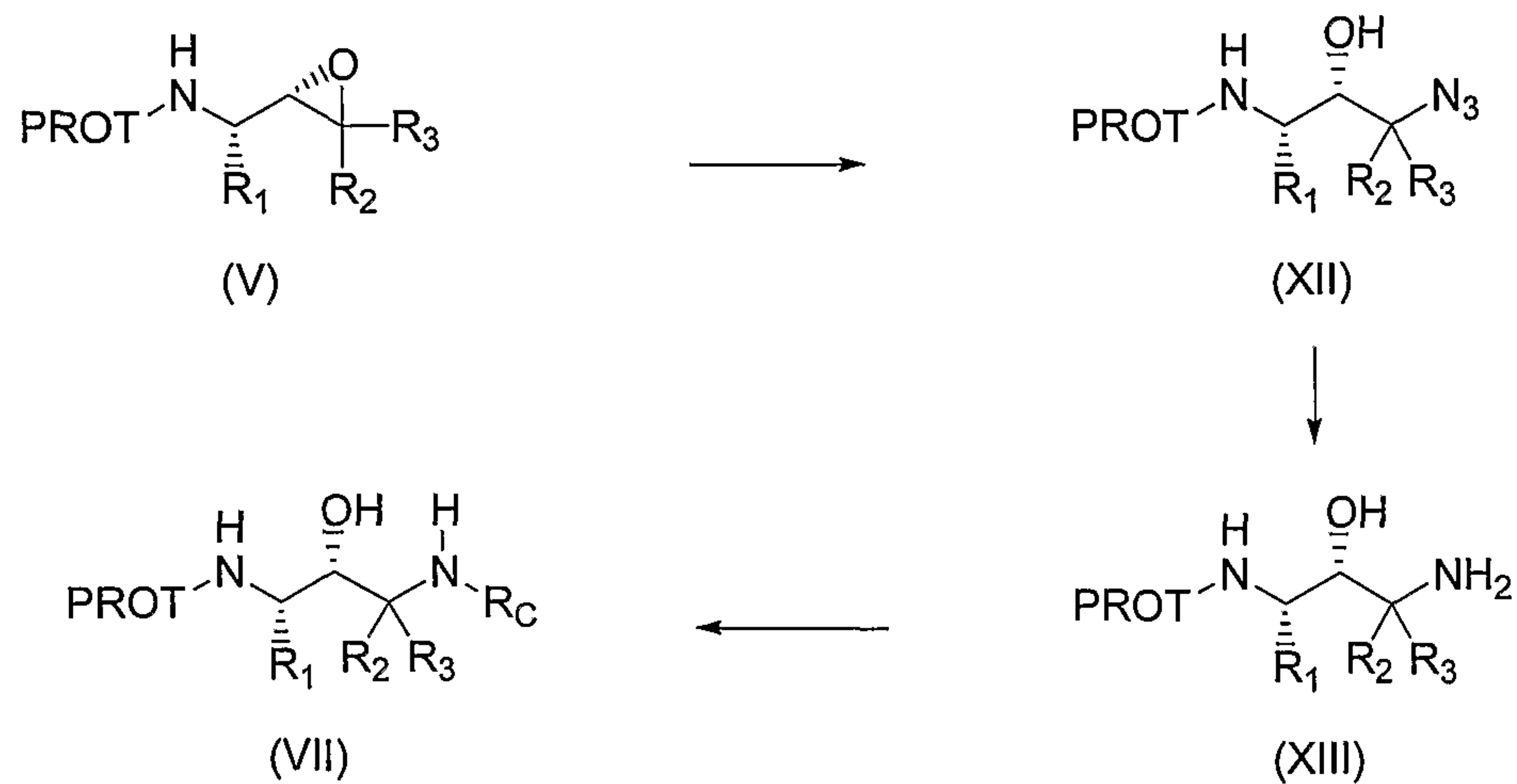


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## SCHEME B

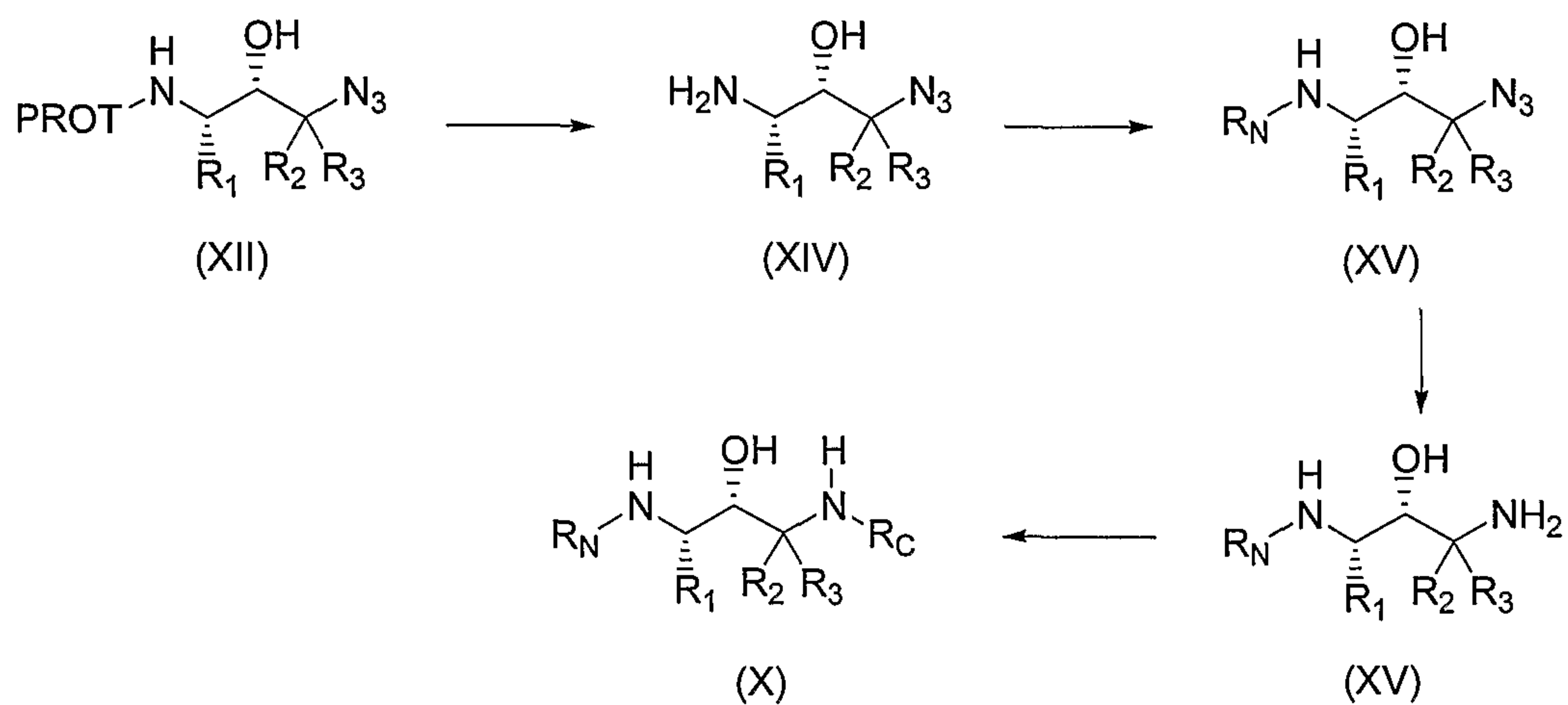


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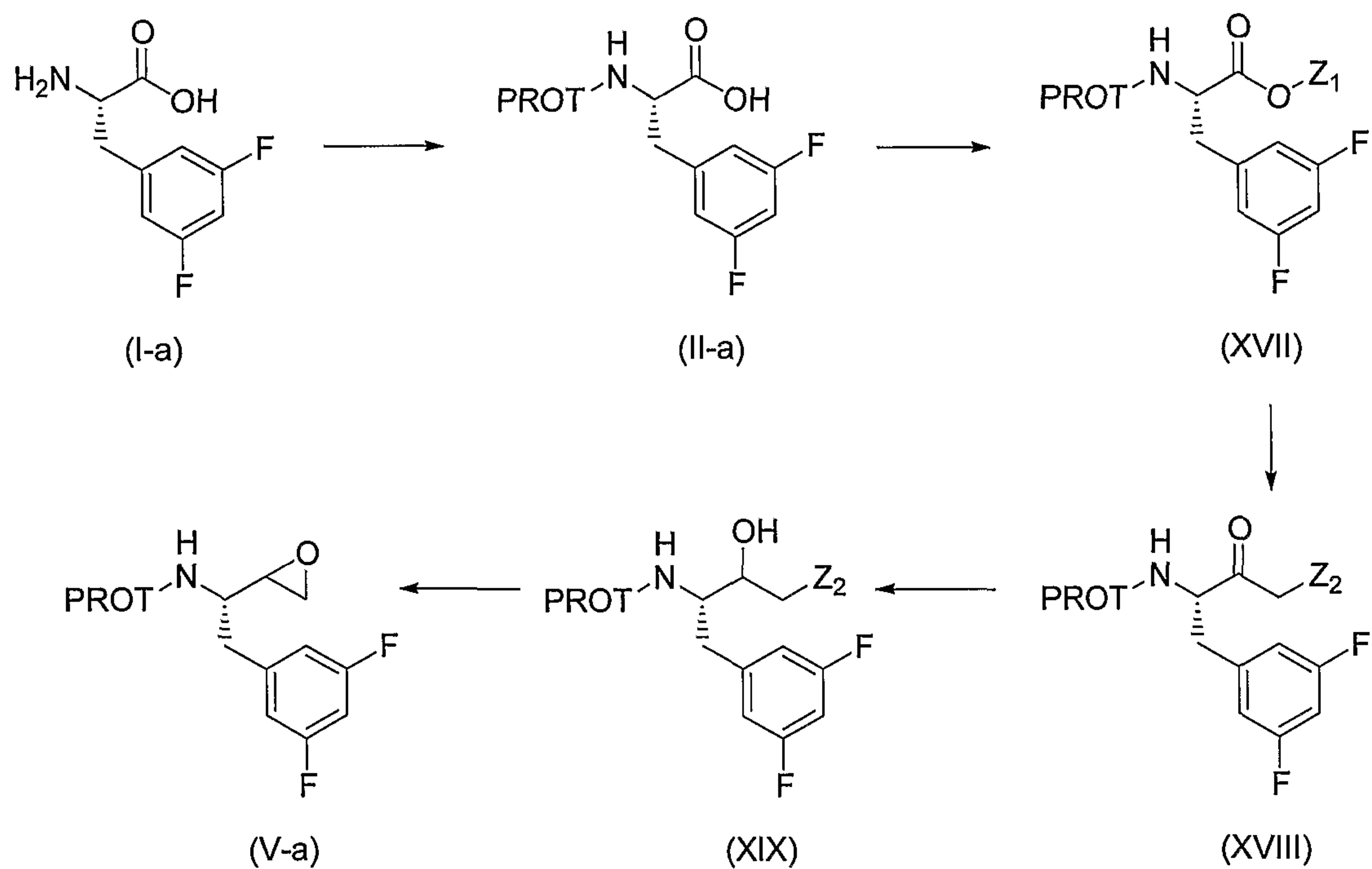


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## SCHEME D

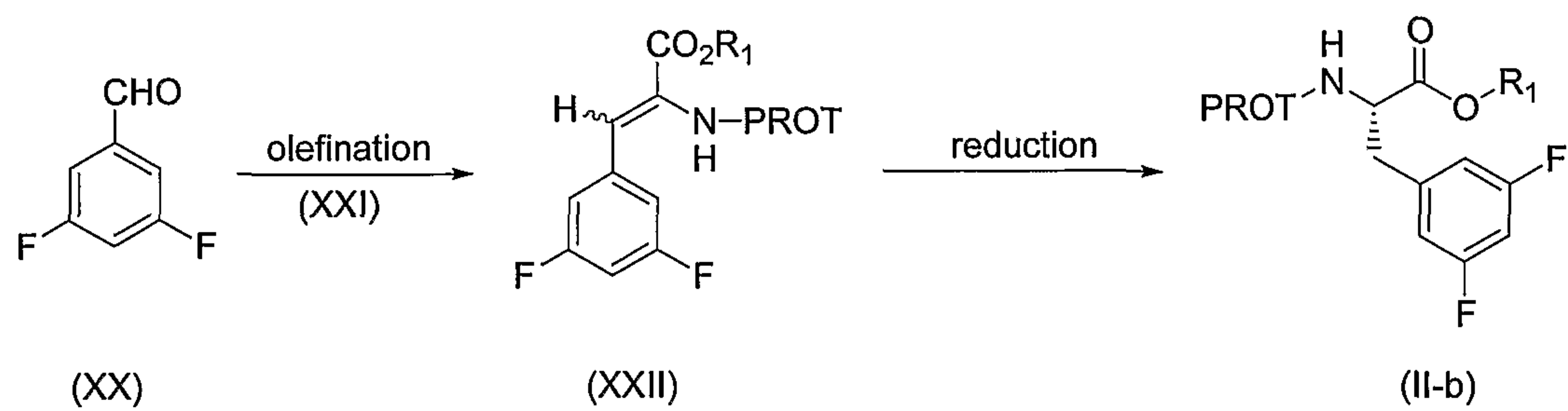


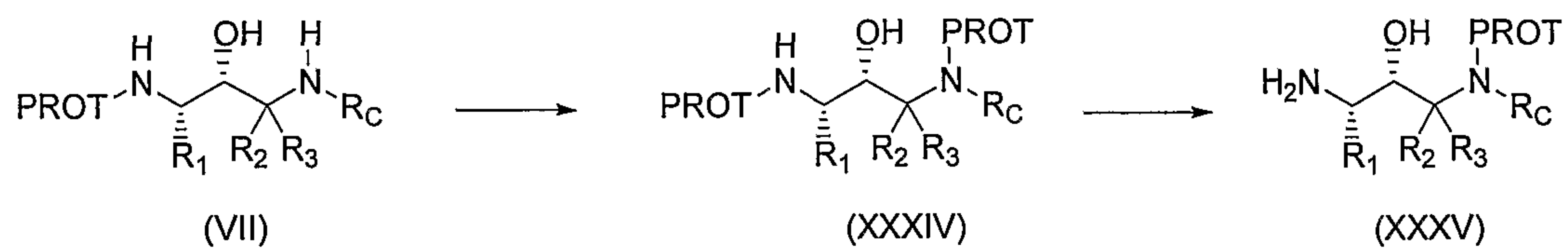
## SCHEME E



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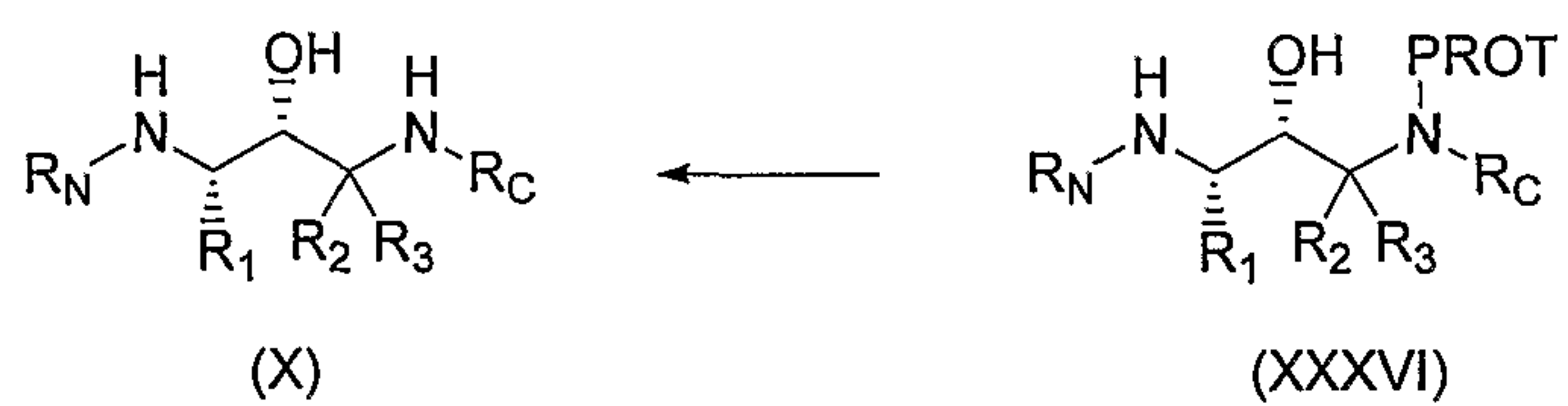
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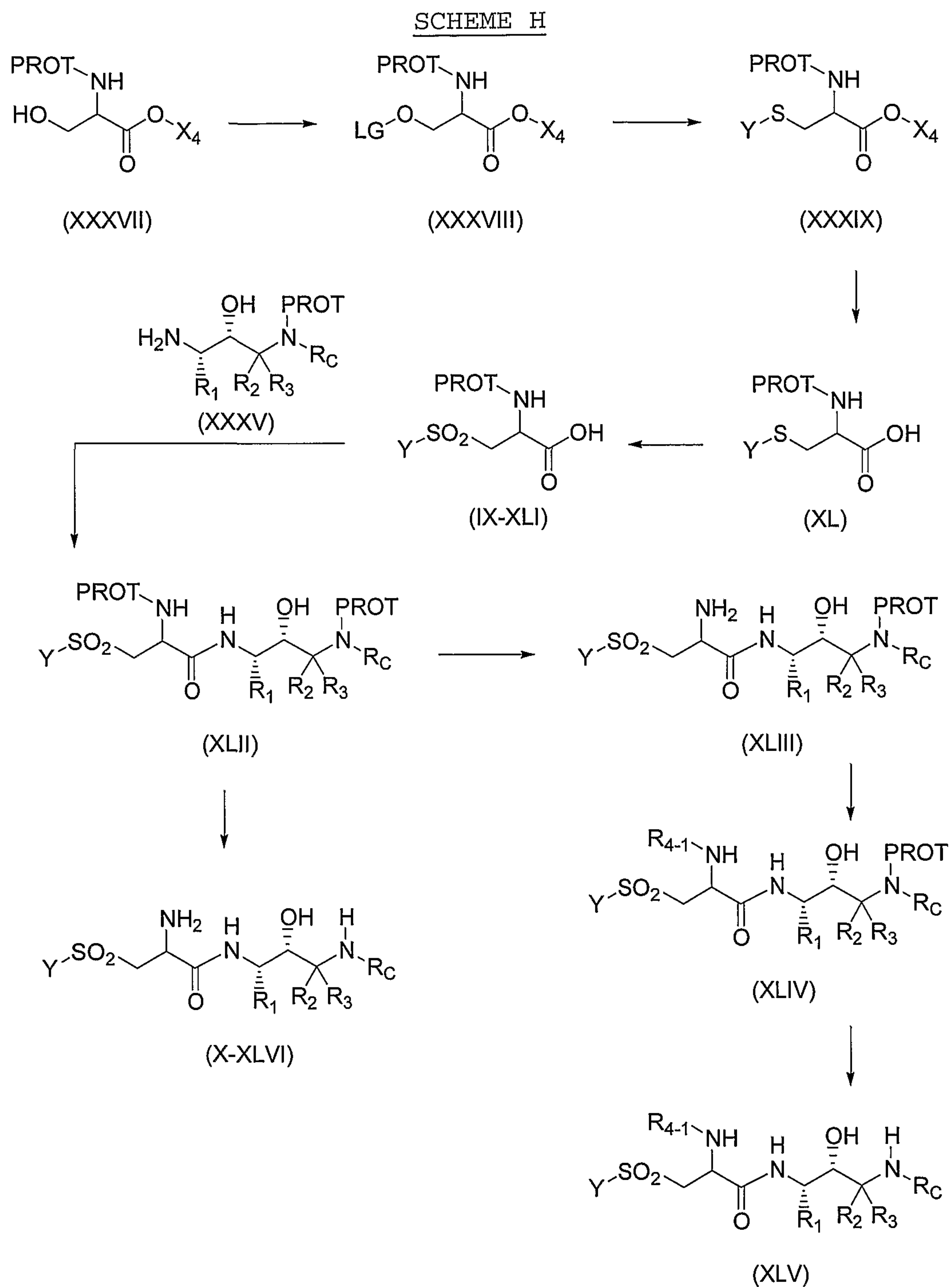


SCHEME G

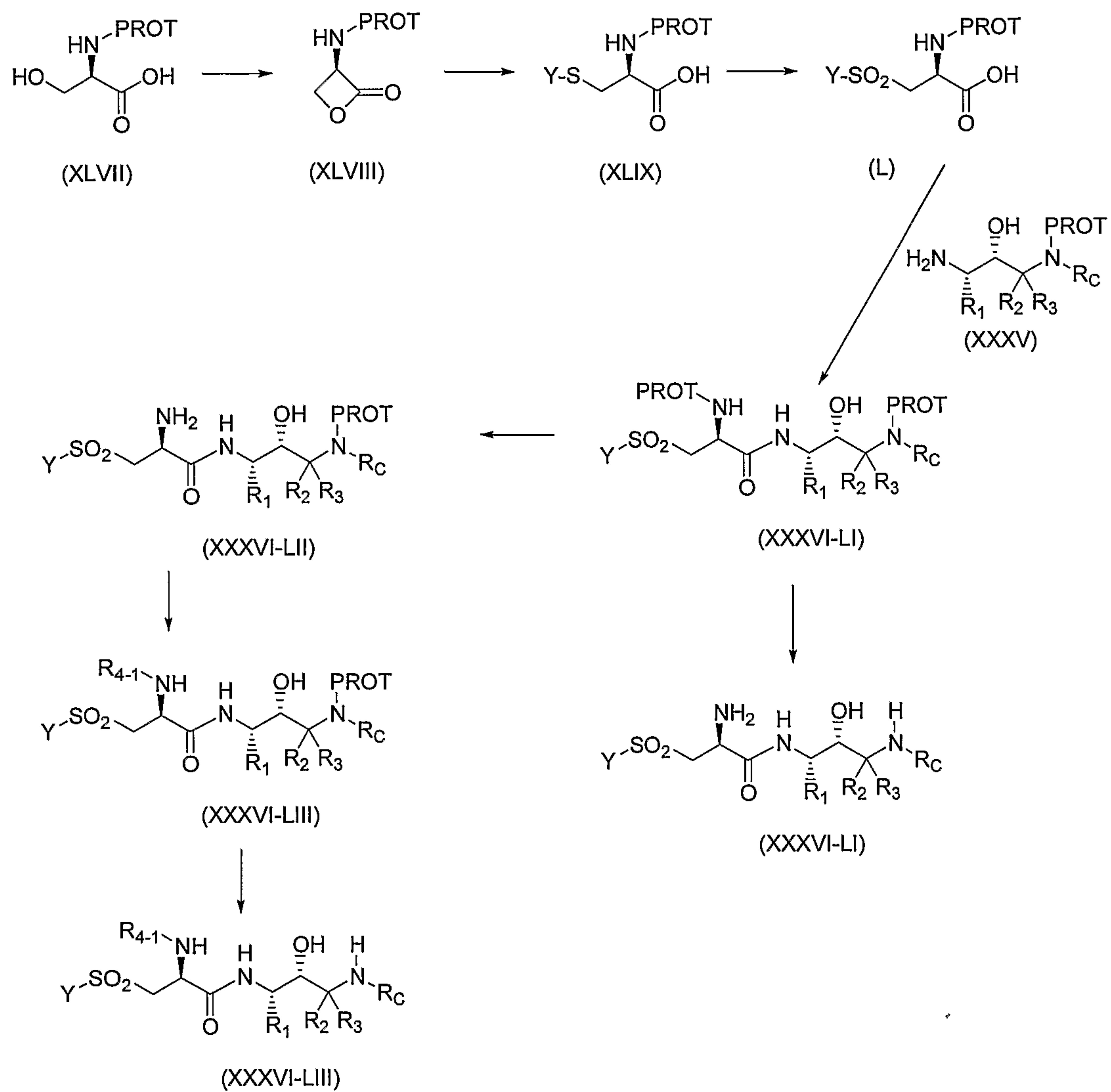
Hal = halogen  
LG = leaving group

$(R_N)_2O, R_NCOCl, R_NSO_2Cl$   
 $R_N-Hal, R_N-O-LG, R_NCO_2H$

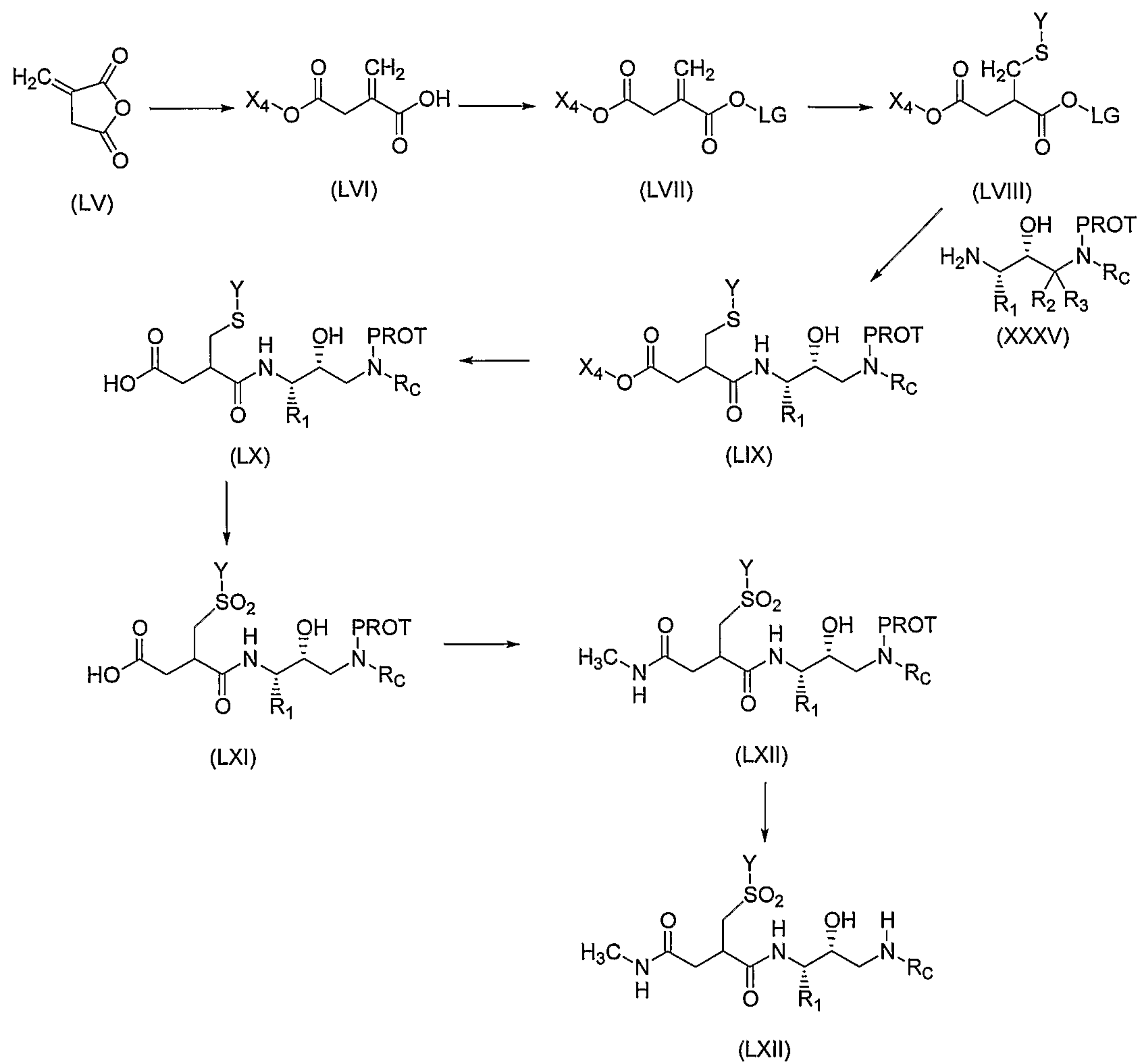




## SCHEME I

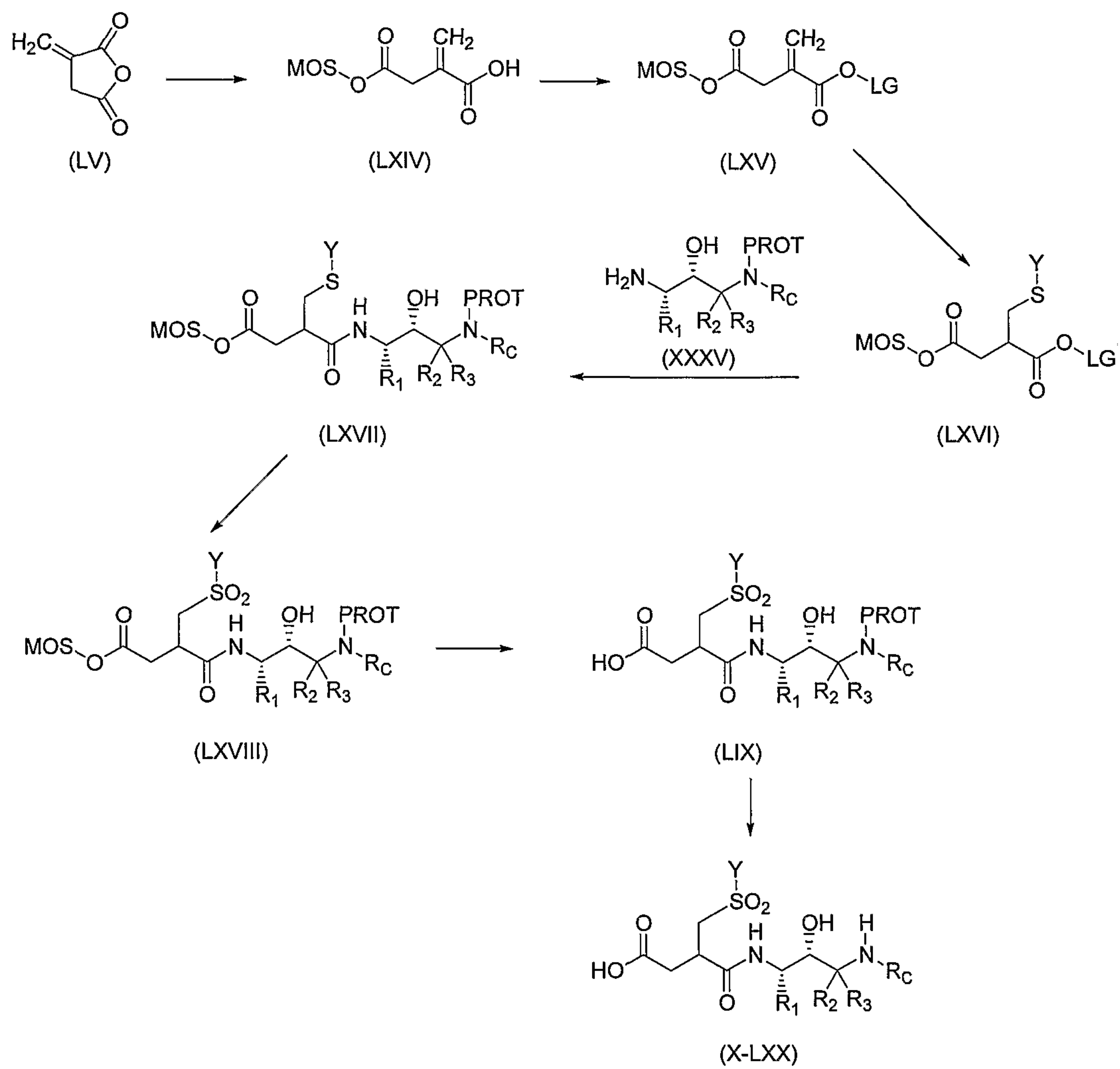


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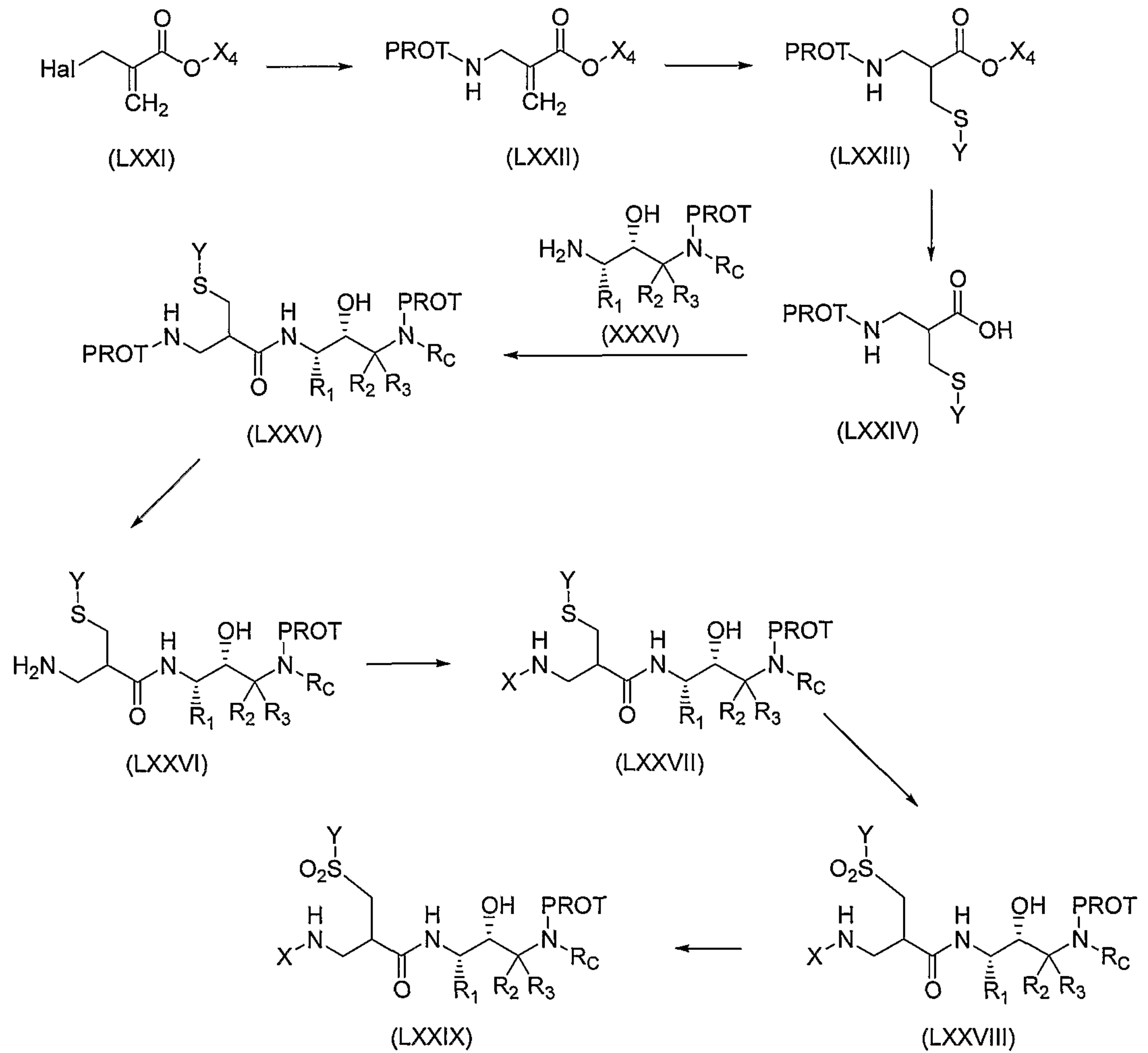




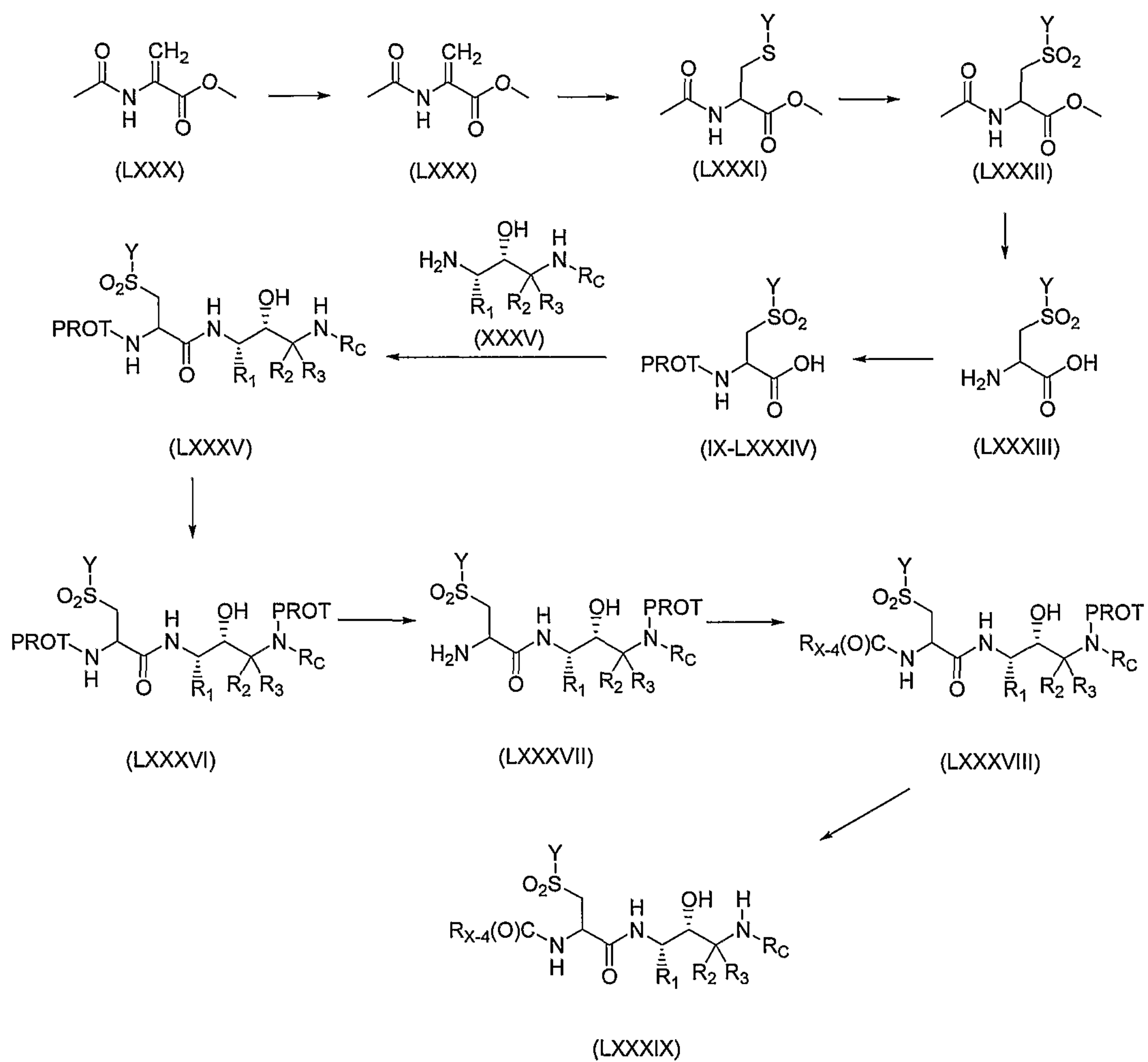
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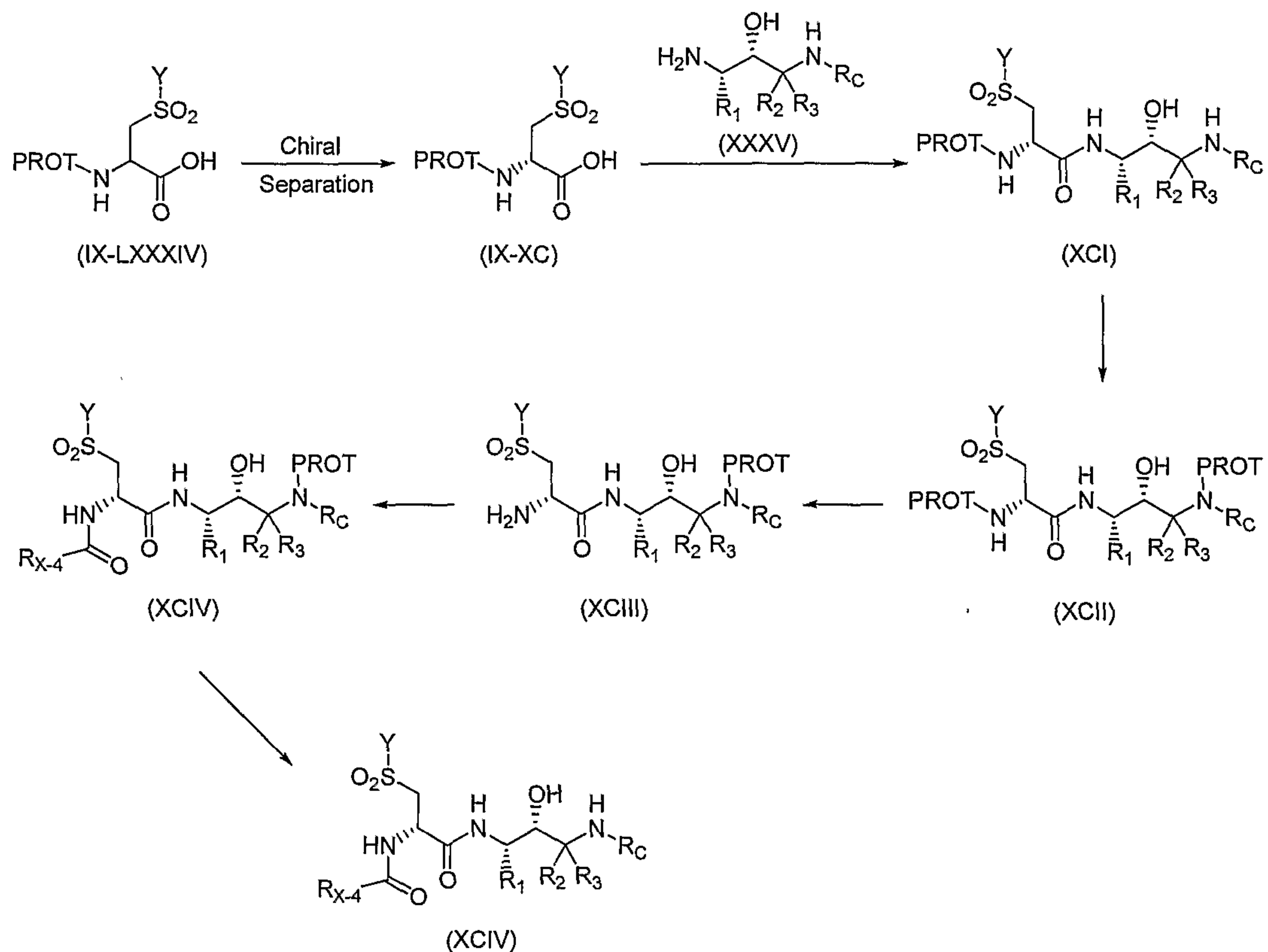
## SCHEME L



## SCHEME M



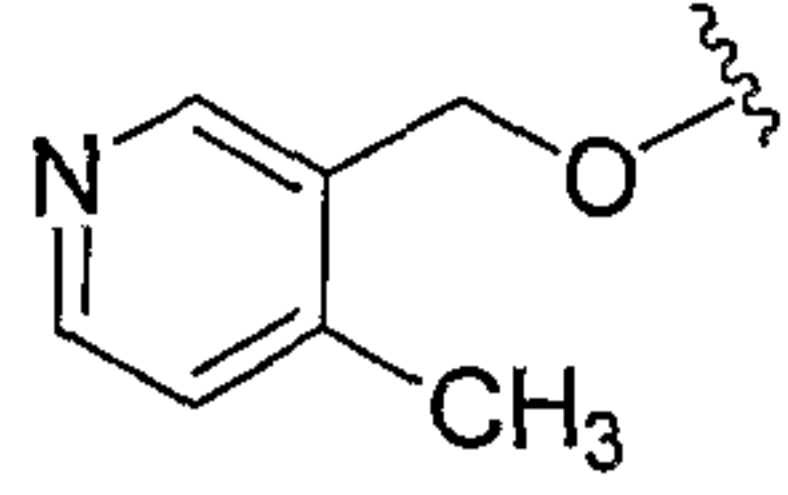
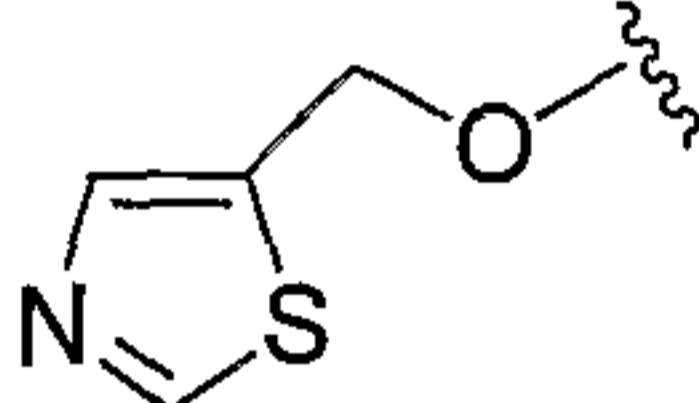
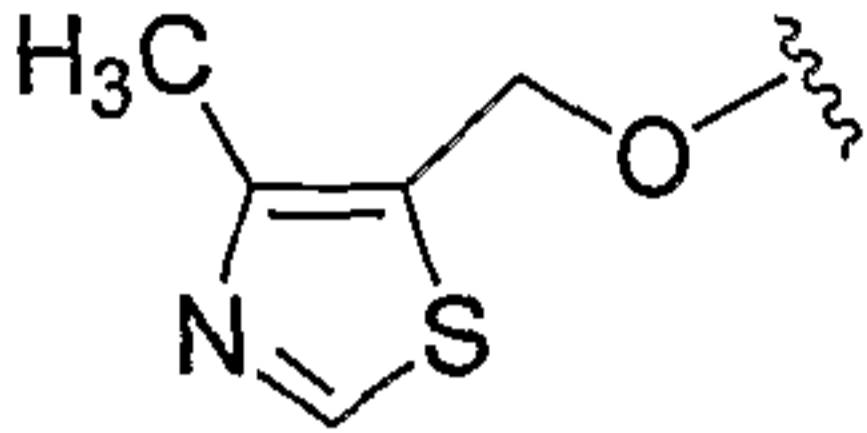
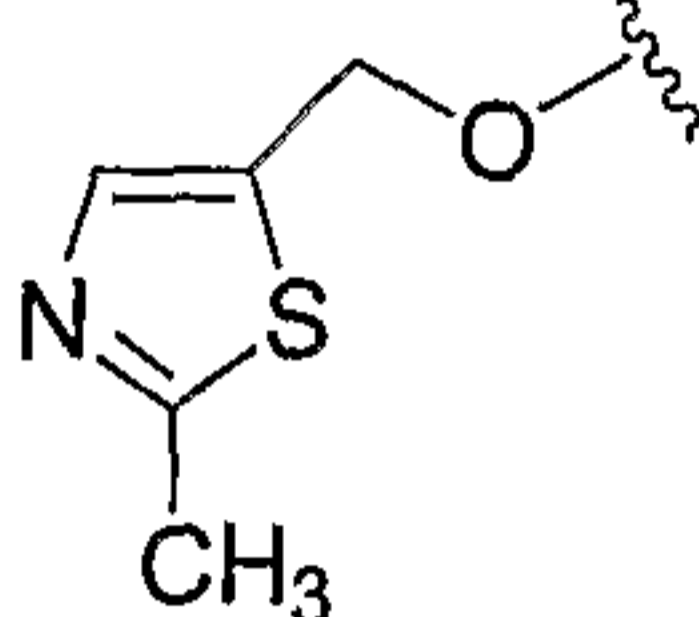
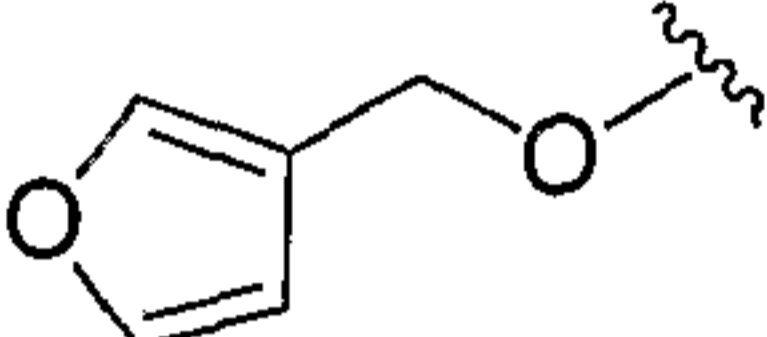
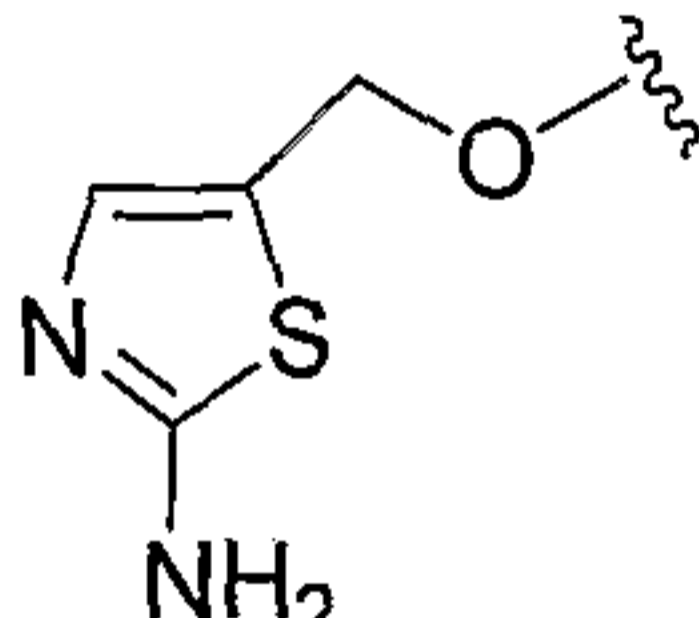
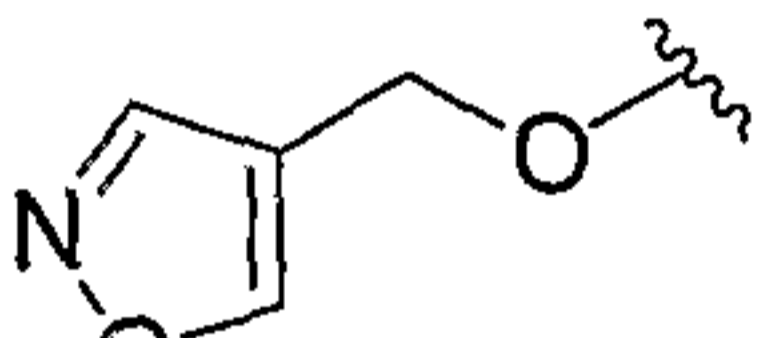
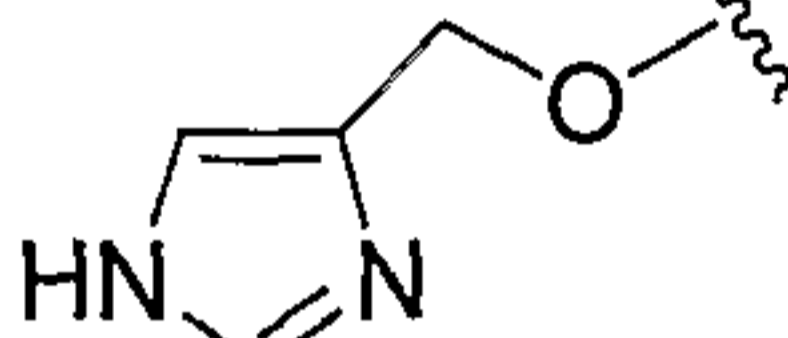
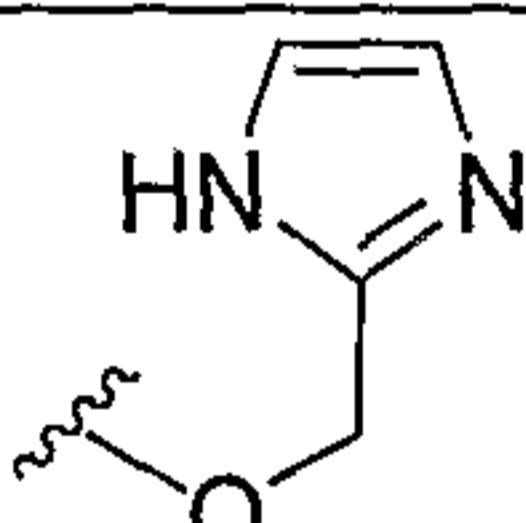
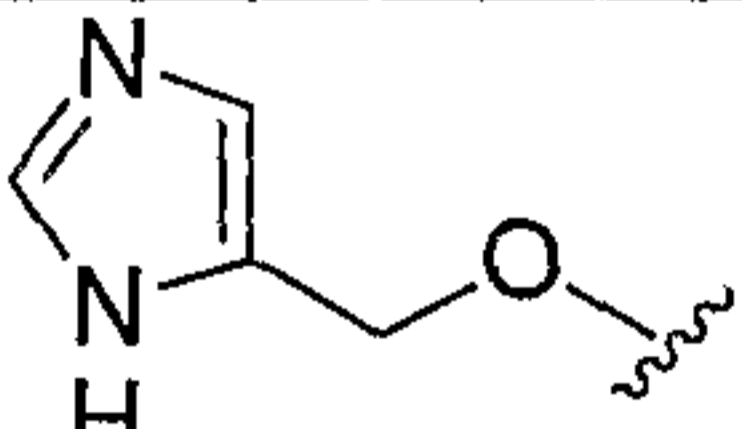
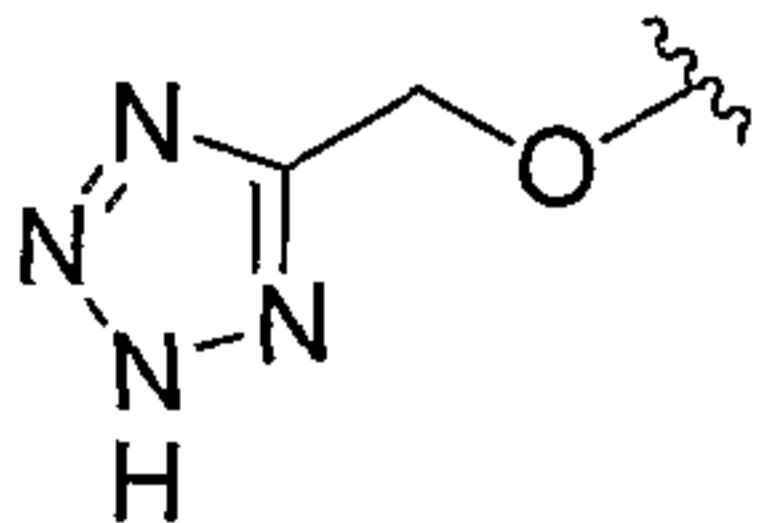
## SCHEME N



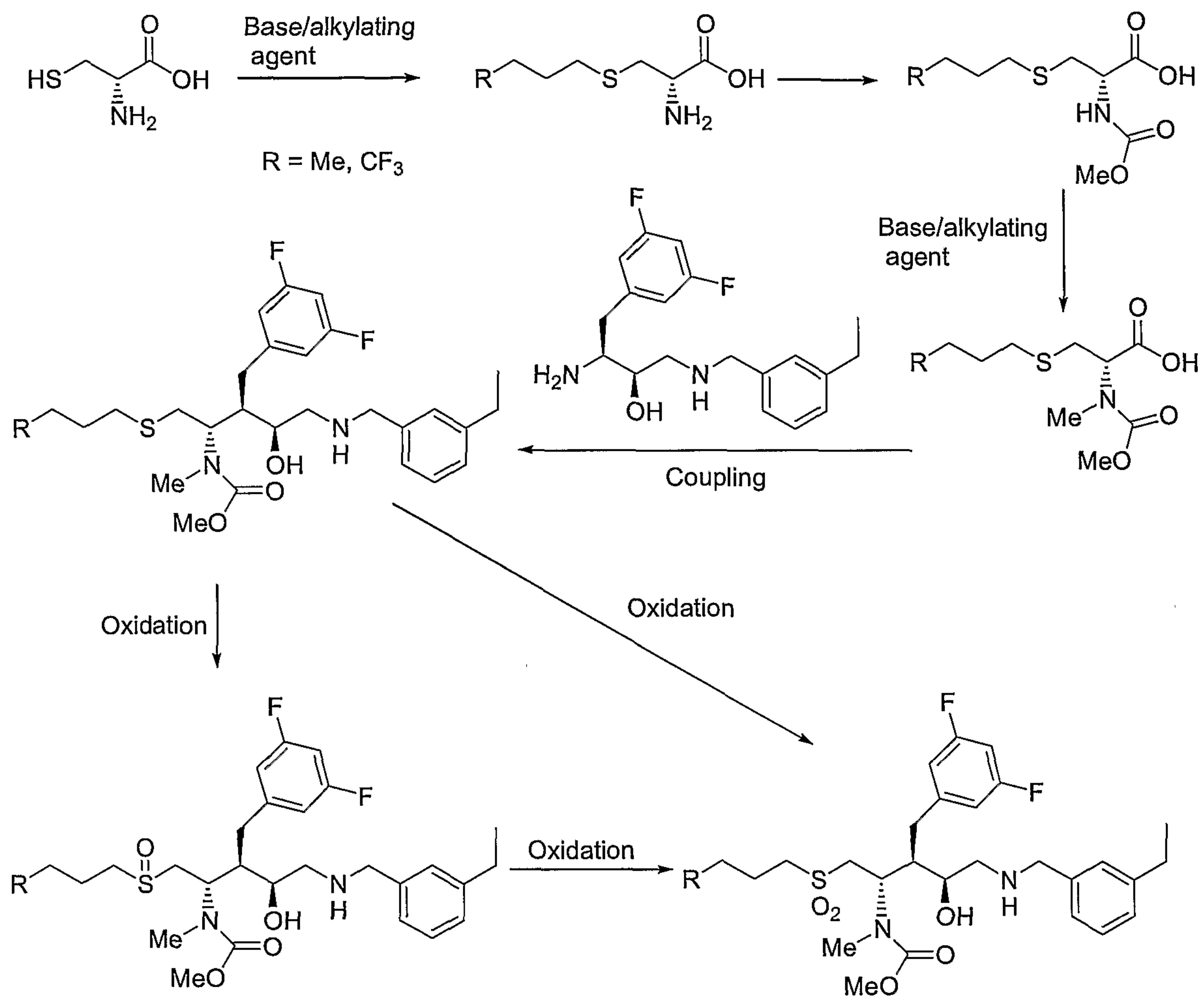
## SCHEME O - Alcohols for Carbamate Formation

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SCHEME P





WO 02/098849

PCT/US02/17698

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Ser Glu Val Lys Met Asp Ala Glu Phe Arg Cys Lys Lys  
 1 5 10

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 <211> 22  
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 <213> Artificial

<220>  
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 <222> (1)..(1)  
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<220>  
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&lt;400&gt; 3

Gly Leu Asn Ile Lys Thr Glu Glu Ile Ser Glu Ile Ser Tyr Glu Val  
 1 5 10 15

Glu Phe Arg Cys Lys Lys  
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<210> 4  
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 <222> (1)..(1)  
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&lt;400&gt; 4

Ala Asp Arg Gly Leu Thr Thr Arg Pro Gly Ser Gly Leu Thr Asn Ile  
 1 5 10 15



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Lys Thr Glu Glu Ile Ser Glu Val Asn Leu Asp Ala Glu Phe Arg Cys  
                   20                                  25                                  30

Lys Lys

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&lt;400&gt; 5

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 1                  5                                  10                                  15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Ala Cys Lys  
                   20                                  25                                  30

Lys

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 <213> Artificial

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PCT/US02/17698

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Cys Gly Gly Ala Asp Arg Gly Leu Thr Thr Arg Pro Gly Ser Gly Leu  
 1 5 10 15

Thr Asn Ile Lys Thr Glu Glu Ile Ser Glu Val Asn Leu Asp Ala Glu  
 20 25 30

Phe

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<400> 7

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Thr Asn Ile Lys Thr Glu Glu Ile Ser Glu Val Asn Leu  
 20 25

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<400> 8

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 1 5

<210> 9  
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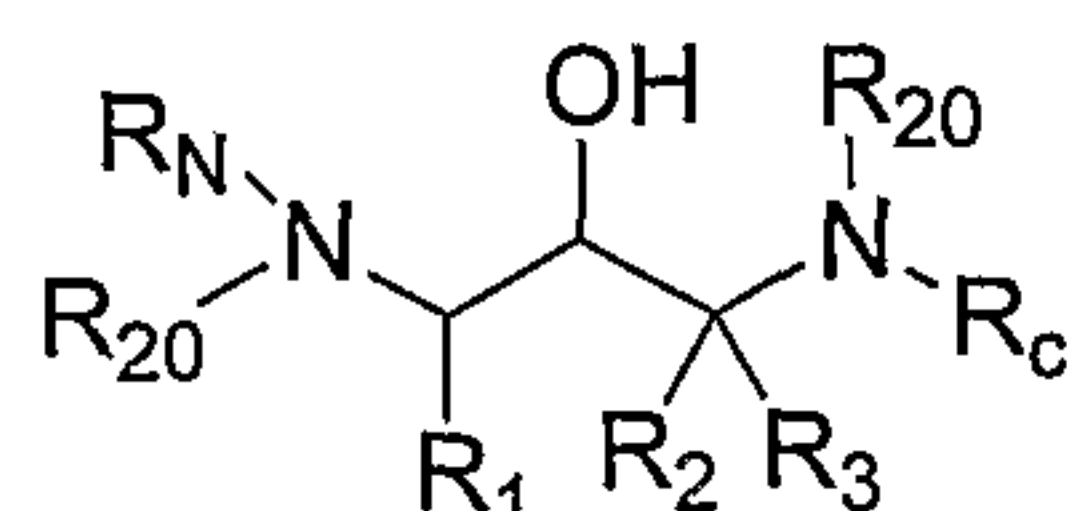
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Ala Asp Arg Gly Leu Thr Thr Arg Pro Gly Ser Gly Leu Thr Asn Ile  
1 5 10 15

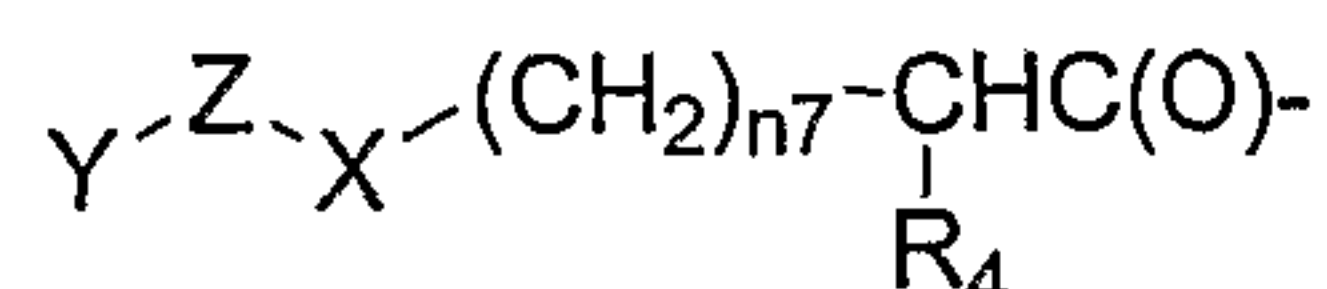
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20 25 30

What is claimed is:

1. A compound of the formula:



- 5 or a pharmaceutically acceptable salt thereof, wherein  
 $R_N$  is:



wherein

- $R_4$  is selected from the group consisting of H;  $NH_2$ ;  $-NH-(CH_2)_{n6}-$   
 10  $R_{4-1}$ ;  $-NHR_8$ ;  $-NR_{50}C(O)R_5$ ;  $C_1-C_4$  alkyl- $NHC(O)R_5$ ;  $-(CH_2)_{0-4}R_8$ ;  $-$   
 $O-C_1-C_4$  alkanoyl; OH;  $C_6-C_{10}$  aryloxy optionally substituted  
 with 1, 2, or 3 groups that are independently halogen,  $C_1-$   
 $C_4$  alkyl,  $-CO_2H$ ,  $-C(O)-C_1-C_4$  alkoxy, or  $C_1-C_4$  alkoxy;  $C_1-C_6$   
 alkoxy; aryl  $C_1-C_4$  alkoxy;  $-NR_{50}CO_2R_{51}$ ;  $-C_1-C_4$  alkyl-  
 15  $NR_{50}CO_2R_{51}$ ;  $-C\equiv N$ ;  $-CF_3$ ;  $-CF_2-CF_3$ ;  $-C\equiv CH$ ;  $-CH_2-CH=CH_2$ ;  $-(CH_2)_{1-}$   
 $4-R_{4-1}$ ;  $-(CH_2)_{1-4}-NH-R_{4-1}$ ;  $-O-(CH_2)_{n6}-R_{4-1}$ ;  $-S-(CH_2)_{n6}-R_{4-1}$ ;  $-$   
 $(CH_2)_{0-4}-NHC(O)-(CH_2)_{0-6}-R_{52}$ ;  $-(CH_2)_{0-4}-R_{53}-(CH_2)_{0-4}-R_{54}$ ;

wherein

$n_6$  is 0, 1, 2, or 3;

- 20  $n_7$  is 0, 1, 2, or 3;

$R_{4-1}$  is selected from the group consisting of  $-SO_2-(C_1-C_8$   
 alkyl),  $-SO-(C_1-C_8$  alkyl),  $-S-(C_1-C_8$  alkyl),  $-S-CO-$   
 $(C_1-C_6$  alkyl),  $-SO_2-NR_{4-2}R_{4-3}$ ;  $-CO-C_1-C_2$  alkyl;  $-CO-NR_{4-}$   
 $3R_{4-4}$ ;

- 25  $R_{4-2}$  and  $R_{4-3}$  are independently H,  $C_1-C_3$  alkyl, or  $C_3-C_6$   
 cycloalkyl;

$R_{4-4}$  is alkyl, arylalkyl, alkanoyl, or arylalkanoyl;

$R_{4-6}$  is H or  $C_1-C_6$  alkyl;

- $R_5$  is selected from the group consisting of  $C_3-C_7$   
 30 cycloalkyl;  $C_1-C_6$  alkyl optionally substituted with  
 1, 2, or 3 groups that are independently halogen,  $-$

NR<sub>6</sub>R<sub>7</sub>, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl, C<sub>5</sub>-C<sub>6</sub>  
 heteroaryl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl,  
 -S-C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>7</sub>, -CO<sub>2</sub>-  
 C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>6</sub>-C<sub>10</sub> aryloxy; heteroaryl optionally  
 5 substituted with 1, 2, or 3 groups that are  
 independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>4</sub>  
 haloalkyl, or OH; heterocycloalkyl optionally  
 substituted with 1, 2, or 3 groups that are  
 independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or  
 10 C<sub>2</sub>-C<sub>4</sub> alkanoyl; aryl optionally substituted with 1,  
 2, 3, or 4 groups that are independently halogen, OH,  
 C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkyl; and -  
 NR<sub>6</sub>R<sub>7</sub>; wherein  
 R<sub>6</sub> and R<sub>7</sub> are independently selected from the group  
 15 consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl,  
 phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl;  
 R<sub>8</sub> is selected from the group consisting of -SO<sub>2</sub>-  
 heteroaryl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heterocycloalkyl, -SO<sub>2</sub>-C<sub>1</sub>-  
 C<sub>10</sub> alkyl, -C(O)NHR<sub>9</sub>, heterocycloalkyl, -S-C<sub>1</sub>-C<sub>6</sub>  
 20 alkyl, -S-C<sub>2</sub>-C<sub>4</sub> alkanoyl, wherein  
 R<sub>9</sub> is aryl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, or H;  
 R<sub>50</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;  
 R<sub>51</sub> is selected from the group consisting of aryl C<sub>1</sub>-C<sub>4</sub>  
 alkyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2,  
 25 or 3 groups that are independently halogen, cyano,  
 heteroaryl, -NR<sub>6</sub>R<sub>7</sub>, -C(O)NR<sub>6</sub>R<sub>7</sub>, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, or  
 -C<sub>1</sub>-C<sub>4</sub> alkoxy; heterocycloalkyl optionally  
 substituted with 1 or 2 groups that are independently  
 C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl,  
 30 aryl C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; alkenyl;  
 alkynyl; heteroaryl optionally substituted with 1, 2,  
 or 3 groups that are independently OH, C<sub>1</sub>-C<sub>4</sub> alkyl,  
 C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub>  
 alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); heteroarylalkyl optionally

substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); aryl; heterocycloalkyl; C<sub>3</sub>-C<sub>8</sub> cycloalkyl; and

5 cycloalkylalkyl; wherein the aryl; heterocycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and cycloalkylalkyl groups are optionally substituted with 1, 2, 3, 4 or 5 groups that are independently halogen, CN, NO<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, hydroxy, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy

10 C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> thioalkoxy, C<sub>1</sub>-C<sub>6</sub> thioalkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkoxy;

R<sub>52</sub> is heterocycloalkyl, heteroaryl, aryl, cycloalkyl, -S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -C(O)NH(alkyl),

15 -C(O)N(alkyl)(alkyl), -CO<sub>2</sub>-alkyl, -NHS(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(alkyl)S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -S(O)<sub>0-2</sub>-heteroaryl, -S(O)<sub>0-2</sub>-aryl, -NH(arylalkyl), -N(alkyl)(arylalkyl), thioalkoxy, or alkoxy, each of which is optionally substituted with 1, 2, 3, 4, or 5

20 groups that are independently alkyl, alkoxy, thioalkoxy, halogen, haloalkyl, haloalkoxy, alkanoyl, NO<sub>2</sub>, CN, alkoxy carbonyl, or aminocarbonyl;

R<sub>53</sub> is absent, -O-, -C(O)-, -NH-, -N(alkyl)-, -NH-S(O)<sub>0-2</sub>-, -N(alkyl)-S(O)<sub>0-2</sub>-, -S(O)<sub>0-2</sub>-NH-, -S(O)<sub>0-2</sub>-N(alkyl)-, -NH-C(S)-, or -N(alkyl)-C(S)-;

25 R<sub>54</sub> is heteroaryl, aryl, arylalkyl, heterocycloalkyl, CO<sub>2</sub>H, -CO<sub>2</sub>-alkyl, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -C(O)NH<sub>2</sub>, C<sub>1</sub>-C<sub>8</sub> alkyl, OH, aryloxy, alkoxy, arylalkoxy, NH<sub>2</sub>, NH(alkyl), N(alkyl)(alkyl), or -C<sub>1</sub>-C<sub>6</sub> alkyl-CO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, each of which is optionally

30 substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, CO<sub>2</sub>H, -CO<sub>2</sub>-alkyl, thioalkoxy, halogen, haloalkyl, haloalkoxy,

hydroxyalkyl, alkanoyl, NO<sub>2</sub>, CN, alkoxy carbonyl, or aminocarbonyl;

X is selected from the group consisting of -C<sub>1</sub>-C<sub>6</sub> alkylidene optionally optionally substituted with 1, 2, or 3 methyl groups; and -NR<sub>4-6</sub>-; or

R<sub>4</sub> and R<sub>4-6</sub> combine to form -(CH<sub>2</sub>)<sub>n<sub>10</sub></sub>-, wherein n<sub>10</sub> is 1, 2, 3, or 4;

Z is selected from the group consisting of a bond; SO<sub>2</sub>; SO; S; and C(O);

Y is selected from the group consisting of H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl; C<sub>6</sub>-C<sub>10</sub> aryl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from the group consisting of halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C<sub>3</sub>-C<sub>8</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, and halogen; alkoxy; aryl optionally substituted with halogen, alkyl, alkoxy, CN or NO<sub>2</sub>; arylalkyl optionally substituted with halogen, alkyl, alkoxy, CN or NO<sub>2</sub>; wherein

Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or

Y<sub>1</sub>, Y<sub>2</sub> and the nitrogen to which they are attached form a ring selected from the group consisting of piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen;

R<sub>20</sub> at each occurrence is independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkanoyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups independently selected from halogen, alkyl, hydroxy, alkoxy, and NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>, wherein

R<sub>26</sub> is selected from the group consisting of -C(O)-, -SO<sub>2</sub>-, -CO<sub>2</sub>-, -C(O)NH-, and -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-;

R<sub>27</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, heterocycloalkyl, and heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, haloalkyl, hydroxyalkyl, -C(O)NH<sub>2</sub>, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);

R<sub>1</sub> is -(CH<sub>2</sub>)<sub>1-2</sub>-S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), or

C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, OH, =O, -SH, -C≡N, -CF<sub>3</sub>, -C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R'-, -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or

C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino, or

aryl, heteroaryl, heterocyclyl, -C<sub>1</sub>-C<sub>6</sub> alkyl-aryl, -C<sub>1</sub>-C<sub>6</sub> alkyl-heteroaryl, or -C<sub>1</sub>-C<sub>6</sub> alkyl-heterocyclyl, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NR<sub>105</sub>R'<sub>105</sub>, -CO<sub>2</sub>R, -N(R)COR', or -N(R)SO<sub>2</sub>R', -C(=O)-(C<sub>1</sub>-C<sub>4</sub>) alkyl, -SO<sub>2</sub>-amino, -SO<sub>2</sub>-



- mono or dialkylamino, -C(=O)-amino, -C(=O)-mono or dialkylamino, -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub>) alkyl, or -C<sub>1</sub>-C<sub>6</sub> alkoxy optionally substituted with 1, 2, or 3 groups which are independently a halogen, or
- 5 C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, -C<sub>1</sub>-C<sub>6</sub> alkyl and mono- or dialkylamino, or
- 10 C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, -C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, mono- or dialkylamino and -C<sub>1</sub>-C<sub>3</sub> alkyl, or
- 15 C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>10</sub> alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, C<sub>1</sub>-C<sub>6</sub> alkyl and mono- or dialkylamino; and
- the heterocyclyl group is optionally further substituted with oxo;
- 20 R and R' independently are hydrogen or C<sub>1</sub>-C<sub>10</sub> alkyl;
- R<sub>2</sub> is selected from the group consisting of H; C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with 1, 2, or 3 substituents that are independently selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy,
- 25 and -NR<sub>1-a</sub>R<sub>1-b</sub>; wherein
- R<sub>1-a</sub> and R<sub>1-b</sub> are -H or C<sub>1</sub>-C<sub>6</sub> alkyl; -(CH<sub>2</sub>)<sub>0-4</sub>-aryl; -(CH<sub>2</sub>)<sub>0-4</sub>-heteroaryl; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkynyl; -CONR<sub>N-2</sub>R<sub>N-3</sub>; -SO<sub>2</sub>NR<sub>N-2</sub>R<sub>N-3</sub>; -CO<sub>2</sub>H; and -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl);
- 30 R<sub>3</sub> is selected from the group consisting of H; C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -

NR<sub>1-a</sub>R<sub>1-b</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-aryl; -(CH<sub>2</sub>)<sub>0-4</sub>-heteroaryl; C<sub>2</sub>-C<sub>6</sub> alkenyl;  
 C<sub>2</sub>-C<sub>6</sub> alkynyl; -CO-NR<sub>N-2</sub>R<sub>N-3</sub>; -SO<sub>2</sub>-NR<sub>N-2</sub>R<sub>N-3</sub>; -CO<sub>2</sub>H; and -CO-  
 O-(C<sub>1</sub>-C<sub>4</sub> alkyl);

or

5 R<sub>2</sub>, R<sub>3</sub> and the carbon to which they are attached form a  
 carbocycle of three thru seven carbon atoms, wherein one  
 carbon atom is optionally replaced by a group selected  
 from-O-, -S-, -SO<sub>2</sub>-, or -NR<sub>N-2</sub>-;

R<sub>c</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>10</sub> alkyl  
 10 optionally substituted with 1, 2, or 3 groups  
 independently selected from the group consisting of R<sub>205</sub>,  
 -OC=ONR<sub>235</sub>R<sub>240</sub>, -S(=O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), -SH, -NR<sub>235</sub>C=ONR<sub>235</sub>R<sub>240</sub>,  
 -C=ONR<sub>235</sub>R<sub>240</sub>, and -S(=O)<sub>2</sub>NR<sub>235</sub>R<sub>240</sub>; -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>8</sub>)  
 cycloalkyl wherein the cycloalkyl is optionally  
 15 substituted with 1, 2, or 3 groups independently selected  
 from the group consisting of R<sub>205</sub>, -CO<sub>2</sub>H, and -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub>  
 alkyl); -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl; -  
 (CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocycloalkyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl-  
 heteroaryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl-heterocycloalkyl;  
 20 -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl-aryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl-aryl; -  
 (CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl-heterocycloalkyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-  
 heteroaryl-heteroaryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocycloalkyl-  
 heteroaryl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocycloalkyl-  
 heterocycloalkyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocycloalkyl-aryl;  
 25 -[C(R<sub>255</sub>)(R<sub>260</sub>)]<sub>1-3</sub>-CO-N-(R<sub>255</sub>)<sub>2</sub>; -CH(aryl)<sub>2</sub>; -CH(heteroaryl)<sub>2</sub>;  
 -CH(heterocycloalkyl)<sub>2</sub>; -CH(aryl)(heteroaryl);  
 cyclopentyl, cyclohexyl, or cycloheptyl ring fused to  
 aryl, heteroaryl, or heterocycloalkyl wherein one carbon  
 of the cyclopentyl, cyclohexyl, or cycloheptyl is  
 30 optionally replaced with NH, NR<sub>215</sub>, O, or S(=O)<sub>0-2</sub>, and  
 wherein the cyclopentyl, cyclohexyl, or cycloheptyl group  
 can be optionally substituted with 1 or 2 groups that are  
 independently R<sub>205</sub> or =O; -CO-NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 C<sub>2</sub>-C<sub>10</sub> alkenyl optionally substituted with 1, 2, or 3 R<sub>205</sub>

groups; C<sub>2</sub>-C<sub>10</sub> alkynyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -(CH<sub>2</sub>)<sub>0-1</sub>-CH((CH<sub>2</sub>)<sub>0-6</sub>-OH)-(CH<sub>2</sub>)<sub>0-1</sub>-aryl; -(CH<sub>2</sub>)<sub>0-1</sub>-CHR<sub>C-6</sub>-(CH<sub>2</sub>)<sub>0-1</sub>-heteroaryl; -CH(-aryl or -heteroaryl)-CO-O(C<sub>1</sub>-C<sub>4</sub> alkyl); -CH(-CH<sub>2</sub>-OH)-CH(OH)-phenyl-NO<sub>2</sub>; (C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-OH; -CH<sub>2</sub>-NH-CH<sub>2</sub>-CH(-O-CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>; -H; and -(CH<sub>2</sub>)<sub>0-6</sub>-C(=NR<sub>235</sub>)(NR<sub>235</sub>R<sub>240</sub>); wherein each aryl is optionally substituted with 1, 2, or 3 R<sub>200</sub>; each heteroaryl is optionally substituted with 1, 2, 3, or 4 R<sub>200</sub>;

each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R<sub>210</sub>;

R<sub>200</sub> at each occurrence is independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; OH; -NO<sub>2</sub>; halogen; -CO<sub>2</sub>H; C≡N; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>220</sub>R<sub>225</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>1</sub>-C<sub>12</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub> alkenyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub> alkynyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO-aryl; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-heteroaryl; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-heterocycloalkyl; -(CH<sub>2</sub>)<sub>0-4</sub>-CO<sub>2</sub>R<sub>215</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-NR<sub>220</sub>R<sub>225</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-SO-(C<sub>1</sub>-C<sub>8</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>12</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>215</sub>)-CO<sub>2</sub>R<sub>215</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>215</sub>)-CO-N(R<sub>215</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-N-CS-N(R<sub>215</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-N(-H or R<sub>215</sub>)-CO-R<sub>220</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-NR<sub>220</sub>R<sub>225</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-O-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-O-P(O)-(OR<sub>240</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-O-CO-N(R<sub>215</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-O-CS-N(R<sub>215</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-O-(R<sub>215</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-O-(R<sub>215</sub>)<sub>2</sub>-COOH; -(CH<sub>2</sub>)<sub>0-4</sub>-S-(R<sub>215</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-O-(C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, or 5 -F); C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>2</sub>-C<sub>6</sub> alkenyl optionally substituted with 1 or 2 R<sub>205</sub> groups; C<sub>2</sub>-C<sub>6</sub> alkynyl optionally substituted with 1 or 2 R<sub>205</sub> groups; -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>215</sub>)-SO<sub>2</sub>-R<sub>220</sub>; and -(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>7</sub> cycloalkyl;

wherein each aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups

that are independently  $R_{205}$ ,  $R_{210}$  or  $C_1-C_6$  alkyl substituted with 1, 2, or 3 groups that are independently  $R_{205}$  or  $R_{210}$ ;

wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently  $R_{210}$ ;

wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently  $R_{205}$ ,  $R_{210}$ , or  $C_1-C_6$  alkyl substituted with 1, 2, or 3 groups that are independently  $R_{205}$  or  $R_{210}$ ;

$R_{205}$  at each occurrence is independently selected from the group consisting of  $C_1-C_6$  alkyl, halogen,  $-OH$ ,  $-O$ -phenyl,  $-SH$ ,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_6$  alkoxy,  $NH_2$ ,  $NH(C_1-C_6$  alkyl), and  $N-(C_1-C_6$  alkyl)( $C_1-C_6$  alkyl);

$R_{210}$  at each occurrence is independently selected from the group consisting of  $C_1-C_6$  alkyl optionally substituted with 1, 2, or 3  $R_{205}$  groups;  $C_2-C_6$  alkenyl optionally substituted with 1, 2, or 3  $R_{205}$  groups;  $C_2-C_6$  alkynyl optionally substituted with 1, 2, or 3  $R_{205}$  groups; halogen;  $C_1-C_6$  alkoxy;  $C_1-C_6$  haloalkoxy;  $-NR_{220}R_{225}$ ;  $OH$ ;  $C\equiv N$ ;  $C_3-C_7$  cycloalkyl optionally substituted with 1, 2, or 3  $R_{205}$  groups;  $-CO-(C_1-C_4$  alkyl);  $-SO_2-NR_{235}R_{240}$ ;  $-CO-NR_{235}R_{240}$ ;  $-SO_2-(C_1-C_4$  alkyl); and  $=O$ ; wherein

$R_{215}$  at each occurrence is independently selected from the group consisting of  $C_1-C_6$  alkyl,  $-(CH_2)_{0-2}-(aryl)$ ,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl,  $C_3-C_7$  cycloalkyl, and  $-(CH_2)_{0-2}-(heteroaryl)$ ,  $-(CH_2)_{0-2}-(heterocycloalkyl)$ ;

wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently  $R_{205}$  or  $R_{210}$ ; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3  $R_{210}$ ; wherein

each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>210</sub>;

R<sub>220</sub> and R<sub>225</sub> at each occurrence are independently selected from the group consisting of -H, -C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, amino C<sub>1</sub>-C<sub>6</sub> alkyl; halo C<sub>1</sub>-C<sub>6</sub> alkyl; -C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>2</sub> alkyl)-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), -C<sub>2</sub>-C<sub>6</sub> alkenyl, -C<sub>2</sub>-C<sub>6</sub> alkynyl, -C<sub>1</sub>-C<sub>6</sub> alkyl chain with one double bond and one triple bond, -aryl, -heteroaryl, and -heterocycloalkyl; wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>270</sub> groups, wherein

R<sub>270</sub> at each occurrence is independently R<sub>205</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; C<sub>2</sub>-C<sub>6</sub> alkenyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; C<sub>2</sub>-C<sub>6</sub> alkynyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; halogen; C<sub>1</sub>-C<sub>6</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkoxy; NR<sub>235</sub>R<sub>240</sub>; OH; C≡N; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); -SO<sub>2</sub>-NR<sub>235</sub>R<sub>240</sub>; -CO-NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); and =O; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R<sub>205</sub> groups;

R<sub>235</sub> and R<sub>240</sub> at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, -(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, aryl C<sub>1</sub>-C<sub>4</sub> alkyl, heteroaryl C<sub>1</sub>-C<sub>4</sub> alkyl, and phenyl; or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6, or 7 carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-, -SO<sub>2</sub>-, and -NR<sub>220</sub>-;

$R_{255}$  and  $R_{260}$  at each occurrence are independently selected from the group consisting of H;  $C_1-C_6$  alkyl optionally substituted with 1, 2, or 3  $R_{205}$  groups;  $C_2-C_6$  alkenyl optionally substituted with 1, 2, or 3  $R_{205}$  groups;  $C_2-C_6$  alkynyl optionally substituted with 1, 2, or 3  $R_{205}$  groups;  $-(CH_2)_{1-2}-S(O)_{0-2}-(C_1-C_6 \text{ alkyl})$ ;  $-(CH_2)_{0-4}-C_3-C_7$  cycloalkyl optionally substituted with 1, 2, or 3  $R_{205}$  groups;  $-(C_1-C_4 \text{ alkyl})$ -aryl;  $-(C_1-C_4 \text{ alkyl})$ -heteroaryl;  $-(C_1-C_4 \text{ alkyl})$ -heterocycloalkyl; -aryl; -heteroaryl; -heterocycloalkyl;  $-(CH_2)_{1-4}-R_{265}-(CH_2)_{0-4}$ -aryl;  $-(CH_2)_{1-4}-R_{265}-(CH_2)_{0-4}$ -heteroaryl; and;  $-(CH_2)_{1-4}-R_{265}-(CH_2)_{0-4}$ -heterocycloalkyl; wherein  $R_{265}$  at each occurrence is independently -O-, -S- or -N( $C_1-C_6$  alkyl)-;

each aryl or phenyl is optionally substituted with 1, 2, or 3 groups that are independently  $R_{205}$ ,  $R_{210}$ , or  $C_1-C_6$  alkyl substituted with 1, 2, or 3 groups that are independently  $R_{205}$  or  $R_{210}$ ;

each heteroaryl is optionally substituted with 1, 2, 3, or 4  $R_{200}$ , each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4  $R_{210}$ .

2. A compound according to claim 1 wherein  $R_1$  is  $(CH_2)_{n_1}-(R_{1-aryl})$  where  $n_1$  is zero or one and  $R_{1-aryl}$  is phenyl optionally substituted with 1, 2, 3, or 4 groups independently selected from  $C_1-C_6$  alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of  $C_1-C_3$  alkyl, halogen, -OH, -SH,  $-NR_{1-a}R_{1-b}$ ,  $-C\equiv N$ ,  $-CF_3$ , and  $C_1-C_3$  alkoxy; halogen;  $C_1-C_6$  alkoxy;  $-NR_{N-2}R_{N-3}$ ; and OH; wherein  $R_{N-2}$  and  $R_{N-3}$  at each occurrence are independently selected from the group consisting of  $-C_1-C_8$  alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of -OH,  $-NH_2$ ,

phenyl and halogen; -C<sub>3</sub>-C<sub>8</sub> cycloalkyl; -(C<sub>1</sub>-C<sub>2</sub> alkyl)-(C<sub>3</sub>-C<sub>8</sub> cycloalkyl); -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl); -C<sub>2</sub>-C<sub>6</sub> alkenyl; -C<sub>2</sub>-C<sub>6</sub> alkynyl; -C<sub>1</sub>-C<sub>6</sub> alkyl chain with one double bond and one triple bond; aryl;

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heteroaryl; heterocycloalkyl;

or

R<sub>N-2</sub>, R<sub>N-3</sub> and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or heteroaryl group, wherein said heterocycloalkyl or heteroaryl group is optionally fused to a benzene, pyridine, or pyrimidine ring, and said groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that at each occurrence are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -OH, -C(O)NH<sub>2</sub>, -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> thioalkoxy, and C<sub>1</sub>-C<sub>6</sub> thioalkoxy C<sub>1</sub>-C<sub>6</sub> alkyl.

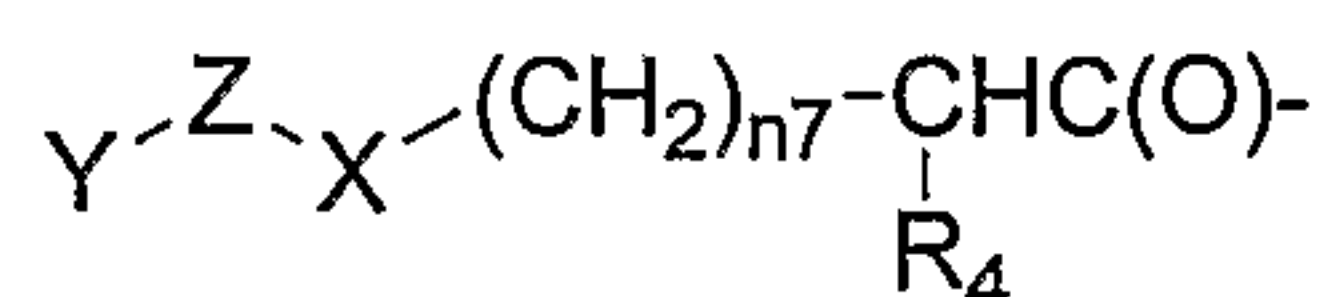
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3. A compound according to claim 2, wherein

R<sub>N</sub> is:



wherein

25 R<sub>4</sub> is NH<sub>2</sub>; -NH-(CH<sub>2</sub>)<sub>n<sub>6</sub></sub>-R<sub>4-1</sub>; -NHR<sub>8</sub>; -NR<sub>50</sub>C(O)R<sub>5</sub>; or -NR<sub>50</sub>CO<sub>2</sub>R<sub>51</sub>;

wherein

n<sub>6</sub> is 0, 1, 2, or 3;

n<sub>7</sub> is 0, 1, 2, or 3;

R<sub>4-1</sub> is selected from the group consisting of -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub>

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alkyl), -SO-(C<sub>1</sub>-C<sub>8</sub> alkyl), -S-(C<sub>1</sub>-C<sub>8</sub> alkyl), -S-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl), -SO<sub>2</sub>-NR<sub>4-2</sub>R<sub>4-3</sub>; -CO-C<sub>1</sub>-C<sub>2</sub> alkyl; -CO-NR<sub>4-3</sub>R<sub>4-4</sub>;

R<sub>4-2</sub> and R<sub>4-3</sub> are independently H, C<sub>1</sub>-C<sub>3</sub> alkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

R<sub>4-4</sub> is alkyl, phenylalkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, or phenylalkanoyl;

5 R<sub>5</sub> is selected from the group consisting of cyclopropyl, cyclopentyl, and cyclohexyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, -NR<sub>6</sub>R<sub>7</sub>, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl, C<sub>5</sub>-C<sub>6</sub> heteroaryl, phenyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -S-C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, -CO<sub>2</sub>H, 10 -CONR<sub>6</sub>R<sub>7</sub>, -CO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, or phenyloxy; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or OH; heterocycloalkyl optionally substituted with 1, 2, or 3 groups that are 15 independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or C<sub>2</sub>-C<sub>4</sub> alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkyl; and 20 -NR<sub>6</sub>R<sub>7</sub>; wherein

R<sub>6</sub> and R<sub>7</sub> are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, and phenyl C<sub>1</sub>-C<sub>4</sub> alkyl;

25 R<sub>8</sub> is selected from the group consisting of -SO<sub>2</sub>-heteroaryl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl or halogen;, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heterocycloalkyl, -C(O)NHR<sub>9</sub>, heterocycloalkyl, -S-C<sub>2</sub>-C<sub>4</sub> alkanoyl, wherein R<sub>9</sub> is phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, or H;

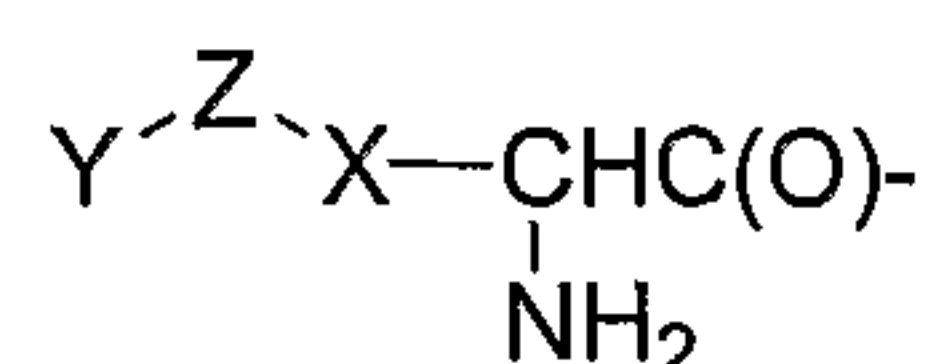
30 R<sub>50</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>51</sub> is selected from the group consisting of phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR<sub>6</sub>R<sub>7</sub>, -C(O)NR<sub>6</sub>R<sub>7</sub>, C<sub>3</sub>-C<sub>7</sub> or -C<sub>1</sub>-C<sub>4</sub> alkoxy;



heterocycloalkyl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; heterocycloalkylalkyl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; alkenyl; alkynyl; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); heteroarylalkyl optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); phenyl; C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and cycloalkylalkyl, wherein the phenyl; C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and cycloalkylalkyl groups are optionally substituted with 1, 2, 3, 4 or 5 groups that are independently halogen, CN, NO<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, hydroxy, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> thioalkoxy, C<sub>1</sub>-C<sub>6</sub> thioalkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkoxy.

4. A compound according to claim 3, wherein



X is C<sub>1</sub>-C<sub>4</sub> alkylidenyl optionally optionally substituted with 1, 2, or 3 methyl groups; or -NR<sub>4-6</sub>-; or R<sub>4</sub> and R<sub>4-6</sub> combine to form -(CH<sub>2</sub>)<sub>n<sub>10</sub></sub>-, wherein n<sub>10</sub> is 1, 2, 3, or 4;

Z is selected from a bond; SO<sub>2</sub>; SO; S; and C(O);

Y is selected from H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl containing at least one N, O, or S; phenyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 thru

3 substituents which can be the same or different and are selected from halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C<sub>3</sub>-C<sub>8</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, and halogen; alkoxy; phenyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; and C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or

-N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen;

R<sub>20</sub> at each occurrence is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkanoyl, each of which is unsubstituted or substituted with 1, or 2 groups independently selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>,

wherein

R<sub>26</sub> is selected from -C(O)-, -SO<sub>2</sub>-, -CO<sub>2</sub>-, -C(O)NH-, and -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-;

R<sub>27</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, heterocycloalkyl, and heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NH<sub>2</sub>, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub>

alkyl) (C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -  
C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl) (C<sub>1</sub>-C<sub>6</sub> alkyl).

5. A compound according to claim 4, wherein

- 5 R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, hydroxy, and C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, or 3 substituents halogen, OH, SH, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N-(C<sub>1</sub>-C<sub>6</sub> alkyl) (C<sub>1</sub>-C<sub>6</sub> alkyl), C≡N, CF<sub>3</sub>;
- 10 R<sub>2</sub> and R<sub>3</sub> are independently selected from H or C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1 substituent selected from halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), and NH(C<sub>1</sub>-C<sub>6</sub> alkyl) (C<sub>1</sub>-C<sub>6</sub> alkyl);
- R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 15 C<sub>1</sub>-C<sub>2</sub> alkoxy C<sub>1</sub>-C<sub>4</sub> alkyl, halo C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, each of which is unsubstituted or substituted with 1 or 2 groups independently selected from halogen, hydroxy, and NH<sub>2</sub>;
- R<sub>C</sub> is C<sub>1</sub>-C<sub>8</sub> alkyl optionally substituted with 1, 2, or 3 groups 20 independently selected from R<sub>205</sub>, -SH, -C=ONR<sub>235</sub>R<sub>240</sub>, and -S(=O)<sub>2</sub>NR<sub>235</sub>R<sub>240</sub>; -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>6</sub>) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from R<sub>205</sub>, -CO<sub>2</sub>H, and -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-phenyl optionally substituted 25 with 1, 2, or 3 R<sub>200</sub>; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyridyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyridazinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrimidinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrazinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-furyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-indolyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-thienyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrrolyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrazolyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-benzoxazolyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>- 30 imidazolyl; each of the above heteroaryl groups is optionally substituted with 1, 2, 3, or 4 R<sub>200</sub>; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-imidazolidinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-tetrahydrofuryl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-tetrahydropyranyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-piperazinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyrrolidinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-piperidinyl; (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-

indolinyl; each of the above heterocycloalkyl groups is optionally substituted with 1, 2, 3, or 4 R<sub>210</sub>; (CH<sub>2</sub>)<sub>0-1</sub>-CH((CH<sub>2</sub>)<sub>0-4</sub>-OH)-(CH<sub>2</sub>)<sub>0-1</sub>-phenyl; -(CH<sub>2</sub>)<sub>0-1</sub>-CH(C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl)-(CH<sub>2</sub>)<sub>0-1</sub>-pyridyl;

5 R<sub>200</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub> groups; OH; -NO<sub>2</sub>; halogen; -CO<sub>2</sub>H; C≡N; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>220</sub>R<sub>225</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>1</sub>-C<sub>8</sub> alkyl); -(CH<sub>2</sub>)<sub>0-4</sub>-CO<sub>2</sub>R<sub>215</sub>; and -(CH<sub>2</sub>)<sub>0-4</sub>-O-(C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 10 2, 3, or 5 -F);

R<sub>205</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, -OH, -O-phenyl, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), and N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);

15 R<sub>210</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1 or 2 R<sub>205</sub> groups; halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> haloalkoxy; -NR<sub>220</sub>R<sub>225</sub>; OH; C≡N; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1 or 2 R<sub>205</sub> groups; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); -SO<sub>2</sub>-NR<sub>235</sub>R<sub>240</sub>; -CO- 20 NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); and =O; wherein

R<sub>215</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(phenyl), C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(pyridyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(pyrrolyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(imidazolyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(pyrimidyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(pyrrolidinyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(imidazolidinyl) 25 -(CH<sub>2</sub>)<sub>0-2</sub>-(piperazinyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(piperidinyl), and -(CH<sub>2</sub>)<sub>0-2</sub>-(morpholinyl); wherein the phenyl group at each occurrence is optionally substituted with 1 or 2 groups that are independently R<sub>205</sub> or R<sub>210</sub>; wherein each heterocycloalkyl group at each occurrence is 30 optionally substituted with 1 or 2 R<sub>210</sub>; wherein each heteroaryl group at each occurrence is optionally substituted with 1 or 2 R<sub>210</sub>;

R<sub>220</sub> and R<sub>225</sub> at each occurrence are independently -H, -C<sub>1</sub>-C<sub>4</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkyl, halo C<sub>1</sub>-C<sub>4</sub> alkyl; -C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-(C<sub>1</sub>-C<sub>2</sub> alkyl);

5 R<sub>235</sub> and R<sub>240</sub> at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, or

10 R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms.

6. A compound according to claim 5, wherein X is -C<sub>1</sub>-C<sub>3</sub> alkylidenyl optionally optionally substituted with 1 methyl group;

Z is SO<sub>2</sub>; SO; S; or C(O);

15 Y is OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); phenyl; benzyl; or C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 or 2 substituents which can be the same or different and are selected from halogen, hydroxy, methoxy, ethoxy, thiomethoxy, thioethoxy, and CF<sub>3</sub>; wherein 20 Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1 or 2 substituents selected from halogen, methoxy, ethoxy, cyclopropyl, and OH; or

25 -N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or halogen;

30 R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, or 3 groups independently selected from methyl, ethyl, n-propyl, isopropyl, hydroxymethyl, monohalomethyl, dihalomethyl, trihalomethyl, -CH<sub>2</sub>CF<sub>3</sub>, methoxymethyl,

halogen, methoxy, ethoxy, n-propyloxy, isopropyloxy, and  
OH;

R<sub>2</sub> and R<sub>3</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl,  
5 or C<sub>2</sub>-C<sub>4</sub> alkanoyl;

R<sub>C</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub>  
groups; cyclopropyl, cyclopropylmethyl, cyclopentyl,  
cyclopentylmethyl, cyclohexyl, cyclohexylmethyl;

10 -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-phenyl optionally substituted with 1 or 2 R<sub>200</sub>  
groups; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyridyl optionally substituted with 1  
or 2 R<sub>200</sub>; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-piperazinyl; or (CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-  
pyrrolidinyl; -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-piperidinyl; each of the above  
heterocycloalkyl groups is optionally substituted with 1  
or 2 R<sub>210</sub> groups;

15 R<sub>200</sub> at each occurrence is independently selected from C<sub>1</sub>-  
C<sub>4</sub> alkyl optionally substituted with 1 or 2 R<sub>205</sub>  
groups; OH; and halogen;

R<sub>205</sub> at each occurrence is independently selected from C<sub>1</sub>-  
C<sub>4</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>4</sub>  
20 alkoxy;

R<sub>210</sub> at each occurrence is independently selected from C<sub>1</sub>-  
C<sub>4</sub> alkyl optionally substituted with 1 or 2 R<sub>205</sub>  
groups; halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; OCF<sub>3</sub>; NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub>  
alkyl); N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); OH; and -CO-(C<sub>1</sub>-C<sub>4</sub>  
25 alkyl); wherein

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently selected  
from H, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or

30 R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which  
they are attached to form a carbocycle of 3, 5, or 6  
carbon atoms.

7. A compound according to claim 4 that is selected from  
S-butyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-  
ethylbenzyl)amino]-2-hydroxypropyl}-D-cysteinamide;

3-(butylsulfinyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-L-alaninamide;

3-(butylsulfonyl)-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-D-alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-L-alaninamide;

N~1~-[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxypropyl-3-(isopentylamino)]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

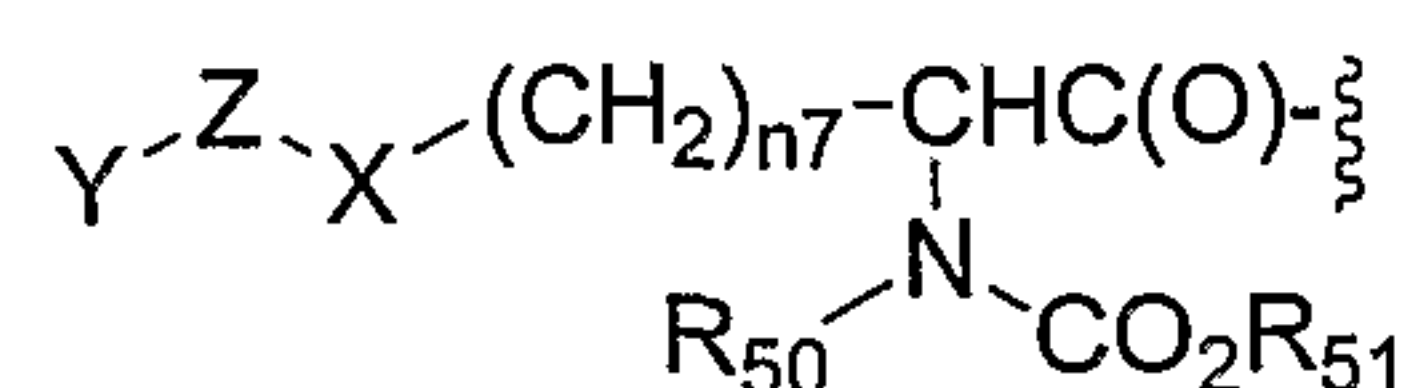
N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide hydrochloride;

(2S)-2-amino-N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-oxo-5-piperidin-1-ylpentanamide; and

(2R)-2-amino-N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-oxo-5-piperidin-1-ylpentanamide .

8. A compound according to claim 3 wherein

R<sub>N</sub> is:



5 n<sub>7</sub> is 0, 1, 2, or 3;

R<sub>50</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>51</sub> is phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted  
 with 1, 2, or 3 groups that are independently halogen,  
 cyano, -NR<sub>6</sub>R<sub>7</sub>, -C(O)NR<sub>6</sub>R<sub>7</sub>, or -C<sub>1</sub>-C<sub>4</sub> alkoxy;  
 heterocycloalkyl optionally substituted with 1 or 2 groups  
 5 that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen,  
 C<sub>2</sub>-C<sub>4</sub> alkanoyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl;  
 heterocycloalkylalkyl optionally substituted with 1 or 2  
 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy,  
 halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub>  
 10 alkyl; alkenyl; alkynyl; heteroaryl optionally substituted  
 with 1, 2, or 3 groups that are independently OH, C<sub>1</sub>-C<sub>4</sub>  
 alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-  
 C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); heteroarylalkyl optionally  
 substituted with 1, 2, or 3 groups that are independently  
 15 C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or  
 N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); phenyl; C<sub>3</sub>-C<sub>8</sub> cycloalkyl; or  
 cycloalkylalkyl; wherein the phenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and  
 cycloalkylalkyl groups are optionally substituted with 1,  
 2, 3, 4 or 5 groups that are independently halogen, CN,  
 20 NO<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>6</sub>  
 haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, hydroxy, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl,  
 C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> thioalkoxy, C<sub>1</sub>-C<sub>6</sub> thioalkoxy  
 C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkoxy;

R<sub>6</sub> and R<sub>7</sub> are independently H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub>  
 25 alkanoyl, phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, or phenyl C<sub>1</sub>-  
 C<sub>4</sub> alkyl;

X is C<sub>1</sub>-C<sub>4</sub> alkylidenyl optionally optionally substituted with  
 1, 2, or 3 methyl groups; or -NR<sub>4-6</sub>-; or

R<sub>4</sub> and R<sub>4-6</sub> combine to form -(CH<sub>2</sub>)<sub>n10</sub>-, wherein  
 30 n<sub>10</sub> is 1, 2, 3, or 4;

Z is a bond; SO<sub>2</sub>; SO; S; or C(O);

Y is H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl containing at  
 least one N, O, or S; phenyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl  
 optionally substituted with 1 thru 3 substituents which



can be the same or different and are selected from  
 halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C<sub>3</sub>-  
 C<sub>8</sub> cycloalkyl optionally substituted with 1, 2, or 3  
 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, and  
 5 halogen; alkoxy; phenyl optionally substituted with  
 halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; or phenyl C<sub>1</sub>-  
 C<sub>4</sub> alkyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl,  
 C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein  
 Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>10</sub> alkyl  
 10 optionally substituted with 1, 2, or 3 substituents  
 selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl,  
 and OH; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-  
 C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub>  
 alkyl; or  
 15 -N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl,  
 piperidinyl, morpholinyl, and pyrrolidinyl, wherein  
 each ring is optionally substituted with 1, 2, 3, or  
 4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
 alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen;  
 20 R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl,  
 C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub>  
 alkanoyl, each of which is unsubstituted or substituted  
 with 1, or 2 groups independently selected from halogen,  
 C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>,  
 25 wherein  
 R<sub>26</sub> is -C(O)-, -SO<sub>2</sub>-, -CO<sub>2</sub>-, -C(O)NH-, or -C(O)N(C<sub>1</sub>-C<sub>6</sub>  
 alkyl)-;  
 R<sub>27</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl C<sub>1</sub>-C<sub>6</sub> alkyl,  
 heterocycloalkyl, or heteroaryl, wherein each of the  
 30 above is unsubstituted or substituted with 1, 2, 3,  
 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-  
 C<sub>4</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub>  
 alkyl, -C(O)NH<sub>2</sub>, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub>

alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -  
C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl).

9. A compound according to claim 8, wherein

5 X is -C<sub>1</sub>-C<sub>3</sub> alkylidenyl;

Z is SO<sub>2</sub>; SO; S; or C(O);

Y is OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); phenyl; benzyl; or C<sub>1</sub>-C<sub>10</sub> alkyl optionally  
substituted with 1 or 2 substituents which can be the same  
or different and are selected from halogen, hydroxy,  
10 methoxy, ethoxy, thiomethoxy, thioethoxy, and CF<sub>3</sub>; wherein  
Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>4</sub> alkyl  
optionally substituted with 1 or 2 substituents  
selected from halogen, methoxy, ethoxy, cyclopropyl,  
and OH; or

15 -N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl,  
piperidinyl, morpholinyl, and pyrrolidinyl, wherein  
each ring is optionally substituted with 1 or 2  
groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub>  
alkoxy, or halogen;

20 R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, or 3  
groups independently selected from methyl, ethyl, n-  
propyl, isopropyl, hydroxymethyl, monohalomethyl,  
dihalomethyl, trihalomethyl, -CH<sub>2</sub>CF<sub>3</sub>, methoxymethyl,  
halogen, methoxy, ethoxy, n-propyloxy, isopropyloxy, and  
25 OH;

R<sub>2</sub> and R<sub>3</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl,

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl,  
or C<sub>2</sub>-C<sub>4</sub> alkanoyl;

R<sub>C</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 R<sub>205</sub>  
30 groups; cyclopropyl, cyclopropylmethyl, cyclopentyl,  
cyclopentylmethyl, cyclohexyl, cyclohexylmethyl;  
-(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-phenyl optionally substituted with 1 or 2 R<sub>200</sub>  
groups; or -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-3</sub>-pyridyl optionally substituted  
with 1 or 2 R<sub>200</sub>;

R<sub>200</sub> at each occurrence is independently C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1 or 2 R<sub>205</sub> groups; OH; or halogen;

R<sub>205</sub> at each occurrence is independently C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, or C<sub>1</sub>-C<sub>4</sub> alkoxy;

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently H, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, or C<sub>1</sub>-C<sub>4</sub> alkoxy, or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3 carbon atoms.

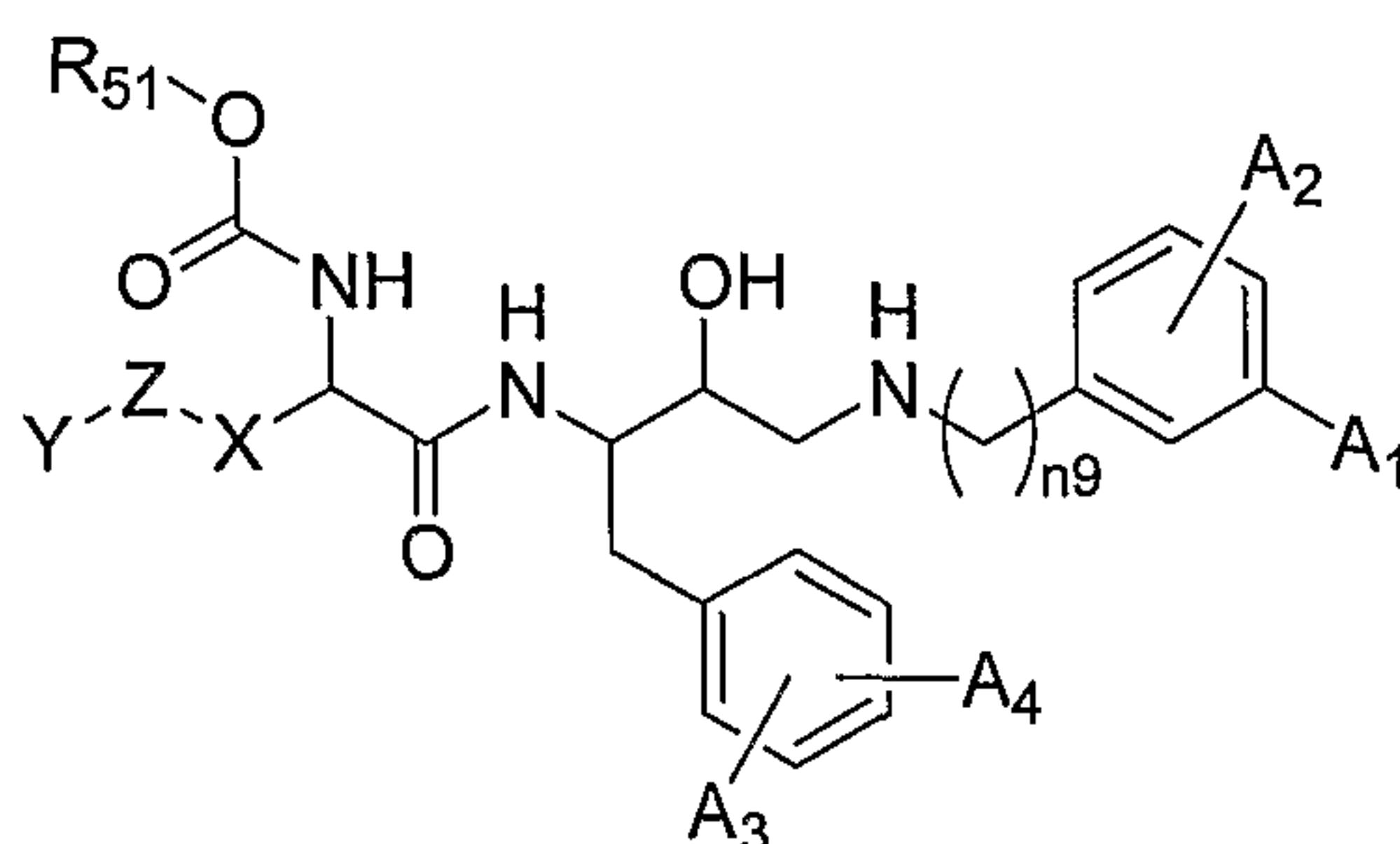
10. A compound according to claim 9, wherein

R<sub>51</sub> is benzyl; phenethyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR<sub>6</sub>R<sub>7</sub>, -C(O)NR<sub>6</sub>R<sub>7</sub>, or -C<sub>1</sub>-C<sub>4</sub> alkoxy; pyrrolidinyl, tetrahydrofuryl, tetrahydro-thienyl 1,1-dioxide, tetrahydrothienyl, pyranyl, piperidinyl, pyrrolidinonyl, each of which is optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, benzyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; pyrrolidinonyl C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>2</sub>-C<sub>4</sub> alkenyl; C<sub>2</sub>-C<sub>4</sub> alkynyl; pyridinyl C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1, or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); cyclopentyl; cyclohexyl; or cyclopropylmethyl; wherein the cycloalkyl, and cycloalkylalkyl groups are optionally substituted with 1, or 2 groups that are independently halogen, CN, NO<sub>2</sub>, methyl, ethyl, methoxy, ethoxy, C<sub>2</sub>-C<sub>4</sub> alkanoyl, CF<sub>3</sub>, OCF<sub>3</sub>, or hydroxy;

R<sub>6</sub> and R<sub>7</sub> are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, or benzyl;

Y is OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); phenyl; benzyl; or C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 or 2 substituents which can be the same or different and are selected from halogen, hydroxy, methoxy, ethoxy, thiomethoxy, thioethoxy, and CF<sub>3</sub>; wherein  
 5 Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H or C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1 or 2 substituents selected from halogen, methoxy, ethoxy, cyclopropyl, and OH.

10 11. A compound according to claim 10 of the formula



wherein

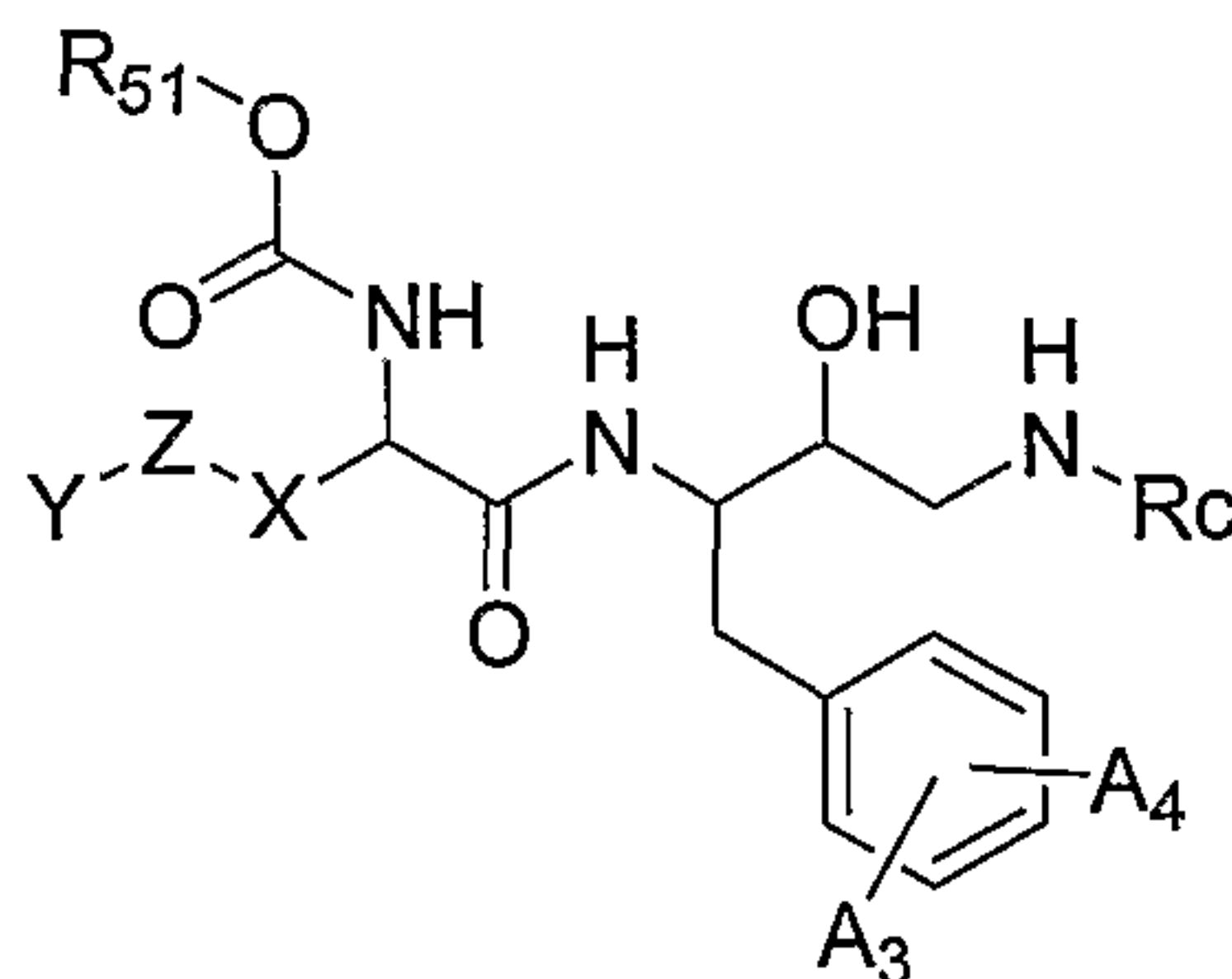
n<sub>9</sub> is 1 or 2;

A<sub>1</sub> and A<sub>2</sub> are independently H, methyl, ethyl, propyl, methoxy,  
 15 F, Cl, Br, I, or CF<sub>3</sub>; or

A<sub>3</sub> and A<sub>4</sub> are independently F, Cl, Br, I, methyl, methoxy, or  
 H.

12. A compound according to claim 8, wherein  
 20 R<sub>c</sub> is C<sub>3</sub>-C<sub>8</sub> alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or -  
 (C<sub>1</sub>-C<sub>4</sub>)alkyl-cyclopropyl.

13. A compound according to claim 12 of the formula



wherein

A<sub>3</sub> and A<sub>4</sub> are independently F, Cl, Br, I, methyl, ethyl, methoxy, ethoxy, or H;

X is C<sub>1</sub> or C<sub>2</sub> alkylidenyl;

5 Z is SO<sub>2</sub>; SO; S; or C(O); and

Y is phenyl, C<sub>1</sub>-C<sub>10</sub> alkyl,; or

Y is -N(Y<sub>1</sub>)(Y<sub>2</sub>); wherein

Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H or C<sub>1</sub>-C<sub>4</sub> alkyl.

10

14. A compound according to claim 8 that is selected from

3-(butylsulfinyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-D-alaninamide;

S-butyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-D-cysteinamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(4,4,4-trifluorobutyl)sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(4,4,4-trifluorobutyl)sulfinyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-S-(4,4,4-trifluorobutyl)-D-cysteinamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(2,2,2-trifluoroethoxy)carbonyl]-D-alaninamide;

N~2~-[(2-cyanoethoxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-

(butylsulfonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3R)-pyrrolidin-3-yl]carbonyl}-D,L-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-D-alaninamide;

N~2~-{[2-(acetamino)ethoxy]carbonyl}-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(pyridin-3-yl)methyl]oxy]carbonyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(pyridin-4-yl)methyl]oxy]carbonyl}-D-alaninamide;

3-(butylsulfonyl)-N~2~-[(methoxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~2~-[(2-cyanoethoxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-D-alaninamide;

N~2~-[(2-cyanoethoxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-{[2-(acetamino)ethoxy]carbonyl}-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[[2-(diethylamino)-2-oxoethoxy]carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(isopropoxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(cyclopropylmethoxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(allyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(2-cyanoethoxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[[2-(acetylamino)ethoxy]carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{[(pyridin-3-yl)methoxy]carbonyl}-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-{[(pyridin-4-yl)methyl]oxy]carbonyl}-D-alaninamide;

benzyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]amino) carbonyl]-3-(methylsulfonyl)propylcarbamate;

N~2~-[(benzyloxy) carbonyl]-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-D-alaninamide trifluoroacetate;

N~2~-[(benzyloxy) carbonyl]-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-L-alaninamide trifluoroacetate;

N~2~-[(benzyloxy) carbonyl]-N~1~-((1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-2-hydroxy-1-phenylethyl]amino)propyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-((1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]amino)propyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-((1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1S)-2-methoxy-1-phenylethyl]amino)propyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl) cyclopropyl] amino]-2-hydroxypropyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-{[(prop-2-ynyl)oxy]carbonyl}-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-(2-methoxyethylcarbonyl)-3-[(1-propylbutyl) sulfonyl]-D-



alaninamide;

N~2~-{ [(3R)-1-acetylpyrrolidin-3-yl] carbonyl }-N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-N~2~-{ [(3S)-tetrahydrofuran-3-yloxy] carbonyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-N~2~-{ [(3S)-tetrahydrofuran-3-yloxy] carbonyl }-3-[(1-propylbutyl) sulfonyl]-L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl) cyclopropyl] amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(cyclopropylmethyl) amino]-2-hydroxypropyl }-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{ (1S,2S)-1-(3,5-

difluorobenzyl)-3-[(3-ethylphenyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)propyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{[(pyridin-3-yl)methyl]oxy}carbonyl}-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3R)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~-{[(3R)-1-acetylpyrrolidin-3-yl]carbonyl}-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{[(3R)-pyrrolidin-3-yl]carbonyl}-D,L-alaninamide;

N~2~-{[(3R)-1-benzylpyrrolidin-3-yl]carbonyl}-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3S)-1,1-dioxidotetrahydrothien-3-yloxy]carbonyl}-3-[(1-

propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrothiophen-3-yloxy]carbonyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~- (cyclopentylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~- (cyclohexylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-[(1-propylbutyl) sulfonyl]-N~2~-{[tetrahydropyran-4-yloxy]carbonyl}-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-{[tetrahydropyran-4-yloxy]carbonyl}-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[1-(methylsulfonyl)piperidin-4-yloxy]carbonyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-{[1-acetylpiperidin-4-yloxy]carbonyl}-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[[[(3S)-5-oxopyrrolidin-3-yl]methyl]oxy]carbonyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[[[(3R)-5-oxopyrrolidin-3-yl]methyl]oxy]carbonyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[[2-methoxyethyl]oxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy)carbonyl]-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl}-N~2~-[(benzyloxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[2-(3-methoxyphenyl)ethyl]amino]propyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~5~,N~5~-dipropyl-L-glutamamide; and

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~5~,N~5~-dipropyl-D-glutamamide;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]-3-oxoheptylcarbamate;

4-butyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(methoxycarbonyl)-D-homoserinamide;

3-(2-butyl-1,3-dioxolan-2-yl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(methoxycarbonyl)-D-alaninamide;

3-(2-butyl-1,3-dioxan-2-yl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(methoxycarbonyl)-D-alaninamide;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]-3,3-difluoroheptylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino) carbonyl]-3-fluoroheptylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino) carbonyl]-4-oxooctylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino) carbonyl]-4-hydroxyoctylcarbamate;

methyl (1R)-3-(2-butyl-1,3-dioxolan-2-yl)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino) carbonyl]propylcarbamate;

methyl (1R)-3-(2-butyl-1,3-dioxan-2-yl)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino) carbonyl]propylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino) carbonyl]-4-fluorooctylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino) carbonyl]-4,4-difluorooctylcarbamate;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-N~2~(methoxycarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-N~2~(methoxycarbonyl)-D-alaninamide;

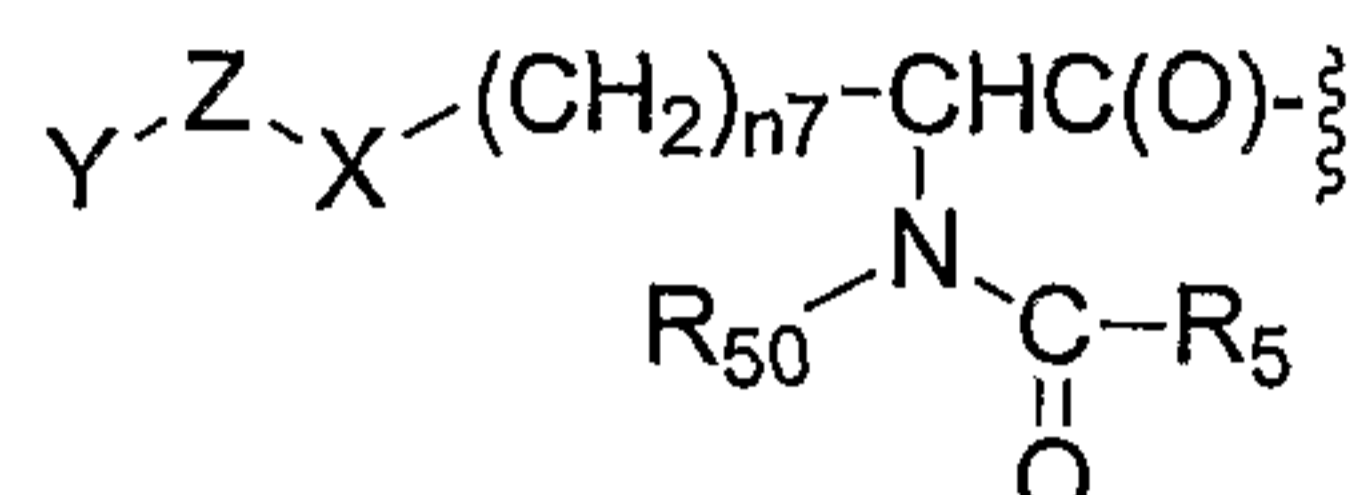
3-(butylsulfonyl)-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-N~2~(methoxycarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-N~2~(methoxycarbonyl)-D-alaninamide; and

3-(butylsulfonyl)-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-

2-hydroxy-3-({1-[3-(trifluoromethyl)phenyl]cyclopropyl}amino)propyl]-N~2~(methoxycarbonyl)-D-alaninamide.

15. A compound according to claim 3, wherein  $R_N$  is:



5 wherein

$n_7$  is 0, 1, 2, or 3;

$R_{50}$  is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

$R_5$  is selected from the group consisting of cyclopropyl;

cyclopentyl; cyclohexyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally

10 substituted with 1, 2, or 3 groups that are independently halogen, -NR<sub>6</sub>R<sub>7</sub>, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl, C<sub>5</sub>-C<sub>6</sub> heteroaryl, phenyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -S-C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>7</sub>, -CO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, or phenyloxy; heteroaryl optionally substituted with 1, 2, or  
 15 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or OH; heterocycloalkyl optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or C<sub>2</sub>-C<sub>4</sub> alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4  
 20 groups that are independently halogen, OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkyl; and -NR<sub>6</sub>R<sub>7</sub>; wherein

$R_6$  and  $R_7$  are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, and phenyl C<sub>1</sub>-C<sub>4</sub> alkyl;

25 X is C<sub>1</sub>-C<sub>4</sub> alkylidanyl optionally optionally substituted with 1, 2, or 3 methyl groups; or -NR<sub>4-6</sub>-; or

$R_4$  and  $R_{4-6}$  combine to form -(CH<sub>2</sub>)<sub>n<sub>10</sub></sub>-, wherein

$n_{10}$  is 1, 2, 3, or 4;

Z is a bond; SO<sub>2</sub>; SO; S; or C(O);

Y is H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl containing at least one N, O, or S; phenyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from

5 halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C<sub>3</sub>-C<sub>8</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, and halogen; alkoxy; phenyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; or phenyl C<sub>1</sub>-

10 C<sub>4</sub> alkyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl,

15 and OH; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or

-N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein

20 each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen; and

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub>

25 alkanoyl, each of which is unsubstituted or substituted with 1, or 2 groups independently selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>, wherein

R<sub>26</sub> is -C(O)-, -SO<sub>2</sub>-, -CO<sub>2</sub>-, -C(O)NH-, or -C(O)N(C<sub>1</sub>-C<sub>6</sub>

30 alkyl)-;

R<sub>27</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-

C<sub>4</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NH<sub>2</sub>, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl).

5

16. A compound according to claim 15, wherein

R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1, or 2 substituents selected from  
 10 halogen, -OH, -SH, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C≡N, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>3</sub> alkoxy; halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; and OH.

17. A compound according to claim 16, wherein

15 X is C<sub>1</sub>-C<sub>3</sub> alkylidanyl optionally optionally substituted with 1 or 2 methyl groups;

Z is SO<sub>2</sub>; SO; S; or C(O);

Y is H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; pyrrolidinyl; piperidinyl; imidazolidinyl; piperazinyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl  
 20 optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> thioalkoxy, and C<sub>1</sub>-C<sub>4</sub> haloalkoxy; C<sub>3</sub>-C<sub>6</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl and halogen; C<sub>1</sub>-C<sub>4</sub> alkoxy; phenyl, benzyl or phenethyl  
 25 each of which is optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

Y<sub>1</sub> and Y<sub>2</sub> are independently H; C<sub>1</sub>-C<sub>6</sub> alkyl optionally

30 substituted with 1, 2, or 3 substituents selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or C<sub>3</sub>-C<sub>6</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or

-N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein

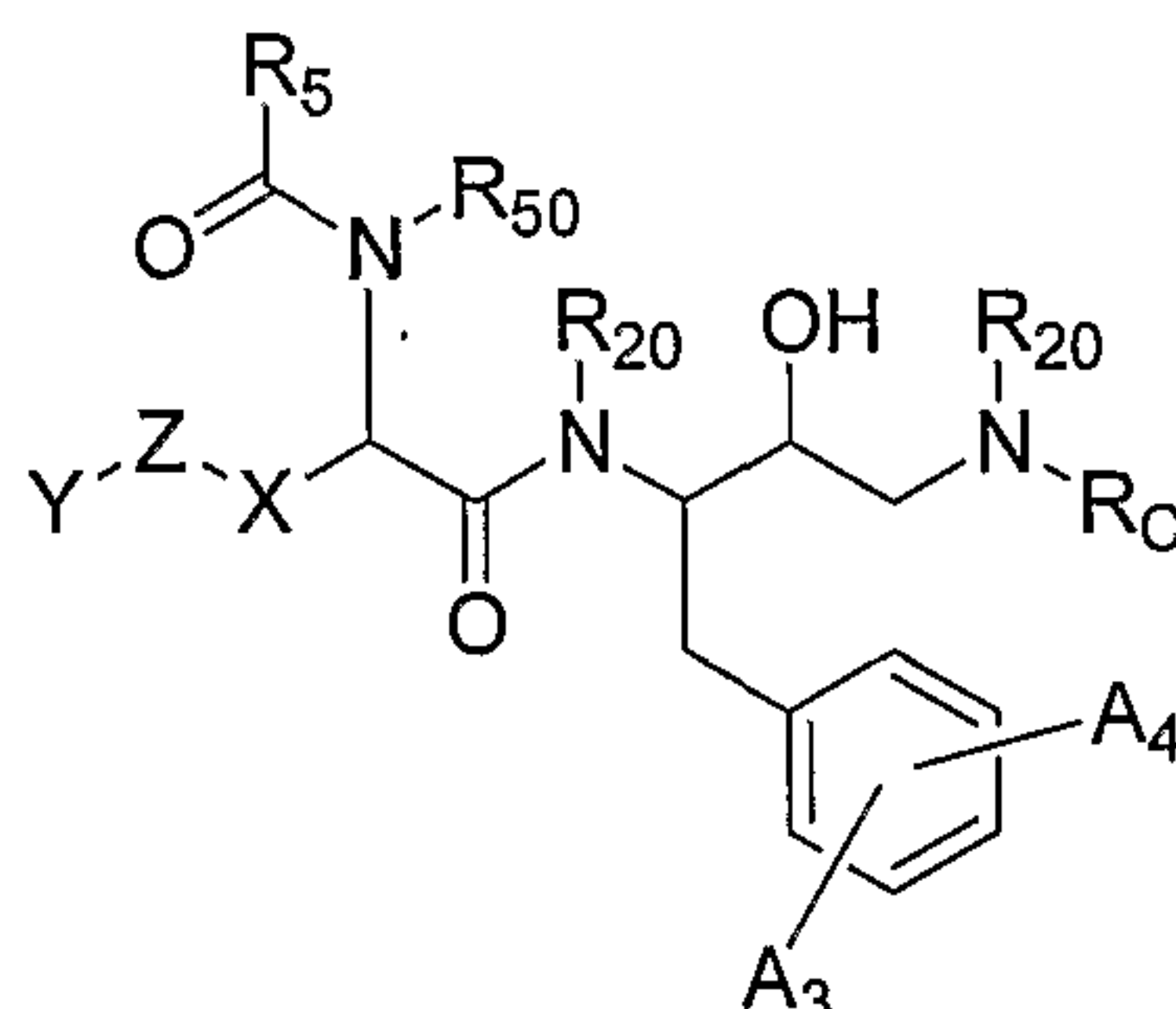


each ring is optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>4</sub> alkyl, or halogen; and R<sub>2</sub> and R<sub>3</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl.

5

18. A compound according to claim 17 wherein R<sub>20</sub> at each occurrence is independently H or C<sub>1</sub>-C<sub>4</sub> alkyl; X is C<sub>1</sub> or C<sub>2</sub> alkylidenyl; Z is SO<sub>2</sub>; SO; S; or C(O); and
- 10 Y is phenyl; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 halogen; or OH; or Y is -N(Y<sub>1</sub>)(Y<sub>2</sub>); wherein Y<sub>1</sub> and Y<sub>2</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl.

- 15 19. A compound according to claim 18, of the formula:

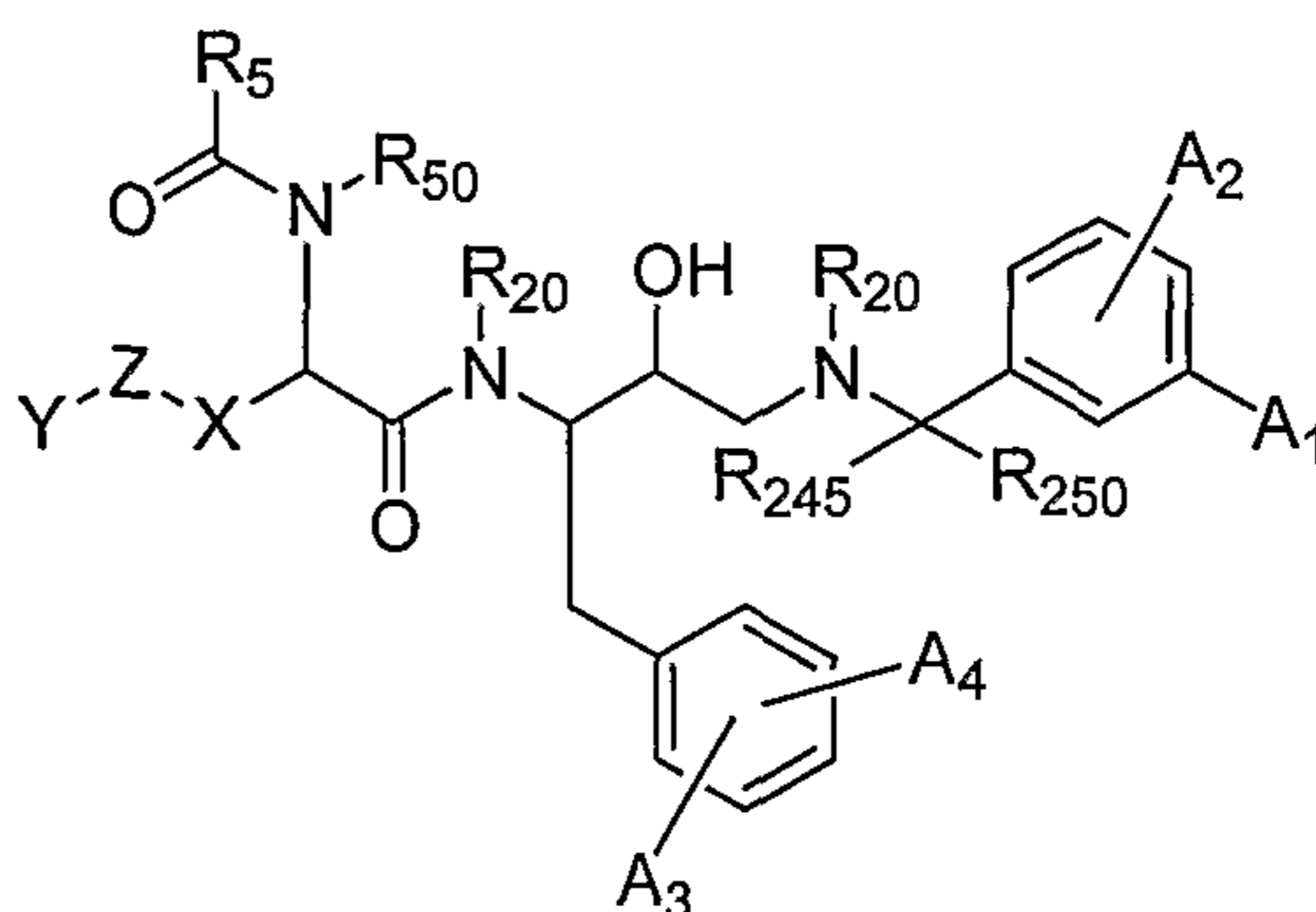


wherein

- R<sub>C</sub> is C<sub>3</sub>-C<sub>8</sub> alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or - (C<sub>1</sub>-C<sub>4</sub>)alkyl-cyclopropyl;
- 20 A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, Br, or I;
- R<sub>5</sub> is selected from cyclopropyl; cyclopentyl; cyclohexyl; pyridyl, thiazolyl, pyrazolyl, or pyrazinyl each of which is optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or OH; piperidinyl, dihydropyridazinonyl, pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl, imidazolyl, or indolyl each of which is optionally substituted with 1, or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or C<sub>2</sub>-C<sub>4</sub> alkanoyl; phenyl

optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>2</sub> haloalkyl.

5 20. A compound according to claim 18, wherein



wherein

A<sub>1</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy;

A<sub>2</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl or OH;

A<sub>3</sub> and A<sub>4</sub> are independently H, F, Cl, Br, or I;

R<sub>5</sub> is selected from cyclopropyl; cyclopentyl; cyclohexyl;

pyridyl, thiazolyl, pyrazolyl, or pyrazinyl each of which is optionally substituted with 1, 2, or 3 groups that are

independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or OH; piperidinyl, dihydropyridazinonyl,

pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl,

imidazolyl, or indolyl each of which is optionally

substituted with 1, or 2 groups that are independently C<sub>1</sub>-

C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or C<sub>2</sub>-C<sub>4</sub> alkanoyl; phenyl

optionally substituted with 1, 2, 3, or 4 groups that are

independently halogen, OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or

C<sub>1</sub>-C<sub>2</sub> haloalkyl.

25 21. A compound according to claim 15 selected from

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-  
[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(3,3,3-  
trifluoropropanoyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(trifluoroacetyl)-D-alaninamide;

N~2~-acetyl-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(pyridin-4-ylcarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~2~-(cyclopropylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~(beta-alanyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~glycyl-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~(N,N-dimethylglycyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~(N,N-dimethyl-beta-alanyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(methoxyacetyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(pyridin-3-ylcarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(2,4-dimethyl-1,3-thiazol-5-yl)carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-

[ (3-ethylbenzyl) amino] -2-hydroxypropyl} -N~2~- { [3-(trifluoromethyl) -1H-pyrazol-4-yl] carbonyl} -D-alaninamide;

3-(butylsulfonyl) -N~1~- { (1S, 2R) -1-(3, 5-difluorobenzyl) -3-[ (3-ethylbenzyl) amino] -2-hydroxypropyl} -N~2~- [ (3-methyl-1H-pyrazol-5-yl) carbonyl] -D-alaninamide;

3-(butylsulfonyl) -N~1~- { (1S, 2R) -1-(3, 5-difluorobenzyl) -3-[ (3-ethylbenzyl) amino] -2-hydroxypropyl} -N~2~- (1H-imidazol-4-ylacetyl) -D-alaninamide;

3-(butylsulfonyl) -N~1~- { (1S, 2R) -1-(3, 5-difluorobenzyl) -3-[ (3-ethylbenzyl) amino] -2-hydroxypropyl} -N~2~- (pyrazin-2-ylcarbonyl) -D-alaninamide;

3-(butylsulfonyl) -N~1~- { (1S, 2R) -1-(3, 5-difluorobenzyl) -3-[ (3-ethylbenzyl) amino] -2-hydroxypropyl} -N~2~- [ (6-hydroxypyridin-3-yl) carbonyl] -D-alaninamide;

N~1~- { (1S, 2R) -1-(3, 5-difluorobenzyl) -3-(cyclopropylamino) -2-hydroxypropyl} -3-[ (1-propylbutyl) sulfonyl] -N~2~- (pyridin-4-ylcarbonyl) -D-alaninamide;

N~2~-acetyl-3-(butylsulfonyl) -N~1~- { (1S, 2R) -1-(3, 5-difluorobenzyl) -3-[ (3-methylbutyl) amino] -2-hydroxypropyl} -D-alaninamide;

N~1~- [ (1S, 2R) -3-(cyclopropylamino) -1-(3, 5-difluorobenzyl) -2-hydroxypropyl] -N~2~- (cyclopropylcarbonyl) -3-[ (1-propylbutyl) sulfonyl] -D-alaninamide;

N~2~-acetyl-N~1~- { (1S, 2R) -1-(3, 5-difluorobenzyl) -3-[ (3-methylbutyl) amino] -2-hydroxypropyl} -3-[ (1-propylbutyl) sulfonyl] -D-alaninamide;

N~1~- { (1S, 2R) -1-(3, 5-difluorobenzyl) -3-[ (3-ethylbenzyl) amino] -2-hydroxypropyl} -3-[ (1-propylbutyl) sulfonyl] -N~2~- (pyridin-4-ylcarbonyl) -D-alaninamide;

N~2~- [ (5-bromoopyridin-3-yl) carbonyl] -N~1~- { (1S, 2R) -1-(3, 5-difluorobenzyl) -3-[ (3-ethylbenzyl) amino] -2-hydroxypropyl} -3-[ (1-propylbutyl) sulfonyl] -D-alaninamide;

N~2~- [(5-chloropyridin-3-yl) carbonyl] -N~1~- { (1S, 2R) -1- (3, 5-difluorobenzyl) -3- [(3-ethylbenzyl) amino] -2-hydroxypropyl} -3- [(1-propylbutyl) sulfonyl] -D-alaninamide;

N~1~- { (1S, 2R) -1- (3, 5-difluorobenzyl) -3- [(3-ethylbenzyl) amino] -2-hydroxypropyl} -N~2~- (3-fluorobenzoyl) -3- [(1-propylbutyl) sulfonyl] -D-alaninamide;

N~1~- { (1S, 2R) -1- (3, 5-difluorobenzyl) -3- [(3-ethylbenzyl) amino] -2-hydroxypropyl} -N~2~- [(5-methylpyridin-3-yl) carbonyl] -3- [(1-propylbutyl) sulfonyl] -D-alaninamide;

N~2~- phenylglycyl -N~1~- { (1S, 2R) -1- (3, 5-difluorobenzyl) -3- [(3-ethylbenzyl) amino] -2-hydroxypropyl} -3- [(1-propylbutyl) sulfonyl] -D-alaninamide;

N~1~- { (1S, 2R) -1- (3, 5-difluorobenzyl) -3- [(3-ethylbenzyl) amino] -2-hydroxypropyl} -3- [(1-propylbutyl) sulfonyl] -N~2~- { [3- (trifluoromethyl) -1H-pyrazol-4-yl] carbonyl} -D-alaninamide;

N~1~- { (1S, 2R) -1- (3, 5-difluorobenzyl) -3- [(3-ethylbenzyl) amino] -2-hydroxypropyl} -N~2~- [(3-methyl-1H-pyrazol-5-yl) carbonyl] -3- [(1-propylbutyl) sulfonyl] -D-alaninamide;

N~1~- { (1S, 2R) -1- (3, 5-difluorobenzyl) -3- [(3-ethylbenzyl) amino] -2-hydroxypropyl} -3- [(1-propylbutyl) sulfonyl] -N~2~- (1, 3-thiazol-4-yl carbonyl) -D-alaninamide;

N~2~- [(1-acetylpiperidin-4-yl) carbonyl] -N~1~- { (1S, 2R) -1- (3, 5-difluorobenzyl) -3- [(3-ethylbenzyl) amino] -2-hydroxypropyl} -3- [(1-propylbutyl) sulfonyl] -D-alaninamide;

N~2~- [4- (acetylamino) butanoyl] -N~1~- { (1S, 2R) -1- (3, 5-difluorobenzyl) -3- [(3-ethylbenzyl) amino] -2-hydroxypropyl} -3- [(1-propylbutyl) sulfonyl] -D-alaninamide;

N~2~- acetyl-beta-alanyl -N~1~- { (1S, 2R) -1- (3, 5-difluorobenzyl) -3- [(3-ethylbenzyl) amino] -2-hydroxypropyl} -3- [(1-propylbutyl) sulfonyl] -D-alaninamide;

N~2~- (chloroacetyl) -N~1~- { (1S, 2R) -1- (3, 5-difluorobenzyl) -3- [(3-ethylbenzyl) amino] -2-hydroxypropyl} -3- [(1-

propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (methoxyacetyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (3-methoxypropanoyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (2,2-dimethylpropanoyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-isobutyryl-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-butyryl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-acetyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl) cyclopropyl] amino]-2-hydroxypropyl)-3-[(1-propylbutyl) sulfonyl]-N~2~-[(pyridin-3-yl) carbonyl]-D-alaninamide trifluoroacetate;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl) cyclopropyl] amino]-2-hydroxypropyl)-3-[(1-propylbutyl) sulfonyl]-N~2~-[(pyridin-4-yl) carbonyl]-D-alaninamide trifluoroacetate;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl) cyclopropyl] amino]-2-hydroxypropyl)-N~2~- (3-hydroxybenzoyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide trifluoroacete;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-[(pyridin-3-yl) carbonyl]-D-

alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-(cyclopropylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-propionyl-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

3-[butylsulfonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(pyridin-3-yl)carbonyl]-D,L-alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-N~2~-(3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoracetate;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N~2~-[(pyridin-4-yl)carbonyl]-D-alaninamide trifluoracetate;

N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]alaninamide hydrochloride;

5-oxo-D-prolyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide;

5-oxo-L-prolyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide;

N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[3-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoyl]-3-[(1-

propylbutyl) sulfonyl] alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(piperidin-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(2,4-dimethyl-1,3-thiazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(2-methyl-4-(trifluoromethyl)-1,3-thiazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(3,5-dimethylisoxazol-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(3-methyl-1H-pyrazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(1H-pyrazol-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(1H-imidazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(1H-imidazol-4-yl)acetyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-[(pyrazin-2-yl)carbonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-



ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(3,5-dihydroxypyridin-4-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(6-hydroxypyridin-3-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~-[(6-chloropyridin-3-yl) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-[(pyridin-4-yl) carbonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(pyridin-3-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-[(pyridin-2-yl) carbonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(1H-indole-6-carbonyl)-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N~2~-[(2,3,4-trimethoxybenzoyl)-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(pyridin-2-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-[(3-hydroxybenzoyl)-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (3-methylbenzoyl)-3-  
[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (3-ethylbenzoyl)-3-  
[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~- (3-chlorobenzoyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-  
[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (4-methylbenzoyl)-3-  
[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (4-methoxybenzoyl)-3-  
[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (4-trifluoromethylbenzoyl)-3-[(1-propylbutyl) sulfonyl]-D,L-  
alaninamide;

N~2~- (cyclohexylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-  
[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~(benzoyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-  
propylbutyl) sulfonyl]-D,L-alaninamide;

N~2~(benzoyl)-N~1~-[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-[(1-  
propylbutyl) sulfonyl]alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (phenylacetyl)-3-[(1-  
propylbutyl) sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~- (3-phenylpropanoyl)-3-  
[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N-(3-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl) amino]-2-hydroxypropyl} amino)-3-oxo-2-[[ (1-propylbutyl) sulfonyl]methyl}propyl) benzamide;

N~1~-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-N~2~- (cyclopropylacetyl)-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N~1~-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-N~2~- [(methylsulfonyl) acetyl]-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N~1~-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-N~2~- [(methylthio) acetyl]-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N~1~-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-N~2~- (4-hydroxy-4-oxobutanoyl)-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N~1~-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-N~2~- [4-(methylamino)-4-oxobutanoyl]-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N~1~-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-N~2~- (4-methoxy-4-oxobutanoyl)-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N-(methylsulfonyl)glycyl-N~1~-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-3-[(1-propylbutyl) sulfonyl]-D, L-alaninamide;

N~2~-acetyl-N~1~-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-3-(phenylsulfonyl)-D, L-alaninamide;

N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}- (2S)-2-[(4-methoxy-4-oxobutanoyl) amino]-5-oxo-5-piperidin-1-ylpentanamide;

(2R)-2-[(benzyloxy) carbonyl] amino}-N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-5-oxo-5-piperidin-1-ylpentanamide;

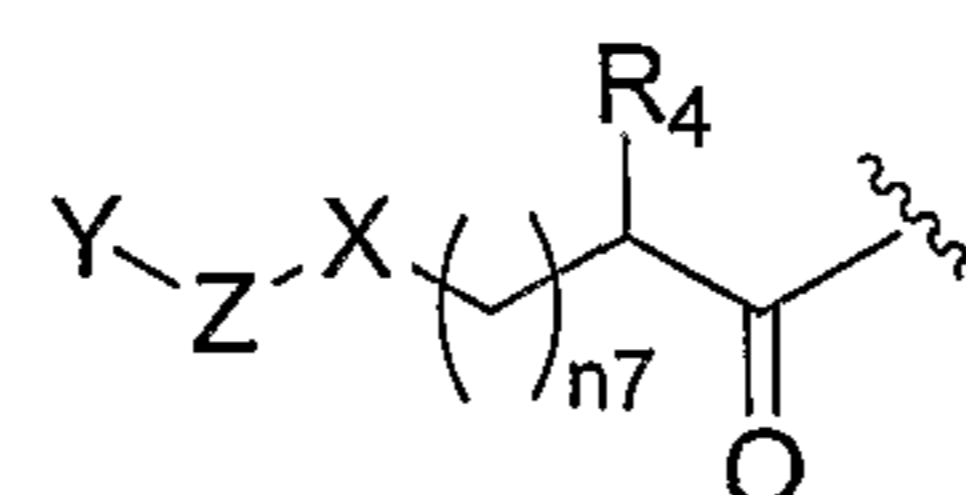
N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}- (2R)-2-[(3-ethoxy-3-oxopropanoyl) amino]-5-oxo-5-piperidin-1-ylpentanamide;

N~1~-{(1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl}-N~2~-(4-methoxy-4-oxobutanoyl)-N~5~,N~5~-dipropyl-D-glutamamide;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-(2R)-2-[(4-methoxy-4-oxobutanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide; and

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-(2R)-2-[(5-methoxy-5-oxopentanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide .

22. A compound according to claim 3, wherein  $R_N$  is of the formula:



5 wherein

$n_7$  is 0, 1, or 2;

$R_4$  is  $-NHR_8$  or  $-NH(CH_2)_{n_6}-R_{4-1}$ ; wherein

$n_6$  is 0, 1, 2, or 3;

10  $R_{4-1}$  is selected from the group consisting of  $-SO_2-(C_1-C_8$  alkyl),  $-SO-(C_1-C_8$  alkyl),  $-S-(C_1-C_8$  alkyl),  $-S-CO-(C_1-C_6$  alkyl),  $-SO_2-NR_{4-2}R_{4-3}$ ;  $-CO-C_1-C_2$  alkyl;  $-CO-NR_{4-3}R_{4-4}$ ;

$R_{4-2}$  and  $R_{4-3}$  are independently H,  $C_1-C_3$  alkyl, or  $C_3-C_6$  cycloalkyl;

15  $R_{4-4}$  is  $C_1-C_4$  alkyl, phenyl  $C_1-C_4$  alkyl,  $C_2-C_4$  alkanoyl, or phenyl  $C_1-C_4$  alkanoyl;

20  $R_8$  is selected from the group consisting of  $-SO_2$ -heteroaryl optionally substituted with 1 or 2 groups that are independently  $C_1-C_4$  alkyl or halogen;  $-SO_2$ -phenyl;  $-SO_2$ -heterocycloalkyl;  $-C(O)NHR_9$ ;

heterocycloalkyl;  $-S-C_2-C_4$  alkanoyl; wherein

$R_9$  is phenyl  $C_1-C_4$  alkyl,  $C_1-C_6$  alkyl, or H;

X is C<sub>1</sub>-C<sub>4</sub> alkylidenyl optionally optionally substituted with  
1, 2, or 3 methyl groups; or -NR<sub>4-6</sub>-; or

R<sub>4</sub> and R<sub>4-6</sub> combine to form -(CH<sub>2</sub>)<sub>n<sub>10</sub></sub>-, wherein

n<sub>10</sub> is 1, 2, 3, or 4;

5 Z is SO<sub>2</sub>; SO; S; or C(O);

Y is H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl containing at  
least one N, O, or S; phenyl; OH; -N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl  
optionally substituted with 1 thru 3 substituents which  
can be the same or different and are selected from

10 halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C<sub>3</sub>-  
C<sub>8</sub> cycloalkyl optionally substituted with 1, 2, or 3  
groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, and  
halogen; alkoxy; phenyl optionally substituted with  
halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; or phenyl C<sub>1</sub>-  
15 C<sub>4</sub> alkyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl,  
C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>10</sub> alkyl  
optionally substituted with 1, 2, or 3 substituents  
selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl,  
20 and OH; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-  
C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; or C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub>  
alkyl; or

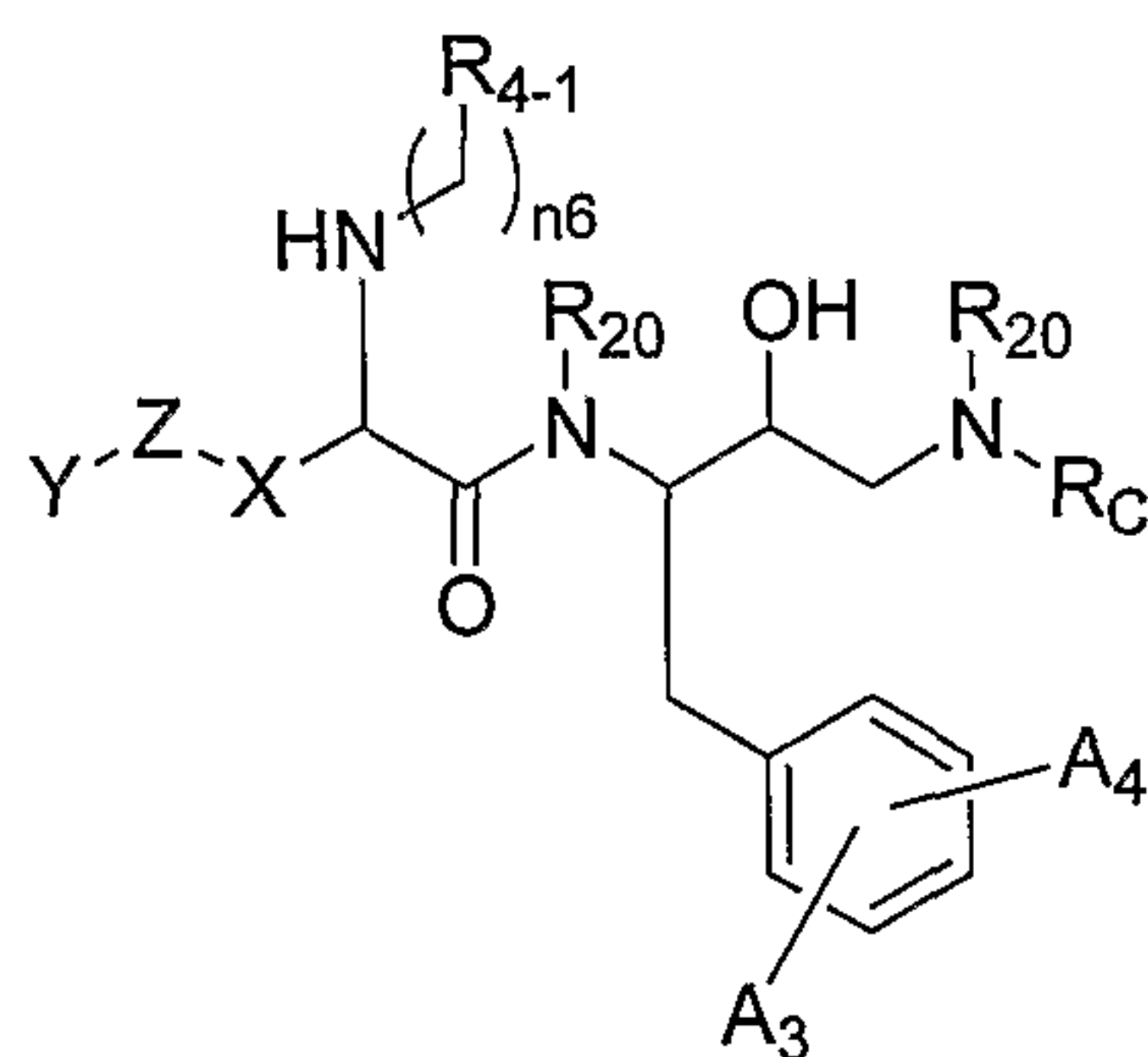
-N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl,  
piperidinyl, morpholinyl, and pyrrolidinyl, wherein  
25 each ring is optionally substituted with 1, 2, 3, or  
4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen; and

R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl,  
C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub>  
30 alkanoyl, each of which is unsubstituted or substituted  
with 1, or 2 groups independently selected from halogen,  
C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>,  
wherein

R<sub>26</sub> is -C(O)-, -SO<sub>2</sub>-, -CO<sub>2</sub>-, -C(O)NH-, or -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-;

R<sub>27</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NH<sub>2</sub>, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl).

23. A compound according to claim 3, of the formula:



wherein

R<sub>C</sub> is C<sub>3</sub>-C<sub>8</sub> alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or - (C<sub>1</sub>-C<sub>4</sub>)alkyl-(C<sub>3</sub>-C<sub>6</sub>) cycloalkyl.

24. A compound according to claim 1, wherein

R<sub>4</sub> is H; C<sub>1</sub>-C<sub>4</sub> alkyl-NHC(O)R<sub>5</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>R<sub>8</sub>; -O-C<sub>1</sub>-C<sub>4</sub> alkanoyl; OH; C<sub>6</sub>-C<sub>10</sub> aryloxy optionally substituted with 1, 2, or 3 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, CO<sub>2</sub>H, -C(O)-C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> alkoxy; aryl C<sub>1</sub>-C<sub>4</sub> alkoxy; -C<sub>1</sub>-C<sub>4</sub> alkyl-NR<sub>50</sub>CO<sub>2</sub>R<sub>51</sub>; -C≡N; -CF<sub>3</sub>; -CF<sub>2</sub>-CF<sub>3</sub>; -C≡CH; -CH<sub>2</sub>-CH=CH<sub>2</sub>; -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>4-1</sub>; -(CH<sub>2</sub>)<sub>1-4</sub>-NH-R<sub>4-1</sub>; -O-(CH<sub>2</sub>)<sub>n6</sub>-R<sub>4-1</sub>; -S-(CH<sub>2</sub>)<sub>n6</sub>-R<sub>4-1</sub>; (CH<sub>2</sub>)<sub>0-4</sub>-NHC(O)-(CH<sub>2</sub>)<sub>0-6</sub>-R<sub>52</sub>; or -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>53</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>54</sub>.

25. A compound according to claim 24, wherein

R<sub>1</sub> is (CH<sub>2</sub>)<sub>n<sub>1</sub></sub>-(R<sub>1-aryl</sub>) where n<sub>1</sub> is zero or one and R<sub>1-aryl</sub> is phenyl optionally substituted with 1, 2, 3, or 4 groups independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -NR<sub>1-a</sub>R<sub>1-b</sub>, -C≡N, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>3</sub> alkoxy; halogen; C<sub>1</sub>-C<sub>6</sub> alkoxy; -NR<sub>N-2</sub>R<sub>N-3</sub>; and OH; wherein

R<sub>N-2</sub> and R<sub>N-3</sub> at each occurrence are independently selected from the group consisting of -C<sub>1</sub>-C<sub>8</sub> alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of -OH, -NH<sub>2</sub>, phenyl and halogen; -C<sub>3</sub>-C<sub>8</sub> cycloalkyl; -(C<sub>1</sub>-C<sub>2</sub> alkyl)-(C<sub>3</sub>-C<sub>8</sub> cycloalkyl); -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl); -C<sub>2</sub>-C<sub>6</sub> alkenyl; -C<sub>2</sub>-C<sub>6</sub> alkynyl; -C<sub>1</sub>-C<sub>6</sub> alkyl chain with one double bond and one triple bond; aryl; heteroaryl; heterocycloalkyl;

or

R<sub>N-2</sub>, R<sub>N-3</sub> and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or heteroaryl group, wherein said heterocycloalkyl or heteroaryl group is optionally fused to a benzene, pyridine, or pyrimidine ring, and said groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that at each occurrence are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -OH, -C(O)NH<sub>2</sub>, -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> thioalkoxy, and C<sub>1</sub>-C<sub>6</sub> thioalkoxy C<sub>1</sub>-C<sub>6</sub> alkyl.

26. A compound according to claim 25, wherein R<sub>20</sub> at each occurrence is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>4</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-

C<sub>4</sub> alkanoyl, each of which is unsubstituted or substituted with 1, or 2 groups independently selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>, wherein

5 R<sub>26</sub> is selected from -C(O)-, -SO<sub>2</sub>-, -CO<sub>2</sub>-;

R<sub>27</sub> is selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, piperidyl, pyrrolyl, and pyridyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NH<sub>2</sub>, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl).

15 27. A compound according to claim 26, wherein

R<sub>4</sub> is H; C<sub>1</sub>-C<sub>4</sub> alkyl-NHC(O)R<sub>5</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>R<sub>8</sub>; -C<sub>1</sub>-C<sub>4</sub> alkyl-NR<sub>50</sub>CO<sub>2</sub>R<sub>51</sub>; -C≡N; -CF<sub>3</sub>; -CF<sub>2</sub>-CF<sub>3</sub>; -C≡CH; -CH<sub>2</sub>-CH=CH<sub>2</sub>; -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>4-1</sub>; -(CH<sub>2</sub>)<sub>1-4</sub>-NH-R<sub>4-1</sub>; (CH<sub>2</sub>)<sub>0-4</sub>-NHC(O)-(CH<sub>2</sub>)<sub>0-6</sub>-R<sub>52</sub>; or -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>53</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>54</sub>.

20

28. A compound according to claim 27, wherein

X is C<sub>1</sub>-C<sub>4</sub> alkylidenyl optionally optionally substituted with 1, 2, or 3 methyl groups; or -NR<sub>4-6</sub>-; or

R<sub>4</sub> and R<sub>4-6</sub> combine to form -(CH<sub>2</sub>)<sub>n10</sub>-, wherein

25 n<sub>10</sub> is 1, 2, 3, or 4;

Z is selected from a bond; SO<sub>2</sub>; SO; S; and C(O);

Y is selected from H; C<sub>1</sub>-C<sub>4</sub> haloalkyl; C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl containing at least one N, O, or S; phenyl; OH; -

30 N(Y<sub>1</sub>)(Y<sub>2</sub>); C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C<sub>3</sub>-C<sub>8</sub> cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, and halogen; alkoxy; phenyl optionally substituted with



halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN or NO<sub>2</sub>; wherein

Y<sub>1</sub> and Y<sub>2</sub> are the same or different and are H; C<sub>1</sub>-C<sub>10</sub> alkyl

5 optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and OH; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkanoyl; phenyl; -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl; phenyl C<sub>1</sub>-C<sub>4</sub> alkyl; and C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl; or

10 -N(Y<sub>1</sub>)(Y<sub>2</sub>) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen.

15

29. A compound according to claim 28, wherein

R<sub>20</sub> at each occurrence is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, tertiary-butoxy carbonyl, and benzyloxycarbonyl;

20 R<sub>1</sub> is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, hydroxy, and C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, or 3 substituents halogen, OH, SH, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N-(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), C≡N, CF<sub>3</sub>;

25 R<sub>2</sub> and R<sub>3</sub> are independently selected from H or C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 1 substituent selected from halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), and NH(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);

30 R<sub>20</sub> at each occurrence is independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> alkoxy C<sub>1</sub>-C<sub>4</sub> alkyl, halo C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, each of which is unsubstituted or substituted with 1 or 2 groups independently selected from halogen, hydroxy, and NH<sub>2</sub>;

$R_C$  is  $C_1$ - $C_8$  alkyl optionally substituted with 1, 2, or 3 groups independently selected from  $R_{205}$ ,  $-SH$ ,  $-C=ONR_{235}R_{240}$ , and  $-S(=O)_2NR_{235}R_{240}$ ;  $-(CH_2)_{0-3}$ - $(C_3-C_6)$  cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from  $R_{205}$ ,  $-CO_2H$ , and  $-CO_2$ - $(C_1-C_4)$  alkyl);  $-(CR_{245}R_{250})_{0-4}$ -phenyl optionally substituted with 1, 2, or 3  $R_{200}$ ;  $-(CR_{245}R_{250})_{0-3}$ -pyridyl;  $-(CR_{245}R_{250})_{0-3}$ -pyridazinyl;  $-(CR_{245}R_{250})_{0-3}$ -pyrimidinyl;  $-(CR_{245}R_{250})_{0-3}$ -pyrazinyl;  $-(CR_{245}R_{250})_{0-3}$ -furyl;  $-(CR_{245}R_{250})_{0-3}$ -indolyl;  $-(CR_{245}R_{250})_{0-3}$ -thienyl;  $-(CR_{245}R_{250})_{0-3}$ -pyrrolyl;  $-(CR_{245}R_{250})_{0-3}$ -pyrazolyl;  $(CR_{245}R_{250})_{0-3}$ -benzoxazolyl;  $-(CR_{245}R_{250})_{0-3}$ -imidazolyl; each of the above heteroaryl groups is optionally substituted with 1, 2, 3, or 4  $R_{200}$ ;  $-(CR_{245}R_{250})_{0-3}$ -imidazolidinyl;  $(CR_{245}R_{250})_{0-3}$ -tetrahydrofuryl;  $(CR_{245}R_{250})_{0-3}$ -tetrahydropyranyl;  $(CR_{245}R_{250})_{0-3}$ -piperazinyl;  $(CR_{245}R_{250})_{0-3}$ -pyrrolidinyl;  $(CR_{245}R_{250})_{0-3}$ -piperidinyl;  $(CR_{245}R_{250})_{0-3}$ -indolinyl; each of the above heterocycloalkyl groups is optionally substituted with 1, 2, 3, or 4  $R_{210}$ ;  $(CH_2)_{0-1}$ - $CH((CH_2)_{0-4}-OH)$ - $(CH_2)_{0-1}$ -phenyl;  $-(CH_2)_{0-1}$ - $CH(C_1-C_4)$  hydroxyalkyl)- $(CH_2)_{0-1}$ -pyridyl;

$R_{200}$  at each occurrence is independently  $C_1$ - $C_6$  alkyl optionally substituted with 1, 2, or 3  $R_{205}$  groups;  $OH$ ;  $-NO_2$ ; halogen;  $-CO_2H$ ;  $C\equiv N$ ;  $-(CH_2)_{0-4}-CO-NR_{220}R_{225}$ ;  $-(CH_2)_{0-4}-CO-(C_1-C_8)$  alkyl);  $-(CH_2)_{0-4}-CO_2R_{215}$ ; and  $-(CH_2)_{0-4}-O-(C_1-C_6)$  alkyl optionally substituted with 1, 2, 3, or 5  $-F$ );

$R_{205}$  at each occurrence is independently  $C_1$ - $C_6$  alkyl, halogen,  $-OH$ ,  $-O$ -phenyl,  $-SH$ ,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1$ - $C_6$  alkoxy,  $NH_2$ ,  $NH(C_1-C_6)$  alkyl), and  $N-(C_1-C_6)$  alkyl)( $C_1-C_6$  alkyl);

$R_{210}$  at each occurrence is independently  $C_1$ - $C_6$  alkyl optionally substituted with 1 or 2  $R_{205}$  groups; halogen;  $C_1$ - $C_4$  alkoxy;  $C_1$ - $C_4$  haloalkoxy;  $-NR_{220}R_{225}$ ;  $OH$ ;  $C\equiv N$ ;  $C_3$ - $C_7$  cycloalkyl optionally substituted with 1

or 2 R<sub>205</sub> groups; -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl); -SO<sub>2</sub>-NR<sub>235</sub>R<sub>240</sub>; -CO-NR<sub>235</sub>R<sub>240</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); and =O; wherein

R<sub>215</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(phenyl), C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(pyridyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(pyrrolyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(imidazolyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(pyrimidyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(pyrrolidinyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(imidazolidinyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(piperazinyl), -(CH<sub>2</sub>)<sub>0-2</sub>-(piperidinyl), and -(CH<sub>2</sub>)<sub>0-2</sub>-(morpholinyl); wherein the phenyl group at each occurrence is optionally substituted with 1 or 2 groups that are independently R<sub>205</sub> or R<sub>210</sub>; wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1 or 2 R<sub>210</sub>; wherein each heteroaryl group at each occurrence is optionally substituted with 1 or 2 R<sub>210</sub>;

R<sub>220</sub> and R<sub>225</sub> at each occurrence are independently -H, -C<sub>1</sub>-C<sub>4</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkyl, halo C<sub>1</sub>-C<sub>4</sub> alkyl; -C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-(C<sub>1</sub>-C<sub>2</sub> alkyl);

R<sub>235</sub> and R<sub>240</sub> at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms.

30. A compound according to claim 29 wherein

R<sub>4</sub> is H; C<sub>1</sub>-C<sub>4</sub> alkyl-NHC(O)R<sub>5</sub>; -(CH<sub>2</sub>)<sub>0-4</sub>R<sub>8</sub>; -C<sub>1</sub>-C<sub>4</sub> alkyl-NR<sub>50</sub>CO<sub>2</sub>R<sub>51</sub>; -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>4-1</sub>; -(CH<sub>2</sub>)<sub>1-4</sub>-NH-R<sub>4-1</sub>; (CH<sub>2</sub>)<sub>1-4</sub>-NHC(O)-(CH<sub>2</sub>)<sub>0-6</sub>-R<sub>52</sub>; or -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>53</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>54</sub>; wherein

R<sub>4-1</sub> is -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub> alkyl), -SO<sub>2</sub>-NR<sub>4-2</sub>R<sub>4-3</sub>; or -CO-NR<sub>4-3</sub>R<sub>4-4</sub>;

wherein

R<sub>4-2</sub> and R<sub>4-3</sub> are independently H, or C<sub>1</sub>-C<sub>3</sub> alkyl;

R<sub>4-4</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, or phenyl C<sub>1</sub>-C<sub>4</sub> alkanoyl;

R<sub>5</sub> is selected from the group consisting of cyclopropyl; cyclopentyl; cyclohexyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally

5 substituted with 1, 2, or 3 groups that are independently halogen, -NR<sub>6</sub>R<sub>7</sub>, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>5</sub>-C<sub>6</sub> heterocycloalkyl, C<sub>5</sub>-C<sub>6</sub> heteroaryl, phenyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -S-C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>7</sub>, -CO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, or phenyloxy; pyridyl,

10 thiazolyl, pyrazolyl, pyrazinyl, optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or OH; piperidinyl, dihydropyridazinonyl, pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl, imidazolyl, indolyl, optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or C<sub>2</sub>-C<sub>4</sub> alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> haloalkyl; wherein

R<sub>6</sub> and R<sub>7</sub> are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl, and phenethyl;

R<sub>8</sub> is -SO<sub>2</sub>-thienyl optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl or halogen; -SO<sub>2</sub>-phenyl, -SO<sub>2</sub>-piperidinyl, -SO<sub>2</sub>-pyrrolidinyl, imidazolidinyyl dione, -C(O)NHR<sub>9</sub>, -S-C<sub>1</sub>-C<sub>6</sub> alkyl, or -S-C<sub>2</sub>-C<sub>4</sub> alkanoyl, wherein

R<sub>9</sub> is phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, or H;

30 R<sub>50</sub> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>51</sub> is selected from benzyl; phenethyl; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR<sub>6</sub>R<sub>7</sub>, -C(O)NR<sub>6</sub>R<sub>7</sub>, or -C<sub>1</sub>-C<sub>4</sub> alkoxy; heterocycloalkyl containing at

least one N, O, or S and optionally substituted with  
 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-  
 C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl, phenyl C<sub>1</sub>-C<sub>4</sub>  
 alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; heterocycloalkylalkyl  
 5 containing at least one N, O, or S and optionally  
 substituted with 1 or 2 groups that are independently  
 C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>2</sub>-C<sub>4</sub> alkanoyl,  
 phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, and -SO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>2</sub>-C<sub>6</sub>  
 alkenyl; C<sub>2</sub>-C<sub>6</sub> alkynyl; heteroaryl optionally  
 10 substituted with 1, 2, or 3 groups that are  
 independently OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen,  
 NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl);  
 heteroarylalkyl containing at least one N, O, or S  
 and optionally substituted with 1, 2, or 3 groups  
 15 that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy,  
 halogen, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl) or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub>  
 alkyl); phenyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl  
 C<sub>1</sub>-C<sub>4</sub> alkyl, wherein the phenyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and  
 C<sub>3</sub>-C<sub>6</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl groups are optionally  
 20 substituted with 1, 2, or 3 groups that are  
 independently halogen, CN, NO<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub>  
 alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub>  
 haloalkoxy, hydroxy, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub>  
 thioalkoxy;

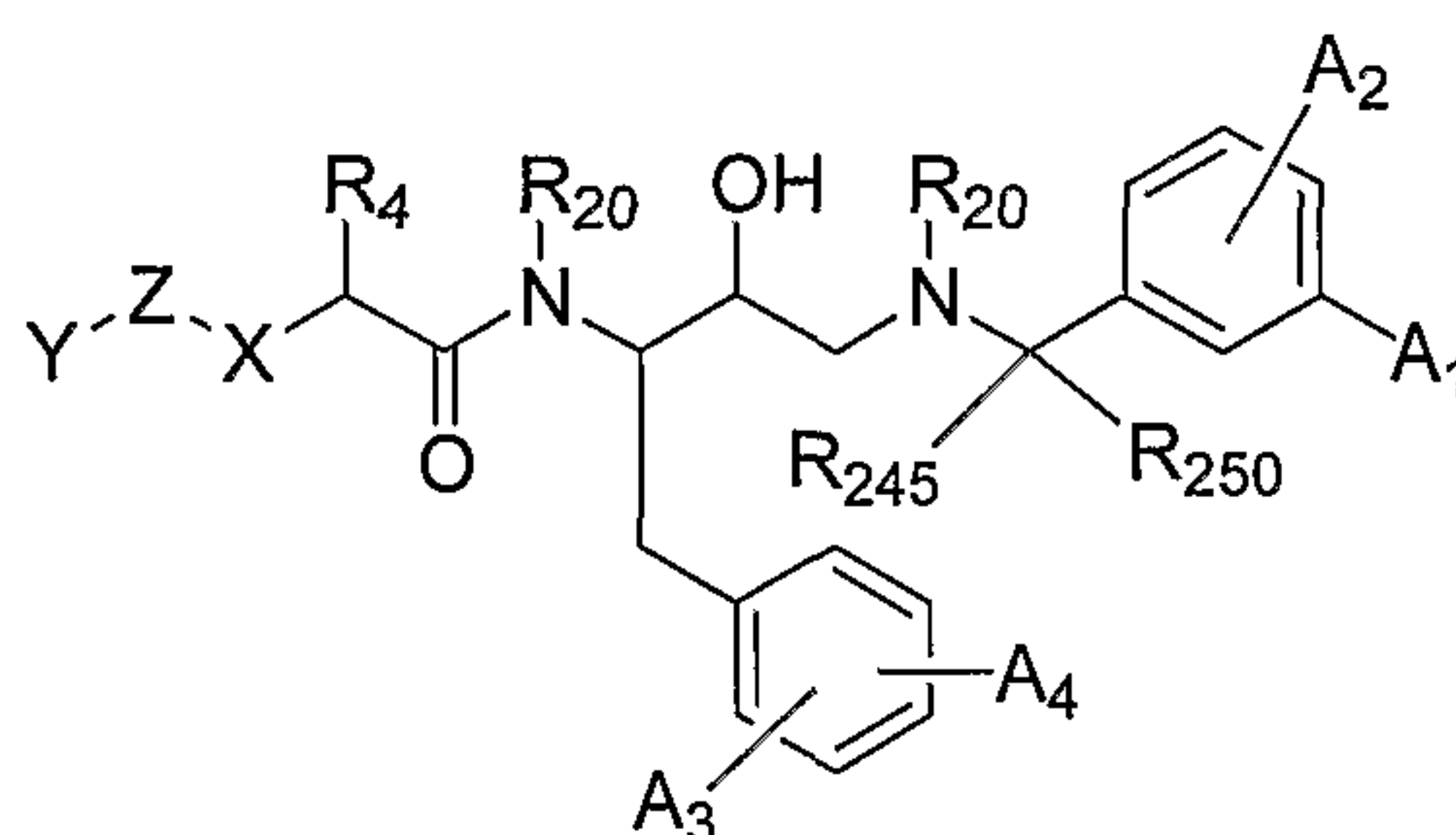
25 R<sub>52</sub> is heterocycloalkyl, heteroaryl, phenyl, C<sub>3</sub>-C<sub>6</sub>  
 cycloalkyl, -S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, CO<sub>2</sub>H, -C(O)NH<sub>2</sub>,  
 -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -CO<sub>2</sub>-alkyl,  
 -NHS(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(alkyl)S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl,  
 -S(O)<sub>0-2</sub>-heteroaryl, -S(O)<sub>0-2</sub>-aryl, -NH(arylalkyl),  
 30 -N(alkyl)(arylalkyl), thioalkoxy, or alkoxy, each of  
 which is optionally substituted with 1, 2, 3, 4, or 5  
 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub>  
 alkoxy, C<sub>1</sub>-C<sub>4</sub> thioalkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl,

haloalkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, NO<sub>2</sub>, CN, C<sub>1</sub>-C<sub>4</sub>  
alkoxycarbonyl, or aminocarbonyl;

R<sub>53</sub> is absent, -O-, -C(O)-, -NH-, -N(alkyl)-, -NH-S(O)<sub>0-2</sub>-,  
-N(alkyl)-S(O)<sub>0-2</sub>-, -S(O)<sub>0-2</sub>-NH-, or -S(O)<sub>0-2</sub>-N(alkyl)-;

5 R<sub>54</sub> is pyridyl, thienyl, imidazolyl, phenyl, phenyl C<sub>1</sub>-C<sub>4</sub>  
alkyl, piperidyl, pyrrolidinyl, imidazolidinyl dione,  
CO<sub>2</sub>H, -CO<sub>2</sub>-alkyl, -C(O)NH(alkyl), -C(O)N(alkyl)  
(alkyl), -C(O)NH<sub>2</sub>, C<sub>1</sub>-C<sub>8</sub> alkyl, OH, phenoxy, alkoxy,  
phenylalkoxy, NH<sub>2</sub>, NH(alkyl), N(alkyl) (alkyl), or -  
10 C<sub>1</sub>-C<sub>6</sub> alkyl-CO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, each of which is  
optionally substituted with 1, 2, 3, 4, or 5 groups  
that are independently alkyl, alkoxy, CO<sub>2</sub>H, -CO<sub>2</sub>-  
alkyl, thioalkoxy, halogen, haloalkyl, haloalkoxy,  
hydroxyalkyl, alkanoyl, NO<sub>2</sub>, CN, alkoxycarbonyl, or  
15 aminocarbonyl.

31. A compound according to claim 30 of the formula:



20 wherein

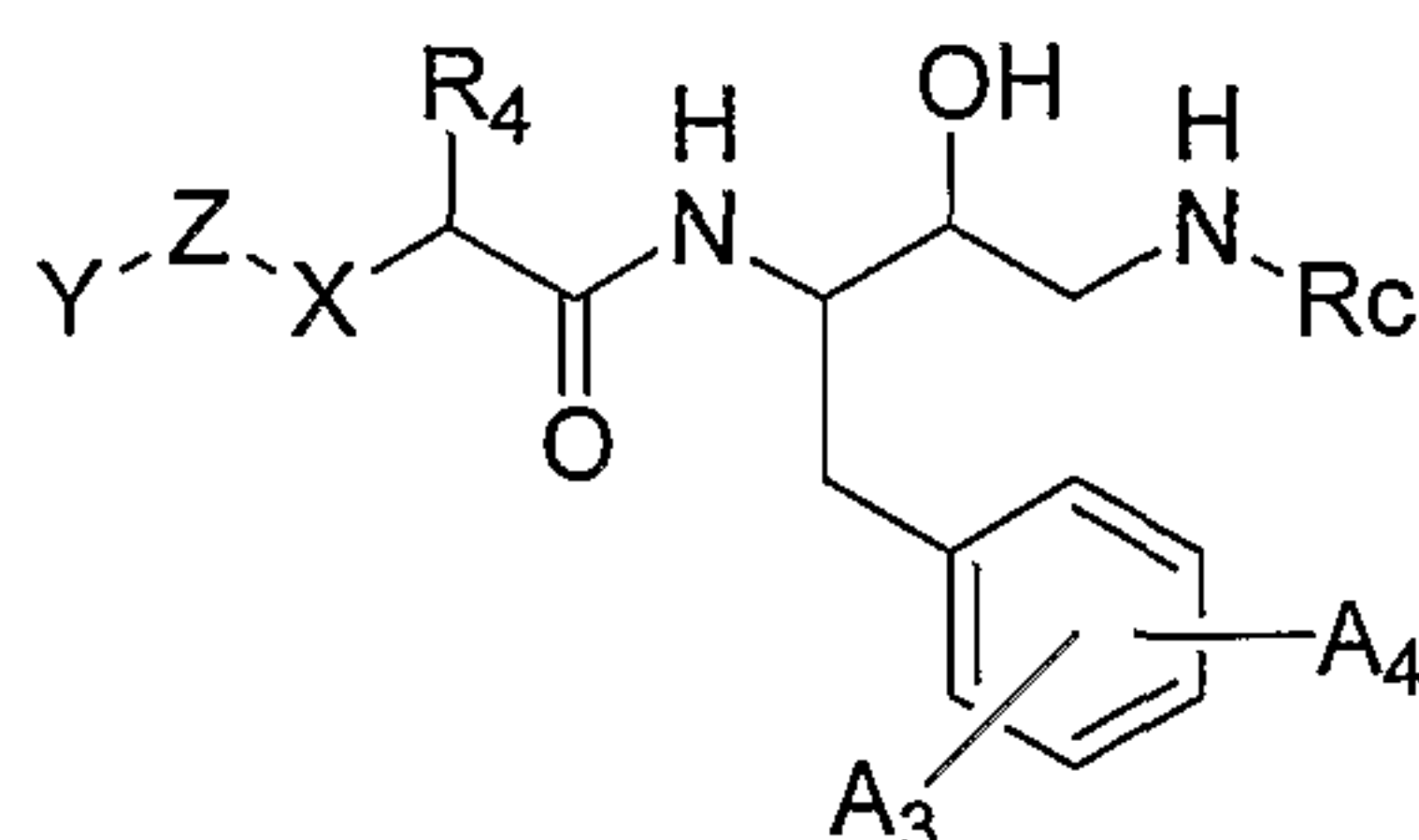
A<sub>1</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy;

A<sub>2</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, C<sub>1</sub>-C<sub>4</sub>  
haloalkyl or OH;

A<sub>3</sub> and A<sub>4</sub> are independently C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, or H.

25

32. A compound according to claim 30 of the formula:



wherein

$R_c$  is  $C_3$ - $C_8$  alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or -  
( $C_1$ - $C_4$ )alkyl-( $C_3$ - $C_6$ ) cycloalkyl; and

5  $A_3$  and  $A_4$  are independently  $C_1$ - $C_4$  alkyl, halogen, or H.

33. A compound according to claim 1, wherein

$R_4$  is  $-C_1$ - $C_4$  alkyl- $NR_{50}CO_2R_{51}$ ;  $-(CH_2)_{1-4}-NH-R_{4-1}$ ; or  $(CH_2)_{1-4}-NHC(O)-$   
( $CH_2$ ) $_{0-6}-R_{52}$ ; wherein

10  $R_{50}$  is H or  $C_1$ - $C_4$  alkyl;

$R_{51}$  is selected from benzyl; phenethyl;  $C_1$ - $C_6$  alkyl

optionally substituted with 1, 2, or 3 groups that  
are independently halogen, cyano,  $-NR_6R_7$ ,  $-C(O)NR_6R_7$ ,  
or  $-C_1$ - $C_4$  alkoxy; heterocycloalkyl containing at

15 least one N, O, or S and optionally substituted with  
1 or 2 groups that are independently  $C_1$ - $C_4$  alkyl,  $C_1$ -  
 $C_4$  alkoxy, halogen,  $C_2$ - $C_4$  alkanoyl, phenyl  $C_1$ - $C_4$   
alkyl, and  $-SO_2$   $C_1$ - $C_4$  alkyl; heterocycloalkylalkyl

20 containing at least one N, O, or S and optionally  
substituted with 1 or 2 groups that are independently  
 $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, halogen,  $C_2$ - $C_4$  alkanoyl,  
phenyl  $C_1$ - $C_4$  alkyl, and  $-SO_2$   $C_1$ - $C_4$  alkyl;  $C_2$ - $C_6$

alkenyl;  $C_2$ - $C_6$  alkynyl; heteroaryl optionally  
substituted with 1, 2, or 3 groups that are

25 independently OH,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, halogen,  
 $NH_2$ ,  $NH(C_1$ - $C_6$  alkyl) or  $N(C_1$ - $C_6$  alkyl)( $C_1$ - $C_6$  alkyl);  
heteroarylalkyl containing at least one N, O, or S  
and optionally substituted with 1, 2, or 3 groups  
that are independently  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,

30 halogen,  $NH_2$ ,  $NH(C_1$ - $C_6$  alkyl) or  $N(C_1$ - $C_6$  alkyl)( $C_1$ - $C_6$

alkyl); phenyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl  
 C<sub>1</sub>-C<sub>4</sub> alkyl, wherein the phenyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and  
 C<sub>3</sub>-C<sub>6</sub> cycloalkyl C<sub>1</sub>-C<sub>4</sub> alkyl groups are optionally  
 substituted with 1, 2, or 3 groups that are  
 5 independently halogen, CN, NO<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub>  
 alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub>  
 haloalkoxy, hydroxy, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub>  
 thioalkoxy;

R<sub>6</sub> and R<sub>7</sub> are independently selected from the group  
 10 consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl,  
 phenyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl, and phenethyl;

R<sub>52</sub> is heterocycloalkyl, heteroaryl, phenyl, C<sub>3</sub>-C<sub>6</sub>  
 cycloalkyl, -S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, CO<sub>2</sub>H, -C(O)NH<sub>2</sub>,  
 -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -CO<sub>2</sub>-alkyl,  
 15 -NHS(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(alkyl)S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl,  
 -S(O)<sub>0-2</sub>-heteroaryl, -S(O)<sub>0-2</sub>-aryl, -NH(arylalkyl),  
 -N(alkyl)(arylalkyl), thioalkoxy, or alkoxy, each of  
 which is optionally substituted with 1, 2, 3, 4, or 5  
 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub>  
 20 alkoxy, C<sub>1</sub>-C<sub>4</sub> thioalkoxy, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl,  
 haloalkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyl, NO<sub>2</sub>, CN, C<sub>1</sub>-C<sub>4</sub>  
 alkoxycarbonyl, or aminocarbonyl.

34. A compound according to claim 33, wherein

25 R<sub>4</sub> is -O-C<sub>1</sub>-C<sub>4</sub> alkanoyl; OH; phenyloxy or naphthyloxy, each of  
 which is optionally substituted with 1, 2, or 3 groups  
 that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, CO<sub>2</sub>H, -C(O)-  
 C<sub>1</sub>-C<sub>4</sub> alkoxy, or C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> alkoxy; phenyl C<sub>1</sub>-C<sub>4</sub>  
 alkoxy; -O-(CH<sub>2</sub>)<sub>n6</sub>-R<sub>4-1</sub>; or -S-(CH<sub>2</sub>)<sub>n6</sub>-R<sub>4-1</sub>

30 R<sub>4-1</sub> is -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub> alkyl), -SO<sub>2</sub>-NR<sub>4-2</sub>R<sub>4-3</sub>; or -CO-NR<sub>4-3</sub>R<sub>4-4</sub>; wherein  
 R<sub>4-2</sub> and R<sub>4-3</sub> are independently H, or C<sub>1</sub>-C<sub>3</sub> alkyl;  
 R<sub>4-4</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, or  
 phenyl C<sub>1</sub>-C<sub>4</sub> alkanoyl;



35. A method for the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative  
5 dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease comprising administration of a  
10 therapeutically effective amount of a compound or salt according to Claim 1, to a patient in need thereof.

36. A method of treatment as in claim 35, wherein the patient is a human.

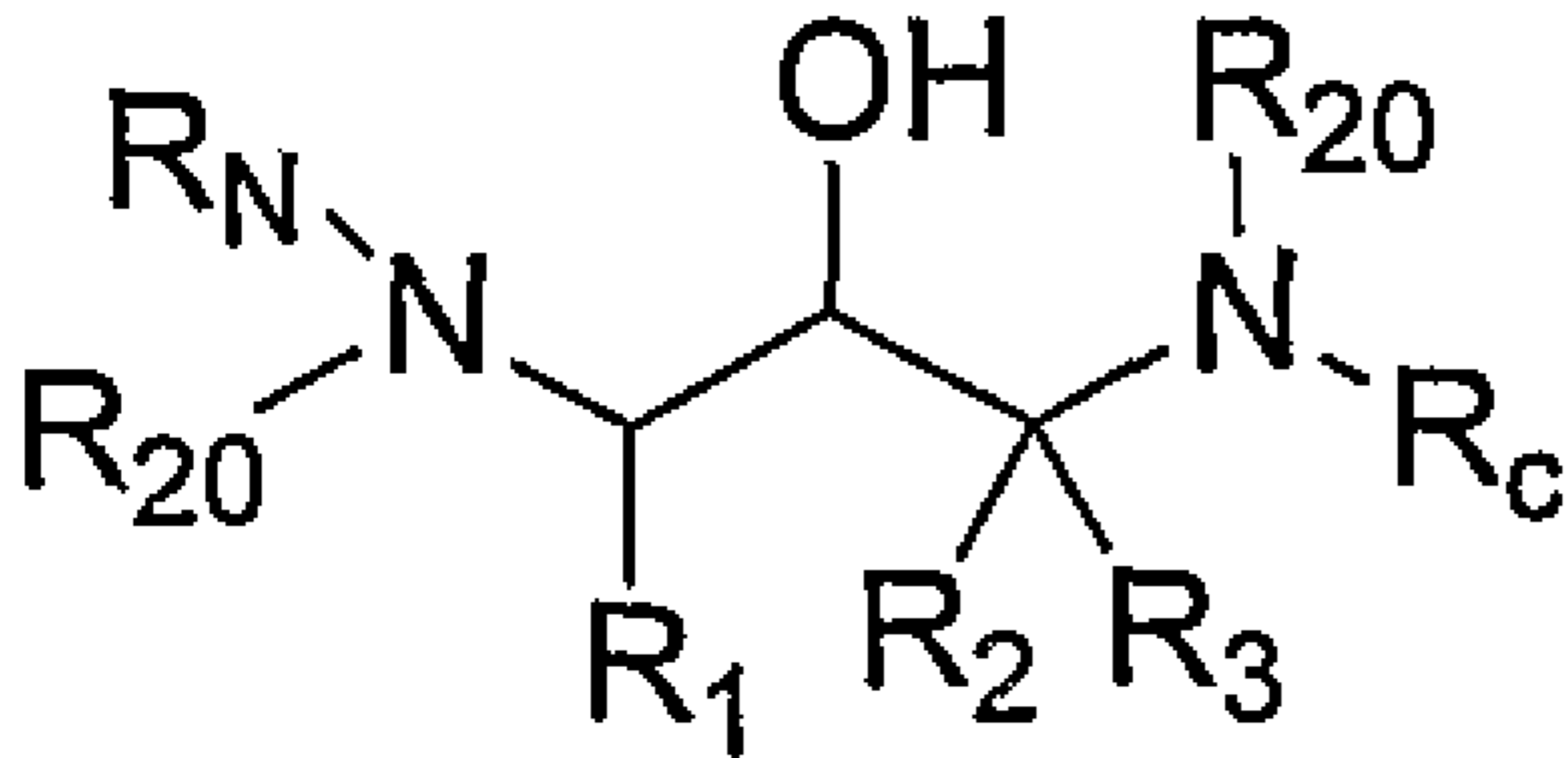
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37. A method of treatment according to claim 35, wherein the disease is dementia.

38. The use of a compound or salt according to claim 1  
20 for the manufacture of a medicament.

39. The use of a compound or salt according to claim 1 for the manufacture of a medicament for use in the treatment or prevention of Alzheimer's disease, mild cognitive impairment  
25 Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear  
30 palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease.

40. A method of preparing a compound of claim 1.



(X)