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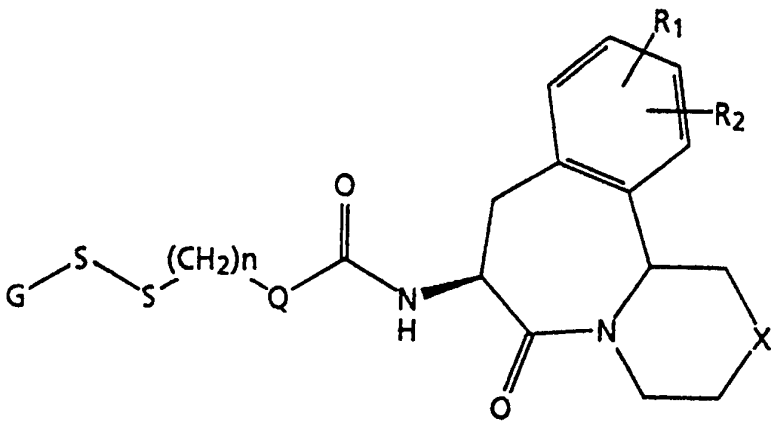
(54) Title: NOVEL INDANE-2-MERCAPTOACETYLAMIDE DISULFIDE DERIVATIVES USEFUL AS INHIBITORS OF ENKEPHALINASE

(57) Abstract

The present invention relates to certain novel indane-2-mercaptoacetylamide disulfide derivatives of formula (I) useful as inhibitors of enkephalinase.



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NOVEL INDANE-2-MERCAPTOACETYLAMIDE DISULFIDE DERIVATIVES USEFUL AS INHIBITORS OF ENKEPHALINASE

BACKGROUND OF THE INVENTION

Enkephalinase or, more specifically, endopeptidase-24.11, is a mammalian ectoenzyme which is involved in the metabolic degradation of certain circulating regulatory peptides. This enzyme, which is a Zn^{+2}-metallopeptidase, exerts its effect by cleaving the extracellular peptides at the amino group of hydrophobic residues and thus inactivates the peptides as regulatory messengers.

Enkephalinase is involved in the metabolic degradation of a variety of circulating regulatory peptides including endorphins, such as β-endorphin and the enkephalins, atrial natriuretic peptide (ANP), and other circulating regulatory peptides.

Endorphins are naturally-occurring polypeptides which bind to opiate receptors in various areas of the brain and thereby provide an analgesic effect by raising the pain threshold. Endorphins occur in various forms including α-endorphin, β-endorphin, γ-endorphin as well as the enkephalins. The enkephalins, i.e., Met-enkephalin and Leu-enkephalin, are pentapeptides which occur in nerve endings

of brain tissue, spinal cord and the gastrointestinal tract. Like the other endorphins, the enkephalins provide an analgesic effect by binding to the opiate receptors in the brain. By inhibiting enkephalinase, the metabolic degradation of the naturally-occurring endorphins and enkephalins are inhibited, thereby providing a potent endorphin- or enkephalin-mediated analgesic effect. Inhibition of enkephalinase would therefore be useful in a patient suffering from acute or chronic pain. Inhibition of enkephalinase would also be useful in providing an antidepressant effect and in providing a reduction in severity of withdrawal symptoms associated with termination of opiate or morphine administration. In addition, inhibition of enkephalinase would also be useful in the treatment of irritable bowel syndrome.

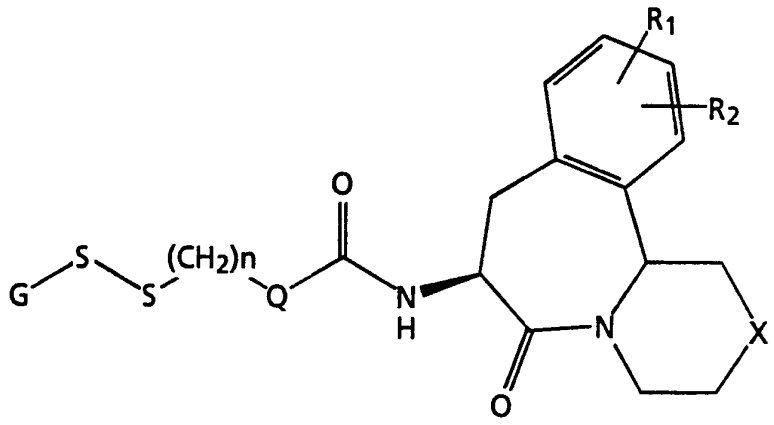
ANP refers to a family of naturally-occurring peptides which are involved in the homeostatic regulation of blood pressure, as well as sodium and water levels. ANP have been found to vary in length from about 21 to about 126 amino acids with a common structural feature being one or more disulfide-looped sequences of 17 amino acids with various amino- and carboxy-terminal sequences attached to the cysteine moiety. ANP have been found to bind to specific binding sites in various tissues including kidney, adrenal, aorta, and vascular smooth muscle with affinities ranging from about 50 pico-molar (pM) to about 500 nano-molar (nM) [Needleman, Hypertension 7, 469 (1985)]. In addition, it is believed that ANP binds to specific receptors in the brain and possibly serves as a neuromodulator as well as a conventional peripheral hormone.

The biological properties of ANP involve potent diuretic/natriuretic and vasodilatory/hypotensive effects as well as an inhibitory effect on renin and aldosterone secretion [deBold, Science 230, 767 (1985)]. By inhibiting enkephalinase, the metabolic degradation of the naturally-

occurring ANP are inhibited, thereby providing a potent ANP-mediated diuretic, natriuretic, hypotensive, hypoaldosteronemic effects. Inhibition of enkephalinase would therefore be useful in a patient suffering from disease states characterized by abnormalities in fluid, electrolyte, blood pressure, intraocular pressure, renin, or aldosterone homeostasis, such as, but not limited to, hypertension, renal diseases, hyperaldosteronemia, cardiac hypertrophy, glaucoma and congestive heart failure.

SUMMARY OF THE INVENTION

The present invention provides novel compounds of the Formula (I)



Formula (I)

wherein

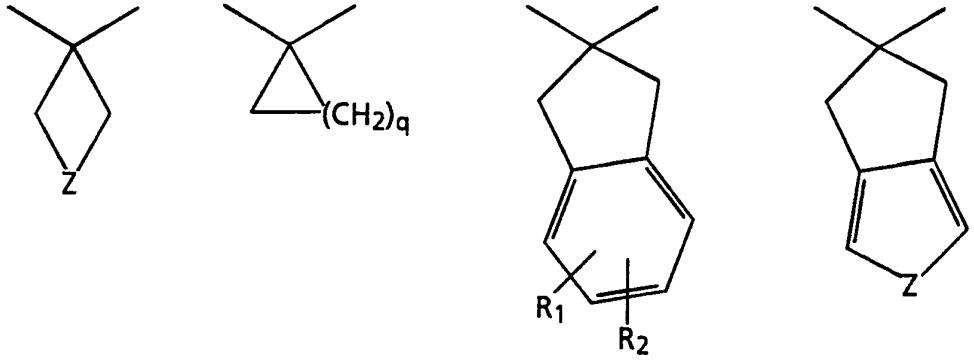
n is an integer from 0 to 3;

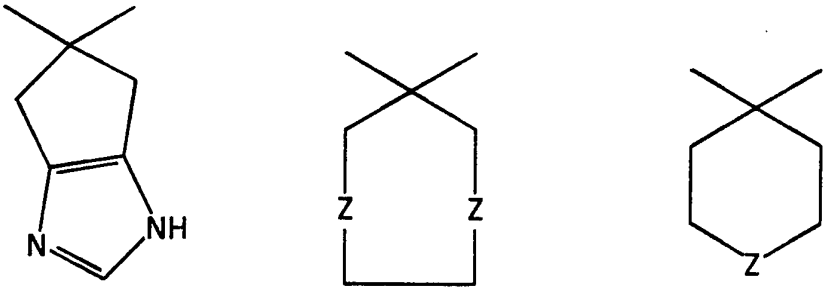
R_1 and R_2 are each time taken independently chosen from the group consisting of: hydrogen, hydroxy, $-OR_3$ wherein R_3 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken

together with said adjacent carbons to form a benzene ring or methylenedioxy;

X is $-(CH_2)_p-$, O, S, NR_4, or $NC(O)R_5$ wherein p is an integer 0 or 1, R_4 is hydrogen, a C_1-C_4 alkyl, or an Ar-Y- group, and R_5 is $-CF_3$, C_1-C_{10} alkyl, or an Ar-Y- group;

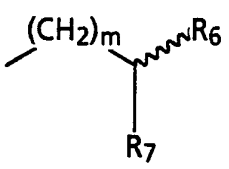
Q is a alkylene radical chosen from the group

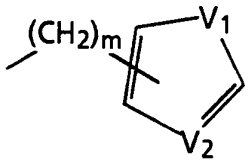


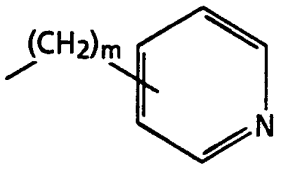


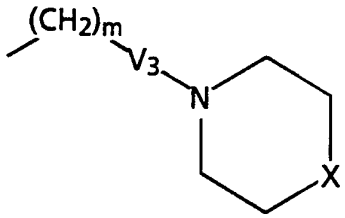
wherein q is an integer from 1 to 5 and Z is O, S, NH;

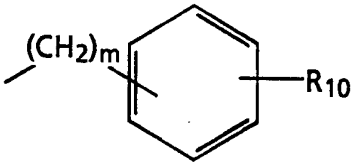
G is a radical chosen from the group;

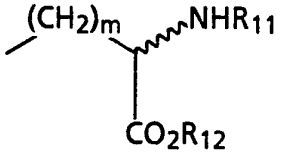


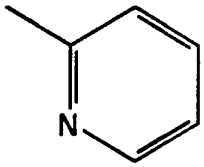












wherein

m is an integer from 1 to 3;

R_6 is hydrogen, C_1-C_6 alkyl, $-CH_2CH_2S(O)_kCH_3$, or Ar-Y- wherein k is an integer form 0 to 2;

R_7 is hydrogen, hydroxy, amino, C_1-C_6 alkyl, N-methylamino, N,N-dimethylamino, $-CO_2R_8$ wherein R_8 is hydrogen, $-CH_2O-C(O)C(CH_3)_3$, or C_1-C_4 alkyl; or $-OC(O)R_9$ wherein R_9 is hydrogen, C_1-C_6 alkyl, or phenyl;

R_{10} is 1 or 2 substituents independently chosen from the group consisting of; hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or halogen;

R_{11} is hydrogen, C_1-C_6 alkyl, or Ar-Y- group;

R_{12} is hydrogen or C_1-C_4 alkyl;

V_1 is O, S, or NH;

V_2 is N or CH;

V_3 is a direct bond or -C(O)-;

or stereoisomers or pharmaceutically acceptable salts thereof.

The present invention further provides a method of inhibiting enkephalinase in a patient in need thereof comprising administering to said patient an effective enkephalinase inhibitory amount of a compound of Formula (I).

In addition, the present invention provides a composition comprising an assayable amount of a compound of Formula (I) in admixture or otherwise in association with an inert carrier. The present invention also provides a pharmaceutical composition comprising an effective inhibitory amount of a compound of Formula (I) in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

DETAILED DESCRIPTION OF THE INVENTION

As used in this application:

a) the term "C_1-C_6 alkyl" refers to a saturated straight or branched chain hydrocarbyl radical of from one to six carbon atoms and includes methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, n-pentyl, cyclo-pentyl, n-hexyl, cyclo-hexyl and the like;

b) the term "C_1-C_4 alkyl" refers to a saturated straight or branched chain hydrocarbyl radical of from one to six carbon atoms and includes methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl;

c) the designation "▬" refers to a bond that protrudes forward out of the plane of the page;

d) the designation "||||||||||" refers to a bond that protrudes backward out of the plane of the page;

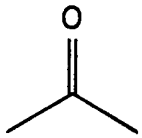
e) the designation "〰" refers to a bond for which the stereochemistry is not designated;

f) the term "halogen", "halo", "halide", or "Hal" refers to chlorine atom, bromine atom, or iodine atom;

g) the terms "C_1-C_8 alkyl" and "C_1-C_{10} alkyl" refer to saturated straight or branched chain hydrocarbyl radicals of one to eight and one to ten carbon atoms, respectively, including methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, pentyl, isopentyl, hexyl, 2,3-dimethyl-2-butyl, heptyl, 2,2-dimethyl-3-pentyl, 2-methyl-2-hexyl, octyl, 4-methyl-3-heptyl and the like;

h) the term "C_1-C_4 alkoxy" refer to a straight or branched alkoxy group containing from 1 to 4 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, t-butoxy, etc;

i) the designation "-C(O)-" refers to a carbonyl group of the formula:



j) the term "Ar-Y-" refers to a radical wherein Ar is an aryl group and Y is a C_0-C_4 alkyl;

k) the term "C_0-C_4 alkyl" refers to a saturated straight or branched chain hydrocarbyl radical of zero to four carbon atoms and includes a bond, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl and the like;

l) the term "Ar" or "aryl group" refers to a phenyl or naphthyl group unsubstituted or substituted with from one to three substituents selected from the group consisting of methylenedioxy, hydroxy, C_1-C_4 alkoxy, fluoro and chloro; specifically included within the scope of the term "arylalkyl" are phenyl, naphthyl, naphthylmethyl, phenylmethyl or benzyl, phenylethyl, p-methoxybenzyl, m-aminophenyl, m-nitrophenyl, p-aminophenyl, p-nitrophenyl, 3,4-methylenedioxybenzyl, p-fluorobenzyl and p-chlorobenzyl;

m) the term "protected amino" refers to either a $-NHPg_1$ or $-NPg_2Pg_3$ wherein Pg_1, Pg_2, and Pg_3 are amino protecting groups as described in Protecting Groups in Organic Synthesis by T. Greene as is well known and appreciated by those skilled in the art which allow for the formation of disulfides and then are removable to afford compounds of Formula (I) in which R_9 in amino;

n) the term "Pg" refers to protecting group;

o) the term "pharmaceutically acceptable salts" refers to either acid addition salts or to base addition salts.

The expression "pharmaceutically acceptable acid addition salts" is intended to apply to any non-toxic organic or inorganic acid addition salt of a compound of Formula (I) or any of its intermediates. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric, and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate, and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono-, di-, and tricarboxylic acids. Illustrative of such acids are for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxy-benzoic, phenylacetic, cinnamic, salicyclic, 2-phenoxy-benzoic, and sulfonic acids such as p-toluenesulfonic acid, methane sulfonic acid and 2-hydroxyethane sulfonic acid. Such salts can exist in either a hydrated or substantially anhydrous form.

The expression "pharmaceutically acceptable basic addition salts" is intended to apply to any non-toxic organic or inorganic basic addition salts of a compound of Formula (I) or any of its intermediates. Illustrative bases which form suitable salts include alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, magnesium, or barium hydroxides; ammonia, and aliphatic, cyclic, or aromatic organic amines such as methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, isopropyldiethylamine, pyridine and picoline.

As is appreciated by one of ordinary skill in the art the compounds of the Formula (I) may exist as stereoisomers. Any reference in this application to one of the compounds of the Formula (I) is meant to encompass either specific stereoisomers or a mixture of stereoisomers. The specific stereoisomers can be prepared by stereospecific synthesis or can be separated and recovered by techniques known in the

art, such as chromatography, chromatography on chiral stationary phases, fractional recrystallization of addition salts formed by reagents used for that purpose, as described in Enantiomers, Racemates, and Resolutions, J. Jacques, A. Collet, and S. H. Wilen, Wiley (1981).

Examples of compounds encompassed by the present invention include:

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-thiopyridine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, benzylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, ethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-hydroxyethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-pyridylmethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-thioacetic acid morpholine carboxamide, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, L-cysteine ethyl ester, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, N-acetyl-L-cysteine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, L-cysteine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (R)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-(2-Thio-ethyl)-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-methyl-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-N-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Thio-1-oxocyclopentane)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5-dihydro-cyclopentimidazole)methylamino]-3,4,6,7,8,12b-hexahydro-6-

oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]furan)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]thiophene)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

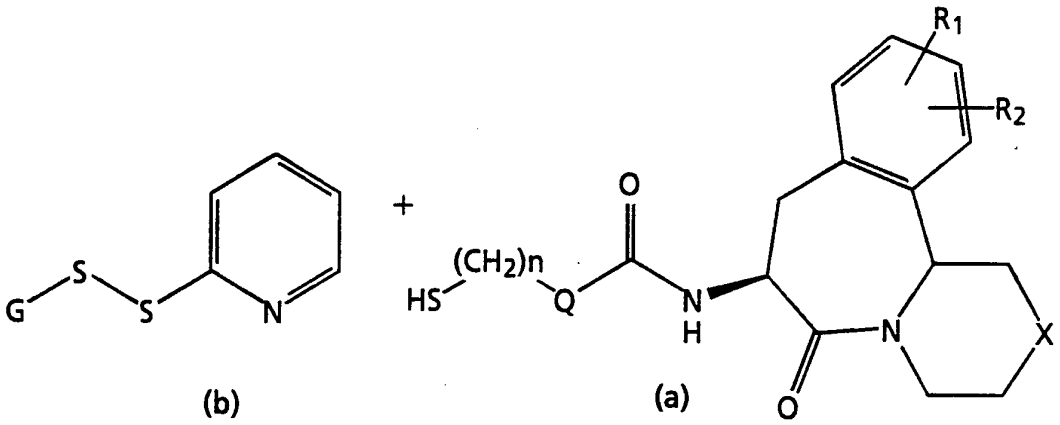
[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-azazino[3,4-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[6α(R*), 11bβ]-6-[(S)-(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

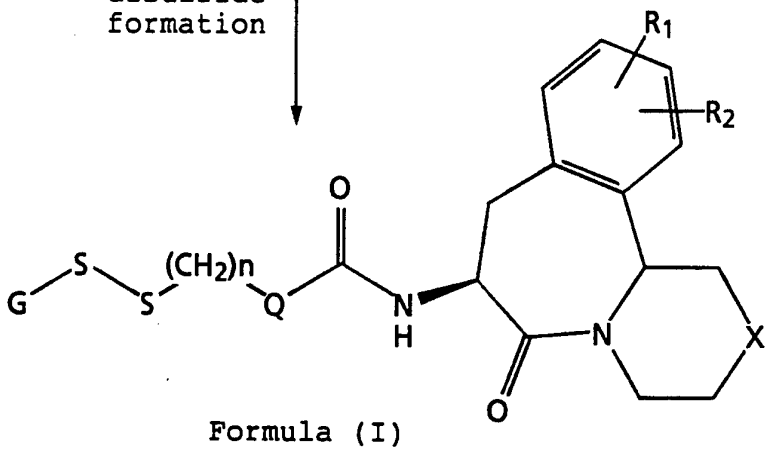
[4S-[4α, 7α(R*), 12bβ]]-7-[(4-Thio-4-oxopiperidine)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

A general synthetic procedure is set forth in Scheme 1 for preparing compounds of Formula (I). In Scheme 1, all substituents unless otherwise indicated, are as previously defined. Starting materials, reagents, techniques, and procedures used in Scheme 1 are well known and appreciated by one of ordinary skill in the art.

SCHEME 1

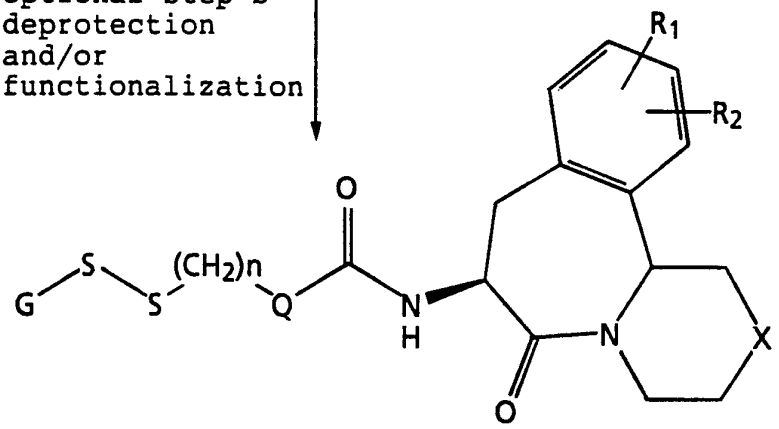


step a
disulfide
formation



Formula (I)
or protected
Formula (I)

optional step b
deprotection
and/or
functionalization



Formula (I)

The disulfide of structure (b) can be obtained by methods known in the art or by methods known analogously in the art, B. P. Roques et al, J. Med. Chem. 33, 2473-2481 (1992). Thiols of structure (a) are prepared in Schemes A, B, and C.

In Scheme 1, step a, an appropriate disulfide of structure (b) is contacted with an appropriate thiol of structure (a) to give a disulfide of Formula (I) or a protected disulfide of Formula (I). An appropriate disulfide of structure (b) is one in which G is as desired in the final product of Formula (I) or gives rise upon deprotection to G as is desired in the final product of Formula (I). An appropriate thiol of the structure (a) is one in which R_1, R_2, Q, X, and n are as desired in the final product of Formula (I) or give rise after deprotection and/or functionalization to R_1, R_2, Q, and X as desired in the final product of Formula (I).

For example, an appropriate disulfide of structure (b) is contacted with an appropriate thiol of structure (a). The reaction is carried out in a suitable solvent, such as ethanol, methanol, dichloromethane, or mixtures of ethanol or methanol and dichloromethane. The solvent is degassed by passing a stream of nitrogen gas through it for 15 minutes before the reaction is carried out. The reaction is carried out using from 1.0 to 4.0 molar equivalents of an appropriate compound of structure (b). The reaction is carried out at temperatures of from 0°C to the refluxing temperature of the solvent, with a temperature of 10°C to 30°C being preferred. The reaction generally requires from 1 to 48 hours. The product can be isolated by techniques well known in the art, such as extraction, evaporation, and precipitation. The product can be purified by chromatography and recrystallization.

In Scheme 1, optional step b, a protected disulfide of Formula (I) is deprotected and or functionalized to give a disulfide of Formula (I).

The selection, use, and removal of protecting groups and the removal of protecting groups in a sequential manner utilizing suitable protecting groups such as those described in Protecting Groups in Organic Synthesis by T. Greene is well known and appreciated by those skilled in the art. The removal of protecting groups or the removal of protecting groups in a sequential manner as required gives disulfides of Formula (I).

A functionalization reaction includes the alkylation or acylation of amines and the formation of esters. These functionalizations can be carried out by methods which are well known in the art. Selective functionalizations using protecting groups in a sequential manner is well known and appeciated in the art.

The following examples present typical syntheses as described in Scheme 1. These examples are understood to be illustrative only and are not intended to limit the scope of the invention in any way. As used in the following examples, the following terms have the meanings indicated: "g" refers to grams, "mmol" refers to millimoles, "mL" refers to milliliters, "°C" refers to degrees Celsius, "R_f" refers to retention factor, "mp" refers to melting point, "dec" refers to decomposition, "M" refers to molar, and "TLC" refers to thin layer chromatography.

EXAMPLE 1

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

Scheme 1, step a:

Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (0.384 g, 0.94 mmol) and (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, 2-thiopyridine, disulfide (0.356 1.04 mmol) in degassed ethanol (8 mL). Stir for 18 hours. Evaporate in vacuo. Chromatograph on silica gel eluting sequentially with 25% ethylacetate/ hexane and then 38% ethylacetate/ hexane to give the title compound as a white solid.

EXAMPLE 2

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-(2-Thio-ethyl)-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;
Scheme 1, step a:

Prepare in a manner similar to Example 1 using [4S-[4α, 7α(R*), 12bβ]]-7-[(2-(2-Mercaptoethyl)-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine.

EXAMPLE 3

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-methyl-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine(S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;
Scheme 1, step a:

Prepare in a manner similar to Example 1 using [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Mercaptomethyl-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine.

EXAMPLE 4

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Thio-1-oxocyclopentane)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

Scheme 1, step a:

Prepare in a manner similar to Example 1 using [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Thio-1-oxocyclopentane)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine.

EXAMPLE 5

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5-dihydro-cyclopentimidazole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

Scheme 1, step a:

Prepare in a manner similar to Example 1 using [4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5-dihydro-cyclopentimidazole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine.

EXAMPLE 6

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]furan)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

Scheme 1, step a:

Prepare in a manner similar to Example 1 using [4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]furan)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine.

EXAMPLE 7

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]thiophene)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

Scheme 1, step a:

Prepare in a manner similar to Example 1 using [4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]thiophene)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine.

EXAMPLE 8

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-azazino[3,4-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

Scheme 1, step a:

Prepare in a manner similar to Example 1 using [4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-azazino[3,4-a][2]benzazepine.

EXAMPLE 9

[6α(R*), 11bβ]-6-[(S)-(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

Scheme 1, step a:

Prepare in a manner similar to Example 1 using [6α(R*), 11bβ]-6-[(S)-(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine.

EXAMPLE 10

[4S-[4α, 7α(R*), 12bβ]]-7-[(4-Thio-4-oxopiperidine)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

Scheme 1, step a:

Prepare in a manner similar to Example 1 using [4S-[4α, 7α(R*), 12bβ]]-7-[(4-Thio-4-oxopiperidine)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine.

EXAMPLE 11

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide trifluoroacetic acid salt; Scheme 1, optional step b:

Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide (0.526 g, 0.825 mmol), and trifluoroacetic acid (1.5 mL) in dichloromethane (7.5 mL). Stir for 3 hours and evaporate *in vacuo*. Repeatedly, add carbon tetrachloride and evaporate *in vacuo* to remove residual trifluoroacetic acid. Evaporation *in vacuo* from hexane/dichloromethane gives the title compound as a solid. Mass spectum CI/CH_4 $M+H^+$ 538.

EXAMPLE 12

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-(2-Thioethyl)-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide trifluoroacetic acid salt; Scheme 1, optional step b:

Prepare in a manner similar to Example 11 using [4S-[4α, 7α(R*), 12bβ]]-7-[(2-(2-Thioethyl)-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

EXAMPLE 13

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thiomethyl-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-

oxopyrido[2,1-a][2]benzazepine, (S)-N-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide trifluoroacetic acid salt;
Scheme 1, optional step b:

Prepare in a manner similar to Example 11 using [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thiomethyl-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine(S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

EXAMPLE 14

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Thio-1-oxocyclopentane)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide trifluoroacetic acid salt;
Scheme 1, optional step b:

Prepare in a manner similar to Example 11 using [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Thio-1-oxocyclopentane)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

EXAMPLE 15

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5-dihydro-cyclopentimidazole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide trifluoroacetic acid salt;
Scheme 1, optional step b:

Prepare in a manner similar to Example 11 using [4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5-dihydro-cyclopentimidazole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

EXAMPLE 16

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]furan)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide trifluoroacetic acid salt;

Scheme 1, optional step b:

Prepare in a manner similar to Example 11 using [4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]furan)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

EXAMPLE 17

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]thiophene)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide trifluoroacetic acid salt;

Scheme 1, optional step b:

Prepare in a manner similar to Example 11 using [4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]thiophene)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

EXAMPLE 18

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-azazino[3,4-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide trifluoroacetic acid salt;

Scheme 1, optional step b:

Prepare in a manner similar to Example 11 using [4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-azazino[3,4-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

EXAMPLE 19

[6α(R*), 11bβ]-6-[(S)-(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide trifluoroacetic acid salt;

Scheme 1, optional step b:

Prepare in a manner similar to Example 11 using [6α(R*), 11bβ]-6-[(S)-(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

EXAMPLE 20

[4S-[4α, 7α(R*), 12bβ]]-7-[(4-Thio-4-oxopiperidine)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide trifluoroacetic acid salt;

Scheme 1, optional step b:

Prepare in a manner similar to Example 11 using [4S-[4α, 7α(R*), 12bβ]]-7-[(4-Thio-4-oxopiperidine)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

EXAMPLE 21

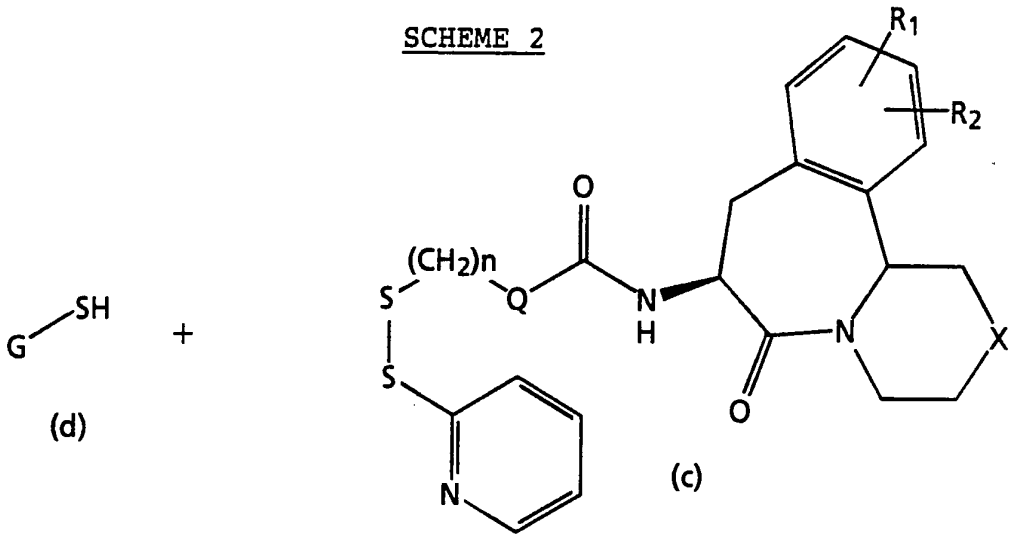
[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-thiopyridine, disulfide;

Scheme 2, step a:

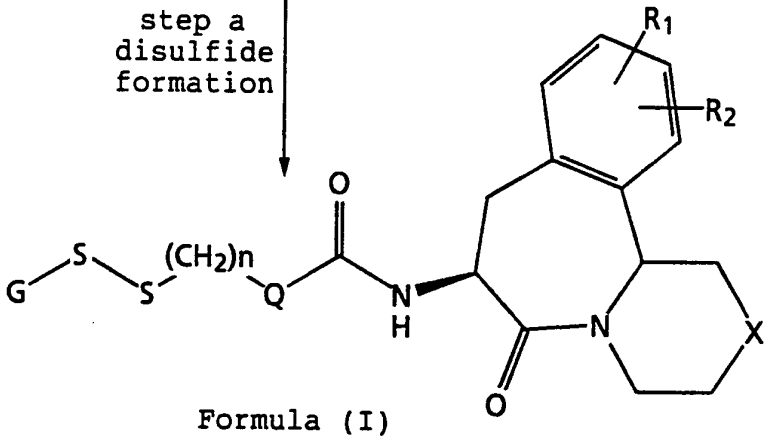
Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (4.0 mmol) and 2,2'-dithiodipyridine (16.0 mmol) is degassed ethanol (24 mL) and dichloromethane (6 mL). Stir under an inert atmosphere at ambient temperature for 20 hours. Evaporate in vacuo to obtain a residue. Chromatograph the residue on silica gel to give the title compound.

An alternate general synthetic procedure is set forth in Scheme 2 for preparing compounds of Formula (I). In Scheme 2, all substituents unless otherwise indicated, are as previously defined. Starting materials, reagents, techniques, and procedures used in Scheme 2 are well known and appreciated by one of ordinary skill in the art.

SCHEME 2

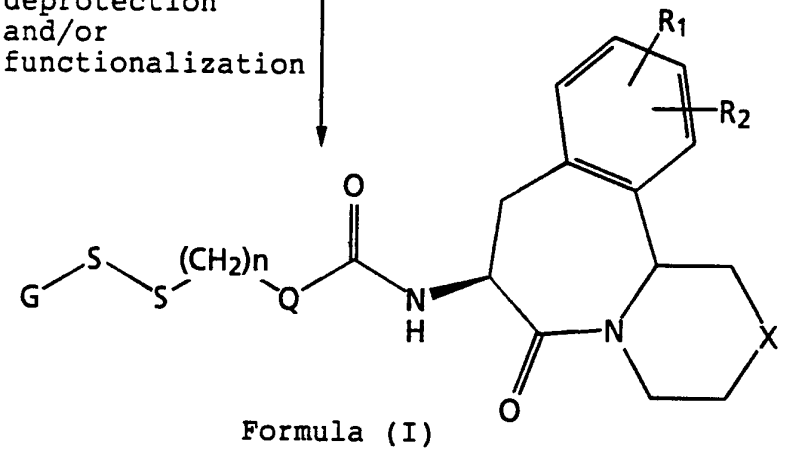


step a
disulfide
formation



Formula (I)
or protected
Formula (I)

optional step b
deprotection
and/or
functionalization



Formula (I)

In Scheme 2, step a, an appropriate thiol of structure (d) is contacted with an appropriate disulfide of structure (c) to give a disulfide of Formula (I) or a protected disulfide of Formula (I) by the method taught above in Scheme 1, step a. An appropriate thiol of structure (d) is one in which G is as desired in the final product of Formula (I) or gives rise after deprotection to G as desired in the final product of Formula (I). An appropriate disulfide of the structure (c) is one in which R_1, R_2, Q, X, and n are as desired in the final product of Formula (I) or give rise after deprotection and/or functionalization to R_1, R_2, Q, and X as desired in the final product of Formula (I). An appropriate disulfide of structure (c) can be prepared by methods known analogously in the art, B. P. Roques et al, J. Med. Chem. 33, 2473-2481 (1992), from compounds of structure (a), prepared below in Schemes A, B, and C.

In Scheme 2, optional step b, a protected disulfide of Formula (I) is deprotectedand/or functionalized to give a disulfide of Formula (I) as taught in Scheme 1 optional, step b above.

The following examples present typical syntheses as described in Scheme 2. These examples are understood to be illustrative only and are not intended to limit the scope of the invention in any way. As used in the following examples, the following terms have the meanings indicated: "g" refers to grams, "mmol" refers to millimoles, "mL" refers to milliliters, "°C" refers to degrees Celsius, "R_f" refers to retention factor, "mp" refers to melting point, "dec" refers to decomposition, "M" refers to molar, and "TLC" refers to thin layer chromatography.

EXAMPLE 22

2-Thiolacetic acid morpholine carboxamide;
Preparation of starting material for Scheme 2, step a:

Combine chloroacetyl chloride (2.00 mL, 25.0 mmol) and N-methylmorpholine (2.76 mL, 25.0 mmol) in dichloromethane (100 mL). Cool in an ice-bath. Add morpholine (2.19 mL, 25.0 mmol) and stir in the ice-bath for 1 hour. Warm to ambient temperature and stir for 1 hour. Extract with cold aqueous 5% sulfuric acid solution, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution. Dry the organic layer over Na_2SO_4, filter, and evaporate *in vacuo* to obtain chloroacetic acid morpholine carboxamide.

Combine chloroacetic acid morpholine carboxamide prepared above (2.88 g, 17.6 mmol) and thiolacetic acid (1.40 mL, 20.0 mmol) in degassed dimethylformamide (10 mL). Slowly add cesium carbonate (3.26 g, 10.0 mmol) providing cooling as needed to keep the temperature of the reaction mixture below 40°C. Stir at ambient temperature for 16 hours. Partition the reaction mixture between water and ethyl acetate. Dry the organic layer over Na_2SO_4, filter, and evaporate *in vacuo* to obtain a residue. Chromatograph the residue on silica gel eluting sequentially with 40% ethyl acetate/hexane and then 66% ethyl acetate/hexane to give 2-acetylthioacetic acid morpholine carboxamide.

Combine 2-acetylthioacetic acid morpholine carboxamide obtained above (2.50 g, 12.0 mmol) and degassed methanol (50 mL). Cool in an ice-bath. Add lithium hydroxide hydrate (1.0 g,24.0 mmol). Stir for 3 hours. Acidify the reaction mixture to pH=1 with 6 M hydrochloric acid solution. Partition the reaction mixture between water and dichloromethane. Extract the organic layer with saturated aqueous ammonium chloride solution. Dry the organic layer

over Na_2SO_4, filter, and evaporate *in vacuo* to obtain a residue. Chromatograph the residue on silica gel eluting with ethyl acetate to give the title compound.

EXAMPLE 23

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, N-(t-butoxycarbonyl)-L-cysteine ethyl ester, disulfide;

Scheme 2, step a:

Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-thiopyridine, disulfide (1.4 mmol) and N-(t-butoxycarbonyl)-L-cysteine ethyl ester (2.0 mmol) in degassed ethanol/dichloromethane (10 mL)/(2 mL). Stir for 18 hours. Evaporate in vacuo to obtain a residue. Chromatograph the residue on silica gel to give the title compound.

EXAMPLE 24

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, benzylthio, disulfide;

Scheme 2, step a:

Prepare in a manner similar to Example 23 using benzylthiol.

EXAMPLE 25

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, ethylthio, disulfide;

Scheme 2, step a:

Prepared in a manner similar to Example 23 using ethylthiol.

EXAMPLE 26

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-hydroxyethylthio, disulfide;

Scheme 2, step a:

Prepare in a manner similar to Example 23 using 2-hydroxyethylthiol.

EXAMPLE 27

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-pyridylmethylthio, disulfide;

Scheme 2, step a:

Prepare in a manner similar to Example 23 using 2-pyridylmethylthiol.

EXAMPLE 28

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-thioacetic acid morpholine carboxamide, disulfide;

Scheme 2, step a:

Prepare in a manner similar to Example 23 using thiolacetic acid morpholine carboxamide.

EXAMPLE 29

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, L-cysteine ethyl ester, disulfide trifluoroacetic acid salt;

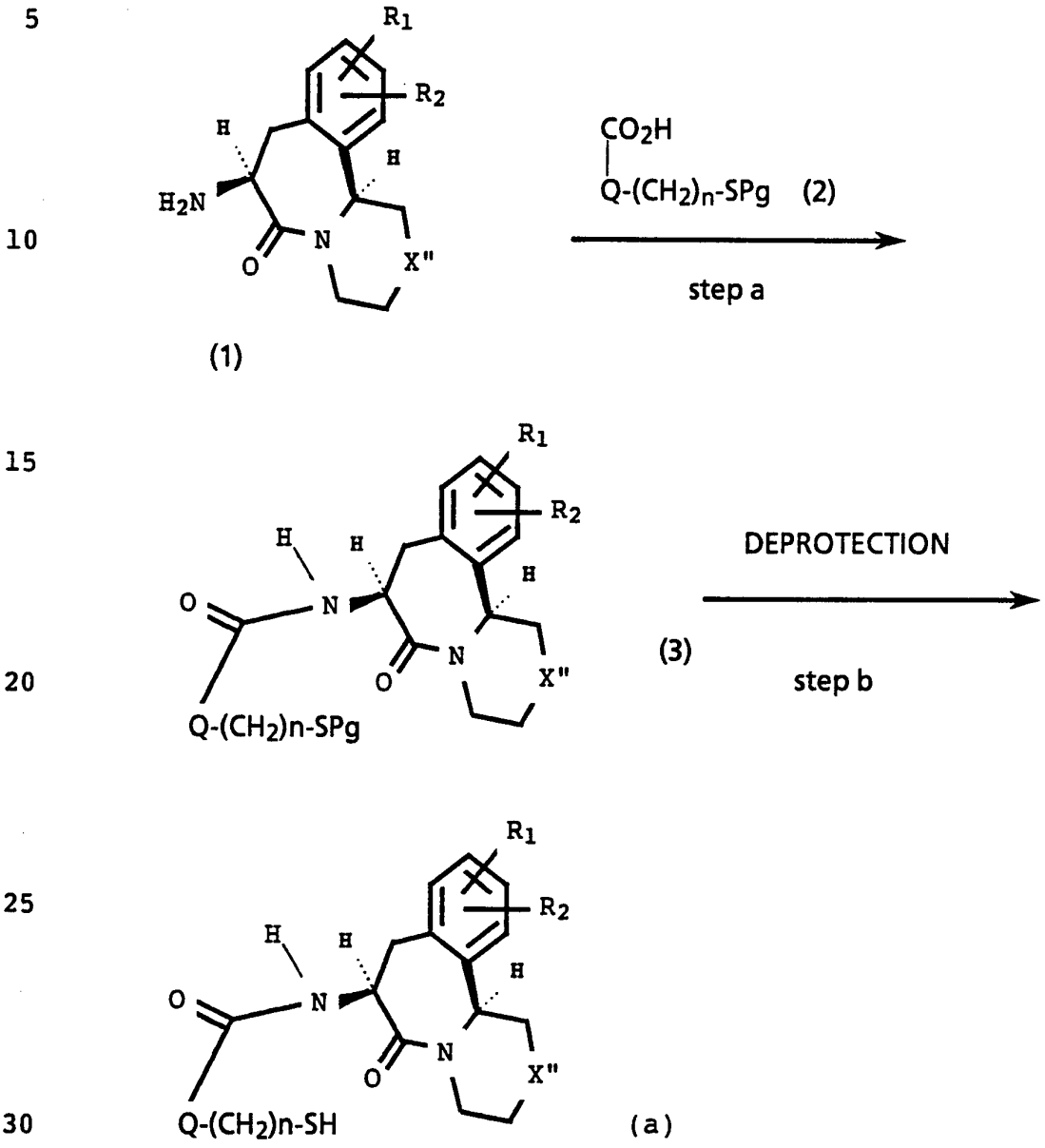
Scheme 2, optional step b:

Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, N-(t-butoxycarbonyl)-L-cysteine ethyl ester, disulfide (1.31 mmol) anisole (1.4 mL, 13.0 mmol) and dichloromethane (15 mL). Cool in an

ice-bath. Add trifluoroacetic acid (3 mL). Stir for 2 hours in the ice-bath and thee warm to ambient temperature and stir an additional 2 hours. Evaporate in vacuo to obtain a residue. Add carbon tetrachloride to the residue and evaporate in vacuo to obtain a residue. Triturate with hexane, filter and dry in vacuo to give the title compound.

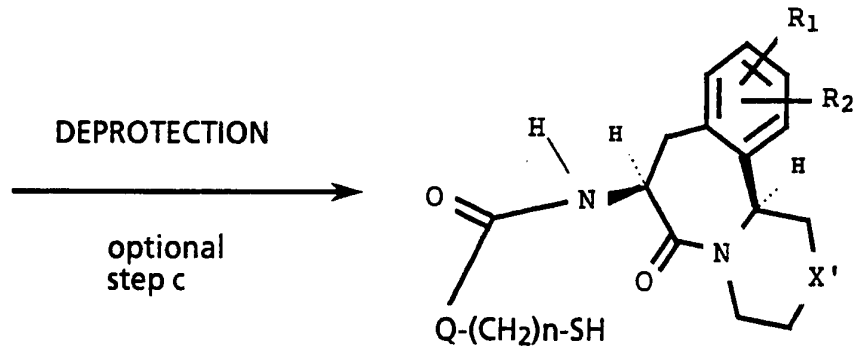
The compounds of structure (a) wherein X is $-(CH_2)_p-$, -O-, -S-, or $-NR_4-$ wherein R_4 is hydrogen can be prepared by utilizing procedures and techniques well known and appreciated by one of ordinary skill in the art. A general synthetic scheme for preparing these compounds is set for in Scheme A wherein all substituents are as previously defined unless otherwise defined.

Scheme A



Scheme A provides a general synthetic procedure for preparing compounds of structure (a) wherein X is $-(CH_2)_p-$, -O-, -S-, or $-NR_4-$ wherein R_4 is hydrogen.

Scheme A Cont.



(a)

X" = $-(CH_2)_p-$, -O-, -S-, or -N-Boc-
X' = -NH-

In step a, the appropriate amino tricyclic compound of structure (1) wherein X is $-(CH_2)_p-$, -O-, -S-, or -N-Boc is reacted with the appropriate protected thiol compound of structure (2) to give the corresponding thiol protected tricyclic compound of structure (3) wherein X is $-(CH_2)_p-$, -O-, -S-, or -N-Boc. For example, the appropriate amino tricyclic compound of structure (1) wherein X is $-(CH_2)_p-$, -O-, -S-, or -N-Boc can be reacted with the appropriate protected thiol compound of structure (2) in the presence of a coupling reagent such as EDC (1-(3-dimethyaminopropyl)-3-ethylcarbodiimide), DCC (1,3-dicyclohexylcarbodiimide), or diethylcyanophosponate in a suitable aprotic solvent, such as methylene chloride to give the appropriate thiol protected tricyclic compound of structure (3) wherein X is $-(CH_2)_p-$, -O-, -S-, or -N-Boc.

Alternatively, the protected thiol compound of structure (2) can be converted to the corresponding acid chloride, followed by reaction with the appropriate amino tricyclic

compound of structure (1) wherein X is $-(CH_2)_p-$, -O-, -S-, or -N-Boc to give the appropriate thiol protected tricyclic compound of structure (3) wherein X is $-(CH_2)_p-$, -O-, -S-, or -N-Boc.

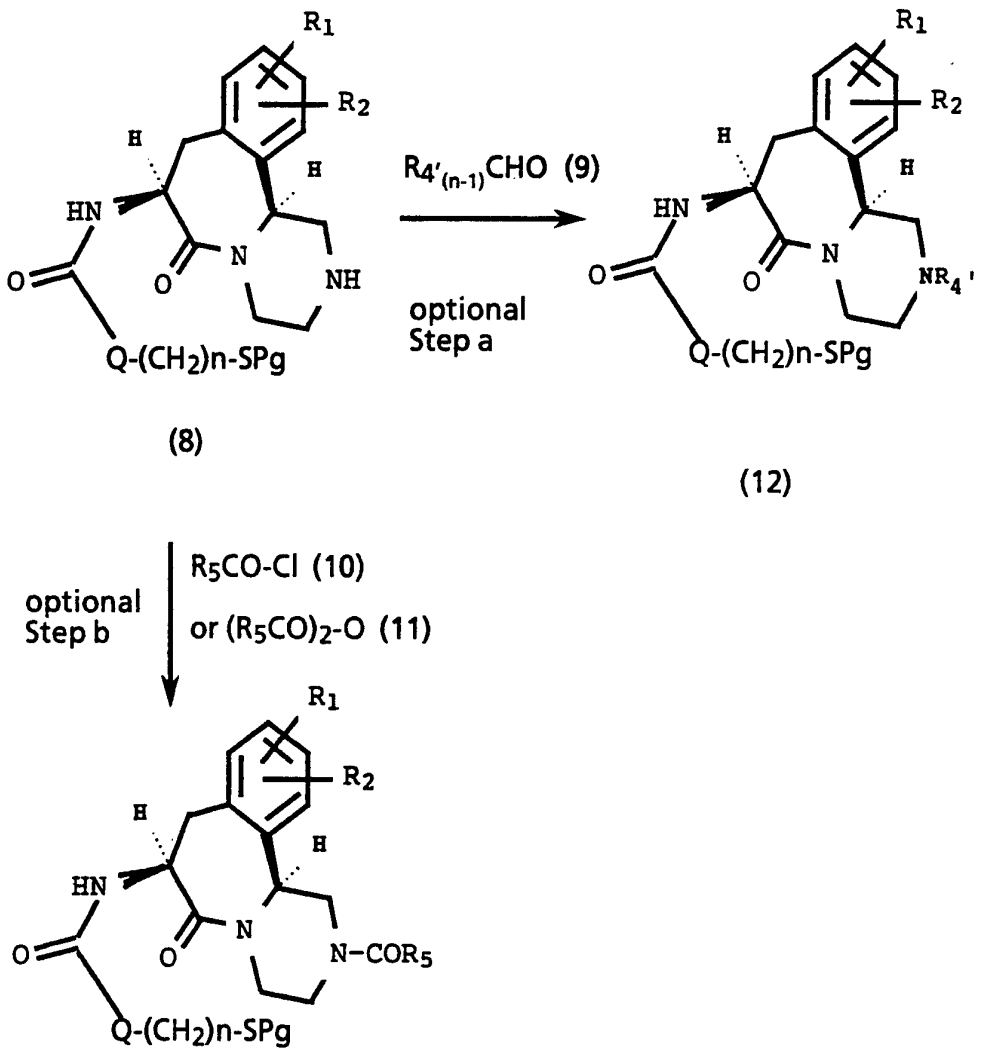
The selection and utilization of suitable thiol protecting groups, such as t-butyl and 4-methoxybenzyl, is well known to one of ordinary skill in the art and are described in "Protective Groups in Organic Syntheses", Theodora W. Greene, Wiley (1981).

In step b, the thiol protecting group is removed by techniques and procedures well known and appreciated by one of ordinary skill in the art, For example, the appropriate thiol protected tricyclic compound of structure (3) wherein X is $-(CH_2)_p-$, -O-, -S-, or -N-Boc is contacted with a molar equivalent of mercuric acetate. The reactants are typically contacted in an appropriate acidic solvent such as trifluoroacetic acid. The reactants are typically stirred together at room temperature for a period of time ranging from 1-24 hours. Mercury is removed from the reaction mixture by the addition of excess hydrogen sulfide. As is well known in the art, acid labile protecting groups may require reintroduction after isolation of an intermediate product. The thiol tricyclic compound of structure (a) wherein X is $-(CH_2)_p-$, -O-, -S-, or -N-Boc is recovered from the reaction zone by extractive methods as is known in the art. It can be purified by silica gel chromatography.

In optional step c, the Boc protecting group on those thiol tricyclic compounds of structure (a) wherein X is -N-Boc, is removed by techniques and procedures well known and appreciated by one of ordinary skill in the art, such as dilute hydrochloric acid to give the corresponding thiol tricyclic compounds of structure (a) wherein X is $-NR_4-$ wherein R_4 is hydrogen.

The compounds of structure (a) wherein X is $-NR_4-$ wherein R_4 is other than hydrogen or wherein X is $-NCOR_5-$ can be prepared by techniques and procedures well known and appreciated by one of ordinary skill in the art. A general synthetic procedure for preparing these compounds is set forth in Scheme B. In Scheme B, all substituents unless otherwise indicated are as previously defined.

Scheme B



Thiol protecting groups, such as t-butyl, p-methoxybenzyl, acetate, and benzoate can be introduced to give compounds of structure (8) from tricyclic compounds of

structure (a) wherein X is $-NR_4-$ wherein R_4 is hydrogen. The selection, use, and removal of protecting groups and the introduction and removal of protecting groups in a sequential manner utilizing suitable protecting groups such as those described in Protecting Groups in Organic Synthesis by T. Greene is well known and appreciated by those skilled in the art.

The thiol protected tricyclic compound of structure (8) wherein X is $-NR_4-$ wherein R_4 is hydrogen can be prepared by removing the Boc protecting group on those thiol tricyclic compounds of structure (a) wherein X is -N-Boc as described previously in Scheme A, optional step c.

In optional step a, the amino functionality of the appropriate thiol protected tricyclic compound of structure (8) wherein X is $-NR_4-$ wherein R_4 is hydrogen is subjected to reductive alkylation with the appropriate aldehyde of structure (9) using sodium cyanoborohydride, as is well known in the art, to give the corresponding thiol protected N-alkyl tricyclic compound of structure (12).

In optional step b, the amino functionality of the appropriate tricyclic compound of structure (8) wherein X is $-NR_4-$ wherein R_4 is hydrogen is acylated using the appropriate acyl chloride of structure (10) or the appropriate anhydride of structure (11), as is well known in the art, to give the corresponding N-acyl tricyclic compound of structure (13).

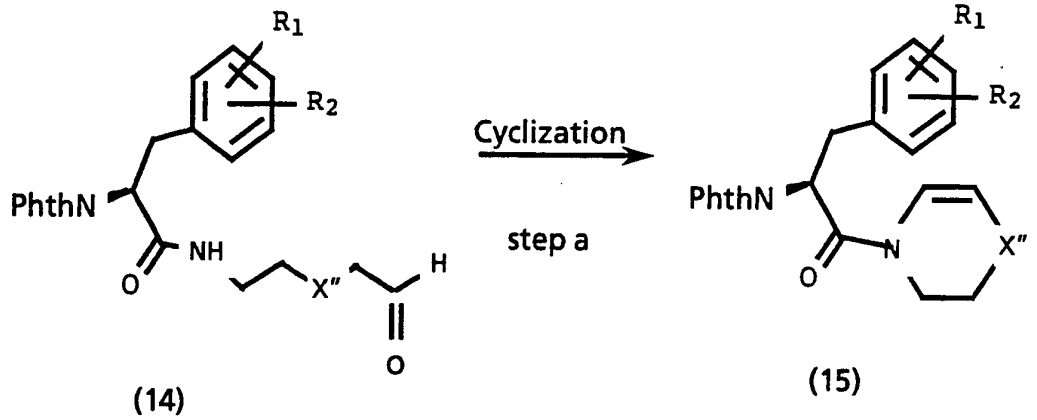
The functionalization of compounds of structure (8) wherein X is $-NR_4$ and Q is a group wherein Z is $-NR_4$ can be carried out by the use of protecting groups in a sequential manner utilizing suitable protecting groups, such as those described in Protecting Groups in Organic Synthesis by T. Greene, as is well known and appreciated by those skilled in the art. Selective functionalization using protecting

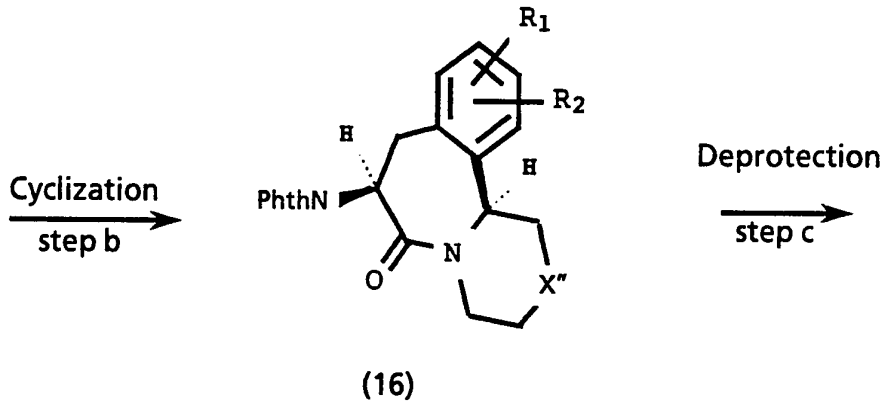
groups in a sequential manner is well known and appreciated in the art. The removal of protecting groups or the removal of protecting groups in a sequential manner as required gives rise to alkylated and acylated compounds of structure (13).

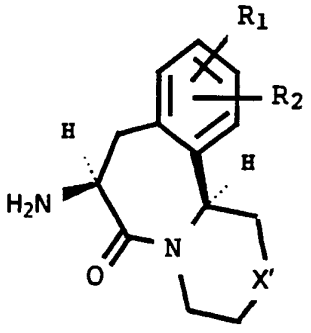
The thiol protecting group of compound (13) may be removed as described previously in Scheme A, step b or by hydrolytic methods described in Protecting Groups in Organic Synthesis by T. Greene.

Amino tricyclic compounds of structure (1) wherein X is $-(CH_2)_p-$, -O-, -S-, or -N-Boc may be prepared as described in Scheme C. In Scheme C, all substituents unless otherwise indicated are as previously defined.

Scheme C







X" = $-(CH_2)_p-$, -O-, -S-, or $-NCOCF_3-$
X' = $-(CH_2)_p-$, -O-, -S-, or -N-Boc-

In step a, the appropriate aldehyde of structure (14) can be cyclized to the appropriate enamine of structure (15) by acid catalysis. For example, the appropriate aldehyde of

structure (14) can be cyclized to the appropriate enamine of structure (15) by treatment with trifluoroacetic acid in a suitable aprotic solvent, such as methylene chloride.

In step b, the appropriate enamine of structure (15) can be converted to the corresponding tricyclic compound of structure (16) by an acid catalyzed Friedel-Crafts reaction. For example, the appropriate enamine of structure (15) can be converted to the corresponding tricyclic compound of structure (16) by treatment with a mixture of trifluoromethane sulfonic acid and trifluoroacetic anhydride in a suitable aprotic solvent, such as methylene chloride.

In step c, for those tricyclic compounds of structure (16) wherein X is $-(CH_2)_p-$, -O-, -S-, or the phthalimide protecting group of the appropriate tricyclic compound of structure (16) wherein X is $-(CH_2)_p-$, -O-, or -S- can be removed using techniques and procedures well known in the art. For example, the phthalimide protecting group of the appropriate tricyclic compound of structure (16) wherein X is $-(CH_2)_p-$, -O-, -S- or a bond can be removed using hydrazine monohydrate in a suitable protic solvent such as methanol, to give the corresponding amino tricyclic compound of structure (1) wherein X is $-(CH_2)_p-$, -O-, or -S-.

For those tricyclic compounds of structure (16) wherein X" is $-NCOCF_3$, the trifluoroacetamide functionality is removed according to the procedure described in Tetrahedron Letters, 32(28), 3301-3304 (1991) to give the corresponding tricyclic compounds of structure (16) wherein X" is -NH. The amino functionality of the appropriate tricyclic compounds of structure (16) wherein X" is -NH is protected with a Boc protecting group by techniques and procedures well known and appreciated in the art to give the corresponding tricyclic compounds of structure (16) wherein X" is -N-Boc. The phthalimide protecting group of the appropriate tricyclic compounds of structure (16) wherein X"

is -N-Boc is then removed using hydrazine as described above in step c to give the corresponding amino tricyclic compound of structure (1) wherein X" is -N-Boc.

Starting materials for use in Schemes A through C are readily available to one of ordinary skill in the art.

The following examples present typical syntheses as described in Schemes A through C. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to grams; "mmol" refers to millimoles; "mL" refers to milliliters; "mol" refers to moles; "bp" refers to boiling point; "mp" refers to melting point; "°C" refers to degrees Celsius; "M" refers to molar, "N" refers to normal, "mm Hg" refers to millimeters of mercury; "µL" refers to microliters; "µg" refers to micrograms; and "µM" refers to micromolar.

EXAMPLE 30

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Scheme C, step a: (R*,R*)]-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-1,2,3,4-tetrahydro-2-pyridine

Mix 5-bromo-1-pentene (31.2 g, 0.209 mol) and potassium cyanide (16.8 g, 0.257 mol) in ethylene glycol (85 mL) and heat at 100°C for 2 hours. Cool, dilute with water (100 mL) and extract into ethyl ether (100 mL). Wash with saturated sodium hydrogen carbonate (35 mL), dry (Na_2SO_4) and distill to give 5-hexenylnitrile as a colorless liquid (16.3 g, 82%); bp 150-156°C.

Suspend lithium aluminum hydride (6.5 g, 0.17 mol) in ethyl ether (350 mL) and add, by dropwise addition over 30

minutes, 5-hexenylnitrile (16.3 g, 0.171 mol). Stir at room temperature for 2 hours, cool in an ice bath and add sequentially, by very slow addition, water (6.8 mL), 20% sodium hydroxide (5.2 mL), then water (24 mL). Decant the ethereal phase and wash the white salts with ether. Combine the ethereal phases and distill at atm. pressure to give 5-hexenylamine as a colorless liquid (10.7 g, 63%); bp 125-135°C.

Dissolve 5-hexenylamine (0.88 g, 8.9 mmol) in methylene chloride (50mL) and treat first with N-phthaloyl-(S)-phenylalanine (2.95 g, 10.0 mmol), then with EEDQ (2.47 g, 10.0 mmol) and stir at room temperature for 6 hours. Evaporate the solvent *in vacuo*, dissolve the residue in ethyl acetate (75 mL) and wash with 5% sulfuric acid (25 mL), saturated sodium hydrogen carbonate (25 mL) and brine (25 mL). Dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by chromatography (hexane/ethyl acetate) to give 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl-5-hexenylamine as a white solid (1.8 g, 55%).

Dissolve 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl-5-hexenylamine (1.2 g, 3.19 mmol) in methylene chloride (40 mL) and methanol (4 mL) and cool to -78°C under a nitrogen atmosphere. Treat with ozone until a blue color persists, degas with nitrogen for 20 minutes and add pyridine (0.2 mL). Quench with dimethylsulfide (4 mL) and stir overnight at room temperature. Dilute with methylene chloride (75 mL) and wash with 5% sulfuric acid (40 mL) and brine (40 mL). Dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by chromatography (hexane/ethyl acetate) to give 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl-5-oxo-pentylamine as a white solid (972 mg, 80%).

Dissolve 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl-5-oxo-pentylamine (153 mg, 0.404 mmol) in

anhydrous methylene chloride (7 mL) and treat with trifluoroacetic acid (0.04 mL, 0.5 mmol). Stir at room temperature for 3 hours, partition between methylene chloride (25 mL) and saturated sodium hydrogen carbonate (15 mL). Dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by chromatography (hexane/ethyl acetate) to give the title compound as a white solid (623 mg, 83%).

Scheme C, step b: [4α, 7α(R*), 12bβ]-7-[(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Dissolve (R*,R*)]-N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-1,2,3,4-tetrahydro-2-pyridine (623 mg, 1.73 mmol) in methylene chloride (14 mL) and add, by dropwise addition, to trifluoromethane sulfonic acid (7 mL). Stir at room temperature for 4.5 hours, cool in an ice bath and quench with water (3 mL). Partition between ethyl acetate (100 mL) and water (30mL). Separate the organic phase and wash with saturated sodium hydrogen carbonate (30 mL). Dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by chromatography (hexane/ethyl acetate) to give the title compound as a white solid (600 mg, 96%).

Scheme C, step c: [4α, 7α(R*), 12bβ]-7-(Amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Dissolve [4α, 7α(R*), 12bβ]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (669 mg, 1.86 mmol) in methanol (15 mL) and treat with hydrazine hydrate (4.6 mL of a 1.0 M solution in methanol, 4.6 mmol). Stir 2.5 days at room temperature, filter through filter aid and condense. Filter again through a mixture of filter aid and $MgSO_4$ and evaporate the solvent *in vacuo* to give the title compound as a white solid (407 mg, 95%).

Scheme A, step a: [4S-[4α, 7α(R*), 12bβ]]-7-[(2-(4-Methoxybenzylthio)-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Dissolve diethylmalonate (15.2 mL, 0.100 mol) in tetrahydrofuran (800 mL). Cool in an ice bath and treat with sodium hydride (3.0 g, 0.10 mol, 80% in mineral oil). Stir until solution attained and add α,α'-dibromo-o-xylene (26.4 g, 0.100 mol). Stir for 30 minutes then add additional sodium hydride (3.0 g, 0.10 mol). Stir at room temperature for 20 hours, filter through filter aid and evaporate the solvent in vacuo. Purify by silica gel chromatography to give 2,2-(dicarboethoxy)indane as a pale yellow oil (16.0g , 61.5%).

Dissolve 2,2-(dicarboethoxy)indane (15.9 g, 60.6 mmol) in dimethylsulfoxide (140 ml). Add water (14mL) and lithium chloride (7.0 g, 0.16 mol). Heat at reflux for 4 hours, cool and partition between water (150 mL) and methylene chloride (2X150 mL). Wash the organic phase with water (150 mL), dry ($MgSO_4$) and pass through a silica gel plug to give 2-(carboethoxy)indane as an amber oil (6.49 g, 56%).

Dissolve 2-(carboethoxy)indane (6.49 g, 34.1 mmol) in ethanol (95%, 150 mL) and water (75 mL). Add potassium hydroxide (9.5 g, 0.17 mol) and stir at room temperature for 1 hour. Partition between water (150 mL) and ethyl ether (2X150 mL). Acidify the aqueous phase with hydrochloric acid to pH 1. Extract with methylene chloride (2X150 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo to give 2-indancarboxylic acid as a tan solid (3.82 g, 69%).

Dissolve 2-indancarboxylic acid (3.82 g, 23.5 mmol) in methanol (60 mL) and treat with dimethoxypropane (5.8mL, 47 mmol) and sulfuric acid (0.8 mL). Stir at room temperature for 6 days. Evaporate the solvent in vacuo, dilute with methylene chloride (75 mL) and wash with saturated sodium hydrogen carbonate (35 mL). Extract the aqueous phase with

methylene chloride (30 mL), wash combined organics with brine (30 mL) and dry (Na_2SO_4). Evaporate the solvent in vacuo and pass through a plug of silica gel to give 2-(carbomethoxy)indane as a yellow oil (3.98 g, 96%).

Mix 4-methoxybenzylthiol (3.0 g, 19 mmol) in sodium hydroxide (20 mL of a 2.5 M aqueous solution) and methanol (10 mL). Add saturated aqueous copper sulfate solution (1.5 mL) and stir at room temperature for 2 hours, blowing air over the top of the mixture. Filter the solid, wash with water and dry to give 4-methoxybenzyl disulfide as a pale yellow powder (2.71 g, 91%).

Cool lithium hexamethyldisilazane (4.2 mL, 4.2 mol, 1.0 M in tetrahydrofuran) to -78°C and treat with a solution of 2-(carbomethoxy)indane (625 mg, 3.55 mmol) in tetrahydrofuran (5 mL). Stir for 1 hour add hexamethylphosphoramide (0.93 mL, 5.3 mmol) and stir for 5 minutes. Add 4-methoxybenzyl disulfide (1.6 g, 5.2 mmol) in tetrahydrofuran (10 mL). Stir for 5 hours at -78°C and quench with a solution of ammonium chloride. Partition between ethyl acetate (75 mL) and brine (30 mL). Dry (Na_2SO_4), evaporate the solvent in vacuo and purify by silica gel chromatography (4:1 hexane/ethyl acetate) to give 2-(carbomethoxy)-2-(4-methoxybenzylthio)indane (2.20 g).

Dissolve 2-(carbomethoxy)-2-(4-methoxybenzylthio)indane (2.20 g, 3.55 mmol) in 95% ethanol (25 mL), water (12 mL) and tetrahydrofuran (15 mL). Treat with potassium hydroxide (1.3g, 23 mmol) and stir at room temperature for 1 hour. Filter and evaporate the solvent in vacuo. Partition between water (125 mL) and ether (75 mL). Separate the aqueous phase and acidify with cold concentrated hydrochloric acid. Extract with methylene chloride (75 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography (2:1 hexane/ethyl acetate) to give

2-carboxy-2-(4-methoxybenzylthio)indane as a yellow solid (0.48 g, 43%).

Dissolve [4α, 7α(R*), 12bβ]-7-(amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (136 mg, 0.59 mmol) and EDC (170 mg, 0.886 mmol) in tetrahydrofuran (5 mL). Treat with 2-carboxy-2-(4-methoxybenzylthio)indane (232 mg, 0.74 mmol). Stir at room temperature under an argon atmosphere for 20 hours and evaporate the solvent in vacuo. Dissolve the residue in ethyl acetate (30 mL) and wash with 5% sulfuric acid (15 ml) then saturated sodium hydrogen carbonate (15 mL). Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography (2:1 hexane/ethyl acetate to 3:2 hexane/ethyl acetate) to give the title compound as a pale yellow foam (205 mg, 65.9%).

Scheme A, step b: [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(2-(4-methoxybenzylthio)-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine[(200 mg, 0.38 mmol) in methylene chloride (6 mL) and cool to 0°C. Treat with trifluoroacetic acid (3 mL), anisole (0.42 mL, 3.8 mmol), and mercuric acetate (155mg, 0.49mmol). Stir at 0°C for 3 hours then bubble hydrogen sulfide gas through the solution for 15 minutes. Filter and wash with methylene chloride. Wash organic phase with water (20 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography (3:2 hexane/ethyl acetate) to give the title compound (128 mg, 83%).

EXAMPLE 31

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-(2-Mercaptoethyl)-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Scheme A, step a: [4S-[4α, 7α(R*), 12bβ]]-7-[(2-[2-(4-Methoxybenzylthio)ethane-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Cool lithium hexamethyldisilazane (4.2 mL 4.2 mmol) in a dry ice/acetone bath and add, by dropwise addition, a solution of 2-(carbomethoxy)indane (625 mg, 3.55 mmol) in tetrahydrofuran (6 mL). Stir for 30 minutes then add hexamethylphosphoramide (1.0 mL, 5.7 mmol). Stir for 45 minutes then add 1-bromo-2-chloroethane (0.37 mL, 4.44 mmol). Stir for 3 hours, remove the ice bath and allow to warm to room temperature. Quench with aqueous ammonium chloride (30 mL) and extract with ethyl acetate (75 mL). Dry (Na_2SO_4) and evaporate the solvent in vacuo. Pass through a plug of silica gel (6:1 hexane/ethyl acetate) to give 2-(carbomethoxy)-2-(2-chloroethane)indane (0.62 g).

Dissolve 4-methoxybenzylthiol (0.7 mL, 5 mmol) in tetrahydrofuran (10 mL) and place under an argon atmosphere. Treat with sodium hydride (144 mg of an 80% dispersion in mineral oil, 4.8 mmol). Stir the suspension for 10 minutes and add tetrabutylammonium iodide (40 mg, 0.11 mmol). Stir for 10 minutes then add a solution of 2-(carbomethoxy)-2-(2-chloroethane)indane (0.6 g, 3.55 mmol) in tetrahydrofuran (5 mL). Stir for 18 hours and partition between aqueous ammonium chloride (15 mL) and ethyl acetate (50 mL). Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography (6:1 hexane/ethyl acetate) to give 2-(carbomethoxy)-2-[2-(4-methoxybenzylthio)ethane]indane (0.75 g).

Dissolve 2-(carbomethoxy)-2-[2-(4-methoxybenzylthio)ethane]indane (0.75 g, 3.55 mmol) in 95% ethanol (16 mL), water (8 mL) and tetrahydrofuran (10 mL). Treat with potassium hydroxide (1.3 g, 23 mmol). Stir for 1 hour and evaporate the solvent in vacuo. Partition between water (50 mL) and ethyl ether (2X35 mL). Cool the aqueous

phase in an ice bath and acidify with concentrated hydrochloric acid to pH 1. Extract with methylene chloride (75 mL), dry ($Na2SO_4$) and evaporate the solvent in vacuo to give 2-carboxy-2-[2-(4-methoxybenzylthio)ethane]indane as a white solid (147 mg).

Dissolve [4α, 7α(R*), 12bβ]-7-(amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (136 mg, 0.59 mmol) and EDC (170 mg, 0.886 mmol) in tetrahydrofuran (5 mL). Treat with 2-carboxy-2-[2-(4-methoxybenzylthio)ethane]indane (0.74 mmol). Stir at room temperature under an argon atmosphere for 20 hours and evaporate the solvent in vacuo. Dissolve the residue in ethyl acetate (30 mL) and wash with 5% sulfuric acid (15 ml) then saturated sodium hydrogen carbonate (15 mL). Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

Scheme A, step b: [4S-[4α, 7α(R*), 12bβ]]-7-[(2-(2-Mercaptoethyl)-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(2-[2-(4-methoxybenzylthio)ethane-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (0.38 mmol) in methylene chloride (6 mL) and cool to 0°C. Treat with trifluoroacetic acid (3 mL), anisole (0.42 mL, 3.8 mmol), and mercuric acetate (155 mg, 0.49 mmol). Stir at 0°C for 3 hours then bubble hydrogen sulfide gas through the solution for 15 minutes. Filter and wash with methylene chloride. Wash organic phase with water (20 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

EXAMPLE 32

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Mercaptomethyl-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Scheme A, step a: [4S-[4α, 7α(R*), 12bβ]]-7-[(2-(t-butylthio)methane-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Dissolve diethyl malonate (7.6 mL, 50 mmol) in anhydrous tetrahydrofuran (500 mL) and place under an argon atmosphere. Cool to 5°C, add sodium hydride (1.2 g, 50 mmol) and stir briefly until homogeneous. Add α,α'-dibromo-o-xylene (13.2 g, 50 mmol) and stir an additional 15 minutes. Add additional sodium hydride (1.2 g, 50 mmol) and stir for 16 hours while warming to room temperature. Filter, evaporate the solvent in vacuo and purify by silica gel chromatography (1:1 methylene chloride/hexane) to give 2,2-dicarboethoxy-indane (9.64 g, 74%).

Dissolve 2,2-dicarboethoxy-indane (5.67 g, 21.7 mmol) in ethanol (150 mL). Add 1N lithium hydroxide (50 mL) and stir overnight at room temperature. Reflux for 1 hour and concentrate the solution in vacuo. Partition between ethyl acetate and 6N hydrochloric acid. Separate the organic phase and wash with brine. Dry ($MgSO_4$) and evaporate the solvent in vacuo to give an off-white solid. Distill (120-160°C @ 0.2-0.5 mmHg) to give 2-carboxy-indan (2.5g, 71%).

Dissolve 2-carboxy-indan (2.5 g, 15.4 mmol) in methanol and cool to 0°C. Saturate with hydrochloride gas then add 2,2-dimethoxypropane (2-3 mL). Stir overnight then evaporate the solvent in vacuo. Purify by silica gel chromatography (2:1 methylene chloride/hexane) to give 2-carbomethoxy-indan as a water white oil. (2.04 g, 75%).

Dissolve diisopropylamine (1.90 mL, 7.8 mmol) in anhydrous tetrahydrofuran (8 mL), cool to -20°C and place under an argon atmosphere. Add, by dropwise addition, n-butyllithium (3.12 mL of a 2.5 M solution in hexanes, 7.8 mmol) and stir for 20 minutes while cooling to -70°C. Add, by dropwise addition, a solution of 2-carbomethoxy-indan (1.34 g, 7.8

mmol) in anhydrous tetrahydrofuran (8 mL). Stir at -70°C for an additional 30 minutes then add trimethylsilyl chloride (freshly distilled from barium oxide, 1.0 mL, 7.8 mmol). Allow to warm to 10°C, evaporate the solvent in vacuo and dry the residue under vacuum for 30 minutes. Suspend the residue in methylene chloride (30 mL), add zinc bromide (300 mg, 1.3 mmol) followed by t-butyl chloromethylsulfide (1.08 g, 7.8 mmol). Stir for 15 minutes at room temperature and add additional zinc bromide (500 mg, 2.2 mmol). Pour onto excess saturated sodium hydrogen carbonate and shake vigorously. Separate the organic phase and extract the aqueous phase with methylene chloride (30 mL). Combine the organic phases, dry ($MgSO_4$) and evaporate the solvent in vacuo to give crude product as a brown oil (2.12 g, 98%). Purify by silica gel chromatography (30-70°C methylene chloride/hexane) and recrystallize (methanol) to give 2-carbomethoxy-2-(t-butyl)thiomethyl-indan as a crystalline solid (1.3 g, 61%).

Dissolve 2-carbomethoxy-2-(t-butyl)thiomethyl-indan (557 mg, 2.0 mmol) in methanol (15 mL) and add 1N lithium hydroxide (3.5 mL). Warm briefly to effect solution then stir at room temperature under an argon atmosphere for 1 hour. Reflux for 6 hours, concentrate in vacuo to a volume of 3 mL and dilute to a volume of 15 mL with water. Wash with methylene chloride and acidify and aqueous phase with excess 2N hydrochloric acid. After 5 minutes, collect the resulting white precipitate by filtration and dry to give 2-carboxy-2-(t-butyl)thiomethyl-indan (506 mg, 96%); mp 158-163°C.

Dissolve [4α, 7α(R*), 12bβ]-7-(amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (136 mg, 0.59 mmol) and EDC (170 mg, 0.886 mmol) in tetrahydrofuran (5 mL). Treat with 2-carboxy-2-(t-butyl)thiomethyl-indan (0.74 mmol). Stir at room temperature under an argon atmosphere for 20 hours and evaporate the solvent in vacuo. Dissolve the residue in ethyl acetate (30 mL) and wash with 5%

sulfuric acid (15 mL) then saturated sodium hydrogen carbonate (15 mL). Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

Scheme A, step b: [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Mercaptomethyl-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(2-(t-butylthio)methane-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (0.38 mmol) in methylene chloride (6 mL) and cool to 0°C. Treat with trifluoroacetic acid (3 mL), anisole (0.42 mL, 3.8 mmol), and mercuric acetate (155 mg, 0.49 mmol). Stir at 0°C for 3 hours then bubble hydrogen sulfide gas through the solution for 15 minutes. Filter and wash with methylene chloride. Wash organic phase with water (20 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

EXAMPLE 33

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Thio-1-oxocyclopentane)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Scheme A, step a: [4S-[4α, 7α(R*), 12bβ]]-7-[(1-(4-methoxybenzylthio)-1-oxo-cyclopentane)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Dissolve diisopropylamine (0.46 mL, 3.3 mmol) in tetrahydrofuran (10 mL) and cool in an ice bath. Add, by dropwise addition, n-butyllithium (1.8 mL of a 1.6M solution in hexanes, 2.9 mmol). Stir for 15 minutes, cool to -78°C and add a solution of methyl cyclopentanecarboxylate (322 mg, 2.51 mmol) in tetrahydrofuran (5 mL). Stir for 1 hour then treat with hexamethylphosphoramide (0.66 mL, 3.8 mmol). Stir for 15 minutes then add 4-methoxybenzyl disulfide ((1.0 g, 3.3 mmol) in tetrahydrofuran (13 mL). Stir for 3

hours at -78°C, quench with saturated aqueous ammonium chloride (5 mL). Partition between water (2X50 mL) and ethyl acetate (100 mL). Dry (Na_2SO_4) and pass through a plug of silica gel (methylene chloride) to give 1-(carbomethoxy)-1-(4-methoxybenzylthio)cyclopentane as a pale yellow oil.

Dissolve 1-(carbomethoxy)-1-(4-methoxylbenzylthio)cyclopentane (3.3 mmol) in 95% ethanol (18 mL), water (9 mL), and tetrahydrofuran (10 mL). Treat with potassium hydroxide (0.91 g, 16 mmol). Stir at room temperature for 2 hours and evaporate the solvent in vacuo. Partition between water (50 mL) and ethyl ether (30 mL). Acidify the aqueous phase with cold concentrated hydrochloric acid and extract with methylene chloride (50 mL). Dry ($MgSO_4$) and evaporate the solvent in vacuo to give 1-(carboxy)-1-(4-methoxybenzylthio)cyclopentane as a pale yellow oil (483 mg, 72%).

Dissolve [4α, 7α(R*), 12bβ]-7-(amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (136 mg, 0.59 mmol) and EDC (170 mg, 0.886 mmol) in tetrahydrofuran (5 mL). Treat with 1-(carboxy)-1-(4-methoxybenzylthio)cyclopentane (0.74 mmol). Stir at room temperature under an argon atmosphere for 20 hours and evaporate the solvent in vacuo. Dissolve the residue in ethyl acetate (30 mL) and wash with 5% sulfuric acid (15 mL) then saturated sodium hydrogen carbonate (15 mL). Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

Scheme A, step b: [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Thio-1-oxocyclopentane)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1-(4-methoxybenzylthio)-1-oxo-cyclopentane)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (0.38 mmol) in methylene chloride (6 mL) and cool to 0°C.

Treat with trifluoroacetic acid (3 mL), anisole (0.42 mL, 3.8 mmol), and mercuric acetate (155 mg, 0.49 mmol). Stir at 0°C for 3 hours then bubble hydrogen sulfide gas through the solution for 15 minutes. Filter and wash with methylene chloride. Wash organic phase with water (20 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

EXAMPLE 34

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5-dihydro-cyclopentimidazole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine

Scheme C, step a: (R*,R*)]-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-3,4-dihydro-2H-1,4-oxazine

Wash sodium hydride (7.75 g, 191 mmol of a 59% dispersion in paraffin) 2 times with dry hexane (2X) under a nitrogen atmosphere. Add anhydrous dimethylformamide (90 mL) and cool with an ice/methanol bath. Add, by portion wise addition, ethanolamine hydrochloride (96.7 mmol), stir for 5 minutes and add potassium iodide (5.2 g, 32 mmol). Add, by dropwise addition, bromoacetaldehyde diethylacetal (14.5 mL, 96.7 mmol), remove the ice bath and stir for 8 hours at room temperature. Add the mixture to a solution of N-phthaloyl-(S)-phenylalanine (14.2g, 48 mmol) and N-carbethoxy-2-ethoxy-1,2-dihydroquinoline (11.9g, 48 mmol) in anhydrous tetrahydrofuran (40 mL). Stir for 18 hours at room temperature, partition between water (200 mL) and diethyl ether (200 mL) and separate the organic phase. Extract the aqueous phase with diethyl ether (200 mL), combine the organic phases and wash with 1N hydrochloric acid (2X200 mL), then saturated sodium hydrogen carbonate (2X200 mL), then brine (50 mL). Dry ($MgSO_4$), filter and evaporate the solvent *in vacuo* to give the intermediate acetal.

Dissolve the intermediate acetal (30.3 mmol) in chloroform (500 mL) and add trifluoroacetic acid (4.5 mL). Reflux for 4 hours under a nitrogen atmosphere, cool and wash with saturated sodium hydrogen carbonate (300 mL) and filter through anhydrous $MgSO_4$. Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Scheme C, step b: [4α, 7α(R*), 12bβ]-7-[(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine

Dissolve (R*,R*)]-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-3,4-dihydro-2H-1,4-oxazine (1.73 mmol) in methylene chloride (14 mL) and add, by dropwise addition, to trifluoromethane sulfonic acid (7 mL). Stir at room temperature for 4.5 hours, cool in an ice bath and quench with water (3 mL). Partition between ethyl acetate (100 mL) and water (30 mL). Separate the organic phase and wash with saturated sodium hydrogen carbonate (30 mL), dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Scheme C, step c: [4α, 7α(R*), 12bβ]-7-(Amino)-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine

Dissolve [4α, 7α(R*), 12bβ]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine (1.86 mmol) in methanol (15 mL) and treat with hydrazine hydrate (4.6 mL of a 1.0M solution in methanol, 4.6 mmol). Stir 2.5 days at room temperature, filter through filter aid and condense. Filter again through a mixture of filter aid and $MgSO_4$ and evaporate the solvent in vacuo to give the title compound.

Scheme A, step a: [4S-[4α, 7α(R*), 12bβ]]-7-[(5-(4-methoxybenzylthio)-5-oxo-1-(carbo-t-butyloxy)-4,5-dihydro-cyclopentimidazole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine

Dissolve 4,5-imidazoledicarboxylic acid (31.2 g, 0.2 mol) in ethanol (500 mL) and treat with concentrated sulfuric acid (0.5 mL). Heat to 60°C for 16 hours, cool and reduce the solvent by 50% in vacuo. Dilute with ethyl ether (500 mL), wash with saturated sodium hydrogen carbonate, then brine. Dry (MgSO4) and evaporate the solvent in vacuo to give 4,5-(dicarboethoxy)imidazole.

Dissolve 4,5-(dicarboethoxy)imidazole (1.06g, 5 mmol) and triethylamine (1.5 mL, 7.5 mmol) in 50/50 dioxane water (25 mL). Add [2-(tert-butyloxycarbonyloxyimino)-2-phenylacetonitrile] (1.36 g, 5.5 mmol) and stir at room temperature for 2 hours. Add water (7.5 mL) and ethyl acetate (10 mL), separate the aqueous phase and wash with ethyl acetate (10 mL). Combine the organic phases, dry ($MgSO_4$) and evaporate the solvent in vacuo. Purify the residue by silica gel chromatography to give N-(carbo-t-butyloxy)-4,5-(dicarboethoxy)imidazole.

Dissolve N-(carbo-t-butyloxy)-4,5-(dicarboethoxy)imidazole (3.12 g, 10 mmol) in anhydrous tetrahydrofuran (30 mL) and cool to -20°C. Treat with lithium borohydride (7 mL of a 2N solution) and stir under a nitrogen atmosphere for several days. Carefully add water and partition between ethyl acetate and 5% hydrochloric acid. Separate the organic phase, wash with brine and dry ($MgSO_4$). Evaporate the solvent in vacuo and purify by silica gel chromatography to give N-(carbo-t-butyloxy)-4,5-(dihydroxymethyl)imidazole.

Dissolve N-bromosuccinimide (1.78 g, 0.01mol) in tetrahydrofuran (60 mL) and add a solution of triphenylphosphine (2.62 g, 0.01mol) in tetrahydrofuran. Add a solution of N-(carbo-t-butyloxy)-4,5-(dihydroxymethyl)imidazole (1.14 g, 5 mmol) in tetrahydrofuran (25 mL) and stir until most of the solid goes into solution. Evaporate the solvent in vacuo and partition the residue between water and ethyl ether.

Separate the organic phase and wash with water. Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give N-(carbo-t-butyloxy)-4,5-(dibromomethyl)imidazole.

Dissolve diethylmalonate (15.2 mL, 0.100 mol) in tetrahydrofuran (800 mL). Cool in an ice bath and treat with sodium hydride (3.0 g, 0.10 mol, 80% in mineral oil). Stir until solution attained and add N-(carbo-t-butyloxy)-4,5-(dibromomethyl)imidazole (35.4 g, 0.100 mol). Stir for 30 minutes then add additional sodium hydride (3.0 g, 0.10 mol). Stir at room temperature for 20 hours, filter through filter aid and evaporate the solvent in vacuo. Purify by silica gel chromatography to give 5,5-(dicarboethoxy)-1-(carbo-t-butyloxy)-4,5-dihydro-cyclopentimidazole.

Dissolve 5,5-(dicarboethoxy)-1-(carbo-t-butyloxy)-4,5-dihydro-cyclopentimidazole (21.3 g, 60.6 mmol) in dimethylsulfoxide (140 mL). Add water (14 mL) and lithium chloride (7.0 g, 0.16 mol). Heat at reflux for 4 hours, cool and partition between water (150 mL) and methylene chloride (2X150 mL). Wash the organic phase with water (150 mL), dry ($MgSO_4$) and pass through a silica gel plug to give 5-(carboethoxy)-1-(carbo-t-butyloxy)-4,5-dihydro-cyclopentimidazole.

Dissolve 5-(carboethoxy)-1-(carbo-t-butyloxy)-4,5-dihydro-cyclopentimidazole (9.5 g, 34.1 mmol) in ethanol (95%, 150 mL) and water (75 mL). Add potassium hydroxide (9.5 g, 0.17 mol) and stir at room temperature for 1 hour. Partition between water (150 mL) and ethyl ether (2X150 mL). Acidify the aqueous phase with hydrochloric acid to pH 1. Extract with methylene chloride (2X150 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo to give 5-(carboxy)-1-(carbo-t-butyloxy)-4,5-dihydro-cyclopentimidazole.

Dissolve 5-(carboxy)-1-(carbo-t-butyloxy)-4,5-dihydro-cyclopentimidazole (5.9 g, 23.5 mmol) in methanol (60 mL) and treat with dimethoxypropane (5.8 mL, 47 mmol) and sulfuric acid (0.8 mL). Stir at room temperature for 1 day. Evaporate the solvent in vacuo, dilute with methylene chloride (75 mL) and wash with saturated sodium hydrogen carbonate (35 mL). Extract the aqueous phase with methylene chloride (30 mL), wash combined organics with brine (30 mL) and dry (Na_2SO_4). Evaporate the solvent in vacuo and pass through a plug of silica gel to give 5-(carbomethoxy)-1-(carbo-t-butyloxy)-4,5-dihydro-cyclopentimidazole.

Mix 4-methoxybenzylthiol (3.0 g, 19 mmol) in sodium hydroxide (20 mL of a 2.5N aqueous solution) and methanol (10 mL). Add saturated aqueous copper sulfate solution (1.5 mL) and stir at room temperature for 2 hours, blowing air over the top of the mixture. Filter, wash solid with water and dry to give 4-methoxybenzyl disulfide as a pale yellow powder (2.71 g, 91%).

Cool lithium hexamethyldisilazane (4.2 mL, 4.2 mmol, 1.0M in tetrahydrofuran) to -78°C and treat with a solution of 5-(carbomethoxy)-1-(carbo-t-butyloxy)-4,5-dihydro-cyclopentimidazole (944 mg, 3.55 mmol) in tetrahydrofuran (5 mL). Stir for 1 hour then add hexamethylphosphoramide (0.93 mL, 5.3 mmol) and stir for 5 minutes. Add 4-methoxybenzyl disulfide (1.6g, 5.2 mmol) in tetrahydrofuran (10 mL). Stir for 5 hours at -78°C and quench with a solution of ammonium chloride. Partition between ethyl acetate (75 mL) and brine (30 mL). Dry (Na_2SO_4), evaporate the solvent in vacuo and purify by silica gel chromatography to give 5-(carbomethoxy)-1-(carbo-t-butyloxy)-5-(4-methoxybenzylthio)-4,5-dihydro-cyclopentimidazole.

Dissolve 5-(carbomethoxy)-1-(carbo-t-butyloxy)-5-(4-methoxybenzylthio)-4,5-dihydro-cyclopentimidazole (1.43 g, 3.55 mmol) in 95% ethanol (25 mL), water (12 mL) and

tetrahydrofuran (15 mL). Treat with potassium hydroxide (1.3g, 23 mmol) and stir at room temperature for 1 hour. Filter and evaporate the solvent in vacuo. Partition between water (125 mL) and ether (75 mL). Separate the aqueous phase and acidify with cold concentrated hydrochloric acid. Extract with methylene chloride (75 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give 5-(carboxy)-1-(carbo-t-butyloxy)-5-(4-methoxybenzylthio)-4,5-dihydro-cyclopentimidazole.

Dissolve [4α, 7α(R*), 12bβ]-7-(amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (136 mg, 0.59 mmol) and EDC (170 mg, 0.886 mmol) in tetrahydrofuran (5 mL). Treat with 5-(carboxy)-1-(carbo-t-butyloxy)-5-(4-methoxybenzylthio)-4,5-dihydro-cyclopentimidazole (0.74 mmol). Stir at room temperature under an argon atmosphere for 20 hours and evaporate the solvent in vacuo. Dissolve the residue in ethyl acetate (30 mL) and wash with 5% sulfuric acid (15 mL) then saturated sodium hydrogen carbonate (15 mL). Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

Scheme A, step b: [4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5-dihydro-cyclopentimidazole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(5-(4-methoxybenzylthio)-5-oxo-1-(carbo-t-butyloxy)-4,5-dihydro-cyclopentimidazole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine (0.38 mmol) in methylene chloride (6 mL) and cool to 0°C. Treat with trifluoroacetic acid (3 mL), anisole (0.42 mL, 3.8 mmol), and mercuric acetate (155 mg, 0.49 mmol). Stir at 0°C for 3 hours then bubble hydrogen sulfide gas through the solution for 15 minutes. Filter and wash with methylene chloride. Wash organic phase with water (20 mL), dry (Na_2SO_4) and

evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

EXAMPLE 35

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]furan)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine

Scheme C, step a: (R*,R*)]-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-3,4-dihydro-2H-1,4-thiazine

Wash sodium hydride (7.7 5g, 191 mmol of a 59% dispersion in paraffin) 2 times with dry hexane (2X) under a nitrogen atmosphere. Add anhydrous dimethylformamide (90 mL) and cool with an ice/methanol bath. Add, by portion wise addition, 2-aminoethanethiol hydrochloride (96.7 mmol), stir for 5 minutes and add potassium iodide (5.2g, 32 mmol). Add, by dropwise addition, bromoacetaldehyde diethylacetal (14.5 mL, 96.7 mmol), remove the ice bath and stir for 8 hours at room temperature. Add to a solution of N-phthaloyl-(S)-phenylalanine (14.2 g, 48 mmol) and N-carbethoxy-2-ethoxy-1,2-dihydroquinoline (11.9g, 48 mmol) in anhydrous tetrahydrofuran (40 mL). Stir for 18 hours at room temperature, partition between water (200 mL) and diethyl ether (200 mL) and separate the organic phase. Extract the aqueous phase with diethyl ether (200 mL), combine the organic phases and wash with 1N hydrochloric acid (2X200 mL), then saturated sodium hydrogen carbonate (2X200 mL), then brine (50 mL). Dry ($MgSO_4$), filter and evaporate the solvent *in vacuo* to give the intermediate acetal.

Dissolve the intermediate acetal (30.3 mmol) in chloroform (500 mL) and add trifluoroacetic acid (4.5 mL). Reflux for 4 hours under a nitrogen atmosphere, cool and wash with saturated sodium hydrogen carbonate (300 mL) and filter through anhydrous $MgSO_4$. Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Scheme C, step b: [4α, 7α(R*), 12bβ]-7-[(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine

Dissolve (R*,R*)]-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-3,4-dihydro-2H-1,4-thiazine (1.73 mmol) in methylene chloride (14 mL) and add, by dropwise addition, to trifluoromethane sulfonic acid (7 mL). Stir at room temperature for 4.5 hours, cool in an ice bath and quench with water (3 mL). Partition between ethyl acetate (100 mL) and water (30 mL). Separate the organic phase and wash with saturated sodium hydrogen carbonate (30 mL), dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Scheme C, step c: [4α, 7α(R*), 12bβ]-7-(Amino)-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine

Dissolve [4α, 7α(R*), 12bβ]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine (1.86 mmol) in methanol (15 mL) and treat with hydrazine hydrate (4.6 mL of a 1.0M solution in methanol, 4.6 mmol). Stir 2.5 days at room temperature, filter through filter aid and condense. Filter again through a mixture of filter aid and $MgSO_4$ and evaporate the solvent in vacuo to give the title compound.

Scheme A, step a: [4S-[4α, 7α(R*), 12bβ]]-7-[(5-(4-methoxybenzylthio)-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]furan)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine

Dissolve 3,4-(dicarboethoxy)furan (21.2 g, 10 mmol) in anhydrous tetrahydrofuran (30 mL) and cool to -20°C. Treat with lithium borohydride (7 mL of a 2N solution) and stir under a nitrogen atmosphere for several days. Carefully add water and partition between ethyl acetate and 5% hydrochloric acid. Separate the organic phase, wash with brine and dry ($MgSO_4$). Evaporate the solvent in vacuo and

purify by silica gel chromatography to give 3,4-(dihydroxymethyl)furan.

Dissolve 3,4-(dihydroxymethyl)furan (11.9 g, 0.093 mol) in 2,4,6-collidine (12.4 g) and add a solution of lithium bromide (7.9 g, 91 mmol) in dimethylformamide (80 mL). Cool to -50°C and place under a nitrogen atmosphere. Add methanesulfonyl chloride (11.8 g) at a rate which keeps the temperature under 0°C. Stir at 0°C for 2 hours and pour onto ice water. Extract with ethyl ether, dry ($MgSO_4$), evaporate the solvent in vacuo and purify by silica gel chromatography to give 3,4-(dibromomethyl)furan.

Dissolve diethylmalonate (15.2 mL, 0.100 mol) in tetrahydrofuran (800 mL). Cool in an ice bath and treat with sodium hydride (3.0 g, 0.10 mol, 80% in mineral oil). Stir until solution attained and add 3,4-(dibromomethyl)furan (23.8g , 0.100 mol). Stir for 30 minutes then add additional sodium hydride (3.0 g, 0.10 mol). Stir at room temperature for 20 hours, filter through filter aid and evaporate the solvent in vacuo. Purify by silica gel chromatography to give 5,5-(dicarboethoxy)-2,4,5,6-tetrahydro-cyclopenta[c]furan.

Dissolve 5,5-(dicarboethoxy)-2,4,5,6-tetrahydro-cyclopenta[c]furan (15.3g , 60.6 mmol) in dimethylsulfoxide (140 mL). Add water (14 mL) and lithium chloride (7.0g, 0.16 mol). Heat at reflux for 4 hours, cool and partition between water (150 mL) and methylene chloride (2X150 mL). Wash the organic phase with water (150 mL), dry ($MgSO_4$) and pass through a silica gel plug to give 5-(carboethoxy)-2,4,5,6-tetrahydro-cyclopenta[c]furan.

Dissolve 5-(carboethoxy)-2,4,5,6-tetrahydro-cyclopenta[c]furan (6.2 g, 34.1 mmol) in ethanol (95%, 150 mL) and water (75 mL). Add potassium hydroxide (9.5 g, 0.17 mol) and stir at room temperature for 1 hour. Partition

between water (150 mL) and ethyl ether (2X150 mL). Acidify the aqueous phase with hydrochloric acid to pH 1. Extract with methylene chloride (2X150 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo to give 5-(carboxy)-2,4,5,6-tetrahydro-cyclopenta[c]furan.

Dissolve 5-(carboxy)-2,4,5,6-tetrahydro-cyclopenta[c]furan (3.6g, 23.5 mmol) in methanol (60 mL) and treat with dimethoxypropane (5.8 mL, 47 mmol) and sulfuric acid (0.8 mL). Stir at room temperature for 1 day. Evaporate the solvent in vacuo, dilute with methylene chloride (75 mL) and wash with saturated sodium hydrogen carbonate (35 mL). Extract the aqueous phase with methylene chloride (30 mL), wash combined organics with brine (30 mL) and dry (Na_2SO_4). Evaporate the solvent in vacuo and pass through a plug of silica gel to give 5-(carbomethoxy)-2,4,5,6-tetrahydro-cyclopenta[c]furan.

Mix 4-methoxybenzylthiol (3.0 g, 19 mmol) in sodium hydroxide (20 mL of a 2.5N aqueous solution) and methanol (10 mL). Add saturated aqueous copper sulfate solution (1.5 mL) and stir at room temperature for 2 hours, blowing air over the top of the mixture. Filter, wash solid with water and dry to give 4-methoxybenzyl disulfide as a pale yellow powder (2.71 g, 91%).

Cool lithium hexamethyldisilazane (4.2 mL, 4.2 mmol, 1.0 M in tetrahydrofuran) to -78°C and treat with a solution of 5-(carbomethoxy)-2,4,5,6-tetrahydro-cyclopenta[c]furan (589 mg, 3.55 mmol) in tetrahydrofuran (5 mL). Stir for 1 hour then add hexamethylphosphoramide (0.93 mL, 5.3 mmol) and stir for 5 minutes. Add 4-methoxybenzyl disulfide (1.6g, 5.2 mmol) in tetrahydrofuran (10 mL). Stir for 5 hours at -78°C and quench with a solution of ammonium chloride. Partition between ethyl acetate (75 mL) and brine (30 mL). Dry (Na_2SO_4), evaporate the solvent in vacuo and purify by silica gel chromatography

to give 5-(carbomethoxy)-5-(4-methoxybenzylthio)-2,4,5,6-tetrahydro-cyclopenta[c]furan.

Dissolve 5-(carbomethoxy)-5-(4-methoxybenzylthio)-2,4,5,6-tetrahydro-cyclopenta[c]furan (1.08 g, 3.55 mmol) in 95% ethanol (25 mL), water (12 mL) and tetrahydrofuran (15 mL). Treat with potassium hydroxide (1.3g, 23 mmol) and stir at room temperature for 1 hour. Filter and evaporate the solvent in vacuo. Partition between water (125 mL) and ether (75 mL). Separate the aqueous phase and acidify with cold concentrated hydrochloric acid. Extract with methylene chloride (75 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give 5-(carboxy)-5-(4-methoxybenzylthio)-2,4,5,6-tetrahydro-cyclopenta[c]furan.

Dissolve [4α, 7α(R*), 12bβ]-7-(amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (136 mg, 0.59 mmol) and EDC (170 mg, 0.886 mmol) in tetrahydrofuran (5 mL). Treat with 5-(carboxy)-5-(4-methoxybenzylthio)-2,4,5,6-tetrahydro-cyclopenta[c]furan (0.74 mmol). Stir at room temperature under an argon atmosphere for 20 hours and evaporate the solvent in vacuo. Dissolve the residue in ethyl acetate (30 mL) and wash with 5% sulfuric acid (15 mL) then saturated sodium hydrogen carbonate (15 mL). Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

Scheme A, step b: [4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]furan)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(5-(4-methoxybenzylthio)-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]furan)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine (0.38 mmol) in methylene chloride (6 mL) and cool to 0°C. Treat with

trifluoroacetic acid (3 mL), anisole (0.42 mL, 3.8 mmol), and mercuric acetate (155 mg, 0.49 mmol). Stir at 0°C for 3 hours then bubble hydrogen sulfide gas through the solution for 15 minutes. Filter and wash with methylene chloride. Wash organic phase with water (20 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

EXAMPLE 36

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]thiophene)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine

Scheme A, step a: [4S-[4α, 7α(R*), 12bβ]]-7-[(5-(4-methoxybenzylthio)-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]thiophene)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine

Dissolve 3,4-(dicarboethoxy)thiophene (2.28 g, 10 mmol) in anhydrous tetrahydrofuran (30 mL) and cool to -20°C. Treat with lithium borohydride (7 mL of a 2N solution) and stir under a nitrogen atmosphere for several days. Carefully add water and partition between ethyl acetate and 5% hydrochloric acid. Separate the organic phase, wash with brine and dry ($MgSO_4$). Evaporate the solvent in vacuo and purify by silica gel chromatography to give 3,4-(dihydroxymethyl)thiophene.

Dissolve 3,4-(dihydroxymethyl)thiophene (13.4 g, 0.093 mol) in 2,4,6-collidine (12.4 g) and add a solution of lithium bromide (7.9 g, 91 mmol) in dimethylformamide (80 mL). Cool to -50°C and place under a nitrogen atmosphere. Add trifluoromethanesulfonyl chloride (11.8 g) at a rate which keeps the temperature under 0°C. Stir at 0°C for 2 hours and pour onto ice water. Extract with ethyl ether, dry ($MgSO_4$), evaporate the solvent in vacuo and purify by silica gel chromatography to give 3,4-(dibromomethyl)thiophene.

Dissolve diethylmalonate (15.2 mL, 0.100 mol) in tetrahydrofuran (800 mL). Cool in an ice bath and treat with sodium hydride (3.0 g, 0.10 mol, 80% in mineral oil). Stir until solution attained and add 3,4-(dibromomethyl)thiophene (25.4 g, 0.100 mol). Stir for 30 minutes then add additional sodium hydride (3.0 g, 0.10 mol). Stir at room temperature for 20 hours, filter through filter aid and evaporate the solvent in vacuo. Purify by silica gel chromatography to give 5,5-(dicarboethoxy)-2,4,5,6-tetrahydro-cyclopenta[c]thiophene.

Dissolve 5,5-(dicarboethoxy)-2,4,5,6-tetrahydro-cyclopenta[c]thiophene (16.2 g, 60.6 mmol) in dimethylsulfoxide (140 mL). Add water (14 mL) and lithium chloride (7.0 g, 0.16 mol). Heat at reflux for 4 hours, cool and partition between water (150 mL) and methylene chloride (2X150 mL). Wash the organic phase with water (150 mL), dry ($MgSO_4$) and pass through a silica gel plug to give 5-(carboethoxy)-2,4,5,6-tetrahydro-cyclopenta[c]thiophene.

Dissolve 5-(carboethoxy)-2,4,5,6-tetrahydro-cyclopenta[c]thiophene (6.68 g, 34.1 mmol) in ethanol (95%, 150 mL) and water (75 mL). Add potassium hydroxide (9.5 g, 0.17 mol) and stir at room temperature for 1 hour. Partition between water (150 mL) and ethyl ether (2X150 mL). Acidify the aqueous phase with hydrochloric acid to pH 1. Extract with methylene chloride (2X150 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo to give 5-(carboxy)-2,4,5,6-tetrahydro-cyclopenta[c]thiophene.

Dissolve 5-(carboxy)-2,4,5,6-tetrahydro-cyclopenta[c]thiophene (3.95 g, 23.5 mmol) in methanol (60 mL) and treat with dimethoxypropane (5.8 mL, 47 mmol) and sulfuric acid (0.8 mL). Stir at room temperature for 1 day. Evaporate the solvent in vacuo, dilute with methylene chloride (75 mL) and wash with saturated sodium hydrogen carbonate (35 mL). Extract the aqueous phase with methylene

chloride (30 mL), wash combined organics with brine (30 mL) and dry (Na_2SO_4). Evaporate the solvent in vacuo and pass through a plug of silica gel to give 5-(carbomethoxy)-2,4,5,6-tetrahydro-cyclopenta[c]thiophene.

Mix 4-methoxybenzylthiol (3.0 g, 19 mmol) in sodium hydroxide (20 mL of a 2.5N aqueous solution) and methanol (10 mL). Add saturated aqueous copper sulfate solution (1.5 mL) and stir at room temperature for 2 hours, blowing air over the top of the mixture. Filter, wash solid with water and dry to give 4-methoxybenzyl disulfide as a pale yellow powder (2.71 g, 91%).

Cool lithium hexamethyldisilazane (4.2 mL, 4.2mol, 1.0 M in tetrahydrofuran) to -78°C and treat with a solution of 5-(carbomethoxy)-2,4,5,6-tetrahydro-cyclopenta[c]thiophene (646 mg, 3.55 mmol) in tetrahydrofuran (5 mL). Stir for 1 hour then add hexamethylphosphoramide (0.93 mL, 5.3 mmol) and stir for 5 minutes. Add 4-methoxybenzyl disulfide (1.6 g, 5.2 mmol) in tetrahydrofuran (10 mL). Stir for 5 hours at -78°C and quench with a solution of ammonium chloride. Partition between ethyl acetate (75 mL) and brine (30 mL). Dry (Na_2SO_4), evaporate the solvent in vacuo and purify by silica gel chromatography to give 5-(carbomethoxy)-5-(4-methoxybenzylthio)-2,4,5,6-tetrahydro-cyclopenta[c]thiophene.

Dissolve 5-(carbomethoxy)-5-(4-methoxybenzylthio)-2,4,5,6-tetrahydro-cyclopenta[c]thiophene (1.14 g, 3.55 mmol) in 95% ethanol (25 mL), water (12 mL) and tetrahydrofuran (15 mL). Treat with potassium hydroxide (1.3g , 23 mmol) and stir at room temperature for 1 hour. Filter and evaporate the solvent in vacuo. Partition between water (125 mL) and ether (75 mL). Separate the aqueous phase and acidify with cold concentrated hydrochloric acid. Extract with methylene chloride (75 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give 5-

(carboxy)-5-(4-methoxybenzylthio)-2,4,5,6-tetrahydro-cyclopenta[c]thiophene.

Dissolve [4α, 7α(R*), 12bβ]-7-(amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (136 mg, 0.59 mmol) and EDC (170 mg, 0.886 mmol) in tetrahydrofuran (5 mL). Treat with 5-(carboxy)-5-(4-methoxybenzylthio)-2,4,5,6-tetrahydro-cyclopenta[c]thiophene (0.74 mmol). Stir at room temperature under an argon atmosphere for 20 hours and evaporate the solvent in vacuo. Dissolve the residue in ethyl acetate (30 mL) and wash with 5% sulfuric acid (15 mL) then saturated sodium hydrogen carbonate (15 mL). Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

Scheme A, step b: [[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-4,5,6-trihydro-cyclopenta[c]thiophene)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine

Dissolve [[4S-[4α, 7α(R*), 12bβ]]-7-[(5-(4-methoxybenzylthio)-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]thiophene)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine (0.38 mmol) in methylene chloride (6 mL) and cool to 0°C. Treat with trifluoroacetic acid (3 mL), anisole (0.42 mL, 3.8 mmol), and mercuric acetate (155 mg, 0.49 mmol). Stir at 0°C for 3 hours then bubble hydrogen sulfide gas through the solution for 15 minutes. Filter and wash with methylene chloride. Wash organic phase with water (20 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

EXAMPLE 37

[4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-azazino[3,4-a][2]benzazepine

Scheme C, step a: [(R*,R*)]-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-3,4-dihydro-2H-4-trifluoracetyl-1,4-azazine

Dissolve ethylenediamine (30 mL, 0.45mol) in dioxane (150 mL). Add, by dropwise addition over 2.5 hours, a solution of di-tert-butyldicarbonate (12.2g, 56.1 mmol) in anhydrous dioxane (150 mL). Stir at room temperature for 22 hours, evaporate the solvent in vacuo and add water (250 mL). Filter and extract the aqueous phase with methylene chloride (3X250 mL). Dry (Na_2SO_4) and evaporate the solvent *in vacuo* to give N-(t-butyloxycarbonyl)ethylenediamine as a colorless oil (8.82g, 98%).

Dissolve N-(t-butyloxycarbonyl)ethylenediamine (8.82 g, 55.1 mmol) in methylene chloride (150 mL). Treat with pyridine (6.7 mL, 83 mmol). Add, by dropwise addition, trifluoroacetic anhydride (11.7 mL, 83 mmol). Stir at room temperature for 2.5 hours and quench with saturated sodium hydrogen carbonate (50 mL). Extract and wash the organic phase with 5% sulfuric acid (50 mL) and again with saturated sodium hydrogen carbonate (50 mL). Dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by chromatography (2:1 ethyl acetate/hexane) to give N-(t-butyloxycarbonyl)-N'-(trifluoroacetyl)-ethylenediamine as a colorless oil (10.1g, 72%).

Dissolve N-(t-butyloxycarbonyl)-N'-(trifluoroacetyl)-ethylenediamine (500 mg, 1.95 mmol) in anhydrous dimethylformamide (10 mL), cool to 0°C and treat with sodium hydride (56 mg, 1.85 mmol, 80% dispersion in mineral oil). Stir for 15 minutes and add allyl bromide (0.25 mL, 2.9 mmol). Stir for 2.5 hours, dilute with ethyl acetate (50 mL) and extract with water (25 mL). Separate the organic phase and wash with brine (2X20 mL). Extract the combined aqueous phases with ethyl acetate (2X5 mL), dry (Na_2SO_4) and evaporate the solvent *in vacuo*. Purify by chromatography (2:1 hexane/ethyl acetate to 3:2 hexane/ethyl acetate) to give

N-(t-butyloxycarbonyl)-N'-(trifluoroacetyl)-N'-(allyl)-ethylenediamine (562 mg, 100%).

Dissolve N-(t-butyloxycarbonyl)-N'-(trifluoroacetyl)-N'-(allyl)-ethylenediamine (1.95 mmol) in methylene chloride (7 mL) and add trifluoroacetic acid (2.6 mL). Stir at room temperature for 1 hour then evaporate the solvent *in vacuo* to give N'-(trifluoroacetyl)-N'-(allyl)-ethylenediamine trifluoroacetate.

Suspend N'-(trifluoroacetyl)-N'-(allyl)-ethylenediamine trifluoroacetate (1.95 mmol) in methylene chloride (7 mL) and add N-phthaloyl-(S)-phenylalanine, acid chloride (3 mL, 2.5 mmol). Cool to -30°C and add, by dropwise addition, N-methylmorpholine (0.46 mL, 4.2 mmol). Stir for 2 hours and dilute with ethyl acetate (50 mL). Wash with 5% sulfuric acid (20 mL), saturated sodium hydrogen carbonate (20 mL) and brine (20 mL). Dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by chromatography (2:1 hexane/ethyl acetate) to give N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-N'-(trifluoroacetyl)-N'-(allyl)-ethylenediamine (540 mg, 58%).

Dissolve N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-N'-(trifluoroacetyl)-N'-(allyl)-ethylenediamine (600 mg, 1.27 mmol) in methylene chloride (22 mL) and methanol (22 mL). Cool to -78°C and treat with ozone until blue. Remove excess ozone with a stream of nitrogen and add pyridine (0.12 mL) followed by dimethylsulfide (2.5 mL) and warm gradually to room temperature overnight. Dilute with ethyl acetate (75 mL) and wash with 5% sulfuric acid (30 mL) and saturated sodium hydrogen carbonate (30 mL). Dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by chromatography (2.5:1 ethyl acetate/hexane) to give 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl-N'-(trifluoroacetyl)-N'-

(1-oxo-ethane)-ethylenediamine as a white foam (489 mg, 81%).

Dissolve 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl-N'-(trifluoroacetyl)-N'-(1-oxo-ethane)-ethylenediamine (200 mg, 0.41 mmol) in methylene chloride (8 mL) and treat with trifluoroacetic acid (0.5 mL, 0.65 mmol). Stir for 2 hours at room temperature and dilute with ethyl acetate (50 mL). Wash with saturated sodium hydrogen carbonate (20 mL), then brine (20 mL) and dry (Na_2SO_4). Evaporate the solvent *in vacuo* and purify by chromatography (2:1 hexane/ethyl acetate) to give the title compound (90 mg, 47%).

Scheme C, step b: [4α, 7α(R*), 12bβ]-7-[(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-4-trifluoroacetyl-[1,4]-azazino[3,4-a][2]benzazepine

Dissolve [(R*,R*)]-N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-3,4-dihydro-2H-4-trifluoroacetyl-1,4-azazine (1.73 mmol) in methylene chloride (14 mL) and add, by dropwise addition, to trifluoromethane sulfonic acid (7 mL). Stir at room temperature for 4.5 days, cool in an ice bath and quench with water (3 mL). Partition between ethyl acetate (100 mL) and water (30 mL). Separate the organic phase and wash with saturated sodium hydrogen carbonate (30 mL), dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Scheme C, step c: [4α, 7α(R*), 12bβ]-7-(Amino)-3,4,6,7,8,12b-hexahydro-6-oxo-1H-4-t-butyloxycarbonyl-[1,4]-azazino[3,4-a][2]benzazepine

Dissolve [4α, 7α(R*), 12bβ]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-4-trifluoroacetyl-[1,4]-azazino[3,4-a][2]benzazepine (9 mmol) in anhydrous tetrahydrofuran (30 mL) and treat with pyrrolidine (10 mmol). Stir at room temperature for 48

hours and evaporate the solvent *in vacuo* to give [4α, 7α(R*), 12bβ]-7-[o-pyrrolidinocarbonylbenzamide]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-4-trifluoroacetyl-[1,4]-azazino[3,4-a][2]benzazepine.

Dissolve [4α, 7α(R*), 12bβ]-7-[o-pyrrolidinocarbonylbenzamide]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-4-trifluoroacetyl-[1,4]-azazino[3,4-a][2]benzazepine (1.5 mmol) in a mixture of ethanol (3 mL) and acetone (3 mL). Add sodium borohydride (1.5 mmol) and stir at room temperature overnight. Pour into water (25 mL) and carefully neutralize with 1N hydrochloric acid. Extract into ethyl acetate (2X), dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give [4α, 7α(R*), 12bβ]-7-[o-pyrrolidinocarbonylbenzamide]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-azazino[3,4-a][2]benzazepine.

Dissolve [4α, 7α(R*), 12bβ]-7-[o-pyrrolidinocarbonylbenzamide]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-azazino[3,4-a][2]benzazepine (1 mmol) in methanolic hydrochloric acid (5 mL) and stir at room temperature overnight. Evaporate the solvent *in vacuo* to give [4α, 7α(R*), 12bβ]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-azazino[3,4-a][2]benzazepine.

Dissolve [4α, 7α(R*), 12bβ]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-azazino[3,4-a][2]benzazepine (5 mmol) in 50/50 dioxane/water (25 mL) and buffer to pH 10 with 1N sodium hydroxide. Add, by dropwise addition, an ether solution of di-t-butyl dicarbonate (1.2 g, 5.5 mmol) at 10°C. Allow to warm to room temperature and buffer occasionally to retain pH 10. Acidify with a sodium citrate/citric acid buffer to pH 5, extract with ether (3X), dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give [4α, 7α(R*), 12bβ]-7-[(1,3-dihydro-

1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-4-t-butyloxycarbonyl-[1,4]-azazino[3,4-a][2]benzazepine.

Dissolve [4α, 7α(R*), 12bβ]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-4-t-butyloxycarbonyl-[1,4]-azazino[3,4-a][2]benzazepine (1.86 mmol) in methanol (15 mL) and treat with hydrazine hydrate (4.6 mL of a 1.0 M solution in methanol, 4.6 mmol). Stir 2.5 days at room temperature, filter through filter aid and condense. Filter again through a mixture of filter aid and $MgSO_4$ and evaporate the solvent *in vacuo* to give the title compound.

Scheme A, step a: [4S-[4α, 7α(R*), 12bβ]]-7-[(5-(4-methoxybenzylthio)-5-oxo-2-(carbo-t-butyloxy)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-4-t-butyloxycarbonyl-[1,4]-azazino[3,4-a][2]benzazepine

Dissolve 3,4-(dicarboethoxy)pyrrole (1.06 g, 5 mmol) in 50/50 dioxane water (25 mL) and buffer to pH 10 with 1N sodium hydroxide. Add, by dropwise addition, an ether solution of di-t-butyl dicarbonate (1.2 g, 5.5 mmol) at 10°C. Allow to warm to room temperature and buffer occasionally to retain pH 10. Acidify with a sodium citrate/citric acid buffer to pH 5, extract with ethyl ether (3X), dry ($MgSO_4$) and evaporate the solvent in vacuo. Purify the residue by silica gel chromatography to give N-(carbo-t-butyloxy)-3,4-(dicarboethoxy)pyrrole.

Dissolve N-(carbo-t-butyloxy)-3,4-(dicarboethoxy)pyrrole (3.11 g, 10 mmol) in anhydrous tetrahydrofuran (30 mL) and cool to -20°C. Treat with lithium borohydride (7 mL of a 2N solution) and stir under a nitrogen atmosphere for several days. Carefully add water and partition between ethyl acetate and 5% hydrochloric acid. Separate the organic phase, wash with brine and dry ($MgSO_4$). Evaporate the

solvent in vacuo and purify by silica gel chromatography to give N-(carbo-t-butyloxy)-3,4-(dihydroxymethyl)pyrrole.

Dissolve N-bromosuccinimide (1.78 g, 0.01 mol) in tetrahydrofuran (60 mL) and add a solution of triphenylphosphine (2.62 g, 0.01 mol) in tetrahydrofuran. Add a solution of N-(carbo-t-butyloxy)-3,4-(dihydroxymethyl)pyrrole (1.14 g, 5 mmol) in tetrahydrofuran (25 mL) and stir until most of the solid goes into solution. Evaporate the solvent in vacuo and partition the residue between water and ethyl ether. Separate the organic phase and wash with water. Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give N-(carbo-t-butyloxy)-3,4-(dibromomethyl)pyrrole.

Dissolve diethylmalonate (15.2 mL, 0.100mol) in tetrahydrofuran (800 mL). Cool in an ice bath and treat with sodium hydride (3.0 g, 0.10 mol, 80% in mineral oil). Stir until solution attained and add N-(carbo-t-butyloxy)-3,4-(dibromomethyl)pyrrole (35.3 g, 0.100 mol). Stir for 30 minutes then add additional sodium hydride (3.0 g, 0.10 mol). Stir at room temperature for 20 hours, filter through filter aid and evaporate the solvent in vacuo. Purify by silica gel chromatography to give 5,5-(dicarboethoxy)-2-(carbo-t-butyloxy)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole.

Dissolve 5,5-(dicarboethoxy)-2-(carbo-t-butyloxy)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole (21.3 g, 60.6 mmol) in dimethylsulfoxide (140 mL). Add water (14 mL) and lithium chloride (7.0 g, 0.16 mol). Heat at reflux for 4 hours, cool and partition between water (150 mL) and methylene chloride (2X150 mL). Wash the organic phase with water (150 mL), dry ($MgSO_4$) and pass through a silica gel plug to give 5-(carboethoxy)-2-(carbo-t-butyloxy)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole.

Dissolve 5-(carboethoxy)-2-(carbo-t-butyloxy)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole (9.5 g, 34.1 mmol) in ethanol (95%, 150 mL) and water (75 mL). Add potassium hydroxide (9.5 g, 0.17 mol) and stir at room temperature for 1 hour. Partition between water (150 mL) and ethyl ether (2X150 mL). Acidify the aqueous phase with hydrochloric acid to pH 1. Extract with methylene chloride (2X150 mL), dry (Na_2SO_4) and evaporate the solvent <u>in vacuo</u> to give 5-(carboxy)-2-(carbo-t-butyloxy)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole.

Dissolve 5-(carboxy)-2-(carbo-t-butyloxy)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole (5.9 g, 23.5 mmol) in methanol (60 mL) and treat with dimethoxypropane (5.8 mL, 47 mmol) and sulfuric acid (0.8 mL). Stir at room temperature for 1 day. Evaporate the solvent <u>in vacuo</u>, dilute with methylene chloride (75 mL) and wash with saturated sodium hydrogen carbonate (35 mL). Extract the aqueous phase with methylene chloride (30 mL), wash combined organics with brine (30 mL) and dry (Na_2SO_4). Evaporate the solvent <u>in vacuo</u> and pass through a plug of silica gel to give 5-(carbomethoxy)-2-(carbo-t-butyloxy)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole.

Mix 4-methoxybenzylthiol (3.0g, 19 mmol) in sodium hydroxide (20 mL of a 2.5 N aqueous solution) and methanol (10 mL). Add saturated aqueous copper sulfate solution (1.5 mL) and stir at room temperature for 2 hours, blowing air over the top of the mixture. Filter, wash solid with water and dry to give 4-methoxybenzyl disulfide as a pale yellow powder (2.71 g, 91%).

Cool lithium hexamethyldisilazane (4.2 mL, 4.2mol, 1.0 M in tetrahydrofuran) to -78°C and treat with a solution of 5-(carbomethoxy)-2-(carbo-t-butyloxy)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole (941 mg, 3.55 mmol) in tetrahydrofuran

(5 mL). Stir for 1 hour then add hexamethylphosphoramide (0.93 mL, 5.3 mmol) and stir for 5 minutes. Add 4-methoxybenzyl disulfide (1.6g, 5.2 mmol) in tetrahydrofuran (10 mL). Stir for 5 hours at -78°C and quench with a solution of ammonium chloride. Partition between ethyl acetate (75 mL) and brine (30 mL). Dry (Na_2SO_4), evaporate the solvent in vacuo and purify by silica gel chromatography to give 5-(carbomethoxy)-2-(carbo-t-butyloxy)-5-(4-methoxybenzylthio)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole.

Dissolve 5-(carbomethoxy)-2-(carbo-t-butyloxy)-5-(4-methoxybenzylthio)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole (1.43 g, 3.55 mmol) in 95% ethanol (25 mL), water (12 mL) and tetrahydrofuran (15 mL). Treat with potassium hydroxide (1.3g, 23 mmol) and stir at room temperature for 1 hour. Filter and evaporate the solvent in vacuo. Partition between water (125 mL) and ether (75 mL). Separate the aqueous phase and acidify with cold concentrated hydrochloric acid. Extract with methylene chloride (75 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give 5-(carboxy)-2-(carbo-t-butyloxy)-5-(4-methoxybenzylthio)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole.

Dissolve [4α, 7α(R*), 12bβ]-7-(amino)-3,4,6,7,8,12b-hexahydro-6-oxo-1H-4-t-butyloxycarbonyl-[1,4]-azazino[3,4-a][2]benzazepine (136 mg, 0.59 mmol) and EDC (170 mg, 0.886 mmol) in tetrahydrofuran (5 mL). Treat with 5-(carboxy)-2-(carbo-t-butyloxy)-5-(4-methoxybenzylthio)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole (0.74 mmol). Stir at room temperature under an argon atmosphere for 20 hours and evaporate the solvent in vacuo. Dissolve the residue in ethyl acetate (30 mL) and wash with 5% sulfuric acid (15 mL) then saturated sodium hydrogen carbonate (15 mL). Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

Scheme A, step b: [4S-[4α, 7α(R*), 12bβ]]-7-[(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-azazino[3,4-a][2]benzazepine

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(5-(4-methoxybenzylthio)-5-oxo-2-(carbo-t-butyloxy)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-4-t-butyloxycarbonyl-[1,4]-azazino[3,4-a][2]benzazepine (0.38 mmol) in methylene chloride (6 mL) and cool to 0°C. Treat with trifluoroacetic acid (3 mL), anisole (0.42 mL, 3.8 mmol), and mercuric acetate (155 mg, 0.49 mmol). Stir at 0°C for 3 hours then bubble hydrogen sulfide gas through the solution for 15 minutes. Filter and wash with methylene chloride. Wash organic phase with water (20 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

EXAMPLE 38

[6α(R*), 11bβ]-6-[(S)-(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine

Scheme C, step a: (R*,R*)-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-1,2,3-trihydro-2-pyrrole

Mix 4-bromo-1-butene (0.209 mol) and potassium cyanide (16.8 g, 0.257 mol) in ethylene glycol (85 mL) and heat at 100°C for 2 hours. Cool, dilute with water (100 mL) and extract into ethyl ether (100 mL). Wash with saturated sodium hydrogen carbonate (35 mL), dry (Na_2SO_4) and distill to give 4-pentenylnitrile.

Suspend lithium aluminum hydride (6.5 g, 0.17 mol) in ethyl ether (350 mL) and add, by dropwise addition over 30 minutes, 4-pentenylnitrile (0.171mol). Stir at room temperature for 2 hours, cool in an ice bath and add, by

very slow addition, water (6.8 mL), then 20% sodium hydroxide (5.2 mL) then water (24 mL). Decant the ethereal phase and wash the white salts with ether. Combine the ethereal phases and distill to give 4-penteneamine.

Dissolve 4-pentenylamine (0.88 g, 8.9 mmol) in methylene chloride (50 mL) and treat first with N-phthaloyl-(S)-phenylalanine (2.95 g, 10.0 mmol), then with EEDQ (2.47 g, 10.0 mmol) and stir at room temperature for 6 hours. Evaporate the solvent *in vacuo*, dissolve the residue in ethyl acetate (75 mL) and wash with 5% sulfuric acid (25 mL), saturated sodium hydrogen carbonate (25 mL) and brine (25 mL). Dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by chromatography to give 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-3-phenylpropionyl-4-pentenylamide.

Dissolve 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-3-phenylpropionyl-4-pentenylamide (3.19 mmol) in methylene chloride (40 mL) and methanol (4 mL), cool to -78°C and place under a nitrogen atmosphere. Treat with ozone until a blue color persists, degas with nitrogen for 20 minutes and add pyridine (0.2 mL). Quench with dimethylsulfide (4 mL) and stir overnight at room temperature. Dilute with methylene chloride (75 mL) and wash with 5% sulfuric acid (40 mL) and brine (40 mL). Dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by chromatography (hexane/ethyl acetate) to give 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-3-phenylpropionyl-4-oxo-butylamide.

Dissolve 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-3-phenylpropionyl-4-oxo-butylamide (0.404 mmol) in anhydrous methylene chloride (7 mL) and treat with trifluoroacetic acid (0.04 mL, 0.5 mmol). Stir at room temperature for 3 hours, partition between methylene chloride (25 mL) and saturated sodium hydrogen carbonate (15 mL). Dry (Na_2SO_4),

evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Scheme C, step b: [6α(R*), 11bβ]-6-[(S)-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine

Dissolve (R*,R*)-N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-1,2,3-trihydro-2-pyrrole (1.73 mmol) in methylene chloride (14 mL) and add, by dropwise addition, to trifluoromethane sulfonic acid (7 mL). Stir at room temperature for 4.5 hours, cool in an ice bath and quench with water (3 mL). Partition between ethyl acetate (100 mL) and water (30 mL). Separate the organic phase and wash with saturated sodium hydrogen carbonate (30 mL), dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Scheme C, step c: [6α(R*), 11bβ]-6-[(S)-Amino]-3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine

Dissolve [6α(R*), 11bβ]-6-[(S)-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine (1.86 mmol) in methanol (15 mL) and treat with hydrazine hydrate (4.6 mL of a 1.0M solution in methanol, 4.6 mmol). Stir 2.5 days at room temperature, filter through filter aid and condense. Filter again through a mixture of filter aid and $MgSO_4$ and evaporate the solvent in vacuo to give the title compound.

Scheme A, step a: [6α(R*), 11bβ]-6-[(S)-(5-(4-Methoxybenzylthio)-5-oxo-2-(carbo-t-butyloxy)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine

Dissolve 5-(carboxy)-2-(carbo-t-butyloxy)-5-(4-methoxybenzylthio)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole (329 mg, 0.845 mmol) in methylene chloride (6 mL), cool in an ice-methanol bath and treat with oxalyl chloride (0.94

mL, 11 mmol). Stir for 1.5 hours, evaporate the solvent in vacuo at 0-5°C. Dilute the residue with methylene chloride (3 mL) and add a solution of [6α(R*), 11bβ]-6-[(S)-Amino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine (0.565 mmol) in methylene chloride (6 mL). Add pyridine (68 µL, 0.85 mmol) and stir for 2 hours. Dilute with ethyl acetate (60 mL) and wash with 1N hydrochloric acid (30 mL) and saturated sodium hydrogen carbonate (2X30 mL). Dry ($MgSO_4$), evaporate the solvent in vacuo and purify by silica gel chromatography to give the title compound.

Scheme A, step b: [6α(R*), 11bβ]-6-[(S)-(5-Thio-5-oxo-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine

Dissolve [6α(R*), 11bβ]-6-[(S)-(5-(4-methoxybenzylthio)-5-oxo-2-(carbo-t-butyloxy)-2,4,5,6-tetrahydro-cyclopenta[c]pyrrole)methylamino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine (105 mg, 0.163 mmol) in methylene chloride (3 mL) and cool to 0°C. Treat with trifluoroacetic acid (1.5 mL), anisole (0.19 mL, 1.7 mmol), and mercuric acetate (65 mg, 0.2 mmol). Stir at 0°C for 3 hours then bubble hydrogen sulfide gas through the solution for 10 minutes. Filter and wash with methylene chloride. Wash organic phase with water (20 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

EXAMPLE 39

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-1-oxo-2-methyl)-2-propylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Dissolve 4-methoxybenzylthiol (14 mL, 0.10 mmol) in anhydrous dimethylformamide (150 mL), degas and purge with nitrogen. Add diisopropylethylamine (20 mL, 0.115 mol),

then treat with ethyl bromoacetate (11.1 mL, 0.10mol). Place the reaction flask in a cooling bath containing cold water and stir to room temperature for 64 hours. Partition between water (300 mL) and ether (250 mL). Separate the aqueous phase and extract with ether (250 mL). Combine the organic phases, wash with water (2X150 mL) and extract the combined aqueous phases with ether (125 mL). Dry (Na_2SO_4) and evaporate the solvent *in vacuo*. Purify by chromatography (6:1 hexane/ethyl acetate) to give 1-(carboethoxy)-1-(4-methoxybenzylthio)methane as a yellow oil (22 g, 92%).

Dissolve lithium hexamethyldisilazane (4.2 mL of a 1.0M solution in tetrahydrofuran, 4.2 mmol) in tetrahydrofuran (9 mL) and cool to -78°C. Treat with a solution of 1-(carboethoxy)-1-(4-methoxybenzylthio)methane (1.0g, 4.2 mmol) in tetrahydrofuran (4 mL). Stir for 45 minutes, add methyliodide (0.26 mL, 4.2 mmol) and stir for 3 hours. Add additional lithium hexamethyldisilazane (4.2 mL of a 1.0 M solution in tetrahydrofuran, 4.2 mmol), stir for 30 minutes and add methyl iodide (0.3 mL, 4.8 mmol). Stir at room temperature overnight. Partition between saturated ammonium chloride (30 mL) and ethyl acetate (50 mL). Separate the organic phase, dry (Na_2SO_4) and evaporate the solvent *in vacuo*. Purify by chromatography (5:1 hexane/ethyl acetate) to give 2-(carboethoxy)-2-(4-methoxybenzylthio)propane as a pale yellow oil (1.05 g, 93.8%).

Dissolve 2-(carboethoxy)-2-(4-methoxybenzylthio)propane (1.05 g, 3.91 mmol) in a mixture of 95% ethanol (18 mL), water (9 mL) and tetrahydrofuran (10 mL). Add potassium hydroxide (1.4g, 25 mmol) and stir at room temperature for 2 hours then at 55°C for 1 hour. Evaporate the solvent *in vacuo* and partition between water (50 mL) and ether (50 mL). Acidify to pH 1 with concentrated hydrochloric acid and extract into methylene chloride (50 mL). Dry (Na_2SO_4) and evaporate the solvent *in vacuo* to give 2-(carboxy)-2-(4-methoxybenzylthio)propane as a tan solid (763 mg).

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-(amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (175 mg) EEDQ (101 mg, 0.41 mmol) and 2-(carboxy)-2-(4-methoxybenzylthio)propane (96 mg, 0.40 mmol in methylene chloride (5 mL). Stir at room temperature for 18 hours and evaporate the solvent in vacuo. Dissolve the residue in ethyl acetate (30 mL) and wash with 5% sulfuric acid (15 mL) then saturated sodium hydrogen carbonate (15 mL). Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give [4S-[4α, 7α(R*), 12bβ]]-7-[(2-(4-methoxybenzylthio)-1-oxo-2-methyl)-2-propylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine.

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(2-(4-methoxybenzylthio)-1-oxo-2-methyl)-2-propylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (260 mg) in methylene chloride (5 mL) and cool to 0°C. Treat with anisole (0.43 mL, 4.0 mmol) and mercuric acetate (159 mg, 0.50 mmol) then with trifluoroacetic acid (2.5 mL). Stir for 3 hours then bubble hydrogen sulfide gas through the solution for 10 minutes. Filter and dilute with methylene chloride. Wash organic phase with water (20 mL), dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound. In a further embodiment, the present invention provides a method of inhibiting enkephalinase in a patient in need thereof comprising administering to said patient an effective enkephalinase inhibitory amount of a compound of Structure (a).

EXAMPLE 40

[4S-[4α, 7α(R*), 12bβ]]-7-[(4-Thio-4-oxopiperidine)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Scheme A, step a: [4S-[4α, 7α(R*), 12bβ]]-7-[(4-(4-Methoxybenzylthio)-4-oxo-1-(carbo-t-butyloxy)-piperidine)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine

Dissolve t-butyldicarbonate (14.14 g, 64.8 mmol) in methylene chloride (600 mL) and add ethyl isonipecotic acid (10 mL, 64.8 mmol). Stir for 1 hour and evaporate the solvent *in vacuo* to give 1-carbo-t-butyloxy-isonipecotic acid, ethyl ester as a pale yellow oil (17.5 g, 99%).

Add, by dropwise addition, 1-carbo-t-butyloxy-isonipecotic acid, ethyl ester (4 g, 15.546 mmol) to a solution of lithium diisopropylamide (27.96 mmol) in tetrahydrofuran at -78°C. Warm to -25°C and add a solution of 4-methoxybenzyl disulfide (8.56g, 27.96 mmol) in tetrahydrofuran (15 mL). Stir at room temperature for 1 hour, dilute with ethyl acetate (200 mL), wash with 10% HCl (2X100 mL) and saturated sodium hydrogen carbonate (100 mL). Dry (Na_2SO_4) and evaporate the solvent *in vacuo*. Purify by silica gel chromatography (1:9 ethyl acetate/hexane) to give (4-(carboethoxy)-4-(4-methoxybenzylthio)-1-(carbo-t-butyloxy)-piperidine.

Dissolve (4-(carboethoxy)-4-(4-methoxybenzylthio)-1-(carbo-t-butyloxy)-piperidine (3 g, 7.5 mmol) in a mixture of methanol, (35 mL) tetrahydrofuran (35 mL) and water (17 mL). Add lithium hydroxide monohydrate (2.2 g, 0.053mol) and heat at 45-60°C for 5 hours. Cool, evaporate the solvent in vacuo and partition the residue between water (200 mL) and ether (200 mL). Separate the aqueous phase, acidify to pH 1 and extract with methylene chloride (200 mL). Dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by silica gel chromatography (9:1 hexane/ethyl acetate) to give (4-(carboxy)-4-(4-methoxybenzylthio)-1-(carbo-t-butyloxy)-piperidine as a white solid (0.5 g, 18%).

Mix (4-(carboxy)-4-(4-methoxybenzylthio)-1-(carbo-t-butyloxy)-piperidine (0.4 g, 1.048 mmol), EDC (0.302 g, 1.57 mmol) and tetrahydrofuran (10 mL). Treat with [4S-[4α, 7α(R*), 12bβ]]-7-(amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (0.242 g, 1.048 mmol) and stir at room temperature for 24 hours. Evaporate the solvent in vacuo, take the residue up in ethyl acetate (60 mL), wash with 5% sulfuric acid, saturated sodium hydrogen carbonate and brine (30 mL). Dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by silica gel chromatography (3:2 hexane/ethyl acetate followed by 1:1 hexane/ethyl acetate) to give the title compound as a white solid (320 mg, 52%).

Scheme A, steps b and c: [4S-[4α, 7α(R*), 12bβ]]-7-[(4-Thio-4-oxopiperidine)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, trifluoroacetate salt

Mix [4S-[4α, 7α(R*), 12bβ]]-7-[(4-(4-Methoxybenzylthio)-4-oxo-1-(carbo-t-butyloxy)-piperidine)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine (320 mg, 0.54 mmol), anisole (0.58 mL, 5.34 mmol), mercuric acetate (214 mg, 0.67 mmol) and methylene chloride (10 mL). Cool in an ice bath and treat with trifluoroacetic acid (3.5 mL). After 3.5 hours, bubble in H_2S gas for 10 minutes, filter and evaporate the solvent *in vacuo*. Triturate the residue with hexane (2X), add methylene chloride and filter. Evaporate the solvent in vacuo, adding carbon tetrachloride to remove excess trifluoroacetic acid. Dissolve the residue in a minimum amount of methylene chloride and pour into vigorously stirring hexane. Collect the precipitate by vacuum filtration and purify by silica gel chromatography (9:1:0.1 methylene chloride/methanol/ammonium hydroxide) to give [4S-[4α, 7α(R*), 12bβ]]-7-[(4-thio-4-oxo-1-(carbo-t-butyloxy)-piperidine)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine. Dissolve in methylene chloride (5 mL) and add trifluoroacetic acid (0.05 mL, 0.669 mmol) to give the title compound after filtration (0.141 mg, 54%).

As used herein, the term "patient" refers to warm-blooded animals or mammals, including mice, rats and humans. A patient is in need of treatment to inhibit enkephalinase when the patient is suffering from acute or chronic pain and is in need of an endorphin- or enkephalin-mediated analgesic effect. In addition, a patient is in need of treatment to inhibit enkephalinase when the patient is suffering from a disease state characterized by abnormalities in fluid, electrolyte, blood pressure, intraocular pressure, renin, or aldosterone homeostasis, such as, but not limited to, hypertension, renal diseases, hyperaldosteronemia, cardiac hypertrophy, glaucoma and congestive heart failure. In these instances the patient is in need of an ANP-mediated diuretic, natriuretic, hypotensive, hypoaldosteronemic effect. Inhibition of enkephalinase would provide an endorphin- or enkephalin-mediated analgesic effect by inhibiting the metabolic degradation of endorphins and enkephalins. Inhibition of enkephalinase would provide an ANP-mediated diuretic, natriuretic, hypotensive, hypoaldosteronemic effect by inhibiting the metabolic degradation of ANP. Inhibition of enkephalinase would also modulate intestinal smooth muscle contractility and would be useful in the treatment of irritable bowel syndrome.

In addition, a patient is in need of treatment to inhibit enkephalinase when the patient is in need of an antidepressant effect or a reduction in severity of withdrawal symptoms associated with termination of opiate or morphine administration.

The identification of those patients who are in need of treatment to inhibit enkephalinase is well within the ability and knowledge of one skilled in the art. A clinician skilled in the art can readily identify, by the

use of clinical tests, physical examination and medical/family history, those patients who are in need of an endorphin- or enkephalin-mediated analgesic effect or who are in need of an ANP-mediated diuretic, natriuretic, hypotensive or hypoaldosteronemic effect.

An effective enkephalinase inhibitory amount of a compound of Formula (I) is an amount which is effective in inhibiting enkephalinase and in thus inhibiting the metabolic degradation of the naturally-occurring circulating regulatory peptides such as the endorphins, including enkephalins, and ANP. Successful treatment is also understood to include prophylaxis in treating a patient in those instances such as, for example, in a pre-operative procedure, where a patient will be suffering from acute or chronic pain in the near future.

An effective enkephalinase inhibitory amount of a compound of Formula (I) is an amount which is effective in inhibiting enkephalinase in a patient in need thereof which results, for example, in endorphin- or enkephalin-mediated analgesic effects or in ANP-mediated diuretic, natriuretic, hypotensive, hypoaldosteronemic effect.

An effective enkephalinase inhibitory dose can be readily determined by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the effective dose, a number of factors are considered including, but not limited to: the species of patient; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; and the use of concomitant medication.

An effective enkephalinase inhibitory amount of a compound of Formula (I) will generally vary from about 0.01 milligram per kilogram of body weight per day (mg/kg/day) to about 20 mg/kg/day. A daily dose of from about 0.1 mg/kg to about 10 mg/kg is preferred.

In effecting treatment of a patient, compounds of Formula (I) can be administered in any form or mode which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, the compound can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred. One skilled in the art of preparing Formulations can readily select the proper form and mode of administration depending upon the disease state to be treated, the stage of the disease, and other relevant circumstances.

Compounds of Formula (I) can be administered in the form of pharmaceutical compositions or medicaments which are made by combining the compounds of Formula (I) with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the chosen route of administration, and standard pharmaceutical practice.

In another embodiment, the present invention provides compositions comprising a compound of Formula (I) in admixture or otherwise in association with one or more inert carriers. These compositions are useful, for example, as assay standards, as convenient means of making bulk shipments, or as pharmaceutical compositions. An assayable amount of a compound of Formula (I) is an amount which is readily measurable by standard assay procedures and techniques as are well known and appreciated by those skilled in the art. Assayable amounts of a compound of

Formula (I) will generally vary from about 0.001% to about 75% of the composition by weight. Inert carriers can be any material which does not degrade or otherwise covalently react with a compound of Formula (I). Examples of suitable inert carriers are water; aqueous buffers, such as those which are generally useful in High Performance Liquid Chromatography (HPLC) analysis; organic solvents, such as acetonitrile, ethyl acetate, hexane and the like; and pharmaceutically acceptable carriers or excipients.

More particularly, the present invention provides pharmaceutical compositions comprising an effective amount of a compound of Formula (I) in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

The pharmaceutical compositions or medicaments are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral or parenteral use and may be administered to the patient in the form of tablets, capsules, suppositories, solution, suspensions, or the like.

The pharmaceutical compositions may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds of Formula (I) may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of Formula (I), the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about

70% of the weight of the unit. The amount of the active ingredient present in compositions is such that a unit dosage form suitable for administration will be obtained.

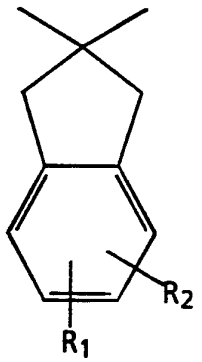
The tablets, pills, capsules, troches and the like may also contain one or more of the following adjuvants: binders, such as microcrystalline cellulose, gum tragacanth or gelatin; excipients, such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants, such as magnesium stearate or Sterotex; glidants, such as colloidal silicon dioxide; and sweetening agents, such as sucrose or saccharin may be added or flavoring agents, such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active ingredient, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral administration, the compounds of Formula (I) may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of a compound of the invention, but may be varied to be between 0.1 and about 50% of the weight thereof. The amount of the active ingredient present in such compositions is such that a suitable dosage will be obtained.

The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils,

polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of toxicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

As with any group of structurally related compounds which possess a particular generic utility, certain groups and configurations are preferred for compounds of Formula (I) in their end-use application. The compounds of Formula (I) wherein R_1 is hydrogen or alkoxy are preferred. The compounds of Formula (I) wherein R_2 is hydrogen or alkoxy are preferred. The compounds of Formula (I) wherein n is 0 are preferred. The compounds of Formula (I) wherein R_3 is hydrogen are preferred. The compounds of Formula (I) wherein Q is



are preferred.

It is, of course, understood that the compounds of Formula (I) may exist in a variety of isomeric configurations including structural as well as stereo isomers. It is further understood that the present invention encompasses those compounds of Formula (I) in each of their various structural and stereo isomeric

configurations as individual isomers and as mixtures of isomers.

The following specific compounds of Formula (I) are particularly preferred in the end-use application of the compounds of the present invention:

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, benzylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, ethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-hydroxyethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-pyridylmethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-thioacetic acid morpholine carboxamide, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, L-cysteine ethyl ester, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

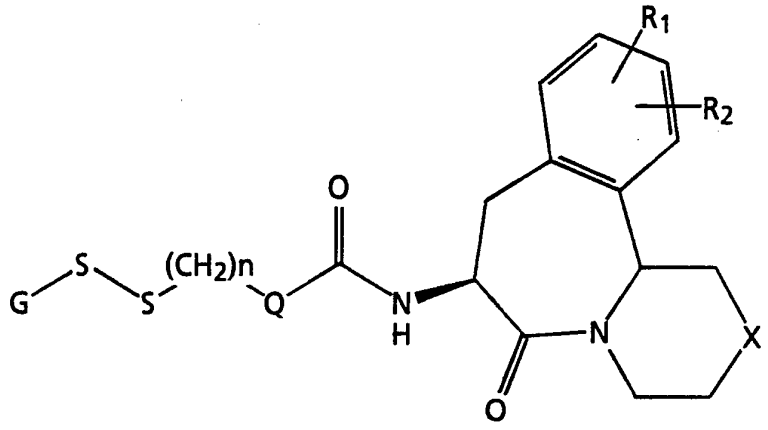
[4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (R)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

The following ex vivo study illustrate the utility of the compounds of the present invention as enkephalinase inhibitors. This study are carried out by the method of J. F. French et al J. Pharmcacol. Exp. Ther., 268(1), 180-186 (1994).

Administer test compound or vehicle (99/1, ethanol/1% sodium bicarbonate solution) to fasted male Sprague-Dawley rats (Charles Rivers Breeding Laboratories Inc.). Administration is carried out by intraperitoneal injection. At 3 hours after administration, sacrifice the rats and remove the kidneys and freeze. Homogenize whole kidneys and carry through the P2 step of the protocol of Booth and Kenny [Biochem. J., 142, 575-581 (1974)] for the preparation of the microvilli fraction. Resuspend P2 material in 50 mM HEPES buffer, pH 8.0, containing 0.3 M NaCl and 0.5% Triton X-100 and keep at -20°C prior to the assay.. The enzyme activity may be measured by the fluorometric methods of Florentin et al Anal. Biochem. 141, 62-69 (1984). The enzyme is assayed in 50mM HEPES buffer (pH 7.4) in a 3.0 mL reaction volume containing 12 μM of the substrate dansyl-D-AlaGly(p-nitro)PheGly-OH (K_m=40μM) at 25°C. The enzyme in a small volume is added to initiate the reaction and the rate of fluorescence increase is recorded continuously using a fluorometer (excitation at 339nm, emission at 562nm). Use Thiorphan (Sigma Chemical Co.) as a standard for NEP inhibition. The effectiveness of the test compound is determined by measuring enzyme activity from kidneys obtained from test compound treated rats compared to enzyme activity from kidneys obtained from vehicle treated rats. The Thiorphan treated animal serve as a positive control.

WHAT IS CLAIMED IS:

1. A compound of the formula



Formula (I)

wherein

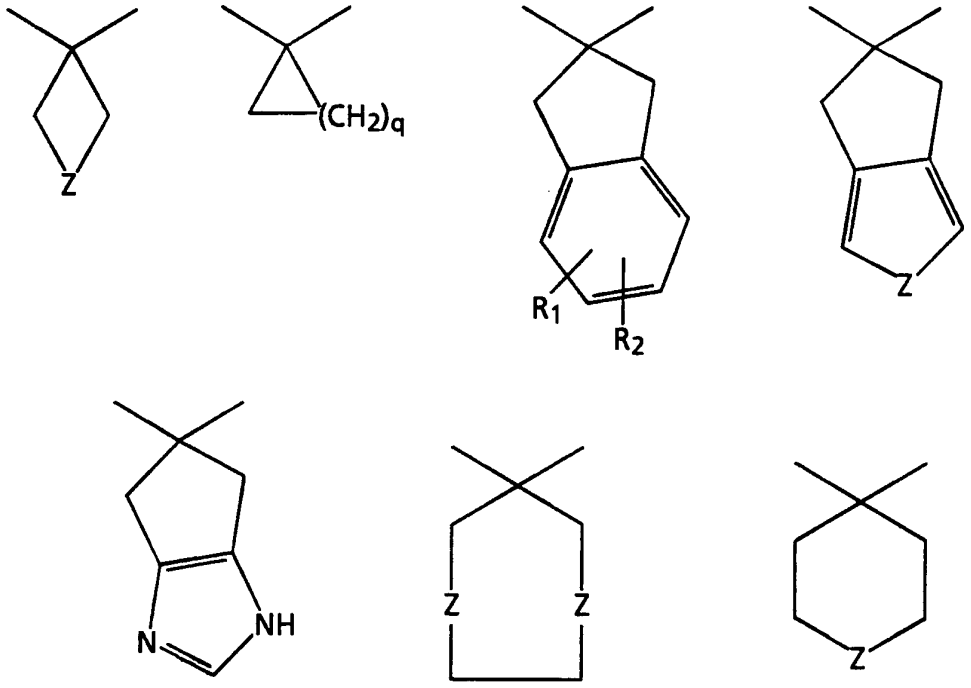
n is an integer from 0 to 3;

R_1 and R_2 are each time taken independently chosen from the group consisting of: hydrogen, hydroxy, $-OR_3$ wherein R_3 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

R_3 is hydrogen $-CH_2O-C(O)C(CH_3)_3$;

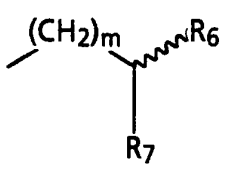
X is $-(CH_2)_p-$, O, S, NR_4, or $NC(O)R_5$ wherein p is an integer 0 or 1, R_4 is hydrogen, a C_1-C_4 alkyl, or an Ar-Y- group, and R_5 is $-CF_3$, C_1-C_{10} alkyl, or an Ar-Y- group;

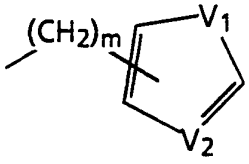
Q is a alkylene radical chosen from the group

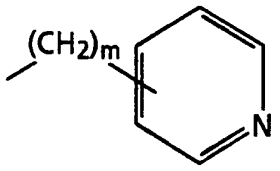


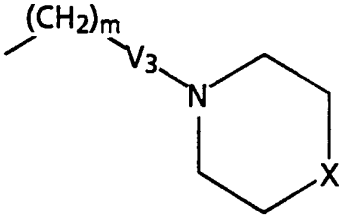
wherein q is an integer from 1 to 5 and Z is O, S, NH;

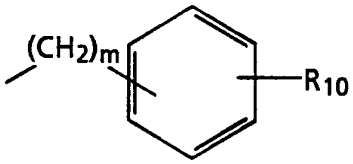
G is a radical chosen from the group;

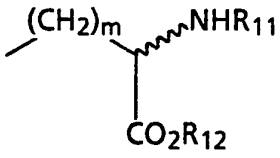


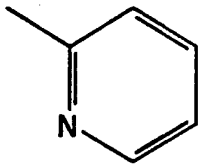












wherein

m is an integer from 1 to 3;

R_6 is hydrogen, C_1-C_6 alkyl, $-CH_2CH_2S(O)_kCH_3$, or Ar-Y- wherein k is an integer form 0 to 2;

R_7 is hydrogen, hydroxy, amino, C_1-C_6 alkyl, N-methylamino, N,N-dimethylamino, $-CO_2R_8$ wherein R_8 is hydrogen, $-CH_2O-C(O)C(CH_3)_3$, or C_1-C_4 alkyl; or $-OC(O)R_9$ wherein R_9 is hydrogen, C_1-C_6 alkyl, or phenyl;

R_{10} is 1 or 2 substituents independently chosen from the group consisting of; hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or halogen;

R_{11} is hydrogen, C_1-C_6 alkyl, or Ar-Y- group;

R_{12} is hydrogen or C_1-C_4 alkyl;

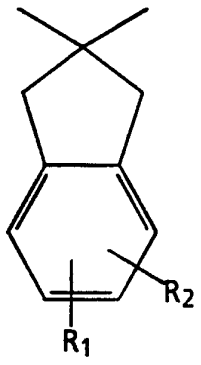
V_1 is O, S, or NH;

V_2 is N or CH;

V_3 is a direct bond or -C(O)-;

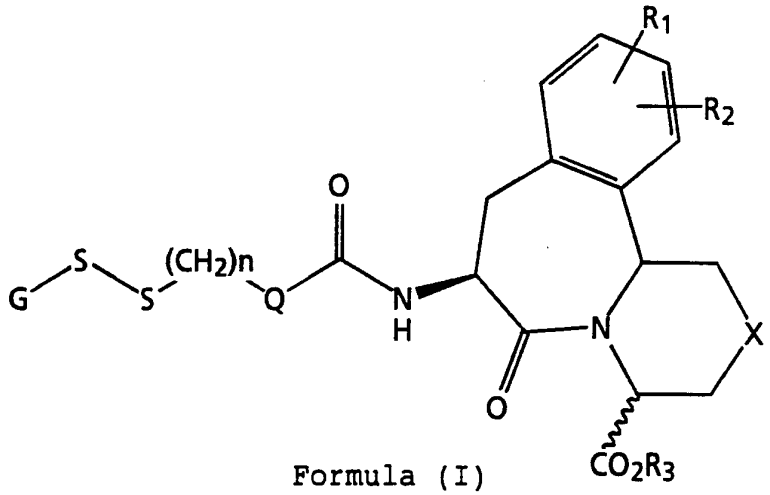
or stereoisomers or pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 wherein Q is



3. A compound of Claim 2 wherein n is 0.

4. A method of inhibiting enkephalinase in a patient in need thereof comprising administering to said patient an effective enkephalinase inhibitory amount of a compound of formula



Formula (I)

wherein

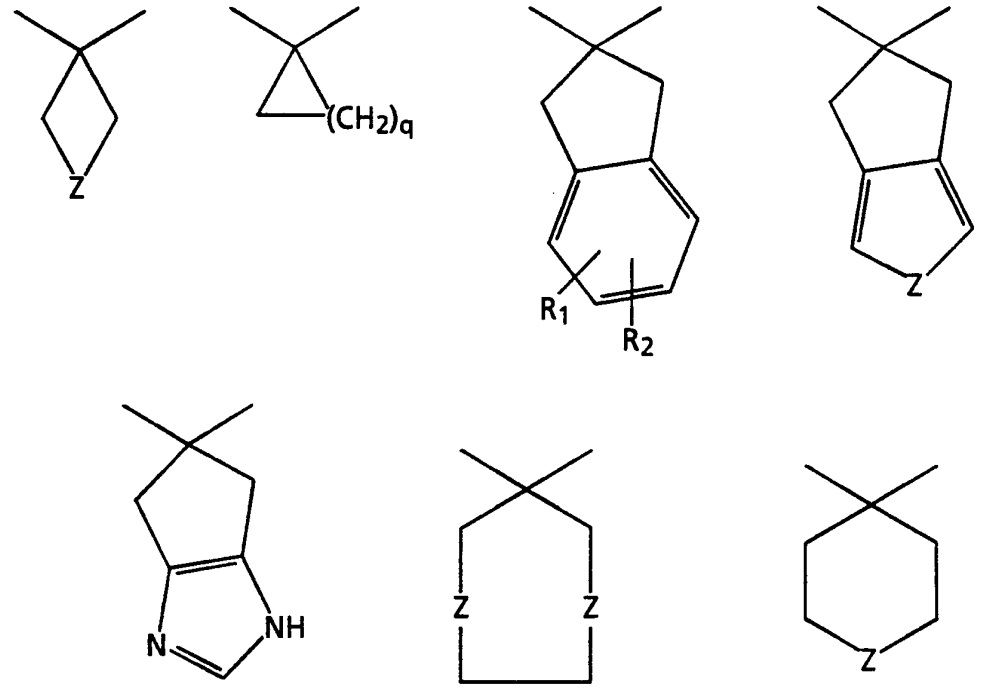
n is an integer from 0 to 3;

R_1 and R_2 are each time taken independently chosen from the group consisting of: hydrogen, hydroxy, $-OR_3$ wherein R_3 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

R_3 is hydrogen $-CH_2O-C(O)C(CH_3)_3$;

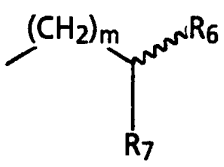
X is $-(CH_2)_p-$, O, S, NR_4, or $NC(O)R_5$ wherein p is an integer 0 or 1, R_4 is hydrogen, a C_1-C_4 alkyl, or an Ar-Y- group, and R_5 is $-CF_3$, C_1-C_{10} alkyl, or an Ar-Y- group;

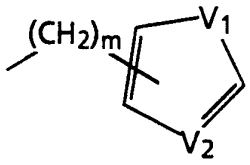
Q is a alkylene radical chosen from the group

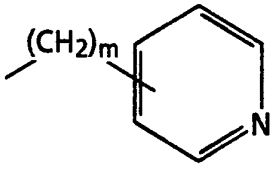


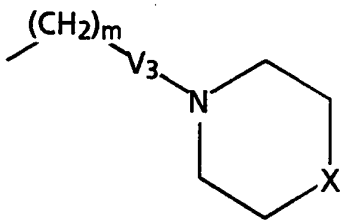
wherein q is an integer from 1 to 5 and Z is O, S, NH;

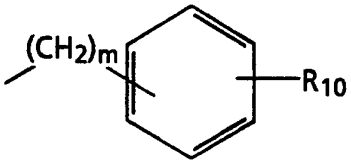
G is a radical chosen from the group;

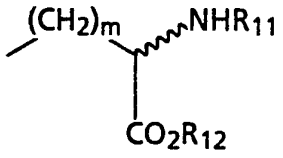


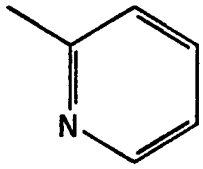












wherein

m is an integer from 1 to 3;

R_6 is hydrogen, C_1-C_6 alkyl, $-CH_2CH_2S(O)_kCH_3$, or Ar-Y- wherein k is an integer form 0 to 2;

R_7 is hydrogen, hydroxy, amino, C_1-C_6 alkyl, N-methylamino, N,N-dimethylamino, $-CO_2R_8$ wherein R_8 is hydrogen, $-CH_2O-C(O)C(CH_3)_3$, or C_1-C_4 alkyl; or $-OC(O)R_9$ wherein R_9 is hydrogen, C_1-C_6 alkyl, or phenyl;

R_{10} is 1 or 2 substituents independently chosen from the group consisting of; hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or halogen;

R_{11} is hydrogen, C_1-C_6 alkyl, or Ar-Y- group;

R_{12} is hydrogen or C_1-C_4 alkyl;

V_1 is O, S, or NH;

V_2 is N or CH;

V_3 is a direct bond or -C(O)-;

or stereoisomers or pharmaceutically acceptable salts thereof.

5. A method according to Claim 4 wherein the patient is in need of an endorphin- or enkephalin-mediated analgesic effect.

6. A method according to Claim 4 wherein the patient is in need of an ANP-mediated hypotensive effect.

7. A method according to Claim 4 wherein the patient is in need of an ANP-mediated diuretic effect.

8. A method according to Claim 4 wherein the patient is suffering from congestive heart failure.

9. A method according to Claim 4 wherein the patient is suffering from irritable bowel syndrome.

10. A composition comprising an assayable amount of a compound of Claim 1 in admixture or otherwise in association with an inert carrier.

11. A pharmaceutical composition comprising an effective immunosuppressive amount of a compound of Claim 1 in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

12. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, benzylthio, disulfide;

13. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, ethylthio, disulfide.

14. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-hydroxyethylthio, disulfide.

15. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-pyridylmethylthio, disulfide.

16. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-thioacetic acid morpholine carboxamide, disulfide.

17. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, L-cysteine ethyl ester, disulfide.

18. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

19. A pharmaceutical composition comprising a compound of Claim 1 in admixture or otherwise in association with one or more inert carriers.

20. A compound according to Claim 1 for use as a pharmaceutically active compound.

21. A compound according to Claim 1 for use as an inhibitor of enkephalinase.

22. A compound according to Claim 1 for use in producing an analgesic effect, a hypotensive effect, or a diuretic effect.

23. A compound according to Claim 1 for use in the treatment of congestive heart failure or irritable bowel syndrome.

24. A pharmaceutical composition according to Claim 21 for inhibition of enkephalinase.

25. A pharmaceutical composition according to Claim 22 for producing an analgesic effect, a hypotensive effect, or a diuretic effect.

26. A pharmaceutical composition according to Claim 23 for the treatment of congestive heart failure or irritable bowel syndrome.

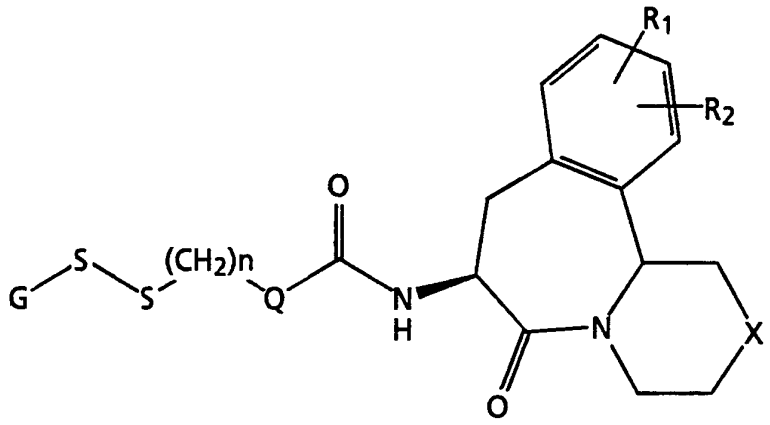
27. The use of a compound of Claim 1, optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a pharmaceutical composition for inhibition of enkephalinase.

28. The use of a compound of Claim 1, optionally in combination with a pharmaceutically acceptable carrier, for

the preparation of a pharmaceutical composition for producing an analgesic effect, a hypotensive effect, or a diuretic effect.

29. The use of a compound of Claim 1, optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a pharmaceutical composition for the treatment of congestive heart failure or irritable bowel syndrome.

30. A process for preparing a compound of the formula



Formula (I)

wherein

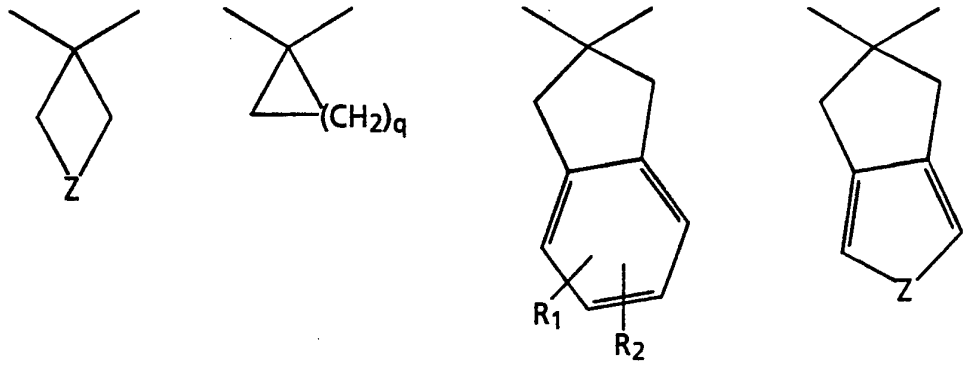
n is an integer from 0 to 3;

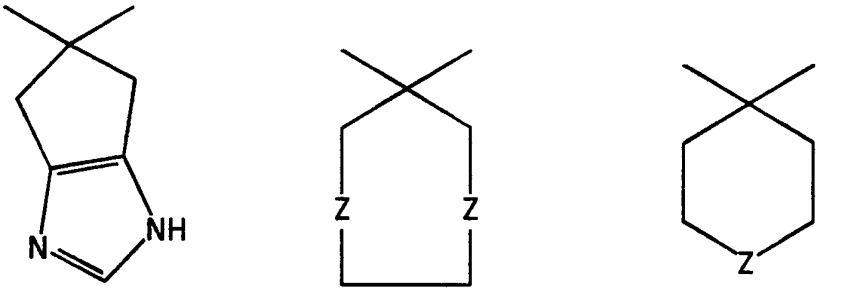
R_1 and R_2 are each time taken independently chosen from the group consisting of: hydrogen, hydroxy, $-OR_3$ wherein R_3 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

R_3 is hydrogen $-CH_2O-C(O)C(CH_3)_3$;

X is $-(CH_2)_p-$, O, S, NR_4, or $NC(O)R_5$ wherein p is an integer 0 or 1, R_4 is hydrogen, a C_1-C_4 alkyl, or an Ar-Y- group, and R_5 is $-CF_3$, C_1-C_{10} alkyl, or an Ar-Y- group;

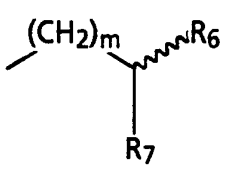
Q is a alkylene radical chosen from the group

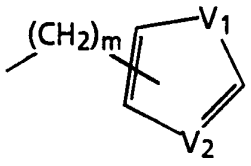


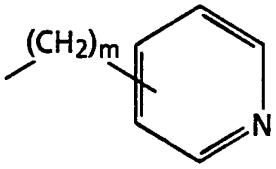


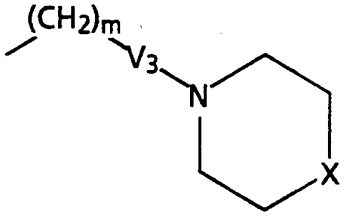
wherein q is an integer from 1 to 5 and Z is O, S, NH;

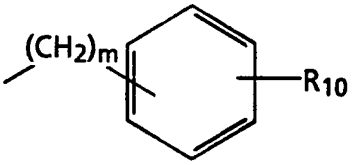
G is a radical chosen from the group;

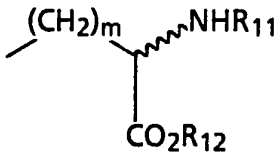


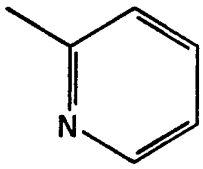












wherein

m is an integer from 1 to 3;

R_6 is hydrogen, C_1-C_6 alkyl, $-CH_2CH_2S(O)_kCH_3$, or Ar-Y- wherein k is an integer form 0 to 2;

R_7 is hydrogen, hydroxy, amino, C_1-C_6 alkyl, N-methylamino, N,N-dimethylamino, $-CO_2R_8$ wherein R_8 is hydrogen, $-CH_2O-C(O)C(CH_3)_3$, or C_1-C_4 alkyl; or $-OC(O)R_9$ wherein R_9 is hydrogen, C_1-C_6 alkyl, or phenyl;

R_{10} is 1 or 2 substituents independently chosen from the group consisting of; hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or halogen;

R_{11} is hydrogen, C_1-C_6 alkyl, or Ar-Y- group;

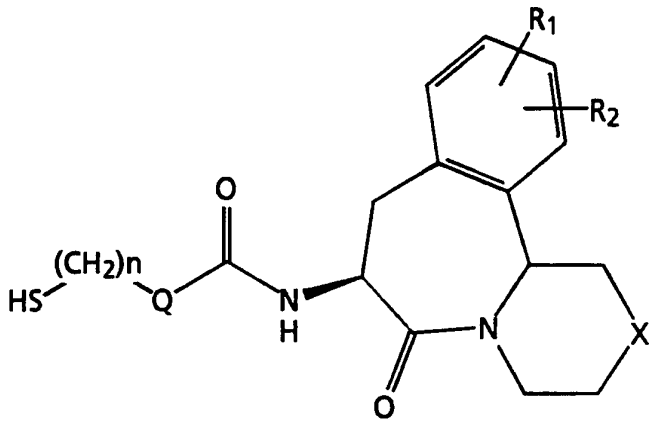
R_{12} is hydrogen or C_1-C_4 alkyl;

V_1 is O, S, or NH;

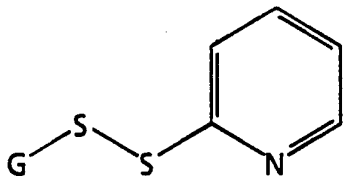
V_2 is N or CH;

V_3 is a direct bond or -C(O)-;

or stereoisomers or pharmaceutically acceptable salts thereof, comprising reacting a compound of the formula



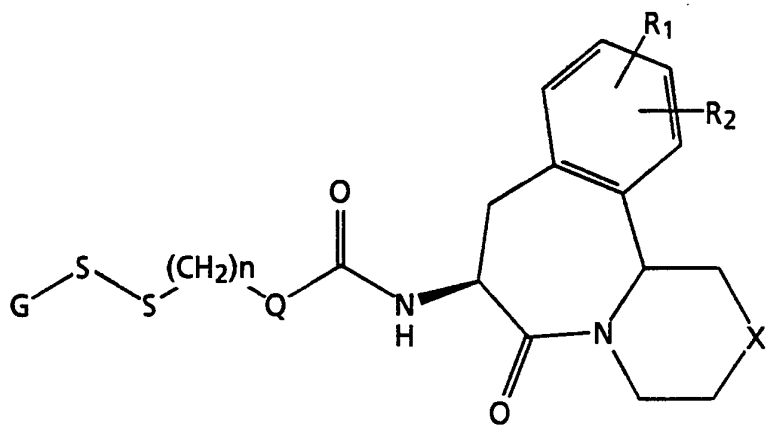
wherein R_1, R_2, Q, n, and X are defined above with a compound of the formula



wherein G is defined above and optionally deprotecting and optionally preparing a pharmaceutically acceptable salt by

further reacting with an acceptable acid or an acceptable base.

31. A process for preparing a compound of the formula



Formula (I)

wherein

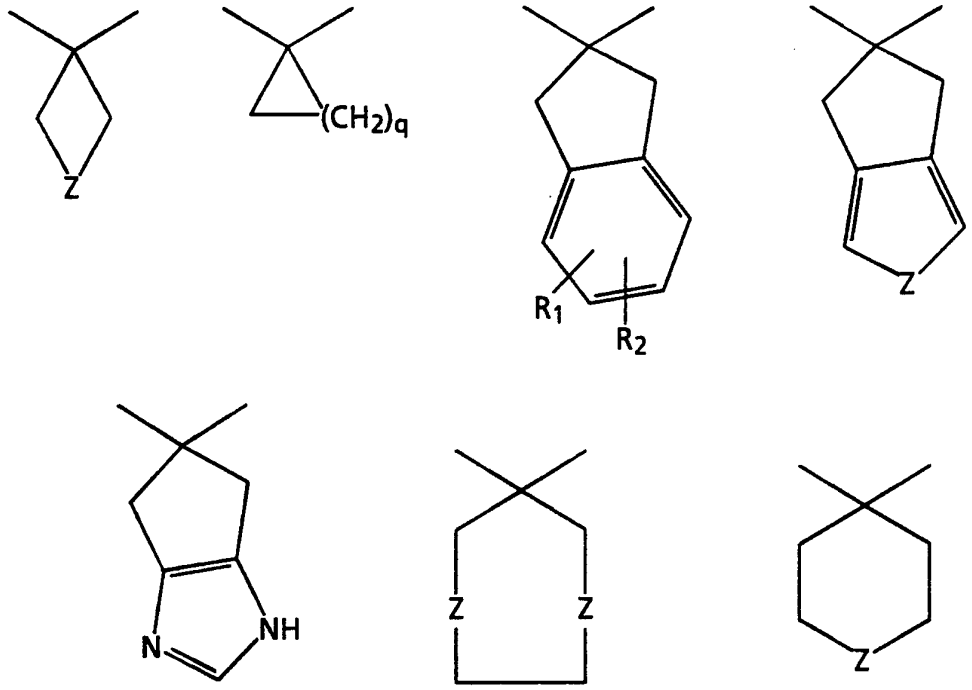
n is an integer from 0 to 3;

R_1 and R_2 are each time taken independently chosen from the group consisting of: hydrogen, hydroxy, $-OR_3$ wherein R_3 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

R_3 is hydrogen $-CH_2O-C(O)C(CH_3)_3$;

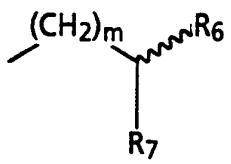
X is $-(CH_2)_p-$, O, S, NR_4, or $NC(O)R_5$ wherein p is an integer 0 or 1, R_4 is hydrogen, a C_1-C_4 alkyl, or an Ar-Y- group, and R_5 is $-CF_3$, C_1-C_{10} alkyl, or an Ar-Y- group;

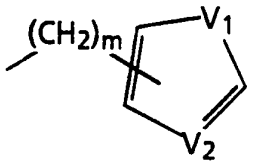
Q is a alkylene radical chosen from the group

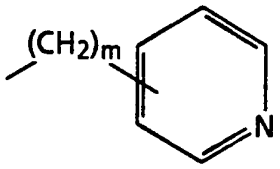


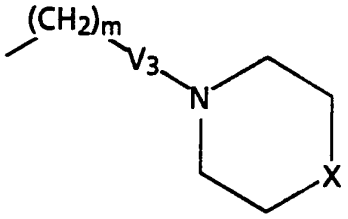
wherein q is an integer from 1 to 5 and Z is O, S, NH;

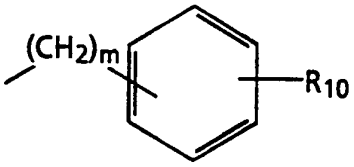
G is a radical chosen from the group;

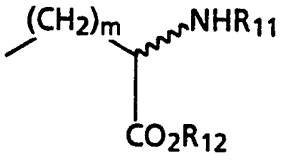


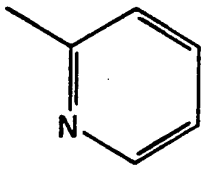












wherein

m is an integer from 1 to 3;

R_6 is hydrogen, C_1-C_6 alkyl, $-CH_2CH_2S(O)_kCH_3$, or Ar-Y- wherein k is an integer form 0 to 2;

R_7 is hydrogen, hydroxy, amino, C_1-C_6 alkyl, N-methylamino, N,N-dimethylamino, $-CO_2R_8$ wherein R_8 is hydrogen, $-CH_2O-C(O)C(CH_3)_3$, or C_1-C_4 alkyl; or $-OC(O)R_9$ wherein R_9 is hydrogen, C_1-C_6 alkyl, or phenyl;

R_{10} is 1 or 2 substituents independently chosen from the group consisting of; hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or halogen;

R_{11} is hydrogen, C_1-C_6 alkyl, or Ar-Y- group;

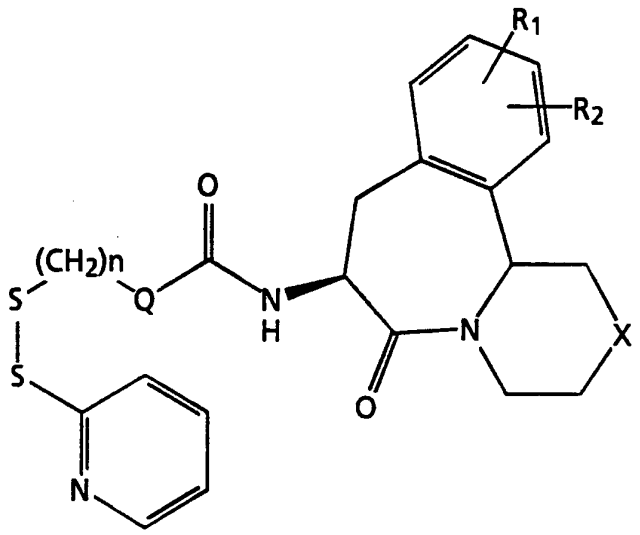
R_{12} is hydrogen or C_1-C_4 alkyl;

V_1 is O, S, or NH;

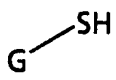
V_2 is N or CH;

V_3 is a direct bond or -C(O)-;

or stereoisomers or pharmaceutically acceptable salts thereof, comprising reacting a compound of the formula



wherein R_1, R_2, Q, n, and X are defined above with a compound of the formula



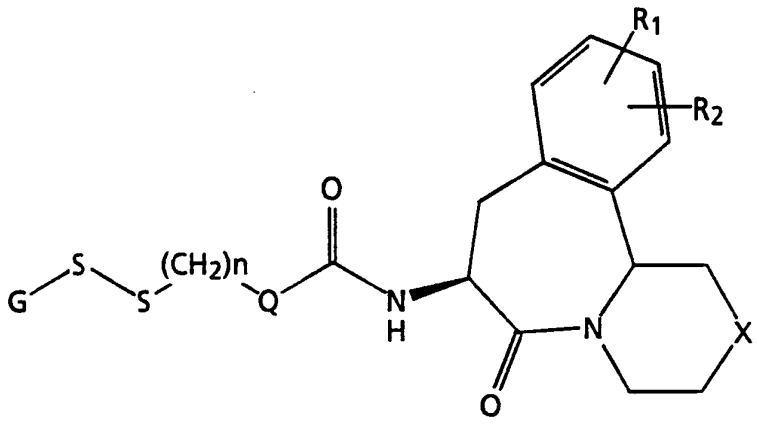
wherein G is defined above and optionally deprotecting and optionally preparing a pharmaceutically acceptable salt by

further reacting with an acceptable acid or an acceptable base.

AMENDED CLAIMS

[received by the International Bureau on 14 June 1995 (14.06.95); original claims 1,4,30 and 31 replaced by amended claims 1,4,30 and 31 (20 pages)]

1. A compound of the formula



Formula (I)

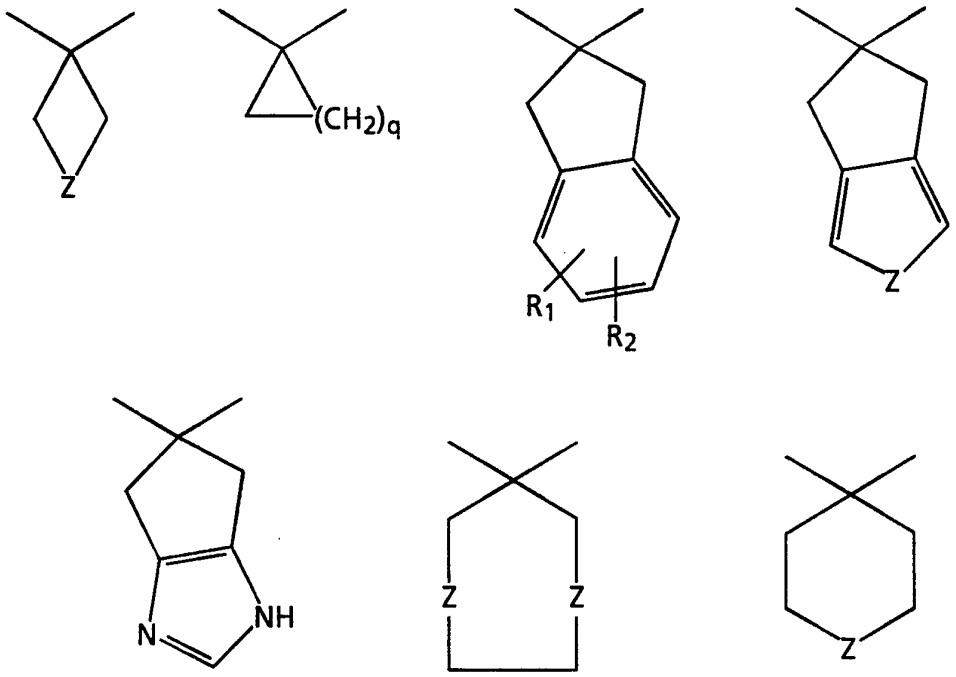
wherein

n is an integer from 0 to 3;

R_1 and R_2 are each time taken independently chosen from the group consisting of: hydrogen, hydroxy, $-OR_3$ wherein R_3 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

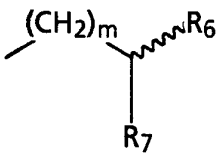
X is $-(CH_2)_p-$, O, S, NR_4, or $NC(O)R_5$ wherein p is an integer 0 or 1, R_4 is hydrogen, a C_1-C_4 alkyl, or an Ar-Y- group, and R_5 is $-CF_3$, C_1-C_{10} alkyl, or an Ar-Y- group;

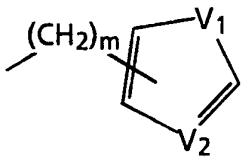
Q is a alkylene radical chosen from the group

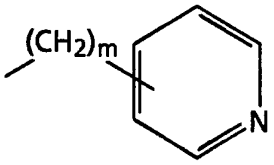


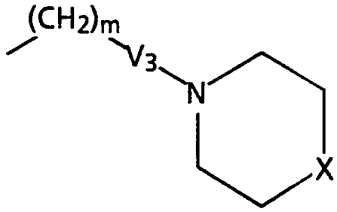
wherein q is an integer from 1 to 5 and Z is O, S, NH;

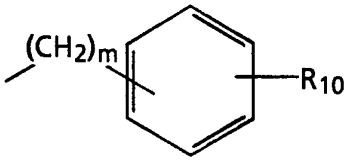
G is a radical chosen from the group;

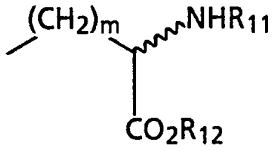


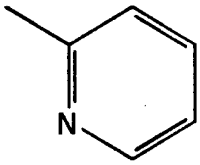












wherein

m is an integer from 1 to 3;

R_6 is hydrogen, C_1-C_6 alkyl, $-CH_2CH_2S(O)_kCH_3$, or Ar-Y- wherein k is an integer form 0 to 2;

R_7 is hydrogen, hydroxy, amino, C_1-C_6 alkyl, N-methylamino, N,N-dimethylamino, $-CO_2R_8$ wherein R_8 is hydrogen, $-CH_2O-C(O)C(CH_3)_3$, or C_1-C_4 alkyl; or $-OC(O)R_9$ wherein R_9 is hydrogen, C_1-C_6 alkyl, or phenyl;

R_{10} is 1 or 2 substituents independently chosen from the group consisting of; hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or halogen;

R_{11} is hydrogen, C_1-C_6 alkyl, or Ar-Y- group;

R_{12} is hydrogen or C_1-C_4 alkyl;

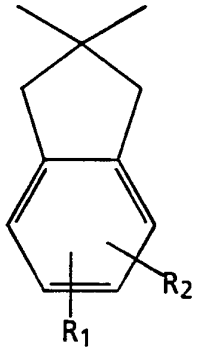
V_1 is O, S, or NH;

V_2 is N or CH;

V_3 is a direct bond or -C(O)-;

or stereoisomers or pharmaceutically acceptable salts thereof.

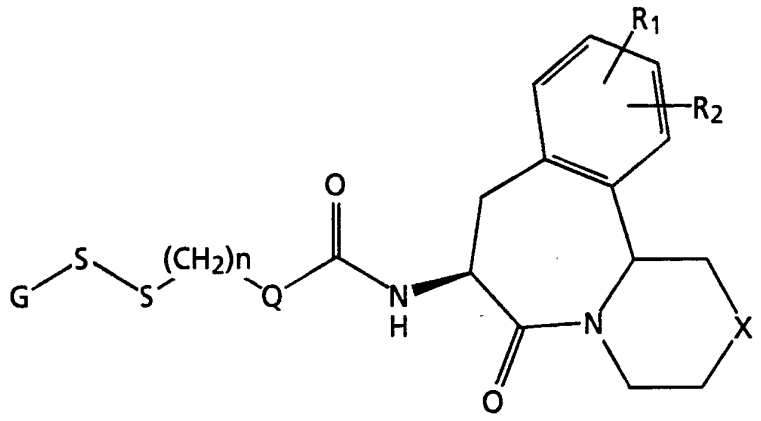
2. A compound of Claim 1 wherein Q is



3. A compound of Claim 2 wherein n is 0.

4. A method of inhibiting enkephalinase in a patient in need thereof comprising administering to said patient an effective enkephalinase inhibitory amount of a compound of formula

wherein



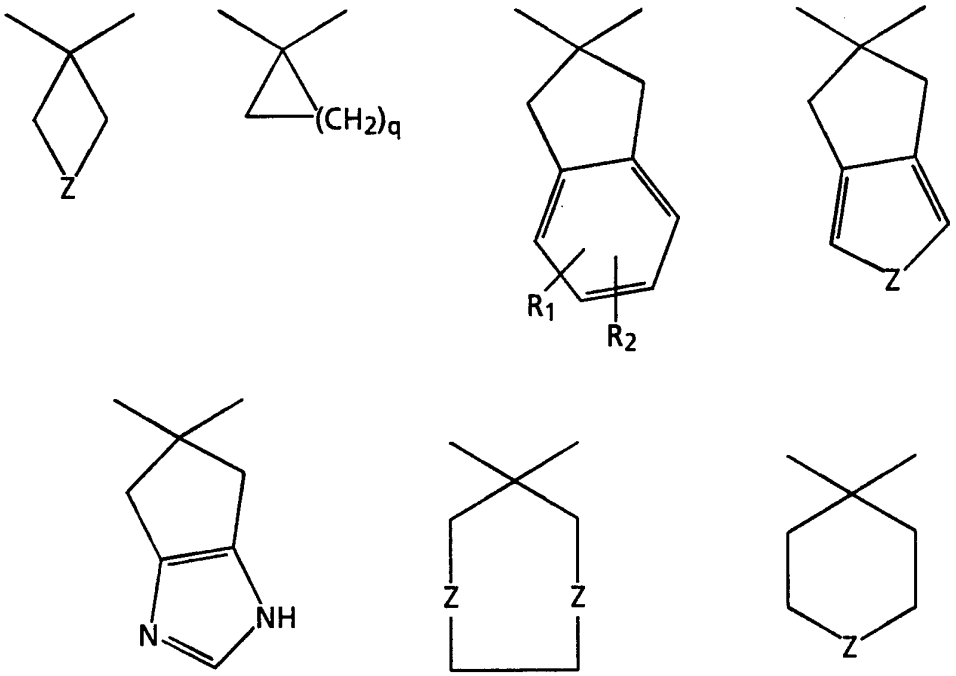
Formula (I)

n is an integer from 0 to 3;

R_1 and R_2 are each time taken independently chosen from the group consisting of: hydrogen, hydroxy, $-OR_3$ wherein R_3 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

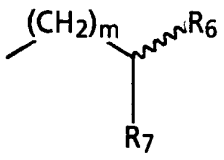
X is $-(CH_2)_p-$, O, S, NR_4, or $NC(O)R_5$ wherein p is an integer 0 or 1, R_4 is hydrogen, a C_1-C_4 alkyl, or an Ar-Y- group, and R_5 is $-CF_3$, C_1-C_{10} alkyl, or an Ar-Y- group;

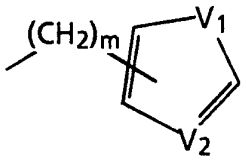
Q is a alkylene radical chosen from the group

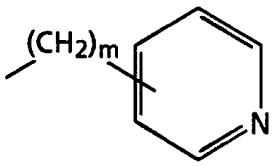


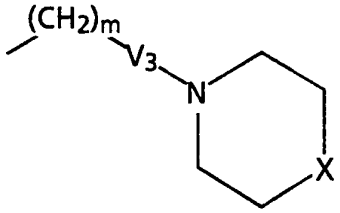
wherein q is an integer from 1 to 5 and Z is O, S, NH;

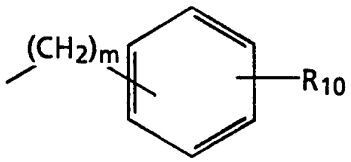
G is a radical chosen from the group;

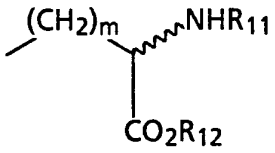


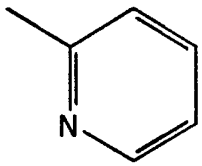












wherein

m is an integer from 1 to 3;

R_6 is hydrogen, C_1-C_6 alkyl, $-CH_2CH_2S(O)_kCH_3$, or Ar-Y- wherein k is an integer form 0 to 2;

R_7 is hydrogen, hydroxy, amino, C_1-C_6 alkyl, N-methylamino, N,N-dimethylamino, $-CO_2R_8$ wherein R_8 is hydrogen, $-CH_2O-C(O)C(CH_3)_3$, or C_1-C_4 alkyl; or $-OC(O)R_9$ wherein R_9 is hydrogen, C_1-C_6 alkyl, or phenyl;

R_{10} is 1 or 2 substituents independently chosen from the group consisting of; hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or halogen;

R_{11} is hydrogen, C_1-C_6 alkyl, or Ar-Y- group;

R_{12} is hydrogen or C_1-C_4 alkyl;

V_1 is O, S, or NH;

V_2 is N or CH;

V_3 is a direct bond or -C(O)-;

or stereoisomers or pharmaceutically acceptable salts thereof.

5. A method according to Claim 4 wherein the patient is in need of an endorphin- or enkephalin-mediated analgesic effect.

6. A method according to Claim 4 wherein the patient is in need of an ANP-mediated hypotensive effect.

7. A method according to Claim 4 wherein the patient is in need of an ANP-mediated diuretic effect.

8. A method according to Claim 4 wherein the patient is suffering from congestive heart failure.

9. A method according to Claim 4 wherein the patient is suffering from irritable bowel syndrome.

10. A composition comprising an assayable amount of a compound of Claim 1 in admixture or otherwise in association with an inert carrier.

11. A pharmaceutical composition comprising an effective immunosuppressive amount of a compound of Claim 1 in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

12. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, benzylthio, disulfide;

13. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, ethylthio, disulfide.

14. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-hydroxyethylthio, disulfide.

15. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-pyridylmethylthio, disulfide.

16. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, 2-thioacetic acid morpholine carboxamide, disulfide.

17. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, L-cysteine ethyl ester, disulfide.

18. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(2-Thio-2-oxoindan)methylamino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

19. A pharmaceutical composition comprising a compound of Claim 1 in admixture or otherwise in association with one or more inert carriers.

20. A compound according to Claim 1 for use as a pharmaceutically active compound.

21. A compound according to Claim 1 for use as an inhibitor of enkephalinase

22. A compound according to Claim 1 for use in producing an analgesic effect, a hypotensive effect, or a diuretic effect.

23. A compound according to Claim 1 for use in the treatment of congestive heart failure or irritable bowel syndrome.

24. A pharmaceutical composition according to Claim 21 for inhibition of enkephalinase.

25. A pharmaceutical composition according to Claim 22 for producing an analgesic effect, a hypotensive effect, or a diuretic effect.

26. A pharmaceutical composition according to Claim 23 for the treatment of congestive heart failure or irritable bowel syndrome.

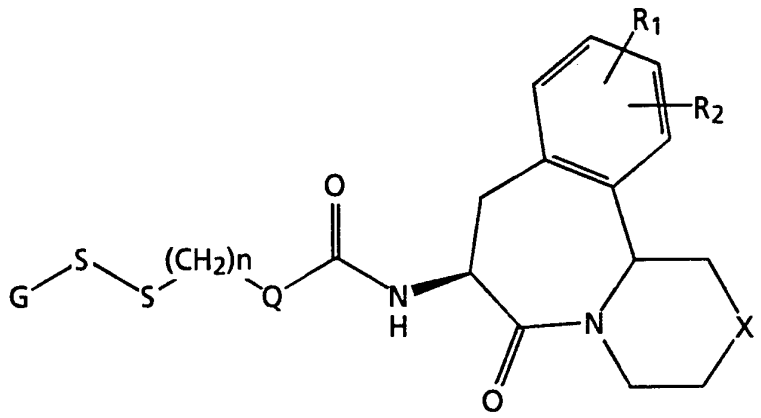
27. The use of a compound of Claim 1, optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a pharmaceutical composition for inhibition of enkephalinase.

28. The use of a compound of Claim 1, optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a pharmaceutical composition for

producing an analgesic effect, a hypotensive effect, or a diuretic effect.

29. The use of a compound of Claim 1, optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a pharmaceutical composition for the treatment of congestive heart failure or irritable bowel syndrome.

30. A process for preparing a compound of the formula



Formula (I)

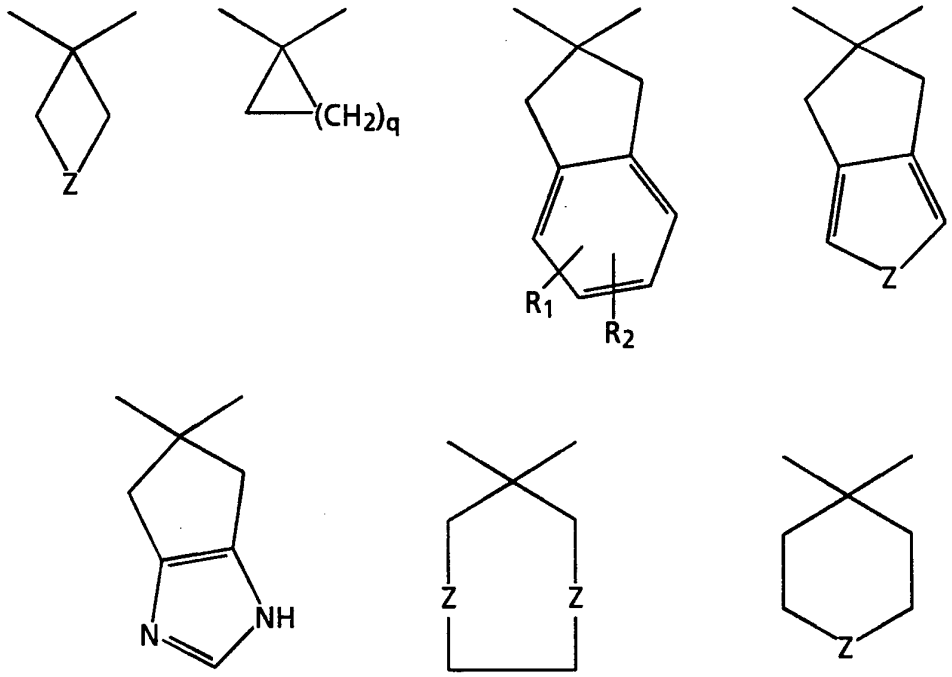
wherein

n is an integer from 0 to 3;

R_1 and R_2 are each time taken independently chosen from the group consisting of: hydrogen, hydroxy, $-OR_3$ wherein R_3 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

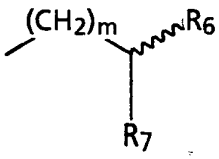
X is $-(CH_2)_p-$, O, S, NR_4, or $NC(O)R_5$ wherein p is an integer 0 or 1, R_4 is hydrogen, a C_1-C_4 alkyl, or an Ar-Y- group, and R_5 is $-CF_3$, C_1-C_{10} alkyl, or an Ar-Y- group;

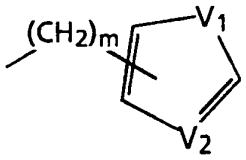
Q is a alkylene radical chosen from the group

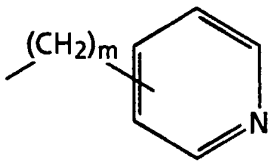


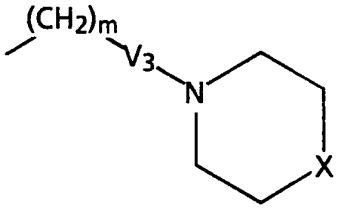
wherein q is an integer from 1 to 5 and Z is O, S, NH;

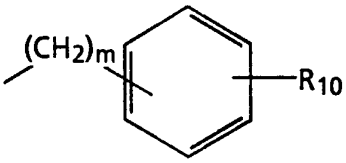
G is a radical chosen from the group;

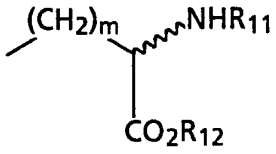


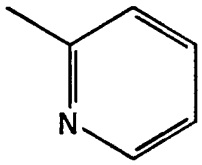












wherein

m is an integer from 1 to 3;

R_6 is hydrogen, C_1-C_6 alkyl, $-CH_2CH_2S(O)_kCH_3$, or Ar-Y- wherein k is an integer form 0 to 2;

R_7 is hydrogen, hydroxy, amino, C_1-C_6 alkyl, N-methylamino, N,N-dimethylamino, $-CO_2R_8$ wherein R_8 is hydrogen, $-CH_2O-C(O)C(CH_3)_3$, or C_1-C_4 alkyl; or $-OC(O)R_9$ wherein R_9 is hydrogen, C_1-C_6 alkyl, or phenyl;

R_{10} is 1 or 2 substituents independently chosen from the group consisting of; hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or halogen;

R_{11} is hydrogen, C_1-C_6 alkyl, or Ar-Y- group;

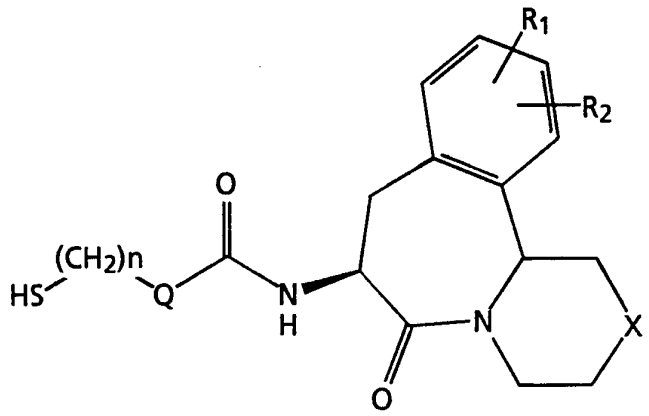
R_{12} is hydrogen or C_1-C_4 alkyl;

V_1 is O, S, or NH;

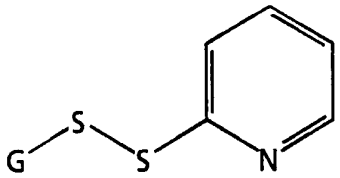
V_2 is N or CH;

V_3 is a direct bond or -C(O)-;

or stereoisomers or pharmaceutically acceptable salts thereof, comprising reacting a compound of the formula



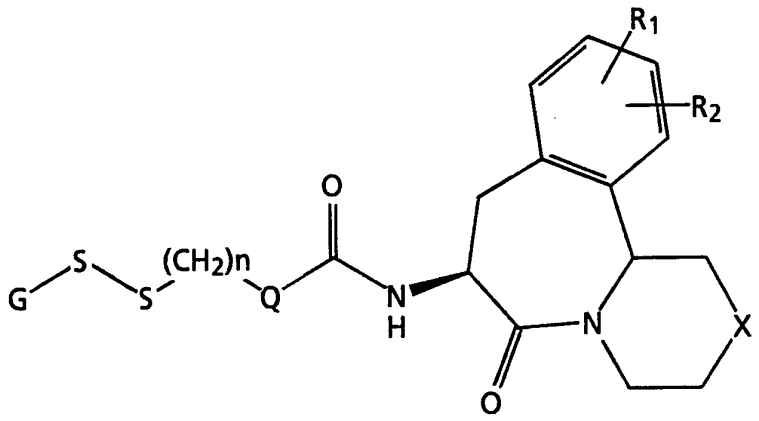
wherein R_1, R_2, Q, n, and X are defined above with a compound of the formula



wherein G is defined above and optionally deprotecting and optionally preparing a pharmaceutically acceptable salt by

further reacting with an acceptable acid or an acceptable base.

31. A process for preparing a compound of the formula



Formula (I)

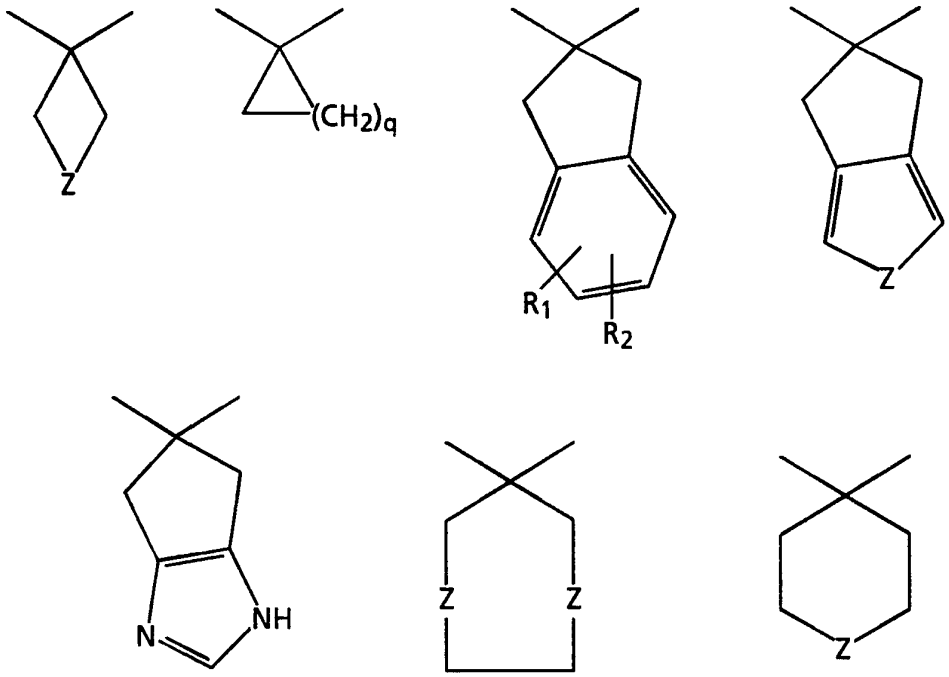
wherein

n is an integer from 0 to 3;

R_1 and R_2 are each time taken independently chosen from the group consisting of: hydrogen, hydroxy, $-OR_3$ wherein R_3 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

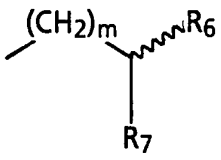
X is $-(CH_2)_p-$, O, S, NR_4, or $NC(O)R_5$ wherein p is an integer 0 or 1, R_4 is hydrogen, a C_1-C_4 alkyl, or an Ar-Y- group, and R_5 is $-CF_3$, C_1-C_{10} alkyl, or an Ar-Y- group;

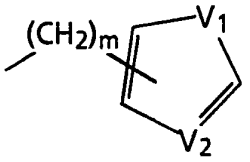
Q is a alkylene radical chosen from the group

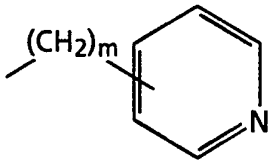


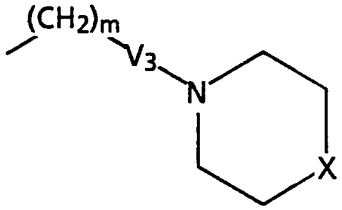
wherein q is an integer from 1 to 5 and Z is O, S, NH;

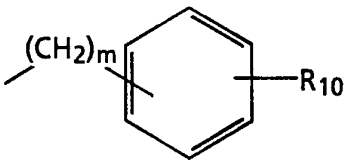
G is a radical chosen from the group;

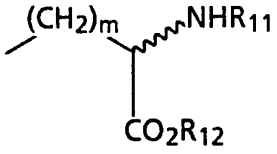


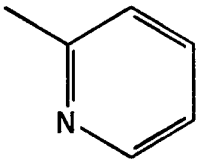












wherein

m is an integer from 1 to 3;

R_6 is hydrogen, C_1-C_6 alkyl, $-CH_2CH_2S(O)_kCH_3$, or Ar-Y- wherein k is an integer form 0 to 2;

R_7 is hydrogen, hydroxy, amino, C_1-C_6 alkyl, N-methylamino, N,N-dimethylamino, $-CO_2R_8$ wherein R_8 is hydrogen, $-CH_2O-C(O)C(CH_3)_3$, or C_1-C_4 alkyl; or $-OC(O)R_9$ wherein R_9 is hydrogen, C_1-C_6 alkyl, or phenyl;

R_{10} is 1 or 2 substituents independently chosen from the group consisting of; hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or halogen;

R_{11} is hydrogen, C_1-C_6 alkyl, or Ar-Y- group;

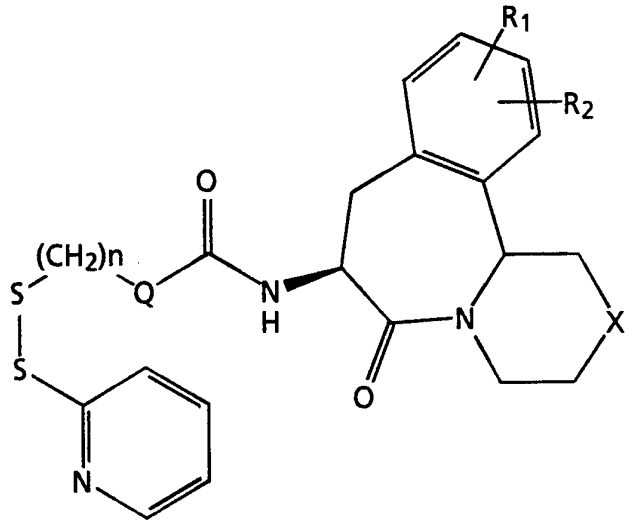
R_{12} is hydrogen or C_1-C_4 alkyl;

V_1 is O, S, or NH;

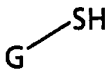
V_2 is N or CH;

V_3 is a direct bond or -C(O)-;

or stereoisomers or pharmaceutically acceptable salts thereof, comprising reacting a compound of the formula



wherein R_1, R_2, Q, n, and X are defined above with a compound of the formula



wherein G is defined above and optionally deprotecting and optionally preparing a pharmaceutically acceptable salt by

further reacting with an acceptable acid or an acceptable base.

INTERNATIONAL SEARCH REPORT

Interna 1 Application No
PCT/US 95/00269

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/55 C07D498/04 C07D513/04 C07D487/04 A61K31/535 A61K31/54 A61K31/495 //(C07D471/04,223:00, 221:00),(C07D498/04,265:00,223:00),(C07D513/04,279:00,223:00),

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

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	EP,A,0 534 363 (MERRELL DOW) 31 March 1993 see page 3, line 43 - line 47; claim 1 ---	1,27
A	WO,A,93 23397 (MERRELL DOW) 25 November 1993 see claims 1,15 -----	1,27

☐ 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
29 March 1995	- 5. 04. 95

Name and mailing address of the ISA	Authorized officer
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	Alfaro Faus, I

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

INTERNATIONAL SEARCH REPORT

Intern: ıl Application No
PCT/US 95/00269

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 (C07D487/04,241:00,223:00),(C07D487/04,223:00,209:00)

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)

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.

☐ 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
29 March 1995	

Name and mailing address of the ISA	Authorized officer
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	Alfaro Faus, I

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

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US95/00269

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 4-9 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:
In claim 1 R3 has two sets of definitions. Formula I of claim 4 does not correspond to Formula I of claim 1. The search has covered the compounds disclosed in the description and generalized in pages 3-6.

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

Interna: :l Application No
PCT/US 95/00269

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0534363	31-03-93	AU-B-	657166	02-03-95
		AU-A-	2524592	01-04-93
		HU-A-	65192	02-05-94
		JP-A-	5294963	09-11-93
		NZ-A-	244461	27-09-94
WO-A-9323397	25-11-93	US-A-	5238932	24-08-93
		AU-B-	4277993	13-12-93
		CA-A-	2135751	25-11-93
		EP-A-	0641343	08-03-95
		FI-A-	945434	18-11-94
		NO-A-	944430	17-01-95