(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 March 2009 (19.03.2009)

PCT

(10) International Publication Number
WO 2009/034432 A2

(51) International Patent Classification:
*C07C 217/60* (2006.01) *A61K 31/137* (2006.01)
*C07C 235/34* (2006.01) *A61K 31/166* (2006.01)
*C07C 311/29* (2006.01) *A61K 31/18* (2006.01)

(21) International Application Number:
PCT/IB2008/002312

(22) International Filing Date:
1 September 2008 (01.09.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/972,282 14 September 2007 (14.09.2007) US

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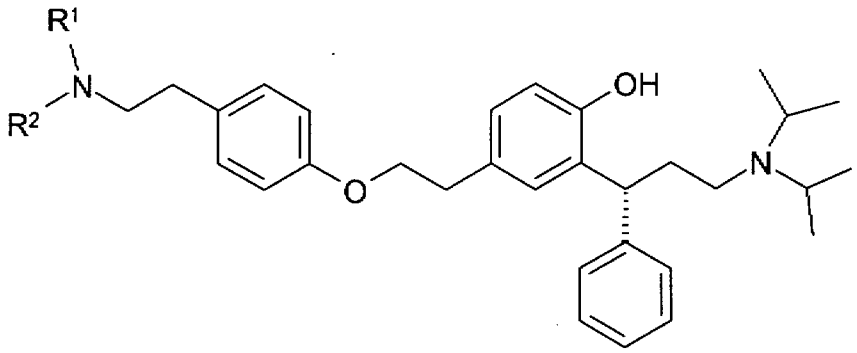
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *without international search report and to be republished upon receipt of that report*

(54) Title: NOVEL COMPOUNDS ACTIVE AS MUSCARINIC RECEPTOR ANTAGONISTS




(I)

(57) Abstract: The invention relates to compounds of formula: (I) processes and intermediates for their preparation, their use as muscarinic antagonists and pharmaceutical compositions containing them.

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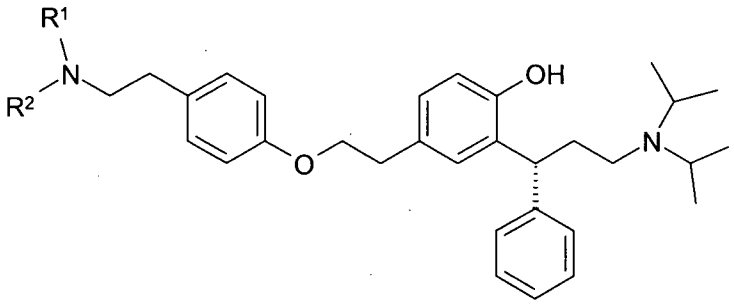
**Novel compounds active as muscarinic receptor antagonists**

This invention relates to compounds of general formula (I):



(I)

in which $R^1$ and $R^2$ have the meanings indicated below, and to processes and intermediates for the preparation of, compositions containing and the uses of such derivatives.

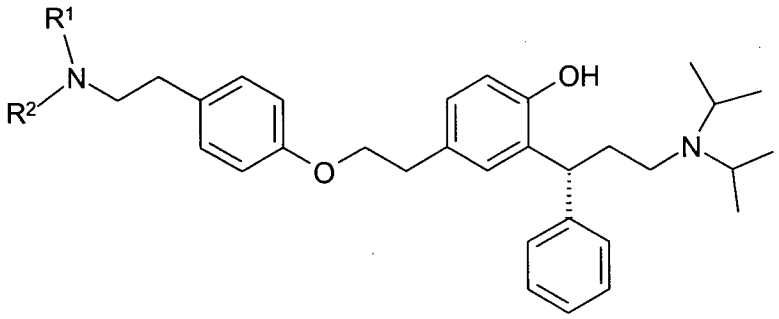
Cholinergic muscarinic receptors are members of the G-protein coupled receptor super-family and are further divided into 5 subtypes, $M_1$ to $M_5$. Muscarinic receptor sub-types are widely and differentially expressed in the body. Genes have been cloned for all 5 sub-types and of these, $M_1$, $M_2$ and $M_3$ receptors have been extensively pharmacologically characterized in animal and human tissue. $M_1$ receptors are expressed in the brain (cortex and hippocampus), glands and in the ganglia of sympathetic and parasympathetic nerves. $M_2$ receptors are expressed in the heart, hindbrain, smooth muscle and in the synapses of the autonomic nervous system. $M_3$ receptors are expressed in the brain, glands and smooth muscle. In the airways, stimulation of $M_3$ receptors evokes contraction of airway smooth muscle leading to bronchoconstriction, while in the salivary gland $M_3$ receptor stimulation increases fluid and mucus secretion leading to increased salivation. $M_2$ receptors expressed on smooth muscle are understood to be pro-contractile while pre-synaptic $M_2$ receptors modulate acetylcholine release from parasympathetic nerves. Stimulation of $M_2$ receptors expressed in the heart produces bradycardia.

Short and long-acting muscarinic antagonists are used in the management of asthma and COPD; these include the short acting agents Atrovent® (ipratropium bromide) and Oxivent® (oxitropium bromide) and the long acting agent Spiriva® (tiotropium bromide). These compounds produce bronchodilation following inhaled administration. In addition to improvements in spirometric values, anti-muscarinic use in chronic obstructive pulmonary disease (COPD) is associated with improvements in health status and quality of life scores.

As a consequence of the wide distribution of muscarinic receptors in the body, significant systemic exposure to muscarinic antagonists is associated with effects such as dry mouth, constipation, mydriasis, urinary retention (all predominantly mediated via blockade of $M_3$ receptors) and tachycardia (mediated by blockade of $M_2$ receptors). A commonly reported side-effect following inhaled administration of therapeutic dose of the current, clinically used non-selective muscarinic antagonists is dry-mouth and while this is reported as only mild in intensity it does limit the dose of inhaled agent given.

Accordingly, there is still a need for improved $M_3$ receptor antagonists that would have an appropriate pharmacological profile, for example in term of potency, pharmacokinetics or duration of action. In this context, the present invention relates to novel $M_3$ receptor antagonists. In particular, there is a need for $M_3$ receptor antagonists that would have a pharmacological profile suitable for an administration by the inhalation route.

The invention relates to a compound of formula (I)



(I)

wherein,

- $R^1$ is H or $C_1$-$C_4$ alkyl;
- $R^2$ is $C_1$-$C_4$ alkyl or a group –X-$R^3$;
- X is a bond, -$CH_2$-, -$SO_2$-, -C(=O)-, or -C(=O)-$CH_2$-;
- $R^3$ is $C_3$-$C_{10}$ cycloalkyl, 2 carbon atoms or more of said cycloalkyl being optionally bridged by one or more carbon atoms, or aryl, said cycloalkyl and aryl being optionally substituted with 1, 2 or 3 groups independently selected from hydroxy, halo, cyano, $C_1$-$C_4$ alkyl, O-($C_1$-$C_4$)alkyl or S-($C_1$-$C_4$)alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

In the here above general formula (I), ($C_1$-$C_4$)alkyl denotes a straight-chain or branched group containing 1, 2, 3 or, 4 carbon atoms. This also applies if they carry substituents or occur as substituents of other radicals, for example in O-($C_1$-$C_4$)alkyl radicals, S-($C_1$-$C_4$)alkyl radicals etc... . Examples of suitable ($C_1$-$C_4$)alkyl radicals are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl.... Examples of suitable O-($C_1$-$C_4$)alkyl radicals are methoxy, ethoxy, *n*-propyloxy, *iso*-propyloxy, *n*-butyloxy, *iso*-butyloxy, *sec*-butyloxy and *tert*-butyloxy...

Preferred $C_3$-$C_{10}$ cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and adamantyl.

Halo denotes a halogen atom selected from the group consisting of fluoro, chloro, bromo and iodo. Preferred halo groups are fluoro or chloro.

Preferred aryl groups are phenyl and naphthyl.

In the above compounds of formula (I), the following definitions and combinations of such definitions are preferred:

Preferably, $R^1$ is H or methyl.

Preferably, $R^2$ is methyl or $-X-R^3$.

Preferably, $R^2$ is $-X-R^3$.

Preferably, $R^3$ is unsubstituted $C_3$-$C_{10}$ cycloalkyl or phenyl optionally substituted with 1, 2 or 3 groups independently selected from hydroxy, halo, cyano, $C_1$-$C_4$ alkyl, O-($C_1$-$C_4$)alkyl or S-($C_1$-$C_4$)alkyl.

Preferably, $R^3$ is unsubstituted $C_3$-$C_{10}$ cycloalkyl or phenyl optionally substituted with 1, 2 or 3 groups independently selected from hydroxy, halo, cyano, methyl or methoxy.

Preferably, $R^3$ is phenyl substituted with OH and optionally substituted with 1 or 2 groups selected from F or Cl.

Preferably, X is $-CH_2-$ or -C(=O)-.

Preferred compounds according to the invention are:

3-Chloro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-4-hydroxy-benzamide;

2-(3-Chloro-4-hydroxy-phenyl)-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-acetamide;

Cyclopentanecarboxylic acid [2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-amide;

2-Cyclopropyl-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-acetamide;

N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-3-fluoro-4-hydroxy-benzamide;

(3S,5S,7S)-N-{2-[4-(2-{3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxyphenyl}ethoxy)phenyl]ethyl}adamantane-1-carboxamide;

2-Chloro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-4-hydroxy-benzamide;

2-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-{2-[4-(2-dimethylamino-ethyl)-phenoxy]-ethyl}-phenol;

4-{2-[4-(2-Benzylamino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol;

4-(2-{4-[2-(3-Chloro-benzylamino)-ethyl]-phenoxy}-ethyl)-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol;

4-{2-[4-(2-Cyclohexylamino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol;

2-chloro-4-[({2-[4-(2-{3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxyphenyl}ethoxy)phenyl]ethyl}amino)methyl]phenol;

2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-[2-(4-{2-[(3-fluoro-4-hydroxybenzyl)amino]ethyl}phenoxy)ethyl]phenol;

2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-[2-(4-{2-[(3-fluoro-2-hydroxybenzyl)amino]ethyl}phenoxy)ethyl]phenol;

4-{[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-2,6-difluoro-phenol;

2,6-Dichloro-4-{[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-phenol;

2-chloro-3-[({2-[4-(2-{3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxyphenyl}ethoxy)phenyl]ethyl}amino)methyl]phenol;

2-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-(2-{4-[2-(3-hydroxy-benzylamino)-ethyl]-phenoxy}-ethyl)-phenol;

3-[({2-[4-(2-{3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxyphenyl}ethoxy)phenyl]ethyl}amino)methyl]-2-fluorophenol;

2-Chloro-4-{[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-6-fluoro-phenol;

5-{[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-benzene-1,3-diol;

2-{[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-4,6-difluoro-phenol;

2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-[2-(4-{2-[(4-fluoro-3-hydroxybenzyl)amino]ethyl}phenoxy)ethyl]phenol;

3,5-Dichloro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-4-hydroxy-benzamide;

4-Fluoro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-3-hydroxy-benzamide;

4-Hydroxy-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-benzamide;

N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-4-hydroxy-benzenesulfonamide;

N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-2-(3-fluoro-4-hydroxy-phenyl)-acetamide;

N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-2,3-difluoro-4-hydroxy-benzamide;

4-Chloro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-3-hydroxy-benzamide;

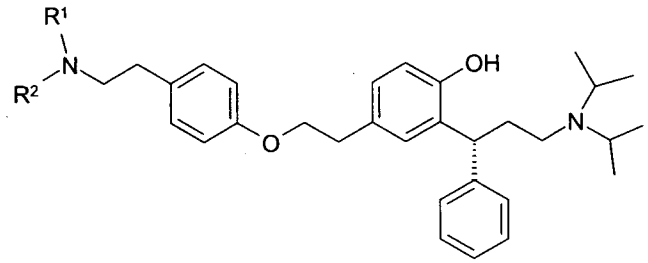
N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-2-fluoro-4-hydroxy-benzamide; and,

N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-3-hydroxy-benzamide;

or pharmaceutically acceptable salts or solvates thereof.

Compounds of formula (I) may be prepared in a variety of ways. The routes below illustrate one such way of preparing these compounds; the skilled person will appreciate that other routes may be equally as practicable.

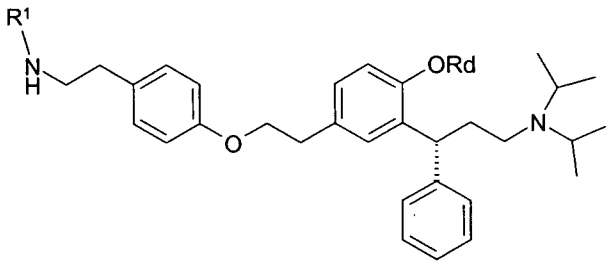
The compounds of the formula (I)



(I)

can be prepared using conventional procedures such as by the following illustrative methods in which $R^1$ and $R^2$ are as previously defined for the compounds of the formula (I) unless otherwise stated.

The amine derivative of the formula (I) may be prepared by reaction of an amine of formula (2):



(2)

wherein Rd is H or Rc,

with a carboxylic acid of formula $R^3CO_2H$ or $R^3CH_2$-$CO_2H$ a sulphonyl chloride of formula $R^3SO_2Cl$ and aldehydes/ketones of formula $R^3C(=O)H$ and $R^3=O$. Rc can be any suitable protecting group described in T. W. Greene, Protective Groups in Organic Synthesis, A. Wiley-Interscience Publication, 1981. Preferred Rc groups are substituted or unsubstituted benzyl. Where Rd is Rc, this group removed by methods described in T. W. Greene, Protective Groups in Organic Synthesis, A. Wiley-Interscience Publication, 1981. When $R^2$ contains a suitably protected phenol, compounds are deprotected to provide the corresponding phenols of formula (I). Suitable protecting groups include benzyl, allyl and tert-butyldimethylsilyl (TBDMS). De-protection may be achieved using standard methodology as described in "Protecting Groups in Organic Synthesis" by T.W. Greene and P. Wutz.

A typical procedure for the formation of amide variants compounds of formula (I) involves reaction of compounds of formula (2) with a carboxylic acid. Reaction of carboxylic acids with compounds of formula (2) involves stirring compounds of formula (2) and the carboxylic acid

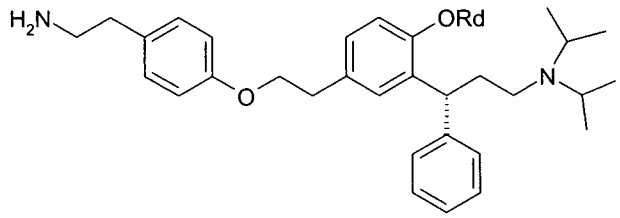
in the presence of a suitable coupling agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, N,N'-carbonyldiimidazole, N,N'-dicyclohexylcarbodiimide, optionally in the presence of a catalyst such as 1-hydroxybenzotriazole hydrate or 1-hydroxy-7-azabenzotriazole, and optionally in the presence of a tertiary amine base such as N-methylmorpholine, triethylamine or N,N-diisopropylethylamine, in a suitable solvent such as dichloromethane, N,N-dimethylformamide, tetrahydrofuran or dimethylsulfoxide, under ambient conditions for 1-48 hours. Alternative methods for the preparation of amido variants of (I) will be obvious to those skilled in the art and include the use of derivatives such as acyl chlorides or acyl fluorides.

A typical procedure for the formation of sulphonamide variants of compounds of formula (I) involves reaction of compounds of formula (2) with a sulphonyl chloride. Reaction of sulphonyl chlorides with compounds of formula (2) involves stirring compounds of formula (2) and the sulphonyl chloride optionally in the presence of pyridine or a tertiary amine base such a triethylamine in suitable solvent such as dichloromethane or tetrahydrofuran at 0°C to 50°C for 1 to 24 hours.

A typical procedure for the formation of amine variants of compounds of formula (I) involves reaction of compounds of formula (2) with an aldehyde or ketone. Reaction of an aldehyde/ketone with compounds of formula (2) involves stirring compounds of formula (2) in the presence of the aldehyde/ketone for 1-4 hours in an inert solvent such as dichloromethane, tetrahydrofuran or N'N'-dimethylformamide, optionally in the presence of a dehydrating agent such as magnesium sulphate and a weak acid such as acetic acid. A reducing agent such as sodium borohydride, sodium triacetoxyborohydride or hydrogen gas and a palladium catalyst is then added and the reaction stirred for 1 to 24 hours at 0°C to 80°C.

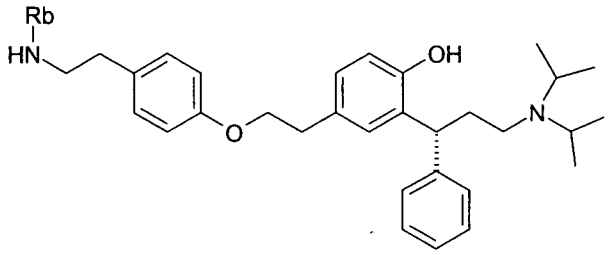
An alternative procedure for the formation of amine variants of compounds of formula (I) involves the reduction of amide variants of compounds of formula (I). A typical procedure for the reduction of an amide to an amine would involve stirring compounds of formula (I) in an inert solvent such as diethylether or tetrahydrofuran with lithium aluminium hydride or borane for 1 to 24 hours at 0°C to 80°C.

When $R^1$ is not H, compounds of formula (2) may be prepared by reactions of compounds of formula (3) with aldehydes/ketones in the presence of a reducing agent or alternatively via formation of an amide and reduction to the corresponding amine according to typical procedures outlined above for compounds of formula (I).




(3)

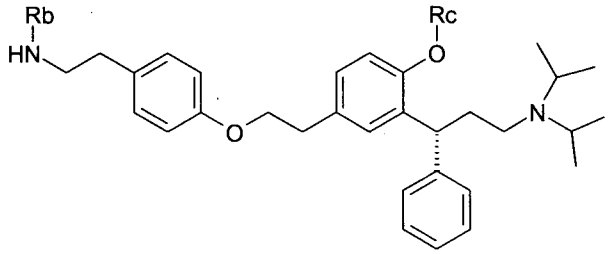
Compounds of formula (3) are prepared by removal of group Rb from compounds of formula (4) or removal of Rb from compounds of formula (5). Rd is H or Rc respectively.



(4)

Rb can be any suitable protecting group described in T. W. Greene, Protective Groups in Organic Synthesis, A. Wiley-Interscience Publication, 1981. Preferred groups include BOC and CBz. Typical procedures for the removal of the Rb protecting group can be found in the text book T. W. Greene, Protective Groups in Organic Synthesis, A. Wiley-Interscience Publication, 1981.

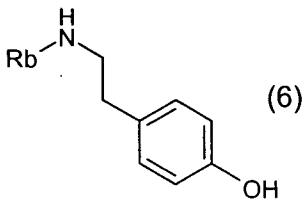
Compounds of formula (4) can be derived from compounds of formula (5)



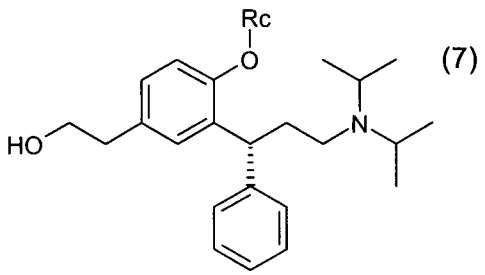
(5)

by removal of the Rc group. Rc can be any suitable protecting group described in T. W. Greene, Protective Groups in Organic Synthesis, A. Wiley-Interscience Publication, 1981. Preferred Rc groups are substituted or unsubstituted benzyl. Typical procedures for the removal of the Rc protecting group can be found in the text book T. W. Greene, Protective Groups in Organic Synthesis, A. Wiley-Interscience Publication, 1981.

Compounds of formula (5) may be derived from the reaction of a compound of formula (6) with a compound of formula (7):



(6)



(7)

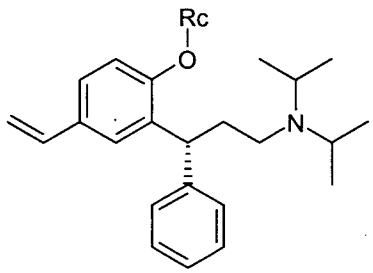
In a typical procedure, the compound of formula (7) is first converted to a halide (e.g. bromide, chloride, iodide) or sulphonate (e.g. mesylate) using standard procedures (e.g. triphenylphospine/iodine; triphenylphosphine/carbon tetrabromide; thionyl chloride; methanesulphonyl chloride/triethylamine) in the presence of a solvent or mixture of solvents (e.g. dimethyl sulphoxide, dichloromethane, toluene, *N*,*N*-dimethylformamide, propionitrile,

acetonitrile). This product is then reacted with the compound of formula (6) in the presence of a solvent or mixture of solvents (e.g. dimethyl sulphoxide, toluene, *N*,*N*-dimethylformamide, acetonitrile, tetrahydrofuran) optionally in the presence of a suitable base (e.g. triethylamine, diisopropylethylamine, potassium carbonate, potassium hydrogen carbonate) at a temperature comprised between 60°C and 120°C, for 4 to 48 hours.

Alternatively, a Mitsunobu protocol may be employed (e.g. diethylazodicarboxylate/ triphenylphosphine) in the presence of a solvent or mixture of solvents (e.g. toluene, acetonitrile, tetrahydrofuran) at a temperature comprised between 25°C and 60°C, for 2 to 4 hours.

Compounds of formula (6) are either commercially available or derived from commercial materials by methods described in the literature.

The compound of formula (7) can be formed from an alkene of formula (8):

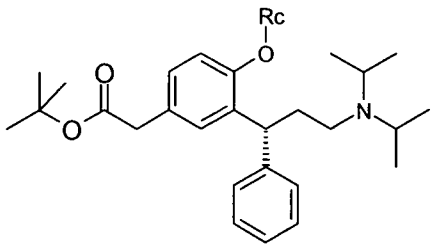



(8)

by reaction with a boronating agent (e.g. borane, 9-Borabicyclo[3.3.1]nonane) in the presence of a suitable solvent (e.g. tetrahydrofuran) at a temperature comprised between 60°C and 100°C for 4 to 24 hours. Followed by oxidation with hydrogen peroxide in a suitable solvent or mixture of solvents (e.g. water, methanol, tetrahydrofuran) with a suitable base (e.g. sodium hydroxide).

The alkene of formula (8) may be formed from the aryl bromide (10) by reaction with a suitable vinyl compound (e.g. vinyltributylstannane; potassium vinyltetrafluoroborate; 2,4,6-trivinylcycloboroxane pyridine complex). In a typical procedure, the aryl halide (10) and the vinyl compound are reacted in the presence of a suitable palladium catalyst (e.g. palladium acetate/ tri-*ortho*-tolylphosphine of formula $Pd(OAc)_2/\{P(o\text{-}Tol)_3\}_2$), in the presence of a solvent or mixture of solvents (e.g. toluene, acetonitrile, hexane) and in the presence of a base (e.g. triethylamine, diisopropylethylamine, potassium carbonate, potassium hydrogen carbonate). Preferably, the reaction is carried out at a temperature comprised between 70°C and 110°C for 4 to 16 hours.

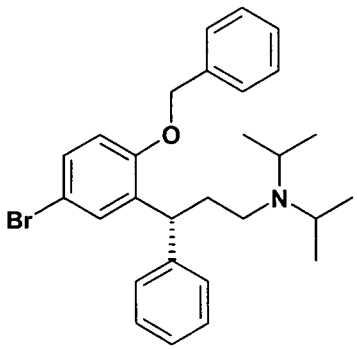
Alternatively, the compound of formula (7) can be formed from an ester of formula (9):




(9)

by reaction with a reducing agent (e.g. lithium aluminium hydride, lithium borohydride) in the presence of a suitable solvent (e.g. tetrahydrofuran) at a temperature comprised between 0°C and 100°C for 4 to 24 hours.

The ester of formula (9) may be formed from the aryl bromide of formula (10) as described by reaction with an anion of tert-butylacetate under palladium catalysis. In a typical procedure, the aryl halide (10) and the ester anion are reacted in the presence of a suitable palladium catalyst (e.g. palladium dibenzylidene acetate or palladium acetate/ tri-*ortho*-tolylphosphine of formula $Pd(OAc)_2/\{P(o\text{-}Tol)_3\}_2$) in the presence of a solvent or mixture of solvents (e.g. toluene, acetonitrile, hexane), and in the presence of a base (e.g. triethylamine, diisopropylethylamine, potassium carbonate, potassium hydrogen carbonate, lithium hexamethyldisilazide). Preferably, the reaction is carried out at a temperature comprised between 0°C and 110°C for 4 to 16 hours.




(10)

The aryl bromide of formula (10) may be prepared according to the method described in WO 1994/11337.

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

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, 1,5-naphtalene disulfonate, 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.

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).

Pharmaceutically acceptable salts of compounds of formula (I) may be prepared by one or more of three methods:

(i) by reacting the compound of formula (I) with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of formula (I) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterised by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterised by a phase change, typically first order ('melting point').

The compounds of the invention may also exist in unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

Also included within the scope of the invention are multi-component complexes (other than salts and solvates) wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallisation, by recrystallisation from solvents, or by physically grinding the components together - see Chem Commun, 17, 1889-1896, by O. Almarsson and M. J. Zaworotko (2004). For a general review of multi-component complexes, see J Pharm Sci, 64 (8), 1269-1288, by Haleblian (August 1975).

The compounds of the invention may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as -$COO^-Na^+$, -$COO^-K^+$, or -$SO_3^-Na^+$) or non-ionic (such as -$N^+(CH_3)_3$) polar head group. For more information, see Crystals and the Polarizing Microscope by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970).

Hereinafter all references to compounds of formula (I) include references to salts, solvates, multi-component complexes and liquid crystals thereof and to solvates, multi-component complexes and liquid crystals of salts thereof.

The compounds of the invention include compounds of formula (I) as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula (I).

As indicated, so-called 'prodrugs' of the compounds of formula (I) are also within the scope of the invention. Thus certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (Ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include

(i) where the compound of formula (I) contains a carboxylic acid functionality (-COOH), an ester thereof, for example, a compound wherein the hydrogen of the carboxylic acid functionality of the compound of formula (I) is replaced by ($C_1$-$C_8$)alkyl;

(ii) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, for example, a compound wherein the hydrogen of the alcohol functionality of the compound of formula (I) is replaced by ($C_1$-$C_6$)alkanoyloxymethyl; and

(iii) where the compound of formula (I) contains a primary or secondary amino functionality (-$NH_2$ or -NHR where R ≠ H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound of formula (I) is/are replaced by ($C_1$-$C_{10}$)alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Moreover, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula I.

Also included within the scope of the invention are metabolites of compounds of formula I, that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the invention include

(i) where the compound of formula (I) contains a methyl group, an hydroxymethyl derivative thereof ($-CH_3$ -> $-CH_2OH$):

(ii) where the compound of formula (I) contains an alkoxy group, an hydroxy derivative thereof (-OR -> -OH);

(iii) where the compound of formula (I) contains a tertiary amino group, a secondary amino derivative thereof ($-NR^1R^2$ -> $-NHR^1$ or $-NHR^2$);

(iv) where the compound of formula (I) contains a secondary amino group, a primary derivative thereof ($-NHR^1$ -> $-NH_2$);

(v) where the compound of formula (I) contains a phenyl moiety, a phenol derivative thereof (-Ph -> -PhOH); and

(vi) where the compound of formula (I) contains an amide group, a carboxylic acid derivative thereof ($-CONH_2$ -> COOH).

Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric *cis/trans* (or Z/E) isomers are possible. Where structural isomers are interconvertible *via* a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula (I) containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula I, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, *d*-lactate or *l*-lysine, or racemic, for example, *dl*-tartrate or *dl*-arginine.

*Cis/trans* isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I)

contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

When any racemate crystallises, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.

While both of the crystal forms present in a racemic mixture have identical physical properties, they may have different physical properties compared to the true racemate. Racemic mixtures may be separated by conventional techniques known to those skilled in the art - see, for example, Stereochemistry of Organic Compounds by E. L. Eliel and S. H. Wilen (Wiley, 1994).

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as $^{2}H$ and $^{3}H$, carbon, such as $^{11}C$, $^{13}C$ and $^{14}C$, chlorine, such as $^{36}Cl$, fluorine, such as $^{18}F$, iodine, such as $^{123}I$ and $^{125}I$, nitrogen, such as $^{13}N$ and $^{15}N$, oxygen, such as $^{15}O$, $^{17}O$ and $^{18}O$, phosphorus, such as $^{32}P$, and sulphur, such as $^{35}S$.

Certain isotopically-labelled compounds of formula I, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* $^{3}H$, and carbon-14, *i.e.* $^{14}C$, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* $^{2}H$, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as $^{11}C$, $^{18}F$, $^{15}O$ and $^{13}N$, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* $D_2O$, $d_6$-acetone, $d_6$-DMSO.

The compounds of formula (I) should be assessed for their biopharmaceutical properties, such as solubility and solution stability (across pH), permeability, *etc.*, in order to select the most appropriate dosage form and route of administration for treatment of the proposed indication.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in Remington's Pharmaceutical Sciences, 19th Edition (Mack Publishing Company, 1995).

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, and/or buccal, lingual, or sublingual administration by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid, semi-solid and liquid systems such as 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.

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).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active

agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in Pharmaceutical Dosage Forms: Tablets, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellable 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.

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

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Pharmaceutical Technology On-line, 25(2), 1-14, by Verma *et al* (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a suspension or as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and semi-solids and suspensions comprising drug-loaded poly(*dl*-lactic-coglycolic)acid (PGLA) microspheres.

The compounds of the invention may also be administered topically, (intra)dermally, or transdermally to the skin or mucosa. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection.

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

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form 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 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 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 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 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.

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.

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-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by a prefilled capsule, blister or pocket or by a system that utilises a gravimetrically fed dosing chamber. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1 to 5000 µg of (compound name here), or a salt thereof. The overall daily dose will typically be in the range 1 µg to 20 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of formula (I) are particularly suitable for an administration by inhalation

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 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 programmed release.

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, gels, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for
example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.
Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Inasmuch as it may 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.

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 0.001mg to 5000mg depending, of course, on the mode of administration. For example, oral administration may require a total daily dose of from 0.1mg to 1000mg, while an intravenous dose may only require from 0.001mg to 100mg. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein.

These dosages are based on an average human subject having a weight of about 60kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

For the avoidance of doubt, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

The compounds of formula (I) have the ability to interact with muscarinic receptors and thereby have a wide range of therapeutic applications, as described further below, because of the essential role which muscarinic receptors play in the physiology of all mammals.

Thus the invention relates to the use of the compounds of formula (I) for the manufacture of a medicament for the treatment or the prevention of diseases, disorders, and conditions in which the M3 receptor is involved. The invention further relates to a method of treatment of a mammal, including a human being, with a M3 antagonist including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, derived form or composition thereof.

Therefore, a further aspect of the present invention relates to the compounds of formula (I), or pharmaceutically acceptable salts, derived forms or compositions thereof, for use in the treatment of diseases, disorders, and conditions in which muscarinic receptors are involved. Examples of such diseases, disorders, and conditions are Inflammatory Bowel Disease, Irritable Bowel Disease, diverticular disease, motion sickness, gastric ulcers,

radiological examination of the bowel, symptomatic treatment of BPH (benign prostatic hyperplasia), NSAID induced gastric ulceration, urinary incontinence (including urgency, frequency, urge incontinence, overactive bladder, nocturia and lower urinary tract symptoms), cycloplegia, mydriatics, parkinsons disease.

More specifically, the present invention also concerns the compounds of formula (I), or pharmaceutically acceptable salts, derived forms or compositions thereof, for use in the treatment of diseases, disorders, and conditions selected from the group consisting of :

- chronic or acute bronchoconstriction, chronic bronchitis, small airways obstruction, and emphysema,
- obstructive or inflammatory airways diseases of whatever type, etiology, or pathogenesis, in particular an obstructive or inflammatory airways disease that is a member selected from the group consisting of chronic eosinophilic pneumonia, chronic obstructive pulmonary disease (COPD), COPD that includes chronic bronchitis, pulmonary emphysema or dyspnea associated or not associated with COPD, COPD that is characterized by irreversible, progressive airways obstruction, adult respiratory distress syndrome (ARDS), exacerbation of airways hyper-reactivity consequent to other drug therapy and airways disease that is associated with pulmonary hypertension,
- bronchitis of whatever type, etiology, or pathogenesis, in particular bronchitis that is a member selected from the group consisting of acute bronchitis, acute laryngotracheal bronchitis, arachidic bronchitis, catarrhal bronchitis, croupus bronchitis, dry bronchitis, infectious asthmatic bronchitis, productive bronchitis, staphylococcus or streptococcal bronchitis and vesicular bronchitis,
- asthma of whatever type, etiology, or pathogenesis, in particular asthma that is a member selected from the group consisting of atopic asthma, non-atopic asthma, allergic asthma, atopic bronchial IgE-mediated asthma, bronchial asthma, essential asthma, true asthma, intrinsic asthma caused by pathophysiologic disturbances, extrinsic asthma caused by environmental factors, essential asthma of unknown or inapparent cause, non-atopic asthma, bronchitic asthma, emphysematous asthma, exercise-induced asthma, allergen induced asthma, cold air induced asthma, occupational asthma, infective asthma caused by bacterial, fungal, protozoal, or viral infection, non-allergic asthma, incipient asthma, wheezy infant syndrome and bronchiolytis,
- acute lung injury,
- bronchiectasis of whatever type, etiology, or pathogenesis, in particular bronchiectasis that is a member selected from the group consisting of cylindric bronchiectasis, sacculated bronchiectasis, fusiform bronchiectasis, capillary bronchiectasis, cystic bronchiectasis, dry bronchiectasis and follicular bronchiectasis.

More specifically, the present invention also concerns the compounds of formula (I), or pharmaceutically acceptable salts, derived forms or compositions thereof, for use in the treatment of COPD or asthma.

Suitable examples of other therapeutic agents which may be used in combination with the compound(s) of formula (I), or pharmaceutically acceptable salts, derived forms or compositions thereof, include, but are by no means limited to:

(a) 5-Lipoxygenase (5-LO) inhibitors or 5-lipoxygenase activating protein (FLAP) antagonists,

(b) Leukotriene antagonists (LTRAs) including antagonists of $LTB_4$, $LTC_4$, $LTD_4$, and $LTE_4$,

(c) Histamine receptor antagonists including H1 and H3 antagonists,

(d) $\alpha_1$- and $\alpha_2$-adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use.

(e) PDE inhibitors, e.g. PDE3, PDE4 and PDE5 inhibitors,

(f) Beta 2 receptor agonists,

(g) Dual compounds active as $\beta_2$ agonists and muscarinic M3 receptor antagonists

(h) Theophylline,

(i) Sodium cromoglycate,

(j) COX inhibitors both non-selective and selective COX-1 or COX-2 inhibitors (NSAIDs),

(k) Prostaglandin receptor antagonists and inhibitors of prostaglandin synthase.

(l) Oral and inhaled glucocorticosteroids, such as Dissociated agonists of the corticoid receptor (DAGR);

(m) Monoclonal antibodies active against endogenous inflammatory entities,

(n) Anti-tumor necrosis factor (anti-TNF-$\alpha$) agents,

(o) Adhesion molecule inhibitors including VLA-4 antagonists,

(p) Kinin-$B_1$- and $B_2$-receptor antagonists,

(q) Immunosuppressive agents, including inhibitors of the IgE pathway and cyclosporine,

(r) Inhibitors of matrix metalloproteases (MMPs),

(s) Tachykinin $NK_1$, $NK_2$ and $NK_3$ receptor antagonists,

(t) Protease inhibitors such as elastase inhibitors,

(u) Adenosine A2a receptor agonists and A2b antagonists,

(v) Inhibitors of urokinase,

(w) Compounds that act on dopamine receptors, such as D2 agonists,

(x) Modulators of the NF$\kappa\beta$ pathway, such as IKK inhibitors,

(y) modulators of cytokine signalling pathyways such as p38 MAP kinase, PI3 kinase, JAK kinase, syk kinase, EGFR or MK-2,

(z) Agents that can be classed as mucolytics or anti-tussive,

(aa)Agents, which enhance responses to inhaled corticosteroids.

(bb)Antibiotics and antivral agents effective against micro-organisms which can colonise the respiratory tract,

(cc) HDAC inhibitors,

(dd)CXCR2 antagonists,

(ee) Integrin antagonists,

(ff) Chemokines,

(gg)Epithelial sodium channel (ENaC) blockers or Epithelial sodium channel (ENaC) inhibitors,

(hh) P2Y2 Agonists and other Nucleotide receptor agonists,

(ii) Inhibitors of thromboxane,

(jj) Inhibitors of $PGD_2$ synthesis and $PGD_2$ receptors (DP1 and DP2/CRTH2);

(kk)Niacin, and

(ll) Adhesion factors including VLAM, ICAM, and ELAM.

Preferred examples of other therapeutic agents which may be used in combination with the compound(s) of formula (I), or pharmaceutically acceptable salts, derived forms or compositions thereof, include:

(a) 5-Lipoxygenase (5-LO) inhibitors or 5-lipoxygenase activating protein (FLAP) antagonists,

(b) Leukotriene antagonists (LTRAs) including antagonists of $LTB_4$, $LTC_4$, $LTD_4$, and $LTE_4$,

(c) Histamine receptor antagonists including H1 and H3 antagonists,

(d) $\alpha_1$- and $\alpha_2$-adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use,

(e) short or long acting $\beta_2$ agonists,

(f) PDE inhibitors, e.g. PDE3, PDE4 and PDE5 inhibitors,

(g) Theophylline,

(h) Sodium cromoglycate,

(i) COX inhibitors both non-selective and selective COX-1 or COX-2 inhibitors (NSAIDs),

(j) Oral and inhaled glucocorticosteroids,

(k) Monoclonal antibodies active against endogenous inflammatory entities,

(l) Anti-tumor necrosis factor (anti-TNF-$\alpha$) agents,

(m) Adhesion molecule inhibitors including VLA-4 antagonists,

(n) Kinin-$B_1$- and $B_2$-receptor antagonists,

(o) Immunosuppressive agents,

(p) Inhibitors of matrix metalloproteases (MMPs),

(q) Tachykinin $NK_1$, $NK_2$ and $NK_3$ receptor antagonists,

(r) Elastase inhibitors,

(s) Adenosine A2a receptor agonists,

(t) Inhibitors of urokinase,

(u) Compounds that act on dopamine receptors, e.g. D2 agonists,

(v) Modulators of the NFκB pathway, e.g. IKK inhibitors,

(w) modulators of cytokine signalling pathyways such as p38 MAP kinase, syk kinase, or JAK kinase inhibitors,

(x) Agents that can be classed as mucolytics or anti-tussive,

(y) Antibiotics,

(z) Prostaglandin antagonists such as DP1, DP2 or CRTH2 antagonists,

(aa) HDAC inhibitors,

(bb)PI3 kinase inhibitors, and,

(cc)CXCR2 antagonists.

According to the present invention, combination of the compounds of formula (I) with :

- H3 antagonists,
- $\beta_2$ agonists,
- PDE4 inhibitors,
- steroids, especially glucocorticosteroids,
- Adenosine A2a receptor agonists,
- Modulators of cytokine signalling pathyways such as p38 MAP kinase or syk kinase, or,
- Leukotriene antagonists (LTRAs) including antagonists of $LTB_4$, $LTC_4$, $LTD_4$, and $LTE_4$,

are preferred.

According to the present invention, combination of the compounds of formula (I) with :

- glucocorticosteroids, in particular inhaled glucocorticosteroids with reduced systemic side effects, including prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide, and mometasone furoate, or
- β2 agonists including in particular salbutamol, terbutaline, bambuterol, fenoterol, salmeterol, formoterol, tulobuterol and their salts.

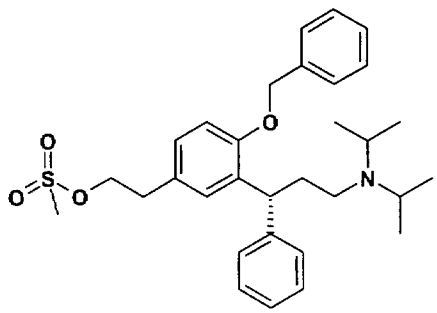
are further preferred.

The following examples illustrate the preparation of the compounds of the formula (I):

**PREPARATIONS**

Preparation 1

2-{4-(benzyloxy)-3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenyl}ethyl methanesulfonate



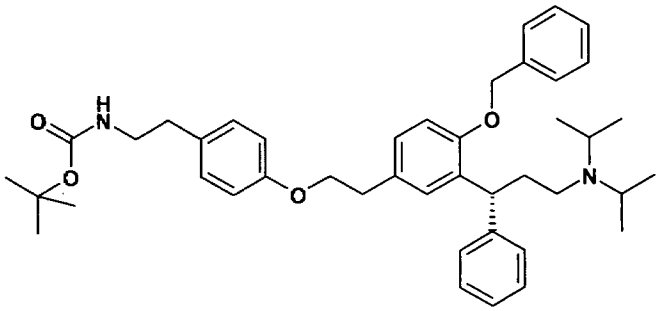
2-{4-(benzyloxy)-3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenyl}ethanol (Prepared according to WO1998/43942, 1.0g, 2.25mmol) was dissolved in dichloromethane (20ml) and N,N-diisopropyl ethylamine (1.8ml, 10mmol) added. The solution was then cooled to 0°C and

methanesulphonyl chloride (0.42ml, 5.4mmol) was added. After stirring for 2 hours at 0°C, the mixture was diluted with dichloromethane (20ml) and washed with water (50ml), brine (50ml) and then dried (magnesium sulphate) and the solvent removed *in vacuo* to yield the title compound as a yellow oil, 1.56g.

LRMS: m/z 524 [M+H]+.

Preparation 2

tert-butyl {2-[4-(2-{4-(benzyloxy)-3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenyl}ethoxy)phenyl]ethyl}carbamate

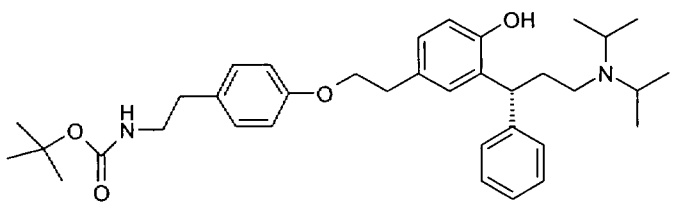


Tert-butyl [2-(4-hydroxyphenyl)ethyl]carbamate (Prepared according to WO1998/43942, 3.8g, 7.3mmol), potassium carbonate (2.6g, 8.0mmol), potassium iodide (1.1g, 7.3mmol) and 2-{4-(benzyloxy)-3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenyl}ethyl methanesulfonate (preparation 1, 1.56g, 2.98mmol) were stirred in toluene (20ml) and stirred at 120°C overnight. After cooling, water (80ml) and ethyl acetate (80ml) were added, organics separated and washed with saturated aqueous sodium hydrogen carbonate (40ml), brine (40ml) then dried (magnesium sulphate) and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (99/1/0.1 to 90/10/1.0 by volume) to furnish the title compound as an oil, 3.4g.

LRMS: m/z 666 [M+H]+

Preparation 3

[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-carbamic acid tert-butyl ester

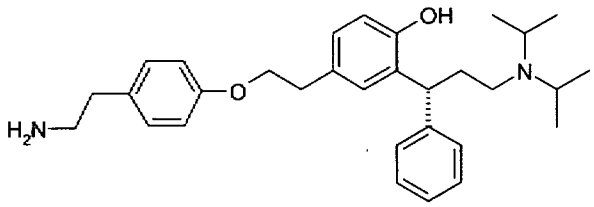


[2-(4-{2-[4-Benzyloxy-3-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenyl]-ethoxy}-phenyl)-ethyl]-carbamic acid tert-butyl ester (preparation 2, 650mg, 0.978mmol) and ammonium formate (394mg, 6.26mmol) were mixed in ethanol (7ml) and heated to 90°C, 20% palladium hydroxide on carbon (96.1mg) was then added and the mixture was stirred for 30 minutes.

Reaction mixture was cooled and filtered through arbocel™ the filtrate was collected and the solvent removed *in vacuo* to furnish the title compound as the formate salt, solid, 600mg.
LRMS: APCI ESI m/z 575 $[M+H]^+$

Preparation 4

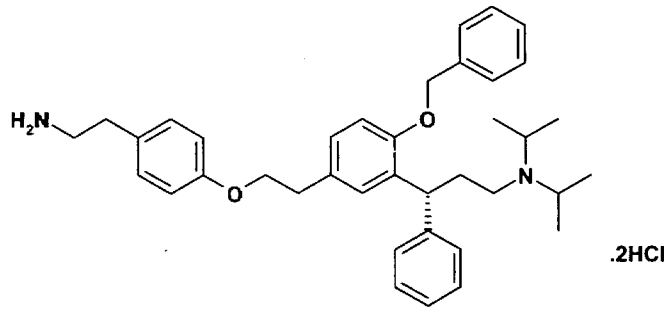
4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol




Hydrogen Chloride (4M in dioxane, 4.59ml, 670mg, 18.4mmol) was added to [2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-carbamic acid tert-butyl ester (preparation 3, 570mg, 0.918mmol) in dioxane (5ml) and stirred for 3 hours under nitrogen at room temperature. The reaction mixture was evaporated in vacuo and diluted with ethyl acetate 25ml and 2 N sodium hydroxide and partitioned. The aqueous layer was washed with 3x ethyl acetate 3x25ml and the combined organic layers were dried over sodium sulphate, filtered and evaporated to furnish the title compound as a brown / amber oil, 490mg.
LRMS: APCI ESI m/z 475 $[M+H]^+$

Preparation 5

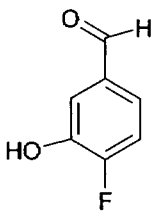
(3R)-3-[5-{2-[4-(2-aminoethyl)phenoxy]ethyl}-2-(benzyloxy)phenyl]-N,N-diisopropyl-3-phenylpropan-1-amine bis hydrochloride salt




Tert-butyl {2-[4-(2-{4-(benzyloxy)-3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenyl}ethoxy) phenyl]ethyl}carbamate (Preparation 2, 3.4g, 5.1mmol) was dissolved in dioxan (20ml) and treated with hydrochloric acid (4M in dioxan, 26ml). After stirring for 4 hours at room temperature the solvent was removed *in vacuo*. The residue was azeotroped twice from dichloromethane to yield the title compound as a brown solid, 3g.
LRMS: m/z 565 [M+H]+.

Preparation 6

4-Fluoro-3-hydroxy-benzaldehyde

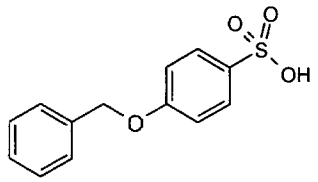


Boron tri-bromide (1M in dichloromethane, 6.5g, 26ml, 26mmol) was added dropwise to an ice-cooled solution of 4-fluoro-3-methoxy-benzaldehyde (2g, 12.98mmol) in dichloromethane (40ml) under nitrogen. Following complete addition, the brown solution was left stirring overnight under nitrogen at room temperature. The reaction was cooled, quenched by dropwise addition of water (26ml) and left to stir overnight at room temperature. The aqueous layer was separated and extracted with dichloromethane (2 x 20ml). The combined organic layers were washed with 2M HCl (15ml), water (15ml), brine (15ml), dried over sodium sulphate, filtered and evaporated to yield a brown oil (3g). The oil was chromatographed over silica gel eluting with ethyl acetate: pentane (1:19 to 1:9 to 1:4) to furnish the title compound as a white solid, 35% yield, 637mg.

$^1$H NMR (400 MHz, METHANOL-$d_4$) $\delta$ ppm 7.2-7.3 (m, 1H), 7.36-7.48 (m, 2H), 9.82 (s, 1H)

Preparation 7

4-Benzyloxybenzene sulphonic acid



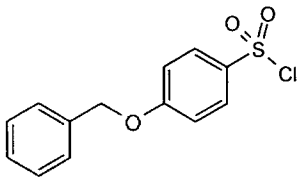
Benzyl bromide (10.3g, 7.13ml, 60.1mmol) in ethanol (60ml) was added dropwise to a stirred solution of 4-hydroxybenzene sulphonic acid sodium salt (8.72g, 50.1mmol) in a 15% aqueous (w/w) sodium hydroxyde solution. The resulting mixture was refluxed at 110°C for 21 hours and then cooled to room temperature. The mixture was filtered under vacuum, washing with ethanol to afford a white solid which was dried under vacuum at 50°C to furnish the title compound in 55% yield, 7.23 g, white solid.

$^1$H NMR (400 MHz, $(CD_3)_2SO$) $\delta$: 5.10 (s, 2 H), 6.90-6.95 (d, 2H), 7.30-7.50 (m, 7H).

LRMS: ESI m/z 263 $[M-H]^-$

Preparation 8

4-Benzyloxybenzene sulphonyl chloride

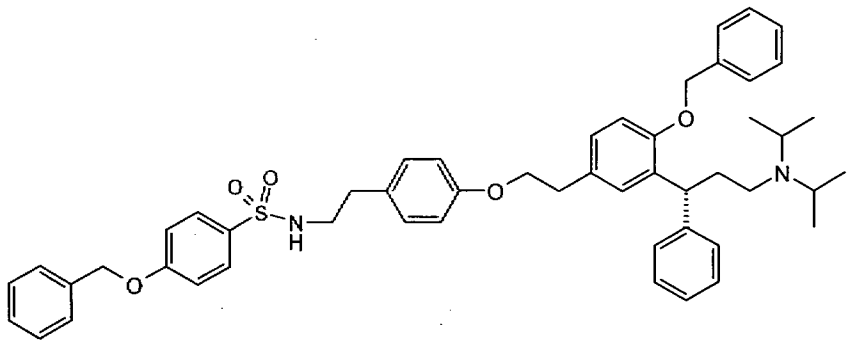


Phosphorous pentachloride (4.41g, 21.19mmol) was added to a stirred solution of 4-Benzyloxybenzene sulfonic acid (the product of preparation 7, 5.6g, 21.19mmol) in

dichloromethane (50ml). The reaction was heated at reflux for 18 hours. The solvent was removed under vacuum and replaced by toluene (50ml) before further phosphorous pentachloride (1.0g, 4.802mmol) was added and reaction heated at 80°C for 1 hour. Reaction mixture cooled and filtered. Solution then used directly in the next reaction without further purification or analysis.

Preparation 9

4-Benzyloxy-N-[2-(4-{2-[4-benzyloxy-3-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenyl]-ethoxy}-phenyl)-ethyl]-benzenesulfonamide



Triethylamine (53.7mg, 0.074ml, 0.530mmol) was added to a stirred solution of (3R)-3-[5-{2-[4-(2-aminoethyl)phenoxy]ethyl}-2-(benzyloxy)phenyl]-N,N-diisopropyl-3-phenylpropan-1-amine bis hydrochloride salt (the product of preparation 5, 165mg, 0.259 mmol) in dichloromethane (5ml) at 0°C under nitrogen. 4-Benzyloxybenzene sulfonyl chloride (product of preparation 8, 81.0mg, 0.285mmol) was then added. The reaction was stirred at 0°C for 2 hours and then warmed to room temperature overnight under nitrogen. The solution was diluted with dichloromethane (10ml) and washed with sodium carbonate (10ml). The organic layer was separated and the aqueous phase washed with a further 10ml dichloromethane. Combined organics were dried (sodium sulphate) and the solvent removed *in vacuo* to yield an orange gum. The oil was purified by column chromatography on silica gel eluting with dichloromethane: methanol: 880 ammonia 97:3:0.3 (by volume) to furnish the title compound in 66% yield, 138mg, colourless gum.

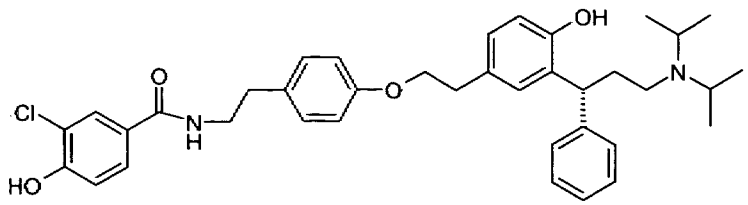
1H NMR (400 MHz, $CD_3OD$) δ: 0.98-1.02 (m, 14 H), 2.2-2.42 (m, 2H), 2.5-2.63 (m, 4H), 2.93 - 3.03 (m, 4H), 4.08-4.12 (m, 2H), 4.39-4.42 (m, 1H), 5.01 (s, 2H), 5.15 (s, 2H), 6.71-6.73 (d, 2H), 6.9-7.45 (m, 22H), 7.68-7.71(d, 2H)

LRMS: ESI m/z 811 $[M+H]^+$

**EXAMPLES**

Example 1

3-Chloro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-4-hydroxy-benzamide



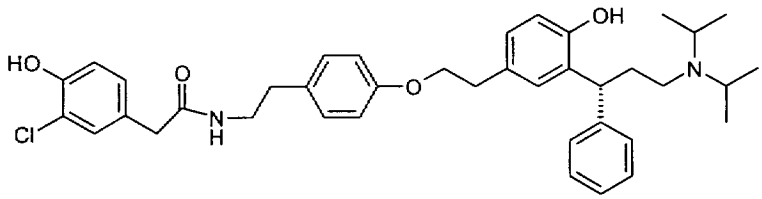
Triethylamine (71.0mg, 0.098ml, 0.702mmol) was added to a stirred suspension of 4-{2-[4-(2-amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (Product of preparation 4, 111mg, 0.234 mmol) in dichloromethane (5ml) at room temperature under nitrogen. 3-chloro-4-hydroxybenzoic acid hemihydrate (46.7mg, 0.257mmol), 1-Hydroxybenzotriazolemonohydrate (43mg, 0.281mmol) and (3-(Dimethylamino) propyl)ethylcarbodimide hydrochloride (53.8mg, 0.281mmol) were then added. The reaction was stirred overnight under nitrogen. The solution was washed with saturated sodium hydrogen carbonate solution (5ml) and water (5ml) and the organics separated, the combined organics were dried (sodium sulphate) and the solvent removed *in vacuo* to yield a pale yellow gum. The oil was purified by column chromatography on silica gel eluting with dichloromethane: methanol: 880 ammonia 99:1:0.1 to 90:10:1 (by volume) to furnish the title compound as a solid, 41% yield, 60mg.

1H NMR (400 MHz, METHANOL-$d_4$) $\delta$ ppm 1.05-1.19 (m, 12 H), 2.2-2.42 (m, 2H), 2.7-2.97 (m, 4H), 3.29 - 3.42 (m, 2H), 3.48-3.6 (m, 4H), 3.95-4.18 (m, 2H), 4.32-4.45 (m, 1H), 6.70-6.80 (m, 4H), 6.9-7.38 (m, 9H), 7.4-7.5(m, 1H), 7.7 (s, 1H).

LRMS: APCI ESI m/z 629 $[M+H]^+$

Example 2

2-(3-Chloro-4-hydroxy-phenyl)-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-acetamide



Triethylamine (53.3mg, 0.073ml, 0.527mmol) was added to a stirred suspension of 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (Product of preparation 4, 50mg, 0.1 mmol) in DCM (5ml) at room temperature under nitrogen. 3-chloro-4-hydroxy-phenylacetic acid (21.6mg, 0.116mmol), 1-Hydroxybenzotriazolemonohydrate (19.4mg, 0.126mmol) and (3-(Dimethylamino)propyl)ethylcarbodimide hydrochloride (24.2mg, 0.126mmol) were then added. The reaction was stirred overnight under Nitrogen. The solution was washed with saturated sodium hydrogen carbonate solution (5ml) and water (5ml) and the organics separated, the combined organics were dried (sodium sulphate) and the solvent removed *in vacuo* to yield a pale yellow gum. The oil was purified by column chromatography

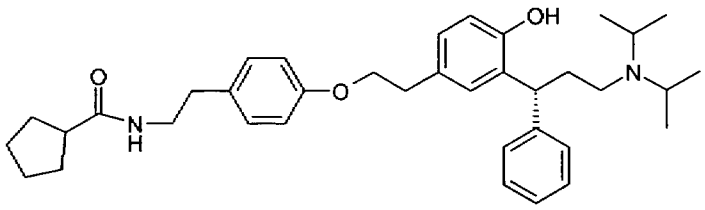
on silica gel eluting with dichloromethane: methanol: 880 ammonia 99:1:0.1 to 90:10:1 (by volume) to furnish the title compound in 37% yield, 25mg, oil

1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 0.95-1.1 (m, 12 H), 2.12-2.36 (m, 3H), 2.53-2.61 (m, 2H), 2.6-2.75 (m, 2H), 2.81-2.95 (m, 2H), 3.1-3.22 (m, 2H), 3.3-3.4 (m, 3H), 3.9-4.15 (m, 2H), 4.3-4.4 (m, 1H), 6.9-7.35 (m, 15 H)

LRMS: APCI ESI m/z 643 $[M+H]^+$

Example 3

Cyclopentanecarboxylic acid [2-{4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-amide



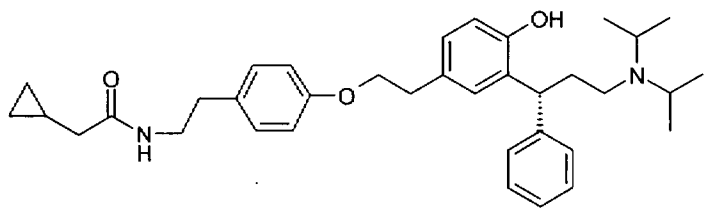
The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (Product of preparation 4, 50mg, 0.1mmol) and cyclopentane carboxylic acid (13.2mg, 0.0126ml, 0.116mmol) using the same method as described in example 2, in 42% yield, 25mg, oil.

1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 0.9-1.03 (m, 12 H), 1.5-1.82 (m, 8H), 2.1-2.25 (m, 2H), 2.4-2.5 (m, 2H), 2.5-2.6 (m, 1H), 2.65-2.75 (m, 2H), 2.82-2.9 (m, 2H), 2.95-3.1 (m, 2H), 3.3-3.4 (m, 2H), 2.95-4.15 (m, 2H), 4.3-4.4 (m, 1H), 6.65-6.75 (m, 1H), 6.7-6.8 (m, 2H), 6.9 (m, 1H), 7.02-7.19 (m, 4H), 7.15-7.28 (m, 2H), 7.3-7.35 (m, 2H).

LRMS: ESI m/z 571 $[M+H]^+$

Example 4

2-Cyclopropyl-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-acetamide



Triethylamine (10.7mg, 0.105mmol) was added to a stirred suspension of 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (Product of preparation 4, 50mg, 0.11 mmol) in dichloromethane (5ml) at room temperature under nitrogen. Cyclopropane acetic acid (10.5mg, 0.105mmol), 1-Hydroxybenzotriazolemonohydrate (16.1mg, 0.105mmol) and (3-(Dimethylamino) propyl)ethylcarbodimide hydrochloride (20.2mg, 0.105mmol) were then added. The reaction was stirred over the weekend under nitrogen. The solution was washed with saturated sodium

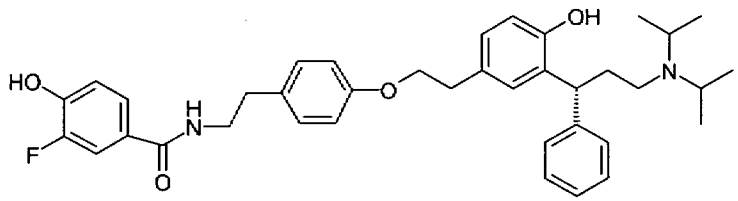
hydrogen carbonate solution (5ml) and water (5ml) and the organics separated, the combined organics were dried (sodium sulphate) and the solvent removed *in vacuo* to yield a pale yellow gum. The oil was purified twice by column chromatography on silica gel eluting with dichloromethane: methanol: 880 ammonia 99:1:0.1 to 90:10:1 (by volume) to furnish the title compound in 17% yield, 10mg, oil

1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 0.1-0.2 (m, 2H), 0.45-0.55 (m, 2H), 0.9-1.1 (m, 13 H), 2.0-2.05 (m, 2H), 2.1-2.3 (m, 2H), 2.5-2.6 (m, 2H), 2.7-2.8 (m, 2H), 2.85-2.95 (m, 2H), 3.1-3.2 (m, 2H), 3.35-3.42 (m, 2H), 3.95-4.15 (m, 2H), 4.3-4.1 (m, 1H), 6.7 (m, 1H), 6.75-6.81 (m, 2H), 6.9-6.95 (m, 1H) 7.05-7.2 (m, 4H), 7.2-7.38 (m, 4H)

LRMS: ESI m/z 558 $[M+H]^+$

Example 5

N-[2-{4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-3-fluoro-4-hydroxy-benzamide



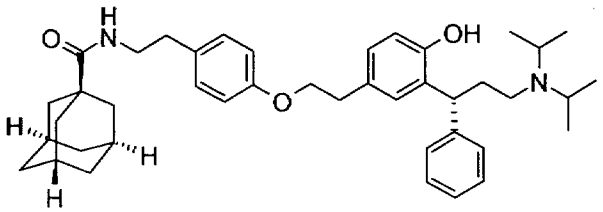

The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (Product of preparation 4, 50mg, 0.1053mmol) and 3-fluoro-4-hydroxybenzoic acid (18.1mg, 0.116mmol) using the same method as described in example 2. Purification was carried out by HPLC using Method A to afford the title compound.

LCMS Method A (acidic conditions): RT 2.81 min (90.83%area), ES m/z 613 $[M+H]^+$.

LRMS: ESI m/z 613 $[M+H]^+$

Example 6

(3S,5S,7S)-N-{2-[4-(2-{3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxyphenyl} ethoxy)phenyl]ethyl}adamantane-1-carboxamide




Triethylamine (53.3mg, 0.073ml, 0.527mmol) was added to a stirred suspension of 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (Product of preparation 4, 50mg, 0.1053 mmol) in dichloromethane (5ml) at room temperature under Nitrogen. 1-Adamantanecarboxylic acid (20.9mg, 0.116mmol), 1-Hydroxybenzotriazolemonohydrate (19.4mg, 0.126mmol) and (3-(Dimethylamino) propyl)ethylcarbodimide hydrochloride (24.2mg, 0.126mmol) were then added. The reaction

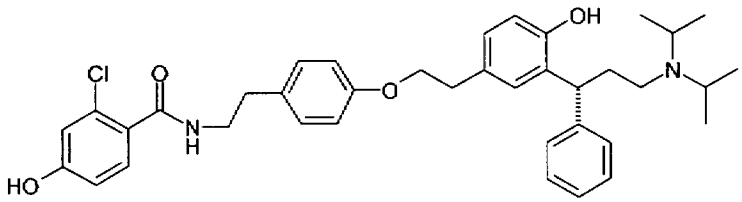
was stirred over the weekend under nitrogen. The solution was washed with saturated sodium hydrogen carbonate solution (5ml) and water (5ml) and the organics separated, the combined organics were dried (sodium sulphate) and the solvent removed *in vacuo* to yield a pale yellow gum. The oil was purified twice by column chromatography on silica gel eluting with dichloromethane: methanol: 880 ammonia 99:1:0.1 to 90:10:1 (by volume) to furnish the title compound in 22% yield, 15mg, solid

1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 1.0-1.18 (m, 12 H), 1.65-1.8 (m, 11 H), 1.95-2.1 (m, 4H), 2.2-2.4 (m, 2H), 2.55-2.65 (m, 2H), 2.65-2.75 (m, 2H), 2.85-2.95 (m, 2H), 3.15-3.3 (m, 2H), 3.3-3.4 (m, 2H), 3.95-4.18 (m, 2H), 4.3-4.42 (m, 1H), 6.7 (m, 1H), 6.75-6.81 (m, 2H), 6.95-7.0 (m, 1H), 7.05-7.2 (m, 4H), 7.2-7.39 (m, 4H).

LRMS: APCI ESI m/z 638 $[M+H]^+$

Example 7

2-Chloro-N-[2-{4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl}-ethyl]-4-hydroxy-benzamide



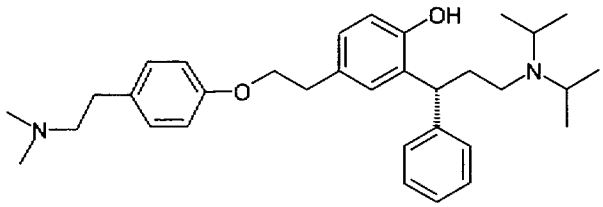

Triethylamine (28.8mg, 0.4ml, 0.285mmol) was added to a stirred suspension of 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (Product of preparation 4, 45mg, 0.095 mmol) in dichloromethane (5ml) at room temperature under nitrogen. 2-chloro-4-hydroxybenzoic acid hydrate (20.0mg, 0.105mmol) 1-Hydroxybenzotriazolemonohydrate (17.5mg, 0.114mmol) and (3-(Dimethylamino) propyl)ethylcarbodimide hydrochloride (31.1mg, 0.114mmol) were then added. The reaction was stirred overnight under nitrogen. The solution was washed with saturated sodium hydrogen carbonate solution (5ml) and water (5ml) and the organics separated, the combined organics were dried (sodium sulphate) and the solvent removed *in vacuo* to yield a pale yellow gum. The oil was purified twice by column chromatography on silica gel eluting with dichloromethane: methanol: 880 ammonia 99:1:0.1 to 90:10:1 (by volume) to furnish the title compound in 18% yield, 10mg, yellow oil.

1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 0.95-1.1 (m, 12 H), 2.1-2.38 (m, 2 H), 2.58-2.7 (m, 2H), 2.79-2.95 (m, 4H), 3.15-3.3 (m, 2H), 3.5-3.6 (m, 2H), 3.98-4.15 (m, 2H), 4.3-4.42 (m, 1H), 6.6-6.82 (m, 5H), 6.9-7.0 (d, 1H), 7-7.1 (s, 1H), 7.1-7.38 (m, 8H)

LRMS: APCI ESI m/z 629 $[M+H]^+$

Example 8

2-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-{2-[4-(2-dimethylamino-ethyl)-phenoxy]-ethyl}-phenol



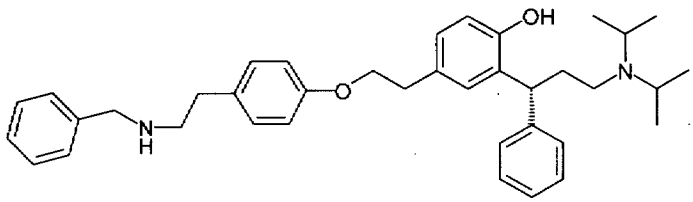
4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (Product of preparation 4, 30mg, 0.063mmol) was dissolved in dichloromethane (5ml) and acetic acid added (in excess of 0.004ml) followed by the addition of formaldehyde (5.96mg, 0.0053ml, 0.19mmol) which was stirred under nitrogen at room temperature for 30 mins. Sodium borohydride was then added (6mg, 0.158mmol) and the reaction stirred overnight under nitrogen at room temperature. The reaction mixture was concentrated in vacuo and re-dissolved in ethyl acetate (30ml) and extracted with saturated sodium hydrogen carbonate solution (10ml). The aqueous layer was washed with 3x40ml ethyl acetate. The combined organic layers were dried over sodium sulphate, filtered and evaporated. Material was purified by column chromatography on silica gel eluting with dichloromethane: methanol: 880 ammonia 90:10:1 to furnish the title compound in 31% yield, 10mg, yellow oil.

1H NMR (400 MHz, METHANOL-$d_4$) $\delta$ ppm 0.83-1.03 (m, 12 H), 2.1-2.25 (m, 2H), 2.25-2.3 (m, 6H), 2.3-2.57 (m, 4 H), 2.6-2.8 (m, 2H), 2.8-2.95 (m, 2H), 2.95-3.1 (m, 2H), 4-4.18 (m, 2H), 4.3-4.4 (m, 1H), 6.62-7.38 (m, 12H)

LRMS: APCI ESI m/z 503 $[M+H]^+$

Example 9

4-{2-[4-(2-Benzylamino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol

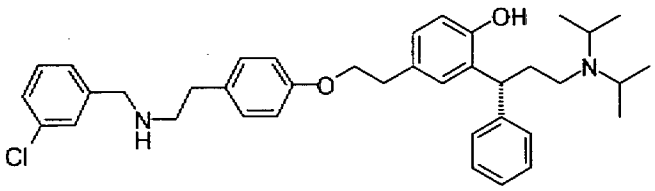


4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (Product of preparation 4, 30mg, 0.063mmol) was dissolved in dichloromethane (5ml) and acetic acid added (in excess of 0.004ml), followed by the addition of benzaldehyde (8.05mg, 0.0758mmol) which was stirred under nitrogen at room temperature for 30 mins. Sodium borohydride was then added (5.98mg, 0.158mmol) and the reaction was stirred overnight under nitrogen at room temperature. The reaction mixture was concentrated in vacuo and re-dissolved in ethyl acetate (30ml) and extracted with saturated sodium hydrogen carbonate solution (10ml). The aqueous was washed with 3x40ml ethyl acetate. The combined organic layers were dried over sodium sulphate, filtered and evaporated. Material was purified by column chromatography on silica gel eluting with dichloromethane: methanol: 880 ammonia 90:10:1 to furnish the title compound in 42% yield, 15mg, yellow oil.

1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 0.9-1.104 (m, 12 H), 2.1-2.3 (m, 2 H), 2.42-2.58 (m, 2 H), 2.7-2.8(m, 4H), 2.8-2.95 (m, 2H), 3-3.18 (m, 2H), 3.77 (s, 2H), 4-4.18 (m, 2H), 4.3-4.4 (m, 1H), 6.7 (d, 1H), 6.75-6.8 (d, 2H), 6.9 (d, 1H), 7.0-7.38 (m, 13H).
LRMS: APCI ESI m/z 565 $[M+H]^+$

Example 10

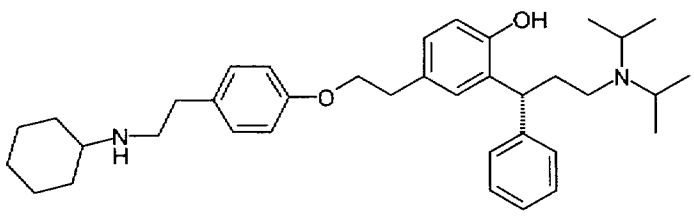
4-{2-{4-[2-(3-Chloro-benzylamino)-ethyl]-phenoxy}-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol




4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (Product of preparation 4, 50mg, 0.11mmol) was dissolved in dichloromethane (5ml) and acetic acid added (in excess of 0.006ml) followed by the addition of 3-chlorobenzaldehyde (14.8mg, 0.012ml, 0.105mmol) which was stirred under nitrogen at room temperature for 30 mins. Sodium borohydride was then added (10.0mg, 0.263mmol) and the reaction was stirred overnight under nitrogen at room temperature. The reaction mixture was concentrated in vacuo and re-dissolved in ethyl acetate (30ml) and extracted with saturated sodium hydrogen carbonate solution (10ml). The aqueous was washed with 3x40ml ethyl acetate. The combined organic layers were dried over sodium sulphate, filtered and evaporated. Material was purified by column chromatography on silica gel eluting with dichloromethane: methanol: 880 ammonia 90:10:1 to furnish the title compound in 40% yield, 25mg, yellow oil.
1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 0.9-1.05 (m, 12 H), 2.1-2.3 (m, 2H), 2.4-2.58 (m, 2H), 2.68-2.8 (m, 4H), 2.8-2.94 (m, 2H), 3.0-3.17 (m, 2H), 3.5-3.7 (m, 2H), 4-4.18 (m, 2H), 4.3-4.4 (m, 1H), 6.62-6.8 (m, 3H), 6.9-7.0 (m, 2H), 7-7.38 (m, 11H).
LRMS: APCI ESI m/z 599 $[M+H]^+$

Example 11

4-{2-[4-(2-Cyclohexylamino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol




4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (Product of preparation 4, 30mg, 0.063mmol) was dissolved in methanol (5ml) and acetic acid added (in excess of 0.004ml) followed by the addition of cyclohexanone (6.2mg, 0.0632mmol)

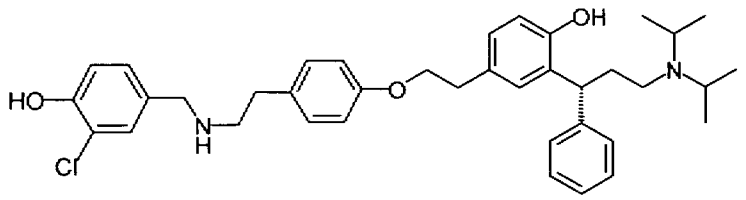
which was stirred under nitrogen at room temperature for 30 mins. It was then evaporated in vacuo and azeotroped twice with methanol: toluene 3:1 (by volume). The residue was re-dissolved in Methanol (5ml) and Sodium borohydride was added (5.98mg, 0.158mmol). The reaction was stirred overnight under nitrogen at room temperature. The reaction mixture was concentrated in vacuo, re-dissolved in ethyl acetate (30ml) and extracted with saturated sodium hydrogen carbonate solution (10ml). The aqueous was washed with 3x40ml ethyl acetate. The combined organic layers were dried over sodium sulphate, filtered and evaporated. Material was purified by column chromatography on silica gel eluting with dichloromethane: methanol: 880 ammonia 90:10:1 to furnish the title compound in 10% yield, 5mg, yellow oil.

1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 0.95-1.02 (m, 13 H), 1.0-1.38 (m, 4 H), 1.6-1.7 (m, 1H), 1.7-1.8 (m, 2H), 1.85-1.95 (m, 2H), 2.1-2.25 (m, 2H) 2.4-2.55 (m, 3 H), 2.65-2.78 (m, 2H), 2.78-2.92 (m, 4 H), 3.0-3.15 (m, 2H), 4.0-4.18 (m, 2H), 4.3-4.4 (m, 1H), 6.7 (d, 1H), 6.7-7.0 (d, 2 H), 6.9(d, 1H), 7.04-7.19 (m, 4H), 7.19-7.28 (m, 2H), 7.28-7.36 (m, 2H).

LRMS: ESI m/z 557 $[M+H]^+$

Example 12

2-chloro-4-[({2-[4-(2-{3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxyphenyl}ethoxy)phenyl]ethyl}amino)methyl]phenol



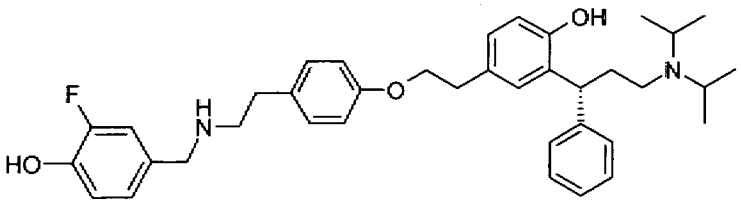

4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (Product of preparation 4, 40mg, 0.084mmol) was dissolved in dichloromethane (5ml) and acetic acid added (in excess of 0.005ml) followed by the addition of 3-chloro-4-hydroxybenzaldehyde (13.2mg, 0.0843mmol) and magnesium sulfate which was stirred under nitrogen at room temperature for 30 mins. Sodium borohydride was then added (6.38mg, 0.169mmol) and the reaction was stirred overnight under nitrogen at room temperature. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution (5ml) and poured through an phase separation cartridge. The organic layer was evaporated in vacuo. Material was purified by column chromatography on silica gel eluting with dichloromethane: methanol: 880 ammonia 99:1:0.1 - 90:10:1 to furnish the title compound in 27% yield, 14mg, solid.

1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 0.9-1.06 (m, 12 H), 2.09-2.28 (m, 2 H), 2.4-2.56 (m, 2H), 2.68-2.82 (m, 4H), 2.8-2.95 (m, 2H), 3.0-3.18 (m, 2H), 3.6-3.62 (s, 2H), 3.95-4.15 (m, 2 H), 4.3-4.41 (m, 1H), 6.67-7.34 (m, 15H).

LRMS: APCI ESI m/z 615 $[M+H]^+$

Example 13

2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-[2-(4-{2-[(3-fluoro-4-hydroxybenzyl)amino]ethyl}phenoxy)ethyl]phenol



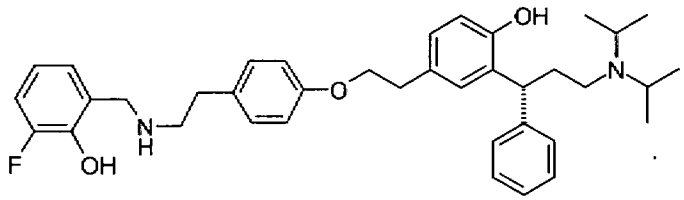
The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 40mg, 0.084mmol) and 3-fluoro-4-hydroxybenzaldehyde (11.8mg, 0.0843mmol) using the same method as described in example 12. (26% yield, 13mg, solid)

1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 0.95-1.05 (m, 12 H), 2.1-2.3 (m, 2 H), 2.4-2.55 (m, 2H), 2.68-2.80 (m, 4H) 2.8-2.95 (m, 2H), 3.0-3.18 (m, 2H), 3.6-3.62 (s, 2H), 3.95-4.18 (m, 2 H), 4.3-4.41 (m, 1H), 6.65-7.35 (m, 15H).

LRMS: APCI ESI m/z 599 $[M+H]^+$

Example14

2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-[2-(4-{2-[(3-fluoro-2-hydroxybenzyl)amino]ethyl}phenoxy)ethyl]phenol

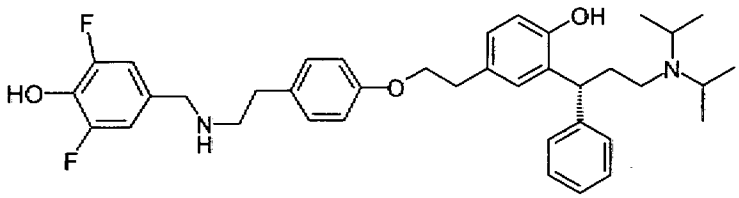


4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (Product of preparation 4, 44mg, 0.093mmol) was dissolved in dichloromethane (5ml) and acetic acid (in excess of 0.0054ml) followed by the addition of 3-fluoro-2-hydroxybenzaldehyde (13mg, 0.0.0927mmol) and magnesium sulphate which was stirred under nitrogen at room temperature for 30 mins. Sodium borohydride was then added (7.02mg, 0.185mmol) and the reaction was stirred over the weekend under nitrogen at room temperature. The reaction was diluted with sodium hydrogen carbonate (5ml) and poured through a phase separator cartridge. The organic layer was evaporated in vacuo. Material was purified by HPLC method B to afford the title compound.

LCMS Method B (acidic conditions) RT 2.25 min (100%area) ES m/z 599 $[M+H]^+$

Example 15

4-{[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-2,6-difluoro-phenol



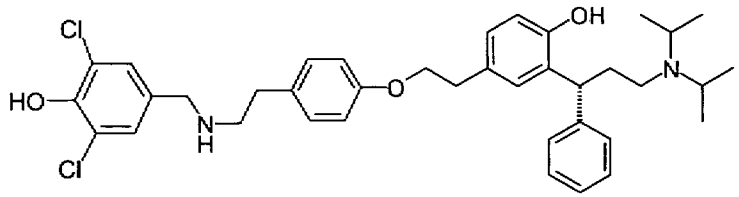
The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 40mg, 0.084mmol) and 3,5-Difluoro-4-hydroxy-benzaldehyde (13.3mg, 0.0843mmol) using the same method as described in example 12.(19% yield, 10mg, solid)

1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 1.01-1.18 (m, 12 H), 2.2-2.42 (m, 2 H), 2.65-2.92 (m, 8H), 3.3-3.4 (m, 2H), 3.6 (s, 2H), 4-4.18 (m, 2H), 4.3-4.48 (m, 1H), 6.7-6.82 (m, 3 H), 6.9-7.38 (m, 11H)

LRMS: APCI ESI m/z 617 $[M+H]^+$

Example 16

2,6-Dichloro-4-{[2-{4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-phenol



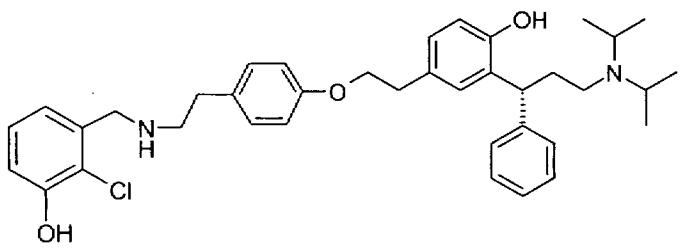
The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 40mg, 0.084mmol) and 3,5-Dichloro-4-hydroxy-benzaldehyde (16.1mg, 0.0843mmol) using the same method as described in example 12.(27% yield, 15mg, solid)

1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 1.01-1.19 (m, 12 H), 2.2-2.40 (m, 2H), 2.60-2.97 (m, 8H), 3.23-3.38 (m, 2H), 3.65 (s, 2H), 3.98-4.15 (m, 2H), 4.33-4.42 (m, 1H), 6.65-6.82 (m, 5 H), 6.9-7.39 (m, 9 H).

LRMS: APCI ESI m/z 649 $[M+H]^+$

Example 17

2-chloro-3-[({2-[4-(2-{3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxyphenyl}ethoxy)phenyl]ethyl}amino)methyl]phenol



The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 40mg, 0.084mmol) and 2-chloro-3-hydroxybenzaldehyde (13.2mg, 0.0843mmol) using the same method as described in example 12, and the crude material was purified by HPLC method C.

LCMS Method C (acidic conditions) RT 2.16 min (100%area) ES m/z 613 $[M-H]^-$

Alternatively, the title compound may be prepared by the following procedure;

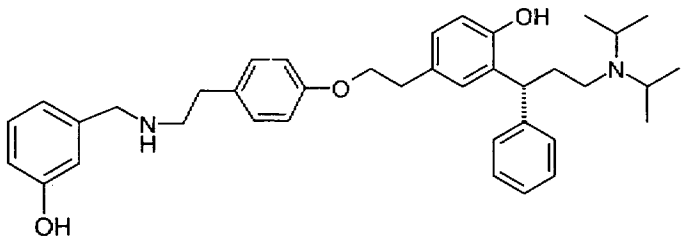
4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 106 mg, 0.223 mmol) was dissolved in ethanol (5 ml), followed by addition of 2-chloro-3-hydroxybenzaldehyde (34.9 mg, 0.223mmol), acetic acid (12.8 µl, 0.223 mmol) and a small spatula of sodium sulphate (drying agent), and the mixture was allowed to stir at room temperature for 18 hours. Sodium borohydride (16.9 mg, 0.446 mmol) was then added and the reaction stirred for 4 hours under nitrogen, then quenched with water (~5 drops) and evaporated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia, 99:1:0.1 to 90:10:1 (by volume), to furnish the title compound as a yellow foam, 71% yield, 98 mg.

$^1$H NMR (400 MHz, METHANOL-$d_4$) δ ppm 0.99 (dd, J=6.63, 3.12 Hz, 12H), 2.14 - 2.26 (m, 2H), 2.50 (t, J=8.19 Hz, 2H), 2.71 - 2.81 (m, 4H), 2.88 (t, J=6.63 Hz, 2H), 3.04 - 3.14 (m, J=6.53, 6.53, 6.53, 6.53 Hz, 2H), 3.81 (s, 2H), 3.98 - 4.09 (m, 2H), 4.35 (t, J=7.80 Hz, 1H), 6.69 - 6.79 (m, 5H), 6.91 (dd, J=8.19, 2.34 Hz, 1H), 7.00-7.30 (m, 9H).

LCMS: APCI ESI m/z 615 $[M+H]^+$

Example 18

2-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-(2-{4-[2-(3-hydroxy-benzylamino)-ethyl]-phenoxy}-ethyl)-phenol

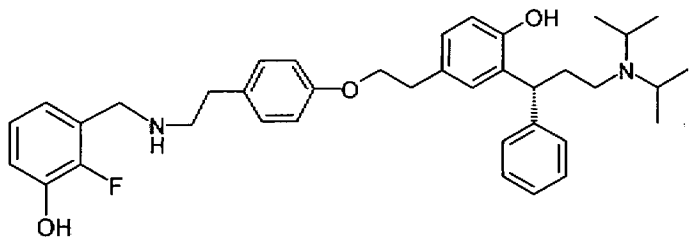



The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 40mg, 0.084mmol) and 3-hydroxybenzaldehyde (10.3mg, 0.0843mmol) using the same method as described in example 12, and the crude material was purified by HPLC method B.

LCMS Method B (acidic conditions) RT 2.31 min (100%area) ES m/z 579 $[M-H]^-$

Example 19

3-[({2-[4-(2-{3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxyphenyl}ethoxy)phenyl]ethyl}amino)methyl]-2-fluorophenol

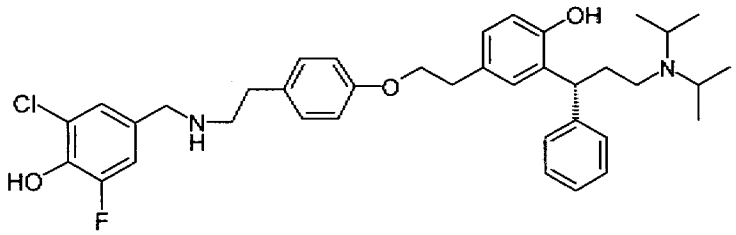


The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 40mg, 0.084mmol) and 2-Fluoro-3-hydroxy-benzaldehyde (11.8mg, 0.0843mmol) using the same method as described in example 12, and the crude material was purified by HPLC method B.

LCMS Method B (acidic conditions) RT 2.2 min (100%area) ES m/z 599 $[M+H]^+$

Example 20

2-Chloro-4-{[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-6-fluoro-phenol



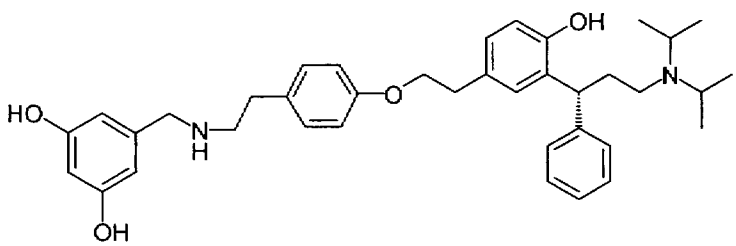
The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 40mg, 0.084mmol) and 3-chloro-5-fluoro-4-hydroxybenzaldehyde (14.7mg, 0.0843mmol) using the same method as described in example 12. (34% yield, 18mg, solid)

1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 1.06-1.2 (m, 12 H), 2.25-2.48 (m, 2H), 2.68-2.95 (m, 8H), 3.3-3.42 (m, 2H), 3.68 (s, 2H), 3.95-4.18 (m, 2H), 4.33-4.42 (m, 1H), 6.7-6.85 (m, 4 H), 6.8-7.38 (m, 10H).

LRMS: APCI ESI m/z 633 $[M+H]^+$

Example 21

5-{[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-benzene-1,3-diol



The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 40mg, 0.084mmol)

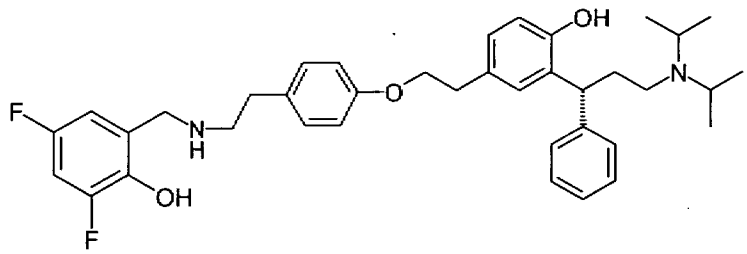
and 3,5-dihydroxybenzaldehyde (11.6mg, 0.0843mmol) using the same method as described in example 12. ( 20% yield, 9mg, oil)

1H NMR (400 MHz, METHANOL-$d_4$) δ ppm 0.95-1.07 (m, 12 H), 2.1-2.23 (m, 2H), 2.45-2.6 (m, 2H), 2.68-2.91 (m, 6H) 3.04-3.2 (m, 2H) 3.6 (s, 2H), 3.95-4.17 (m, 2H), 4.3-4.42 (m, 1H), 6.14-6.25 (m, 3H), 6.68-6.82 (m, 3H), 6.86-7.38 (m, 9H)

LRMS: APCI ESI m/z 597 $[M+H]^+$

Example 22

2-{[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-4,6-difluoro-phenol

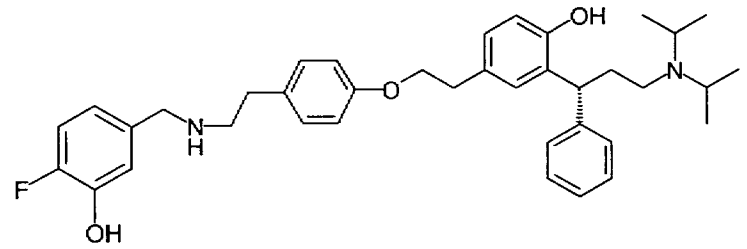


The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 40mg, 0.084mmol) and 3,5-difluorosalicylaldehyde (13.3mg, 0.0843mmol) using the same method as described in example 12, and the crude material was purified by HPLC method B.

LCMS Method B (acidic conditions) RT 2.29 min (100% area) ES m/z 617 $[M+H]^+$

Example 23

2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-[2-(4-{2-[(4-fluoro-3-hydroxybenzyl)amino]ethyl}phenoxy)ethyl]phenol

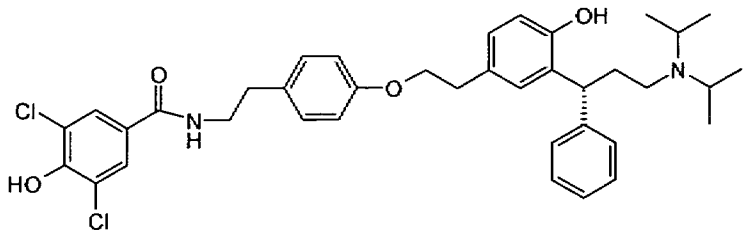


The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 40mg, 0.084mmol) and 4-fluoro-3-hydroxy-benzaldehyde (product of preparation 6, 11.8mg, 0.0843mmol) using the same method as described in example 12, and the crude material was purified by HPLC method B.

LCMS Method B (acidic conditions) RT 2.27 min (100%area) ES m/z 599 $[M+H]^+$

Example 24

3,5-Dichloro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-4-hydroxy-benzamide



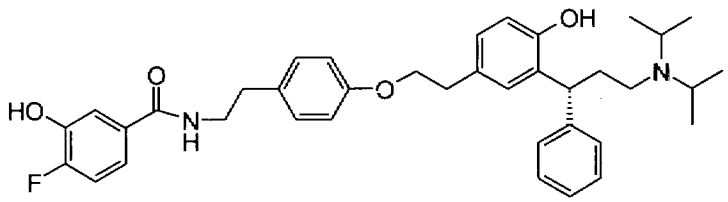
Triethylamine (8.95mg, 0.012ml, 0.089mmol) was added to a stirred suspension of 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 35mg, 0.074 mmol) in dichloromethane (3ml) at room temperature under nitrogen. 3,5-Dichloro-4-hydroxy benzoic acid (14.1mg, 0.081mmol), 1-Hydroxybenzotriazole monohydrate (13.5mg, 0.089mmol) and (3-(Dimethylamino)propyl)ethylcarbodimide hydrochloride (17.0mg, 0.089mmol) were then added. The reaction was stirred for 18 hours under nitrogen. Saturated sodium hydrogen carbonate solution (5ml) and dichloromethane (5ml) were added and the biphasic solution poured through a phase separation cartridge. The organic layer was reduced *in vacuo* and the crude material was purified by HPLC method A to afford the title compound.

LCMS Method A (acidic conditions) RT 2.67 (100%area) min ES m/z 663 $[M+H]^+$

LRMS: ESI m/z 663 $[M+H]^+$

Example 25

4-Fluoro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-3-hydroxy-benzamide



The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 35mg, 0.074mmol) and 3-Hydroxy-4-Fluoro benzoic acid (12.7mg, 0.081mmol) using the same method as described in example 24.

LCMS Method A (acidic conditions) RT 2.59 (100%area) min ES m/z 613 $[M+H]^+$

LRMS: ESI m/z 613 $[M+H]^+$ ES m/z 611 $[M-H]^-$

Alternatively, the title compound may be prepared by the following procedure;

(3-(Dimethylamino)propyl)ethylcarbodimide hydrochloride (1.29 g, 5.62 mmol) and N,N-diisopropylethylamine (2.45 ml, 14.1 mmol) was added to a mixture of 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (product of preparation 4,

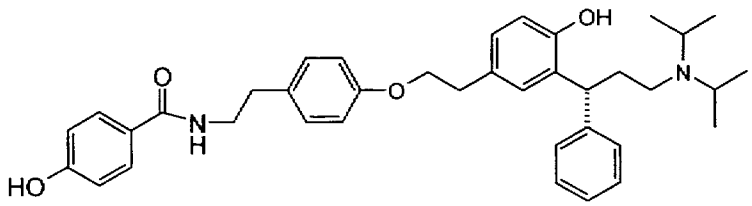
2.67 g, 5.62 mmol), 4-fluoro-3-hydroxybenzoic acid (878 mg, 5.62 mmol) and 1-hydroxybenzotriazolemonohydrate (1.03g, 6.75 mmol) in N-methylpyrrolidinone (25 ml) and stirred at room temperature for 18 hours. The solvent was removed *in vacuo* to yield a crude residue that was purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia, 96:4:0.4 to 94:6:0.6 (by volume), to furnish the title compound as a white foam, 41% yield, 1.40 g.

$^1$H NMR (400 MHz, METHANOL-$d_4$) δ ppm 1.04 (dd, J=6.63, 3.51 Hz, 12H), 2.16-2.32 (m, 2H), 2.60 (t, J=8.39 Hz, 2H), 2.79 - 2.90 (m, 4H), 3.13 - 3.24 (m, J=6.63, 6.63, 6.63, 6.63 Hz, 2H), 3.51 (t, J=7.22 Hz, 2H), 3.98 - 4.09 (m, 2H), 4.36 (t, J=7.61 Hz, 1H), 6.69 - 6.78 (m, 3H), 6.91-7.30 (m, 12H).

LCMS: APCI ESI m/z 613 $[M+H]^+$

Example 26

4-Hydroxy-N-[2-{4-[2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-benzamide




The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 35mg, 0.074mmol) and 4-Hydroxy benzoic acid (11.2mg, 0.081mmol) using the same method as described in example 24.

LCMS Method A (acidic conditions) RT 2.52 (100%area) min ES m/z 595 $[M+H]^+$

LRMS: ESI m/z 595 $[M+H]^+$ ES m/z 593 $[M-H]^-$

Alternatively, the title compound may be prepared by the following procedure;

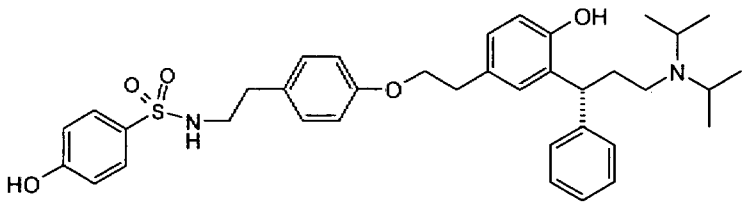
The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 100 mg, 0.211 mol) and 4-hydroxybenzoic acid (72.7 mg, 0.526 mmol) using the same method as described in example 32, and the crude residue purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia, 98:2:0.2 to 90:10:1 (by volume), to furnish the title compound as a yellow foam in 18% yield, 60mg.

$^1$H NMR (400 MHz, METHANOL-$d_4$) δ ppm 0.99 (dd, J=6.63, 2.73 Hz, 12H), 2.13 - 2.24 (m, 2H), 2.49 (t, J=8.19 Hz, 2H), 2.79 - 2.90 (m, 4H), 3.04 - 3.13 (m, J=6.53, 6.53, 6.53, 6.53 Hz, 2H), 3.49-3.53 (m, 2H), 3.98 - 4.09 (m, 2H), 4.35 (t, J=7.61 Hz, 1H), 6.69 (d, J=8.19 Hz, 1H), 6.77 (d, J=8.97 Hz, 4H), 6.91 (dd, J=8.19, 2.34 Hz, 1H), 7.06-7.30 (m, 8H), 7.63 (d, J=8.58 Hz, 2H).

LCMS: ESI m/z 593 [M-H]$^-$

Example 27

N-[2-{4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-4-hydroxy-benzenesulfonamide



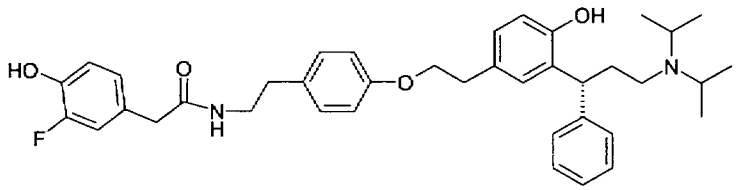
Palladium (II) Hydroxide (11.7mg, 0.016mmol) and Ammonium Formate (52.5mg, 0.832mmol) were added to a stirred solution of 4-Benzyloxy-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-benzenesulfonamide (the product of preparation 9, 135mg, 0.164 mmol) in ethanol (5ml) at reflux. The reaction was stirred as such for 1 hour. The catalyst was filtered from solution through Arbocel and the organic solution reduced under vacuum to afford an almost colourless gum. Material was taken up in 2ml DMSO, to which was added 0.023ml triethylamine and solution was purified by HPLC method A to afford the title compound.

LCMS Method A (acidic conditions) RT 2.55 (100%area) min ES m/z 629 [M-H]$^-$

LRMS: ESI m/z 631 [M+H]$^+$ ES m/z 629 [M-H]$^-$

Example 28

N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-2-(3-fluoro-4-hydroxy-phenyl)-acetamide



The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-(1-phenyl-propyl)-phenol (the product of preparation 4, 35.0mg, 0.074mmol) and 3-Fluoro-4-hydroxyphenyl acetic acid (13.8mg, 0.081mmol) using the same method as described in example 24.

LCMS Method A (acidic conditions) RT 2.64 (100%area) min ES m/z 627 [M+H]$^+$

Alternatively, the title compound may be prepared by the following procedure;

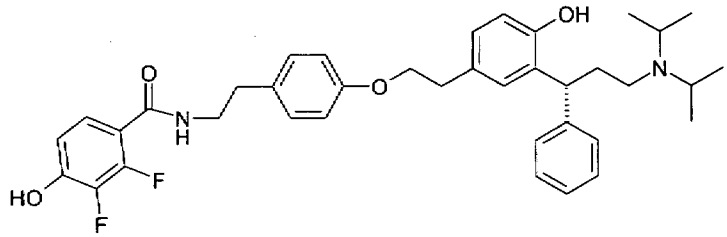
The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 100 mg, 0.211 mol) and (3-fluoro-4-hydroxy-phenyl)-acetic acid (34 mg, 0.20 mmol) using the same method as described in example 30, as a yellow foam in 34% yield, 45mg.

$^1$H NMR (400 MHz, METHANOL-$d_4$) δ ppm 1.00-1.05 (m, 12H), 2.17-2.31 (m, 2H), 2.56 (t, J=8.19 Hz, 2H), 2.67 (t, J=7.02 Hz, 2H), 2.89 (t, J=6.83 Hz, 2H), 3.10-3.20 (m, 2H), 3.29 - 3.36 (m, 4H), 3.98 - 4.09 (m, 2H), 4.35 (t, J=7.80 Hz, 1H), 6.69-7.31 (m, 15H).

LCMS: APCI ESI m/z 627 $[M+H]^+$

Example 29

N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-2,3-difluoro-4-hydroxy-benzamide



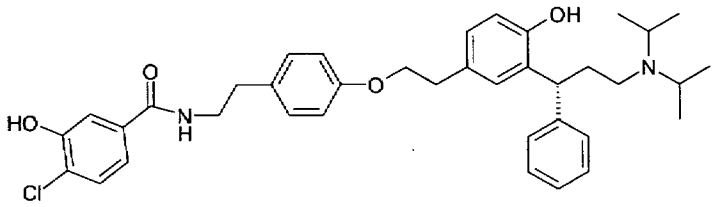
The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-(3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 35.0mg, 0.074mmol) and 2,3-Difluoro-4-hydroxybenzoic acid (14.1mg, 0.081mmol) using the same method as described in example 24.

LCMS Method A (acidic conditions) RT 2.65 (100%area) min ES m/z 631 $[M+H]^+$

LRMS: ESI m/z 631 $[M+H]^+$

Example 30

4-Chloro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-3-hydroxy-benzamide



The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-(3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 35.0mg, 0.074mmol) and 4-Chloro-3-hydroxybenzoic acid (14.0mg, 0.081mmol) using the same method as described in example 24.

LCMS Method A (acidic conditions) RT 2.65 (100%area) min ES m/z 629 $[M+H]^+$

LRMS: ESI m/z 629 $[M+H]^+$

Alternatively, the title compound may be prepared by the following procedure;

(3-(Dimethylamino)propyl)ethylcarbodimide hydrochloride (38 mg, 0.200 mmol) was added to a solution of 4-chloro-3-hydroxy-benzoic acid (34.5 mg, 0.200 mmol) in dimethylformamide (1 ml). The mixture was allowed to stir for 30 minutes before adding 1-hydroxybenzotriazolemonohydrate (31 mg, 0.200 mmol). The mixture was allowed to stir for

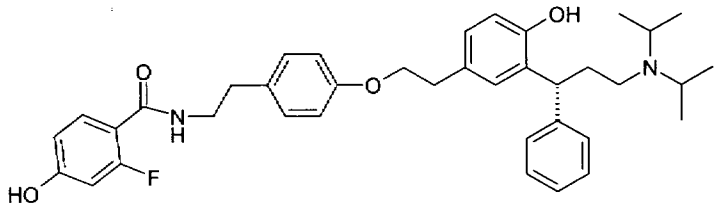
10 minutes before adding a solution of 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 100 mg, 0.211 mol) in dimethylformamide (2ml) and the reaction stirred at room temperature for 18 hours. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (20 ml) and saturated sodium hydrogen carbonate solution (20 ml). The layers were separated and the aqueous layer extracted with further dichloromethane (2×20 ml). The combined organic layers were dried (magnesium sulphate), filtered and the solvent removed *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with ethyl acetate: methanol: 880 ammonia, 99:1:0.1 to 90:10:1 (by volume), to furnish the title compound as a yellow foam, 22% yield, 29 mg.

$^1$H NMR (400 MHz, METHANOL-$d_4$) δ ppm: 1.05 (dd, J=6.63, 3.90 Hz, 12H), 2.17-2.34 (m, 2H), 2.63 (t, J=8.39 Hz, 2H), 2.81 (t, J=7.22 Hz, 2H), 2.87 (t, J=6.63 Hz, 2H), 3.18-3.25 (m, 2H), 3.51 (t, J=7.41 Hz, 2H), 3.98 - 4.10 (m, 2H), 4.35-4.38 (m, 1H), 6.76 (d, J=8.58 Hz, 2H), 6.71 (d, J=7.80 Hz, 1H), 6.93 (dd, J=8.19, 2.34 Hz, 1H), 7.03 (dd, J=17.75, 2.15 Hz, 1H), 7.05 -7.30 (m, 10H)

LCMS: APCI ESI m/z 629 $[M+H]^+$

Example 31

N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-2-fluoro-4-hydroxy-benzamide



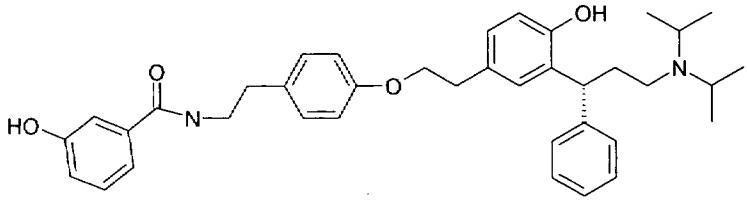

The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-(3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 35.0mg, 0.074mmol) and 2-Fluoro-4-hydroxybenzoic acid (12.7mg, 0.081mmol) using the same method as described in example 24.

LCMS Method A (acidic conditions) RT 2.61 (100%area) min ES m/z 613 $[M+H]^+$

LRMS: ESI m/z 613 $[M+H]^+$ ES m/z 611 $[M-H]^-$

Example 32

N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-3-hydroxy-benzamide




The title compound was prepared from 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-(3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 35.0mg, 0.074mmol)

and 3-Hydroxybenzoic acid (11.3mg, 0.081mmol) using the same method as described in example 24.

LCMS Method A (acidic conditions) RT 2.64 (100%area) min ES m/z 595 $[M+H]^+$

LRMS: ESI m/z 595 $[M+H]^+$

Alternatively, the title compound may be prepared by the following procedure;

(3-(Dimethylamino)propyl)ethylcarbodimide hydrochloride (142 mg, 0.738 mmol) was added to a solution of 4-{2-[4-(2-Amino-ethyl)-phenoxy]-ethyl}-2-(1R)-3-diisopropylamino-1-phenyl-propyl)-phenol (the product of preparation 4, 250 mg, 0.527 mmol), 3-hydroxybenzoic acid (69.2 mg, 0.50 mmol) and 1-hydroxybenzotriazolemonohydrate (85 mg, 0.553 mmol) in a mixture of dichloromethane (2 ml) and dimethylformamide (1 ml) and the reaction stirred at room temperature for 18 hours. The solution was partitioned between dichloromethane (30 ml) and saturated sodium hydrogen carbonate solution (20 ml). The layers were separated and the aqueous layer extracted with further dichloromethane (30 ml). The combined organic layers were dried (magnesium sulphate) and the solvent removed *in vacuo* to yield a crude residue that was purified by HPLC method D to afford the title compound as a white solid in 8 % yield, 25 mg.

$^1$H NMR (400 MHz, METHANOL-$d_4$) δ ppm 1.02 (dd, J=6.63, 3.12 Hz, 12H), 2.14-2.30 (m, 2H), 2.55 (t, J=8.19 Hz, 2H), 2.80 - 2.90 (m, 4H), 3.11 - 3.18 (m, J=6.53, 6.53, 6.53, 6.53 Hz, 2H), 3.52 (t, J=7.41 Hz, 2H), 3.98 - 4.09 (m, 2H), 4.35 (t, J=7.80 Hz, 1H), 6.70 (d, J=8.19 Hz, 1H), 6.77 (d, J=8.58 Hz, 2H), 6.90-6.94 (m, 2H), 7.06 -7.31 (m, 11H).

LCMS: APCI ESI m/z 595 $[M+H]^+$

**HPLC methodology**

Method A:

| **HPLC conditions** | **Analytical (QC)** | | **Preparative conditions** | |
|---|---|---|---|---|
| Column | XTerra C18 5µm 4.6 x 50mm | | Sunfire Prep C18 OBD 5µm 19 x 50mm | |
| Temperature | Ambient | | Ambient | |
| Detection | UV 225nm - ELSD - MS | | ELSD-MS | |
| System/Data file | CTC - MUX1 | | Fractionlynx 2 | |
| Injection volume | ~20µL | | 1000µL | |
| Flow rate | 1.5mL/min | | 18 mL/min | |
| Mobile phase | A: H2O + 0.1% ammonia B: MeCN + 0.1% ammonia | | A: H2O + 0.1% formic acid B: MeCN + 0.1% formic acid | |
| **Gradient** | **Time (min)** | **%B** | **Time (min)** | **%B** |
| | 0 | 5 | 0-1.0 | 5 |
| | 0-3.0 | 5-95 | 1.0-7.0 | 5-98 |
| | 3.0-4.0 | 95 | 7.0-9.0 | 98 |
| | 4.0-4.1 | 95-5 | 9.0-9.10 | 98-5 |
| | 4.1-5.0 | 5 | 9.10-10 | 5 |

Method B:

| HPLC conditions | Analytical (QC) | | Preparative conditions | |
|---|---|---|---|---|
| Column | 5µm 4.6 x 50mm | | Sunfire Prep C18 OBD 5µm 19 x 100mm | |
| Temperature | Ambient | | Ambient | |
| Detection | UV 225nm - ELSD - MS | | ELSD-MS | |
| System/Data file | | | | |
| Injection volume | 5µL | | 1000µL | |
| Flow rate | 1.5mL/min | | 18 mL/min | |
| Mobile phase | | | A: H2O + 0.1% formic acid<br>B: MeCN + 0.1% formic acid | |
| **Gradient** | **Time (min)** | **%B** | **Time (min)** | **%B** |
| | 0 | 5 | 0-1.0 | 5 |
| | 0-3.0 | 5-95 | 1.0-7.0 | 5-98 |
| | 3.0-4.0 | 95 | 7.0-9.0 | 98 |
| | 4.0-4.1 | 95-5 | 9.0-9.10 | 98-5 |
| | 4.1-5.0 | 5 | 9.10-10 | 5 |

Method C:

| HPLC conditions | Analytical (QC) | | Preparative conditions | |
|---|---|---|---|---|
| Column | 5µm 4.6 x 50mm | | Sunfire Prep C18 OBD 5µm 19 x 100mm | |
| Temperature | Ambient | | Ambient | |
| Detection | UV 225nm - ELSD - MS | | ELSD-MS | |
| System/Data file | CTC - MUX1 | | Fractionlynx 4 | |
| Injection volume | 5µL | | 1000µL | |
| Flow rate | 1.5mL/min | | 10 mL/min | |
| Mobile phase | | | A: H2O + 0.1% formic acid<br>B: MeCN + 0.1% formic acid | |
| **Gradient** | **Time (min)** | **%B** | **Time (min)** | **%B** |
| | 0 | 5 | 0-1.0 | 5 |
| | 0-3.0 | 5-95 | 1.0-7.0 | 5-98 |
| | 3.0-4.0 | 95 | 7.0-9.0 | 98 |
| | 4.0-4.1 | 95-5 | 9.0-9.10 | 98-5 |
| | 4.1-5.0 | 5 | 9.10-10 | 5 |

Method D:

| HPLC conditions | Preparative conditions | | | |
|---|---|---|---|---|
| Column | Phenomenex Luna 10u C18(2) 150 x 21.2 (mm) 10 micron | | | |
| Temperature | Ambient | | | |
| Detection | Waters Photodiode Array (PDA) Micromass Mass Spectrometer (MS) | | | |
| Injection volume | 1000µL | | | |
| Flow rate | 25 mL/min | | | |
| Mobile phase | A: H2O B: MeCN C: 2% formic acid | | | |
| **Gradient** | **Time (min)** | **%A** | **%B** | **%C** |
| | 0-0.6 | 90 | 5 | 5 |
| | 0.6-8.5 | 90-5 | 5-90 | 5 |
| | 8.5-11.5 | 5 | 90 | 5 |
| | 11.5-11.6 | 5-90 | 90-5 | 5 |
| | 11.6-14.0 | 90 | 5 | 5 |

**Cell based potency assessment at the human recombinant $M_3$ muscarinic receptor**

$M_3$ potency was determined in CHO-K1 cells transfected with the NFAT-Betalactamase gene. CHO (Chinese Hamster Ovary) cells recombinantly expressing the human muscarinic $M_3$ receptor were transfected with the NFAT_β-Lac_Zeo plasmid. Cells were grown in DMEM with Glutamax-1, supplemented with 25mM HEPES(Life Technologies 32430-027), containing 10% FCS (Foetal Calf Serum; Sigma F-7524), 1nM Sodium pyruvate (Sigma S-8636), NEAA (non-Essential Amino Acids; Invitrogen 11140-035) and 200µg/ml Zeocin (Invitrogen R250-01).

$hM_3$ β-Lactamase Assay Protocol

Cells were harvested for assay when they reached 80-90% confluency using enzyme free cell Dissociation Solution (Life technologies 13151-014) incubated with the cells for 5 min at 37°C in an atmosphere containing 5% $CO_2$. Detached cells were collected in warmed growth media and centrifuged at 2000rpm for 10min, washed in PBS (Phosphate Buffered Saline; Life Technologies 14190-094) and centrifuged again as just described. The cells were re-suspended at $2x10^5$ cells/ml in growth medium (composition as described above). 20µl of this cell suspension was added to each well of a 384 well black clear bottomed plate (Greiner Bio One 781091-PFI). The assay buffer used was PBS supplemented with 0.05% Pluronic F-127 (Sigma 9003-11-6) and 2.5% DMSO. Muscarinic $M_3$ receptor signalling was stimulated using 80nM carbamyl choline (Aldrich N240-9) incubated with the cells for 4h at 37°C /5% $CO_2$ and monitored at the end of the incubation period using a Tecan SpectraFluor+ plate reader (λ -

excitation 405nm, emission 450nm and 503nm). $M_3$ receptor antagonists under test were added to the assay at the beginning of the 4h incubation period and compound activity measured as the concentration dependent inhibition of the carbamyl choline induced signal. Inhibition curves were plotted and $IC_{50}$ values generated using a 4-parameter sigmoid fit and converted to Ki values using the Cheng-Prusoff correction and the $K_D$ value for carbamyl choline in the assay.

**Binding affinity assessment at the human recombinant $M_3$ muscarinic receptor**

Membrane preparation

Cell Pellets from CHO (Chinese Hamster Ovary) cells recombinantly expressing the human muscarinic $M_3$ receptor were homogenised in 20mM HEPES (pH7.4) and centrifuged at 48000 x g for 20min at 4°C. The pellet was re-suspended in buffer and the homogenisation and centrifugation steps repeated. The resulting pellet was re-suspended in 1ml buffer per 1ml original packed cell volume and the homogenisation step repeated. Protein estimation was carried out on the suspension and 1ml aliquots of ~1mg/ml frozen at -80°C.

$hM_3$ competition binding Assay Protocol

Membranes (5µg/well) were incubated with $^3$H-NMS (at a concentration 5 x $K_D$) plus/minus test compound for 24hr at RT (room temperature) in a 1ml polystyrene 96-well deep well block. The final assay volume was 200µl, comprising of: 20µl plus/minus test compound; 20µl $^3$H-NMS (Perkin Elmer NEN 636) and 160µl membrane solution. Total Binding was defined with 0.1% DMSO; Non-Specific Binding was defined with 1µM Atropine. Assay buffer was 20mM Hepes (pH 7.4).

Once all assay components were added, plates were covered and incubated at room temperature for 24 hrs with shaking. The assay was terminated by rapidly filtering through GF/B Unifilter plates pre-soaked with 0.5% polyethylenimine, using a Packard filtermate harvester, the filter plate was then washed with 3x1ml 4°C assay buffer. The filter plates were dried at 45°C for 1hour. The bottoms of the filter plates were sealed and 50µl/well of Microscint '0' added, the top of the plates were sealed with a Topseal. Following 90mins, the plates were read on an NXT Topcount (1 minute read time per well).

The resulting data was expressed as a percentage of the specific binding (Specific binding = Total binding – Non-Specific Binding). % specific binding versus test compound concentration was plotted to determine an $IC_{50}$ from a sigmoid curve using an in-house data analysis programme. $IC_{50}$ values corrected to Ki values by applying the Cheng-Prussoff equation:

Cheng-Prussoff equation: $$K_i = \frac{IC_{50}}{1 + [L]/K_D}$$

Where $IC_{50}$ is the concentration of unlabelled drug which inhibits by 50% the specific radioligand binding. [L] is the free radioligand concentrations and $K_D$ and $K_i$ are the equilibrium dissociation constants of the radioligand and unlabelled drug respectively.

It has thus been found that compounds of formula (I) according to the present invention that have been tested in the above assays show $hM_3$ receptor antagonist activity as listed in the table below:

| Example Number | CHO cell β-lactamase $hM_3$ Ki (nM) | CHO cell binding assay $hM_3$ Ki (nM) |
|---|---|---|
| 1 | 0.512 | 2.45 |
| 2 | 1.70 | 2.70 |
| 3 | 3.59 | |
| 4 | 1.19 | 0.738 |
| 5 | 5.36 | 4.30 |
| 6 | 4.99 | |
| 7 | 0.727 | 1.38 |
| 8 | 1.40 | 0.152 |
| 9 | 0.785 | 1.35 |
| 10 | 7.73 | |
| 11 | 6.06 | |
| 12 | >12.5 | 0.574 |
| 13 | >12.1 | 0.821 |
| 14 | 1.40 | 0.286 |
| 15 | 1.55 | 0.933 |
| 16 | >6.87 | 0.305 |
| 17 | 1.00 | 0.339 |
| 18 | >10.4 | 0.697 |
| 19 | 2.69 | 0.197 |
| 20 | >5.89 | 0.423 |
| 21 | >5.75 | |
| 22 | 7.11 | |
| 23 | >6.66 | 0.689 |
| 24 | 2.15 | 4.06 |
| 25 | 0.751 | 0.734 |
| 26 | 0.705 | 0.559 |
| 27 | 1.32 | 0.501 |
| 28 | | 0.600 |
| 29 | | 5.08 |
| 30 | | 0.626 |
| 31 | | 1.07 |
| 32 | | 2.30 |

**Guinea Pig Trachea assay**

Male, Dunkin-Hartley guinea-pigs weighing 350-450g are culled in a rising concentration of $CO_2$, followed by exsanguinations of the vena cava. Tracheas are dissected from the larynx to the entry point into the chest cavity and then placed in fresh, oxygenated, modified Krebs buffer solution (Krebs containing 10μM propranolol, 10μM guanethidine and 3μM indomethacin) at room temperature. The tracheas are opened by cutting through the cartilage opposite the trachealis muscle. Strips approximately 3-5 cartilage rings wide are cut. A cotton thread is attached to the cartilage at one end of the strip for attachment to the

force transducer and a cotton loop made at the other end to anchor the tissue in the organ bath. The strips are mounted in 5ml organ baths filled with warm (37°C) aerated modified Krebs. The pump flow rate is set to 1.0 ml/ min and the tissues washed continuously. Tissues are placed under an initial tension of 1000mg. Tissues are re-tensioned after 15 and 30 minutes, then allowed to equilibrate for a further 30-45 minutes.

Tissues are subjected to electrical field stimulation (EFS) of the following parameters: 10s trains every 2 minutes, 0.1ms pulse width, 10Hz and 10-30V. The voltage is raised 5V every 10min within the stated range until a maximum contractile response for each tissue is observed. This just maximum voltage for each tissue is then used throughout the remainder of the experiment. Following equilibration to EFS for 20min, the pump is stopped, and after 15min control readings are taken over a 8-10 min period (4-5 responses). Compound is then added to each tissue as a bolus dose at 30xKi (determined at the human $M_3$ receptor expressed in CHO cells in a filtration binding assay), and left to incubate for 2h. Compound is then washed from tissues using a rapid wash with modified Krebs for 1min and flow is restored to 1ml/min for the remainder of the experiment. At the end of the experiment tissues are challenged with histamine (1μM) to determine viability. Readings taken during the experiment are automatically collected using Notocord ® software. The raw data are converted into percent response taking into account measurements of inhibition of the EFS response. After starting washout, the times taken for the tissue to recover by 25% from the inhibition induced are recorded and used as a measure of compound duration of action. Tissue viability limits the duration of the experiment to 16h post-compound washout. Compounds are typically tested at n=2 to 5 to estimate duration of action.

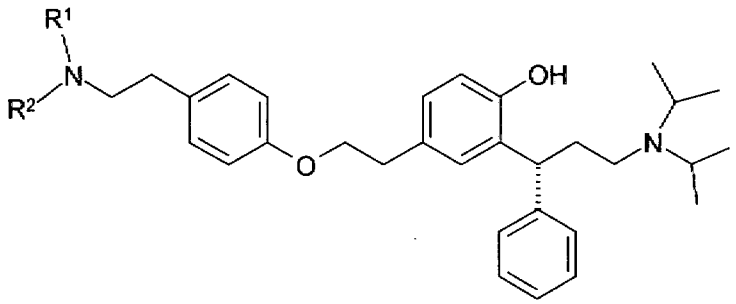
**Alternatively the following Guinea Pig Trachea assay can also be used:**

Trachea were removed from male Dunkin-Hartley guinea-pigs (wt 350-450g) and following removal of adherent connective tissue, an incision was made through the cartilage opposite the trachealis muscle and tracheal strips 3-5 cartilage rings wide prepared. The tracheal strips were suspended between an isometric strain gauge and a fixed tissue hook with the muscle in the horizontal plane in 5ml tissue baths under an initial tension of 1g and bathed in warmed (37°C) aerated (95%$O_2$/5%$CO_2$) Krebs solution containing 3μM indomethacin and 10μM guanethidine. The tissues were positioned between parallel platinum wire electrodes (~1cm gap). A constant 1ml/min flow of fresh Krebs solution (of the above composition) was maintained through the tissue baths using peristaltic pumps. The tissues were allowed to equilibrate for an hour with re-tensioning to 1g at 15min and 30min from the start of the equilibration period. At the end of the equilibration, tissues were electrically field stimulated (EFS) using the following parameters: 10V, 10Hz 0.1ms pulse width with 10sec trains every 2 min. In each tissue a voltage response curve was constructed over the range 10v – 30V (keeping all other stimulation parameters constant) to determine a just maximal stimulation. Using these stimulation parameters EFS responses were 100% nerve mediated and 100% cholinergic as confirmed by blockade by 1μM tetrodotoxin or 1μM atropine. Tissues were

then repeatedly stimulated at 2 min intervals until the responses were reproducible. The peristaltic pump was stopped 20 min prior to the addition of the study compound and the average twitch contraction over the last 10min recorded as the control response. The study compound was added to the tissue baths, with each tissue receiving a single concentration of compound and allowed to equilibrate for 2h. At 2h post addition the inhibition of the EFS response was recorded and $IC_{50}$ curves generated using a range of compound concentrations over tracheal strips from the same animal. The tissues were then rapidly washed and the 1ml/min perfusion with Krebs solution re-established. Tissues were stimulated for a further 16h and recovery of the EFS response recorded. At the end of the 16h, 10μM histamine was added to the baths to confirm tissue viability. The just max concentration (tested concentration giving a response > 70% inhibition but less than 100%) of antagonist was identified from the $IC_{50}$ curve and the time to 25% recovery of the induced inhibition ($T_{25}$) calculated in tissues receiving this concentration. Compounds are typically tested at n=2 to 5 to estimate duration of action.

Claims

1. A compound of formula (I)



(I)

wherein,

- $R^1$ is H or $C_1$-$C_4$ alkyl;
- $R^2$ is $C_1$-$C_4$ alkyl or a group –X-$R^3$;
- X is a bond, -$CH_2$-, -$SO_2$-, -C(=O)-, or -C(=O)-$CH_2$-;
- $R^3$ is $C_3$-$C_{10}$ cycloalkyl, 2 carbon atoms or more of said cycloalkyl being optionally bridged by one or more carbon atoms, or aryl, said cycloalkyl and aryl being optionally substituted with 1, 2 or 3 groups independently selected from hydroxy, halo, cyano, $C_1$-$C_4$ alkyl, O-($C_1$-$C_4$)alkyl or S-($C_1$-$C_4$)alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, where $R^1$ is H or methyl.

3. A compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, where $R^1$ is H.

4. A compound according to anyone of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, where $R^2$ is methyl or –X-$R^3$.

5. A compound according to anyone of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, where $R^2$ is –X-$R^3$.

6. A compound according to anyone of claims 1 to 5, or a pharmaceutically acceptable salt or solvate thereof, where $R^3$ is unsubstituted $C_3$-$C_{10}$ cycloalkyl or phenyl optionally substituted with 1, 2 or 3 groups independently selected from hydroxy, halo, cyano, $C_1$-$C_4$ alkyl, O-($C_1$-$C_4$)alkyl or S-($C_1$-$C_4$)alkyl.

7. A compound according to anyone of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, where $R^3$ is phenyl substituted with OH and optionally substituted with 1 or 2 groups selected from F or Cl.

8. A compound according to anyone of claims 1 to 7, or a pharmaceutically acceptable salt or solvate thereof, where X is -$CH_2$- or -C(=O)-.

9. A compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, said compound being selected from:

3-Chloro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-4-hydroxy-benzamide;

2-(3-Chloro-4-hydroxy-phenyl)-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-acetamide;
Cyclopentanecarboxylic acid [2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-amide;
2-Cyclopropyl-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-acetamide;
N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-3-fluoro-4-hydroxy-benzamide;
(3S,5S,7S)-N-{2-[4-(2-{3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxyphenyl}ethoxy)phenyl]ethyl}adamantane-1-carboxamide;
2-Chloro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-4-hydroxy-benzamide;
2-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-{2-[4-(2-dimethylamino-ethyl)-phenoxy]-ethyl}-phenol;
4-{2-[4-(2-Benzylamino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol;
4-(2-{4-[2-(3-Chloro-benzylamino)-ethyl]-phenoxy}-ethyl)-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol;
4-{2-[4-(2-Cyclohexylamino-ethyl)-phenoxy]-ethyl}-2-((1R)-3-diisopropylamino-1-phenyl-propyl)-phenol;
2-chloro-4-[({2-[4-(2-{3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxyphenyl}ethoxy)phenyl]ethyl}amino)methyl]phenol;
2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-[2-(4-{2-[(3-fluoro-4-hydroxybenzyl)amino]ethyl}phenoxy)ethyl]phenol;
2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-[2-(4-{2-[(3-fluoro-2-hydroxybenzyl)amino]ethyl}phenoxy)ethyl]phenol;
4-{[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-2,6-difluoro-phenol;
2,6-Dichloro-4-{[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-phenol;
2-chloro-3-[({2-[4-(2-{3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxyphenyl}ethoxy)phenyl]ethyl}amino)methyl]phenol;
2-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-(2-{4-[2-(3-hydroxy-benzylamino)-ethyl]-phenoxy}-ethyl)-phenol;
3-[({2-[4-(2-{3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxyphenyl}ethoxy)phenyl]ethyl}amino)methyl]-2-fluorophenol;
2-Chloro-4-{[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-6-fluoro-phenol;
5-{[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-benzene-1,3-diol;

2-{[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethylamino]-methyl}-4,6-difluoro-phenol;

2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-[2-(4-{2-[(4-fluoro-3-hydroxybenzyl)amino]ethyl}phenoxy)ethyl]phenol;

3,5-Dichloro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-4-hydroxy-benzamide;

4-Fluoro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-3-hydroxy-benzamide;

4-Hydroxy-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-benzamide;

N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-4-hydroxy-benzenesulfonamide;

N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-2-(3-fluoro-4-hydroxy-phenyl)-acetamide;

N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-2,3-difluoro-4-hydroxy-benzamide;

4-Chloro-N-[2-(4-{2-[3-((1R)-3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-3-hydroxy-benzamide;

N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-2-fluoro-4-hydroxy-benzamide; and,

N-[2-(4-{2-[3-((1R)-3-Diisopropylamino-1-phenyl-propyl)-4-hydroxy-phenyl]-ethoxy}-phenyl)-ethyl]-3-hydroxy-benzamide;

or a pharmaceutically acceptable salt or solvate thereof.

10. A pharmaceutical composition comprising at least an effective amount of a compound of the formula (I) as described in any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof.

11. A compound of the formula (I) as described in any one of claims 1 to 9, or a pharmaceutically acceptable salt or solvate thereof, for use as a medicament.

12. The use of a compound of the formula (I) as described in any one of claims 1 to 9, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a drug for the treatment of treatment of diseases, disorders, and conditions selected from the group consisting of

- chronic or acute bronchoconstriction, chronic bronchitis, small airways obstruction, and emphysema,
- obstructive or inflammatory airways diseases of whatever type, etiology, or pathogenesis, in particular an obstructive or inflammatory airways disease that is a member selected from the group consisting of chronic eosinophilic pneumonia, chronic obstructive pulmonary disease (COPD), COPD that includes chronic bronchitis, pulmonary emphysema or dyspnea associated or not associated with COPD, COPD that is characterized by irreversible, progressive airways obstruction, adult respiratory distress syndrome (ARDS), exacerbation of

airways hyper-reactivity consequent to other drug therapy and airways disease that is associated with pulmonary hypertension,

- bronchitis of whatever type, etiology, or pathogenesis, in particular bronchitis that is a member selected from the group consisting of acute bronchitis, acute laryngotracheal bronchitis, arachidic bronchitis, catarrhal bronchitis, croupus bronchitis, dry bronchitis, infectious asthmatic bronchitis, productive bronchitis, staphylococcus or streptococcal bronchitis and vesicular bronchitis,

- asthma of whatever type, etiology, or pathogenesis, in particular asthma that is a member selected from the group consisting of atopic asthma, non-atopic asthma, allergic asthma, atopic bronchial IgE-mediated asthma, bronchial asthma, essential asthma, true asthma, intrinsic asthma caused by pathophysiologic disturbances, extrinsic asthma caused by environmental factors, essential asthma of unknown or inapparent cause, non-atopic asthma, bronchitic asthma, emphysematous asthma, exercise-induced asthma, allergen induced asthma, cold air induced asthma, occupational asthma, infective asthma caused by bacterial, fungal, protozoal, or viral infection, non-allergic asthma, incipient asthma, wheezy infant syndrome and bronchiolytis,

- acute lung injury,

- bronchiectasis of whatever type, etiology, or pathogenesis, in particular bronchiectasis that is a member selected from the group consisting of cylindric bronchiectasis, sacculated bronchiectasis, fusiform bronchiectasis, capillary bronchiectasis, cystic bronchiectasis, dry bronchiectasis and follicular bronchiectasis.

13. Combination of a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof, with other therapeutic agent(s) selected from:

(a) 5-Lipoxygenase (5-LO) inhibitors or 5-lipoxygenase activating protein (FLAP) antagonists,

(b) Leukotriene antagonists (LTRAs) including antagonists of $LTB_4$, $LTC_4$, $LTD_4$, and $LTE_4$,

(c) Histamine receptor antagonists including H1 and H3 antagonists,

(d) $\alpha_1$- and $\alpha_2$-adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use.

(e) PDE inhibitors, e.g. PDE3, PDE4 and PDE5 inhibitors,

(f) Beta 2 receptor agonists,

(g) Dual compounds active as $\beta_2$ agonists and muscarinic M3 receptor antagonists

(h) Theophylline,

(i) Sodium cromoglycate,

(j) COX inhibitors both non-selective and selective COX-1 or COX-2 inhibitors (NSAIDs),

(k) Prostaglandin receptor antagonists and inhibitors of prostaglandin synthase.

(l) Oral and inhaled glucocorticosteroids, such as Dissociated agonists of the corticoid receptor (DAGR);

(m) Monoclonal antibodies active against endogenous inflammatory entities,

(n) Anti-tumor necrosis factor (anti-TNF-$\alpha$) agents,

(o) Adhesion molecule inhibitors including VLA-4 antagonists,

(p) Kinin-$B_1$ - and $B_2$ -receptor antagonists,

(q) Immunosuppressive agents, including inhibitors of the IgE pathway and cyclosporine,

(r) Inhibitors of matrix metalloproteases (MMPs),

(s) Tachykinin $NK_1$, $NK_2$ and $NK_3$ receptor antagonists,

(t) Protease inhibitors such as elastase inhibitors,

(u) Adenosine A2a receptor agonists and A2b antagonists,

(v) Inhibitors of urokinase,

(w) Compounds that act on dopamine receptors, such as D2 agonists,

(x) Modulators of the NFκβ pathway, such as IKK inhibitors,

(y) modulators of cytokine signalling pathyways such as p38 MAP kinase, PI3 kinase, JAK kinase, syk kinase, EGFR or MK-2,

(z) Agents that can be classed as mucolytics or anti-tussive,

(aa)Agents, which enhance responses to inhaled corticosteroids.

(bb)Antibiotics and antivral agents effective against micro-organisms which can colonise the respiratory tract,

(cc) HDAC inhibitors,

(dd)CXCR2 antagonists,

(ee) Integrin antagonists,

(ff) Chemokines,

(gg)Epithelial sodium channel (ENaC) blockers or Epithelial sodium channel (ENaC) inhibitors,

(hh) P2Y2 Agonists and other Nucleotide receptor agonists,

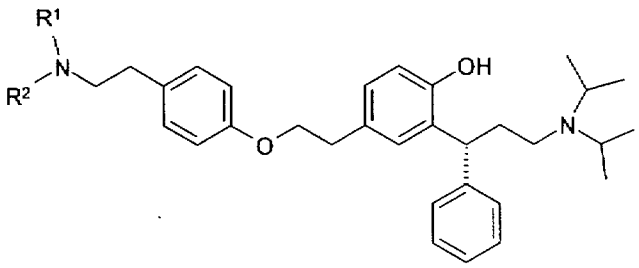
(ii) Inhibitors of thromboxane,

(jj) Inhibitors of $PGD_2$ synthesis and $PGD_2$ receptors (DP1 and DP2/CRTH2);

(kk)Niacin, and

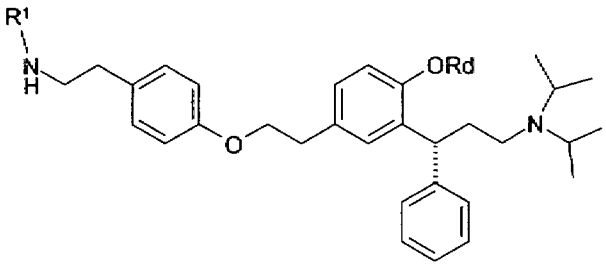
(ll) Adhesion factors including VLAM, ICAM, and ELAM.

14. A process for the preparation of a compound of formula (I)




(I)

where $R^1$ and $R^2$ are as defined in claim 1, said process comprising the step of reacting a compound of formula (2)

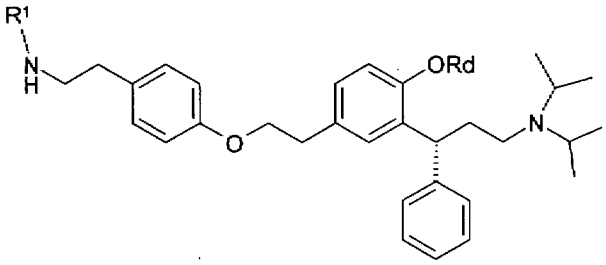


(2)

wherein Rd is H or Rc wherein Rc is a suitable protecting group,

with a carboxylic acid of formula $R^3CO_2H$ or $R^3CH_2$-$CO_2H$, a sulphonyl chloride of formula $R^3SO_2Cl$ or aldehydes/ketones of formula $R^3C(=O)H$ and $R^3=O$.

15. A compound of formula (2)



(2)

wherein Rd is H or Rc, where Rc is a suitable protecting group such as benzyl and $R^1$ is as defined in claim 1.