



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

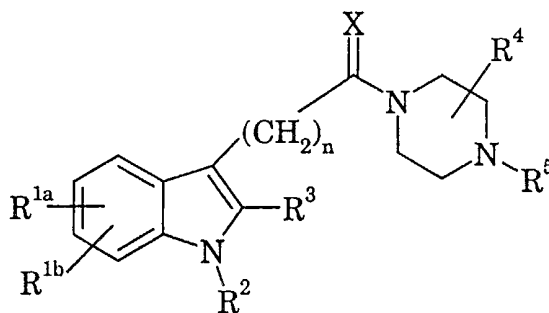
<p>(51) International Patent Classification ⁷ : C07D 209/18, A61K 31/40, A61P 25/24, C07D 405/12, 487/08, 401/12, 403/12, 403/06 // (C07D 487/08, 209:00, 209:00)</p>	A1	<p>(11) International Publication Number: WO 00/51984</p> <p>(43) International Publication Date: 8 September 2000 (08.09.00)</p>
<p>(21) International Application Number: PCT/GB00/00650</p> <p>(22) International Filing Date: 23 February 2000 (23.02.00)</p> <p>(30) Priority Data: 9905010.6 4 March 1999 (04.03.99) GB</p> <p>(71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): CHAPMAN, Kevin, T. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). DINNELL, Kevin [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). ELLIOTT, Jason, Matthew [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). HOLLINGWORTH, Gregory, John [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). HUTCHINS, Steven, Michael [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SHAW, Duncan, Edward [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). WILLOUGHBY, Christopher, Alan [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p>	<p>(74) Agent: HISCOCK, Ian, James; Merck & Co., Inc., European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p> <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>	

(54) Title: 2-ARYL INDOLE DERIVATIVES AS ANTAGONISTS OF TACHYKININS

(57) Abstract

The present invention relates to compounds of formula (I) wherein R^{1a} and R^{1b} represent a variety of substituents; R³ represents an optionally substituted phenyl, biphenyl or naphthyl group; R⁴ represents hydrogen, C₁₋₆alkyl, carbonyl (=O), (CH₂)_pphenyl or a C₁₋₂alkylene bridge across the piperazine ring; R⁵ represents

C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, C₂₋₆alkenyl, phenyl, naphthyl, fluorenyl, heteroaryl, (CH₂)_pphenyl, (CH₂)_pheteroaryl, CH(phenyl)₂, CH(C₁₋₆alkyl)(phenyl), C₂₋₄alkenyl(phenyl), (CH₂)_pNR^cR^d, (CH₂)_pCONR^cR^d, (CH₂)_mCOR^c, (CH₂)_mCO₂R^c or (CH₂)_pOH; X represents an oxygen or a sulfur atom; m is zero or an integer from 1 to 4; n is an integer from 1 to 4; p is an integer from 1 to 4; or a pharmaceutically acceptable salt thereof. The compounds are of particular use in the treatment or prevention of depression, anxiety, pain, inflammation, migraine, emesis or postherpetic neuralgia.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

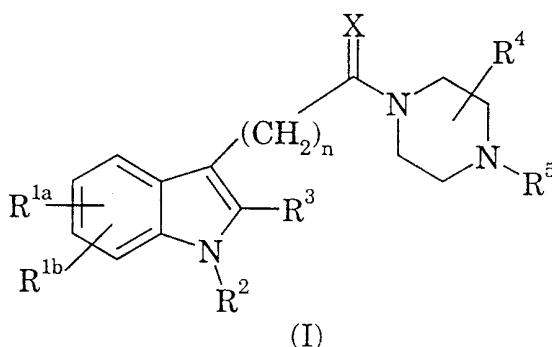
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

2-ARYL INDOLE DERIVATIVES AS ANTAGONISTS OF TACHYKININS

This invention relates to indole derivatives and their use as
 5 tachykinin antagonists, and in particular as neurokinin-1 receptor
 antagonists.

We have now found a class of indole derivatives which are potent
 receptor antagonists of tachykinins, especially of the neurokinin-1
 (substance P) receptor.

10 The present invention accordingly provides the compounds of the
 formula (I):



wherein

- 15 R^{1a} and R^{1b} each independently represent hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy,
 fluoroC₁₋₆alkyl, fluoroC₁₋₆alkoxy, halogen, cyano, NR^aR^b, SR^a, SOR^a,
 SO₂R^a, OSO₂R^a, NR^aCOR^b, COR^a, CO₂R^a or CONR^aR^b;
- R² represents hydrogen, C₁₋₆alkyl, fluoroC₁₋₆alkyl, (CH₂)_mCOR^a,
 (CH₂)_pCO₂R^a, (CH₂)_pOH, (CH₂)_mCONR^aR^b, (CH₂)_mphenyl or SO₂C₁₋₆alkyl;
- 20 R³ represents phenyl, biphenyl or naphthyl, wherein said phenyl, biphenyl
 or naphthyl group may be optionally substituted by one, two or three
 groups independently selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy,
 fluoroC₁₋₆alkyl, fluoroC₁₋₆alkoxy, NO₂, cyano, SR^a, SOR^a, SO₂R^a, COR^a,
 CO₂R^a, CONR^aR^b, C₂₋₆alkenyl, C₂₋₆alkynyl or C₁₋₄alkoxyC₁₋₄alkyl;
- 25 R⁴ represents hydrogen, C₁₋₆alkyl, carbonyl (=O), (CH₂)_pphenyl or a
 C₁₋₂alkylene bridge across the piperazine ring;

- R⁵ represents C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, C₂₋₆alkenyl, phenyl, naphthyl, fluorenyl, heteroaryl, (CH₂)_pphenyl, (CH₂)_pheteroaryl, CH(phenyl)₂, CH(C₁₋₆alkyl)(phenyl), C₂₋₄alkenyl(phenyl), (CH₂)_pNR^cR^d, (CH₂)_pCONR^cR^d, (CH₂)_mCOR^c, (CH₂)_mCO₂R^c or (CH₂)_pOH;
- 5 R^a and R^b each independently represent hydrogen, C₁₋₄alkyl or fluoroC₁₋₄alkyl;
- R^c and R^d each independently represent hydrogen, C₁₋₄alkyl, fluoroC₁₋₄alkyl, C₂₋₄alkenyl, phenyl or benzyl or R^c and R^d, together with the nitrogen atom to which they are attached, form a heteroaliphatic ring
- 10 of 4 to 7 atoms, to which ring there may optionally be fused a benzene ring, and wherein said phenyl, naphthyl, fluorenyl or heteroaryl groups may be optionally substituted by one, two or three groups independently selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy, fluoroC₁₋₆alkyl, fluoroC₁₋₆alkoxy, NO₂, cyano, SR^a, SOR^a, SO₂R^a, COR^a, CO₂R^a, CONR^aR^b,
- 15 C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₄alkoxyC₁₋₄alkyl or -O(CH₂)₁₋₂O-;
- X represents an oxygen or a sulfur atom;
- m is zero or an integer from 1 to 4;
- n is an integer from 1 to 4;
- p is an integer from 1 to 4;
- 20 or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of formula (I) is that wherein R^{1a} and R^{1b} each independently represent hydrogen, C₁₋₆alkyl, fluoroC₁₋₆alkoxy or halogen. Where R^{1a} and R^{1b} are both other than hydrogen, preferably R^{1a} and R^{1b} are the same. Where R^{1a} is other than hydrogen and R^{1b} is

25 hydrogen, R^{1a} is preferably attached to the indole ring at the 5-position.

A particularly preferred group of compounds of formula (I) is that wherein R^{1a} and R^{1b} each independently represent hydrogen, methyl, trifluoromethoxy, fluorine or chlorine.

As especially preferred group of compounds of formula (I) is that

30 wherein R^{1a} represents 5-methyl or 5-chloro, and R^{1b} is hydrogen.

A further preferred group of compounds of formula (I) is that wherein R^2 represents hydrogen, C_{1-6} alkyl, fluoro C_{1-6} alkyl, $(CH_2)_mCOR^a$, $(CH_2)_pCOR^a$, $(CH_2)_pOH$ or $(CH_2)_m$ phenyl.

5 A particularly preferred group of compounds of formula (I) is that wherein R^2 represents C_{1-3} alkyl (especially methyl, ethyl or isopropyl), fluoro C_{1-3} alkyl (especially trifluoromethyl or 2,2,2-trifluoroethyl), $COCH_3$, CH_2CO_2H , $CH_2CO_2CH_3$, $(CH_2)_{1-2}OH$ (especially CH_2CH_2OH) or benzyl.

An especially preferred group of compounds of formula (I) is that wherein R^2 is hydrogen or methyl.

10 Another preferred group of compounds of formula (I) is that wherein R^3 represents phenyl, biphenyl or naphthyl (especially 2-naphthyl) wherein said phenyl group is optionally substituted by one or two groups selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, trifluoro C_{1-6} alkyl, fluoro C_{1-6} alkoxy or C_{2-6} alkenyl.

15 A particularly preferred class of compounds of formula (I) is that wherein R^3 represents phenyl, biphenyl or naphthyl (especially 2-naphthyl) wherein said phenyl group is optionally substituted by one or two groups selected from chlorine, bromine, C_{1-4} alkyl (especially isopropyl or tertiary butyl), methoxy, trifluoromethyl, trifluoromethoxy or vinyl.

20 An especially preferred group of compounds of formula (I) is that wherein R^3 represents phenyl optionally substituted by one or two groups selected from chlorine, bromine, C_{1-4} alkyl (especially isopropyl or tertiary butyl), methoxy, trifluoromethyl, trifluoromethoxy or vinyl.

25 A further preferred group of compounds of formula (I) is that wherein R^4 represents hydrogen, methyl, carbonyl, benzyl or a methylene bridge across the 2,5-positions on the piperazine ring.

As especially preferred group of compounds of formula (I) is that wherein R^4 is hydrogen.

30 Another preferred group of compounds of formula (I) is that wherein R^5 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, C_{2-6} alkenyl, phenyl, naphthyl, fluorenyl, heteroaryl, $(CH_2)_p$ phenyl, $(CH_2)_p$ heteroaryl,

CH(phenyl)₂, CH(C₁₋₆alkyl)(phenyl), C₂₋₄alkenyl(phenyl), (CH₂)_pNR^cR^d,
 (CH₂)_pCONR^cR^d, (CH₂)_mCOR^c or (CH₂)_mCO₂R^c wherein said phenyl or
 heteroaryl group is optionally substituted by one or two substituents
 selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy, fluoroC₁₋₆alkyl,
 5 fluoroC₁₋₆alkoxy, NO₂, cyano, SR^a or -O(CH₂)₁₋₂O-.

A particularly preferred group of compounds of formula (I) is that
 wherein R⁵ represents C₃₋₆alkyl (especially propyl, isopropyl or isopentyl),
 C₅₋₇cycloalkyl (especially cyclohexyl), C₃₋₇cycloalkylC₁₋₂alkyl (especially
 cyclopropylmethyl, cyclohexylmethyl or 2-cyclohexylethyl), C₂₋₄alkenyl
 10 (especially vinyl), phenyl, naphthyl (especially 1-naphthyl), fluorenyl
 (especially 9-fluorenyl), heteroaryl, (CH₂)_pphenyl (especially wherein p is 1
 or 2), (CH₂)_pheteroaryl (especially wherein p is 1), CH(phenyl)₂,
 CH(C₁₋₂alkyl)(phenyl), C₂₋₄alkenyl(phenyl) (especially CH₂-CH=CHphenyl),
 (CH₂)_pNR^cR^d (especially where R^c and R^d each represent C₂₋₄alkenyl; and
 especially wherein p is 2), (CH₂)_pCONR^cR^d (especially wherein R^c and R^d
 15 each independently represent hydrogen, C₁₋₄alkyl, C₂₋₄alkenyl, phenyl or
 benzyl or R^c and R^d, together with the nitrogen atom to which they are
 attached, form a heteroaliphatic ring of 5 or 6 atoms to which ring there is
 fused a benzene ring; and especially wherein p is 1), (CH₂)_mCOR^c
 20 (especially wherein R^c represents phenyl; and especially wherein m is zero)
 or (CH₂)_mCO₂R^c (especially wherein R^c represents hydrogen or C₁₋₄alkyl;
 and especially wherein m is zero or 1), wherein said phenyl or heteroaryl
 groups may be substituted by one or two groups independently selected
 from halogen, C₁₋₄alkyl, C₁₋₄alkoxy, fluoroC₁₋₄alkyl, fluoroC₁₋₄alkoxy, NO₂,
 25 cyano and SR^a (especially wherein R^a represents C₁₋₄alkyl), or said phenyl
 or heteroaryl group may be substituted by the group -O(CH₂)₁₋₂O-.

Particularly preferred are compounds in which said phenyl groups are
 unsubstituted or substituted by one or two substituents independently
 selected from fluorine, chlorine, methyl, ethyl, methoxy, ethoxy,
 30 isopropoxy, trifluoromethoxy, nitro, cyano and thiomethyl, or said phenyl
 is substituted by -OCH₂O-. Also preferred are compounds in which said

heteroaryl groups are unsubstituted or are monosubstituted by methyl or trifluoromethyl.

Another preferred group of compounds of formula (I) is that wherein X represents an oxygen atom.

5 A further preferred group of compounds of formula (I) is that wherein n is 2, 3 or 4, and especially wherein n is 2.

When any variable occurs more than one time in formula (I) or in any substituent, its definition on each occurrence is independent of its definition at every other occurrence.

10 As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

15 As used herein, the terms "fluoroC₁₋₆alkyl" and "fluoroC₁₋₆alkoxy" means a C₁₋₆alkyl or C₁₋₆alkoxy group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by fluorine atoms. Similarly, the term "fluoroC₁₋₄alkyl" means a C₁₋₄alkyl group in which one or more (in particular 1 to 3) hydrogen atoms have been replaced by fluorine atoms.
20 Particularly preferred are fluoroC₁₋₃alkyl and fluoroC₁₋₃alkoxy groups, for example, CF₃, CH₂CH₂F, CH₂CHF₂, CH₂CF₃, OCF₃, OCH₂CH₂F, OCH₂CHF₂ or OCH₂CF₃, and most especially CF₃, OCF₃ and OCH₂CF₃.

The cycloalkyl groups referred to herein may represent, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. A suitable
25 cycloalkylalkyl group may be, for example, cyclopropylmethyl.

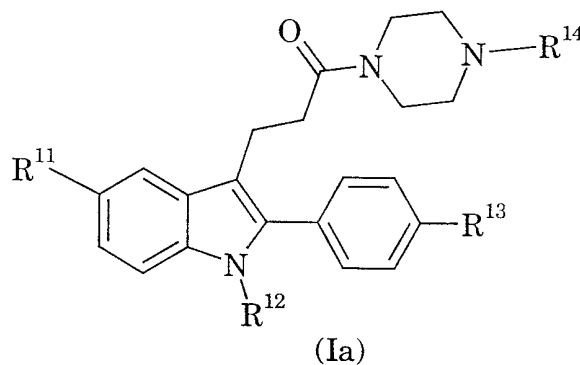
Similarly cycloalkoxy groups referred to herein may represent, for example, cyclopropoxy or cyclobutoxy.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part of a group means that the group is straight or branched. Examples of
30 suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is propargyl.

As used herein, the term "heteroaryl" as a group or part of a group means a 5- or 6-membered heteroaromatic ring containing 1 to 4 heteroatoms selected from N, O and S. Examples of such groups include pyrrolyl, furanyl, thienyl, pyridyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, oxadiazolyl, thiadiazolyl, triazinyl, and tetrazolyl. Particularly preferred examples of "heteroaryl" groups include pyridyl and triazolyl, especially 2-pyridyl and 1,2,4-triazol-3-yl.

When used herein the term "halogen" means fluorine, chlorine, bromine and iodine. The most apt halogens are fluorine and chlorine of which fluorine is preferred, unless otherwise stated.

A particularly preferred compound of the present invention is the compound of formula (Ia)



or a pharmaceutically acceptable salt thereof wherein

R¹¹ represents a chlorine atom or a methyl group;

R¹² represents a hydrogen atom or a group selected from C₁₋₃alkyl, fluoroC₁₋₃alkyl, COCH₃, or (CH₂)₂OH;

R¹³ represents a halogen atom or a group selected from C₁₋₄alkyl, C₂₋₄alkenyl, fluoroC₁₋₄alkyl, C₁₋₄alkoxy or fluoroC₁₋₄alkoxy; and

R¹⁴ represents a group selected from C₃₋₆alkyl, C₅₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₂alkyl, phenyl, naphthyl, benzyl, α-methylbenzyl,

phenylethyl, $-\text{CH}_2\text{CON}(\text{CH}_3)\text{phenyl}$, $-\text{CH}_2\text{CON}(\text{CH}_3)\text{benzyl}$, $-\text{CH}_2\text{CONR}^c\text{R}^d$
(where R^c and R^d , together with the nitrogen atom to which they are
attached, form a heteroaliphatic ring of 5 or 6 atoms to which ring there is
fused a benzene ring), $-\text{CH}_2\text{CON}(\text{CH}_3)\text{C}_{2-4}\text{alkenyl}$, or $-(\text{CH}_2)_m\text{CO}_2\text{R}^c$ (where
5 R^c is hydrogen or $\text{C}_{1-4}\text{alkyl}$ and m is zero or 1), wherein said phenyl and
benzyl groups may be substituted by a group selected from halogen,
 $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkoxy}$, $\text{fluoroC}_{1-3}\text{alkyl}$, $\text{fluoroC}_{1-3}\text{alkoxy}$, NO_2 , cyano, and $-\text{S}-$
 $\text{C}_{1-3}\text{alkyl}$ or said phenyl and benzyl groups may be substituted by the
group $-\text{O}-\text{CH}_2-\text{O}-$.

10 Particularly preferred compounds of formula (Ia) are those wherein
 R^{12} represents hydrogen, methyl, COCH_3 or $-(\text{CH}_2)_2\text{OH}$, especially
hydrogen or methyl.

Another preferred class of compounds of formula (Ia) is that wherein
 R^{13} represents chlorine, bromine, methyl, ethyl, isopropyl, trifluoromethyl
15 or vinyl, especially chlorine or bromine.

A further preferred class of compounds of formula (Ia) is that
wherein R^{14} represents phenyl, benzyl, cyclohexyl, cyclohexylmethyl,
cyclopropylmethyl, isopentyl, $-\text{CH}_2\text{CON}(\text{CH}_3)\text{phenyl}$,
 $-\text{CH}_2\text{CON}(\text{CH}_3)\text{benzyl}$, or $-\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_3$, wherein said phenyl and
20 benzyl groups may be substituted by a group selected from fluorine,
chlorine, methyl, methoxy, trifluoromethoxy, NO_2 , methylthio or by the
group $-\text{O}-\text{CH}_2-\text{O}-$.

An especially preferred class of compound of formula (Ia) is that
wherein R^{14} represents 2-methoxyphenyl.

25 In a further aspect of the present invention, the compounds of
formula (I) may be prepared in the form of a pharmaceutically acceptable
salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula (I) will be
non-toxic pharmaceutically acceptable salts. Other salts may, however, be
30 useful in the preparation of the compounds according to the invention or of
their non-toxic pharmaceutically acceptable salts. Suitable

pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention may have at least one asymmetric centre, and may exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier or excipient.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, wafers, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation. Oral compositions such as tablets, pills, capsules or wafers, are particularly preferred.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as

tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Preferred compositions for administration by injection include those comprising a compound of formula (I), as the active ingredient, in
5 association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may
10 contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the
15 nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

20 The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide
25 variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity.

Thus, for example, an excess of tachykinin, and in particular substance P, activity is implicated in a variety of disorders of the central nervous system. Such disorders include mood disorders, such as
30 depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders,

or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and
cyclothymic disorder; anxiety disorders, such as panic disorder with or
without agoraphobia, agoraphobia without history of panic disorder,
specific phobias, for example, specific animal phobias, social phobias,
5 obsessive-compulsive disorder, stress disorders including post-traumatic
stress disorder and acute stress disorder, and generalised anxiety
disorders; schizophrenia and other psychotic disorders, for example,
schizophreniform disorders, schizoaffective disorders, delusional disorders,
brief psychotic disorders, shared psychotic disorders and psychotic
10 disorders with delusions or hallucinations; delerium, dementia, and
amnesic and other cognitive or neurodegenerative disorders, such as
Alzheimer's disease, senile dementia, dementia of the Alzheimer's type,
vascular dementia, and other dementias, for example, due to HIV disease,
head trauma, Parkinson's disease, Huntington's disease, Pick's disease,
15 Creutzfeldt-Jakob disease, or due to multiple aetiologies; Parkinson's
disease and other extra-pyramidal movement disorders such as
medication-induced movement disorders, for example, neuroleptic-induced
parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute
dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive
20 dyskinesia and medication-induced postural tremour; substance-related
disorders arising from the use of alcohol, amphetamines (or amphetamine-
like substances) caffeine, cannabis, cocaine, hallucinogens, inhalants and
aerosol propellants, nicotine, opioids, phenylglycidine derivatives,
sedatives, hypnotics, and anxiolytics, which substance-related disorders
25 include dependence and abuse, intoxication, withdrawal, intoxication
delerium, withdrawal delerium, persisting dementia, psychotic disorders,
mood disorders, anxiety disorders, sexual dysfunction and sleep disorders;
epilepsy; Down's syndrome; demyelinating diseases such as MS and ALS
and other neuropathological disorders such as peripheral neuropathy, for
30 example diabetic and chemotherapy-induced neuropathy, and postherpetic
neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and

other neuralgias; and cerebral vascular disorders due to acute or chronic cerebrovascular damage such as cerebral infarction, subarachnoid haemorrhage or cerebral oedema.

Tachykinin, and in particular substance P, activity is also involved
5 in nociception and pain. The compounds of the present invention will therefore be of use in the prevention or treatment of diseases and conditions in which pain predominates, including soft tissue and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain,
10 myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for example, dysmenorrhoea, and labour pain; pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for
15 example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; pain associated with carcinoma, often referred to as cancer pain; central nervous system pain, such as pain due to spinal cord or brain stem damage; low back pain; sciatica; ankylosing spondylitis,
20 gout; and scar pain.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive
25 airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, bronchospasm and cough; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal
30 conjunctivitis, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases

such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of neoplasms, including breast tumours,
5 neuroganglioblastomas and small cell carcinomas such as small cell lung cancer.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of gastrointestinal (GI) disorders, including inflammatory disorders and diseases of the GI tract such as gastritis,
10 gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed or anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for
15 example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intracranial pressure, gastro-oesophageal reflux disease, acid indigestion, over indulgence in food or drink, acid stomach, waterbrash or regurgitation, heartburn, for example, episodic, nocturnal or meal-induced heartburn, and dyspepsia.

20 Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of a variety of other conditions including stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune
25 enhancement or suppression such as systemic lupus erythematosus; plasma extravasation resulting from cytokine chemotherapy, disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia and incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; disorders of blood flow caused by vasodilation and
30 vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; and pain or nociception attributable to or associated

with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of
5 combined post-operative pain and post-operative nausea and vomiting.

The compounds of formula (I) are particularly useful in the treatment of emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in
10 intercranial pressure. Most especially, the compounds of formula (I) are of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents, including those routinely used in cancer chemotherapy, and emesis induced by other pharmacological agents, for example, rolipram.

Examples of such chemotherapeutic agents include alkylating
15 agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic
20 antibiotics.

Particular examples of chemotherapeutic agents are described, for instance, by D. J. Stewart in *Nausea and Vomiting: Recent Research and Clinical Advances*, Eds. J. Kucharczyk *et al*, CRC Press Inc., Boca Raton, Florida, USA (1991) pages 177-203, especially page 188. Commonly used
25 chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin
30 and chlorambucil [R. J. Gralla *et al* in *Cancer Treatment Reports* (1984) 68(1), 163-172].

The compounds of formula (I) are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer, or radiation sickness; and in the treatment of post-operative nausea and vomiting.

5 It will be appreciated that the compounds of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use for the relief of emesis. Such combined preparations may be, for example, in the form of a twin pack.

10 A further aspect of the present invention comprises the compounds of formula (I) in combination with a 5-HT₃ antagonist, such as ondansetron, granisetron or tropisetron, or other anti-emetic medicaments, for example, a dopamine antagonist such as metoclopramide or domperidone or GABA_B receptor agonists such as baclofen.

15 Additionally, a compound of formula (I), either alone or in combination with one or more other anti-emetic therapeutic agents, may be administered in combination with an anti-inflammatory corticosteroid, such as dexamethasone, betamethasone, triamcinolone, triamcinolone acetone, flunisolide, budesonide, or others such as those disclosed in US
20 patent nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712. Dexamethasone (Decadron™) is particularly preferred. Furthermore, a compound of formula (I) may be administered in combination with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor or cytotoxic antibiotic,
25 as described above. In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

Suitable methods for determining the anti-emetic effects of compounds of the present invention are well known in the art, for example, using the ferret model of cisplatin-induced emesis described by
30 F. D. Tattersall *et al*, in *Eur. J. Pharmacol.*, (1993) 250, R5-R6.

The compounds of formula (I) are also particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, 5 asthma, osteoarthritis, rheumatoid arthritis and headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain.

The compounds of formula (I) are also particularly useful in the treatment of depression including depressive disorders, for example, single 10 episodic or recurrent major depressive disorders, and dysthymic disorders, depressive neurosis, and neurotic depression; melancholic depression including anorexia, weight loss, insomnia and early morning waking, and psychomotor retardation; atypical depression (or reactive depression) including increased appetite, hypersomnia, psychomotor agitation or 15 irritability, anxiety and phobias; seasonal affective disorder; or depression.

The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a 20 medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of 25 tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

According to a further aspect of the present invention, it may be desirable to treat any of the aforementioned conditions with a combination 30 of a compound according to the present invention and one or more other pharmacologically active agents suitable for the treatment of the specific

condition. The compound of formula (I) and the other pharmacologically active agent(s) may be administered to a patient simultaneously, sequentially or in combination.

Thus, for example, for the treatment of respiratory diseases such as
5 asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2 -adrenergic receptor agonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

10 Likewise, a compound of the present invention may be employed with a leukotriene antagonists, such as a leukotriene D₄ antagonist such as a compound selected from those disclosed in European patent specification nos. 0 480 717 and 0 604 114 and in US patent nos. 4,859,692 and 5,270,324. This combination is particularly useful in the treatment of
15 respiratory diseases such as asthma, chronic bronchitis and cough.

The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a
20 bronchodilator.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of
25 migraine, a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT₁ agonists, especially sumatriptan, naratriptan, zolmatriptan or rizatriptan.

Likewise, for the treatment of behavioural hyperalgesia, a compound of the present invention may be used in conjunction with an
30 antagonist of N-methyl D-aspartate (NMDA), such as dizocilpine.

For the treatment or prevention of inflammatory conditions in the lower urinary tract, especially cystitis, a compound of the present invention may be used in conjunction with an anti-inflammatory agent such as a bradykinin receptor antagonist.

5 The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of pain or nociception, a compound of the present invention may be used in
10 conjunction with other analgesics, such as acetaminophen (paracetamol), aspirin and other NSAIDs and, in particular, opioid analgesics, especially morphine. Specific anti-inflammatory agents include diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam and sulindac. Suitable opioid analgesics of use in conjunction with a compound of the
15 present invention include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine; or a pharmaceutically acceptable salt thereof.

20 Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an analgesic, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is
25 provided a product comprising a compound of the present invention and an analgesic as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of pain or nociception.

It will be appreciated that for the treatment of depression or anxiety, a compound of the present invention may be used in conjunction
30 with other anti-depressant or anti-anxiety agents.

Suitable classes of anti-depressant agent include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α -adrenoreceptor antagonists and atypical anti-depressants.

Suitable norepinephrine reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Suitable examples of tertiary amine tricyclics include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine, and pharmaceutically acceptable salts thereof. Suitable examples of secondary amine tricyclics include: amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof.

Suitable selective serotonin reuptake inhibitors include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

Suitable monoamine oxidase inhibitors include: isocarboxazid, phenelzine, tranylcypromine and selegiline, and pharmaceutically acceptable salts thereof.

Suitable reversible inhibitors of monoamine oxidase include: moclobemide, and pharmaceutically acceptable salts thereof.

Suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include: venlafaxine, and pharmaceutically acceptable salts thereof.

Suitable CRF antagonists include those compounds described in International Patent Specification Nos. WO 94/13643, WO 94/13644, WO 94/13661, WO 94/13676 and WO 94/13677.

Suitable atypical anti-depressants include: bupropion, lithium, nefazodone, trazodone and viloxazine, and pharmaceutically acceptable salts thereof.

Suitable classes of anti-anxiety agent include benzodiazepines and 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists.

Suitable benzodiazepines include: alprazolam, chlordiazepoxide, 5 clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam, and pharmaceutically acceptable salts thereof.

Suitable 5-HT_{1A} receptor agonists or antagonists include, in particular, the 5-HT_{1A} receptor partial agonists buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

10 Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an anti-depressant or anti-anxiety agent, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is 15 provided a product comprising a compound of the present invention and an anti-depressant or anti-anxiety agent as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of depression and/or anxiety.

It will be appreciated that for the treatment or prevention of eating 20 disorders, including obesity, bulimia nervosa and compulsive eating disorders, a compound of the present invention may be used in conjunction with other anorectic agents.

The present invention accordingly provides the use of a compound of formula (I) and an anorectic agent for the manufacture of a medicament 25 for the treatment or prevention of eating disorders, including obesity, bulimia nervosa and compulsive eating disorders.

The present invention also provides a method for the treatment or prevention of eating disorders, including obesity, bulimia nervosa and compulsive eating disorders, which method comprises administration to a 30 patient in need of such treatment an amount of a compound of formula (I)

and an amount of an anorectic agent, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of formula (I) and an
5 anorectic agent, together with at least one pharmaceutically acceptable carrier or excipient.

It will be appreciated that the compound of formula (I) and anorectic agent may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention
10 of eating disorders. Such combined preparations may be, for example, in the form of a twin pack.

In a further or alternative aspect of the present invention, there is therefore provided a product comprising a compound of formula (I) and an anorectic agent as a combined preparation for simultaneous, separate or
15 sequential use in the treatment or prevention of eating disorders.

Suitable anorectic agents of use in combination with a compound of the present invention include, but are not limited to, aminorex, amphechloral, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclexedrine,
20 dexfenfluramine, dextroamphetamine, diethylpropion, diphemethoxidine, *N*-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex, fludorex, fluminorex, furfurylmethylamphetamine, levamfetamine, levophacetoperane, mazindol, mefenorex, metamfepramone, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine,
25 phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine; and pharmaceutically acceptable salts thereof.

A particularly suitable class of anorectic agent are the halogenated amphetamine derivatives, including chlorphentermine, cloforex, clortermine, dexfenfluramine, fenfluramine, picilorex and sibutramine;
30 and pharmaceutically acceptable salts thereof.

Particularly preferred halogenated amphetamine derivatives of use in combination with a compound of the present invention include: fenfluramine and dexfenfluramine, and pharmaceutically acceptable salts thereof.

5 It will be appreciated that for the treatment or prevention of obesity, the compounds of the present invention may also be used in combination with a selective serotonin reuptake inhibitor (SSRI).

The present invention accordingly provides the use of a compound of formula (I) and an SSRI for the manufacture of a medicament for the
10 treatment or prevention of obesity.

The present invention also provides a method for the treatment or prevention of obesity, which method comprises administration to a patient in need of such treatment an amount of a compound of formula (I) and an amount of an SSRI, such that together they give effective relief.

15 In a further aspect of the present invention, there is provided a pharmaceutical composition for the treatment or prevention of obesity comprising a compound of formula (I) and an SSRI, together with at least one pharmaceutically acceptable carrier or excipient.

It will be appreciated that the compound of formula (I) and SSRI
20 may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of obesity. Such combined preparations may be, for example, in the form of a twin pack.

In a further or alternative aspect of the present invention, there is therefore provided a product comprising a compound of formula (I) and an
25 SSRI as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of obesity.

Suitable selective serotonin reuptake inhibitors of use in combination with a compound of the present invention include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable
30 salts thereof.

As used herein "obesity" refers to a condition whereby a mammal has a Body Mass Index (BMI), which is calculated as weight per height squared (kg/m^2), of at least 25.9. Conventionally, those persons with normal weight, have a BMI of 19.9 to less than 25.9.

5 The obesity herein may be due to any cause, whether genetic or environmental. Examples of disorders that may result in obesity or be the cause of obesity include overeating and bulimia, polycystic ovarian disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, Type II diabetes, GH-deficient subjects, normal variant short
10 stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g, children with acute lymphoblastic leukemia.

"Treatment" (of obesity) refers to reducing the BMI of the mammal
15 to less than about 25.9, and maintaining that weight for at least 6 months. The treatment suitably results in a reduction in food or calorie intake by the mammal.

"Prevention" (of obesity) refers to preventing obesity from occurring if the treatment is administered prior to the onset of the obese condition.
20 Moreover, if treatment is commenced in already obese subjects, such treatment is expected to prevent, or to prevent the progression of, the medical sequelae of obesity, such as, e.g., arteriosclerosis, Type II diabetes, polycystic ovarian disease, cardiovascular diseases, osteoarthritis, dermatological disorders, hypertension, insulin resistance,
25 hypercholesterolemia, hypertriglyceridemia, and cholelithiasis.

A further aspect of the present invention comprises the use of a compound of formula (I) for achieving a chronobiologic (circadian rhythm phase-shifting) effect and alleviating circadian rhythm disorders in a mammal. The present invention is further directed to the use of a
30 compound of formula (I) for blocking the phase-shifting effects of light in a mammal.

The present invention further relates to the use of a compound of formula (I) for enhancing or improving sleep quality, in particular by increasing sleep efficiency and augmenting sleep maintenance, as well as for preventing and treating sleep disorders and sleep disturbances, in a mammal.

In a preferred embodiment, the present invention provides a method for the phase advance or phase delay in the circadian rhythm of a subject which comprises administering to the subject an appropriate amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of emesis, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 3 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of psychiatric disorders, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 3 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of

administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

Several methods for preparing the compounds of the present invention are illustrated in the following schemes and Examples wherein
5 R¹, R², R³, R⁴, R⁵, X and n are as defined above unless otherwise specified.

Abbreviations used in the Schemes

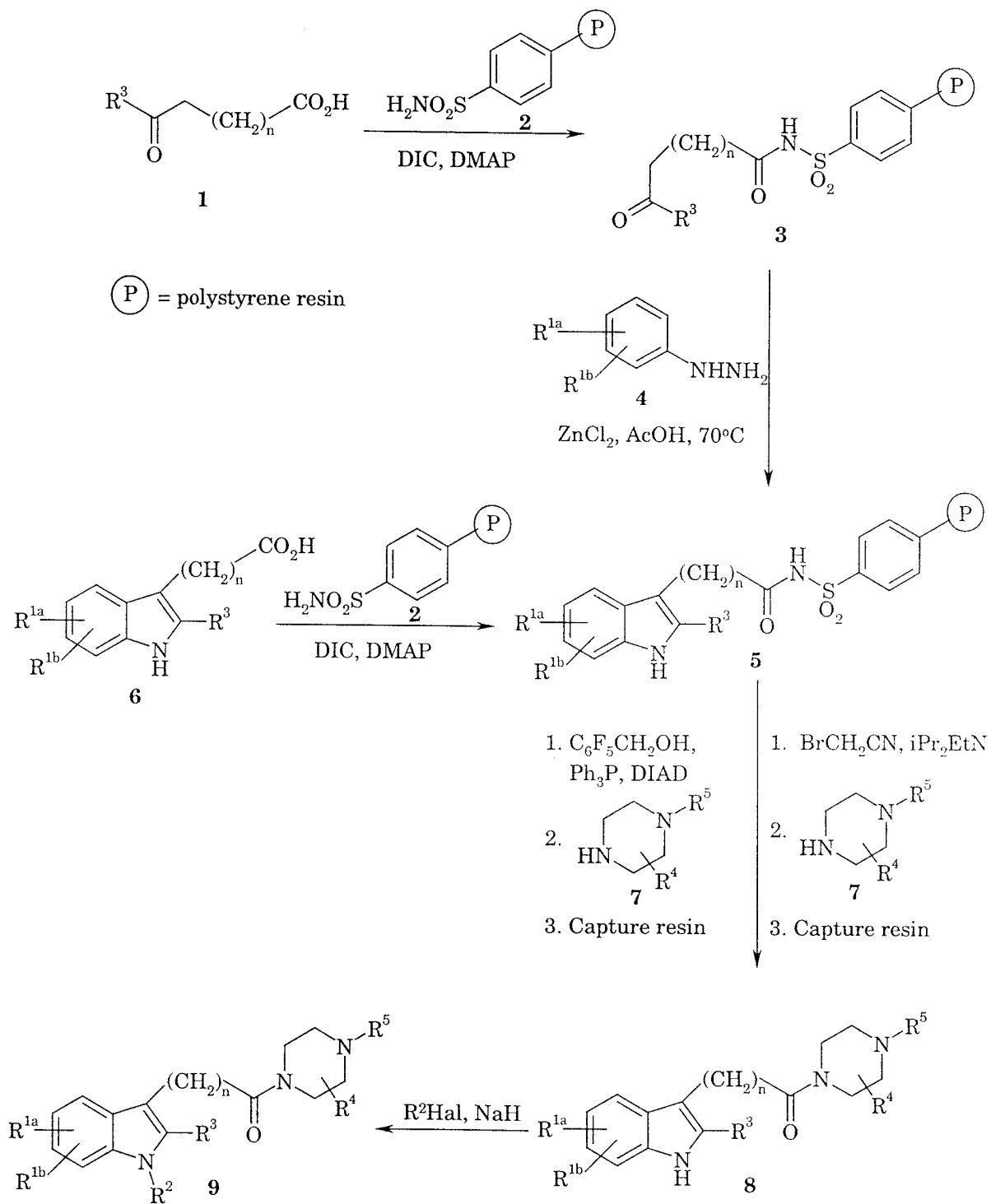
Reagents

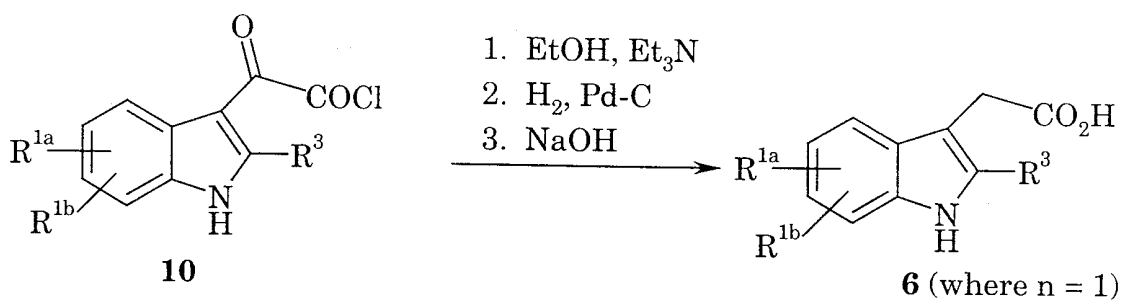
AcCl	acetyl chloride
AcOH	acetic acid
BH ₃ .THF	borane-tetrahydrofuran complex
BrCH ₂ CN	bromoacetonitrile
C ₆ F ₅ CH ₂ OH	pentafluorobenzyl alcohol
CDI	carbonyldiimidazole
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIC	2-dimethylaminoisopropyl chloride hydrochloride
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
(DPPB)PdCl ₂	[1,4-butanediylbis(diphenylphosphine)] dichloropalladium
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et ₃ N	triethylamine
EtOH	ethanol
H ₂ , Pd-C	catalytic hydrogenation using palladium on carbon
HCl	hydrochloric acid
HOBT	1-hydroxybenzotriazole hydrate
iPr ₂ EtN	diisopropylethylamine

K_2CO_3	potassium carbonate
KOt-Bu	potassium <i>tert</i> -butoxide
MeOH	methanol
$Na(AcO)_3BH$	sodium triacetoxyborohydride
NaH	sodium hydride
NaOH	sodium hydroxide
$Pd_2(DBA)_3$	tris(dibenzylideneacetone)dipalladium (0)
Ph_3P	triphenylphosphine
(RS)-BINAP	(<i>R,S</i>)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
TFA	trifluoroacetic acid
TMSBr	bromotrimethylsilane
$ZnCl_2$	zinc chloride

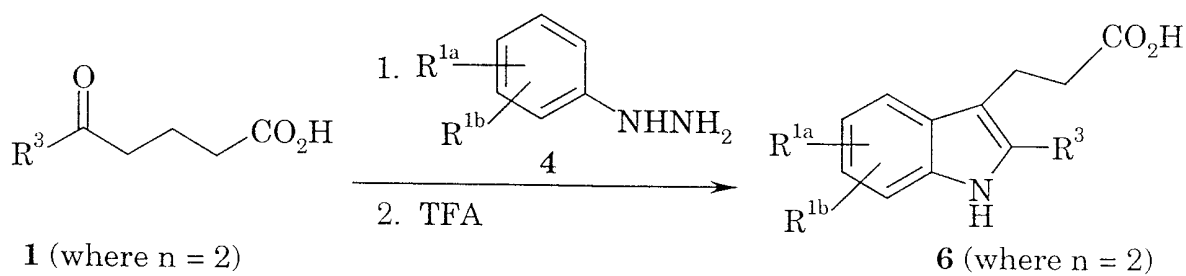
Scheme 1

Resin bound synthesis of compounds of formula (I) wherein X = O



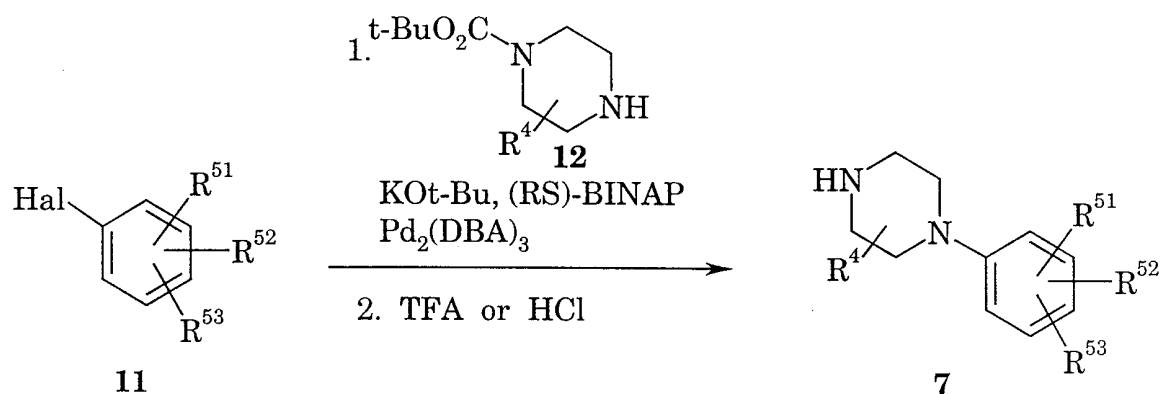
Scheme 2Synthesis of acid **6** where $n = 1$ 

5

Scheme 3Synthesis of acid **6** where $n = 2$ 

10

Scheme 4

Synthesis of amines 7 (where R⁵ is substituted phenyl)

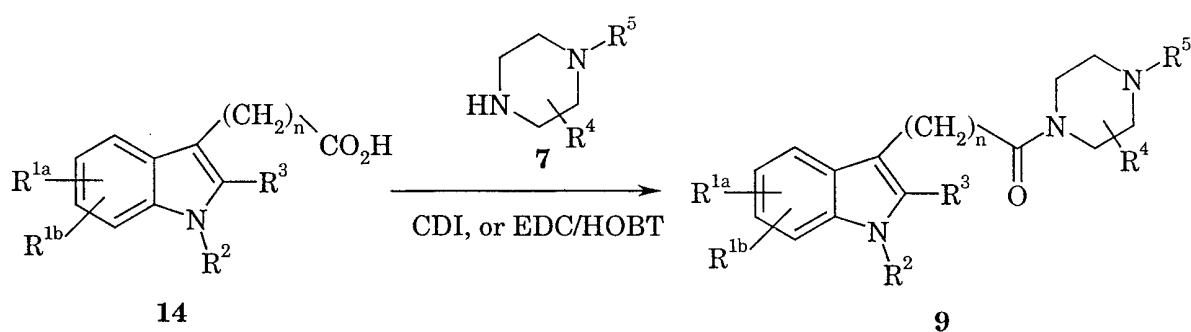
where R⁵¹, R⁵² and R⁵³ represent one, two or three optional substituents as defined in formula (I) and Hal is a leaving group such as bromine or iodine

(where R⁵ is substituted phenyl)

5

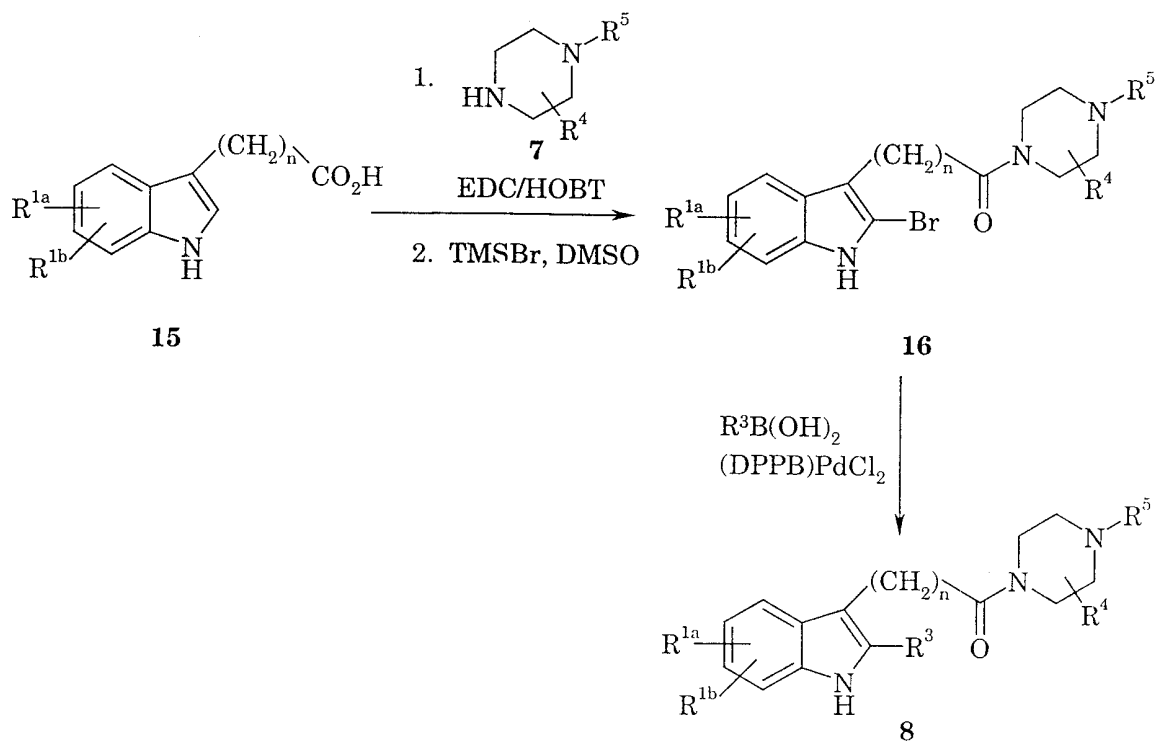
Scheme 5

Coupling reaction (where X = O)

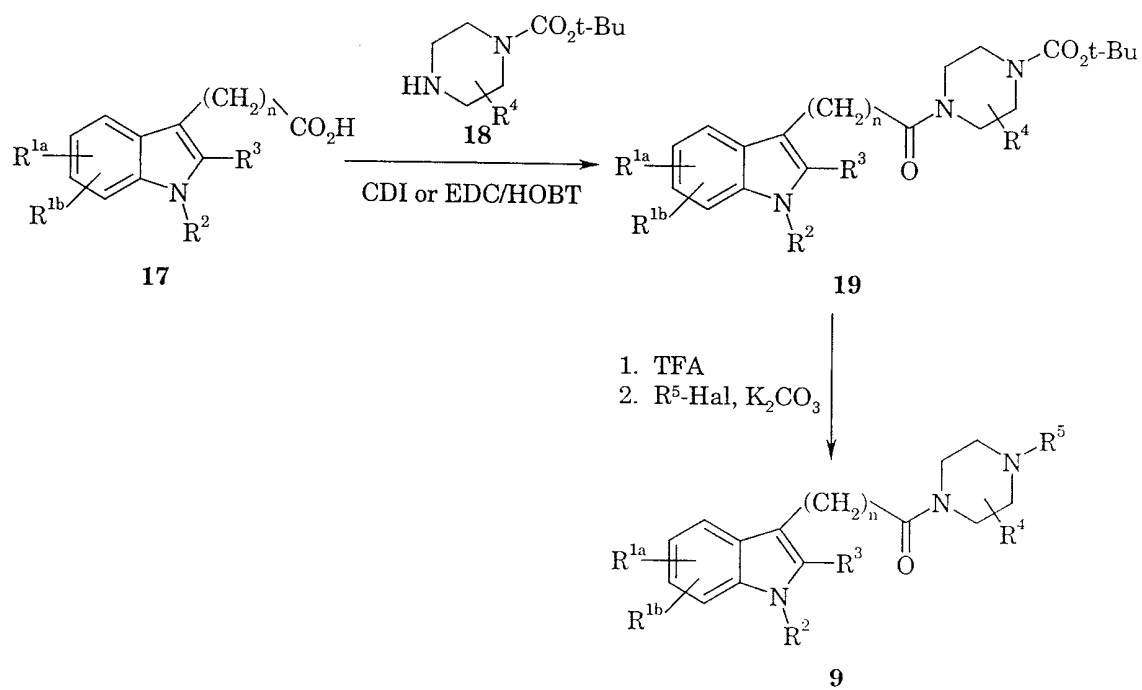


10

Scheme 6

Coupling reaction (addition of R³) (where X = O)

Scheme 7

Coupling reaction (addition of R⁵) (where X = O)

The compounds of the present invention in which X = O may be prepared by the general route outlined in Scheme 1 or by methods analogous thereto. Thus, the appropriate carboxylic acid **1** is loaded onto a resin **2**, for example, 4-sulfamylbutyryl AM resin (Novabiochem), using a suitable coupling agent such as 1,3-diisopropylcarbodiimide. The reaction is conveniently effected in the presence of an organic base such as 4-dimethylaminopyridine. The resultant loaded resin **3** may then be reacted with phenyl hydrazine or with a variety of mono- or disubstituted phenyl hydrazines **4** to prepare the indole intermediate **5** which, at this stage, is still bound to the resin. Reaction with the hydrazine is an example of the well-known Fischer indole synthesis, conveniently effected in glacial acetic acid in the presence of a suitable catalyst, for example, a Lewis acid such as zinc chloride.

An alternative route to the resin bound indoles **5** involves the coupling of a preformed indole carboxylic acid **6** with the resin **2** using the conditions described above.

Preparation of the compounds of formula (I) is completed by an exchange reaction that liberates the resin and introduces the substituted piperazine moiety. This exchange reaction may be effected using a variety of conditions such as pentafluorobenzyl alcohol, triphenylphosphine and diisopropyl azodicarboxylate to introduce the substituted piperazine **7**. Alternatively, the reaction may be effected in the presence of diisopropylethylamine and bromoacetonitrile.

The compound of formula (I) **8** is readily modified on the indole nitrogen using conventional methodology. Thus, for example, where R² is an alkyl group, reaction with an appropriate alkyl halide in the presence of a hydride, affords further compounds of formula (I) **9**.

The indole-3-acetic acid intermediates **6** (where n = 1) may be prepared by the general route outlined in Scheme 2 or by methods analogous thereto. Thus, an appropriately substituted α -oxo-indole-3-

acetyl chloride **10** may be converted to the corresponding ester by reaction with, for example, ethanol, in the presence of a base, such as triethylamine. The resultant α -oxo ester is then reduced using, for example, catalytic hydrogenation using a transition metal catalyst such as palladium on carbon, followed by hydrolysis using, for example, a hydroxide such as sodium hydroxide, to afford the acetic acid compound **6**.

The indole-3-propanoic acid intermediates **6** (where $n = 2$) may be prepared by the general route outlined in Scheme 3 or by methods analogous thereto. Thus, an appropriately substituted δ -oxopentanoic acid **1** (where $n = 2$) may be reacted with phenyl hydrazine or with a mono- or disubstituted phenyl hydrazine under conventional conditions for the Fischer indole synthesis or by heating the mixture at reflux in the presence of trifluoroacetic acid. The reaction is conveniently effected in a solvent, for example, triethylamine.

Other indole-3-carboxylic acids in which n is 3 or 4 may be prepared by methods analogous to those described in Scheme 3 or by other methods well known to a person of ordinary skill in the art.

The piperazine intermediates **7** (where $R^5 =$ substituted phenyl) may be prepared by the general route outlined in Scheme 4 or by methods analogous thereto. Thus, an appropriately substituted phenyl halide **11** may be coupled to a protected piperazine derivative **12** using conventional coupling conditions such as mixing with sodium or potassium *tert*-butoxide, to which mixture is added (*R,S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and tris(dibenzylideneacetone)dipalladium (0). The reaction is conveniently effected in an aromatic hydrocarbon solvent such as toluene. Deprotection of the phenylpiperazine compound may be effected in a conventional manner, for example, by treatment with an organic acid such as trifluoroacetic acid or an inorganic acid, such as hydrochloric acid to afford an amine **7**, where R^5 is a substituted phenyl group.

Other piperazine intermediates **7** in which R^5 is other than a substituted phenyl group may be prepared by methods analogous to those

described in Scheme 4 or by other methods well known to a person of ordinary skill in the art.

In an alternative method, compounds of the present invention in which X = O may be prepared by the general route outlined in Scheme 5 or
5 by methods analogous thereto. A 2-aryl-indole-3-carboxylic acid intermediate **14** may be coupled to a piperazine intermediate **7** using conventional coupling conditions such as treating the carboxylic acid with 1,1-carbonyldiimidazole, followed by reaction with the piperazine. The reaction is conveniently effected in a suitable solvent such as an ether, for
10 example, tetrahydrofuran. The treatment with CDI is preferably effected at the reflux temperature of the solvent whereas reaction with the piperazine is preferably effected at about room temperature.

Alternative coupling conditions comprise mixing the 2-aryl-indole-3-carboxylic acid **14** and the piperazine **7** with 1-hydroxybenzotriazole,
15 followed by addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The reaction is conveniently effected in a suitable solvent such as an ether, for example, tetrahydrofuran, and preferably at about room temperature, to afford the compound of formula (I) **9**.

In a further alternative method, compounds of the present invention in which X = O may be prepared by the general route outlined in Scheme 6
20 or by methods analogous thereto. An indole-3-carboxylic acid **15** may be coupled to a piperazine intermediate **7**, according to the general methods described in relation to Scheme 5. The resultant intermediate indole may then be brominated at the 2-position by treatment with a suitable
25 brominating agent such as bromotrimethylsilane. The reaction is preferably effected in a suitable organic solvent such as dimethylsulfoxide, conveniently at about room temperature, to afford the 2-bromo-indole intermediate **16**.

Reaction of the 2-bromo-indole **16** with an appropriate aryl boronic
30 acid using the conventional conditions of a Suzuki coupling, for example, using a catalyst such as [1,4-butanediylbis(diphenylphosphine)]-

dichloropalladium. The reaction is preferably effected in the presence of an alkali metal carbonate such as aqueous sodium carbonate and at an elevated temperature, for example, between 70°C and 95°C, to afford the compound of formula (I) **8**.

5 The boronic acids of use in the coupling described in Scheme 6 are commercially available or may be prepared by methods well known to a person of ordinary skill in the art.

 In another alternative method, compounds of the present invention in which X = O may be prepared by the general route outlined in Scheme 7
10 or by methods analogous thereto. Thus, a 2-aryl-indole-3-carboxylic acid **17** may be reacted with a mono-protected piperazine **18** to afford the N-protected intermediate **19**. The coupling may be effected according to the general methods described in relation to Scheme 5. The resultant N-protected piperazine **19** may then be deprotected using acidic conditions,
15 for example, trifluoroacetic acid and then N-substituted using a variety of reagents of the formula R⁵-Hal where Hal is a halogen atom, preferably bromine or chlorine. The reaction is preferably effected in the presence of an inorganic base such as potassium carbonate, conveniently in a solvent such as an ester, for example, acetone, conveniently at room temperature.

20 This method is particularly useful for the preparation of compounds of the present invention in which R⁵ is an alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl, heteroaryl, aralkyl or heteroaralkyl group.

 The halides of formula R⁵-Hal of use in the methods described in Scheme 7 are commercially available or may be prepared by methods well
25 known to a person of ordinary skill in the art.

 It will be appreciated that, where appropriate, a combination of the general methodology described in Schemes 1 to 7 may be applied to prepare further compounds of the present invention.

 The compounds of formula (I) prepared according to the methods
30 described above may be isolated and purified in a conventional manner,

for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography or a combination thereof.

Although the reaction schemes described herein are reasonably general, it will be understood by those skilled in the art of organic synthesis that one or more functional groups present in a given compound of formula (I) may render the molecule incompatible with a particular synthetic sequence.

In such a case an alternative route, an altered order of steps, or a strategy of protection and deprotection may be employed. In all cases the particular reaction conditions, including reagents, solvent, temperature, and time, should be chosen so that they are consistent with the nature of the functionality present in the molecule.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165. The compounds were found to be active with IC₅₀ at the NK₁ receptor of less than 100nM on said test method.

The following non-limiting Examples serve to illustrate the preparation of compounds of the present invention:

DESCRIPTION 1Scavenger Resin

A solution of pentafluorophenyl chlorothionoformate (0.5 M) and diisopropylethylamine (0.5 M) in tetrahydrofuran-dichloromethane (1:1, 20 mL per 1 gram of resin) was added to aminomethylated polystyrene HL resin (Novabiochem, product no. 01-64-0010) and the mixture was stirred at room temperature for 1 h. The resin was washed with tetrahydrofuran-dichloromethane (1:1, 4 x) and dimethylformamide (4 x), then a solution of triethylamine in dimethylformamide (0.5M, 20 mL per 1 g of resin) was added. The mixture was stirred at room temperature for 30 min., then the resin was washed with dimethylformamide (4 x), tetrahydrofuran-dichloromethane (1:1, 4 x), dichloromethane (4 x) and ether (2 x). The resin was then dried *in vacuo* for 1 h. and used immediately.

15

DESCRIPTION 2Loaded Resin

1,3-Diisopropylcarbodiimide (3.47 g) was added to 4-bromo- δ -oxobenzenepentanoic acid (*J. Org. Chem.* **1948**, *13*, 284; *J. Org. Chem.* **1984**, *49*, 3170; 14.91 g) in dichloromethane (55 mL) and the mixture was stirred at room temperature for 30 min. The mixture was added to 4-sulfamylbutyryl AM resin (Novabiochem, product no. 01-64-0152, 1 mmol/g loading, 5.5 g), 4-dimethylaminopyridine (671 mg) was added and the mixture was stirred at room temperature for 18 h. The mixture was filtered and the resin was washed with dimethylformamide (50 mL), dichloromethane (50 mL), methanol (50 mL) and ether (50 mL) and dried *in vacuo*. A dispersion of (4-methylphenyl)hydrazine hydrochloride (9.2 g) in glacial acetic acid (135 mL) then zinc chloride (10.8 g) were added and the mixture was heated to 75 °C for 18 h. The mixture was cooled to room temperature, filtered and washed with glacial acetic acid-tetrahydrofuran (1:1, 50 mL), dichloromethane (50 mL), dimethylformamide (50 mL), methanol (50 mL) and ether (50 mL) and dried *in vacuo*.

DESCRIPTION 3

Determination of Resin Loading by preparation of N,N-Dimethyl-[2-(4-bromophenyl)-5-methyl-1H-indol-3-yl]propanamide

5 Diisopropylethylamine (65 mg) and bromoacetonitrile (288 mg) were added to the resin of Description 2 (100 mg) in N-methylpyrrolidinone (1 mL) and the mixture was allowed to stand at room temperature for 18 h. The mixture was filtered and the resin was washed with N-methylpyrrolidinone (5 mL) and tetrahydrofuran (5 mL). A solution of dimethylamine in
10 tetrahydrofuran (2M, 2 mL) was added and the mixture was allowed to stand at room temperature for 18 h. The mixture was filtered and the filtrate was collected. The solvent was evaporated under reduced pressure and the residue was dried *in vacuo* to give the title compound as a pale brown solid (20 mg), consistent with a resin loading of 0.52 mmol/g prior to activation and cleavage.

15

DESCRIPTION 4

Ethyl 5-Methyl- α -oxo-2-phenyl-1H-indole-3-acetate

5-Methyl- α -oxo-2-phenyl-1H-indole-3-acetyl chloride (*Ind. J. Chem. Sec. B. 1995*, 796-801; 2.5 g, 12 mmol) was added to a solution of triethylamine
20 (25 mL) in ethanol (150 mL). The solvent was evaporated under reduced pressure, water was added and the mixture was extracted with ethyl acetate. The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure to give the title compound as a pale brown solid (3.8 g, 98%). ¹H NMR (250MHz, CDCl₃) δ 1.03 (3H, t, *J* 7 Hz), 2.53 (3H, s),
25 3.60-3.84 (2H, m), 7.18-7.20 (1H, m), 7.30-7.35 (2H, m), 7.40-7.57 (5H, m), and 8.23 (1H, s).

DESCRIPTION 5

Ethyl 5-Methyl-2-phenyl-1H-indole-3-acetate

30 A suspension of palladium on carbon (10%, 1 g) in dioxane (50 mL) was added to a solution of ethyl 5-methyl- α -oxo-2-phenyl-1H-indole-3-acetate

(Description 4, 3.66 g) in dioxane (250 mL). A solution of sodium hypophosphite (10 g) in water (10 mL) was added and the mixture was heated under reflux for 10 h. Further palladium on carbon (10%, 1 g) and sodium hypophosphite (10 g) were added and the mixture was heated under reflux for 24 h. Further
5 palladium on carbon (10%, 1 g) and sodium hypophosphite (10 g) were added and the mixture was heated under reflux for 24 h. The mixture was cooled, filtered through celite and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc (90:10) to give the title compound as a colourless solid
10 (1.6 g, 47%). ¹H NMR (360MHz, CDCl₃) δ 0.86 (3H, t, *J* 7 Hz), 2.43 (3H, s), 3.73 (2H, s), 4.11-4.16 (2H, m), 6.96 (1H, dd, *J* 8, 1.8 Hz), 7.18 (1H, d, *J* 10.8 Hz), 7.28-7.46 (5H, m), 7.58 (1H, d, *J* 7.2 Hz), and 7.98 (1H, br s). *m/z* (ES⁺) 294 (M+1).

15

DESCRIPTION 6

5-Methyl-2-phenyl-1*H*-indole-3-acetic Acid

Aqueous sodium hydroxide (4M, 75 mL) was added to ethyl
5-methyl-2-phenyl-1*H*-indole-3-acetate (Description 5, 1.61 g) in methanol (150 mL) and the mixture was stirred at room temperature for 2 h. The mixture
20 was cooled to 0 °C, the pH was adjusted to 3.0 with hydrochloric acid (2M) and the mixture was extracted with ethyl acetate. The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was recrystallized from ether to give the title compound as a
colourless solid (1.1 g, 76%). ¹H NMR (360MHz, CDCl₃) δ 2.47 (3H, s), 3.85 (3H,
25 s), 7.05 (1H, dd, *J* 8.3, 1.4 Hz), 7.27 (1H, d, *J* 11.2 Hz), 7.36-7.49 (4H, m), 7.62 (1H, d, *J* 9.2 Hz), and 8.05 (1H, br s). *m/z* (ES⁺) 266 (M+1).

DESCRIPTION 7

5-Methyl-2-phenyl-1*H*-indole-3-propanoic Acid

30 Triethylamine (1.4 mL, 10 mmol) was added to a stirred suspension of δ-oxobenzepentanoic acid (1.92 g, 10 mmol) and (4-methylphenyl)hydrazine

hydrochloride (1.59 g, 10 mmol) in ethanol (16 mL) and the mixture was stirred at room temperature for 4 h. Ether (100 mL) was added, the mixture was filtered and the solvent was evaporated under reduced pressure. The residue was added slowly to trifluoroacetic acid (15 mL) and the mixture was heated under reflux for 2 h. The mixture was cooled, water (100 mL) was added and the mixture was extracted with ethyl acetate (100 mL). The organic fraction was washed with brine (30 mL), dried (MgSO₄) and the volume was reduced to *Ca.* 10 mL by evaporation under reduced pressure. The precipitate was collected and recrystallized from ether to give the title compound as a pale solid (1.51 g, 54%). ¹H NMR (360MHz, DMSO-d₆) δ 2.39 (3H, s), 2.50-2.58 (2H, m), 3.03-3.09 (2H, m), 6.91-6.95 (1H, m), 7.23-7.25 (1H, m), 7.34-7.40 (2H, m), 7.47-7.63 (4H, m), 11.4 (1H, br s), and 12.25 (1H, br s). *m/z* (ES⁺) 280 (M+1).

DESCRIPTION 8

15 5-Chloro-2-phenyl-1*H*-indole-3-propanoic Acid

Prepared from δ-oxobenzene-pentanoic acid and (4-chlorophenyl)hydrazine hydrochloride according to the method of Description 7. ¹H NMR (360MHz, CDCl₃) (Contains 20% δ-oxobenzene-pentanoic acid) δ 8.02 (1H, s), 7.52-7.33 (6H, m), 7.23-7.18 (1H, m), 7.10-7.07 (1H, m), 3.16-3.11 (2H, m), and 2.65-2.60 (2H, m).

DESCRIPTION 9

25 5-Fluoro-2-phenyl-1*H*-indole-3-propanoic Acid

Prepared from δ-oxobenzene-pentanoic acid and (4-fluorophenyl)hydrazine hydrochloride according to the method of Description 7. ¹H NMR (360MHz, CDCl₃) (Contains 40% δ-oxobenzene-pentanoic acid) δ 8.04 (1H, s), 7.56-7.39 (5H, m), 7.30-7.25 (2H, m), 6.98-6.93 (1H, m), 3.23-3.18 (2H, m), and 2.71-2.67 (2H, m).

DESCRIPTION 105,6-Dimethyl-2-phenyl-1H-indole-3-propanoic Acid and 4,5-Dimethyl-2-phenyl-1H-indole-3-propanoic Acid

- Prepared from δ -oxobenzene-pentanoic acid and
- 5 (3,4-dimethylphenyl)hydrazine hydrochloride according to the method of Description 7 as a 2:1 mixture of isomers. ^1H NMR (360MHz, CDCl_3) (Contains 29% δ -oxobenzene-pentanoic acid); *5,6-dimethyl-2-phenyl-1H-indole-3-propanoic acid* (Major Isomer) δ 7.85 (1H, s), 7.58-7.33 (5H, m), 7.37 (1H, s), 7.16 (1H, s), 3.25-3.20 (2H, m), 2.75-2.67 (2H, m), and 2.38 (6H, s); *4,5-dimethyl-*
- 10 *2-phenyl-1H-indole-3-propanoic acid* (Minor Isomer) δ 7.92 (1H, s), 7.58-7.33 (5H, m), 7.12 (1H, t, J 8.2 Hz), 7.02 (1H, t, J 8.2 Hz), 3.35-3.31 (2H, m), 2.75-2.67 (2H, m), 2.64 (3H, s), and 2.39 (3H, s).

DESCRIPTION 1115 5-Chloro-2-(4-chlorophenyl)-1H-indole-3-propanoic Acid

- Prepared from 4-chloro- δ -oxobenzene-pentanoic acid and (4-chlorophenyl)hydrazine hydrochloride according to the method of Description 7. ^1H NMR (250MHz, DMSO-d_6) δ 2.55-2.61 (2H, m), 3.07-3.13 (2H, m), 7.16 (2H, d, J 12.6 Hz), 7.41 (2H, d, J 12.6 Hz), 7.62-7.71 (3H, m), 11.52 (1H, br s),
- 20 and 12.19 (1H, br s). m/z (ES^+) 331, 333 ($\text{M}+1$).

DESCRIPTION 125-Chloro-2-(4-chlorophenyl)-1-methyl-1H-indole-3-propanoic Acid

- Sodium hydride (60% suspension in mineral oil, 5.98 g) was added in
- 25 portions to a stirred, cooled (0 °C) solution of 5-chloro-2-(4-chlorophenyl)-1H-indole-3-propanoic acid (Description 11, 10 g, 30 mmol) in dimethylformamide (100 mL) and the mixture was stirred at 0 °C for 30 min. Iodomethane (9 mL) was added and the mixture was stirred at room temperature for 30 min. Water (1.5 L) was added and the mixture was
- 30 extracted with ether (3 x 400 mL). The combined organic fractions were dried (MgSO_4) and the solvent was evaporated under reduced pressure. The residue

was dissolved in methanol (240 mL) and aqueous sodium hydroxide (4M, 60 mL) was added. The mixture was heated under reflux for 1 h., cooled and the pH was adjusted to 1.0 with hydrochloric acid (2M). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic
5 fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was triturated with hexane and the solid was collected and dried *in vacuo* to give the the title compound (7.5 g, 72%). ¹H NMR (360MHz, CDCl₃) δ 2.54-2.59 (2H, m), 2.96-3.00 (2H, m), 3.53 (3H, s), 7.18-7.30 (4H, m), 7.44-7.48 (2H, m), and 7.58 (1H, d, *J* 1.8 Hz).

10

DESCRIPTION 13

Loaded Resin

1,3-Diisopropylcarbodiimide (1.21 g) was added to 5-chloro-2-(4-chlorophenyl)-1*H*-indole-3-propanoic acid (Description 11, 6.4 g, 19.2 mmol) in
15 tetrahydrofuran-dichloromethane (1:1, 80 mL) and the mixture was stirred at room temperature for 30 min. The mixture was added to 4-sulfamylbutyryl AM resin (Novabiochem, product no. 01-64-0152, 1 mmol/g loading, 8.3 g), 4-dimethylaminopyridine (292 mg) was added and the mixture was stirred at room temperature for 16 h. The mixture was filtered and the resin was washed
20 with tetrahydrofuran-dichloromethane (1:1), methanol (50 mL) and tetrahydrofuran (3x) and dried *in vacuo*.

DESCRIPTION 14

Determination of Resin Loading by preparation of N,N-Dimethyl-[2-(4-bromophenyl)-5-methyl-1*H*-indol-3-yl]propanamide
25

The loading of the resin of Description 13 was determined to be 0.51 mmol/g by the method of Description 3.

DESCRIPTION 152-Bromo-4-(trifluoromethoxy)phenol

A solution of bromine (32 g, 0.2 mol) in chloroform (50 mL) was added dropwise to a stirred, cooled (0 °C) solution of 4-(trifluoromethoxy)phenol (35.6 g, 0.2 mol) in chloroform (280 mL). The mixture was stirred at 0 °C for 1 h. and at room temperature for 2 h. Dichloromethane (200 mL) and water (400 mL) were added and the layers were separated. The organic fraction was washed with water (400 mL) and brine (200 mL), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by distillation under reduced pressure to give the title compound as a colorless oil. ¹H NMR (250MHz, CDCl₃) δ 7.38 (1H, d, *J* 2.1 Hz), 7.13 (1H, dd, *J* 9.1, 2.1 Hz), 7.03 (1H, d, *J* 9.1 Hz), and 5.53 (1H, s).

DESCRIPTION 162-Bromo-1-methoxy-4-(trifluoromethoxy)benzene

Iodomethane (14.94 mL, 0.24 mol) was added to a solution of 2-bromo-4-(trifluoromethoxy)phenol (Description 15, 7.2 g) and potassium carbonate (11.6 g, 0.084 mol) in dimethylformamide (60 mL) and the mixture was stirred at room temperature for 15 h. Water (400 mL) and ether (200 mL) were added and the layers were separated. The organic fraction was washed with water (4 x 200 mL), saturated aqueous sodium hydrogen carbonate (2 x 200 mL) and brine (200 mL), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/EtOAc (100:0 increasing to 98:2), to give the title compound. ¹H NMR (250MHz, CDCl₃) δ 7.45 (1H, d, *J* 2.8 Hz), 7.16 (1H, dd, *J* 9.0, 2.8 Hz), 6.88 (1H, d, *J* 9.0 Hz), and 3.90 (3H, s).

DESCRIPTION 171,1-Dimethylethyl 4-[2-Methoxy-4-(trifluoromethoxy)phenyl]-1-piperazinecarboxylate

A solution of 2-bromo-1-methoxy-4-(trifluoromethoxy)benzene
5 (Description 16, 3 g, 11 mmol), 1,1-dimethylethyl 1-piperazinecarboxylate
(2.47 g) and sodium tert-butoxide (1.49 g) in toluene (100 mL) was degassed
with bubbling argon. (*RS*)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (56 mg)
and tris(dibenzylideneacetone)dipalladium (0) (13.8 mg) were added and the
mixture was degassed and stirred at 80 °C for 72 h. The mixture was cooled,
10 diluted with ether (150 mL) and filtered through celite. The solvent was
evaporated under reduced pressure and the residue was purified by flash
column chromatography on silica gel, eluting with hexane/EtOAc (95:5
increasing to 85:15), to give the title compound (3.4 g, 82%). ¹H NMR (250MHz,
CDCl₃) δ 1.48 (9H, s), 2.98-3.01 (4H, m), 3.58-3.61 (4H, m), 3.87 (3H, s), and
15 6.74-6.85 (3H, m). m/z (ES⁺) 377 (M+1).

DESCRIPTION 181-[2-Methoxy-4-(trifluoromethoxy)phenyl]piperazine

Trifluoroacetic acid (90 mL) was added to a stirred, cooled (0 °C) solution
20 of 1,1-dimethylethyl
4-[2-methoxy-4-(trifluoromethoxy)phenyl]-1-piperazinecarboxylate (Description
17, 3.4 g) in dichloromethane (135 mL) and the mixture was stirred at room
temperature for 1 h. The mixture was allowed to warm to room temperature,
saturated aqueous sodium bicarbonate solution (380 mL) was added and the
25 mixture was extracted with dichloromethane. The combined organic fractions
were dried (MgSO₄) and the solvent was evaporated under reduced pressure to
give the title compound as a pale brown solid (1.84 g, 74%). ¹H NMR (250MHz,
CDCl₃) δ 3.28-3.58 (8H, m), 3.87 (3H, s), 6.77 (1H, d, *J* 1.9 Hz), 6.84 (1H, d, *J*
8.9 Hz), and 6.91-6.95 (1H, m).

DESCRIPTION 191-[2-(Trifluoromethoxy)phenyl]piperazine Hydrochloride

A solution of 1-iodo-2-(trifluoromethoxy)benzene (23.2 g, 80.6 mmol), 1,1-dimethylethyl 1-piperazinecarboxylate (10 g, 53.7 mmol) and sodium tert-butoxide (7.2 g, 75.2 mmol) in toluene was degassed with bubbling nitrogen. (RS)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (334 mg, 0.54 mmol) and tris(dibenzylideneacetone)dipalladium (0) (492 mg, 0.54 mmol) were added, and the mixture was degassed and stirred at 80 °C for 48 h. The mixture was cooled, poured into water and extracted with ethyl acetate. The combined organic fractions were dried (MgSO₄), filtered through a plug of silica gel, eluting with ethyl acetate, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL), hydrochloric acid (5M, 100 mL) was added and the mixture was stirred at room temperature overnight. The layers were separated and the organic layer was extracted with hydrochloric acid (5M). The combined aqueous extracts were washed with ether, basified with aqueous sodium hydroxide (4N) and extracted with ethyl acetate. The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate-ether (1:1) and ethereal hydrogen chloride (1M, 40 mL) was added. The solid was collected and dried *in vacuo* to give the title compound as a light brown solid (9.5 g, 62%). ¹H NMR (360MHz, D₂O) δ 7.41-7.35 (2H, m), 7.26-7.19 (2H, m), 3.45-3.42 (4H, m), and 3.34-3.32 (4H, m). m/z (ES⁺) 247 (M+1).

DESCRIPTION 201,1-Dimethylethyl 4-[3-(Phenylmethoxy)phenyl]-1-piperazinecarboxylate

Prepared from 1-iodo-3-(phenylmethoxy)benzene and 1,1-dimethylethyl 1-piperazinecarboxylate according to the method of Description 17. m/z (ES⁺) 369 (M+1).

DESCRIPTION 211,1-Dimethylethyl 4-(3-Hydroxyphenyl)-1-piperazinecarboxylate

A slurry of palladium hydroxide on carbon (330 mg) in methanol (10 mL) was added to a solution of 1,1-dimethylethyl
5 4-[3-(phenylmethoxy)phenyl]-1-piperazinecarboxylate (Description 20, 3.25 g, 8.8 mmol) in ethyl acetate/methanol (1:9) and the mixture was shaken under an atmosphere of hydrogen (40 psi) for 48 h. The mixture was filtered through celite and the solvent was evaporated under reduced pressure to give the title compound (2.28 g, 93%). ¹H NMR (360MHz, CDCl₃) δ 1.48 (9H, s), 3.10-3.13
10 (4H, m), 3.54-3.57 (4H, m), 6.34 (1H, dd, *J* 7.9, 2.2 Hz), 6.41 (1H, t, *J* 2.0 Hz), 6.34 (1H, dd, *J* 8.3, 2.2 Hz), and 7.11 (1H, t, *J* 7.9 Hz).

DESCRIPTION 221-(3-Ethoxyphenyl)piperazine

15 Bromoethane (0.7 mL) was added to a mixture of 1,1-dimethylethyl 4-(3-hydroxy phenyl)-1-piperazinecarboxylate (Description 21, 500 mg, 1.8 mmol) and potassium carbonate (495 mg) in acetone (50 mL) and the mixture was heated under reflux for 13 h. The mixture was cooled, water (100 mL) was added and the mixture was extracted with ether (3 x 100 mL).
20 The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/EtOAc (95:5). The residue was dissolved in dichloromethane (14 mL), cooled to 0 °C and trifluoroacetic acid (9 mL) was added. The mixture was stirred at 0 °C for 1 h., then allowed to
25 warm to room temperature and saturated aqueous sodium bicarbonate solution (40 mL) was added. The mixture was extracted with dichloromethane, the combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure to give the title compound as a pale brown solid
(210 mg, 46%). ¹H NMR (250MHz, CDCl₃) δ 1.43 (3H, t, *J* 7.6 Hz), 3.65-3.82
30 (8H, m), 3.98-4.13 (2H, m), 6.84-6.91 (2H, m), and 7.34-7.40 (1H, m).

DESCRIPTION 231-[3-(1-Methylethoxy)phenyl]piperazine

Prepared from 1,1-dimethylethyl

4-(3-hydroxyphenyl)-1-piperazinecarboxylate (Description 21) and

5 2-iodopropane according to the method of Description 22. ¹H NMR (250MHz, CDCl₃) δ 1.34 (6H, d, *J* 6 Hz), 3.63-3.78 (8H, m), 4.51-4.60 (1H, m), 6.78-6.84 (2H, m), and 7.30-7.37 (1H, m).

DESCRIPTION 2410 5-Methyl-1*H*-indole-3-propanoic Acid

Acrylic acid (16.5 mL, 240.6 mmol) was added to a solution of 5-methyl-1*H*-indole (10.5 g, 80.2 mmol) in acetic acid (20 mL) and acetic anhydride (20 mL) and the mixture was stirred at room temperature for 1 week. Aqueous sodium hydroxide (4N, 100 mL) was added and the mixture was
15 washed with ethyl acetate. The aqueous fraction was acidified to pH 1 with hydrochloric acid (5M) and extracted with ethyl acetate. The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure to give the title compound as a brown solid (7 g, 43%). ¹H NMR (360MHz, CDCl₃) δ 7.85 (1H, br s), 7.38 (1H, s), 7.24 (1H, d, *J* 8.3 Hz), 7.02 (1H,
20 dd, *J* 8.3, 2.3 Hz), 6.97 (1H, d, *J* 2.3 Hz), 3.09 (2H, t, *J* 7.6 Hz), 2.76 (2H, t, *J* 7.6 Hz), and 2.46 (3H, s).

DESCRIPTION 251-[3-(1*H*-Indol-3-yl)-1-oxopropyl]-4-(2-methoxyphenyl)piperazine

25 Triethylamine (1.46 mL, 10.5 mmol) was added to a mixture of 1*H*-indole-3-propanoic acid (1.36 g, 7.2 mmol), 1-(2-methoxyphenyl)piperazine hydrochloride (1.5 g, 6.55 mmol) and 1-hydroxybenzotriazole (1.33g, 7.86 mmol) in tetrahydrofuran (20 mL) and the mixture was stirred at room temperature for 10 min. 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride
30 (1.89 g, 9.8 mmol) was added and the mixture was stirred at room temperature for 2 h. The mixture was poured into water and extracted with ethyl acetate.

The combined organic fractions were washed with saturated aqueous sodium carbonate and water, dried (MgSO₄), and the solvent was evaporated under reduced pressure. The residue was triturated with hexane to give the title compound as a colorless solid (2.1 g, 88%). ¹H NMR (360MHz, CDCl₃) δ 8.00 (1H, br s), 7.63 (1H, d, *J* 7.6 Hz), 7.36 (1H, d, *J* 8.0 Hz), 7.10-7.00 (2H, m), 6.94-6.80 (3H, m), 3.85 (3H, s), 3.80 (2H, t, *J* 5.0 Hz), 3.52 (2H, t, *J* 5.0 Hz), 3.14 (2H, m), 2.95 (2H, t, *J* 5.0 Hz), and 2.77 (4H, m). *m/z* (ES⁺) 364 (M+1).

DESCRIPTION 26

10 4-(2-Methoxyphenyl)-1-[3-(5-methyl-1*H*-indol-3-yl)-1-oxopropyl]piperazine

Prepared from 5-methyl-1*H*-indole-3-propanoic acid (Description 24) and 1-(2-methoxyphenyl)piperazine hydrochloride according to the method of Description 25. ¹H NMR (360MHz, CDCl₃) δ 7.89 (1H, br s), 7.40 (1H, s), 7.24 (1H, d, *J* 8.3 Hz), 7.04-7.00 (3H, m), 6.94-6.81 (3H, m), 3.86 (3H, s), 3.81 (2H, t, *J* 5.0 Hz), 3.53 (2H, t, *J* 5.0 Hz), 3.13 (2H, t, *J* 7.6 Hz), 2.96 (2H, t, *J* 5.0 Hz), 2.80 (2H, t, *J* 5.0 Hz), 2.77-2.73 (2H, m), and 2.46 (3H, s).

DESCRIPTION 27

20 1-[3-(2-Bromo-1*H*-indol-3-yl)-1-oxopropyl]-4-(2-methoxyphenyl)piperazine

A solution of bromotrimethylsilane (0.27 mL, 2.62 mmol) in dimethylsulfoxide (5 mL) was added dropwise to a solution of 1-[3-(1*H*-indol-3-yl)-1-oxopropyl]-4-(2-methoxyphenyl)piperazine (Description 25, 0.5 g, 1.38 mmol) in dimethylsulfoxide (10 mL) and the mixture was stirred at room temperature for 2 h. The mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The combined organic fractions were washed with water, dried (MgSO₄), and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/EtOAc (40:60) to give the title compound as a colorless solid (415 mg, 68%). ¹H NMR (360MHz, CDCl₃) δ 8.09 (1H, br s), 7.56 (1H, d, *J* 8.1 Hz), 7.27 (1H, m), 7.19-7.12 (2H, m), 7.01 (1H, dd, *J* 1.6, 7.7 Hz), 6.93-6.85 (2H, m), 6.80 (1H, dd, *J* 1.6, 7.8 Hz), 3.85 (3H, s),

3.79 (2H, t, *J* 5.0 Hz), 3.48 (2H, m), 3.12 (2H, m), 2.90 (2H, t, *J* 5.0 Hz), 2.76 (2H, t, *J* 5.0 Hz), and 2.69 (2H, m). *m/z* (ES⁺) 442, 444 (M+1).

DESCRIPTION 28

5 1-[3-(2-Bromo-5-methyl-1*H*-indol-3-yl)-1-oxopropyl]-4-(2-methoxyphenyl)piperazine

Prepared from 4-(2-methoxyphenyl)-1-[3-(5-methyl-1*H*-indol-3-yl)-1-oxopropyl]piperazine (Description 26) according to the method of Description 27. ¹H NMR (360MHz, CDCl₃) δ 7.96 (1H, br s), 7.34 (1H, s), 7.16 (1H, d, *J* 8.3 Hz), 7.04-6.98 (2H, m), 6.93-6.80 (3H, m), 3.86 (3H, s), 3.80 (2H, t, *J* 5.0 Hz), 10 3.50 (2H, t, *J* 5.0 Hz), 3.08 (2H, m), 2.93 (2H, t, *J* 5.0 Hz), 2.79 (2H, t, *J* 5.0 Hz), 2.67 (2H, m), and 2.38 (3H, s). *m/z* (ES⁺) 456, 458 (M+1).

DESCRIPTION 29

15 [2-Methoxy-5-(trifluoromethoxy)phenyl]boronic Acid

n-Butyllithium (1.6M in hexanes, 3.8 mL, 6 mmol) was added dropwise to a cooled (-78 °C) solution of 2-bromo-1-methoxy-4-(trifluoromethoxy)benzene (Description 16, 1.5 g, 5.5 mmol) in tetrahydrofuran (prefiltered through alumina, 18 mL) [internal temperature < -70 °C]. The mixture was stirred at 20 -78 °C for 15 min., then trimethylborate (2 mL, 17.6 mmol) was added dropwise [internal temperature < -70 °C]. The mixture was stirred at -78 °C for 30 min., then hydrochloric acid (1M, 6 mL) was added. The mixture was warmed to room temperature and stirred for 30 min. Water (25 mL) was added and the mixture was extracted with ethyl acetate (2 x 40 mL). The combined organic fractions 25 were washed with water (20 mL) and brine (20 mL), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was triturated with hexane and the solid was collected and dried *in vacuo* at 40 °C to give the title compound as an off white solid (366 mg, 28%). ¹H NMR (360MHz, CDCl₃) δ 3.93 (3H, s), 5.84 (2H, s), 6.90 (1H, d, *J* 9.0Hz), 7.29 (1H, m) and 7.70 (1H, d, *J* 30 2.6 Hz).

DESCRIPTION 301-{3-[5-Chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}piperazine

Trifluoroacetic acid (20 mL) was added to a stirred, cooled (0 °C) solution of 1,1-dimethylethyl 4-{3-[5-chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}-1-piperazinecarboxylate (Example 80, 600 mg) in dichloromethane (30 mL) and the mixture was stirred at 0 °C for 1 h. The mixture was allowed to warm to room temperature, saturated aqueous sodium bicarbonate solution (80 mL) was added and the mixture was extracted with dichloromethane. The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure to give the title compound as a pale solid (390 mg, 81%). ¹H NMR (360MHz, CD₃OD) δ 2.65-2.69 (4H, m), 2.91-2.95 (2H, m), 3.23-3.28 (2H, m), 3.44-3.47 (2H, m), 3.71-3.75 (2H, m), 7.12 (1H, dd, *J* 8.7, 2.1 Hz), 7.35 (1H, d, *J* 7.9 Hz), and 7.46-7.58 (5H, m). *m/z* (ES⁺) 402, 404 (M+1).

15

DESCRIPTION 311-{3-[5-Chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indol-3-yl]-1-oxopropyl}piperazine

Prepared from 1,1-dimethylethyl 4-{3-[5-chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indol-3-yl]-1-oxopropyl}-1-piperazinecarboxylate (Example 95) according to the method of Description 30. ¹H NMR (360MHz, CDCl₃) δ 2.47-2.52 (2H, m), 2.65-2.68 (2H, m), 2.83-2.85 (2H, m), 2.97-3.01 (2H, m), 3.26-3.30 (2H, m), 3.39 (1H, br s), 3.55 (3H, s), 3.59-3.62 (2H, m), 7.19-7.32 (4H, m), 7.49 (2H, d, *J* 8.3Hz), and 7.57 (1H, s). *m/z* (ES⁺) 416, 418 (M+1).

25

DESCRIPTION 32(*S*)-*N*-(2-{*N*-[(1,1-Dimethylethoxy)carbonyl]methylamino}-1-oxo-3-phenylpropyl)glycine methyl ester

N-[(1,1-Dimethylethoxy)carbonyl]-*N*-methyl-*L*-phenylalanine dicyclohexylamine salt (3.0 g, 6.5 mmol) was partitioned between dichloromethane (100 mL) and aqueous hydrochloric acid (0.1M, 100 mL). The layers were separated and the organic fraction was washed with aqueous

30

hydrochloric acid (0.1M, 100 mL), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (30 mL), cooled to 0 °C and N-methylmorpholine (0.72 mL, 0.66 g, 6.5 mmol) then isobutyl chloroformate (0.84 mL, 0.89 g, 6.5 mmol) were added. The mixture was stirred at 0 °C for 10 min., then N-methylmorpholine (0.72 mL, 0.66 g, 6.5 mmol) and glycine methyl ester hydrochloride (0.82 g, 6.5 mmol) were added. The mixture was stirred at 0 °C for 1 h., then at room temperature for 2 h. Water (100 mL) was added and the mixture was extracted with ethyl acetate (100 mL). The organic fraction was dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/EtOAc (50:50), to give the title compound as a colorless gum (2.28 g, 100%). ¹H NMR (250MHz, CDCl₃) mixture of two amide rotamers; δ 7.28-7.23 (5H, m), 6.66, 6.40 (total 1H, each br s), 5.01, 4.80 (total 1H, each m), 4.24-3.82 (2H, m), 3.75 (3H, s), 3.39 (1H, m), 2.94 (1H, m), 2.81, 2.76 (total 3H, each s), and 1.37, 1.27 (total 9H, each s). m/z (ES⁺) 351 (M+1).

DESCRIPTION 33

(S)-N-[2-(Methylamino)-1-oxo-3-phenylpropyl]glycine methyl ester

Trifluoroacetic acid (5 mL) was added to a solution of (S)-N-(2-{N-[(1,1-dimethylethoxy)carbonyl]methylamino}-1-oxo-3-phenylpropyl)glycine methyl ester (Description 32, 2.28 g, 6.5 mmol) in dichloromethane (50 mL) and the mixture was stirred at room temperature for 3.5 h. The solvent was evaporated under reduced pressure, then toluene was added and evaporated under reduced pressure. Aqueous sodium carbonate (10%, 100 mL) was added and the mixture was extracted with dichloromethane (2 x 100 mL). The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH₂Cl₂/MeOH (95:5), to give the title compound as a colorless oil (1.59 g, 98%). ¹H NMR (250MHz, CDCl₃) δ 7.71 (1H, br s), 7.61-7.21 (5H, m), 4.15 (1H, dd, *J* 18.3, 6.1 Hz), 4.02 (1H, dd, *J* 18.3, 5.5 Hz), 3.76 (3H, s), 3.25

(2H, m), 2.69 (1H, dd, J 14.7, 10.9 Hz), 2.31 (3H, s), and 1.30 (1H, br s). m/z (ES⁺) 251 (M+1).

DESCRIPTION 34

5 (6S)-1-Methyl-6-(phenylmethyl)-2,5-piperazinedione

A solution of (S)-N-[2-(methylamino)-1-oxo-3-phenylpropyl]glycine methyl ester (Description 33, 1.59 g, 6.4 mmol) in toluene (15 mL) was heated at 170 °C in a sealed tube for 42 h. The mixture was cooled, the solvent was evaporated under reduced pressure and the residue was purified by flash
10 column chromatography on silica gel, eluting with CH₂Cl₂/MeOH/NH₃(aq.) (95:5:1), to give the title compound as a colorless solid (1.19 g, 86%). ¹H NMR (360MHz, CDCl₃) δ 7.31 (3H, m), 7.14 (2H, m), 5.93 (1H, br s), 4.16 (1H, m), 3.44 (1H, dd, J 17.0, 3.6 Hz), 3.27 (1H, dd, J 13.9, 3.7 Hz), 3.16 (1H, dd, J 13.9, 4.6 Hz), 3.06 (3H, s), and 2.48 (1H, d, J 17.0 Hz). m/z (ES⁺) 218 (M+1).

15

DESCRIPTION 35

(2S)-1-Methyl-2-(phenylmethyl)piperazine

Lithium aluminium hydride (1.0M in ether, 20.2 mL, 20.2 mmol) was added to a stirred, cooled (0 °C) suspension of (6S)-1-methyl-6-(phenylmethyl)-2,5-
20 piperazinedione (Description 34, 1.1 g, 5.0 mmol) in THF (60 mL) and the mixture was heated under reflux for 1 h. The mixture was cooled to -20 °C and saturated aqueous sodium sulfate (20.2 mL) was added. The mixture was stirred at room temperature for 15 min., filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column
25 chromatography on silica gel, eluting with CH₂Cl₂/MeOH/NH₃(aq.) (90:10:1), to give the title compound as a yellow oil (0.83 g, 87%). ¹H NMR (250MHz, CDCl₃) δ 7.31-7.15 (5H, m), 3.17 (1H, dd, J 13.3, 3.9 Hz), 2.92-2.70 (4H, m), 2.46 (2H, m), 2.43 (3H, s), 2.27 (2H, m) and 1.51 (1H, br s). m/z (ES⁺) 191 (M+1).

EXAMPLE 11-[3-[2-(4-Bromophenyl)-5-methyl-1*H*-indol-3-yl]-1-oxopropyl]-4-(2-methoxyphenyl)piperazine

4-Bromo- δ -oxobenzenepentanoic acid (*J. Org. Chem.* **1948**, *13*, 284; *J. Org. Chem.* **1984**, *49*, 3170; 6.2 g, 23 mmol) was added to a solution of 1,3-diisopropylcarbodiimide (1.8 mL, 11.5 mmol) in tetrahydrofuran-dichloromethane (1:1, 40 mL) and the mixture was allowed to stand at room temperature for 20 min. The mixture was added to 4-sulfamylbenzoyl AM resin (Novabiochem, product no. 01-64-0121, 1.15 mmol/g loading; 2 g) in a 70 mL solid phase extraction cartridge equipped with a frit and stopcock. 4-Dimethylaminopyridine (138 mg, 1.1 mmol) was added and the mixture was allowed to stand overnight at room temperature. The resin was washed with tetrahydrofuran-dichloromethane (1:1, 3 x), dimethylformamide (3 x), dichloromethane (3 x) and acetic acid (3 x). A solution of (4-methylphenyl)hydrazine hydrochloride (3.2 g, 20 mmol) and zinc chloride (2.7 g, 20 mmol) in glacial acetic acid (40 mL) was added and the mixture was heated to 70 °C for 1 h. The mixture was vented, mixed manually and heated overnight at 70 °C. The mixture was cooled and the resin was washed with acetic acid (3 x), tetrahydrofuran-dichloromethane (1:1, 3 x), dimethylformamide (3 x) and tetrahydrofuran-dichloromethane (1:1, 4 x). A solution of pentafluorobenzyl alcohol (2.3 g, 11.5 mmol), triphenylphosphine (3 g, 11.5 mmol) and diisopropyl azodicarboxylate (2.3 mL, 11.5 mmol) in tetrahydrofuran-dichloromethane (1:1, 40 mL) was added and the mixture was stirred at room temperature for 3 h. The resin was washed with tetrahydrofuran-dichloromethane (1:1, 4 x), dimethylformamide (4 x), tetrahydrofuran-dichloromethane (1:1, 4 x), dichloromethane (4 x) and ether (2 x), then dried under a stream of nitrogen and transferred from the cartridge to a round bottom flask. A solution of 1-(2-methoxyphenyl)piperazine (884 mg, 4.6 mmol) in tetrahydrofuran (40 mL) was added and the mixture was left to stand at room temperature for 24 h. Scavenger resin (description 1, 2.4 g) and sufficient tetrahydrofuran to cover the additional swollen resin were added and

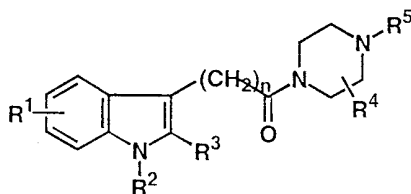
the mixture was left to stand at room temperature for 24 h. The mixture was filtered and the resin washed with tetrahydrofuran. The combined filtrates were evaporated under reduced pressure and the residue was purified by

5 hexane-ethyl acetate (1:1) to give the title compound (494 mg, 40%). ¹H NMR (360MHz, CDCl₃) δ 8.00 (1H, br s), 7.59-7.57 (2H, m), 7.45-7.32 (3H, m), 7.27-7.25 (1H, m), 7.06-7.00 (2H, m), 6.93-6.80 (3H, m), 3.85 (3H, s), 3.77 (2H, t, *J* 5.0 Hz), 3.43 (2H, t, *J* 5.0 Hz), 3.26 (2H, m), 2.93 (2H, t, *J* 5.0 Hz), 2.76 (2H, t, *J* 5.0 Hz), and 2.69 (2H, m). *m/z* (ES⁺) 532, 534 (M+1).

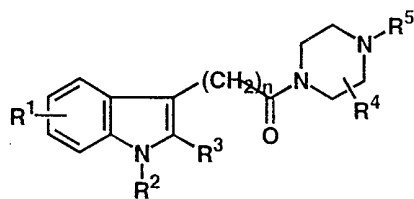
10

The following compounds were prepared according to the method of Example 1, substituting an appropriate keto acid for 4-bromo-δ-oxobenzenepentanoic acid and an appropriate hydrazine for (4-methylphenyl)hydrazine hydrochloride

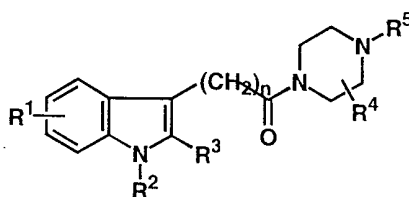
15

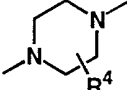
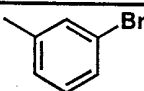
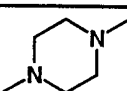
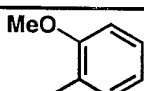
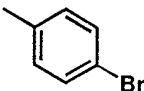
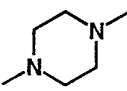
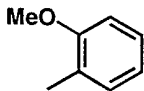
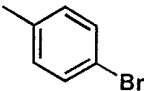
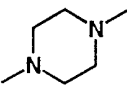
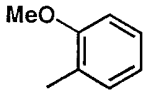
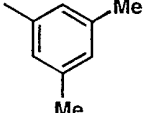
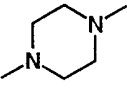
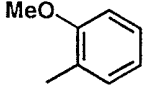


Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	<i>m/z</i> (ES ⁺) (M+1).
2	5-Methyl	H		2			C ₂₉ H ₃₁ N ₃ O ₂	453	454
3	5-Methyl	H		3			C ₃₀ H ₃₃ N ₃ O ₂	467	468
4	5-Methyl	H		4			C ₃₁ H ₃₅ N ₃ O ₂	481	482
5	5-Methyl	H		2			C ₃₃ H ₃₃ N ₃ O ₂	503	504



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES ⁺) (M+1).
6	5-Methyl	H		3			C ₃₄ H ₃₅ N ₃ O ₂	517	518
7	5-Methyl	H		4			C ₃₅ H ₃₇ N ₃ O ₂	531	532
8	5-Methyl	H		3			C ₃₀ H ₃₂ BrN ₃ O ₂	545 547	546 548
9	5-Methyl	H		4			C ₃₁ H ₃₄ BrN ₃ O ₂	559 561	560 562
10	5-Methyl	H		3			C ₃₀ H ₃₂ BrN ₃ O ₂	545 547	546 548
11	5-Methyl	H		4			C ₃₁ H ₃₄ BrN ₃ O ₂	559 561	560 562
12	5-Methyl	H		2			C ₃₁ H ₃₅ N ₃ O ₂	481	482
13	H	Me		2			C ₂₉ H ₃₁ N ₃ O ₂	453	454
14	H	Me		2			C ₃₃ H ₃₃ N ₃ O ₂	503	504
15	H	Me		3			C ₃₄ H ₃₅ N ₃ O ₂	517	518



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES ⁺) (M+1).
16	H	 Me		2			C ₂₉ H ₃₀ BrN ₃ O ₂	531	532
								533	534
17	H	 Me		2			C ₂₉ H ₃₀ BrN ₃ O ₂	531	532
								533	534
18	H	 Me		3			C ₃₀ H ₃₂ BrN ₃ O ₂	545	546
								547	548
19	H	 Me		2			C ₃₁ H ₃₅ N ₃ O ₂	481	482

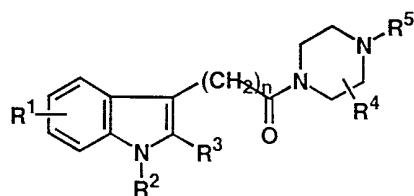
EXAMPLE 20

1-{3-[2-(4-Bromophenyl)-5-methyl-1H-indol-3-yl]-1-oxopropyl}-4-(3,5-dimethoxyphenyl)piperazine

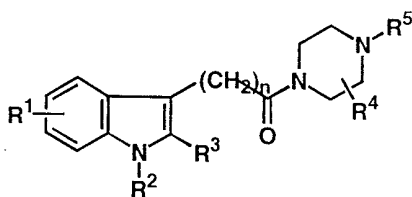
- 5 Diisopropylethylamine (32 mg) and bromoacetonitrile (145 mg) were added to the resin of Description 2 (50 mg) in N-methylpyrrolidinone (1.2 mL) and the mixture was allowed to stand at room temperature for 24 h. The mixture was filtered and the resin was washed with N-methylpyrrolidinone (5 mL) and tetrahydrofuran (5 mL). A solution of
- 10 1-(3,5-dimethoxyphenyl)piperazine (5.2 mg) in tetrahydrofuran (1.6 mL) was added and the mixture was allowed to stand at room temperature for 24 h. The mixture was filtered, washing with tetrahydrofuran (0.5 mL) and the filtrate was collected. The solvent was evaporated under reduced pressure and the residue was dried *in vacuo* to give the title compound (6.8 mg). ¹H NMR
- 15 (360MHz, DMSO-d₆) δ 1.88-1.94 (2H, m), 2.17-2.21 (3H, m), 2.40 (3H, s), 2.68 (1H, m), 2.90 (2H, m), 3.01 (2H, m), 3.06-3.10 (2H, m), 3.70 (6H, s), 5.98 (1H, s),

6.03 (2H, s), 6.95 (1H, d, *J* 10 Hz), 7.25 (1H, d, *J* 10 Hz), 7.35 (1H, s), 7.58 (2H, d, *J* 10 Hz), and 7.70 (2H, d, *J* 10 Hz). *m/z* (ES⁺) 562, 564 (M+1).

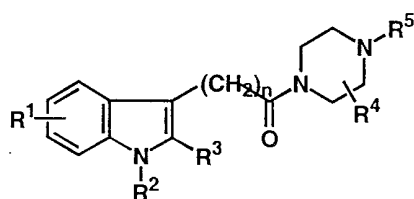
The following compounds were prepared according to the methods of Description 2 and Example 20, substituting an appropriate keto acid for 4-bromo- δ -oxobenzene-pentanoic acid, an appropriate hydrazine for (4-methylphenyl)hydrazine hydrochloride and an appropriate amine for 1-(3,5-dimethoxyphenyl)piperazine.



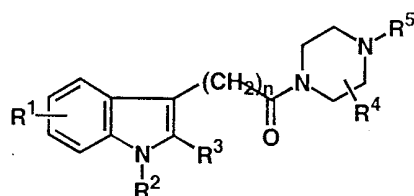
Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	<i>m/z</i> (ES ⁺) (M+1).
21	5-Methyl	H		2			C ₃₀ H ₃₂ BrN ₃ O	529	530
								531	532
22	5-Methyl	H		2			C ₂₉ H ₂₈ BrN ₃ O ₃	545	546
								547	548
23	5-Methyl	H		2	(±)		C ₃₀ H ₃₀ BrN ₃ O	527	528
								529	530
24	5-Methyl	H		2			C ₂₈ H ₂₆ BrF ₃ N ₄ O	570	571
								572	573
25	5-Methyl	H		2			C ₂₈ H ₂₇ BrFN ₃ O	519	520
								521	522
26	5-Methyl	H		2	(±)		C ₃₀ H ₃₂ BrN ₃ O	529	530
								531	532



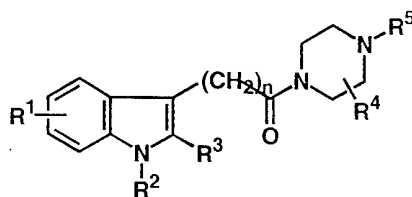
Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES ⁺) (M+1).
27	5-Methyl	H		2			C ₂₈ H ₂₆ BrF ₃ N ₄ O	570 572	571 573
28	5-Methyl	H		2			C ₃₅ H ₃₃ BrClN ₃ O	625 627	626 628
29	5-Methyl	H		2			C ₃₀ H ₃₂ BrN ₃ O	529 531	530 532
30	5-Methyl	H		2			C ₃₀ H ₃₂ BrN ₃ O ₂	545 547	546 548
31	5-Methyl	H		2			C ₂₈ H ₂₇ BrClN ₃ O	535 537	536 538
32	5-Methyl	H		2			C ₃₀ H ₃₂ BrN ₃ O	529 531	530 532
33	5-Methyl	H		2			C ₃₅ H ₃₂ BrF ₂ N ₃ O	627 629	628 630
34	5-Methyl	H		2			C ₂₉ H ₂₉ BrClN ₃ O	549 551	550 552
35	5-Methyl	H		2			C ₂₈ H ₃₄ BrN ₃ O	507 509	508 510
36	5-Methyl	H		2			C ₃₀ H ₃₂ BrN ₃ O	529 531	530 532



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES ⁺) (M+1).
37	5-Methyl	H		2			C ₃₀ H ₃₂ BrN ₃ O ₃	561 563	562 564
38	5-Methyl	H		2			C ₃₀ H ₃₂ BrN ₃ O	529 531	530 532
39	5-Methyl	H		2			C ₂₉ H ₃₀ BrN ₃ O	515 517	516 518
40	5-Methyl	H		2			C ₃₀ H ₃₂ BrN ₃ O	529 531	530 532
41	5-Methyl	H		2			C ₂₉ H ₃₀ BrN ₃ OS	547 549	548 550
42	5-Methyl	H		2			C ₂₈ H ₂₇ BrClN ₃ O	535 537	536 538
43	5-Methyl	H		2			C ₂₅ H ₂₈ BrN ₃ O	465 467	466 468
44	5-Methyl	H		2			C ₃₀ H ₃₇ BrN ₄ O	548 550	549 551
45	5-Methyl	H		2			C ₂₈ H ₂₇ BrN ₄ O ₃	546 548	547 549
46	5-Methyl	H		2			C ₃₁ H ₃₃ BrN ₄ O ₂	572 574	573 575



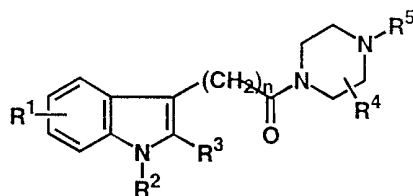
Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES ⁺) (M+1).
47	5-Methyl	 H		2			C ₃₁ H ₃₄ BrN ₃ O ₂	559	560
								561	562
48	5-Methyl	 H		2			C ₃₀ H ₃₈ BrN ₃ O	535	536
								537	538
49	5-Methyl	 H		2			C ₃₀ H ₃₂ BrN ₃ O ₃	561	562
								563	564
50	5-Methyl	 H		2			C ₃₀ H ₃₂ BrN ₃ O ₂	545	546
								547	548
51	5-Methyl	 H		2			C ₂₉ H ₃₀ BrN ₃ O	515	516
								517	518
52	5-Methyl	 H		2			C ₂₉ H ₃₀ BrN ₃ O	515	516
								517	518
53	5-Methyl	 H		2			C ₂₉ H ₂₇ BrN ₄ O	526	527
								528	529
54	5-Methyl	 H		2	(±)		C ₂₉ H ₂₉ BrClN ₃ O	549	550
								551	552
55 ¹	4-Chloro 6-Chloro	 H		2			C ₂₈ H ₂₇ Cl ₂ N ₃ O ₂	507	508
								509	510
56 ¹	4,5- Dichloro 5,6- Dichloro	 H		2			C ₂₈ H ₂₆ Cl ₃ N ₃ O ₂	541	542
								543	544



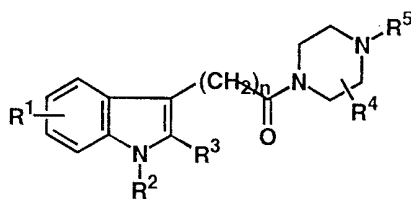
Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES ⁺) (M+1).
57	5,7-Dichloro	H		2			C ₂₈ H ₂₆ Cl ₃ N ₃ O ₂	541	542
								543	544
58	5-Trifluoromethoxy	H		2			C ₂₉ H ₂₇ ClF ₃ N ₃ O ₃	557	558
								559	560

1:1 Mixture of isomers

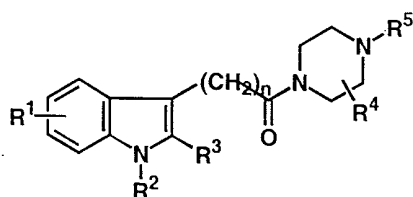
The following compounds were prepared from 5-chloro-2-(4-chlorophenyl)-1*H*-indole-3-propanoic acid (Description 11) or 5-methyl-2-phenyl-1*H*-indole-3-propanoic acid (Description 7) according to the methods of Description 13 and Example 20, substituting an appropriate amine for 1-(3,5-dimethoxyphenyl)piperazine.



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES ⁺) (M+1).
59	5-Methyl	H		2			C ₂₈ H ₂₈ ClN ₃ O	457	458
								459	460
60	5-Methyl	H		2			C ₂₈ H ₂₈ FN ₃ O	441	442



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES ⁺) (M+1).
61	5-Methyl	H		2			C ₂₉ H ₃₁ N ₃ O	437	438
62	5-Methyl	H		2			C ₂₉ H ₃₁ N ₃ O ₂	453	454
63	5-Methyl	H		2			C ₃₀ H ₃₃ N ₃ O	451	452
64	5-Methyl	H		2			C ₃₀ H ₃₃ N ₃ O	451	452
65 ¹	5-Methyl	H		2			C ₃₀ H ₃₃ N ₃ O	451	452
66 ²	5-Methyl	H		2			C ₃₀ H ₃₀ F ₃ N ₃ O ₃	537	538
67	5-Methyl	H		2			C ₂₉ H ₃₁ N ₃ O ₂	453	454
68	5-Methyl	H		2			C ₂₉ H ₃₁ N ₃ O	437	438
69	5-Methyl	H		2			C ₂₈ H ₂₈ ClN ₃ O	457	458
								459	460
70	5-Methyl	H		2			C ₂₉ H ₂₈ F ₃ N ₃ O	491	492



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES ⁺) (M+1).
71	5-Chloro	H		2			C ₂₈ H ₂₇ Cl ₂ N ₃ O	491 493	492 494
72 ¹	5-Chloro	H		2			C ₂₉ H ₂₉ Cl ₂ N ₃ O	505 507	506 508
73	5-Chloro	H		2			C ₂₇ H ₂₃ Cl ₂ F ₂ N ₃ O	513 515	514 516
74	5-Chloro	H		2			C ₂₉ H ₂₇ Cl ₂ N ₃ O ₃	535 537	536 538
75	5-Chloro	H		2			C ₃₀ H ₂₉ Cl ₂ N ₃ O	517 519	518 520
76	5-Chloro	H		2			C ₂₈ H ₂₇ Cl ₂ N ₃ O ₂	507 509	508 510
77 ³	5-Chloro	H		2			C ₂₉ H ₂₉ Cl ₂ N ₃ O ₂	521 523	522 524
78 ⁴	5-Chloro	H		2			C ₃₀ H ₃₁ Cl ₂ N ₃ O ₂	535 537	536 538

¹1-(3,5-Dimethylphenyl)piperazine; *Bull Soc Chim Fr.* **1987**, *1*, 205-211.

²1-[2-Methoxy-4-(trifluoromethoxy)phenyl]piperazine; Description 18

³1-(3-Ethoxyphenyl)piperazine; Description 22.

5 ⁴1-[3-(1-Methylethoxy)phenyl]piperazine; Description 23.

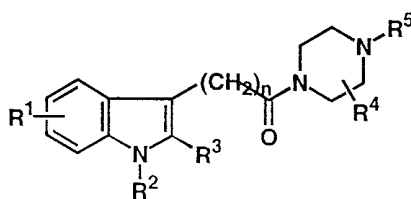
EXAMPLE 791-{3-[5-Chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indol-3-yl]-1-oxopropyl}-4-(phenylmethyl)piperazine

1,1-Carbonyl diimidazole (47 mg, 0.29 mmol) was added to a solution of
5 5-chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indole-3-propanoic acid (Description
12, 100 mg, 0.29 mmol) in tetrahydrofuran (4 mL) and the mixture was heated
under reflux for 2 h. The mixture was cooled and 1-(phenylmethyl)piperazine
(48 mg, 0.27 mmol) was added. The mixture was stirred at room temperature
overnight and the solvent was evaporated under reduced pressure. Water
10 (4 mL) was added and the mixture was stirred at 80 °C for 2 h. The mixture
was cooled, the water was decanted and the residue was dissolved in
dichloromethane. Using a Bond Elut™ cartridge to separate the layers the
solution was washed with hydrochloric acid (1M), and aqueous sodium
hydroxide (2M). The organic fraction was evaporated under reduced pressure to
15 a small volume and filtered through a plug of silica on a Bond Elut™ cartridge,
eluting with hexane/EtOAc (85:15 increasing to 70:30), to give the title
compound as a colorless solid (95 mg, 65%). ¹H NMR (360MHz, CDCl₃) δ
2.10-2.13 (2H, m), 2.25-2.28 (2H, m), 2.40-2.43 (2H, m), 2.89-2.93 (2H, m),
3.13-3.16 (2H, m), 3.78 (2H, s), 3.46 (3H, s), 3.48-3.51 (2H, m), 7.10-7.26 (9H,
20 m), 7.40 (2H, d, *J* 8.3 Hz), and 7.50 (1H, s). *m/z* (ES⁺) 506, 508 (M+1).

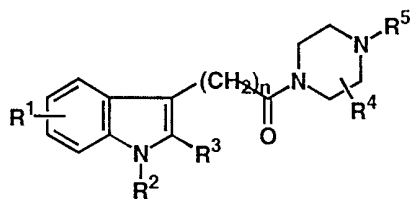
EXAMPLE 801,1-Dimethylethyl 4-{3-[5-Chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}-1-piperazinecarboxylate

25 Prepared from 5-chloro-2-(4-chlorophenyl)-1*H*-indole-3-propanoic acid
(Description 11) and 1,1-dimethylethyl 1-piperazinecarboxylate according to the
method of Example 79. ¹H NMR (360MHz, CDCl₃) δ 1.45 (9H, s), 2.60-2.65 (2H,
m), 3.19-3.24 (6H, m), 3.30-3.33 (2H, m), 3.53-3.57 (2H, m), 7.16 (1H, dd, *J* 8.6,
1.8 Hz), 7.26 (1H, d, *J* 8.6 Hz), 7.43-7.50 (4H, m), 7.56(1H, d, *J* 1.8 Hz), and 8.08
30 (1H, s).

The following compounds were prepared according to the method of Example 79, substituting an appropriate acid for 5-chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indole-3-propanoic acid and an appropriate amine, or amine hydrochloride for 1-(phenylmethyl)piperazine. If an amine hydrochloride was used, triethylamine (1 eq.) was added to the reaction mixture. If the product contained a strongly basic group, the hydrochloric acid wash was omitted.



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES ⁺) (M+1).
81	5-Methyl	 H		1			C ₂₈ H ₂₉ N ₃ O ₂	439	440
82	5-Chloro	 H		2			C ₂₈ H ₂₈ ClN ₃ O ₂	473 475	474 476
83	5-Fluoro	 H		2			C ₂₈ H ₂₈ FN ₃ O ₂	457	458
84 ¹	5,6-Dimethyl	 H		2			C ₃₀ H ₃₃ N ₃ O ₂	467	468
85	5-Chloro	 H		2			C ₂₈ H ₂₇ Cl ₂ N ₃ O ₂	507 509	508 510
86	5-Chloro	 Me		2			C ₃₂ H ₂₉ Cl ₂ N ₃ O	541 543	542 544
87	5-Chloro	 Me		2			C ₂₈ H ₃₃ Cl ₂ N ₃ O	497 499	598 500



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES') (M+1).
88	5-Chloro	 Me		2			C ₂₅ H ₂₉ Cl ₂ N ₃ O	457 459	458 460
89	5-Chloro	 Me		2			C ₂₅ H ₂₉ Cl ₂ N ₃ O	457 459	458 460
90	5-Chloro	 Me		2			C ₃₅ H ₃₁ Cl ₂ N ₃ O	579 581	580 582
91	5-Chloro	 Me		2			C ₃₀ H ₃₁ Cl ₂ N ₃ O	519 521	520 522
92 ²	5-Chloro	 Me		2			C ₂₆ H ₂₉ Cl ₂ N ₃ O	469 471	470 472
93 ³	5-Chloro	 Me		2			C ₂₉ H ₃₅ Cl ₂ N ₃ O	511 513	512 514
94	5-Chloro	 Me		2			C ₃₁ H ₃₂ Cl ₂ N ₄ O ₂	562 564	563 565
95	5-Chloro	 Me		2		CO ₂ ^t Bu	C ₂₇ H ₃₁ Cl ₂ N ₃ O ₃	515 517	516 518
96	5-Chloro	 Me		2		CO ₂ Et	C ₂₆ H ₂₉ Cl ₂ N ₃ O ₃	501 503	502 504

12:1 Mixture of isomers.

²1-(Cyclopropylmethyl)piperazine; *J. Med. Chem.* **1996**, *39*, 2068-2080.

³1-(Cyclohexylmethyl)piperazine; *J. Med. Chem.* **1992**, *35*, 2688-2696.

EXAMPLE 97

1-{3-[5-Chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indol-3-yl]-1-oxopropyl}-4-[2-(trifluoromethoxy)phenyl]piperazine

5 Prepared from 5-chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indole-3-propanoic acid (Description 12) and 1-[2-(trifluoromethoxy)phenyl]piperazine hydrochloride (Description 19) according to the method of Description 25. ¹H NMR (360MHz, CDCl₃) δ 7.60 (1H, d, *J* 1.7 Hz), 7.49 (2H, m), 7.32 (2H, m), 7.24-7.18 (4H, m), 7.04-7.00 (1H, m), 6.93 (1H, dd, *J* 1.3, 8.0 Hz), 3.71 (2H, t, *J* 5.0 Hz), 3.54 (3H, s), 3.37 (2H, t, *J* 5.0 Hz), 3.02 (2H, m), 2.95 (2H, t, *J* 5.0 Hz), 2.80 (2H, t, *J* 5.0 Hz), and 2.54 (2H, m). *m/z* (ES⁺) 576, 578 (M+1).

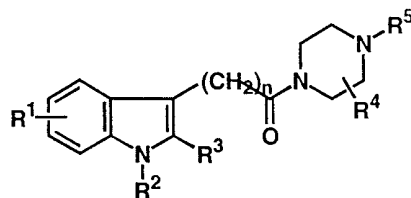
EXAMPLE 98

4-[[3,5-Bis(trifluoromethyl)phenyl]methyl]-1-{3-[5-chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}piperazine

15 1-(Bromomethyl)-3,5-bis(trifluoromethyl)benzene (83 mg) was added to a mixture of 1-{3-[5-chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}piperazine (Description 30, 35 mg) and potassium carbonate (36 mg) in acetone (3 mL) and the mixture was stirred at room temperature for 2 h. 20 Methanol (1 mL) and ethyl acetate (10 mL) were added and the mixture was washed with water. The organic fraction was filtered through a plug of silica in a Bond Elut™ cartridge, eluting with hexane/EtOAc (80:20 increasing to 60:40), to give the title compound as a colorless solid (49 mg, 89%). ¹H NMR (360MHz, CDCl₃) δ 2.16-2.19 (2H, m), 2.33-2.36 (2H, m), 2.59-2.63 (2H, m), 3.15-3.20 (2H, m), 3.28-3.30 (2H, m), 3.53 (2H, s), 3.58-3.61 (2H, m), 7.13 (1H, dd, *J* 8.7, 1.8 Hz), 7.25 (1H, d, *J* 8.3 Hz), 7.36-7.53 (6H, m), 7.77 (2H, s), and 8.51 (1H, s). *m/z* (ES⁺) 628, 630 (M+1).

30 The following compounds were prepared from 1-{3-[5-chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}piperazine (Description 30) or 1-{3-[5-chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indol-3-yl]-

1-oxopropyl}piperazine (Description 31) according to the method of Example 98, substituting an appropriate alkyl bromide or chloride for 1-(bromomethyl)-3,5-bis(trifluoromethyl)benzene.



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES ⁺) (M+1).
99	5-Chloro	H		2			C ₂₉ H ₂₉ Cl ₂ N ₃ O ₂	521	522
								523	524
100	5-Chloro	H		2			C ₂₉ H ₂₉ Cl ₂ N ₃ O ₂	521	522
								523	524
101	5-Chloro	H		2			C ₂₈ H ₂₆ Cl ₃ N ₃ O	525	526
								527	528
102	5-Chloro	H		2			C ₂₈ H ₂₆ Cl ₃ N ₃ O	525	526
								527	528
103	5-Chloro	H		2			C ₂₈ H ₂₆ Cl ₂ FN ₃ O	509	510
								511	
104	5-Chloro	H		2			C ₂₈ H ₂₆ Cl ₂ N ₄ O ₃	536	537
								538	539
105	5-Chloro	H		2			C ₂₈ H ₂₆ Cl ₂ N ₄ O ₃	536	537
								538	539
106	5-Chloro	Me		2			C ₂₇ H ₃₃ Cl ₂ N ₃ O	485	486
								487	488
107 ¹	5-Chloro	Me		2			C ₂₆ H ₂₈ Cl ₂ N ₆ O	510	511
								512	513

¹⁵-Chloromethyl-1-methyl-1,2,4-triazole hydrochloride; EP-170073.

EXAMPLE 108

4-Benzoyl-1-{3-[5-chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}piperazine

5

Benzoyl chloride (0.011 mL) was added to a stirred solution of 1-{3-[5-chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}piperazine (Description 30, 35 mg) in pyridine (0.5 mL) and the mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure, hydrochloric acid (2M, 5 mL) and ethyl acetate (5 mL) were added and the layers were separated. The organic layer was dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was crystallized from dichloromethane/ethyl acetate (4:1) to give the title compound as a colorless solid (25 mg, 58%). ¹H NMR (360MHz, CDCl₃) δ 2.56-2.68 (2H, m), 3.02-3.67 (10H, m), 7.17 (1H, dd, *J* 8.6, 1.8 Hz), 7.28 (1H, d, *J* 8.6 Hz), 7.33-7.50 (9H, m), 7.56 (1H, s), and 8.13 (1H, s). *m/z* (ES⁺) 506, 508 (M+1).

10

15

EXAMPLE 109

Ethyl 4-{3-[5-Chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}piperazine-1-acetate

20

Prepared from 5-chloro-2-(4-chlorophenyl)-1*H*-indole-3-propanoic acid (Description 11) and ethyl 1-piperazinecarboxylate according to the method of Example 79. ¹H NMR (250MHz, CDCl₃) δ 1.26 (3H, t, *J* 7.3 Hz), 2.34 (2H, t, *J* 4.8 Hz), 2.48 (2H, t, *J* 5.3 Hz), 2.62 (2H, t, *J* 7.8 Hz), 3.16 (2H, s), 3.18-3.23 (2H, m), 3.29-3.35 (2H, m), 3.64 (2H, t, *J* 5.0 Hz), 4.17 (2H, dd, *J* 14.0, 7.3 Hz), 7.16 (1H, dd, *J* 8.5, 1.8 Hz), 7.28 (1H, d, *J* 8.8 Hz), 7.42-7.50 (4H, m), 7.56 (1H, d, *J* 1.8 Hz), and 8.13 (1H, s).

25

EXAMPLE 110

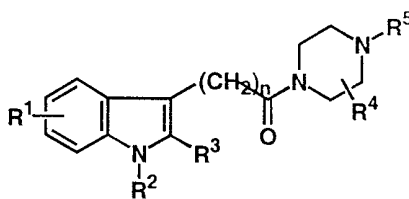
4-{3-[5-Chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}piperazine-1-acetic acid

Potassium hydroxide (320 mg) was added to a solution of ethyl
 5 4-{3-[5-chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}piperazine-1-
 acetate (Example 109, 350 mg, 0.72 mmol) in methanol and the mixture was
 stirred at room temperature overnight. Water was added and the pH was
 adjusted to 7.0 with hydrochloric acid (2M). The mixture was extracted with
 ethyl acetate, the combined organic fractions were dried (MgSO₄) and the
 10 solvent was evaporated under reduced pressure. The residue was crystallised
 from ethyl acetate:methanol (99:1) to give the title compound as a pale solid
 (300 mg, 90%). ¹H NMR (250MHz, CD₃OD) δ 2.20-2.26 (2H, m), 2.92-2.97 (2H,
 m), 3.10-3.25 (4H, m), 3.55-3.60 (2H, m), 3.90-4.01 (4H, m), 7.10 (1H, dd, *J* 8.8,
 2.0 Hz), 7.38 (1H, d, *J* 8.8 Hz), and 7.45-7.60 (5H, m). *m/z* (ES⁺) 460, 462 (M+1).

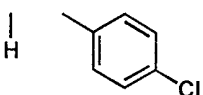
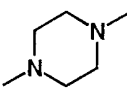
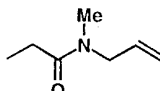
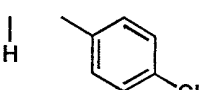
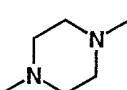
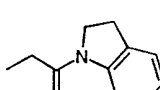
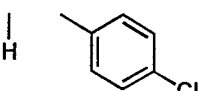
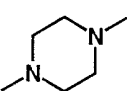
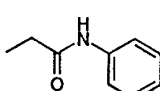
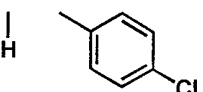
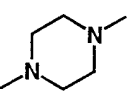
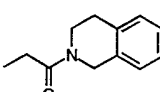
15

The following compounds were prepared from
 4-{3-[5-chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}piperazine-1-acetic
 acid (Example 110) according to the method of Example 79, substituting an
 appropriate amine for 1-(phenylmethyl)piperazine.

20



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	<i>m/z</i> (ES ⁺)
111	5-Chloro	H		2			C ₃₀ H ₃₀ Cl ₂ N ₄ O ₂	548 550	549 551
112	5-Chloro	H		2			C ₃₀ H ₃₀ Cl ₂ N ₄ O ₂	548 550	549 551

113	5-Chloro		2			C27H30Cl2N4O2	512	513
							514	515
114	5-Chloro		2			C31H30Cl2N4O2	560	561
							562	563
115	5-Chloro		2			C29H28Cl2N4O2	534	535
							536	537
116	5-Chloro		2			C32H32Cl2N4O2	574	575
							576	577

EXAMPLE 117

4-(2-Methoxyphenyl)-1-[3-[5-methyl-2-(4-methylphenyl)-1H-indol-3-yl]-1-oxopropyl]piperazine Hydrochloride

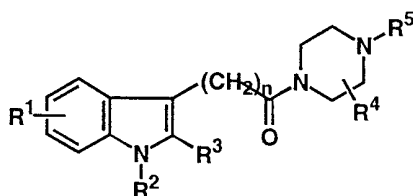
5 Aqueous sodium carbonate (2M, 3 mL) was added to a solution of 1-[3-(2-bromo-5-methyl-1H-indol-3-yl)-1-oxopropyl]-4-(2-methoxyphenyl)piperazine (Description 28, 70 mg, 0.15 mmol) and (4-methylphenyl)boronic acid (42 mg, 0.3 mmol) in DME (10 mL) and the mixture was degassed with bubbling nitrogen. [1,4-Butanediylbis(diphenylphosphine-κP)]

10 dichloropalladium (*Organometallics* **1998**, *17*, 661; 10 mg) was added and the mixture was degassed and stirred at 85 °C for 18 h. The reaction mixture was cooled, poured into water and extracted with ethyl acetate. The combined organic fractions were dried (MgSO₄), the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography

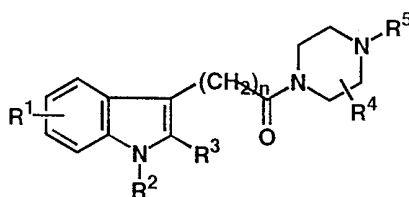
15 on silica gel, eluting with hexane/EtOAc (35:65). The residue was dissolved in ethyl acetate and ethereal hydrogen chloride (1M, 0.5 mL) was added. The solid was collected and dried *in vacuo* to give the title compound as a colorless solid (30 mg, 40%). ¹H NMR (360MHz, DMSO-d₆) δ 10.79 (1H, br s), 7.32 (2H, d, *J* 8.1 Hz), 7.11 (3H, m), 7.03 (1H, d, *J* 8.1 Hz), 6.92-6.85 (3H, m), 6.77-6.70 (2H, m), 3.61 (3H, s), 3.47 (2H, m), 3.33 (2H, m), 2.88 (2H, m), 2.79 (2H, m), 2.70

20 (2H, m), 2.48 (2H, m), 2.19 (3H, s), and 2.16 (3H, s). *m/z* (ES⁺) 468 (M+1).

The following compounds were prepared from
 1-[3-(2-bromo-1*H*-indol-3-yl)-1-oxopropyl]-4-(2-methoxyphenyl)piperazine
 (Description 27) or 1-[3-(2-bromo-5-methyl-1*H*-indol-3-yl)-1-oxopropyl]-4-
 (2-methoxyphenyl)piperazine (Description 28) and an appropriately substituted
 5 phenylboronic acid according to the method of Example 117.



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES ⁺) (M+1).
118	H	H		2			C ₂₈ H ₂₈ CIN ₃ O ₂	473 475	474 476
119	5-Methyl	H		2			C ₂₉ H ₃₀ CIN ₃ O ₂	487 489	488 490
120	5-Methyl	H		2			C ₃₀ H ₃₃ N ₃ O ₃	483	484
121	5-Methyl	H		2			C ₂₉ H ₃₀ CIN ₃ O ₂	487 489	488 490
122	5-Methyl	H		2			C ₃₀ H ₃₃ N ₃ O ₃	483	484
123	5-Methyl	H		2			C ₃₀ H ₃₃ N ₃ O ₃	483	484
124'	5-Methyl	H		2			C ₃₁ H ₃₂ F ₃ N ₃ O ₄	567	568
125	5-Methyl	H		2			C ₃₂ H ₃₇ N ₃ O ₂	495	496



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W.	m/z (ES ⁺) (M+1).
126	5-Methyl	H		2			C ₃₃ H ₃₉ N ₃ O ₂	509	510
127	5-Methyl	H		2			C ₃₁ H ₃₃ N ₃ O ₂	479	480
128	5-Methyl	H		2			C ₃₀ H ₃₀ F ₃ N ₃ O ₂	521	522

¹[2-Methoxy-5-(trifluoromethoxy)phenyl]boronic Acid; Description 29.

EXAMPLE 129

5 4-(2-Methoxyphenyl)-1-{3-[5-methyl-2-(4-phenylphenyl)-1H-indol-3-yl]-1-oxopropyl}piperazine

Prepared from 1-{3-[2-(4-bromophenyl)-5-methyl-1H-indol-3-yl]-1-oxopropyl}-4-(2-methoxyphenyl)piperazine (Example 1) and phenylboronic acid according to the method of Example 117. ¹H NMR (360MHz, CDCl₃) δ 8.05 (1H, br s), 7.71-7.61 (6H, m), 7.48-7.44 (3H, m), 7.39-7.35 (1H, m), 7.29-7.25 (1H, m),
 10 7.06-6.98 (2H, m), 6.90-6.77 (3H, m), 3.82 (3H, s), 3.78 (2H, t, *J* 5.0 Hz), 3.46 (2H, t, *J* 5.0 Hz), 3.33 (2H, m), 2.92 (2H, t, *J* 5.0 Hz), 2.74 (4H, m), and 2.48 (3H, s). m/z (ES⁺) 530 (M+1).

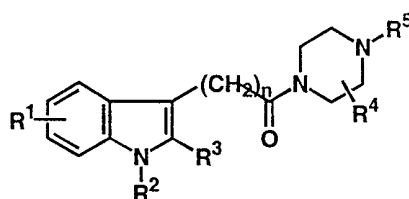
EXAMPLE 130

15 1-{3-[2-(4-Chlorophenyl)-1,5-dimethyl-1H-indol-3-yl]-1-oxopropyl}-4-(2-methoxyphenyl)piperazine

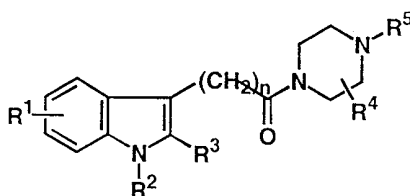
Sodium hydride (60% dispersion in mineral oil, 2.5 mg, 0.062 mmol) was added to a solution of 1-{3-[2-(4-chlorophenyl)-5-methyl-1H-indol-3-yl]-1-

oxopropyl}-4-(2-methoxyphenyl)piperazine (Example 119, 20 mg, 0.041 mmol) in N,N-dimethylformamide (1 mL) and the mixture was stirred at room temperature for 10 min. Iodomethane (5 μ l, 0.12 mmol) was added and the mixture was stirred at room temperature for 10 min. Water (25 mL) was added and the mixture was extracted with ethyl acetate. The combined organic fractions were dried (MgSO₄), the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with hexane/ether (35:65) to give the title compound as a pale yellow foam (20 mg, 97%). ¹H NMR (360MHz, CDCl₃) δ 7.48-7.43 (3H, m), 7.33-7.31 (2H, m), 7.24-7.21 (1H, m), 7.11-7.02 (2H, m), 6.91-6.84 (3H, m), 3.86 (3H, s), 3.76 (2H, m), 3.53 (3H, s), 3.38 (2H, m), 3.04 (2H, m), 2.94 (2H, m), 2.77 (2H, m), 2.57 (2H, m), and 2.49 (3H, s). m/z (ES⁺) 502, 504 (M+1).

The following compounds were prepared according to the method of Example 130, substituting an appropriate 1*H*-indole for 1-{3-[2-(4-chlorophenyl)-5-methyl-1*H*-indol-3-yl]-1-oxopropyl}-4-(2-methoxyphenyl)piperazine and acetyl chloride, 2-bromopropane, benzyl bromide, or (2,2,2-trifluoroethyl)trichloromethanesulfonate for iodomethane.



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W. (ES ⁺)	m/z (M+1)
131 ¹	5-Methyl			2			C ₃₃ H ₃₉ N ₃ O ₂	509	510
132 ²	5-Methyl			2			C ₃₄ H ₄₁ N ₃ O ₂	523	524



Ex.	R ¹	R ²	R ³	n		R ⁵	Formula	M.W. (ES ⁺)	m/z
									(M+1)
133 ³	5-Methyl			2			C ₃₁ H ₃₂ F ₃ N ₃ O ₂	535	536
134 ⁴	5-Methyl			2			C ₃₀ H ₃₂ BrN ₃ O ₂	545	546
								547	548
135 ⁴	5-Methyl			2			C ₃₁ H ₃₂ BrN ₃ O ₃	573	574
								575	576
136 ⁵	5-Chloro			2			C ₃₁ H ₃₃ Cl ₂ N ₃ O ₂	549	550
								551	552
137 ⁵	5-Chloro			2			C ₃₅ H ₃₃ Cl ₂ N ₃ O ₂	597	598
								599	600
138 ⁵	5-Chloro			2			C ₃₀ H ₂₈ Cl ₂ F ₃ N ₃ O ₂	589	590
								591	592
139 ⁵	5-Chloro			2			C ₃₀ H ₂₉ Cl ₂ N ₃ O ₂	533	534
								535	536

¹ 1-(3-[5-Methyl-2-[4-(1-methylethyl)phenyl]-1*H*-indol-3-yl]-1-oxopropyl)-4-(2-methoxyphenyl)piperazine; Example 125.

² 1-(3-[2-[4-(1,1-Dimethylethyl)phenyl]-5-methyl-1*H*-indol-3-yl]-1-oxopropyl)-4-(2-methoxyphenyl)piperazine; Example 126.

5 ³ 1-(3-[5-Methyl-2-[4-(trifluoromethyl)phenyl]-1*H*-indol-3-yl]-1-oxopropyl)-4-(2-methoxyphenyl)piperazine; Example 128.

⁴ 1-[3-[2-(4-Bromophenyl)-5-methyl-1*H*-indol-3-yl]-1-oxopropyl]-4-(2-methoxyphenyl)piperazine; Example 1.

⁵ 1-{3-[5-Chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}-4-(2-methoxyphenyl)piperazine; Example 85.

EXAMPLE 140

5 Methyl 5-Chloro-2-(4-chlorophenyl)-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]-3-oxoprop-1-yl}-1*H*-indole-1-acetate and 5-Chloro-2-(4-chlorophenyl)-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]-3-oxoprop-1-yl}-1*H*-indole-1-acetic acid
Hydrochloride

Sodium hydride (60% dispersion in mineral oil, 35 mg) was added to a
10 solution of 1-{3-[5-chloro-2-(4-chlorophenyl)-1*H*-indol-3-yl]-1-oxopropyl}-4-(2-methoxyphenyl)piperazine (Example 85, 149 mg) in *N,N*-dimethylformamide (3 mL) and the mixture was stirred at room temperature for 5 min. Methyl bromoacetate (58 mg) was added and the mixture was stirred at room
15 temperature for 5 min. Water (25 mL) was added and the mixture was extracted with ethyl acetate (25 mL). The organic fraction was washed with water (25 mL) dried (Na_2SO_4), the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with hexane/EtOAc (50:50) then with EtOAc/AcOH (99:1).
The first product to elute was crystallized from hexane/EtOAc and the solid was
20 collected and dried *in vacuo* to give *methyl 5-chloro-2-(4-chlorophenyl)-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]-3-oxoprop-1-yl}-1*H*-indole-1-acetate* (22 mg).
m/z (ES^+) 580, 582 ($\text{M}+1$).

The second product to elute was dissolved in ethanol (2 mL) and ethereal
hydrogen chloride (1M, 100 μl) was added. The solvent was evaporated under
25 reduced pressure and the residue was crystallized from hexane/EtOAc. The solid was collected and dried *in vacuo* to give *5-chloro-2-(4-chlorophenyl)-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]-3-oxoprop-1-yl}-1*H*-indole-1-acetic acid hydrochloride* (34 mg). *m/z* (ES^+) 566, 568 ($\text{M}+1$).

EXAMPLE 1415-Chloro-2-(4-chlorophenyl)-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]-3-oxoprop-1-yl}-1H-indole-1-ethanol

Lithium borohydride (5 mg) was added in one portion to a solution of methyl 5-chloro-2-(4-chlorophenyl)-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]-3-oxoprop-1-yl}-1H-indole-1-acetate (Example 140, 43 mg) in THF (2 mL) and toluene (1 mL) and the mixture was stirred at room temperature for 15min., then at 60 °C for 45 min. The mixture was cooled, hydrochloric acid (1M, 2 mL) was added and the mixture was stirred at room temperature for 10 min.

Potassium carbonate and ethyl acetate (30 mL) were added and the layers were separated. The organic phase was dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was recrystallised from ethyl acetate and the solid was collected and dried *in vacuo* to give the title compound as a colorless solid (21 mg). m/z (ES⁺) 552, 554 (M+1).

15

EXAMPLE 142Phenylmethyl 4-{3-[5-Chloro-2-(4-chlorophenyl)-1-methyl-1H-indol-3-yl]-1-oxopropyl}-3-oxo-1-piperazinecarboxylate

Oxalyl chloride (0.08 mL, 114 mg, 0.9 mmol) was added dropwise to a stirred, cooled (0 °C) solution of 5-chloro-2-(4-chlorophenyl)-1-methyl-1H-indole-3-propanoic acid (Description 12, 330 mg, 0.95 mmol) and DMF (1 drop) in toluene (15 mL) and the mixture was stirred at room temperature for 2 h. to give a solution of 5-chloro-2-(4-chlorophenyl)-1-methyl-1H-indole-3-propanoyl chloride. Sodium hydride (60% dispersion in mineral oil, 19 mg, 0.48 mmol) was added to a solution of phenylmethyl 3-oxo-1-piperazinecarboxylate (*Eur.J.Med.Chem.* **1981**, *16*, 229-232) (111 mg, 0.48 mmol) in DMF (3 mL) and the mixture was stirred at room temperature for 30 min. A portion of the solution of 5-chloro-2-(4-chlorophenyl)-1-methyl-1H-indole-3-propanoyl chloride (7.5 mL) was added dropwise and the mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with ether. The combined organic fractions were dried (MgSO₄) and the solvent was evaporated

30

under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/EtOAc (80:20). The fractions containing product were combined, washed with aqueous sodium hydroxide (4M) and water, dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane and washed with aqueous hydrochloric acid (2M), saturated aqueous sodium carbonate and water, dried (MgSO₄) and the solvent was evaporated under reduced pressure to give the title compound as a colorless oil (14 mg, 5%). δ 7.58 (1H, s), 7.47 (2H, d, J 8.4 Hz), 7.39-7.16 (9H, m), 5.15 (2H, s), 4.22 (2H, s), 3.81 (2H, m), 3.61 (2H, m), 3.53 (3H, s), 3.15 (2H, m), and 3.00 (2H, m). m/z (ES⁺) 564, 566 (M+1).

EXAMPLE 143

4-{3-[5-Chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indol-3-yl]-1-oxopropyl}-1-(phenylmethyl)piperazinone

Oxalyl chloride (0.08 mL, 114 mg, 0.9 mmol) was added dropwise to a stirred, cooled (0 °C) solution of 5-chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indole-3-propanoic acid (Description 12, 330 mg, 0.95 mmol) and DMF (1 drop) in toluene (15 mL) and the mixture was stirred at room temperature for 2 h. to give a solution of 5-chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indole-3-propanoyl chloride. A sample (7.5 mL) was added to a solution of 1-(phenylmethyl)piperazinone (*Tet.Lett.* **1996**, *37*, 7339-7342) (90 mg, 0.48 mmol) and triethylamine (0.1 mL, 73 mg, 0.72 mmol) in THF (5 mL) and the mixture was stirred at room temperature. Water was added and the mixture was extracted with ethyl acetate. The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/EtOAc (80:20) to give the title compound as a colorless foam. ¹H NMR (360MHz, CDCl₃) mixture of two amide rotamers; major isomer, δ 7.57-7.18 (12H, m), 4.38 (2H, s), 3.86 (2H, s), 3.63 (2H, t, J 5.3 Hz), 3.55 (3H, s), 3.08-2.96 (4H, m), and 2.43 (2H, t, J 7.4 Hz); minor isomer, δ 7.57-7.18 (12H, m), 4.57

(2H, s), 4.26 (2H, s), 3.50 (3H, s), 3.37 (2H, t, *J* 5.3 Hz), 3.08-2.96 (4H, m), and 2.48 (2H, t, *J* 7.4 Hz). *m/z* (ES⁺) 520, 522 (M+1).

EXAMPLE 144

5 1-{3-[5-Chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indol-3-yl]-1-thiopropyl}-4-(phenylmethyl)piperazine

2,4-Bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (2.5 mg, 6 μmol) was added to a solution of 1-{3-[5-chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indol-3-yl]-1-oxopropyl}-4-(phenylmethyl)piperazine (Example 79, 10 6.0 mg, 12 μmol) in dioxane (3 mL) and the mixture was heated under reflux for 1 h. The mixture was cooled, water was added and the mixture was extracted with ethyl acetate. The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel, eluting with CH₂Cl₂/MeOH (98:2) to give the title 15 compound (2 mg, 33%). ¹H NMR (360MHz, CDCl₃) δ 7.64 (1H, s), 7.47 (2H, d, *J* 8.3 Hz), 7.32-7.23 (9H, m), 4.27 (2H, m), 3.54 (3H, s), 3.45 (2H, s), 3.38 (2H, m), 3.08 (2H, m), 3.00 (2H, m), 2.45 (2H, m), and 2.11 (2H, m). *m/z* (ES⁺) 522, 524 (M+1).

20

EXAMPLE 145

1-{3-[5-Chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indol-3-yl]-1-oxopropyl}-4-(2,2-dimethylpropyl)piperazine

Sodium triacetoxyborohydride (127 mg, 0.6 mmol) was added to a mixture of 1-{3-[5-chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indol-3-yl]-1-oxopropyl}piperazine (Description 31, 50 mg, 0.12 mmol), 2,2-dimethylpropanal 25 (16 μL, 12 mg, 0.14 mmol) and acetic acid (34 μL, 36 mg, 0.6 mmol) in 1,2-dichloroethane (5 mL) and the mixture was stirred at room temperature for 18 h. Saturated aqueous sodium hydrogen carbonate (20 mL) was added and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined 30 organic fractions were washed with brine (20 mL), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by

column chromatography on silica gel, eluting with hexane/EtOAc (80:20), to give the title compound as a brown foam (37 mg, 63%). ¹H NMR (360MHz, CDCl₃) δ 7.58 (1H, d, *J* 1.8 Hz), 7.47 (2H, d, *J* 6.5 Hz), 7.31 (2H, d, *J* 6.5 Hz), 7.24 (1H, d, *J* 8.6 Hz), 7.22 (1H, dd, *J* 8.6, 1.8 Hz), 3.54 (3H, s), 3.53 (2H, m), 5 3.19 (2H, m), 2.98 (2H, m), 2.48 (2H, m), 2.41 (2H, m), 2.28 (2H, m), 2.01 (2H, s), and 0.85 (9H, s). *m/z* (ES⁺) 486, 488 (M+1).

EXAMPLE 146

10 1-{3-[5-Chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indol-3-yl]-1-oxopropyl}-4-(3,3-dimethylbutyl)piperazine

Prepared from 1-{3-[5-chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indol-3-yl]-1-oxopropyl}piperazine (Description 31) and 3,3-dimethylbutanal according to the method of Example 145. ¹H NMR (360MHz, CDCl₃) δ 7.58 (1H, d, *J* 1.7 Hz), 7.48 (2H, d, *J* 6.5 Hz), 7.31 (2H, d, *J* 6.5 Hz), 7.24 (1H, d, *J* 8.6 Hz), 7.20 (1H, 15 dd, *J* 8.6, 1.7 Hz), 3.58 (2H, m), 3.54 (3H, s), 3.23 (2H, m), 2.98 (2H, m), 2.50 (2H, m), 2.33 (2H, m), 2.28 (2H, m), 2.20 (2H, m), 1.37 (2H, m), and 0.90 (9H, s). *m/z* (ES⁺) 500, 502 (M+1).

EXAMPLE 147

20 (3*S*)-1-{3-[5-Chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indol-3-yl]-1-oxopropyl}-4-methyl-3-(phenylmethyl)piperazine

Prepared from 5-chloro-2-(4-chlorophenyl)-1-methyl-1*H*-indole-3-propanoic acid (Description 12) and (2*S*)-1-methyl-2-(phenylmethyl)piperazine (Description 35) according to the method of Description 25. ¹H NMR (400MHz, 25 CDCl₃) mixture of two amide rotamers; δ 7.56-6.98 (12H, m), 4.09, 3.93 (total 1H, each d, *J* 13.1 Hz), 3.53, 3.47 (total 3H, each s), 3.20-1.98 (12H, m), and 2.39, 2.38 (total 3H, each s). *m/z* (ES⁺) 520, 522 (M+1).

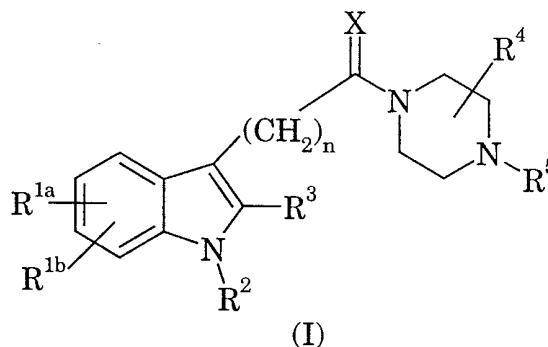
EXAMPLE 148

1-{3-[2-(5-Chloro-4-chlorophenyl)-1-(methylsulfonyl)-1H-indol-3-yl]-1-oxopropyl}-4-(2-methoxyphenyl)piperazine

Sodium hydride (60% dispersion in mineral oil, 13 mg, 0.3 mmol) was added to a solution of 1-{3-[2-(5-chloro-4-chlorophenyl)-1H-indol-3-yl]-1-oxopropyl}-4-(2-methoxyphenyl)piperazine (Example 85, 52 mg, 0.1 mmol) in N,N-dimethylformamide (1 mL) and the mixture was stirred at room temperature for 5 min. Methanesulfonyl chloride (10 μ l, 15 mg, 0.13 mmol) was added and the mixture was stirred at room temperature for 10 min. Further sodium hydride (60% dispersion in mineral oil, 50 mg, 1.2 mmol) and methanesulfonyl chloride (20 μ l, 30 mg, 0.26 mmol) were added and the mixture was stirred at room temperature for 10 min. Saturated aqueous ammonium chloride (10 mL) was added and the mixture was extracted with ethyl acetate. The combined organic fractions were washed with aqueous ammonium chloride (10%, 10 mL) dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/ether (50:50) to give the title compound as a colorless glass (30 mg, 51%). ¹H NMR (360MHz, CDCl₃) δ 8.04 (1H, d, *J* 8.8 Hz), 7.62 (1H, d, *J* 2.1 Hz), 7.45 (2H, d, *J* 8.5 Hz), 7.37 (2H, d, *J* 8.5 Hz), 7.36 (1H, dd, *J* 8.8, 2.1 Hz), 7.03 (1H, t, *J* 7.7 Hz), 6.94-6.85 (3H, m), 3.87 (3H, s), 3.75 (2H, m), 3.38 (2H, m), 2.98-2.86 (6H, m), 2.81 (3H, s), and 2.45 (2H, m). m/z (ES⁺) 586, 588 (M+1).

CLAIMS:

1. A compound of the formula (I):



5

wherein

- R^{1a} and R^{1b} each independently represent hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, fluoro C_{1-6} alkyl, fluoro C_{1-6} alkoxy, halogen, cyano, NR^aR^b , SR^a , SOR^a , SO_2R^a , OSO_2R^a , NR^aCOR^b , COR^a , CO_2R^a or $CONR^aR^b$;
- 10 R^2 represents hydrogen, C_{1-6} alkyl, fluoro C_{1-6} alkyl, $(CH_2)_mCOR^a$, $(CH_2)_pCO_2R^a$, $(CH_2)_pOH$, $(CH_2)_mCONR^aR^b$, $(CH_2)_m$ phenyl or SO_2C_{1-6} alkyl;
- R^3 represents phenyl, biphenyl or naphthyl, wherein said phenyl, biphenyl or naphthyl group may be optionally substituted by one, two or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy,
- 15 fluoro C_{1-6} alkyl, fluoro C_{1-6} alkoxy, NO_2 , cyano, SR^a , SOR^a , SO_2R^a , COR^a , CO_2R^a , $CONR^aR^b$, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{1-4} alkoxy C_{1-4} alkyl;
- R^4 represents hydrogen, C_{1-6} alkyl, carbonyl (=O), $(CH_2)_p$ phenyl or a C_{1-2} alkylene bridge across the piperazine ring;
- R^5 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, C_{2-6} alkenyl,
- 20 phenyl, naphthyl, fluorenyl, heteroaryl, $(CH_2)_p$ phenyl, $(CH_2)_p$ heteroaryl, $CH(phenyl)_2$, $CH(C_{1-6}alkyl)(phenyl)$, C_{2-4} alkenyl(phenyl), $(CH_2)_pNR^cR^d$, $(CH_2)_pCONR^cR^d$, $(CH_2)_mCOR^c$, $(CH_2)_mCO_2R^c$ or $(CH_2)_pOH$;
- R^a and R^b each independently represent hydrogen, C_{1-4} alkyl or fluoro C_{1-4} alkyl;
- 25 R^c and R^d each independently represent hydrogen, C_{1-4} alkyl, fluoro C_{1-4} alkyl, C_{2-4} alkenyl, phenyl or benzyl or R^c and R^d , together with

the nitrogen atom to which they are attached, form a heteroaliphatic ring of 4 to 7 atoms, to which ring there may optionally be fused a benzene ring, and wherein said phenyl, naphthyl, fluorenyl or heteroaryl groups may be optionally substituted by one, two or three groups independently
5 selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy, fluoroC₁₋₆alkyl, fluoroC₁₋₆alkoxy, NO₂, cyano, SR^a, SOR^a, SO₂R^a, COR^a, CO₂R^a, CONR^aR^b, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₄alkoxyC₁₋₄alkyl or -O(CH₂)₁₋₂O-;
X represents an oxygen or a sulfur atom;
m is zero or an integer from 1 to 4;
10 n is an integer from 1 to 4;
p is an integer from 1 to 4;
or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in Claim 1 wherein R^{1a} and R^{1b} each
15 independently represent hydrogen, C₁₋₆alkyl, fluoroC₁₋₆alkoxy or halogen.

3. A compound as claimed in Claim 1 or Claim 2 wherein R²
represents hydrogen, C₁₋₆alkyl, fluoroC₁₋₆alkyl, (CH₂)_mCOR^a, (CH₂)_pCOR^a,
(CH₂)_pOH or (CH₂)_mphenyl.
20

4. A compound as claimed in any one of Claims 1 to 3 wherein
R³ represents phenyl, biphenyl or naphthyl wherein said phenyl group is
optionally substituted by one or two groups selected from halogen,
C₁₋₆alkyl, C₁₋₆alkoxy, trifluoroC₁₋₆alkyl, fluoroC₁₋₆alkoxy or C₂₋₆alkenyl.
25

5. A compound as claimed in any one of Claims 1 to 4 wherein
R⁴ represents hydrogen, methyl, carbonyl, benzyl or a methylene bridge
across the 2,5-positions on the piperazine ring.

6. A compound as claimed in any one of Claims 1 to 5 wherein
30 R⁵ represents C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, C₂₋₆alkenyl,

phenyl, naphthyl, fluorenyl, heteroaryl, $(\text{CH}_2)_p$ phenyl, $(\text{CH}_2)_p$ heteroaryl, $\text{CH}(\text{phenyl})_2$, $\text{CH}(\text{C}_{1-6}\text{alkyl})(\text{phenyl})$, $\text{C}_{2-4}\text{alkenyl}(\text{phenyl})$, $(\text{CH}_2)_p\text{NR}^c\text{R}^d$, $(\text{CH}_2)_p\text{CONR}^c\text{R}^d$, $(\text{CH}_2)_m\text{COR}^c$ or $(\text{CH}_2)_m\text{CO}_2\text{R}^c$ wherein said phenyl or heteroaryl group is optionally substituted by one or two substituents
 5 selected from halogen, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkoxy}$, fluoro $\text{C}_{1-6}\text{alkyl}$, fluoro $\text{C}_{1-6}\text{alkoxy}$, NO_2 , cyano, SR^a or $-\text{O}(\text{CH}_2)_{1-2}\text{O}-$.

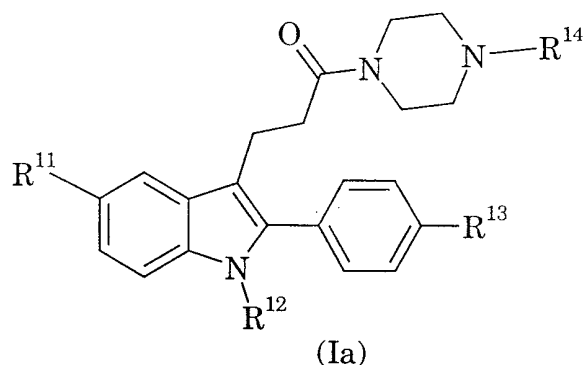
7. A compound as claimed in any one of Claims 1 to 6 wherein X represents an oxygen atom.

10

8. A compound as claimed in any one of Claims 1 to 7 wherein n is 2, 3 or 4.

9. A compound of the formula (Ia)

15



or a pharmaceutically acceptable salt thereof wherein

20 R^{11} represents a chlorine atom or a methyl group;
 R^{12} represents a hydrogen atom or a group selected from $\text{C}_{1-3}\text{alkyl}$, fluoro $\text{C}_{1-3}\text{alkyl}$, COCH_3 , or $(\text{CH}_2)_2\text{OH}$;
 R^{13} represents a halogen atom or a group selected from $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{2-4}\text{alkenyl}$, fluoro $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkoxy}$ or fluoro $\text{C}_{1-4}\text{alkoxy}$; and

R¹⁴ represents a group selected from C₃₋₆alkyl, C₅₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₂alkyl, phenyl, naphthyl, benzyl, α -methylbenzyl, phenylethyl, -CH₂CON(CH₃)phenyl, -CH₂CON(CH₃)benzyl, -CH₂CONR^cR^d (where R^c and R^d, together with the nitrogen atom to which they are
5 attached, form a heteroaliphatic ring of 5 or 6 atoms to which ring there is fused a benzene ring), -CH₂CON(CH₃)C₂₋₄alkenyl, or -(CH₂)_mCO₂R^c (where R^c is hydrogen or C₁₋₄alkyl and m is zero or 1), wherein said phenyl and benzyl groups may be substituted by a group selected from halogen, C₁₋₃alkyl, C₁₋₃alkoxy, fluoroC₁₋₃alkyl, fluoroC₁₋₃alkoxy, NO₂, cyano, and -S-
10 C₁₋₃alkyl or said phenyl and benzyl groups may be substituted by the group -O-CH₂-O-.

10. A compound as claimed in any preceding claim for use in therapy.

15

11. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 9, together with at least one pharmaceutically acceptable carrier or excipient.

12. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound according to claim 1.

13. A method according to claim 12 for the treatment or prevention of pain or inflammation, migraine, emesis, postherpetic neuralgia, depression or anxiety.

14. The use of a compound as claimed in any one of claims 1 to 9
30 for the manufacture of a medicament for the treatment or prevention of a physiological disorder associated with an excess of tachykinins.

15. The use of a compound as claimed in any one of claims 1 to 9 for the manufacture of a medicament for the treatment or prevention of pain or inflammation, migraine, emesis, postherpetic neuralgia,
5 depression or anxiety.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/00650

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/18 A61K31/40 A61P25/24 C07D405/12 C07D487/08
 C07D401/12 C07D403/12 C07D403/06 //(C07D487/08,209:00,
 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)

IPC 7 C07D A61K A61P

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	GB 2 311 523 A (MERCK & CO., INC.) 1 October 1997 (1997-10-01) claims ---	1, 14
A	EP 0 655 442 A (FUJISAWA PHARMACEUTICAL CO.,LTD.) 31 May 1995 (1995-05-31) page 3, line 1 - line 20; claim 1 -----	1, 14

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

25 May 2000

Date of mailing of the international search report

07/06/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/00650

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2311523 A	01-10-1997	US 5869489 A	09-02-1999
EP 655442 A	31-05-1995	AU 689504 B	02-04-1998
		AU 7911194 A	08-06-1995
		CA 2136712 A	30-05-1995
		CN 1107149 A, B	23-08-1995
		HU 71348 A	28-11-1995
		IL 111730 A	06-12-1998
		JP 7242641 A	19-09-1995
		US 5670505 A	23-09-1997
		US 5883098 A	16-03-1999
		ZA 9409228 A	01-08-1995
		BR 9500539 A	31-10-1995