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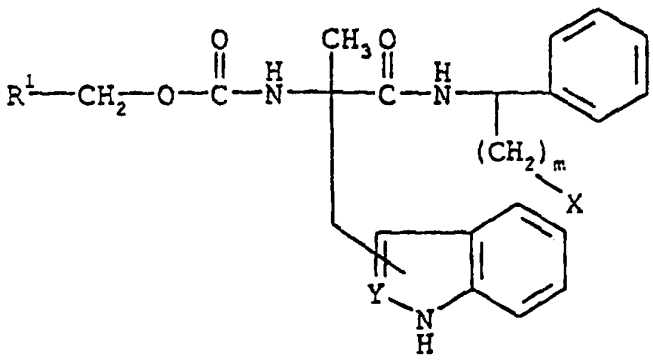
(54) Title: TACHYKININ (NK_1) RECEPTOR ANTAGONISTS

(57) Abstract

A compound of formula (I) or a pharmaceutically acceptable salt thereof wherein: R^1 is phenyl, pyridine, thiophene, furan, naphthalene, indole, benzofuran, or benzothiophene each unsubstituted, mono-, di-, or trisubstituted by alkyl, hydroxy, alkoxy, nitro, halogen, amino, or trifluoromethyl; X is OR^2, wherein R^2 is hydrogen, $(CH_2)_nNR^3R^4$, or a promoiety, or X is NH_2, NHCO-promoiety, $NHCO(CH_2)_nNR^3R^4$, NR^3R^4, or $(CH_2)_nNR^3R^4$ wherein n is an integer of from 0 to 5 and R^3 and R^4 are each independently selected from hydrogen and methyl or R^3 and R^4 form a ring together with the N to which they are attached; m is an integer of from 1 to 6; and Y is CH, CCH_3, CF, CCl, CBr, $CSCH_3$, or N. The invention concerns tachykinin antagonists. The compounds are alcohols, amines and prodrugs of nonpeptides which have utility in treating disorders mediated by tachykinins. Such disorders are respiratory, inflammatory, gastrointestinal, ophthalmic, allergies, pain, vascular, diseases of the central nervous system, and migraine. Methods of preparing compounds and novel intermediates are also included. The compounds are expected to be especially useful in asthma, multiple sclerosis, rheumatoid arthritis, the management of pain, migraine, and antiemetic agents.



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TACHYKININ (NK_1) RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

Over the last decade, major advances have been made in the understanding of the biology of the mammalian tachykinin neuropeptides. It is now well established that substance-P (1), neurokinin A (NKA) (2), and neurokinin B (NKB) (3), all of which share a common C-terminal sequence Phe-X-Gly-Leu-Met-NH_2, (Nakanishi S., Physiol. Rev., 67:117 (1987)), are widely distributed throughout the periphery and central nervous system (CNS) where they appear to interact with at least three receptor types referred to as NK_1, NK_2, and NK_3 (Guard S., et al., Neurosci. Int., 18:149 (1991)). Substance-P displays highest affinity for NK_1 receptors, whereas NKA and NKB bind preferentially to NK_2 and NK_3 receptors, respectively. Recently, all three receptors have been cloned and sequenced and shown to be members of the G-protein-linked "super family" of receptors (Nakanishi S., Annu. Rev. Neurosci., 14:123 (1991)).

Substance-P is the best known of the mammalian tachykinins and has been shown to display preferential affinity for the NK_1 tachykinin receptor (Guard S., Watson S.P., Neurochem. Int., 18:149 (1991)). Substance-P and the other tachykinins are suggested to play a major role in a variety of biological processes including pain transmission, vasodilation, bronchoconstriction, activation of the immune system, and neurogenic inflammation (Maggi C.A., et al., Auton. Pharmacol., 13:23 (1993)).

However, to date, a detailed understanding of the physiological roles of tachykinin neuropeptides has been severely hampered by a lack of selective, high

affinity, metabolically stable tachykinin receptor antagonists that possess both good bioavailability and CNS penetration. Although several tachykinin receptor antagonists have been described (Tomczuk B.E., et al., Current Opinions in Therapeutic Patents, 1:197 (1991)), most have been developed through the modification and/or deletion of one or more of the amino acids that comprise the endogenous mammalian tachykinins such that the resulting molecules are still peptides that possess poor pharmacokinetic properties and limited in vivo activities.

Since 1991, a number of high-affinity nonpeptide NK_1 tachykinin receptor antagonists have been identified primarily as a result of the screening of large compound collections using high throughput radioligand binding assays. These include the following: the quinuclidine derivative, CP-96345 (Snider R.M., et al., (Science, 251:435 (1991)); the piperidine derivative, CP-99994 (McLean S., et al., J. Reg. Peptides, S120 (1992); the perhydroisoindoione derivative, RP-67580 (Garret C., et al., Natl. Acad. Sci., U.S.A., 88:10208 (1991)); the steroid derivative, WIN 51708 (Lawrence K.B., et al., J. Med. Chem., 35:1273 (1992)); the piperidine derivative, SR-140333 (Oury-Donat F., et al., Neuropeptides, 24:233 (1993)); and a tryptophan derivative (Macleod A.M., et al., J. Med. Chem., 36:2044 (1993)).

FK888, a di-peptide with high affinity for the NK_1 receptor, was rationally designed from the octapeptide [D-Pro^4, D-Trp^{7,9,10}, Phe^{11}]SP(4-11) (Fujii T., et al., Neuropeptides, 22:24 (1992)). Schilling, et al., have described a series of piperidines as NK_1 receptor antagonists derived from a peptide/template approach (Schilling W., et al., XIIth International Symposium on Medicinal Chemistry, Basel, September 1992, Abstract ML-11.3).

Substance-P is widely distributed throughout the periphery and central nervous system. It is believed to mediate a variety of biological actions, via an interaction with three receptor types referred to as NK_1, NK_2, and NK_3, including smooth muscle contraction, pain transmission, neuronal excitation, secretion of saliva, angiogenesis, broncho-constriction, activation of the immune system and neurogenic inflammation.

Accordingly, compounds capable of antagonizing the effects of substance-P at NK_1 receptors will be useful in treating or preventing a variety of brain disorders including pain, anxiety, panic, depression, schizophrenia, neuralgia, and addiction disorders; inflammatory diseases such as arthritis, asthma, and psoriasis; gastrointestinal disorders including colitis, Crohn's disease, irritable bowel syndrome, and satiety; allergic responses such as eczema and rhinitis; vascular disorders such as angina and migraine; neuropathological disorders including Parkinson's disease, multiple sclerosis, and Alzheimer's disease; and ophthalmic diseases including scleroderma.

The compounds of the invention, NK_1 receptor antagonists, are useful as anti-angiogenic agents for the treatment of conditions associated with aberrant neovascularization such as rheumatoid arthritis, atherosclerosis, and tumor cell growth. They will also be useful as agents for imaging NK_1 receptors in vivo in conditions such as ulcerative colitis and Crohn's disease.

They will also be useful as antiemetics versus emergens such as cisplatin.

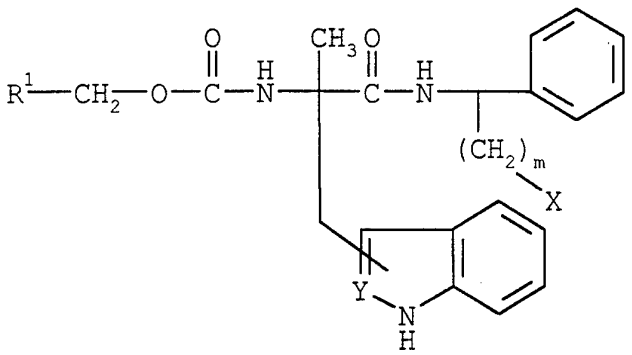
International Publication Numbers WO 93/01169, WO 93/01165, and WO 93/001160 cover certain nonpeptide tachykinin receptor antagonists.

Copending United States Application 08/097,264 filed July 23, 1993 covers certain NK_1 receptor antagonists which are unique in the alkylation/ substitution pattern along the backbone. That application is hereby incorporated by reference.

SUMMARY OF THE INVENTION

The invention covers tachykinin antagonists. The compounds are nonpeptides which have proved to be highly selective and functional tachykinin antagonists. These compounds are unique in the alkylation/ substitution pattern along their backbone and in the alcohol, promoieties (prodrug), and amine groups which are expected to improve pharmacokinetic properties such as increased water solubility and absolute oral bioavailability.

Compounds of the invention are those of formula



I

or a pharmaceutically acceptable salt thereof wherein

R^1 is phenyl, pyridine, thiophene, furan, naphthalene, indole, benzofuran, or benzothiophene each unsubstituted, mono-, di-, or trisubstituted by alkyl, hydroxy, alkoxy, nitro, halogen, amino, or trifluoromethyl;

X is OR^2 wherein R^2 is hydrogen, $(CH_2)_nNR^3R^4$ or a promoiety, or

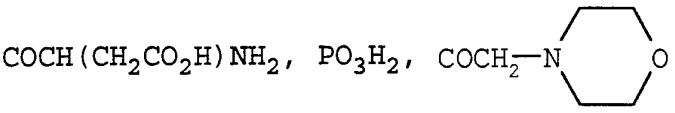
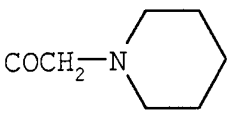
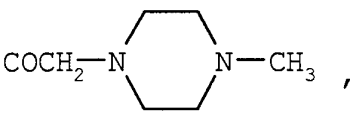
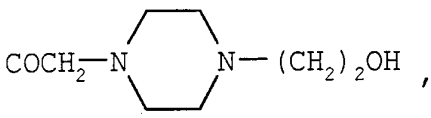
X is NH_2,
NHCO-promoiety,
$NHCO(CH_2)_nNR^3R^4$,
NR^3R^4, or
$(CH_2)_nNR^3R^4$ wherein n is an integer of from 0 to 5 and R^3 and R^4 are each independently selected from hydrogen and methyl or R^3 and R^4 form a ring together with the N to which they are attached;

m is an integer of from 1 to 6; and

Y is CH, CCH_3, CF, CCl, CBr, $CSCH_3$, or N.

Preferred compounds of the instant invention are those of Formula I above wherein

R^1 is phenyl, pyridine, thiophene, furan, naphthalene, indole, benzofuran, or benzothienyl each unsubstituted or mono-, di-, or trisubstituted by alkyl, hydroxy, alkoxy, nitro, halogen, amino, or trifluoromethyl;

X is OR^2 wherein R^2 is hydrogen, $COCH_2N(CH_3)_2$, $COC(CH_3)_2N(CH_3)_2$, $COCH[CH_2CH(CH_3)_2]NH_2$, $COCH(CH_2CO_2H)NH_2$, PO_3H_2,  ,  ,  ,  , $(CH_2)_nNR^3R^4$, or

X is $NHCO(CH_2)_nNR^3R^4$ or NR^3R^4 wherein n is an integer of from 0 to 5 and R^3 and R^4 are each independently hydrogen or methyl;

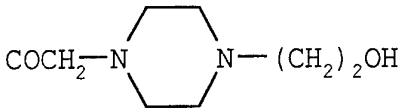
m is 1; and

Y is CH, CCH_3, CF, CCl, CBr, $CSCH_3$, or N.

More preferred compounds of the instant invention are those of Formula I above wherein

R^1 is phenyl, 2-benzofuran, 2-fluorophenyl, 2,5-difluorophenyl, 2-benzothienyl, or 4-CH_3-2-fluorophenyl;

X is OR^2 wherein R^2 is hydrogen, $COCH[(CH_2CH(CH_3)_2)NH_2]$, or $COCH_2N(CH_3)_2$,



, or

X is NH_2 or $NHCH_3$;

m is 1; and

Y is CH.

Most preferred compounds of the invention are:

Carbamic acid, [2-[(2-hydroxy-1-phenylethyl)-amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-benzofuranylmethyl ester, [R-(R*,R*)]-;

Carbamic acid, [2-[(2-hydroxy-1-phenylethyl)-amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, (2-fluorophenyl)methyl ester, [R-(R*,R*)]-;

Carbamic acid, [2-[(2-hydroxy-1-phenylethyl)-amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, (2,5-difluorophenyl)methyl ester, [R-(R*,R*)]-(+)-isomer;

Carbamic acid, [2-[(2-hydroxy-1-phenylethyl)-amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, benzo[b]thien-2-ylmethyl ester, [R-(R*,R*)]-;

Glycine, N,N-dimethyl-, 2-[[2-[[(2-benzofuranyl-methoxy)carbonyl]amino]-3-(1H-indol-3-yl)-2-methyl-1-oxopropyl]amino]-2-phenylethyl ester, monohydrochloride, [R-(R*,R*)]-;

L-Leucine, 2-[[2-[[(2-benzofuranylmethoxy)-carbonyl]amino]-3-(1H-indol-3-yl)-2-methyl-1-oxopropyl]amino]-2-phenylethyl ester, [R-(R*,R*)]-;

Carbamic acid, [2-[(2-amino-1-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-benzofuranylmethyl ester, [R-(R*,R*)]-;

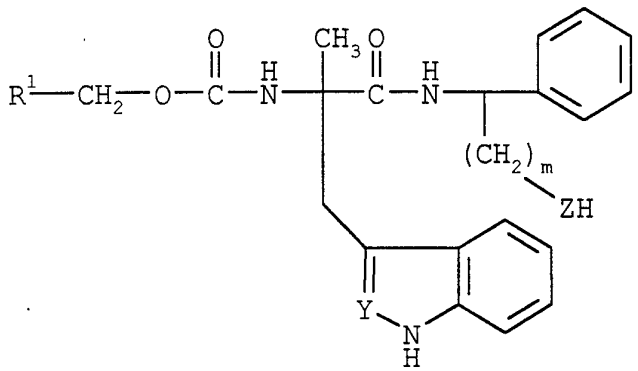
Carbamic acid, [2-[(2-amino-1-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-benzofuranylmethyl ester, [R-(R*,R*)]-;

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, phenylmethyl ester, [R-(R*,R*)]-;

Carbamic acid, [2-(2-hydroxy-1-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-benzofuranylmethyl ester, [R-(R*,R*)]-; and

Carbamic acid, [2-[[(2-[[(dimethylamino)acetyl]-amino]-1-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-benzofuranylmethyl ester, monohydrochloride, [R-(R*,R*)]-.

Novel intermediates of the final products are also included. They are compounds of Formula II



II

wherein

R^1 is phenyl, pyridine, thiophene, furan, naphthalene, indole, benzofuran, or benzothienyl each unsubstituted or mono-, di-, or trisubstituted by alkyl, hydroxy, alkoxy, nitro, halogen, amino, or trifluoromethyl; m is an integer of from 1 to 6; and,

Y is CH, CCH_3, CF, CCl, CBr, $CSCH_3$, or N; and

Z is oxygen or NH.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective to treat respiratory disorders in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

Another aspect of the invention is a method for treating respiratory disorders in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective to treat inflammation in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

Another aspect of the invention is a method for treating inflammation in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective to treat gastrointestinal disorders in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

Another aspect of the invention is a method for treating gastrointestinal disorders in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective to treat eye diseases such as dry eye and conjunctivitis in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

Another aspect of the invention is a method for treating eye diseases in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective to treat allergies in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

Another aspect of the invention is a method for treating allergies in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective to treat diseases of the central nervous system in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

Another aspect of the invention is a method for treating diseases of the central nervous system in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective to treat migraine in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

Another aspect of the invention is a method for treating migraine in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

Another aspect of the invention is a pharmaceutical composition comprising an amount of compound according to Formula I effective to treat pain

arising from neurogenic inflammation or inflammatory pain.

Another aspect of the invention is a method for treating pain such as pain arising from neurogenic inflammation in inflammatory pain status.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective in treating conditions associated with aberrant neovascularization: rheumatoid arthritis, multiple sclerosis, atherosclerosis, and tumor cell growth.

Another aspect of the invention is a method of treating conditions associated with aberrant neovascularization: rheumatoid arthritis, multiple sclerosis, atherosclerosis, and tumor cell growth.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective in treating emesis associated with such emergins as cisplatin.

Another aspect of the invention is a method of treating conditions associated with emesis.

Another aspect of the invention is using the compounds as imaging agents for imaging NK_1 receptors in vivo.

Processes for preparing the compounds and novel intermediates are included in the invention.

DETAILED DESCRIPTION OF THE INVENTION

The following terms are descriptive of the compounds of the instant invention.

The alkyl groups contemplated by the invention include straight or branched carbon chains of from 1 to 8 carbon atoms except where specifically stated otherwise. Representative groups are methyl, ethyl,

propyl, isopropyl, n-propyl, n-butyl, iso-butyl, sec-butyl, 2-methylhexyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl, and the like.

The alkoxy groups contemplated by the invention comprise both straight and branched carbon chains of from 1 to 6 carbon atoms unless otherwise stated. Representative groups are methoxy, ethoxy, propoxy, i-propoxy, t-butoxy, and hexoxy.

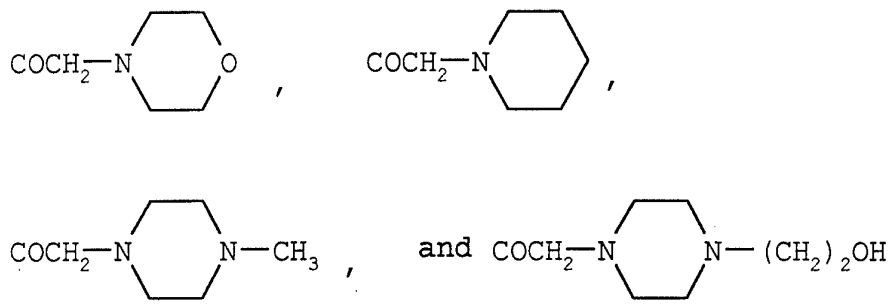
The term halogen is intended to include fluorine, chlorine, bromine, and iodine.

R^1 is an aryl or a heterocycle which is unsubstituted or bears from 1 to 3 substituents. Aryl groups include phenyl, naphthyl, biphenyl, and indanyl. Preferred aryl groups are phenyl and naphthyl.

Heterocyclic groups include pyridyl, 2- or 3-indolyl, benzofuranyl, furanyl, benzothienyl, thienyl. Preferred heterocyclic groups are: benzofuranyl and benzothienyl.

The substituents in the above are selected from alkyl, hydroxy, alkoxy, nitro, halogen, amino, and trifluoromethyl. From 1 to 3 substituents are considered. Preferred substituents are fluorine, methoxy, methyl, and amino; most preferred is 1,2-dimethoxy.

The promoiety of the instant invention are found in the X term of Formula I above. These moieties are useful in that they provide improved drug stability, improved water solubility, enhanced absorption, allow for site-specific delivery, mask side effects, and/or extend the duration of action (Bundgaard H., Elsevier E., Design of Prodrugs, 1985). In the instant invention, various promoieties are useful: $COCH_2N(CH_3)_2$, $COC(CH_3)_2N(CH_3)_2$, $COCH[(CH_2CH(CH_3)_2)]NH_2$, $COCH(CH_2CO_2H)NH_2$, PO_3H_2,



Others as would occur to a skilled artisan are also included.

As shown in Table I below, the compounds of the invention are tachykinin NK_1 receptor antagonists in an in vitro NK_1 preparation, i.e., the compound antagonizes the pharmacological action of the selective NK_1 receptor agonist substance-P methylester on this tissue. Therefore, it is expected to be useful in the therapeutic disorders when the attenuation of the NK_1 receptor response is the appropriate form of intervention.

TABLE I

NK_1 Antagonist Activity

Example	K_B (nM) Guinea Pig Ileum*
6	1.3
16	10.6
17	9.3
18	6.3
9	6.2
12	22
8	16

* McKnight A.T., et al., Br. J. Pharmacol., 104:355-360 (1991)

These compounds are active in vivo as NK_1 receptor antagonists as shown in Table II below. They antagonize the ability of a NK_1 receptor selective agonist (SPOMe) to induce plasma protein extravasation

in the guinea pig bladder. The protocol is similar to that described by Eglezos, et al., Eur. J. Pharmacol., 209:277-279 (1991).

TABLE II

Guinea Pig Plasma Extravasation (Bladder)

Example	ID_{50} (mg/kg IV)	ID_{50} (mg/kg PO)
6	0.16	30
9	0.16	4.4

As can be seen from the binding data below (Table III), several of these compounds have high affinity for the NK_1 receptor.

TABLE III

NK_1 Binding in Human IM9 Lymphoma Cells

Example	IC_{50} (nM)
6	1.2
9	12
12	16
10	84
8	13
15	58
16	3.3
17	3.9
18	9

Table III above shows the concentration of the compounds of the present invention which is needed to displace 50% of a specific radioligand ([^{125}I]Bolton Hunter Substance-P) from tachykinin NK_1 receptor sites in human IM9 lymphoma cells (Boyle S., et al., Rational design of high affinity tachykinin NK_1 receptor antagonists. Bioorg. Med. Chem., 1994, in press).

Compounds of the invention are expected to be useful in treating disorders mediated by tachykinins such as respiratory disorders, especially asthma.

They are also expected to be useful in treating inflammation such as arthritis, gastrointestinal disorders such as colitis, Crohn's disease, and irritable bowel syndrome.

They are further expected to be useful in treating and/or preventing eye diseases such as dry eye and conjunctivitis.

They are further expected to be useful in treating allergies such as rhinitis (common cold), and eczema.

The compounds are expected to treat vascular disorders such as angina and migraine.

They are further expected to be useful in preventing and/or treating diseases of the central nervous system such as schizophrenia.

They are further expected to be useful in the management of pain.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository preparations, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

The powders and tablets preferably contain 5% to about 70% of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The compounds of the invention include solvates, hydrates, pharmaceutically acceptable salts, and polymorphs (different crystalline lattice descriptors) of the compounds of Formula I.

The compounds of the present invention can have multiple chiral centers in the above Formula I depending on their structures. In particular the compounds of the present invention may exist as diastereomers, mixtures of diastereomers, or as the mixed or the individual optical enantiomers. The present invention contemplates all such forms of the compounds. The mixtures of diastereomers are typically obtained as a result of the reactions described more fully below. Individual diastereomers may be separated from mixtures of the diastereomers by conventional techniques such as column chromatography or repetitive recrystallizations. Individual enantiomers may be separated by conventional methods well known in the art such as conversion to a salt with an optically active compound, followed by separation by chromatography or recrystallization and reconversion to the nonsalt form.

Where it is appropriate to form a salt, the pharmaceutically acceptable salts are acetate,

benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycoloylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, theoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc.

Cyclodextrin is one suitable inclusion in a pharmaceutical preparation.

The term "preparation" is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

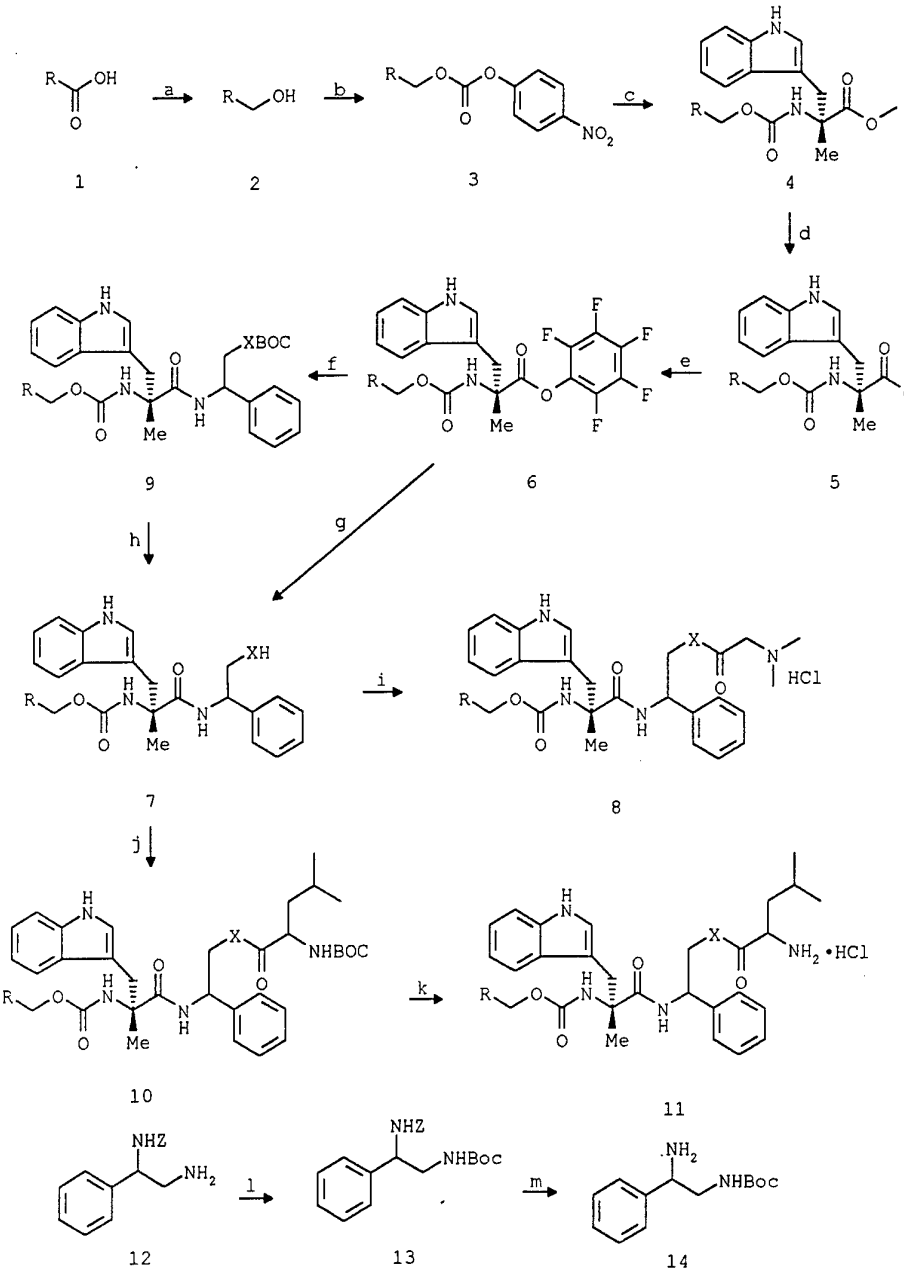
Liquid form preparations include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

The compounds of the instant invention are prepared as summarized below in Scheme I and as described below in Examples 1-18. The examples are not intended to be limiting, rather, they are illustrative.

SCHEME I



Compounds 1 to 7: (i) X = O, R = Ph; (ii) X = O, R = 2-F,Ph; (iii) X = O, R = 2,5-DiF,Ph; (iv) X = O, R = 2-benzofuran; (v) X = O, R = 2-benzothiophene; (vi) X = NH, R = 2-benzofuran.

Compounds 8 and 9: (i) X = O, R = 2-benzofuran; (ii) X = NH, R = 2-benzofuran.

Compounds 10 and 11: (i) X = O, R = 2-benzofuran.

Reagents and conditions: (a) $LiAlH_4$, THF, -5°C to 25°C; (b) Pyridine, CH_2Cl_2, p-NO_2PhOCOCl; (c) (R)αMeTrp(OMe), DMAP, DMF; (d) LiOH, THF, MeOH, H_2O; (e) DCCI, PFP, EtOAc; (f) (R)β NH_2, N-BocPhenethylamine 14, EtOAc; (g) (R)Phenylglycinol, EtOAc; (h) Formic acid; (i) N,N-DiMe_2Gly, DCCl, DMAP, CH_2CH_2; (j) Boc-(L)-Leu(OH).

EXAMPLE 1

Compound 2 (iv)

To a suspension of lithium aluminum hydride (2.82 g, 63 mmol) in dry THF (150 mL) at -5°C under nitrogen was added dropwise a solution of benzofuran-2-carboxylic acid (10.2 g, 63 mmol) in THF (100 mL). The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. 1N HCl was added slowly with cooling (cardice-acetone bath) and the resulting solution was washed with 1N HCl, $NaHCO_{3(aq)}$, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography on silica eluting with a mixture of hexane:EtOAc (1:1) to give 2 (iv) as a yellow oil (7.2 g, 77%).

^1H NMR ($CDCl_3$): δ 2.68 (1H, s, OH), 4.70 (2H, s, CHHOH), 6.58 (1H, s, ArH3), 7.15-7.27 (2H, m, ArH), 7.42 (1H, d, 8.1 Hz, ArH), 7.48-7.51 (1H, m, ArH); Anal. $C_9H_8O_2$: C,H,N.

EXAMPLE 2

Compound 3 (iv)

To a stirred solution of 2 (iv) (8.58 g, 58 mmol) and pyridine (4.82 mL, 58 mmol) in CH_2Cl_2 (150 mL) at 10°C was added dropwise a solution of p-nitrophenyl chloroformate (14 g, 70 mmol) in CH_2Cl_2 (150 mL). The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The solvent was removed in vacuo and the residue taken up in EtOAc, washed with 1N HCl, $NaHCO_{3(aq)}$, dried ($MgSO_4$), and concentrated in vacuo. The resultant yellow solid was purified using hexane:ether (9:1) as eluant to give 3 (iv) as a cream solid (9.8 g, 54%).

^1H NMR ($CDCl_3$): δ 5.41 (2H, s, CHHO), 6.90 (1H, s, H2 of benzofuran), 7.21-7.42 (2H, m, ArH), 7.39 (2H, d, 9.2 Hz, H2, H6 of phenyl), 7.52 (1H, d, 7.8 Hz, ArH),

7.60 (1H, d, 7.1 Hz, ArH), 8.28 (2H, d, 9.2 Hz, H3, H5 of phenyl);
IR: 3119.0, 1770.0, 1617.0, 1594.0, 1524.0, 1346.0, 1251.0, 1213.0, 862.0, 753.0 cm^{-1};
mp 90.5-92.5°C;
Anal. $C_{16}H_{11}NO_6$: C,H,N.

EXAMPLE 3

Compound 4 (iv)

The mixed carbonate 3 (iv) (7 g, 22 mmol), (R)α-methyltryptophan, methyl ester (5.2 g, 22 mmol), and dimethylaminopyridine (2.7 g, 22 mmol) were stirred in DMF (60 mL) at room temperature overnight. The reaction mixture was taken up in ether, washed with $NaCO_{3(aq)}$, 1N HCl, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with hexane:EtOAc (7:3) to give 4 (iv) as a yellow sticky solid (8.57 g, 96%).

^1H NMR ($CDCl_3$): δ 1.70 (3H, s, αCH_3), 3.36 (1H, d, 14.6 Hz, CHH indole), 3.54 (1H, bd, 13.9 Hz, CHH indole), 3.67 (3H, s, CO_2CH_3), 5.17 (1H, d, 13.4 Hz, CHHOCONH), 5.27 (1H, d, 13.2 Hz, CHHOCONH), 5.58 (1H, bs, OCONH), 6.78 (1H, s, ArH), 6.81 (1H, s, ArH), 7.00 (1H, t, 7.6 Hz, ArH), 7.12 (1H, t, 7.3 Hz, ArH), 7.23-7.34 (3H, m, ArH), 7.47-7.50 (2H, m, ArH), 7.81 (1H, bs, indole NH).

EXAMPLE 4

Compound 5 (iv)

To a solution of 4 (iv) (8.57 g, 21 mmol) in THF (90 mL) was added lithium hydroxide (30 mL, 10 M), methanol (30 mL) and water (60 mL) and the reaction was stirred at room temperature for 2 days. The volatiles were removed in vacuo and the aqueous mixture was acidified with 1N HCl, and extracted with EtOAc. The

organic phase was washed with water, dried ($MgSO_4$), and concentrated in vacuo to yield 5 (iv) as a yellow oil (8.23 g, 100%) which was used without further purification in the next step.

EXAMPLE 5

Compound 6 (iv)

To a solution of 5 (iv) (8.23 g, 21 mmol) in EtOAc was added dicyclohexylcarbodiimide (4.3 g, 21 mmol) followed by pentafluorophenol (3.86 g, 21 mmol) and the mixture was stirred at room temperature for 16 hours. The mixture was cooled to 0°C for 30 minutes and the resulting precipitate of dicyclohexylurea was removed by filtration. The filtrate was washed with 1N HCl, $NaCO_{3(aq)}$, dried ($MgSO_4$), and the solvents removed in vacuo. The residue was purified by flash chromatography on silica gel eluting with a mixture of hexane:EtOAc (9:1) to give 6 (iv) as a cream solid (7.5 g, 64%).

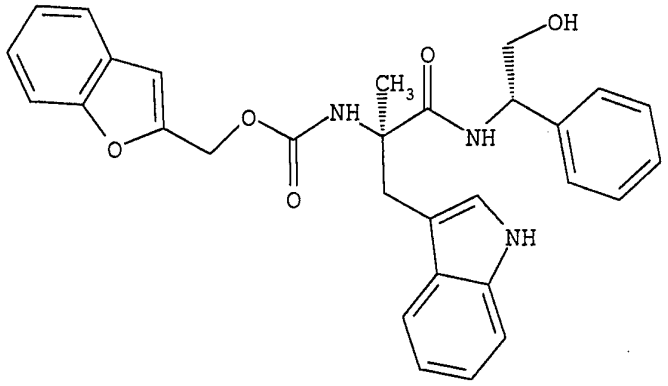
^1H NMR ($CDCl_3$): δ 1.74 (3H, s, αCH_3), 3.44 (1H, d, 14.9 Hz, CHH indole), 3.66 (1H, d, 14.6 Hz, CHH indole), 5.18-5.29 (3H, m, CHHOCONH), 6.79 (1H, s, ArH), 7.0 (1H, s, ArH), 7.04 (1H, t, 7.6 Hz, ArH), 7.18 (1H, t, 7.5 Hz, ArH), 7.21-7.36 (3H, m, ArH), 7.46 (1H, d, 8.1 Hz, ArH), 7.55-7.58 (2H, m, ArH), 8.02 (1H, bs, indole NH);

IR: 3418.0, 1785.0, 1707.0, 1652.0, 1520.0, 1455.0, 1254.0 cm^{-1};

MS m/e (CI) 559 (M+H);

Anal. $C_{28}H_{19}F_5N_2O_5$: C,H,N.

EXAMPLE 6



Carbamic acid, [2-[(2-hydroxy-1-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-benzofuranylmethyl ester, [R-(R*,R*)]-

Compound 7 (IV)

The pentafluoroester 6 (iv) (5 g, 9.0 mmol) and (R)-phenylglycinol (1.27 g, 9.0 mmol) were stirred at room temperature in EtOAc (400 mL) for 24 hours. The reaction mixture was washed with 1N HCl, $NaCO_{3\,(aq)}$, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified on silica gel by flash chromatography, eluting with a gradient of hexane:EtOAc (1:1) to EtOAc. The alcohol 7 (iv) was obtained as a white solid (3.61 g, 79%).

^1H NMR ($CDCl_3$): δ 1.68 (3H, s, $\alpha C\underline{H}_3$), 2.58 (1H, bs, O$\underline{H}$), 3.23 (1H, d, 14.8 Hz, CH$\underline{H}$ indole), 3.42 (1H, d, 14.8 Hz, CH$\underline{H}$ indole), 3.63-3.72 (1H, m, CH$\underline{H}$OH), 3.73-3.81 (1H, m, CH$\underline{H}$OH), 5.00 (1H, m, $C\underline{H}CH_2OH$), 5.13 (1H, d, 13.2 Hz, C$\underline{H}$HOCONH), 5.25 (1H, d, 13.2 Hz, CH$\underline{H}$OCONH), 5.45 (1H, s, N$\underline{H}$CO), 6.52 (1H, d, 7.7 Hz, N$\underline{H}$CHCHHOH), 6.77 (1H, s, Ar$\underline{H}$), 6.90 (1H, d, 2.0 Hz, Ar$\underline{H}$), 7.07-7.34 (10H, m, Ar$\underline{H}$), 7.46 (1H, d, 7.6 Hz, Ar$\underline{H}$), 7.57 (2H, t, 8.8 Hz, Ar$\underline{H}$), 7.59 (1H, s, indole N$\underline{H}$);

IR: 3383.0, 1713.0, 1652.0, 1495.0, 1455.0, 1250.0, 1070.0 cm^{-1};
MS m/e (FAB) 512.0 (M+H), 534.0 (M+Na);
$[\alpha_D]$ = +34.67 (MEOH, c = 0.075);
mp 77-85°C;
HPLC R.T. = 11.943, C^{18} reverse phase, 40-100% MeCN:TFA/water:TFA.
Anal. $C_{30}H_{29}N_3O_5 \cdot 0.35H_2O$: C,H,N.

EXAMPLE 7

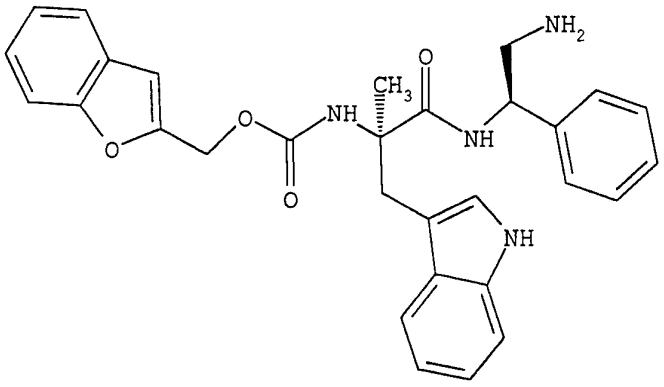
Compound 9 (ii)

The pentafluorophenyl ester 6 (iv) (1.0 g, 1.80 mmol), and α-amino, N-Boc-phenethylamine (14) (0.57 g, 2.00 mmol) were stirred at room temperature in EtOAc (100 mL) for 2 days. The reaction mixture was washed with 1N HCl, $NaHCO_{3(aq)}$, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified on silica gel by flash chromatography, eluting with a gradient of hexane:EtOAc (1:1) to EtOAc. The N-protected amine was obtained as a white solid (0.87 g, 80%).
^1H NMR ($CDCl_3$): δ 1.41 (9H, s, ^{t}butyl), 1.67 (3H, s, αC$\underline{H}_3$), 3.25-3.31 (1H, m, CH$\underline{H}$NHBoc), 3.42-3.39 (3H, m, CH$\underline{H}$NHBoc, C$\underline{H}\underline{H}$ indole), 4.91-5.00 (2H, m, C$\underline{H}$CH_2N$\underline{H}$Boc), 5.16 (1H, d, 13.2 Hz, C$\underline{H}$HOCONH), 5.23 (1H, d, 13.4 Hz, CH$\underline{H}$OCONH), 5.56 (1H, s, N$\underline{H}$CO_2CH_2), 6.76 (1H, s, Ar$\underline{H}$), 6.81 (1H, s, Ar$\underline{H}$), 7.04 (1H, t, 7.3 Hz, Ar$\underline{H}$), 7.12-7.32 (9H, m, 8 Ar$\underline{H}$, CON$\underline{H}$CHHPh), 7.44-7.60 (4H, m, Ar$\underline{H}$), 7.82 (1H, s, indole N$\underline{H}$);
IR: 3354.0, 1700.3, 1652.0, 1495.0, 1455.0, 1367.0, 1251.0, 1167.0, 1069.0 cm^{-1};
MS m/e (FAB) 610 (M), 611.3 (M+H), 633.1 (M+Na);
α^D = +7.62 (MEOH, c = 0.105 g, 100 mL^{-1});
mp 79-83°C;

HPLC R.T.= 15.767, C^{18} reverse phase, 40-100% MeCN:TFA/water:TFA;

Anal. $C_{35}H_{38}N_4O_6$: C,H,N.

EXAMPLE 8



Carbamic acid, [2-[(2-amino-1-phenylethyl)aminol-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-benzofuranylmethyl ester, [R-(R*,R*)]-

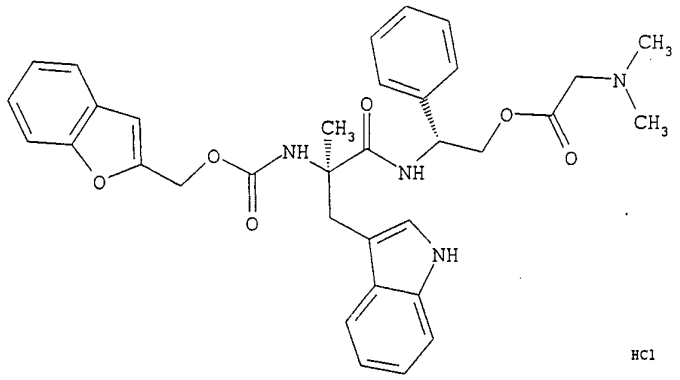
Compound 7 (VI)

A solution of formic acid (20 mL) and 9 (ii) (0.87 g, 1.43 mmol) was stirred for 1 hour. The solvent was removed and the residue was taken up in EtOAc and washed with $NaHCO_{3(aq)}$, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was triturated with EtOAc to yield the free amine as a white solid (38 mg, 52%).

^1H NMR ($CDCl_3$): δ 1.69 (3H, s, $\alpha C\underline{H}_3$), 2.74 (1H, dd, 4.6, 12.7 Hz, $CH\underline{H}NH_2$), 2.84 (1H, dd, 5.86, 12.94 Hz, $CH\underline{H}NH_2$), 3.29 (1H, d, 14.7 Hz, CHH indole), 3.44 (1H, d, 14.9 Hz, CHH indole), 4.88 (1H, m, $C\underline{H}CH_2NH_2$), 5.15 (1H, d, 13.2 Hz, $C\underline{H}HOCONH$), 5.23 (1H, d, 13.4 Hz, $CH\underline{H}OCONH$), 5.58 (1H, s, $N\underline{H}CO_2CH_2$), 6.76 (1H, s, Ar$\underline{H}$), 6.83 (1H, s, Ar$\underline{H}$), 6.88 (1H, d, 7.6 Hz, $CON\underline{H}CH$), 7.05-7.32 (12H, m, 10 Ar$\underline{H}$, $N\underline{H}_2$), 7.46 (1H, d, 8.1 Hz,

ArH), 7.56 (2H, t, 8.3 Hz, ArH), 8.00 (1H, s, indole NH);
IR: 3299.0, 1719.0, 1655.0, 1493.0, 1454.0, 1250.0 cm^{-1};
MS m/e (FAB) 511.5 (M+H);
α^D = 0.00 (MEOH, c = 0.105 g, 100 mL^{-1});
mp 166-167°C;
Anal. $C_{30}H_{30}N_4O_4$: C,H,N.

EXAMPLE 9



Glycine, N,N-dimethyl-, 2-[[2-[[(2-benzofuranyl-methoxy)carbonyl]amino]-3-(1H-indol-3-yl)-2-methyl-1-oxopropyl]amino]-2-phenylethyl ester, monohydrochloride, [R-(R*,R*)]-;

Compound 8 (i)

To a stirred solution of 7 (iv) (0.3 g, 0.59 mmol) in CH_2Cl_2 (100 mL) was added N,N-dimethylglycine (0.24 g, 2.3 mmol), dicyclohexylcarbodiimide (0.19 g, 1.8 mmol) and dimethylaminopyridine (72 mg, 0.59 mmol) and the reaction mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo and the residue, taken up in EtOAc and chilled at 4°C for 30 minutes. The resulting white precipitate of dicyclohexylurea was removed by filtration and the filtrate was washed, dried ($MgSO_4$), and concentrated

in vacuo. The residue was purified by flash chromatography on silica gel using a hexane:EtOAc (1:1) to EtOAc gradient as eluant. The sticky solid obtained was triturated with ether to produce the free dimethylamine as a white solid. To a solution of the free amine in EtOAc was added one equivalent of HCl in dioxan (0.3 mL, 4 M) causing the hydrochloride salt to precipitate out. The salt was filtered and washed thoroughly with ether before repeated triturations with EtOAc/ether mixtures yielded 8 (i) as a crystalline white solid (0.17 g, 48%).

^{1}H NMR (DMSO): δ 1.27 (3H, s, αCH_3), 3.14 (1H, d, 14.8 Hz, CHH indole), 2.77 (6H, s, $N(CH_3)_2$), 3.40 (1H, d, 14.8 Hz, CHH indole), 3.95-4.10 (2H, m, $OCOCHHN(CH_3)_2$), 4.30-4.44 (2H, m, CHCHHOCO), 5.14-5.25 (3H, m $CHCH_2OCO$, CHHOCONH), 6.80 (1H, t, 7.2 Hz, ArH), 6.89-6.97 (3H, m, ArH), 7.13 (1H, s, ArH), 7.22-7.41 (8H, m, ArH), 7.52 (1H, d, 8.0 Hz, ArH or NHCH), 7.61 (1H, d, 8.0 Hz, NHCH or ArH), 8.31 (1H, d, 8.4 Hz, NHCH or ArH), 10.18 (1H, bs OCONH), 10.84 (1H, s, indole NH);

IR: 3346.0, 2363.0, 1721.0, 1654.0, 1455.0, 1250.0 cm^{-1};

MS m/e (CI) 597.2 (M-Cl);

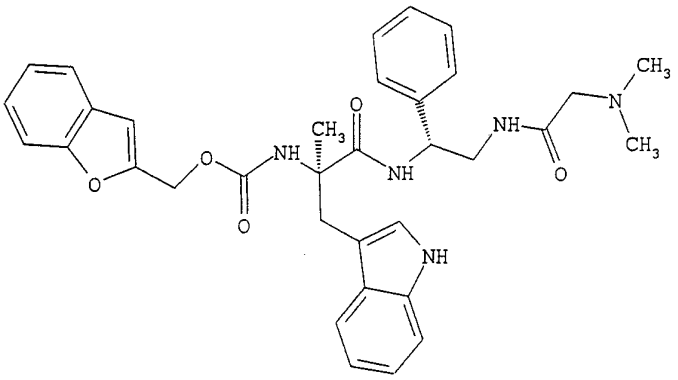
α^D = +14.74 (MEOH, c = 0.286);

mp 107-111°C;

HPLC R.T.= 16.613, C^{18} reverse phase, 20-80% MeCN:TFA/water:TFA;

Anal. $C_{34}H_{37}N_4O_6Cl \cdot 1.0H_2O$: C,H,N.

EXAMPLE 10



Carbamic acid, [2-[[(2-[[(dimethylamino)acetyl]amino]-1-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-benzofuranylmethyl ester, monohydrochloride, [R-(R*,R*)]-

Compound 8 (ii)

To a stirred solution of N,N-dimethylglycine (51.5 mg, 0.5 mmol) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) (51.5 mg, 0.50 mmol) in DMF (50 mL) at room temperature was added diisopropylethylamine (180 mL, 1.00 mmol). After 10 minutes, 7 (vi) (255 mg, 0.50 mmol) and diisopropylethylamine (90 mL, 0.50 mmol) were added to the reaction mixture which was stirred for a further 10 hours. The solvent was removed under reduced pressure and the residue was taken up in EtOAc and washed with $NaHCO_{3\,(aq)}$, water, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using a EtOAc to 10% MeOH/DCM gradient as eluant. To a solution of the free amine in EtOAc was added one equivalent of HCl in dioxan (0.125 mL, 4 M) causing the hydrochloride salt to precipitate out. The salt was filtered and washed thoroughly with ether before repeated triturations with

EtOAc/ether mixtures yielded 8 (ii) as a crystalline white solid (0.117 g, 41%).

^{1}H NMR (DMSO): δ 1.27 (3H, s, $\alpha C\underline{H}_3$), 2.68 (6H, bs, $N(C\underline{H}_3)_2$), 3.12 (1H, d, 14.6 Hz, C<u>H</u>H indole), 3.31-3.36 (1H, m, (obscured by water peak) CH<u>H</u>NHCO), 3.37 (1H, d, 14.2 Hz, C<u>H</u>H indole), 3.49-3.56 (1H, m, CH<u>H</u>NHCO), 3.72 (1H, d, 15.6 Hz, $OCOC\underline{H}HN(CH_3)_2$), 3.81 (1H, d, 15.6 Hz, $OCOC\underline{H}HN(CH_3)_2$), 5.03 (1H, q, 8.1, 14.4 Hz, $NHC\underline{H}CHHNH$), 5.13 (1H, d, 13.4 Hz, C<u>H</u>HOCONH), 5.19 (1H, d, 13.4 Hz, CH<u>H</u>OCONH), 6.79 (1H, t, 7.3 Hz, Ar<u>H</u>), 6.87 (1H, s, OCON<u>H</u>), 6.95 (2H, t, 7.1 Hz, Ar<u>H</u>), 7.17-7.31 (9H, m, Ar<u>H</u>), 7.40 (1H, d, 7.8 Hz, Ar<u>H</u>), 7.52 (1H, d, 7.8 Hz, Ar<u>H</u>), 7.61 (1H, d, 7.6 Hz, Ar<u>H</u>), 8.16 (1H, d, 8.5 Hz, CON<u>H</u>CH), 8.48 (1H, m, CHHN<u>H</u>CO), 9.68 (1H, s, <u>H</u>$^+$Cl-), 10.82 (1H, s, indole N<u>H</u>);

IR: 3334.0, 1715.7, 1682.0, 1652.0, 1540.3, 1455.0, 1252.0 cm^{-1};

α^D = -46.45, (MEOH, c = 0.155 g, 100 mL^{-1});

mp 126-128°C;

Anal. $C_{34}H_{38}ClN_5O_5 \cdot 1.0H_2O$: C,H,N.

EXAMPLE 11

<u>Compound 10 (i)</u>

To a stirred solution of boc-(L)-leu(OH) (0.32 g, 1.37 mmol) and 2-(1H-benzotriazol-1-yl)1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) (0.52 g, 1.37 mmol) in DMF (10 mL) at room temperature was added diisopropylethylamine (238 μL, 1.37 mmol). After 10 minutes, 7 (vi) (799 mg, 1.37 mmol), diisopropylethylamine (238 μL, 1.37 mmol), and dimethylaminopyridine (167 mg, 1.37 mmol) were added to the reaction mixture which was stirred for a further 10 hours. The solvent was removed under reduced pressure and the residue was taken up in EtOAc and washed with 10% citric acid solution, water, $NaHCO_3$(aq), water, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue

was chromatographed on silica gel eluting with CH_2Cl_2 to give 10 (i) (695 mg, 70%).

^1H NMR ($CDCl_3$): δ 0.83-0.90 (6H, m, $CH(C\underline{H}_3)_2$), 1.42 (9H, s, ^{t}butyl), 1.63 (3H, s, $\alpha C\underline{H}_3$), 1.40-1.65 (3H, m, $C\underline{H}C\underline{H}_2(CH_3)_2$), 3.30 (1H, d, 14.6 Hz, $CH\underline{H}$ indole), 3.53 (1H, d, 14.6 Hz, $CH\underline{H}$ indole), 4.20-4.30 (3H, m, $C\underline{H}\underline{H}O$, $COC\underline{H}NH$), 4.94 (1H, bd, 7.8 Hz, $OCON\underline{H}CH$), 5.16 (1H, d, 13.2 Hz, $C\underline{H}HOCONH$), 5.24 (1H, d, 13.4 Hz, $CH\underline{H}OCONH$), 5.20-5.25 (1H, m, $PhC\underline{H}NH$), 5.58 (1H, s, $OCON\underline{H}C$), 6.77 (1H, s, $Ar\underline{H}$), 6.83 (2H, s, $Ar\underline{H}$, $CON\underline{H}CHPh$), 7.03-7.08 (1H, m, $Ar\underline{H}$), 7.13-7.33 (9H, m, $Ar\underline{H}$), 7.47 (1H, d, 8.1 Hz, $Ar\underline{H}$), 7.55-7.60 (2H, m, $Ar\underline{H}$), 8.23 (1H, s, indole $N\underline{H}$);

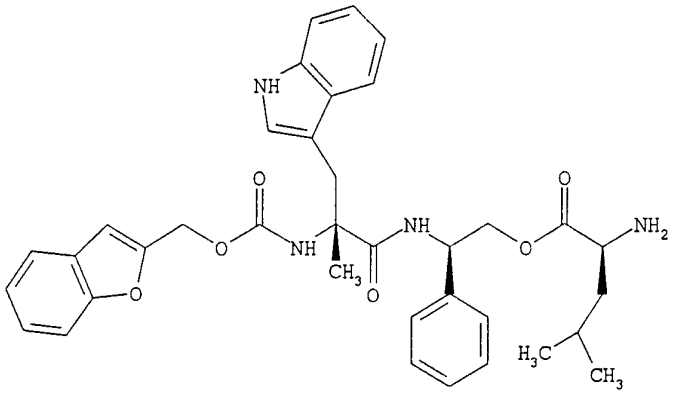
IR: 3346.0, 2959.0, 1714.0, 1665.0, 1505.0, 1455.0, 1368.0, 1250.0, 1162.0, 1070.0, 742.0 cm^{-1};

α^D = +10.9 (MEOH, c = 0.5 g, 100 mL^{-1});

mp 73-78°C;

Anal. $C_{41}H_{48}N_4O_8$: C,H,N.

EXAMPLE 12



L-Leucine, 2-[[2-[[(2-benzofuranylmethoxy)carbonyl]-amino]-3-(1H-indol-3-yl)-2-methyl-1-oxopropyl]amino]-2-phenylethyl ester, [R-(R*,R*)]-

Compound 11 (i)

To a solution of formic acid (20 mL), anisole (1 mL), and water (1 mL) was added 10 (i) (0.63 g, 0.87 mmol) and the mixture was stirred for 2 hours. The solvent was removed and the residue was taken up in EtOAc and washed with $NaHCO_{3\,(aq)}$, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with EtOAc to yield the free amine (608 mg, 80%). To a solution of the free amine (538 mg, 0.86 mmol) in ether (80 mL) was added a solution of HCl in dioxan (0.25 mL, 1 mmol) causing the hydrochloride salt, 11 (i), to precipitate out immediately as a white solid. The mixture was stirred for 20 minutes before the solid was removed by filtration to give 11 (i) (520 mg, 91%).

^1H NMR ($CDCl_3$): δ 0.70-0.80 (6H, m, $CH(C\underline{H}_3)_2$), 1.50-1.80 (6H, m, $C\underline{H}C\underline{H}_2(CH_3)_2$, αCH_3), 3.31 (1H, d, 14.9 Hz, C<u>H</u>H indole), 3.48 (1H, d, 14.4 Hz, CH<u>H</u> indole), 3.80-3.90 (1H, m, $C\underline{H}NH_3^+$), 3.98-4.18 (1H, m, CHCH<u>H</u>O), 4.37-4.43 (1H, m, CHCH<u>H</u>O), 5.10-5.25 (3H, m, C<u>H</u>HOCONH, PhC<u>H</u>NH), 5.80-6.00 (1H, bs, OCON<u>H</u>), 6.72 (1H,

s, ArH), 6.80-7.00 (1H, bs, CONHCHPh), 6.95-7.30 (11H, m, ArH), 7.42 (1H, d, 8.3 Hz, ArH), 7.48-7.54 (2H, m, ArH), 8.55 (1H, s, indole NH);
IR: 3350.0-3100.0, 2961.0, 1732.0, 1661.0, 1505.0, 1455.0, 1250.0, 1135.0, 1070.0, 742.0 cm^{-1};
MS m/e (CI) 625 (M+H), 624 (M);
α^D = +2.30° (MEOH, c = 0.5 g, 100 mL^{-1});
mp 110-115°C;
HPLC R.T. = 10.85, C^{18} reverse phase, 40-100% MeCN:TFA/H_2O:TFA;
Anal. $C_{36}H_{40}N_4O_6 \cdot HCl$: C,H,N.

EXAMPLE 13

Compound 13

The carbonate salt of the amine (12) (Horwell, et al., J. Med. Chem. 34:404 (1991)) (1.0 g, 3.3 mmol) was suspended in dioxan (20 mL) containing water (2 mL) and cooled to 0°C. Potassium Hydroxide pellets (0.5 g, 8.9 mmol) and ditertbutylcarbonate (1.3 g, 6.0 mmol) were then added to the reaction mixture which was stirred at 0°C for 1 hour and at room temperature for a further hour. The reaction mixture was poured onto water (150 mL), extracted with EtOAc (2 x 75 mL), dried ($MgSO_4$), and evaporated in vacuo to yield an oily residue. The residue was purified by flash chromatography using EtOAc/hexane 0-100% gradient as eluant to give the desired Product 13 as a white solid (1.12 g, 82%).
^1H NMR (DMSO): δ 1.33 (9H, s, Boc), 3.17 (2H, t, 6.24 Hz, CH_2NH_2), 4.69 (1H, q, 7.4, 15.5 Hz, CHCHH), 4.96 (1H, d, 12.6 Hz, PhCHHOCON), 5.02 (1H, d, 12.6 Hz, PhCHHOCON), 6.84 (1H, m, NHBoc), 7.08-7.33 (10H, m, ArH), 7.72 (1H, d, 8.4 Hz, NHCOOCHH);
IR: 271.0, 240.0, 91.0 cm^{-1};
MS m/e (CI) 371 (M+H);
Anal. $C_{21}H_{26}N_2O_4$: C,H,N.

EXAMPLE 14

Compound 14

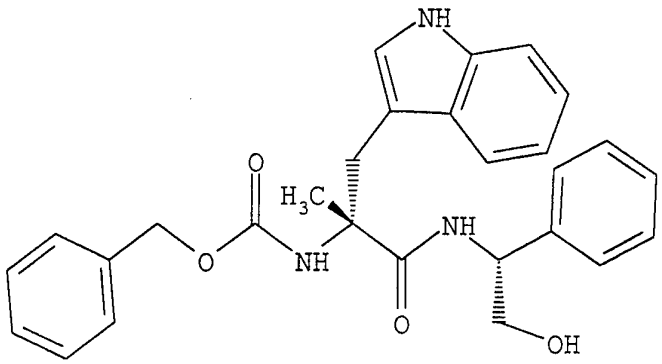
The protected diamine (13) (0.5 g, 1.4 mmol) was dissolved in MeOH (50 mL) and hydrogenated at 45 psi/30°C in a parr apparatus using 10% palladium on carbon (50 mg) as the catalyst. The reaction was complete after 2 hours and the catalyst was removed by filtration through celite and the solvent removed in vacuo to yield 14 as a viscous brown oil (0.32 g, 100%).

^{1}H NMR (DMSO): δ 1.36 (9H, s, Boc), 2.89-2.98 (1H, m, CHHNHBoc), 3.07-3.17 (1H, m, CHHNHBoc), 3.85-3.89 (1H, m CHCHH), 6.44-6.78 (1H, m NHBoc), 7.17-7.35 (6H, m, ArH, NHH);

IR: 164.0, 106.0;

MS m/e (CI) 237 (M+H), 181 (100%).

EXAMPLE 15



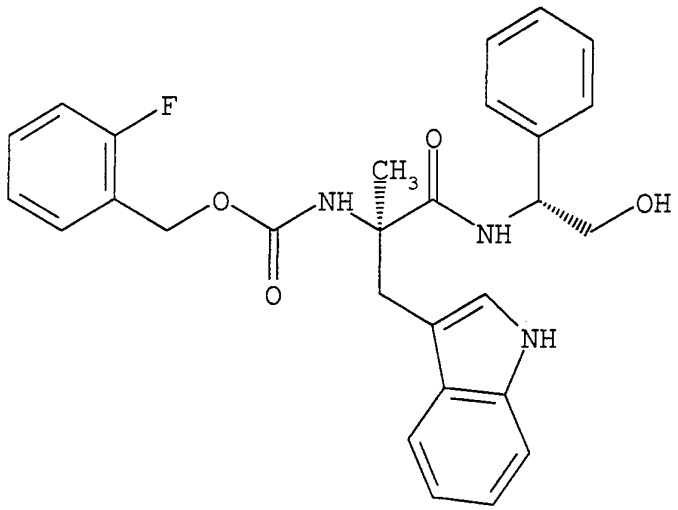
Carbamic acid, [2-[(2-hydroxy-1-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, phenylmethyl ester, [R-(R*,R*)]-

Compound 7 (i)

^{1}H NMR ($CDCl_3$): δ 1.67 (3H, s, αCH_3), 2.60 (1H, bs, OH), 3.23 (1H, d, 14.7 Hz, CHH indole), 3.42 (1H, d, 14.7 Hz, CHH indole), 3.61-3.74 (2H, m, CHHOH), 5.00 (1H, m, $CHCH_2OH$), 5.04 (1H, d, 12.4 Hz, CHHOCONH),

5.11 (1H, d, 12.2 Hz, CHHOCONH), 5.41 (1H, s, $NHCO_2CH_2$), 6.54 (1H, d, 7.6 Hz, CONHCH), 6.89 (1H, s, ArH), 7.10-7.36 (13H, m, ArH), 7.59 (1H, d, 7.9 Hz, ArH), 8.05 (1H, s, indole NH);
IR: 3807.0, 1704.0, 1632.0, 1504.0, 1455.0, 1253.0, 1105.0, 1073, 740.0, 697.0 cm^{-1};
Anal. $C_{28}H_{29}N_3O_4$: C,H,N.

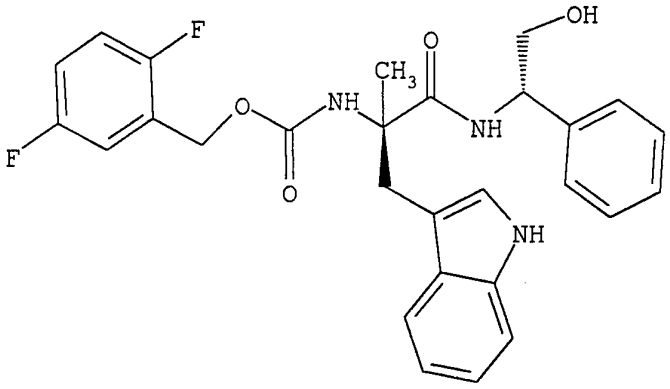
EXAMPLE 16



Carbamic acid, [2-[(2-hydroxy-1-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, (2-fluorophenyl)methyl ester, [R-(R*,R*)]-
Compound 7 (ii)
^1H NMR ($CDCl_3$): δ 1.66 (3H, s, αCH_3), 2.65 (1H, bs, OH), 3.25 (1H, d, 14.4 Hz, CHH indole), 3.42 (1H, d, 14.8 Hz, CHH indole), 3.62-3.68 (1H, m CHHOH), 3.70-3.80 (1H, m, CHHOH), 5.00 (1H, m, $CHCH_2OH$), 5.12 (1H, d, 12.4 Hz, CHHOCONH), 5.20 (1H, d, 12.4 Hz, CHHOCONH), 5.45 (1H, s, $NHCO_2CH_2$), 6.56 (1H, d, 8.0 Hz, CONHCH), 6.92 (1H, d, 2.4 Hz, ArH), 7.05-7.39 (12H, m, ArH), 7.59 (1H, d, 8.0 Hz, ArH), 8.12 (1H, s, indole NH);

IR: 3340.0, 1709.0, 1660.0, 1495.0, 1456.0, 1234.0, 1073.0 cm^{-1};
MS m/e (FAB) 490.4 (M+H), 512.3 (M+Na);
α^D = +25.53 (MEOH, c = 0.38 g, 100 mL^{-1});
mp 146.5-147.5°C;
HPLC R.T. = 11.208, C^{18} reverse phase, 40-100% MeCN:TFA/water:TFA;
Anal. $C_{28}H_{28}FN_3O_4 \cdot 0.6H_2O$: C,H,N.

EXAMPLE 17



Carbamic acid, [2-[(2-hydroxy-1-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, (2,5-difluorophenyl)methyl ester, [R-(R*,R*)]

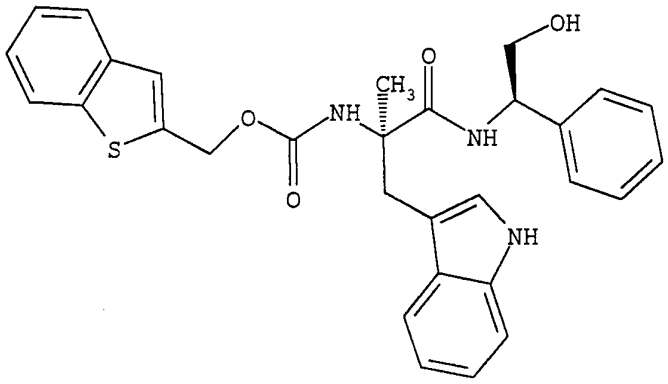
Compound 7 (iii)

^1H NMR ($CDCl_3$): δ 1.70 (3H, s, αCH_3), 2.42 (1H, bs, OH), 3.28 (1H, d, 14.4 Hz, CHH indole), 3.46 (1H, d, 14.8 Hz, CHH indole), 3.66-3.80 (2H, m, CHHOH), 5.00 (1H, m, $CHCH_2OH$), 5.10 (1H, d, 13.0 Hz, CHHOCONH), 5.16 (1H, d, 12.8 Hz, CHHOCONH), 5.53 (1H, s, $NHCO_2CH_2$), 6.53 (1H, d, 7.5 Hz, CONHCH), 6.97-7.36 (11H, m, ArH), 7.37 (1H, d, 8.1 Hz, ArH), 7.61 (1H, d, 7.9 Hz, ArH), 8.00 (1H, s, indole NH);
IR: 3332.0, 1714.0, 1660.7, 1496.0, 1248.0, 1072 cm^{-1};
MS m/e (FAB) 508.5 (M+H);
α^D = +20.00 (MEOH, c = 0.045 g, 100 mL^{-1});

mp 136-139°C;

Anal. $C_{28}H_{27}F_2N_3O_4$: C,H,N.

EXAMPLE 18



Carbamic acid, [2-[(2-hydroxy-1-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, benzo[b]thien-2-ylmethyl ester, [R-(R*,R*)]-

Compound 7 (v)

^{1}H NMR ($CDCl_3$): δ 1.69 (3H, s, $\alpha C\underline{H}_3$), 2.53 (1H, bs, O$\underline{H}$), 3.24 (1H, d, 14.8 Hz, CH$\underline{H}$ indole), 3.43 (1H, d, 14.8 Hz, CH$\underline{H}$ indole), 3.60-3.68 (1H, m, CH$\underline{H}$OH), 3.70-3.79 (1H, m, CH$\underline{H}$OH), 5.00 (1H, m, $C\underline{H}CH_2OH$), 5.26 (1H, d, 12.8 Hz, C$\underline{H}$HOCONH), 5.37 (1H, d, 12.8 Hz, CH$\underline{H}$OCONH), 5.46 (1H, s, $N\underline{H}CO_2CH_2$), 6.49 (1H, d, 7.6 Hz, CON$\underline{H}$CH), 6.91 (1H, s, Ar$\underline{H}$), 7.09-7.36 (11H, m, Ar$\underline{H}$), 7.59 (1H, d, 7.8 Hz, Ar$\underline{H}$), 7.74 (1H, dd, 6.35, 5.37 Hz, Ar$\underline{H}$), 7.79 (1H, dd, 6.35 Hz, Ar$\underline{H}$), 7.96 (1H, s, indole N$\underline{H}$);

IR: 3375.0, 1705.0, 1653.0, 1495.0, 1457.0 cm^{-1};

MS m/e (FAB) 528.0 (M+H), 550.6 (M+Na);

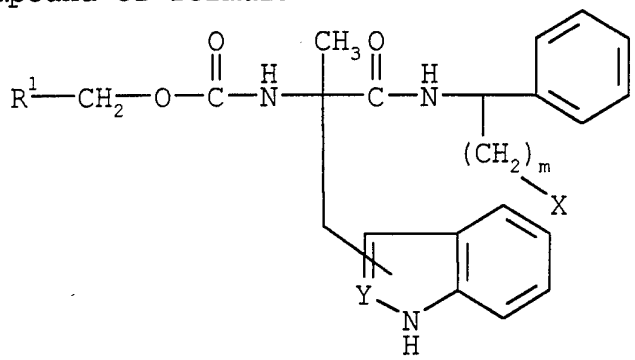
α^D = +31.43 (MEOH, c = 0.07 g, 100 mL^{-1});

mp 77-82°C;

Anal. $C_{30}H_{29}N_3O_4S$: C,H,N.

CLAIMS

1. A compound of formula



I

or a pharmaceutically acceptable salt thereof wherein

R^1 is phenyl, pyridine, thiophene, furan, naphthalene, indole, benzofuran, or benzothiophene each unsubstituted, mono-, di-, or trisubstituted by alkyl, hydroxy, alkoxy, nitro, halogen, amino, or trifluoromethyl;

X is OR^2 wherein R^2 is hydrogen, $(CH_2)_nNR^3R^4$, or a promoiety, or

X is NH_2,
NHCO-promoiety,
$NHCO(CH_2)_nNR^3R^4$,
NR^3R^4, or
$(CH_2)_nNR^3R^4$ wherein n is an integer of from 0 to 5 and R^3 and R^4 are each independently selected from hydrogen and methyl or R^3 and R^4 form a ring together with the N to which they are attached;

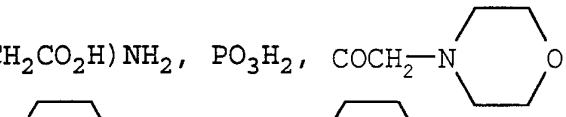
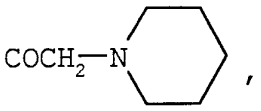
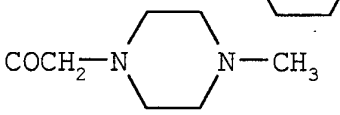
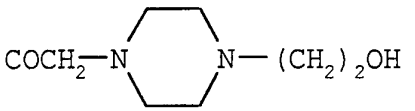
m is an integer of from 1 to 6; and

Y is CH, CCH_3, CF, CCl, CBr, $CSCH_3$, or N.

2. A compound according to Claim 1 wherein

R^1 is phenyl, pyridine, thiophene, furan, naphthalene, indole, benzofuran, or

benzothienyl each unsubstituted or mono-, di-, or trisubstituted by alkyl, hydroxy, alkoxy, nitro, halogen, amino, or trifluoromethyl;

X is OR^2 wherein R^2 is hydrogen or a promoiety selected from: $COCH_2N(CH_3)_2$, $COC(CH_3)_2N(CH_3)_2$, $COCH[CH_2CH(CH_3)_2]NH_2$, $COCH(CH_2CO_2H)NH_2$, PO_3H_2,  ,  ,  ,  , and $(CH_2)_nNR^3R^4$, or

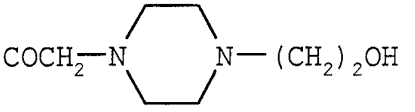
X is $NHCO(CH_2)_nNR^3R^4$ or NR^3R^4 wherein n is an integer of from 0 to 5 and R^3 and R^4 are each independently hydrogen or methyl;

m is 1; and

Y is CH, CCH_3, CF, CCl, CBr, $CSCH_3$, or N.

3. A compound according to Claim 1 wherein

R^1 is phenyl, 2-benzofuran, 2-fluorophenyl, 2,5-difluorophenyl, 2-benzothienyl, or 4-CH_3; 2-fluorophenyl;

X is OR^2 wherein R^2 is hydrogen, or a promoiety selected from: $COCH(CH_2(CH_3)_2)NH_2$, or $COCH_2N(CH_3)_2$,  , or

or X is NH_2 or $NHCH_3$;

m is 1; and

Y is CH.

4. A compound according to Claim 1 selected from

Carbamic acid, [2-[(2-hydroxy-1-phenylethyl)-amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-benzofuranylmethyl ester, [R-(R*,R*)]-;

Carbamic acid, [2-[(2-hydroxy-1-phenylethyl)-amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, (2-fluorophenyl)methyl ester, [R-(R*,R*)]-;

Carbamic acid, [2-[(2-hydroxy-1-phenylethyl)-amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, benzo[b]thien-2-ylmethyl ester, [R-(R*,R*)]-;

L-Leucine, 2-[[2-[[(2-benzofuranyl-methoxy)carbonyl]amino]-3-(1H-indol-3-yl)-2-methyl-1-oxopropyl]amino]-2-phenylethyl ester, [R-(R*,R*)]-;

Carbamic acid, [2-[(2-amino-1-phenylethyl)-amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-benzofuranylmethyl ester, [R-(R*,R*)]-;

Carbamic acid, [2-[(2-amino-1-phenylethyl)-amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-benzofuranylmethyl ester, [R-(R*,R*)]-;

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, phenylmethyl ester, [R-(R*,R*)]-;

Carbamic acid, [2-(2-hydroxy-1-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-benzofuranylmethyl ester, [R-(R*,R*)]-;

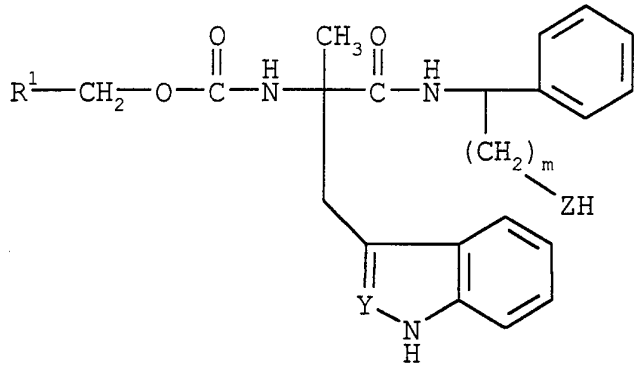
Carbamic acid, [2-[[(2-[[(dimethylamino)-acetyl]amino]-1-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-benzofuranyl-methyl ester, monohydrochloride, [R-(R*,R*)]-.

5. A compound selected from:

Carbamic acid, [2-[(2-hydroxy-1-phenylethyl)-amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, (2,5-difluorophenyl)methyl ester, [R-(R*,R*)]; and

Glycine, N,N-dimethyl-, 2-[[2-[[(2-benzofuranylmethoxy)carbonyl]amino]-3-(1H-indol-3-yl)-2-methyl-1-oxopropyl]amino]-2-phenylethyl ester, monohydrochloride, [R-(R*,R*)]-.

6. A compound of formula



II

wherein

R^1 is phenyl, pyridine, thiophene, furan, naphthalene, indole, benzofuran, or benzothienyl each unsubstituted or mono-, di-, or trisubstituted by alkyl, hydroxy, alkoxy, nitro, halogen, amino, or trifluoromethyl;

m is an integer of from 1 to 6; and,

Y is CH_2, CCH_3, CF, CCl, CB_5, $CSCH_3$, or N; and Z is oxygen or NH.

7. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat respiratory disorders in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

8. A method for treating respiratory disorders in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.

9. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat asthma in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

10. A method for treating asthma in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.

11. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat inflammation in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

12. A method for treating inflammation in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.

13. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat arthritis in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

14. A method for treating arthritis in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.

15. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat gastrointestinal disorders in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

16. A method for treating gastrointestinal disorders in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.

17. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat ophthalmic diseases in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

18. A method for treating ophthalmic diseases in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.

19. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat allergies in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

20. A method for treating allergies in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.

21. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat diseases of the central nervous system in a

mammal suffering therefrom, and a pharmaceutically acceptable carrier.

22. A method for treating diseases of the central nervous system in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.

23. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat migraine in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

24. A method for treating migraine in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.

25. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat inflammatory pain or neurogenic inflammation in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

26. A method for treating inflammatory pain or neurogenic inflammation in a mammal comprising administration of therapeutically effective amounts of a compound according to Claim 1.

27. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat rheumatoid arthritis in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

28. A method for treating rheumatoid arthritis in a mammal comprising administration of therapeutically effective amounts of a compound according to Claim 1.

29. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat atherosclerosis in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

30. A method for treating atherosclerosis in a mammal comprising administration of therapeutically effective amounts of a compound according to Claim 1.

31. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat tumor cell growth in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

32. A method for treating tumor cell growth in a mammal comprising administration of therapeutically effective amounts of a compound according to Claim 1.

33. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat emesis in a mammal suffering therefrom and a pharmaceutically acceptable carrier.

34. A method for treating and/or preventing emesis in a mammal comprising administration of a therapeutically effective amount of a compound according to Claim 1.

35. A pharmaceutical composition comprising an amount of a compound accordance to Claim 1 effect to treat multiple sclerosis in a mammal suffering therefrom and a pharmaceutically acceptable carrier.

36. A method for treating multiple sclerosis in a mammal comprising administration of a therapeutically effective amount of a compound according to Claim 1.

37. A diagnostic useful in imaging NK_1 receptors in vivo.

38. A method of antagonizing NK_1 receptors by administering a compound according to Claim 1.

INTERNATIONAL SEARCH REPORT

Intc. ...nal Application No
PCT/US 95/06289

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D405/12 A61K31/40 C07D209/20 C07D409/12

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)
IPC 6 C07D A61K

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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 04494 (WARNER-LAMBERT COMPANY) 3 March 1994 cited in the application see claims ---	1,7
A	WO,A,93 01169 (MERCK SHARP & DOHME LTD.) 21 January 1993 cited in the application see claims -----	1,7

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

☒ Patent family members are listed in 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 document but 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	Date of mailing of the international search report
7 August 1995	18.08.95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I ...national application No.
PCT/US95/06289

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

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely: 32
Although claims 8,10,12,14,16,18,20,22,24,26,28,30,34,36 and 38 are directed to a method of treatment of(diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/ composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inte ɔnal Application No
PCT/US 95/06289

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9404494	03-03-94	AU-B-	5005593	15-03-94
		EP-A-	0655055	31-05-95
WO-A-9301169	21-01-93	CA-A-	2110514	21-01-93
		EP-A-	0593559	27-04-94
		JP-T-	6509087	13-10-94
		AU-A-	2244092	11-02-93
		CA-A-	2110513	21-01-93
		CA-A-	2110725	21-01-93
		EP-A-	0522808	13-01-93
		EP-A-	0593557	27-04-94
		EP-A-	0593615	27-04-94
		WO-A-	9301159	21-01-93
		WO-A-	9301160	21-01-93
		WO-A-	9301165	21-01-93
		JP-T-	6509332	20-10-94
		JP-T-	6509090	13-10-94