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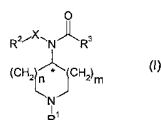
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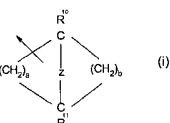
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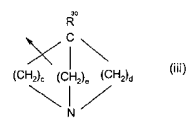
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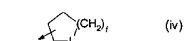
(i)



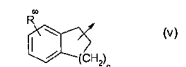
(ii)



(iii)



(iv)



(v)

(57) Abstract: A compound of Formula (I) and pharmaceutically and/or veterinarily acceptable derivatives thereof, wherein: R^1 is H, C_{1-6} alkyl, $-C(A)Y$, C_{3-8} cycloalkyl, aryl, het, aryl- C_{1-4} alkyl or het- C_{1-4} alkyl, wherein the cycloalkyl, aryl or het groups are optionally substituted; A is S or O; Y is H, C_{1-6} alkyl, aryl, het, aryl- C_{1-4} alkyl or het- C_{1-4} alkyl; aryl is independently selected from phenyl, naphthyl, anthracyl or phenanthryl; het is independently selected from an aromatic or non-aromatic 4-, 5- or 6- membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to a 5- or 6- membered carbocyclic group or a second 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom; R^2 is aryl¹ or het¹, each optionally substituted; aryl¹ is independently selected from phenyl, naphthyl, anthracyl, phenanthryl, or indanyl; het¹ is an aromatic 5 to 10 membered heterocyclic ring system which contains at least one N, O or S heteroatom, optionally containing an aryl group; R^3 is H, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-6} alkyl, C_{1-8} alkylSC₁₋₈alkyl, het³, or het³- C_{1-4} alkyl, wherein the alkyl, cycloalkyl and het³ groups are each optionally substituted; het³ is a non-aromatic 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to a 5- or 6-membered carbocyclic group or a second 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom; or R^3 is $(CH_2)_aK$, wherein a' is 0, 1 or 2 and K is a group selected from: Formula (i) wherein: Z is O, S, NR¹², $(CH_2)_v$ or a bond; a is 1, 2, 3 or 4; b is 1, 2 or 3; v is 1 or 2; R¹⁰ and R¹¹ are each independently H or C_{1-4} alkyl; R¹² is H, C_{1-6} alkyl, C(O) C_{1-6} alkyl, SO₂- C_{1-6} alkyl; and wherein one or more pairs of hydrogen atoms on adjacent carbon or nitrogen atoms may be replaced by a corresponding number of double bonds, provided the ring system is not aromatic; Formula (ii) a carbocyclic spiro group containing 6 to 12 carbon atoms; Formula (iii) wherein: c is 1, 2, 3 or 4; d is 1, 2 or 3; e is 1 or 2; and R³⁰ is H or C_{1-4} alkyl; and wherein one or more pairs of hydrogen atoms on adjacent carbon atoms may be replaced by a corresponding number of double bonds, provided the ring system is not aromatic; Formula (iv) wherein: f is 0, 1, 2 or 3; L is SO, SO₂ or NR⁴⁰; and R⁴⁰ is H, C_{1-6} alkyl, C(O) C_{1-6} alkyl, SO₂- C_{1-6} alkyl; and wherein one or more pairs of hydrogen atoms on adjacent carbon atoms may be replaced by a corresponding number of double bonds, provided the ring system is not aromatic; Formula (v) wherein: g is 0, 1, 2 or 3; and R⁵⁰ is H, C_{1-8} alkyl, C_{1-8} alkoxy, OH, halo, CF₃, OCHF₂, OCF₃, SCF₃, hydroxy- C_{1-6} alkyl, C_{1-4} alkoxy- C_{1-6} alkyl and C_{1-4} alkyl-S- C_{1-4} alkyl; and Formula (vi) CH(cyclopropane)₂; X is a covalent bond, C_{1-8} alkyl or C_{3-8} cycloalkyl, wherein if X is C_{3-8} cycloalkyl, then R²-X may form a fused aryl-cycloalkyl ring system; and n is 1 or 2, provided that when n is 1, m is 0 or 1 and when n is 2, m is 0, wherein if m is 0, then * represents a chiral centre.

responding number of double bonds, provided the ring system is not aromatic; Formula (v) wherein: g is 0, 1, 2 or 3; and R⁵⁰ is H, C_{1-8} alkyl, C_{1-8} alkoxy, OH, halo, CF₃, OCHF₂, OCF₃, SCF₃, hydroxy- C_{1-6} alkyl, C_{1-4} alkoxy- C_{1-6} alkyl and C_{1-4} alkyl-S- C_{1-4} alkyl; and Formula (vi) CH(cyclopropane)₂; X is a covalent bond, C_{1-8} alkyl or C_{3-8} cycloalkyl, wherein if X is C_{3-8} cycloalkyl, then R²-X may form a fused aryl-cycloalkyl ring system; and n is 1 or 2, provided that when n is 1, m is 0 or 1 and when n is 2, m is 0, wherein if m is 0, then * represents a chiral centre.



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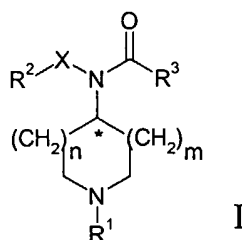
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Novel Compounds

This invention relates to novel amide compounds which inhibit monoamine re-uptake, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

The compounds of the invention exhibit activity as serotonin and/or noradrenaline re-uptake inhibitors and therefore have utility in a variety of therapeutic areas. For example, the compounds of the invention are of use in the treatment of disorders in which the regulation of monoamine transporter function is implicated, more particularly disorders in which inhibition of re-uptake of serotonin or noradrenaline is implicated. Furthermore, the compounds of the invention are of use in disorders in which inhibition of both serotonin and noradrenaline is implicated, such as urinary incontinence. Additionally, the compounds of the invention are of use in disorders in which it may be desired to inhibit preferentially the reuptake of one of noradrenaline or serotonin compared with the other, such as pain, depression, premature ejaculation; ADHD or fibromyalgia.

According to a first aspect, the invention provides a compound of Formula (I)



and pharmaceutically and/or veterinarily acceptable derivatives thereof, wherein:

R¹ is -H, -C₁₋₆alkyl, -C(A)Y, -C₃₋₈cycloalkyl, -aryl, -het, aryl-C₁₋₄alkyl- or het-C₁₋₄alkyl-, wherein the cycloalkyl, aryl or het groups are optionally substituted by at least one substituent independently selected from B;

A is S or O;

Y is -H, -C₁₋₆alkyl, -aryl, -het, aryl-C₁₋₄alkyl- or het-C₁₋₄alkyl-;

aryl is independently selected from phenyl, naphthyl, anthracyl or phenanthryl;

het is independently selected from an aromatic or non-aromatic 4-, 5- or 6- membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to a 5- or 6-membered carbocyclic group or a second 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom;

B represents C₁₋₈alkyl-, C₁₋₈alkoxy-, -OH, -halo, -CF₃, -CHF₂, -OCF₃, -OCHF₂, -SCF₃, hydroxy-C₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₆alkyl- and C₁₋₄alkyl-S-C₁₋₄alkyl-;

R² is aryl¹ or het¹, each optionally substituted by at least one substituent independently selected from D;

aryl¹ is independently selected from phenyl, naphthyl, anthracyl, phenanthryl, or indanyl;

het¹ is an aromatic 5 to 10 membered heterocyclic ring system which contains at least one N, O or S heteroatom, optionally containing an aryl group;

D represents C₁₋₆alkyl-, C₁₋₈alkoxy-, -OH, -halo, -CF₃, -CHF₂, -OCF₃, -OCHF₂, -SCF₃, hydroxy-C₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₆alkyl-, -SC₁₋₈alkyl, C₁₋₄alkyl-S-C₁₋₄alkyl-, -aryl², -het², -Oaryl², -Ohet², -Saryl², -Shet², -CF₂CF₃, -CH₂CF₃, -CF₂CH₃, -OCF₂CHF₂, C₃₋₈cycloalkyl-, C₃₋₆cycloalkyl-C₁₋₄alkyl-, C₃₋₆cycloalkyl-C₁₋₄alkoxy-, C₃₋₆cycloalkyl-O-C₁₋₄alkyl-, C₃₋₆cycloalkyl-C₁₋₄alkoxy-C₁₋₄alkyl-, -OC₃₋₆cycloalkyl, -OC₁₋₈alkyl-C₃₋₈cycloalkyl and -SC₃₋₆cycloalkyl, wherein the aryl² and het² groups are optionally substituted by at least one group selected from E;

aryl² is independently selected from phenyl, naphthyl, anthracyl or phenanthryl;

het² is independently selected from an aromatic or non-aromatic 4-, 5- or 6- membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to a 5- or 6- membered carbocyclic group or a second 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom;

E represents C₁₋₆alkyl-, C₃₋₈cycloalkyl-, C₁₋₆alkoxy-, -OC₃₋₆cycloalkyl, -halo, -CN, -OH, -CF₃, -CHF₂, -OCF₃, -OCHF₂, hydroxyC₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₄alkyl-, -SC₁₋₆alkyl and -SCF₃;

R³ is -H, C₁₋₈alkyl-, C₃₋₈cycloalkyl-, C₃₋₈cycloalkyl-C₁₋₆alkyl-, C₁₋₈alkylSC₁₋₈alkyl-, -het³, or het³-C₁₋₄alkyl-, wherein the alkyl, cycloalkyl and het³ groups are each optionally substituted by at least one substituent independently selected from G;

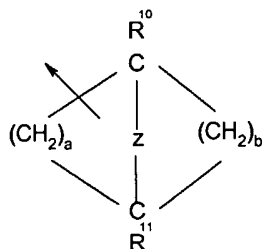
het³ is a non-aromatic 4-, 5- or 6- membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to a 5- or 6- membered carbocyclic group or a second 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom;

G represents C₁₋₈alkyl-, C₁₋₆alkoxy-, -OH, -halo, -CF₃, -OCHF₂, -OCF₃, -SCF₃, -CN, -CF₂CF₃, -CF₂-C₁₋₄alkyl, hydroxy-C₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₆alkyl- and C₁₋₄alkyl-S-C₁₋₄alkyl-; and the alkyl groups being optionally substituted by at least one substituent independently selected from J;

J represents C₁₋₆alkoxy-, -OH, -halo, -CF₃, -OCHF₂, -OCF₃, -SCF₃, -CN, -CF₂CF₃, -CF₂-C₁₋₄alkyl, hydroxy-C₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₆alkyl- and C₁₋₄alkyl-S-C₁₋₄alkyl-;

or R³ is (CH₂)_aK, wherein a' is 0, 1 or 2 and K is a group selected from:

(i)



wherein:

Z is O, S, NR¹², (CH₂)_v or a bond;

a is 1, 2, 3 or 4;

b is 1, 2 or 3;

v is 1 or 2;

R¹⁰ and R¹¹ are each independently -H or C₁₋₄ alkyl-;

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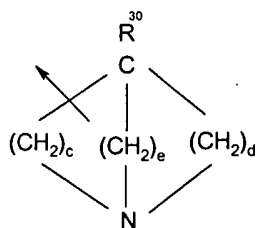
R^{12} is -H, C_{1-6} alkyl-, $-C(O)C_{1-6}$ alkyl-, $-SO_2-C_{1-6}$ alkyl;

and wherein one or more pairs of hydrogen atoms on adjacent carbon or nitrogen atoms may be replaced by a corresponding number of double bonds, provided the ring system is not aromatic;

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(ii) a carbocyclic spiro group containing 6 to 12 carbon atoms;

(iii)



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wherein:

c is 1, 2, 3 or 4;

d is 1, 2 or 3;

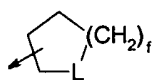
e is 1 or 2; and

R^{30} is -H or C_{1-4} alkyl-;

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and wherein one or more pairs of hydrogen atoms on adjacent carbon atoms may be replaced by a corresponding number of double bonds, provided the ring system is not aromatic;

(iv)



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wherein:

f is 0, 1, 2 or 3;

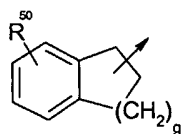
L is SO, SO_2 or NR^{40} ; and

R^{40} is -H, C_{1-6} alkyl-, $-C(O)C_{1-6}$ alkyl-, $-SO_2-C_{1-6}$ alkyl;

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and wherein one or more pairs of hydrogen atoms on adjacent carbon atoms may be replaced by a corresponding number of double bonds, provided the ring system is not aromatic;

(v)



30

wherein:

g is 0, 1, 2 or 3; and

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R^{50} is -H, C_{1-8} alkyl-, C_{1-8} alkoxy-, -OH, -halo, -CF₃, -OCHF₂, -OCF₃, -SCF₃, hydroxy- C_{1-6} alkyl-, C_{1-4} alkoxy- C_{1-6} alkyl- and C_{1-4} alkyl-S- C_{1-4} alkyl-; and

(vi) -CH(cyclopropane)₂;

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X is a covalent bond, C_{1-8} alkyl- or C_{3-8} cycloalkyl-, wherein if X is C_{3-8} cycloalkyl, then R^2 -X may form a fused aryl-cycloalkyl ring system; and

n is 1 or 2, provided that:

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when n is 1, m is 0 or 1; and

when n is 2, m is 0;

wherein if m is 0, then * represents a chiral centre.

In an embodiment of the invention, R^1 is -H.

15

In a further embodiment of the invention, m is 0. Where m is 0, * represents the R or S enantiomeric configuration. Thus, in a further embodiment, m is 0; and * represents the S enantiomer. In a yet further embodiment, n is 1 and m is 0 or 1.

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In a yet further embodiment, X represents a covalent bond and C_{1-8} alkyl-; preferably C_{1-8} alkyl represents C_{1-6} alkyl, more preferably C_{1-4} alkyl, more preferably C_{1-2} alkyl, and most preferably represents -CH₂-.

In a further embodiment, aryl¹ represents phenyl, naphthyl, and indanyl.

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In a yet further embodiment, het¹ represents furyl, thienyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzoxazolyl, benzothiazinyl, benzofuranyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, benzothiazolyl, cinnolinyl, phthalzinyl, indolyl and isoindolyl; preferably it represents quinolinyl, isoquinolinyl or pyridinyl; preferably it represents quinolinyl.

30

In a further embodiment R^2 is aryl¹ or het¹, each optionally substituted by between one and three substituents independently selected from D.

In a yet further embodiment D represents -halo, C_{1-8} alkyl-, SC_{1-8} alkyl-, C_{1-8} alkyloxy-, C_{1-4} alkoxy- C_{1-6} alkyl-, -aryl², -Oaryl², -het², C_{3-8} cycloalkyl-, -OC₁₋₈alkyl- C_{3-8} cycloalkyl-, -CF₃, -SCF₃, -OCHF₂, -CHF₂, -OCF₂CHF₂,
 35 and -OCF₃; preferably halo represents fluoro, chloro, and bromo; preferably C_{1-8} alkyl represents C_{1-4} alkyl; preferably C_{1-8} alkyloxy represents methoxy, ethoxy, and propoxy; preferably aryl² represents phenyl; preferably Oaryl² represents OPh; preferably het² represents pyridinyl; preferably SC_{1-8} alkyl represents SMe and SEt; preferably C_{3-8} cycloalkyl represents cyclopropyl, cyclobutyl and cyclopentyl; preferably C_{1-4} alkoxy- C_{1-6} alkyl represents CH₂OMe; and preferably OC₁₋₈alkyl- C_{3-8} cycloalkyl represents OCH₂-
 40 cyclopropyl.

In a further embodiment D represents -halo, C₁₋₈alkyl-, SC₁₋₈alkyl-, C₁₋₈alkyloxy-, C₁₋₄alkoxy-C₁₋₆alkyl-, -aryl², -Oaryl², C₃₋₈cycloalkyl-, -OC₁₋₈alkyl-C₃₋₈cycloalkyl-, -CF₃, -SCF₃, -OCF₂CHF₂, and -OCF₃; preferably halo represents fluoro, chloro, and bromo; preferably C₁₋₈alkyl represents C₁₋₃alkyl; preferably C₁₋₈alkyloxy represents methoxy, ethoxy, and propoxy; preferably aryl² represents phenyl; preferably Oaryl² represents OPh; preferably SC₁₋₈alkyl represents SMe and SEt; preferably C₃₋₈cycloalkyl represents cyclopropyl, cyclobutyl and cyclopentyl; preferably C₁₋₄alkoxy-C₁₋₆alkyl represents CH₂OMe; and preferably OC₁₋₈alkyl-C₃₋₈cycloalkyl represents OCH₂-cyclopropyl.

In a yet further embodiment D represents -halo, C₁₋₈alkyl-, -SC₁₋₈alkyl, C₁₋₈alkyloxy-, -aryl², -Oaryl², C₃₋₈cycloalkyl-, -OC₁₋₈alkyl-C₃₋₈cycloalkyl, -CF₃, -OCF₂CHF₂, and -OCF₃; preferably halo represents fluoro, chloro, and bromo; preferably C₁₋₈alkyl represents C₁₋₃alkyl; preferably C₁₋₈alkyloxy represents methoxy and ethoxy; preferably aryl² represents phenyl; preferably Oaryl² represents OPh; preferably SC₁₋₈alkyl represents SMe and SEt; preferably C₃₋₈cycloalkyl represents cyclopropyl; and preferably OC₁₋₈alkyl-C₃₋₈cycloalkyl represents OCH₂-cyclopropyl.

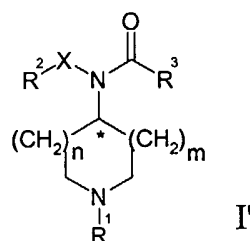
In a further embodiment E represents halo; preferably chloro and fluoro; preferably fluoro.

In a still further embodiment R³ represents C₁₋₈alkyl-, C₃₋₈cycloalkyl-, C₃₋₈cycloalkyl-C₁₋₆alkyl-, and C₁₋₈alkylSC₁₋₈alkyl-; preferably C₁₋₈alkyl represents C₁₋₆alkyl; preferably C₃₋₈cycloalkyl represents C₃₋₆cycloalkyl; preferably C₃₋₈cycloalkyl-C₁₋₆alkyl represents cyclopentylmethyl; and preferably C₁₋₈alkylSC₁₋₈alkyl represents CH₂SMe.

In a yet further embodiment, G represents C₁₋₆alkoxy-, -halo, -OH, and -CF₃; preferably halo represents fluoro; preferably C₁₋₆alkoxy represents methoxy and ethoxy. In a further embodiment, G represents CF₃.

In a further embodiment het³ represents a non-aromatic 6- membered heterocycle which contains at least one N, O or S heteroatom; preferably it represents a non-aromatic 6- membered heterocycle which contains at least one O heteroatom; preferably it represents tetrahydropyranyl.

According to an alternative aspect, the invention provides a compound of Formula (I')



and pharmaceutically and/or veterinarily acceptable derivatives thereof, wherein:

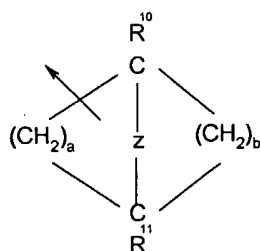
R¹ is -H, C₁₋₆alkyl-, -C(A)Y, C₃₋₈cycloalkyl-, -aryl, -het, aryl-C₁₋₄alkyl- or het-C₁₋₄alkyl-, wherein the cycloalkyl, aryl or het groups are optionally substituted by at least one substituent independently selected from C₁₋₈alkyl-, C₁₋₈alkoxy-, -OH, -halo, -CF₃, -CHF₂, -OCF₃, -OCHF₂, -SCF₃, hydroxy-C₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₆alkyl- and C₁₋₄alkyl-S-C₁₋₄alkyl-;

R^2 is aryl or heteroaryl, each optionally substituted by at least one substituent independently selected from C_{1-8} alkyl-, C_{1-8} alkoxy-, -OH, -halo, -CF₃, -CHF₂, -OCF₃, -OCHF₂, -SCF₃, hydroxy- C_{1-6} alkyl-, C_{1-4} alkoxy- C_{1-6} alkyl-, C_{1-4} alkyl-S- C_{1-4} alkyl-, -aryl¹, -het¹, -Oaryl¹, -Ohet¹, -Saryl¹, -Shet¹, -CF₂CF₃, -CH₂CF₃, -CF₂CH₃, C_{3-8} cycloalkyl-, C_{3-6} cycloalkyl- C_{1-4} alkyl-, C_{3-6} cycloalkyl- C_{1-4} alkoxy-, C_{3-6} cycloalkyl-O- C_{1-4} alkyl-, C_{3-6} cycloalkyl- C_{1-4} alkoxy- C_{1-4} alkyl-, -OC₃₋₆cycloalkyl and -SC₃₋₆cycloalkyl, wherein the aryl¹ and het¹ groups are optionally substituted by at least one group selected from C_{1-6} alkyl-, C_{3-6} cycloalkyl-, C_{1-6} alkoxy-, -OC₃₋₆cycloalkyl, -halo, -CN, -OH, -CF₃, -CHF₂, -OCF₃, -OCHF₂, hydroxy- C_{1-6} alkyl-, C_{1-4} alkoxy- C_{1-4} alkyl-, -SC₁₋₆alkyl and -SCF₃;

R^3 is -H, C_{1-8} alkyl-, C_{3-8} cycloalkyl-, C_{3-8} cycloalkyl- C_{1-6} alkyl-, -heterocycle, or heterocycle- C_{1-4} alkyl-, wherein the cycloalkyl and heterocycle groups are each optionally substituted by at least one substituent independently selected from C_{1-8} alkyl-, C_{1-6} alkoxy-, -OH, -halo, -CF₃, -OCHF₂, -OCF₃, -SCF₃, -CN, -CF₂CF₃, -CF₂- C_{1-4} alkyl, hydroxy- C_{1-6} alkyl-, C_{1-4} alkoxy- C_{1-6} alkyl- and C_{1-4} alkyl-S- C_{1-4} alkyl-; and the alkyl groups are optionally substituted by at least one substituent independently selected from C_{1-6} alkoxy-, -OH, -halo, -CF₃, -OCHF₂, -OCF₃, -SCF₃, -CN, -CF₂CF₃, -CF₂- C_{1-4} alkyl, hydroxy- C_{1-6} alkyl-, C_{1-4} alkoxy- C_{1-6} alkyl- and C_{1-4} alkyl-S- C_{1-4} alkyl-;

or R^3 is $(CH_2)_aE$, wherein a' is 0, 1 or 2 and E is a group selected from:

(i)



wherein:

Z is O, S, NR¹², $(CH_2)_v$, or a bond;

a is 1, 2, 3 or 4;

b is 1, 2 or 3;

v is 1 or 2;

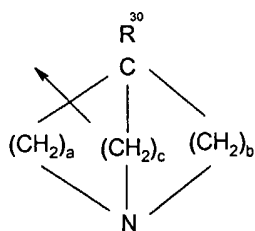
R^{10} and R^{11} are each independently -H or C_{1-4} alkyl-; and

R^{12} is -H, C_{1-6} alkyl-, -C(O) C_{1-6} alkyl, -SO₂- C_{1-6} alkyl;

and wherein one or more pairs of hydrogen atoms on adjacent carbon or nitrogen atoms may be replaced by a corresponding number of double bonds, provided the ring system is not aromatic;

(ii) a carbocyclic spiro group containing 6 to 12 carbon atoms;

(iii)



wherein:

a is 1, 2, 3 or 4;

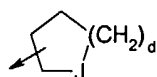
b is 1, 2 or 3;

c is 1 or 2; and

 R^{30} is -H or C_{1-4} alkyl-;

and wherein one or more pairs of hydrogen atoms on adjacent carbon atoms may be replaced by a corresponding number of double bonds, provided the ring system is not aromatic;

(iv)



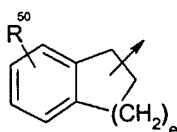
wherein:

d is 0, 1, 2 or 3;

J is SO, SO₂ or NR⁴⁰; and R^{40} is -H, C_{1-6} alkyl-, C(O) C_{1-6} alkyl-, -SO₂- C_{1-6} alkyl-;

and wherein one or more pairs of hydrogen atoms on adjacent carbon atoms may be replaced by a corresponding number of double bonds, provided the ring system is not aromatic;

(v)



wherein:

e is 0, 1, 2 or 3; and

R^{50} is -H, C_{1-8} alkyl-, C_{1-8} alkoxy-, -OH, -halo, -CF₃, -OCHF₂, -OCF₃, -SCF₃, hydroxy- C_{1-6} alkyl-, C_{1-4} alkoxy- C_{1-6} alkyl- and C_{1-4} alkyl-S- C_{1-4} alkyl-; and

(vi) -CH(cyclopropane)₂;

X is a covalent bond, C_{1-8} alkyl- or C_{3-8} cycloalkyl-, wherein if X is C_{3-8} cycloalkyl, then R^2 -X may form a fused aryl-cycloalkyl ring system;

A is S or O;

Y is -H, C₁₋₆alkyl-, -aryl-, -het-, aryl-C₁₋₄alkyl- or het-C₁₋₄alkyl-;

n is 1 or 2, provided that when n is 1, m is 0 or 1 and when n is 2, m is 0, wherein if m is 0, then * represents a chiral centre;

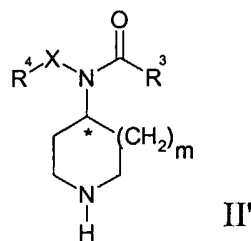
aryl and aryl¹ are each independently selected from phenyl, naphthyl, anthracyl or phenanthryl;

5 heteroaryl is an aromatic 5- or 6- membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to an aryl group;

heterocycle is a non-aromatic 4-, 5- or 6- membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to a 5- or 6- membered carbocyclic group or a second 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom; and

10 het and het¹ are each independently selected from an aromatic or non-aromatic 4-, 5- or 6- membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to a 5- or 6- membered carbocyclic group or a second 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom.

15 In a yet further embodiment of the invention, there is provided a compound of Formula II'



and pharmaceutically and/or veterinarily acceptable derivatives thereof, wherein:

R³ is as defined above in any embodiment;

20 R⁴ is phenyl, naphthyl, or quinoliny, each optionally substituted by at least one substituent independently selected from C₁₋₈alkyl-, C₁₋₈alkoxy-, -OH, -halo, -CF₃, -CHF₂, -OCF₃, -OCHF₂, -SCF₃, hydroxy-C₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₆alkyl-, C₁₋₄alkyl-S-C₁₋₄alkyl-, -aryl¹, -het¹, -Oaryl¹, -Ohet¹, -Saryl¹, -Shet¹, -CF₂CF₃, -CH₂CF₃, -CF₂CH₃, C₃₋₆cycloalkyl-, C₃₋₆cycloalkyl-C₁₋₄alkyl-, C₃₋₆cycloalkyl-C₁₋₄alkoxy-, C₃₋₆cycloalkyl-O-C₁₋₄alkyl-, C₃₋₆cycloalkyl-C₁₋₄alkoxy-C₁₋₄alkyl-, -OC₃₋₆cycloalkyl and -SC₃₋₆cycloalkyl, wherein the aryl¹ and het¹ groups are optionally substituted by at least one group selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkoxy, OC₃₋₆cycloalkyl, halo, CN, OH, CF₃, CHF₂, OCF₃, OCHF₂, hydroxyC₁₋₆alkyl, C₁₋₄alkoxy-C₁₋₄alkyl, SC₁₋₆alkyl and SCF₃;

25 X is a covalent bond, C₁₋₈alkyl- or C₃₋₈cycloalkyl-, wherein if X is C₃₋₈cycloalkyl, then R⁴-X may form a fused aryl-cycloalkyl ring system; and

m is 0 or 1, wherein if m is 0, then * represents the R or S enantiomer.

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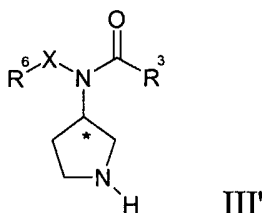
In a further embodiment, R⁴ is phenyl, 1-naphthyl or 2-naphthyl, each optionally substituted by at least one substituent independently selected from C₁₋₈alkyl-, C₁₋₈alkoxy-, -OH, -halo, -CF₃, -CHF₂, -OCF₃, -OCHF₂, -SCF₃, hydroxy-C₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₆alkyl-, C₁₋₄alkyl-S-C₁₋₄alkyl-, -aryl¹, -het¹, -Oaryl¹, -Ohet¹, -Saryl¹, -Shet¹, -CF₂CF₃, -CH₂CF₃, -CF₂CH₃, C₃₋₆cycloalkyl-, C₃₋₆cycloalkyl-C₁₋₄alkyl-, C₃₋₆cycloalkyl-C₁₋₄alkoxy-, C₃₋₆cycloalkyl-O-C₁₋₄alkyl-, C₃₋₆cycloalkyl-C₁₋₄alkoxy-C₁₋₄alkyl-, -OC₃₋₆cycloalkyl and -SC₃₋₆cycloalkyl, wherein the aryl¹ and het¹ groups are optionally substituted by at least one group selected

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from C₁₋₆alkyl-, C₃₋₆cycloalkyl-, C₁₋₆alkoxy-, -OC₃₋₆cycloalkyl-, -halo, -CN, -OH, -CF₃, -CHF₂, -OCF₃, -OCHF₂, hydroxyC₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₄alkyl-, -SC₁₋₆alkyl and -SCF₃. The phenyl or naphthyl groups may be substituted by one, two or three substituents.

- 5 In a yet still further embodiment, m is 0. In this embodiment, * represents the R or S enantiomer. In a further embodiment, m is 0 and * represents the S enantiomer.

In a still further embodiment, there is provided a compound of Formula III'



- 10 and pharmaceutically and/or veterinarily acceptable derivatives thereof, wherein:

R³ is as defined above in any embodiment;

- R⁶ is phenyl, naphthyl or quinoliny, each optionally substituted by at least one substituent independently selected from C₁₋₈alkyl-, C₁₋₈alkoxy-, -OH, -halo, -CF₃, -CHF₂, -OCF₃, -OCHF₂, -SCF₃, hydroxy-C₁₋₆alkyl-,
 15 C₁₋₄alkoxy-C₁₋₆alkyl-, C₁₋₄alkyl-S-C₁₋₄alkyl-, -aryl¹, -het¹, -Oaryl¹, -Ohet¹, -Saryl¹, -Shet¹, -CF₂CF₃, -CH₂CF₃, -CF₂CH₃, C₃₋₆cycloalkyl-, C₃₋₆cycloalkyl-C₁₋₄alkyl-, C₃₋₆cycloalkyl-C₁₋₄alkoxy-, C₃₋₆cycloalkyl-O-C₁₋₄alkyl-, C₃₋₆cycloalkyl-C₁₋₄alkoxy-C₁₋₄alkyl-, -OC₃₋₆cycloalkyl and -SC₃₋₆cycloalkyl, wherein the aryl¹ and het¹ groups are optionally substituted by at least one group selected from C₁₋₆alkyl-, C₃₋₆cycloalkyl-, C₁₋₆alkoxy-, -OC₃₋₆cycloalkyl, -halo, -CN, -OH, -CF₃, -CHF₂, -OCF₃, -OCHF₂, hydroxyC₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₄alkyl-, -SC₁₋₆alkyl and -SCF₃;

- 20 X is a covalent bond, C₁₋₈alkyl- or C₃₋₈cycloalkyl-, wherein if X is C₃₋₈cycloalkyl, then R⁶-X may form a fused aryl-cycloalkyl ring system; and
 * represents the R or S enantiomer.

- 25 In a further embodiment, R⁶ is phenyl, 1-naphthyl or 2-naphthyl, each optionally substituted by at least one substituent independently selected from C₁₋₈alkyl-, C₁₋₈alkoxy-, -OH, -halo, -CF₃, -CHF₂, -OCF₃, -OCHF₂, -SCF₃, hydroxy-C₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₆alkyl-, C₁₋₄alkyl-S-C₁₋₄alkyl-, -aryl¹, -het¹, -Oaryl¹, -Ohet¹, -Saryl¹, -Shet¹, -CF₂CF₃, -CH₂CF₃, -CF₂CH₃, C₃₋₆cycloalkyl-, C₃₋₆cycloalkyl-C₁₋₄alkyl-, C₃₋₆cycloalkyl-C₁₋₄alkoxy-, C₃₋₆cycloalkyl-O-C₁₋₄alkyl-, C₃₋₆cycloalkyl-C₁₋₄alkoxy-C₁₋₄alkyl-, -OC₃₋₆cycloalkyl and -SC₃₋₆cycloalkyl, wherein the aryl¹ and het¹ groups are optionally substituted by at least one group selected from C₁₋₆alkyl-, C₃₋₆cycloalkyl-, C₁₋₆alkoxy-, -OC₃₋₆cycloalkyl, -halo, -CN, -OH, -CF₃, -CHF₂, -OCF₃, -OCHF₂, hydroxyC₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₄alkyl-, -SC₁₋₆alkyl and -SCF₃.

In a yet further embodiment, * represents the S enantiomer.

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In a further embodiment, the invention provides a compound selected from:
 N-(Biphenyl-2-ylmethyl)-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide;

- N*-(2,4-Dichlorobenzyl)-3-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
N-(2,4-Dichlorobenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(2,3-Dichlorobenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(2-Naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]acetamide;
- 5 *N*-[(2'-fluorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-[(3'-fluorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(biphenyl-2-ylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
N-(biphenyl-2-ylmethyl)-3-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
N-[(4'-chlorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
- 10 *N*-(biphenyl-2-ylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-[2-(ethylthio)benzyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(4-chloro-2-methoxybenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
2-methyl-*N*-(2-phenoxybenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-[(4'-fluorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
- 15 *N*-[(2',4'-difluorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]-*N*-[2-(1,1,2,2-tetrafluoroethoxy)benzyl]propanamide;
N-(2-bromobenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(4-chloro-2-methoxybenzyl)-3-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]-*N*-[2-(trifluoromethyl)benzyl]propanamide;
- 20 2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]-*N*-(2,3,4-trichlorobenzyl)propanamide;
2-methyl-*N*-[2-(methylthio)benzyl]-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-[(3'-fluorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*R*)-pyrrolidin-3-yl]propanamide;
2-methyl-*N*-(3-phenoxybenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-[(3'-chlorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
- 25 *N*-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopentanecarboxamide;
N-(2-cyclopropylbenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(2-bromobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopropanecarboxamide;
N-[(3*S*)-pyrrolidin-3-yl]-*N*-[2-(trifluoromethyl)benzyl]cyclopropanecarboxamide;
N-[(3',4'-difluorobiphenyl-2-yl)methyl]-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
- 30 *N*-(2,3-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
N-[(3*S*)-pyrrolidin-3-yl]-*N*-[2-(trifluoromethyl)benzyl]cyclopentanecarboxamide;
N-[2-(cyclopropylmethoxy)benzyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(4-chloro-2-ethoxybenzyl)-3-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
N-(2,4-dichlorobenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
- 35 *N*-(2,4-dichlorobenzyl)-2-ethyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
N-(4-chloro-2-methylbenzyl)-3-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
N-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclohexanecarboxamide;
N-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
N-(2,4-dichlorobenzyl)-3,3-dimethyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
- 40 *N*-(2,3-dichlorobenzyl)-3-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
N-(2,3-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]pentanamide;

- N*-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]pentanamide;
2-cyclopropyl-*N*-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]acetamide;
N-(2,4-dichlorobenzyl)-4-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]pentanamide;
2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]-*N*-[3-(trifluoromethoxy)benzyl]propanamide;
5 2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]-*N*-(2,3,5-trichlorobenzyl)propanamide;
N-(2-naphthylmethyl)-*N*-[(3*R*)-pyrrolidin-3-yl]acetamide;
N-(2-naphthylmethyl)-*N*-[(3*R*)-pyrrolidin-3-yl]cyclohexanecarboxamide;
N-(2-naphthylmethyl)-*N*-[(3*R*)-pyrrolidin-3-yl]propanamide;
N-(2-naphthylmethyl)-*N*-[(3*R*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
10 3-methyl-*N*-(2-naphthylmethyl)-*N*-[(3*R*)-pyrrolidin-3-yl]butanamide;
N-(2-naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopentanecarboxamide;
N-(2-naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(2-naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
3-methyl-*N*-(2-naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
15 *N*-(2-naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclohexanecarboxamide;
2-methyl-*N*-(2-naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-[(1-methyl-2-naphthyl)methyl]-*N*-[(3*S*)-pyrrolidin-3-yl]acetamide;
N-[(1-methyl-2-naphthyl)methyl]-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-[(6-fluoro-1-methyl-2-naphthyl)methyl]-*N*-[(3*R*)-pyrrolidin-3-yl]acetamide;
20 *N*-[(6-fluoro-1-methyl-2-naphthyl)methyl]-*N*-[(3*R*)-pyrrolidin-3-yl]propanamide;
N-[(6-fluoro-1-methyl-2-naphthyl)methyl]-*N*-[(3*S*)-pyrrolidin-3-yl]acetamide;
N-[(6-fluoro-1-methyl-2-naphthyl)methyl]-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
2-(methylthio)-*N*-(2-naphthylmethyl)-*N*-[(3*R*)-pyrrolidin-3-yl]acetamide;
N-[(3*R*)-pyrrolidin-3-yl]-*N*-(quinolin-6-ylmethyl)pentanamide;
25 *N*-[(3*S*)-pyrrolidin-3-yl]-*N*-(quinolin-6-ylmethyl)pentanamide;
N-[(3*S*)-pyrrolidin-3-yl]-*N*-(quinolin-6-ylmethyl)butanamide;
N-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopropanecarboxamide;
N-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
4,4,4-trifluoro-*N*-[(3*R*)-pyrrolidin-3-yl]-*N*-(quinolin-6-ylmethyl)butanamide;
30 4,4,4-trifluoro-*N*-[(3*S*)-pyrrolidin-3-yl]-*N*-(quinolin-6-ylmethyl)butanamide;
N-(2,4-dimethylbenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
N-(4-chloro-2-fluorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
N-(3-chloro-2-methylbenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopropanecarboxamide;
N-(2,4-dimethylbenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopropanecarboxamide;
35 *N*-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
N-(2,3-dimethylbenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopropanecarboxamide;
N-(3-chloro-4-methylbenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
N-[2-fluoro-4-(trifluoromethyl)benzyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(2-chloro-4-fluorobenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
40 *N*-(2,3-dichlorobenzyl)-2-methyl-*N*-[(3*R*)-pyrrolidin-3-yl]propanamide;
N-(4-chloro-2-ethoxybenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;

- N*-[2-methoxy-4-(trifluoromethyl)benzyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(5-chloro-2,3-dihydro-1*H*-inden-1-yl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(2-naphthylmethyl)-*N*-piperidin-4-ylacetamide;
N-[(1-methyl-2-naphthyl)methyl]-*N*-piperidin-4-ylacetamide;
5 *N*-(2-naphthylmethyl)-*N*-piperidin-4-ylpropanamide;
N-(2-naphthylmethyl)-*N*-piperidin-4-ylbutanamide;
3-methyl-*N*-(1-naphthylmethyl)-*N*-piperidin-4-ylbutanamide;
N-piperidin-4-yl-*N*-(quinolin-6-ylmethyl)propanamide;
N-piperidin-4-yl-*N*-(quinolin-6-ylmethyl)butanamide;
10 2-methyl-*N*-piperidin-4-yl-*N*-(quinolin-6-ylmethyl)propanamide;
N-[(1-ethyl-2-naphthyl)methyl]-*N*-piperidin-4-ylacetamide;
N-[(7-methoxy-1-methyl-2-naphthyl)methyl]-*N*-piperidin-4-ylacetamide;
N-[(7-methoxy-1-methyl-2-naphthyl)methyl]-*N*-piperidin-4-ylpropanamide;
2-hydroxy-*N*-(2-naphthylmethyl)-*N*-piperidin-4-ylpropanamide;
15 *N*-(2,3-dichlorobenzyl)-2-methyl-*N*-piperidin-4-ylpropanamide;
N-(2,4-dichlorobenzyl)-2-methyl-*N*-piperidin-4-ylpropanamide;
and pharmaceutically and/or veterinarily acceptable derivatives thereof.

The above described embodiments of the invention may be combined with one or more further
20 embodiments such that further embodiments are provided wherein two or more variables are defined
more specifically in combination. For example, within the scope of the invention is a further embodiment
wherein the variables R^1 , R^2 , R^3 , X, m and n all have the more limited definitions assigned to them in the
more specific embodiments described above. All such combinations of the more specific embodiments
described and defined above are within the scope of the invention

25 By pharmaceutically and/or veterinarily acceptable derivative it is meant any pharmaceutically or
veterinarily acceptable salt, solvate, ester or amide, or salt or solvate of such ester or amide, complex,
polymorph, stereoisomer, geometric isomer, tautomeric form, or isotopic variation, of the compounds of
formula (I), (I'), (II) or (III) or any other compound which upon administration to the recipient is capable of
30 providing (directly or indirectly) a compound of formula (I), (I'), (II') or (III') or an active metabolite or
residue thereof. Preferably, pharmaceutically acceptable derivatives are salts, solvates, esters and
amides of the compounds of formula (I), (I'), (II') or (III'). More preferably, pharmaceutically acceptable
derivatives are salts and solvates.

35 For pharmaceutical or veterinary use, the salts referred to above will be the pharmaceutically or
veterinarily acceptable salts, but other salts may find use, for example in the preparation of compounds of
formula (I), (I'), (II') or (III') and the pharmaceutically or veterinarily acceptable salts thereof.

The aforementioned pharmaceutically or veterinarily acceptable salts include the acid addition and base
40 salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, camsylate, citrate, hemicitrate, edisylate, hemiedisylate, esylate, fumarate, gluceptate, gluconate, glucuronate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, 2-napsylate, nicotinate, nitrate, orotate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate and tosylate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

A pharmaceutically acceptable salt of a compound of formula (I), (I'), (II') or (III') may be readily prepared by mixing together solutions of the compound and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the salt may vary from completely ionised to almost non-ionised.

Pharmaceutically acceptable solvates in accordance with the invention include hydrates and solvates of the compounds of formula (I), (I'), (II') or (III').

Also within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included in this invention are complexes of the pharmaceutical drug which contain two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Halebian (August 1975).

The compounds of formula (I), (I'), (II') or (III') may be modified to provide pharmaceutically or veterinarily acceptable derivatives thereof at any of the functional groups in the compounds. Examples of such derivatives are described in: Drugs of Today, Volume 19, Number 9, 1983, pp 499 – 538; Topics in Chemistry, Chapter 31, pp 306 – 316; and in "Design of Prodrugs" by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference) and include: esters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, sulphonamides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals and ketals.

It will be further appreciated by those skilled in the art, that certain moieties, known in the art as "pro-moieties", for example as described by H. Bundgaard in "Design of Prodrugs" (ibid) may be placed on appropriate functionalities when such functionalities are present within compounds of the invention.

The compounds of formula (I), (I'), (II') or (III') may contain one or more chiral centres, by virtue of the asymmetric carbon atom defined by certain meanings of the "R" groups (e.g. s-butyl), or the value of the integer m. Such compounds exist in a number of stereoisomeric forms (e.g. in the form of a pair of optical isomers, or enantiomers). It is to be understood that the present invention encompasses all isomers of the compounds of the invention, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. tautomeric or racemic mixtures).

The compounds of the invention may exist in one or more tautomeric forms. All tautomers and mixtures thereof are included in the scope of the present invention. For example, a claim to 2-hydroxypyridinyl would also cover its tautomeric form α -pyridonyl.

It is to be understood that the present invention includes radio labelled compounds of formula (I), (I'), (II') or (III').

The compounds of formula (I), (I'), (II') or (III') and their pharmaceutically and veterinarily acceptable derivatives may also be able to exist in more than one crystal form, a characteristic known as polymorphism. All such polymorphic forms ("polymorphs") are encompassed within the scope of the invention. Polymorphism generally can occur as a response to changes in temperature or pressure or both, and can also result from variations in the crystallisation process. Polymorphs can be distinguished by various physical characteristics, and typically the x-ray diffraction patterns, solubility behaviour, and melting point of the compound are used to distinguish polymorphs.

Unless otherwise indicated, any alkyl group may be straight or branched and is of 1 to 8 carbon atoms, such as 1 to 6 carbon atoms or 1 to 4 carbon atoms, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group. Where the alkyl group contains more than one carbon atom, it may be unsaturated. Thus, the term C₁₋₆ alkyl includes C₂₋₆ alkenyl and C₂₋₆ alkynyl. Similarly, the term C₁₋₈ alkyl includes C₂₋₈ alkenyl and C₂₋₈ alkynyl, and the term C₁₋₄ alkyl includes C₂₋₄ alkenyl and C₂₋₄ alkynyl.

The term halogen is used to represent fluorine, chlorine, bromine or iodine.

Unless otherwise indicated, the term het includes any aromatic, saturated or unsaturated 4-, 5- or 6-membered heterocycle which contains up to 4 heteroatoms selected from N, O and S. Examples of such heterocyclic groups included furyl, thienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, dioxolanyl, oxazolyl, thiazolyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyranyl, tetrahydropyranyl, pyridyl, piperidinyl, dioxanyl, morpholino, dithianyl, thiomorpholino, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, sulfolanyl, tetrazolyl, triazinyl, azepinyl, oxazapinyl, thiazepinyl, diazepinyl and thiazolinyl. In addition, the term heterocycle includes fused heterocyclyl groups, for example benzimidazolyl, benzoxazolyl, imidazopyridinyl, benzoxazinyl, benzothiazinyl, oxazolopyridinyl, benzofuranyl, quinolinyl, quinazolinyl, quinoxalinyl, dihydroquinazdinyl, benzothiazolyl, phthalimido, benzodiazepinyl, indolyl and isoindolyl.

For the avoidance of doubt, unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different. Further, the term independently means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

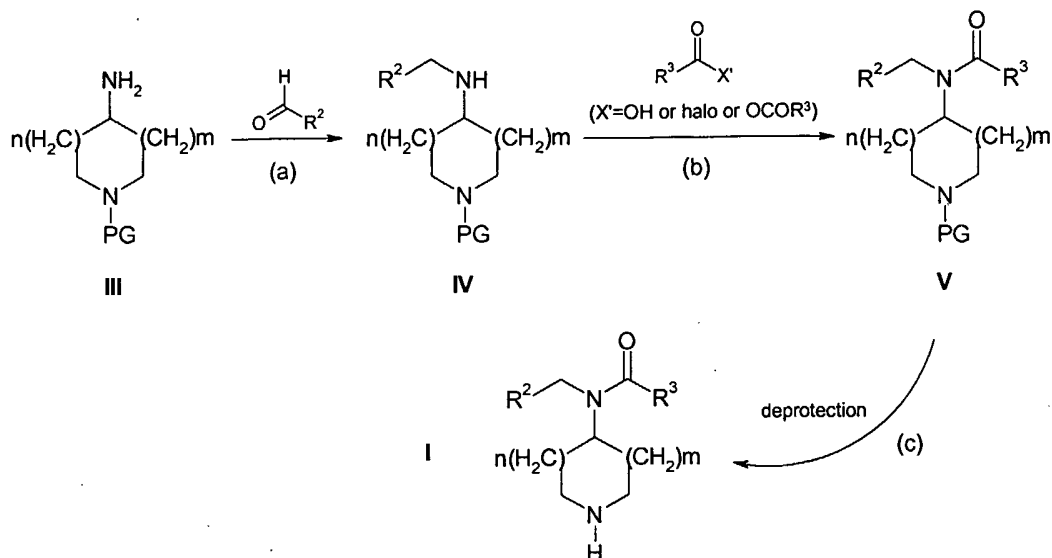
Hereinafter, the compounds of formula (I), (I'), (II') or (III') and their pharmaceutically and veterinarily acceptable derivatives, the radio labelled analogues of the foregoing, the isomers of the foregoing, and the polymorphs of the foregoing, are referred to as "compounds of the invention".

In one embodiment of the invention, the compounds of the invention are the pharmaceutically and veterinarily acceptable derivatives of compounds of formula (I), (I'), (II') or (III'), such as the pharmaceutically or veterinarily acceptable salts or solvates of compounds of formula (I), (I'), (II') or (III'), (e.g. pharmaceutically or veterinarily acceptable salts of compounds of formula (I), (I'), (II') or (III')).

In a still further embodiment of the invention, there is provided a compound of the invention which is an inhibitor of serotonin and/or noradrenaline monoamine re-uptake, having SRI or NRI IC_{50}/K_i values of 500nM or less, preferably 400nM or less, more preferably 200nM or less. In a further embodiment, the compound has SRI and/or NRI IC_{50}/K_i values of 100nM or less. In a yet further embodiment, the compound has SRI and/or NRI IC_{50}/K_i values of 50nM or less. In a still yet further embodiment, the compound has SRI and/or NRI IC_{50}/K_i values of 25nM or less.

Without wishing to be bound by theory, it is believed that for certain of the diseases or conditions for which the compounds of the invention are indicated it is useful for the compound to be a more potent inhibitor of the reuptake of one of serotonin or noradrenaline than the other. Thus, in an embodiment of the invention, the reuptake of noradrenaline is inhibited to greater degree than the reuptake of serotonin. In an alternative embodiment, the reuptake of serotonin is inhibited to a greater degree than the reuptake of noradrenaline. For example, in the treatment of pain, it is believed that compounds of the invention which inhibit the reuptake of noradrenaline have good efficacy. Thus, an embodiment of the invention provides a method of treating pain which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound according to the invention which is capable of inhibiting the reuptake of noradrenaline. In this embodiment, the compound of the invention may selectively inhibit the reuptake of noradrenaline or it may inhibit the reuptake of noradrenaline preferentially to the inhibition of serotonin reuptake or it may inhibit the reuptake of serotonin preferentially to the inhibition of noradrenaline reuptake. In a further embodiment of the invention, there provided compounds which are more potent noradrenalin reuptake inhibitors than serotonin reuptake inhibitors. Accordingly, such an embodiment of the invention provides a method of treating pain which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound according to the invention which is capable of inhibiting the reuptake of noradrenaline to a greater extent than the reuptake of serotonin.

According to **Scheme 1**, compounds of Formula (I) may be prepared from compounds of Formula (III) by reaction with an aldehyde, $R^2\text{CHO}$ (or a suitable ketone), in the presence of a reducing agent, followed by reaction with an acid or anhydride or acid chloride $R^3\text{COX}'$, where X' is OH or halo or OCOR^3 , or alternatively with an acid mixed anhydride, and deprotection.



Scheme 1

In the above scheme, R^3 , R^2 , m and n are as defined above, X is CH_2 and PG is a protecting group.

(a) – Reductive Amination

- 10 The reaction of the 1° amine (III) with the aldehyde $R^2\text{CHO}$ to form the 2° amine (IV) is a reductive amination reaction, in which the dehydration of the amine and the aldehyde is followed by reduction of the formed imine by a metal hydride reagent or hydrogenation, in a suitable solvent at room temperature.

- 15 In this reaction, equimolar amounts of amine and aldehyde are typically treated with either sodium triacetoxyborohydride (STAB), NaBH_3CN or NaBH_4 , in a suitable solvent (e.g. DCM, THF) at room temperature for 1 to 24 hours. Alternatively, an excess of a reducing agent (e.g. NaBH_4 , LiAlH_4 , STAB) in a suitable solvent (e.g. THF, MeOH, EtOH, toluene) is added after the amine and aldehyde have been mixed for 1-18 hours, optionally in the presence of a drying agent (e.g. molecular sieve) or with the removal of water using Dean-Stark apparatus with a suitable solvent (e.g. toluene, xylene). A further
- 20 alternative involves catalytic hydrogenation in the presence of a palladium or nickel catalyst (e.g. Pd/C, Raney® Ni) under an atmosphere of H_2 , optionally at elevated temperature and pressure, in a suitable solvent (e.g. EtOH).

- 25 A more specific example of the reductive amination involves treatment of the amine with the aldehyde in the presence of either 10% Pd/C, optionally in the presence of triethylamine, in ethanol under about 415 kPa (about 60psi) of hydrogen at room temperature for 18 hours.

Another more specific example of the reductive amination is treatment of the amine with the aldehyde in toluene at reflux under Dean-Stark conditions for 18 hours and then after concentration, treatment with an excess of sodium borohydride in methanol at room temperature for 3 hours.

- 5 Suitable aldehydes are either, known and available from commercial sources, or, are derivable from commercially available materials using known techniques; for example, 7-methoxy-1-methyl-naphtalene-2-carbaldehyde can be prepared using the preparation described in WO 2004/111003.

(b) – Amide Formation

- 10 The formation of an amide bond between the acid or acid halide or anhydride (R^3COX') and the amine (IV) may be undertaken by using either:
- (i) the acyl halide or anhydride and the amine (IV), with an excess of acid acceptor in a suitable solvent; or
- (ii) the acid, optionally with a conventional coupling agent, and the amine (IV), optionally in the presence of a catalyst, with an excess of acid acceptor in a suitable solvent.
- 15

Examples of such reactions are as follows:

- (a) An acid chloride (optionally generated *in situ*) or anhydride is reacted with an excess of the amine (IV), optionally with an excess of 3° amine (such as Et_3N , Hünig's base, pyridine or NMM), in DCM (or dioxane), optionally at an elevated temperature for between 1 and 24 hours;
- 20 (b) An acid, WSCDI (or DCCI, or TBTU) and HOBT (or HOAT) is reacted with an excess of amine (IV) and an excess of NMM (or Et_3N , or Hünig's base) in THF (or DCM, or EtOAc), at room temperature for between 4 and 48 hours; or
- (c) An acid and PYBOP® (or PyBrOP®, or Mukaiyama's reagent) is reacted with an excess of amine (IV) and an excess of NMM (or Et_3N , or Hünig's base) in THF (or DCM, or EtOAc), at room temperature for between 4 and 24 hours.
- 25

- Where the acid halide is an acid chloride (i.e. $X'=Cl$), this may be generated *in situ* by standard methodology and then reacted with the amine (IV) in the presence of triethylamine in dichloromethane at room temperature for 1 hour.
- 30

Suitable acids, anhydrides and acid chlorides are either, known and available from commercial sources, or, are derivable from commercially available materials using known techniques.

35 (c) – Deprotection

Where PG is a suitable amine-protecting group, preferably BOC, trifluoroacetate, benzyloxycarbonyl (Bz) or benzyl (Bn), the removal of PG from (V), to form the unprotected amine (I), is performed by a method selective to the protecting group as detailed in "Protective Groups in Organic Synthesis", 3rd edition, by TW Greene and PGM Wuts. John Wiley and Sons, Inc., 1999, incorporated herein by reference.

Examples of such deprotection reactions are as follows:

When PG is BOC, the deprotection involves treatment of (V) with an excess of strong acid (e.g. HCl, TFA) at room temperature in a suitable solvent (e.g. DCM, EtOAc, dioxane).

5 When PG is trifluoroacetate, the deprotection involves treatment of (V) with a base (e.g. K_2CO_3 , Na_2CO_3 , NH_3 , $Ba(OH)_2$) in an alcoholic solvent (e.g. MeOH, EtOH), optionally with water and optionally at elevated temperature. More specifically, when PG is trifluoroacetate, the deprotection involves treatment with K_2CO_3 in methanol:water mixture (5:1 to 10:1) at room temperature for 18 hours (WO 2004110995).

10 When PG is Bn or Bz, the deprotection involves either transfer hydrogenation with a transition metal or transition metal salt hydrogenation catalyst (e.g. Pd/C, $Pd(OH)_2$) in the presence of a hydrogen donor (e.g. $NH_4^+HCO_2^-$) in a polar solvent (e.g. THF, EtOH, MeOH) optionally at elevated temperature and/or pressure, or catalytic hydrogenation in the presence of a palladium or nickel catalyst (e.g. Pd/C, Raney[®] Ni) under an atmosphere of H_2 , optionally at elevated temperature and pressure, in a suitable solvent.

15

More specifically:

When PG is BOC, the deprotection involves treatment with either an excess of 4M hydrogen chloride in dioxane for 18 hours at room temperature or with TFA in DCM for 20 hours at room temperature.

20 When PG is trifluoroacetate, the deprotection involves treatment with K_2CO_3 in methanol:water mixture (5:1 to 10:1) at room temperature for 18 hours.

When PG is Bn or Bz, the deprotection involves treatment with $NH_4^+HCO_2^-$ and 10% Pd/C in ethanol under gentle reflux for between 4 and 20 hours.

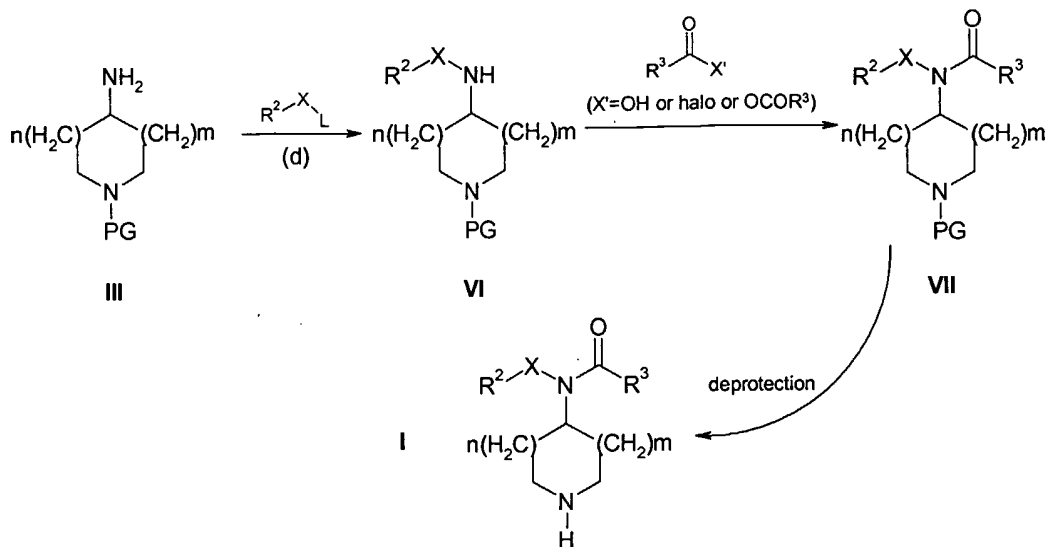
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When PG is trifluoroacetate, the deprotection involves treatment of (V) with a base (e.g. K_2CO_3 , Na_2CO_3 , NH_3 , $Ba(OH)_2$) in an alcoholic solvent (e.g. MeOH, EtOH), optionally with water and optionally at an elevated temperature.

30 More specifically, when PG is trifluoroacetate, the deprotection involves treatment with K_2CO_3 in methanol:water mixture (5:1 to 10:1) at room temperature for 18 hours (examples of such deprotection are described in WO 2004110995).

35 According to **Scheme 2**, compounds of Formula (I) may be prepared from compounds of Formula (III) by reaction with R^2-X-L , where L is a leaving group, under suitable conditions. The resulting compound of Formula (VI) may then be converted to a compound of Formula (I) by amide formation and deprotection in a manner analogous to that described above in relation to **Scheme 1**.

19



Scheme 2

In the above scheme, R^2 , R^3 , X, m and n are as defined above, PG is a suitable protecting group and L is a leaving group, whose meaning will depend, *inter alia*, on the nature of the reaction and the specific reaction conditions employed. Suitable leaving groups will be readily apparent to the skilled person and are described in many standard organic chemistry texts, for example: "Advanced Organic Chemistry", Jerry March, Third Edition, Wiley (1985), page 587, incorporated herein by reference; they include halogen (e.g. Br) and sulfonate esters (e.g. methanesulfonate or trifluoromethanesulfonate).

Conveniently, R^2 is an aryl group, X is alkyl, L is Br and reaction (d) is carried out in a suitable solvent, at elevated temperatures, in the presence of a 3° amine (such as Et_3N , or Hünig's base, or NMM, or an inorganic base).

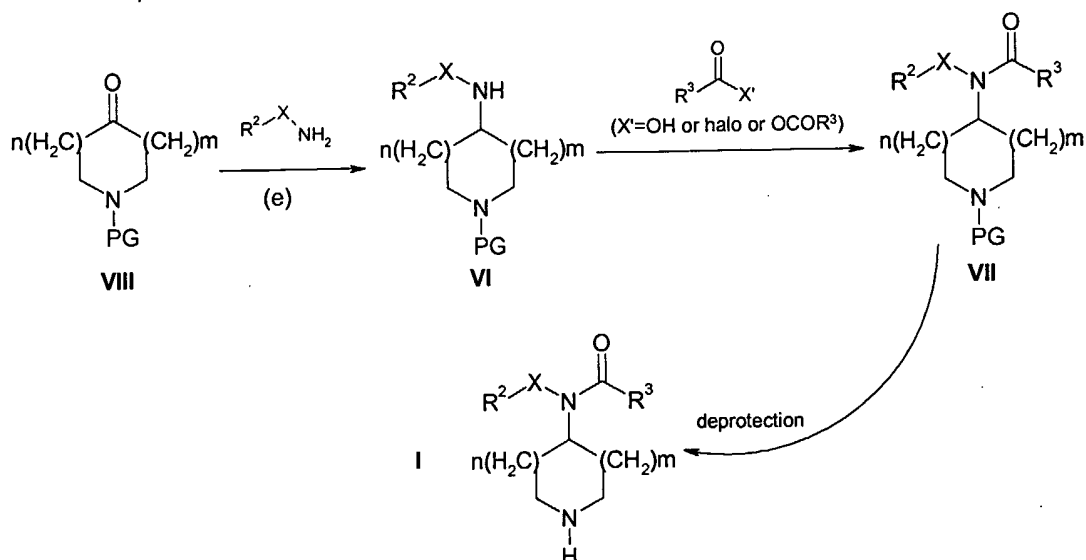
In a more specific example of a process according to **Scheme 2**, amine (III) is treated with the arylalkylbromide in acetonitrile under gentle reflux for between 1 and 20 hours in the presence of potassium carbonate.

Alternatively, where R^2 is an aryl group, X is a covalent bond and L is Br, reaction (d) may be carried out in a suitable solvent, at elevated temperatures, in the presence of a palladium catalyst. Such palladium mediated aryl amination reactions are well known to those skilled in the art.

More specifically, this involves the treatment of an aryl bromide with an amine of Formula (III) in the presence of tris(dibenzylideneacetone)dipalladium, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and sodium *tert*-butoxide in toluene at 100°C for 18 hours.

Suitable alkyl halides are either, known and available from commercial sources, or are derivable from commercially available materials using known techniques.

According to **Scheme 3**, compounds of Formula (VI) may be prepared from a ketone of Formula (VIII) by reaction with a primary amine R^2-X-NH_2 in the presence of a reducing agent, under suitable conditions. The resulting compound of Formula (VI) may then be converted to a compound of Formula (I) by amide formation and deprotection in a manner analogous to that described above in relation to **Scheme 1**.



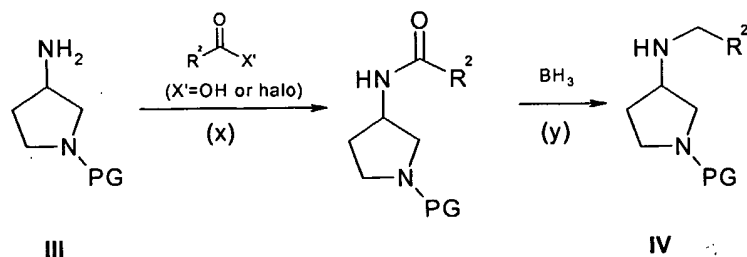
In the above scheme, R^3 , R^2 , X , m and n are as defined above and PG is a suitable protecting group.

Scheme 3

The reaction (e) of the primary amine R^2-X-NH_2 with the ketone (VIII) may conveniently be a reductive amination reaction in which the dehydration of the amine and the ketone is followed by reduction of the resultant imine, for example by a metal hydride reagent or hydrogenation, under suitable conditions.

Conveniently, the reaction of the amine and the ketone is carried out in the presence of titanium (IV) tetraisopropoxide in THF at room temperature for 18 hours, followed by reduction by an excess of sodium borohydride in methanol at room temperature for 5 hours.

Suitable amines are either, known and available from commercial sources, or are derivable from commercially available materials using known techniques.



Scheme 4.

In the above scheme, R^2 is as defined above and PG is a protecting group.

According to **Scheme 4**, compounds of Formula (IV) may be prepared from a 1° amine of Formula (III) by reaction with a carboxylic acid or acid halide, optionally prepared *in situ*, R²COX' (where X' is OH or halo), followed by reaction with a reducing agent, such as borane.

- 5 The formation of an amide bond between the acid or acid halide and the 1° amine (III) may be undertaken by using either:
- (i) the acyl halide (or the acid or acid anhydride) and the amine (III), with an excess of acid acceptor in a suitable solvent, or
 - (ii) the acid, optionally with a conventional coupling agent, and the amine (III), optionally in the presence
- 10 of a catalyst, with an excess of acid acceptor in a suitable solvent.

Examples of such reactions are as follows:

- (a) An acid chloride (optionally generated *in situ*) is reacted with an excess of the amine (III), optionally with an excess of 3° amine (such as Et₃N, Hünig's base or NMM), in DCM (or dioxane),
15 optionally at an elevated temperature for between 1 and 24 hours;
- (b) An acid, WSCDI (or DCCI, or TBTU) and HOBt (or HOAT) is reacted with an excess of amine (III) and an excess of NMM (or Et₃N, or Hünig's base) in THF (or DCM, or EtOAc), at room temperature for between 4 and 48 hours; or
- (c) An acid and 1-propyl phosphonic ester cyclic anhydride (or PYBOP®, or PyBrOP®, or
20 Mukaiyama's reagent) is reacted with an excess of amine (III) and an excess of NMM (or Et₃N, or Hünig's base) in THF (or DCM, or EtOAc), at room temperature for between 1 and 24 hours.

A more specific example of the amide formation involves treatment of the acid with the amine in the presence of 1-propyl phosphonic ester cyclic anhydride and in the presence of triethylamine in DCM at
25 room temperature for 1 hour.

Where the acid halide is an acid chloride (i.e. X'=Cl), this may be generated *in situ* by standard methodology and then reacted with the amine (III) and triethylamine in dichloromethane at 70°C for 90
30 minutes

The reaction (y) is a reduction of the amide to amine (IV) for example by a hydride reducing agent under suitable conditions.

Conveniently, the reduction of the amide is carried out in the presence of Borane in THF at reflux for 2
35 hours, followed by addition of methanol and optionally of aqueous ammonium chloride and further reflux for 4 hours before isolation of the amine (IV).

The skilled person is able to select the most appropriate synthetic route to the desired compound according to Formula (I), (II) or (III). The above schemes may of course be modified as appropriate in
40 accordance with the common general knowledge of those skilled in the art.

For example, the skilled person will of course appreciate that the hydrogen attached to the piperidine or pyrrolidine nitrogen (depending upon the value of m) of the deprotected amide (I) can be replaced with alternative groups as desired to form an alternative compound of Formula (I) where n is 1 and m is 0 or 1 by the use of conventional synthetic methodologies.

5

In addition, compounds of Formula (I) where n is 2 and m is 0 can be prepared by analogous processes to those described above using the appropriate starting materials.

10

It will be appreciated by those skilled in the art that one or more sensitive functional groups may need to be protected and deprotected during the synthesis of a compound of Formula (I), (II) or (III). This may be achieved by conventional techniques, for example as described in "Protective Groups in Organic Synthesis", 3rd edition, by TW Greene and PGM Wuts. John Wiley and Sons, Inc., 1999, incorporated herein by reference, which also describes methods for the removal of such groups.

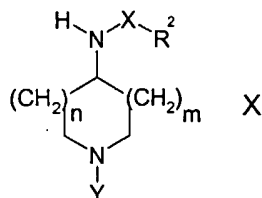
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It will be apparent to those skilled in the art that certain protected derivatives of compounds of the invention, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolized in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as prodrugs. Further, certain compounds of the invention may act

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as prodrugs of other compounds of the invention.

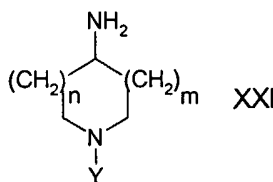
According to a further aspect of the invention, there is provided a process for preparing compounds of Formula (I), (I'), (II') or (III'), which comprises reacting a compound of formula (X):



25

wherein R^2 , n and m are as defined above and Y is R^1 or a protecting group, with an acid or acyl halide: R^3COX , wherein X is OH or halo, or an acid anhydride: $(R^3CO)_2O$, and deprotecting if necessary.

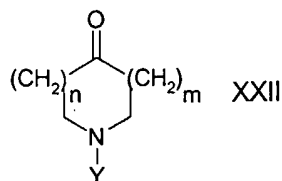
Where X is CH_2 , then the compound of Formula (X) may be prepared by reacting a compound of Formula (XXI) with an aldehyde: R^2CHO in the presence of a reducing agent.



30

Alternatively, the compound of Formula (X) may be prepared by reacting a compound of Formula (XXI) with a compound R^2-X-L , where L is a leaving group, optionally selected from halide, methanesulfonate and trifluoromethanesulfonate.

Furthermore, the compound of Formula (X) may be prepared by reacting a compound of Formula (XXII) with a compound R^2-X-NH_2 in the presence of a reducing agent.



Certain intermediates described above are novel compounds and it is to be understood that all novel intermediates herein form further aspects of the present invention.

Racemic compounds may be separated either using preparative HPLC and a column with a chiral stationary phase, or resolved to yield individual enantiomers utilizing methods known to those skilled in the art. In addition, racemic chiral intermediate compounds may be resolved and used to prepare enantio-enriched chiral compounds of the invention.

According to a further aspect of the invention, there is provided one or more metabolites of the compounds of the invention when formed *in vivo*.

The compounds of the invention may have the advantage that they are more potent, have a longer duration of action, have a broader range of activity, are more stable, have fewer side effects or are more selective, or have other more useful properties than the compounds of the prior art.

The compounds of the invention are useful because they have pharmacological activity in mammals, including humans. Thus, they are useful in the treatment or prevention of disorders in which the regulation of monoamine transporter function is implicated, more particularly disorders in which inhibition of re-uptake of serotonin or noradrenaline is implicated. Furthermore, the compounds of the invention are of use in disorders in which inhibition of both serotonin and noradrenaline is implicated, such as urinary incontinence. Additionally, the compounds of the invention are of use in disorders in which it may be desired to inhibit preferentially the reuptake of one of noradrenaline or serotonin compared with the other, such as pain.

Accordingly the compounds of the invention are useful in the treatment of urinary incontinence, such as genuine stress incontinence (GSI), stress urinary incontinence (SUI) or urinary incontinence in the elderly; overactive bladder (OAB), including idiopathic detrusor instability, detrusor overactivity secondary to neurological diseases (e.g. Parkinson's disease, multiple sclerosis, spinal cord injury and stroke) and detrusor overactivity secondary to bladder outflow obstruction (e.g. benign prostatic hyperplasia (BPH), urethral stricture or stenosis); nocturnal enuresis; urinary incontinence due to a combination of the above conditions (e.g. stress incontinence associated with overactive bladder); and lower urinary tract symptoms, such as frequency and urgency. The term OAB is intended to encompass both OAB wet and OAB dry.

In view of their aforementioned pharmacological activity the compounds of the invention are also useful in the treatment of depression, such as major depression, recurrent depression, single episode depression, subsyndromal symptomatic depression, depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, paediatric depression, child abuse induced depression, depression in infertile women, post partum depression, premenstrual dysphoria and grumpy old man syndrome.

In view of their aforementioned pharmacological activity the compounds of the invention are also useful in the treatment of cognitive disorders such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease) and vascular dementia (including multi-infarct dementia), as well as dementia associated with intracranial space occupying lesions, trauma, infections and related conditions (including HIV infection), metabolism, toxins, anoxia and vitamin deficiency; mild cognitive impairment associated with ageing, particularly age associated memory impairment (AAMI), amnesic disorder and age-related cognitive decline (ARCD); psychotic disorders, such as schizophrenia and mania; anxiety disorders, such as generalised anxiety disorder, phobias (e.g. agoraphobia, social phobia and simple phobias), panic disorder, obsessive compulsive disorder, post traumatic stress disorder, mixed anxiety and depression; personality disorders such as avoidant personality disorder and attention deficit hyperactivity disorder (ADHD); sexual dysfunction, such as premature ejaculation, male erectile dysfunction (MED) and female sexual dysfunction (FSD) (e.g. female sexual arousal disorder (FSAD)); premenstrual syndrome; seasonal affective disorder (SAD); eating disorders, such as anorexia nervosa and bulimia nervosa; obesity; appetite suppression; chemical dependencies resulting from addiction to drugs or substances of abuse, such as addictions to nicotine, alcohol, cocaine, heroin, phenobarbital and benzodiazepines; withdrawal syndromes, such as those that may arise from the aforementioned chemical dependencies; cephalic pain, such as migraine, cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, headache associated with chemical dependencies or withdrawal syndromes resulting from chemical dependencies, and tension headache; pain; Parkinson's diseases, such as dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias; endocrine disorders, such as hyperprolactinaemia; vasospasm, such as in the cerebral vasculature; cerebellar ataxia; Tourette's syndrome; trichotillomania; kleptomania; emotional lability; pathological crying; sleep disorder (cataplexy); and shock.

In view of their aforementioned pharmacological activity the compounds of the invention are also useful in the treatment of a number of other conditions or disorders, including hypotension; gastrointestinal tract disorders (involving changes in motility and secretion) such as irritable bowel syndrome (IBS), ileus (e.g. post-operative ileus and ileus during sepsis), gastroparesis (e.g. diabetic gastroparesis), peptic ulcer, gastroesophageal reflux disease (GORD, or its synonym GERD), flatulence and other functional bowel disorders, such as dyspepsia (e.g. non-ulcerative dyspepsia (NUD)) and non-cardiac chest pain (NCCP); and fibromyalgia syndrome.

The compounds of the invention, being serotonin and/or noradrenaline reuptake inhibitors are potentially useful in the treatment of a range of disorders, including pain.

Physiological pain is an important protective mechanism designed to warn of danger from potentially injurious stimuli from the external environment. The system operates through a specific set of primary sensory neurones and is activated by noxious stimuli via peripheral transducing mechanisms (see Millan, 1999, Prog. Neurobiol., 57, 1-164 for a review). These sensory fibres are known as nociceptors and are characteristically small diameter axons with slow conduction velocities. Nociceptors encode the intensity, duration and quality of noxious stimulus and by virtue of their topographically organised projection to the spinal cord, the location of the stimulus. The nociceptors are found on nociceptive nerve fibres of which there are two main types, A-delta fibres (myelinated) and C fibres (non-myelinated). The activity generated by nociceptor input is transferred, after complex processing in the dorsal horn, either directly, or via brain stem relay nuclei, to the ventrobasal thalamus and then on to the cortex, where the sensation of pain is generated.

Pain may generally be classified as acute or chronic: Acute pain begins suddenly and is short-lived (usually in twelve weeks or less). It is usually associated with a specific cause such as a specific injury and is often sharp and severe. It is the kind of pain that can occur after specific injuries resulting from surgery, dental work, a strain or a sprain. Acute pain does not generally result in any persistent psychological response. In contrast, chronic pain is long-term pain, typically persisting for more than three months and leading to significant psychological and emotional problems. Common examples of chronic pain are neuropathic pain (e.g. painful diabetic neuropathy, postherpetic neuralgia), carpal tunnel syndrome, back pain, headache, cancer pain, arthritic pain and chronic post-surgical pain.

When a substantial injury occurs to body tissue, via disease or trauma, the characteristics of nociceptor activation are altered and there is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. These effects lead to a heightened sensation of pain. In acute pain these mechanisms can be useful, in promoting protective behaviours which may better enable repair processes to take place. The normal expectation would be that sensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is often due to nervous system injury. This injury often leads to abnormalities in sensory nerve fibres associated with maladaptation and aberrant activity (Woolf & Salter, 2000, Science, 288, 1765-1768).

Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. Patients tend to be quite heterogeneous and may present with various pain symptoms. Such symptoms include: 1) spontaneous pain which may be dull, burning, or stabbing; 2) exaggerated pain responses to noxious stimuli (hyperalgesia); and 3) pain produced by normally innocuous stimuli (allodynia - Meyer et al., 1994, Textbook of Pain, 13-44). Although patients suffering from various forms of acute and chronic pain may have similar symptoms, the underlying mechanisms may be different and may, therefore, require different treatment strategies. Pain can also therefore be divided into a number of different

subtypes according to differing pathophysiology, including nociceptive, inflammatory and neuropathic pain.

Nociceptive pain is induced by tissue injury or by intense stimuli with the potential to cause injury. Pain afferents are activated by transduction of stimuli by nociceptors at the site of injury and activate neurons in the spinal cord at the level of their termination. This is then relayed up the spinal tracts to the brain where pain is perceived (Meyer et al., 1994, Textbook of Pain, 13-44). The activation of nociceptors activates two types of afferent nerve fibres. Myelinated A-delta fibres transmit rapidly and are responsible for sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey a dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of pain from central nervous system trauma, strains/sprains, burns, myocardial infarction and acute pancreatitis, post-operative pain (pain following any type of surgical procedure), posttraumatic pain, renal colic, cancer pain and back pain. Cancer pain may be chronic pain such as tumour related pain (e.g. bone pain, headache, facial pain or visceral pain) or pain associated with cancer therapy (e.g. postchemotherapy syndrome, chronic postsurgical pain syndrome or post radiation syndrome). Cancer pain may also occur in response to chemotherapy, immunotherapy, hormonal therapy or radiotherapy. Back pain may be due to herniated or ruptured intervertebral discs or abnormalities of the lumbar facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament. Back pain may resolve naturally but in some patients, where it lasts over 12 weeks, it becomes a chronic condition which can be particularly debilitating.

Neuropathic pain is currently defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system. Nerve damage can be caused by trauma and disease and thus the term 'neuropathic pain' encompasses many disorders with diverse aetiologies. These include, but are not limited to, peripheral neuropathy, diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, back pain, cancer neuropathy, HIV neuropathy, phantom limb pain, carpal tunnel syndrome, central post-stroke pain and pain associated with chronic alcoholism, hypothyroidism, uremia, multiple sclerosis, spinal cord injury, Parkinson's disease, epilepsy and vitamin deficiency. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patient's quality of life (Woolf and Mannion, 1999, Lancet, 353, 1959-1964). The symptoms of neuropathic pain are difficult to treat, as they are often heterogeneous even between patients with the same disease (Woolf & Decosterd, 1999, Pain Supp., 6, S141-S147; Woolf and Mannion, 1999, Lancet, 353, 1959-1964). They include spontaneous pain, which can be continuous, and paroxysmal or abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

The inflammatory process is a complex series of biochemical and cellular events, activated in response to tissue injury or the presence of foreign substances, which results in swelling and pain (Levine and Taiwo, 1994, Textbook of Pain, 45-56). Arthritic pain is the most common inflammatory pain. Rheumatoid disease is one of the commonest chronic inflammatory conditions in developed countries and rheumatoid arthritis is a common cause of disability. The exact aetiology of rheumatoid arthritis is unknown, but current hypotheses suggest that both genetic and microbiological factors may be important (Grennan &

Jayson, 1994, Textbook of Pain, 397-407). It has been estimated that almost 16 million Americans have symptomatic osteoarthritis (OA) or degenerative joint disease, most of whom are over 60 years of age, and this is expected to increase to 40 million as the age of the population increases, making this a public health problem of enormous magnitude (Houge & Mersfelder, 2002, Ann Pharmacother., 36, 679-686; McCarthy et al., 1994, Textbook of Pain, 387-395). Most patients with osteoarthritis seek medical attention because of the associated pain. Arthritis has a significant impact on psychosocial and physical function and is known to be the leading cause of disability in later life. Ankylosing spondylitis is also a rheumatic disease that causes arthritis of the spine and sacroiliac joints. It varies from intermittent episodes of back pain that occur throughout life to a severe chronic disease that attacks the spine, peripheral joints and other body organs.

Another type of inflammatory pain is visceral pain which includes pain associated with inflammatory bowel disease (IBD). Visceral pain is pain associated with the viscera, which encompass the organs of the abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain associated with the viscera can be divided into digestive visceral pain and non-digestive visceral pain. Commonly encountered gastrointestinal (GI) disorders that cause pain include functional bowel disorder (FBD) and inflammatory bowel disease (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including, in respect of FBD, gastro-esophageal reflux, dyspepsia, irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and, in respect of IBD, Crohn's disease, ileitis and ulcerative colitis, all of which regularly produce visceral pain. Other types of visceral pain include the pain associated with dysmenorrhoea, cystitis and pancreatitis and pelvic pain.

It should be noted that some types of pain have multiple aetiologies and thus can be classified in more than one area, e.g. back pain and cancer pain have both nociceptive and neuropathic components.

Other types of pain include:

- pain resulting from musculo-skeletal disorders, including myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, glycogenolysis, polymyositis and pyomyositis;
- heart and vascular pain, including pain caused by angina, myocardical infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleredoma and skeletal muscle ischemia;
- head pain, such as migraine (including migraine with aura and migraine without aura), cluster headache, tension-type headache mixed headache and headache associated with vascular disorders; and
- orofacial pain, including dental pain, otic pain, burning mouth syndrome and temporomandibular myofascial pain.

Disorders of particular interest include urinary incontinence, such as mixed incontinence, GSI and USI; pain; depression; anxiety disorders, such as obsessive-compulsive disorder and post traumatic stress

disorder; personality disorders, such as ADHD; sexual dysfunction; and chemical dependencies and withdrawal syndromes resulting from chemical dependencies.

Thus, according to further aspects, the invention provides:

- i) a compound of the invention for use in human or veterinary medicine;
- ii) a compound of the invention for use in the treatment of a disorder in which the regulation of monoamine transporter function is implicated, such as urinary incontinence;
- iii) the use of a compound of the invention in the manufacture of a medicament for the treatment of a disorder in which the regulation of monoamine transporter function is implicated;
- iv) a compound of the invention for use in the treatment of a disorder in which the regulation of serotonin or noradrenaline is implicated;
- v) the use of a compound of the invention in the manufacture of a medicament for the treatment of a disorder in which the regulation of serotonin or noradrenaline is implicated;
- vi) a compound of the invention for use in the treatment of a disorder in which the regulation of serotonin and noradrenaline is implicated;
- vii) the use of a compound of the invention in the manufacture of a medicament for the treatment of a disorder in which the regulation of serotonin and noradrenaline is implicated;
- viii) a compound of the invention for use in the treatment of pain or urinary incontinence;
- ix) the use of a compound of the invention in the manufacture of a medicament for the treatment of pain or urinary incontinence;
- x) a method of treatment of a disorder in which the regulation of monoamine transporter function is implicated which comprises administering a therapeutically effective amount of a compound of the invention to a patient in need of such treatment;
- xi) a method of treatment of a disorder in which the inhibition of the reuptake of serotonin or noradrenaline is implicated which comprises administering a therapeutically effective amount of a compound of the invention to a patient in need of such treatment;
- xii) a method of treatment of a disorder in which the inhibition of the reuptake of serotonin and noradrenaline is implicated which comprises administering a therapeutically effective amount of a compound of the invention to a patient in need of such treatment; and

- xiii) a method of treating pain or urinary incontinence, such as GSI or USI, which comprises administering a therapeutically effective amount of a compound of the invention to a patient in need of such treatment.

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It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment, unless explicitly stated otherwise.

The compounds of the invention may be administered alone or as part of a combination therapy. If a combination of therapeutic agents is administered, then the active ingredients may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

Examples of suitable agents for adjunctive therapy include:

- an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;
- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;
- a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, theamylal or thiopental;
- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;
- an H₁ antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphenadrine;
- an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex[®], a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (–)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(1H)-quinolinone};
- an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, phentolamine, terazasin, prazosin or 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;

- a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;
- an anticonvulsant, e.g. carbamazepine, lamotrigine, topiramate or valproate;
- a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (α R,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-
- 5 [1,4]diazocino[2,1-g][1,7]-naphthyridine-6-13-dione (TAK-637), 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);
- a muscarinic antagonist, e.g. oxybutynin, tolterodine, propiverine, trospium chloride, darifenacin,
- 10 solifenacin, temiverine and ipratropium;
- a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;
- a coal-tar analgesic, in particular paracetamol;
- a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine,
- 15 mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonopiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, medlinertant, Miraxion® or sarizotan;
- a vanilloid receptor agonist (e.g. resiniferatoxin) or antagonist (e.g. capsazepine);
- 20 • a beta-adrenergic such as propranolol;
- a local anaesthetic such as mexiletine;
- a corticosteroid such as dexamethasone;
- a 5-HT receptor agonist or antagonist, particularly a 5-HT_{1B/1D} agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;
- 25 • a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);
- a cholinergic (nicotinic) analgesic, such as ispronicline (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidylmethoxy)-2-chloropyridine (ABT-594) or nicotine;
- Tramadol®;
- 30 • a PDEV inhibitor, such as 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-
- 35 2-(1-ethyl-3-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(1-methyl-7-

oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;

- an alpha-2-delta ligand such as gabapentin, pregabalin, 3-methylgabapentin, (1 α ,3 α ,5 α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid;
- a cannabinoid;
- metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;
- a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone;
- a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupropion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;
- a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and imipramine;
- an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chloro-3-pyridinecarbonitrile; 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine, or guanidinoethyldisulfide;
- an acetylcholinesterase inhibitor such as donepezil;
- a prostaglandin E₂ subtype 4 (EP4) antagonist such as N-[(2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl)amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[(1S)-1-([5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl)amino]ethyl]benzoic acid;

- a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870,
- a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl),1,4-benzoquinone (CV-6504);
- a sodium channel blocker, such as lidocaine;
- a 5-HT₃ antagonist, such as ondansetron, granisetron, tropisetron, azasetron, dolasetron or alosetron;
- an oestrogen agonist or selective oestrogen receptor modulator (e.g. HRT therapies or lasofoxifene);
- an alpha-adrenergic receptor agonist, such as phenylpropanolamine or R-450;
- a dopamine receptor agonist (e.g. apomorphine, teachings on the use of which as a pharmaceutical may be found in US-A-5945117), including a dopamine D₂ receptor agonist (e.g. premiprival, Pharmacia Upjohn compound number PNU95666; or ropinirole);
- a PGE₁ agonist (e.g. alprostadil);

and the pharmaceutically acceptable salts and solvates thereof.

- 20 The invention thus provides, in a further aspect, a combination comprising a compound of the invention together with a further therapeutic agent.

For human use the compounds of the invention can be administered alone, but in human therapy will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of the invention, can be administered orally, buccally or sublingually in the form of tablets, capsules (including soft gel capsules), ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, dual-, controlled-release or pulsatile delivery applications. The compounds of the invention may also be administered via intracavernosal injection. The compounds of the invention may also be administered via fast dispersing or fast dissolving dosage forms.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine, and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycolate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the invention, and their pharmaceutically acceptable salts, may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

Modified release and pulsatile release dosage forms may contain excipients such as those detailed for immediate release dosage forms together with additional excipients that act as release rate modifiers, these being coated on and/or included in the body of the device. Release rate modifiers include, but are not exclusively limited to, hydroxypropylmethyl cellulose, methyl cellulose, sodium carboxymethylcellulose, ethyl cellulose, cellulose acetate, polyethylene oxide, Xanthan gum, Carbomer, ammonio methacrylate copolymer, hydrogenated castor oil, carnauba wax, paraffin wax, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, methacrylic acid copolymer and mixtures thereof. Modified release and pulsatile release dosage forms may contain one or a combination of release rate modifying excipients. Release rate modifying excipients may be present both within the dosage form i.e. within the matrix, and/or on the dosage form, i.e. upon the surface or coating.

Fast dispersing or dissolving dosage formulations (FDDFs) may contain the following ingredients: aspartame, acesulfame potassium, citric acid, croscarmellose sodium, crospovidone, diascorbic acid, ethyl acrylate, ethyl cellulose, gelatin, hydroxypropylmethyl cellulose, magnesium stearate, mannitol, methyl methacrylate, mint flavouring, polyethylene glycol, fumed silica, silicon dioxide, sodium starch glycolate, sodium stearyl fumarate, sorbitol, xylitol. The terms dispersing or dissolving as used herein to describe FDDFs are dependent upon the solubility of the drug substance used i.e. where the drug substance is insoluble a fast dispersing dosage form can be prepared and where the drug substance is soluble a fast dissolving dosage form can be prepared.

The compounds of the invention can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the invention or salts or solvates thereof will usually be from 10 to 500 mg (in single or divided doses).

Thus, for example, tablets or capsules of the compounds of the invention or salts or solvates thereof may contain from 5 mg to 250 mg of active compound for administration singly or two or more at a time, as

appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention. The skilled person will also appreciate that, in the treatment of certain conditions (including PE), compounds of the invention may be taken as a single dose on an "as required" basis (i.e. as needed or desired).

Example Tablet Formulation

In general a tablet formulation could typically contain between about 0.01mg and 500mg of a compound according to the present invention (or a salt thereof) whilst tablet fill weights may range from 50mg to 1000mg. An example formulation for a 10mg tablet is illustrated:

<u>Ingredient</u>	<u>%w/w</u>
Free base or salt of compound	10.000*
Lactose	64.125
Starch	21.375
Croscarmellose Sodium	3.000
Magnesium Stearate	1.500

* This quantity is typically adjusted in accordance with drug activity and is based on the weight of the free base.

The compounds of the invention can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebulizer with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra- fluoro-ethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray or nebulizer may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 to 50 mg of a compound of the invention for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1 to 50 mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

The compounds of the invention may also be formulated for delivery via an atomiser. Formulations for atomiser devices may contain the following ingredients as solubilisers, emulsifiers or suspending agents: water, ethanol, glycerol, propylene glycol, low molecular weight polyethylene glycols, sodium chloride, fluorocarbons, polyethylene glycol ethers, sorbitan trioleate, oleic acid.

Alternatively, the compounds of the invention can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of the invention may also be dermally or transdermally administered, for example, by the use of a skin patch. They may also be administered by the ocular, pulmonary or rectal routes.

For ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

For application topically to the skin, the compounds of the invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters, wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of the invention may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

For oral or parenteral administration to human patients the daily dosage levels of compounds of formula (I), (I'), (II'), (III'), and their pharmaceutically acceptable salts, will be from 0.01 to 30 mg/kg (in single or divided doses) and preferably will be in the range 0.01 to 5 mg/kg. Thus tablets will contain 1mg to 0.4g of compound for administration singly or two or more at a time, as appropriate. The physician will in any event determine the actual dosage which will be most suitable for any particular patient and it will vary with the age, weight and response of the particular patient. The above dosages are, of course only exemplary of the average case and there may be instances where higher or lower doses are merited, and such are within the scope of the invention.

Oral administration is preferred.

- For veterinary use, a compound of the invention is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

Thus according to a further aspect, the invention provides a pharmaceutical formulation containing a compound of the invention and a pharmaceutically acceptable adjuvant, diluent or carrier.

- The combinations referred to above may also conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable adjuvant, diluent or carrier comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

- When a compound of the invention is used in combination with a second therapeutic the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

- The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions may be used:

APCI	Atmospheric pressure chemical ionisation
Arbocel®	filter agent
br	Broad
BOC	<i>tert</i> -butoxycarbonyl
CDI	carbonyldiimidazole
δ	chemical shift
d	doublet
dd	doublet of doublets
Δ	heat
DCCI	dicyclohexylcarbodiimide
DCM	dichloromethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
ES ⁺	electrospray ionisation positive scan
ES ⁻	electrospray ionisation negative scan
h	hours
HOAT	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography

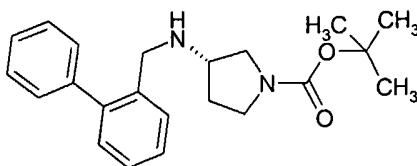
LRMS	Low resolution mass spectrum
m/z	mass spectrum peak
min	minutes
NMM	<i>N</i> -methyl morpholine
NMR	nuclear magnetic resonance
q	quartet
s	singlet
t	triplet
TBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
WSCDI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

The Preparations and Examples that follow illustrate the invention but do not limit the invention in any way. All temperatures are in °C. Flash column chromatography was carried out using Merck silica gel 60 (9385). Solid Phase Extraction (SPE) chromatography was carried out using Varian Mega Bond Elut (Si) cartridges (Anachem) under 15mmHg vacuum. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 plates (5729). Melting points were determined using a Gallenkamp MPD350 apparatus and are uncorrected. NMR was carried out using a Varian-Unity Inova 400MHz NMR spectrometer or a Varian Mercury 400MHz NMR spectrometer. Mass spectroscopy was carried out using a Finnigan Navigator single quadrupole electrospray mass spectrometer or a Finnigan aQa APCI mass spectrometer.

Conveniently, compounds of the invention are isolated following work-up in the form of the free base, but pharmaceutically acceptable acid addition salts of the compounds of the invention may be prepared using conventional means. Solvates (e.g. hydrates) of a compound of the invention may be formed during the work-up procedure of one of the aforementioned process steps.

Where it is stated that compounds were prepared in the manner described for an earlier Preparation or Example, the skilled person will appreciate that reaction times, number of equivalents of reagents and reaction temperatures may be modified for each specific reaction, and that it may nevertheless be necessary or desirable to employ different work-up or purification conditions.

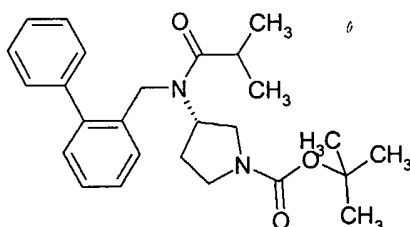
Preparation 1: *tert*-Butyl (3S)-3-[(biphenyl-2-ylmethyl)amino]pyrrolidine-1-carboxylate



Biphenyl-2-carbaldehyde (270mg, 1.45mmol) was added to a solution of tert-butyl (3S)-3-aminopyrrolidine-1-carboxylate (270mg, 1.45mmol) in methanol (5ml), under nitrogen, at room temperature. The reaction mixture was stirred at room temperature for 16 hours, and sodium borohydride (110mg, 2.90mmol) was then added. The reaction mixture was stirred at room temperature for a further 3 hours, after which time it was quenched with a saturated sodium bicarbonate solution (25ml), diluted with water (25ml) and extracted into ethyl acetate (2x100ml). The organic extracts were combined, washed with brine (50ml), dried over magnesium sulphate and concentrated *in vacuo* to yield the title compound (448mg, 87%) as a colourless gum.

¹H-NMR (CDCl₃, 400MHz): 1.44(s, 9H), 1.56(m, 1H), 1.83(m, 1H), 2.91(m, 0.5H), 3.01(m, 0.5H), 3.15(m, 1H), 3.24(m, 1H), 3.31-3.38(m, 2H), 3.76(s, 2H), 7.33-7.42(m, 8H), 7.48(m, 1H); LRMS APCI⁺ m/z 353 [MH]⁺.

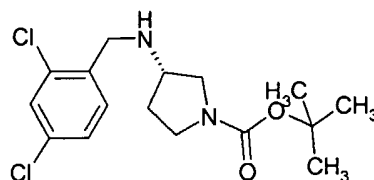
Preparation 2: tert-Butyl (3S)-3-[(biphenyl-2-ylmethyl)(isobutyryl)amino]pyrrolidine-1-carboxylate



Isobutyryl chloride (220μl, 2.1mmol) was added to a solution of the amine described in **preparation 1** (448mg, 1.27mmol), and triethylamine (480μl, 3.44mmol), in dioxane (15ml). The reaction mixture was heated at 70°C for 2 hours, after which time it was concentrated *in vacuo*. The resulting product was taken up in ethyl acetate and washed with water, 2M hydrochloric acid, 1M sodium hydroxide and brine. The organic extracts were dried over magnesium sulphate, filtered and concentrated *in vacuo* to yield the title compound (608mg, 100%) as a gum.

¹H-NMR (CDCl₃, 400MHz): 1.03-1.06(m, 6H), 1.41(s, 9H), 1.72(m, 1H), 1.93(m, 1H), 2.50(m, 1H), 2.93(m, 1H), 3.20(m, 1H), 3.37(m, 1H), 3.54(m, 1H), 4.27-4.35(m, 2H), 5.04(m, 1H), 7.15(m, 1H), 7.27-7.46(m, 8H); LRMS APCI⁺ m/z 323 [(M-BOC)H]⁺.

Preparation 3: tert-Butyl (3S)-3-[(2,4-dichlorobenzyl)amino]pyrrolidine-1-carboxylate

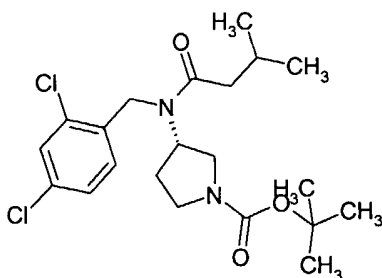


2,4-Dichlorobenzaldehyde (1.88g, 10.74mmol) was added to a solution of tert-butyl (3S)-3-aminopyrrolidine-1-carboxylate (2g, 10.74mmol) in toluene (50ml). The reaction mixture was heated at reflux under Dean-Stark conditions for 18 hours, under nitrogen. It was then concentrated *in vacuo* and the residue was taken up in methanol (50ml). The mixture was cooled down to 0°C and then sodium borohydride (812mg, 21.48mmol) was added portionwise. The solution was stirred at 0°C for 30 minutes and then at room temperature for 1.5 hours. It was then quenched with water (10ml) and concentrated *in vacuo*. The resulting residue was partitioned between water (40ml) and dichloromethane (40ml). The

layers were separated and the aqueous layer was further extracted with dichloromethane (2x10ml). The organic extracts were combined, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with ethyl acetate:pentane (1:5 to 1:3 by volume) to yield the title compound (3.58g, 96%).

- 5 $^1\text{H-NMR}$ (CDCl_3 , 400MHz): 1.45(s, 9H), 1.58(brs, 1H), 1.76(m, 1H), 2.03(m, 1H), 3.11-3.20(brm, 1H), 3.32(brs, 2H), 3.44-3.56(m, 2H), 3.86(s, 2H), 7.23(d, 1H), 7.35-7.38(m, 2H); LRMS APCI $^+$ m/z 289 [MH-isobutylene] $^+$.

Preparation 4: *tert*-Butyl (3S)-3-[(2,4-dichlorobenzyl)(3-methylbutanoyl)amino]pyrrolidine-1-carboxylate

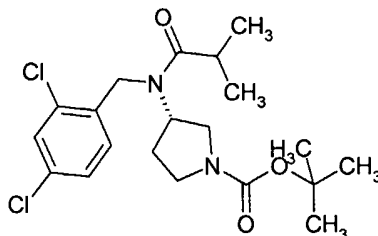


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The title compound (208mg, 84%) was prepared by a method similar to that described in **preparation 2** using the amine described in **preparation 3** and isovaleryl chloride (3-methylbutanoyl chloride).

- 15 $^1\text{H-NMR}$ (CDCl_3 , 400MHz, rotamers): 0.99(d, 6H), 1.43(s, 9H), 1.96-2.03(m, 2H), 2.11(m, 1H), 2.23(d, 2H), 3.03(m, 1H), 3.26(m, 1H), 3.45(m, 1H), 3.59(m, 1H), 4.47-4.58(brm, 2H), 5.16(m, 1H), 6.95-7.05(m, 1H), 7.17-7.27(m, 1H), 7.35-7.43(m, 1H); LRMS APCI $^+$ m/z 329 [MH-BOC] $^+$.

Preparation 5: *tert*-Butyl (3S)-3-[(2,4-dichlorobenzyl)(isobutyryl)amino]pyrrolidine-1-carboxylate

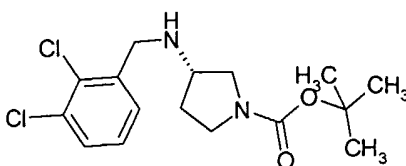


- 20 The title compound (458mg, 94%) was prepared by a method similar to that described in **preparation 2** using the amine described in **preparation 3** and isobutyryl chloride.

$^1\text{H-NMR}$ (CDCl_3 , 400MHz, rotamers): 1.08(d, 3H), 1.19(d, 3H), 1.42(s, 9H), 1.76(m, 1H), 1.98(m, 1H), 2.39(m, 1H), 3.01(m, 1H), 3.26(m, 1H), 3.45(m, 1H), 3.58(m, 1H), 4.47(brs, 1.5H), 4.61(brs, 0.5H), 5.18(m, 1H), 6.86(d, 0.5H), 7.01(d, 0.5H), 7.16(d, 0.5H), 7.28(m, 0.5H), 7.35(s, 0.5H), 7.42(s, 0.5H); LRMS APCI $^+$ m/z 315 [MH-BOC] $^+$.

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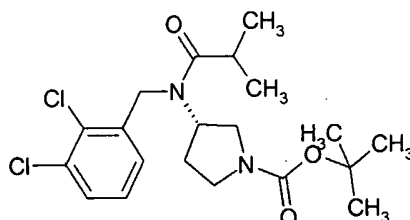
Preparation 6: *tert*-Butyl (3S)-3-[(2,3-dichlorobenzyl)amino]pyrrolidine-1-carboxylate



The title compound (1.55g, 85%) was prepared by a method similar to that described in **preparation 3** using tert-butyl (3S)-3-aminopyrrolidine-1-carboxylate and 2,3-dichlorobenzaldehyde.

¹H-NMR (CDCl₃, 400MHz): 1.45(s, 9H), 1.64(brs, 1H, NH), 1.76(m, 1H), 2.04(m, 1H), 3.10-3.20(brm, 1H), 3.33(brs, 2H), 3.44-3.56(m, 2H), 3.92(s, 2H), 7.18(t, 1H), 7.32(brs, 1H), 7.38(d, 1H); LRMS APCI⁺ m/z 345 [MH]⁺.

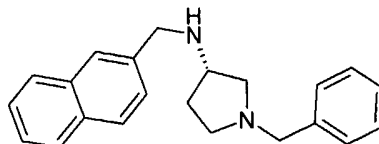
Preparation 7: *tert*-Butyl (3S)-3-[(2,3-dichlorobenzyl)(isobutyryl)amino]pyrrolidine-1-carboxylate



The title compound (592mg, 100%) was prepared by a method similar to that described in **preparation 2** using the amine described in **preparation 6** and isobutyryl chloride.

¹H-NMR (CDCl₃, 400MHz, rotamers): 1.08(d, 4H), 1.23-1.27(m, 2H), 1.42(s, 9H), 1.76(m, 1H), 1.98(m, 1H), 2.39(m, 1H), 3.02(m, 1H), 3.26(m, 1H), 3.45(m, 1H), 3.59(m, 1H), 4.52 (brs, 1.5H), 4.64 (m, 0.5H), 5.20(m, 1H), 6.83(d, 0.5H), 7.01(d, 0.5H), 7.13(t, 0.5H), 7.23(m, 0.5H), 7.33(d, 0.5H), 7.43(d, 0.5H); LRMS APCI⁺ m/z 415 [MH]⁺.

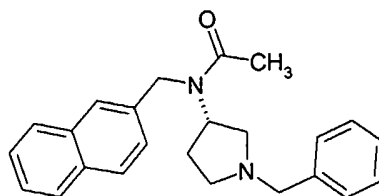
Preparation 8: (3S)-1-Benzyl-N-(2-naphthylmethyl)pyrrolidin-3-amine



The title compound (4.1g, 100%) was prepared by a method similar to that described in **preparation 1** using (3S)-1-benzylpyrrolidin-3-amine and 2-naphthaldehyde.

¹H-NMR (CDCl₃, 400MHz): 1.69(m, 1H), 1.80(brs, 1H, NH), 2.17(m, 1H), 2.48(m, 1H), 2.56(m, 1H), 2.70(m, 1H), 2.78(m, 1H), 3.42(m, 1H), 3.64(q, 2H), 3.91(s, 2H), 7.26(m, 1H), 7.31-7.33(m, 4H), 7.44-7.46(m, 3H), 7.74(s, 1H), 7.79-7.82(m, 3H); LRMS APCI⁺ m/z 317 [MH]⁺.

Preparation 9: *N*-[(3S)-1-Benzylpyrrolidin-3-yl]-*N*-(2-naphthylmethyl)acetamide



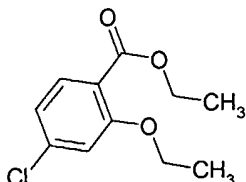
Acetic anhydride (270μl, 2.84mmol) was added to a solution of the amine described in **preparation 8** (300mg, 0.948mmol) and pyridine (460μl, 5.68mmol), in dichloromethane (5ml). The reaction mixture was stirred at room temperature for 16 hours, after which time it was washed with water and brine. The organic extracts were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude

product was purified by column chromatography on silica gel eluting with dichloromethane:methanol (100:0 to 98:2, by volume) to yield the title compound (330mg, 97%).

LRMS ESI⁺ m/z 359 [MH]⁺.

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Preparation 10: Ethyl 4-chloro-2-ethoxybenzoate



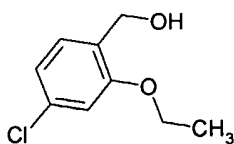
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4-Chloro-2-hydroxybenzoic acid (5g, 29mmol), iodoethane (11.7ml, 145mmol) and potassium carbonate (20g, 145mmol) were combined in acetone (100ml) and the reaction mixture was heated at reflux for 18 hours. The acetone was then evaporated *in vacuo*. The resulting residue was partitioned between water (100ml) and ethyl acetate (150ml). The layers were separated and the aqueous layer was further extracted with ethyl acetate (150ml). The organic extracts were combined, dried over sodium sulphate, filtered and evaporated *in vacuo*. The title compound was obtained as an orange solid (6.66g, 100%).

¹H-NMR (CDCl₃, 400MHz) δ: 1.18 (t, 3H), 1.23 (t, 3H), 4.10 (q, 2H), 4.38 (q, 2H), 6.95 (m, 2H), 7.75 (d, 1H).

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Preparation 11: (4-Chloro-2-ethoxyphenyl)methanol



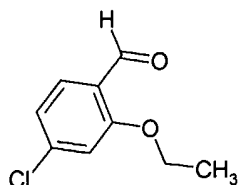
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A 1M solution of lithium aluminium hydride (5ml) was added dropwise to a solution of the compound described in **preparation 10** (1.14g, 5mmol) in tetrahydrofuran (10ml), at room temperature, under nitrogen. The reaction mixture was stirred at room temperature for 3 hours, after which time it was quenched with 2M hydrochloric acid (20ml). The solution was extracted with ethyl acetate (2x30ml), and the combined organic extracts were combined, dried over magnesium sulphate and evaporated *in vacuo* to yield the title compound (780mg, 84%).

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¹H-NMR (CDCl₃, 400MHz) δ: 1.43 (t, 3H), 2.32 (bs, 1H), 4.05(q, 2H), 4.62 (s, 2H), 6.84 (s, 1H), 6.92 (d, 1H), 7.20 (d, 1H).

Preparation 12: 4-Chloro-2-ethoxybenzaldehyde



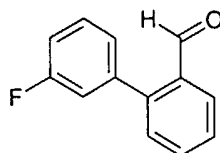
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Manganese dioxide (1.8g, 21.2mmol) was added to a solution of 4-chloro-2-ethoxyphenyl)methanol (described in **preparation 11**) (1g, 5.3mmol) in dichloromethane (15ml), and the reaction mixture was heated at reflux for 72 hours. It was then filtered through arboce[®] and the filtrate was evaporated *in vacuo*. The crude material was purified by column chromatography using an ISCO[®] silica cartridge,

eluting with a solvent gradient of pentane changing to pentane: ethyl acetate (80:20 by volume). The title compound was obtained as a yellow solid (965mg, 5.2mmol, 98%).

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 1.45 (t, 3H), 4.17 (q, 2H), 6.99 (m, 2H), 7.78 (d, 1H), 10.42 (s, 1H).

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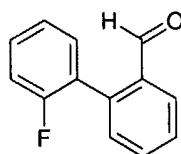
Preparation 13: 3'-Fluorobiphenyl-2-carbaldehyde

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2-Bromo-benzaldehyde (1.24g, 6.7mmol), 3-fluorophenylboronic acid (1.12g, 8.04mmol), tris(dibenzylideneacetone)dipalladium (0) (92mg, 0.1mmol), tricyclohexylphosphine (85mg, 0.30mmol) and potassium phosphate (2.84g, 13.4mmol) were combined in toluene (20ml) and the reaction mixture was heated at 100°C for 18 hours. The suspension was then filtered through arboce[®] and the filtrate was evaporated *in vacuo*. The crude material was purified by column chromatography over silica gel eluting with a solvent gradient of pentane changing to pentane: ethyl acetate (90:10 by volume). The title compound was obtained as a yellow oil (756mg, 3.7mmol, 55%).

15

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 7.12 (m, 3H), 7.42 (m, 2H), 7.51 (t, 1H), 7.64 (t, 1H), 8.03 (d, 1H), 10.00 (s, 1H).

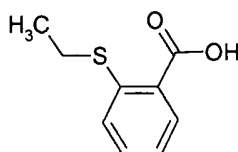
Preparation 14: 2'-Fluorobiphenyl-2-carbaldehyde

20

2-Bromobenzaldehyde (1g, 5.4mmol), 2-fluorophenylboronic acid (909mg, 6.5mmol), tris(dibenzylideneacetone)dipalladium (0) (73mg, 0.08mmol), tricyclohexylphosphine (67mg, 0.24mmol) and potassium phosphate (2.3g, 10.8mmol) were combined in toluene (20ml) and the reaction mixture was heated at 100°C for 18 hours. The suspension was filtered through arboce[®] and the filtrate was evaporated *in vacuo*. The residue was dissolved in diethyl ether, washed with 1M sodium hydroxide, dried over magnesium sulphate, filtered and evaporated *in vacuo*. The title compound was obtained as a yellow oil (1.1g, 5.5mmol, 84%).

25

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 7.18 (t, 1H), 7.26 (t, 1H), 7.34 (t, 1H), 7.43 (m, 2H), 7.54 (t, 1H), 7.67 (t, 1H), 8.04 (d, 1H), 9.92 (s, 1H); LRMS APCI⁺ m/z 201 [MH]⁺.

Preparation 15: 2-(ethylthio)benzoic acid

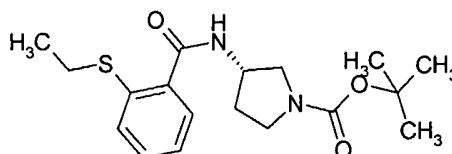
30

A 1M sodium hydroxide solution (10ml) was added to 2-mercaptobenzoic acid (1g, 6.4mmol) in ethanol (10ml), followed by iodoethane (1g, 6.4mmol). The reaction mixture was stirred for 72 hours, after which

time the ethanol was evaporated under reduced pressure. The reaction mixture was then cooled in an ice bath and acidified to pH 1 with 2N aqueous hydrochloric acid. The resulting precipitate was collected by filtration, washed with water and dried under reduced pressure to afford the title compound, (1.09g, 98%).

- 5 $^1\text{H-NMR}$ (400MHz, CD_3OD) δ : 1.32(t, 3H), 2.9(q, 2H), 7.13(t, 1H), 7.38(d, 1H), 7.43 (t, 1H), 7.88 (d, 1H); LRMS APCI $^-$ m/z 181 [M-H] $^-$

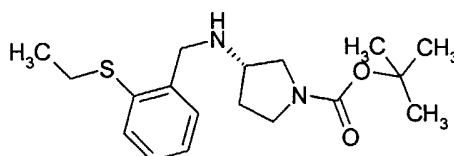
Preparation 16: Tert-butyl (3S)-3-[[2-(ethylthio)benzoyl]amino]pyrrolidine-1-carboxylate



- 10 A 50% solution of 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P $^{\text{®}}$) (50% solution in ethyl acetate by weight, 9.7ml, 16.5mmol) was added dropwise to a solution of 2-(ethylthio)benzoic acid (described in **preparation 15**) (3.0g, 16.5mmol), tert-butyl (3S)-3-aminopyrrolidine-1-carboxylate (2.79g, 15mmol) and triethylamine (5.2ml, 33.5mmol) in dichloromethane (75ml). The reaction mixture was stirred at room temperature for 18 hours. An aqueous solution of potassium carbonate (50ml) was then added and the reaction mixture was stirred at room temperature for a further 18 hours. The layers were separated and the organic phase was washed with an aqueous solution of potassium carbonate, dried over magnesium sulphate, filtered and evaporated *in vacuo*. The title compound was obtained as a brown gum (4.02g, 11.6mmol, 77%).
- 15 LRMS APCI $^+$ m/z 351 [MH] $^+$.

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Preparation 17: Tert-butyl (3S)-3-[[2-(ethylthio)benzyl]amino]pyrrolidine-1-carboxylate

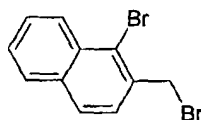


- A 1M solution of borane in tetrahydrofuran (38ml, 38.3mmol) was added dropwise to a solution of the compound described in **preparation 16** (4.02g, 11.6mmol) in tetrahydrofuran (35ml). The reaction mixture was heated at reflux for 2.5 hours after which time it was allowed to cool to room temperature. The mixture was quenched with methanol and the solvent was evaporated *in vacuo*. The resulting residue was dissolved in methanol (80ml) and the solution was heated at reflux for 4 hours. The methanol was then evaporated *in vacuo* and the crude material was purified by column chromatography over silica gel eluting with a solvent gradient of pentane: ethyl acetate (90:10 by volume) changing to pentane: ethyl acetate (50:50, by volume). The title compound was obtained as a colourless oil (2.34g, 6.96mmol, 60%).
- 25
- 30

$^1\text{H-NMR}$ (CDCl_3 , 400MHz): δ : 1.31 (t, 3H), 1.44 (s, 9H), 1.76 (m, 2H), 2.02 (m, 1H), 2.94 (q, 2H), 3.07-3.23 (m, 1H), 3.32 (s, 2H), 3.40-3.60 (m, 2H), 3.87 (s, 2H), 7.14 (t, 1H), 7.22 (t, 1H), 7.28-7.34 (m, 2H); LRMS APCI $^+$ m/z 337 [MH] $^+$.

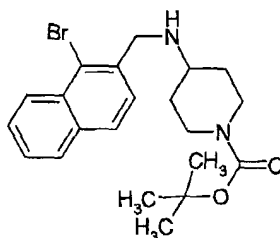
35

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Preparation 18: 1-Bromo-2-(bromomethyl)naphthalene

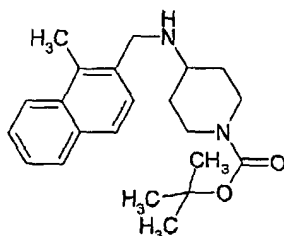
N-bromosuccinimide (4.4g, 24.8mmol) was added to a solution of 1-bromo-2-methylnaphthalene (5.0g, 22.6mmol) in trichloroethane (100ml). Benzoyl peroxide (44mg, 0.18mmol) was then added, and the reaction mixture was heated at 85°C for 21 hours. It was then quenched with a saturated aqueous solution of sodium hydrogen carbonate (100ml). The organic phase was separated, washed with brine (150ml), dried over magnesium sulphate, filtered and evaporated *in vacuo*. The yellow solid was triturated with pentane to yield the title compound (4.42g, 14.7mmol, 65%).

¹H-NMR (CDCl₃, 400MHz) δ : 4.85 (s, 2H), 7.50-7.65 (m, 3H), 7.80 (m, 2H), 8.38 (d, 1H).

Preparation 19: Tert-butyl 4-[[[1-bromo-2-naphthyl)methyl]amino]piperidine-1-carboxylate

The compound described in **preparation 18** (200mg, 0.66mmol), tert-butyl 4-aminopiperidine-1-carboxylate (200mg, 1mmol) and potassium carbonate (182mg, 1.31mmol) were combined in acetonitrile (4ml), and the reaction mixture was heated at reflux for 18 hours. The solvent was evaporated *in vacuo* and the resulting residue was partitioned between water (50ml) and ethyl acetate (50ml). The organic layer was washed with brine (30ml), dried over magnesium sulphate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography over silica gel eluting with a solvent gradient of pentane: ethyl acetate (50:50 by volume) changing to pentane: ethyl acetate (10:90 by volume) to yield the title compound (220mg, 0.52mmol, 78%).

¹H-NMR (CDCl₃, 400MHz) δ : 1.40 (m, 2H), 1.45 (s, 9H), 1.90 (m, 2H), 2.74 (m, 1H), 2.82(m, 2H), 4.05 (brs, 2H), 4.15 (s, 2H), 7.50 (m, 1H), 7.60 (m, 2H), 7.80 (t, 2H), 8.30 (d, 1H); LRMS ESI⁺ m/z 421 [MH]⁺.

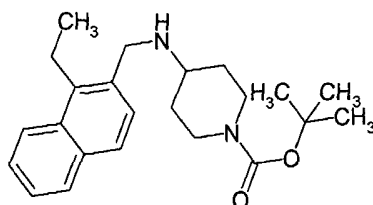
Preparation 20: Tert-butyl 4-[[[1-methyl-2-naphthyl)methyl]amino]piperidine-1-carboxylate

The compound described in **preparation 19** (215mg, 0.51mmol), potassium carbonate (283mg, 2.05mmol), tetrakis(triphenylphosphine)palladium (0) (58mg, 0.05mmol) and trimethylboroxin (0.110ml, 0.79mmol) were combined in 1,4- dioxane (2ml). The reaction mixture was heated at 100°C for 18 hours.

It was then filtered through arbocel[®] and the filtrate was extracted from water (30ml) into ethyl acetate, which was dried over magnesium sulphate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography over silica gel eluting with a solvent gradient of pentane: ethyl acetate (50:50 by volume) changing to pentane: ethyl acetate (10:90 by volume). The title compound was

obtained as a colourless oil (110mg, 0.31mmol, 61%).
¹H-NMR (CDCl₃, 400MHz) δ : 1.40 (m, 2H), 1.48 (s, 9H), 1.92 (m, 2H), 2.70 (s, 3H), 2.75-2.95 (m, 3H), 4.00 (s, 2H), 4.05 (m, 2H), 7.40-7.55 (m, 3H), 7.68 (d, 1H), 7.82 (d, 1H), 8.06 (d, 1H).

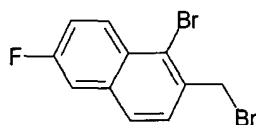
Preparation 21: tert-Butyl 4-[[[1-ethyl-2-naphthyl)methyl]amino]piperidine-1-carboxylate



Diethyl zinc bromide (3.6ml of a 1M solution in hexane, 3.6mmol) was added dropwise to a mixture of the compound described in **preparation 19** (500mg, 1.19mmol) and [1,3bis(diphenylphosphino)propane] dichloronickel(II) (96 mg, 0.18 mmol) in tetrahydrofuran (3 ml) at 0°C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred then for 1.5 hours, before being cooled to 0°C and quenched by the addition of aqueous ammonium chloride (10mL). The mixture was diluted with ethyl acetate (30ml) and filtered through Celite[®] before being washed with brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography over silica gel eluting with a solvent gradient of ethyl acetate:pentane 2:3 by volume, changing to ethyl acetate:pentane 3:2 by volume to give the title compound (130mg, 29%) as an oil.

LRMS APCI⁺ m/z 369 [MH]⁺.

Preparation 22: 1-Bromo-2-(bromomethyl)-6-fluoronaphthalene

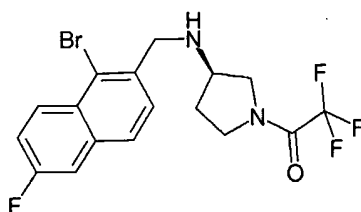


A mixture of 1,1'-azobis(cyclohexanecarbonitrile) (VAZO[®] catalyst 88) (200mg, 0.8mmol), 1-bromo-6-fluoro-2-methylnaphthalene (prepared according to *J. Med. Chem.*, 1993, **36**, 2485) (4.12g, 17.2mmol) and N-bromosuccinimide (3.1g, 17.2mmol) in carbon tetrachloride (35ml) was heated at reflux for 6 hours then was stirred at room temperature for a further 18 hours. The reaction mixture was diluted with dichloromethane, washed with water, dried over sodium sulphate and evaporated *in vacuo*. The residue was triturated with pentane to yield the title compound as an off white solid (2.96g, 54%)

¹H-NMR (CDCl₃, 400MHz): δ 4.85 (s, 2H), 7.38 (m, 1H), 7.45 (dd, 1H), 7.53 (d, 1H), 7.74 (d, 1H), 8.36 (dd, 1H).

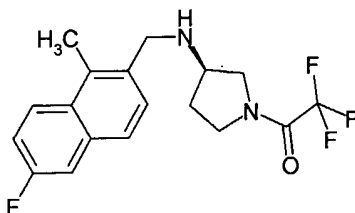
46

Preparation 23: (3R)-N-[(1-Bromo-6-fluoro-2-naphthyl)methyl]-1-(trifluoroacetyl)pyrrolidin-3-amine



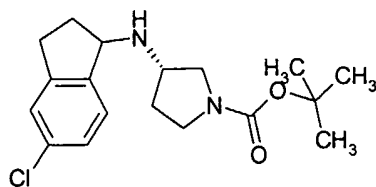
A mixture of the compound described in **preparation 22** (2.75g, 8.65mmol), (3R)-1-(trifluoroacetyl)pyrrolidin-3-amine (2.27g, 10.4mmol) and potassium carbonate (2.38g, 17.2mmol) in acetonitrile (30ml) was heated at reflux for 16 hours. The solvent was then removed in vacuo and the resulting residue was applied directly to a silica column. Elution with dichloromethane:methanol (100:0 increasing polarity to 97:3 by volume) gave the title compound (2.22g, 61%) as an oil.
LRMS APCI⁺ m/z 419, 421 [MH]⁺.

Preparation 24: (3R)-N-[(6-Fluoro-1-methyl-2-naphthyl)methyl]-1-(trifluoroacetyl)pyrrolidin-3-amine



A mixture of the compound described in **preparation 23** (2.21g, 5.27mmol), trimethylboroxine (1.32g, 11.4mmol), potassium carbonate (2.91g, 21.1mmol) and tetrakis(triphenylphosphine)palladium(0) (1.22g, 1.06mmol) in 1,4-dioxane (30ml) was heated at reflux under nitrogen for 3 hours. The reaction mixture was then cooled to room temperature and partitioned between ethyl acetate (100 ml) and water (100 ml). The organic layer was washed with brine, dried (MgSO₄) and evaporated. The resulting residue was purified by column chromatography (silica, eluting with dichloromethane, increasing polarity to dichloromethane:methanol 95:5 by volume) to give the title compound (1.87g, 100%) as an oil.
LRMS APCI⁺ m/z 355 [MH]⁺.

Preparation 25: tert-butyl (3S)-3-[(5-chloro-2,3-dihydro-1H-inden-1-yl)amino]pyrrolidine-1-carboxylate



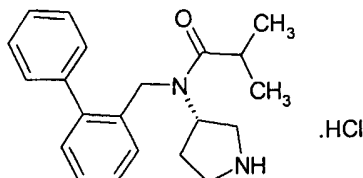
The title compound (0.252g, 70%) was prepared as a mixture of diastereoisomers by a method similar to that described in **preparation 1** using tert-butyl (3S)-3-aminopyrrolidine-1-carboxylate and 5-chloroindan-1-one.

Modified work-up and purification procedure: The reaction mixture was quenched with water (40ml) and extracted into dichloromethane (5x30ml). The organic extracts were combined, dried over magnesium

sulphate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography over silica gel eluting with 50:50 ethyl acetate: pentane to give the title compound as an oil.

LRMS EI⁺ m/z 337 [MH]⁺.

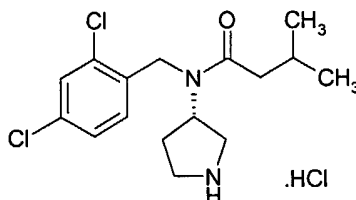
5 **Example 1:** *N*-(Biphenyl-2-ylmethyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide hydrochloride



The Boc protected amine described in **preparation 2** (608mg, 1.3mmol) was dissolved in dichloromethane (15ml) under nitrogen, and the mixture was treated with trifluoroacetic acid (10ml). The reaction mixture was then stirred at room temperature under nitrogen for 20 hours. It was then concentrated *in vacuo* and the resulting residue was taken up in dichloromethane (50ml) and washed with 1M sodium hydroxide solution (25ml). The organic phase was separated, dried over magnesium sulphate and concentrated *in vacuo*. The resulting residue was suspended in diethyl ether (10ml) and 1M hydrogen chloride in diethyl ether (5ml) was added. The mixture was concentrated *in vacuo* and dried under high vacuum to yield the title compound (388mg, 83%) as a white foam.

15 ¹H-NMR (CD₃OD, 400MHz): 0.96-0.98(m, 6H), 2.09(m, 1H), 2.18(m, 1H), 2.55(m, 1H), 3.07(q, 1H), 3.24(m, 1H), 3.37(m, 1H), 3.60(m, 1H), 4.06(m, 1H), 4.61(q, 2H), 7.27-7.34(m, 4H), 7.39-7.49(m, 5H); LRMS APCI⁺ m/z 323 [MH]⁺.

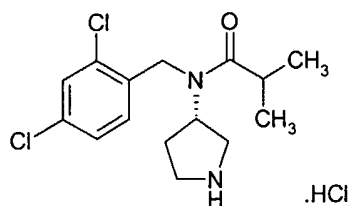
Example 2: *N*-(2,4-Dichlorobenzyl)-3-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide hydrochloride



20 A solution of 4M hydrogen chloride in dioxane (2.5ml) was added to a solution of the Boc protected amine described in **preparation 4** (208mg, 0.48mmol), in dichloromethane (2ml), and the reaction mixture was stirred at room temperature for 18 hours. It was then concentrated *in vacuo* and the resulting residue was azeotroped with dichloromethane (x3) and diethyl ether (x3). The resulting gum was dissolved in diethyl ether:isopropanol (20:1, 2ml) at 30°C then cooled in a solid carbon dioxide bath for 5 minutes, until a solid precipitated. This solid was triturated with another 2ml of diethyl ether:isopropanol (20:1), the solution was concentrated and the resulting product was dried under high vacuum to yield the title compound (124mg, 70%) as a solid.

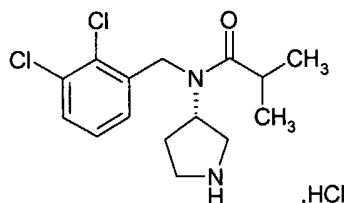
25 ¹H-NMR (CD₃OD, 400MHz): 0.94(d, 6H), 2.13-2.28(m, 5H), 3.12(q, 1H), 3.35(m, 1H), 3.53(m, 1H), 3.67(m, 1H), 4.15(m, 1H), 4.72(s, 2H), 7.27(d, 1H), 7.42(d, 1H), 7.56(s, 1H); LRMS APCI⁺ m/z 329 [MH]⁺; Microanalysis: Found: C, 52.51; H, 6.32; N, 7.57%. C₁₆H₂₂N₂OCl₂.HCl requires C, 52.55; H, 6.34; N, 7.66%.

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Example 3: *N*-(2,4-Dichlorobenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide hydrochloride

A solution of 4M hydrogen chloride in dioxane (1.5ml) was added to a solution of the Boc protected amine described in **preparation 5** (450mg, 1.08mmol), in dichloromethane (3ml), and the reaction mixture was stirred at room temperature for 2 hours. It was then concentrated *in vacuo*, and the resulting residue was partitioned between 2M sodium hydroxide and dichloromethane. The layers were separated and the aqueous layer was extracted twice with dichloromethane. The organic extracts were combined, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5, by volume) to yield the title product as the free base. This was taken up in dichloromethane, and 1M hydrogen chloride in diethyl ether was added. The reaction mixture was stirred at room temperature for 2 hours and then concentrated *in vacuo*. The solid was azeotroped twice with diethyl ether to yield the title compound (331mg, 86%) as an off-white solid.

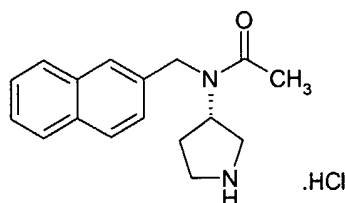
¹H-NMR (CD₃OD, 400MHz): 1.11(d, 6H), 2.14-2.30(m, 2H), 2.79(m, 1H), 3.12(q, 1H), 3.34(m, 1H), 3.49(m, 1H), 3.67(m, 1H), 4.16(m, 1H), 4.76(s, 2H), 7.27(d, 1H), 7.43(d, 1H), 7.55(s, 1H); LRMS APCI⁺ m/z 315 [MH]⁺; Microanalysis: Found: C, 49.58; H, 6.14; N, 7.72%. C₁₅H₂₀N₂OCl₂·HCl·2/3H₂O requires C, 49.55; H, 6.19; N, 7.70%.

Example 4: *N*-(2,3-Dichlorobenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide hydrochloride

The title compound was prepared by a method similar to that described in **example 2** using the Boc protected amine described in **preparation 7**. Trituration with diethyl ether yielded the title compound (487mg, 100%) as a solid.

¹H-NMR (CD₃OD, 400MHz): 1.11 (d, 6H), 2.16-2.31 (m, 2H), 2.75 (m, 1H), 3.12 (q, 1H), 3.36 (m, 1H), 3.52 (m, 1H), 3.67 (m, 1H), 4.19 (m, 1H), 4.81(s, 2H), 7.21 (d, 1H), 7.39 (t, 1H), 7.55 (d, 1H); LRMS APCI⁺ m/z 315 [MH]⁺; Microanalysis: Found : C, 50.33; H, 6.21; N, 7.68%. C₁₅H₂₀N₂OCl₂·HCl·1/3H₂O requires C, 50.38; H, 6.10; N, 7.83%.

49

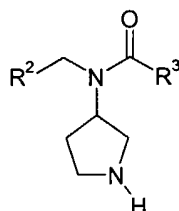
Example 5: *N*-(2-Naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]acetamide hydrochloride

A solution of the benzyl protected product described in **preparation 9** (320mg, 0.893mmol), ammonium formate (56.3mg, 8.93mmol) and 10% Pd/C (40mg) in ethanol (5ml) was heated at reflux under nitrogen for 4.5 hours. The reaction mixture was then filtered through Arbocel[®], washed through with ethanol and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (100:0:0 to 90:10:1, by volume). The free base of the product was dissolved in dichloromethane, minimal volume of 1M hydrogen chloride in diethyl ether was added and the mixture was concentrated *in vacuo*. The solid was triturated in diethyl ether (x3) and dried under vacuum to yield the title compound (80mg, 28%).

¹H-NMR (DMSO-D₆, 400MHz): 1.90-1.97(m, 2H), 2.98-3.13(m, 2H), 3.24-3.34(m, 2H), 3.81(s, 3H), 4.71(m, 1H), 4.80(s, 2H), 7.36(m, 1H), 7.46-7.49(m, 2H), 7.63-7.69(m, 1H), 7.84(m, 1H), 7.81-7.93(m, 2H); MS APCI+ *m/z* 269 [MH]⁺; Microanalysis: Found: C, 63.41; H, 7.20; N, 8.64%. C₁₇H₂₀N₂O.HCl.H₂O requires C, 63.24; H, 7.18; N, 8.68%.

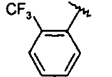
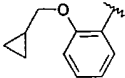
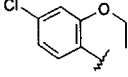
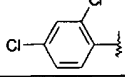
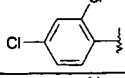
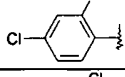
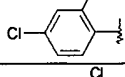
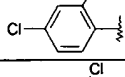
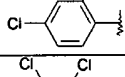
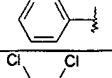
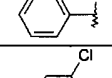
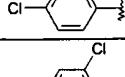
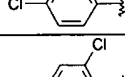
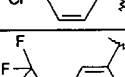
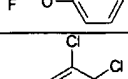
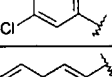
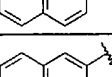
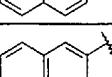
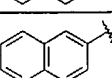
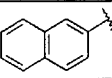
Examples 6-84

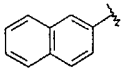
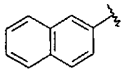
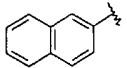
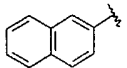
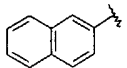
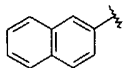
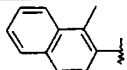
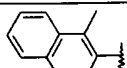
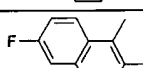
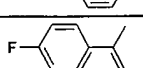
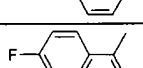
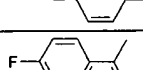
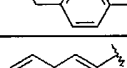
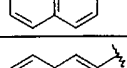
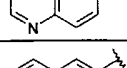
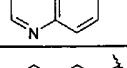
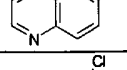
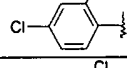
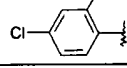
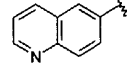
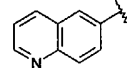
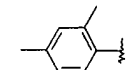
The following tabulated examples were made using analogous methods to those described in the Examples and Preparations described above.



Eg		R ²	R ³	
6	N-[(2'-fluorobiphenyl-2-yl)methyl]-2-methyl-N-[(3 <i>S</i>)-pyrrolidin-3-yl]propanamide			APCI <i>m/z</i> : 341 (MH ⁺)
7	N-[(3'-fluorobiphenyl-2-yl)methyl]-2-methyl-N-[(3 <i>S</i>)-pyrrolidin-3-yl]propanamide			APCI <i>m/z</i> : 341 (MH ⁺)
8	N-(biphenyl-2-ylmethyl)-N-[(3 <i>S</i>)-pyrrolidin-3-yl]butanamide hydrochloride			APCI <i>m/z</i> : 323 (MH ⁺)
9	N-(biphenyl-2-ylmethyl)-3-methyl-N-[(3 <i>S</i>)-pyrrolidin-3-yl]butanamide hydrochloride			APCI <i>m/z</i> : 335 (MH ⁺)
10	N-[(4'-chlorobiphenyl-2-yl)methyl]-2-methyl-N-[(3 <i>S</i>)-pyrrolidin-3-yl]propanamide			APCI <i>m/z</i> : 357 (MH ⁺)
11	N-(biphenyl-2-ylmethyl)-N-[(3 <i>S</i>)-pyrrolidin-3-yl]propanamide hydrochloride			APCI <i>m/z</i> : 309 (MH ⁺)

12	N-[2-(ethylthio)benzyl]-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 307 (MH+)
13	N-(4-chloro-2-methoxybenzyl)-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 311 (MH+)
14	2-methyl-N-(2-phenoxybenzyl)-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 339 (MH+)
15	N-[(4'-fluorobiphenyl-2-yl)methyl]-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide			APCI m/z: 341 (MH+)
16	N-[(2',4'-difluorobiphenyl-2-yl)methyl]-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide			APCI m/z: 359 (MH+)
17	2-methyl-N-[(3S)-pyrrolidin-3-yl]-N-[2-(1,1,2,2-tetrafluoroethoxy)benzyl]propanamide			APCI m/z: 363 (MH+)
18	N-(2-bromobenzyl)-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 325, 327 (MH+)
19	N-(4-chloro-2-methoxybenzyl)-3-methyl-N-[(3S)-pyrrolidin-3-yl]butanamide hydrochloride			APCI m/z: 325 (MH+)
20	2-methyl-N-[(3S)-pyrrolidin-3-yl]-N-[2-(trifluoromethyl)benzyl]propanamide hydrochloride			APCI m/z: 339 (MH+)
21	2-methyl-N-[(3S)-pyrrolidin-3-yl]-N-(2,3,4-trichlorobenzyl)propanamide hydrochloride			APCI m/z: 349 (MH+)
22	2-methyl-N-[2-(methylthio)benzyl]-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 293 (MH+)
23	N-[(3'-fluorobiphenyl-2-yl)methyl]-2-methyl-N-[(3R)-pyrrolidin-3-yl]propanamide			APCI m/z: 341 (MH+)
24	2-methyl-N-(3-phenoxybenzyl)-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 339 (MH+)
25	N-[(3'-chlorobiphenyl-2-yl)methyl]-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide			APCI m/z: 357 (MH+)
26	N-(2,4-dichlorobenzyl)-N-[(3S)-pyrrolidin-3-yl]cyclopentanecarboxamide hydrochloride			APCI m/z: 341 (MH+)
27	N-(2-cyclopropylbenzyl)-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 287 (MH+)
28	N-(2-bromobenzyl)-N-[(3S)-pyrrolidin-3-yl]cyclopropanecarboxamide hydrochloride			APCI m/z: 323, 325 (MH+)
29	N-[(3S)-pyrrolidin-3-yl]-N-[2-(trifluoromethyl)benzyl]cyclopropanecarboxamide hydrochloride			APCI m/z: 313 (MH+)
30	N-[(3',4'-difluorobiphenyl-2-yl)methyl]-N-[(3S)-pyrrolidin-3-yl]cyclobutanecarboxamide			APCI m/z: 371 (MH+)
31	N-(2,3-dichlorobenzyl)-N-[(3S)-pyrrolidin-3-yl]cyclobutanecarboxamide hydrochloride			APCI m/z: 327 (MH+)

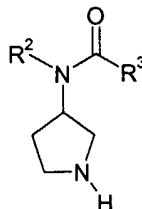
32	N-[(3S)-pyrrolidin-3-yl]-N-[2-(trifluoromethyl)benzyl]cyclopentanecarboxamide hydrochloride			APCI m/z: 341 (MH+)
33	N-[2-(cyclopropylmethoxy)benzyl]-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 317 (MH+)
34	N-(4-chloro-2-ethoxybenzyl)-3-methyl-N-[(3S)-pyrrolidin-3-yl]butanamide hydrochloride			APCI m/z: 339 (MH+)
35	N-(2,4-dichlorobenzyl)-2-methyl-N-[(3S)-pyrrolidin-3-yl]butanamide hydrochloride			APCI m/z: 329 (MH+)
36	N-(2,4-dichlorobenzyl)-2-ethyl-N-[(3S)-pyrrolidin-3-yl]butanamide hydrochloride			APCI m/z: 343 (MH+)
37	N-(4-chloro-2-methylbenzyl)-3-methyl-N-[(3S)-pyrrolidin-3-yl]butanamide hydrochloride			APCI m/z: 309 (MH+)
38	N-(2,4-dichlorobenzyl)-N-[(3S)-pyrrolidin-3-yl]cyclohexanecarboxamide hydrochloride			APCI m/z: 355 (MH+)
39	N-(2,4-dichlorobenzyl)-N-[(3S)-pyrrolidin-3-yl]butanamide hydrochloride			APCI m/z: 315 (MH+)
40	N-(2,4-dichlorobenzyl)-3,3-dimethyl-N-[(3S)-pyrrolidin-3-yl]butanamide hydrochloride			APCI m/z: 343 (MH+)
41	N-(2,3-dichlorobenzyl)-3-methyl-N-[(3S)-pyrrolidin-3-yl]butanamide hydrochloride			APCI m/z: 329 (MH+)
42	N-(2,3-dichlorobenzyl)-N-[(3S)-pyrrolidin-3-yl]pentanamide hydrochloride			APCI m/z: 329 (MH+)
43	N-(2,4-dichlorobenzyl)-N-[(3S)-pyrrolidin-3-yl]pentanamide hydrochloride			APCI m/z: 329 (MH+)
44	2-cyclopropyl-N-(2,4-dichlorobenzyl)-N-[(3S)-pyrrolidin-3-yl]acetamide hydrochloride			APCI m/z: 327 (MH+)
45	N-(2,4-dichlorobenzyl)-4-methyl-N-[(3S)-pyrrolidin-3-yl]pentanamide hydrochloride			APCI m/z: 343 (MH+)
46	2-methyl-N-[(3S)-pyrrolidin-3-yl]-N-[3-(trifluoromethoxy)benzyl]propanamide hydrochloride			APCI m/z: 331 (MH+)
47	2-methyl-N-[(3S)-pyrrolidin-3-yl]-N-(2,3,5-trichlorobenzyl)propanamide hydrochloride			APCI m/z: 349 (MH+)
48	N-(2-naphthylmethyl)-N-[(3R)-pyrrolidin-3-yl]acetamide hydrochloride		Me	APCI m/z: 269 (MH+)
49	N-(2-naphthylmethyl)-N-[(3R)-pyrrolidin-3-yl]cyclohexanecarboxamide hydrochloride			APCI m/z: 337 (MH+)
50	N-(2-naphthylmethyl)-N-[(3R)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 283 (MH+)
51	N-(2-naphthylmethyl)-N-[(3R)-pyrrolidin-3-yl]cyclobutanecarboxamide hydrochloride			APCI m/z: 309 (MH+)
52	3-methyl-N-(2-naphthylmethyl)-N-[(3R)-pyrrolidin-3-yl]butanamide hydrochloride			APCI m/z: 311 (MH+)

53	N-(2-naphthylmethyl)-N-[(3S)-pyrrolidin-3-yl]cyclopentanecarboxamide hydrochloride			APCI m/z: 323 (MH+)
54	N-(2-naphthylmethyl)-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 283 (MH+)
55	N-(2-naphthylmethyl)-N-[(3S)-pyrrolidin-3-yl]cyclobutanecarboxamide hydrochloride			APCI m/z: 309 (MH+)
56	3-methyl-N-(2-naphthylmethyl)-N-[(3S)-pyrrolidin-3-yl]butanamide hydrochloride			APCI m/z: 311 (MH+)
57	N-(2-naphthylmethyl)-N-[(3S)-pyrrolidin-3-yl]cyclohexanecarboxamide hydrochloride			APCI m/z: 337 (MH+)
58	2-methyl-N-(2-naphthylmethyl)-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 297 (MH+)
59	N-[(1-methyl-2-naphthyl)methyl]-N-[(3S)-pyrrolidin-3-yl]acetamide hydrochloride		Me	APCI m/z: 283 (MH+)
60	N-[(1-methyl-2-naphthyl)methyl]-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 297 (MH+)
61	N-[(6-fluoro-1-methyl-2-naphthyl)methyl]-N-[(3R)-pyrrolidin-3-yl]acetamide hydrochloride		Me	APCI m/z: 301 (MH+)
62	N-[(6-fluoro-1-methyl-2-naphthyl)methyl]-N-[(3R)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 315 (MH+)
63	N-[(6-fluoro-1-methyl-2-naphthyl)methyl]-N-[(3S)-pyrrolidin-3-yl]acetamide hydrochloride		Me	APCI m/z: 301 (MH+)
64	N-[(6-fluoro-1-methyl-2-naphthyl)methyl]-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 315 (MH+)
65	2-(methylthio)-N-(2-naphthylmethyl)-N-[(3R)-pyrrolidin-3-yl]acetamide hydrochloride			El m/z: 315 (MH+)
66	N-[(3R)-pyrrolidin-3-yl]-N-(quinolin-6-ylmethyl)pentanamide hydrochloride			APCI m/z: 312 (MH+)
67	N-[(3S)-pyrrolidin-3-yl]-N-(quinolin-6-ylmethyl)pentanamide hydrochloride			APCI m/z: 312 (MH+)
68	N-[(3S)-pyrrolidin-3-yl]-N-(quinolin-6-ylmethyl)butanamide hydrochloride			APCI m/z: 298 (MH+)
69	N-(2,4-dichlorobenzyl)-N-[(3S)-pyrrolidin-3-yl]cyclopropanecarboxamide hydrochloride			APCI m/z: 313 (MH+)
70	N-(2,4-dichlorobenzyl)-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 301 (MH+)
71	4,4,4-trifluoro-N-[(3R)-pyrrolidin-3-yl]-N-(quinolin-6-ylmethyl)butanamide L-(+)-tartrate			El m/z: 352 (MH+)
72	4,4,4-trifluoro-N-[(3S)-pyrrolidin-3-yl]-N-(quinolin-6-ylmethyl)butanamide L-(+)-tartrate			APCI m/z: 352 (MH+)
73	N-(2,4-dimethylbenzyl)-N-[(3S)-pyrrolidin-3-yl]cyclobutanecarboxamide hydrochloride			APCI m/z: 287 (MH+)
74	N-(3-chloro-2-methylbenzyl)-N-[(3S)-pyrrolidin-3-yl]cyclopropanecarboxamide hydrochloride			APCI m/z: 293 (MH+)

75	N-(2,4-dimethylbenzyl)-N-[(3S)-pyrrolidin-3-yl]cyclopropanecarboxamide hydrochloride			APCI m/z: 273 (MH+)
76	N-(2,4-dichlorobenzyl)-N-[(3S)-pyrrolidin-3-yl]cyclobutanecarboxamide hydrochloride			APCI m/z: 327 (MH+)
77	N-(2,3-dimethylbenzyl)-N-[(3S)-pyrrolidin-3-yl]cyclopropanecarboxamide hydrochloride			APCI m/z: 273 (MH+)
78	N-(3-chloro-4-methylbenzyl)-N-[(3S)-pyrrolidin-3-yl]cyclobutanecarboxamide hydrochloride			EI m/z: 307 (MH+)
79	N-[2-fluoro-4-(trifluoromethyl)benzyl]-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 333 (MH+)
80	N-(2-chloro-4-fluorobenzyl)-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 299 (MH+)
81	N-(2,3-dichlorobenzyl)-2-methyl-N-[(3R)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 315 (MH+)
82	N-(4-chloro-2-ethoxybenzyl)-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 326 (MH+)
83	N-[2-methoxy-4-(trifluoromethyl)benzyl]-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 345 (MH+)

Example 84

The following tabulated example was made using analogous methods to those described in the Examples and Preparations described above.

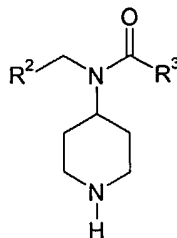


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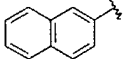
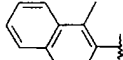
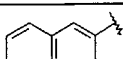
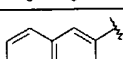
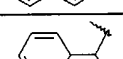
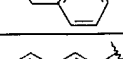
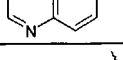
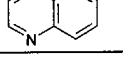
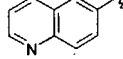
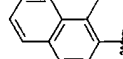
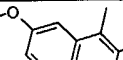
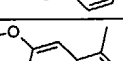
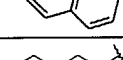
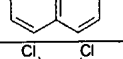
Eg		R ²	R ³	
84	N-(5-chloro-2,3-dihydro-1H-inden-1-yl)-2-methyl-N-[(3S)-pyrrolidin-3-yl]propanamide hydrochloride			APCI m/z: 307 (MH+)

Examples 85-98

The following tabulated examples were made using analogous methods to those described in the Examples and Preparations described above.



10

Eg		R ²	R ³	
85	N-(2-naphthylmethyl)-N-piperidin-4-ylacetamide hydrochloride		Me	APCI m/z: 283 (MH ⁺)
86	N-[(1-methyl-2-naphthyl)methyl]-N-piperidin-4-yl acetamide hydrochloride		Me	ES m/z: 297 (MH ⁺)
87	N-(2-naphthylmethyl)-N-piperidin-4-yl propanamide hydrochloride			EI m/z: 297 (MH ⁺)
88	N-(2-naphthylmethyl)-N-piperidin-4-ylbutanamide hydrochloride			EI m/z: 311 (MH ⁺)
89	3-methyl-N-(1-naphthylmethyl)-N-piperidin-4-yl butanamide oxalate			APCI m/z: 325 (MH ⁺)
90	N-piperidin-4-yl-N-(quinolin-6-ylmethyl) propanamide hydrochloride			EI m/z: 298 (MH ⁺)
91	N-piperidin-4-yl-N-(quinolin-6-ylmethyl) butanamide hydrochloride			EI m/z: 312 (MH ⁺)
92	2-methyl-N-piperidin-4-yl-N-(quinolin-6-ylmethyl) propanamide hydrochloride			EI m/z: 312 (MH ⁺)
93	N-[(1-ethyl-2-naphthyl)methyl]-N-piperidin-4-yl acetamide hydrochloride		Me	APCI m/z: 311 (MH ⁺)
94	N-[(7-methoxy-1-methyl-2-naphthyl)methyl]-N-piperidin-4-ylacetamide hydrochloride		Me	APCI m/z: 327 (MH ⁺)
95	N-[(7-methoxy-1-methyl-2-naphthyl)methyl]-N-piperidin-4-ylpropanamide hydrochloride			APCI m/z: 341 (MH ⁺)
96	2-hydroxy-N-(2-naphthylmethyl)-N-piperidin-4-yl propanamide hydrochloride			APCI m/z: 313 (MH ⁺)
97	N-(2,3-dichlorobenzyl)-2-methyl-N-piperidin-4-yl propanamide hydrochloride			APCI m/z: 329 (MH ⁺)
98	N-(2,4-dichlorobenzyl)-2-methyl-N-piperidin-4-yl propanamide hydrochloride			APCI m/z: 329 (MH ⁺)

The compounds of the invention were evaluated for biological activity by measuring the functional inhibition of monoamine reuptake by the cognate human monoamine transporter protein in a whole cell assay (**Method 1**). Alternatively, the activity of a compound was determined by measuring its affinity for the human monoamine transporter protein as a function of its ability to bind and hence displace a specific ligand (**Method 2**).

Method 1:

- 10 The NRI and SRI IC₅₀ values of the exemplified compounds were determined as described below. A selection of the results is set out below in **Table 1**. All of the exemplified compounds exhibited an NRI IC₅₀ value and/or an SRI IC₅₀ value of less than 100 nM; a selection are characterized in table 1.

	SRI IC ₅₀ (nM)	NRI IC ₅₀ (nM)
Example 1	>400	14
Example 2	93	31
Example 3	14	28
Example 4	12	23
Example 5	2.6	243

Table 1.

The compounds were tested for biological activity by their ability to inhibit the uptake of serotonin and/or noradrenaline by human serotonin and/or noradrenaline transporters as follows.

5 (i) **Cell Culture**

Human embryonic kidney cells (HEK-293), stably transfected with the human recombinant cDNA encoding either the human serotonin transporter (hSERT, TRAN0105) or the noradrenaline transporter (hNET, TRAN0107), were cultured under standard cell culture techniques. Specifically, cells were grown at 37°C and 5% CO₂ in Dulbecco's Modified Eagle's Medium (DMEM) culture media supplemented with 10% dialysed foetal calf serum (FCS), 2mM L-glutamine and 250µg/ml geneticin. Prior to assay, cells were harvested by utilising cell dissociation solution (Sigma) and centrifugation, and resuspended in standard assay buffer (see below) at a viable cell density of 750,000 cells/ml.

15 (ii) **Determination of inhibitor potency**

All test compounds were dissolved in 100% DMSO at 4mM and diluted down in 1% DMSO in water to give appropriate test concentrations. Assays were carried out in 96-well filter bottom plates. Cells expressing the appropriate human transporter protein (75,000 cells/assay well) were pre-incubated at 25°C in standard assay buffer containing either test compound, a standard inhibitor (positive control) or compound vehicle (DMSO in water; final DMSO concentration was 0.1% in each assay well) for 5 minutes. Reactions were started by addition of either ³H-serotonin or ³H-noradrenaline substrates. All reactions were carried out at 25°C in a shaking incubator. Incubation times were 5 minutes for the hSERT and 15 minutes for the hNET assay. Reactions were terminated by addition of ice-cold wash buffer (see below), followed by filtration of the assay mixture using a vacuum manifold and rapid washing with ice-cold wash buffer. The quantity of ³H-substrate incorporated into the cells was then quantified. Filtered/washed assay plates were dried at 45°C for 1 hour, scintillation fluid added, and radioactivity measured by scintillation counting. Potency of test compounds was quantified as IC₅₀ values (concentration of test compound required to inhibit the specific uptake of radiolabelled substrate into the cells by 50% relative to maximum (compound vehicle only) and minimum (complete inhibition by standard inhibitor) responses).

(iii) **Standard Assay Buffer Composition:**

Tris (hydroxymethyl) amino methane hydrochloride (26mM)

NaCl (124mM)

KCl (4.5mM)

5 KH₂PO₄ (1.2mM)

MgCl₂·6H₂O (1.3mM)

Ascorbic acid (1.136mM)

Glucose (5.55mM)

pH 7.40

10 CaCl₂ (2.8mM)

Pargyline (100μM)

Note: The pH of the buffer was adjusted to 7.40 with 1M NaOH before addition of CaCl₂ and pargyline.

15 Wash Buffer Composition:

Tris (hydroxymethyl) methylamine (26mM)

NaCl (124mM)

KCl (4.5mM)

KH₂PO₄ (1.2mM)

20 MgCl₂·6H₂O (1.3mM)

Ascorbic acid (1.136mM)

pH 7.40 at 4°C with 6M HCl

(iv) **Summary of Assay Parameters**

	hSERT Assay	hNET Assay
Cells per assay well.	75,000	75,000
Substrate Concentration.	³ H-5HT (50nM)	³ H-Noradrenaline (200nM)
Incubation time (minutes)	5	15

25

Method 2:

The NRI and SRI Ki values of the exemplified compounds were determined as described below. A selection of the results is set out below in **Table 2**. All of the exemplified compounds exhibited an NRI Ki value and/or an SRI Ki value of less than 100 nM; a selection are characterized below.

Compound	SRI Ki (nM)	NRI Ki (nM)
Example 1	960	5.8
Example 2	14	44
Example 4	9.5	52

Table 2

30

The compounds were tested for biological activity by their ability to inhibit binding of selective tritiated radioligands at the human serotonin and noradrenaline transporters (SERT and NET, respectively), using scintillation proximity assay (SPA) technology. The SPA binding was performed using cellular membranes prepared from cell lines expressing human cDNA encoding either SERT or NET (hSERT, hNET), using the radioligands ^3H -citalopram and ^3H -nisoxetine respectively.

i) Cell culture methodology

Human embryonic kidney cells (HEK-293) expressing each transporter were maintained as a continuous culture, using standard cell culture techniques, in 50 mL of growth medium (see Media and Buffers for composition) in 225 cm² flasks, at 37 °C in a humidified atmosphere with 5 % CO₂ present. Cells were passaged from a 90 % confluent monolayer at a ratio of approximately 1:3.

For cell harvesting, the growth medium was removed from the monolayer and the cells were incubated with cell dissociation solution (Sigma) until signs of dissociation were observed. The cells were subsequently knocked from the base of the flask and pelleted by centrifugation for storage (frozen at - 80 °C) prior to further use.

ii) Cellular membrane preparation

Cell pellets were thawed on ice and resuspended in 3 mL of membrane preparation buffer (see Media and Buffers for composition) per 1 mL of packed cell volume, using a vortex mixer to disperse the cell pellet.

After incubation on ice for 10 minutes, the suspension was homogenised for four individual 10 second intervals using a hand-held homogeniser. The homogenate was then centrifuged at 1,075 x g for 20 minutes at 4 °C.

The supernatants were then collected and retained. Initial cell & nuclei pellets (P1) were subsequently rehomogenised and centrifuged using the conditions cited above, and the supernatants collected and pooled with those retained from the first spin.

The pooled supernatants were centrifuged at 35,000 x g for 30 minutes at 4 °C, and the supernatants discarded. The pellets (P2) were then resuspended in 1 mL of membrane preparation buffer per 1 mL of the original packed cell volume. Protein concentrations were subsequently measured and the membrane suspension was finally frozen in aliquots of set volume and stored at - 80 °C prior to use in assays.

iii) Assay methodology

A. Determination of Optimal Assay Conditions for Individual Membrane Batches

The specific SPA bead type differed for each transporter studied, wheat germ agglutinin-coated yttrium silicate (YSi WGA) SPA beads were used for hSERT and WGA-coated polystyrene (PVT WGA) SPA beads for hNET assays. For each batch of membrane used, optimal concentrations of bead and membrane were determined.

Tritiated radioligands specific to each transporter (^3H -citalopram for hSERT and ^3H -nisoxetine for hNET) were used. The assay free radioligand concentration was expressed as a percentage of the total free radioligand concentration to give an estimate of the radioligand depletion. The radioligand depletion in assays for both transporters was less than 30% to ensure that there was sufficient radioligand available for binding. The ligand depletion value was also used for selecting the optimal assay conditions when using new batches of membranes.

The affinity of the specific radioligand for the respective transporter was determined for each membrane batch at the selected protein and bead concentrations. This was achieved by the determination of the K_D , the concentration of free radioligand at which 50 % of the transporter binding sites were occupied. The mean K_D for a radioligand at a batch of membranes was determined from data from a minimum of three separate assays. The mean K_D was subsequently used for all assays using the membrane batch profiled to enable determination of K_i values of compounds studied using the method determined by Cheng and Prusoff (Cheng YC and Prusoff WH. Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50% inhibition of an enzymatic reaction. *Biochem Pharmacol* 1973; 22:2099-3108.)

B. Assay protocol

Bead/membrane complex preparation

The required amount of membrane was thawed on ice and added to a pre-determined volume of bead suspension in assay buffer. The beads were then pre-coupled by incubating the predetermined protein quantity per mg of bead on a shaker at a temperature of 4°C for 2 hours. Subsequently, the bead/membrane complex was spun down at 865 x g for 5 minutes. The resulting pellet was resuspended in assay buffer and this spin/wash step was then repeated. The final pellet was then resuspended in assay buffer at the specific concentration required for the final assay.

Ligand preparation

An aliquot of [^3H]-radioligand stock was diluted in assay buffer to give a pre-determined final assay concentration less than the equilibrium dissociation constant (K_D) value.

Compound plate preparation

All test compounds were prepared at a concentration of 4 mM in 100 % dimethyl sulphoxide (DMSO) from dry samples. Compounds were diluted in 0.75 % DMSO in ddH₂O to give appropriate test concentrations in a 384 well plate to give a final volume of 20 μL .

The same volume of assay buffer was added to specific wells of the plate to enable subsequent measurement of total radioligand binding. Furthermore, 20 μL of a high concentration of compound specific to each transporter assay was subsequently added to pre-determined wells to determine non-specific binding (NSB). Fluoxetine (10 μM final assay concentration) was used for hSERT and desipramine (40 μM final assay concentration) for hNET.

For each individual transporter assay, 20 μ L of the prepared specific radioligand was added to each well of the final assay plates (containing compound solutions). Subsequently, 20 μ L of the corresponding bead/membrane complex was added to each well of the final assay plate, ensuring that the suspension was mixed well. The plates were then sealed and incubated, with shaking, for 1 hour at room temperature. The plates were subsequently incubated for an additional 6 hours, with dark adaptation, prior to reading.

C. Data analysis

The assay window (specific binding) per plate was calculated by subtracting the mean NSB readings (in counts per minute, or cpm) from the mean of total binding readings. Subsequently the cpm read per well (with mean NSB subtracted) were expressed as a percentage of the plate window to determine the amount of radioligand bound to the transporter.

These values were plotted against the concentration of the compound tested and a sigmoidal inhibitory concentration effect curve was fitted to the data using a four-parameter logistic equation and free-fitting parameters to give an IC_{50} value (the concentration of compound required to inhibit 50% of the specific binding at the neurotransmitter transporter).

The inhibitory dissociation constant (K_i) value was then calculated from the IC_{50} value using the Cheng-Prusoff equation.

Following determination of individual K_i values for compounds tested, an overall geometric mean was calculated together with 95% confidence intervals and n values, where n is the total number of individual K_i values.

iv) **Media and Buffers**

hSERT and hNET Cell Growth Medium

DMEM, 10 % (w/v) dialysed FCS

2 mM L-glutamine (diluted from 200 mM stock)

25 mM HEPES (diluted from 1 M stock)

250 μ g/mL genetecin

MEMBRANE PREPARATION BUFFER

20 mM HEPES (diluted from 1M stock with ddH₂O), pH 7.4 at room temperature, stored at 4°C. Prior to use, one complete protease inhibitor tablet was dissolved per 50 mL of buffer.

Assay Buffer (1.5 x final assay concentration)

30 mM HEPES (diluted from 1 M stock with ddH₂O) and 180 mM NaCl (diluted from 5 M stock with ddH₂O), pH 7.4 at room temperature, stored at 4 °C.

The compounds can also be tested in specific disease models, such as the pain models as follows:

6.2 Neuropathic pain

The activity of a compound in the treatment of neuropathic pain may be measured according to the following test protocol.

Animals: Male Sprague Dawley rats are housed in appropriately sized groups. All animals are kept under a 12h light/dark cycle (lights on at 07h 00min) with food and water ad libitum. All experiments are carried out by an observer blind to the treatments and in accordance with the Home Office Animals (Scientific Procedures) Act 1986.

Chronic constriction injury (CCI) rat model of neuropathic pain

The CCI of sciatic nerve is performed as previously described by Bennett and Xie (Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain*:33:87-107, 1988). Animals are anaesthetised with a 2% isoflurane/O₂ mixture. The right hind thigh is shaved and swabbed with 1% iodine. Animals are then transferred to a homeothermic blanket for the duration of the procedure and anaesthesia maintained during surgery via a nose cone. The skin is cut along the line of the thighbone. The common sciatic nerve is exposed at the middle of the thigh by blunt dissection through biceps femoris. About 7mm of nerve is freed proximal to the sciatic trifurcation, by inserting forceps under the nerve and the nerve gently lifted out of the thigh. Suture is pulled under the nerve using forceps and tied in a simple knot until slight resistance is felt and then double knotted. The procedure is repeated until 4 ligatures (4-0 silk) are tied loosely around the nerve with approx 1mm spacing. The incision is closed in layers and the wound treated with topical antibiotics.

Streptozocin (STZ)-induced diabetes neuropathy in the rat

Diabetes is induced by a single intraperitoneal injection of streptozotocin (50mg/kg) freshly dissolved in 0.9% sterile saline. Streptozotocin injection induces a reproducible mechanical allodynia within 3 weeks, lasting for at least 7 weeks (Chen and Pan, (Chen SR and Pan HL. Hypersensitivity of Spinothalamic Tract Neurons Associated With Diabetic Neuropathic Pain in Rats. *J Neurophysiol* 87: 2726-2733, 2002).

Assessment of static and dynamic allodynia

Static allodynia.

Animals are habituated to wire bottom test cages prior to the assessment of allodynia. Static allodynia is evaluated by application of von Frey hairs (Stoelting, Wood Dale, Illinois, USA.) in ascending order of force (0.6, 1, 1.4, 2, 4, 6, 8, 10, 15 and 26 grams) to the plantar surface of hind paws. Each von Frey hair is applied to the paw for a maximum of 6 sec, or until a withdrawal response occurred. Once a withdrawal response to a von Frey hair is established, the paw is re-tested, starting with the filament below the one that produced a withdrawal, and subsequently with the remaining filaments in descending force sequence until no withdrawal occurs. The highest force of 26g lifts the paw as well as eliciting a response, thus represented the cut off point. Each animal has both hind paws tested in this manner. The lowest amount of force required to elicit a response is recorded as paw withdrawal threshold (PWT) in grams. Static

allodynia is defined as present if animals respond to a stimulus of, or less than, 4g, which is innocuous in naive rats (Field MJ, Bramwell S, Hughes J, Singh L. Detection of static and dynamic components of mechanical allodynia in rat models of neuropathic pain: are they signalled by distinct primary sensory neurones? Pain, 1999;83:303-11).

5

Dynamic allodynia

Dynamic allodynia is assessed by lightly stroking the plantar surface of the hind paw with a cotton bud. To avoid recording general motor activity, care is taken to perform this procedure in fully habituated rats that are not active. At least two measurements are taken at each time point, the mean of which represents the paw withdrawal latency (PWL). If no reaction is exhibited within 15 sec the procedure is terminated and animals are assigned this withdrawal time. A pain withdrawal response is often accompanied with repeated flinching or licking of the paw. Dynamic allodynia is considered to be present if animals respond to the cotton stimulus within 8 sec of commencing stroking (Field et al, 1999).

10

15 **6.3 Nociceptive pain**

The activity of a compound in the treatment of nociceptive pain may be measured according to the following test protocols.

Hotplate

20

Experimental Procedure: Male Sprague Dawley rats are placed on a hot plate (Ugo Basile, Italy) maintained at $55 \pm 5^\circ\text{C}$. The time between placement of the animal on the hot plate and occurrence of either licking of fore or hind paw, shaking or jumping off the surface is measured. Baseline measurements are made and animals reassessed following drug administration. The cut off time for hot plate latencies is set at 20 seconds to prevent tissue damage.

25

Ovariectomy (OVX)

Experimental Procedure: Female Sprague Dawley rats are placed into an anaesthetic chamber and anaesthetised with a 2% isoflurane O_2 mixture. During surgery, anaesthesia is maintained via a nose cone. OVX is performed via a midline incision (2cm in length) in the linea alba, whilst the animal is on a heat blanket. The ovarian ligaments and cervix are ligated with 5-0 silk, using a single clamp technique. The ovaries and uterus are then removed. The abdominal wall is closed using 4 simple interrupted sutures and the skin closed using 4 wound clips. Immediately after surgery animals are placed in individual plexiglass chambers. Once the animal has recovered from the anaesthetic the abdominal body postures are recorded in 30 min bins at various time points. Postures scored are humpback position, contraction of the muscle of the abdomen associated with inward movements of the hind limb, stretching of the body and squashing of the lower abdomen against the floor. Each of these behaviours is scored as one posture.

30

35

Brennan

40

Experimental Procedure: Male Sprague Dawley rats are placed into an anaesthetic chamber and anaesthetised with a 2% isoflurane O_2 mixture. During surgery, anaesthesia is maintained via a nose

cone. The plantar aspect of the right hind paw is cleaned with 50% ethanol. A 1cm long longitudinal incision is made with a number 11 blade through the skin and fascia of the plantar aspect of the foot, starting 0.5cm from the proximal edge of the heel and extending toward the toes. The plantaris muscle is elevated using forceps and incised longitudinally, the muscle origin and insertion remain intact. After haemostasis with gentle pressure, the skin is closed with two simple sutures of braided silk.

Mono-Iodoacetate (MIA)-induced OA model

Male 6 weeks-old Sprague-Dawley (SD, Japan SLC or Charles River Japan) rats are anesthetized with pentobarbital. Injection site is shaved and cleaned with 70% ethanol. 25 µl of MIA solution or saline is injected in the right knee joint using a 29G needle. 7, 14, 19 and 20 days after the MIA injection, train rats to measure the weight bearing (WB) without their stress. 21 days after the MIA injection, the WB on two of each hind paw is measured and the WB deficit is calculated. Define the WB deficit value as "pre value". Arrange for experimental group evenly in consideration of pre value and prepre value. After the administration of test compounds or vehicle, the WB on two of each hind paw was measured.

Cancer pain model

These experiments use adult male C3H/HeN mice (Nihon SLC, Shizuoka, Japan). The mice are housed in accordance with National Institutes of Health guidelines in a vivarium maintained at 22 °C with a 12-hour alternating light-dark cycle, and were given food and water ad libitum. The sarcoma injection protocol which is used has been described. After induction of general anesthesia with an inhalation of isofluran (2%), a superficial incision is made in the skin overlying the patella, using Mora scissors. The patellar ligament is then cut, exposing the condyles of the distal femur. A 30-gauge needle is inserted at the level of the intercondylar notch and into the medullary canal to create an initial core pathway. After the initial core is made, a 29-gauge needle is used to make the final pathway into the bone. A 0.5-mm depression is then made using a half-round bur in a pneumatic dental high speed handpiece, to serve as mechanical retention for the dental resin plug. Then, 20 µl α-minimum essential media (Sigma; sham injection) or 20 µl media containing 1×10^5 2472 osteolytic sarcoma cells (American Type Culture Collection, Rockville, Maryland; sarcoma injection) is injected using a 29-gauge needle and a .25 cc syringe. To prevent leakage of cells outside the bone, the injection site is closed with dental resin, followed by copious irrigation with filtered water. Wound closure is achieved using auto wound clips (Becton Dickinson, San Jose, California). Wound clips are removed at day 5 to prevent interference with behavioral testing.

Assessment of static and dynamic allodynia

Static allodynia.

Animals are habituated to wire bottom test cages prior to the assessment of allodynia. Static allodynia is evaluated by application of von Frey hairs (Stoelting, Wood Dale, Illinois, USA.) in ascending order of force (0.6, 1, 1.4, 2, 4, 6, 8, 10, 15 and 26 grams) to the plantar surface of hind paws. Each von Frey hair is applied to the paw for a maximum of 6 sec, or until a withdrawal response occurs. Once a withdrawal response to a von Frey hair is established, the paw is re-tested, starting with the filament below the one

that produces a withdrawal, and subsequently with the remaining filaments in descending force sequence until no withdrawal occurs. The highest force of 26g lifts the paw as well as eliciting a response, thus represents the cut off point. Each animal has both hind paws tested in this manner. The lowest amount of force required to elicit a response is recorded as paw withdrawal threshold (PWT) in grams. Static allodynia is defined as present if animals respond to a stimulus of, or less than, 4g, which is innocuous in naive rats (Field MJ, Bramwell S, Hughes J, Singh L. Detection of static and dynamic components of mechanical allodynia in rat models of neuropathic pain: are they signalled by distinct primary sensory neurones? Pain, 1999;83:303-11).

10 Dynamic allodynia

Dynamic allodynia is assessed by lightly stroking the plantar surface of the hind paw with a cotton bud. To avoid recording general motor activity, care is taken to perform this procedure in fully habituated rats that are not active. At least two measurements are taken at each time point, the mean of which represents the paw withdrawal latency (PWL). If no reaction is exhibited within 15 sec the procedure is terminated and animals are assigned this withdrawal time. A pain withdrawal response is often accompanied with repeated flinching or licking of the paw. Dynamic allodynia is considered to be present if animals respond to the cotton stimulus within 8 sec of commencing stroking (Field et al, 1999).

Radiant heat paw withdrawal

20 Experimental procedure: Thermal paw withdrawal is assessed using the rat plantar test (Ugo Basile, Italy) following a modified method of Hargreaves et al., 1988. Rats are habituated to the apparatus that consists of three individual perspex boxes on an elevated glass table. A mobile radiant heat source is located under the table and focused onto the hind paw and paw withdrawal latencies (PWL) are recorded. There is an automatic cut off point of 22.5 s to prevent tissue damage. PWL are taken 2–3 times for both hind paws of each animal, the mean of which represents baselines for right and left hind paws. The apparatus is calibrated to give a PWL of approximately 10 s.

Weight bearing

30 Experimental procedure: Animals are examined for hypersensitivity in the weight-bearing test, using an "incapacitance tester" (Linton Instruments, Diss, Norfolk, U.K.). Rats were positioned with their fore limbs up on a perspex slope and hind limb weight distribution was measured via force transducers under each of the hind paws. Each animal is placed in the apparatus and the weight load exerted by the hind paws is noted. The difference in weight bearing is calculated by subtracting the ipsilateral (injured) paw from the contralateral paw (normal) and this constitutes the raw data.

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6.4 Inflammatory pain

The activity of compound in the treatment of inflammatory pain may be measured according to the following test protocol.

40

CFA-induced weight bearing deficits in rats

Male 7-week-old SD rats are fasted overnight. CFA (300 µg of Mycobacterium Tuberculosis H37 RA (Difco Laboratories) in 100 µL of liquid paraffin (Wako)) is injected into the rat's right hind footpad. Two days after the administration of CFA, the changes in hind paw weight distribution between the left (ipsilateral) and the right (contralateral) limbs are measured as an index of pain by using Linton Incapacitance tester (Linton Instrumentation, UK). The test compound suspended in 0.1% MC (Wako) is administered orally in a volume of 1 mL per 100 g body weight. Each animal is placed in the apparatus and the weight load exerted by the hind paws is measured before, 1, 2 and 4 hours after drug administration.

Carrageenin-induced mechanical hyperalgesia in rats

Male 4-week-old SD rats are fasted overnight. Hyperalgesia is induced by intraplantar injection of Lambda-carrageenin (0.1 ml of 1% w/v solution in saline, Zushikagaku). The test compound (1ml of 0.1% methylcellulose/100g body weight) is given orally at 5.5 hours after the carrageenin injection. The paw withdrawal threshold (gram) is measured by analgesimeter (Ugo Basile) at 3.5, 4.5, 6.5 and 7.5 hours after the carrageenin injection. (Randall L.O. & Selitto I.J., Arch. Int. Pharmacodyn. 111, 409-419, 1957)

Carrageenan-Induced Thermal Hyperalgesia (CITH) in the Rat

Thermal hyperalgesia is assessed using the rat plantar test (Ugo Basile, Comerio, Italy), according to a method modified by Hargreaves et al. (1988). Briefly, rats are habituated to the apparatus that consists of three individual Perspex boxes on a glass table. A mobile radiant heat source is located under the table and focused onto the desired paw. Paw withdrawal latencies (PWLs) are recorded three times for both hind paws of each animal, the mean of which represents baseline for left and right hind paws. The apparatus is calibrated to give a PWL of approximately 10 s in naïve rats. To prevent tissue damage of the plantar zone, a 22.5 sec cut-off is observed. Lambda carrageenan is injected intraplantarly (100 µl, 20 mg/ml) the right hind paw and baseline recordings of PWT are taken 2 hr post administration.

6.5 Visceral pain

The activity of a compound in the treatment of visceral pain may be measured according to the following test protocols.

Several models are available to determine if a compound is effective in treating disorders of the viscera. These models include a LPS model (Eutamene H et al, *J Pharmacol Exp Ther* 2000 295 (1):162-7), a TNBS model (Diop L. et al, *Gastroenterology* 1999, 116, 4(2): A986), a IBD model (Clemett D, Markham A, *Drugs* 2000 Apr;59(4):929-56), a pancreatic pain model (Isla AM, *Hosp Med* 2000 Jun;61(6):386-9) and a visceral non digestive pain model (Boucher M et al, *J Urol* 2000 Jul;164(1):203-8).

TNBS-induced chronic visceral allodynia in rats

In this experimental model of colonic distension in awake rats, previous injection of trinitrobenzenesulfonic acid (TNBS) into the proximal colon lowered the visceral pain threshold.

Materials and methods: Male Sprague-Dawley rats are used. The animals are housed 3 per cage in a regulated environment ($20 \pm 1^\circ\text{C}$, $50 \pm 5\%$ humidity, with light 8:00 am to 8:00 pm). At day 0, under anesthesia (ketamine 80 mg/kg i.p.; acepromazine 12 mg/kg i.p.), the injection of TNBS (50 mg/kg in ethanol 30 %), or saline (1.5 ml/kg) for control rats, is performed into the proximal colon wall (1 cm from the cecum). After the surgery, animals are individually housed in polypropylene cages and kept in a regulated environment ($20 \pm 1^\circ\text{C}$, $50 \pm 5\%$ humidity, with light 8:00 a.m. to 8:00 p.m.) during 7 days. At day 7 after TNBS administration, a balloon (5-6 cm length) is inserted by anus, and kept in position (tip of balloon 5 cm from the anus) by taping the catheter to the base of the tail. Oral administration of the test compound is performed 1 h before the colonic distension cycle: the balloon is progressively inflated by steps of 5 mm Hg (0.667 kPa), from 0 to 75 mm Hg, each step of inflation lasting 30 s. Each cycle of colonic distension is controlled by a standard barostat. The threshold (mm Hg) corresponds to the pressure which produced the first abdominal contraction, and the cycle of distension is then discontinued. The colonic threshold is determined after performance of four cycles of distension on the same animal.

15 LPS-induced rectal hypersensitivity in rats

Intraperitoneal injection of bacterial lipo-polysaccharide (LPS) has been shown to induce rectal hyperalgesia in awake rats.

Materials and methods: Animals are surgically prepared for electromyography: rats are anaesthetized by intraperitoneal injection of acepromazine (0.6 mg/kg) and ketamine (120 mg/kg). Three groups of three electrodes are implanted in the abdominal external oblique musculature, just superior to the inguinal ligament. Electrodes are exteriorized on the back of the neck and protected by a glass tube attached to the skin. Animals are individually housed in polypropylene cages and kept in a temperature-controlled room (21°C). Food (UAR pellets, Epinay, France) and water are provided ad libitum.

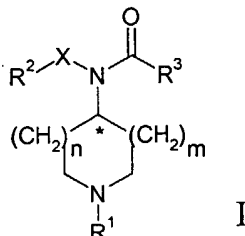
Electromyographic recordings begin five days after surgery. The electrical activity of abdominal striated muscles is recorded with an electroencephalograph machine (Mini VIII Alvar, Paris, France) using a short time constant (0.03 s) to remove low-frequency signals ($< 3\text{ Hz}$) and a paper speed of 3.6 cm/min. Spike bursts are recorded as an index of abdominal contractions.

Distension procedure: Rats are placed in plastic tunnels (6 cm diameter x 25 cm long), where they cannot move, escape, or turn around, in order to prevent damage to the balloon. Animals are accustomed to this procedure for four days before rectal distension in order to minimize stress reactions during experiments. The balloon used for distension is an arterial embolectomy catheter (Fogarty, Edwards Laboratories Inc.).

Rectal distension is performed by insertion of the balloon (2 mm diameter x 2 cm long) into the rectum, at 1 cm from the anus, and catheter is fixed at the base of the tail. It is inflated progressively with tepid water by steps of 0.4 ml, from 0 to 1.2 ml, each step of inflation lasting 5 min. To detect possible leakage, the volume of water introduced in the balloon is checked by complete removal with a syringe at the end of the distension period.

Claims:

1. A compound of Formula (I)



and pharmaceutically and/or veterinarily acceptable derivatives thereof, wherein:

R¹ is -H, -C₁₋₆alkyl, -C(A)Y, -C₃₋₈cycloalkyl, -aryl, -het, aryl-C₁₋₄alkyl- or het-C₁₋₄alkyl-, wherein the cycloalkyl, aryl or het groups are optionally substituted by at least one substituent independently selected from B;

A is S or O;

Y is H, -C₁₋₆alkyl, -aryl, -het, aryl-C₁₋₄alkyl- or het-C₁₋₄alkyl-;

aryl is independently selected from phenyl, naphthyl, anthracyl or phenanthryl;

het is independently selected from an aromatic or non-aromatic 4-, 5- or 6- membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to a 5- or 6- membered carbocyclic group or a second 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom;

B represents -C₁₋₈alkyl, -C₁₋₈alkoxy, -OH, -halo, -CF₃, -CHF₂, -OCF₃, -OCHF₂, -SCF₃, hydroxy-C₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₆alkyl- and C₁₋₄alkyl-S-C₁₋₄alkyl-;

R² is aryl¹ or het¹, each optionally substituted by at least one substituent independently selected from D;

aryl¹ is independently selected from phenyl, naphthyl, anthracyl, phenanthryl, or indanyl;

het¹ is an aromatic 5 to 10 membered heterocyclic ring system which contains at least one N, O or S heteroatom, optionally containing an aryl group;

D represents -C₁₋₈alkyl, -C₁₋₈alkoxy, -OH, -halo, -CF₃, -CHF₂, -OCF₃, -OCHF₂, -SCF₃, hydroxy-C₁₋₆alkyl-, C₁₋₄alkoxy-C₁₋₆alkyl-, -SC₁₋₈alkyl, C₁₋₄alkyl-S-C₁₋₄alkyl-, -aryl², -het², -Oaryl², -Ohet², -Saryl², -Shet², -CF₂CF₃, -CH₂CF₃, -CF₂CH₃, -OCF₂CHF₂, -C₃₋₈cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl-, C₃₋₆cycloalkyl-C₁₋₄alkoxy-, C₃₋₆cycloalkyl-O-C₁₋₄alkyl-, C₃₋₆cycloalkyl-C₁₋₄alkoxy-C₁₋₄alkyl-, -OC₃₋₆cycloalkyl, -OC₁₋₈alkyl-C₃₋₈cycloalkyl and -SC₃₋₆cycloalkyl, wherein the aryl² and het² groups are optionally substituted by at least one group selected from E;

aryl² is independently selected from phenyl, naphthyl, anthracyl or phenanthryl;

het² is independently selected from an aromatic or non-aromatic 4-, 5- or 6- membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to a 5- or 6- membered carbocyclic group or a second 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom;

E represents $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ alkoxy, $-OC_{3-6}$ cycloalkyl, -halo, -CN, -OH, $-CF_3$, $-CHF_2$, $-OCF_3$, $-OCHF_2$, hydroxy C_{1-6} alkyl-, C_{1-4} alkoxy- C_{1-4} alkyl-, $-SC_{1-6}$ alkyl and $-SCF_3$;

5 R^3 is -H, $-C_{1-8}$ alkyl, $-C_{3-8}$ cycloalkyl, C_{3-8} cycloalkyl- C_{1-6} alkyl-, $-C_{1-8}$ alkyl SC_{1-8} alkyl-, -het³, or het³- C_{1-4} alkyl-, wherein the alkyl, cycloalkyl and het³ groups are each optionally substituted by at least one substituent independently selected from G;

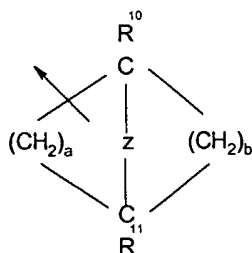
het³ is a non-aromatic 4-, 5- or 6- membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to a 5- or 6- membered carbocyclic group or a second 4-, 5- or 6- membered heterocycle which contains at least one N, O or S heteroatom;

10 G represents $-C_{1-8}$ alkyl, $-C_{1-6}$ alkoxy, -OH, -halo, $-CF_3$, $-OCHF_2$, $-OCF_3$, $-SCF_3$, -CN, $-CF_2CF_3$, $-CF_2-C_{1-4}$ alkyl, hydroxy- C_{1-6} alkyl-, C_{1-4} alkoxy- C_{1-6} alkyl- and C_{1-4} alkyl-S- C_{1-4} alkyl-; and the alkyl groups being optionally substituted by at least one substituent independently selected from J;

J represents C_{1-6} alkoxy-, -OH, -halo, $-CF_3$, $-OCHF_2$, $-OCF_3$, $-SCF_3$, -CN, $-CF_2CF_3$, $-CF_2-$
15 C_{1-4} alkyl, hydroxy- C_{1-6} alkyl-, C_{1-4} alkoxy- C_{1-6} alkyl- and C_{1-4} alkyl-S- C_{1-4} alkyl-;

or R^3 is $-(CH_2)_{a'}K$, wherein a' is 0, 1 or 2 and K is a group selected from:

(i)



20 wherein:

Z is O, S, NR^{12} , $(CH_2)_v$ or a bond;

a is 1, 2, 3 or 4;

b is 1, 2 or 3;

v is 1 or 2;

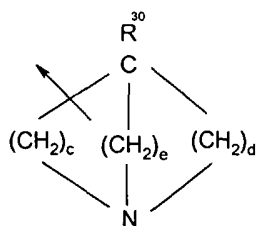
25 R^{10} and R^{11} are each independently -H or $-C_{1-4}$ alkyl;

R^{12} is -H, $-C_{1-6}$ alkyl, $-C(O)C_{1-6}$ alkyl, $-SO_2-C_{1-6}$ alkyl;

and wherein one or more pairs of hydrogen atoms on adjacent carbon or nitrogen atoms may be replaced by a corresponding number of double bonds, provided the ring system is not aromatic;

30 (iii) a carbocyclic spiro group containing 6 to 12 carbon atoms;

(iii)



wherein:

c is 1, 2, 3 or 4;

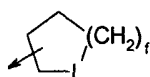
d is 1, 2 or 3;

e is 1 or 2; and

R^{30} is -H or -C₁₋₄ alkyl;

and wherein one or more pairs of hydrogen atoms on adjacent carbon atoms may be replaced by a corresponding number of double bonds, provided the ring system is not aromatic;

(iv)



wherein:

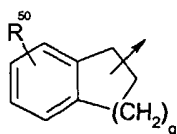
f is 0, 1, 2 or 3;

L is SO, SO₂ or NR⁴⁰; and

R^{40} is -H, -C₁₋₆ alkyl, -C(O)C₁₋₆ alkyl, -SO₂-C₁₋₆ alkyl;

and wherein one or more pairs of hydrogen atoms on adjacent carbon atoms may be replaced by a corresponding number of double bonds, provided the ring system is not aromatic;

(v)



wherein:

g is 0, 1, 2 or 3; and

R^{50} is -H, -C₁₋₈ alkyl, -C₁₋₈ alkoxy, -OH, -halo, -CF₃, -OCHF₂, -OCF₃, -SCF₃, hydroxy-C₁₋₆ alkyl-, C₁₋₄ alkoxy-C₁₋₆ alkyl- and C₁₋₄ alkyl-S-C₁₋₄ alkyl-; and

(vi) -CH(cyclopropane)₂;

X is a covalent bond, -C₁₋₈ alkyl or -C₃₋₈ cycloalkyl, wherein if X is C₃₋₈ cycloalkyl, then R²-X may form a fused aryl-cycloalkyl ring system; and

n is 1 or 2, provided that:

when n is 1, m is 0 or 1; and

when n is 2, m is 0;

wherein if m is 0, then * represents a chiral centre.

- 5 2. A compound according to Claim 1, wherein R¹ is H.
3. A compound according to Claim 1 or Claim 2, wherein R² is aryl¹ or het¹, each optionally substituted by between one and three substituents independently selected from D.
- 10 4. A compound according to Claim 3, wherein D is -halo, -C₁₋₈alkyl, -SC₁₋₈alkyl, C₁₋₈alkyloxy-, C₁₋₄alkoxy-C₁₋₆alkyl-, -aryl², -Oaryl², -het², -C₃₋₈cycloalkyl, -OC₁₋₈alkyl-C₃₋₈cycloalkyl, -CF₃, -SCF₃, -OCHF₂, -CHF₂, -OCF₂CHF₂, or -OCF₃.
- 15 5. A compound according to any of Claims 1 to 4, wherein R³ is -C₁₋₈alkyl, -C₃₋₈cycloalkyl, C₃₋₈cycloalkyl-C₁₋₆alkyl-, or C₁₋₈alkylSC₁₋₈alkyl-.
6. A compound according to any of Claims 1 to 5, wherein X is a covalent bond or -C₁₋₈alkyl.
7. A compound according to any of Claims 1 to 6, wherein m is 0 and * represents the R or S enantiomer.
- 20 8. A compound according to Claim 7, wherein * represents the S enantiomer.
9. A compound according to Claim 1, selected from:
 - 25 *N*-(Biphenyl-2-ylmethyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
 - N*-(2,4-Dichlorobenzyl)-3-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
 - N*-(2,4-Dichlorobenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
 - N*-(2,3-Dichlorobenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
 - N*-(2-Naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]acetamide;
 - 30 *N*-[(2'-fluorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
 - N*-[(3'-fluorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
 - N*-(biphenyl-2-ylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
 - N*-(biphenyl-2-ylmethyl)-3-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
 - N*-[(4'-chlorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
 - 35 *N*-(biphenyl-2-ylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
 - N*-[2-(ethylthio)benzyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
 - N*-(4-chloro-2-methoxybenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
 - 2-methyl-*N*-(2-phenoxybenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
 - N*-[(4'-fluorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
 - 40 *N*-[(2',4'-difluorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
 - 2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]-*N*-[2-(1,1,2,2-tetrafluoroethoxy)benzyl]propanamide;

- N*-(2-bromobenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(4-chloro-2-methoxybenzyl)-3-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]-*N*-[2-(trifluoromethyl)benzyl]propanamide;
2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]-*N*-(2,3,4-trichlorobenzyl)propanamide;
5 2-methyl-*N*-[2-(methylthio)benzyl]-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-[(3'-fluorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*R*)-pyrrolidin-3-yl]propanamide;
2-methyl-*N*-(3-phenoxybenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-[(3'-chlorobiphenyl-2-yl)methyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopentanecarboxamide;
10 *N*-(2-cyclopropylbenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(2-bromobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopropanecarboxamide;
N-[(3*S*)-pyrrolidin-3-yl]-*N*-[2-(trifluoromethyl)benzyl]cyclopropanecarboxamide;
N-[(3',4'-difluorobiphenyl-2-yl)methyl]-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
N-(2,3-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
15 *N*-[(3*S*)-pyrrolidin-3-yl]-*N*-[2-(trifluoromethyl)benzyl]cyclopentanecarboxamide;
N-[2-(cyclopropylmethoxy)benzyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(4-chloro-2-ethoxybenzyl)-3-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
N-(2,4-dichlorobenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
N-(2,4-dichlorobenzyl)-2-ethyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
20 *N*-(4-chloro-2-methylbenzyl)-3-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
N-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclohexanecarboxamide;
N-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
N-(2,4-dichlorobenzyl)-3,3-dimethyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
N-(2,3-dichlorobenzyl)-3-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
25 *N*-(2,3-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]pentanamide;
N-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]pentanamide;
2-cyclopropyl-*N*-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]acetamide;
N-(2,4-dichlorobenzyl)-4-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]pentanamide;
2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]-*N*-[3-(trifluoromethoxy)benzyl]propanamide;
30 2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]-*N*-(2,3,5-trichlorobenzyl)propanamide;
N-(2-naphthylmethyl)-*N*-[(3*R*)-pyrrolidin-3-yl]acetamide;
N-(2-naphthylmethyl)-*N*-[(3*R*)-pyrrolidin-3-yl]cyclohexanecarboxamide;
N-(2-naphthylmethyl)-*N*-[(3*R*)-pyrrolidin-3-yl]propanamide;
N-(2-naphthylmethyl)-*N*-[(3*R*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
35 3-methyl-*N*-(2-naphthylmethyl)-*N*-[(3*R*)-pyrrolidin-3-yl]butanamide;
N-(2-naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopentanecarboxamide;
N-(2-naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(2-naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
3-methyl-*N*-(2-naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]butanamide;
40 *N*-(2-naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclohexanecarboxamide;
2-methyl-*N*-(2-naphthylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;

- N*-[(1-methyl-2-naphthyl)methyl]-*N*-[(3*S*)-pyrrolidin-3-yl]acetamide;
N-[(1-methyl-2-naphthyl)methyl]-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-[(6-fluoro-1-methyl-2-naphthyl)methyl]-*N*-[(3*R*)-pyrrolidin-3-yl]acetamide;
N-[(6-fluoro-1-methyl-2-naphthyl)methyl]-*N*-[(3*R*)-pyrrolidin-3-yl]propanamide;
5 *N*-[(6-fluoro-1-methyl-2-naphthyl)methyl]-*N*-[(3*S*)-pyrrolidin-3-yl]acetamide;
N-[(6-fluoro-1-methyl-2-naphthyl)methyl]-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
2-(methylthio)-*N*-(2-naphthylmethyl)-*N*-[(3*R*)-pyrrolidin-3-yl]acetamide;
N-[(3*R*)-pyrrolidin-3-yl]-*N*-(quinolin-6-ylmethyl)pentanamide;
N-[(3*S*)-pyrrolidin-3-yl]-*N*-(quinolin-6-ylmethyl)pentanamide;
10 *N*-[(3*S*)-pyrrolidin-3-yl]-*N*-(quinolin-6-ylmethyl)butanamide;
N-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopropanecarboxamide;
N-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
4,4,4-trifluoro-*N*-[(3*R*)-pyrrolidin-3-yl]-*N*-(quinolin-6-ylmethyl)butanamide;
4,4,4-trifluoro-*N*-[(3*S*)-pyrrolidin-3-yl]-*N*-(quinolin-6-ylmethyl)butanamide;
15 *N*-(2,4-dimethylbenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
N-(4-chloro-2-fluorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
N-(3-chloro-2-methylbenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopropanecarboxamide;
N-(2,4-dimethylbenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopropanecarboxamide;
N-(2,4-dichlorobenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
20 *N*-(2,3-dimethylbenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclopropanecarboxamide;
N-(3-chloro-4-methylbenzyl)-*N*-[(3*S*)-pyrrolidin-3-yl]cyclobutanecarboxamide;
N-[2-fluoro-4-(trifluoromethyl)benzyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(2-chloro-4-fluorobenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(2,3-dichlorobenzyl)-2-methyl-*N*-[(3*R*)-pyrrolidin-3-yl]propanamide;
25 *N*-(4-chloro-2-ethoxybenzyl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-[2-methoxy-4-(trifluoromethyl)benzyl]-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(5-chloro-2,3-dihydro-1*H*-inden-1-yl)-2-methyl-*N*-[(3*S*)-pyrrolidin-3-yl]propanamide;
N-(2-naphthylmethyl)-*N*-piperidin-4-ylacetamide;
N-[(1-methyl-2-naphthyl)methyl]-*N*-piperidin-4-ylacetamide;
30 *N*-(2-naphthylmethyl)-*N*-piperidin-4-ylpropanamide;
N-(2-naphthylmethyl)-*N*-piperidin-4-ylbutanamide;
3-methyl-*N*-(1-naphthylmethyl)-*N*-piperidin-4-ylbutanamide;
N-piperidin-4-yl-*N*-(quinolin-6-ylmethyl)propanamide;
N-piperidin-4-yl-*N*-(quinolin-6-ylmethyl)butanamide;
35 2-methyl-*N*-piperidin-4-yl-*N*-(quinolin-6-ylmethyl)propanamide;
N-[(1-ethyl-2-naphthyl)methyl]-*N*-piperidin-4-ylacetamide;
N-[(7-methoxy-1-methyl-2-naphthyl)methyl]-*N*-piperidin-4-ylacetamide;
N-[(7-methoxy-1-methyl-2-naphthyl)methyl]-*N*-piperidin-4-ylpropanamide;
2-hydroxy-*N*-(2-naphthylmethyl)-*N*-piperidin-4-ylpropanamide;
40 *N*-(2,3-dichlorobenzyl)-2-methyl-*N*-piperidin-4-ylpropanamide;
N-(2,4-dichlorobenzyl)-2-methyl-*N*-piperidin-4-ylpropanamide;

and pharmaceutically and/or veterinarily acceptable derivatives thereof.

10. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 9 and a pharmaceutically acceptable adjuvant, diluent or carrier.

5

11. A compound according to any one of Claims 1 to 9 for use as a medicament.

12. Use of a compound according to any one of Claims 1 to 9 in the manufacture of a medicament for the treatment of a disorder in which the regulation of monoamine transporter function in mammals is implicated.

10

13. Use of a compound according to any one of Claims 1 to 9 in the manufacture of a medicament for the treatment of a disorder in which the regulation of serotonin or noradrenaline in mammals is implicated.

15

14. Use according to Claim 13, wherein the regulation of serotonin and noradrenaline is implicated.

15. Use of a compound according to any one of Claims 1 to 9 in the manufacture of a medicament for the treatment of urinary disorders, depression, pain, premature ejaculation, ADHD or fibromyalgia in mammals.

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16. Use of a compound according to Claim 15, for the treatment of urinary incontinence, or OAB.

17. Use of a compound according to Claim 15, for the treatment of ADHD.

25

18. A method of treatment of a disorder in which the regulation of monoamine transporter function is implicated which comprises administering a therapeutically effective amount of a compound according to any one of Claims 1 to 9 to a patient in need of such treatment.

19. A method of treatment of a disorder in which the regulation of serotonin or noradrenaline is implicated which comprises administering a therapeutically effective amount of a compound according to any one of Claims 1 to 9 to a patient in need of such treatment.

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20. A method according to Claim 19, wherein the regulation of serotonin and noradrenaline is implicated.

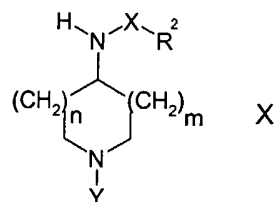
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21. A method of treatment of urinary disorders, depression, pain, premature ejaculation, ADHD or fibromyalgia, which comprises administering a therapeutically effective amount of a compound according to any one of Claims 1 to 9 to a patient in need of such treatment.

40

22. A method according to Claim 21 for the treatment of urinary disorders, wherein the urinary disorder is urinary incontinence.

23. A method according to Claim 21 for the treatment of pain
24. A process for preparing a compound according to any one of Claims 1 to 9 comprising reacting a compound of formula (X):



5

wherein R^2 , n and m are as defined in any of Claims 1 to 9 and Y is R^1 or a protecting group, with an acid or acyl halide: R^3COX , wherein X is OH or halo, or an acid anhydride $(R^3CO)_2O$, wherein R^1 and R^3 are as defined in any of Claims 1 to 9; and deprotecting if necessary or desired.