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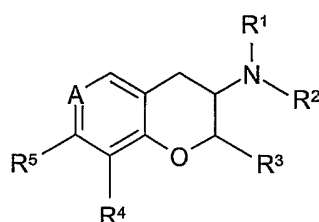
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(54) Title: CHROMAN COMPOUNDS



(I)

(57) Abstract: PC26133A The present invention provides for compounds of formula (I) wherein A, R¹, R², R³, R⁴ and R⁵ are defined herein. The compounds of formula (I) are a class of dopamine agonists, more particularly a class of agonists that are selective for D3 over D2. These compounds are useful for the treatment and/or prevention of neuropsychiatric disorders, neurodegenerative disorders, pain and sexual dysfunction.

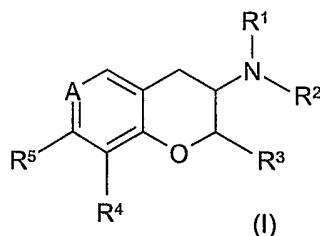
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Chroman compounds

The present invention relates to a class of dopamine agonists, more particularly a class of agonists that are selective for D3 over D2. These compounds are useful for the treatment and/or prevention of neuropsychiatric disorders, neurodegenerative disorders, pain and sexual dysfunction, for example female sexual dysfunction (FSD), in particular female sexual arousal disorder (FSAD), and male sexual dysfunction, in particular male erectile dysfunction (MED). Male sexual dysfunction as referred to herein includes ejaculatory disorders such as premature ejaculation, anorgasmia (inability to achieve orgasm) or desire disorders such as hypoactive sexual desire disorder (HSDD; lack of interest in sex).

The present invention encompasses compounds which belong to the chemical class of chromans. Other examples of chroman species may be found in publications including WO 96/30333, *European Journal of Medicinal Chemistry* (1976), 11(3), 251-6; *Journal of Medicinal Chemistry* (2004), 47(16), 3927-30; *Bioorganic and Medicinal Chemistry* (1999), 7(2), 335-341; *Journal of Chromatography*, A, (1995), 704(1), 83-7; *Journal of Medicinal Chemistry* (1994), 37(24), 4245-50; *European Journal of Medicinal Chemistry* (1991), 26(5), 497-504; *Journal of Labelled Compounds and Radiopharmaceuticals* (1998), 25(8), 833-54; *European Journal of Medicinal Chemistry* (1976), 11(3), 257-62; WO 90/12795; *Journal of Medicinal Chemistry* (1972), 15(8), 863-5; and US 4,801,605.

The present invention provides for compounds of formula (I)



wherein:

A is C-R⁶;

R¹ is selected from H, (C₁-C₆)alkyl and (C₃-C₈)cyclic alkyl;

R² is selected from (C₁-C₆)alkyl and (C₃-C₈)cyclic alkyl, wherein said (C₁-C₆)alkyl is optionally substituted by phenyl or Het;

R³ is selected from H or (C₁-C₆)alkyl;

R⁴ is selected from H, CN, O(C₁-C₆)alkyl, C(O)NH₂, Cl, F and (C₁-C₆)alkyl, wherein said (C₁-C₆)alkyl is optionally substituted by OH;

R⁵ is selected from H, OH, O(C₁-C₆)alkyl, C(O)NH₂, CN, NH₂ and Het;

R⁶ is selected from H, (C₁-C₆)alkyl, C(O)NH₂, CN, Cl, F, and Het, wherein said (C₁-C₆)alkyl is optionally substituted by OH or NH₂;

wherein Het is a 5 or 6 membered aromatic heterocycle, containing 1 to 3 heteroatoms, each independently selected from N, O and S, wherein said heterocycle is optionally substituted by 1 to 3 (C₁-C₆)alkyl groups;

wherein phenyl is optionally substituted by 1 to 5 groups independently selected from (C₁-C₆)alkyl, O(C₁-C₆)alkyl, Cl or F;

- 5 and pharmaceutically acceptable salts, solvates and prodrugs thereof;
with the provisos that:
- a) R⁴, R⁵ and R⁶ cannot all simultaneously represent H;
 - b) when R³, R⁵ and R⁶ are H then R⁴ cannot be OCH₃;
 - c) when R³, R⁴ and R⁶ are H then R⁵ cannot be OCH₃;
 - 10 d) when R³, R⁴ and R⁵ are H then R⁶ cannot be CH₃;
 - e) when R¹ and R² are n-propyl, R³ is H, R⁴ is H and R⁵ is H then R⁶ cannot be C(O)NH₂;
 - f) when R¹ and R² are n-propyl, R³ is H, R⁴ and R⁵ are OCH₃ then R⁶ cannot be H;
 - g) when R¹, R³ and R⁵ are H, R² and R⁴ are CH₃ then R⁶ cannot be CH₃;
 - h) when R¹ and R² are n-propyl, R³ is H, R⁴ is H and R⁵ is H then R⁶ cannot be CH₂OH;
 - 15 i) when R¹ and R² are n-propyl, R³ is H, R⁴ is H and R⁶ is H then R⁵ cannot be OH; and
 - j) when R¹ is H, R² is ethyl, R³ is H, R⁴ is H and R⁵ is H then R⁶ cannot be Cl.

In the above definitions alkyl groups, containing the requisite number of carbon atoms, can be unbranched or branched. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of cyclic alkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

A pharmaceutically acceptable salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) 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.

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

- 5 Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

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

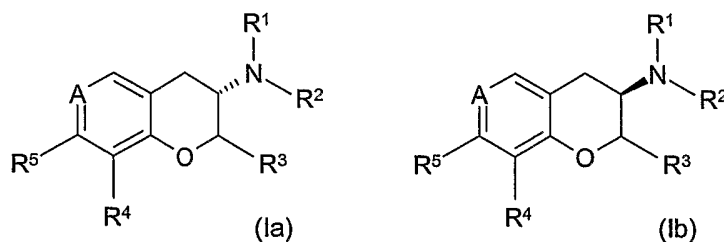
- 10 The pharmaceutically acceptable solvates of the compounds of the formula (I) include the hydrates thereof.

Also included within the present scope of the compounds of the formula (I) are polymorphs thereof.

- 15 A compound of the formula (I) contains one or more asymmetric carbon atoms and therefore exists in two or more stereoisomeric forms.

Separation of diastereoisomers can be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

- 20 Diastereoisomers of the present invention include compounds of formula (Ia) and (Ib):



25

It is to be understood that references in this document to compounds of formula (I) also encompass the compounds of formula (Ia) and (Ib).

- 30 One embodiment of the present invention comprises compounds of formula (Ia) and (Ib).

In an alternative embodiment, the present invention comprises compounds of formula (Ia).

In a further alternative embodiment, the present invention comprises compounds of formula (Ib).

In a first alternative embodiment R^1 is selected from H and (C_1-C_6) alkyl.

- 35 In a second alternative embodiment R^1 is selected from H, methyl, ethyl and propyl.

In a third alternative embodiment R^1 is selected from H, ethyl and n-propyl.

In a fourth alternative embodiment R^1 is H.

In a first alternative embodiment R^2 is selected from (C_1-C_6) alkyl and (C_3-C_8) cyclic alkyl, wherein said (C_1-C_6) alkyl is optionally substituted by phenyl.

5 In a second alternative embodiment R^2 is (C_1-C_6) alkyl, wherein said (C_1-C_6) alkyl is optionally substituted by phenyl.

In a third alternative embodiment R^2 is (C_1-C_3) alkyl, wherein said (C_1-C_3) alkyl is optionally substituted by phenyl.

In a fourth alternative embodiment still R^2 is (C_1-C_3) alkyl.

10 In a fifth alternative embodiment R^2 is n-propyl.

In a first alternative embodiment R^3 is selected from H, methyl or ethyl.

In a second alternative embodiment R^3 is H.

15 In a first alternative embodiment R^4 is selected from H, CN, $O(C_1-C_6)$ alkyl, $C(O)NH_2$, Cl, and F.

In a second alternative embodiment R^4 is selected from H, CN, OCH_3 , $C(O)NH_2$, Cl, F.

In a third alternative embodiment R^4 is selected from H, CN, Cl and F.

In a fourth alternative embodiment, R^4 is selected from H, Cl and F.

In a fifth alternative embodiment R^4 is selected from H and F.

20 In a sixth alternative embodiment R^4 is H.

In a first alternative embodiment R^5 is selected from H, OH, $O(C_1-C_6)$ alkyl, $C(O)NH_2$, CN, and NH_2 .

In a second alternative embodiment R^5 is selected from H, OH, $C(O)NH_2$, CN, and NH_2 .

In a third alternative embodiment R^5 is selected from H, OH, $C(O)NH_2$ and CN.

25 In a fourth alternative embodiment R^5 is selected from H, OH and $C(O)NH_2$.

In a fifth alternative embodiment R^5 is selected from H and OH.

In a sixth alternative embodiment R^5 is OH.

30 In a first alternative embodiment R^6 is selected from H, (C_1-C_6) alkyl, $C(O)NH_2$, CN, Cl, F, and Het, wherein said (C_1-C_6) alkyl is optionally substituted by OH.

In a second alternative embodiment R^6 is selected from H, $C(O)NH_2$, CN, F, and Het.

In a third alternative embodiment R^6 is selected from H, $C(O)NH_2$, CN and Het.

In a fourth alternative embodiment R^6 is selected from H, $C(O)NH_2$, and CN.

In a fifth alternative embodiment R^6 is selected from H, $C(O)NH_2$ and CN.

35 In a sixth alternative embodiment R^6 is selected from $C(O)NH_2$ and CN.

In a seventh alternative embodiment R^6 is $C(O)NH_2$.

40 In a first alternative embodiment, Het is a 5 membered aromatic heterocycle containing 1 to 3 heteroatoms, each independently selected from N, O and S, said heterocycle optionally substituted by (C_1-C_6) alkyl.

In a second alternative embodiment, Het is a 5 to 6 membered aromatic heterocycle containing 1 to 2 heteroatoms, each independently selected from N and O, said heterocycle optionally substituted by (C₁-C₆)alkyl.

- 5 In a third alternative embodiment Het is a 5 membered aromatic heterocycle containing 1 to 2 heteroatoms, each independently selected from N and O, said heterocycle optionally substituted by (C₁-C₃)alkyl.

- 10 In a fourth alternative embodiment Het is a 5 membered aromatic heterocycle containing 2 heteroatoms, each independently selected from N and O, said heterocycle optionally substituted by methyl.

In a fifth alternative embodiment, Het is imidazolyl or 5-methyl-2-oxazolyl.

- 15 It is to be understood that the invention covers all combinations of particular embodiments of the invention as described hereinabove, consistent with the definition of compounds of formula (I).

Representative compounds of the invention include:

- | | | |
|----|---|---------------|
| | 3-(diethylamino)chromane-6-carboxamide | (Example 4); |
| 20 | 3-[ethyl(propyl)amino]chromane-6-carboxamide | (Example 5); |
| | 3-[ethyl(propyl)amino]chromane-6-carbonitrile | (Example 13); |
| | 3-(dipropylamino)chromane-6-carbonitrile | (Example 14); |
| | 7-hydroxy-3-(propylamino)chromane-6-carboxamide | (Example 16); |
| | 3-[ethyl(propyl)amino]-7-hydroxychromane-6-carboxamide | (Example 17); |
| 25 | 3-(dipropylamino)-7-hydroxychromane-6-carboxamide | (Example 18); |
| | 3-(dipropylamino)chromane-7-carboxamide | (Example 19); |
| | 3-(dipropylamino)-8-fluorochromane-6-carboxamide | (Example 22); |
| | N-ethyl-6-(1H-imidazol-2-yl)-N-propylchroman-3-amine | (Example 23); |
| | and pharmaceutically acceptable salts, solvates and prodrugs thereof. | |

30

Further representative compounds of the invention include:

- | | | |
|----|---|---------------|
| | (3S)-3-(diethylamino)chromane-6-carboxamide | (Example 4); |
| | (3S)-3-[ethyl(propyl)amino]chromane-6-carboxamide | (Example 5); |
| 35 | (3S)-3-[ethyl(propyl)amino]chromane-6-carbonitrile | (Example 13); |
| | (3S)-7-hydroxy-3-(propylamino)chromane-6-carboxamide | (Example 16); |
| | (3S)-3-[ethyl(propyl)amino]-7-hydroxychromane-6-carboxamide | (Example 17); |
| | (3S)-3-(dipropylamino)-7-hydroxychromane-6-carboxamide | (Example 18); |
| | (3S)-3-(dipropylamino)chromane-7-carboxamide | (Example 19); |
| 40 | (3S)-N-ethyl-6-(1H-imidazol-2-yl)-N-propylchroman-3-amine | (Example 23); |
| | and pharmaceutically acceptable salts, solvates and prodrugs thereof. | |

Yet further representative compounds of the invention include:

- (3*S*)-3-(diethylamino)chromane-6-carboxamide (Example 4);
 5 (3*S*)-3-[ethyl(propyl)amino]chromane-6-carboxamide (Example 5);
 (3*R*)-7-hydroxy-3-(propylamino)chromane-6-carboxamide (Example 16);
 (3*R*)-3-[ethyl(propyl)amino]-7-hydroxychromane-6-carboxamide (Example 17);
 (3*R*)-3-(dipropylamino)-7-hydroxychromane-6-carboxamide (Example 18);
 and pharmaceutically acceptable salts, solvates and prodrugs thereof.

10

In a further embodiment, the present invention encompasses compounds of formula (I) wherein:

A is selected from C-R⁶ and N;

R¹ and R² are each independently selected from H, (C₁-C₆)alkyl, said alkyl optionally substituted by Ph;

15 and (C₃-C₈) cyclic alkyl;

R³ is as previously defined above;

R⁴ is selected from H and halo;

R⁵ is selected from H, OH, O(C₁-C₆)alkyl or in combination with R⁶ may form a (C₂-C₅) alkylene link, said link optionally incorporating an alkene group, said link optionally incorporating 1-2 heteroatoms each

20 independently selected from N, O and S; and

R⁶ is selected from H, C(O)NH₂, CO₂H, C(O)O(C₁-C₆)alkyl, NHSO₂(C₁-C₆)alkyl, NHC(O)(C₁-C₆)alkyl, halo, a 5-6 membered aromatic heterocycle containing 1-3 heteroatoms each independently selected from N, O and S; (C₁-C₆)alkyl, said alkyl optionally substituted by OH; or in combination with R⁵ may form

a (C₂-C₅) alkylene link, said link optionally incorporating an alkene group, said link optionally

25 incorporating 1-2 heteroatoms each independently selected from N, O and S;

and pharmaceutically acceptable salts, solvates and prodrugs thereof;

with the provisos that when:

A is CR⁶, R¹ and R² are propyl, R³ is H, R⁴ is OH, R⁵ is H then R⁶ cannot be H;

A is CR⁶, R¹ and R² are propyl, R³ is H, R⁴ is H, R⁵ is H then R⁶ cannot be Br, H, CO₂H, C(O)NH₂ or OMe;

30 A is CR⁶, R¹ and R² are propyl, R³ is H, R⁴ is H, then R⁵ and R⁶ cannot be a -O-CH-CH- link;

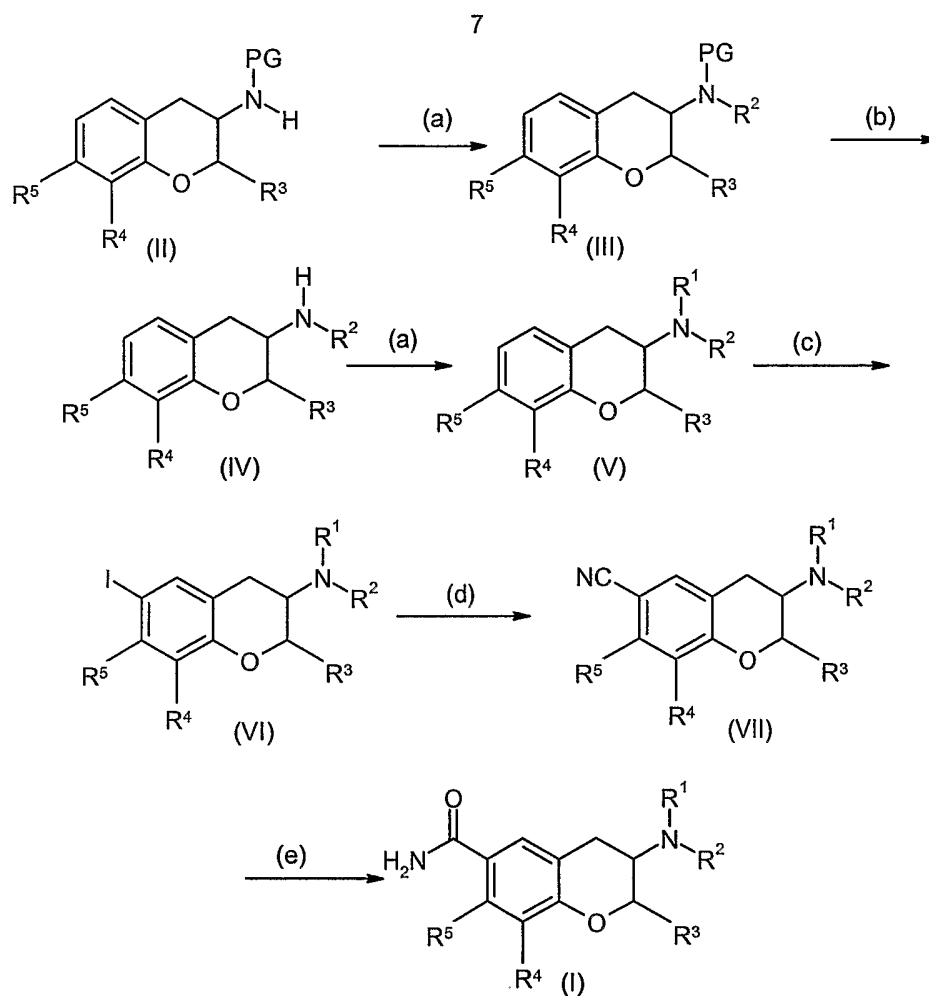
A is CR⁶, R¹ is H, R² is H or propyl, R³ is H, R⁵ is H, R⁶ is H then R⁴ cannot be Br;

A is CR⁶, R¹ is n-propyl or methylcyclopropyl, R² is n-propyl, R³ is H, R⁵ is H, R⁶ is H then R⁴ cannot be Br.

35 Compounds of the invention may be prepared, in a known manner, in a variety of ways. The routes below illustrate methods of synthesising compounds of formula (I); the skilled man will appreciate that the compounds of formula (Ia) and (Ib) can be isolated with appropriate resolution techniques.

Compounds of formula (I), wherein R¹ to R⁵ are as described, R⁶ is CN or CONH₂ can be prepared

40 according to the methods described in scheme 1, below.



Compounds of formula (II) can be obtained by analogy with the methods of van Niet et. al. (J. Med.

Chem. 2000; 43; 3549), or Brisander et. al. (J. Org. Chem. 1998; 63; 5362) or Andersson et. al. (WO 9012795).

PG represents a suitable N protecting group, typically benzyl or allyl, more typically benzyl.

Step (a): Reductive amination

Amine (II) is reacted with an excess of aldehyde, $R^2(O)H$ (or $R^1(O)H$ or an excess of a ketone of a (C_3 - C_8) cyclic alkyl) in the presence of a reducing agent, such as sodium triacetoxyborohydride or sodium cyanoborohydride, and optionally in the presence of acetic acid, to give the compound of formula (III). PG is a suitable N protecting group, as described in "Protecting Groups in Organic Synthesis" by T.W. Greene and P. Wutz.

This reaction may be carried out by, stirring the starting materials at temperatures such as 20°C to 80°C for 1 to 72 hours in a suitable solvent such as dichloromethane or tetrahydrofuran or heating amine (II) with excess $R^2(O)H$ (or an excess of $R^1(O)H$ or a ketone of a (C_3 - C_8) cyclic alkyl) with a suitable Lewis acid catalyst such as titanium tetrachloride or titanium tetraisopropoxide at temperatures such as 50°C to 100°C in a suitable solvent such as dichloroethane or ethanol for 1 to 18 hours, followed by reduction of

the intermediate imine/iminium species with a suitable reducing agent, such as sodium borohydride, or hydrogenation over a suitable catalyst, such as platinum oxide or palladium on carbon.

Typical conditions are:

- 5 1.4 to 20 molar equivalents (eq) $R^2(O)H$ (or $R^1(O)H$ or a ketone of a (C_3-C_8) cyclic alkyl), 1.5 to 3.5 eq $Na(OAc)_3BH$, optionally in the presence of 1eq AcOH in tetrahydrofuran (THF) at room temperature (rt) for between 5 and 72 hours (hrs).

Step (b)-Deprotection

- 10 Deprotection of compound (III) to provide the compound of formula (IV) is undertaken using standard methodology, as described in "Protecting Groups in Organic Synthesis" by T.W. Greene and P. Wutz.

In one embodiment PG is benzyl. Typical conditions for such a deprotection are:

- 5 to 10 eq ammonium formate, 10% Pd/C in methanol or ethanol at about the reflux temp of the reaction
15 for between 1 and 26 hours,
or, 10% Pd/C in ethanol at 40°C under 1atm H_2 , for about 3 hrs.

Compounds of formula (V) can be prepared by reaction of the amine of formula (IV) with aldehyde $R^1(O)H$, using the methods described previously in step (a).

20

Step (c)-Iodination

Iodination of the compound of formula (V) using a suitable mild iodinating agent such as N-iodosuccinimide, optionally in the presence of a catalyst such as trifluoromethanesulphonic (triflic) acid or trifluoroacetic acid optionally in a suitable solvent (eg MeCN) at room temperature (rt) provides the

- 25 compound of formula (VI)

Typical conditions are:

1 eq N-iodosuccinimide in trifluoroacetic acid at rt for 18 hrs.

Step (d)-Cyanation reaction

- 30 Cyanation of the iodide of formula (VI), according to the method of Tschaen et. al. (Syn. Comm. 1994; 24; 887) provides the compound of formula (VII).

Typical conditions are:

0.45 to 0.7 eq $Zn(CN)_2$, about 0.05eq $Pd(PPh_3)_4$, in N,N-dimethylformamide at between 90 to 100°C for between 4 and 18 hrs,

- 35 Or, $Zn(CN)_2$, Tris(dibenzylideneacetone)dipalladium(0) 1,1'-Bis(diphenylphosphino)ferrocene ($Pd_2(dba)_3$ dppf) in N,N-dimethylformamide at 100°C for 2 hrs.

Step (e) – Nitrile hydrolysis

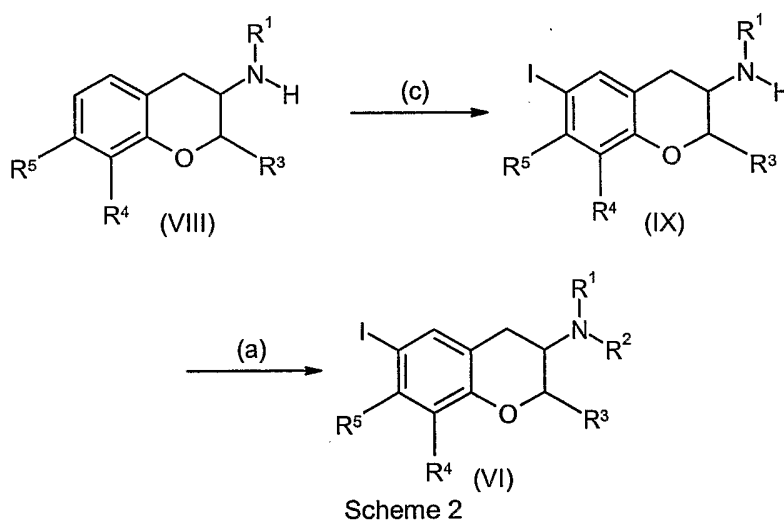
Hydrolysis of the nitrile of formula (VII) may be achieved in the presence of acid or base, in a suitable
40 solvent, optionally at elevated temperature to afford the amide of formula (I). Typically the nitrile of

formula (I) is treated with a metal hydroxide (eg Li, K or Cs) in alcoholic solvent (eg 2-methyl-2-propanol) at between rt and the reflux temperature of the reaction.

Typical conditions are:

- 5 Excess KOH, nitrile (VII) in 2-methyl-2-propanol at reflux for up to 72 hrs.

Compounds of formula (VI) wherein R^1 to R^5 are as described herein can alternatively be prepared, according to scheme 2 below:

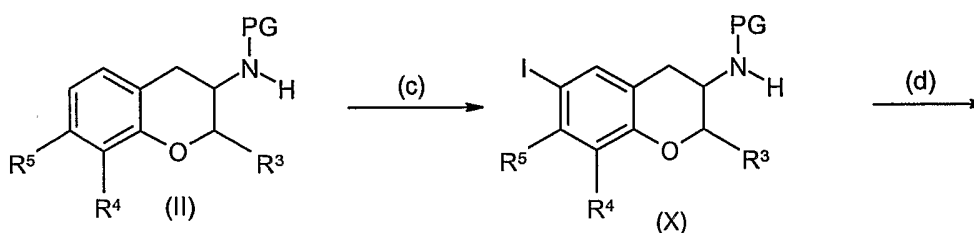


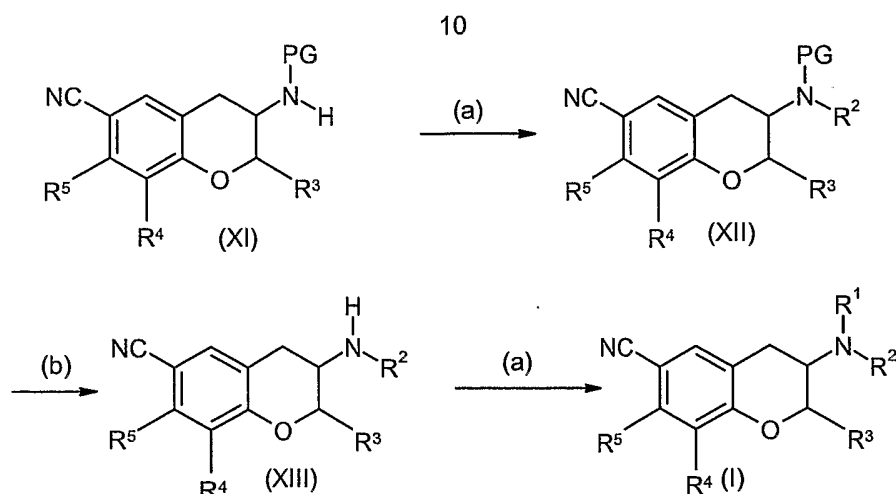
- 15 Compounds of formula (VIII) can be obtained by analogy with the methods of van Niet et. al. (J. Med. Chem. 2000; 43; 3549), or Brisander et. al. (J. Org. Chem. 1998; 63; 5362) or Andersson et. al. (WO 9012795).

20 Iodination of the compound of formula (VIII) as described previously for step (c) provides the compound of formula (IX).

Reaction of the compounds of formula (IX) with $R^2(O)H$ (or a ketone of a (C_3-C_8) cyclic alkyl), as described previously in step (a) provides the compounds of formula (VI).

- 25 Compounds of formula (I), wherein R^1 to R^5 are as described herein, and R^6 is CN can alternatively be prepared according to scheme 3 below.





5

Iodination of the compound of formula (II) using the methods described previously in step (c) provides the compound of formula (X).

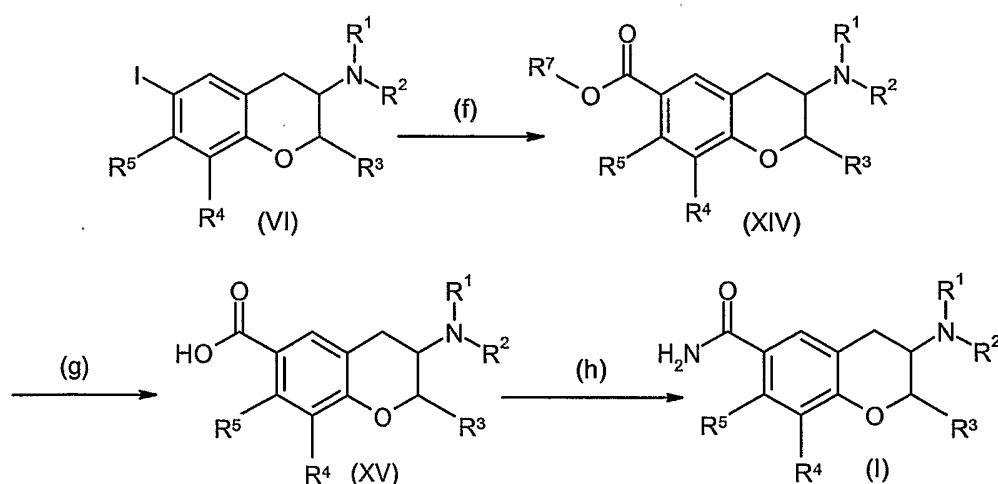
Cyanation of compounds of the formula (X) according to the method described in step (d) above provides the compound of formula (XI).

- 10 Reductive amination of the compound of formula (XI) with $R^2(O)H$ (or a ketone of a (C_3-C_8) cyclic alkyl) as described previously for step (a) provides the compound of formula (XII).

Deprotection of the compound of formula (XII) as described previously for step (b) provides the compound of formula (XIII).

- 15 Reductive amination of the compound of formula (XIII) with $R^1(O)H$ as described previously in step (a), provides the compound of formula (I).

Compounds of formula (I), wherein R^1 to R^5 are as described herein, and R^6 is $CONH_2$ can be prepared according to scheme 4 below.



- 25 R^7 represents C_1-C_6 alkyl or benzyl, typically C_1-C_4 alkyl and more typically CH_3

Step (f)-Carbonylation

Carbonylation of the iodide of formula (VI) using a suitable transition metal catalyst (eg Pd or Ni) in the presence of R^7OH , a suitable base, such as Et_3N , under an atmosphere of CO, in a suitable solvent, such as DMF, at elevated temperature provides compounds of the formula (XIV).

5 Typical conditions are:

0.2eq Pd(dppf) $Cl_2 \cdot CH_2Cl_2$, 2 eq Et_3N in N,N-dimethylformamide and MeOH under $CO_{(g)}$ at 90°C for 8 hrs.

Step (g)-Hydrolysis

10 Hydrolysis of the ester of formula (XIV) can be achieved in the presence of acid or base, in a suitable solvent, optionally at elevated temperature to afford the acid (XV). Typically the ester of formula (XIV) is treated with a metal hydroxide (Li, Na, K or Cs) in aqueous solvent (MeOH, EtOH, dioxan, THF) at between rt and the reflux temperature of the reaction.

15 Typical conditions are:

Excess aqueous NaOH, ester of formula (XIV) in dioxan at rt for up to 72 hrs.

Step (h)-Amide synthesis

Conversion of carboxylic acid of formula (XV) into amide (I) using either

20 (i) an acyl chloride derivative of acid of formula (XV) + ammonia, optionally with an excess of acid acceptor in a suitable solvent, or

(ii) the acid of formula (XV) with a conventional coupling agent (e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSCDI), dicyclohexylcarbodiimide (DCC)) + ammonia, optionally in the presence of 1-hydroxybenzotriazole (HOBT) or 1-hydroxy-7-azabenzotriazole (HOAT), with an excess of

25 acid acceptor in a suitable solvent (e.g. EtOAc, DCM).

Typical conditions are:

Acid chloride of acid (XV) (generated *in-situ*), an excess of ammonia, optionally with an excess of 3° amine such as Et_3N , Hünig's base or N-methylmorpholine (NMM), in DCM or THF, without heating for 1 to 24 hrs,

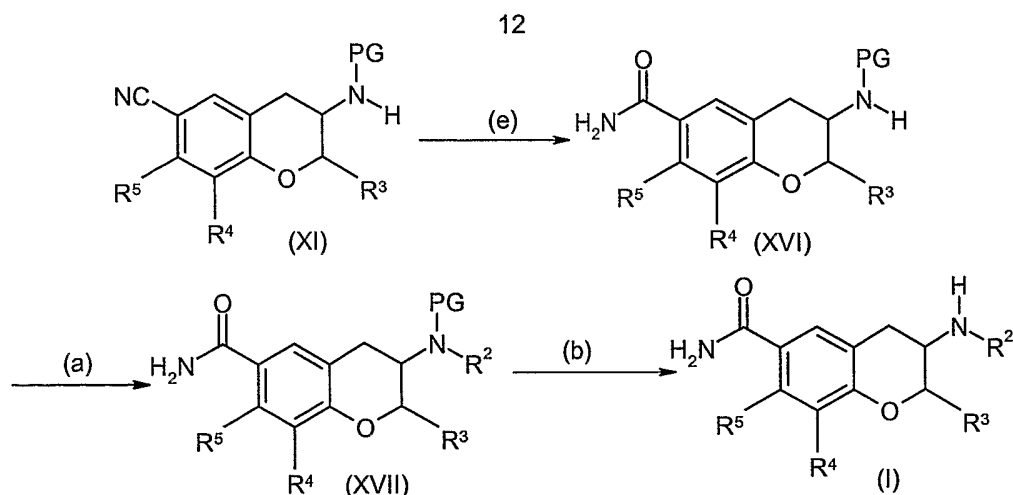
30

More typical conditions are:

Treatment of acid (XV) with $SOCl_2$ in DCM at between 50°C and the reflux temperature of the reaction for 2 hours, followed by addition of 0.88 ammonia or gaseous ammonia, and stirring at room temperature for 2 to 18 hours.

35

Compounds of the formula (I) wherein R^1 represents H and R^2 R^3 to R^5 are as described herein, PG is as previously described and R^6 is $CONH_2$ can be prepared according to the methods described in scheme 5, below.



Scheme 5

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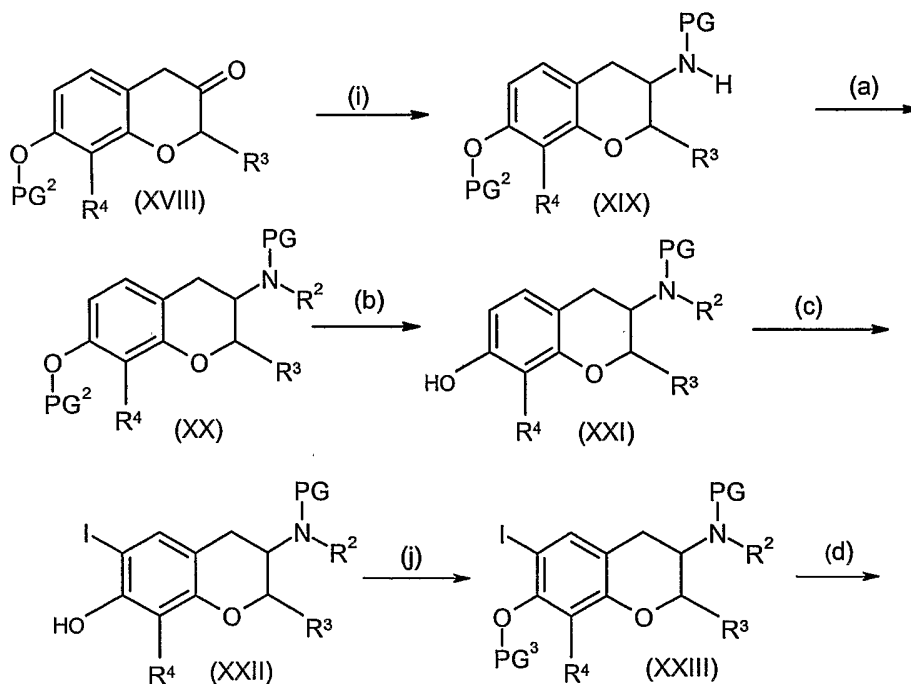
Hydrolysis of the compound of formula (XI) using the methods described previously in step (e) provides the compound of formula (XVI).

Reductive amination with an aldehyde of formula R²(O)H (or a ketone of a (C₃-C₈) cyclic alkyl) according to the method described in step (a) above provides the compound of formula (XVII).

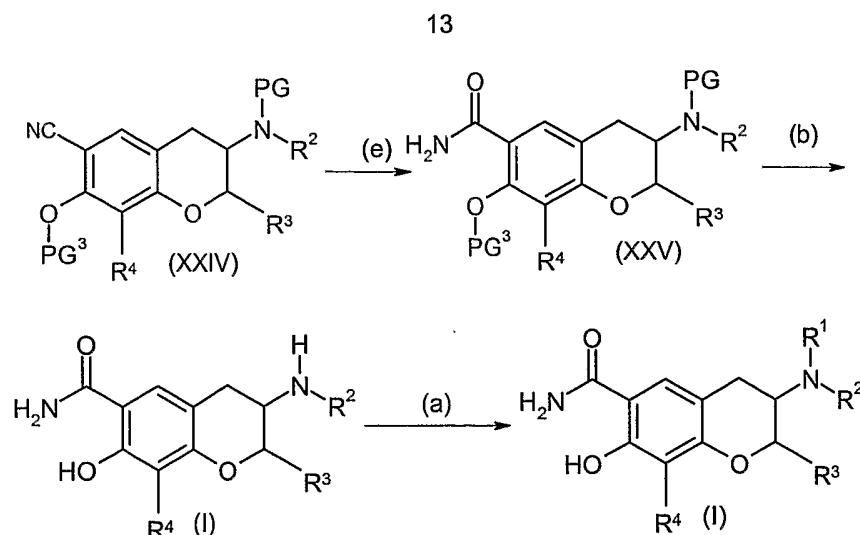
10 Deprotection of the compound of formula (XVII) as described previously for step (b) provides the compound of formula (I).

Compounds of formula (I), wherein R¹ and R² are as described herein, R³ and R⁴ are H, R⁵ is OH and R⁶ is CN or CONH₂ can be prepared according to the methods described in scheme 6, below.

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PG² represents a suitable O protecting group, typically a C₁-C₄ alkyl group, more typically methyl.
 PG³ represents a suitable O protecting group and is typically benzyl.

Compounds of formula (XVIII) can be obtained by analogy with the methods of van Niet et. al. (J. Med.
 Chem. 2000; 43; 3549), or Brisander et. al. (J. Org. Chem. 1998; 63; 5362) or Andersson et. al. (WO
 9012795) or Corey et al. (J. Am. Chem. Soc. (1993), 115(20), 9327-8).

Step (i): Reductive amination

Ketone (XVIII) is reacted with an amine PGNH₂ of in the presence of a reducing agent, such as sodium
 triacetoxyborohydride or sodium cyanoborohydride, and optionally in the presence of acetic acid, to give
 the compound of formula (XIX). PG is a suitable N protecting group, as described in "Protecting Groups
 in Organic Synthesis" by T.W. Greene and P. Wutz. Typically PG is benzyl or allyl, more typically benzyl.

This reaction may be carried out by, stirring the starting materials at temperatures such as 0°C to 80°C
 for 1 to 72 hours in a suitable solvent such as dichloromethane or tetrahydrofuran or heating the ketone
 of formula (XVIII) with PGNH₂ with a suitable Lewis acid catalyst such titanium tetrachloride or titanium
 tetraisopropoxide at temperatures such as 50°C to 100°C in a suitable solvent such as dichloroethane or
 ethanol for 1 to 18 hours, followed by reduction of the intermediate imine/iminium species with a suitable
 reducing agent, such as sodium borohydride, or hydrogenolysis over a suitable catalyst, such as
 platinum oxide or palladium on carbon.

Typical conditions are:

1.0 to 5 eq PGNH₂, 1.5 to 3.5 eq Na(OAc)₃BH, optionally in the presence of 1eq AcOH in tetrahydrofuran
 at rt for between 5 and 72 hrs.

30

Reductive amination of the compound of formula (XIX) with R²(O)H as described previously in step (a),
 provides the compound of formula (XX).

Step (b)-Deprotection

Deprotection of the compound of formula (XX) to provide the compound of formula (XXI) is undertaken using standard methodology, as described in "Protecting Groups in Organic Synthesis" by T.W. Greene and P. Wutz.

- 5 Typically PG² is methyl. The typical conditions for such a deprotection are:
48% hydrobromic acid at about 80°C for between 1 and 48 hours.

Iodination of the compound of formula (XXI) using the methods described previously in step (c) provides the compound of formula (XXII).

10

Step (j)-Protection

Protection of the compound of formula (XXII) using a suitable electrophile such as benzyl bromide in the presence of a base such as potassium carbonate in a suitable solvent (eg N,N-dimethylformamide) at room temperature provides the compound of formula (XXIII).

- 15 Typical conditions are:

1.05 eq benzyl bromide, 3 eq potassium carbonate in N,N-dimethylformamide at rt for 18 hrs.

Cyanation according to the method described in step (d) above provides the compound of formula (XXIV)

20

Hydrolysis of the compound of formula (XXIV) can be achieved by analogy with the method previously described in step (e), to provide the compound of formula (XXV).

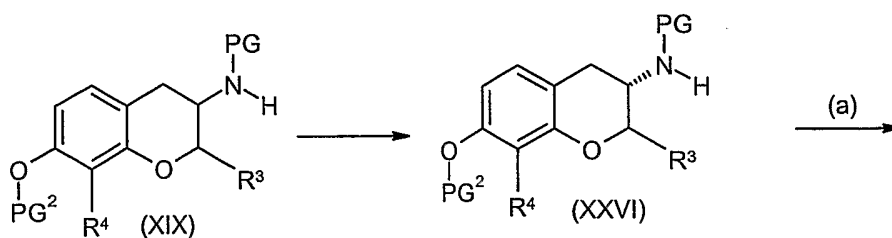
- 25 Deprotection of the compound of formula (XXV) as described previously for step (b) provides the compound of formula (I).

When R¹ does not represent H, then compounds of formula (I) may be prepared by reaction with a suitable carbonyl compound, as described previously in step (a).

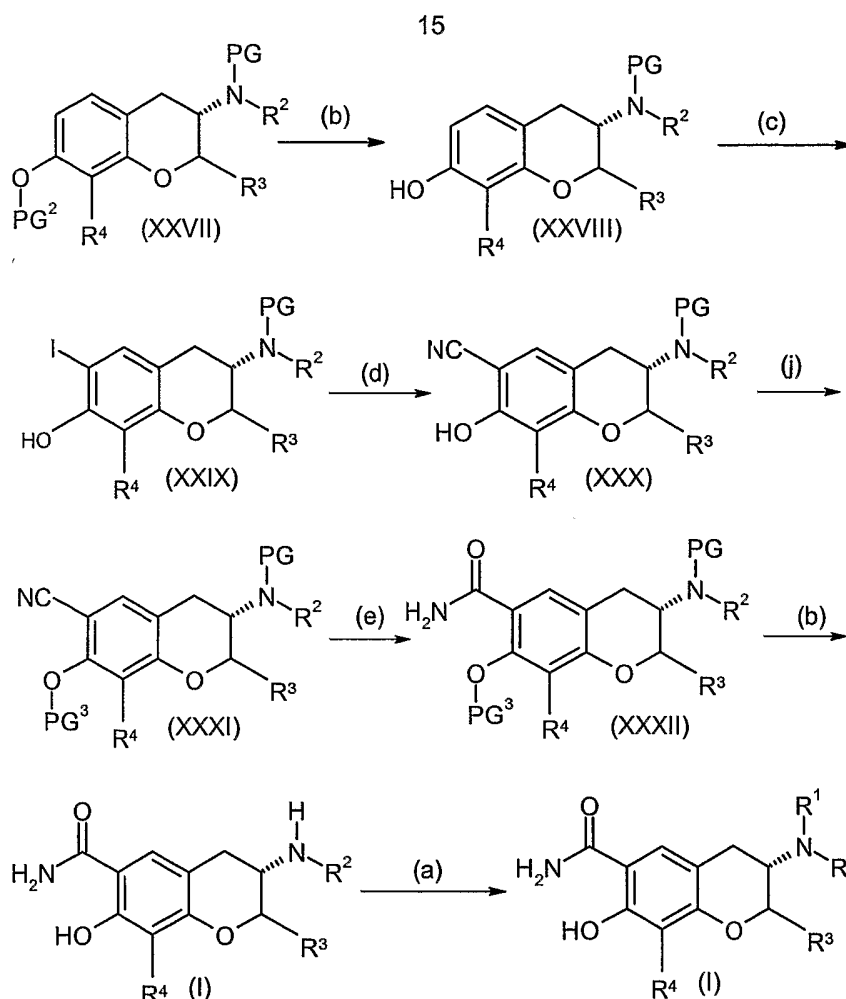
It will be appreciated by those skilled in the art that, compounds of formula (I), wherein R⁶ represents CN, can be prepared directly from the compound of formula (XXIV) by reaction according to steps (b) and (a)

- 30 as previously described.

Alternatively, compounds of the formula (I), wherein R¹ and R² are as described herein, R³ and R⁴ are H, R⁵ is as described herein but not H, and R⁶ is CN or CONH₂ can be prepared according to the methods described in scheme 7, below.



35



Compounds of the formula (XXVI) may be prepared from compounds of the formula (XIX) by chiral HPLC or classical salt resolution methodology.

Compounds of formula (XXVII) may be prepared from compounds of formula (XXVI) by analogy with the methods previously described for step (a).

Compounds of formula (XXVIII) may be prepared from compounds of formula (XXVII) by analogy with the methods previously described for step (b).

Compounds of formula (XXIX) may be prepared from compounds of formula (XXVIII) by analogy with the methods previously described for step (c).

Compounds of formula (XXX) may be prepared from compounds of formula (XXIX) by analogy with the methods previously described for step (d).

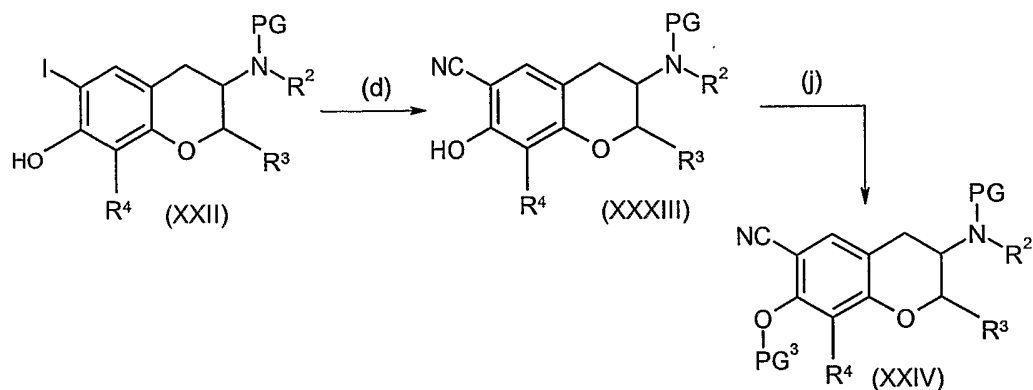
Compounds of formula (XXXI) may be prepared from compounds of formula (XXX) by analogy with the methods previously described for step (j).

Compounds of formula (XXXII) may be prepared from compounds of formula (XXXI) by analogy with the methods previously described for step (e).

Compounds of formula (I) may be prepared from compounds of formula (XXXII) by analogy with the methods previously described for step (b).

Compounds of formula (I) may be prepared from compounds of formula (I) by analogy with the methods previously described for step (a).

Alternatively, compounds of formula (XXIV) can be prepared from compounds of formula (XXII) as shown in scheme 8 below.



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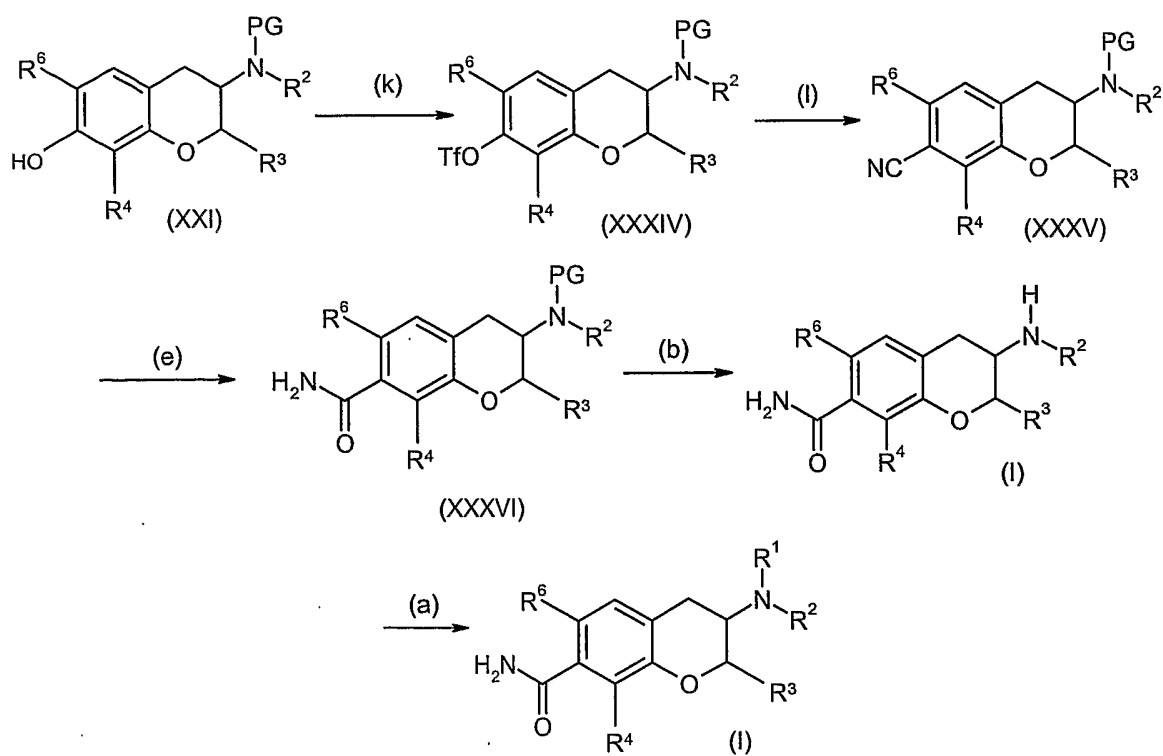
Scheme 8

Compounds of formula (XXXIII) may be prepared from compounds of formula (XXII) by analogy with the methods previously described for step (d).

Compounds of formula (XXIV) may be prepared from compounds of formula (XXXIII) by analogy with the methods previously described for step (j).

10

Compounds of formula (I), wherein R^1 to R^4 and R^6 are as described herein, and R^5 represents CN or CONH_2 can be prepared according to the methods described in scheme 9, below.



15

Scheme 9

Step (k) – Triflate formation

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Conversion of compound (XXI) into its triflate (XXXIV) may be accomplished by reaction with a triflating reagent such as N-phenylbis(trifluoromethanesulphonimide) or trifluoromethanesulfonic anhydride in the presence of a suitable base such as Et₃N or N-ethyl-diisopropylamine in a suitable solvent such as DCM or THF.

5

Typical conditions for this transformation are 1.05 eq N-phenylbis(trifluoromethanesulphonimide) and 1.1 eq Et₃N in DCM at room temperature for 18 hrs.

Step (l)-Cyanation reaction

- 10 Cyanation of the triflate of formula (XXXIV), according to the method of Tschaen et. al. (Syn. Comm. 1994; 24; 887) provides the compound of formula (XXXV).

Typical conditions are:

0.7 eq Zn(CN)₂, 0.1eq Pd(PPh₃)₄, 0.2 eq. dppf, 1eq. LiCl in N,N-dimethylformamide at about 100°C for about 3 hrs.

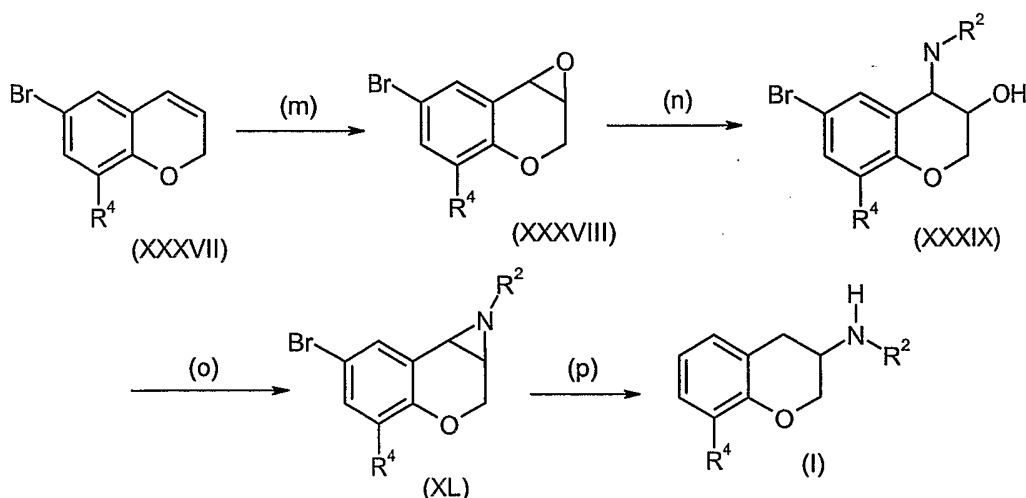
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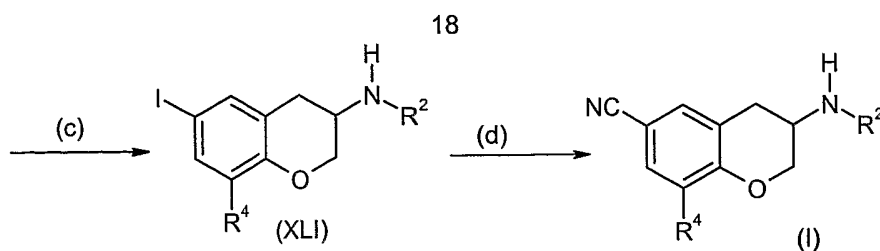
The carboxamide of formula (XXXVI) may be prepared from the nitrile of formula (XXXV) by hydrolysis as previously described for step (e).

- 20 The amine of formula (I) may be prepared from the carboxamide of formula (XXXV) by a deprotection reaction as previously described for step (b).

The compounds of formula (I), wherein R¹ does not represent H, may be prepared by reductive amination as previously described in step (a).

- 25 Compounds of formula (I), wherein R¹ to R⁵ are as described herein, and R⁶ is H or CN, can be prepared according to the methods described in scheme 10, below.





Scheme 10

Compounds of formula (XXXVII) are either available commercially or can be obtained by analogy with the methods of Sawada et. al (Pest. Manag. Sci. Vol 59; (1); 2002; 36-48).

Step (m)-Epoxidation.

Compounds of formula (XXXVIII) may be obtained by epoxidation of the compound of formula (XXXVII) using the methods of Yang et al (J. Org. Chem. 1995; 60; 3887).

Typical conditions are:

10eq 1,1,1-trifluoroacetone, excess EDTANa₂, 7.7eq NaHCO₃, 5 eq. Oxone[®] in MeCN at about 0°C for about 1 hr.

Step (n)-Ring Opening

The compound of formula (XXXIX) may be prepared by reaction of the epoxide of formula (XXXVIII) with the amine of formula R²NH₂ in a suitable solvent (eg MeOH, EtOH) at elevated temperature for up to 18 hrs.

Typical conditions are:

1 eq R²NH₂ in EtOH at reflux for about 2 hrs.

Step (o)-Aziridine formation

The aziridine of formula (XL) may be prepared by reaction of the compound of formula (XXXIX), under standard Mitsunobu conditions, as described in J. Org. Chem. 2003; 68(13); 5160.

Typical conditions are:

1eq (XXXIX), 1.5 eq diethylazodicarboxylate (DEAD), 1.5 eq. PPh₃ in THF for about 2 hrs at rt.

Step (p)-Hydrogenation.

The compound of formula (I), wherein R⁶ is H, are prepared by hydrogenation of the compound of formula (XL). Typically this may be achieved by catalytic hydrogenation in the presence of a suitable catalyst e.g. Pd/C, in a suitable alcoholic solvent, e.g. H₂O, MeOH, or EtOH at between rt and about 60°C under an atmosphere of H₂.

Typical conditions are:

10% Palladium on charcoal in EtOH at 1atm H₂, at rt for about 3 hrs.

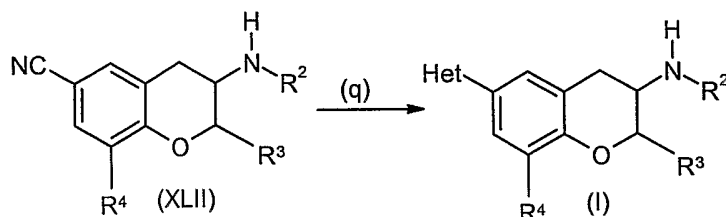
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The compound of formula (XLI) are prepared from the compound of formula (I), wherein R^6 is H, by using the methods previously described in step (c).

The compound of formula (I), wherein R^6 is CN, are prepared from the compound of formula (XLI) by using the methods previously described in step (d).

5

Compounds of formula (I), wherein R^1 to R^5 are as described herein, and R^6 represents Het, may be prepared according to the methods described in scheme 11, below.



Scheme 11

10

Step (q)-Heterocycle formation

Compounds of formula (I) may be prepared from compounds of formula (XLII), using standard chemical transformations, or by analogy with the methods described in Comprehensive Heterocyclic Chemistry I and II; published by Pergamon press 1984 and 1996, and the methods cited therein.

15

Compounds of formula (I) may also be converted to alternative compounds of formula (I) using standard chemical reactions and transformations.

For example, when R^2 is also a protecting group, typically benzyl, removal of this protecting group affords compounds of formula (I) where R^1 represents H, as described previously in step (b). This is exemplified in examples 3 and 7 to 10

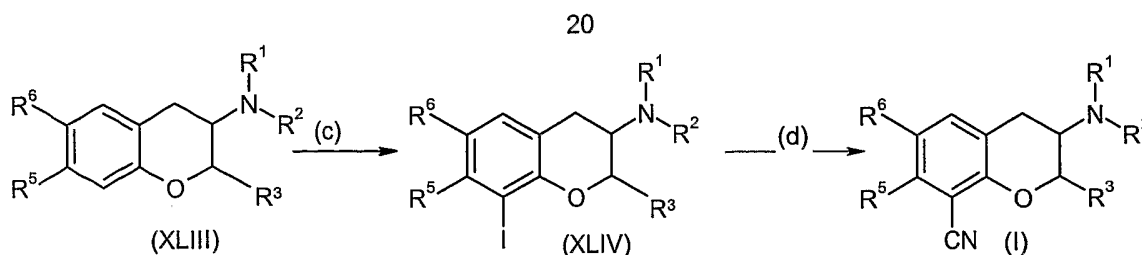
When R^1 is not H, compounds of formula (I) may be obtained from compounds of formula (I), where R^1 is H, by a reductive amination reaction with the aldehyde $R^1C(O)H$, as previously described in step (a).

This is exemplified by example 4.

When R^6 represents $CONH_2$, compounds of formula (I) may be prepared from compounds of formula (I) where R^6 represents CN, by hydrolysis. This may be achieved under acidic (eg conc. H_2SO_4 , $AcOH/BF_3$) or basic conditions (eg KOH in t-butanol). Typically, the nitrile compound is treated with 6 eq KOH in t-butanol, at the reflux temperature of the reaction for about 18 hrs. This is exemplified by example 11.

30

Compounds of formula (I), wherein R^1 to R^3 & R^5 to R^6 are as described herein, and R^4 represents CN, can be prepared according to the methods described in scheme 12, below.



Scheme 12

Iodination of the compound of formula (XLIII) using the methods described previously in step (c) provides the compound of formula (XLIV).

- 5 Cyanation of compounds of the formula (XLIV) according to the method described in step (d) above provides the compound of formula (I).

It will be appreciated by those skilled in the art, that the order of steps described in the schemes above may, where appropriate to the synthesis, be modified. In addition, a suitable protection/deprotection strategy may need to be employed.

It will be further appreciated by those skilled in the art that, in the schemes above, certain compounds of formula (II), (XI), (XVI), (XIX) and (XXVI) are encompassed within the definition of compounds of formula (I), as are the compounds of formula (IV), (V), (VII), (XIII), (XLII) and (XLIII). Alternative numbering of these compounds was adopted merely to enhance the clarity of the schemes.

All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the Examples and Preparations hereto. Furthermore, it will be clear to the skilled person that the compounds of formula (I) may be synthesised either directly from, or by analogy to, the schemes, literature precedents and the Examples and Preparations herein described, as well as the common general knowledge.

The compounds of the present invention have utility as selective D3 agonists in the treatment of disease states. There are a number of prior art compounds with activity as both D2 and D3 agonists; however the use of such compounds is associated with a large number of side effects including nausea, emesis, syncope, hypotension and bradycardia, some of which are a cause for serious concern.

It was previously held that the efficacy of the said prior art compounds stemmed from their ability to agonise D2; however, without being bound by any theory, it has been postulated that D2 agonism could be implicated as a cause of the side effects detailed above.

The present invention provides a class of selective D3 agonists. These have been found to be efficacious, whilst reducing the side effects associated with unselective prior art compounds.

Accordingly a further aspect of the invention provides a compound of formula (I) for use as a medicament. In the following embodiments, references to compounds of formula (I) include the said compounds with or without provisos a) to j) defined hereinabove.

- 5 Compounds of the present invention are particularly useful in treating sexual dysfunction, female sexual dysfunction, including hypoactive sexual desire disorder, female sexual arousal disorder, female orgasmic disorder and sexual pain disorder; male erectile dysfunction, hypertension, neurodegeneration, depression, pain and psychiatric disorders.
- 10 Accordingly, the present invention provides for the use of a compound of formula (I), in the preparation of a medicament for the treatment or prevention of sexual dysfunction.

The compounds of the present invention are useful in male sexual dysfunction, including male erectile dysfunction. Male erectile dysfunction (MED), otherwise known as male erectile disorder, is defined as:

15

"the inability to achieve and/or maintain a penile erection for satisfactory sexual performance"
(NIH Consensus Development Panel on Impotence, 1993)"

- It has been estimated that the prevalence of erectile dysfunction (ED) of all degrees (minimal, moderate and complete impotence) is 52% in men 40 to 70 years old, with higher rates in those older than 70 (Melman *et al* 1999, J. Urology, 161, p5-11). The condition has a significant negative impact on the quality of life of the individual and their partner, often resulting in increased anxiety and tension which leads to depression and low self-esteem. Whereas two decades ago, MED was primarily considered to be a psychological disorder (Benet *et al* 1994 Comp. Ther., 20: 669-673), it is now known that for the majority of individuals there is an underlying organic cause. As a result, much progress has been made in identifying the mechanism of normal penile erection and the pathophysiologies of MED.

- Penile erection is a haemodynamic event which is dependent upon the balance of contraction and relaxation of the corpus cavernosal smooth muscle and vasculature of the penis (Lerner *et al* 1993, J. Urology, 149, 1256-1255). Corpus cavernosal smooth muscle is also referred to herein as corporal smooth muscle or in the plural sense corpus cavernosa. Relaxation of the corpus cavernosal smooth muscle leads to an increased blood flow into the trabecular spaces of the corpus cavernosa, causing them to expand against the surrounding tunica and compress the draining veins. This produces a vast elevation in blood pressure which results in an erection (Naylor, 1998, J. Urology, 81, 424-431).

35

- The changes that occur during the erectile process are complex and require a high degree of coordinated control involving the peripheral and central nervous systems, and the endocrine system (Naylor, 1998, J. Urology, 81, 424-431). Corporal smooth muscle contraction is modulated by sympathetic noradrenergic innervation via activation of postsynaptic α_1 adrenoceptors. MED may be associated with an increase in the endogenous smooth muscle tone of the corpus cavernosum. However, the process of corporal smooth muscle relaxation is mediated partly by non-adrenergic, non-

40

cholinergic (NANC) neurotransmission. There are a number of other NANC neurotransmitters found in the penis, other than NO, such as calcitonin gene related peptide (CGRP) and vasoactive intestinal peptide (VIP). The main relaxing factor responsible for mediating this relaxation is nitric oxide (NO), which is synthesised from L-arginine by nitric oxide synthase (NOS) (Taub *et al* 1993 Urology, 42, 698-704). It is thought that reducing corporal smooth muscle tone may aid NO to induce relaxation of the corpus cavernosum. During sexual arousal in the male, NO is released from neurones and the endothelium and binds to and activates soluble guanylate cyclase (sGC) located in the smooth muscle cells and endothelium, leading to an elevation in intracellular cyclic guanosine 3',5'-monophosphate (cGMP) levels. This rise in cGMP leads to a relaxation of the corpus cavernosum due to a reduction in the intracellular calcium concentration ($[Ca^{2+}]_i$), via unknown mechanisms thought to involve protein kinase G activation (possibly due to activation of Ca^{2+} pumps and Ca^{2+} -activated K^+ channels).

Multiple potential sites have been identified within the central nervous system for the modulation of sexual behaviour. The key neurotransmitters are thought to be serotonin, norepinephrine, oxytocin, nitric oxide and dopamine. By mimicking the actions of one of these key neurotransmitters sexual function may be adjusted. Dopamine D3 receptors are expressed almost exclusively in the limbic area of the brain, regions involved in the reward, emotional and cognitive processes.

Without being bound by any theory, it appears that "due to its role in the control of locomotor activity, the integrity of the nigrostriatal dopaminergic pathway is also essential for the display of copulatory behaviour. Somehow, more specific to sexual function, it is likely that dopamine can trigger penile erection by acting on oxytocinergic neurons located in the paraventricular nucleus of the hypothalamus, and perhaps on the pro-erectile sacral parasympathetic nucleus within the spinal cord". It now appears that a significant site is D3 and not as previously thought, D2 alone.

In essence, agonism of the D3 receptor initiates of sexual behaviour.

Accordingly, the present invention provides for the use of a compound of formula (I), in the preparation of a medicament for the treatment or prevention of male sexual dysfunction, particularly, but not limited to, male erectile dysfunction.

Patients with mild to moderate MED should benefit from treatment with the compounds according to the present invention, and patients with severe MED may also respond. However, early investigations suggest that the responder rate of patients with mild, moderate and severe MED may be greater with a selective D3 agonist/PDE5 inhibitor combination. Mild, moderate and severe MED will be terms known to the man skilled in the art, but guidance can be found in The Journal of Urology, vol. 151, 54-61 (Jan 1994).

Early investigations suggest the below mentioned MED patient groups should benefit from treatment with a selective D3 agonist and a PDE5i and/or a NEPi (or other combination set out hereinafter). These patient groups, which are described in more detail in Clinical Andrology vol. 23, no.4, p773-782 and

chapter 3 of the book by I. Eardley and K. Sethia "Erectile Dysfunction-Current Investigation and Management", published by Mosby-Wolfe, are as follows: psychogenic, organic, vascular, endocrinologic, neurogenic, arteriogenic, drug-induced sexual dysfunction (lactogenic) and sexual dysfunction related to cavernosal factors, particularly venogenic causes.

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Accordingly the present invention provides for the use of a compound of formula (I), in the preparation of a medicament in combination with a PDE5 inhibitor; particularly for, but not limited to, the treatment of erectile dysfunction

Suitable PDE5 inhibitors are described herein.

10

In another embodiment, the compounds of the present invention are useful in the treatment or prevention of female sexual dysfunction (FSD), including FSAD.

In accordance with the invention, FSD can be defined as the difficulty or inability of a woman to find satisfaction in sexual expression. FSD is a collective term for several diverse female sexual disorders (Leiblum, S.R. (1998) - Definition and classification of female sexual disorders. *Int. J. Impotence Res.*, **10**, S104-S106; Berman, J.R., Berman, L. & Goldstein, I. (1999) - Female sexual dysfunction: Incidence, pathophysiology, evaluations and treatment options. *Urology*, **54**, 385-391). The woman may have lack of desire, difficulty with arousal or orgasm, pain with intercourse or a combination of these problems. Several types of disease, medications, injuries or psychological problems can cause FSD. Treatments in development are targeted to treat specific subtypes of FSD, predominantly desire and arousal disorders.

The categories of FSD are best defined by contrasting them to the phases of normal female sexual response: desire, arousal and orgasm (Leiblum, S.R. (1998) - Definition and classification of female sexual disorders. *Int. J. Impotence Res.*, **10**, S104-S106). Desire or libido is the drive for sexual expression. Its manifestations often include sexual thoughts either when in the company of an interested partner or when exposed to other erotic stimuli. Arousal is the vascular response to sexual stimulation, an important component of which is genital engorgement and includes increased vaginal lubrication, elongation of the vagina and increased genital sensation/sensitivity. Orgasm is the release of sexual tension that has culminated during arousal.

Hence, FSD occurs when a woman has an inadequate or unsatisfactory response in any of these phases, usually desire, arousal or orgasm. FSD categories include hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorders and sexual pain disorders. Although the compounds of the invention will improve the genital response to sexual stimulation (as in female sexual arousal disorder), in doing so it may also improve the associated pain, distress and discomfort associated with intercourse and so treat other female sexual disorders.

Hypoactive sexual desire disorder is present if a woman has no or little desire to be sexual, and has no or few sexual thoughts or fantasies. This type of FSD can be caused by low testosterone levels, due

either to natural menopause or to surgical menopause. Other causes include illness, medications, fatigue, depression and anxiety.

Female sexual arousal disorder (FSAD) is characterised by inadequate genital response to sexual stimulation. The genitalia do not undergo the engorgement that characterises normal sexual arousal. The vaginal walls are poorly lubricated, so that intercourse is painful. Orgasms may be impeded. Arousal disorder can be caused by reduced oestrogen at menopause or after childbirth and during lactation, as well as by illnesses, with vascular components such as diabetes and atherosclerosis. Other causes result from treatment with diuretics, antihistamines, antidepressants e.g. selective serotonin re-uptake inhibitors (SSRIs) or antihypertensive agents.

Sexual pain disorders (includes dyspareunia and vaginismus) is characterised by pain resulting from penetration and may be caused by medications which reduce lubrication, endometriosis, pelvic inflammatory disease, inflammatory bowel disease or urinary tract problems.

As previously discussed, D3 is thought to be an initiator of sexual behaviour. The clitoris is considered to be a homologue of the penis (Levin, R.J. (1991), *Exp. Clin. Endocrinol.*, **98**, 61-69); the same mechanism that provides an erectile response in the male produces an increase in genital blood flow in the female with an associated effect upon FSD. In addition there are changes in proceptivity and receptivity.

Thus, in accordance with one embodiment of the invention, there is provided the use of a compound of formula (I), in the preparation of a medicament for the treatment or prophylaxis of female sexual dysfunction, including hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder or sexual pain disorder.

In one embodiment the compounds of formula (I) are useful in the treatment or prophylaxis of sexual arousal disorder, orgasmic disorder, and hypoactive sexual desire disorder, and in a further embodiment, in the treatment or prophylaxis of sexual arousal disorder.

In a further embodiment the compounds of formula (I), are useful in the treatment of a subject with female sexual arousal disorder and concomitant hypoactive sexual desire disorder.

The Diagnostic and Statistical Manual (DSM) IV of the American Psychiatric Association defines Female Sexual Arousal Disorder (FSAD) as being:

"... a persistent or recurrent inability to attain or to maintain until completion of the sexual activity adequate lubrication-swelling response of sexual excitement. The disturbance must cause marked distress or interpersonal difficulty. ..."

The arousal response consists of vasocongestion in the pelvis, vaginal lubrication and expansion and swelling of the external genitalia. The disturbance causes marked distress and/or interpersonal difficulty.

FSAD is a highly prevalent sexual disorder affecting pre-, peri- and post-menopausal ($\pm$ hormone replacement therapy (HRT)) women. It is associated with concomitant disorders such as depression, cardiovascular diseases, diabetes and urogenital (UG) disorders.

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The primary consequences of FSAD are lack of engorgement/swelling, lack of lubrication and lack of pleasurable genital sensation. The secondary consequences of FSAD are reduced sexual desire, pain during intercourse and difficulty in achieving an orgasm.

- 10 It has recently been hypothesised that there is a vascular basis for at least a proportion of patients with symptoms of FSAD (Goldstein *et al.*, Int. J. Impot. Res., 10, S84-S90, 1998) with animal data supporting this view (Park *et al.*, Int. J. Impot. Res., 9, 27-37, 1997).

- 15 R.J. Levin teaches us that because "... male and female genitalia develop embryologically from the common tissue anlagen, [that] male and female genital structures are argued to be homologues of one another. Thus the clitoris is the penile homologue and the labia homologues of the scrotal sac. ..." (Levin, R.J. (1991), *Exp. Clin. Endocrinol.*, **98**, 61-69).

- 20 Drug candidates for treating FSAD, which are under investigation for efficacy, are primarily erectile dysfunction therapies that promote circulation to male genitalia.

- 25 The compounds of the present invention are advantageous by providing a means for restoring a normal sexual arousal response - namely increased genital blood flow leading to vaginal, clitoral and labial engorgement. This will result in increased vaginal lubrication via plasma transudation, increased vaginal compliance and increased genital sensitivity. Hence, the present invention provides a means to restore, or potentiate, the normal sexual arousal response.

- 30 Thus, in one embodiment of the invention, there is provided the use of a compound of formula (I), in the preparation of a medicament for the treatment or prophylaxis of female sexual arousal disorder.

- 35 By female genitalia herein we mean: "The genital organs consist of an internal and external group. The internal organs are situated within the pelvis and consist of ovaries, the uterine tubes, uterus and the vagina. The external organs are superficial to the urogenital diaphragm and below the pelvic arch. They comprise the mons pubis, the labia majora and minora pudendi, the clitoris, the vestibule, the bulb of the vestibule, and the greater vestibular glands" (Gray's Anatomy, C.D. Clemente, 13th American Edition).

- 40 The compounds of the invention find application in the following sub-populations of patients with FSD: the young, the elderly, pre-menopausal, peri-menopausal, post-menopausal women with or without hormone replacement therapy.

The compounds of the invention find application in patients with FSD arising from:-

- i) Vasculogenic etiologies e.g. cardiovascular or atherosclerotic diseases, hypercholesterolemia, cigarette smoking, diabetes, hypertension, radiation and perineal trauma, traumatic injury to the iliohypogastric pudendal vascular system.
- 5 ii) Neurogenic etiologies such as spinal cord injuries or diseases of the central nervous system including multiple sclerosis, diabetes, Parkinsonism, cerebrovascular accidents, peripheral neuropathies, trauma or radical pelvic surgery.
- 10 iii) Hormonal/endocrine etiologies such as dysfunction of the hypothalamic/pituitary/gonadal axis, or dysfunction of the ovaries, dysfunction of the pancreas, surgical or medical castration, androgen deficiency, high circulating levels of prolactin e.g. hyperprolactinemia, natural menopause, premature ovarian failure, hyper and hypothyroidism.
- iv) Psychogenic etiologies such as depression, obsessive compulsive disorder, anxiety disorder, postnatal depression/"Baby Blues", emotional and relational issues, performance anxiety, marital discord, dysfunctional attitudes, sexual phobias, religious inhibition or a traumatic past experiences.
- 15 v) Drug-induced sexual dysfunction resulting from therapy with selective serotonin reuptake inhibitors (SSRIs) and other antidepressant therapies (tricyclics and major tranquillizers), anti-hypertensive therapies, sympatholytic drugs, chronic oral contraceptive pill therapy.

The Compounds of the present invention are also useful in the treatment of depression.

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Dopamine D3 receptors are expressed almost exclusively in the limbic area of the brain, regions involved in reward, emotional and cognitive processes. Chronic treatment with several classes of antidepressants are known to increase the expression of D3 in the limbic area, and antidepressant effects of desipramine can be blocked by sulpride (D2/D3 antagonist) when injected to nucleus accumbens (area rich in D3) but not caudate-putamen (area rich in dopamine D2 receptors). In addition, antidepressant effects were observed preclinical models of depression and in patients treated with pramipexole, a D3-preferring agonist. The available information suggests that D3 receptors mediate the anti-depressant activity and that selective D3 receptor agonists represent a new class of antidepressant drugs. Since antidepressants are known to be effective in other psychiatric disorders, D3 agonists would have the potential to treat psychiatric diseases.

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Suitable conditions include depression (e.g. depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, paediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression and grumpy old man syndrome), generalized anxiety disorder, phobias (e.g. agoraphobia, social phobia and simple phobias), posttraumatic stress syndrome, avoidant personality disorder, eating disorders (e.g. anorexia nervosa and bulimia nervosa), chemical dependencies (e.g. addictions to alcohol, cocaine, heroin, phenobarbital, nicotine and benzodiazepines), Alzheimer's disease, obsessive-compulsive disorder, panic disorder, memory disorders (e.g. dementia, amnesic disorders, and age-related cognitive decline (ARCD)), Parkinson's diseases (e.g. dementia in Parkinson's disease, neuroleptic-induced parkinsonism and

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tardive dyskinesias), endocrine disorders (e.g. hyperprolactinaemia), negative symptoms of schizophrenia, Tourette's syndrome, trichotillomania, kleptomania, attention deficit hyperactivity disorder (ADHD), emotional lability, pathological crying, sleeping disorder (cataplexy) and shock.

- 5 In a further embodiment, the present invention provides for the use of a compound of formula (I) in the preparation of a medicament for the treatment of depression or psychiatric disorders.

Suitable depressive conditions and psychiatric disorders are described above.

- 10 The compounds of the present invention also have utility in the treatment of neurodegeneration; sources of neurodegeneration include neurotoxin poisoning; vision loss caused by neurodegeneration of the visual pathway, such as by a stroke in the visual pathway eg in retina, optic nerve and/or occipital lobe; epileptic seizures; and from impairment of glucose and/or oxygen supply to the brain.
- 15 Accordingly the present invention provides for the use of a compound of formula (I) in the preparation of a medicament for the treatment or prevention of neurodegeneration.

The compounds of the present invention also have utility in the treatment of pain, particularly, but not limited to, chronic nociceptive pain.

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- 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
- 25 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,
- 30 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
- 35 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
- 40 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 dysmenorrhea, 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:

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- 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
10 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
15 temporomandibular myofascial pain.

Accordingly the present invention provides for the use of a compound of formula (I), in the preparation of a medicament for the treatment or prevention of pain. In a further embodiment the present invention
20 provides for the use of a compound of formula (I), in the preparation of a medicament for the treatment or prevention of chronic nociceptive pain.

In addition to their role in treating sexual dysfunction, depression, neurodegeneration, pain and psychiatric disorders, the compounds of the present invention are likely to be efficacious in a number of
25 additional indications. Accordingly, the present invention provides for the use of compounds of formula (I) in the preparation of a medicament for the treatment of hypertension, premature ejaculation, obesity, cluster headache, migraine, pain, endocrine disorders (e.g. hyperprolactinaemia), vasospasm (particularly in the cerebral vasculature), cerebellar ataxia, gastrointestinal tract disorders (involving changes in motility and secretion), premenstrual syndrome, fibromyalgia syndrome, stress incontinence,
30 chronic paroxysmal hemicrania, and headache (associated with vascular disorders).

In another embodiment, the present invention provides a method for treating or preventing the conditions, diseases or disorders mentioned herein above, which comprises administering to a mammalian subject, including a human, in need thereof, an effective amount of a compound of formula
35 (I) or a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof.

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

40 D3/D2 AGONIST BINDING ASSAY

Gonzalez *et al* (Eup. J Pharmacology 272 (1995) R1-R3) discloses an assay for determining the binding capability of a compound at D3 and/or D2 dopamine receptors and thus the binding selectivity of such compounds. This assay is, thus, herein referred to as a binding assay.

5 D3/D2 AGONIST FUNCTIONAL ASSAY

A suitable assay for determining functionally the activity of a compound at D3 and/or D2 dopamine receptors is published in WO2004/052372.

- 10 Using the functional assay described above, the compounds of the present invention all exhibit a functional potency at D3 receptor expressed as an EC₅₀, lower than 1000nM and a 10 fold selectivity for D3 over D2. For example, the compounds of examples 1, 4, 5, 12, 13, 14, 16, 18 and 19 to 24, all exhibit a functional potency at D3 receptor expressed as an EC₅₀ lower than 500nM and a greater than 20 fold selectivity for D3 over D2.

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- The compound of example 5 has a functional potency at D3 receptor expressed as an EC₅₀, of 83nM and 120 fold selectivity for D3 over D2. The compound of example 14 has a functional potency at D3 receptor expressed as an EC₅₀, of 27nM and 370 fold selectivity for D3 over D2. The compound of example 16 has a functional potency at D3 receptor expressed as an EC₅₀, of 10nM and 118 fold selectivity for D3 over D2. The compound of example 23 has a functional potency at D3 receptor expressed as an EC₅₀, of 33nM and 303 fold selectivity for D3 over D2. Selectivity is calculated as the D2 EC₅₀ value divided by the D3 EC₅₀ value. Where the value of the D2 EC₅₀ was >10000, a figure of 10000 was used in the calculation.

25 PAIN ASSAYS

Suitable assays for determining the utility of the compounds of the invention in various pain conditions are described below.

30 **Neuropathic pain**

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

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

40 Chronic constriction injury (CCI) rat model of neuropathic pain

The CCI of sciatic nerve was 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 were anaesthetised with a 2% isoflurane/O₂ mixture. The right hind thigh was shaved and swabbed with 1% iodine. Animals were then transferred to a homeothermic blanket for the duration of the procedure and anaesthesia maintained during surgery via a nose cone. The skin was cut along the line of the thighbone. The common sciatic nerve was exposed at the middle of the thigh by blunt dissection through biceps femoris. About 7mm of nerve was freed proximal to the sciatic trifurcation, by inserting forceps under the nerve and the nerve gently lifted out of the thigh. Suture was pulled under the nerve using forceps and tied in a simple knot until slight resistance was felt and then double knotted. The procedure was repeated until 4 ligatures (4-0 silk) were tied loosely around the nerve with approx 1mm spacing. The incision was closed in layers and the wound treated with topical antibiotics.

Streptozocin (STZ)-induced diabetes neuropathy in the rat

Diabetes was 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 were habituated to wire bottom test cages prior to the assessment of allodynia. Static allodynia was 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 was 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 was established, the paw was 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 occurred. The highest force of 26g lifted the paw as well as eliciting a response, thus represented the cut off point. Each animal had both hind paws tested in this manner. The lowest amount of force required to elicit a response was recorded as paw withdrawal threshold (PWT) in grams. Static allodynia was defined as present if animals responded 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).

Dynamic allodynia

Dynamic allodynia was assessed by lightly stroking the plantar surface of the hind paw with a cotton bud. To avoid recording general motor activity, care was taken to perform this procedure in fully habituated rats that were not active. At least two measurements were taken at each time point, the mean of which represented the paw withdrawal latency (PWL). If no reaction was exhibited within 15 sec the procedure

was terminated and animals were assigned this withdrawal time. A pain withdrawal response was often accompanied with repeated flinching or licking of the paw. Dynamic allodynia was considered to be present if animals responded to the cotton stimulus within 8 sec of commencing stroking (Field et al, 1999).

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Nociceptive pain

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

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Hotplate

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 will be made and animals reassessed following drug administration. The cut off time for hot plate latencies is set at 20 seconds to prevent tissue damage.

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Ovariectomy (OVX)

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Experimental Procedure: Female Sprague Dawley rats are placed into an anaesthetic chamber and anaesthetised with a 2% isoflurane / O₂ 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.

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Brennan

Experimental Procedure: Male Sprague Dawley rats are placed into an anaesthetic chamber and anaesthetised with a 2% isoflurane / O₂ 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.

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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 as in 10.2. 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 used adult male C3H/HeN mice (Nihon SLC, Shizuoka, Japan). The mice were 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 used has been described. After induction of general anesthesia with an inhalation of isoflurane (2%), a superficial incision was made in the skin overlying the patella, using Mora scissors. The patellar ligament was then cut, exposing the condyles of the distal femur. A 30-gauge needle was inserted at the level of the intercondylar notch and into the medullary canal to create an initial core pathway. After the initial core was made, a 29-gauge needle was used to make the final pathway into the bone. A 0.5-mm depression was 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) was injected using a 29-gauge needle and a .25 cc syringe. To prevent leakage of cells outside the bone, the injection site was closed with dental resin, followed by copious irrigation with filtered water. Wound closure was achieved using auto wound clips (Becton Dickinson, San Jose, California). Wound clips were removed at day 5 to prevent interference with behavioral testing.

Assessment of static and dynamic allodyniaStatic allodynia.

Procedure as described above for neuropathic pain.

Dynamic allodynia

Procedure as described above for neuropathic pain.

Radiant heat paw withdrawal

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

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.

Inflammatory pain

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

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

- 5 Thermal hyperalgesia was assessed using the rat plantar test (Ugo Basile, Comerio, Italy), according to a method modified by Hargreaves et al. (1988). Briefly, rats were habituated to the apparatus that consisted of three individual Perspex boxes on a glass table. A mobile radiant heat source was located under the table and focused onto the desired paw. Paw withdrawal latencies (PWLs) were recorded three times for both hind paws of each animal, the mean of which represented baseline for left and right
- 10 hind paws. The apparatus was 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 was observed. Lambda carrageenan was injected intraplantarly (100 µl, 20 mg/ml) the right hind paw and baseline recordings of PWT were taken 2 hr post administration.

15 **Visceral pain**

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

- 20 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).

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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.

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- Materials and methods: Male Sprague-Dawley rats are used. The animals are housed 3 per cage in a regulated environment (20 ± 1°C, 50 ± 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 ± 1°C, 50 ± 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
- 35 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
- 40

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.

5 LPS-induced rectal hypersensitivity in rats

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

- 10 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
- 15 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 Hz) and a paper speed of 3.6 cm/min.

- 20 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

- 25 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
- 30 removal with a syringe at the end of the distension period.

Suitable auxiliary active agents for use in combination with the compounds of the present invention include:

35

- 1) Naturally occurring or synthetic prostaglandins or esters thereof. Suitable prostaglandins for use herein include compounds such as alprostadil, prostaglandin E₁, prostaglandin E₀, 13, 14 - dihydroprosta glandin E₁, prostaglandin E₂, eprostinol, natural synthetic and semi-synthetic prostaglandins and derivatives thereof including those described in WO-00033825 and/or US
- 40 6,037,346 issued on 14th March 2000 all incorporated herein by reference, PGE₀, PGE₁, PGA₁, PGB₁, PGF₁ α, 19-hydroxy PGA₁, 19-hydroxy - PGB₁, PGE₂, PGB₂, 19-hydroxy-PGA₂, 19-

hydroxy-PGB₂, PGE₃ α , carboprost tromethamine dinoprost, tromethamine, dinoprostone, lipo prost, gemeprost, metenoprost, sulprostone, tiaprost and moxislyate;

- 2) α - adrenergic receptor antagonist compounds also known as α - adrenoceptors or α -receptors or α -blockers. Suitable compounds for use herein include: the α -adrenergic receptor blockers as described in PCT application WO99/30697 published on 14th June 1998, the disclosures of which relating to α -adrenergic receptors are incorporated herein by reference and include, selective α_1 -adrenoceptor or α_2 -adrenoceptor blockers and non-selective adrenoceptor blockers, suitable α_1 -adrenoceptor blockers include: phentolamine, phentolamine mesylate, trazodone, alfuzosin, indoramin, naftopidil, tamsulosin, dapiprazole, phenoxybenzamine, idazoxan, efaraxan, yohimbine, rauwolfia alkaloids, Recordati 15/2739, SNAP 1069, SNAP 5089, RS17053, SL 89.0591, doxazosin, terazosin, abanoquil and prazosin; α_2 -blocker blockers from US 6,037,346 [14th March 2000] dibenarnine, tolazoline, trimazosin and dibenarnine; α -adrenergic receptors as described in US patents: 4,188,390; 4,026,894; 3,511,836; 4,315,007; 3,527,761; 3,997,666; 2,503,059; 4,703,063; 3,381,009; 4,252,721 and 2,599,000 each of which is incorporated herein by reference; α_2 -Adrenoceptor blockers include: clonidine, papaverine, papaverine hydrochloride, optionally in the presence of a cariotonic agent such as pirxamine;
- 3) NO-donor (NO-agonist) compounds. Suitable NO-donor compounds for use herein include organic nitrates, such as mono- di or tri-nitrates or organic nitrate esters including glyceryl trinitrate (also known as nitroglycerin), isosorbide 5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside (SNP), 3-morpholinosydnonimine molsidomine, S-nitroso- N-acetyl penicilliamine (SNAP) S-nitroso-N-glutathione (SNO-GLU), N-hydroxy - L-arginine, amylnitrate, linsidomine, linsidomine chlorohydrate, (SIN-1) S-nitroso - N-cysteine, diazenium diolates,(NONOates), 1,5-pentanedinitrate, L-arginene, ginseng, zizphi fructus, molsidomine, Re - 2047, nitrosylated maxislyte derivatives such as NMI-678-11 and NMI-937 as described in published PCT application WO 0012075;
- 4) Potassium channel openers or modulators. Suitable potassium channel openers/modulators for use herein include nicorandil, cromokalim, levromakalim, lemakalim, pinacidil, cliazoxide, minoxidil, charybdotoxin, glyburide, 4-amini pyridine, BaCl₂;
- 5) Vasodilator agents. Suitable vasodilator agents for use herein include nimodipine, pinacidil, cycandelate, isoxsuprine, chloroprumazine, , Rec 15/2739, trazodone;
- 6) Thromboxane A₂ agonists;
- 7) CNS active agents;

- 8) Ergot alkaloids; Suitable ergot alkaloids are described in US patent 6,037,346 issued on 14th March 2000 and include acetergamine, brazergoline, bromerguride, cianergoline, delorgotrile, disulergine, ergonovine maleate, ergotamine tartrate, etisulergine, lergotrile, lysergide, mesulergine, metergoline, metergotamine, nicergoline, pergolide, propisergide, proterguride and terguride;
- 9) Compounds which modulate the action of naturetic factors in particular atrial naturetic factor (also known as atrial naturetic peptide), B type and C type naturetic factors such as inhibitors or neutral endopeptidase;
- 10) Compounds which inhibit angiotensin-converting enzyme such as enapril, and combined inhibitors of angiotensin-converting enzyme and neutral endopeptidase such as omapatrilat.
- 11) Angiotensin receptor antagonists such as losartan;
- 12) Substrates for NO-synthase, such as L-arginine;
- 13) Calcium channel blockers such as amlodipine;
- 14) Antagonists of endothelin receptors and inhibitors of endothelin-converting enzyme;
- 15) Cholesterol lowering agents such as statins (e.g. atorvastatin/ Lipitor- trade mark) and fibrates;
- 16) Antiplatelet and antithrombotic agents, e.g. tPA, uPA, warfarin, hirudin and other thrombin inhibitors, heparin, thromboplastin activating factor inhibitors;
- 17) Insulin sensitising agents such as rezulin and hypoglycaemic agents such as glipizide;
- 18) Acetylcholinesterase inhibitors such as donezipil;
- 19) Steroidal or non-steroidal anti-inflammatory agents;
- 20) Estrogen receptor modulators and/or estrogen agonists and/or estrogen antagonists, for example raloxifene or lasofoxifene, (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol and pharmaceutically acceptable salts thereof the preparation of which is detailed in WO 96/21656;
- 21) A PDE inhibitor, more particularly a PDE 2, 3, 4, 5, 7 or 8 inhibitor, typically a PDE2 or PDE5 inhibitor and most typically a PDE5 inhibitor (see hereinafter), said inhibitors preferably having an IC₅₀ against the respective enzyme of less than 100nM (with the proviso that PDE 3 and 4 inhibitors are only administered topically or by injection to the penis);

- 22) Vasoactive intestinal protein (VIP), VIP mimetic, VIP analogue, more particularly mediated by one or more of the VIP receptor subtypes VPAC1, VPAC or PACAP (pituitary adenylate cyclase activating peptide), one or more of a VIP receptor agonist or a VIP analogue (e.g. Ro-125-1553) or a VIP fragment, one or more of a α -adrenoceptor antagonist with VIP combination (e.g. Invicorp, Aviptadil);
- 23) A melanocortin receptor (particularly of the MC3 or MC4 subtype) agonist or modulator or melanocortin enhance, such as melanotan II, PT-14, PT-141 or compounds claimed in WO-09964002, WO-00074679, WO-09955679, WO-00105401, WO-00058361, WO-00114879, WO-00113112, WO-09954358;
- 24) A serotonin receptor agonist, antagonist or modulator, more particularly agonists, antagonists or modulators for 5HT1A (including VML 670), 5HT2A, 5HT2C, 5HT3 and/or 5HT6 receptors, including those described in WO-09902159, WO-00002550 and/or WO-00028993;
- 25) A testosterone replacement agent (including dehydroandrostendione), testosterone (Tostrelle), dihydrotestosterone or a testosterone implant;
- 26) Estrogen, estrogen and medroxyprogesterone or medroxyprogesterone acetate (MPA) (i.e. as a combination), or estrogen and methyl testosterone hormone replacement therapy agent (e.g. HRT especially Premarin, Cenestin, Oestrofeminal, Equin, Estrace, Estrofem, Elleste Solo, Estring, Estraderm TTS, Estraderm Matrix, Dermestril, Premphase, Preempro, Prempak, Premique, Estratest, Estratest HS, Tibolone);
- 27) A modulator of transporters for noradrenaline, dopamine and/or serotonin, such as bupropion, GW-320659;
- 28) A purinergic receptor agonist and/or modulator;
- 29) A neurokinin (NK) receptor antagonist, including those described in WO-09964008;
- 30) An opioid receptor agonist, antagonist or modulator, preferably agonists for the ORL-1 receptor;
- 31) An agonist, antagonist or modulator for oxytocin receptors, preferably a selective oxytocin agonist or modulator;
- 32) Modulators of cannabinoid receptors;
- 33) A SEP inhibitor (SEPi), for instance a SEPi having an IC_{50} at less than 100 nanomolar, more preferably, at less than 50 nanomolar.

Preferably, the SEP inhibitors according to the present invention have greater than 30-fold, more preferably greater than 50-fold selectivity for SEP over neutral endopeptidase NEP EC 3.4.24.11 and angiotensin converting enzyme (ACE). Preferably the SEPI also has a greater than 100-fold selectivity over endothelin converting enzyme (ECE).

34) An antagonist or modulator for the NPY (particularly Y1 and Y5 subtype) receptor.

35) A Sex Hormone Binding Globulin antagonist or modulator that inhibits estrogens and/or androgens from being bound.

36) An arginase II inhibitor,

37) An agonist, antagonist or modulator for vassopressin receptors, preferably selective for the V1a receptor

38) A PDE5 Inhibitor. Suitable PDE5 inhibitors include:

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), particularly sildenafil citrate;

(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-2-(1-ethyl-3-azetidiny)-

2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; 5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidiny)-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 (TA-1790); 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 (DA 8159) and pharmaceutically acceptable salts thereof.

39) A selective dopamine D4 receptor agonist such as 2-[(4-pyridin-2-ylpiperazin-1-yl)methyl]-1H-benzimidazole (ABT724).

40) One or more selective serotonin reuptake inhibitors (SSRIs) such as dapoxetine, paroxetine, 3-[(dimethylamino)methyl]-4-[4-(methylsulfonyl)phenoxy]benzenesulfonamide (Example 28, WO 0172687), 3-[(dimethylamino)methyl]-4-[3-methyl-4-(methylsulfonyl)phenoxy]

benzenesulfonamide (Example 12, WO 0218333), N-methyl-N-[(3-[3-methyl-4-(methylsulfonyl)phenoxy]-4-pyridinyl)methyl]amine (Example 38, PCT Application no PCT/IB02/01032).

41) one or more NEP inhibitors, preferably wherein said NEP is EC 3.4.24.11 and more preferably wherein said NEP inhibitor is a selective inhibitor for EC 3.4.24.11, more preferably a selective NEP inhibitor is a selective inhibitor for EC 3.4.24.11, which has an IC_{50} of less than 100nM (e.g. omapatrilat, sampatrilat) suitable NEP inhibitor compounds are described in EP-A-1097719; IC_{50} values against NEP and ACE may be determined using methods described in published patent application EP1097719-A1, paragraphs [0368] to [0376];

42) Melanocortin receptor agonists (e.g. Melanotan II and PT141) and selective MC3 and MC4 agonists (e.g. THIQ).

43) Mono amine transport inhibitors, particularly Noradrenaline Re-uptake Inhibitors (NRIs) (e.g. Reboxetine).

By cross reference herein to compounds contained in patents and patent applications which can be used in accordance with invention, we mean the therapeutically active compounds as defined in the claims (in particular of claim 1) and the specific examples (all of which is incorporated herein by reference).

The foregoing combinations have particular utility in the treatment of sexual dysfunction.

If a combination of active agents is administered, then they may be administered simultaneously, separately or sequentially.

The compounds of the formula (I) can be administered alone but 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.

Accordingly the present invention provides for a composition comprising a compound of formula (I) and a pharmaceutically acceptable diluent or carrier.

For example, the compounds of the formula (I) can be administered orally, buccally or sublingually in the form of tablets; soft or hard capsules containing multi- or nano-particulates, liquids, or powders; lozenges (including liquid-filled); chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal/mucoadhesive patches, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, 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 formula (I) 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.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules (made, for example, from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellaable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula (I), a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabiliser or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

The compound of formula (I) may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 weight % to 80 weight %, more typically from 20 weight % to 50 weight %, of the solutes. Less soluble compounds may comprise a greater proportion of the composition, typically up to 88 weight % of the solutes. Alternatively, the compound of formula (I) may be in the form of multiparticulate beads.

The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %.

Other possible ingredients include anti-oxidants, colorants, flavourings and flavour enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

- 5 The compounds of the formula (I) 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
- 10 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.

- The compounds of formula (I) can also be administered intranasally or by inhalation, typically in the form
- 15 of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler, as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, or as nasal
- 20 drops. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

- The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable
- 25 alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

- Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate
- 30 comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

- Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the
- 35 invention, a suitable powder base such as lactose or starch and a performance modifier such as l-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

- 40 A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of the invention per actuation and the actuation volume

may vary from 1µl to 100µl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

- 5 Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

- Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include delayed-, sustained-, pulsed-,
10 controlled-, targeted and programmed release.

- The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives
15 may be used as appropriate.

- Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and
20 programmed release.

- They may also be administered by the ocular route. For ophthalmic use, the compounds can be formulated as micronised 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.

- 25 For application topically to the skin, the compounds of the formula (I) 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
30 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 formula (I) may also be used in combination with a cyclodextrin. Cyclodextrins are
35 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-
40 cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

Inasmuch as it may be desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula I in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

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

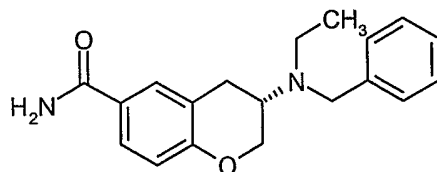
α_D	optical rotation at 587nm.
Ac ₂ O	acetic anhydride
APCI	atmospheric pressure chemical ionisation
Arbacel®	filter agent
br	broad
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
CDCl ₃	chloroform-d1
CD ₃ OD	methanol-d4
δ	chemical shift
d	doublet
dd	double doublet
DCM	dichloromethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
eq	(molar) equivalents
ESI	electrospray ionisation
Et	ethyl
EtOAc	ethyl acetate

h	hours
HCl	hydrogen chloride
HPLC	high performance liquid chromatography
HR M/S	high resolution mass spectrum
IPA	isopropylalcohol
KOAc	potassium acetate
m	multiplet
Me	methyl
MeCN	acetonitrile
M/S	mass spectrum
min	minutes
NMR	nuclear magnetic resonance
q	quartet
r.t.	room temperature
s	singlet
sat	saturated
t	triplet
td	triplet of doublets
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC/t.l.c	thin layer chromatography

¹H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million δ_H downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used for common solvents: CDCl₃, deuteriochloroform; DMSO, dimethylsulfoxide. The abbreviation psi means pounds per square inch and LRMS means low resolution mass spectrometry. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 F₂₅₄ plates, R_f is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate.

Example 1

(3S)-3-[Benzyl(ethyl)amino]chromane-6-carboxamide



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Thionyl chloride (1.30ml, 17.82mmol) was added to a solution of the acid from preparation 11 (620mg, 1.78mmol) in dichloromethane (20ml) and the solution heated under reflux for 1 hour. The cooled mixture was evaporated under reduced pressure and the residual solid was dissolved in dichloromethane (10ml) and treated with 0.88 ammonia (15ml). The reaction was stirred for an hour at room temperature, then the phases separated. The organic layer was washed with brine (15ml), dried (MgSO₄) and evaporated under reduced pressure to afford the title compound as a pale orange powder, 454mg.

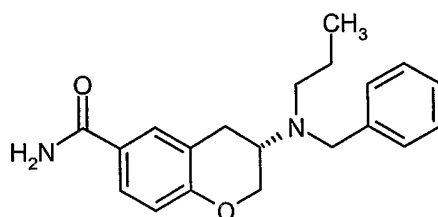
¹H NMR (CD₃OD, 400MHz) δ : 1.04 (t, 3H), 2.69 (m, 2H), 2.97 (d, 2H), 3.20 (m, 1H), 3.77 (s, 2H), 3.99 (dd, 1H), 4.32 (dd, 1H), 6.78 (d, 1H), 7.20 (dd, 1H), 7.25 (dd, 2H), 7.34 (d, 2H), 7.60 (dd, 1H), 7.62 (s, 1H).

LRMS : m/z APCI⁺ 311 [MH]⁺

$[\alpha]_D = +101.17$ (c = 0.11 in methanol)

Example 2

(3S)-3-[Benzyl(propyl)amino]chromane-6-carboxamide



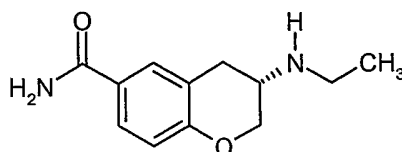
Thionyl chloride (1.0 ml) was added to a solution of the acid from preparation 12 (120mg, 0.36mmol) in dichloromethane (5ml) and the solution stirred at 50°C for 2 hours. The solution was evaporated under reduced pressure, the residue redissolved in dichloromethane (5ml) and this solution cooled in an ice bath. Ammonia was bubbled through the solution for 10 minutes and the reaction stirred for 18 hours at room temperature. The reaction mixture was evaporated under reduced pressure and the residue partitioned between dichloromethane (50ml) and water (50ml). The layers were separated, the organic phase dried (MgSO₄) and evaporated under reduced pressure to afford the title compound as a yellow oil, 69mg.

¹H NMR (CDCl₃, 400MHz) δ : 0.87 (t, 3H), 1.47 (q, 2H), 2.54 (m, 2H), 2.90 (d, 2H), 3.20 (m, 1H), 3.75 (s, 2H), 3.93 (dd, 1H), 4.31 (d, 1H), 6.79 (d, 1H), 7.22-7.34 (m, 5H), 7.50 (d, 1H), 7.59 (s, 1H).

LRMS : m/z APCI⁺ 325 [MH]⁺

Example 3

(3S)-3-(Ethylamino)chromane-6-carboxamide



A mixture of the compound from example 1 (420mg, 1.35mmol), 10% Pd/C (42mg) and ammonium formate (623mg, 13.5mmol) in ethanol (15ml) was heated under reflux for 26 hours. The cooled mixture

49

was filtered through Arbocel® and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (95:5:0 to 90:10:1 to 0:100:0). The product was suspended in a dichloromethane:methanol (95:5) solution, the insoluble material filtered off and the filtrate evaporated under reduced pressure to give the title compound, 290mg.

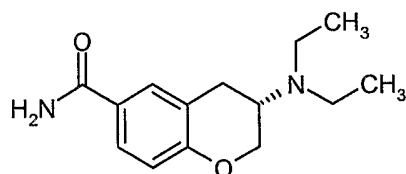
¹H NMR (CD₃OD, 400MHz) δ: 1.33 (t, 3H), 2.99 (dd, 1H), 3.15 (q, 2H), 3.37 (m, 1H), 3.71 (m, 1H), 4.27-4.40 (m, 2H), 6.93 (d, 1H), 7.70 (m, 1H), 8.46 (s, 1H).

LRMS : m/z APCI⁺ 221 [MH]⁺

[α]_D = +5.40 (c = 0.10 in methanol)

Example 4

(3S)-3-(Diethylamino)chromane-6-carboxamide



Acetaldehyde (0.41ml, 7.26mmol) was added to a solution of the amine from example 3 (80mg, 0.36mmol) in tetrahydrofuran (15ml) and the solution stirred for 10 minutes. Acetic acid (22mg, 0.36mmol) and sodium triacetoxyborohydride (115mg, 0.55mmol) were added and the reaction stoppered and stirred at room temperature for 5 hours. The reaction was quenched by the addition of 1N sodium hydroxide solution (15ml) and the mixture extracted with ethyl acetate (2x15ml). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure. The residual orange oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (95:5 to 90:10:1) to afford the title compound as a gum, 61mg.

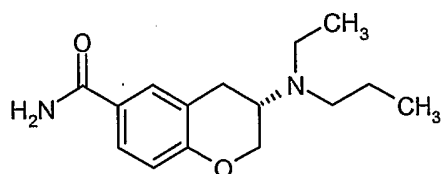
¹H NMR (CD₃OD, 400MHz) δ: 1.05 (t, 6H), 2.71 (q, 4H), 2.83-2.98 (m, 2H), 3.17 (m, 1H), 3.93 (dd, 1H), 4.38 (d, 1H), 6.80 (d, 1H), 7.60 (d, 1H), 7.65 (s, 1H).

LRMS : m/z APCI⁺ 249 [MH]⁺

[α]_D = +87.35 (c = 0.12 in methanol)

Example 5

(3S)-3-[Ethyl(propyl)amino]chromane-6-carboxamide



The title compound was obtained as a pale yellow solid from the amine from example 3 and propionaldehyde, following a similar procedure to that described in example 4.

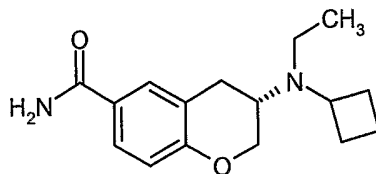
¹H NMR (CD₃OD, 400MHz) δ: 0.92 (t, 3H), 1.08 (t, 3H), 1.48 (m, 2H), 2.58 (t, 2H), 2.70 (q, 2H), 2.84-2.99 (m, 2H), 3.17 (m, 1H), 3.91 (dd, 1H), 4.35 (d, 1H), 6.80 (d, 1H), 7.60 (d, 1H), 7.65 (s, 1H).

LRMS : m/z APCI⁺ 263 [MH]⁺

$[\alpha]_D = +65.41$ ($c = 0.10$ in methanol)

Example 6

(3S)-3-[Cyclobutyl(ethyl)amino]chromane-6-carboxamide



5

Cyclobutanone (69mg, 0.99mmol) was added to a solution of the amine from example 3 (67mg, 0.30mmol) in tetrahydrofuran (15ml) and the solution stirred for 10 minutes. Acetic acid (18mg, 0.30mmol) and sodium triacetoxyborohydride (96mg, 0.46mmol) were added and the reaction stirred at room temperature for 18 hours. TLC analysis showed starting material remaining, so the reaction was filtered and the filtrate concentrated under reduced pressure. The residue was suspended in cyclobutanone (1ml) and stirred at room temperature for 72 hours. Sodium triacetoxyborohydride (96mg, 0.46mmol) was added and the reaction stirred for a further 18 hours. The reaction was quenched by the addition of 1N sodium hydroxide solution (15ml) and the mixture extracted with ethyl acetate (2x15ml). The combined organic solutions were dried (MgSO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0 to 90:10:1) to give the title compound as a colourless gum, 44mg.

10

15

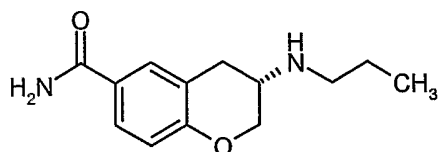
^1H NMR (CD_3OD , 400MHz) δ : 1.02 (t, 3H), 1.63 (m, 2H), 1.90-2.07 (m, 4H), 2.65 (q, 2H), 2.81-2.94 (m, 2H), 3.18 (m, 1H), 3.41 (m, 1H), 3.90 (m, 1H), 4.27 (dd, 1H), 6.78 (d, 1H), 7.59 (d, 1H), 7.61 (s, 1H).
LRMS : m/z APCI $^+$ 275 $[\text{MH}]^+$

20

$[\alpha]_D = +79.11$ ($c = 0.11$ in methanol)

Example 7

(3S)-3-(Propylamino)chromane-6-carboxamide



25

Ammonium formate (41mg, 0.66mmol) was added to a solution of the compound from example 2 (43mg, 0.13mmol) and 10% Pd/C (21mg) in methanol (5ml) and the mixture heated under reflux for 2 hours. The cooled mixture was filtered through Arbocel®, washing through with additional methanol. The filtrate was evaporated under reduced pressure and the residue purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (95:5:0.5 to 90:10:1) to give the title compound as a colourless oil, 25mg.

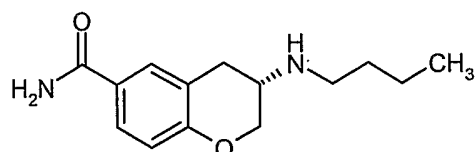
30

^1H NMR (CD_3OD , 400MHz) δ : 0.93 (t, 3H), 1.53 (m, 2H), 2.69 (m, 3H), 3.04 (dd, 1H), 3.17 (m, 1H), 3.96 (m, 1H), 4.25 (d, 1H), 6.84 (d, 1H), 7.52 (d, 1H), 7.60 (s, 1H).
LRMS : m/z APCI $^+$ 235 $[\text{MH}]^+$

$[\alpha]_D = +28.01$ ($c = 0.10$ in methanol)

Example 8

(3S)-3-(Butylamino)chromane-6-carboxamide



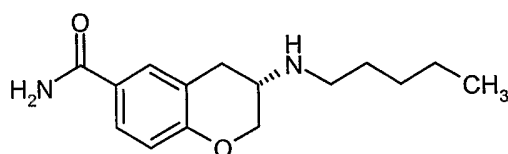
- 5 The title compound was obtained as an off-white foam, from the compound from preparation 20, following a similar procedure to that described in example 7, except the product was not purified by column chromatography on silica gel.

^1H NMR (CD_3OD , 400MHz) δ : 0.95 (t, 3H), 1.39 (m, 2H), 1.52 (m, 2H), 2.72 (m, 3H), 3.13 (m, 2H), 3.92 (m, 1H), 4.28 (d, 1H), 6.82 (d, 1H), 7.63 (dd, 2H).

- 10 LRMS : m/z APCI $^+$ 249 $[\text{MH}]^+$
 $[\alpha]_D = +21.8$ ($c = 0.10$ in methanol)

Example 9

(3S)-3-(Pentylamino)chromane-6-carboxamide



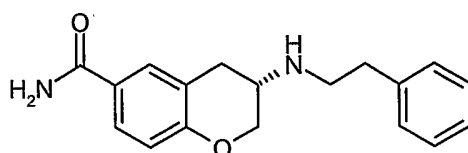
- 15 The title compound was obtained as a white solid in 77% yield, from the compound from preparation 21, following the procedure described in example 7.

^1H NMR (CD_3OD , 400MHz) δ : 0.92 (t, 3H), 1.35 (m, 4H), 1.54 (q, 2H), 2.70 (m, 3H), 3.10 (m, 2H), 3.91 (m, 1H), 4.28 (d, 1H), 6.82 (d, 1H), 7.63 (dd, 2H).

- 20 LRMS : m/z APCI $^+$ 263 $[\text{MH}]^+$

Example 10

(3S)-3-[(2-Phenylethyl)amino]chromane-6-carboxamide



- 25 The title compound was obtained as a white solid in 50% yield, from the compound from preparation 22, following the procedure described in example 7.

^1H NMR (CD_3OD , 400MHz) δ : 2.69 (dd, 1H), 2.83 (t, 2H), 2.97 (t, 2H), 3.07 (dd, 1H), 3.17 (m, 1H), 3.94 (m, 1H), 4.27 (d, 1H), 6.79 (d, 1H), 7.15-7.30 (m, 5H), 7.60 (d, 1H), 7.62 (s, 1H).

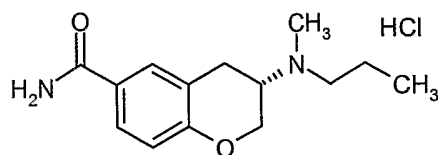
LRMS : m/z APCI $^+$ 319 $[\text{MNa}]^+$

- 30 $[\alpha]_D = +9.4$ ($c = 0.10$ in methanol)

Example 11

52

(3S)-3-[Methyl(propyl)amino]chromane-6-carboxamide hydrochloride



A mixture of the compound from preparation 14 (1.37g, 5.9mmol) and potassium hydroxide (1g, 17.8mmol) in 2-methyl-2-propanol (20ml) was heated under reflux for 18 hours. TLC analysis showed starting material remaining, so additional potassium hydroxide (333mg, 5.9mmol) was added and the mixture stirred for a further 2 hours. The cooled mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate (300ml) and water (200ml). The layers were separated, the organic phase dried (MgSO₄) and evaporated under reduced pressure. The residual yellow oil was pre-adsorbed onto silica gel and purified by column chromatography on silica gel using dichloromethane:methanol (90:10). The product was dissolved in dichloromethane (50ml), hydrogen chloride gas bubbled through for 10 minutes, and the solution evaporated under reduced pressure to afford the title compound as a white solid, 1.15g.

¹H NMR (CD₃OD, 400MHz, rotamers) δ : 1.04 (t, 3H), 1.80 (m, 2H), 2.92, 2.96 (2xs, 3H), 3.20 (m, 3H), 3.40 (m, 1H), 3.96 (m, 1H), 4.43 (d, 1H), 4.58 (m, 1H), 6.95 (d, 1H), 7.70 (d, 1H), 7.77 (s, 1H).

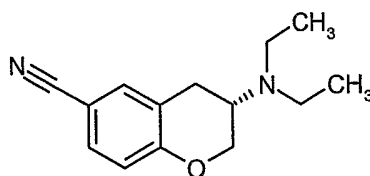
LRMS : m/z APCI⁺ 249 [MH]⁺

$[\alpha]_D = -83.83$ (c = 0.1 in methanol)

Microanalysis: C, 51.94; H, 7.44; N, 8.55. C₁₄H₂₀N₂O₂·HCl;2H₂O requires C, 52.41; 7.85; N, 8.73%.

Example 12

(3S)-3-(Diethylamino)chromane-6-carbonitrile



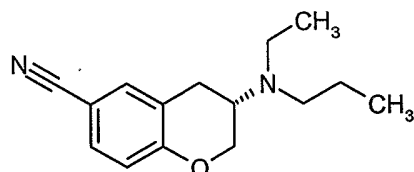
Acetaldehyde (0.1ml, 1.73mmol) was added to an ice-cold solution of the amine from preparation 17 (35mg, 0.17mmol) in tetrahydrofuran (5ml), the solution stoppered and stirred for 30 minutes. Sodium triacetoxyborohydride (13mg, 0.2mmol) was added and the reaction stirred at room temperature for 3 hours. TLC analysis showed starting material remaining, so additional acetaldehyde (0.1ml, 1.73mmol) was added and the reaction stirred for a further hour at 0°C. The reaction mixture was concentrated under reduced pressure and the residue dissolved in ethyl acetate (75ml) and washed with brine (50ml). The organic solution was dried (MgSO₄) and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (98:2 to 95:5), and repeated using ethyl acetate:pentane (50:50) as eluant to afford the title compound, 39mg.

¹H NMR (CDCl₃, 400MHz) δ : 1.06 (t, 6H), 2.67 (q, 4H), 2.86 (m, 2H), 3.15 (m, 1H), 3.90 (t, 1H), 4.36 (d, 1H), 6.84 (d, 1H), 7.37 (s, 2H).

LRMS : m/z APCI⁺ 231 [MH]⁺

Example 13

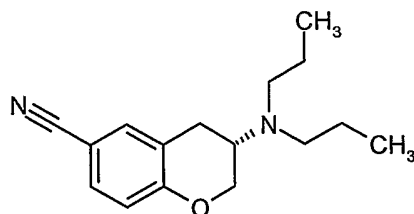
(3S)-3-[Ethyl(propyl)amino]chromane-6-carbonitrile



- 5 Acetaldehyde (0.2ml, 3.7mmol) followed by sodium triacetoxyborohydride (56mg, 0.89mmol) was added to a cooled (-10°C) solution of the amine from preparation 18 (80mg, 0.37mmol) in tetrahydrofuran (5ml) and the reaction stirred at room temperature for 72 hours. The mixture was partitioned between ethyl acetate (80ml) and brine (40ml) and the layers separated. The organic phase was dried (MgSO₄) and evaporated under reduced pressure. The residual yellow oil was purified by column chromatography on
- 10 silica gel using dichloromethane:methanol (98:2) as eluant to afford the title compound, 34mg.
- ¹H NMR (CDCl₃, 400MHz) δ: 0.88 (t, 3H), 1.05 (t, 3H), 1.45 (q, 2H), 2.52 (t, 2H), 2.63 (q, 2H), 2.86 (m, 2H), 3.15 (m, 1H), 3.90 (t, 1H), 4.35 (d, 1H), 6.83 (d, 1H), 7.35 (s, 2H).
- LRMS : m/z APCI⁺ 245 [MH]⁺

Example 14

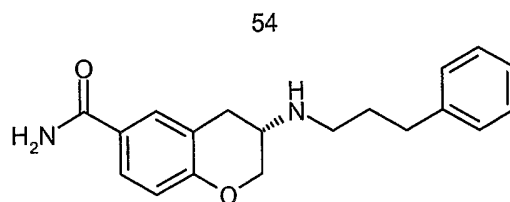
(3S)-3-(Dipropylamino)chromane-6-carbonitrile



- Propionaldehyde (52μl, 0.72mmol) was added to a solution of the amine from preparation 18 (130mg, 0.60mmol) in tetrahydrofuran (5ml) and the solution stirred at room temperature for 1.5 hours. Sodium
- 20 triacetoxyborohydride (178mg, 0.84mmol) was added and the reaction stirred at room temperature for 18 hours. The reaction was diluted with ethyl acetate (100ml), the mixture washed with saturated sodium bicarbonate solution (50ml), brine (50ml) and dried (MgSO₄) and evaporated under reduced pressure. The residual yellow oil was purified by column chromatography on silica gel using an elution gradient of ethyl acetate:pentane (10:90 to 20:80) to give the title compound as a white solid, 115mg.
- 25 ¹H NMR (CDCl₃, 400MHz) δ: 0.88 (t, 6H), 1.45 (m, 4H), 2.50 (m, 2H), 2.84 (d, 2H), 3.13 (m, 1H), 3.88 (t, 1H), 4.34 (dd, 1H), 6.83 (d, 1H), 7.37 (m, 2H).
- LRMS : m/z APCI⁺ 259 [MH]⁺
- [α]_D = +89.42 (c = 0.1, methanol)

Example 15

(3S)-3-[(2-Phenylpropyl)amino]chromane-6-carboxamide

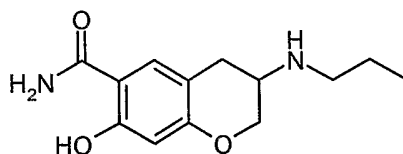


The title compound was obtained as a white solid in quantitative yield, from the compound from preparation 23, following the procedure described in example 7 to give the product as a colourless oil 83mg.

- 5 ^1H NMR (CD_3OD , 400MHz) δ : 1.85 (m, 2H), 2.68 (dt, 5H), 3.07 (m, 2H), 3.9 (t, 1H), 4.27 (d, 1H), 6.81 (d, 1H), 7.2 (m, 5H), 7.63 (d, 2H).
 LRMS : m/z APCI $^+$ 311 $[\text{M}+\text{H}]^+$
 $[\alpha]_D = +11.4$ ($c = 0.10$ in methanol)

10 Example 16

7-hydroxy-3-(propylamino)chromane-6-carboxamide



- 15 A mixture of *N*-benzyl-*N*-(6-carboxamide-7-benzyloxy-3,4-dihydro-2*H*-chromen-3-yl)-*N*-propylamine from preparation 30 (60mg, 0.14mmol), ammonium formate (150mg, 2.3mmol) and 10% palladium on charcoal (50mg) in methanol (5ml) was heated at 80°C for 15 minutes. The cooled mixture was filtered through Arbocel®, washing through with methanol then dichloromethane. The filtrate was evaporated under reduced pressure and the residue purified by column chromatography on silica with dichloromethane:methanol:ammonia hydroxide 90:10:1 to afford the title compound as a white solid 29mg.

- 20 ^1H NMR (CDCl_3 , 400MHz) δ : 0.9 (t, 3H), 1.45-1.55 (m, 2H), 2.6-2.8 (m, 3H), 2.9 (dd, 1H), 3.1-3.2 (m, 1H), 3.9 (dt, 1H), 4.2 (d, 1H), 6.4 (s, 1H), 7.05 (s, 1H).
 LRMS : m/z APCI $^+$ 251 $[\text{MH}]^+$

- This mixture of isomers was separated on a Chiralpak AD-H (150*21.5mm) HPLC column. Mobile phase 30% iso-propyl alcohol, Hexane (70%), trifluoroacetic acid (0.3%) and diethylamine (0.2%), flow rate 25 15ml/min.

Sample preparation 163mg dissolved in 1ml IPA, $\text{X}_{\mu\text{L}}$ injection.

Two major peaks were obtained, with retention times 3.996 min (example 16A) and 7.042 min (example 16B).

- 30 The crude pure samples were partitioned between dichloromethane (20ml) and ammonium hydroxide solution (5ml) with added sodium chloride, the organic layer was dried over MgSO_4 and concentrated under reduced pressure. The sample was further purified by column chromatography on silica with dichloromethane:methanol (90:10 to 60:30) afford example 16A as a pale yellow powder 99mg (contaminated with 0.43 eq diethylamine) and example 16B as an off-white solid 131mg (contaminated with 0.79 eq diethylamine).

Example 16A: ^1H NMR (CD_3OD , 400MHz) δ : 0.98 (t, 3H), 1.60 (m, 2H), 2.70 (dd, 1H), 2.81 (t, 2H), 3.08 (dd, 1H), 3.37 (br, m, 1H), 4.06 (m, 1H), 4.23 (d, 1H), 6.28 (s, 1H), 7.57 (s, 1H).

LRMS : m/z APCI $^+$ 251 [MH] $^+$

5 $[\alpha]_D = -18.0$ (c = 0.1185 in methanol)

Example 16B: ^1H NMR (CD_3OD , 400MHz) δ : 0.98 (t, 3H), 1.61 (m, 2H), 2.75 (dd, 1H), 2.87 (t, 2H), 3.13 (dd, 1H), 3.43 (br, m, 1H), 4.14 (dd, 1H), 4.23 (d, 1H), 6.30 (s, 1H), 7.57 (s, 1H).

LRMS : m/z APCI $^+$ 251 [MH] $^+$

10 $[\alpha]_D = +16.8$ (c = 0.1415 in methanol)

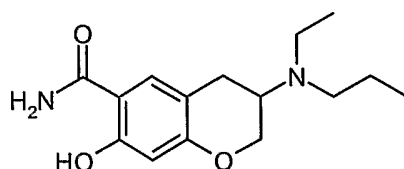
Alternatively, example 16A was obtained directly as a single enantiomer from the compound from preparation 53 (2.95g, 6.86mmol), by reaction with ammonium formate (4.32g, 68.6mmol) and 10% palladium on charcoal (300mg) in methanol (100ml) at 80°C for 3h. The cooled mixture was filtered through Arbocel®, washing through with methanol. The filtrate was evaporated under reduced pressure and the residue purified by column chromatography on silica eluting with 10% MeOH/EtOAc followed by EtOAc:methanol:ammonia hydroxide 90:10:1 to afford the title compound as a pale yellow solid 1.70g.

LRMS : m/z APCI $^+$ 251 [MH] $^+$

TLC 10% MeOH/EtOAc Rf=0.1

20 **Example 17**

3-[ethyl(propyl)amino]-7-hydroxychromane-6-carboxamide



Acetaldehyde (0.10ml, 1.80mmol) was added to a solution of 7-hydroxy-3-(propylamino)chromane-6-carboxamide from example 16 (30mg, 0.12mmol) in tetrahydrofuran (5ml) and then acetic acid (7mg, 0.12mmol) followed by Sodium triacetoxyborohydride (38mg, 0.18mmol) was added and the reaction stirred at room temperature for 18 hours. Water (10ml) was added then ammonia solution (1ml), and the mixture extracted with ethyl acetate (2x20ml). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure, the residue was purified by column chromatography on silica with dichloromethane:methanol (98:2 to 90:10) to afford the title compound as an off-white crystalline solid, 23mg.

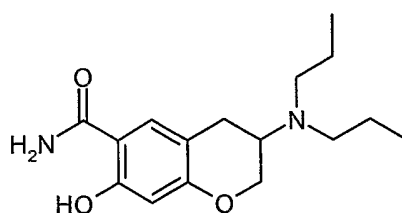
MP 139-141°C; ^1H NMR (CD_3OD , 400MHz) δ : 0.86 (t, 3H), 1.03 (t, 3H), 1.46 (m, 2H), 2.55 (t, 2H), 2.68 (m, 2H), 2.73-2.87 (m, 2H), 3.09 (m, 1H), 3.86 (t, 1H), 4.28 (dd, 1H), 6.21 (s, 1H), 7.50+7.59 (2s, 1H).

LRMS : m/z APCI $^+$ 279 [MH] $^+$

35 **Example 18**

3-(dipropylamino)-7-hydroxychromane-6-carboxamide

56



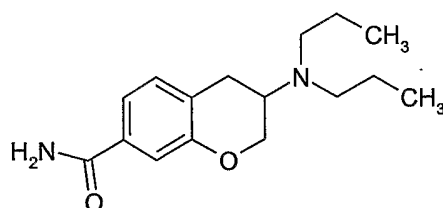
Propionaldehyde (8mg, 0.132mmol) was added to a solution of 7-hydroxy-3-(propylamino)chromane-6-carboxamide from example 16 (30mg, 0.12mmol) in tetrahydrofuran (5ml) and then acetic acid (7mg, 0.12mmol) followed by Sodium triacetoxyborohydride (38mg, 0.18mmol) was added and the reaction stirred at room temperature for 18 hours. Water (10ml) was added then ammonia solution (1ml), and the mixture extracted with ethyl acetate (2x20ml). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure, the residue was purified by column chromatography on silica with dichloromethane:methanol (95:5 to 90:10) to afford the title compound as an off-white crystalline solid, 15mg.

MP 153-156°C; ¹H NMR (CD₃OD, 400MHz) δ: 0.82-0.98 (m, 6H), 1.40-1.57 (m, 4H), 2.47-2.61 (m, 4H), 2.71-2.88 (m, 2H), 3.09 (m, 1H), 3.89 (t, 1H), 4.28 (d, 1H), 6.22 (s, 1H), 7.52 (s, 1H).

LRMS : m/z APCI⁺ 293 [MH]⁺

Example 19

(3S)-3-(Dipropylamino)chromane-7-carboxamide

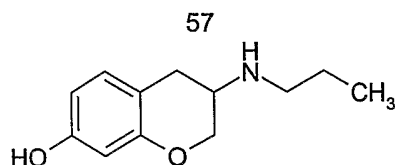


A mixture of the compound from preparation 42 (240mg, 1.0mmol), propionaldehyde (81μl, 1.1mmol), acetic acid (59μl, 1.0mmol) and sodium triacetoxyborohydride (326mg, 1.5mmol) in dichloromethane (10ml) was stirred at room temperature for 18 hours. The mixture was partitioned between water (50ml) and dichloromethane (50ml) and the layers separated. The aqueous phase was extracted further with dichloromethane (50ml) and the combined organic solutions dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (100:0:0 to 90:10:1) to afford a white solid, 100mg. This was further purified by HPLC using a Chiralpak AS-H column and an eluant of isopropanol:hexane:diethylamine (30:70:0.1) to provide enantiomer 1, as a white solid, 8mg. Further elution provided enantiomer 2, the title compound as a white solid, 12mg.

¹H NMR (CD₃OD, 400MHz) δ: 0.90 (t, 6H), 1.42-1.55 (m, 4H), 2.58 (m, 4H), 2.96 (m, 2H), 3.17 (m, 1H), 3.90 (dd, 1H), 4.34 (m, 1H), 7.18 (d, 1H), 7.25 (d, 1H), 7.38 (dd, 1H). LRMS : m/z APCI⁺ 277 [MH]⁺

Example 20

3-(Propylamino)chroman-7-ol

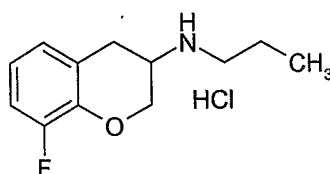


Ammonium formate (424mg, 6.7mmol) was added portionwise to a mixture of the compound from preparation 26 (200mg, 0.67mmol) and 10% palladium on charcoal (20mg) in ethanol (10ml) and the mixture heated under nitrogen at 100°C for 3 hours. The cooled mixture was filtered through a pad of Arbocel® and the filtrate evaporated under reduced pressure. The crude product was purified by column chromatography using Dowex® 50W8-X200 ion exchange resin and an elution gradient of water:0.88 ammonia (100:0 to 95:5) to afford the title compound as a clear gum.

¹H NMR (CD₃OD, 400MHz) δ: 0.97 (t, 3H), 1.50-1.60 (m, 2H), 2.54-2.59 (dd, 1H), 2.66 (dd, 2H), 2.90-2.98 (m, 1H), 3.06 (m, 1H), 3.30 (m, 1H), 3.80 (dd, 1H), 4.18 (dd, 1H), 6.20 (s, 1H), 6.32 (d, 1H), 6.82 (d, 1H). LRMS : m/z APCI⁺ 208 [MH]⁺

Example 21

(+)-8-Fluoro-*N*-propylchroman-3-amine hydrochloride



A mixture of the compound from preparation 38 (2.85g, 1.0mmol) and 10% palladium on charcoal (250mg) in ethanol (70ml) was hydrogenated at 1 atm. and room temperature for 3 hours. The mixture was filtered through Arbocel® and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate:pentane (25:75) as eluant to provide a yellow oil, 1.58g.

A sample of this (150mg), was further purified by HPLC using a Chiralpak AD-H 250x20mm column, with detection at 220nm and hexane:isopropanol:diethylamine:trifluoroacetic acid (70:30:0.2:0.3) as eluant to provide enantiomer 1.

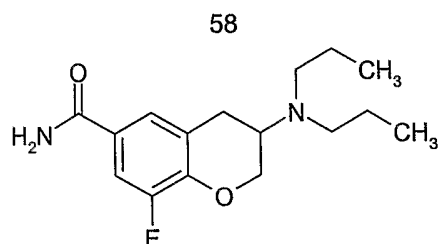
Further elution provided enantiomer 2. The compound containing fractions were evaporated under reduced pressure, the product dissolved in dichloromethane (10ml), the solution washed with potassium carbonate solution, dried (MgSO₄) and evaporated under reduced pressure. The product was re-dissolved in ether, ethereal hydrochloric acid added, and the solution evaporated under reduced pressure to afford the title compound as a white solid, 39mg.

¹H NMR (CD₃OD, 400MHz) δ: 1.00 (t, 3H), 1.68-1.77 (m, 2H), 2.98-3.12 (m, 3H), 3.34-3.40 (m, 1H), 3.80 (m, 1H), 4.26 (m, 1H), 4.44 (m, 1H), 6.85-7.01 (m, 3H). LRMS : m/z APCI⁺ 210 [MH]⁺

[α]_D = +38.92, (c = 0.0925, methanol)

Example 22

3-(Dipropylamino)-8-fluorochromane-6-carboxamide



A mixture of the compound from preparation 41 (398mg, 1.44mmol) and potassium hydroxide (323mg, 5.77mmol) in *tert*-butanol (8ml) was heated under reflux for 4 hours. The cooled reaction mixture was partitioned between ethyl acetate (50ml) and water (50ml) and the layers separated. The aqueous solution was extracted with further ethyl acetate (50ml), the combined organic solutions dried (MgSO₄) and evaporated under reduced pressure to provide a beige solid, 260mg. This was purified by HPLC using a Chiralpak AD-H column and methanol:ethanol (50:50) as eluant to provide enantiomer 1, 27mg. Further elution provided enantiomer 2, the title compound, 30mg.

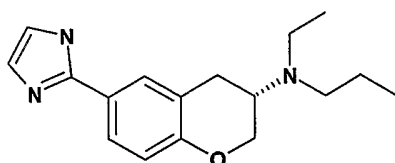
¹H NMR (CD₃OD, 400MHz) δ : 0.92 (t, 6H), 1.42-1.57 (m, 4H), 2.58 (m, 4H), 2.98 (m, 2H), 3.19 (m, 1H), 4.00 (dd, 1H), 4.40 (dd, 1H), 7.42-7.50 (m, 2H).

LRMS : m/z APCI⁺ 295 [MH]⁺

$[\alpha]_D = +68.48$, (c = 0.165, methanol)

Example 23

(S)-Ethyl-[6-(1H-imidazol-2-yl)-chroman-3-yl]-propylamine



The material from preparation 43 (84mg, 0.3mmol) was dissolved in MeOH (8ml) and aminoacetaldehyde dimethyl acetal (0.32mmol, 1.05eq) was added. The mixture was heated to reflux for 4h. The solvent was evaporated, 6M HCl_(aq) (8ml) added, and the mixture heated to reflux for 2h.

The mixture was cooled in an ice/water bath and neutralised by cautious addition of 0.880 NH_{3(aq)}. The formed suspension was extracted with dichloromethane (3x20ml) and evaporated to give a colourless oil (22mg)

¹H NMR (CD₃OD, 400MHz) δ : 0.92 (t, 3H), 1.09 (t, 3H), 1.51 (m, 2H), 2.59 (m, 2H), 2.76 (m, 2H), 2.95 (m, 2H), 3.18 (m, 1H), 3.93 (t, 1H), 4.34 (d, 1H), 6.82 (d, 1H), 7.06 (s, 2H), 7.56 (d, 1H), 7.59 (s, 1H)

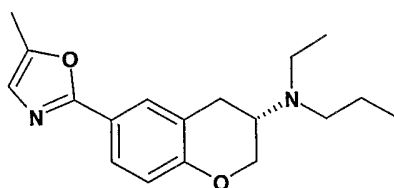
LRMS: m/z APCI⁺ 286 (MH⁺)

TLC 95/5/0.5 CH₂Cl₂/MeOH/NH₃ R_f = 0.1

Example 24

(S)-Ethyl-[6-(5-methyloxazol-2-yl)-chroman-3-yl]-propylamine

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The material from preparation 46 (0.612 mmol assumed) was taken up in THF and Burgess reagent ((methoxycarbonylsulfamoyl)triethylammonium hydroxide 507mg, 3eq) was added. The mixture was heated to reflux for 4h, allowed to cool, diluted with MeOH and evaporated *in vacuo* to give a brown oil.

- 5 This was purified by flash column chromatography on a SiO₂ column with a gradient elution from 2% MeOH/CH₂Cl₂ to 10% 2% MeOH/CH₂Cl₂ to give the title compound as a yellow oil. (79mg 37% over 2 steps).

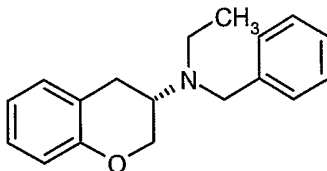
¹H NMR (CD₃OD, 400MHz) δ : 0.91 (t, 3H), 1.09 (t, 3H), 1.49 (m, 2H), 2.39 (s, 3H), 2.55-2.63 (m, 2H), 2.68-2.77 (m, 2H), 2.86-3.01 (m, 2H), 3.15-3.22 (m, 1H), 3.93-3.98 (m, 1H), 4.32-4.39 (m, 1H), 6.84 (m,

10 2H), 7.66 (m, 1H), 7.71 (s, 1H)

The following preparations illustrate the synthesis of certain intermediates used in the preparation of the preceding examples:

15 Preparation 1

N-Benzyl-*N*-[(3*S*)-3,4-dihydro-2*H*-chromen-3-yl]-*N*-ethylamine



Acetaldehyde (8.67ml, 154.6mmol) was added to a solution of (*S*)-3-(benzylamino)chroman (J. Org. Chem. 63; 16; 1998; 5365) (1.85g, 7.73mmol) in tetrahydrofuran (15ml) and the solution stirred at room temperature for 20 minutes. Acetic acid (0.44ml, 7.73mmol) and sodium triacetoxyborohydride (2.46g, 11.60mmol) were added, the flask stoppered, and the reaction stirred at room temperature for 18 hours. The reaction was quenched by the addition of 1N sodium hydroxide solution (30ml) and the mixture extracted with ethyl acetate (2x25ml). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (99:1 to 98:2) to give the title compound as a yellow oil, 1.82g.

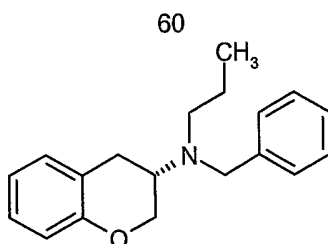
¹H NMR (CDCl₃, 400MHz) δ : 1.05 (t, 3H), 2.65 (m, 2H), 2.90 (m, 2H), 3.24 (m, 1H), 3.76 (s, 2H), 3.86 (t, 1H), 4.32 (dd, 1H), 6.79 (d, 1H), 6.82 (dd, 1H), 7.04 (m, 2H), 7.20-7.39 (m, 5H).

LRMS : *m/z* APCI⁺ 268 [MH]⁺

30 microanalysis found: C, 80.69; H, 7.93; N, 5.24. C₁₈H₂₁NO requires C, 80.86; H, 7.92; N, 5.24%.

Preparation 2

N-Benzyl-*N*-[(3*S*)-3,4-dihydro-2*H*-chromen-3-yl]-*N*-propylamine

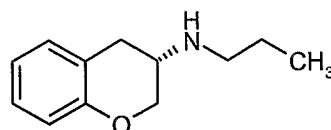


Propionaldehyde (3.17ml, 44.0mmol) was added to a solution of (S)-3-(benzylamino)chroman (J. Org. Chem. 63, 16, 1998, 5365) (7.5g, 31.3mmol), acetic acid (1.8ml, 31.0mmol) and sodium triacetoxyborohydride (18.6g, 87.7mmol) in tetrahydrofuran (200ml), and the reaction stirred at room temperature for 20 hours. The reaction was quenched by the addition of sodium bicarbonate solution (750ml) and the mixture extracted with ethyl acetate (2x300ml). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure, to afford the title compound as a colourless oil, 8.76g.

¹H NMR (CDCl₃, 400MHz) δ : 0.88 (t, 3H), 1.48 (m, 2H), 2.56 (q, 2H), 2.90 (m, 2H), 3.22 (m, 1H), 3.75 (s, 2H), 3.87 (t, 1H), 4.32 (dd, 1H), 6.80 (d, 1H), 6.85 (dd, 1H), 7.07 (m, 2H), 7.20-7.40 (m, 5H).
LRMS : m/z APCI⁺ 282 [MH]⁺

Preparation 3

(S)-3-(Propylamino)chroman

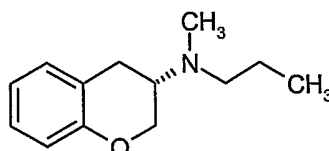


A mixture of the compound from preparation 2 (2.5g, 8.9mmol), ammonium formate (2.8g, 44.0mmol) and 10% palladium on charcoal (250mg) in methanol (50ml) was heated at 100°C for 1 hour. The cooled mixture was filtered through Arbocel®, washing through with methanol. The filtrate was evaporated under reduced pressure to afford the title compound as a yellow oil, 1.9g.

¹H NMR (CD₃OD, 400MHz) δ : 0.96 (t, 3H), 1.57 (m, 2H), 2.70 (m, 1H), 2.76 (t, 2H), 3.10 (dd, 1H), 3.23 (m, 1H), 3.94 (dd, 1H), 4.23 (d, 1H), 6.78 (d, 1H), 6.85 (dd, 1H), 7.05 (m, 2H).
LRMS : m/z APCI⁺ 192 [MH]⁺

Preparation 4

N-Methyl-N-[(3S)-3,4-dihydro-2H-chromen-3-yl]-N-propylamine



Formaldehyde (3.8ml, 37% aq, 44.5mmol) was added to a solution of the amine from preparation 3 (1.7g, 8.9mmol) in tetrahydrofuran (50ml) and the solution stirred at room temperature for 1 hour.

Sodium triacetoxyborohydride (4.7g, 22mmol) was added and the reaction stirred at room temperature for 18 hours. Saturated sodium bicarbonate solution (300ml) was added, and the mixture extracted with

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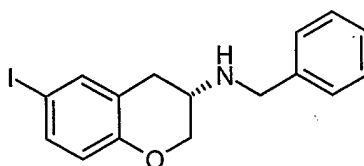
ethyl acetate (2x200ml). The combined organic solutions were dried (MgSO_4) and evaporated under reduced pressure to afford the title compound as a colourless oil, 1.76g.

^1H NMR (CD_3OD , 400MHz) δ : 0.92 (t, 3H), 1.55 (m, 2H), 2.38 (s, 3H), 2.56 (m, 2H), 2.82-3.01 (m, 3H), 3.90 (dd, 1H), 4.32 (dd, 1H), 6.73 (d, 1H), 6.82 (dd, 1H), 7.06 (m, 2H).

5 LRMS : m/z APCI $^+$ 206 $[\text{MH}]^+$

Preparation 5

N-Benzyl-*N*-[(3*S*)-6-iodo-3,4-dihydro-2*H*-chromen-3-yl]amine



10 *N*-Iodosuccinimide (1.5g, 6.7mmol) was added portionwise to an ice-cooled solution of (*S*)-3-(benzylamino)chroman (J. Org. Chem. 63, 16, 1998, 5365) (1.6g, 6.7mmol) in trifluoroacetic acid (30ml) and the reaction then stirred for 18 hours at room temperature. The reaction was poured onto ice, the mixture diluted with ethyl acetate (200ml), then basified carefully to pH 8-9 using solid sodium bicarbonate. The layers were separated, the organic phase dried (MgSO_4) and evaporated under

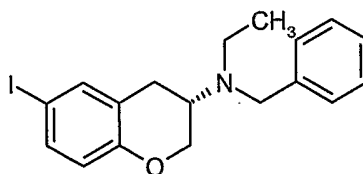
15 reduced pressure to give the title compound as a yellow oil, 2.76g.

^1H NMR (CD_3OD , 400MHz) δ : 2.65 (m, 1H), 2.98 (dd, 1H), 3.08 (m, 1H), 3.88 (m, 3H), 4.20 (dd, 1H), 6.56 (d, 1H), 7.25 (d, 1H), 7.27-7.40 (m, 6H).

LRMS : m/z APCI $^+$ 366 $[\text{MH}]^+$

20 Preparation 6

N-Benzyl-*N*-ethyl-*N*-[(3*S*)-6-iodo-3,4-dihydro-2*H*-chromen-3-yl]amine



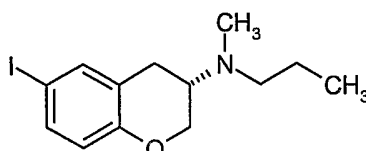
The title compound was obtained as a brown oil in 88% yield from the compound from preparation 1, following the procedure described in preparation 5.

25 ^1H NMR (CD_3OD , 400MHz) δ : 1.02 (t, 3H), 2.63 (q, 2H), 2.83 (d, 2H), 3.11 (m, 1H), 3.71 (s, 2H), 3.86 (t, 1H), 4.23 (dd, 1H), 6.48 (d, 1H), 7.17-7.37 (m, 7H).

LRMS : m/z APCI $^+$ 394 $[\text{MH}]^+$

Preparation 7

30 *N*-[(3*S*)-6-iodo-3,4-dihydro-2*H*-chromen-3-yl]-*N*-methyl-*N*-propylamine



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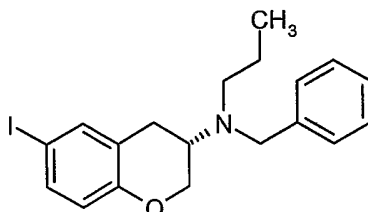
The title compound was obtained as a brown solid, from the compound from preparation 4, following the procedure described in preparation 5.

^1H NMR (CD_3OD , 400MHz) δ : 0.92 (t, 3H), 1.54 (m, 2H), 2.38 (s, 3H), 2.57 (m, 2H), 2.80-3.00 (m, 3H), 3.95 (m, 1H), 4.30 (d, 1H), 6.55 (d, 1H), 7.34 (d, 1H), 7.42 (s, 1H).

5 LRMS : m/z APCI $^+$ 332 $[\text{MH}]^+$

Preparation 8

N-Benzyl-*N*-[(3*S*)-6-iodo-3,4-dihydro-2*H*-chromen-3-yl]-*N*-propylamine



10 Propionaldehyde (0.83ml, 11.5mmol) was added to a solution of the amine from preparation 5 (3g, 8.2mmol) in tetrahydrofuran (100ml), and the solution stirred at room temperature for 2 hours. Acetic acid (0.47ml, 8.2mmol) and sodium triacetoxyborohydride (4.8g, 23mmol) were added and the reaction stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate (200ml), washed with sodium bicarbonate solution (200ml) and brine (150ml) then dried (MgSO_4) and evaporated under

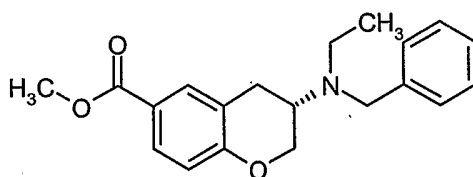
15 reduced pressure, to give the title compound as a colourless oil, 3.15g.

^1H NMR (CDCl_3 , 400MHz) δ : 0.88 (t, 3H), 1.49 (m, 2H), 2.55 (m, 2H), 2.84 (m, 2H), 3.19 (m, 1H), 3.74 (s, 2H), 3.86 (m, 1H), 4.28 (dd, 1H), 6.54 (d, 1H), 7.20-7.35 (m, 7H).

LRMS : m/z APCI $^+$ 408 $[\text{MH}]^+$

20 Preparation 9

Methyl (3*S*)-3-[benzyl(ethyl)amino]chromane-6-carboxylate



Methanol (15ml), triethylamine (1.62ml, 11.6mmol) and dichloro[1,1'-

25 bis(diphenylphosphino)ferrocene]palladium dichloromethane adduct (0.95g, 1.16mmol) were added to the iodide from preparation 6 (2.28g, 5.80mmol) in *N,N*-dimethylformamide (30ml). Carbon monoxide was bubbled through the solution until saturated, and then purged a further 3 times with carbon monoxide. The reaction was then heated to 90°C under an atmosphere of carbon monoxide for 8 hours and stirred for a further 18 hours at room temperature. The reaction was concentrated under reduced

30 pressure and the residue partitioned between ethyl acetate (30ml) and saturated sodium bicarbonate solution (15ml). The layers were separated, the organic phase dried (MgSO_4) and evaporated under reduced pressure. The residual red/brown solid was purified by column chromatography on silica gel

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using an elution gradient of pentane:ethyl acetate (100:0 to 80:20) to afford the title compound as a yellow oil, 650mg.

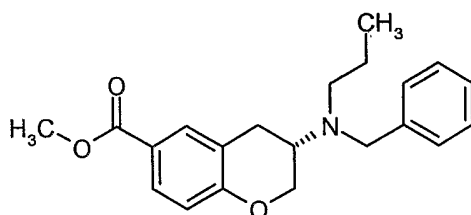
^1H NMR (CD_3OD , 400MHz) δ : 1.03 (t, 3H), 2.68 (q, 2H), 2.97 (d, 2H), 3.19 (m, 1H), 3.78 (s, 2H), 3.82 (s, 3H), 4.00 (t, 1H), 4.35 (dd, 1H), 6.78 (d, 1H), 7.20 (dd, 1H), 7.26 (dd, 2H), 7.34 (d, 2H), 7.70 (d, 1H), 7.77 (s, 1H).

LRMS : m/z APCI $^+$ 326 [MH] $^+$

$[\alpha]_D = +94.4$ (c = 0.113 in ethanol)

Preparation 10

10 Methyl (3S)-3-[benzyl(propyl)amino]chromane-6-carboxylate

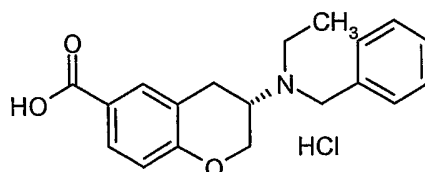


The title compound was obtained from the iodide from preparation 8, following the procedure described in preparation 9.

^1H NMR (CDCl_3 , 400MHz) δ : 0.84 (t, 3H), 1.47 (m, 2H), 2.53 (m, 2H), 2.90 (d, 2H), 3.18 (m, 1H), 3.72 (s, 2H), 3.84 (s, 3H), 3.90 (t, 1H), 4.32 (dd, 1H), 6.75 (d, 1H), 7.20-7.30 (m, 5H), 7.72 (d, 1H), 7.75 (s, 1H).
LRMS : m/z ES $^+$ 340 [MH] $^+$

Preparation 11

(3S)-3-[Benzyl(ethyl)amino]chromane-6-carboxylic acid hydrochloride



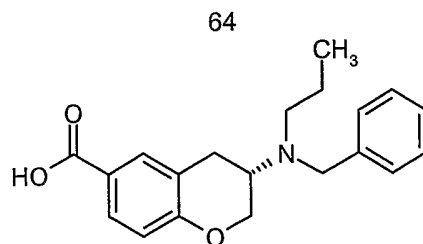
Sodium hydroxide solution (20ml, 2N, 40mmol) was added to a solution of the ester from preparation 9 (595mg, 1.83mmol) in dioxan (20ml) and the solution stirred at room temperature for 72 hours. The mixture was concentrated under reduced pressure and the residue dissolved in water (25ml). The solution was acidified to pH 1 using concentrated hydrochloric acid, and then concentrated under reduced pressure. The solid was triturated with hot isopropyl alcohol (2x), the insoluble material filtered off and the filtrate evaporated under reduced pressure to give the title compound as an orange oil, 620mg.

^1H NMR (CD_3OD , 400MHz) δ : 1.16 (t, 3H), 2.82 (q, 2H), 3.05 (d, 2H), 3.40 (m, 1H), 3.95 (m, 2H), 4.13 (t, 1H), 4.39 (dd, 1H), 6.80 (d, 1H), 7.23-7.36 (m, 3H), 7.39 (d, 2H), 7.74 (d, 1H), 7.80 (s, 1H).

LRMS : m/z APCI $^+$ 312 [MH] $^+$

Preparation 12

(3S)-3-[Benzyl(propyl)amino]chromane-6-carboxylic acid



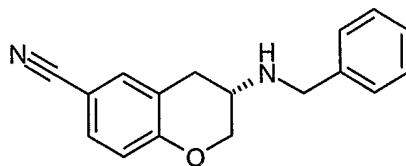
A mixture of the ester from preparation 10 (620mg, 1.8mmol) in sodium hydroxide solution (20ml, 2N) and methanol (10ml) was heated under reflux for 18 hours. The cooled solution was concentrated under reduced pressure and the residue partitioned between water (10ml) and dichloromethane (20ml). The aqueous layer was acidified to pH 6-7 using 1M hydrochloric acid, and this extracted with a dichloromethane:methanol (90:10 by volume)(40ml in total). solution. These organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the title compound as a brown oil, 428mg.

¹H NMR (CD₃OD, 400MHz) δ : 0.85 (t, 3H), 1.50 (m, 2H), 2.64 (m, 2H), 2.99 (d, 2H), 3.26 (m, 1H), 3.84 (s, 2H), 4.04 (t, 1H), 4.34 (dd, 1H), 6.77 (d, 1H), 7.20-7.37 (m, 5H), 7.39 (d, 2H), 7.72 (d, 1H), 7.77 (s, 1H).

LRMS : m/z APCI⁺ 324 [MH]⁺

Preparation 13

(3S)-3-(Benzylamino)chromane-6-carbonitrile



Tetrakis(triphenylphosphine)palladium (505mg, 0.44mmol), followed by zinc cyanide (456mg, 3.9mmol) were added to a solution of the iodide from preparation 5 (2.9g, 8.0mmol) in N,N-dimethylformamide (20ml) and the reaction stirred at 90°C for 4 hours. The cooled reaction mixture was partitioned between ethyl acetate (250ml) and water (250ml) and the layers separated. The aqueous phase was extracted with additional ethyl acetate (200ml) and the combined organic solutions were dried (MgSO₄) and evaporated under reduced pressure. The residual brown oil was purified by column chromatography on silica gel using dichloromethane:methanol (100:0 to 98:2) as eluant to give the title compound, 1.26g.

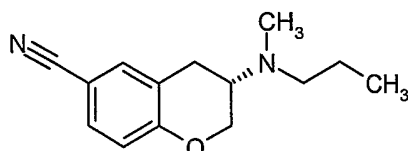
¹H NMR (CDCl₃, 400MHz) δ : 2.70 (m, 1H), 3.00 (dd, 1H), 3.20 (m, 1H), 3.92 (s, 2H), 4.05 (m, 1H), 4.26 (d, 1H), 6.85 (d, 1H), 7.27 (m, 1H), 7.35 (m, 5H), 7.39 (d, 1H).

LRMS : m/z APCI⁺ 265 [MH]⁺

$[\alpha]_D = +47.8$ (c = 0.1 in methanol)

Preparation 14

(3S)-3-[Methyl(propyl)amino]chromane-6-carbonitrile



65

Tetrakis(triphenylphosphine)palladium (460mg, 0.39mmol), followed by zinc cyanide (655mg, 5.6mmol) were added to a solution of the iodide from preparation 7 (2.64g, 7.97mmol) in N,N-dimethylformamide (25ml) and the reaction stirred at 100°C for 18 hours. The cooled reaction mixture was partitioned between ethyl acetate (250ml) and water (200ml) and the layers separated. The organic phase was washed with brine (200ml), dried (MgSO₄) and evaporated under reduced pressure. The residual brown oil was pre-adsorbed onto silica gel, and this was purified by column chromatography on silica gel using ethyl acetate:pentane (25:75) as eluant to give the title compound as a yellow oil, 1.54g.

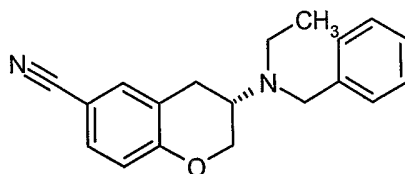
¹H NMR (CD₃OD, 400MHz) δ: 0.91 (t, 3H), 1.52 (m, 2H), 2.35 (s, 3H), 2.54 (m, 2H), 2.80-2.90 (m, 3H), 4.05 (dd, 1H), 4.38 (d, 1H), 6.87 (d, 1H), 7.40 (d, 1H), 7.48 (s, 1H).

LRMS : m/z APCI⁺ 231 [MH]⁺

[α]_D = 67.85 (c = 0.1 in methanol)

Preparation 15

(3S)-3-[Benzyl(ethyl)amino]chromane-6-carbonitrile



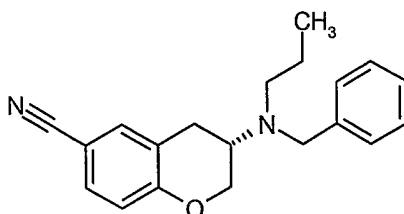
Acetaldehyde (0.32ml, 5.7mmol) was added to an ice-cooled solution of the amine from preparation 13 (150mg, 0.57mmol) in tetrahydrofuran (10ml) and the solution stirred for 30 minutes. Sodium triacetoxyborohydride (43mg, 0.68mmol) was added and the reaction stirred at room temperature for 2 hours. TLC analysis showed starting material remaining, so additional acetaldehyde (0.64ml, 11.4mmol) was added and the reaction stirred at room temperature for a further 18 hours. Further acetaldehyde (0.32ml, 5.7mmol) and sodium triacetoxyborohydride (72mg, 1.14mmol) were added and the reaction stirred for 2 hours. The mixture was partitioned between dichloromethane (100ml) and water (100ml) and the layers separated. The organic phase was washed with brine (50ml), dried (MgSO₄) and evaporated under reduced pressure. The residual yellow oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 98:2) to afford the title compound, 125mg.

¹H NMR (CDCl₃, 400MHz) δ: 1.08 (t, 3H), 2.69 (q, 2H), 2.91 (d, 2H), 3.24 (m, 1H), 3.76 (s, 2H), 3.96 (dd, 1H), 4.35 (dd, 1H), 6.81 (d, 1H), 7.23-7.35 (m, 7H).

LRMS : m/z APCI⁺ 315 [MNa]⁺

Preparation 16

(3S)-3-[Benzyl(propyl)amino]chromane-6-carbonitrile



66

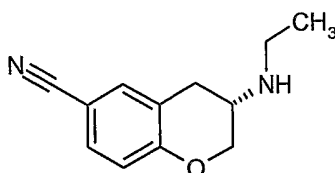
Propionaldehyde (446 μ l, 6.18mmol) and sodium triacetoxyborohydride (389mg, 6.21mmol) were added to a solution of the amine from preparation 13 (681mg, 2.6mmol) in tetrahydrofuran (30ml) and the reaction stirred at room temperature for 72 hours. The reaction was partitioned between ethyl acetate (150ml) and saturated aqueous sodium bicarbonate solution (100ml). The layers were separated, the organic phase washed with brine (100ml), dried (MgSO₄) and evaporated under reduced pressure. The residual yellow oil was purified by column chromatography on silica gel using an elution gradient of ethyl acetate:pentane (5:95 to 10:90) to give the title compound as a colourless oil, 455mg.

¹H NMR (CDCl₃, 400MHz) δ : 0.87 (t, 3H), 1.48 (q, 2H), 2.56 (m, 2H), 2.88 (d, 2H), 3.20 (m, 1H), 3.75 (s, 2H), 3.94 (t, 1H), 4.34 (d, 1H), 6.81 (d, 1H), 7.23-7.37 (m, 7H).

LRMS : m/z APCI⁺ 307 [MH]⁺

Preparation 17

(3S)-3-(Ethylamino)chromane-6-carbonitrile



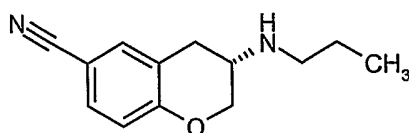
A mixture of the compound from preparation 15 (110mg, 0.37mmol) and 10% Pd/C (50mg) in ethanol (30ml) was hydrogenated at 1 atm, and 40°C for 3 hours. The mixture was filtered through Arbocel®, washing through with additional ethanol and the filtrate concentrated under reduced pressure. The residual yellow oil was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (98:2:0.2 to 96:4:0.4) to afford the title compound as a colourless oil, 42.5mg.

¹H NMR (CD₃OD, 400MHz) δ : 1.16 (t, 3H), 2.67 (m, 1H), 2.77 (q, 2H), 3.10 (m, 2H), 3.96 (dd, 1H), 4.31 (d, 1H), 6.88 (d, 1H), 7.42 (d, 1H), 7.46 (s, 1H).

LRMS : m/z APCI⁺ 203 [MH]⁺

Preparation 18

(3S)-3-(Propylamino)chromane-6-carbonitrile



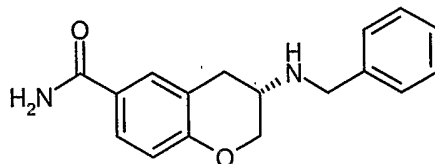
Ammonium formate (469mg, 7.43mmol) was added to a mixture of the compound from preparation 16 (455mg, 1.49mmol) and 10% palladium on charcoal (220mg) in methanol (10ml) and the reaction stirred under reflux for 1.5 hours. The cooled reaction was filtered through Arbocel® washing through with methanol. The filtrate was evaporated under reduced pressure and the residue partitioned between dichloromethane (100ml) and ammonia (60ml). The layers were separated, the organic phase dried (MgSO₄) and evaporated under reduced pressure to give the title compound as a colourless oil, 287mg.

¹H NMR (CD₃OD, 400MHz) δ : 1.05 (t, 3H), 1.77 (m, 2H), 3.09 (m, 2H), 3.35 (m, 2H), 3.84 (m, 1H), 4.38 (d, 1H), 4.48 (d, 1H), 7.01 (d, 1H), 7.51 (d, 1H), 7.58 (s, 1H).

LRMS : m/z APCI⁺ 217 [MH]⁺

Preparation 19

(3S)-3-(Benzylamino)chromane-6-carboxamide



5

A mixture of the nitrile from preparation 13 (1.46g, 5.5mmol) and potassium hydroxide (927mg, 16.5mmol) in 2-methyl-2-propanol (20ml) was heated under reflux for 18 hours. TLC analysis showed starting material remaining, so additional potassium hydroxide (927mg, 16.5mmol) and 2-methyl-2-propanol (10ml) were added and the reaction heated for a further 3 hours. The cooled reaction mixture was evaporated under reduced pressure and the residue partitioned between ethyl acetate (250ml) and water (150ml). The layers were separated, the organic phase dried (MgSO₄) and evaporated under reduced pressure to afford the title compound as a white solid, 1.17g.

10

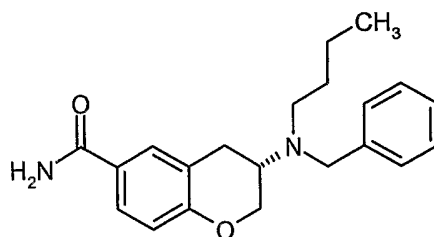
¹H NMR (CD₃OD, 400MHz) δ: 2.71 (m, 1H), 3.10 (m, 2H), 3.89 (s, 2H), 3.91 (m, 1H), 4.28 (d, 1H), 6.81 (d, 1H), 7.25-7.38 (m, 5H), 7.62 (dd, 2H).

15

LRMS : m/z APCI⁺ 283 [MH]⁺

Preparation 20

(3S)-3-[Benzyl(butyl)amino]chromane-6-carboxamide



20

Butyraldehyde (0.09ml, 1.0mmol) followed by acetic acid (0.04ml, 0.71mmol) and sodium triacetoxyborohydride (420mg, 1.9mmol) were added to a solution of the amine from preparation 19 (200mg, 0.71mmol) in tetrahydrofuran (10ml) and the reaction stirred at room temperature for 18 hours. The mixture was partitioned between ethyl acetate (100ml) and sodium bicarbonate solution (75ml) and the layers separated. The organic phase was dried (MgSO₄) and evaporated under reduced pressure to give the title compound as a colourless oil, 252mg.

25

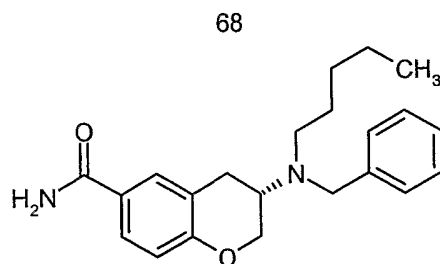
¹H NMR (CD₃OD, 400MHz) δ: 0.86 (t, 3H), 1.31 (m, 2H), 1.43 (m, 2H), 2.63 (m, 2H), 2.96 (m, 2H), 3.16 (m, 1H), 3.77 (s, 2H), 4.00 (m, 1H), 4.32 (d, 1H), 6.77 (d, 1H), 7.20 (dd, 1H), 7.28 (dd, 2H), 7.33 (d, 2H), 7.60 (d, 1H), 7.63 (s, 1H).

LRMS : m/z APCI⁺ 339 [MH]⁺

30

Preparation 21

(3S)-3-[Benzyl(pentyl)amino]chromane-6-carboxamide



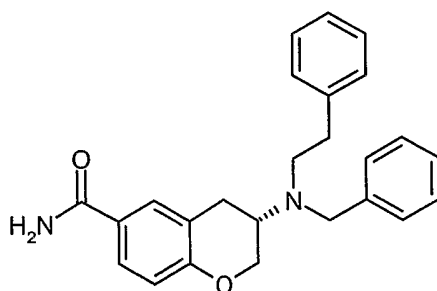
The title compound was obtained as a colourless oil, from the amine from preparation 19 and valeraldehyde, following the procedure described in preparation 20.

¹H NMR (CD₃OD, 400MHz) δ: 0.92 (t, 3H), 1.35-1.55 (m, 6H), 2.61 (m, 2H), 2.98 (m, 2H), 3.19 (m, 1H), 3.55 (m, 1H), 3.78 (s, 2H), 4.32 (d, 1H), 6.78 (d, 1H), 7.20 (dd, 1H), 7.27 (dd, 2H), 7.33 (d, 2H), 7.60 (d, 1H), 7.63 (s, 1H).

LRMS : m/z APCI⁺ 353 [MH]⁺

Preparation 22

10 (3S)-3-[Benzyl(2-phenylethyl)amino]chromane-6-carboxamide



Phenylacetaldehyde (0.10ml, 0.89mmol) was added to a solution of the amine from preparation 19 (180mg, 0.64mmol) in tetrahydrofuran (10ml) and the solution stirred for 1 hour. Acetic acid (36μl, 0.64mmol) and sodium triacetoxyborohydride (378mg, 1.78mmol) were added and the reaction stirred at room temperature for 18 hours. TLC analysis showed starting material remaining, so additional phenylacetaldehyde (0.10ml, 0.89mmol) followed by sodium triacetoxyborohydride (189mg, 0.89mmol) were added and the reaction stirred for a further 18 hours. The mixture was partitioned between ethyl acetate (100ml) and saturated sodium bicarbonate solution (100ml) and the layers separated. The organic phase was dried (MgSO₄) and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel using dichloromethane:methanol (98:2) as eluant to afford the title compound.

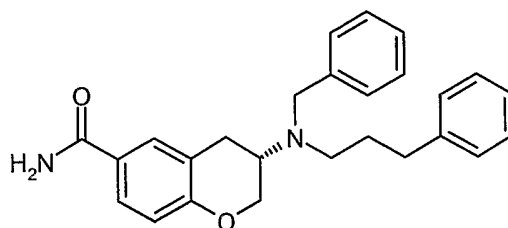
¹H NMR (CD₃OD, 400MHz) δ: 2.72 (t, 2H), 2.84 (m, 2H), 2.93 (d, 2H), 3.20 (m, 1H), 3.86 (s, 2H), 3.96 (t, 1H), 4.26 (d, 1H), 6.75 (d, 1H), 7.09-7.32 (m, 10H), 7.57 (d, 1H), 7.62 (s, 1H).

LRMS : m/z APCI⁺ 387 [MH]⁺

Preparation 23

(3S)-3-[Benzyl(2-phenylpropyl)amino]chromane-6-carboxamide

69



Phenylpropionaldehyde (0.085ml, 0.65mmol) was added to a solution of the amine from preparation 19 (130mg, 0.46mmol) in tetrahydrofuran (10ml) and the solution stirred for 2 hours. Acetic acid (26 μ l, 0.46mmol) and sodium triacetoxyborohydride (273mg, 1.3mmol) were added and the reaction stirred at room temperature for 18 hours. The mixture was partitioned between ethyl acetate (100ml) and saturated sodium bicarbonate solution (100ml) and the layers separated. The organic phase was dried (MgSO₄) and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel using dichloromethane:methanol (98:2) as eluant to afford the title compound.

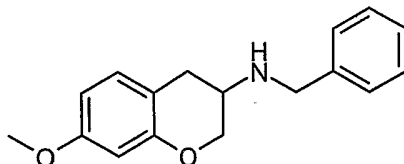
¹H NMR (CD₃OD, 400MHz) δ : 1.8 (m, 2H), 2.62 (m, 4H), 2.89 (d, 2H), 3.20 (m, 1H), 3.76 (s, 2H), 3.91 (t, 1H), 4.26 (d, 1H), 6.79 (d, 1H), 7.0-7.4 (m, 10H), 7.5 (d, 1H), 7.57 (s, 1H).

LRMS : m/z APCI⁺ 401 [MH]⁺

[α]_D = +85.2 (c = 0.1 in methanol)

Preparation 24

N-Benzyl-*N*-[7-Methoxy-3,4-dihydro-2*H*-chromen-3-yl]amine



Benzyl amine (4.06ml, 37.1mmol) was added dropwise to a solution of 7-methoxy-2*H*-chromen-3(4*H*)-one (J. Am. Chem. Soc. (1993), 115(20), 9327-8) (6.02g, 33.8mmol) in tetrahydrofuran (100ml). Then acetic acid (1.93ml, 33.8mmol) and sodium triacetoxyborohydride (10.73g, 50.63mmol) were added and the reaction stirred at room temperature for 20 hours under nitrogen. The reaction was quenched by the addition of sodium bicarbonate solution (40ml) and the mixture extracted with ethyl acetate (2x80ml).

The combined organic layers were extracted with 2M HCl (3x50ml) before the aqueous extracts were adjusted to pH 10 with potassium carbonate (s) before been re-extracted with ethyl acetate (3x80ml).

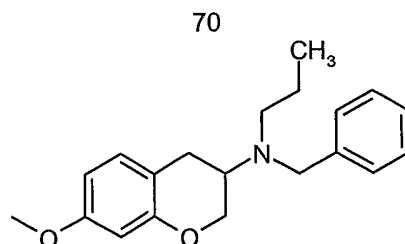
The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure, the crude residue was purified by column chromatography on silica gel using ethyl acetate:pentane (10:90 to 30:70) as eluant to give the title compound as a mixture of free base 2.34g and acetic acid salt 1.01g.

¹H NMR (CD₃OD, 400MHz) δ : 2.58 (dd, 2H), 2.96 (dd, 1H), 3.04 (m, 1H), 3.68 (s, 3H), 3.80 (q, 1H), 3.85 (s, 2H), 4.20 (dd, 1H), 6.31 (d, 1H), 6.42 (dd, 1H), 6.92 (d, 1H), 7.24 (m, 1H), 7.20-7.40 (m, 4H).

LRMS : m/z APCI⁺ 270 [MH]⁺

Preparation 25

N-Benzyl-*N*-[7-Methoxy-3,4-dihydro-2*H*-chromen-3-yl]-*N*-propylamine



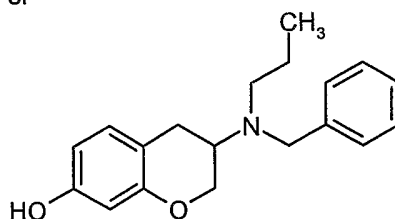
Propionaldehyde (0.85ml, 11.7mmol) was added to a solution of (*N*-Benzyl-*N*-[7-Methoxy-3,4-dihydro-2*H*-chromen-3-yl]amine from preparation 24 (3.02g, 11.2mmol), acetic acid (0.64ml, 11.2mmol) and sodium triacetoxyborohydride (3.56g, 16.8mmol) in tetrahydrofuran (50ml), and the reaction stirred at room temperature for 48 hours. The reaction was quenched by the addition of 1M sodium hydroxide solution (40ml) and the mixture extracted with ethyl acetate (2x50ml). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure, to afford the title compound as a colourless oil, 3.25g.

¹H NMR (CD₃OD, 400MHz) δ : 0.84 (t, 3H), 1.45 (m, 2H), 2.56 (m, 2H), 2.81 (m, 2H), 3.10 (m, 1H), 3.67 (s, 3H), 3.75 (s, 2H), 3.84 (t, 1H), 4.23 (dd, 1H), 6.26 (s, 1H), 6.40 (d, 1H), 6.92 (d, 1H), 7.20 (t, 2H), 7.25 (t, 2H).

LRMS : m/z APCI⁺ 312 [MH]⁺

Preparation 26

3-[benzyl(propyl)amino]chroman-7-ol



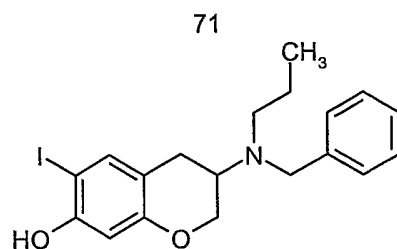
N-Benzyl-*N*-[7-Methoxy-3,4-dihydro-2*H*-chromen-3-yl]-*N*-propylamine from preparation 25 (3.23g, 10.37mmol) was refluxed for 18h in 48% hydrobromic acid (30ml) before being allowed to cool. The reaction mixture was allowed to cool before being concentrated *N*-Benzyl-*N*-[7-Methoxy-3,4-dihydro-2*H*-chromen-3-yl]-*N*-propylamine *in vacuo*, and azeotroped with toluene. The residue was portioned between dichloromethane (80ml) and water (80ml) and adjusted to pH 11 with ammonia solution. The aqueous was extracted with dichloromethane (2x30ml) and the combined organic layers dried with MgSO₄ and concentrated to give a dark red residue. The residue was purified by column chromatography on silica using ether: pentane (5:95 to 2:8) to afford the title compound as a brown oil 2.13g.

¹H NMR (CD₃OD, 400MHz) δ : 0.85 (t, 3H), 1.44 (m, 2H), 2.56 (m, 2H), 2.78 (m, 2H), 3.07 (m, 1H), 3.74 (s, 2H), 3.81 (t, 1H), 4.20 (dd, 1H), 6.17 (s, 1H), 6.26 (dd, 1H), 6.82 (d, 1H), 7.19 (t, 1H), 7.26 (t, 2H), 7.34 (d, 2H).

LRMS : m/z APCI⁺ 298 [MH]⁺

Preparation 27

3-[benzyl(propyl)amino]-6-iodochroman-7-ol



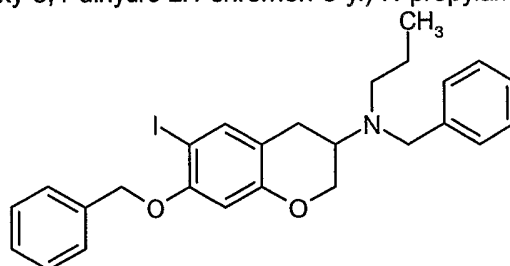
3-[benzyl(propyl)amino]chroman-7-ol from preparation 26 (2.34g, 7.87mmol) was dissolved in trifluoroacetic acid (20ml) and cooled to -10°C . N-iodosuccinimide (1.77g, 7.87mmol) was added and the reaction stirred for 1h at -10°C and then at rt for 8h. The reaction was quenched with ice and sodium bicarbonate solution until pH8 was reached. The aqueous was extracted with ethyl acetate (2x80ml) and the combined organic layers were dried over MgSO_4 and concentrated to give a brown residue. This was purified by column chromatography MeOH/dichloromethane (2/98) to afford the title compound as a red oil, 2.37g.

^1H NMR (CD_3OD , 400MHz) δ : 0.84 (t, 3H), 1.43 (m, 2H), 2.46-2.59 (m, 2H), 2.70-2.80 (m, 2H), 3.05 (m, 1H), 3.69 (s, 2H), 3.81 (t, 1H), 4.19 (dd, 1H), 6.23 (s, 1H), 7.19 (t, 1H), 7.22-7.36 (m, 5H).

LRMS : m/z APCI $^+$ 424 $[\text{MH}]^+$

Preparation 28

N-benzyl-*N*-(6-iodo-7-benzyloxy-3,4-dihydro-2*H*-chromen-3-yl)-*N*-propylamine



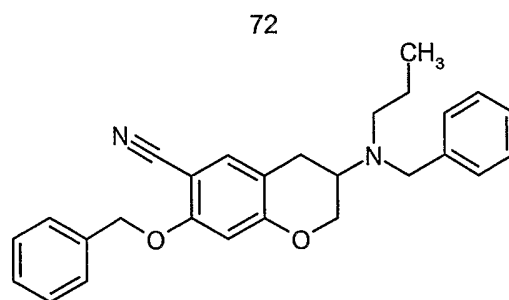
3-[benzyl(propyl)amino]chroman-7-ol from preparation 27 (145g, 0.34mmol) was dissolved in dimethylformamide (5ml) with potassium carbonate (140mg, 1mmol) to which was added benzyl bromide (0.043ml, 0.36mmol) and the reaction mixture was stirred for 18h under nitrogen. The reaction mixture was concentrated *in vacuo* and the residue separated between dichloromethane (50ml) and water (10ml). The aqueous layer was extracted with dichloromethane (2x10ml) and the combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica ethyl acetate:pentane 1:20 to give the product as a colourless oil 124mg.

^1H NMR (CDCl_3 , 400MHz) δ : 0.9 (t, 3H), 1.5 (m, 2H), 2.5 (m, 2H), 2.80 (d, 2H), 3.1-3.2 (m, 1H), 3.7 (s, 2H), 3.8 (t, 1H), 4.25 (dd, 1H), 5.05 (s, 2H), 6.3 (s, 1H), 7.2-7.5 (m, 10H), 8.0 (s, 5H).

LRMS : m/z APCI $^+$ 514 $[\text{MH}]^+$

Preparation 29

N-benzyl-*N*-(6-carbonitrile-7-benzyloxy-3,4-dihydro-2*H*-chromen-3-yl)-*N*-propylamine



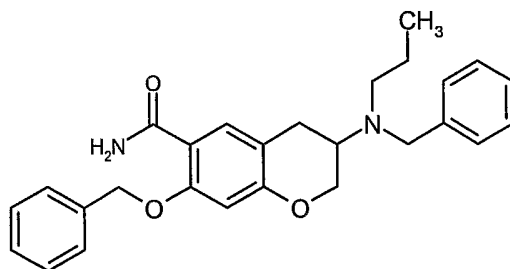
Tetrakis(triphenylphosphine)palladium (50mg, 0.04mmol) and zinc cyanide (30mg, 0.26mmol) were added to a solution of *N*-benzyl-*N*-(6-iodo-7-benzyloxy-3,4-dihydro-2*H*-chromen-3-yl)-*N*-propylamine from preparation 28 (224mg, 0.44mmol) in *N,N*-dimethylformamide (5ml) and the reaction stirred at 90°C for 0.5h. A second aliquot of tetrakis(triphenylphosphine)palladium (50mg, 0.04mmol), and zinc cyanide (30mg, 0.26mmol) was added and the reaction heated for 0.5h after which time extra tetrakis(triphenylphosphine)palladium (50mg, 0.04mmol) was added, this was repeated four times and the reaction then stirred at 90°C for 18h. The reaction was cooled and evaporated under reduced pressure. The residual yellow oil was purified by column chromatography on silica using ethyl acetate:pentane (10:90) as eluant to give the title compound as a viscous oil which slowly crystallised 63mg.

¹H NMR (CDCl₃, 400MHz) δ: 0.9 (t, 3H), 1.45-1.55 (m, 2H), 2.5-2.6 (m, 2H), 2.8 (d, 2H), 3.15 (dq, 1H), 3.7 (s, 2H), 3.97 (t, 1H), 4.3 (dd, 1H), 5.1 (s, 2H), 6.2 (s, 1H), 7.2-7.5 (m, 11H).

LRMS : m/z APCI⁺ 413 [MH]⁺

Preparation 30

N-benzyl-*N*-(6-carboxamide-7-benzyloxy-3,4-dihydro-2*H*-chromen-3-yl)-*N*-propylamine



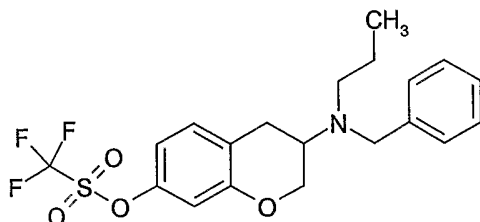
A mixture of *N*-benzyl-*N*-(6-carbonitrile-7-benzyloxy-3,4-dihydro-2*H*-chromen-3-yl)-*N*-propylamine from preparation 29 (63mg, 0.15mmol) and potassium hydroxide (25mg, 0.46mmol) in 2-methyl-2-propanol (3ml) was heated under reflux for 18 hours. TLC analysis showed starting material remaining, so additional potassium hydroxide (40mg) was added and the reaction heated for a further 3 hours. The cooled reaction mixture was evaporated under reduced pressure and the residue partitioned between dichloromethane (2x10ml) and water (5ml). The layers were separated, the organic phase dried (MgSO₄), and evaporated under reduced pressure to afford the title compound, 60mg.

¹H NMR (CDCl₃, 400MHz) δ: 0.9 (t, 3H), 1.45-1.55 (m, 2H), 2.5-2.6 (m, 2H), 2.8-2.95 (m, 2H), 3.1-3.2 (m, 1H), 3.7-3.8 (m, 2H), 3.9 (t, 1H), 4.3 (dd, 1H), 5.1 (s, 2H), 5.6 (bs, 1H), 6.4 (s, 1H), 7.2-7.4 (m, 10H), 7.6 (bs, 1H), 8.0 (s, 1H).

LRMS : m/z APCI⁺ 431 [MH]⁺

Preparation 31

3-[Benzyl(propyl)amino]-3,4-dihydro-2H-chromen-7-yl trifluoromethanesulfonate



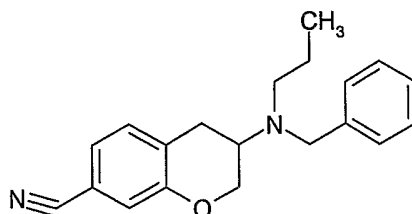
A mixture of the alcohol from preparation 26 (1g, 3.37mmol), N-phenylbis(trifluoromethanesulphonimide) (1.26g, 3.54mmol) and triethylamine (516μl, 3.7mmol) in dichloromethane (20ml) was stirred at room temperature for 18 hours. The mixture was partitioned between dichloromethane (50ml) and aqueous potassium carbonate solution and the layers separated. The aqueous solution was extracted with further dichloromethane (50ml) and the combined organic solutions dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:pentane (30:70 to 100:0) to afford the title compound as a clear oil, 1.3g.

¹H NMR (CDCl₃, 400MHz) δ: 0.83 (t, 3H), 1.42-1.53 (m, 2H), 2.58 (m, 2H), 2.96 (m, 2H), 3.12 (m, 1H), 3.78 (s, 2H), 3.99 (dd, 1H), 4.32 (m, 1H), 6.70 (d, 1H), 6.80 (dd, 1H), 7.19 (m, 2H), 7.24 (m, 2H), 7.35 (m, 2H).

LRMS : m/z APCI⁺ 430 [MH]⁺

Preparation 32

3-[Benzyl(propyl)amino]chromane-7-carbonitrile

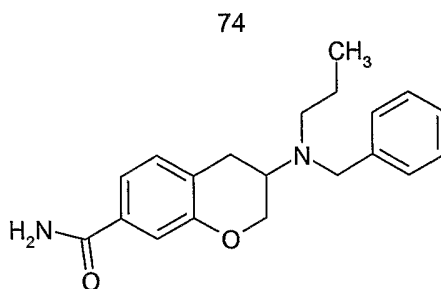


A mixture of the compound from preparation 31 (1.3g, 3.03mmol), zinc cyanide (249mg, 2.12mmol), tris(dibenzylideneacetone)dipalladium(0) (174mg, 0.3mmol), 1,1'-bis(diphenylphosphino)ferrocene (336mg, 0.6mmol) and lithium chloride (128mg, 3.03mmol) in N,N-dimethylformamide (2ml) was stirred at 100°C for 3 hours. The cooled mixture was diluted with water and extracted with ether (2x50ml). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure. The crude product was pre-adsorbed onto silica gel and purified by column chromatography on silica gel using an elution gradient of dichloromethane:pentane (30:70 to 50:50) to afford the title compound as a brown crystalline solid, 730mg.

¹H NMR (DMSO-d₆, 400MHz) δ: 0.78 (t, 3H), 1.36-1.41 (m, 2H), 2.48 (m, 2H), 2.95 (m, 2H), 3.00-3.10 (m, 2H), 3.68 (s, 2H), 3.99 (dd, 1H), 4.26 (m, 1H), 7.17-7.35 (m, 8H). LRMS : m/z APCI⁺ 307 [MH]⁺

Preparation 33

3-[Benzyl(propyl)amino]chromane-7-carboxamide

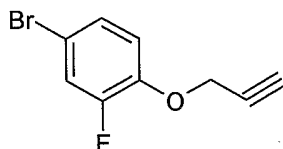


A mixture of the compound from preparation 32 (720mg, 2.35mmol) and potassium hydroxide (527mg, 9.4mmol) in *tert*-butanol (15ml) was heated under reflux for 2 hours. The cooled solution was diluted with water (50ml) and the mixture partitioned between brine (50ml) and ethyl acetate (50ml). The layers were separated, the aqueous phase extracted with further ethyl acetate (50ml) and the combined organic solutions dried (MgSO₄) and evaporated under reduced pressure to give a beige solid, 740mg.

¹H NMR (CD₃OD, 400MHz) δ : 0.83 (t, 3H), 1.42-1.54 (m, 2H), 2.36 (m, 2H), 2.98 (m, 2H), 3.18 (m, 1H), 3.78 (s, 2H), 3.97 (dd, 1H), 4.30 (m, 1H), 7.15-7.38 (m, 8H). LRMS : m/z APCI⁺ 325 [MH]⁺

10 Preparation 34

4-Bromo-2-fluoro-1-(prop-2-yn-1-yloxy)benzene

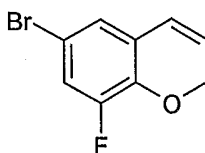


Propargyl bromide (14.9ml, 100mmol), followed by potassium carbonate (27.6g, 200mmol) were added to a solution of 4-bromo-2-fluorophenol (10.9ml, 100mmol) in acetone (400ml) and the reaction stirred at room temperature for 72 hours. The reaction was diluted with water (300ml) and the mixture extracted with ether (2x500ml). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to provide the title compound as a yellow oil, 23g.

¹H NMR (CDCl₃, 400MHz) δ : 2.58 (s, 1H), 4.78 (s, 2H), 7.00 (dd, 1H), 7.20 (m, 1H), 7.25 (m, 1H).

20 Preparation 35

6-Bromo-8-fluoro-2H-chromene



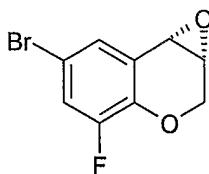
A solution of the compound from preparation 34 (5g, 21.9mmol) in N,N-diethylaniline (50ml) was heated to 220°C (reaction temperature) for 4 hours, then allowed to cool. The mixture was partitioned between 2M hydrochloric acid (100ml) and ether (100ml) and the layers separated. The organic phase was washed with further 2M hydrochloric acid (100ml), then dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using ethyl acetate:pentane (2:98) to afford the title compound as a brown oil, 2.8g.

¹H NMR (CDCl₃, 400MHz) δ : 4.90 (s, 2H), 5.85 (m, 1H), 6.38 (d, 1H), 6.88 (s, 1H), 7.06 (d, 1H).

75

Preparation 36

6-Bromo-4-fluoro-1a,7b-dihydro-2H-oxireno[c]chromene

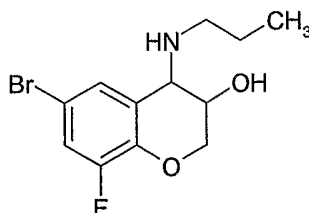


1,1,1-Trifluoroacetone (20ml, 275mmol) was added to an ice-cooled solution of the compound from preparation 35 (6.3g, 27.5mmol) and ethylenediamine tetraacetic acid disodium salt (0.4M, 100ml) in acetonitrile (150ml). A mixture of sodium bicarbonate (18g, 213mmol) and Oxone® (84.5g, 137mmol) was added portionwise over 1 hour, and once addition was complete the reaction was stirred at 0°C for an hour. The reaction was partitioned between dichloromethane (500ml) and water (500ml) and the layers separated. The organic layer was dried (MgSO₄) and evaporated under reduced pressure to afford the title compound, 8.7g.

¹H NMR (CDCl₃, 400MHz) δ: 3.83 (dd, 2H), 4.20 (d, 1H), 4.64 (d, 1H), 7.20-7.35 (m, 2H). LRMS : m/z APCI⁺ 264 [MNH₄]⁺

Preparation 37

6-Bromo-8-fluoro-4-(propylamino)chroman-3-ol

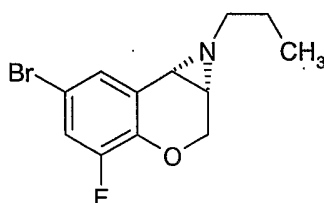


A mixture of the compound from preparation 36 (8.7g, 27.5mmol) and propylamine (2.25ml, 27.5mmol) in ethanol (100ml) was heated under reflux for 2 hours. The mixture was concentrated under reduced pressure and the residue purified by column chromatography on silica gel using an elution gradient of ethyl acetate:pentane (5:95 to 50:50) to afford the title compound as a brown oil, 4.48g.

¹H NMR (CDCl₃, 400MHz) δ: 0.96 (t, 3H), 1.57 (m, 2H), 2.63 (m, 1H), 2.78 (m, 1H), 4.00 (m, 1H), 4.20 (m, 1H), 4.41 (d, 1H), 7.18 (m, 2H). LRMS : m/z APCI⁺ 304, 306 [MH]⁺

Preparation 38

6-Bromo-4-fluoro-1-propyl-1a,2,7b-tetrahydrochromeno[3,4-b]azirene



Diisopropyl azodicarboxylate (4.3ml, 21.7mmol) was added to a solution of the compound from preparation 37 (4.4g, 14.5mmol) and triphenylphosphine (5.7g, 21.7mmol) in tetrahydrofuran (100ml) and the reaction stirred at room temperature for 2 hours. The reaction was concentrated under reduced

76

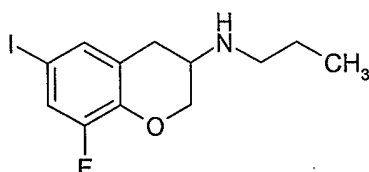
pressure and the residue purified by column chromatography on silica gel using an elution gradient of ethyl acetate:pentane (5:95 to 10:90) to afford the title compound as a white solid, 2.3g.

^1H NMR (CDCl_3 , 400MHz) δ : 0.94 (t, 3H), 1.61 (m, 2H), 2.30-2.46 (m, 4H), 3.90 (d, 1H), 4.54 (d, 1H), 7.08 (d, 1H), 7.19 (s, 1H). LRMS : m/z APCI $^+$ 286, 288 $[\text{MH}]^+$

5

Preparation 39

8-Fluoro-6-iodo-*N*-propylchroman-3-amine

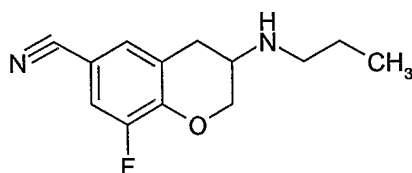


N-Iodosuccinimide (1.04g, 4.6mmol) was added portionwise to solution of the compound from example 22 (970mg, 4.6mmol) in tetrahydrofuran (15ml) at 0°C. The reaction was allowed to warm to room temperature and stirred for a further 18 hours. The reaction was carefully poured onto ice, the mixture basified using potassium carbonate then extracted with ethyl acetate (2x200ml). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to provide the title compound as a brown oil in quantitative yield.

^1H NMR (CDCl_3 , 400MHz) δ : 0.96 (t, 3H), 1.58 (m, 2H), 2.74 (m, 4H), 3.01 (m, 1H), 3.21 (m, 1H), 4.02 (m, 1H), 4.28 (m, 1H), 7.18 (s, 1H), 7.21 (d, 1H). LRMS : m/z APCI $^+$ 336 $[\text{MH}]^+$

Preparation 40

8-Fluoro-3-(propylamino)chromane-6-carbonitrile



20

A mixture of the compound from preparation 39 (1.54g, 4.6mmol), zinc cyanide (378mg, 3.2mmol), tris(dibenzylideneacetone)dipalladium(0) (265mg, 0.46mmol) and 1,1'-bis(diphenylphosphino)ferrocene (510mg, 0.92mmol) in *N,N*-dimethylformamide (15ml) was heated at 100°C for 2 hours. The mixture was allowed to cool and evaporated under reduced pressure. The residue was dissolved in toluene and purified by column chromatography on silica gel using an elution gradient of ethyl acetate:pentane (40:60 to 100:0) to afford the title compound as a brown oil, 600mg.

25

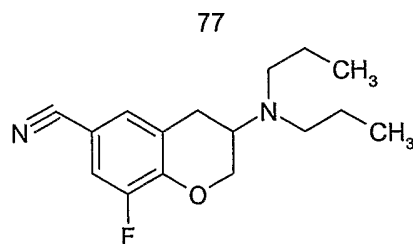
^1H NMR (CDCl_3 , 400MHz) δ : 0.96 (t, 3H), 1.57 (m, 2H), 2.70 (m, 4H), 3.02 (m, 1H), 3.21 (m, 1H), 4.08 (m, 1H), 4.38 (m, 1H), 7.17-7.22 (m, 2H).

LRMS : m/z APCI $^+$ 235 $[\text{MH}]^+$

30

Preparation 41

3-(Dipropylamino)-8-fluorochromane-6-carbonitrile



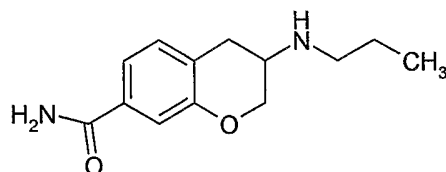
A mixture of the compound from preparation 40 (600mg, 2.56mmol), propionaldehyde (280 μ l, 3.84mmol) and sodium triacetoxymethylborohydride (815mg, 3.84mmol) in dichloromethane (10ml) was stirred at room temperature for 72 hours. The reaction was quenched by the addition of water (30ml) and the mixture extracted with dichloromethane (2x30ml). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of ethyl acetate:pentane (5:95 to 10:90) to afford the title compound as an oil, 588mg.

¹H NMR (CDCl₃, 400MHz) δ : 0.86 (t, 6H), 1.42 (m, 4H), 2.50 (m, 4H), 2.84 (m, 2H), 3.18 (m, 1H), 3.95 (m, 1H), 4.42 (m, 1H), 7.19 (m, 2H).

LRMS : m/z APCI⁺ 277 [MH]⁺

Preparation 42

3-(Propylamino)chromane-7-carboxamide



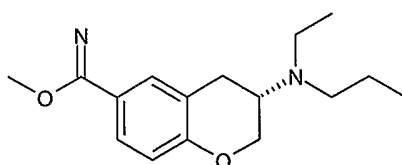
Ammonium formate (1.36g, 21.6mmol) was added portionwise to a mixture of the compound from preparation 33 (700mg, 2.16mmol) and 10% palladium on charcoal (70mg) in ethanol (30ml) and the mixture heated under nitrogen at 100°C for 3 hours. Further ammonium formate (500mg, 7.94mmol) was added and the reaction continued for a further hour. The cooled mixture was filtered through a pad of Celite® and Arbocel® and the filtrate evaporated under reduced pressure. The residual orange solid was pre-adsorbed onto silica gel and purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5) as eluant to afford a pale orange solid, 410mg.

¹H NMR (CD₃OD, 400MHz) δ : 0.97 (t, 3H), 1.50-1.60 (m, 2H), 2.63-2.74 (m, 3H), 3.06-3.15 (m, 2H), 3.88 (m, 1H), 4.26 (m, 1H), 7.18 (d, 1H), 7.27 (d, 1H), 7.38 (dd, 1H).

LRMS : m/z APCI⁺ 235 [MH]⁺

Preparation 43

(3S)-3-Ethyl-propyl-amino)-chroman-6-carboximidic acid methyl ester



78

HCl gas was bubbled through a solution of the compound from Example 13 (87mg, 0.35mmol) in MeOH (10ml) for 5 min. The reaction was then allowed to stir at room temperature for 1h. The mixture was evaporated to dryness and the resulting solid partitioned between dichloromethane (50ml) and NaHCO₃ (sat'd aq - 40ml). The organic layer was dried over MgSO₄, filtered and evaporated to give the title

compound as an off-white solid (87mg).

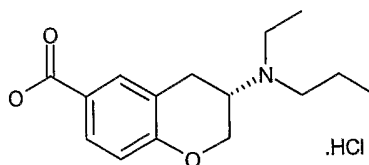
¹H NMR (CDCl₃, 400MHz) δ : 1.0 (t, 3H), 1.45 (br, 3H), 1.9 (br, 2H), 3.0 (br, 2H), 3.2 (br, 2H), 3.4 (br, 2H), 3.74 (br, 1H), 4.03 (s, 3H), 4.55 (br, 2H), 6.9 (d, 1H), 7.42 (s, 1H), 7.66 (d, 1H), 7.76 (br, 1H)

LRMS m/z APCI+ 277 (MH⁺)

TLC 95/5/0.5 CH₂Cl₂/MeOH/NH₃ R_f = 0.29

Preparation 44

(3S)-3-(Ethylpropylamino)-chroman-6-carboxylic acid



The compound from example 13 (600mg 2.456mmol, 1eq) was taken up in 6M HCl (aq) (20ml) and heated to reflux for 20h. The reaction was allowed to cool, evaporated *in vacuo*, and azeotroped three times with toluene. The solid residue was triturated twice with IPA and the insoluble material filtered off. The filtrate was evaporated *in vacuo* to give a brown solid, which was azeotroped with toluene x3 to give a pale brown hygroscopic foam (708mg, 96%)

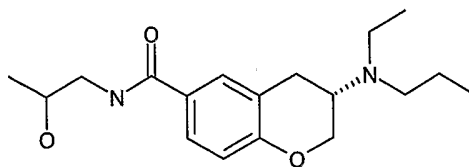
¹H NMR (CD₃OD, 400MHz) δ : 1.00 (t, 3H), 1.37 (t, 3H), 1.78 (m, 2H), 3.21 (m, 3H), 3.37 (m, 3H), 3.99 (m, 1H), 4.42-4.55 (m, 2H), 6.92 (d, 1H), 7.82 (d, 1H), 7.88 (s, 1H).

LRMS m/z ES+ 264 (MH⁺)

TLC 15% MeOH/CH₂Cl₂ R_f 0.03

Preparation 45

(3S)-3-(Ethylpropylamino)-chroman-6-carboxylic acid (2-hydroxypropyl) amide



The compound from preparation 44 (285mg, 0.951mmol, 1eq) was suspended in CH₂Cl₂ (15ml) and thionyl chloride (0.69ml, 9.510mmol, 10eq) added heated to reflux for 3h. The mixture was cooled to room temperature and evaporated *in vacuo*. The residue was taken up in dichloromethane (15ml) and 1-aminopropan-2-ol (86mg, 1.14mmol, 1.2eq) was added followed by a solution of Na₂CO₃ (302mg) in water (15ml). The biphasic mixture was stirred for 72h at room temperature, the layers then separated, the organic layer dried over MgSO₄, filtered and the solvent removed *in vacuo*. The brown residue was purified by flash column chromatography on SiO₂ column with a gradient elution from 5% MeOH/CH₂Cl₂ to 90/10/1 CH₂Cl₂/MeOH, NH₃ to give a pale brown oil (200mg, 66%, mixture of diastereoisomers).

79

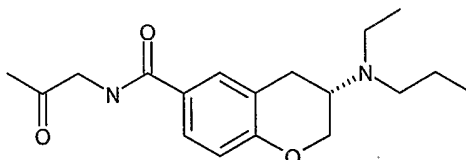
^1H NMR (CD_3OD , 400MHz) δ : 0.90 (t, 3H), 1.06 (m, 3H), 1.19 (m, 3H), 1.30 (m, 1H), 1.48 (m, 2H), 2.58 (m, 2H), 2.70 (m, 2H), 2.82-3.00 (m, 2H), 3.17 (m, 1H), 3.37 (m, 1H), 3.89-3.97 (m, 2H), 4.35 (m, 1H), 6.74-6.81 (m, 1H), 7.57-7.63 (m, 2H)

LRMS m/z APCI+, 321 (MH+)

5

Preparation 46

(3S)-3-(Ethylpropylamino)- chroman-6 carboxylic acid – 2-oxopropyl)-amide



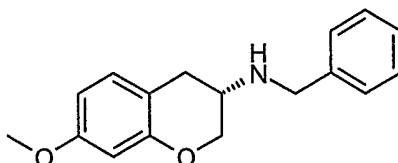
The compound from preparation 45 (196mg, 0.612mmol, 1eq) was taken up in dichloromethane (15ml) and 4A molecular sieves (excess) were added. N-methylmorpholine-N-oxide (124mg, 0.917mmol, 1.5eq) and tetrapropylammonium perruthenate (23mg, 0.122mmol, 0.2eq) were added. And the reaction stirred at room temperature overnight. The mixture was filtered through a plug of arboceel and evaporated *in vacuo* to give a dark brown oil. This material was carried forward to prepare example 25 without further purification.

15 LRMS m/z APCI+ 319 (MH+)

LRMS m/z APCI- 317 (MH+)

Preparation 47

(S)-(+)-N-Benzyl-N-[7-Methoxy-3,4-dihydro-2H-chromen-3-yl]amine



20

The material from preparation 24 was separated into individual enantiomers on by HPLC on a Chiralpak-AS-H column with a mobile phase of MeCN, flow rate 15ml/min, to give the title compound.

RT = 5.22min

^1H NMR (CD_3OD , 400MHz) δ : 2.58 (dd, 2H), 2.96 (dd, 1H), 3.04 (m, 1H), 3.68 (s, 3H), 3.80 (q, 1H), 3.85 (s, 2H), 4.20 (dd, 1H), 6.31 (d, 1H), 6.42 (dd, 1H), 6.92 (d, 1H), 7.24 (m, 1H), 7.20-7.40 (m, 4H).

25

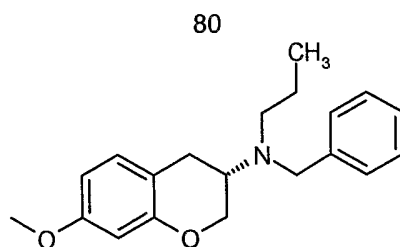
$[\alpha]_D = +57.86$ (c = 4.8mg/ml in methanol)

t.l.c. 10% EtOAc/Pentane R_f = 0.5

Preparation 48

(S)-N-Benzyl-N-[7-Methoxy-3,4-dihydro-2H-chromen-3-yl]-N-propylamine

30



The compound from preparation 47 (1.75g, 6.5mmol) was treated to analogous conditions to those described in preparation 25 to yield the title compound as a white solid (1.59g, 79%)

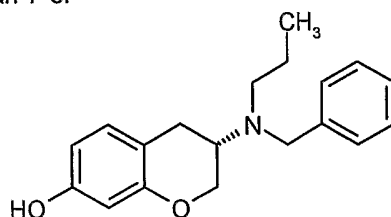
¹H NMR (CD₃OD, 400MHz) δ: 0.84 (t, 3H), 1.45 (m, 2H), 2.56 (m, 2H), 2.81 (m, 2H), 3.10 (m, 1H), 3.67 (s, 3H), 3.75 (s, 2H), 3.84 (t, 1H), 4.23 (dd, 1H), 6.26 (s, 1H), 6.40 (d, 1H), 6.92 (d, 1H), 7.20 (t, 2H), 7.25 (t, 2H).

LRMS : m/z APCI⁺ 312 [MH]⁺

TLC 2% MeOH/DCM R_f=0.9

10 Preparation 49

(S)-3-[benzyl(propyl)amino]chroman-7-ol



The compound from preparation 48 (5.8g, 18.6mmol) was subjected to analogous conditions to those described in preparation 26. After work-up the reaction yielded the title compound as a pale brown oil

15 which was taken forward without further purification.

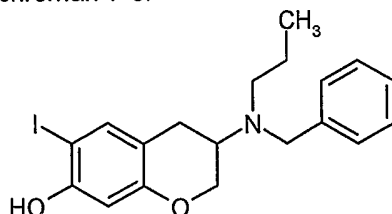
TLC 5% MeOH/DCM R_f=0.55

¹H NMR (CD₃OD, 400MHz) δ: 0.84 (t, 3H), 1.41-1.52 (m, 2H), 2.46-2.61 (m, 2H), 2.73-2.82 (m, 2H), 3.06-3.16 (m, 1H), 3.73 (s, 2H), 3.79-3.86 (m, 1H), 4.17-4.23 (m, 1H), 6.17 (s, 1H), 6.28 (d, 1H), 6.84 (d, 1H), 7.15-7.37 (m, 5H)

20 LRMS : m/z ES⁺ 298 [MH]⁺

Preparation 50

(S)-3-[benzyl(propyl)amino]-6-iodochroman-7-ol



25 The compound from preparation 49 (18.6mmol) was subjected to conditions analogous to those described in preparation 27. After work-up the material was purified by pre-absorption onto SiO₂ and flash chromatography on a SiO₂ column with a gradient elution from 10% to 30% Et₂O/Pentane to yield the title compound as a pale oil (6.52g)

TLC 10% Et₂O/Pentane R_f=0.05

81

^1H NMR (CD_3OD , 400MHz) δ : 0.84 (t, 3H), 1.41-1.54 (m, 2H), 2.50-2.61 (m, 2H), 2.74-2.84 (m, 2H), 3.05-3.16 (m, 1H), 3.74 (s, 2H), 3.80-3.90 (m, 1H), 4.19-4.25 (m, 1H), 6.25 (s, 1H), 7.16-7.38 (m, 6H)

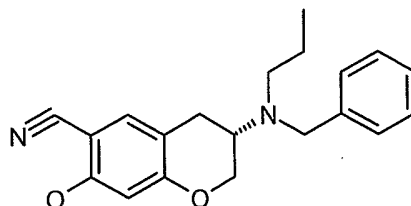
LRMS : m/z ES^+ 424 $[\text{MH}]^+$

ES^- 422 $[\text{M}-\text{H}]$

5

Preparation 51

(S)-3-[Benzyl(propyl)amino]-7-hydroxy chroman-6-carbonitrile



The compound from preparation 50 (6.5g, 15.4 mmol) zinc cyanide (1.26g, 10.76 mmol),
 10 tris(dibenzylideneacetone)dipalladium(0) (883mg, 1.53mmol) and 1,1'-bis(diphenylphosphino)ferrocene
 (1.7g, 3.07mmol) in N,N-dimethylformamide (80ml) was heated at 100°C for 18 hours. The mixture was
 allowed to cool and evaporated under reduced pressure. The residue was azeotroped with toluene (x2),
 and partitioned between H_2O (2x100ml) and Et_2O (4x250ml), organics combined, dried over MgSO_4 ,
 filtered and the solvent removed *in vacuo*. The crude material was dissolved in toluene and purified by
 15 column chromatography on silica gel using an elution gradient of ethyl acetate:pentane (10:90 to 40:60).
 Product containing fractions were evaporated & triturated with 50% EtOAc/pentane to give a pale green
 solid (3.2g)

t.l.c 20% EtOAc/pentane R_f =0.45

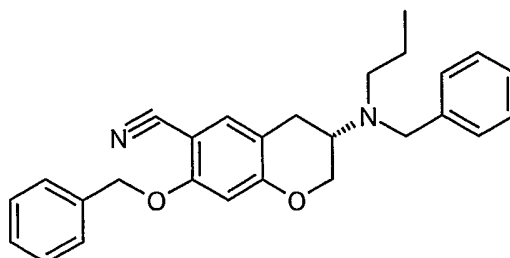
$[\alpha]_D = +124.90$ ($c = 2.6\text{mg/ml}$ in methanol)

20 ^1H NMR (CD_3OD , 400MHz) δ : 0.85 (t, 3H), 1.41-1.54 (m, 2H), 2.50-2.63 (m, 2H), 2.82 (d, 2H), 3.07-3.16
 (m, 1H), 3.75 (s, 2H), 3.94-4.00 (m, 1H), 4.25-4.33 (m, 1H), 6.28 (s, 1H), 7.16-7.26 (m, 6H)

LRMS : m/z APCI^+ 323 $[\text{MH}]^+$

Preparation 52

25 (S)-N-benzyl-N-(6-carbonitrile-7-benzyloxy-3,4-dihydro-2H-chromen-3-yl)-N-propylamine



The material from preparation 51 (3.2g, 9.9mmol) was dissolved in dimethylformamide (140ml) with
 potassium carbonate (2.06mg, 14.9mmol) to which was added benzyl bromide (1.24ml, 10.4mmol) and
 the reaction mixture was heated to 60°C for 2h under nitrogen. The reaction mixture was concentrated *in*
 30 *vacuo* and the residue separated between diethylether (2x300ml) and water (300ml), the combined
 organic layers were dried over MgSO_4 and concentrated *in vacuo* and azeotroped x2 with toluene to give

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a green oil. The residue was purified by column chromatography on silica with a gradient elution from 100% pentane to ethyl acetate:pentane 1:5 to give the product as a pale oil 4.05g.

^1H NMR ($\text{d}_6\text{-DMSO}$, 400MHz) δ : 0.76(t, 3H), 1.30-1.42 (m, 2H), 2.41-2.53 (m, 2H), 2.79 (d, 2H), 2.96-3.07 (m, 1H), 3.67 (s, 2H), 3.97-4.07 (m, 1H), 4.24-4.32 (dd, 1H), 5.18 (s, 2H), 6.63 (s, 1H), 7.15-7.47 (m, 11H).

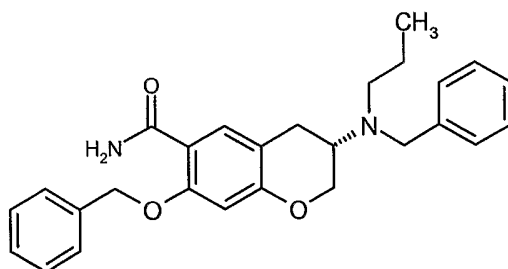
LRMS : m/z APCI $^+$ 413 [MH] $^+$

TLC 10% EtOAc/pentane Rf=0.4

$[\alpha]_D = +46.44$ (c = 4mg/ml in methanol)

10 Preparation 53

(S)-N-benzyl-N-(6-carboxamide-7-benzyloxy-3,4-dihydro-2H-chromen-3-yl)-N-propylamine



A mixture of the material from preparation 52 (4.05g, 9.8 mmol) and potassium hydroxide (3.3g, 59mmol) in 2-methyl-2-propanol (75ml) was heated under reflux for 18 hours. The cooled reaction mixture was evaporated under reduced pressure and the residue partitioned between EtOAc (2x300ml) and water (300ml). The layers were separated, the organic phase dried (MgSO_4), and evaporated under reduced pressure. The crude material was dissolved in toluene and purified by column chromatography on silica gel using an elution gradient of ethyl acetate:pentane (10:90 to 60:40). Product containing fractions were evaporated to give a white solid (2.95g).

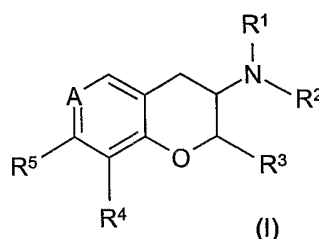
TLC 20% EtOAc/pentane Rf=0.05

^1H NMR (CD_3OD , 400MHz) δ : 0.85(t, 3H), 1.42-1.54 (m, 2H), 2.50-2.63 (m, 2H), 2.87 (d, 2H), 3.09-3.17 (m, 1H), 3.76 (s, 2H), 3.93-4.01 (m, 1H), 4.27-4.33 (dd, 1H), 5.17 (s, 2H), 6.56 (s, 1H), 7.17-7.48 (m, 10H), 7.76 (s, 1H)

LRMS : m/z APCI $^+$ 431 [MH] $^+$

Claims

1. A compound of formula (I)



wherein:

A is C-R⁶;

R¹ is selected from H, (C₁-C₆)alkyl and (C₃-C₈)cyclic alkyl;

- 10 R² is selected from (C₁-C₆)alkyl and (C₃-C₈)cyclic alkyl, wherein said (C₁-C₆)alkyl is optionally substituted by phenyl or Het;

R³ is selected from H or (C₁-C₆)alkyl;

R⁴ is selected from H, CN, O(C₁-C₆)alkyl, C(O)NH₂, Cl, F and (C₁-C₆)alkyl, wherein said (C₁-C₆)alkyl is optionally substituted by OH;

- 15 R⁵ is selected from H, OH, O(C₁-C₆)alkyl, C(O)NH₂, CN, NH₂ and Het;

R⁶ is selected from H, (C₁-C₆)alkyl, C(O)NH₂, CN, Cl, F, and Het, wherein said (C₁-C₆)alkyl is optionally substituted by OH or NH₂;

wherein Het is a 5 or 6 membered aromatic heterocycle, containing 1 to 3 heteroatoms, each
20 independently selected from N, O and S, wherein said heterocycle is optionally substituted by 1 to 3 (C₁-C₆)alkyl groups;

wherein phenyl is optionally substituted by 1 to 5 groups independently selected from (C₁-C₆)alkyl, O(C₁-C₆)alkyl, Cl or F;

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and pharmaceutically acceptable salts, solvates and prodrugs thereof;

with the provisos that:

- a) R⁴, R⁵ and R⁶ cannot all simultaneously represent H;
- b) when R³, R⁵ and R⁶ are H then R⁴ cannot be OCH₃;
- 30 c) when R³, R⁴ and R⁶ are H then R⁵ cannot be OCH₃;
- d) when R³, R⁴ and R⁵ are H then R⁶ cannot be CH₃;
- e) when R¹ and R² are n-propyl, R³ is H, R⁴ is H and R⁵ is H then R⁶ cannot be C(O)NH₂;
- f) when R¹ and R² are n-propyl, R³ is H, R⁴ and R⁵ are OCH₃ then R⁶ cannot be H;
- g) when R¹, R³ and R⁵ are H, R² and R⁴ are CH₃ then R⁶ cannot be CH₃;
- 35 h) when R¹ and R² are n-propyl, R³ is H, R⁴ is H and R⁵ is H then R⁶ cannot be CH₂OH;
- i) when R¹ and R² are n-propyl, R³ is H, R⁴ is H and R⁶ is H then R⁵ cannot be OH; and

j) when R¹ is H, R² is ethyl, R³ is H, R⁴ is H and R⁵ is H then R⁶ cannot be Cl.

2. A compound according to claim 1 wherein R³ is H, and pharmaceutically acceptable salts, solvates and prodrugs thereof.

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3. A compound according to claims 1 or 2 wherein:

R¹ is selected from H, methyl, ethyl and propyl;

R² is (C₁-C₆)alkyl, wherein said (C₁-C₆)alkyl is optionally substituted by phenyl;

R⁴ is selected from H, CN, Cl and F;

10 R⁵ is selected from H, OH, C(O)NH₂, CN, and NH₂;

R⁶ is selected from H, C(O)NH₂, CN and Het;

and pharmaceutically acceptable salts, solvates and prodrugs thereof.

4. A compound according to claims 1 or 2 selected from:

15 (3S)-3-(diethylamino)chromane-6-carboxamide;

(3S)-3-[ethyl(propyl)amino]chromane-6-carboxamide;

(3S)-3-[ethyl(propyl)amino]chromane-6-carbonitrile;

3-(dipropylamino)chromane-6-carbonitrile;

7-hydroxy-3-(propylamino)chromane-6-carboxamide;

20 3-[ethyl(propyl)amino]-7-hydroxychromane-6-carboxamide;

3-(dipropylamino)-7-hydroxychromane-6-carboxamide;

(3S)-3-(dipropylamino)chromane-7-carboxamide;

3-(dipropylamino)-8-fluorochromane-6-carboxamide; and

(3S)-N-ethyl-6-(1H-imidazol-2-yl)-N-propylchroman-3-amine;

25 and pharmaceutically acceptable salts, solvates and prodrugs thereof.

5. A compound according to any of claims 1 to 4, or a pharmaceutically acceptable salt, solvate or prodrug thereof, for use as a medicament.

30 6. A compound according to any of claims 1 to 4, or a pharmaceutically acceptable salt, solvate or prodrug thereof, for use as a medicament in the treatment or prevention of a disease or condition mediated by the dopamine D3 receptor.

7. The use of a compound according to any of claims 1 to 4, or a pharmaceutically acceptable salt, solvate or prodrug thereof, without proviso, in the preparation of a medicament for the treatment or prevention of sexual dysfunction.

8. The use according to claim 7 wherein the sexual dysfunction is male erectile dysfunction.

40 9. The use according to claim 7 wherein the sexual dysfunction is female sexual dysfunction.

10. The use according to claim 9 wherein the female sexual dysfunction is selected from hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder or sexual pain disorder.

11. The use of a compound according to any of claims 1 to 4, or a pharmaceutically acceptable salt, solvate or prodrug thereof, in the preparation of a medicament for the treatment of depression or psychiatric disorders.

12. The use of a compound according to any of claims 1 to 4, or a pharmaceutically acceptable salt, solvate or prodrug thereof, in the preparation of a medicament for the treatment or prevention of neurodegeneration.

13. The use of a compound according to any of claims 1 to 4, or a pharmaceutically acceptable salt, solvate or prodrug thereof, without proviso, in the preparation of a medicament for the treatment or prevention of pain.

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14. A method for treating or preventing a condition, disease or disorder selected from male sexual dysfunction, female sexual dysfunction, neurodegeneration, depression or psychiatric disorders, and pain, which comprises administering to a mammalian subject, including a human, in need thereof, an effective amount of a compound according to any of claims 1 to 4 or a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof.

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15. A pharmaceutical composition comprising a compound according to any of claims 1 to 4, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable diluent or carrier.

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