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(54) Title: PROLINE BIS-AMIDE OREXIN RECEPTOR ANTAGONISTS

(57) Abstract: The present invention is directed to proline bis-amide compounds which are antagonists of orexin receptors, and which are useful in the treatment or prevention of neurological and psychiatric disorders and diseases in which orexin receptors are involved. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which orexin receptors are involved.

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TITLE OF THE INVENTION

PROLINE BIS-AMIDE OREXIN RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

The orexins (hypocretins) comprise two neuropeptides produced in the hypothalamus: the orexin A (OX-A) (a 33 amino acid peptide) and the orexin B (OX-B) (a 28 amino acid peptide) (Sakurai T. et al., Cell, 1998, 92, 573-585). Orexins are found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in the central feedback mechanism that regulates feeding behaviour (Sakurai T. et al., Cell, 1998, 92, 573-585). Orexins also regulate states of sleep and wakefulness opening potentially novel therapeutic approaches for narcoleptic or insomniac patients (Chemelli R.M. et al., Cell, 1999, 98, 437-451). Two orexin receptors have been cloned and characterized in mammals. They belong to the super family of G-protein coupled receptors (Sakurai T. et al., Cell, 1998, 92, 573-585): the orexin-1 receptor (OX or OX1R) is selective for OX-A and the orexin-2 receptor (OX2 or OX2R) is capable to bind OX-A as well as OX-B. The physiological actions in which orexins are presumed to participate are thought to be expressed via one or both of OX 1 receptor and OX 2 receptor as the two subtypes of orexin receptors.

Orexin receptors are found in the mammalian brain and may have numerous implications in pathologies such as depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis; depressive neurosis; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; schizophrenia; manic depression; delirium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Tourette syndrome; eating disorders such as anorexia, bulimia, cachexia, and obesity; cardiovascular diseases; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome/disease; basophile adenoma; prolactinoma; hyperprolactinemia; hypophysis tumour/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric diskinesia; gastric ulcers; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; I(allman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic- adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardinal infarction; ischemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine;

hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute I pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain such as irritable bowel syndrome, and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; migraine; sleep apnea; narcolepsy; insomnia; parasomnia; jet lag syndrome; and neurodegenerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration epilepsy; seizure disorders and other diseases related to general orexin system dysfunction.

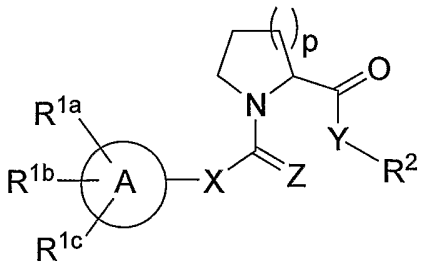
Certain orexin receptor antagonists are disclosed in PCT patent publications WO 99/09024, WO 99/58533, WO 00/47576, WO 00/47577, WO 00/47580, WO 01/68609, WO 01/85693, WO 2002/051232, WO 2002/051838, WO 2003/002559, WO 2003/002561, WO 2003/032991, WO 2003/037847, WO 2003/041711, WO 2003/051872, WO 2003/051873, WO 2004/004733, WO 2004/033418, WO 2004/083218, WO 2004/085403, WO 2005/060959, WO2005/118548. 2-Amino-methylpiperidine derivatives (WO 01/96302), 3-aminomethyl morpholine derivatives (WO 02/44172) and N-aroyl cyclic amines (WO 02/090355, WO 02/089800 and WO 03/051368) are disclosed as orexin receptor antagonists.

SUMMARY OF THE INVENTION

The present invention is directed to proline bis-amide compounds which are antagonists of orexin receptors, and which are useful in the treatment or prevention of neurological and psychiatric disorders and diseases in which orexin receptors are involved. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which orexin receptors are involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of the formula I:



wherein:

A is selected from the group consisting of phenyl, napthyl and heteroaryl;
X is selected from -S-CH_2-, -CH_2-S-, -CH_2-, -CH_2CH_2-, -CH=CH-, -$CH_2CH_2CH_2$-, -O-CH_2-, -CH_2-O-, -(CO)-cyclohexyl-, -NH-CH_2-, -CH_2-NH-, -$CH_2N(C_{1-6}alkyl)$-, -$N(C_{1-6}alkyl)CH_2$-, -$CH_2N(C_{3-6}cycloalkyl)$-, -$N(C_{3-6}cycloalkyl)CH_2$-, -S(O)CH_2-, -$S(O)_2CH_2$-, -C≡C-, and a bond;
Y is selected from -NH-, -$N(C_{1-6}alkyl)$-, -$N(C_{3-6}cycloalkyl)$-, -CH_2-, -$CH(C_{1-6}alkyl)$- and -O-;
Z is selected from O and H,H;
p is 0, 1, 2 or 3;
R^{1a}, R^{1b} and R^{1c} may be absent if the valency of A does not permit such substitution and are independently selected from the group consisting of:

(1) hydrogen,
(2) halogen,
(3) hydroxyl,
(4) -$(C=O)_m$-O_n-C_{1-6}alkyl, where m is 0 or 1, n is 0 or 1 (wherein if m is 0 or n is 0, a bond is present) and where the alkyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(5) -$(C=O)_m$-O_n-C_{3-6}cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(6) -$(C=O)_m$-C_{2-4}alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(7) -$(C=O)_m$-O_n-phenyl or -$(C=O)_m$-O_n-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(8) -$(C=O)_m$-O_n-heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{13},
(9) -$(C=O)_m$-$NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently selected from the group consisting of:
    (a) hydrogen,
    (b) C_{1-6}alkyl, which is unsubstituted or substituted with R^{13},
    (c) C_{3-6}alkenyl, which is unsubstituted or substituted with R^{13},
    (d) C_{3-6}cycloalkyl which is unsubstituted or substituted with R^{13},
    (e) phenyl, which is unsubstituted or substituted with R^{13}, and
    (f) heterocycle, which is unsubstituted or substituted with R^{13},
(10) -$S(O)_2$-$NR^{10}R^{11}$,
(11) -$S(O)_q$-R^{12}, where q is 0, 1 or 2 and where R^{12} is selected from the definitions of R^{10} and R^{11},
(12) -CO_2H,

(13) -CN, and

(14) $-NO_2$;

R^2 is selected from the group consisting of:

(1) -phenyl, which is substituted with R^{7a}, R^{7b} and R^{7c},

(2) -heterocycle, which is substituted with R^{7a}, R^{7b} and R^{7c},

(3) C_{1-6}alkyl, which is unsubstituted or substituted with one or more substituents selected from R^{13}, and

(4) C_{3-6}cycloalkyl, which may be fused to a phenyl ring and which is unsubstituted or substituted with one or more substituents selected from R^{13};

R^{7a}, R^{7b} and R^{7c} may be absent if the valency of the group to which they are attached does not permit such substitution and are independently selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) $-(C=O)_m-O_n-C_{1-6}$alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(5) $-(C=O)_m-O_n-C_{3-6}$cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(6) $-(C=O)_m-C_{2-4}$alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(7) $-(C=O)_m-O_n$-phenyl or $-(C=O)_m-O_n$-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(8) $-(C=O)_m-O_n$-heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{13},

(9) $-(C=O)_m-NR^{10}R^{11}$,

(10) $-S(O)_2-NR^{10}R^{11}$,

(11) $-S(O)_q-R^{12}$,

(12) $-CO_2H$,

(13) -CN, and

(14) $-NO_2$;

R^{13} is selected from the group consisting of:

(1) halogen,

(2) hydroxyl,

(3) $-(C=O)_m-O_n-C_{1-6}$alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R^{14},

(4) $-O_n-(C_{1-3})$perfluoroalkyl,

(5) $-(C=O)_m-O_n-C_{3-6}$cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R^{14},

(6) $-(C=O)_m-C_{2-4}$alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R^{14},

(7) $-(C=O)_m-O_n$-phenyl or $-(C=O)_m-O_n$-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents selected from R^{14},

(8) $-(C=O)_m-O_n$-heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{14},

(9) $-(C=O)_m-NR^{10}R^{11}$,

(10) $-S(O)_2-NR^{10}R^{11}$,

(11) $-S(O)_q-R^{12}$,

(12) $-CO_2H$,

(13) -CN, and

(14) $-NO_2$;

R^{14} is selected from the group consisting of:

(1) hydroxyl,

(2) halogen,

(3) C_{1-6}alkyl,

(4) $-C_{3-6}$cycloalkyl,

(5) $-O-C_{1-6}$alkyl,

(6) $-O(C=O)-C_{1-6}$alkyl,

(7) $-NH-C_{1-6}$alkyl,

(8) phenyl,

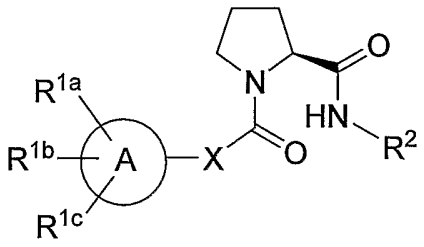
(9) heterocycle,

(10) $-CO_2H$, and

(11) -CN;

or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

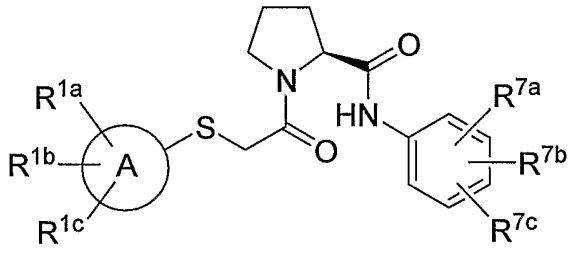
An embodiment of the present invention includes compounds of the formula Ia:



Ia

wherein X, R^{1a}, R^{1b}, R^{1c} and R^2 are defined herein; or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

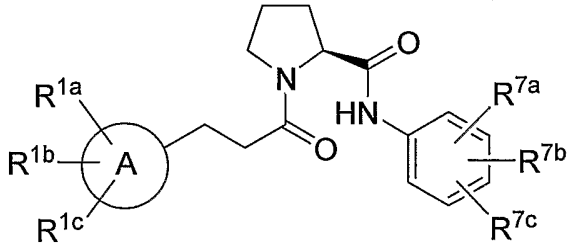
An embodiment of the present invention includes compounds of the formula Ib:



Ib

wherein X, R^{1a}, R^{1b}, R^{1c}, R^{7a}, R^{7b} and R^{7c} are defined herein; or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

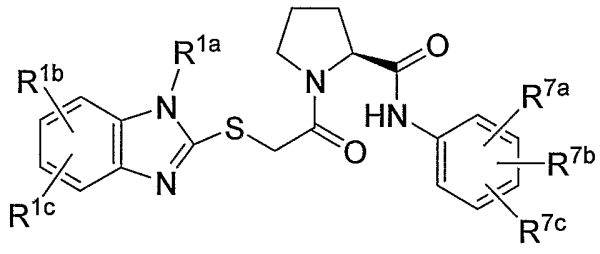
An embodiment of the present invention includes compounds of the formula Ic:



Ic

wherein R^{1a}, R^{1b}, R^{1c}, R^{7a}, R^{7b} and R^{7c} are defined herein; or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

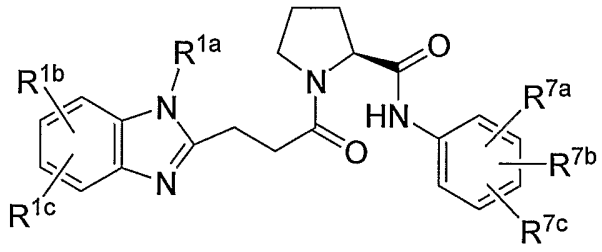
An embodiment of the present invention includes compounds of the formula Id:



Id

wherein R^{1a}, R^{1b}, R^{1c}, R^{7a}, R^{7b} and R^{7c} are defined herein; or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

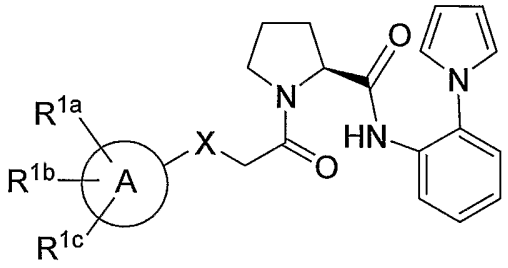
An embodiment of the present invention includes compounds of the formula Ie:



Ie

wherein R^{1a}, R^{1b}, R^{1c}, R^{7a}, R^{7b} and R^{7c} are defined herein; or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

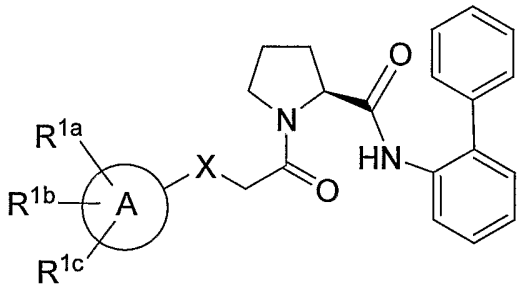
An embodiment of the present invention includes compounds of the formula If:



If

wherein X, R^{1a}, R^{1b} and R^{1c} are defined herein; or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

An embodiment of the present invention includes compounds of the formula Ig:



Ig

wherein X, R^{1a}, R^{1b} and R^{1c} are defined herein; or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

An embodiment of the present invention includes compounds wherein p is 1. An embodiment of the present invention includes compounds wherein X is -S-CH_2- or -CH_2CH_2-. An

embodiment of the present invention includes compounds wherein Y is -NH-. An embodiment of the present invention includes compounds wherein Z is -O-.

An embodiment of the present invention includes compounds wherein A is selected from the group consisting of benzimidazole, N-methylbenzimidazole, benzthiazole and benzoxazole.

An embodiment of the present invention includes compounds wherein A is benzimidazole , R^{1a} is hydrogen or C_{1-6}alkyl, R^{1b} is hydrogen and R^{1c} is hydrogen.

An embodiment of the present invention includes compounds wherein R^2 is phenyl or pyridyl which is substituted with R^{7a}, R^{7b} and R^{7c}.

An embodiment of the present invention includes compounds wherein R^{7a}, R^{7b} and R^{7c} are independently selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) C_{1-6}alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl or napthyl,

(5) -O-C_{1-6}alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl,

(6) heteroaryl, wherein heteroaryl is selected from pyrrolyl, imidazolyl, indolyl, pyridyl, and pyrimidinyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl or-NO_2,

(7) phenyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl or-NO_2,

(8) -O-phenyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl or-NO_2, and

(9) -NH-phenyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl or-NO_2.

An embodiment of the present invention includes compounds wherein R^{7b} is hydrogen, R^{7c} is hydrogen and R^{7a} is selected from the group consisting of:

(1) 2-phenyl,

(2) 2-pyrrole, and

(3) 2-(3-pyridyl).

An embodiment of the present invention includes compounds wherein R^2 is phenyl which is substituted with pyrrolyl.

Specific embodiments of the present invention include a compound which is selected from the group consisting of the subject compounds of the Examples herein or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds. Formula I shows the structure of the class of compounds without preferred stereochemistry.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diasteromeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

As appreciated by those of skill in the art, halogen or halo as used herein are intended to include fluoro, chloro, bromo and iodo. Similarly, C_{1-6}, as in C_{1-6}alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C_{1-8}alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and hexyl. A group which is designated as being independently substituted with substituents may be independently substituted with multiple numbers of such substituents. The term "heterocycle" as used herein includes both unsaturated and saturated heterocyclic moieties, wherein the unsaturated heterocyclic moieties (i.e. "heteroaryl") include benzoimidazolyl, benzimidazolonyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl,

isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, and N-oxides thereof, and wherein the saturated heterocyclic moieties include azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, thiomorpholinyl, and tetrahydrothienyl, and N-oxides thereof.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein. Specific compounds within the present invention include a compound which selected from the group consisting of the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

The subject compounds are useful in a method of antagonizing orexin receptor activity in a patient such as a mammal in need of such inhibition comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein

as antagonists of orexin receptor activity. In addition to primates, especially humans, a variety of other mammals can be treated according to the method of the present invention.

The present invention is further directed to a method for the manufacture of a medicament for antagonizing orexin receptor activity or treating the disorders and diseases noted herein in humans and animals comprising combining a compound of the present invention or a pharmaceutically acceptable salt thereof with a pharmaceutical carrier or diluent.

The subject treated in the present methods is generally a mammal, preferably a human being, male or female. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. It is recognized that one skilled in the art may affect the neurological and psychiatric disorders by treating a patient presently afflicted with the disorders or by prophylactically treating a patient afflicted with the disorders with an effective amount of the compound of the present invention. As used herein, the terms "treatment" and "treating" refer to all processes wherein there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of the neurological and psychiatric disorders described herein, but does not necessarily indicate a total elimination of all disorder symptoms, as well as the prophylactic therapy of the mentioned conditions, particularly in a patient who is predisposed to such disease or disorder. The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need thereof.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The utility of the compounds in accordance with the present invention as orexin receptor OX1R and/or OX2R antagonists may be readily determined without undue experimentation by methodology well known in the art, including the "FLIPR Ca^{2+} Flux Assay" (Okumura et al., Biochem. Biophys. Res. Comm. 280:976-981, 2001). In a typical experiment the OX1 and OX2 receptor

antagonistic activity of the compounds of the present invention was determined in accordance with the following experimental method. For intracellular calcium measurements, Chinese hamster ovary (CHO) cells expressing the rat orexin-1 receptor or the human orexin-2 receptor, are grown in Iscove's modified DMEM containing 2 mM L-glutamine, 0.5 g/ml G418, 1% hypoxanthine-thymidine supplement, 100 U/ml penicillin, 100 ug/ml streptomycin and 10 % heat-inactivated fetal calf serum (FCS). The cells are seeded at 20,000 cells / well into Becton-Dickinson black 384-well clear bottom sterile plates coated with poly-D-lysine. All reagents were from GIBCO-Invitrogen Corp. The seeded plates are incubated overnight at 37°C and 5% CO2. $Ala^{6,12}$ human orexin-A as the agonist is prepared as a 1 mM stock solution in 1% bovine serum albumin (BSA) and diluted in assay buffer (HBSS containing 20 mM HEPES, 0.1% BSA and 2.5mM probenecid, pH7.4) for use in the assay at a final concentration of 70pM. Test compounds are prepared as 10 mM stock solution in DMSO, then diluted in 384-well plates, first in DMSO, then assay buffer. On the day of the assay, cells are washed 3 times with 100 ul assay buffer and then incubated for 60 min (37° C, 5% CO2) in 60 ul assay buffer containing 1 uM Fluo-4AM ester , 0.02 % pluronic acid, and 1 % BSA. The dye loading solution is then aspirated and cells are washed 3 times with 100 ul assay buffer. 30 ul of that same buffer is left in each well. Within the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices), test compounds are added to the plate in a volume of 25 ul , incubated for 5 min and finally 25 ul of agonist is added. Fluorescence is measured for each well at 1 second intervals for 5 minutes and the height of each fluorescence peak is compared to the height of the fluorescence peak induced by 70 pM $Ala^{6,12}$ orexin-A with buffer in place of antagonist. For each antagonist, IC50 value (the concentration of compound needed to inhibit 50 % of the agonist response) is determined. The intrinsic orexin receptor antagonist activity of a compound which may be used in the present invention may be determined by these assays.

In particular, the compounds of the following examples had activity in antagonizing the rat orexin-1 receptor and/or the human orexin-2 receptor in the aforementioned assays, generally with an IC_{50} of less than about 50 μM. Preferred compounds within the present invention had activity in antagonizing the rat orexin-1 receptor and/or the human orexin-2 receptor in the aforementioned assays with an IC_{50} of less than about 100 nM. Such a result is indicative of the intrinsic activity of the compounds in use as antagonists of orexin-1 receptor and/or the orexin-2 receptor. The present invention also includes compounds within the generic scope of the invention which possess activity as agonists of the orexin-1 receptor and/or the orexin-2 receptor.

The orexin receptors have been implicated in a wide range of biological functions. This has suggested a potential role for these receptors in a variety of disease processes in humans or other species. The compounds of the present invention have utility in treating, preventing, ameliorating, controlling or reducing the risk of a variety of neurological and psychiatric disorders associated with orexin receptors, including one or more of the following conditions or diseases: sleep disorders, sleep

disturbances, including enhancing sleep quality, improving sleep quality, increasing sleep efficiency, augmenting sleep maintenance; increasing the value which is calculated from the time that a subject sleeps divided by the time that a subject is attempting to sleep; improving sleep initiation; decreasing sleep latency or onset (the time it takes to fall asleep); decreasing difficulties in falling asleep; increasing sleep continuity; decreasing the number of awakenings during sleep; decreasing intermittent wakings during sleep; decreasing nocturnal arousals; decreasing the time spent awake following the initial onset of sleep; increasing the total amount of sleep; reducing the fragmentation of sleep; altering the timing, frequency or duration of REM sleep bouts; altering the timing, frequency or duration of slow wave (i.e. stages 3 or 4) sleep bouts; increasing the amount and percentage of stage 2 sleep; promoting slow wave sleep; enhancing EEG-delta activity during sleep; decreasing nocturnal arousals, especially early morning awakenings; increasing daytime alertness; reducing daytime drowsiness; treating or reducing excessive daytime sleepiness; increasing satisfaction with the intensity of sleep; increasing sleep maintenance; idiopathic insomnia; sleep problems; insomnia, hypersomnia, idiopathic hypersomnia, repeatability hypersomnia, intrinsic hypersomnia, narcolepsy, interrupted sleep, sleep apnea, wakefulness, nocturnal myoclonus, REM sleep interruptions, jet-lag, shift workers' sleep disturbances, dyssomnias, night terror, insomnias associated with depression, emotional/mood disorders, Alzheimer's disease or cognitive impairment, as well as sleep walking and enuresis, and sleep disorders which accompany aging; Alzheimer's sundowning; conditions associated with circadian rhythmicity as well as mental and physical disorders associated with travel across time zones and with rotating shift-work schedules, conditions due to drugs which cause reductions in REM sleep as a side effect; fibromyalgia; syndromes which are manifested by non-restorative sleep and muscle pain or sleep apnea which is associated with respiratory disturbances during sleep; conditions which result from a diminished quality of sleep; eating disorders associated with excessive food intake and complications associated therewith, compulsive eating disorders, obesity (due to any cause, whether genetic or environmental), obesity-related disorders including overeating and bulimia nervosa, hypertension, diabetes, elevated plasma insulin concentrations and insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms and arrythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovary disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g, children with acute lymphoblastic leukemia, metabolic syndrome, also known as syndrome X, insulin resistance syndrome, reproductive hormone abnormalities, sexual and reproductive dysfunction, such as impaired fertility, infertility, hypogonadism in males and hirsutism in females, fetal defects associated with maternal obesity, gastrointestinal motility disorders,

such as obesity-related gastro-esophageal reflux, respiratory disorders, such as obesity-hypoventilation syndrome (Pickwickian syndrome), breathlessness, cardiovascular disorders, inflammation, such as systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, kidney cancer, increased anesthetic risk, reducing the risk of secondary outcomes of obesity, such as reducing the risk of left ventricular hypertrophy; diseases or disorders where abnormal oscillatory activity occurs in the brain, including depression, migraine, neuropathic pain, Parkinson's disease, psychosis and schizophrenia, as well as diseases or disorders where there is abnormal coupling of activity, particularly through the thalamus; enhancing cognitive function; enhancing memory; increasing memory retention; increasing immune response; increasing immune function; hot flashes; night sweats; extending life span; schizophrenia; muscle-related disorders that are controlled by the excitation/relaxation rhythms imposed by the neural system such as cardiac rhythm and other disorders of the cardiovascular system; conditions related to proliferation of cells such as vasodilation or vasorestriction and blood pressure; cancer; cardiac arrhythmia; hypertension; congestive heart failure; conditions of the genital/urinary system; disorders of sexual function and fertility; adequacy of renal function; responsivity to anesthetics; mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder, mood disorders due to a general medical condition, and substance-induced mood disorders; anxiety disorders including acute stress disorder, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic attack, panic disorder, post-traumatic stress disorder, separation anxiety disorder, social phobia, specific phobia, substance-induced anxiety disorder and anxiety due to a general medical condition; acute neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, ischemic stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage; Huntington's Chorea; amyotrophic lateral sclerosis; multiple sclerosis; ocular damage; retinopathy; cognitive disorders; idiopathic and drug-induced Parkinson's disease; muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions; cognitive disorders including dementia (associated with Alzheimer's disease, ischemia, trauma, vascular problems or stroke, HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jacob disease, perinatal hypoxia, other general medical conditions or substance abuse); delirium, amnestic disorders or age related cognitive decline; schizophrenia or psychosis including schizophrenia (paranoid, disorganized, catatonic or undifferentiated), schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition and substance-induced psychotic disorder; substance-related disorders and addictive behaviors (including substance-induced delirium, persisting dementia, persisting amnestic

disorder, psychotic disorder or anxiety disorder; tolerance, dependence or withdrawal from substances including alcohol, amphetamines, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, sedatives, hypnotics or anxiolytics); movement disorders, including akinesias and akinetic-rigid syndromes (including Parkinson's disease, drug-induced parkinsonism, postencephalitic parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, parkinsonism-ALS dementia complex and basal ganglia calcification), chronic fatigue syndrome, fatigue, including Parkinson's fatigue, multiple sclerosis fatigue, fatigue caused by a sleep disorder or a circadian rhythm disorder, medication-induced parkinsonism (such as neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremor), Gilles de la Tourette's syndrome, epilepsy, and dyskinesias [including tremor (such as rest tremor, essential tremor, postural tremor and intention tremor), chorea (such as Sydenham's chorea, Huntington's disease, benign hereditary chorea, neuroacanthocytosis, symptomatic chorea, drug-induced chorea and hemiballism), myoclonus (including generalised myoclonus and focal myoclonus), tics (including simple tics, complex tics and symptomatic tics), restless leg syndrome and dystonia (including generalised dystonia such as iodiopathic dystonia, drug-induced dystonia, symptomatic dystonia and paroxymal dystonia, and focal dystonia such as blepharospasm, oromandibular dystonia, spasmodic dysphonia, spasmodic torticollis, axial dystonia, dystonic writer's cramp and hemiplegic dystonia); attention deficit/hyperactivity disorder (ADHD); conduct disorder; migraine (including migraine headache); urinary incontinence; substance tolerance, substance withdrawal (including, substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.); psychosis; schizophrenia; anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder); mood disorders (including depression, mania, bipolar disorders); trigeminal neuralgia; hearing loss; tinnitus; neuronal damage including ocular damage; retinopathy; macular degeneration of the eye; emesis; brain edema; pain, including acute and chronic pain states, severe pain, intractable pain, inflammatory pain, neuropathic pain, post-traumatic pain, bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological), chronic pain, neuropathic pain, post-traumatic pain, trigeminal neuralgia, migraine and migraine headache.

Thus, in preferred embodiments the present invention provides methods for: enhancing the quality of sleep; augmenting sleep maintenance; increasing REM sleep; increasing stage 2 sleep; decreasing fragmentation of sleep patterns; treating insomnia; enhancing cognition; increasing memory retention; treating or controlling obesity; treating or controlling depression; treating, controlling, ameliorating or reducing the risk of epilepsy, including absence epilepsy; treating or controlling pain, including neuropathic pain; treating or controlling Parkinson's disease; treating or controlling psychosis;

or treating, controlling, ameliorating or reducing the risk of schizophrenia, in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of a compound of the present invention.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein. The dosage of active ingredient in the compositions of this invention may be varied, however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The active ingredient may be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. The dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize. Generally, dosage levels of between 0.0001 to 10 mg/kg. of body weight daily are administered to the patient, e.g., humans and elderly humans, to obtain effective antagonism of orexin receptors. The dosage range will generally be about 0.5 mg to 1.0 g. per patient per day which may be administered in single or multiple doses. Preferably, the dosage range will be about 0.5 mg to 500 mg per patient per day; more preferably about 0.5 mg to 200 mg per patient per day; and even more preferably about 5 mg to 50 mg per patient per day. Pharmaceutical compositions of the present invention may be provided in a solid dosage formulation preferably comprising about 0.5 mg to 500 mg active ingredient, more preferably comprising about 1 mg to 250 mg active ingredient. The pharmaceutical composition is preferably provided in a solid dosage formulation comprising about 1 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg or 250 mg active ingredient. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of the present invention or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of the present invention is preferred. However, the

combination therapy may also includes therapies in which the compound of the present invention and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of the present invention. The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds.

Likewise, compounds of the present invention may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used. In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered in conbination with other compounds which are known in the art to be useful for enhancing sleep quality and preventing and treating sleep disorders and sleep disturbances, including e.g., sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, antihistamines, benzodiazepines, barbiturates, cyclopyrrolones, GABA agonists, 5HT-2 antagonists including 5HT-2A antagonists and 5HT-2A/2C antagonists, histamine antagonists including histamine H3 antagonists, histamine H3 inverse agonists, imidazopyridines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, other orexin antagonists, orexin agonists, prokineticin agonists and antagonists, pyrazolopyrimidines, T-type

calcium channel antagonists, triazolopyridines, and the like, such as: adinazolam, allobarbital, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, armodafinil, APD-125, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capromorelin, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, clonazepam, cloperidone, clorazepate, clorethate, clozapine, conazepam, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, EMD-281014, eplivanserin, estazolam, eszopiclone, ethchlorynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, gaboxadol, glutethimide, halazepam, hydroxyzine, ibutamoren, imipramine, indiplon, lithium, lorazepam, lormetazepam, LY-156735, maprotiline, MDL-100907, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, methyprylon, midaflur, midazolam, modafinil, nefazodone, NGD-2-73, nisobamate, nitrazepam, nortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, ramelteon, reclazepam, roletamide, secobarbital, sertraline, suproclone, TAK-375, temazepam, thioridazine, tiagabine, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zopiclone, zolpidem, and salts thereof, and combinations thereof, and the like, or the compound of the present invention may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

In another embodiment, the subject compound may be employed in combination with other compounds which are known in the art, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: insulin sensitizers including (i) PPARγ antagonists such as glitazones (e.g. ciglitazone; darglitazone; englitazone; isaglitazone (MCC-555); pioglitazone; rosiglitazone; troglitazone; tularik; BRL49653; CLX-0921; 5-BTZD), GW-0207, LG-100641, and LY-300512, and the like); (iii) biguanides such as metformin and phenformin; (b) insulin or insulin mimetics, such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente); Lys-Pro insulin, GLP-1 (73-7) (insulintropin); and GLP-1 (7-36)-NH_2); (c) sulfonylureas, such as acetohexamide; chlorpropamide; diabinese; glibenclamide; glipizide; glyburide; glimepiride; gliclazide; glipentide; gliquidone; glisolamide; tolazamide; and tolbutamide; (d) α-glucosidase inhibitors, such as acarbose, adiposine; camiglibose; emiglitate; miglitol; voglibose; pradimicin-Q; salbostatin; CKD-711; MDL-25,637; MDL-73,945; and MOR 14, and the like; (e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (atorvastatin, itavastatin, fluvastatin, lovastatin, pravastatin, rivastatin, rosuvastatin, simvastatin, and other statins), (ii) bile acid absorbers/sequestrants, such as cholestyramine, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran; Colestid®; LoCholest®, and the like, (ii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iii) proliferator-activater receptor α agonists such as fenofibric acid derivatives (gemfibrozil,

clofibrate, fenofibrate and benzafibrate), (iv) inhibitors of cholesterol absorption such as stanol esters, beta-sitosterol, sterol glycosides such as tiqueside; and azetidinones such as ezetimibe, and the like, and (acyl CoA:cholesterol acyltransferase (ACAT)) inhibitors such as avasimibe, and melinamide, (v) anti-oxidants, such as probucol, (vi) vitamin E, and (vii) thyromimetics; (f) PPARα agonists such as beclofibrate, benzafibrate, ciprofibrate, clofibrate, etofibrate, fenofibrate, and gemfibrozil; and other fibric acid derivatives, such as Atromid®, Lopid® and Tricor®, and the like, and PPARα agonists as described in WO 97/36579 by Glaxo; (g) PPARδ agonists; (h) PPAR α/δ agonists, such as muraglitazar, and the compounds disclosed in US 6,414,002; and (i) anti-obesity agents, such as (1) growth hormone secretagogues, growth hormone secretagogue receptor agonists/antagonists, such as NN703, hexarelin, MK-0677, SM-130686, CP-424,391, L-692,429, and L-163,255; (2) protein tyrosine phosphatase-1B (PTP-1B) inhibitors; (3) cannabinoid receptor ligands, such as cannabinoid CB_1 receptor antagonists or inverse agonists, such as rimonabant (Sanofi Synthelabo), AMT-251, and SR-14778 and SR 141716A (Sanofi Synthelabo), SLV-319 (Solvay), BAY 65-2520 (Bayer); (4) anti-obesity serotonergic agents, such as fenfluramine, dexfenfluramine, phentermine, and sibutramine; (5) β3-adrenoreceptor agonists, such as AD9677/TAK677 (Dainippon/Takeda), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, Trecadrine, Zeneca D7114, SR 59119A; (6) pancreatic lipase inhibitors, such as orlistat (Xenical®), Triton WR1339, RHC80267, lipstatin, tetrahydrolipstatin, teasaponin, diethylumbelliferyl phosphate; (7) neuropeptide Y1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI-264879A; (8) neuropeptide Y5 antagonists, such as GW-569180A, GW-594884A, GW-587081X, GW-548118X, FR226928, FR 240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, PD-160170, SR-120562A, SR-120819A and JCF-104; (9) melanin-concentrating hormone (MCH) receptor antagonists; (10) melanin-concentrating hormone 1 receptor (MCH1R) antagonists, such as T-226296 (Takeda); (11) melanin-concentrating hormone 2 receptor (MCH2R) agonist/antagonists; (12) orexin receptor antagonists, such as SB-334867-A, and those disclosed in patent publications herein; (13) serotonin reuptake inhibitors such as fluoxetine, paroxetine, and sertraline; (14) melanocortin agonists, such as Melanotan II; (15) other Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), ME-10142, and ME-10145 (Melacure), CHIR86036 (Chiron); PT-141, and PT-14 (Palatin); (16) 5HT-2 agonists; (17) 5HT2C (serotonin receptor 2C) agonists, such as BVT933, DPCA37215, WAY161503, R-1065; (18) galanin antagonists; (19) CCK agonists; (20) CCK-A (cholecystokinin-A) agonists, such as AR-R 15849, GI 181771, JMV-180, A-71378, A-71623 and SR14613; (22) corticotropin-releasing hormone agonists; (23) histamine receptor-3 (H3) modulators; (24) histamine receptor-3 (H3) antagonists/inverse agonists, such as hioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate, clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and O-[3-(1H-imidazol-4-yl)propanol]-carbamates; (25) β-hydroxy steroid dehydrogenase-1 inhibitors (β-HSD-1); 26) PDE (phosphodiesterase) inhibitors, such as

theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram, and cilomilast; (27) phosphodiesterase-3B (PDE3B) inhibitors; (28) NE (norepinephrine) transport inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine; (29) ghrelin receptor antagonists; (30) leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); (31) leptin derivatives; (32) BRS3 (bombesin receptor subtype 3) agonists such as [D-Phe6,beta-Ala11,Phe13,Nle14]Bn(6-14) and [D-Phe6,Phe13]Bn(6-13)propylamide, and those compounds disclosed in Pept. Sci. 2002 Aug; 8(8): 461-75); (33) CNTF (Ciliary neurotrophic factors), such as GI-181771 (Glaxo-SmithKline), SR146131 (Sanofi Synthelabo), butabindide, PD170,292, and PD 149164 (Pfizer); (34) CNTF derivatives, such as axokine (Regeneron); (35) monoamine reuptake inhibitors, such as sibutramine; (36) UCP-1 (uncoupling protein-1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-napthalenyl)-1-propenyl]benzoic acid (TTNPB), retinoic acid; (37) thyroid hormone β agonists, such as KB-2611 (KaroBioBMS); (38) FAS (fatty acid synthase) inhibitors, such as Cerulenin and C75; (39) DGAT1 (diacylglycerol acyltransferase 1) inhibitors; (40) DGAT2 (diacylglycerol acyltransferase 2) inhibitors; (41) ACC2 (acetyl-CoA carboxylase-2) inhibitors; (42) glucocorticoid antagonists; (43) acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al., Obesity Research, 9:202-9 (2001); (44) dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, NVP-DPP728, LAF237, MK-431, P93/01, TSL 225, TMC-2A/2B/2C, FE 999011, P9310/K364, VIP 0177, SDZ 274-444; (46) dicarboxylate transporter inhibitors; (47) glucose transporter inhibitors; (48) phosphate transporter inhibitors; (49) Metformin (Glucophage®); and (50) Topiramate (Topimax®); and (50) peptide YY, PYY 3-36, peptide YY analogs, derivatives, and fragments such as BIM-43073D, BIM-43004C (Olitvak, D.A. et al., Dig. Dis. Sci. 44(3):643-48 (1999)); (51) Neuropeptide Y2 (NPY2) receptor agonists such NPY3-36, N acetyl [Leu(28,31)] NPY 24-36, TASP-V, and cyclo-(28/32)-Ac-[Lys28-Glu32]-(25-36)-pNPY; (52) Neuropeptide Y4 (NPY4) agonists such as pancreatic peptide (PP), and other Y4 agonists such as 1229U91; (54) cyclooxygenase-2 inhibitors such as etoricoxib, celecoxib, valdecoxib, parecoxib, lumiracoxib, BMS347070, tiracoxib or JTE522, ABT963, CS502 and GW406381, and pharmaceutically acceptable salts thereof; (55) Neuropeptide Y1 (NPY1) antagonists such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI-264879A; (56) Opioid antagonists such as nalmefene (Revex ®), 3-methoxynaltrexone, naloxone, naltrexone; (57) 11β HSD-1 (11-beta hydroxy steroid dehydrogenase type 1) inhibitor such as BVT 3498, BVT 2733; (58) aminorex; (59) amphechloral; (60) amphetamine; (61) benzphetamine; (62) chlorphentermine; (63) clobenzorex; (64) cloforex; (65) clominorex; (66) clortermine; (67) cyclexedrine; (68) dextroamphetamine; (69) diphemethoxidine, (70) N-ethylamphetamine; (71) fenbutrazate; (72) fenisorex; (73) fenproporex; (74) fludorex; (75) fluminorex; (76) furfurylmethylamphetamine; (77) levamfetamine; (78) levophacetoperane; (79) mefenorex; (80)

metamfepramone; (81) methamphetamine; (82) norpseudoephedrine; (83) pentorex; (84) phendimetrazine; (85) phenmetrazine; (86) picilorex; (87) phytopharm 57; and (88) zonisamide.

In another embodiment, the subject compound may be employed in combination with an anti-depressant or anti-anxiety agent, including norepinephrine reuptake inhibitors (including tertiary amine tricyclics and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists, neurokinin-1 receptor antagonists, atypical anti-depressants, benzodiazepines, 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists. Specific agents include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine; amoxapine, desipramine, maprotiline, nortriptyline and protriptyline; fluoxetine, fluvoxamine, paroxetine and sertraline; isocarboxazid, phenelzine, tranylcypromine and selegiline; moclobemide: venlafaxine; aprepitant; bupropion, lithium, nefazodone, trazodone and viloxazine; alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam; buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

In another embodiment, the subject compound may be employed in combination with anti-Alzheimer's agents; beta-secretase inhibitors; gamma-secretase inhibitors; growth hormone secretagogues; recombinant growth hormone; HMG-CoA reductase inhibitors; NSAID's including ibuprofen; vitamin E; anti-amyloid antibodies; CB-1 receptor antagonists or CB-1 receptor inverse agonists; antibiotics such as doxycycline and rifampin; N-methyl-D-aspartate (NMDA) receptor antagonists, such as memantine; cholinesterase inhibitors such as galantamine, rivastigmine, donepezil, and tacrine; growth hormone secretagogues such as ibutamoren, ibutamoren mesylate, and capromorelin; histamine H_3 antagonists; AMPA agonists; PDE IV inhibitors; $GABA_A$ inverse agonists; or neuronal nicotinic agonists.

In another embodiment, the subject compound may be employed in combination with sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbiturates, 5HT-2 antagonists, and the like, such as: adinazolam, allobarbital, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, clonazepam, cloperidone, clorazepate, clorethate, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, hydroxyzine, imipramine, lithium, lorazepam,

lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, reclazepam, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zolpidem, and salts thereof, and combinations thereof, and the like, or the subject compound may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

In another embodiment, the subject compound may be employed in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor such as carbidopa or benserazide), anticholinergics such as biperiden (optionally as its hydrochloride or lactate salt) and trihexyphenidyl (benzhexol) hydrochloride, COMT inhibitors such as entacapone, MOA-B inhibitors, antioxidants, A2a adenosine receptor antagonists, cholinergic agonists, NMDA receptor antagonists, serotonin receptor antagonists and dopamine receptor agonists such as alentemol, bromocriptine, fenoldopam, lisuride, naxagolide, pergolide and pramipexole. It will be appreciated that the dopamine agonist may be in the form of a pharmaceutically acceptable salt, for example, alentemol hydrobromide, bromocriptine mesylate, fenoldopam mesylate, naxagolide hydrochloride and pergolide mesylate. Lisuride and pramipexol are commonly used in a non-salt form.

In another embodiment, the subject compound may be employed in combination with acetophenazine, alentemol, benzhexol, bromocriptine, biperiden, chlorpromazine, chlorprothixene, clozapine, diazepam, fenoldopam, fluphenazine, haloperidol, levodopa, levodopa with benserazide, levodopa with carbidopa, lisuride, loxapine, mesoridazine, molindolone, naxagolide, olanzapine, pergolide, perphenazine, pimozide, pramipexole, risperidone, sulpiride, tetrabenazine, trihexyphenidyl, thioridazine, thiothixene or trifluoperazine.

In another embodiment, the subject compound may be employed in combination with a compound from the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of neuroleptic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. An example of a dibenzazepine is clozapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozide. An example of an indolone is molindolone. Other neuroleptic agents include loxapine, sulpiride and risperidone. It will be appreciated that the neuroleptic agents when used in combination with thesubject compound may be in the form of a pharmaceutically acceptable salt, for example, chlorpromazine hydrochloride, mesoridazine besylate, thioridazine

hydrochloride, acetophenazine maleate, fluphenazine hydrochloride, flurphenazine enathate, fluphenazine decanoate, trifluoperazine hydrochloride, thiothixene hydrochloride, haloperidol decanoate, loxapine succinate and molindone hydrochloride. Perphenazine, chlorprothixene, clozapine, haloperidol, pimozide and risperidone are commonly used in a non-salt form.

In another embodiment, the subject compound may be employed in combination with an anoretic agent such as aminorex, amphechloral, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclexedrine, dexfenfluramine, dextroamphetamine, diethylpropion, diphemethoxidine, N-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex, fludorex, fluminorex, furfurylmethylamphetamine, levamfetamine, levophacetoperane, mazindol, mefenorex, metamfepramone, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine; selective serotonin reuptake inhibitor (SSRI); halogenated amphetamine derivatives, including chlorphentermine, cloforex, clortermine, dexfenfluramine, fenfluramine, picilorex and sibutramine; and pharmaceutically acceptble salts thereof

In another embodiment, the subject compound may be employed in combination with an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent, for example with a compound such as acetaminophen, asprin, codiene, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap, and the like. Similarly, the subject compound may be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antiitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a sedating or non-sedating antihistamine.

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

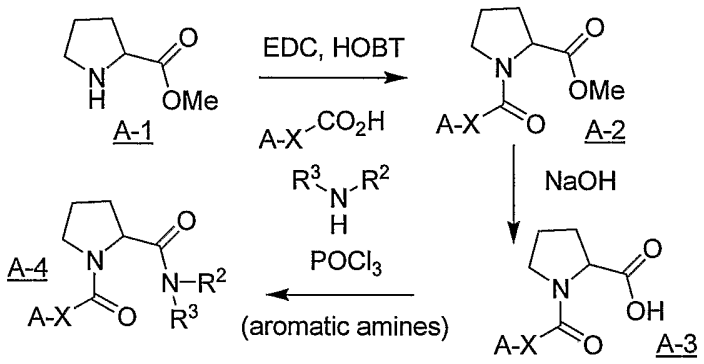
The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Pharmaceutical 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 which 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. Compositions 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. Oily suspensions may be formulated by suspending the active ingredient in a suitable oil. Oil-in-water emulsions may also be employed. 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. Pharmaceutical compositions of the present compounds may be in the form of a sterile injectable aqueous or oleagenous suspension. The compounds of the present invention may also be administered in the form of suppositories for rectal administration. For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention may be employed. The compounds of the present invention may

also be formulated for administered by inhalation. The compounds of the present invention may also be administered by a transdermal patch by methods known in the art.

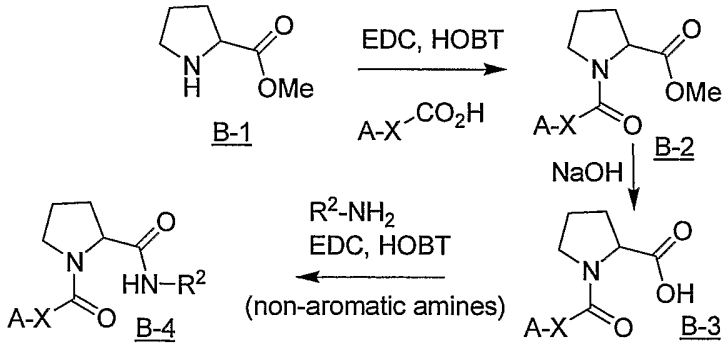
Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein. The following abbreviations are used herein: Me: methyl; Et: ethyl; t-Bu: *tert*-butyl; Ar: aryl; Ph: phenyl; Bn: benzyl; Ac: acetyl; THF: tetrahydrofuran; DEAD: diethylazodicarboxylate; DMSO: dimethylsulfoxide; EDC: N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide; HOBT: hydroxybenzotriazole; Boc: tert-butyloxy carbonyl; Et_3N: triethylamine; DCM: dichloromethane; DCE: dichloroethane; BSA: bovine serum albumin; TFA: trifluoracetic acid; DMF: N,N-dimethylformamide; MTBE: methyl tert-butyl ether;$SOCl_2$: thionyl chloride; CDI: carbonyl diimidazole; rt: room temperature; HPLC: high performance liquid chromatography. The compounds of the present invention can be prepared in a variety of fashions.

REACTION SCHEME A



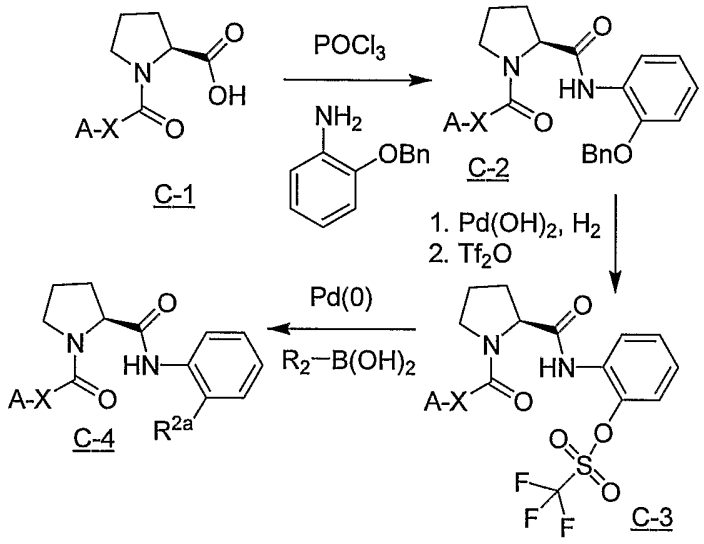
L-proline can be acylated under EDC-mediated coupling conditions to afford acyl-proline esters (A-2). These esters can be hydrolyzed and further functionalized using phosphorous oxychloride to couple aromatic amines to generate the desired proline bis-amides (A-4).

REACTION SCHEME B



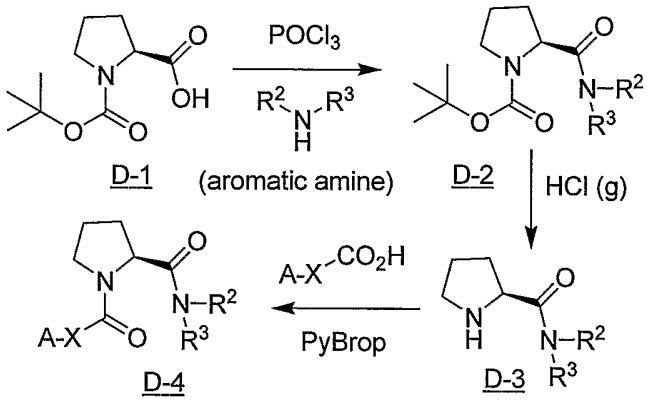
L-proline can be acylated under EDC-mediated coupling conditions to afford acyl-proline esters (B2). These esters can be hydrolyzed and further functionalized using a second EDC coupling using non-aromatic amines to generate the desired proline bis-amides (B-4).

REACTION SCHEME C



Acylated proline carboxylic acids (C-1) and 2-benzyloxyaniline can be coupled with phosphorous oxychloride to afford the anilide, C-2. This anilide can be deprotected under standard hydrogenolysis conditions and converted to the aryl triflate under the action of trifluoromethanesulfonic anhydride. Various boronic acids can be used in the subsequent Suzuki reaction to afford the desired proline bis-amides (C-4).

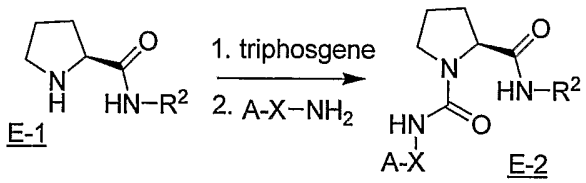
REACTION SCHEME D



Boc-L-proline can be reacted with an aromatic amine under the action of phosphorous oxychloride to afford protected anilides, D-2. These coupled products can be deprotected with gaseous

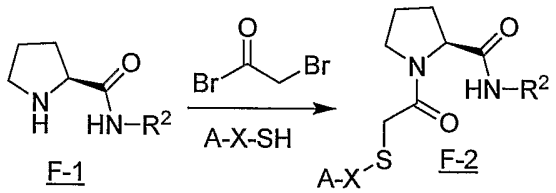
hydrogen chloride and the resulting amine can be coupled with various acids under the action of PyBrop to give proline bis-amides, D-4.

REACTION SCHEME E



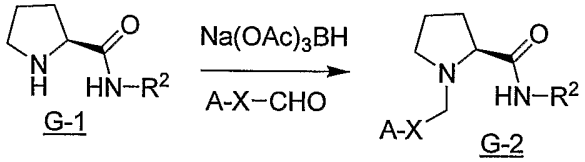
Proline mono-amides (E-1) can be reacted with triphosgene to afford an intermediate carbamoyl chloride which when treated with various amines can give ureas (E-2).

REACTION SCHEME F



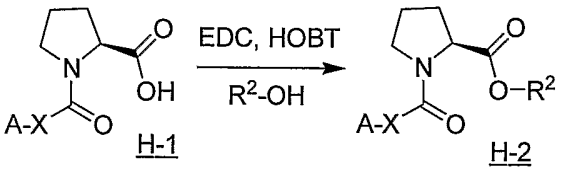
Proline mono-amides (F-1) can be reacted with alpha-bromoacetylbromide and then subsequently treated with thiols to afford proline bis-amides containing thioether functionality (F-2).

REACTION SCHEME G



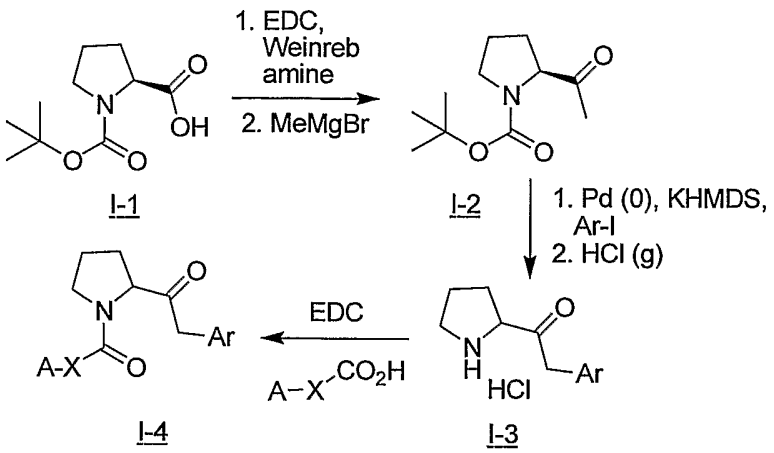
Proline mono-amides (G-1) can be treated under standard reductive amination conditions using various aldehydes to afford N-alkylated products (G-2).

REACTION SCHEME H



Proline mono-amide carboxylic acid derivatives can be esterified under standard amide coupling conditions to afford esters (H-2).

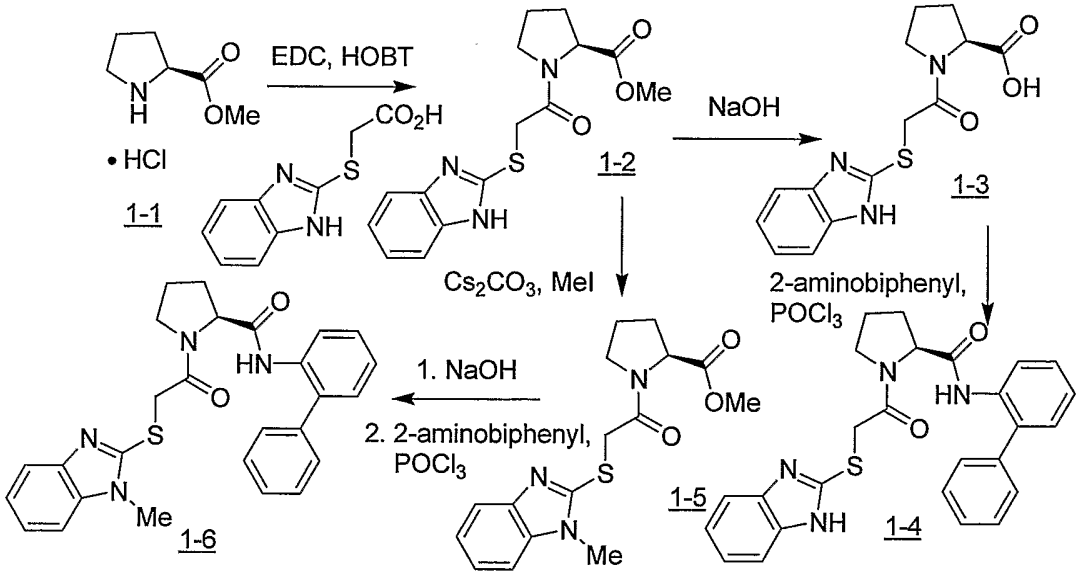
REACTION SCHEME I



Keto-prolines (I-2) can be transformed into arylated keto-prolines via palladium catalyzed arylation conditions and then modified under standard amide coupling conditions to afford compounds (I-4).

In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

EXAMPLE 1



Methyl 1-[(1H-benzimidazol-2-ylthio)acetyl]-L-prolinate (1-2)

To a solution of L-proline methyl ester hydrochloride (3.0 g, 18.1 mmol) and (2-benzimidazolylthio)acetic acid (4.1 g, 19.9 mmol) in DMF (35 mL) was added triethylamine (5.1 mL, 36.2 mmol), EDC (4.2 g, 21.7 mmol), and HOBT (2.9 g, 21.7 mmol), and the reaction was heated to 100 °C for 1 h. The reaction was cooled to ambient temperature and quenched with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organics were dried organics over $MgSO_4$ and concentrated. The crude reaction was purified by column chromatography (50% EtOAc in hexanes to 25% MeOH in EtOAc) to give 1-2 as an oil. Data for 1-2: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.70-7.4 (m, 2H), 7.23-7.16 (m, 2H), 4.58 (dd, J = 8.5, 3.5 Hz, 1H), 3.90-3.84 (m, 2H), 3.76-3.71 (m, 1H), 3.75 (s, 3 H, overlapping signals), 3.68-3.63 (m, 1H), 2.34-2.24 (m, 1 H), 2.13-2.06 (m, 3H) ppm; ESI MS [M+H] for $C_{15}H_{17}N_3O_3S$ = 320.1

1-[(1H-benzimidazol-2-ylthio)acetyl]-N-(1,1'-biphenyl-2-yl)-L-prolinamide (1-4)

To a solution of 1-2 (3.8 g, 11.9 mmol) in THF (40 mL) was added NaOH (0.57 g, 14.3 mmol) in water (2mL) at 25 °C. The reaction was stirred for 12 h and 0.5 equiv NaOH (0.24 g, 0.60 mmol) in water (1.3 mL). The reaction was complete after 36 h. The reaction was acidified to pH 5 with concentrated HCl, and the solvent was evaporated to dryness. The residue was azeotroped with toluene (3 x 100 mL) to afford a brown solid which was used without further purification. To a solution of carboxylic acid 1-3 (0.15 g, 0.49 mmol) and 2-aminobiphenyl (0.17 g, 0.98 mmol) in pyridine (1.5 mL) at 0°C was added phosphorous oxychloride (0.11 g, 0.74 mmol) dropwise. The reaction was stirred 20 minutes, and the reaction was quenched with water. The reaction was diluted with EtOAc (20 mL) and washed with water (1 x 20 mL). The combined organics were dried over $MgSO_4$ and concentrated. The crude reaction was purified by column chromatography (0 to 25% MeOH in EtOAc) to afford 1-4 as a brown solid. Data for 1-4: ^{1}HNMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.09 (d, J = 7.5 Hz, 1H), 7.44-7.14 (m, 14H), 4.50 (d, J = 4.5 Hz, 1H), 3.18-3.64 (m, 2H), 3.54-3.44 (m, 2H), 2.30-2.18 (m, 1H), 2.01-1.90 (m, 3H) ppm; ESI MS [M+H] for $C_{26}H_{24}N_4O_sS$ = 457.2

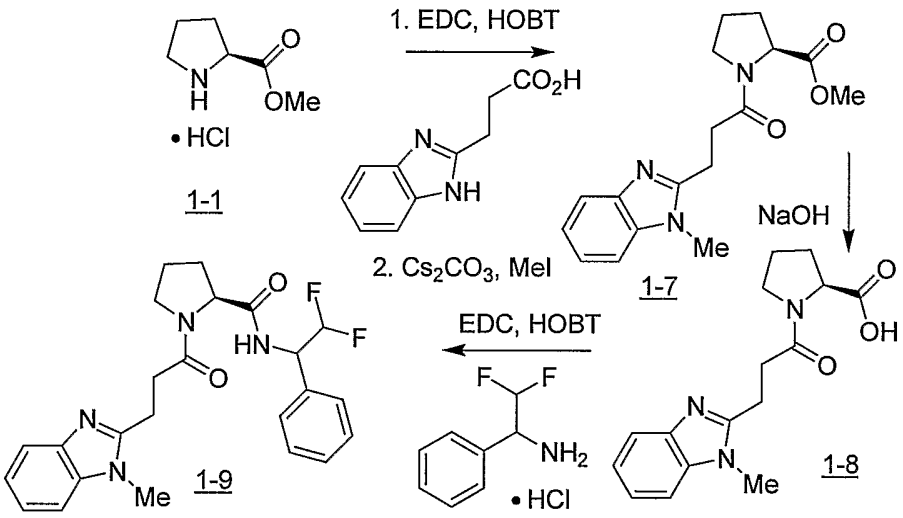
Methyl 1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinate (1-5)

To a solution of ester 1-2 (5.0 g, 15.7 mmol) in DMF (40 mL) at 25 °C was added Cs_2CO_3 (7.7 g, 23.5 mmol) and iodomethane (2.9 g, 20.4 mmol). After 1.5 h, the reaction was diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organics were dried over $MgSO_4$ and concentrated. The crude reaction was purified by column chromatography (50% EtOAc in hexanes to 30% MeOH in EtOAc) to afford 1-5 as an oil. Data for 1-5: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.64-7.61 (m, 1H), 7.28-7.18 (m, 3H), 4.52 (dd, J = 8.5, 4.0 Hz, 1H), 4.46 (d, J = 14.5, 1H), 4.29 (d, J = 14.5 Hz, 1H), 3.84-3.80 (m, 2 H), 3.73 (s, 3H), 3.71 (s, 3H), 2.31-2.00 (m, 4H) ppm; ESI MS [M+H] for $C_{16}H_{19}N_3O_3S$ 334.2

N-(1,1'-biphenyl-2-yl)-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide (1-6)

To a solution of ester 1-5 (1.2 g, 3.6 mmol) in THF (15 mL) was added NaOH (0.22 g, 5.4 mmol) in water (1mL) at 25 °C. The reaction was stirred for 12 h and the reaction was complete. The reaction was acidified to pH 5 with concentrated HCl, and the solvent was evaporated to dryness. The residue was azeotroped with toluene (3 x 50 mL) to afford a solid which was used without further purification. To a solution of the carboxylic acid (0.18 g, 0.56 mmol) and 2-aminobiphenyl (0.11 g, 0.68 mmol) in pyridine (1.5 mL) at 0 °C was added phosphorous oxychloride (0.10 g, 0.68 mmol) dropwise. The reaction was stirred 20 minutes, and the reaction was quenched with water (10 mL). The reaction was diluted with EtOAc (20 mL) and washed with water (1 x 10 mL). The combined organics were dried over $MgSO_4$ and concentrated. The crude reaction was purified by column chromatography (0 to 25% MeOH in EtOAc) to afford 1-6 as a brown solid. Data for 1-6: ^{1}HNMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.43-7.09 (m, 11H), 4.59 (d, J = 7.0 Hz, 1H), 4.17 (d, J = 15.0 Hz, 1H), 3.94 (d, J = 15.0 Hz, 1H), 3.69 (s, 3H), 3.65-3.56 (m, 2H), 2.39-2.31 (m, 1H), 2.02-1.91 (m, 3H) ppm; HRMS [M+H] for $C_{24}H_{26}N_4O_2S$ calc'd 471.1842, found 471.1849.

EXAMPLE 2



Methyl 1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinate (1-7)

To a solution of L-proline methyl ester hydrochloride (5.0 g, 30.2 mmol) and 2-benzimidazole propionic acid (8.6 g, 45.3 mmol) in DMF (50 mL) was added HOBT (6.1 g, 45.3 mmol), EDC (8.7 g, 45.3 mmol), and triethylamine (9.2 g, 90.6 mmol), and the reaction was heated to 105 °C. After 15 minutes, all reagents went soluble, and after 1.5 h the reaction was complete. The reaction was partitioned between EtOAc (200 mL) and water (200 mL). The reaction was extracted with EtOAc (2 x 200 mL), and the combined organics were dried organics over $MgSO_4$ and concentrated. The crude reaction was purified by column chromatography (0 to 30% MeOH in EtOAc) to afford a white foam. To

a solution of the obtained ester (6.4 g, 21.2 mmol) in DMF (50 mL) at 25 °C was added Cs_2CO_3 (10.4 g, 31.9 mmol) and iodomethane (3.6 g, 25.5 mmol). After 1.5h, the reaction was diluted with water (150 mL) and extracted with EtOAc (2 x 150 mL). The combined organics were dried over $MgSO_4$ and concentrated. The crude reaction was purified by column chromatography (50% EtOAc in hexanes to 30% MeOH in EtOAc) to afford 1-7 as an oil. Data for 1-7: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 7.5 Hz, 1H), 7.32-7.20 (m, 3H), 4.48 (dd, J = 9.0, 4.0 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.74-3.69 (m, 1H), 3.67-3.61 (m, 1H), 3.32-2.98 (m, 4H), 2.22-1.95 (m, 4H) ppm; ESI MS [M+H] for $C_{17}H_{21}N_3O_3$ = 316.2

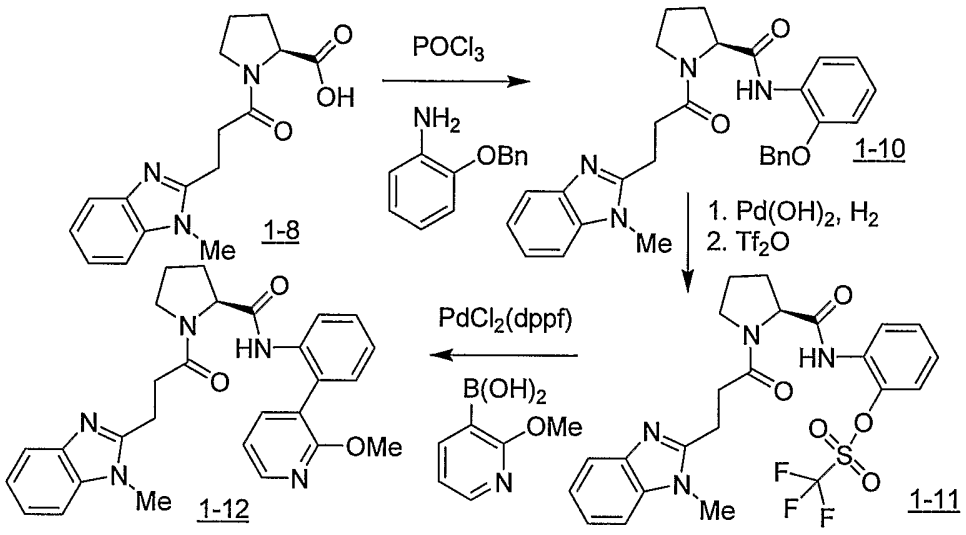
1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-proline (1-8)

To a solution of ester 1-7 (4.3 g, 13.6 mmol) in THF (30 mL) was added NaOH (0.82 g, 20.5 mmol) in water (1.5mL) at 25 °C. The reaction was stirred for 2 h and acidified to pH 5 with concentrated HCl and the solvent was evaporated to dryness. The residue was azeotroped with toluene (3 x 150 mL) to afford a white solid (1-8) which was used without further purification. Data for 1-8: ESI MS [M+H] for $C_{16}H_{19}N_3O_3$ = 302.2

N-(2,2-difluoro-1-phenylethyl)-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide (1-9)

To a solution of carboxylic acid 1-8 (0.10 g, 0.33 mmol), α-difluoromethylbenzylamine (0.063 g, 0.40 mmol) and triethylamine (0.067 g, 0.66 mmol) in DMF (2 mL) at 25 °C was added EDC (0.095 g, 0.50 mmol) and HOBT (0.076 g, 0.50 mmol), and the reaction was heated to 150 °C in the microwave for 10 minutes and the reaction was complete. The reaction was cooled to ambient temperature and quenched with water (5 mL). The crude reaction mixture was diluted with EtOAc (20 mL) and washed with water (4 x 10 mL). The combined organics were dried over $MgSO_4$ and concentrated. The crude reaction was purified by column chromatography (50% EtOAc in hexanes to 40% MeOH in EtOAc) to afford 1-9 as an oil as a 1:1 mixture of diastereomers. Data for 1-9: HRMS [M+H] for $C_{24}H_{26}F_2N_4O_2$ calc'd 441.2097, found 441.2100.

EXAMPLE 3



N-[2-(benzyloxy)phenyl]-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide (1-10)

To a solution of 1-[3-methyl-1-benzimidazol-2-yl)propanoyl]-L-proline (4.30 g, 14.26 mmol) and 2-(benzyloxy)aniline (2.84 g, 14.26 mmol) in pyridine at -10°C was added $POCl_3$ (1.43 mL, 15.69 mmol) and stirred for 0.5h. The system was warmed to 0 °C and quenched with 20 mL of ice-water, extracted with DCM, washed with water and dried over magnesium sulfate. The crude reaction mixture was purified using normal phase conditions (0%→8% MeOH(10% NH_4OH):DCM) to afford the title compound (1-10) as an orange foam. Data for 1-10: ESI+ MS $[MH]^+$ $C_{29}H_{30}N_4O_3$ = 483.4.

N-(2-hydroxyphenyl)-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide (1-11; step 1)

To a solution of N-[2-(benzyloxy)phenyl]-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide (2.60 g, 5.38 mmol) in methanol was added 20 wt% $Pd(OH)_2$ (1.3 g, 1.80 mmol) and stirred under a hydrogen balloon at room temperature. After 2h, the reaction contents were filtered through a pad of celite and concentrated to afford the title compound as a beige foam. Data for 1-11 (step 1): ESI+ MS $[MH]^+$ $C_{22}H_{24}N_4O_3$ = 393.2.

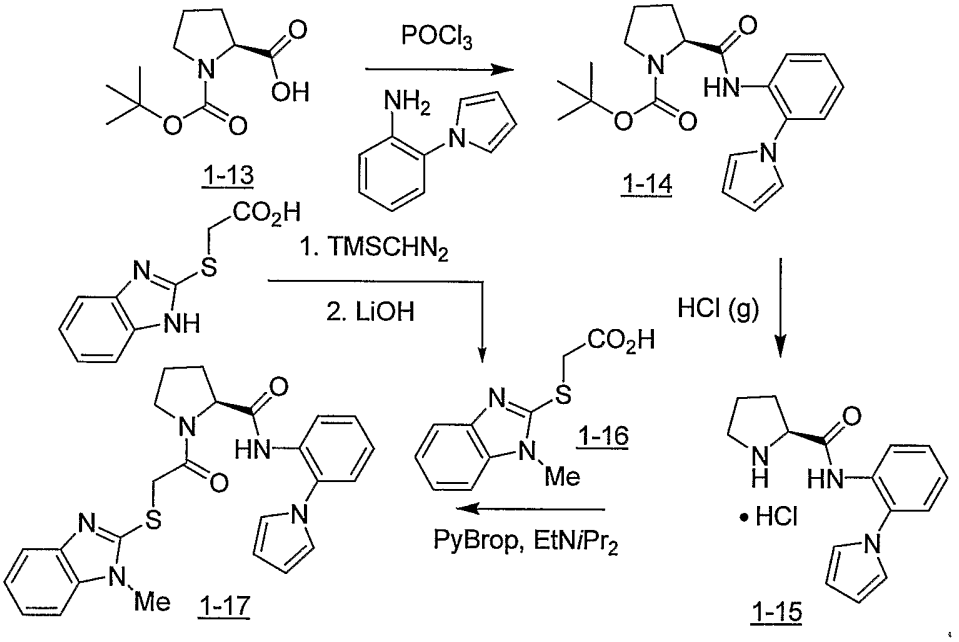
2-({1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolyl}amino)phenyl trifluoromethanesulfonate (1-11; step 2)

To a solution of N-(2-hydroxyphenyl)-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide (2.10 g, 5.37 mmol) in pyridine at 0 °C was added triflic anhydride (0.995 mL, 5.91 mmol) and stirred for 0.5h. The system is extracted with EtOAc, washed with water and dried over magnesium sulfate. The crude residue was purified using normal phase conditions (0%→8% MeOH(10% NH_4OH):DCM) to afford the title compound (1-11) as a yellow foam. Data for 1-11: HRMS [M+H] $C_{23}H_{23}F_3N_4O_5S$ calc'd 525.5228 , found 525.1419.

N-[2-(2-methoxypyridin-3-yl)phenyl]-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide (1-12)

To a solution of 2-({1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolyl}amino)phenyl trifluoromethanesulfonate (0.100 g, 0.191 mmol) and (2-methoxypyridin-3-yl)boronic acid (0.029 g, 0.191 mmol) in THF (1.0 mL) was added cesium carbonate (0.267 g, 0.820 mmol) and $PdCl_2$(dppf) (0.014 g, 0.019 mmol) and heated in a microwave to 160 °C for 10 minutes. The system was cooled to room temperature, extracted with EtOAc, washed with water and dried over sodium sulfate. The crude reaction mixture was purified using reverse phase conditions (5%→95% 0.1% TFA in water: 0.1% TFA in ACN) followed by free base extraction with saturated sodium carbonate to afford the title compound (1-12) as a white semi-solid. Data for 1-12: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.79-1.87 (m, 1H), 1.90-1.96 (m, 1H), 2.30-2.33 (m, 1H), 2.75-2.80 (m, 1H), 3.12 (m, 2H), 3.51 (m, 2H), 3.79 (m, 2H), 3.83 (s, 3H), 3.96 (s, 3H), 4.55 (m, 1H), 6.96 (m, 1H), 7.14-7.21 (m, 3H), 7.34-7.35 (m, 2H), 7.40-7.43 (m, 1H), 7.62 (m, 1H), 7.91 (m, 1H), 8.20 (br s, 1H), 8.64 (m, 1H). HRMS [M+H] $C_{28}H_{29}F_3N_5O_3$ calc'd 484.2270, found 484.2332.

EXAMPLE 4



1-(tert-butoxycarbonyl)-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide (1-14)

Phosporus oxychloride (468 μL, 5.11 mmol) was added to a stirring a solution of L-BOC-proline (1g, 4.65 mmol) and 1-(2-aminophenyl)pyrrole (735mg, 4.65 mmol) in dry pyridine (15mL). After 20 minutes the reaction was complete and quenched by slow addition of ice/water (50mL). The reaction was extracted with EtOAc, washed with saturated sodium bicarbonate and brine. The

combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified on silica by normal phase preparative chromatography (7-30% ethyl acetate/heptane) to give the title compound (1-14) as a solid. Data for 1-14: ESI+ MS: 256.1[MH-BOC]$^+$.

N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide hydrochloride (1-15)

Hydrogen chloride gas was bubbled through a solution of (1-14) in of EtOAc (25 mL) cooled to 0°C for 3 minutes. The reaction was stirred for 30 minutes and concentrated *in vacuo* to give the title compound (1-15) as a solid. Data for 1-15: ESI+ MS: 256.0[MH]$^+$.

Methyl [(1-methyl-1H-benzimidazol-2-yl)thio]acetate (1-16; step 1)

(2-Benzimidazolythio)acetic acid (1g, 4.8 mmol) and 2M TMS-diazomethane (7.2 mL, 14.4 mmol) were stirred in benzene/methanol (2:1, 30 mL) overnight. Additional TMS-diazomethane (3mL, 6 mmol) were added and reaction stirred another 24 hours. Additional TMS-diazomethane (2 mL, 4 mmol) was added and the reaction stirred an additional 24 hours. The reaction was diluted with EtOAc, saturated sodium bicarbonate and brine. The organics were dried over Na_2SO_4 and concentrated *in vacuo.* to give the title compound (1-16; step 1). Data for 1-16; step 1: ESI+ MS: 237[MH]$^+$.

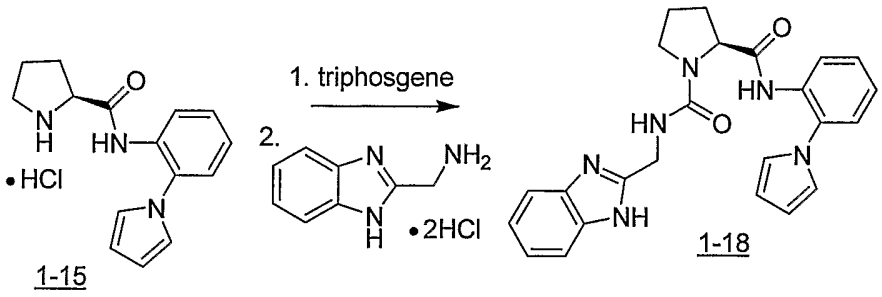
[(1-methyl-1H-benzimidazol-2-yl)thio]acetic acid (1-16; step 2)

Compound 1-16 (step 1) (450mg, 1.9 mmol) was taken up in THF (5mL) and the LiOH (200mg, 4.76 mmol) in water (5mL) was added. The reaction stirred at room temperature overnight, was made slightly acidic (pH 5-6) with concentrated HCl, stripped to dryness and azeotroped from toluene to give the titled compound (1-16) as a mixture with in organic salts. Data for 1-16: ESI+ MS: 223[MH]$^+$.

1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide (1-17)

The amine salt (1-15) (100mg, 0.343 mmol), the acid (1-16) (114 mg, 0.514 mmol), PyBrOP (240mg, 0.514 mmol) and diisopropylethylamine (198 µL, 1.2 mmol) were stirred in DMF (3 mL) at room temperature for 20 minutes. The reaction was diluted with EtOAc, washed with water, saturated sodium bicarbonate and brine. The combined organics were dried over Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by reverse phase preparative chromatography (C-18, 0.5% TFA 95-5% water in acetonitrile) to give the title compound (1-17) as the bis(trifluoromethyl)acetic acid salt. Data for 1-17: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d J=8.3 Hz, 1H), 7.93-7.91 (m, 1H), 7.81 (Br s, 1H), 7.47-7.41 (m, 3H), 7.36 (t J=7.7 Hz, 1H), 7.17 (t J=7.5 Hz, 1H), 6.75 (s, 2H), 6.37 (s, 2H), 4.84 (d J=16.1 Hz, 1H), 4.49 (d J=5.9 Hz, 1H), 4.38 (d J=16.1 Hz, 1H), 3.92 (s, 3H), 3.64-3.56 (m, 2H), 2.27-2.23 (m, 1H), 2.09-1.93 (m, 3H); EI HRMS exact mass calculated for $C_{24}H_{22}N_4O_2S_2$ 463.1257 found 463.1249.

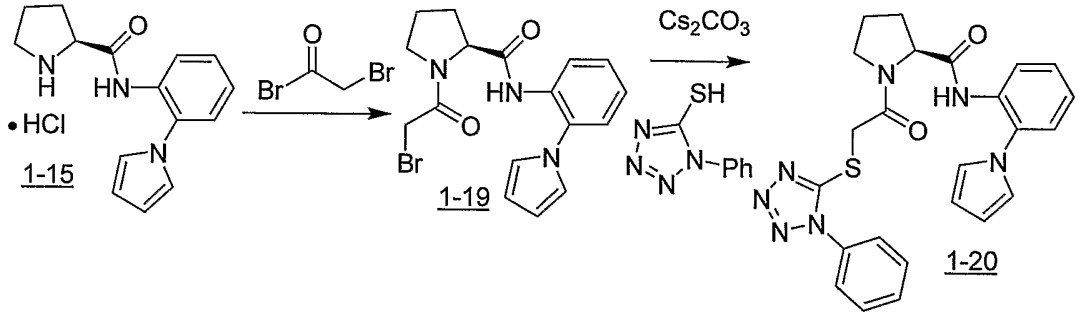
EXAMPLE 5



(2S)-N-1-(1H-benzimidazol-2-ylmethyl)-N-2-[2-(1H-pyrrol-1-yl)phenyl]pyrrolidine-1,2-dicarboxamide (1-18)

To a suspension of the amine salt (1-15) (62mg, 0.212 mmol) and triethylamine (30 μL, 0.212 mmol) in THF (2 mL) at 0°C, triphosgene (21mg, 0.071 mmol) was added followed by more triethylamine (30 μL, 0.212 mmol). The reaction stirred for 10 minutes and 1-(1H-benzimidazol-2-yl)methanamine dihydrochloride (47mg, 0.212 mmol) was added followed by triethylamine (45 uL, 0.218 mmol). The reaction stirred for 45min at 0°C and warmed to room temperature. The reaction was diluted with EtOAc, washed with water, saturated sodium bicarbonate and brine. The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by reverse phase preparative chromatography (C-18, 0.5% TFA 95-5% water in acetonitrile) to give the title compound (1-18) as a solid. Data for 1-18: ^{1}H NMR (500 MHz, d_6-DMSO) δ 8.96 (s, 1H), 7.73-7.71 (m, 2H), 7.47-7.46 (m, 2H), 7.34 (d J=13.7Hz, 2H), 7.28-7.26 (m, 2H), 6.91 (s, 2H), 6.18 (d J=4.2 Hz, 2H), 4.70-4.56 (m, 2H), 4.28 (dd J=8.5 Hz and 2.4 Hz, 1H), 3.40-3.34 (m, 3H), 2.04-2.01 (m, 1H), 1.89-1.88 (m, 2H), 1.84-1.82 (m, 1H); EI HRMS exact mass calculated for $C_{24}H_{24}N_6O_2$ 463.1257 found 463.1249.

EXAMPLE 6



1-(bromoacetyl)-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide (1-19)

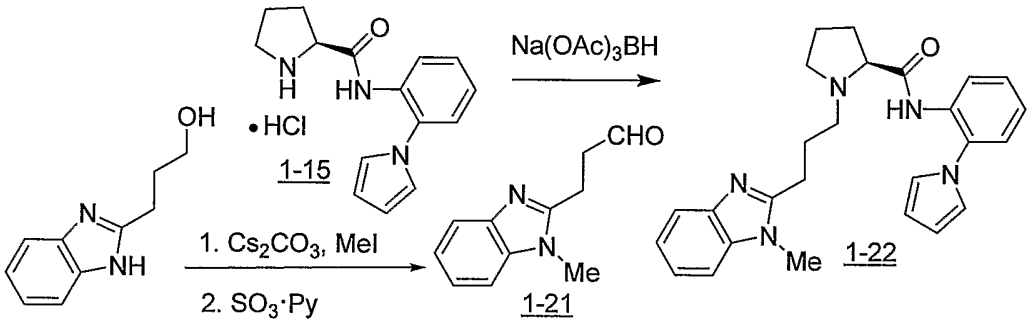
To the amine salt (1-15) (500mg) and triethylamine (597 μL, 4.28 mmol) in DCM (15 mL) at 0°C, bromoacetyl bromide (164 μL, 1.88 mmol) was added and the reaction stirred for 20

minutes. The reaction was diluted with EtOAc, washed with water, saturated sodium bicarbonate and brine. The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (1-19) as a foamy solid. Data for 1-19: ESI+ MS: 376, 378.1$[MH]^+$.

1-{[(1-phenyl-1H-tetraazol-5-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide (1-20)

The bromoamide (1-19) (60mg, 0.159 mmol), 1-phenyl-1H-tetrazole-5-thiol (57mg, 0.319 mmol) and cesium carbonate (156 mg, 0.478 mmol) in DMF (2 mL) were heated in a microwave apparatus to 60°C for 10 minutes. The reaction was filtered and put directly on a reverse phase preparative HPLC system (C-18, 0.5% TFA 95-5% water in acetonitrile) to give the titled compound (1-20) as a solid. Data for 1-20: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d J=8.1 Hz, 1H), 7.84 (s, 1H), 7.63-7.55 (m, 5H), 7.38 (t J=7.9 Hz, 1H), 7.17 (t J=7.6 Hz, 1H), 6.76 (s, 1H), 6.35 (s, 2H), 4.57 (d J=8.1 Hz, 1H), 4.39 (d J=15.6, 1H), 4.22 (d J=15.8 Hz, 1H), 3.63-3.57 (m, 2H), 2.34-2.30 (m, 1H), 2.06-1.97 (m, 3H); HRMS exact mass calculated for $C_{24}H_{23}N_7O_2S$ 474.1707 found 474.1715.

EXAMPLE 7



3-(1-methyl-1H-benzimidazol-2-yl)propan-1-ol (1-21; step 1)

Methyl Iodide (839μL, 13.48 mmol) was added to a mixture of the 3-(1H-benzimidazol-2-yl)propan-1-ol (2.5g, 14.19 mmol) and Et_3N (2.16mL, 15.6 mmol) in DCM (100 mL) at 0°C. The reaction stirred for 40 minutes, was warmed to room temperature and stirred 1 hour. DMF (50 mL) was added and continued stirring for 1 hour. Cesium carbonate (4.62g, 14.19 mmol) and methyl iodide (839μL, 13.48 mmol) were added and the reaction stirred overnight. The reaction was diluted with EtOAc, washed with water, saturated sodium bicarbonate and brine. The combined organics were dried over Na_2SO_4 and concentrated *in vacuo.* The crude solids were triturated with ethyl ether/hexane (1:2) to give the title compound (1-21; step 1) as a solid. Data for 1-21; step 1: ESI+ MS: 191.1$[MH]^+$.

3-(1-methyl-1H-benzimidazol-2-yl)propanal (1-21; step 2)

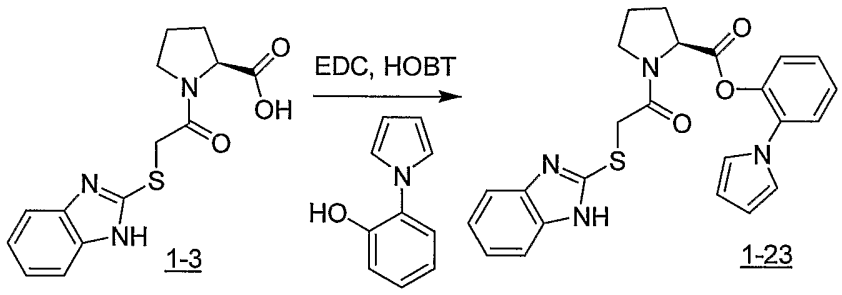
The alcohol (1-21; step 1) (150mg, 0.79 mmol), triethylamine (440 μL, 3.15 mmol) and sulfur trioxide-pyridine complex (314mg, 1.97 mmol) in DMSO (5 mL) were stirred at room temperature for 2.4 hours. Additional triethylamine (440 μL, 3.15 mmol) and sulfur trioxide-pyridine complex

(314mg, 1.97 mmol) were added and the reaction stirred 30 minutes more. The reaction was diluted with EtOAc, washed with water and brine. The organics were dried over Na_2SO_4 and concentrated *in vacuo.* to give the title compound (1-21) as an oil. Data for 1-21: ESI+ MS: 189$[MH]^+$.

1-[3-(1-methyl-1H-benzimidazol-2-yl)propyl]-N-[2-(1H-pyrrol-1yl)phenyl]-L-prolinamide (1-22)

The aldehyde (1-21) (53mg, 0.282 mmol), the amine salt (1-15) (82mg, 0.282 mmol), sodium triacetoxyborohydride (90mg, 0.422 mmol) and powdered 4Å sieves (100mg) were combined in dichloroethane (2 mL) and stirred at room temperature for 30 minutes. Additional aldehyde (40mg, 0.21 mmol) in dichloroethane (0.5 mL) was added and the reaction stirred 20 minutes more. The reaction was diluted with EtOAc, washed with water, saturated sodium bicarbonate and brine. The combined organics were dried over Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by reverse phase preparative chromatography (C-18, 0.5% TFA 95-5% water in acetonitrile) to give the title compound as the bis(trifluoroacetic acid) salt (1-22). Data for 1-22: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.87 (m,1H), 7.65 (d J=7.6 Hz, 1H), 7.61-7.57 (m, 3H), 7.35-7.31 (m, 1H), 7.29 (d J=4.2 Hz, 2H), 6.78-6.77 (m, 2H), 6.19 (s, 2H), 4.75 (Br s, 1H), 3.98 (s, 3H), 3.86 (br s, 1H), 3.48-3.45 (m, 2H), 3.37-3.27 (m, 3H), 2.47-2.45 (m, 1H), 2.34 (Br s, 2H), 2.17-2.14 (m, 3H); EI HRMS exact mass calculated for $C_{26}H_{29}N_5O$ 463.1257 found 463.1249.

EXAMPLE 8



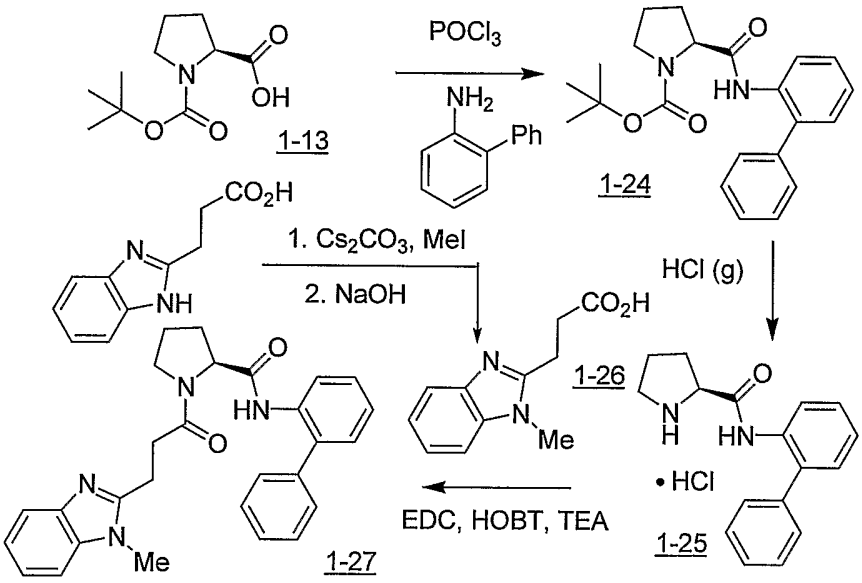
1-3 1-23

2-(1H-pyrrol-1-yl)phenyl 1-[(1H-benzimidazol-2-ylthio)acetyl]-L-prolinate (1-23)

To a solution of carboxylic acid 1-3 (0.10 g, 0.327 mmol), 2-(1H-pyrrol-1-yl)benzenol (0.052 g, 0.327 mmol) and triethylamine (0.066 g, 0.655 mmol) at 25 °C was added EDC (0.094 g, 0.491 mmol) and HOBT (0.075 g, 0.491 mmol) at 25 °C and heated to 90 °C. After 1 h, the reaction was cooled and quenched with water and diluted with EtOAc (15 mL). The organics were washed with water, dried over MgSO4 and concentrated. The crude reaction mixture was purified by column chromatography (50:50 EtOAc in hexanes to 20% MeOH in EtOAc to afford 1-23 as a beige foam. Data for 1-23: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.42-7.15 (m, 8H), 6.82-7.76 (m, 2H), 6.30-6.24 (m, 2H), 4.66 (dd, J = 9.0,

4.5 Hz, 1H), 3.92-3.88 (m, 2H), 3.71-3.55 (m, 2H), 2.20-2.11 (m, 1H), 1.97-1.80 (m, 3H) ppm; HRMS [M+H] for $C_{24}H_{22}N_4O_3S$ calc'd 447.1486, found 447.1486.

EXAMPLE 9



1-(tert-butoxycarbonyl)-N-[2-aminobiphenyl]-L-prolinamide (1-24)

Phosporus oxychloride (14.0 mL, 153 mmol) was added to a stirred solution of L-BOC-proline (30 g, 139 mmol)) and 2-aminobiphenyl (25.9 g, 153 mmol) in dry pyridine (200 mL). After 30 minutes the reaction was complete and quenched by slow addition of ice/water (200 mL). The reaction was diluted with EtOAc and washed with water once. The combined organics were dried over Na_2SO_4 and concentrated. The crude product was purified on silica by normal phase chromatography (0 to 100% ethyl acetate in hexanes) to give the titled compound (1-24) as an oil. ESI+ MS: 367.1$[M+H]^+$.

N-[2-aminobiphenyl]-L-prolinamide hydrochloride (1-25)

Hydrogen chloride gas was bubbled through a solution of (1-24) in of EtOAc (1000 mL) cooled to 0°C for 5 minutes. The reaction was stirred for 18 hours and concentrated to give the titled compound (1-25) as a solid. ESI+ MS: 267.3 $[M+H]^+$.

3-(1-methyl-1*H*-benzimidazol-2-yl)propanoic acid (1-26)

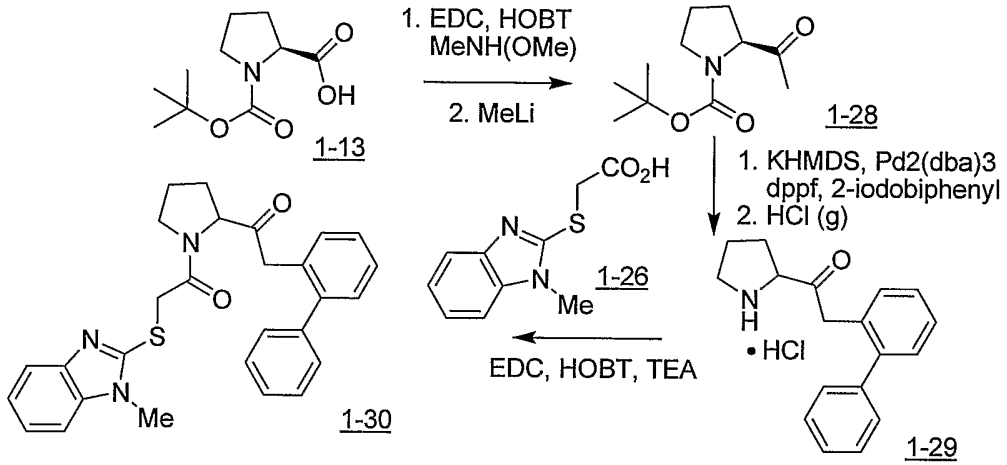
To a solution of 2-benzimidazolepropionic acid (20.5g, 108 mmol) in DMF (200 mL) at 25 °C was added cesium carbonate (52.7 g, 162 mmol) and iodomethane (23.0 g, 162 mmol) and the reaction was stirred vigorously for 24h. The reaction was quenched with water (200 mL) and extracted with ethyl acetate (2 x 200mL). The combined organics were dried over $MgSO_4$ and the residue was concentrated. The residue was further azeotroped with toluene (3 x 400mL) to afford a solid which was used without further purification. To a solution of the resulting solid in THF/MeOH (1:1, 200 mL) at 25 °C was added potassium hydroxide (5.0 g, 90 mmol) in water (54 mL) and the reaction was stirred for

24h. Concentrated hydrochloric acid (7.4 mL) was then added slowly and the reaction mixture was concentrated. The residue was azeotroped with toluene (3 x 300 mL) to give the titled compound (1-26) as an off-white solid. ESI+ MS: 205 $[M+H]^+$.

N-biphenyl-2-yl-1-[3-(1-methyl-1*H*-benzimidazol-2-yl)propanoyl]-L-prolinamide (1-27)

The amine salt (1-25) (18.8 g, 62.1 mmol), the acid (1-26) (19.0 g, 68.3 mmol), EDC (15.5 g, 81.0 mmol), HOBT (12.4 g, 81.0 mmol), and triethylamine (87.0 mL, 621 mmol) were stirred in DMF (300 mL) at 90 °C for 3h. The reaction was diluted with EtOAc (1000 mL), washed with water (2 x 500 mL), saturated sodium bicarbonate (3 x 500 mL) and brine (500 mL). The combined organics were dried over Na_2SO_4 and concentrated. The crude product was purified by normal phase silica gel chromatography (0 to 35% MeOH in ethyl acetate) to give the titled compound (1-27) as a solid. EI HRMS exact mass calculated for $C_{28}H_{28}N_4O_2$ $[M+H]^+$ 453.2292 found 453.2268. ^1H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.56-7.10 (m, 12H), 4.58-4.52 (m, 1H), 3.71 (s, 3H), 3.52-3.45 (m, 2H), 3.08-2.82 (m, 3H), 2.78-2.68 (m, 1H), 2.35-2.30 (m, 1H), 1.95-1.87 (m, 3H)

EXAMPLE 10



tert-butyl (2*S*)-2-acetylpyrrolidine-1-carboxylate (1-28)

To a solution of Boc-L-proline (5.0 g, 23.2 mmol) and Weinreb amine hydrochloride (4.1 g, 41.8 mmol) in DMF (90 mL) at ambient temperature was added EDC (6.7 g, 34.8 mmol), HOBT (4.7 g, 34.8 mmol) and triethylamine (7.1 g, 69.7 mmol). The reaction was heated to 100 °C for 3h, cooled and quenched with water (50 mL) and saturated sodium bicarbonate (50 mL). The mixture was diluted with EtOAc (400 mL) and washed with saturated sodium bicarbonate (3 x 100 mL), water (3 x 100 mL), and brine (1 x 100 mL). The combined organics were dried over Na_2SO_4 and concentrated. The crude oil was then diluted in THF (80 mL) and cooled to 0 °C. To the reaction was added methylmagnesium bromide (8.9 g, 74.5 mmol, 3M solution in THF) and the reaction was stirred for 2h. The reaction was then quenched with brine (100mL) and extracted with EtOAc (3 x 100 mL). The

combined organics were dried over Na2SO4 and concentrated. The resulting oil (1-28) was >95% pure crude and used without further purification. ESI+ MS: 236.0 $[M+Na]^+$.

2-biphenyl-2-yl-1-[(R/*S*)-pyrrolidin-2-yl]ethanone hydrochloride (1-29)

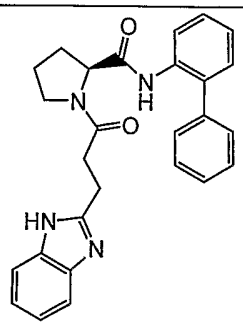
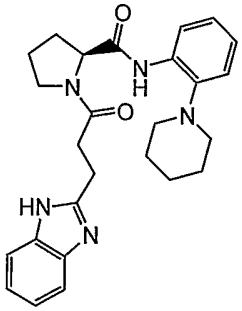
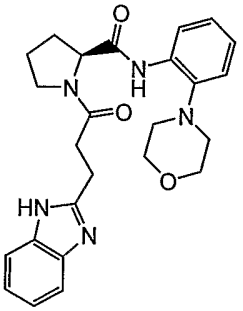
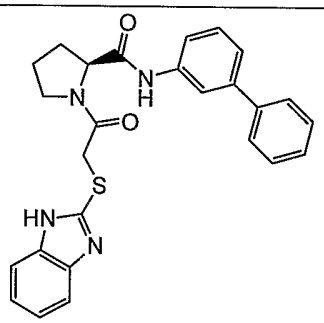
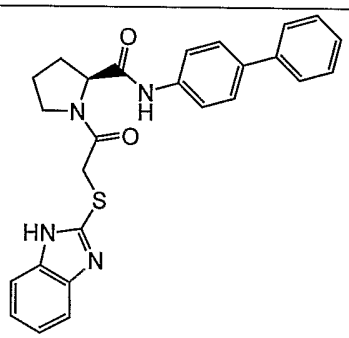
To a solution of *tert*-butyl (2*S*)-2-acetylpyrrolidine-1-carboxylate (0.50g, 2.3 mmol) and 2-iodobiphenyl (0.66g, 2.3 mmol) in THF (10 mL) at ambient temperature was added KHMDS (1.0 g, 5.2 mmol), $Pd_2(dba)_3$ (0.18g, 0.19 mmol), and diphenylphosphinoferrocene (0.13 g, 0.23 mmol) and the reaction was heated to reflux for 3 h. The reaction was then cooled and quenched with brine (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were dried over $MgSO_4$ and concentrated. The crude reaction mixture was purified by silica gel column chromatography to afford an oil. The resulting oil was dissolved in ethyl acetate (10 mL) and cooled to 0 °C. Gaseous hydrochloric acid was bubbled through the solution for 1 minute. After 2h the reaction mixture was concentrated directly to give a brown solid (1-29) used without further purification. ESI+ MS: 266.1 $[M+H]^+$.

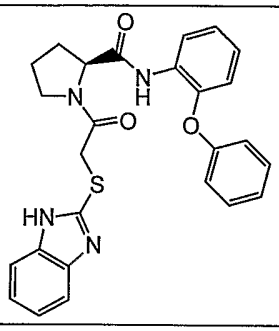
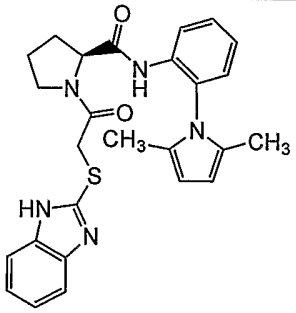
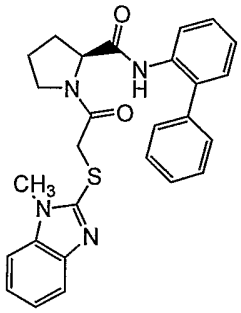
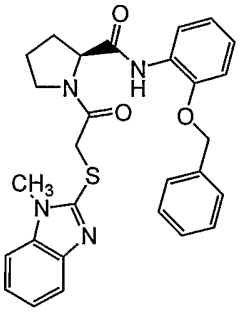
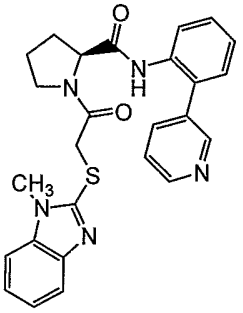
2-biphenyl-2-yl-1-(1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}pyrrolidin-2-yl)ethanone (1-30)

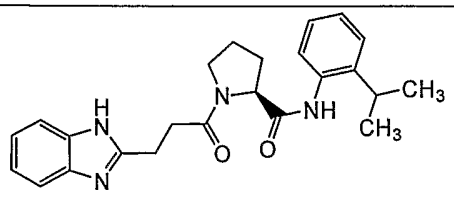
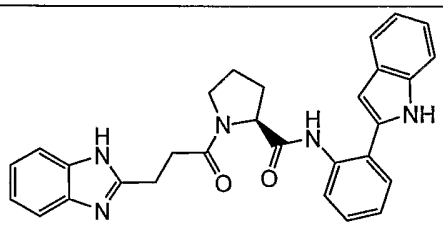
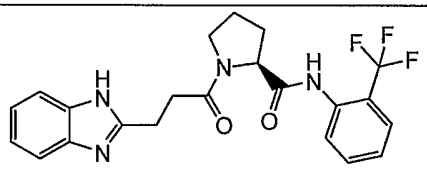
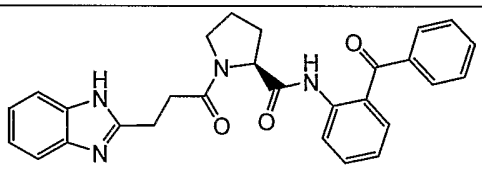
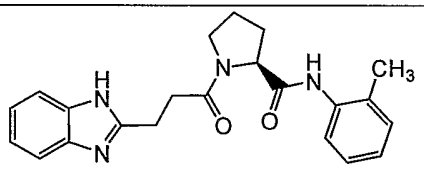
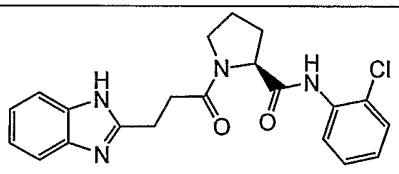
The amine salt (1-29) (30mg, 0.099 mmol), the acid (1-26) (55 mg, 0.248 mmol), EDC (48mg, 0.248 mmol), HOBT (34 mg, 0.248 mmol), and triethylamine (0.070 mL, 0.50 mmol) were stirred in DMF (2 mL) at 90 °C for 3h. The reaction was diluted with EtOAc (10 mL), washed with water (10 mL), saturated sodium bicarbonate (2 x 20 mL) and brine (10 mL). The combined organics were dried over Na_2SO_4 and concentrated. The crude product was purified by normal phase silica gel chromatography (0 to 35% MeOH in ethyl acetate) to give the titled compound (1-30) as a solid. EI HRMS exact mass calculated for $C_{28}H_{27}N_3O_2S$ $[M+H]^+$ 470.1897 found 470.1901. ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 6 Hz, 1H), 7.38-7.17 (M, 12H), 4.50-4.46 (m, 1H), 4.37 (d, J = 15 Hz, 1H), 4.20 (d, J = 15 Hz, 1H), 3.88 – 3.79 (m, 2H), 3.75-3.71 (m, 1H), 3.70 (s, 3H) 3.68-3.63 (m, 1H), 3.52-3.40 (m, 2H), 1.88-1.74 (m, 2H), 1.38-1.24 (m, 2H)

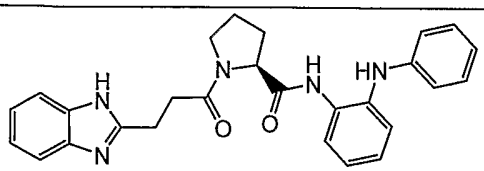
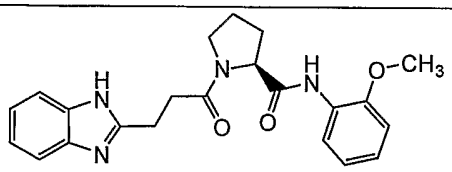
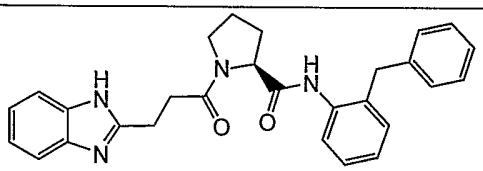
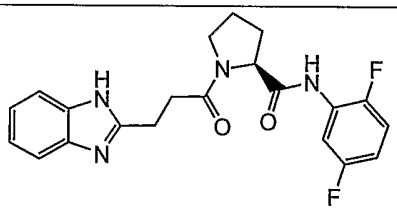
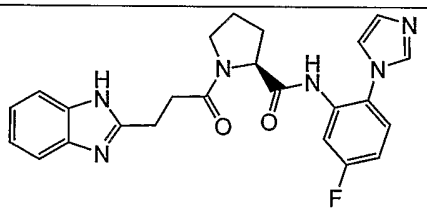
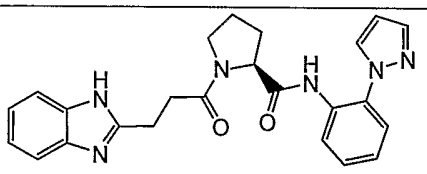
The following compounds were prepared using the foregoing methodology, but substituting the appropriately substituted reagent, such as organometallic or amine, as described in the foregoing Reaction Schemes and Examples. The requisite starting materials were commercialy available, described in the literature or readily synthesized by one skilled in the art of organic synthesis without undue experimentation.

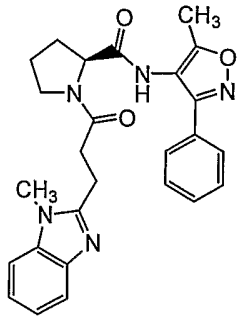
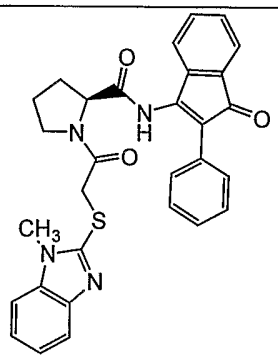
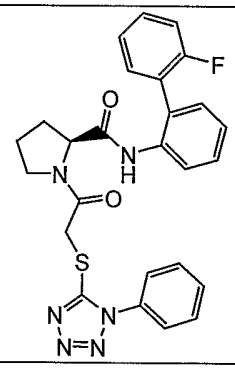
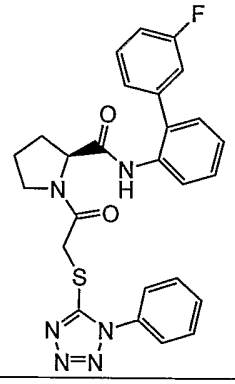
Structure	Found Mass (M+1)	Chemical Name

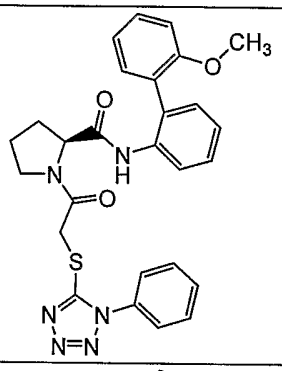
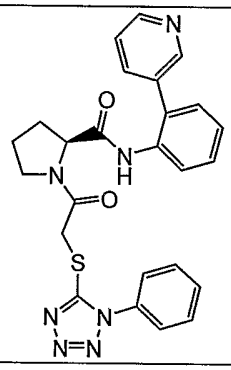
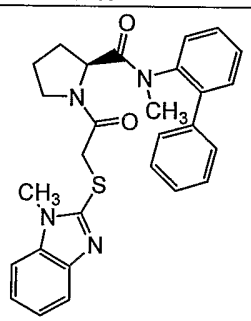
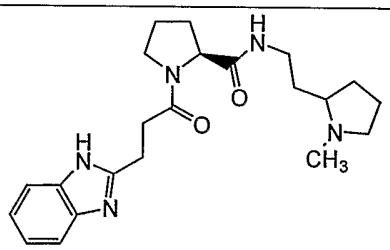
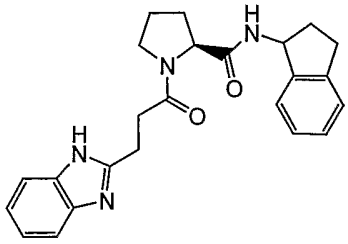
	439.2125	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-biphenyl-2-yl-L-prolinamide
	446.2522	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-piperidin-1-ylphenyl)-L-prolinamide
	448.2135	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-morpholin-4-ylphenyl)-L-prolinamide
	457.1705	1-[(1H-benzimidazol-2-ylthio)acetyl]-N-biphenyl-3-yl-L-prolinamide
	457.1702	1-[(1H-benzimidazol-2-ylthio)acetyl]-N-biphenyl-4-yl-L-prolinamide

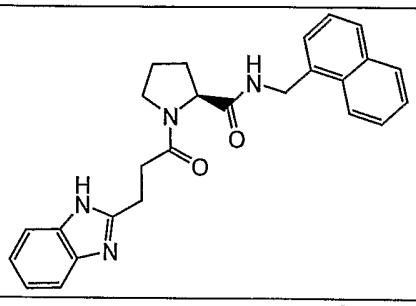
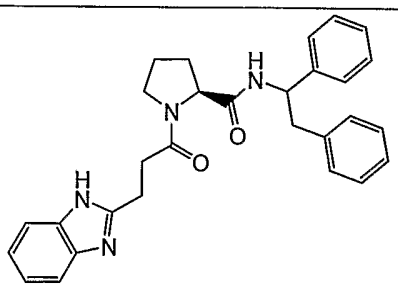
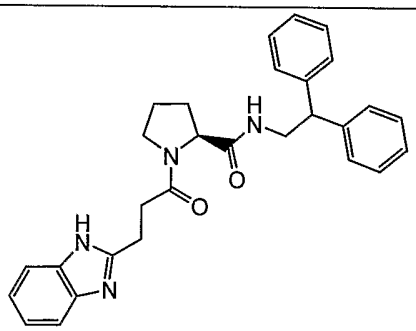
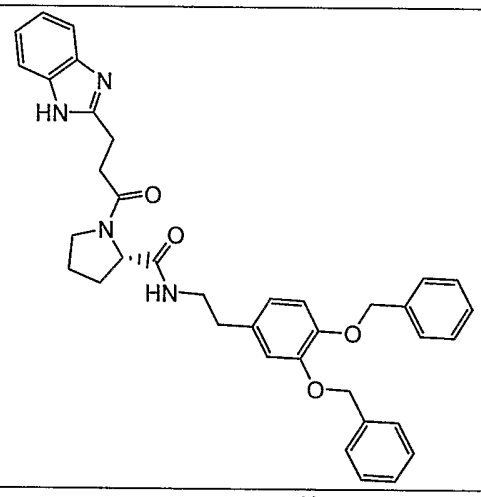
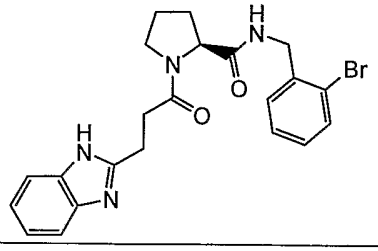
	473.1634	1-[(1H-benzimidazol-2-ylthio)acetyl]-N-(2-phenoxyphenyl)-L-prolinamide
	474.1952	1-[(1H-benzimidazol-2-ylthio)acetyl]-N-[2-(2,5-dimethyl-1H-pyrrol-1-yl)phenyl]-L-prolinamide
	471.1842	N-biphenyl-2-yl-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide
	501.1955	N-[2-(benzyloxy)phenyl]-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide
	472.1803	1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(2-pyridin-3-ylphenyl)-L-prolinamide

	405.2301	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-ISOPROPYLPHENYL)-L-PROLINAMIDE
	478.2237	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-[2-(1H-INDOL-2-YL)PHENYL]-L-PROLINAMIDE
	431.1692	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-[2-(TRIFLUOROMETHYL)PHENYL]-L-PROLINAMIDE
	467.2077	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-BENZOYLPHENYL)-L-PROLINAMIDE
	377.1983	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-METHYLPHENYL)-L-PROLINAMIDE
	397.141	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-CHLOROPHENYL)-L-PROLINAMIDE

	454.2214	N-(2-ANILINOPHENYL)-1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-L-PROLINAMIDE
	393.1908	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-METHOXYPHENYL)-L-PROLINAMIDE
	453.2277	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-BENZYLPHENYL)-L-PROLINAMIDE
	399.1631	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2,5-DIFLUOROPHENYL)-L-PROLINAMIDE
	447.1923	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-[5-FLUORO-2-(1H-IMIDAZOL-1-YL)PHENYL]-L-PROLINAMIDE
	449.2037	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-[2-(1H-PYRAZOL-1-YL)PHENYL]-L-PROLINAMIDE

	458.2187	1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-N-(5-methyl-3-phenylisoxazol-4-yl)-L-prolinamide
	523.177	1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(1-oxo-2-phenyl-1H-inden-3-yl)-L-prolinamide
	503.1672	N-(2'-fluorobiphenyl-2-yl)-1-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl}-L-prolinamide
	503.1684	N-(3'-fluorobiphenyl-2-yl)-1-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl}-L-prolinamide

	515.1838	N-(2'-methoxybiphenyl-2-yl)-1-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl}-L-prolinamide
	486.1695	1-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl}-N-(2-pyridin-3-ylphenyl)-L-prolinamide
	485.201	N-biphenyl-2-yl-N-methyl-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide
	398.254	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[2-(1-methylpyrrolidinium-2-yl)ethyl]-L-prolinamide
	403.2122	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,3-dihydro-1H-inden-1-yl)-L-prolinamide

	427.2119	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(1-naphthylmethyl)-L-prolinamide
	467.2437	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(1,2-diphenylethyl)-L-prolinamide
	467.2439	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,2-diphenylethyl)-L-prolinamide
	603.2957	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,2-diphenylethyl)-L-prolinamide
	455.107	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2-bromobenzyl)-L-

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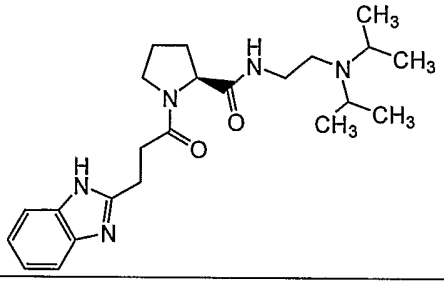
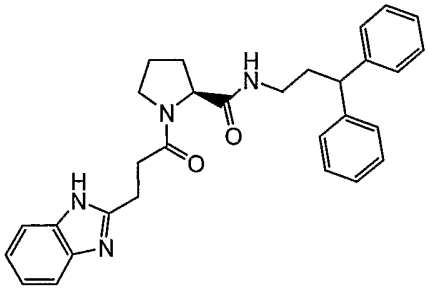
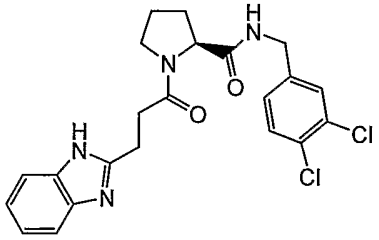
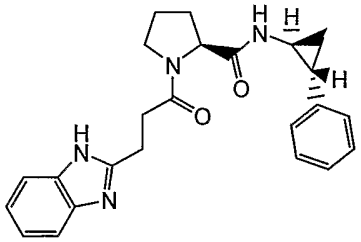
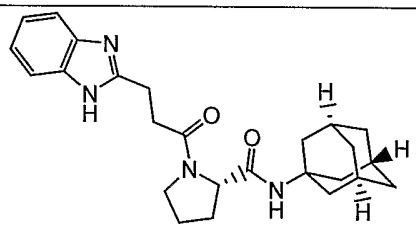
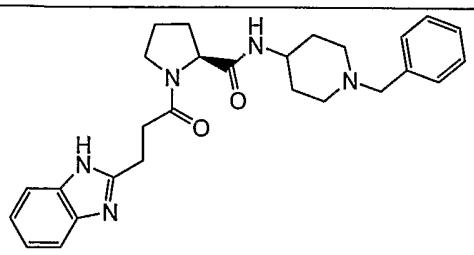
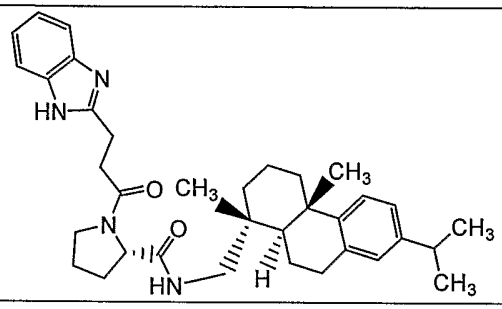
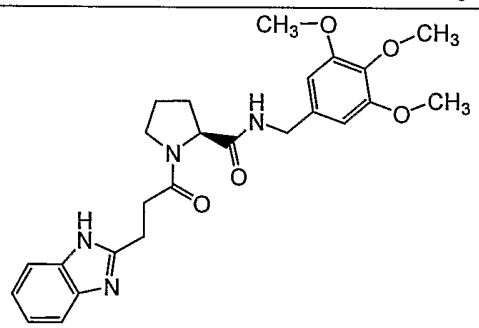
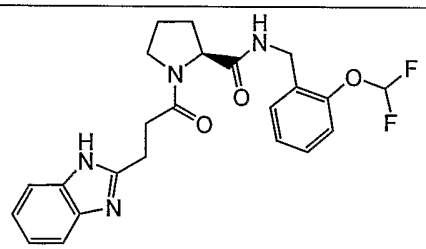
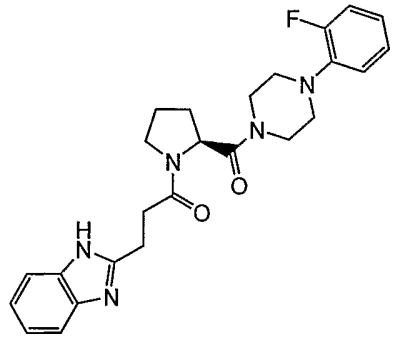
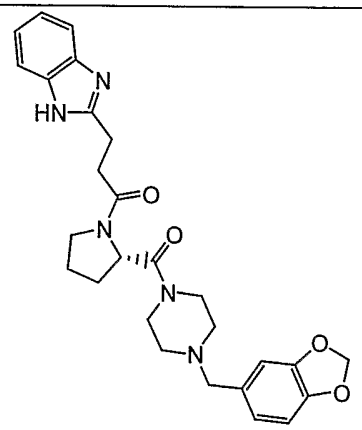
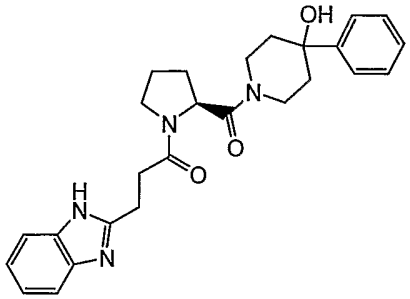
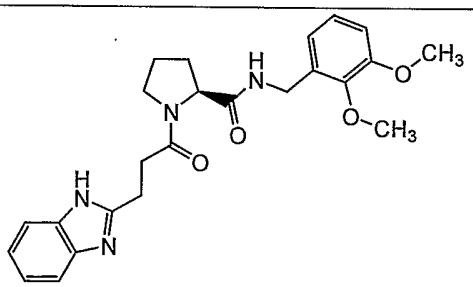
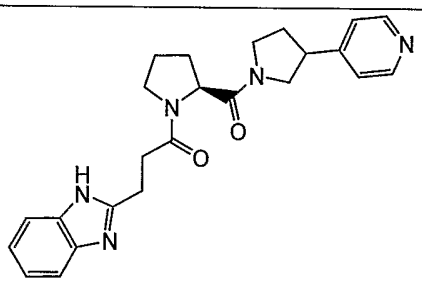
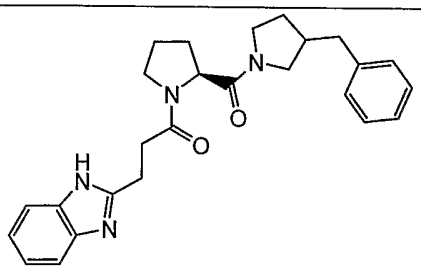
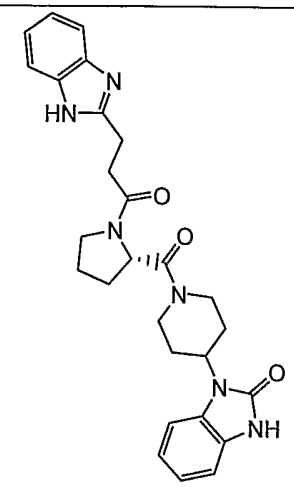
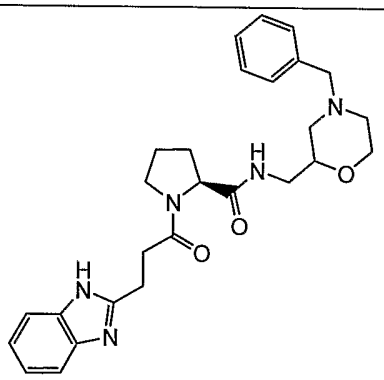
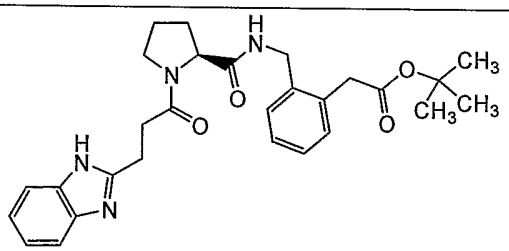
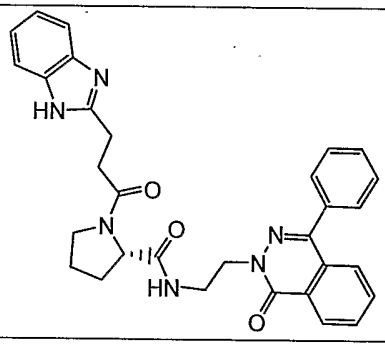
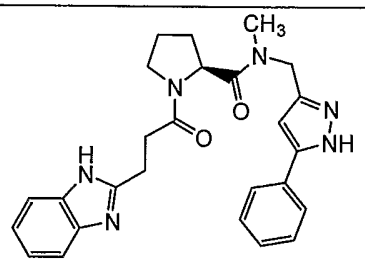
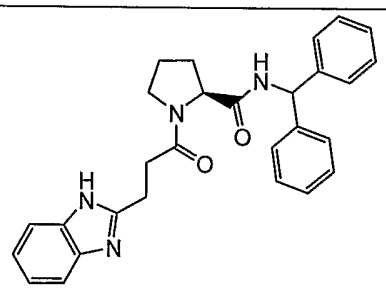
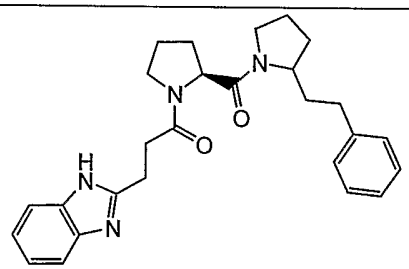
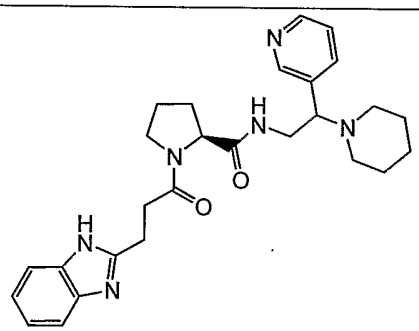
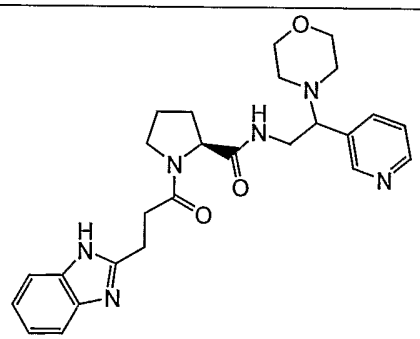
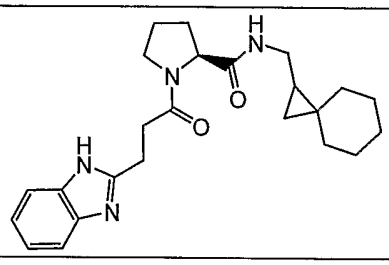
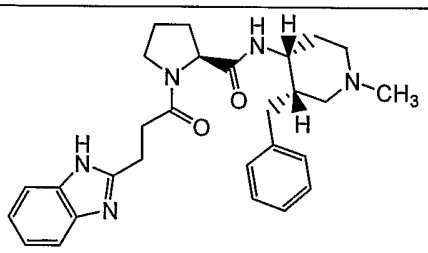
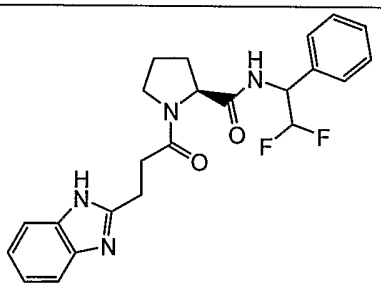
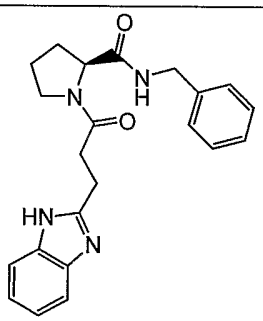
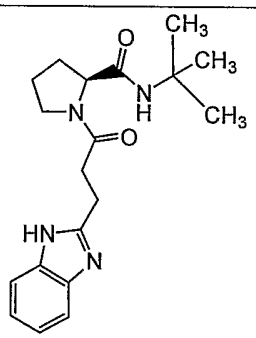
	414.2856	N-[2-({1-[3-(1H-benzimidazol-2-yl)propanoyl]-L-prolyl}amino)ethyl]-N-isopropylpropan-2-aminium
	481.2595	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(3,3-diphenylpropyl)-L-prolinamide
	445.119	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(3,4-dichlorobenzyl)-L-prolinamide
	403.2122	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-[(1S,2R)-2-phenylcyclopropyl]-L-prolinamide
	421.2591	N-1-adamantyl-1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-L-prolinamide

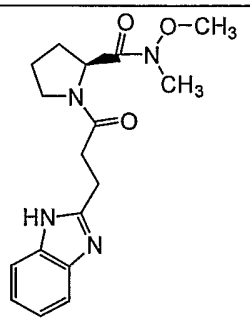
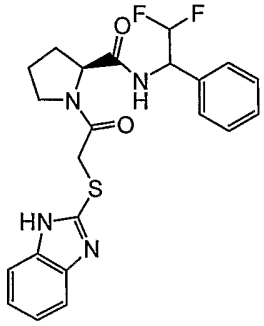
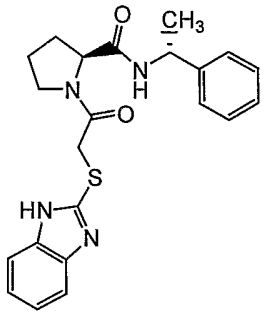
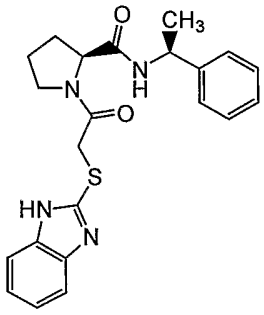
	460.2707	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(1-benzylpiperidinium-4-yl)-L-prolinamide
	555.3705	N-beta-8(14),9(11),12-trien-18-yl-1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-L-prolinamide
	467.2283	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(3,4,5-trimethoxybenzyl)-L-prolinamide
	443.1882	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-[2-(difluoromethoxy)benzyl]-L-prolinamide
	450.229	4-{1-[3-(1H-benzimidazol-2-yl)propanoyl]-L-prolyl}-1-(2-fluoro-phenyl)piperazin-1-ium

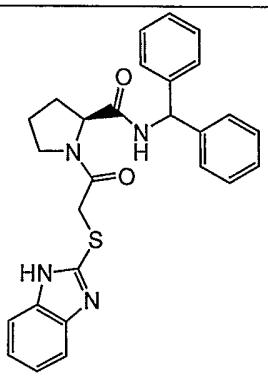
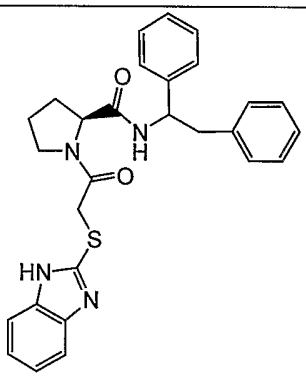
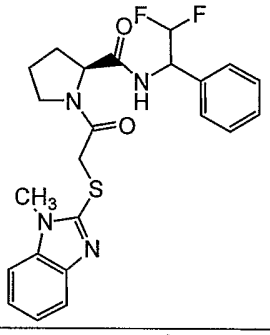
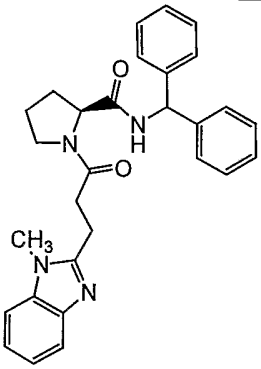
	490.2444	4-{1-[3-(1H-benzimidazol-2-yl)propanoyl]-L-prolyl}-1-(1,3-benzodioxol-5-ylmethyl)piperazin-1-ium
	447.2382	1-{1-[3-(1H-benzimidazol-2-yl)propanoyl]-L-prolyl}-4-hydroxy-4-phenyl-piperidin-1-ium
	437.2173	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,3-dimethoxybenzyl)-L-prolinamide
	418.2235	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,3-dimethoxybenzyl)-L-prolinamide
	431.2435	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,3-dimethoxybenzyl)-L-prolinamide

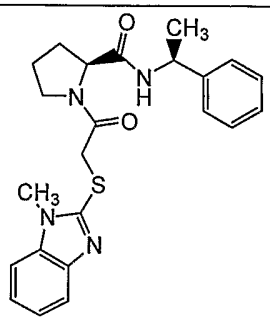
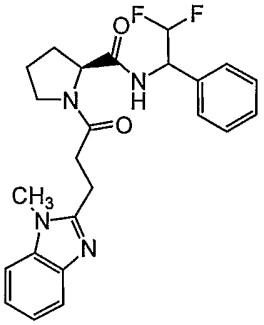
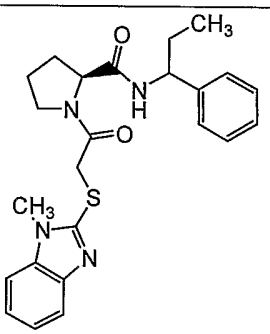
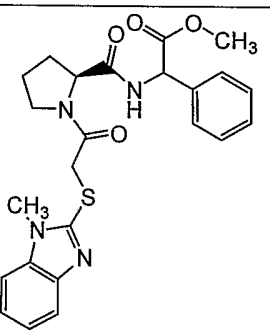
	487.2451	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,3-dimethoxybenzyl)-L-prolinamide
	467.2652	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[(4-benzylmorpholin-4-ium-2-yl)methyl]-L-prolinamide
	491.2653	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[(4-benzylmorpholin-4-ium-2-yl)methyl]-L-prolinamide
	535.2454	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-[2-(1-oxo-4-phenylphthalazin-2(1H)-yl)ethyl]-L-prolinamide

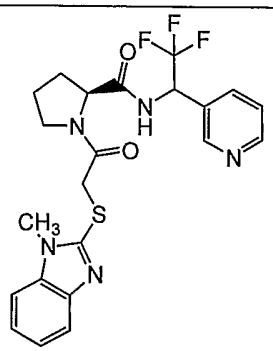
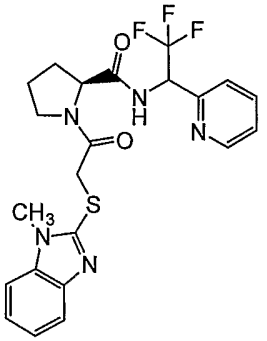
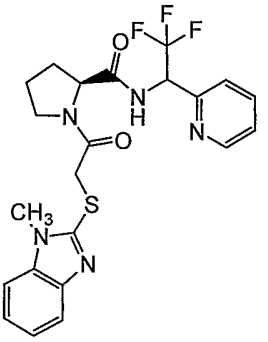
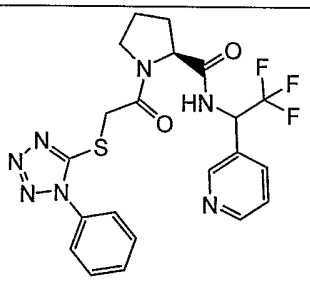
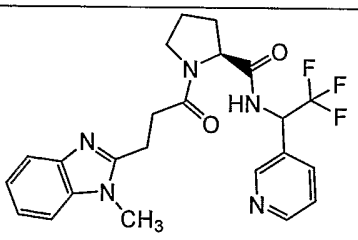
	457.2334	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-methyl-N-[(5-phenyl-1H-pyrazol-3-yl)methyl]-L-prolinamide
	453.2276	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(diphenylmethyl)-L-prolinamide
	445.2594	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(diphenylmethyl)-L-prolinamide
	475.2811	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-piperidinium-1-yl-2-pyridin-3-ylethyl)-L-prolinamide
	477.2602	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-morpholin-4-ium-4-yl-2-pyridin-3-ylethyl)-L-prolinamide

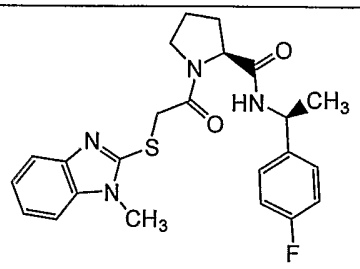
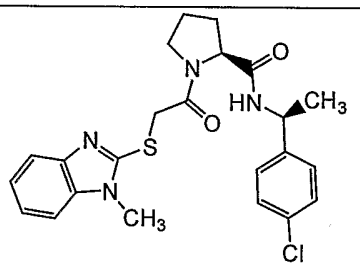
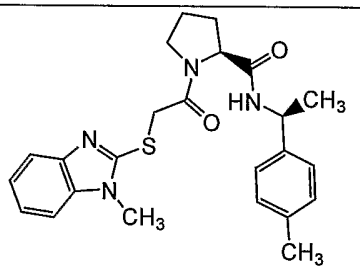
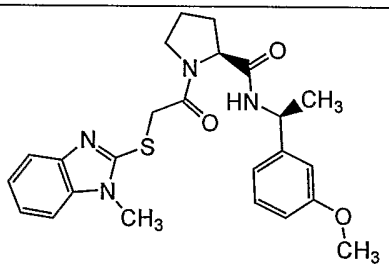
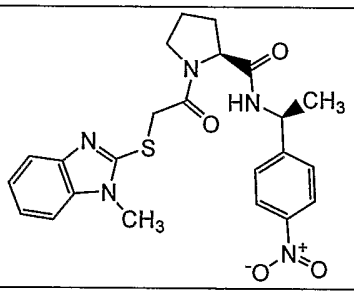
	452.3016	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(spiro[2.5]oct-1-ylmethyl)-L-prolinamide
	474.2864	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[(3S,4R)-3-benzyl-1-methylpiperidinium-4-yl]-L-prolinamide
	427.1932	1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,2-difluoro-1-phenylethyl)-L-prolinamide
	377.1998	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-benzyl-L-prolinamide
	343.2131	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(tert-butyl)-L-prolinamide

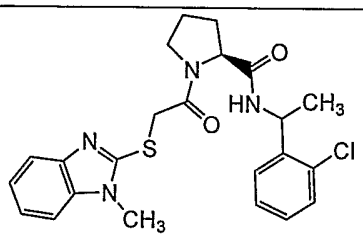
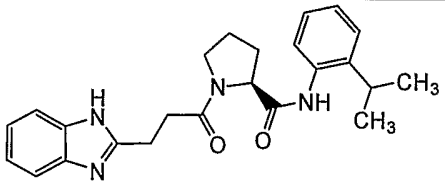
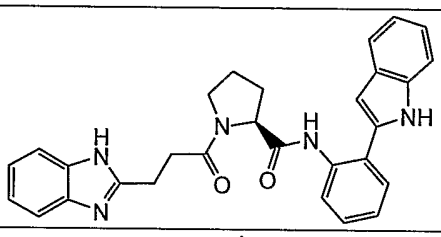
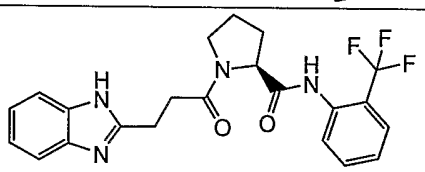
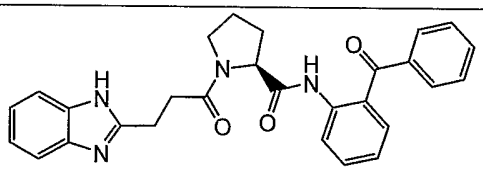
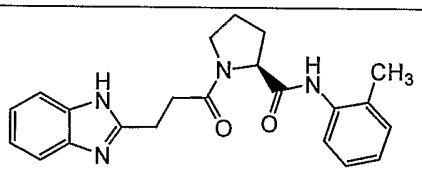
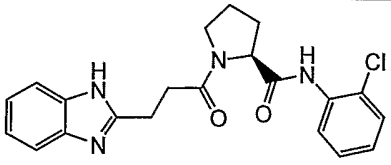
	331.1757	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-methoxy-N-methyl-L-prolinamide
	445.1498	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-methoxy-N-methyl-L-prolinamide
	409.1693	1-[(1H-benzimidazol-2-ylthio)acetyl]-N-[(1R)-1-phenylethyl]-L-prolinamide
	409.1694	1-[(1H-benzimidazol-2-ylthio)acetyl]-N-[(1S)-1-phenylethyl]-L-prolinamide

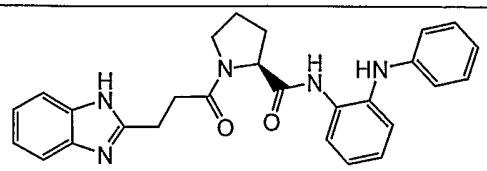
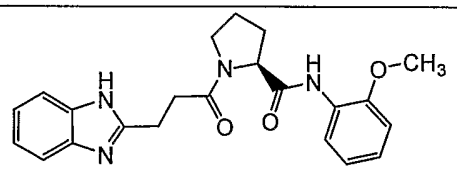
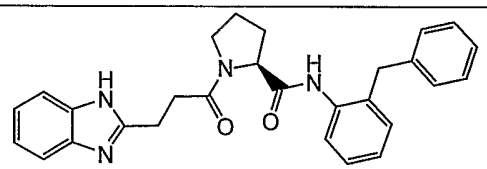
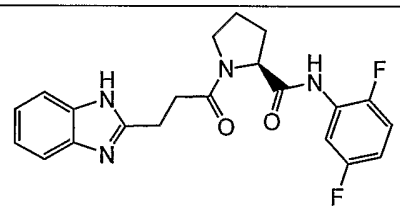
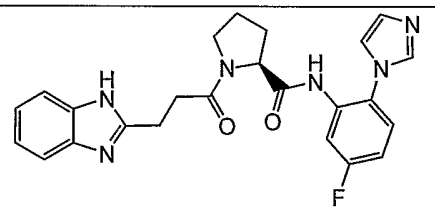
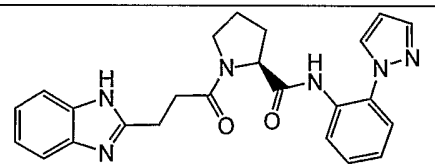
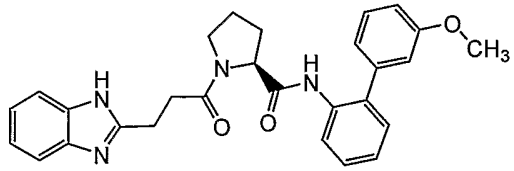
	471.1849	1-[(1H-benzimidazol-2-ylthio)acetyl]-N-(diphenylmethyl)-L-prolinamide
	485.2005	1-[(1H-benzimidazol-2-ylthio)acetyl]-N-(1,2-diphenylethyl)-L-prolinamide
	459.1658	N-(2,2-difluoro-1-phenylethyl)-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide
	467.2434	N-(diphenylmethyl)-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide

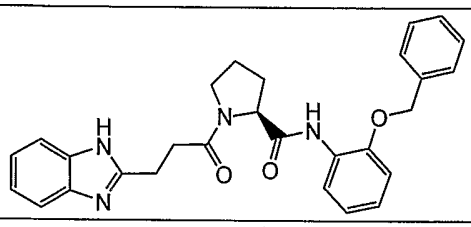
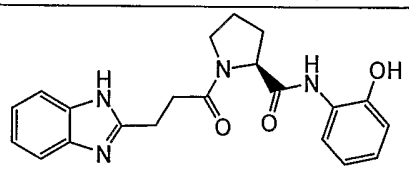
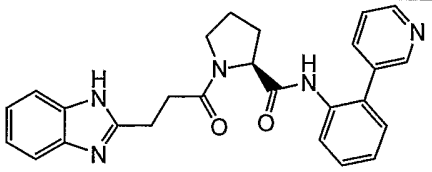
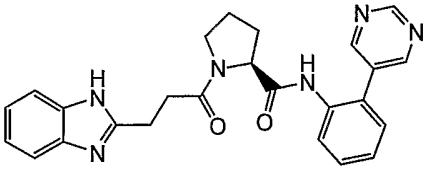
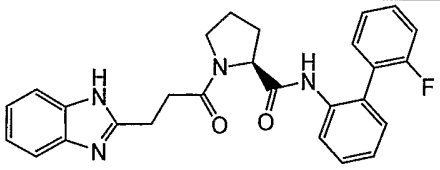
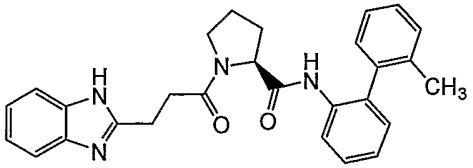
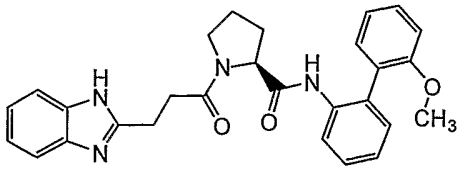
	423.1854	1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[(1S)-1-phenylethyl]-L-prolinamide
	441.21	1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[(1S)-1-phenylethyl]-L-prolinamide
	437.2013	1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(1-phenylpropyl)-L-prolinamide
	467.1748	1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(1-phenylpropyl)-L-prolinamide

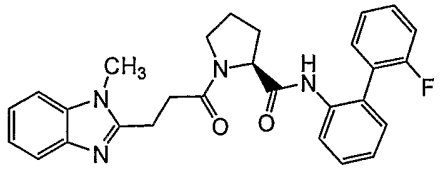
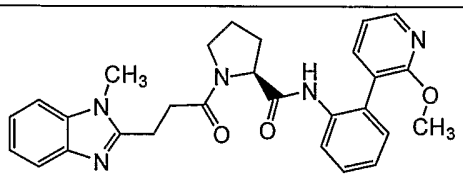
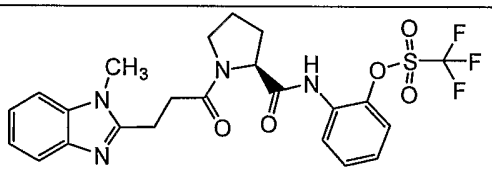
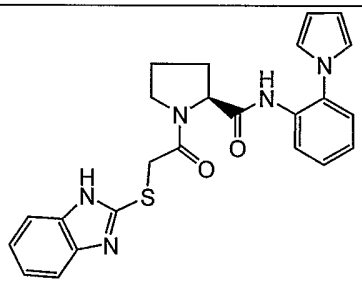
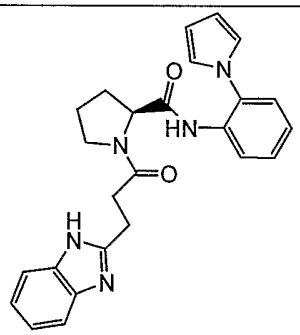
	478.1515	1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(2,2,2-trifluoro-1-pyridin-3-ylethyl)-L-prolinamide
	478.1525	1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(2,2,2-trifluoro-1-pyridin-2-ylethyl)-L-prolinamide
	478.152	1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(2,2,2-trifluoro-1-pyridin-2-ylethyl)-L-prolinamide
	492.1434	1-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl}-N-(2,2,2-trifluoro-1-pyridin-3-ylethyl)-L-prolinamide
	460.1951	1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-N-(2,2,2-trifluoro-1-pyridin-3-ylethyl)-L-prolinamide

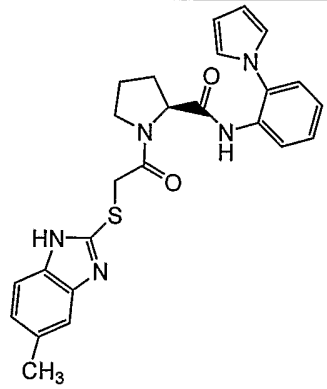
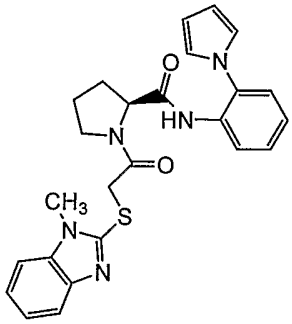
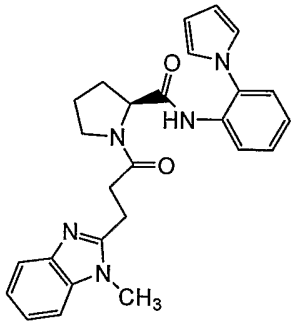
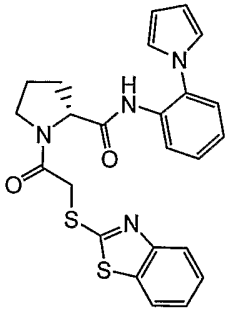
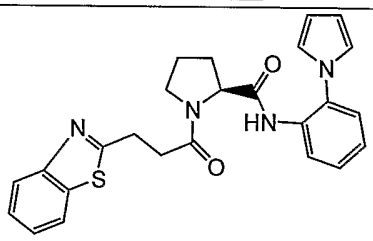
	441.177	N-[(1S)-1-(4-fluorophenyl)ethyl]-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide
	457.1476	N-[(1S)-1-(4-chlorophenyl)ethyl]-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide
	437.2018	1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[(1S)-1-(4-methylphenyl)ethyl]-L-prolinamide
	453.1965	N-[(1S)-1-(3-methoxyphenyl)ethyl]-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide
	468.1706	1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[(1S)-1-(4-nitrophenyl)ethyl]-L-prolinamide

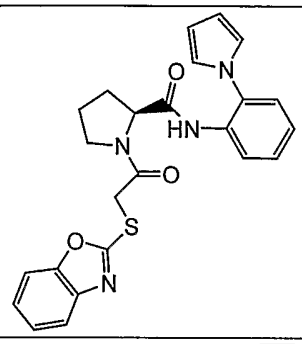
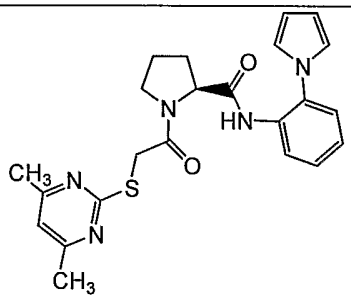
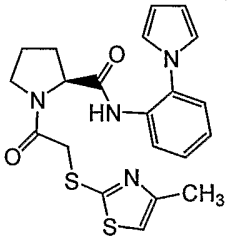
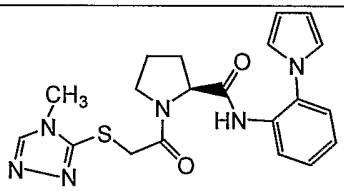
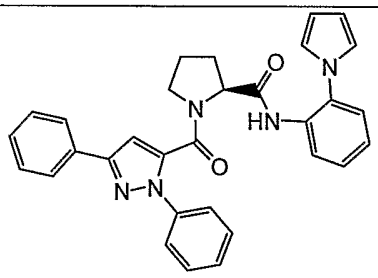
	457.1464	N-[1-(2-chlorophenyl)ethyl]-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide
	405.2301	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-ISOPROPYLPHENYL)-L-PROLINAMIDE
	478.2237	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-[2-(1H-INDOL-2-YL)PHENYL]-L-PROLINAMIDE
	431.1692	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-[2-(TRIFLUOROMETHYL)PHENYL]-L-PROLINAMIDE
	467.2077	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-BENZOYLPHENYL)-L-PROLINAMIDE
	377.1983	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-METHYLPHENYL)-L-PROLINAMIDE
	397.141	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-CHLOROPHENYL)-L-PROLINAMIDE

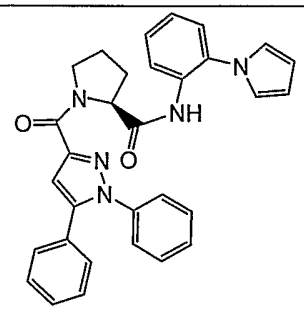
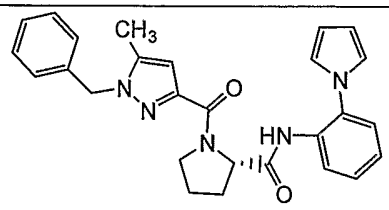
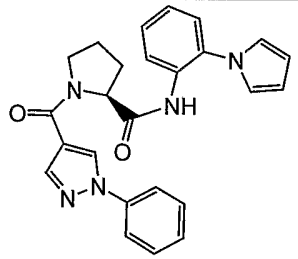
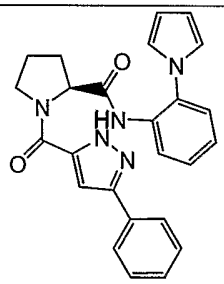
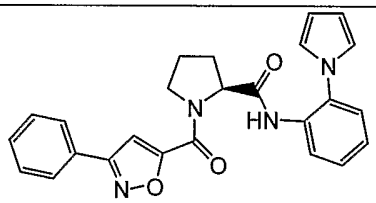
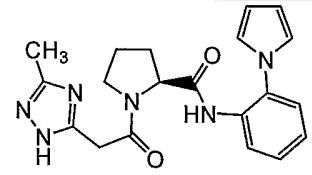
	454.2214	N-(2-ANILINOPHENYL)-1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-L-PROLINAMIDE
	393.1908	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-METHOXYPHENYL)-L-PROLINAMIDE
	453.2277	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-BENZYLPHENYL)-L-PROLINAMIDE
	399.1631	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2,5-DIFLUOROPHENYL)-L-PROLINAMIDE
	447.1923	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-[5-FLUORO-2-(1H-IMIDAZOL-1-YL)PHENYL]-L-PROLINAMIDE
	449.2037	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-[2-(1H-PYRAZOL-1-YL)PHENYL]-L-PROLINAMIDE
	469.2234	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(3'-METHOXY-1,1'-BIPHENYL-2-YL)-L-PROLINAMIDE

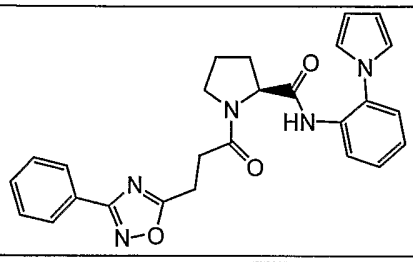
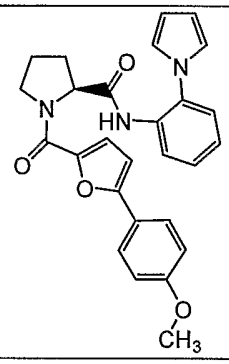
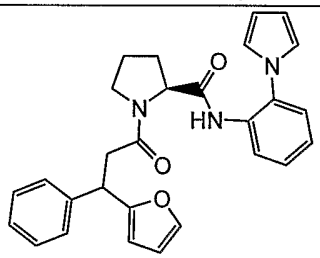
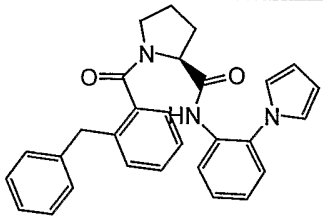
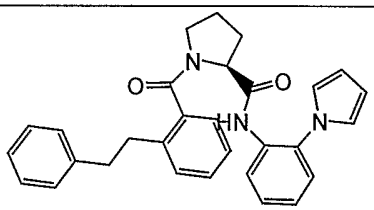
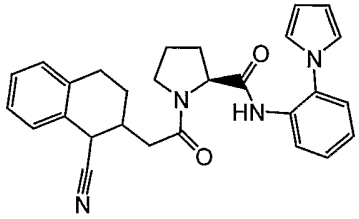
	469.2234	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-[2-(BENZYLOXY)PHENYL]-L-PROLINAMIDE
	379.1765	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-HYDROXYPHENYL)-L-PROLINAMIDE
	440.2081	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-PYRIDIN-3-YLPHENYL)-L-PROLINAMIDE
	440.2034	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2-PYRIMIDIN-5-YLPHENYL)-L-PROLINAMIDE
	457.2034	1-[3-(1H-BENZIMIDAZOL-2-YL)PROPANOYL]-N-(2'-FLUORO-1,1'-BIPHENYL-2-YL)-L-PROLINAMIDE
	453.2235	1-[3-(1H-BENZIMIDAZOL-1-IUM-2-YL)PROPANOYL]-N-(2'-METHYL-1,1'-BIPHENYL-2-YL)-L-PROLINAMIDE
	469.2235	1-[3-(1H-BENZIMIDAZOL-1-IUM-2-YL)PROPANOYL]-N-(2'-METHOXY-1,1'-BIPHENYL-2-YL)-L-PROLINAMIDE

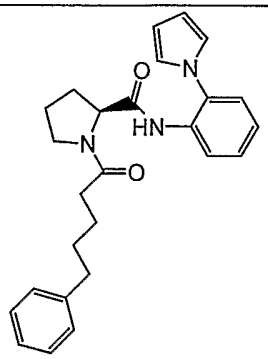
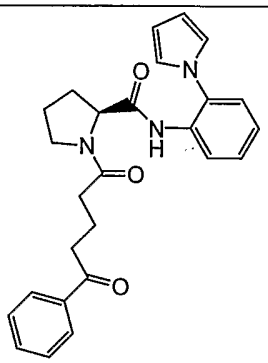
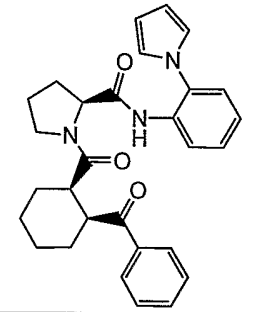
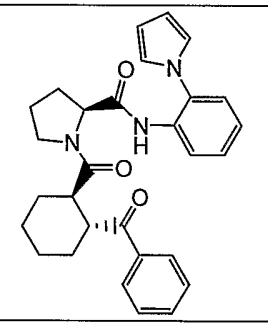
	471.2191	N-(2'-FLUORO-1,1'-BIPHENYL-2-YL)-1-[3-(1-METHYL-1H-BENZIMIDAZOL-2-YL)PROPANOYL]-L-PROLINAMIDE
	484.2332	N-[2-(2-METHOXYPYRIDIN-3-YL)PHENYL]-1-[3-(1-METHYL-1H-BENZIMIDAZOL-2-YL)PROPANOYL]-L-PROLINAMIDE
	525.1419	2-({1-[3-(1-METHYL-1H-BENZIMIDAZOL-2-YL)PROPANOYL]-L-PROLYL}AMINO)PHENYL-TRIFLUOROMETHANESULFONATE
	446.1686	1-[(1H-benzimidazol-2-ylthio)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	428.2069	1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide

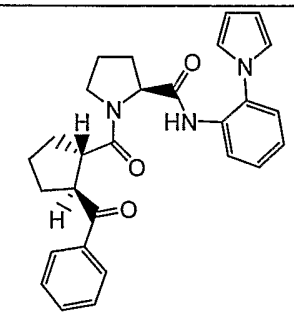
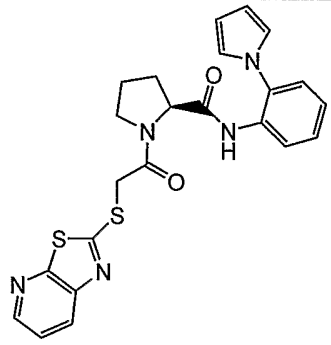
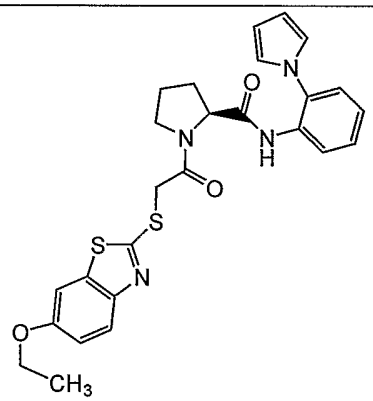
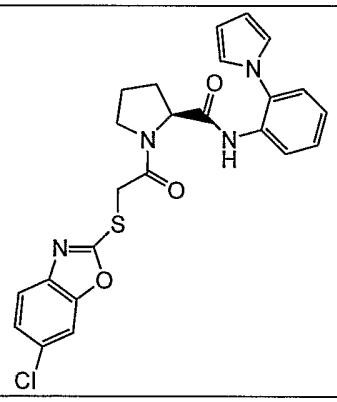
	460.179	1-{[(5-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	460.1793	1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	442.2239	1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	463.1249	1-[(1,3-benzothiazol-2-ylthio)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-D-prolinamide
	489.228	1-[3-(1,3-benzothiazol-2-yl)propanoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide

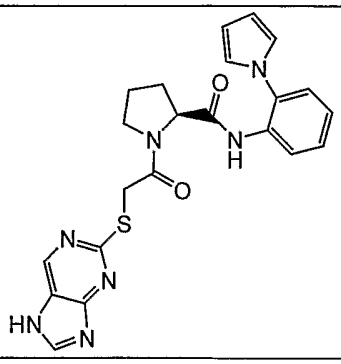
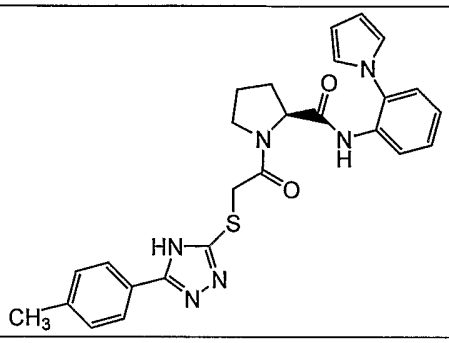
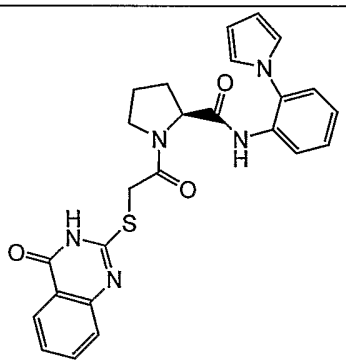
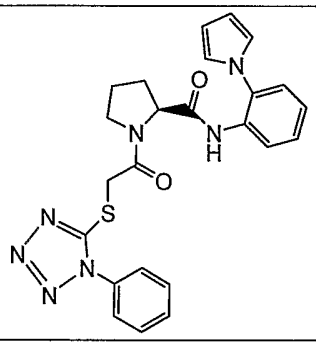
	447.1477	1-[(1,3-benzoxazol-2-ylthio)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	480.2276	1-{[(4,6-dimethylpyrimidin-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	426.1918	1-{[(4-methyl-1,3-thiazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	468.2003	1-{[(4-methyl-4H-1,2,4-triazol-3-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	502.2233	1-[(1,3-diphenyl-1H-pyrazol-5-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide

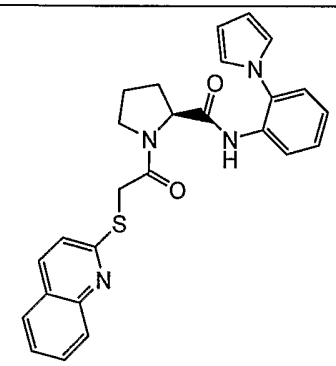
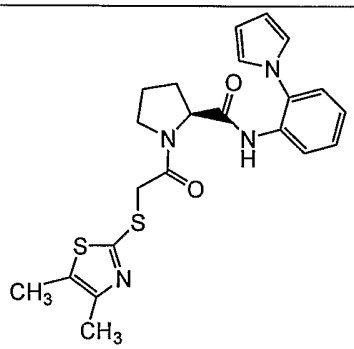
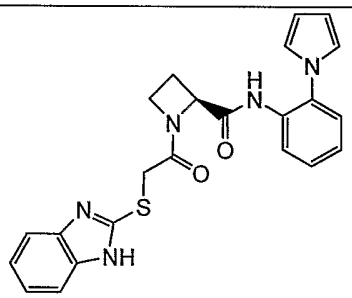
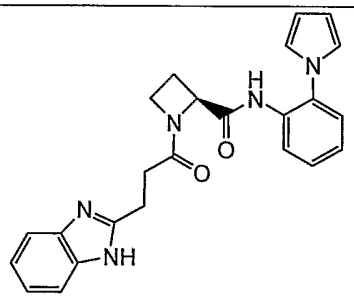
	502.2233	1-[(1,5-diphenyl-1H-pyrazol-3-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	454.2247	1-[(1-benzyl-5-methyl-1H-pyrazol-3-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	426.1935	1-[(1-phenyl-1H-pyrazol-4-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	426.1933	1-[(3-phenyl-1H-pyrazol-5-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	427.1769	1-[(3-phenylisoxazol-5-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	379.1877	1-[(3-methyl-1H-1,2,4-triazol-5-yl)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide

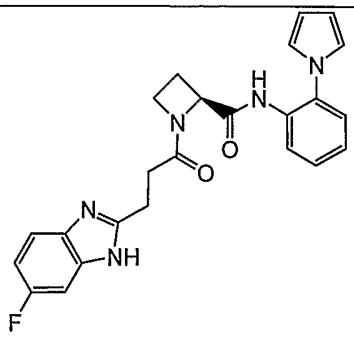
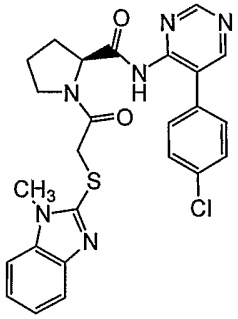
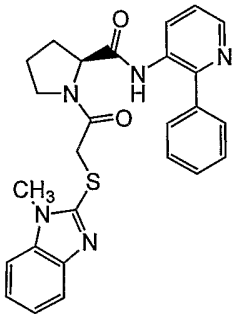
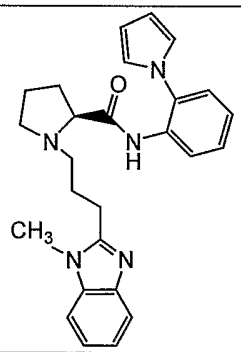
	456.2038	1-[3-(3-phenyl-1,2,4-oxadiazol-5-yl)propanoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	456.1923	N-[2-(divinylamino)phenyl]-1-[5-(4-methoxyphenyl)-2-furoyl]-L-prolinamide
	454.213	1-[3-(2-furyl)-3-phenylpropanoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	450.2171	1-(2-benzylbenzoyl)-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	464.2324	1-[2-(2-phenylethyl)benzoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	453.2281	1-[(1-cyano-1,2,3,4-tetrahydronaphthalen-2-yl)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide

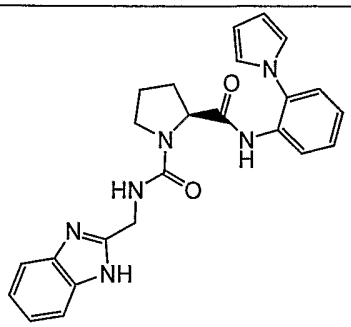
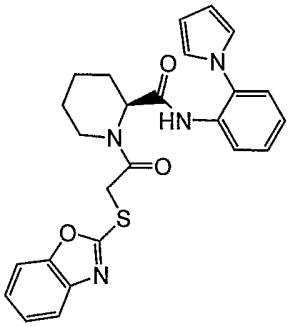
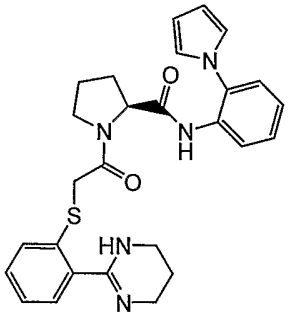
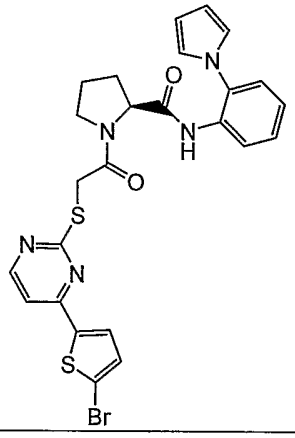
	416.2331	1-(5-PHENYLPENTANOYL)-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	430.2141	1-(5-OXO-5-PHENYLPENTANOYL)-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	470.2433	1-{[(1R,2S)-2-benzoylcyclohexyl]carbonyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	470.2432	1-{[(1R,2R)-2-benzoylcyclohexyl]carbonyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide

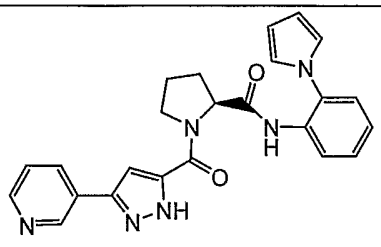
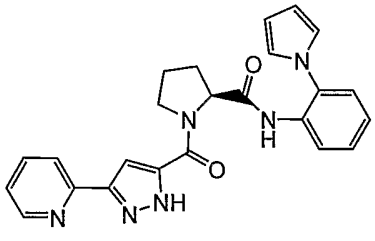
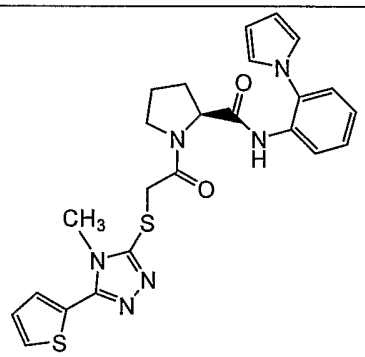
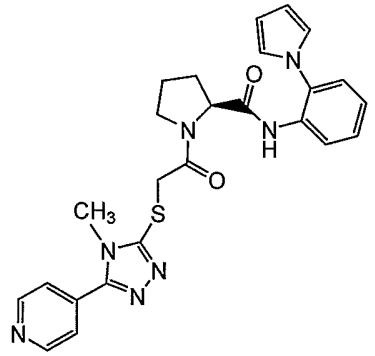
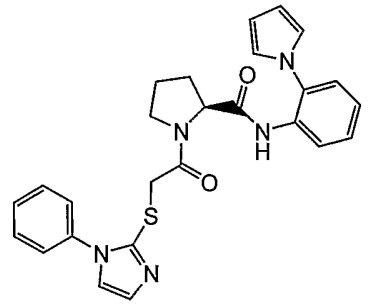
	456.228	1-{[(1S,2S)-2-benzoylcyclopentyl]carbonyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	464.1222	N-[2-(1H-pyrrol-1-yl)phenyl]-1-[([1,3]thiazolo[5,4-b]pyridin-2-ylthio)acetyl]-L-prolinamide
	529.1327	1-{[(6-ethoxy-1,3-benzothiazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	481.1095	1-{[(6-chloro-1,3-benzoxazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide

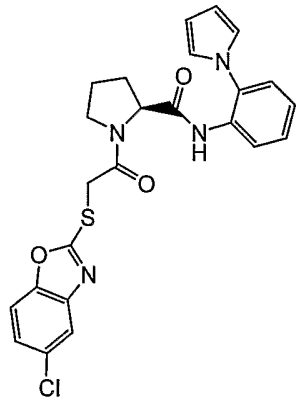
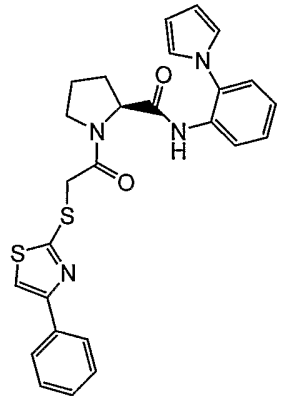
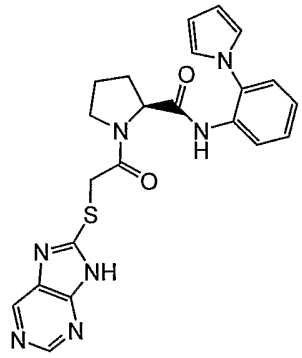
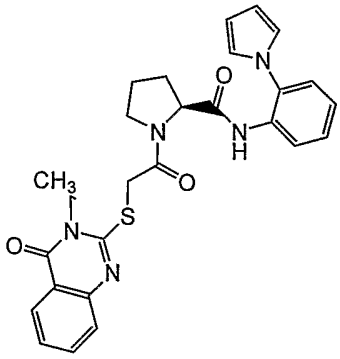
	448.1555	1-[(7H-purin-2-ylthio)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	487.1913	1-({[5-(4-methylphenyl)-4H-1,2,4-triazol-3-yl]thio}acetyl)-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	496.1407[MNa]+	1-{[(4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	474.1715	1-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide

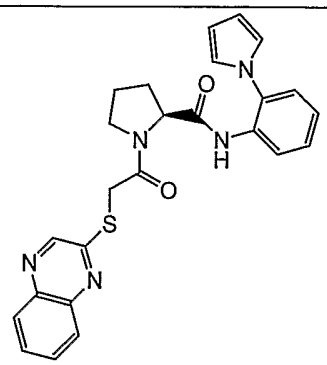
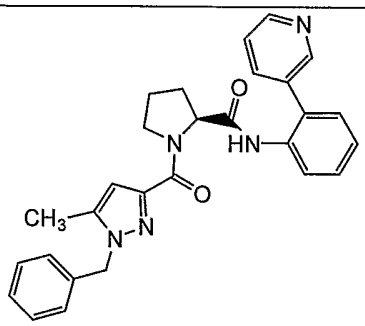
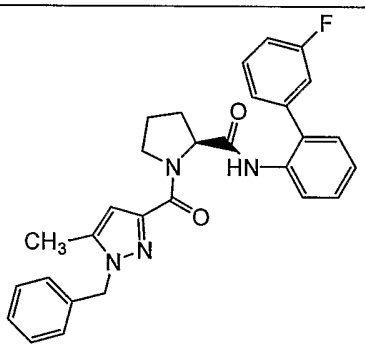
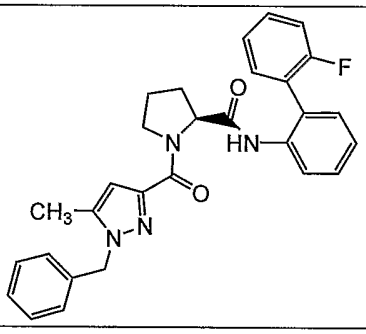
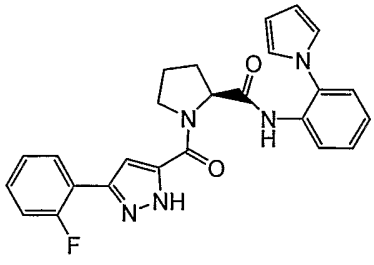
	474.1701	N-[2-(1H-pyrrol-1-yl)phenyl]-1-[(quinolin-2-ylthio)acetyl]-L-prolinamide
	441.1376	1-{[(4,5-dimethyl-1,3-thiazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide
	432.1443	2-({2-oxo-2-[(2S)-2-({[2-(1H-pyrrol-1-yl)phenyl]amino}carbonyl)azetidin-1-yl]ethyl}thio)-1H-3,1-benzimidazol-3-ium
	414.1688	2-{3-oxo-3-[(2S)-2-({[2-(1H-pyrrol-1-yl)phenyl]amino}carbonyl)azetidin-1-yl]propyl}-1H-3,1-benzimidazol-3-ium

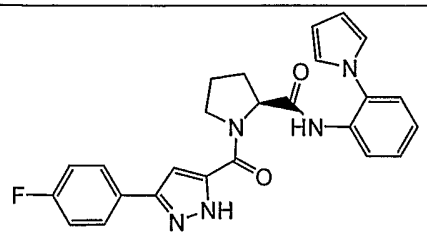
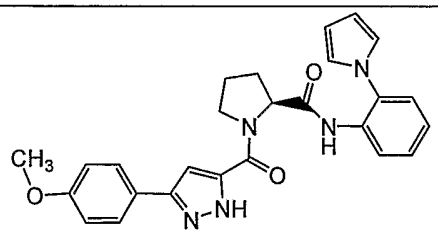
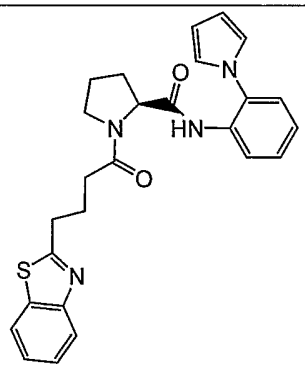
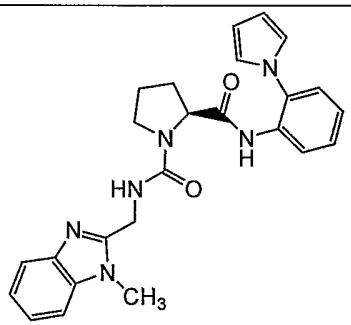
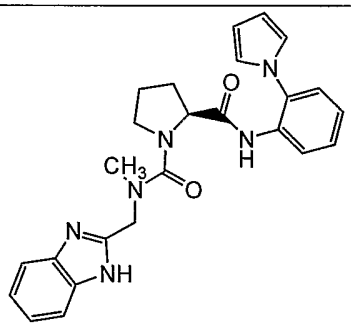
	432.1798	6-fluoro-2-{3-oxo-3-[(2S)-2-({[2-(1H-pyrrol-1-yl)phenyl]amino}carbonyl)azetidin-1-yl]propyl}-1H-3,1-benzimidazol-3-ium
	507.1374	N-[5-(4-chlorophenyl)pyrimidin-4-yl]-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide
	472.1744	1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(2-phenylpyridin-3-yl)-L-prolinamide
	428.2453	1-[3-(1-methyl-1H-benzimidazol-2-yl)propyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide

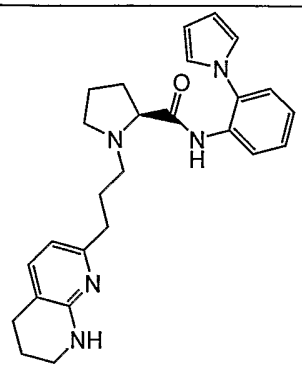
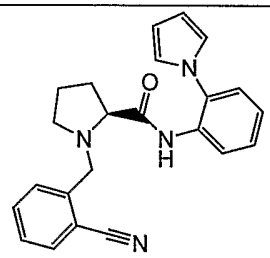
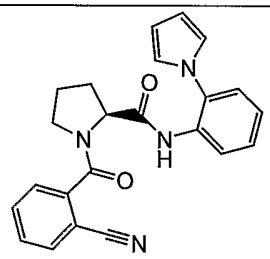
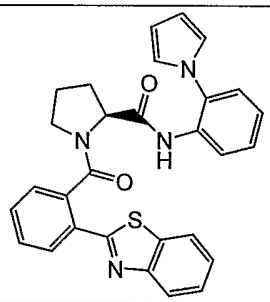
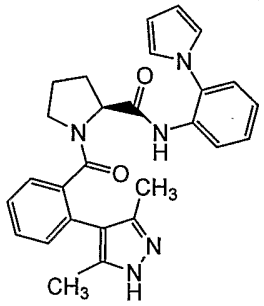
	429.2043	(2S)-N-1-(1H-benzimidazol-2-ylmethyl)-N-2-[2-(1H-pyrrol-1-yl)phenyl]pyrrolidine-1,2-dicarboxamide
	461.164	(2S)-1-[(1,3-BENZOXAZOL-2-YLTHIO)ACETYL]-N-[2-(1H-PYRROL-1-YL)PHENYL]PIPERIDINE-2-CARBOXAMIDE
	488.2108	N-[2-(1H-PYRROL-1-YL)PHENYL]-1-({[2-(1,4,5,6-TETRAHYDROPYRIMIDIN-2-YL)PHENYL]THIO}ACETYL)-L-PROLINAMIDE
	568.0478	1-({[4-(5-BROMOTHIEN-2-YL)PYRIMIDIN-2-YL]THIO}ACETYL)-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE

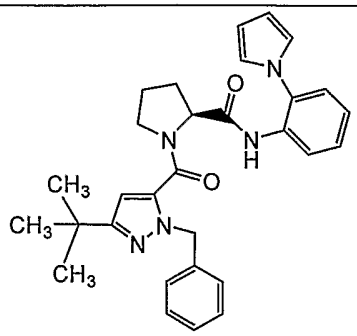
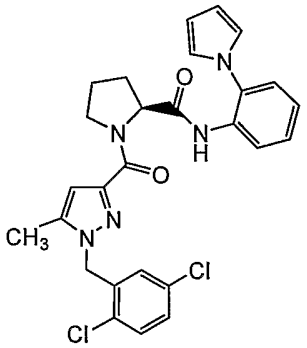
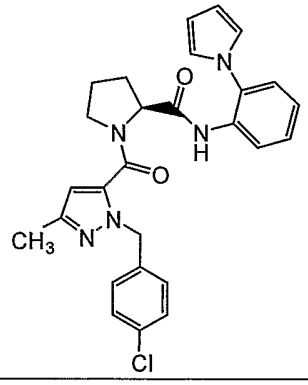
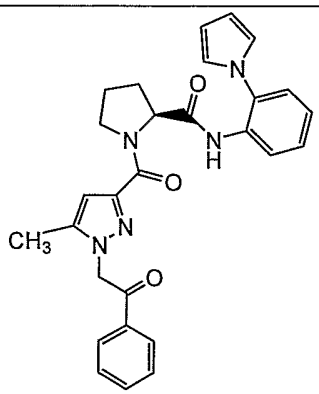
	427.1886	1-[(3-PYRIDIN-3-YL-1H-PYRAZOL-5-YL)CARBONYL]-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	427.1894	1-[(3-PYRIDIN-2-YL-1H-PYRAZOL-5-YL)CARBONYL]-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	492.1476	1-{[(4-METHYL-5-THIEN-2-YL-4H-1,2,4-TRIAZOL-3-YL)THIO]ACETYL}-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	487.1869	1-{[(4-METHYL-5-PYRIDIN-4-YL-4H-1,2,4-TRIAZOL-3-YL)THIO]ACETYL}-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	471.181	1-{[(1-PHENYL-1H-IMIDAZOL-2-YL)THIO]ACETYL}-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE

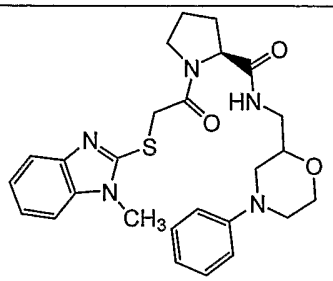
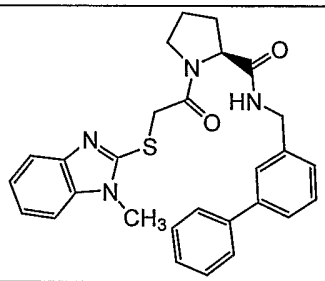
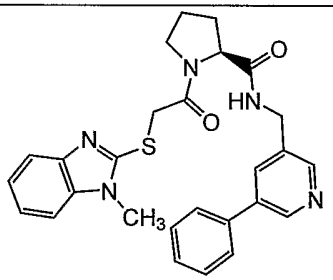
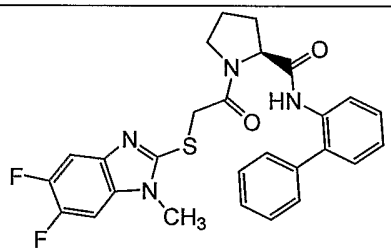
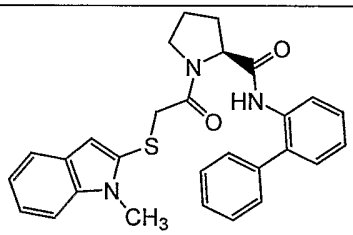
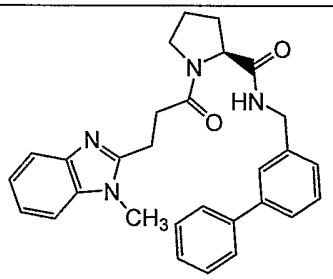
	480.11	1-{[(5-CHLORO-1,3-BENZOXAZOL-2-YL)THIO]ACETYL}-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	488.1413	1-{[(4-PHENYL-1,3-THIAZOL-2-YL)THIO]ACETYL}-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	447.1556	1-[(9H-PURIN-8-YLTHIO)ACETYL]-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	502.1954	1-{[(3-ETHYL-4-OXO-3,4-DIHYDROQUINAZOLIN-2-YL)THIO]ACETYL}-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE

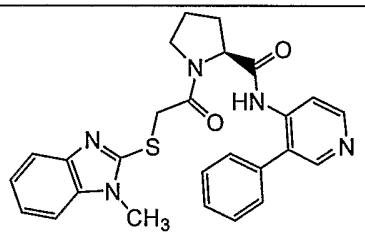
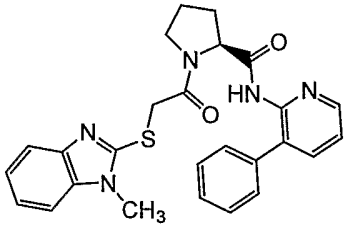
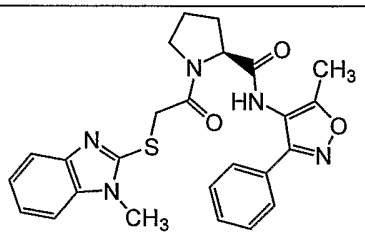
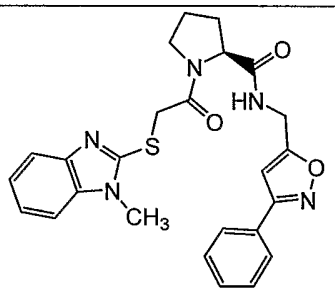
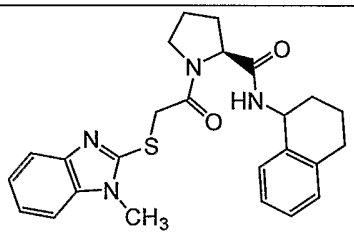
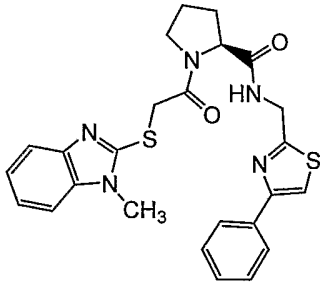
	458.1665	N-[2-(1H-PYRROL-1-YL)PHENYL]-1-[(QUINOXALIN-2-YLTHIO)ACETYL]-L-PROLINAMIDE
	466.2213	1-[(1-BENZYL-5-METHYL-1H-PYRAZOL-3-YL)CARBONYL]-N-(2-PYRIDIN-3-YLPHENYL)-L-PROLINAMIDE
	483.2181	1-[(1-BENZYL-5-METHYL-1H-PYRAZOL-3-YL)CARBONYL]-N-(3'-FLUORO-1,1'-BIPHENYL-2-YL)-L-PROLINAMIDE
	483.2175	1-[(1-BENZYL-5-METHYL-1H-PYRAZOL-3-YL)CARBONYL]-N-(2'-FLUORO-1,1'-BIPHENYL-2-YL)-L-PROLINAMIDE
	444.1836	1-{[3-(2-FLUOROPHENYL)-1H-PYRAZOL-5-YL]CARBONYL}-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE

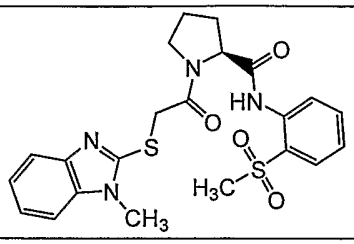
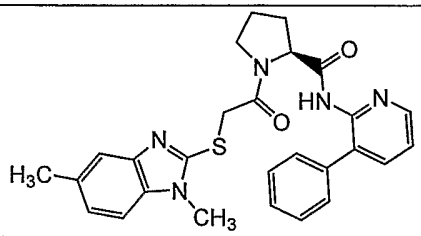
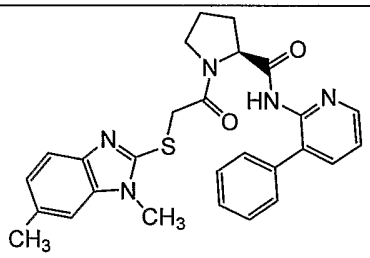
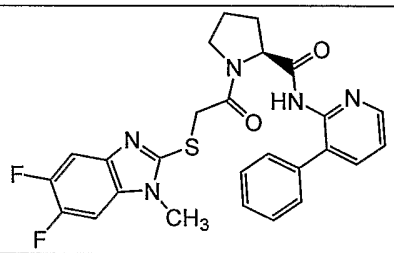
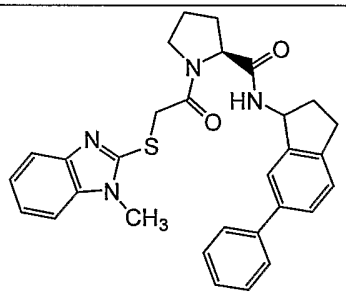
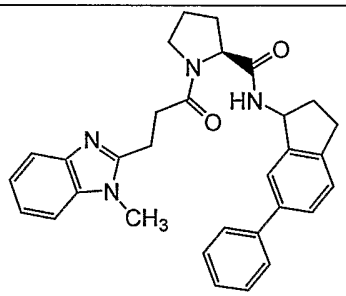
	444.1834	1-{[3-(4-FLUOROPHENYL)-1H-PYRAZOL-5-YL]CARBONYL}-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	456.2063	1-{[3-(4-METHOXYPHENYL)-1H-PYRAZOL-5-YL]CARBONYL}-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	459.1827	1-[4-(1,3-BENZOTHIAZOL-2-YL)BUTANOYL]-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	443.2173	(2S)-N-1-[(1-METHYL-1H-BENZIMIDAZOL-2-YL)METHYL]-N-2-[2-(1H-PYRROL-1-YL)PHENYL]PYRROLIDINE-1,2-DICARBOXAMIDE
	443.2166	(2S)-N-1-(1H-BENZIMIDAZOL-2-YLMETHYL)-N-1-METHYL-N-2-[2-(1H-PYRROL-1-YL)PHENYL]PYRROLIDINE-1,2-DICARBOXAMIDE

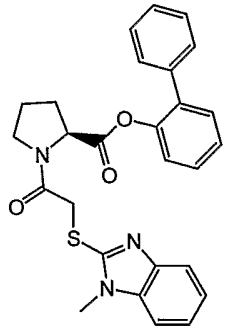
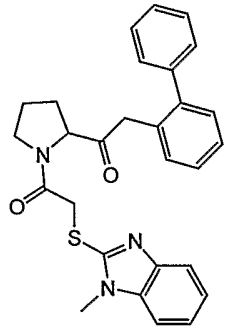
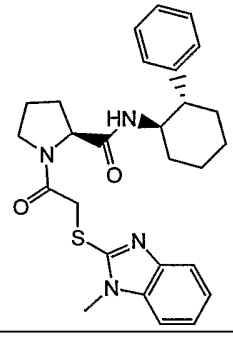
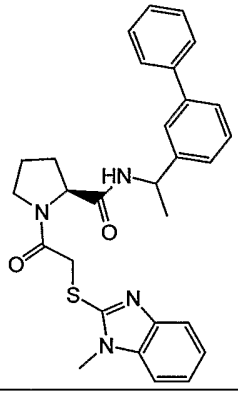
	430.2594	N-[2-(1H-PYRROL-1-YL)PHENYL]-1-[3-(5,6,7,8-TETRAHYDRO-1,8-NAPHTHYRIDIN-2-YL)PROPYL]-L-PROLINAMIDE
	371.1868	1-(2-CYANOBENZYL)-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	385.166	1-(2-CYANOBENZOYL)-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	493.1691	1-[2-(1,3-BENZOTHIAZOL-2-YL)BENZOYL]-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	454.2241	1-[2-(3,5-DIMETHYL-1H-PYRAZOL-4-YL)BENZOYL]-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE

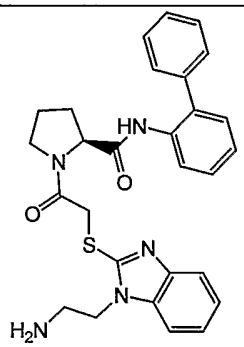
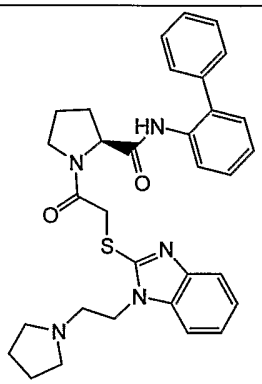
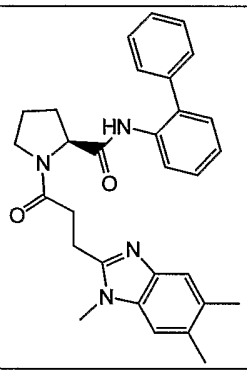
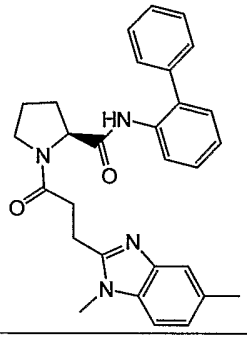
	496.2721	1-[(1-BENZYL-3-TERT-BUTYL-1H-PYRAZOL-5-YL)CARBONYL]-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	522.1468	1-{[1-(2,5-DICHLOROBENZYL)-5-METHYL-1H-PYRAZOL-3-YL]CARBONYL}-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	488.1867	1-{[1-(4-CHLOROBENZYL)-3-METHYL-1H-PYRAZOL-5-YL]CARBONYL}-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE
	482.2188	1-{[5-METHYL-1-(2-OXO-2-PHENYLETHYL)-1H-PYRAZOL-3-YL]CARBONYL}-N-[2-(1H-PYRROL-1-YL)PHENYL]-L-PROLINAMIDE

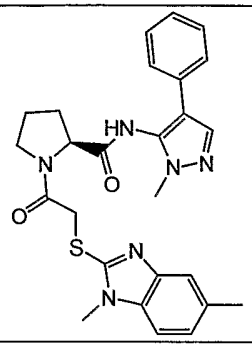
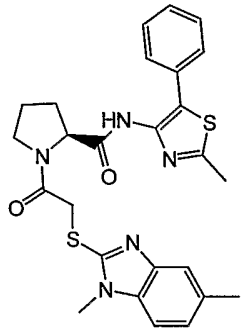
	494.2243	1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-[(4-phenylmorpholin-2-yl)methyl]-L-prolinamide
	485.2015	*N*-(biphenyl-3-ylmethyl)-1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-L-prolinamide
	486.1962	1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-[(5-phenylpyridin-3-yl)methyl]-L-prolinamide
	507.1675	*N*-biphenyl-2-yl-1-{[(5,6-difluoro-1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-L-prolinamide
	470.1904	*N*-biphenyl-2-yl-1-{[(1-methyl-1*H*-indol-2-yl)thio]acetyl}-L-prolinamide
	467.2427	*N*-(biphenyl-3-ylmethyl)-1-[3-(1-methyl-1*H*-benzimidazol-2-yl)propanoyl]-L-prolinamide

	472.1804	1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-(3-phenylpyridin-4-yl)-L-prolinamide
	472.1792	1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-(3-phenylpyridin-2-yl)-L-prolinamide
	476.1737	1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-(5-methyl-3-phenylisoxazol-4-yl)-L-prolinamide
	476.1756	1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-[(3-phenylisoxazol-5-yl)methyl]-L-prolinamide
	449.2013	1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-L-prolinamide
	492.1513	1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-[(4-phenyl-1,3-thiazol-2-yl)methyl]-L-prolinamide

	473.1314	1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-[2-(methylsulfonyl)phenyl]-L-prolinamide
	486.1962	1-{[(1,5-dimethyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-(3-phenylpyridin-2-yl)-L-prolinamide
	486.1966	1-{[(1,6-dimethyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-(3-phenylpyridin-2-yl)-L-prolinamide
	508.1636	1-{[(5,6-difluoro-1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-(3-phenylpyridin-2-yl)-L-prolinamide
	511.2166	1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-(6-phenyl-2,3-dihydro-1*H*-inden-1-yl)-L-prolinamide
	493.2600	1-[3-(1-methyl-1*H*-benzimidazol-2-yl)propanoyl]-*N*-(6-phenyl-2,3-dihydro-1*H*-inden-1-yl)-L-prolinamide

	472.1690	biphenyl-2-yl 1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-L-prolinate
	470.1901	2-biphenyl-2-yl-1-(1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}pyrrolidin-2-yl)ethanone
	477.2287	1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-[(1*R*,2*S*)-2-phenylcyclohexyl]-L-prolinamide
	499.2170	*N*-(1-biphenyl-3-ylethyl)-1-{[(1-methyl-1*H*-benzimidazol-2-yl)thio]acetyl}-L-prolinamide

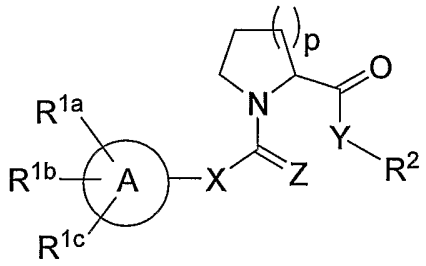
	500.2116	1-({[1-(2-aminoethyl)-1*H*-benzimidazol-2-yl]thio}acetyl)-*N*-biphenyl-2-yl-L-prolinamide
	554.2589	*N*-biphenyl-2-yl-1-({[1-(2-pyrrolidin-1-ylethyl)-1*H*-benzimidazol-2-yl]thio}acetyl)-L-prolinamide
	481.2600	*N*-biphenyl-2-yl-1-[3-(1,5,6-trimethyl-1*H*-benzimidazol-2-yl)propanoyl]-L-prolinamide
	467.2452	*N*-biphenyl-2-yl-1-[3-(1,5-dimethyl-1*H*-benzimidazol-2-yl)propanoyl]-L-prolinamide

	489.2050	1-{[(1,5-dimethyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-(1-methyl-4-phenyl-1*H*-pyrazol-5-yl)-L-prolinamide
	506.1658	1-{[(1,5-dimethyl-1*H*-benzimidazol-2-yl)thio]acetyl}-*N*-(2-methyl-5-phenyl-1,3-thiazol-4-yl)-L-prolinamide

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



A is selected from the group consisting of phenyl, napthyl and heteroaryl;
X is selected from -S-CH_2-, -CH_2-S-, -CH_2-, -CH_2CH_2-, -CH=CH-, -$CH_2CH_2CH_2$-, -O-CH_2-, -CH_2-O-, -(CO)-cyclohexyl-, -NH-CH_2-, -CH_2-NH-, -$CH_2N(C_{1-6}alkyl)$-, -$N(C_{1-6}alkyl)CH_2$-, -$CH_2N(C_{3-6}cycloalkyl)$-, -$N(C_{3-6}cycloalkyl)CH_2$-, -$S(O)CH_2$-, -$S(O)_2CH_2$-, -C≡C-, and a bond;
Y is selected from -NH-, -$N(C_{1-6}alkyl)$-, -$N(C_{3-6}cycloalkyl)$-, -CH_2-, -$CH(C_{1-6}alkyl)$- and -O-;
Z is selected from O and H,H;
p is 0, 1, 2 or 3;
R^{1a}, R^{1b} and R^{1c} may be absent if the valency of A does not permit such substitution and are independently selected from the group consisting of:

(1) hydrogen,
(2) halogen,
(3) hydroxyl,
(4) -$(C=O)_m$-O_n-C_{1-6}alkyl, where m is 0 or 1, n is 0 or 1 (wherein if m is 0 or n is 0, a bond is present) and where the alkyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(5) -$(C=O)_m$-O_n-C_{3-6}cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(6) -$(C=O)_m$-C_{2-4}alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(7) -$(C=O)_m$-O_n-phenyl or -$(C=O)_m$-O_n-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(8) -$(C=O)_m$-O_n-heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{13},

(9) -$(C=O)_m$-$NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently selected from the group consisting of:
  (a) hydrogen,
  (b) C_{1-6}alkyl, which is unsubstituted or substituted with R^{13},
  (c) C_{3-6}alkenyl, which is unsubstituted or substituted with R^{13},
  (d) C_{3-6}cycloalkyl which is unsubstituted or substituted with R^{13},
  (e) phenyl, which is unsubstituted or substituted with R^{13}, and
  (f) heterocycle, which is unsubstituted or substituted with R^{13},
(10) -$S(O)_2$-$NR^{10}R^{11}$,
(11) -$S(O)_q$-R^{12}, where q is 0, 1 or 2 and where R^{12} is selected from the definitions of R^{10} and R^{11},
(12) -CO_2H,
(13) -CN, and
(14) -NO_2;

R^2 is selected from the group consisting of:
(1) -phenyl, which is substituted with R^{7a}, R^{7b} and R^{7c},
(2) -heterocycle, which is substituted with R^{7a}, R^{7b} and R^{7c},
(3) C_{1-6}alkyl, which is unsubstituted or substituted with one or more substituents selected from R^{13}, and
(4) C_{3-6}cycloalkyl, which may be fused to a phenyl ring and which is unsubstituted or substituted with one or more substituents selected from R^{13};

R^{7a}, R^{7b} and R^{7c} may be absent if the valency of the group to which they are attached does not permit such substitution and are independently selected from the group consisting of:
(1) hydrogen,
(2) halogen,
(3) hydroxyl,
(4) -$(C=O)_m$-O_n-C_{1-6}alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(5) -$(C=O)_m$-O_n-C_{3-6}cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(6) -$(C=O)_m$-C_{2-4}alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(7) -$(C=O)_m$-O_n-phenyl or -$(C=O)_m$-O_n-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(8) -$(C=O)_m$-O_n-heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{13},

(9) -$(C=O)_m$-$NR^{10}R^{11}$,

(10) -$S(O)_2$-$NR^{10}R^{11}$,

(11) -$S(O)_q$-R^{12},

(12) -CO_2H,

(13) -CN, and

(14) -NO_2;

R^{13} is selected from the group consisting of:

(1) halogen,

(2) hydroxyl,

(3) -$(C=O)_m$-O_n-C_{1-6}alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R^{14},

(4) -O_n-(C_{1-3})perfluoroalkyl,

(5) -$(C=O)_m$-O_n-C_{3-6}cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R^{14},

(6) -$(C=O)_m$-C_{2-4}alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R^{14},

(7) -$(C=O)_m$-O_n-phenyl or -$(C=O)_m$-O_n-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents selected from R^{14},

(8) -$(C=O)_m$-O_n-heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{14},

(9) -$(C=O)_m$-$NR^{10}R^{11}$,

(10) -$S(O)_2$-$NR^{10}R^{11}$,

(11) -$S(O)_q$-R^{12},

(12) -CO_2H,

(13) -CN, and

(14) -NO_2;

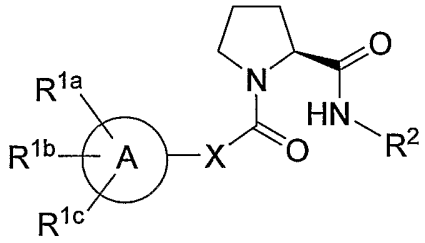
R^{14} is selected from the group consisting of:

(1) hydroxyl,

(2) halogen,
(3) C_{1-6}alkyl,
(4) -C_{3-6}cycloalkyl,
(5) -O-C_{1-6}alkyl,
(6) -O(C=O)-C_{1-6}alkyl,
(7) -NH-C_{1-6}alkyl,
(8) phenyl,
(9) heterocycle,
(10) -CO_2H, and
(11) -CN;

or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

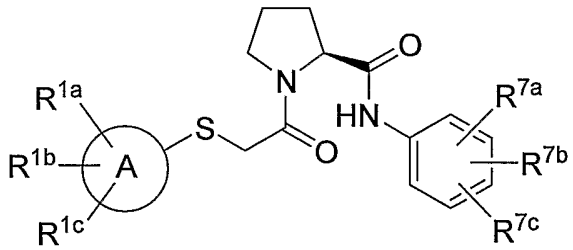
2. The compound of Claim 1 of the formula Ia:



Ia

or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

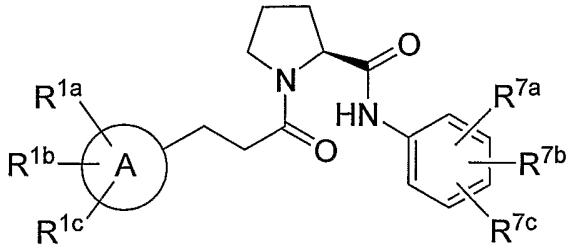
3. The compound of Claim 1 of the formula Ib:



Ib

or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

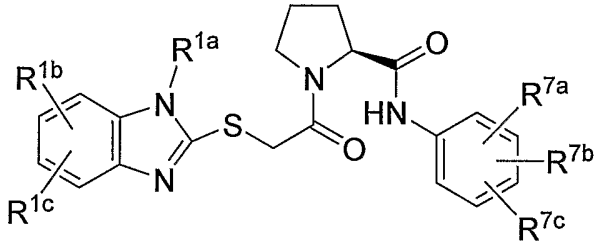
4. The compound of Claim 1 of the formula Ic:



Ic

or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

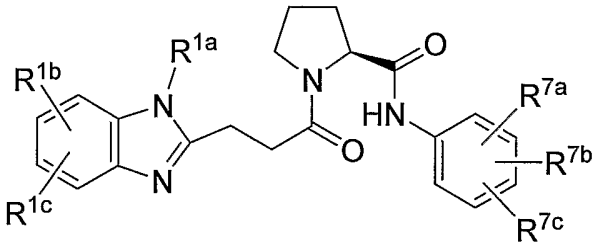
5. The compound of Claim 1 of the formula Id:



Id

or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

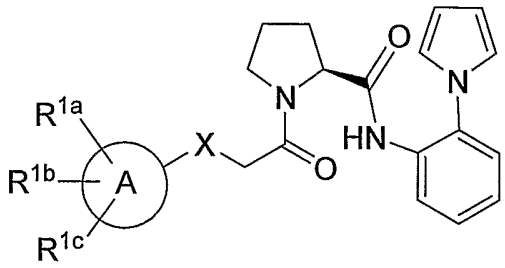
6. The compound of Claim 1 of the formula Ie:



Ie

or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

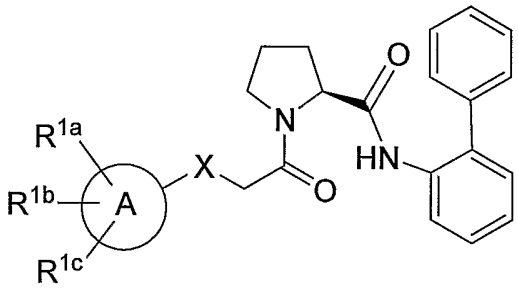
7. The compound of Claim 1 of the formula If:



If

or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

8. The compound of Claim 1 of the formula Ig:



Ig

or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

9. The compound of Claim 1 wherein p is 1.

10. The compound of Claim 1 wherein X is -S-CH_2- or -CH_2CH_2-.

11. The compound of Claim 1 wherein Y is -NH-.

12. The compound of Claim 1 wherein Z is -O-.

13. The compound of Claim 1 wherein A is selected from the group consisting of benzimidazole, N-methylbenzimidazole, benzthiazole and benzoxazole.

14. The compound of Claim 1 wherein A is benzimidazole , R^{1a} is hydrogen or C_{1-6}alkyl, R^{1b} is hydrogen and R^{1c} is hydrogen.

15. The compound of Claim 1 wherein R^2 is phenyl or pyridyl which is substituted with R^{7a}, R^{7b} and R^{7c}.

16. The compound of Claim 1 wherein R^{7a}, R^{7b} and R^{7c} are independently selected from the group consisting of:

(1) hydrogen,
(2) halogen,
(3) hydroxyl,
(4) C_{1-6}alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl or napthyl,
(5) -O-C_{1-6}alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl,
(6) heteroaryl, wherein heteroaryl is selected from pyrrolyl, imidazolyl, indolyl, pyridyl, and pyrimidinyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl or-NO_2,
(7) phenyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl or-NO_2,
(8) -O-phenyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl or-NO_2, and
(9) -NH-phenyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl or-NO_2.

17. The compound of Claim 1 wherein R^{7b} is hydrogen, R^{7c} is hydrogen and R^{7a} is selected from the group consisting of:

(1) 2-phenyl,
(2) 2-pyrrole, and
(3) 2-(3-pyridyl).

18. The compound of Claim 1 wherein R^2 is phenyl which is substituted with pyrrolyl.

19. A compound which is selected from the group consisting of:
N-(1,1'-biphenyl-2-yl)-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide;
N-(2,2-difluoro-1-phenylethyl)-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide;
N-[2-(2-methoxypyridin-3-yl)phenyl]-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;

(2S)-N-1-(1H-benzimidazol-2-ylmethyl)-N-2-[2-(1H-pyrrol-1-yl)phenyl]pyrrolidine-1,2-dicarboxamide;
1-{[(1-phenyl-1H-tetraazol-5-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[3-(1-methyl-1H-benzimidazol-2-yl)propyl]-N-[2-(1H-pyrrol-1yl)phenyl]-L-prolinamide;
2-(1H-pyrrol-1-yl)phenyl-1-[(1H-benzimidazol-2-ylthio)acetyl]-L-prolinate;
N-biphenyl-2-yl-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide;
2-biphenyl-2-yl-1-(1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}pyrrolidin-2-yl)ethanone;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-biphenyl-2-yl-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-piperidin-1-ylphenyl)-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-morpholin-4-ylphenyl)-L-prolinamide;
1-[(1H-benzimidazol-2-ylthio)acetyl]-N-biphenyl-3-yl-L-prolinamide;
1-[(1H-benzimidazol-2-ylthio)acetyl]-N-biphenyl-4-yl-L-prolinamide;
1-[(1H-benzimidazol-2-ylthio)acetyl]-N-(2-phenoxyphenyl)-L-prolinamide;
1-[(1H-benzimidazol-2-ylthio)acetyl]-N-[2-(2,5-dimethyl-1H-pyrrol-1-yl)phenyl]-L-prolinamide;
N-biphenyl-2-yl-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide;
N-[2-(benzyloxy)phenyl]-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(2-pyridin-3-ylphenyl)-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-isopropylphenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[2-(1H-indol-2-yl)phenyl]-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[2-(trifluoromethyl)phenyl]-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-benzoylphenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-methylphenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-chlorophenyl)-l-prolinamide;
N-(2-anilinophenyl)-1-[3-(1H-benzimidazol-2-yl)propanoyl]-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-methoxyphenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-benzylphenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2,5-difluorophenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[5-fluoro-2-(1H-imidazol-1-yl)phenyl]-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[2-(1H-pyrazol-1-yl)phenyl]-l-prolinamide;
1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-N-(5-methyl-3-phenylisoxazol-4-yl)-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(1-oxo-2-phenyl-1H-inden-3-yl)-L-prolinamide;
N-(2'-fluorobiphenyl-2-yl)-1-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl}-L-prolinamide;
N-(3'-fluorobiphenyl-2-yl)-1-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl}-L-prolinamide;
N-(2'-methoxybiphenyl-2-yl)-1-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl}-L-prolinamide;
1-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl}-N-(2-pyridin-3-ylphenyl)-L-prolinamide;
N-biphenyl-2-yl-N-methyl-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide;

1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[2-(1-methylpyrrolidinium-2-yl)ethyl]-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,3-dihydro-1H-inden-1-yl)-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(1-naphthylmethyl)-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(1,2-diphenylethyl)-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,2-diphenylethyl)-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,2-diphenylethyl)-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2-bromobenzyl)-L-prolinamide;
N-[2-({1-[3-(1H-benzimidazol-2-yl)propanoyl]-L-prolyl}amino)ethyl]-N-isopropylpropan-2-aminium;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(3,3-diphenylpropyl)-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(3,4-dichlorobenzyl)-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-[(1S,2R)-2-phenylcyclopropyl]-L-prolinamide;
N-1-adamantyl-1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(1-benzylpiperidinium-4-yl)-L-prolinamide;
N-beta-8(14),9(11),12-trien-18-yl-1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(3,4,5-trimethoxybenzyl)-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-[2-(difluoromethoxy)benzyl]-L-prolinamide;
4-{1-[3-(1H-benzimidazol-2-yl)propanoyl]-L-prolyl}-1-(2-fluoro-phenyl)piperazin-1-ium;
4-{1-[3-(1H-benzimidazol-2-yl)propanoyl]-L-prolyl}-1-(1,3-benzodioxol-5-ylmethyl)piperazin-1-ium;
1-{1-[3-(1H-benzimidazol-2-yl)propanoyl]-L-prolyl}-4-hydroxy-4-phenyl-piperidin-1-ium;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,3-dimethoxybenzyl)-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,3-dimethoxybenzyl)-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,3-dimethoxybenzyl)-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,3-dimethoxybenzyl)-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[(4-benzylmorpholin-4-ium-2-yl)methyl]-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[(4-benzylmorpholin-4-ium-2-yl)methyl]-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-[2-(1-oxo-4-phenylphthalazin-2(1H)-yl)ethyl]-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-methyl-N-[(5-phenyl-1H-pyrazol-3-yl)methyl]-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(diphenylmethyl)-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(diphenylmethyl)-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-piperidinium-1-yl-2-pyridin-3-ylethyl)-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-morpholin-4-ium-4-yl-2-pyridin-3-ylethyl)-L-prolinamide;
1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(spiro[2.5]oct-1-ylmethyl)-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[(3S,4R)-3-benzyl-1-methylpiperidinium-4-yl]-L-prolinamide;

1-[3-(1H-3,1-benzimidazol-3-ium-2-yl)propanoyl]-N-(2,2-difluoro-1-phenylethyl)-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-benzyl-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(tert-butyl)-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-methoxy-N-methyl-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-methoxy-N-methyl-L-prolinamide;
1-[(1H-benzimidazol-2-ylthio)acetyl]-N-[(1R)-1-phenylethyl]-L-prolinamide;
1-[(1H-benzimidazol-2-ylthio)acetyl]-N-[(1S)-1-phenylethyl]-L-prolinamide;
1-[(1H-benzimidazol-2-ylthio)acetyl]-N-(diphenylmethyl)-L-prolinamide;
1-[(1H-benzimidazol-2-ylthio)acetyl]-N-(1,2-diphenylethyl)-L-prolinamide;
N-(2,2-difluoro-1-phenylethyl)-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide;
N-(diphenylmethyl)-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[(1S)-1-phenylethyl]-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[(1S)-1-phenylethyl]-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(1-phenylpropyl)-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(1-phenylpropyl)-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(2,2,2-trifluoro-1-pyridin-3-ylethyl)-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(2,2,2-trifluoro-1-pyridin-2-ylethyl)-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(2,2,2-trifluoro-1-pyridin-2-ylethyl)-L-prolinamide;
1-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl}-N-(2,2,2-trifluoro-1-pyridin-3-ylethyl)-L-prolinamide;
1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-N-(2,2,2-trifluoro-1-pyridin-3-ylethyl)-L-prolinamide;
N-[(1S)-1-(4-fluorophenyl)ethyl]-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide;
N-[(1S)-1-(4-chlorophenyl)ethyl]-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[(1S)-1-(4-methylphenyl)ethyl]-L-prolinamide;
N-[(1S)-1-(3-methoxyphenyl)ethyl]-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[(1S)-1-(4-nitrophenyl)ethyl]-L-prolinamide;
N-[1-(2-chlorophenyl)ethyl]-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-isopropylphenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[2-(1H-indol-2-yl)phenyl]-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[2-(trifluoromethyl)phenyl]-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-benzoylphenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-methylphenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-chlorophenyl)-l-prolinamide;
N-(2-anilinophenyl)-1-[3-(1H-benzimidazol-2-yl)propanoyl]-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-methoxyphenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-benzylphenyl)-l-prolinamide;

1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2,5-difluorophenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[5-fluoro-2-(1H-imidazol-1-yl)phenyl]-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[2-(1H-pyrazol-1-yl)phenyl]-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(3'-methoxy-1,1'-biphenyl-2-yl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[2-(benzyloxy)phenyl]-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-hydroxyphenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-pyridin-3-ylphenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2-pyrimidin-5-ylphenyl)-l-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-(2'-fluoro-1,1'-biphenyl-2-yl)-l-prolinamide;
1-[3-(1H-benzimidazol-1-ium-2-yl)propanoyl]-N-(2'-methyl-1,1'-biphenyl-2-yl)-l-prolinamide;
1-[3-(1H-benzimidazol-1-ium-2-yl)propanoyl]-N-(2'-methoxy-1,1'-biphenyl-2-yl)-l-prolinamide;
N-(2'-fluoro-1,1'-biphenyl-2-yl)-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-l-prolinamide;
N-[2-(2-methoxypyridin-3-yl)phenyl]-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-l-prolinamide;
2-({1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-l-prolyl}amino)-phenyl-trifluoromethanesulfonate;
1-[(1H-benzimidazol-2-ylthio)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[3-(1H-benzimidazol-2-yl)propanoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-{[(5-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[(1,3-benzothiazol-2-ylthio)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-D-prolinamide;
1-[3-(1,3-benzothiazol-2-yl)propanoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[(1,3-benzoxazol-2-ylthio)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-{[(4,6-dimethylpyrimidin-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-{[(4-methyl-1,3-thiazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-{[(4-methyl-4H-1,2,4-triazol-3-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[(1,3-diphenyl-1H-pyrazol-5-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[(1,5-diphenyl-1H-pyrazol-3-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[(1-benzyl-5-methyl-1H-pyrazol-3-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[(1-phenyl-1H-pyrazol-4-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[(3-phenyl-1H-pyrazol-5-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[(3-phenylisoxazol-5-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[(3-methyl-1H-1,2,4-triazol-5-yl)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[3-(3-phenyl-1,2,4-oxadiazol-5-yl)propanoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
N-[2-(divinylamino)phenyl]-1-[5-(4-methoxyphenyl)-2-furoyl]-L-prolinamide;
1-[3-(2-furyl)-3-phenylpropanoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;

1-(2-benzylbenzoyl)-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[2-(2-phenylethyl)benzoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[(1-cyano-1,2,3,4-tetrahydronaphthalen-2-yl)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-(5-phenylpentanoyl)-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-(5-oxo-5-phenylpentanoyl)-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-{[(1R,2S)-2-benzoylcyclohexyl]carbonyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-{[(1R,2R)-2-benzoylcyclohexyl]carbonyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-{[(1S,2S)-2-benzoylcyclopentyl]carbonyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
N-[2-(1H-pyrrol-1-yl)phenyl]-1-[([1,3]thiazolo[5,4-b]pyridin-2-ylthio)acetyl]-L-prolinamide;
1-{[(6-ethoxy-1,3-benzothiazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-{[(6-chloro-1,3-benzoxazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-[(7H-purin-2-ylthio)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-({[5-(4-methylphenyl)-4H-1,2,4-triazol-3-yl]thio}acetyl)-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-{[(4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
1-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
N-[2-(1H-pyrrol-1-yl)phenyl]-1-[(quinolin-2-ylthio)acetyl]-L-prolinamide;
1-{[(4,5-dimethyl-1,3-thiazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
2-({2-oxo-2-[(2S)-2-({[2-(1H-pyrrol-1-yl)phenyl]amino}carbonyl)azetidin-1-yl]ethyl}thio)-1H-3,1-benzimidazol-3-ium;
2-{3-oxo-3-[(2S)-2-({[2-(1H-pyrrol-1-yl)phenyl]amino}carbonyl)azetidin-1-yl]propyl}-1H-3,1-benzimidazol-3-ium;
6-fluoro-2-{3-oxo-3-[(2S)-2-({[2-(1H-pyrrol-1-yl)phenyl]amino}carbonyl)azetidin-1-yl]propyl}-1H-3,1-benzimidazol-3-ium;
N-[5-(4-chlorophenyl)pyrimidin-4-yl]-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(2-phenylpyridin-3-yl)-L-prolinamide;
1-[3-(1-methyl-1H-benzimidazol-2-yl)propyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide;
(2S)-N-1-(1H-benzimidazol-2-ylmethyl)-N-2-[2-(1H-pyrrol-1-yl)phenyl]pyrrolidine-1,2-dicarboxamide;
(2S)-1-[(1,3-benzoxazol-2-ylthio)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]piperidine-2-carboxamide;
N-[2-(1H-pyrrol-1-yl)phenyl]-1-({[2-(1,4,5,6-tetrahydropyrimidin-2-yl)phenyl]thio}acetyl)-l-prolinamide;
1-({[4-(5-bromothien-2-yl)pyrimidin-2-yl]thio}acetyl)-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-[(3-pyridin-3-yl-1H-pyrazol-5-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-[(3-pyridin-2-yl-1H-pyrazol-5-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-{[(4-methyl-5-thien-2-yl-4h-1,2,4-triazol-3-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;

1-{[(4-methyl-5-pyridin-4-yl-4h-1,2,4-triazol-3-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-{[(1-phenyl-1H-imidazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-{[(5-chloro-1,3-benzoxazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-{[(4-phenyl-1,3-thiazol-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-[(9H-purin-8-ylthio)acetyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-{[(3-ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
N-[2-(1H-pyrrol-1-yl)phenyl]-1-[(quinoxalin-2-ylthio)acetyl]-l-prolinamide;
1-[(1-benzyl-5-methyl-1H-pyrazol-3-yl)carbonyl]-N-(2-pyridin-3-ylphenyl)-l-prolinamide;
1-[(1-benzyl-5-methyl-1H-pyrazol-3-yl)carbonyl]-N-(3'-fluoro-1,1'-biphenyl-2-yl)-l-prolinamide;
1-[(1-benzyl-5-methyl-1H-pyrazol-3-yl)carbonyl]-N-(2'-fluoro-1,1'-biphenyl-2-yl)-l-prolinamide;
1-{[3-(2-fluorophenyl)-1H-pyrazol-5-yl]carbonyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-{[3-(4-fluorophenyl)-1H-pyrazol-5-yl]carbonyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-{[3-(4-methoxyphenyl)-1H-pyrazol-5-yl]carbonyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-[4-(1,3-benzothiazol-2-yl)butanoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
(2S)-N-1-[(1-methyl-1H-benzimidazol-2-yl)methyl]-N-2-[2-(1H-pyrrol-1-yl)phenyl]pyrrolidine-1,2-dicarboxamide;
(2S)-N-1-(1H-benzimidazol-2-ylmethyl)-N-1-methyl-N-2-[2-(1H-pyrrol-1-yl)phenyl]pyrrolidine-1,2-dicarboxamide;
N-[2-(1H-pyrrol-1-yl)phenyl]-1-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-l-prolinamide;
1-(2-cyanobenzyl)-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-(2-cyanobenzoyl)-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-[2-(1,3-benzothiazol-2-yl)benzoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-[2-(3,5-dimethyl-1H-pyrazol-4-yl)benzoyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-[(1-benzyl-3-tert-butyl-1H-pyrazol-5-yl)carbonyl]-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-{[1-(2,5-dichlorobenzyl)-5-methyl-1H-pyrazol-3-yl]carbonyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-{[1-(4-chlorobenzyl)-3-methyl-1H-pyrazol-5-yl]carbonyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-{[5-methyl-1-(2-oxo-2-phenylethyl)-1H-pyrazol-3-yl]carbonyl}-N-[2-(1H-pyrrol-1-yl)phenyl]-l-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[(4-phenylmorpholin-2-yl)methyl]-L-prolinamide;
N-(biphenyl-3-ylmethyl)-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[(5-phenylpyridin-3-yl)methyl]-L-prolinamide;
N-biphenyl-2-yl-1-{[(5,6-difluoro-1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide;
N-biphenyl-2-yl-1-{[(1-methyl-1H-indol-2-yl)thio]acetyl}-L-prolinamide;

N-(biphenyl-3-ylmethyl)-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(3-phenylpyridin-4-yl)-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(3-phenylpyridin-2-yl)-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(5-methyl-3-phenylisoxazol-4-yl)-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[(3-phenylisoxazol-5-yl)methyl]-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[(4-phenyl-1,3-thiazol-2-yl)methyl]-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[2-(methylsulfonyl)phenyl]-L-prolinamide;
1-{[(1,5-dimethyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(3-phenylpyridin-2-yl)-L-prolinamide;
1-{[(1,6-dimethyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(3-phenylpyridin-2-yl)-L-prolinamide;
1-{[(5,6-difluoro-1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(3-phenylpyridin-2-yl)-L-prolinamide;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(6-phenyl-2,3-dihydro-1H-inden-1-yl)-L-prolinamide;
1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-N-(6-phenyl-2,3-dihydro-1H-inden-1-yl)-L-prolinamide
biphenyl-2-yl 1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinate;
2-biphenyl-2-yl-1-(1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}pyrrolidin-2-yl)ethanone;
1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-N-[(1R,2S)-2-phenylcyclohexyl]-L-prolinamide;
N-(1-biphenyl-3-ylethyl)-1-{[(1-methyl-1H-benzimidazol-2-yl)thio]acetyl}-L-prolinamide;
1-({[1-(2-aminoethyl)-1H-benzimidazol-2-yl]thio}acetyl)-N-biphenyl-2-yl-L-prolinamide;
N-biphenyl-2-yl-1-({[1-(2-pyrrolidin-1-ylethyl)-1H-benzimidazol-2-yl]thio}acetyl)-L-prolinamide;
N-biphenyl-2-yl-1-[3-(1,5,6-trimethyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide;
N-biphenyl-2-yl-1-[3-(1,5-dimethyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide;
1-{[(1,5-dimethyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-L-prolinamide;
1-{[(1,5-dimethyl-1H-benzimidazol-2-yl)thio]acetyl}-N-(2-methyl-5-phenyl-1,3-thiazol-4-yl)-L-prolinamide;
or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition which comprises an inert carrier and the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

21. A method for the manufacture of a medicament for antagonizing orexin receptor activity in a mammalian patient comprising combining the compound of Claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutical carrier or diluent.

22. A method for the manufacture of a medicament for treating a sleep disorder in a mammalian patient comprising combining the compound of Claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutical carrier or diluent.

23. A method for the manufacture of a medicament for treating or controlling obesity in a mammalian patient comprising combining the compound of Claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutical carrier or diluent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/19649

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **C07D 403/12**(2006.01)

USPC: 548/306.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 548/306.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database CAS ONLINE on STN, Chem. Abstr., Accession No 1995:218781, REISTAD et al., 'In vitro formation and degradation of 2-amino1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) protein adducts'. Carcinogenesis (1994), 15(11), 2547-52, abstract.	19

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search
03 August 2006 (03.08.2006)

Date of mailing of the international search report
25 AUG 2006

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/19649

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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:

2. ☒ Claims Nos.: 1-18 and 20-23
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:
Please See Continuation Sheet

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 No. III Observations where unity of invention is lacking (Continuation of item 3 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 additional fees, this Authority did not invite payment of any additional fees.
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 and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

] INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/19649

Continuation of Box II Reason 2:
The numerous variables, e.g. (A, X, Y, Z, p, R1a, R1b, R1c, R2, R7a, R7b, R7c, R13, R14, etc.) and their voluminous, complex meanings and their virtual incomprehensible permutations make it impossible to determine the full scope and complete meaning of the claimed subject matter. As presented the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus it is impossible to carry out a meaningful search on same. A search will be carried out on the first discernable invention of claim 19 which is the first listed compound; N-(1,1'-biphenyl-2-yl)-1-{[(1-methyl-1H-benzimidazol-2-yl)thio[acetyl}-L-prolinamide.

Continuation of B. FIELDS SEARCHED Item 3:
CAS ONLINE
STN structure search