

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
16 January 2003 (16.01.2003)

PCT

(10) International Publication Number  
WO 03/004018 A1

(51) International Patent Classification<sup>7</sup>: A61K 31/40,  
C07D 209/52, 401/12, 487/04, 401/14, A61K 31/403,  
A61P 25/00, C07D 209/42

Corporation., 35 Northeast Industrial Road, Branford, CT  
06405 (US).

(21) International Application Number: PCT/IB02/02499

(74) Agents: LUMB, J. Trevor et al.; c/o Simpson, Alison,  
Urquhart-Dykes & Lord, 30 Welbeck Street, London, W1G  
8ER (GB).

(22) International Filing Date: 27 June 2002 (27.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/303,467 6 July 2001 (06.07.2001) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,  
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,  
VN, YU, ZA, ZM, ZW.

(71) Applicants (*for all designated States except US*): PFIZER  
PRODUCTS INC. [US/US]; Eastern Point Road, Gro-  
ton, CT 06340 (US). NEUROGEN CORPORATION  
[US/US]; 35 Northeast Industrial Road, Branford, CT  
06405 (US).

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,  
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent  
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,  
NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): YOHANNES,  
Daniel [ER/US]; Pfizer Global Research and Develop-  
ment, Eastern Po, Eastern Point Road, Groton, CT 06340  
(US). LIU, Xiaojun [CN/US]; Pfizer Global Research  
and Development, Eastern Point Road, Groton, CT 06340  
(US). MAYNARD, George, Daniel [US/US]; Neurogen

Published:

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: CYCLOALKYLPYRROLE-3-CARBOXYLIC ACID DERIVATIVES AND HETEROCYCLOALKYLPYRROLE-3-CARBOXYLIC ACID DERIVATIVES AS GABA-A RECEPTOR LIGANDS

(57) Abstract: This invention relates to cycloalkylpyrrole-3-carboxylic acid derivatives and heterocycloalkylpyrrole-3-carboxylic acid derivatives that bind with high selectivity and/or high affinity to the benzodiazepine site of GABA<sub>A</sub> receptors. This invention also relates to pharmaceutical compositions comprising such compounds and to the use of such compounds in the treatment of central nervous system (CNS) diseases. This invention also relates to the use of these cycloalkylpyrrole-3-carboxylic acid derivatives and heterocycloalkylpyrrole-3-carboxylic acid derivatives in combination with one or more other CNS agents to potentiate the effects of the other CNS agents. Additionally this invention relates to the use such compounds as probes for the detection of GABA<sub>A</sub> receptors in tissue samples.



WO 03/004018 A1

**Cycloalkylpyrrole-3-Carboxylic Acid Derivatives and Heterocycloalkylpyrrole-3-Carboxylic Acid Derivatives**

**Field of the Invention**

This invention relates to a certain cycloalkylpyrrole-3-carboxylic acid derivatives and  
5 heterocycloalkylpyrrole-3-carboxylic acids derivatives that bind with high selectively and/or  
high affinity to the benzodiazepine site of GABA<sub>A</sub> receptors. This invention also relates to  
pharmaceutical compositions comprising such compounds and to the use of such compounds  
in the treatment of central nervous system (CNS) diseases. This invention also relates to the  
use of these cycloalkylpyrrole-3-carboxylic acid derivative and heterocycloalkylpyrrole-3-  
10 carboxylic acids derivative compounds in combination with one or more other CNS agents to  
potentiate the effects of the other CNS agents. Additionally this invention relates to the use  
such compounds as probes for the localization of GABA<sub>A</sub> receptors in tissue sections.

**Background**

The GABA<sub>A</sub> receptor superfamily represents one of the classes of receptors through  
15 which the major inhibitory neurotransmitter,  $\gamma$ -aminobutyric acid, or GABA, acts. Widely,  
although unequally, distributed throughout the mammalian brain, GABA mediates many of its  
actions through a complex of proteins called the GABA<sub>A</sub> receptor, which causes alteration in  
chloride conductance and membrane polarization. In addition to being the site of  
neurotransmitter action, a number of drugs including the anxiolytic and sedating  
20 benzodiazepines bind to this receptor. The GABA<sub>A</sub> receptor comprises a chloride channel  
that generally, but not invariably, opens in response to GABA, allowing chloride to enter the  
cell. This, in turn, effects a slowing of neuronal activity through hyperpolarization of the cell  
membrane potential.

GABA<sub>A</sub> receptors are composed of five protein subunits. A number of cDNAs for  
25 these GABA<sub>A</sub> receptor subunits have been cloned and their primary structures determined.  
While these subunits share a basic motif of 4 membrane-spanning helices, there is sufficient  
sequence diversity to classify them into several groups. To date at least 6 $\alpha$ , 3 $\beta$ , 3 $\gamma$ , 1 $\epsilon$ , 1 $\delta$   
and 2 $\rho$  subunits have been identified. Native GABA<sub>A</sub> receptors are typically composed of 2 $\alpha$ ,  
2 $\beta$ , and 1 $\gamma$ . Various lines of evidence (such as message distribution, genome localization and  
30 biochemical study results) suggest that the major naturally occurring receptor combinations  
are  $\alpha_1\beta_2\gamma_2$ ,  $\alpha_2\beta_3\gamma_2$ ,  $\alpha_3\beta_3\gamma_2$ , and  $\alpha_5\beta_3\gamma_2$  (Mohler *et al.*, *Neuroch. Res.* 1995; 20(5):631-36).

The GABA<sub>A</sub> receptor binding sites for GABA (2 per receptor complex) are formed by  
amino acids from the  $\alpha$  and  $\beta$  subunits. Amino acids from the  $\alpha$  and  $\gamma$  subunits together form  
one benzodiazepine site per receptor. Benzodiazepines exert their pharmacological actions  
35 by interacting with the benzodiazepine binding sites associated with the GABA<sub>A</sub> receptor. In  
addition to the benzodiazepine site (sometimes referred to as the benzodiazepine or BDZ  
receptor), the GABA<sub>A</sub> receptor contains sites of interaction for several other classes of drugs.

These include a steroid binding site, a picrotoxin site, and a barbiturate site. The benzodiazepine site of the GABA<sub>A</sub> receptor is a distinct site on the receptor complex that does not overlap with the site of interaction for other classes of drugs that bind to the receptor or for GABA (see, e.g., Cooper, et al., *The Biochemical Basis of Neuropharmacology*, 6<sup>th</sup> ed., 1991, pp. 145-148, Oxford University Press, New York).

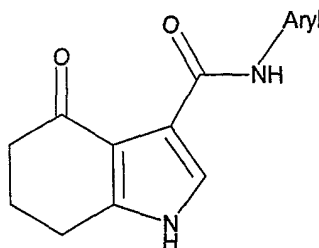
In a classic allosteric mechanism, the binding of a drug to the benzodiazepine site increases the affinity of the GABA receptor for GABA. Benzodiazepines and related drugs that enhance the ability of GABA to open GABA<sub>A</sub> receptor channels are known as agonists or partial agonists depending on the level of GABA enhancement. Other classes of drugs, such as β-carboline derivatives, that occupy the same site and negatively modulate the action of GABA are called inverse agonists. A third class of compounds exists which occupy the same site as both the agonists and inverse agonists and yet have little or no effect on GABA activity. These compounds will, however, block the action of agonists or inverse agonists and are thus referred to as GABA<sub>A</sub> receptor antagonists.

The important allosteric modulatory effects of drugs acting at the benzodiazepine site were recognized early, and the distribution of activities at different subtype receptors has been an area of intense pharmacological discovery. Agonists that act at the benzodiazepine site are known to exhibit anxiolytic, sedative, and hypnotic effects, while compounds that act as inverse agonists at this site elicit anxiogenic, cognition enhancing, and proconvulsant effects. While benzodiazepines have enjoyed long pharmaceutical use as anxiolytics, these compounds are known to exhibit a number of unwanted side effects. These may include cognitive impairment, sedation, ataxia, potentiation of ethanol effects, and a tendency for tolerance and drug dependence.

GABA<sub>A</sub> selective ligands may also act to potentiate the effects of certain other CNS active compounds. For example, there is evidence that selective serotonin reuptake inhibitors (SSRIs) may show greater antidepressant activity when used in combination with GABA<sub>A</sub> selective ligands than when used alone.

#### Description of the Related Art

Cyclohexanone pyrrole carboxamide compounds of the following general Formula A have been previously disclosed as modulators of GABA<sub>A</sub> receptors.



Formula A

PCT publications WO 95/11885, WO 97/26243, WO 9734870, WO 98/02420, and WO 00/23862U.S. Patent Nos. 5,484,944, 5,608,079, 5,750,702, 5,925,770, 5,637,724, 5,804,686, 5,849,927, 6,080,873, and 6,211,365, all of which are assigned to Neurogen Corporation, disclose structures of Formula A.

5

#### Summary of the Invention

This invention relates to certain novel cycloalkylpyrrole-3-carboxylic acid derivatives and heterocycloalkylpyrrole-3-carboxylic acid derivatives that bind with high affinity and high selectivity to the benzodiazepine site of GABA<sub>A</sub> receptors, including human GABA<sub>A</sub> receptors. Compounds of the invention bind with high selectivity and/or high affinity to GABA<sub>A</sub> receptors and thereby act as agonists, antagonists or inverse agonists of such receptors. As such, they are useful in the treatment of various CNS disorders.

10

The invention provides novel compounds of Formula I (shown below), and pharmaceutical compositions comprising compounds of Formula I.

The invention further comprises methods of treating patients suffering from certain CNS disorders with an effective amount of a compound of the invention. The patient may be a human or other mammal. Treatment of humans, domesticated companion animals (pets) or livestock animals suffering from certain CNS disorders with an effective amount of a compound of the invention is encompassed by the invention.

15

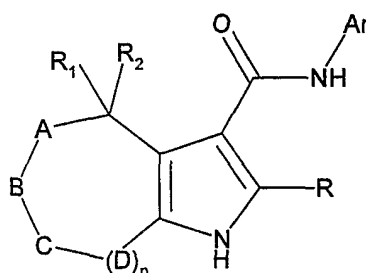
In a separate aspect, the invention provides a method of potentiating the actions of other CNS active compounds. This method comprises administering an effective amount of a compound of the invention in conjunction with the administration of another CNS active compound.

20

Additionally this invention relates to the use of compounds of Formula I as probes for the localization of GABA<sub>A</sub> receptors in tissue sections.

25

Accordingly, in a broad aspect the invention is directed to compounds of Formula I,



Formula I

and the pharmaceutically acceptable salts thereof, wherein:

R is selected from halogen, cyano, nitro, and amino;

30

R<sub>1</sub> is chosen from amino, fluoro, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, arylamino, heteroaryl amino, aryloxy, or heteroaryloxy; and

R<sub>2</sub> is chosen from hydrogen, fluoro, C<sub>1</sub>-C<sub>6</sub> alkyl, and aryl(C<sub>1</sub>-C<sub>4</sub>alkyl); or

R<sub>1</sub> and R<sub>2</sub> together represent an oxo group; or

R<sub>1</sub> and R<sub>2</sub> are joined to form a saturated, or partially unsaturated ring of from 4 to 8 members containing 1 or more heteroatoms, preferably from 1 to 4 heteroatoms, independently chosen from N, S, and O, with the proviso that no two heteroatoms, with the  
5 exception of amino groups (forming a hydrazino group) are adjacent to each other;

n is 0, 1, or 2;

A is chosen from O, NR<sub>3</sub>, and CR<sub>3</sub>R<sub>3</sub>';

B is chosen from O, NR<sub>4</sub>, and CR<sub>4</sub>R<sub>4</sub>';

C is chosen from O, NR<sub>5</sub>, and CR<sub>5</sub>R<sub>5</sub>';

10 each D is independently selected from O, NR<sub>6</sub>, and CR<sub>6</sub>R<sub>6</sub>';

each R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>, C<sub>2</sub>-C<sub>6</sub>alkenyl<sub>1</sub>, C<sub>2</sub>-C<sub>6</sub>alkynyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heterocycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>), amino(C<sub>2</sub>-C<sub>6</sub> alkyl<sub>1</sub>), aryl<sub>1</sub>, aryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heteroaryl<sub>1</sub>, and heteroaryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>);

15 each R<sub>3</sub>, R<sub>3</sub>', R<sub>4</sub>, R<sub>4</sub>', R<sub>5</sub>, R<sub>5</sub>', R<sub>6</sub>, and R<sub>6</sub>' is independently selected from hydrogen, halogen, hydroxy, amino, cyano, nitro, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy<sub>1</sub>, C<sub>2</sub>-C<sub>6</sub>alkenyl<sub>1</sub>, C<sub>2</sub>-C<sub>6</sub>alkynyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heterocycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), halo(C<sub>1</sub>-C<sub>6</sub>)alkyl<sub>1</sub>, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy<sub>1</sub>, hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>), amino(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>), mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>)amino, mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>)amino(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>), aryl<sub>1</sub>, aryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heteroaryl<sub>1</sub>, and heteroaryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>);

20 wherein each alkyl<sub>1</sub>, alkenyl<sub>1</sub>, alkynyl<sub>1</sub>, alkoxy<sub>1</sub>, cycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>, aryl<sub>1</sub>, and heteroaryl<sub>1</sub> is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and mono- or di-(C<sub>1</sub>-C<sub>6</sub>alkyl)amino;

25 with the proviso that :

a) at least one of B, C, and D is nitrogen and is substituted by C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heterocycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>), amino(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>), aryl<sub>1</sub>, aryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heteroaryl<sub>1</sub>, and heteroaryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>);  
or

30 b) at least one of B, C, and D are carbon and is substituted by halogen, hydroxy, amino, cyano, nitro, oxo, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heterocycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), halo(C<sub>1</sub>-C<sub>6</sub>)alkyl<sub>1</sub>, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy<sub>1</sub>, hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>), amino(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>), mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>)amino, mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>)amino(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>), aryl<sub>1</sub>, aryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heteroaryl<sub>1</sub>, and heteroaryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>); or

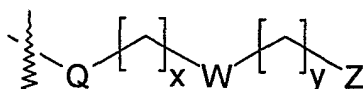
35 c) A is carbon and is substituted by halogen, hydroxy, amino, cyano, nitro, oxo, C<sub>1</sub>-C<sub>6</sub>alkoxy, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl<sub>1</sub>, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy<sub>1</sub>, hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>), or

d) n is 1 or 2 and at least one of B, C, or D is nitrogen or oxygen; or

e) any of  $R_3$  and  $R_3$ ,  $R_4$  and  $R_4$ ,  $R_5$  and  $R_5$ , and  $R_6$ , and  $R_6$  may be joined to form a saturated, partially unsaturated, or unsaturated carbocyclic or heterocyclic ring of from a 4-8 membered ring<sub>1</sub>;

wherein said ring<sub>1</sub> is a saturated, partially unsaturated, or unsaturated carbocyclic or heterocyclic ring of from 3-8 ring members which contains 0, 1, or 2 heteroatoms independently chosen from O, N, and S, and said ring<sub>1</sub> is unsubstituted or is substituted by 1, 2, or 3 substituents independently chosen from halogen, hydroxy, amino, cyano, nitro, oxo, 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>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl), amino(C<sub>1</sub>-C<sub>6</sub> alkyl), mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, and mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino(C<sub>1</sub>-C<sub>6</sub>alkyl);

Ar is a group of the formula



Q is an optionally substituted carbocyclic aryl or optionally substituted heteroaryl group having from 1 to 3 rings, 5 to 6 members in each ring and from 1 to 3 heteroatoms;

W is hydrogen, oxygen, nitrogen, sulfur, or CR<sup>7</sup>R<sup>8</sup> where R<sup>7</sup> and R<sup>8</sup> are the same or different and represent hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, or R<sup>7</sup> and R<sup>8</sup> may be taken together to represent a cyclic moiety having 3-7 carbon atoms;

Z is hydrogen, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub>alkoxy), amino, mono or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, or NR<sup>9</sup>COR<sup>10</sup> where R<sup>9</sup> and R<sup>10</sup> are the same or different and represent hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl, or R<sup>9</sup> and R<sup>10</sup> may be joined to form a C<sub>3</sub>-C<sub>7</sub> cycloalkyl ring, or

Z is optionally substituted carbocyclic aryl or optionally substituted heteroaryl group having from 1 to 3 rings, 5 to 6 members in each ring and from 1 to 3 heteroatoms;



and represent carbon chains which are independently unsubstituted or substituted with halogen, cyano, nitro, amino, mono or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, 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>alkoxy, trihalomethyl, trihalomethoxy, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>3</sub>-C<sub>7</sub> cycloalkyl,

x is 0, 1, 2, or 3; and

y is 0, 1, 2, or 3.

The novel compounds encompassed by the invention are described by the general Formula I (set forth above) and the pharmaceutically acceptable non-toxic salts thereof.

The invention further encompasses compounds of Formula I, above, in which

R, R<sub>1</sub>, R<sub>2</sub>, A, B, C, D, and n are as defined above and

Q is chosen from phenyl, naphthyl, quinolinyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl, oxazolyl, isoxazolyl, symmetrical or unsymmetrical oxadiazolyl, symmetrical or unsymmetrical thiadiazolyl, symmetrical or unsymmetrical triazolyl, pyrazolyl, furanyl, diazenyl, triazenyl, or triazolopyrazinyl group;

5 each of which is unsubstituted or substituted with up to three substituents independently selected from i) and ii) wherein

i) is hydroxy, cyano, halogen, nitro, amino, mono or 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>alkoxy, trihalomethyl, and trihalomethoxy;

10 ii) is C<sub>1</sub>-C<sub>6</sub>alkyl optionally containing heteroatoms and optionally substituted with one or more carbocyclic or heterocyclic group;

W is hydrogen, oxygen, nitrogen, sulfur, or CR<sup>7</sup>R<sup>8</sup> where R<sup>7</sup> and R<sup>8</sup> are the same or different and represent hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or R<sup>7</sup> and R<sup>8</sup> may be taken together to represent a cyclic moiety having 3-7 carbon atoms;

15 Z is hydrogen, hydroxy, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>3</sub>-C<sub>7</sub>cycloalkyl, C<sub>3</sub>-C<sub>7</sub>cycloalkyl(C<sub>1-3</sub>alkoxy), amino, mono or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, a carbocyclic or heterocyclic group, or NR<sup>9</sup>COR<sup>10</sup> where R<sup>9</sup> and R<sup>10</sup> are the same or different and represent hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl, or R<sup>9</sup> and R<sup>10</sup> may be joined to form a C<sub>3</sub>-C<sub>7</sub> cycloalkyl ring, or

20 Z is a phenyl, naphthyl, quinolinyl, thienyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, pyrazolyl, pyrazinyl, pyridizynyl, piperidinyl, oxazolyl, isoxazolyl, symmetrical or unsymmetrical thiadiazolyl, symmetrical or unsymmetrical triazolyl, symmetrical or unsymmetrical oxadiazolyl, pyrrolyl, furanyl, pyrimidinyl, diazenyl, triazenyl, 1, 2, 4-triazolone, 4,5-dihydroimidazolyl, or a 1,4,5,6-tetrahydropyrimidinyl group;



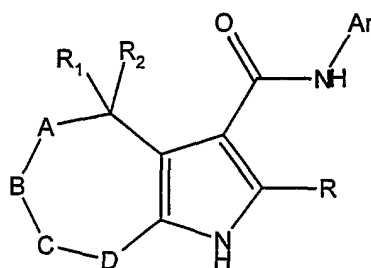
25 and represent carbon chains which are unsubstituted or substituted with up to three groups independently chosen from halogen, cyano, nitro, amino, mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, trihalomethyl, trihalomethoxy, straight or branched chain C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>3</sub>-C<sub>7</sub>cycloalkyl, and

m is 0, 1, 2, or 3; and

n is 0, 1, 2, or 3.

Such compounds will be referred to as compounds of Formula Ia.

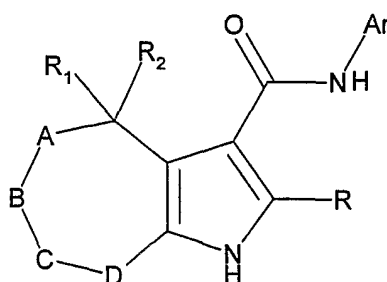
30 Also particularly provided by the invention are compounds of Formula II:



Formula II

i.e. compounds in which  $n$ , shown in Formula 1, is 1 and  $R$ ,  $R_1$ ,  $R_2$ ,  $A$ ,  $B$ ,  $C$ ,  $D$ , and  $Ar$  are as defined either for Formula I or more preferably as defined for Formula Ia.

5 Further provided by the invention are compounds of Formula III:



Formula III

wherein  $R$ ,  $Ar$ , and  $A$ ,  $B$ ,  $C$ , and  $D$  are as defined either for Formula I or more preferably as defined for Formula Ia.

10 Particularly embodied by the invention are compounds of Formula III in which

$A$  is chosen from  $NR_3$  and  $CR_3R_3'$ ;

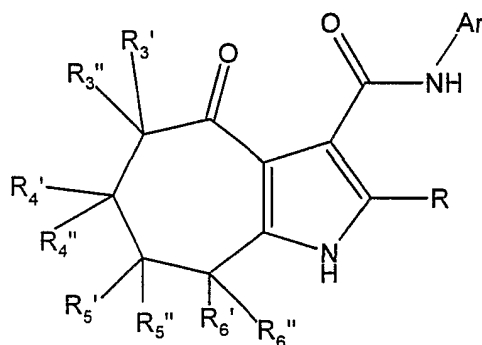
$B$  is chosen from  $NR_4$  and  $CR_4R_4'$ ;

$C$  is chosen from  $NR_5$  and  $CR_5R_5'$ ;

$D$  is chosen from  $NR_6$  and  $CR_6R_6'$ ; and not more than 2 members of the ring

15 containing  $A$ ,  $B$ ,  $C$ , and  $D$  are nitrogen.

Another embodiment of the invention includes compounds of Formula IV



Formula IV

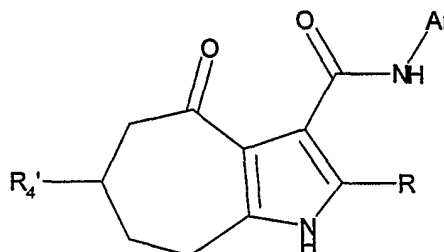


wherein R, Ar, R<sub>3</sub>, R<sub>3</sub>R<sub>3</sub>', R<sub>4</sub>, R<sub>4</sub>R<sub>4</sub>', R<sub>5</sub>, R<sub>5</sub>R<sub>5</sub>', R<sub>6</sub>, R<sub>6</sub>' and R<sub>6</sub>' are as are as defined either for Formula I or more preferably as defined for Formula Ia.

Particular embodiments of the invention include compounds of Formula IV in which Ar is phenyl, pyridyl or pyrimidinyl,

5 each of which is unsubstituted or substituted with up to three substituents independently selected from hydroxy, cyano, halogen, nitro, amino, mono or 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>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, trihalomethyl, or trihalomethoxy.

Another specific embodiment of the invention includes compounds of Formula V



10

Formula V

wherein R is are as defined either for Formula I or more preferably as defined for Formula Ia;

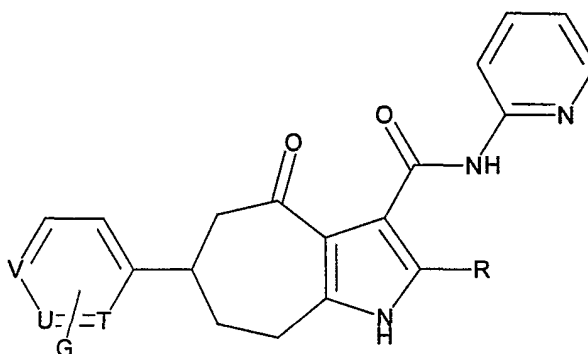
Ar is chosen from phenyl, pyridyl and pyrimidinyl,

15 each of which is unsubstituted or substituted with up to three substituents independently selected from hydroxy, cyano, halogen, nitro, amino, mono or 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>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, trihalomethyl, or trihalomethoxy; and

20 R<sub>4</sub>' is chosen from C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heterocycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), aryl<sub>1</sub>, aryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heteroaryl<sub>1</sub>, and heteroaryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>);

wherein each alkyl<sub>1</sub>, cycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>, aryl<sub>1</sub>, and heteroaryl<sub>1</sub> is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, amino(C<sub>1</sub>-C<sub>6</sub>alkyl); mono- or di-(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, and mono- or di-(C<sub>1</sub>-C<sub>6</sub>alkyl)amino(C<sub>1</sub>-C<sub>6</sub>alkyl).

25 Also included in the invention are compounds and salts of Formula VI



Formula VI

wherein

R is selected from hydrogen, halogen, methyl, and ethyl; V, U, and T, independently  
 5 represent N or CH; and G represents up to 3 groups independently chosen from hydrogen,  
 hydroxy, oxo, halogen, amino, cyano, nitro, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and mono- or di-  
 amino(C<sub>1</sub>-C<sub>6</sub>alkyl).

Another preferred embodiment of the invention includes compounds of Formula I, as  
 set forth above, wherein R, R<sub>1</sub>, R<sub>2</sub>, Ar, A, B, C, D, n and Ar are as defined for Formula I:

10 with the proviso that either R<sub>3</sub> or R<sub>3</sub>' and R<sub>4</sub> or R<sub>4</sub>' form an unsaturated, partially  
 saturated, or saturated ring of from 5 to 7 members or R<sub>4</sub> or R<sub>4</sub>' and R<sub>5</sub> or R<sub>5</sub>' form an  
 unsaturated, partially saturated, or saturated ring of from 5 to 7 members, wherein said  
 unsaturated, partially saturated, or saturated ring contains 0, 1, or 2 heteroatoms  
 independently chosen from S, O, or N and said unsaturated, partially saturated, or saturated  
 15 ring is unsubstituted or substituted with up to 3 substituents independently chosen from:

halogen, hydroxy, amino, cyano, nitro, oxo, 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>alkenyl, C<sub>2</sub>-  
 C<sub>6</sub>alkynyl, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>2</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), heterocycloalkyl<sub>2</sub>,  
 heterocycloalkyl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl),  
 amino(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub>amino, aryl<sub>2</sub>, aryl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), heteroaryl<sub>2</sub>, and  
 20 heteroaryl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl);

wherein each cycloalkyl<sub>2</sub>, heterocycloalkyl<sub>2</sub>, aryl<sub>2</sub>, and heteroaryl<sub>2</sub> is unsubstituted or  
 substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino,  
 cyano, nitro, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and mono- or di-amino(C<sub>1</sub>-C<sub>6</sub>alkyl).

Such compounds will be referred to as compounds of Formula VII.

25 Particularly preferred compounds of this class are those compounds wherein n is 1 or  
 2, but preferably 1, and the variables Q, W, and Z, which are part of the group Ar are defined  
 as follows:

Q is a phenyl, naphthyl, quinoliny, thienyl, pyridyl, pyrimidinyl, pyrazinyl, oxazolyl,  
 isoxazolyl, symmetrical or unsymmetrical oxadiazolyl, symmetrical or unsymmetrical

thiadiazolyl, symmetrical or unsymmetrical triazolyl, pyrazolyl, furanyl, diazenyl, triazenyl, or triazolopyrazinyl group;

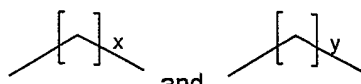
each of which is unsubstituted or substituted with up to three substituents independently selected from i) and ii) wherein

- 5 i) represents hydroxy, cyano, halogen, nitro, amino, mono or 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>alkoxy, trihalomethyl, or trihalomethoxy;
- ii) represents C<sub>1</sub>-C<sub>6</sub>alkyl optionally containing heteroatoms and optionally substituted with one or more carbocyclic or heterocyclic group;

10 W is hydrogen, oxygen, nitrogen, sulfur, or CR<sup>7</sup>R<sup>8</sup> where R<sup>7</sup> and R<sup>8</sup> are the same or different and represent hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or R<sup>7</sup> and R<sup>8</sup> may be taken together to represent a cyclic moiety having 3-7 carbon atoms;

Z is hydrogen, hydroxy, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>3</sub>-C<sub>7</sub>cycloalkyl, C<sub>3</sub>-C<sub>7</sub>cycloalkyl(C<sub>1-3</sub>alkoxy), amino, mono or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, a carbocyclic or heterocyclic group, or NR<sup>9</sup>COR<sup>10</sup> where R<sup>9</sup> and R<sup>10</sup> are the same or different and represent hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl, or R<sup>9</sup> and R<sup>10</sup> may  
15 be joined to form a C<sub>3</sub>-C<sub>7</sub> cycloalkyl ring, or

Z is a phenyl, naphthyl, quinoliny, thienyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, pyrazolyl, pyrazinyl, pyridiziny, piperidiny, oxazolyl, isoxazolyl, symmetrical or unsymmetrical thiadiazolyl, symmetrical or unsymmetrical triazolyl, symmetrical or unsymmetrical  
20 oxadiazolyl, pyrrolyl, furanyl, pyrimidinyl, diazenyl, triazenyl, 1, 2, 4-triazolone, 4,5-dihydroimidazolyl, or a 1,4,5,6-tetrahydropyrimidinyl group;



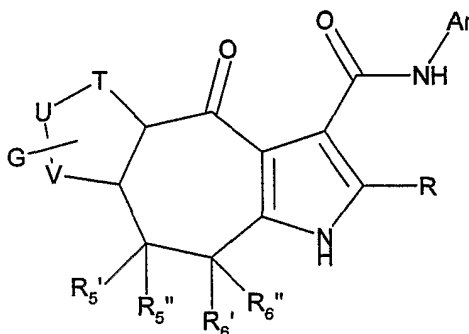
represent carbon chains which is unsubstituted or substituted with up to three groups independently chosen from halogen, cyano, nitro, amino, mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, trihalomethyl, trihalomethoxy, straight or branched chain C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>3</sub>-C<sub>7</sub>cycloalkyl, and

- 25 x is 0, 1, 2, or 3; and  
y is 0, 1, 2, or 3.

Such compounds will be referred to a compounds of Formula VIIa. Preferred compounds of Formula VIIa are those compounds wherein n is 1 and R<sub>1</sub> and R<sub>2</sub> form an oxo group. Other preferred compounds of Formula VIIa are those compounds in which n is 1, R<sub>1</sub> and R<sub>2</sub> form an oxo group, A is chosen from NR<sub>3</sub> and CR<sub>3</sub>R<sub>3</sub>'; B is chosen from NR<sub>4</sub> and CR<sub>4</sub>R<sub>4</sub>', C is chosen from NR<sub>5</sub> and CR<sub>5</sub>R<sub>5</sub>', D is chosen from NR<sub>6</sub> and CR<sub>6</sub>R<sub>6</sub>', and not more than 2 members of the ring containing A, B, C, and D are nitrogen. Still other specific  
30 embodiments of the invention include compounds in which n is 1, R<sub>1</sub> and R<sub>2</sub> form an oxo group, and A is CR<sub>3</sub>R<sub>3</sub>'; B is CR<sub>4</sub>R<sub>4</sub>'; C is CR<sub>5</sub>R<sub>5</sub>'; and D is CR<sub>6</sub>R<sub>6</sub>'. Also included in the  
35 invention are compounds of Formula VIIa wherein n is 1, R<sub>1</sub> and R<sub>2</sub> form an oxo group, and A

is  $CR_3R_3$ ; B is  $CR_4R_4$ ; C is  $CR_5R_5$ ; and D is  $CR_6R_6$ , Ar is phenyl, pyridyl or pyrimidinyl, each of which may be unsubstituted or substituted with up to three substituents independently selected from hydroxy, cyano, halogen, nitro, amino, mono or 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>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, trihalomethyl, or trihalomethoxy.

5 Also included in the invention are compounds and salts of Formula VIII



Formula VIII

wherein:

R is as defined in as for Specific Embodiment VIIa

10  $R_5$ ,  $R_5'$ ,  $R_6$ , and  $R_6'$  are independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, oxo, 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>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl), amino(C<sub>1</sub>-C<sub>6</sub> alkyl), mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino;

T, U, and V are independently chosen from O, S, CH<sub>2</sub>, and NH;

15 G represents 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, nitro, oxo, 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>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>2</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), heterocycloalkyl<sub>2</sub>, heterocycloalkyl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl), amino(C<sub>1</sub>-C<sub>6</sub> alkyl), mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub>amino, aryl<sub>2</sub>, aryl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), heteroaryl<sub>2</sub>, and heteroaryl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl);

20 wherein each cycloalkyl<sub>2</sub>, heterocycloalkyl<sub>2</sub>, aryl<sub>2</sub>, and heteroaryl<sub>2</sub> is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and mono- or di-amino(C<sub>1</sub>-C<sub>6</sub>alkyl); and

Ar is phenyl, pyridyl or pyrimidinyl,

25 each of which is unsubstituted or substituted with up to three substituents independently selected from hydroxy, cyano, halogen, nitro, amino, mono or 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>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, trihalomethyl, or trihalomethoxy.

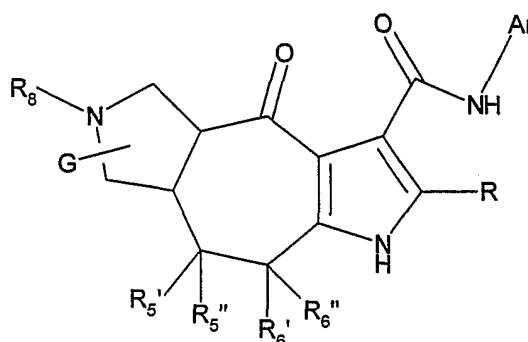
30 Preferred compounds and salts of Formula VIII are those compounds in which  $R_5$ ,  $R_5'$ ,  $R_6$ , and  $R_6'$  are all hydrogen, Ar is as defined for compounds of Formula VIIa; R is chosen from hydrogen, halogen, methyl, and ethyl;

T', U', and V' are independently chosen from O, S, CH<sub>2</sub>, and NH; and

G' represents up to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, nitro, oxo, 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>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>2</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), heterocycloalkyl<sub>2</sub>, heterocycloalkyl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl), amino(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>2</sub>, mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>2</sub>)amino, aryl<sub>2</sub>, aryl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), heteroaryl<sub>2</sub>, and heteroaryl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl);

wherein each cycloalkyl<sub>2</sub>, heterocycloalkyl<sub>2</sub>, aryl<sub>2</sub>, and heteroaryl<sub>2</sub> is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and mono- or di-amino(C<sub>1</sub>-C<sub>6</sub>alkyl).

Another embodiment of the invention is directed to compounds and salts of Formula IX



Formula IX

wherein Ar is as defined for compounds of Formula VIIa;

R is chosen from hydrogen, halogen, methyl, and ethyl;

R<sub>5</sub>', R<sub>5</sub>'', R<sub>6</sub>', and R<sub>6</sub>'' are independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, trihalomethyl, and trifluoromethoxy; and

G represents 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, nitro, oxo, 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>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>2</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), heterocycloalkyl<sub>2</sub>, heterocycloalkyl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl), amino(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>2</sub>, mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>2</sub>)amino, aryl<sub>2</sub>, aryl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), heteroaryl<sub>2</sub>, and heteroaryl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl);

wherein each cycloalkyl<sub>2</sub>, heterocycloalkyl<sub>2</sub>, aryl<sub>2</sub>, and heteroaryl<sub>2</sub> is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and mono- or di-amino(C<sub>1</sub>-C<sub>6</sub>alkyl); and

R<sub>8</sub> is chosen from hydrogen and C<sub>1</sub>-C<sub>6</sub>alkyl. Preferred compounds of Formula IX are those compounds in which Ar represents phenyl, pyridyl, or pyrimidinyl each or which may be unsubstituted or substituted with 1, 2, or 3, substituents chosen from hydroxy, halogen, amino, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, trihalomethyl, trihalomethoxy, amino(C<sub>1</sub>-C<sub>6</sub> alkyl), mono- or di(C<sub>1</sub>-C<sub>6</sub> alkyl)amino, and mono- or di(C<sub>1</sub>-C<sub>6</sub> alkyl)amino(C<sub>1</sub>-C<sub>6</sub> alkyl).

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds set forth in Examples 1 to 8 and their pharmaceutically acceptable acid and base addition salts. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanolic such as acetic,  $\text{HOOC}-(\text{CH}_2)_n-\text{ACOOH}$  where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the acylated prodrugs of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies that may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I. The invention further encompasses all enantiomers and diastereomers of the disclosed compounds. Those of ordinary skill in the art will readily recognize methods by which mixtures of enantiomers and diastereomers may be resolved. The definition of Formula I as used in herein include possible isomers, such as tautomers and rotamers.

This invention relates to novel cycloalkylpyrrole-3-carboxylic acid derivatives and heterocycloalkylpyrrole-3-carboxylic acid derivatives preferred examples of which bind with high affinity to the benzodiazepine site of  $\text{GABA}_A$  receptors, including human  $\text{GABA}_A$  receptors. Preferred cycloalkylpyrrole-3-carboxylic acid derivatives and heterocycloalkylpyrrole-3-carboxylic acid derivatives, that bind with high selectivity to the benzodiazepine site of  $\text{GABA}_A$  receptors, including human  $\text{GABA}_A$  receptors, are also included in this invention. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of Formula I with the benzodiazepine site results in the pharmaceutical utility of these compounds.

The invention further comprises methods of treating patients in need of such treatment with an amount of a compound of the invention sufficient to alter the symptoms of a CNS disorder. Compounds of the inventions that act as agonists at  $\alpha_2\beta_3\gamma_2$  and  $\alpha_3\beta_3\gamma_2$  receptor subtypes are useful in treating anxiety disorders such as panic disorder, obsessive compulsive disorder and generalized anxiety disorder; stress disorders including post-traumatic stress, and acute stress disorders. Compounds of the inventions that act as agonists at  $\alpha_2\beta_3\gamma_2$  and  $\alpha_3\beta_3\beta_2$  receptor subtypes are also useful in treating depressive or

bipolar disorders and in treating sleep disorders. Compounds of the invention that act as inverse agonists at the  $\alpha_5\beta_3\gamma_2$  receptor subtype or  $\alpha_1\beta_2\gamma_2$  and  $\alpha_5\beta_3\gamma_2$  receptor subtypes are useful in treating cognitive disorders including those resulting from Down Syndrome, neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, and stroke related dementia. Compounds of the invention that act as agonists at the  $\alpha_1\beta_2\gamma_2$  receptor subtype are useful in treating convulsive disorders such as epilepsy. Compounds that act as antagonists at the benzodiazepine site are useful in reversing the effect of benzodiazepine overdose and in treating drug and alcohol addiction.

The diseases and/ or disorders that can also be treated using compounds and compositions according to the invention include:

Depression, e.g. depression, atypical depression, bipolar disorder, depressed phase of bipolar disorder.

Anxiety, e.g. general anxiety disorder (GAD), agoraphobia, panic disorder +/- agoraphobia, social phobia, specific phobia, Post traumatic stress disorder, obsessive compulsive disorder (OCD), dysthymia, adjustment disorders with disturbance of mood and anxiety, separation anxiety disorder, anticipatory anxiety acute stress disorder, adjustment disorders, cyclothymia.

Sleep disorders, e.g. sleep disorders including primary insomnia, circadian rhythm sleep disorder, dyssomnia NOS, parasomnias, including nightmare disorder, sleep terror disorder, sleep disorders secondary to depression and/or anxiety or other mental disorders, substance induced sleep disorder.

Cognition Impairment, e.g. cognition impairment, Alzheimer's disease, Parkinson's disease, mild cognitive impairment (MCI), age-related cognitive decline (ARCD), stroke, traumatic brain injury, AIDS associated dementia, and dementia associated with depression, anxiety or psychosis.

Attention Deficit Disorder, e.g. attention deficit disorder (ADD), and attention deficit and hyperactivity disorder (ADHD).

Speech disorders, e.g. stuttering, including motor tic, clonic stuttering, dysfluency, speech blockage, dysarthria, Tourette syndrome or logospasm.

The invention also provides pharmaceutical compositions comprising one or more compounds of the invention together with a pharmaceutically acceptable carrier or excipient, for treating disorders responsive to GABA<sub>A</sub> receptor modulation, e.g., treatment of anxiety, depression, sleep disorders or cognitive impairment by GABA<sub>A</sub> receptor modulation. Pharmaceutical compositions include packaged pharmaceutical compositions comprising a container holding a therapeutically effective amount of at least one GABA<sub>A</sub> receptor modulator as described supra and instructions (e.g., labeling) indicating the contained GABA<sub>A</sub> receptor

ligand is to be used for treating a disorder responsive to GABA<sub>A</sub> receptor modulation in the patient.

In a separate aspect, the invention provides a method of potentiating the actions of other CNS active compounds, which comprises administering an effective amount of a compound of the invention in combination with another CNS active compound. Such CNS active compounds include, but are not limited to the following: for anxiety, serotonin receptor (e.g. 5-HT<sub>1A</sub>) agonists and antagonists; for anxiety and depression, neurokinin receptor antagonists or corticotropin releasing factor receptor (CRF<sub>1</sub>) antagonists; for sleep disorders, melatonin receptor agonists; and for neurodegenerative disorders, such as Alzheimer's dementia, nicotinic agonists, muscarinic agents, acetylcholinesterase inhibitors and dopamine receptor agonists. Particularly the invention provides a method of potentiating the antidepressant activity of selective serotonin reuptake inhibitors (SSRIs) by administering an effective amount of a GABA agonist compound of the invention in combination with an SSRI.

Combination administration can be carried out in a fashion analogous to that disclosed in Da-Rocha, et al., *J. Psychopharmacology* (1997) 11(3) 211-218; Smith, et al., *Am. J. Psychiatry* (1998) 155(10) 1339-45; or Le, et al., *Alcohol and Alcoholism* (1996) 31 Suppl. 127-132. Also see, the discussion of the use of the GABA<sub>A</sub> receptor ligand 3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl) methoxy-1,2,4-triazolo [3,4-a]phthalazine in combination with nicotinic agonists, muscarinic agonists, and acetylcholinesterase inhibitors, in PCT International publications Nos. WO 99/47142, WO 99/47171, and WO 99/47131, respectively. Also see in this regard PCT International publication No. WO 99/37303 for its discussion of the use of a class of GABA<sub>A</sub> receptor ligands, 1,2,4-triazolo[4,3-b]pyridazines, in combination with SSRIs.

The present invention also pertains to methods of inhibiting the binding of benzodiazepine compounds, such as Ro15-1788, or GABA to the GABA<sub>A</sub> receptors which methods involve contacting a solution containing compound of the invention with cells expressing GABA<sub>A</sub> receptors, wherein the compound is present at a concentration sufficient to inhibit benzodiazepine binding or GABA binding to GABA<sub>A</sub> receptors *in vitro*. This method includes inhibiting the binding of benzodiazepine compounds to GABA<sub>A</sub> receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to inhibit the binding of benzodiazepine compounds or GABA to GABA<sub>A</sub> receptors *in vitro*. In one embodiment, such methods are useful in treating benzodiazepine drug overdose. The amount of a compound that would be sufficient to inhibit the binding of a benzodiazepine compound to the GABA<sub>A</sub> receptor may be readily determined via a GABA<sub>A</sub> receptor binding assay, such as the assay described in Example 13. The GABA<sub>A</sub> receptors used to determine *in vitro* binding may be obtained from a variety of sources, for example from preparations of rat cortex or from cells expressing cloned human GABA<sub>A</sub> receptors.



The present invention also pertains to methods for altering the signal-transducing activity, particularly the chloride ion conductance of GABA<sub>A</sub> receptors, said method comprising exposing cells expressing such receptors to an effective amount of a compound of the invention. This method includes altering the signal-transducing activity of GABA<sub>A</sub> receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to alter the signal-transducing activity of GABA<sub>A</sub> receptors *in vitro*. The amount of a compound that would be sufficient to alter the signal-transducing activity of GABA<sub>A</sub> receptors may be determined via a GABA<sub>A</sub> receptor signal transduction assay, such as the assay described in Example 14. The cells expressing the GABA receptors *in vivo* may be, but are not limited to, neuronal cells or brain cells. Such cells may be contacted with compounds of the invention through contact with a body fluid containing the compound, for example through contact with cerebrospinal fluid. Alteration of the signal-transducing activity of GABA<sub>A</sub> receptors *in vitro* may be determined from a detectable change in the electrophysiology of cells expressing GABA<sub>A</sub> receptors, when such cells are contacted with a compound of the invention in the presence of GABA.

Intracellular recording or patch-clamp recording may be used to quantitate changes in electrophysiology of cells. A reproducible change in behavior of an animal given a compound of the invention may also be used to indicate that changes in the electrophysiology of the animal's cells expressing GABA<sub>A</sub> receptors has occurred.

The GABA<sub>A</sub> receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the GABA<sub>A</sub> receptor. Radiolabeled derivatives the GABA<sub>A</sub> receptor ligands provided by this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT).

The compounds herein described may have one or more asymmetric centers or planes. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms (racemates), by asymmetric synthesis, or by synthesis from optically active starting materials. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. *Cis* and *trans* geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral (enantiomeric and diastereomeric), and racemic forms, as well as all geometric isomeric

forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0 to 3 R<sup>\*</sup>, (where R<sup>\*</sup> indicates any variable group such as R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, etc.) then said group may optionally be substituted with up to three R<sup>\*</sup> groups and R<sup>\*</sup> at each occurrence is selected independently from the definition of R<sup>\*</sup>. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both branched and straight-chain aliphatic hydrocarbon groups, having the specified number of carbon atoms. Alkyl groups of 2 or more carbon atoms may contain double or triple bonds. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. Preferred alkyl groups are C<sub>1</sub>-C<sub>6</sub> alkyl groups. "C<sub>1</sub>-C<sub>6</sub> alkyl" indicates alkyl groups having from 1 to about 6 carbon atoms.

As used herein, "alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. "C<sub>1</sub>-C<sub>6</sub> alkoxy" indicates alkoxy groups having from 1 to about 6 carbon atoms.

"Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl. Alkenyl groups typically will have 2 to about 12 carbon atoms, more typically 2 to about 8 carbon atoms.

"Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl. Alkynyl groups typically will have 2 to about 12 carbon atoms, more typically 2 to about 8 carbon atoms.

"Aryl" is intended to include groups that, in accordance with the theory of Hückel, have a cyclic, delocalized (4n + 2) pi-electron system. Examples of aryl groups include, but are not limited to, arenes and their substitution products, e.g. phenyl, naphthyl and tolyl, among numerous others.

"Carbocyclic Aryl" refers to optionally substituted aromatic groups having 1 or more rings, wherein the members of the aromatic ring or rings are carbon. Such groups include optionally substituted phenyl and optionally substituted naphthyl.

The term "heteroaryl" is intended to include aromatic heterocyclic groups and includes the non-limiting examples thiophenyl, pyridyl, pyrimidyl, pyridazyl, oxazolyl, isooxazolyl, thiazolyl and isothiazolyl, among others.

5 The term "Cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. Cycloalkyl groups typically will have 3 to about 8 ring members.

In the term "(cycloalkyl)alkyl", Cycloalkyl and alkyl are as defined above and the point of attachment is on the alkyl group. This term encompasses, but is not limited to, cyclopropylmethyl, cyclohexylmethyl, cyclohexylmethyl.

10 As used herein, "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example  $-C_vF_w$  where  $v = 1$  to  $3$  and  $w = 1$  to  $(2v+1)$ ). Examples of haloalkyl include, but are not limited to, trifluoromethyl, difluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl.

15 As used herein, "haloalkoxy" indicates a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of haloalkoxy groups include, but are not limited to, trifluoromethoxy and trichloromethoxy.

20 As used herein, the terms "heterocyclic ring" and "heterocyclic group" are intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated ("heteroaryl"), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The term or "heterocycloalkyl" is used to refer to saturated

25 heterocyclic groups.

The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable

30 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in

35 the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 5 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indoliziny, indolyl, 3*H*-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl;- 1,2,5oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, 10 pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenaziny, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazoliny, quinolinyl, 4*H*-quinoliziny, quinoxaliny, quinuclidinyl, tetrahydrofuranyl, 15 tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

Preferred heterocyclic groups include, but are not limited to, pyridinyl, pyrimidinyl, 20 furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, and imidazolyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The term "oxo" indicates a carbonyl group. When an oxo group appears as a substituent the allowed valence of the substituted position is not exceeded.

25 The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings or animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. As used herein, 30 "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic 35 salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic,

phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, malefic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC-(CH<sub>2</sub>)<sub>n</sub>-COOH where n is 0-4, and the like. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17<sup>th</sup> ed., Mack Publishing Company, Easton, PA, p. 1418 (1985).

The terms "trihaloalkyl" and "trihaloalkoxy" refer to particular types of haloalkyl and haloalkoxy groups that contain three halogen atoms, e.g., trichloromethyl, trifluoromethoxy.

The term "protecting group" is used to describe a group which is unreactive (inert) under certain reaction conditions which are used to produce final compounds according to the present invention or to intermediates which are used to synthesize compounds according to the present invention. Protecting groups according to the present invention may be readily removed under selective conditions (acid, base, fluoride anion, zinc, etc.) as is well-known in the art. This term is well-known in the art and is given its art recognized definition in describing the present invention and in particular, methods of synthesizing compounds according to the present invention.

The term "potentiate" is used to describe the pharmacological activity of compounds according to the present invention in increasing the activity of CNS agents which are co-administered with compounds according to the present invention. It is an unexpected result that compounds according to the present invention may be coadministered with other CNS agents and produce a combined effect which is more than additive (synergistic). Other CNS agents which may be administered in combination with compounds according to the present invention include the non-limiting examples, for anxiety, serotonin receptor (e.g., 5HT1A) agonists and antagonists; for anxiety and depression, neurokinin receptor antagonists or corticotropin releasing factor receptor (CRF1) antagonists; for sleep disorders, melatonin receptor agonists; and for neurodegenerative disorders, such as Alzheimer's dementia, nicotinic agonists, muscarinic agents, acetylcholinesterase inhibitors and dopamine receptor agonists. In particular aspects, the present invention provides a method of potentiating the antidepressant activity of selective serotonin inhibitors (SSRIs) by administering an effective amount of a GABA agonist compound of the invention in combination with an SSRI.

Combination therapy or administration may be carried out analogously according to the method of any one or more of Da-Rocha, et al., *J. Psychopharmacology* (1997) 11 (3) 211-218; Smith, et al., *Am. J. Psychiatry* (1988) 155(10) 1339-45; or Le, et al., *Alcohol and Alcoholism* (1996) 31 Suppl. 127-132. Also see, the discussion of the use of the GABAA receptor ligand 3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl)methoxy-1,2,4-triazolo [3,4-a]phthalazine in combination with nicotinic agonists, muscarinic agonists, and acetylcholinesterase inhibitors, in international patent applications WO 99/47142, WO 99/47171 and WO 99/47131, respectively. Also, see in this regard international application No. WO 99/37303 for its discussion of the use of a class of GABAA receptor ligands, such as the 1,2,4-triazolo[4,3-b]pyridazines, in combination with SSRIs.

The term "effective" is used to describe amounts or concentrations of compounds according to the present invention which are used in pharmaceutical compositions and/or methods of treatment or use according to the present invention consistent with the intended use of the compound. An effective amount or concentration is that amount or concentration which produces an intended effect.

#### Detailed Description of the Invention

An illustration of the preparation of compounds of the present invention is given in the following reaction schemes. The reactions shown below show specific methods for the synthesis of 3 types of compounds of the invention. However, one of ordinary skill in the art will recognize that reagents and reaction conditions may be varied to obtain specific end products. For example, a variety of methods for protecting amine groups, in addition to the BOC protection method shown, will be readily understood.

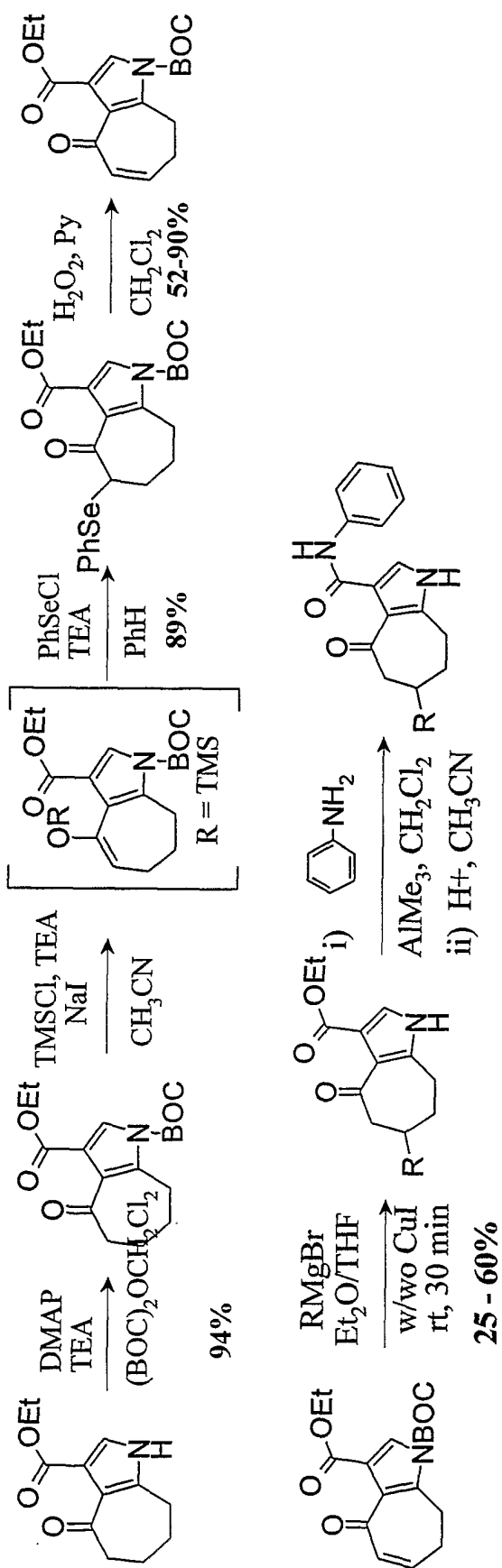
In general, synthesis of the compounds according to the present invention occur in a step-wise fashion in which the basic bicyclic structure (seven-membered ring fused to a substituted pyrrole; preferably an ester substituted pyrrole) is first substituted on the seven-membered ring where applicable (including creating a third ring structure) and the ester group (or other leaving group such as an active ester, tosyl, or halogen such as an acyl halide) on the pyrrole moiety of the molecule is then reacted with an appropriate amine (preferably, an aryl amine as defined or otherwise indicated herein) to produce the corresponding amide derivative (final compound). These compounds may be prepared in a number of ways using methods which are well-known in the art. By way of example, the final substituted bicyclic phenamide compounds of the schemes, may be prepared by the illustrated methods or by analogous methods readily available in the art.

By way of example, according to the method of Scheme I, the initial bicyclic ketone compound is N-Boc protected on the pyrrole group and subsequently phenylselenated at the position  $\alpha$  to the ketone in the seven membered ring. Reaction of the phenylselenated derivative with hydrogen peroxide/pyridine in methylene chloride produces the eneone group

in the seven-membered ring. Subsequent reaction of the enone with a Grignard reagent in ether/THF produces the saturated substituted ester derivative, which is reacted with aniline in the presence of a Lewis acid ( $\text{AlCl}_3$ ), followed by acid in acetonitrile provides the substituted bicyclic phenamide.

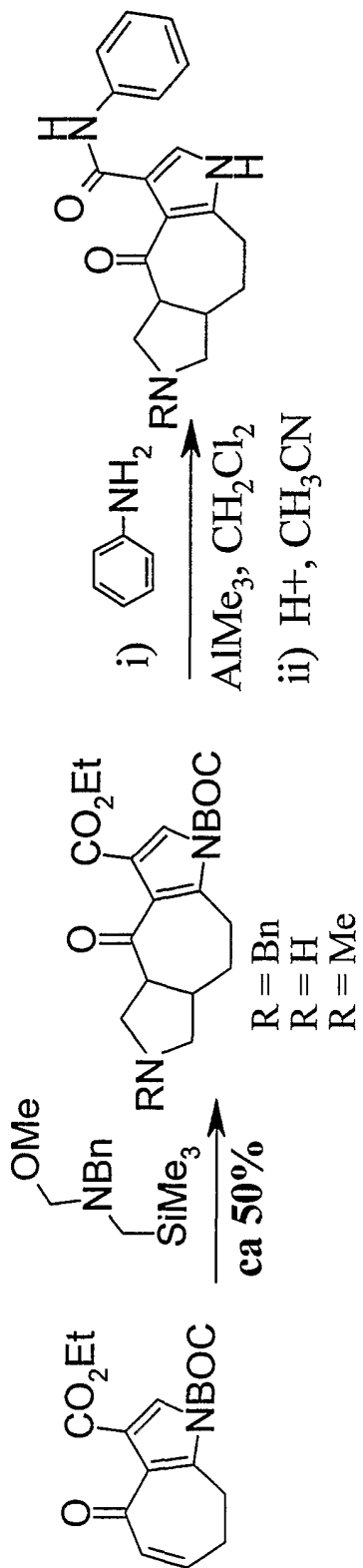
5           In scheme II, the tricyclic phenamide is prepared from the N-boc protected enone using the benzyl-methoxymethyltrimethylsilylmethyl-amine or analogous substituted reagent to produce the N-substituted tricyclic intermediate which is subsequently reacted with aniline in the presence of a Lewis acid ( $\text{AlCl}_3$ ) in methylene chloride, followed by acid in acetonitrile to provide the substituted tricyclic phenamide. In scheme III, the substituted bicyclic  
10 phenamide is prepared from the ketone by introducing substitution in the position  $\alpha$  to the ketone in the seven-membered ring using trimethylsilylchloride in the presence of triethylamine and sodium iodide in acetonitrile, followed by reaction of the ester with aniline in the presence of  $\text{AlCl}_3$  (Lewis acid) in methylene chloride followed by acid in acetonitrile. Other approaches will be readily apparent to the person of ordinary skill in synthetic  
15 chemistry.

**Scheme I**





Scheme II





In pharmacological aspects of the present invention, the compounds of the present invention may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred. The term parenteral as used herein includes subcutaneous injections, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intrathecal injection or like injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example,

lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium

chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

5           The compounds of general Formulas I may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

10           Compounds of general Formulas I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

15           For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It will be convenient to formulate these animal feed and drinking water compositions so that the animal takes in an appropriate quantity of the composition along with its diet. It will also be convenient to present the composition as a premix for addition to the feed or drinking water.

20           Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

25           Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of anxiety, depression, or cognitive impairment a dosage regimen of 1 or 2 times daily is particularly preferred. For the treatment of sleep disorders a single dose that rapidly reaches effective concentrations is desirable.

30           It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

35           Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to high solubility (preferably 500 ng/ ml or more) in aqueous solutions, oral bioavailability, low toxicity, low serum protein binding, lack of clinically

relevant EKG effects, and desirable *in vitro* and *in vivo* half-lives. Penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of compounds used to treat peripheral disorders are often preferred.

Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocytes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously.

Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová, et al. (Journal of Chromatography B (1996) volume 677, pages 1-27).

Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127).

The present invention is now described by way of the following non-limiting examples.

#### EXAMPLES

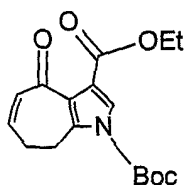
##### Preparation of starting materials and intermediates

The starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well known synthetic methods. Unless otherwise specified standard, commercial grade reagents are used without further purification. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present inventions.

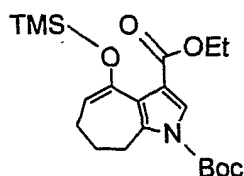
Representative examples of methods for preparing intermediates of the invention are set forth below.

##### Example 1

##### Preparation of 4-Oxo-7,8-dihydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester



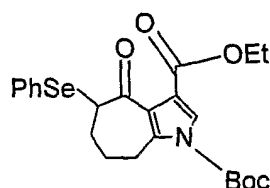
Step 1: 4-Trimethylsilyloxy-7,8-dihydro-6H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester



TMSCl (4.03 ml, 31.74 mmol) is added slowly to a solution of 4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (6.0 g, 18.67 mmol), NaI (4.76g, 31.74 mmol) and TEA (7.8ml, 56mmol) in CH<sub>3</sub>CN (100ml) at room temperature. The reaction mixture is stirred at room temperature for 18h. It is then quenched with saturated NaHCO<sub>3</sub> (aq., 70 ml). The layers are separated and the aqueous phase extracted with 1:1 EtOAc/hexanes. The organic layers are combined, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated to afford the title compound as a brown oil. The title compound is used in the next step without further purification.

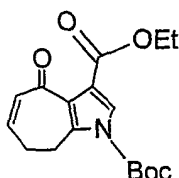
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.12 (9H, s), 1.31 (3H, t), 1.59 (9H, s), 1.90 (2H, m), 2.02 (2H, m), 2.97 (2H, t), 4.25 (2H, q), 5.35 (1H, t), 7.62 (1H, s). MS (ES<sup>+</sup>) 394 (M+1).

Step 2: 4-Oxo-5-phenylselanyl-5,6,7,8-tetrahydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester



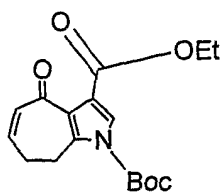
TEA (55.3 ml, 0.396 mol) is added to a solution of 4-trimethylsilyloxy-7,8-dihydro-6H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (103.3 g, 0.264mol) in benzene (1 L) at room temperature, followed by addition of PhSeCl (55.5g, 0.29 mol) in benzene over 45 min. The reaction mixture is stirred at room temperature for 4 h. The solvent is removed in *vacuo*. The residue is purified by flash chromatograph (3:1 hexane/EtOAc) to provide the title compound as a light brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.86 (1H, t), 1.21 (3H, t), 1.58 (9H, s), 1.72 (1H, m), 1.82 (1H, m), 2.05 (1H, m), 2.35 (1H, m), 3.01-3.30 (2H, m), 4.20 (2H, q), 7.26 (3H, m), 7.63 (2H, m), 7.74 (1H, s). MS (ES<sup>+</sup>) 478 (M+1)

Step 3: 4-Oxo-7,8-dihydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester



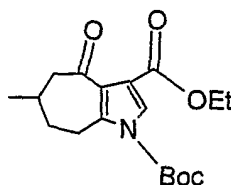
Pyridine (30ml, 0.37mol) is added to a solution of 4-oxo-5-phenylselanyl-5,6,7,8-tetrahydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester ( 59g, 0.124 mol) in CH<sub>2</sub>Cl<sub>2</sub> at room temperature. A solution of H<sub>2</sub>O<sub>2</sub> (30% in water, 225 ml) is then added dropwise. After the addition, reaction mixture is allowed to stir at room temperature for another hour and then quenched with saturated NaHCO<sub>3</sub> (aq., 250ml). The aqueous layer is extracted with CH<sub>2</sub>Cl<sub>2</sub> (10mlx2), the organic layers combined, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue is purified by chromatograph to provide the title compound as yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.30 (3H, t), 1.58 (9H, s), 2.55 (2H, m), 3.40 (2H, t), 4.31 (2H, q), 6.19 (1H, d), 6.60 (1H, m), 7.48 (1H, s). MS (ES<sup>+</sup>) 320 (M+1)

10

Example 2Preparation of 6-Methyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid pyridin-2-ylamide

Step 1: 6-Methyl-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester

15



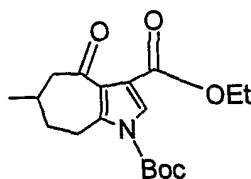
MeLi (1.4M in ether, 2ml) is added dropwise to a stirred suspension of CuI (268mg, 1.40mmol) in Et<sub>2</sub>O at 0 °C. The reaction mixture is kept at 0 °C for 15 min. 4-oxo-7,8-dihydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (300mg, 0.94mmol) in THF is added slowly to the solution at 0°C, the reaction mixture is allowed to warm up to room temperature over a period of 30 min and then quenched with saturated NH<sub>4</sub>Cl( aq., 30ml). 50 ml Et<sub>2</sub>O is added and stirring is continued for 5 min. The layers are separated; the organic layer is washed with water (20ml), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. Flash chromatography (30% EtOAc / hexanes) provides the title compound as white powder. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.02 (3H, d), 1.28 (3H, t), 1.56 (9H+1H, s+m), 1.92 (1H, m), 2.15 (1H, m), 2.48 (1H, q), 2.80 (1H, q), 3.15-3.25 (2H, m), 4.24 (2H, q), 7.57 (1H, s). MS (ES<sup>+</sup>) 336 (M+1)

20

25

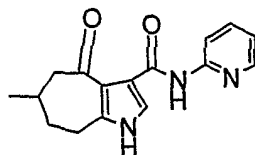
Step 2: 6-Methyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid ethyl ester





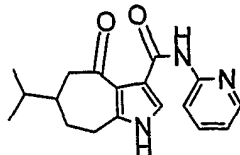
6-Methyl-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester ( 273 mg, 0.814mmol) is dissolved in 1:1 mixture of TFA and CH<sub>2</sub>Cl<sub>2</sub> (4ml). The reaction mixture is stirred at room temperature for 3h. Solvents are removed in vacuo and the residue is put on a column (1:1 EtOAc / hexanes) to provide the title compound as white solid. . <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.01 (3H, d), 1.26 (3H, t), 1.1-1.50 (1H, m), 1.96 (1H, m), 2.12 (1H, m), 2.54 (1H, q), 2.70-2.90 (3H, m), 4.20 (2H, q), 7.17 (1H, s). MS (ES<sup>+</sup>) 236 (M+1)

Step 3: 6-Methyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid pyridin-2-ylamide

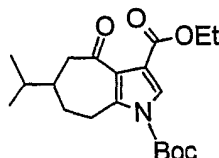


AlMe<sub>3</sub> (2M in toluene, 0.85ml, 1.7ml) is added dropwise to 2-aminopyridine (199.9mg, 2.12mmol) in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. The reaction mixture is stirred at room temperature for 0.5h, it is then transferred to a solution of 6-methyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid ethyl ester (100mg, 0.425mmol) in CH<sub>2</sub>Cl<sub>2</sub> via syringe. The reaction mixture is heated at 40 °C for 10h. 5 ml water is added, stirring continued for 10 min. The solid residue is filtered off with celite, the layers separated, the aqueous phase extracted with CH<sub>2</sub>Cl<sub>2</sub> (10mlx2), and the combined organic phases are dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated.

The residue obtained from last step is dissolved in CH<sub>3</sub>CN (2ml) and saturated NaH<sub>2</sub>PO<sub>4</sub> (aq., 4 ml). The reaction mixture is stirred at room temperature for 5h. The solution is basified with saturated NaHCO<sub>3</sub> (aq.), and 10 ml CH<sub>2</sub>Cl<sub>2</sub> are added. Layers separated, aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10mlx2). Combined organic phases are dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. Flash chromatography (60% EtOAc / hexanes) provides the title compound as white powder. This compound may be salted as HCl salt. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 1.1.05 (3H, d), 1.45 (1H, m), 2.06-2.17 (2H, m), 2.70 (1H, m), 2.80-3.01 (3H, m), 7.07 (1H, q), 7.51 (1H, s), 7.75 (1H, m), 8.22 (1H, d), 8.28 (1H, m). MS (ES<sup>+</sup>) 284 (M+1)

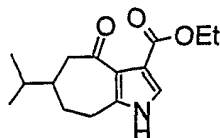
Example 3Preparation of 6-Isopropyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid  
pyridin-2-ylamide

5            Step 1: 6-Methyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid  
pyridin-2-ylamide



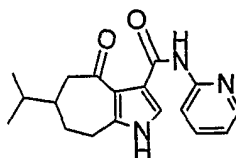
The title compound may be obtained as a white solid by the method described in  
Example 2, Step 1, using isopropylmagnesium chloride as the organometallic reagent. <sup>1</sup>H  
10 NMR (400 MHz, CDCl<sub>3</sub>) δ 0.89 (6H, m), 1.28 (3H, t), 1.56 (9H+2H, s+m), 1.78 (1H, m), 1.97  
(1H, m), 2.60 (1H, q), 2.75 (1H, m), 3.19 (2H, m), 4.25 (2H, q), 7.59 (1H, s). MS (ES<sup>+</sup>) 364  
(M+1)

Step 2: 6-Isopropyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic  
acid ethyl ester



15            The title compound may be obtained as white solid by the methods described in  
Example 2, Step 2. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.87 (6H, m), 1.25 (3H, t), 1.60 (2H, m),  
1.75 (1H, m), 1.89 (1H, m), 2.64 (2H, m), 2.88 (2H, m), 4.20 (2H, q), 7.20 (1H, s). MS (ES<sup>+</sup>)  
264 (M+1)

20            Step 3  
6-Isopropyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic            acid  
pyridin-2-ylamide



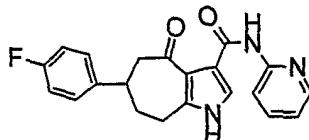
25            The title compound may be obtained as a white solid and salted as HCl salt by the  
methods given in Example 2, Step 3. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.97 (6H, m), 1.65 (2H,

m), 1.70 (1H, m), 2.01 (1H, m), 2.72–2.90 (4H, m), 7.07 (1H, q), 7.51 (1H, s), 7.75 (1H, m), 8.22 (1H, d), 8.28 (1H, m). MS (ES<sup>+</sup>) 312 (M+1).

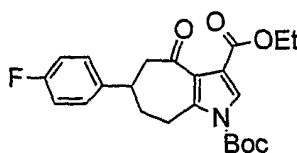
#### Example 4

#### Preparation of 6-(4-Fluoro-phenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid pyridin-2-ylamide

5

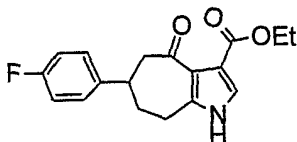


Step 1: 6-(4-Fluoro-phenyl)-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester



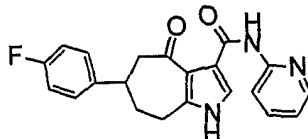
10 The title compound may be obtained as a slightly colored solid by the methods described in Example 2, Step 1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.27 (3H, t), 1.59 (9H, s), 2.07 (1H, m), 2.20 (1H, m), 2.92-3.37 (5H, m), 4.24 (2H, q), 6.93 (2H, m), 7.14 (2H, m), 7.63 (1H, s). MS (ES<sup>+</sup>) 416 (M+1)

15 Step 2: 6-(4-Fluoro-phenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid ethyl ester



20 The title compound (190mg, 74%) may be obtained as white powder by the procedure described in Example 2, Step 2.. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.26 (3H, t), 1.95 (1H, m), 2.19 (1H, m), 2.85-3.00 (4H, m), 3.18 (1H, m), 4.23 (2H, q), 6.93 (2H, m), 7.11(2H, m), 7.21 (1H, s). MS (ES<sup>+</sup>) 316 (M+1).

Step 3: 6-(4-Fluoro-phenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid pyridin-2-ylamide



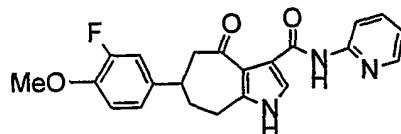
25 The title compound may be obtained as white solid and salted as HCl salt by the methods described in Example 2, Step 3, <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 1.95 (1H, m), 2.31

(1H, m), 3.02 (2H, m), 3.19 (3H, m), 6.99 (2H, m), 7.07 (1H, m), 7.26 (2H, m), 7.40 (1H, m), 7.56 (1H, s), 7.78 (1H, m), 7.83 (1H, m), MS (ES<sup>+</sup>) 364 (M+1).

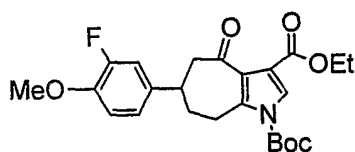
**Example 5**

**Preparation of 6-(3-Fluoro-4-methoxy-phenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid pyridin-2-ylamide**

5

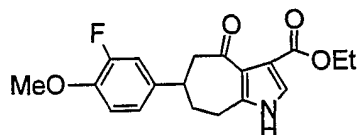


Step 1: 6-(3-Fluoro-4-methoxy-phenyl)-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester



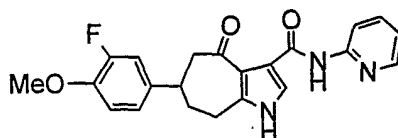
10 The title compound may be obtained as a white solid by the procedures described in Example 2, Step 1, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.28 (3H, t), 1.57 (9H, s), 2.01 (1H, m), 2.19 (1H, m), 2.89-3.35 (5H, m), 3.83 (3H, s), 4.25 (2H, q), 6.83-6.95 (3H, m), 7.62 (1H, s). MS (ES<sup>+</sup>) 446 (M+1)

15 Step 2: 6-(3-Fluoro-4-methoxy-phenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid ethyl ester



The title product was obtained as white solid by the methods described in Example 2, Step 2. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.26 (3H, t), 1.96 (1H, m), 2.17 (1H, m), 2.84-3.12 (5H, m), 3.82 (3H, s), 4.09 (2H, q), 6.80-6.91 (3H, m), 7.20 (1H, s). MS (ES<sup>+</sup>) 346 (M+1).

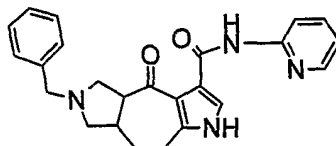
20 Step 3: 6-(3-Fluoro-4-methoxy-phenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid pyridin-2-ylamide



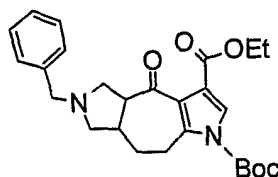
25 The title compound may be obtained as white solid and salted as HCl salt by the methods described in Example 2, Step 3. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 1.90 (1H, m), 2.28 (1H, m), 2.94-3.20 (5H, m), 3.80 (3H, s), 6.95-7.08 (4H, m), 7.56 (1H, s), 7.75 (1H, t), 8.12 (2H, m). MS (ES<sup>+</sup>) 394 (M+1)

Example 6

Preparation of 6-Benzyl-4-oxo-4,4a,5,6,7,7a,8,9-octahydro-1H-1,6-diaza-cyclopenta[f]azulene-3-carboxylic acid pyridin-2-ylamide

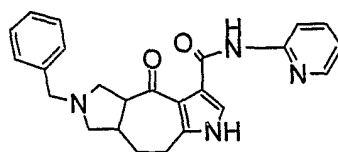


- 5                    Step 1: 6-Benzyl-4-oxo-4,4a,5,6,7,7a,8,9-octahydro-1,6-diaza-cyclopenta[f]azulene-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester



- 10                    4-Oxo-7,8-dihydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (2.92g, 9.15mmol), LiF ( 296mg, 11.4 mmol) and benzyl-methoxymethyl-trimethylsilanylmethyl-amine are mixed together in CH<sub>3</sub>CN (10 ml). The reaction mixture is sonicated under N<sub>2</sub>. The water bath is kept under 35 °C with ice. After 6h, solvents are removed in vacuo. The residue is put on a column (1:1 EtOAc / hexanes) to afford the title compound as clear oil, which solidified upon standing. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.23 (3H, t), 1.56 (9H, s), 1.88-2.00 (2H, m), 2.65 (1H, m), 2.92-3.02 (4H, m), 3.24 (1H, m), 3.50-3.59 (3H, m), 4.06 (1H, q), 4.19 (2H, q), 7.18 –7.27 (5H, m), 7.62 (1H, s). MS (ES<sup>+</sup>) 453 (M+1)
- 15

- Step            2:                    6-Benzyl-4-oxo-4,4a,5,6,7,7a,8,9-octahydro-1H-1,6-diaza-cyclopenta[f]azulene-3-carboxylic acid pyridin-2-ylamide



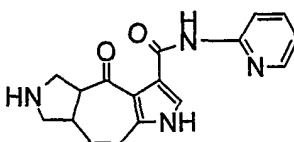
- 20                    6-Benzyl-4-oxo-4,4a,5,6,7,7a,8,9-octahydro-1,6-diaza-cyclopenta[f]azulene-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (350 mg, 0.773mmol) are used for the amination reaction. The amination is carried out via the methods described in Example 2, Step 3. The crude products are used in the next step without further purification.

- 25                    The crude products obtained from step a) are dissolved in a 1:1 mixture of TFA and CH<sub>2</sub>Cl<sub>2</sub> (4ml). The reaction mixture is stirred at room temperature for 3h. The solvents are removed in vacuo and the residue was put on a column (4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to provide the title compound as white solid. This compound is salted as an HCl salt. <sup>1</sup>H NMR (400 MHz,

CD<sub>3</sub>OD)  $\delta$  1.88-2.00 (2H, m), 2.55 (1H, m), 2.92-3.02 (4H, m), 3.34 (1H, m), 3.50-3.59 (3H, m), 3.95 (1H, m), 6.95 (1H, m), 7.18-7.26 (5H, m), 7.61 (2H, m), 8.35 (2H, m). MS (ES<sup>+</sup>) 401 (M+1)

#### Example 7

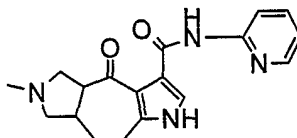
#### 5 Preparation of 4-Oxo-4,4a,5,6,7,7a,8,9-octahydro-1H-1,6-diaza-cyclopenta[f]azulene-3-carboxylic acid pyridin-2-ylamide



Pd(OH)<sub>2</sub> (Pearlman's catalyst, 30mg) is added to a solution of 6-benzyl-4-oxo-4,4a,5,6,7,7a,8,9-octahydro-1H-1,6-diaza-cyclopenta[f]azulene-3-carboxylic acid pyridin-2-ylamide (65mg, 0.16 mmol) and HCOONH<sub>4</sub> (204mg, 3.24mmol) in EtOH (10ml). The reaction mixture is heated at 78 °C for 20 min. Pd catalyst is filtered off with celite. The solvent is removed by rotavapor. The residue is loaded on a column (0.5% TEA + 19.5% MeOH + 80% CH<sub>3</sub>CN) to provide the title compound (20 mg, 40%) as white solid. This compound may be salted as HCl salt. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  1.98 (1H, m), 2.01-2.16 (2H, m), 2.65 (1H, m), 3.02-3.25 (5H, m), 3.76 (1H, m), 7.09 (1H, m), 7.57 (1H, s), 7.78 (1H, m), 8.27 (2H, m). MS (ES<sup>+</sup>) 311 (M+1)

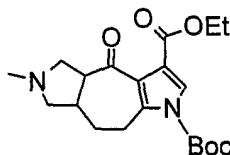
#### Example 8

#### Preparation of 6-Methyl-4-oxo-4,4a,5,6,7,7a,8,9-octahydro-1H-1,6-diaza-cyclopenta[f]azulene-3-carboxylic acid pyridin-2-ylamide



20

Step 1: 6-Methyl-4-oxo-4,4a,5,6,7,7a,8,9-octahydro-1,6-diaza-cyclopenta[f]azulene-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester

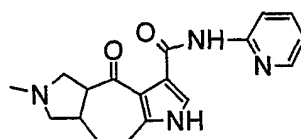


MeI (5.7mL, 93 mmol) is added to 6-benzyl-4-oxo-4,4a,5,6,7,7a,8,9-octahydro-1,6-diaza-cyclopenta[f]azulene-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester ( 2.8 g, 6.2 mmol) in acetone (100mL) at room temperature. The reaction mixture is stirred at room temperature for 4 h. The solvent and excessive MeI are removed under reduced pressure. The resulting solid is used in the next step without further purification.

25

The solid obtained above is dissolved in EtOH (700mL). Pd/C (1g, 10% Pd on activated carbon) is added. The reaction mixture was shaken under H<sub>2</sub> (40 psi) at 65-70°C for 10h. Pd/C is filtered off with Celite. EtOH is removed under reduced pressure. The residue was loaded on a column (9:1:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH) to provide the title compound (1.15g, 40%) as slightly colored solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.68 (1H, s), 4.17 (2H, q), 3.60 (1H, m), 3.31 (1H, m), 3.06-2.68 (4H, m), 2.34 (3H, s), 2.03-1.97 (2H, m), 1.58 (9H, s), 1.25 (3H, t). MS (ES<sup>+</sup>) 377 (M+1).

Step 2: 6-Methyl-4-oxo-4,4a,5,6,7,7a,8,9-octahydro-1H-1,6-diazacyclopenta[f]azulene-3-carboxylic acid pyridin-2-ylamide.



10

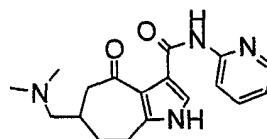
(a) 6-Methyl-4-oxo-4,4a,5,6,7,7a,8,9-octahydro-1,6-diazacyclopenta[f]azulene-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (150mg, 0.398mmol) is used for the amination reaction. The amination reaction is carried out in the same way as described in Example 2, Step 3. The crude products are put into next step without further purification.

(b) The crude products obtained from the previous step are dissolved in 1:1 mixture of TFA and CH<sub>2</sub>Cl<sub>2</sub> (4ml). The reaction mixture is stirred at room temperature for 3h. The solvents are removed under reduced pressure, and the residue was put on a column (4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to provide the title compound (52 mg, 40%) as white solid. It title compound may be salted as HCl salt. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD); δ 8.29-8.23 (2H, m), 7.76 (1H, m), 7.58 (1H, s), 7.08 (1H, m), 3.65 (1H, m), 3.37-2.99 (4H, m), 2.77 (1H, m), 2.48 (1H, m), 2.43 (3H, s), 2.29 (1H, m), 2.04 (1H, m), 1.79 (1H, m). MS (ES<sup>+</sup>) 325 (M+1)

20

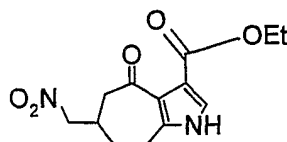
#### Example 9

#### Preparation of 6-Dimethylaminomethyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid pyridin-2-ylamide



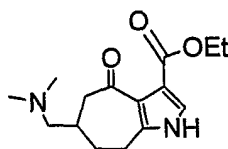
25

Step 1: 6-Nitromethyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid ethyl ester



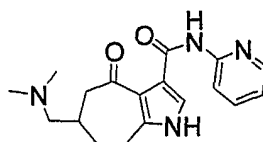
4-Oxo-7,8-dihydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (6.81g, 21.3mmol) is dissolved in  $\text{CH}_3\text{NO}_2$  (50ml), Triton B (40% aqueous, 2.5 mL) is added quickly. The reaction mixture was kept at 80 °C for 8h. The mixture is cooled and the solvent removed under reduced pressure. The residue is taken into 50 ml  $\text{CH}_2\text{Cl}_2$  and 25 ml  $\text{H}_2\text{O}$ . The aqueous phase is adjusted to slightly basic with 1N HCl and sat.  $\text{NaHCO}_3$ , and extracted with  $\text{CH}_2\text{Cl}_2$  (30mL x 4). Organic phases are combined, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. Flash chromatography (1:1 hexanes /EtOAc) provides the title compound (5.6g, 93%) as white solid. .  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.21 (1H, s), 4.45 (2H, d), 4.20 (2H, q), 2.97-2.62 (5H, m), 2.04 (1H, m), 1.65 (1H, m), 1.27 (3H, t).  $\text{MS (ES}^+)$  281 (M+1)

Step 2: Dimethylaminomethyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid ethyl ester.



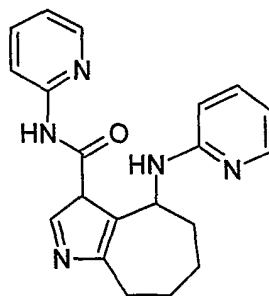
6-Nitromethyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid ethyl ester (350mg, 1.25mmol) is dissolved in EtOH /THF (50mL/13mL). Raney-Ni (50% aqueous slurry, 350mg) and HCHO (37% in  $\text{H}_2\text{O}$ , 2.04g, 25mmol) are added to the solution. The reaction mixture is shaken under  $\text{H}_2$  (40psi) at room temperature for 24h. The catalyst is filtered off with Celite and the solvents are removed under reduced pressure. Flash chromatography (4% MeOH + 95%  $\text{CH}_2\text{Cl}_2$  + 1%  $\text{NH}_4\text{OH}$ ) provides the title compound (180mg, 52%) as white solid. .  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$ : 7.32 (1H, s), 4.18 (2H, q), 3.01-2.75 (3H, m), 2.54 (1H, m), 2.26-2.17 (9H, m), 2.02 (1H, m), 1.57 (1H, m), 1.25 (3H, t).  $\text{MS (ES}^+)$  279 (M+1)

Step 3 : 6-Dimethylaminomethyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid pyridin-2-ylamide



In the same way as described in Example 2, Step 3, the title compound (125mg, 50%) is obtained as a white solid. It may be salted as an HCl salt.  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.31-8.24 (2H, m), 7.79 (1H, m), 7.54 (1H, s), 7.10 (1H, m), 3.04-2.73 (4H, m), 2.28-2.18 (9H, m), 2.07 (1H, m), 1.56 (1H, m).  $\text{MS (ES}^+)$  327 (M+1)



Example 10

4-(Pyridin-2-ylamino)-3,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid  
pyridin-2-ylamide

- 5 This compound is prepared by the reductive amination of the imine (Schiff Base) which is prepared by reaction of the corresponding unsubstituted ketone (see example 1, step 1 with minor modification) with 2-aminopyridine. Reduction of the resulting imine using standard reduction conditions (LiAlH<sub>4</sub>, NaBH<sub>4</sub>, sodium acetoxy borohydride, H<sub>2</sub>/catalyst) affords the above compound. The preferred reducing agent is sodium acetoxy borohydride.
- 10 These compounds have limited stability due to the presence of the secondary amine group. Other compounds, similar to the above compound (having an amine substituent on the seven-membered ring) may be synthesized using modifications of the disclosed methods .

Example 11Preparation of radiolabeled probe compounds of the invention

- 15 The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. The radioisotope is preferably selected from of at least one of carbon (preferably <sup>14</sup>C), hydrogen (preferably <sup>3</sup>H), sulfur (preferably <sup>35</sup>S), or iodine (preferably <sup>125</sup>I). Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of
- 20 radiolabeled probe compounds. Such suppliers include Amersham Corporation, Arlington Heights, IL; Cambridge Isotope Laboratories, Inc. Andover, MA; SRI International, Menlo Park, CA; Wizard Laboratories, West Sacramento, CA; ChemSyn Laboratories, Lexena, KS; American Radiolabeled Chemicals, Inc., St. Louis, MO; and Moravek Biochemicals Inc., Brea, CA.
- 25 Tritium labeled probe compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas. Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate. In addition,
- 30 certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate.

EXAMPLE 12Receptor autoradiography

Receptor autoradiography (receptor mapping) is carried out in vitro as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention prepared as described in the preceding Example.

EXAMPLE 13Binding Assay

The high affinity and high selectivity of compounds of this invention for the benzodiazepine site of the GABA<sub>A</sub> receptor was confirmed using the binding assay described by Thomas and Tallman (*J. Bio. Chem.* 1981; 156:9838-9842, and *J. Neurosci.* 1983; 3:433-440).

Rat cortical tissue was dissected and homogenized in 25 volumes (w/v) of Buffer A (0.05 M Tris HCl buffer, pH 7.4 at 4 °C). The tissue homogenate was centrifuged in the cold (4 °C) at 20,000 x g for 20 minutes. The supernatant was decanted, the pellet rehomogenized in the same volume of buffer, and centrifuged again at 20,000 x g. The supernatant of this centrifugation step was decanted and the pellet stored at -20 °C overnight. The pellet was then thawed and resuspended in 25 volumes of Buffer A (original wt/vol), centrifuged at 20,000 x g and the supernatant decanted. This wash step was repeated once. The pellet was finally resuspended in 50 volumes of Buffer A.

Incubations contained 100 µl of tissue homogenate, 100 µl of radioligand, (0.5 nM <sup>3</sup>H-Ro15-1788 [<sup>3</sup>H-Flumazenil], specific activity 80 Ci/mmol), and test compound or control (see below), and were brought to a total volume of 500 µl with Buffer A. Incubations were carried for 30 min at 4°C and then rapidly filtered through Whatman GFB filters to separate free and bound ligand. Filters were washed twice with fresh Buffer A and counted in a liquid scintillation counter. Nonspecific binding (control) is determined by displacement of <sup>3</sup>H Ro15-1788 with 10 µM Diazepam (Research Biochemicals International, Natick, MA). Data were collected in triplicate, averaged, and percent inhibition of total specific binding (Total Specific Binding = Total - Nonspecific) was calculated for each compound.

A competition binding curve was obtained with up to 11 points spanning the compound concentration range from 10<sup>-12</sup>M to 10<sup>-5</sup>M obtained per curve by the method described above for determining percent inhibition. K<sub>i</sub> values were calculated according the Cheng-Prusoff equation. Each of the compounds set forth in Examples 1-10 as compounds was tested in this fashion and each was found to have a K<sub>i</sub> of < 4µM. Preferred compounds of the invention exhibit K<sub>i</sub> values of less than 100 nM and more preferred compounds of the invention exhibit K<sub>i</sub> values of less than 10 nM.

The results for the above-described compounds in the binding assay are presented below.

- Example 2: 2nM  
Example 3: 1 nM  
5 Example 4: 7nM  
Example 5: 8 nM  
Example 6: 4 nM  
Example 7: 7 nM  
Example 8: 8 nM  
10 Example 9: 23 nM  
Example 10: 24 nM

#### EXAMPLE 14

##### Electrophysiology

The following assay is used to determine if a compound of the invention acts as an  
15 agonist, an antagonist, or an inverse agonist at the benzodiazepine site of the GABA<sub>A</sub> receptor.

Assays are carried out as described in White and Gurley (NeuroReport 6: 1313-1316, 1995) and White, Gurley, Hartnett, Stirling, and Gregory (Receptors and Channels 3: 1-5, 1995) with modifications. Electrophysiological recordings are carried out using the two  
20 electrode voltage-clamp technique at a membrane holding potential of -70 mV. *Xenopus Laevis* oocytes are enzymatically isolated and injected with non-polyadenylated cRNA mixed in a ratio of 4:1:4 for  $\alpha$ ,  $\beta$  and  $\gamma$  subunits, respectively. Of the nine combinations of  $\alpha$ ,  $\beta$  and  $\gamma$  subunits described in the White et al. publications, preferred combinations are  $\alpha_1\beta_2\gamma_2$ ,  $\alpha_2\beta_3\gamma_2$ ,  $\alpha_3\beta_3\gamma_2$ , and  $\alpha_5\beta_3\gamma_2$ . Preferably all of the subunit cRNAs in each combination are human clones  
25 or all are rat clones. The sequence of each of these cloned subunits is available from GENBANK, e.g., human  $\alpha_1$ , GENBANK accession no. X14766, human  $\alpha_2$ , GENBANK accession no. A28100; human  $\alpha_3$ , GENBANK accession no. A28102; human  $\alpha_5$ , GENBANK accession no. A28104; human  $\beta_2$ , GENBANK accession no. M82919; human  $\beta_3$ , GENBANK accession no. Z20136; human  $\gamma_2$ , GENBANK accession no. X15376; rat  $\alpha_1$ , GENBANK  
30 accession no. L08490, rat  $\alpha_2$ , GENBANK accession no. L08491; rat  $\alpha_3$ , GENBANK accession no. L08492; rat  $\alpha_5$ , GENBANK accession no. L08494; rat  $\beta_2$ , GENBANK accession no. X15467; rat  $\beta_3$ , GENBANK accession no. X15468; and rat  $\gamma_2$ , GENBANK accession no. L08497. For each subunit combination, sufficient message for each constituent subunit is injected to provide current amplitudes of >10 nA when 1  $\mu$ M GABA is applied.

35 Compounds are evaluated against a GABA concentration that evokes <10% of the maximal evokable GABA current (e.g. 1 $\mu$ M–9 $\mu$ M). Each oocyte is exposed to increasing concentrations of a compound being evaluated (test compound) in order to evaluate a

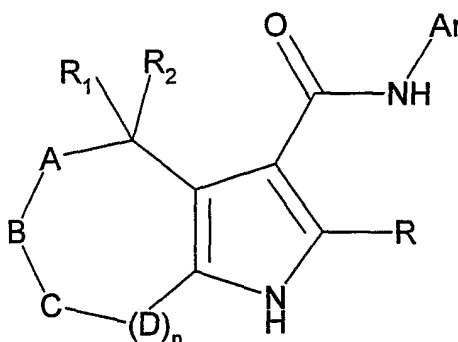
concentration/effect relationship. Test compound efficacy is calculated as a percent-change in current amplitude:  $100*((I_c/I)-1)$ , where  $I_c$  is the GABA evoked current amplitude observed in the presence of test compound and  $I$  is the GABA evoked current amplitude observed in the absence of the test compound.

5            Specificity of a test compound for the benzodiazepine site is determined following completion of a concentration/effect curve. After washing the oocyte sufficiently to remove previously applied test compound, the oocyte is exposed to GABA + 1  $\mu$ M RO15-1788, followed by exposure to GABA + 1  $\mu$ M RO15-1788 + test compound. Percent change due to addition of compound is calculated as described above. Any percent change observed in the  
10           presence of RO15-1788 is subtracted from the percent changes in current amplitude observed in the absence of 1  $\mu$ M RO15-1788. These net values are used for the calculation of average efficacy and  $EC_{50}$  values by standard methods. To evaluate average efficacy and  $EC_{50}$  values, the concentration/effect data are averaged across cells and fit to the logistic equation.

15           It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the scope of the present invention as set forth in the following claims.

## CLAIMS

1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

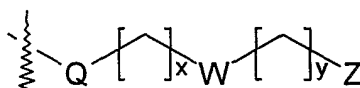
- 5 R is selected from halogen, cyano, nitro, and amino;  
 R<sub>1</sub> is chosen from amino, fluoro, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, arylamino, heteroarylamino, aryloxy, or heteroaryloxy, and  
 R<sub>2</sub> is chosen from hydrogen, fluoro, C<sub>1</sub>-C<sub>6</sub> alkyl, and aryl(C<sub>1</sub>-C<sub>4</sub>alkyl); or  
 R<sub>1</sub> and R<sub>2</sub> together represent an oxo group; or  
 10 R<sub>1</sub> and R<sub>2</sub> are joined to form a saturated, or partially unsaturated ring of from 4 to 8 members containing 1 or more heteroatoms independently chosen from N, S, and O;  
 n is 0, 1, or 2;  
 A is chosen from O, NR<sub>3</sub>, and CR<sub>3</sub>R<sub>3</sub>;  
 B is chosen from O, NR<sub>4</sub>, and CR<sub>4</sub>R<sub>4</sub>;  
 15 C is chosen from O, NR<sub>5</sub>, and CR<sub>5</sub>R<sub>5</sub>;  
 D is independently chosen at each occurrence from O, NR<sub>6</sub>, and CR<sub>6</sub>R<sub>6</sub>;  
 R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently chosen at each occurrence from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>, C<sub>2</sub>-C<sub>6</sub>alkenyl<sub>1</sub>, C<sub>2</sub>-C<sub>6</sub>alkynyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heterocycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>), amino(C<sub>2</sub>-C<sub>6</sub> alkyl<sub>1</sub>),  
 20 aryl<sub>1</sub>, aryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heteroaryl<sub>1</sub>, and heteroaryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>);  
 R<sub>3</sub>, R<sub>3</sub><sup>\*</sup>, R<sub>4</sub>, R<sub>4</sub><sup>\*</sup>, R<sub>5</sub>, R<sub>5</sub><sup>\*</sup>, R<sub>6</sub>, and R<sub>6</sub><sup>\*</sup> are independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy<sub>1</sub>, C<sub>2</sub>-C<sub>6</sub>alkenyl<sub>1</sub>, C<sub>2</sub>-C<sub>6</sub>alkynyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heterocycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), halo(C<sub>1</sub>-C<sub>6</sub>)alkyl<sub>1</sub>, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy<sub>1</sub>, hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>),  
 25 amino(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>), mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>)amino, mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>)amino(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>), aryl<sub>1</sub>, aryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heteroaryl<sub>1</sub>, and heteroaryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>);  
 wherein each alkyl<sub>1</sub>, alkenyl<sub>1</sub>, alkynyl<sub>1</sub>, alkoxy<sub>1</sub>, cycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>, aryl<sub>1</sub>, and heteroaryl<sub>1</sub> is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and mono- or di-(C<sub>1</sub>-C<sub>6</sub>alkyl)amino;  
 30 C<sub>6</sub>alkyl)amino;

with the proviso that

- a) at least one of B, C, and D is nitrogen and is substituted by C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heterocycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), hydroxy(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>), amino(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>), aryl<sub>1</sub>, aryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heteroaryl<sub>1</sub>, and heteroaryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>),  
 5 or
- b) at least one of B, C, and D are carbon and is substituted by halogen, hydroxy, amino, cyano, nitro, oxo, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heterocycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), halo(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>), halo(C<sub>1</sub>-C<sub>6</sub>alkoxy<sub>1</sub>), hydroxy(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>), amino(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>), mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>)amino, mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>)amino(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>), aryl<sub>1</sub>, aryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heteroaryl<sub>1</sub>, and heteroaryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>),  
 10 or
- c) A is carbon and is substituted by halogen, hydroxy, amino, cyano, nitro, oxo, C<sub>1</sub>-C<sub>6</sub>alkoxy, halo(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>), halo(C<sub>1</sub>-C<sub>6</sub>alkoxy<sub>1</sub>), hydroxy(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>), or
- d) n is 1 or 2 and at least one of B, C, or D is nitrogen or oxygen; or  
 15 any of R<sub>3'</sub> and R<sub>3''</sub>, R<sub>4'</sub> and R<sub>4''</sub>, R<sub>5'</sub> and R<sub>5''</sub>, and R<sub>6'</sub> and R<sub>6''</sub> may be joined to form a saturated, partially unsaturated, or unsaturated carbocyclic or heterocyclic ring<sub>1</sub>;

wherein said ring<sub>1</sub> is a saturated, partially unsaturated, or unsaturated carbocyclic or heterocyclic ring of from 3-8 ring members which contains 0, 1, or 2 heteroatoms independently chosen from O, N, and S, and said ring<sub>1</sub> is unsubstituted or is substituted by 1,  
 20 2, or 3 substituents independently chosen from halogen, hydroxy, amino, cyano, nitro, oxo, 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>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, halo(C<sub>1</sub>-C<sub>6</sub>alkyl), halo(C<sub>1</sub>-C<sub>6</sub>alkoxy), hydroxy(C<sub>1</sub>-C<sub>6</sub>alkyl), amino(C<sub>1</sub>-C<sub>6</sub>alkyl), mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, and mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino(C<sub>1</sub>-C<sub>6</sub>alkyl);

Ar is a group of the formula

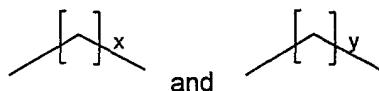


Q is an optionally substituted carbocyclic aryl or optionally substituted heteroaryl group having from 1 to 3 rings, 5 to 6 members in each ring and from 1 to 3 heteroatoms;

W is hydrogen, oxygen, nitrogen, sulfur, or CR<sup>7</sup>R<sup>8</sup> where R<sup>7</sup> and R<sup>8</sup> are the same or different and represent hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or R<sup>7</sup> and R<sup>8</sup> may be taken together to  
 30 represent a cyclic moiety having 3-7 carbon atoms;

Z is hydrogen, hydroxy, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>3</sub>-C<sub>7</sub>cycloalkyl, C<sub>3</sub>-C<sub>7</sub>cycloalkyl(C<sub>1</sub>-C<sub>4</sub>alkoxy), amino, mono or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, or NR<sup>9</sup>COR<sup>10</sup> where R<sup>9</sup> and R<sup>10</sup> are the same or different and represent hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl, or R<sup>9</sup> and R<sup>10</sup> may be joined to form a C<sub>3</sub>-C<sub>7</sub>cycloalkyl ring, or

Z is optionally substituted carbocyclic aryl or optionally substituted heteroaryl group having from 1 to 3 rings, 5 to 6 members in each ring and from 1 to 3 heteroatoms;



represent carbon chains which are independently unsubstituted or substituted with halogen, cyano, nitro, amino, mono or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, 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>alkoxy, trihalomethyl, trihalomethoxy, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>3</sub>-C<sub>7</sub>cycloalkyl,

x is 0, 1, 2, or 3; and

y is 0, 1, 2, or 3.

2. A compound or salt according to Claim 1, wherein:

10 R, R<sub>1</sub>, R<sub>2</sub>, A, B, C, D, and n are as defined in Claim 1 and

Q is a phenyl, naphthyl, quinolinyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl, oxazolyl, isoxazolyl, symmetrical or unsymmetrical oxadiazolyl, symmetrical or unsymmetrical thiadiazolyl, symmetrical or unsymmetrical triazolyl, pyrazolyl, furanyl, diazenyl, triazenyl, or triazolopyrazinyl group;

15 each of which is unsubstituted or substituted with up to three substituents independently selected from i) and ii) wherein

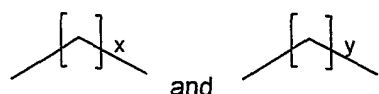
i) is hydroxy, cyano, halogen, nitro, amino, mono or di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, trihalomethyl, and trihalomethoxy;

20 ii) is C<sub>1</sub>-C<sub>6</sub>alkyl optionally containing heteroatoms and optionally substituted with one or more carbocyclic or heterocyclic group;

W is hydrogen, oxygen, nitrogen, sulfur, or CR<sup>7</sup>R<sup>8</sup> where R<sup>7</sup> and R<sup>8</sup> are the same or different and represent hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or R<sup>7</sup> and R<sup>8</sup> may be taken together to represent a cyclic moiety having 3-7 carbon atoms;

25 Z is hydrogen, hydroxy, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>3</sub>-C<sub>7</sub>cycloalkyl, C<sub>3</sub>-C<sub>7</sub>cycloalkyl(C<sub>1-3</sub>alkoxy), amino, mono or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, a carbocyclic or heterocyclic group, or NR<sup>9</sup>COR<sup>10</sup> where R<sup>9</sup> and R<sup>10</sup> are the same or different and represent hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl, or R<sup>9</sup> and R<sup>10</sup> may be joined to form a C<sub>3</sub>-C<sub>7</sub> cycloalkyl ring, or

30 Z is a phenyl, naphthyl, quinolinyl, thienyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, pyrazolyl, pyrazinyl, pyridizynyl, piperidinyl, oxazolyl, isoxazolyl, symmetrical or unsymmetrical thiadiazolyl, symmetrical or unsymmetrical triazolyl, symmetrical or unsymmetrical oxadiazolyl, pyrrolyl, furanyl, pyrimidinyl, diazenyl, triazenyl, 1, 2, 4-triazolone, 4,5-dihydroimidazolyl, or a 1,4,5,6-tetrahydropyrimidinyl group;



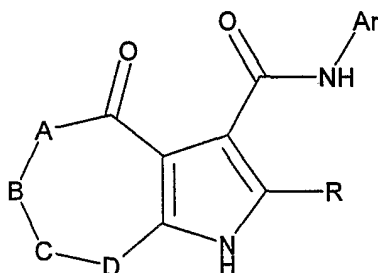
represent carbon chains which are unsubstituted or substituted with up to three groups independently chosen from halogen, cyano, nitro, amino,

mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, 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>alkoxy, trihalomethyl, trihalomethoxy, straight or branched chain C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>3</sub>-C<sub>7</sub>cycloalkyl, and

m is 0, 1, 2, or 3; and

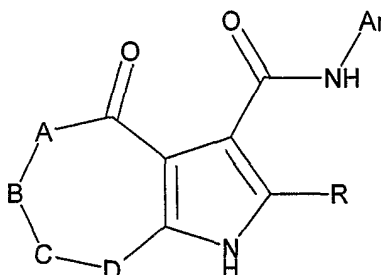
n is 0, 1, 2, or 3.

- 5 3. A compound or salt according to Claim 2, wherein n is 1 and R, R<sub>1</sub>, R<sub>2</sub>, A, B, C, D, and Ar are as defined in Claim 2.
4. A compound or salt according to Claim 2, of the formula



wherein R, Ar, and A, B, C, and D are as defined in Claim 2.

- 10 5. A compound or salt according to Claim 2, of the formula



wherein R, Ar, are as defined in Claim 2;

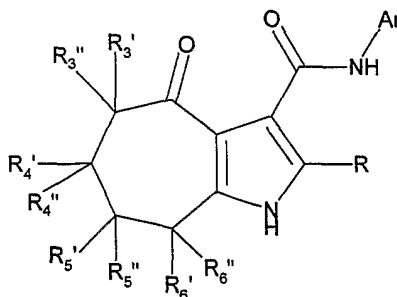
A is chosen from NR<sub>3</sub> and CR<sub>3</sub>R<sub>3</sub>';

B is chosen from NR<sub>4</sub> and CR<sub>4</sub>R<sub>4</sub>';

- 15 C is chosen from NR<sub>5</sub> and CR<sub>5</sub>R<sub>5</sub>';

D is chosen from NR<sub>6</sub> and CR<sub>6</sub>R<sub>6</sub>'; and not more than 2 members of the ring containing A, B, C, and D are nitrogen.

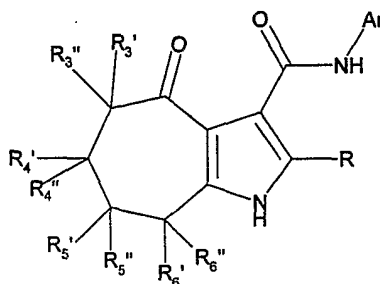
6. A compound or salt according to Claim 2, of the formula



- 20 wherein R, Ar, R<sub>3</sub>, R<sub>3</sub>R<sub>3</sub>', R<sub>4</sub>, R<sub>4</sub>R<sub>4</sub>', R<sub>5</sub>, R<sub>5</sub>R<sub>5</sub>', R<sub>6</sub>, R<sub>6</sub>' and R<sub>6</sub>'' are as defined in Claim 2.



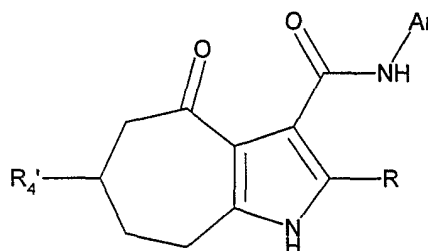
7. A compound or salt according to Claim 2, of the formula



wherein R, R<sub>3</sub>, R<sub>3</sub>R<sub>3</sub>', R<sub>4</sub>, R<sub>4</sub>R<sub>4</sub>', R<sub>5</sub>, R<sub>5</sub>R<sub>5</sub>', R<sub>6</sub>, R<sub>6</sub> and R<sub>6</sub>' are as defined in Claim 2; and  
Ar is phenyl, pyridyl or pyrimidinyl,

- 5 each of which is unsubstituted or substituted with up to three substituents independently selected from hydroxy, cyano, halogen, nitro, amino, mono or 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>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, trihalomethyl, or trihalomethoxy.

8. A compound or salt according to Claim 2, of the formula



10

wherein R is as defined in Claim 2; and

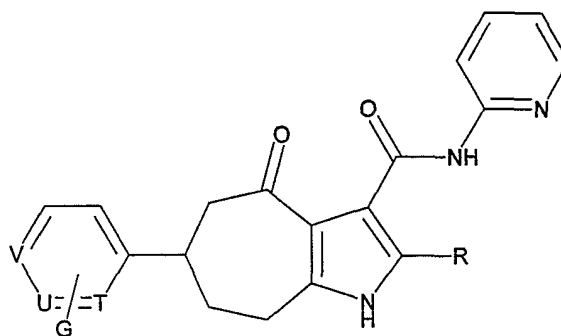
Ar is phenyl, pyridyl or pyrimidinyl,

- each of which is unsubstituted or substituted with up to three substituents independently selected from hydroxy, cyano, halogen, nitro, amino, mono or 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>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, trihalomethyl, or trihalomethoxy; and

15 R<sub>4</sub>' is chosen from C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heterocycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), aryl<sub>1</sub>, aryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heteroaryl<sub>1</sub>, and heteroaryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>);

20 wherein each alkyl<sub>1</sub>, cycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>, aryl<sub>1</sub>, and heteroaryl<sub>1</sub> is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, amino(C<sub>1</sub>-C<sub>6</sub>alkyl); mono- or di-(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, and mono- or di-(C<sub>1</sub>-C<sub>6</sub>alkyl)amino(C<sub>1</sub>-C<sub>6</sub>alkyl).

9. A compound or salt according to Claim 2, of the formula



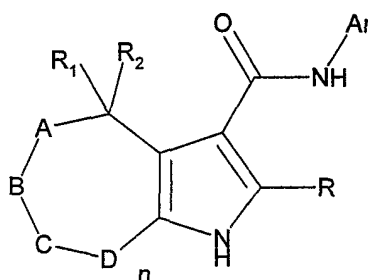
wherein

R is selected from hydrogen, halogen, methyl, and ethyl;

V, U, and T, independently represent N or CH; and

5 G represents up to 3 groups independently chosen from hydrogen, hydroxy, oxo, halogen, amino, cyano, nitro, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and mono- or di-amino(C<sub>1</sub>-C<sub>6</sub>alkyl).

10. A compound of the formula



or a pharmaceutically acceptable salt, wherein:

10 R is selected from hydrogen, halogen, cyano, nitro, and amino;

R<sub>1</sub> is chosen from amino, fluoro, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, arylamino, heteroaryl amino, aryloxy, or heteroaryloxy, and

R<sub>2</sub> is chosen from hydrogen, fluoro, C<sub>1</sub>-C<sub>6</sub> alkyl, and aryl(C<sub>1</sub>-C<sub>4</sub>alkyl); or

R<sub>1</sub> and R<sub>2</sub> together represent an oxo group; or

15 R<sub>1</sub> and R<sub>2</sub> are joined to form a saturated, or partially unsaturated ring of from 4 to 8 members containing 1 or more heteroatoms independently chosen from N, S, and O;

n is 0, 1, or 2;

A is chosen from O, NR<sub>3</sub>, and CR<sub>3</sub>R<sub>3</sub>;

B is chosen from O, NR<sub>4</sub>, and CR<sub>4</sub>R<sub>4</sub>;

20 C is chosen from O, NR<sub>5</sub>, and CR<sub>5</sub>R<sub>5</sub>;

D is independently chosen at each occurrence from O, NR<sub>6</sub>, and CR<sub>6</sub>R<sub>6</sub>;

R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently chosen at each occurrence from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>, C<sub>2</sub>-C<sub>6</sub>alkenyl<sub>1</sub>, C<sub>2</sub>-C<sub>6</sub>alkynyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heterocycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>), amino(C<sub>2</sub>-C<sub>6</sub> alkyl<sub>1</sub>), aryl<sub>1</sub>, aryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heteroaryl<sub>1</sub>, and heteroaryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>);

$R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $R_5$ ,  $R_5'$ ,  $R_6$ , and  $R_6'$  are independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy<sub>1</sub>, C<sub>2</sub>-C<sub>6</sub> alkenyl<sub>1</sub>, C<sub>2</sub>-C<sub>6</sub> alkynyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub> cycloalkyl<sub>1</sub>, C<sub>3</sub>-C<sub>7</sub> cycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heterocycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), halo(C<sub>1</sub>-C<sub>6</sub>)alkyl<sub>1</sub>, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy<sub>1</sub>, hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>), amino(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>1</sub>), mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>)amino, mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>)amino(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>1</sub>), aryl<sub>1</sub>, aryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>), heteroaryl<sub>1</sub>, and heteroaryl<sub>1</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl<sub>1</sub>);

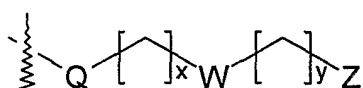
wherein each alkyl<sub>1</sub>, alkenyl<sub>1</sub>, alkynyl<sub>1</sub>, alkoxy<sub>1</sub>, cycloalkyl<sub>1</sub>, heterocycloalkyl<sub>1</sub>, aryl<sub>1</sub>, and heteroaryl<sub>1</sub> is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and mono- or di-amino(C<sub>1</sub>-C<sub>6</sub>alkyl);

with the proviso that either  $R_3$  or  $R_3'$  and  $R_4$  or  $R_4'$  form an unsaturated, partially saturated, or saturated ring of from 5 to 7 members or  $R_4$  or  $R_4'$  and  $R_5$  or  $R_5'$  form an unsaturated, partially saturated, or saturated ring of from 5 to 7 members, wherein said unsaturated, partially saturated, or saturated ring contains 0, 1, or 2 heteroatoms independently chosen from S, O, or N and said unsaturated, partially saturated, or saturated ring is unsubstituted or substituted with up to 3 substituents independently chosen from:

halogen, hydroxy, amino, cyano, nitro, oxo, 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>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>2</sub>, C<sub>3</sub>-C<sub>7</sub>cycloalkyl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), heterocycloalkyl<sub>2</sub>, heterocycloalkyl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy(C<sub>1</sub>-C<sub>6</sub> alkyl), amino(C<sub>1</sub>-C<sub>6</sub> alkyl<sub>2</sub>, mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl<sub>2</sub>)amino, aryl<sub>2</sub>, aryl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), heteroaryl<sub>2</sub>, and heteroaryl<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl);

wherein each cycloalkyl<sub>2</sub>, heterocycloalkyl<sub>2</sub>, aryl<sub>2</sub>, and heteroaryl<sub>2</sub> is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and mono- or di-amino(C<sub>1</sub>-C<sub>6</sub>alkyl);

Ar is a group of the formula

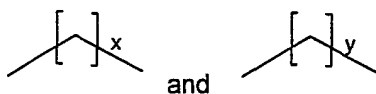


Q is an optionally substituted carbocyclic aryl or optionally substituted heteroaryl group having from 1 to 3 rings, 5 to 6 members in each ring and from 1 to 3 heteroatoms;

W is hydrogen, oxygen, nitrogen, sulfur, or CR<sup>7</sup>R<sup>8</sup> where R<sup>7</sup> and R<sup>8</sup> are the same or different and represent hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, or R<sup>7</sup> and R<sup>8</sup> may be taken together to represent a cyclic moiety having 3-7 carbon atoms;

Z is hydrogen, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub>alkoxy), amino, mono or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, or NR<sup>9</sup>COR<sup>10</sup> where R<sup>9</sup> and R<sup>10</sup> are the same or different and represent hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl, or R<sup>9</sup> and R<sup>10</sup> may be joined to form a C<sub>3</sub>-C<sub>7</sub> cycloalkyl ring, or

Z is optionally substituted carbocyclic aryl or optionally substituted heteroaryl group having from 1 to 3 rings, 5 to 6 members in each ring and from 1 to 3 heteroatoms;



and represent carbon chains which are independently unsubstituted or substituted with halogen, cyano, nitro, amino, mono or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, mono or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino(C<sub>1</sub>-C<sub>6</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>alkoxy, trihalomethyl, trihalomethoxy, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and

x is 0, 1, 2, or 3; and

y is 0, 1, 2, or 3.

11. A compound or salt according to Claim 10, wherein:

10 R, R<sub>1</sub>, R<sub>2</sub>, A, B, C, D, and n are as defined in Claim 1 and

Q is a phenyl, naphthyl, quinoliny, thienyl, pyridyl, pyrimidinyl, pyrazinyl, oxazolyl, isoxazolyl, symmetrical or unsymmetrical oxadiazolyl, symmetrical or unsymmetrical thiadiazolyl, symmetrical or unsymmetrical triazolyl, pyrazolyl, furanyl, diazenyl, triazenyl, or triazolopyrazinyl group;

15 each of which is unsubstituted or substituted with up to three substituents independently selected from i) and ii) wherein

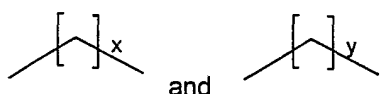
i) represents hydroxy, cyano, halogen, nitro, amino, mono or di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, trihalomethyl, or trihalomethoxy;

10 ii) represents C<sub>1</sub>-C<sub>6</sub>alkyl optionally containing heteroatoms and optionally substituted with one or more carbocyclic or heterocyclic group;

W is hydrogen, oxygen, nitrogen, sulfur, or CR<sup>7</sup>R<sup>8</sup> where R<sup>7</sup> and R<sup>8</sup> are the same or different and represent hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or R<sup>7</sup> and R<sup>8</sup> may be taken together to represent a cyclic moiety having 3-7 carbon atoms;

25 Z is hydrogen, hydroxy, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>3</sub>-C<sub>7</sub>cycloalkyl, C<sub>3</sub>-C<sub>7</sub>cycloalkyl(C<sub>1-3</sub>alkoxy), amino, mono or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, a carbocyclic or heterocyclic group, or NR<sup>9</sup>COR<sup>10</sup> where R<sup>9</sup> and R<sup>10</sup> are the same or different and represent hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl, or R<sup>9</sup> and R<sup>10</sup> may be joined to form a C<sub>3</sub>-C<sub>7</sub> cycloalkyl ring, or

30 Z is a phenyl, naphthyl, quinoliny, thienyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, pyrazolyl, pyrazinyl, pyridiziny, piperidinyl, oxazolyl, isoxazolyl, symmetrical or unsymmetrical thiadiazolyl, symmetrical or unsymmetrical triazolyl, symmetrical or unsymmetrical oxadiazolyl, pyrrolyl, furanyl, pyrimidinyl, diazenyl, triazenyl, 1, 2, 4-triazolone, 4,5-dihydroimidazolyl, or a 1,4,5,6-tetrahydropyrimidinyl group;



and represent carbon chains which is unsubstituted or substituted with up to three groups independently chosen from halogen, cyano, nitro, amino,

mono- or di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, 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>alkoxy, trihalomethyl, trihalomethoxy, straight or branched chain C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>3</sub>-C<sub>7</sub>cycloalkyl, and

x is 0, 1, 2, or 3; and

y is 0, 1, 2, or 3.

- 5           12.    A compound or salt according to Claim 11, wherein Ar represents phenyl, pyridyl, or pyrimidinyl each or which may be unsubstituted or substituted with 1, 2, or 3, substituents chosen from hydroxy, halogen, amino, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, trihalomethyl, trihalomethoxy, amino(C<sub>1</sub>-C<sub>6</sub> alkyl), mono- or di(C<sub>1</sub>-C<sub>6</sub> alkyl)amino, and mono- or di(C<sub>1</sub>-C<sub>6</sub> alkyl)amino(C<sub>1</sub>-C<sub>6</sub> alkyl).
- 10           13.    A pharmaceutical composition comprising an effective amount of a compound according to any of claims 1-12 with at least one pharmaceutically acceptable carrier or excipient.
- 15           14.    A method for the treatment of anxiety, depression, a sleep disorder, attention deficit disorder, or Alzheimer's dementia, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claims 1 to 12.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 02/02499

<p>A. CLASSIFICATION OF SUBJECT MATTER                  IPC 7 A61K31/40 C07D209/52 C07D401/12 C07D487/04 C07D401/14                  A61K31/403 A61P25/00 C07D209/42</p>		
<p>According to International Patent Classification (IPC) or to both national classification and IPC</p>		
<p>B. FIELDS SEARCHED</p>		
<p>Minimum documentation searched (classification system followed by classification symbols)                  IPC 7 C07D</p>		
<p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p>		
<p>Electronic data base consulted during the international search (name of data base and, where practical, search terms used)                  EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data</p>		
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p>		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 16103 A (NEUROGEN CORP ;ALBAUGH PAMELA (US); HUTCHISON ALAN (US); SHAW KENN) 8 March 2001 (2001-03-08) claims 1,25,70,71; examples ---	1-14
X	US 5 925 770 A (ALBAUGH PAMELA ET AL) 20 July 1999 (1999-07-20) cited in the application column 9, line 1 -column 10, line 36 examples ---	1-14
X	WO 95 11885 A (NEUROGEN CORP ;ALBAUGH PAMELA (US); HUTCHISON ALAN (US)) 4 May 1995 (1995-05-04) cited in the application page 1, line 14 - line 22; claim 1 examples ---	1-14
	-/--	
<p><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.</p>		
<p>° Special categories of cited documents :</p>		
<p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p>		<p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p>
<p>Date of the actual completion of the international search  2 September 2002</p>		<p>Date of mailing of the international search report  20/09/2002</p>
<p>Name and mailing address of the ISA                  European Patent Office, P.B. 5818 Patentlaan 2                  NL - 2280 HV Rijswijk                  Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,                  Fax: (+31-70) 340-3016</p>		<p>Authorized officer  Seymour, L</p>

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 02/02499

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 34870 A (NEUROGEN CORP ;ALBAUGH PAMELA (US); HUTCHISON ALAN (US); LIU GANG) 25 September 1997 (1997-09-25) cited in the application page 1, line 7 - line 10; claim 1 examples -----	1-14

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB 02/02499

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  

Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.



## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 02/02499

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0116103	A	08-03-2001	AU 7092800 A	26-03-2001
			BR 0013664 A	14-05-2002
			EP 1210328 A1	05-06-2002
			NO 20020948 A	28-02-2002
			TR 200200544 T2	21-06-2002
			WO 0116103 A1	08-03-2001
US 5925770	A	20-07-1999	US 5750702 A	12-05-1998
			US 5608079 A	04-03-1997
			US 5484944 A	16-01-1996
			AU 2832897 A	09-02-1998
			AU 3660497 A	09-02-1998
			HR 970385 A1	31-08-1998
			WO 9802433 A1	22-01-1998
			WO 9802420 A1	22-01-1998
			ZA 9706244 A	21-01-1999
			AT 168673 T	15-08-1998
			AU 701151 B2	21-01-1999
			AU 8126594 A	22-05-1995
			CA 2175204 A1	11-05-1995
			CN 1143953 A	26-02-1997
			CZ 9601129 A3	16-04-1997
			DE 69411939 D1	27-08-1998
			DE 69411939 T2	25-03-1999
			DK 725775 T3	26-04-1999
			EP 0725775 A1	14-08-1996
			EP 0825193 A1	25-02-1998
			ES 2122504 T3	16-12-1998
			FI 961776 A	14-06-1996
			HU 76064 A2	30-06-1997
			JP 9506082 T	17-06-1997
			KR 181383 B1	20-03-1999
			NO 961655 A	10-06-1996
			NZ 275968 A	27-05-1998
			NZ 330023 A	29-11-1999
			PL 314136 A1	19-08-1996
RU 2125989 C1	10-02-1999			
RU 2157367 C2	10-10-2000			
SE 9601563 A	22-05-1996			
SE 9902648 A	09-07-1999			
SK 52496 A3	09-07-1997			
WO 9511885 A1	04-05-1995			
WO 9511885	A	04-05-1995	US 5484944 A	16-01-1996
			AT 168673 T	15-08-1998
			AU 701151 B2	21-01-1999
			AU 8126594 A	22-05-1995
			CA 2175204 A1	11-05-1995
			CN 1143953 A	26-02-1997
			CZ 9601129 A3	16-04-1997
			DE 69411939 D1	27-08-1998
			DE 69411939 T2	25-03-1999
			DK 725775 T3	26-04-1999
			EP 0725775 A1	14-08-1996
			EP 0825193 A1	25-02-1998
			ES 2122504 T3	16-12-1998
			FI 961776 A	14-06-1996
HU 76064 A2	30-06-1997			

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 02/02499

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9511885	A	JP 9506082 T	17-06-1997
		KR 181383 B1	20-03-1999
		NO 961655 A	10-06-1996
		NZ 275968 A	27-05-1998
		NZ 330023 A	29-11-1999
		PL 314136 A1	19-08-1996
		RU 2125989 C1	10-02-1999
		RU 2157367 C2	10-10-2000
		SE 9601563 A	22-05-1996
		SE 9902648 A	09-07-1999
		SK 52496 A3	09-07-1997
		US 5925770 A	20-07-1999
		WO 9511885 A1	04-05-1995
		US 5608079 A	04-03-1997
		US 5750702 A	12-05-1998
WO 9734870	A	25-09-1997	
		AU 2218997 A	10-10-1997
		CA 2249562 A1	25-09-1997
		EP 0888300 A1	07-01-1999
		US 2001020035 A1	06-09-2001
WO 9734870 A1	25-09-1997		