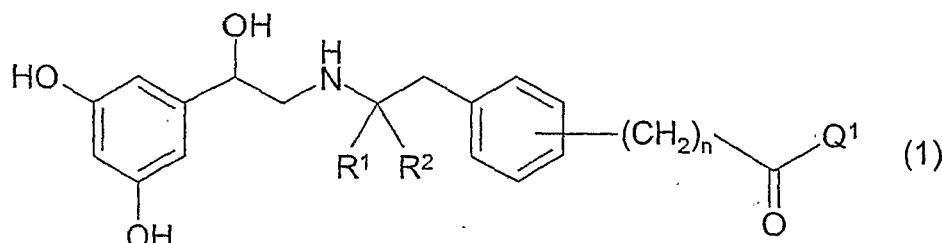


COMPOUNDS FOR THE TREATMENT OF DISEASES

This invention relates to β 2 agonists of general formula:



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

Adrenoceptors are members of the large G-protein coupled receptor super-family. The adrenoceptor subfamily is itself divided into the α and β subfamilies with the β sub-family being composed of at least 3 receptor sub-
 10 types: β 1, β 2 and β 3. These receptors exhibit differential expression patterns in tissues of various systems and organs of mammals. β 2 adrenergic (β 2) receptors are mainly expressed in smooth muscle cells (e.g. vascular, bronchial, uterine or intestinal smooth muscles), whereas β 3 adrenergic receptors are mainly expressed in fat tissues (therefore β 3 agonists could
 15 potentially be useful in the treatment of obesity and diabetes) and β 1 adrenergic receptors are mainly expressed in cardiac tissues (therefore β 1 agonists are mainly used as cardiac stimulants).

The pathophysiology and treatments of airway diseases have been extensively reviewed in the literature (for reference see Barnes, P.J. Chest,
 20 1997, 111:2, pp 17S-26S and Bryan, S.A. et al, Expert Opinion on investigational drugs, 2000, 9:1, pp25-42) and therefore only a brief summary will be included here to provide some background information.

Glucocorticosteroids, anti-leukotrienes, theophylline, cromones, anti-cholinergics and β 2 agonists constitute drug classes that are currently used to

treat allergic and non-allergic airways diseases such as asthma and chronic obstructive airways disease (COPD). Treatment guidelines for these diseases include both short and long acting inhaled $\beta 2$ agonists. Short acting, rapid onset $\beta 2$ agonists are used for "rescue" bronchodilation, whereas, long-acting forms
5 provide sustained relief and are used as maintenance therapy.

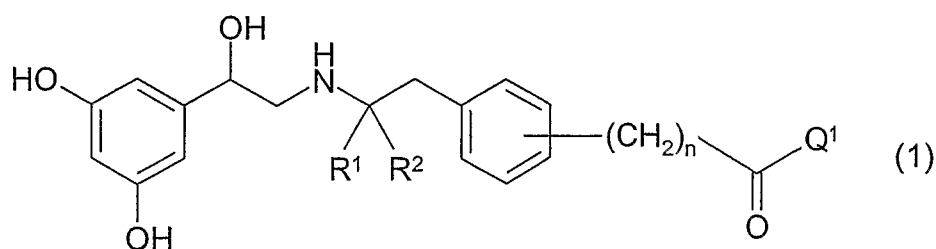
Bronchodilation is mediated via agonism of the $\beta 2$ adrenoceptor expressed on airway smooth muscle cells, which results in relaxation and hence bronchodilation. Thus, as functional antagonists, $\beta 2$ agonists can prevent and reverse the effects of all bronchoconstrictor substances, including
10 leukotriene D₄ (LTD₄), acetylcholine, bradykinin, prostaglandins, histamine and endothelins. Because $\beta 2$ receptors are so widely distributed in the airway, $\beta 2$ agonists may also affect other types of cells that play a role in asthma. For example, it has been reported that $\beta 2$ agonists may stabilize mast cells. The inhibition of the release of bronchoconstrictor substances may be how $\beta 2$
15 agonists block the bronchoconstriction induced by allergens, exercise and cold air. Furthermore, $\beta 2$ agonists inhibit cholinergic neurotransmission in the human airway, which can result in reduced cholinergic-reflex bronchoconstriction.

In addition to the airways, it has also been established that $\beta 2$ adrenoceptors are also expressed in other organs and tissues and thus $\beta 2$
20 agonists, such as those described in the present invention, may have application in the treatment of other diseases such as, but not limited to those of the nervous system, premature labor, congestive heart failure, depression, inflammatory and allergic skin diseases, psoriasis, proliferative skin diseases, glaucoma and in conditions where there is an advantage in lowering gastric
25 acidity, particularly in gastric and peptic ulceration.

However, numerous $\beta 2$ agonists are limited in their use due to their low selectivity or adverse side-effects driven by high systemic exposure and mainly mediated through action at $\beta 2$ adrenoreceptors expressed outside the airways (muscle tremor, tachycardia, palpitations, restlessness). Therefore there is a
30 need for improved agents in this class.

Accordingly, there is still a need for novel β_2 agonists that would have an appropriate pharmacological profile, for example in terms of potency, selectivity, pharmacokinetics or duration of action. In this context, the present invention relates to novel β_2 agonists.

5 The invention relates to the compounds of general formula (1):

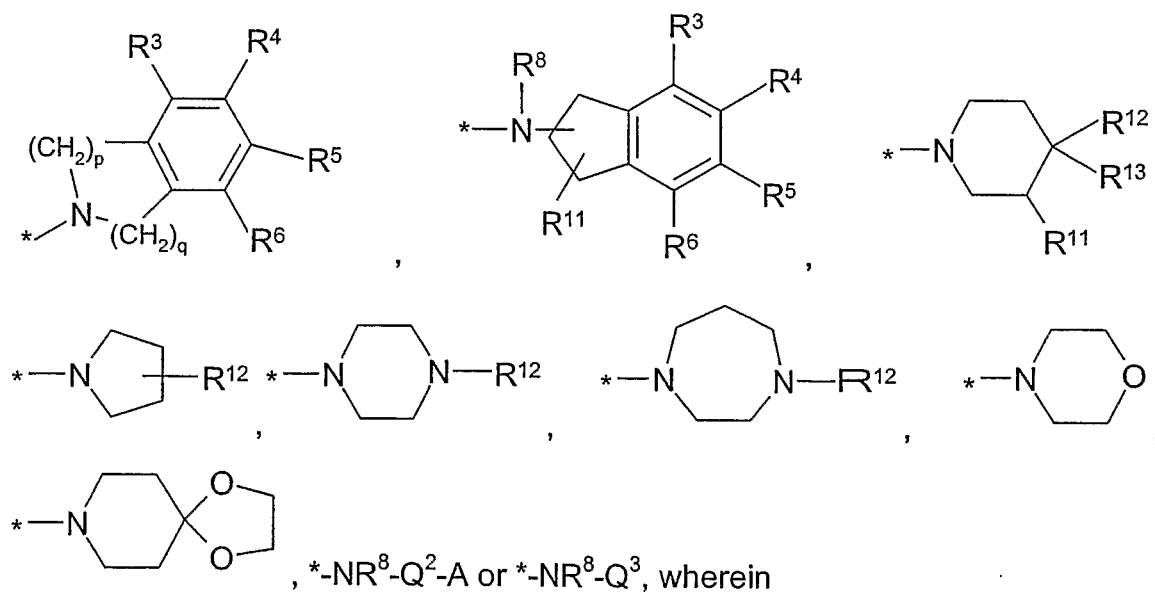


wherein the $(\text{CH}_2)_n\text{-C(=O)Q}^1$ group is in the meta or para position,

- R¹ and R² are independently selected from H and C₁-C₄ alkyl.

- n is 0, 1 or 2 and

10 - Q^1 is a group selected from,



- p is 1 or 2 and q is 1 or 2.

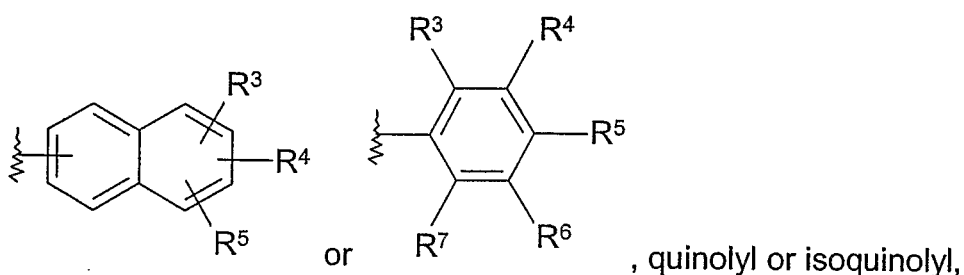
15 - Q² is a single bond or a C₁-C₄ alkylene optionally substituted with OH,

- R⁸ is H or C₁-C₄ alkyl and,

- Q³ is C₁-C₆ alkyl optionally substituted with NR⁹R¹⁰, OR⁹ or phenoxy,

- A is selected from:

- 5
- C₃-C₁₀ cycloalkyl, said cycloalkyl being optionally bridged by one or more, preferably 1, 2, 3 or 4, carbon atoms, and being optionally substituted with one hydroxy group,
 - a 5 to 6 membered heterocyclic group, optionally aromatic, containing one or two heteroatoms selected from O, N or S, optionally substituted by one or two substituents selected from C₁-C₄ alkyl, benzyl and cyclopropylmethyl or
 - a group



- 10 - R³, R⁴, R⁵, R⁶ and R⁷ are the same or different and are selected from H, C₁-C₄ alkyl, OR⁹, SR⁹, SOR⁹, SO₂R⁹, halo, CN, CF₃, OCF₃, SO₂NR⁹R¹⁰, COOR⁹, CONR⁹R¹⁰, NR⁹R¹⁰, NHCOR¹⁰ and phenyl optionally substituted with OH,
- R⁹ and R¹⁰ are the same or different and are selected from H or C₁-C₄ alkyl,
- R¹¹ is selected from H or OH, and,
- 15 - R¹² and R¹³ are the same or different and are selected from H, C₁-C₄ alkyl optionally substituted with OR⁹, OR⁹, C(=O)NH₂, C(=O)CH₃, N(CH₃)C(=O)CH₃, C(=O)OR⁹, phenyl optionally substituted with halogen, pyridyl optionally substituted with CN, oxadiazolyl optionally substituted with C₁-C₄ alkyl, and,
- * represents the attachment point to the carbonyl group;
- 20 or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof.

The compounds of formula (1) are agonists of the β₂ receptors, that are particularly useful for the treatment of β₂-mediated diseases and/or conditions, by showing excellent potency, in particular when administered via the inhalation route.

25

In the here above general formula (1), C₁-C₄ alkyl and C₁-C₄ alkylene denote a straight-chain or branched group containing 1, 2, 3 or 4 carbon atoms.

C₁-C₆ alkyl denotes a straight-chain or branched group containing 1, 2, 3, 4, 5 or 6 carbon atoms. This also applies if they carry substituents or occur as substituents of other radicals, for example in O-(C₁-C₄)alkyl radicals, S-(C₁-C₄)alkyl radicals etc... . Examples of suitable (C₁-C₄)alkyl radicals are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl.... Examples of suitable O-(C₁-C₄)alkyl radicals are methoxy, ethoxy, *n*-propyloxy, *iso*-propyloxy, *n*-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy....

The C₃-C₁₀ cycloalkyl wherein 2 carbon atoms or more are optionally bridged by one or more carbon atoms include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane. Preferred cycloalkyl groups are cyclohexyl and adamantyl.

Non limitative examples of "5 to 6 membered heterocyclic group, optionally aromatic, containing one or two heteroatoms selected from O, N or S" are morpholinyl, pyrrolidinyl, piperidyl, piperazinyl, pyrazolyl, thienyl, furanyl, imidazolyl, isothiazolyl, thiazolyl, isoxazolyl, oxazolyl, pyridyl and pyrimidyl.

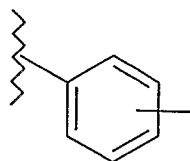
Preferably, said heterocyclic group contains one nitrogen, two nitrogens or one nitrogen and one oxygen atom.

Preferred aromatic 5 to 6 membered heterocyclic groups are pyrazolyl and pyridyl.

Preferred non aromatic 5 to 6 membered heterocyclic groups are morpholinyl, pyrrolidinyl, piperidyl and piperazinyl.

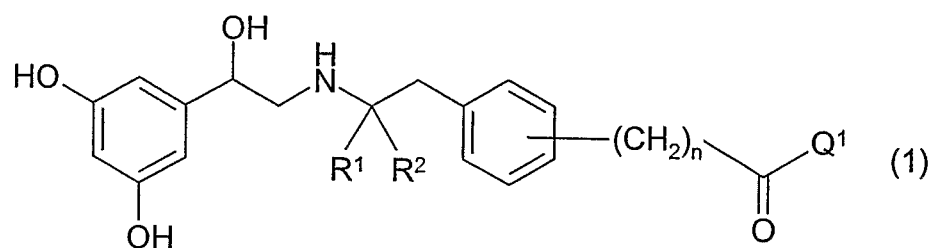
Finally, halo denotes a halogen atom selected from the group consisting of fluoro, chloro, bromo and iodo in particular fluoro or chloro.

In the following, the free bond on the phenyl group such as in the structure below,



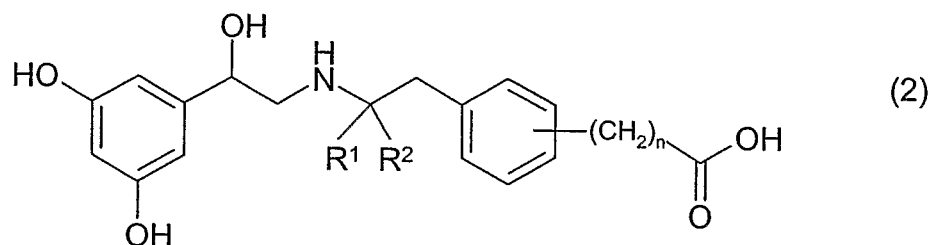
means that the phenyl can be substituted in the meta or para position.

The compounds of the formula (1)



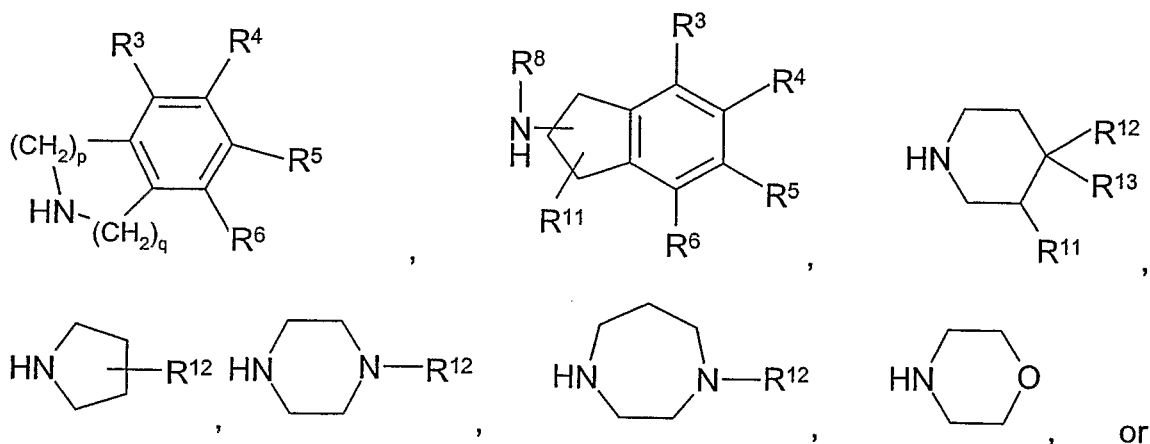
- 5 can be prepared using conventional procedures such as by the following illustrative methods in which Q^1 , Q^2 , R^1 , R^2 , A and n are as previously defined for the compounds of the formula (1) unless otherwise stated.

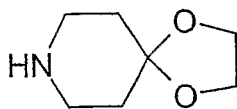
The amide derivatives of the formula (1) may be prepared by coupling an acid of formula (2):



10

with an amine of formula NHR^8-Q^2-A , NHR^8-Q^3

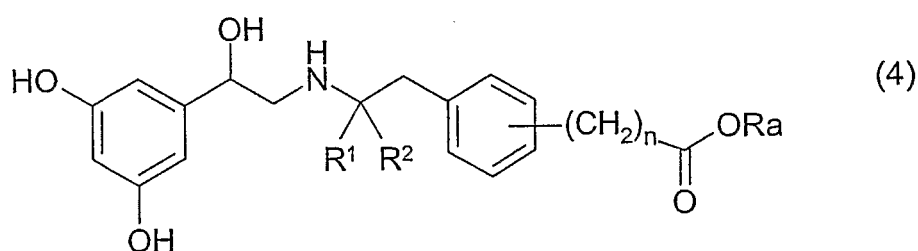




The coupling is generally carried out in an excess of said amine as an acid receptor, with a conventional coupling agent (e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride or *N, N'*-dicyclohexylcarbodiimide), optionally in the presence of a catalyst (e.g. 1-hydroxybenzotriazole hydrate or 1-hydroxy-7-azabenzotriazole), and optionally in the presence of a tertiary amine base (e.g. *N*-methyldimorpholine, triethylamine or diisopropylethylamine). The reaction may be undertaken in a suitable solvent such as pyridine, dimethylformamide, tetrahydrofuran, dimethylsulfoxide, dichloromethane, *N,N*-dimethylacetamide, or ethyl acetate, and at temperature comprised between 10°C and 40°C (room temperature) for a period of 1-24 hours.

Said amines (are either commercially available or may be prepared by conventional methods well known to the one skilled in the art (e.g. reduction, oxidation, alkylation, transition metal-mediated coupling, protection, deprotection etc...)) from commercially available material.

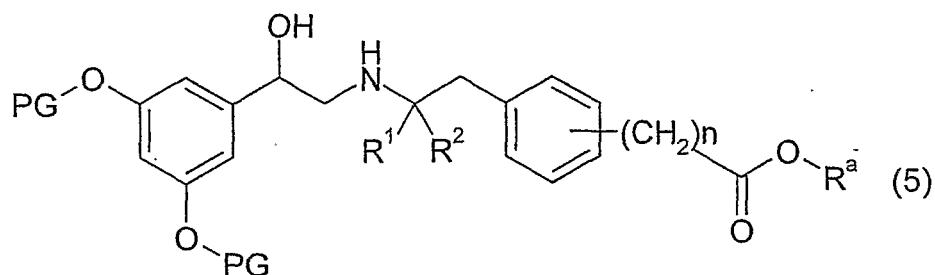
The acid of formula (2) may be prepared from the corresponding ester of formula (4):



wherein *R_a* is a suitable acid protecting group, preferably a (C₁-C₄)alkyl group, which includes, but is not limited to, methyl and ethyl, according to any method well-known to the one skilled in the art to prepare an acid from an ester, without modifying the rest of the molecule. For example, the ester may be hydrolysed by treatment with aqueous acid or base (e.g. hydrogen chloride, potassium hydroxide, sodium hydroxide or lithium hydroxide), optionally in the presence of a solvent or mixture of solvents (e.g. water, 1,4-dioxan, tetrahydrofuran/water),

at a temperature comprised between 20°C and 100°C, for a period of 1 to 40 hours.

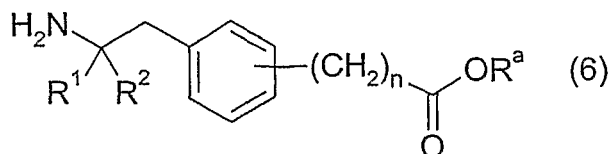
- The ester of formula (4) may be prepared by removal of the phenolic protecting group of the compound of formula (5), where PG is defined as a suitable phenol protecting group, typically an alkyl or alkoxy ether (eg. methyl, benzyl, methoxymethyl) and is preferably benzyl:



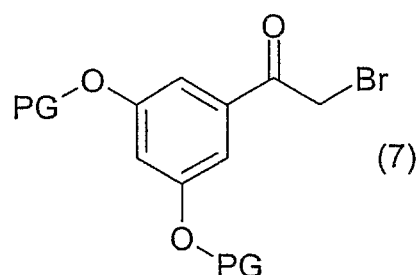
- Reagents suitable to achieve this deprotection are described in the text book T.W. GREENE, *Protective Groups in Organic Synthesis*, A. Wiley-Interscience Publication, 1981. In a typical procedure, when PG represents benzyl, this may be achieved by hydrogenation using a suitable catalyst (eg. palladium hydroxide or palladium on charcoal) in a suitable solvent such as ethanol or methanol under an atmosphere of hydrogen, optionally at elevated pressure (eg 60 psi) and at a temperature between room temperature and 60°C for 8-24 hours.

Alternatively transfer hydrogenation can be used with a suitable catalyst (eg palladium hydroxide) and ammonium formate as a hydrogen source in a suitable solvent such as ethanol and at a temperature between room temperature and 60°C.

- The ester of formula (5) may be prepared by reaction of an amine of formula (6):

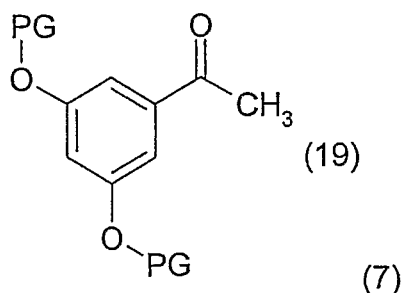


wherein Ra and n are as previously defined, with a bromide of formula (7) :



In a typical procedure, the amine of formula (6) is reacted with a bromide of formula (7) optionally in the presence of a solvent or mixture of solvents (e.g. dimethylsulfoxide, toluene, *N,N*-dimethylformamide, acetonitrile, THF), optionally in the presence of a suitable base (e.g. triethylamine, diisopropylethylamine, potassium carbonate) at a temperature comprised between 60°C and 120°C, for 12 to 120 hours. The resulting intermediate amino ketone can then be reduced using a suitable reducing agent such as sodium borohydride or diisobutyl aluminium hydride.

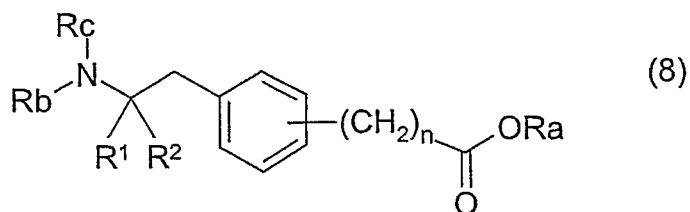
The bromide of formula (7) may be prepared from the ketone of formula (19):



by bromination with a suitable bromine source. In a typical procedure the ketone is treated with a brominating agent (e.g. Et₄NBr₃) in a suitable solvent such as THF and methanol at room temperature for about 24 hours.

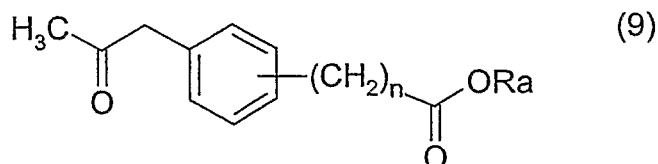
The ketone of formula (19) is commercially available.

The amine of formula (6), where R¹ is Me and R² is H, may be prepared as either the (*R*) or (*S*) enantiomer from the corresponding protected amine of formula (8) :



wherein Ra and n are as previously defined and Rb and Rc represent any suitable substituents so that HNRbRc is a chiral amine (for example, Rb may be hydrogen and Rc may be α -methylbenzyl), provided that the bonds between N and Rb and N and Rc can be easily cleaved to give the free amine of formula (5) using standard methodology for cleaving nitrogen protecting groups, such as those found in the text book T.W. GREENE, Protective Groups in Organic Synthesis, A. Wiley-Interscience Publication, 1981.

The amine of formula (8) may be prepared as a single diastereomer by reaction of an amine of formula HNRbRc with a ketone of formula (9):

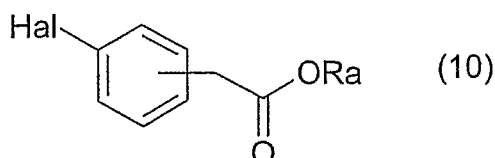


wherein Ra, Rb, Rc and n are as previously defined.

In a typical procedure, the reaction of the ketone of formula (9) with the amine of formula HNRbRc leads to a chiral intermediate which is in turn reduced by a suitable reducing agent (e.g. sodium cyanoborohydride of formula NaCNBH₃ or sodium triacetoxyborohydride of formula Na(OAc)₃BH) optionally in the presence of a drying agent (e.g. molecular sieves, magnesium sulfate) and optionally in the presence of an acid catalyst (e.g. acetic acid) to give the amine of formula (8) as a mixture of diastereomers. The reaction is generally done in a solvent such as tetrahydrofuran or dichloromethane at a temperature comprised between 20°C and 80°C for 3 to 72 hours. The resulting product is then converted to the hydrochloride salt and selectively crystallised from a suitable solvent or mixture of solvents (e.g. isopropanol, ethanol, methanol,

diisopropyl ether or diisopropyl ether/methanol) to give (8) as a single diastereomer.

The ketone of formula (9) where $n=1$ may be prepared by palladium mediated coupling of an aryl halide of formula (10):



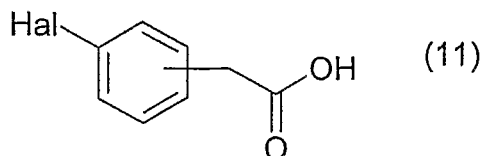
5

wherein Ra is as previously defined and Hal represents an halogen atom, which includes, but is not limited to bromo and iodo, with an enolate or enolate equivalent.

In a typical procedure, the aryl halide of formula (10) is reacted with a tin enolate generated in-situ by treatment of isopropenyl acetate with tri-n-butyltin methoxide of formula Bu_3SnOMe in the presence of a suitable palladium catalyst (palladium acetate/ tri-*ortho*-tolylphosphine of formula $\text{Pd}(\text{OAc})_2/\text{P}(\text{o-Tol})_3$) in a non-polar solvent (e.g. toluene, benzene, hexane). Preferably, the reaction is carried out at a temperature comprised between 80°C and 110°C for 6 to 16 hours.

15

The aryl halide of formula (10) may be obtained by esterification of the corresponding acid of formula (11):



wherein Hal is as previously defined, according to any method well-known to the one skilled in the art to prepare an ester from an acid, without modifying the rest of the molecule.

20

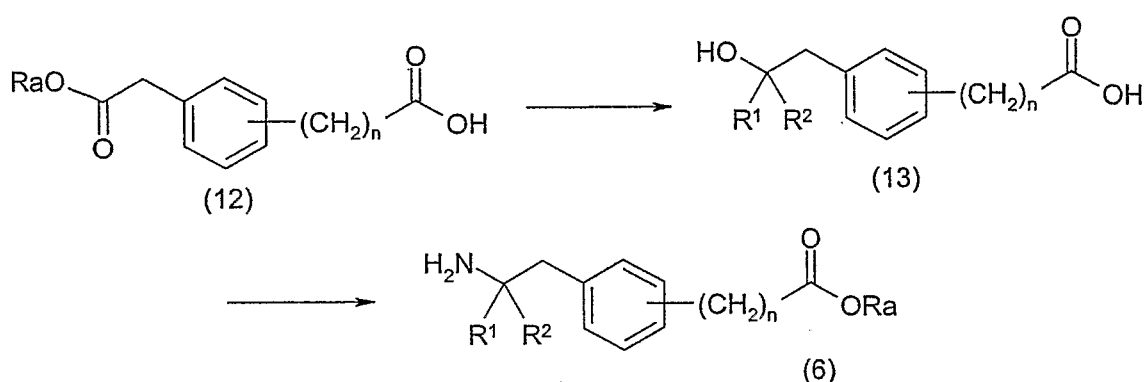
In a typical procedure, the acid of formula (11) is reacted with an alcoholic solvent of formula RaOH , wherein Ra is as previously defined, in the

presence of an acid such as hydrogen chloride at a temperature between 10°C and 40°C (room temperature) for 8 to 16 hours.

The acid of formula (11) is a commercial product.

The amine of formula (6), where R^1 and R^2 are both C_1 - C_4 alkyl, may be prepared according to the following scheme:

Scheme 1



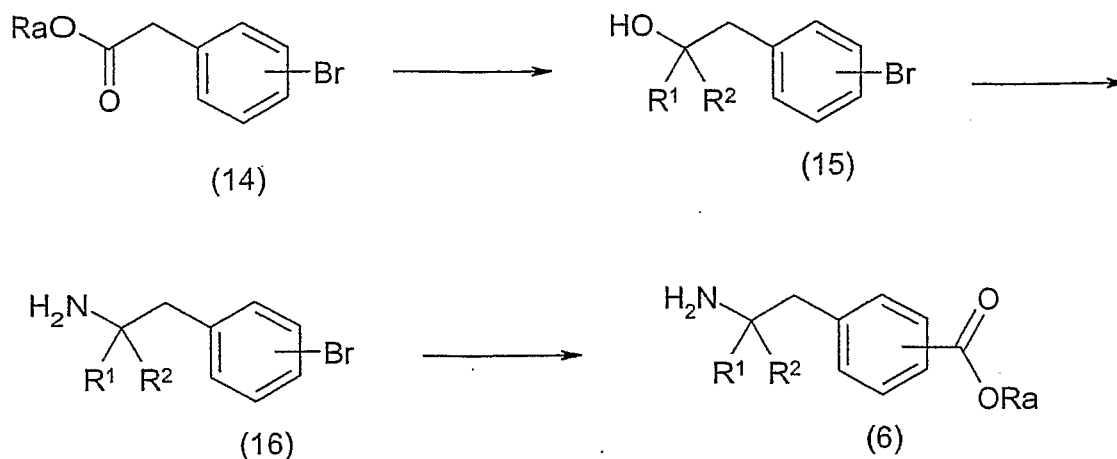
wherein R^1 , R^2 and Ra are as previously defined.

In a typical procedure, the ester of formula (12) is reacted with an "activated" alkyl (organometallic alkyl such as R^2MgBr , R^2MgCl or R^2Li) to give the corresponding tertiary alcohol of formula (13) using the method described above.

Said tertiary alcohol of formula (13) is then treated with an alkyl nitrile (e.g. acetonitrile, chloroacetonitrile) in the presence of an acid (e.g. sulphuric acid, acetic acid) to give a protected intermediate which is in turn cleaved using standard methodology for cleaving nitrogen protecting group such as those mentioned in textbooks. The resulting amino acid is then esterified using the method described herein to give the amine of formula (6).

Alternatively, the amine of formula (6), where R^1 and R^2 both C_1 - C_4 alkyl and $n=0$, may be prepared according to the following scheme:

Scheme 2



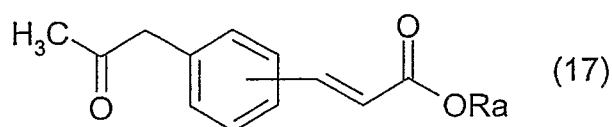
wherein R^1 , R^2 and Ra are as previously defined.

In a typical procedure, the ester of formula (14) is reacted with an "activated" alkyl (organometallic alkyl such as R^2MgBr , R^2MgCl or R^2Li) to give the corresponding tertiary alcohol of formula (15) using the method described above.

Said tertiary alcohol of formula (15) is then treated with an alkyl nitrile (e.g. acetonitrile, chloroacetonitrile) in the presence of an acid (e.g. sulphuric acid, acetic acid) to give a protected intermediate which is in turn cleaved using standard methodology for cleaving nitrogen protecting group such as those mentioned in textbooks to give the bromo amine (16).

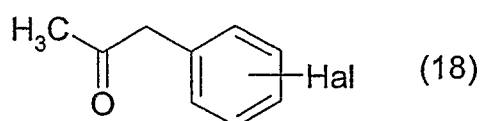
The resulting bromo amine (16) is treated with a suitable palladium catalyst (e.g. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) under an atmosphere of carbon monoxide using RaOH as solvent (e.g. MeOH, EtOH) at elevated temperature (100°C) and pressure (100psi) to give the ester of formula (6).

The ketone of formula (9) where $n=2$ may be prepared by reduction of an alkene of formula (17) :



In a typical procedure, a solution of the olefin of formula (17) in a suitable solvent (e.g. methanol, ethanol, ethyl acetate) is treated with a palladium catalyst (e.g. 10% palladium on charcoal) and stirred under an atmosphere of hydrogen, optionally at elevated pressure (e.g. 60 psi), at temperature between
5 room temperature and 60°C for 8-24 hours.

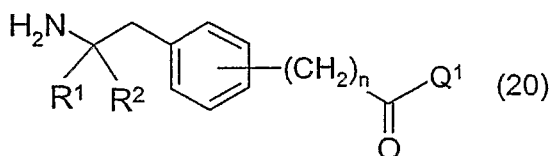
The alkene of formula (17) may be prepared by a palladium mediated coupling of an activated olefin with an aryl halide of formula (18):



In a typical procedure, the aryl halide (18) is coupled with a vinyl ester
10 (e.g. methyl acrylate) in the presence of a suitable palladium catalyst (e.g. tetrakis(triphenylphosphine)palladium(0) of formula $\text{Pd}(\text{PPh}_3)_4$, palladium acetate/tri-*ortho*-tolylphosphine of formula $\text{Pd}(\text{OAc})_2/\text{P}(\text{o-tol})_3$ or (diphenylphosphino)ferrocenyl palladium chloride of formula dppfPdCl_2) in a suitable solvent (e.g. acetonitrile, *N,N*-dimethylformamide, toluene), optionally
15 in the presence of a base such as triethylamine at a temperature between 40°C and 110°C for 8 to 24 hours.

The ketone of formula (18) is a commercial product.

Alternatively a compound of formula (1) may be prepared by reaction of a bromide of formula (7) and an amine of formula (20):

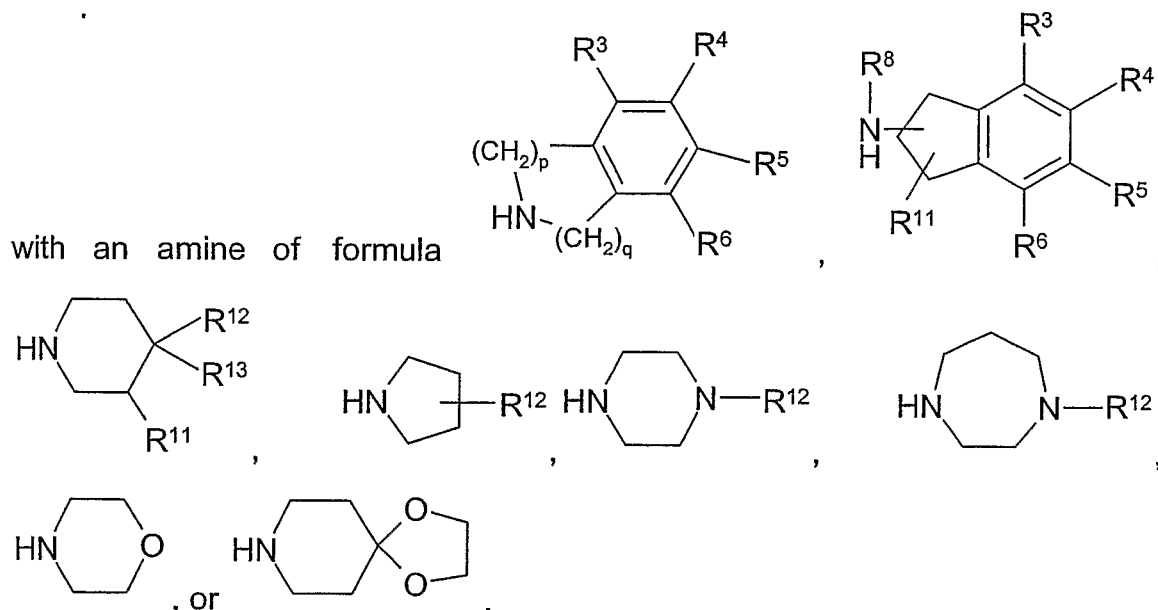
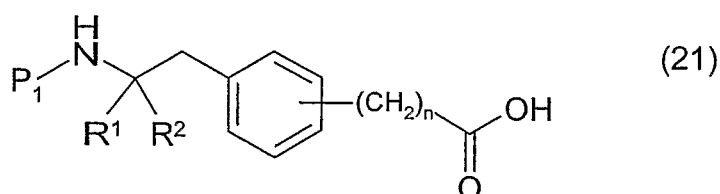


20

where R^1 , R^2 , Q^1 and n are as previously defined for the compounds of the formula (1) unless otherwise stated.

In a typical procedure, the amine of formula (20) is reacted with a bromide of formula (7) optionally in the presence of a solvent or mixture of solvents (e.g. dimethylsulfoxide, toluene, *N,N*-dimethylformamide, acetonitrile), optionally in the presence of a suitable base (e.g. triethylamine, diisopropylethylamine, potassium carbonate) at a temperature comprised between 60°C and 120°C, for 12 to 48 hours. The resulting intermediate amino ketone can then be reduced using a suitable reducing agent such as sodium borohydride or diisobutyl aluminium hydride.

The amide of formula (20) may be prepared by coupling an acid of formula (21) incorporating a suitable amine protecting group P1:



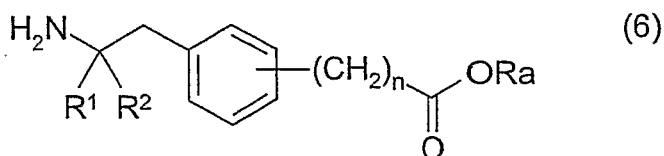
The coupling is generally carried out in an excess of said amine as an acid receptor, with a conventional coupling agent (e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride or *N,N'*-dicyclohexylcarbodiimide), optionally in the presence of a catalyst (e.g. 1-hydroxybenzotriazole hydrate or 1-hydroxy-7-azabenzotriazole), and optionally in the presence of a tertiary amine base (e.g. *N*-methylmorpholine, triethylamine or diisopropylethylamine). The reaction may

be undertaken in a suitable solvent such as pyridine, dimethylformamide, tetrahydrofuran, dimethylsulfoxide, dichloromethane or ethyl acetate, and at temperature comprised between 10°C and 40°C (room temperature) for a period of 1-24 hours.

- 5 Said amine is either commercially available or may be prepared by conventional methods well known to the one skilled in the art (e.g. reduction, oxidation, alkylation, transition metal-mediated coupling, protection, deprotection etc...) from commercially available material.

10 The acid of formula (21) may be prepared from the corresponding ester of formula (6).

The acid of formula (21), where R¹ and R² are both C₁-C₄ alkyl, may be prepared from the ester (6) incorporating a suitable amine protecting group P1 either before or after the acid formation:

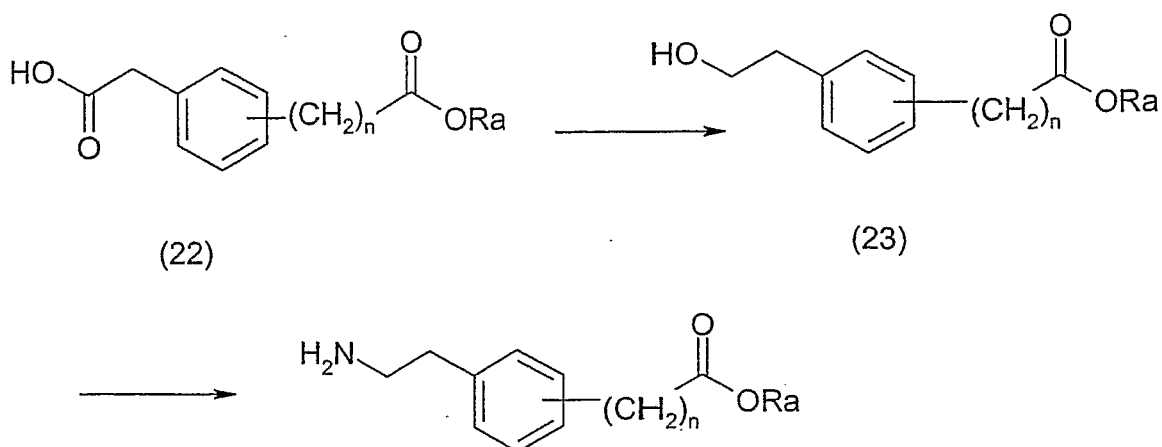


- 15 wherein Ra is a suitable acid protecting group, preferably a (C₁-C₄)alkyl group, which includes, but is not limited to, methyl and ethyl, according to any method well-known to the one skilled in the art to prepare an acid from an ester, without modifying the rest of the molecule. For example, the ester may be hydrolysed by treatment with aqueous acid or base (e.g. hydrogen chloride, potassium
- 20 hydroxide, sodium hydroxide or lithium hydroxide), optionally in the presence of a solvent or mixture of solvents (e.g. water, 1,4-dioxan, tetrahydrofuran/water), at a temperature comprised between 20°C and 100°C, for a period of 1 to 40 hours.

The amine of formula (6), where R¹ and R² are both H, may be prepared

25 according to the following scheme:

Scheme 3



wherein R^1 , R^2 and Ra are as previously defined.

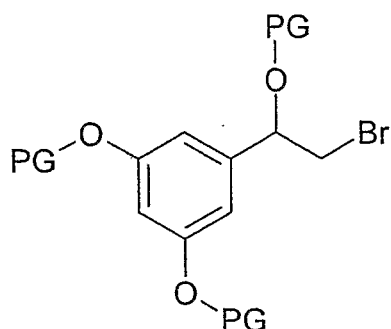
In a typical procedure, the acid of formula (22) is preferentially reduced
 5 to the corresponding alcohol (23) in the presence of the ester. This may be performed by formation of the acyl imidazole or mixed anhydride and subsequent reduction with sodium borohydride or another suitable reducing agent.

Said primary alcohol of formula (23) is then converted into a leaving
 10 group such as mesylate, tosylate, bromide or iodide and displaced with appropriate amine nucleophile. The preferred nucleophile is azide ion which can then be reduced to the primary amine *via* hydrogenation or triphenylphosphine. Alternative nucleophiles could include ammonia or alkylamines such as benzylamine or allylamine and subsequent cleavage of the
 15 alkyl group to furnish the amine.

For some of the steps of the here above described process of preparation of the compounds of formula (1), it may be necessary to protect potential reactive functions that are not wished to react, and to cleave said protecting groups in
 20 consequence. In such a case, any compatible protecting radical can be used. In particular methods of protection and deprotection such as those described by T.W. GREENE (*Protective Groups in Organic Synthesis*, A. Wiley-Interscience

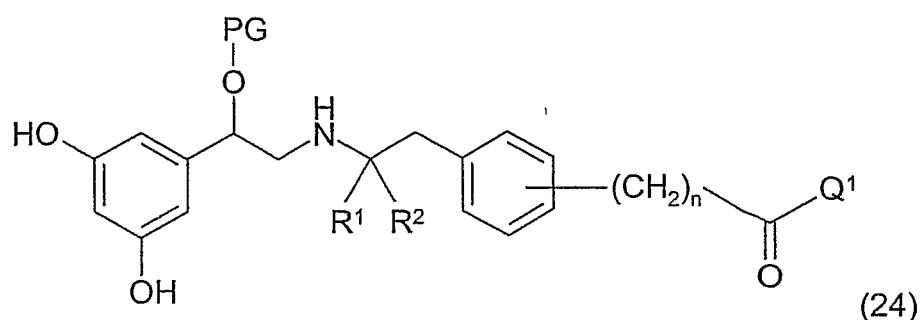
Publication, 1981) or by P. J. Kocienski (*Protecting groups*, Georg Thieme Verlag, 1994), can be used.

For example, in the above processes, the bromine of formula (7) may be replaced by a protected bromine of formula



The bromide may be prepared in a racemic fashion using a reducing agent such as sodium borohydride in a suitable solvent such as ethanol. Alternatively the alcohol may be prepared as either the (R) or (S) enantiomer according to methods well described in the literature (Tetrahedron Letters 1994, 35(50), 9375).¹

The compound of formula (I) would then be obtained by deprotection of a compound of formula



wherein PG represents a suitable alcohol protecting group, typically a silyl group such as TBDMS or TMS, and preferably TBDMS.

The deprotection may be carried out according to the methods described in standard text-books such as "Protective Groups in Organic Synthesis" by T.W.Greene, A.Wiley-Interscience Publication, 1981. In a typical procedure, where PG represents TBDMS, compound of formula (24) is treated with 10-18

eq ammonium fluoride in aqueous methanol, at about 45°C for between 18 and 42 hours. An alternative agent for deprotection would be one equivalent of triethylamine trihydrofluoride in tetrahydrofuran or suitable solvent at room temperature for 12 hours.

- 5 All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the examples and
10 preparations hereto.

Also, the compounds of formula (1) as well as intermediate for the preparation thereof can be purified according to various well-known methods, such as for example crystallization or chromatography.

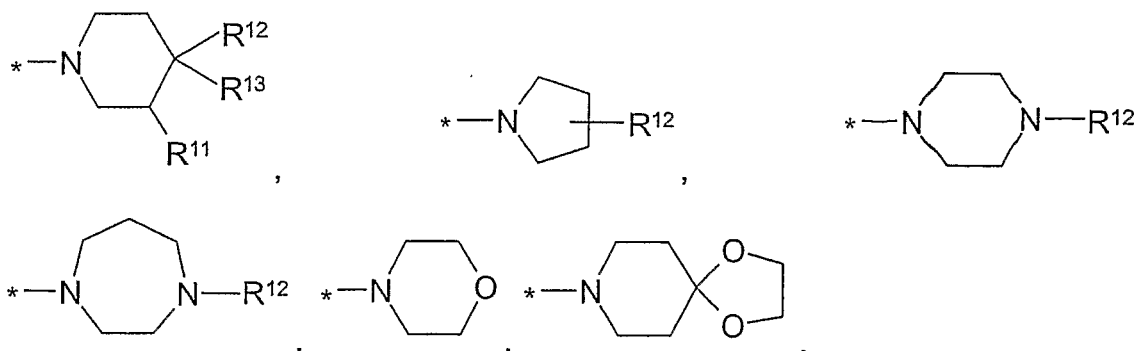
In a preferred embodiment of the invention, Q^2 is a single bond.

- 15 In a preferred embodiment of the invention, A is selected from morpholinyl, pyrrolidinyl, piperidyl, piperazinyl or pyrazolyl, optionally substituted by a methyl group.

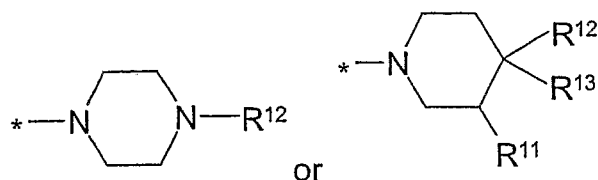
In a preferred embodiment of the invention, A is selected from pyrazolyl optionally substituted by one or two C_1 - C_4 alkyl group.

- 20 In a preferred embodiment of the invention, Q^1 is $^*-NR^8-Q^3$.

In a preferred embodiment of the invention, Q^1 is a group selected from,

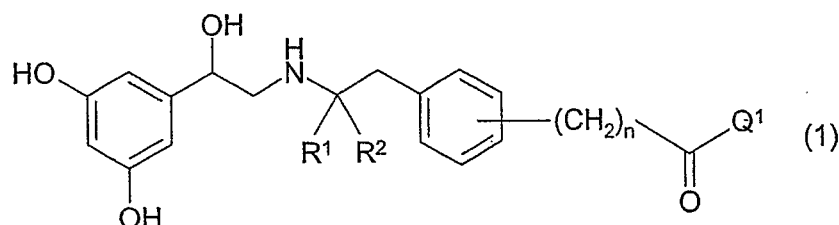


In a preferred embodiment, Q¹ is a group



wherein R¹¹ and R¹³ are H and R¹² is pyridyl or oxadiazolyl optionally substituted with a C₁-C₄ alkyl.

5 The following group of compounds of formula (1) is more preferred:

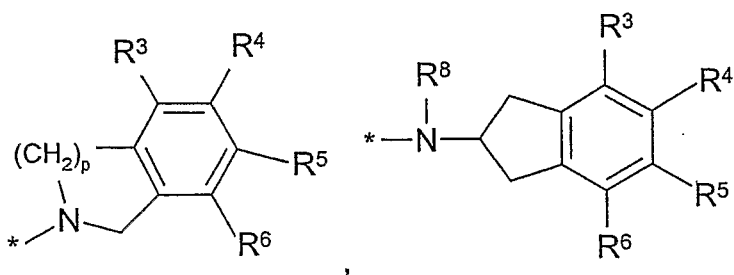


wherein the (CH₂)_n-C(=O)Q¹ group is in the meta or para position,

- R¹ and R² are independently selected from H and C₁-C₄ alkyl,

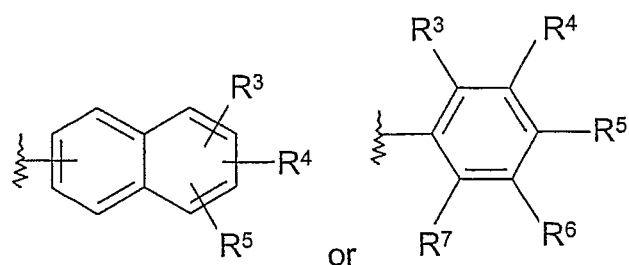
- n is 0, 1 or 2 and

10 - Q¹ is a group selected from,



and a group *-NR⁸-Q²-A, wherein p is 1 or 2, Q² is a C₁-C₄ alkylene, R⁸ is H or C₁-C₄ alkyl and A is pyridyl, C₃-C₁₀ cycloalkyl, said cycloalkyl being optionally bridged by 1, 2, 3 or 4 carbon atoms, preferably 1 or 2 carbon atoms,

15 tetrahydropyranyl, piperidinyl, tetrahydrothiopyranyl or a group



- R^3 , R^4 , R^5 , R^6 and R^7 are the same or different and are selected from H, C_1 - C_4 alkyl, OR^9 , SR^9 , SOR^9 , SO_2R^9 , halo, CN, CF_3 , OCF_3 , $SO_2NR^9R^{10}$, $COOR^9$, $CONR^9R^{10}$, NR^9R^{10} , $NHCOR^{10}$ and phenyl optionally substituted with OH;

- R^9 and R^{10} are the same or different and are selected from H or C_1 - C_4 alkyl

5 and,

- * represents the attachment point to the carbonyl group;

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof.

10 The compounds of formula (1) containing the following substituents are preferred:

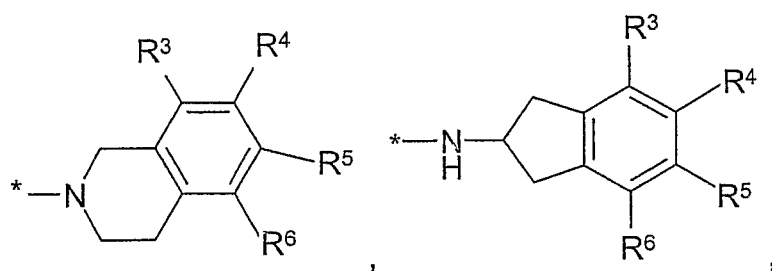
Preferably Q^1 is a group $^*-NH-Q^2-A$, wherein A is cyclopropyl, cyclohexyl, cycloheptyl or adamantyl.

More preferably Q^1 is a group $^*-NH-Q^2-A$, wherein A is cyclohexyl or adamantyl.

Preferably, A is naphthyl optionally substituted with OR^9 .

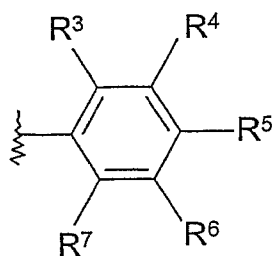
15 Preferably R^8 is H or CH_3 . More preferably, R^8 is H

Preferably, Q^1 is



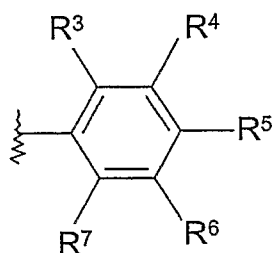
wherein R_3 , R_4 , R_5 and R_6 are H.

Preferably, Q^1 is a group $^*-NH-Q^2-A$, wherein A is a group



- wherein R^3 , R^4 , R^5 , R^6 and R^7 are the same or different and are selected from H, C_1 - C_4 alkyl, OR^9 , SR^9 , halo, CN, CF_3 , OCF_3 , $SO_2NR^9R^{10}$, $COOR^9$, $CONR^9R^{10}$, NR^9R^{10} , $NHCOR^{10}$ and phenyl optionally substituted with OH,
 5 provided at least 2 of R^3 to R^7 are equal to H;
 wherein R^9 and R^{10} are the same or different and are selected from H or C_1 - C_4 alkyl.

More preferably, Q^1 is a group $^*-NH-Q^2-A$, wherein A is a group



- 10 wherein R^3 , R^4 , R^5 , R^6 and R^7 are the same or different and are selected from H, CH_3 , OCH_3 , OCH_2CH_3 , SCH_3 , halo, CF_3 , provided at least 2 of R^3 to R^7 are equal to H.

In the above groups of compounds, the following substituents are particularly preferred:

- 15 Q^2 is $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH(CH_3)-$, $-CH_2CH(CH_3)-$ or $(CH(CH_3)_2)-$, preferably $-CH_2-$.

R^1 is H or C_1 - C_4 alkyl and R^2 is C_1 - C_4 alkyl. More preferably, R^1 is H or CH_3 and R^2 is CH_3 .

n is 1.

- 20 R^1 is H and R^2 is CH_3 and n is 1.

R¹ is CH₃, R² is CH₃ and n is 1.

The following compounds, which can be prepared according to the processes disclosed herein, are preferred:

- 5 *N*-benzyl-2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]acetamide;
N-cyclopropyl-2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]acetamide;
2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-[(1*R*,2*S*)-2-(hydroxymethyl)cyclohexyl]acetamide;
10 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-(3-morpholin-4-ylpropyl)acetamide;
2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-(pyridin-2-ylmethyl)acetamide;
15 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-(2-morpholin-4-ylethyl)acetamide;
2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-isopropylacetamide;
N-(4-chlorobenzyl)-2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]acetamide;
20 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-[2-(dimethylamino)ethyl]acetamide;
N-[2-(diethylamino)ethyl]-2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]acetamide;
25 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-[3-(dimethylamino)propyl]acetamide;
2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-pentylacetamide;
2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-(2-pyrrolidin-1-ylethyl)acetamide;
30 *N*-(2,4-dichlorobenzyl)-2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]acetamide;

- N*-(3,4-dichlorobenzyl)-2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]acetamide;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(4-methoxybenzyl)acetamide;
- 5 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(2-hydroxyethyl)acetamide;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-propylacetamide;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(3-methoxypropyl)acetamide;
- 10 *N*-cyclobutyl-2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]acetamide;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[(1*R*)-1-(1-naphthyl)ethyl]acetamide;
- 15 *N*-2,3-dihydro-1*H*-inden-1-yl-2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]acetamide;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[2-(1-methylpyrrolidin-2-yl)ethyl]acetamide
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(4-fluorobenzyl)acetamide;
- 20 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(4-phenylbutyl)acetamide;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(3-methoxybenzyl)acetamide;
- 25 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(3-ethoxypropyl)acetamide;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(3,4,5-trimethoxybenzyl)acetamide;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[4-(trifluoromethyl)benzyl]acetamide;
- 30 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[2-(trifluoromethyl)benzyl]acetamide;

- 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(3,5-dimethoxybenzyl)acetamide;
2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(2-phenoxyethyl)acetamide;
- 5 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-[(1*S*)-2-hydroxy-1-methylethyl]acetamide;
2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]acetamide;
2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-
- 10 methylpropyl)phenyl]-*N*-[(1*S*,2*S*)-1-(hydroxymethyl)-2-methylbutyl]acetamide;
N-[(1*R*)-1-benzyl-2-hydroxyethyl]-2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]acetamide;
2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-[(1*R*)-1-(hydroxymethyl)propyl]acetamide;
- 15 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]acetamide;
N-[(1*S*)-2-cyclohexyl-1-(hydroxymethyl)ethyl]-2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]acetamide;
2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-
- 20 methylpropyl)phenyl]-*N*-[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetamide;
2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(2-propoxyethyl)acetamide;
2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-
- 25 methylpropyl)phenyl]-*N*-(4-hydroxycyclohexyl)acetamide;
2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(3-propoxypropyl)acetamide;
2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-ethyl-*N*-(2-hydroxyethyl)acetamide;
- 30 1-([3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]acetyl)piperidine-4-carboxamide;

- 5-{2-[(2-{3-[2-(4-acetylpiperazin-1-yl)-2-oxoethyl]phenyl}-1,1-dimethylethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 5-{2-[(2-{3-[2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]phenyl}-1,1-dimethylethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 5 *N*-benzyl-2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-methylacetamide;
- 5-(1-hydroxy-2-{[2-(3-{2-[4-(2-hydroxyethyl)piperazin-1-yl]-2-oxoethyl}phenyl)-1,1-dimethylethyl]amino}ethyl)benzene-1,3-diol;
- 5-(2-{[2-(3-{2-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-2-oxoethyl}phenyl)-1,1-dimethylethyl]amino}-1-hydroxyethyl)benzene-1,3-diol;
- 10 5-{2-[(1,1-dimethyl-2-{3-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]phenyl}ethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-methyl-*N*-(2-phenylethyl)acetamide;
- 15 5-{2-[(1,1-dimethyl-2-{3-[2-oxo-2-(4-pyridin-2-yl)piperazin-1-yl)ethyl]phenyl}ethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[3-(dimethylamino)propyl]-*N*-methylacetamide;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(2-hydroxyethyl)-*N*-propylacetamide;
- 20 *N*-[2-(diethylamino)ethyl]-2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-methylacetamide;
- 5-{2-[(1,1-dimethyl-2-{3-[2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl]phenyl}ethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 25 5-[2-({1,1-dimethyl-2-[3-(2-morpholin-4-yl)-2-oxoethyl]phenyl}ethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-methyl-*N*-[(1*S*)-1-phenylethyl]acetamide;
- 5-[2-({1,1-dimethyl-2-[3-(2-oxo-2-piperidin-1-ylethyl)phenyl]ethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 30 5-(1-hydroxy-2-{[2-(3-{2-[(3*R*)-3-hydroxypyrrolidin-1-yl]-2-oxoethyl}phenyl)-1,1-dimethylethyl]amino}ethyl)benzene-1,3-diol;

- 5-(1-hydroxy-2-{{2-(3-{2-[(3*R*)-3-hydroxypiperidin-1-yl]-2-oxoethyl}phenyl)-1,1-dimethylethyl}amino}ethyl)benzene-1,3-diol;
- 5-{2-[(2-{3-[2-(4-acetyl-1,4-diazepan-1-yl)-2-oxoethyl]phenyl)-1,1-dimethylethyl}amino]-1-hydroxyethyl}benzene-1,3-diol;
- 5 5-(1-hydroxy-2-{{2-(3-{2-[4-(hydroxymethyl)piperidin-1-yl]-2-oxoethyl}phenyl)-1,1-dimethylethyl}amino}ethyl)benzene-1,3-diol;
- N*-(1-{{3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]acetyl}pyrrolidin-3-yl)-*N*-methylacetamide;
- 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-(2-methoxyethyl)-*N*-propylacetamide;
- 10 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-ethyl-*N*-(2-methoxyethyl)acetamide;
- 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-[3-(dimethylamino)-2,2-dimethylpropyl]acetamide;
- 15 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-[3-fluoro-5-(trifluoromethyl)benzyl]acetamide;
- 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-[(1*S*)-1-(hydroxymethyl)-3-methylbutyl]acetamide;
- 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-(1*S*)-2-hydroxy-1-phenylethyl]acetamide;
- 20 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N,N*-diethylacetamide;
- 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-1*H*-pyrazol-5-ylacetamide;
- 25 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-(5-methyl-1*H*-pyrazol-3-yl)acetamide;
- N*-(cyclohexylmethyl)-2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]acetamide;
- ethyl 4-{{3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]acetyl}piperazine-1-carboxylate;
- 30 *N*-(5-chloropyridin-2-yl)-2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]acetamide;

- 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(6-methylpyridin-2-yl)acetamide;
- 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(3-methylpyridin-2-yl)acetamide;
- 5 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-isoquinolin-1-ylacetamide;
- 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(4,6-dimethylpyridin-2-yl)acetamide;
- 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(2-methoxybenzyl)acetamide;
- 10 *N*-[(1*S*)-1-benzyl-2-hydroxyethyl]-2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]acetamide;
- 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(1-ethyl-1*H*-pyrazol-5-yl)acetamide;
- 15 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl)acetamide;
- 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(3-fluorobenzyl)acetamide;
- 1-([3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]acetyl)-*L*-prolinamide;
- 20 5-{2-[(2-{3-[2-(5-amino-3-*tert*-butyl-1*H*-pyrazol-1-yl)-2-oxoethyl]phenyl}-1,1-dimethylethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-[(1*S*)-1-phenylethyl]acetamide;
- 25 5-{2-[(2-{3-[2-(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)-2-oxoethyl]phenyl}-1,1-dimethylethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- N*-[2-(4-Chloro-phenyl)-ethyl]-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide;
- N*-Adamantan-1-yl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 30 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-*N*-[2-(3-fluoro-phenyl)-ethyl]-benzamide;

- N-[2-(2-Chloro-phenyl)-ethyl]-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide;
3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-N-[2-(2,3-dimethyl-phenyl)-ethyl]-benzamide;
- 5 N-[2-(2-Chloro-4-fluoro-phenyl)-ethyl]-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide;
3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-N-[2-(4-methoxy-2,3-dimethyl-phenyl)-ethyl]-benzamide;
N-(3,4-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-
- 10 ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
N-(3,4-Dichloro-benzyl)-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide;
N-(4-Chloro-benzyl)-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide;
- 15 N-Adamantan-1-yl-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide;
N-(4-Chloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
N-(4-Trifluoromethoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-
- 20 ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-pyridin-2-ylmethyl-acetamide;
N-(3,4-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 25 N-(Benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
N-Cyclohexylmethyl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
1-(3,4-Dihydro-1H-isoquinolin-2-yl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-
- 30 ethylamino]-propyl}-phenyl)-ethanone;
N-Benzyl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-methyl-acetamide;

- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(2-hydroxy-benzyl)-acetamide;
- N-(4-Cyano-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- 5 N-(2,4-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-(Benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-(2-Chlorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- 10 N-(3-Methoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-(Cyclohexylmethyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- 15 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-phenethyl-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-chlorophenethyl)-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-phenylphenethyl)-acetamide;
- 20 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4'-hydroxy-biphenyl-3-ylmethyl)-acetamide;
- N-Cycloheptyl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- 25 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-phenethyl-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(2-methylsulfanyl-benzyl)-acetamide;
- N-(2,6-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 30 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-indan-2-yl-acetamide;

- N-(2-Chloro-6-fluorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- N-(4-Chlorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 5 N-(2,5-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-(3,5-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-(2,6-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-
- 10 ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-Biphenyl-2-ylmethyl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-(2-Chlorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 15 N-(3-Methoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- N-(3-Trifluoromethylbenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- N-(3,4-Difluorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-
- 20 propyl}-phenyl)-acetamide;
- N-(2-Methoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- N-(3,4-Dimethylbenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 25 N-(3,4-Dimethoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 4-[[2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetylamino]-methyl]-benzamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-
- 30 indan-1-yl-acetamide;
- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(3-fluoro-phenyl)-ethyl]-benzamide;

- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-chloro-phenyl)-ethyl]-benzamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-naphthalen-1-ylmethyl-acetamide;
- 5 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(2-fluoro-5-trifluoromethyl-benzyl)-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(3-chlorobenzyl)-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(4-10 fluoro-3-trifluoromethyl-benzyl)-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2-methylsulfanyl-benzyl)-acetamide;
- 4-{[2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetyl-amino]-methyl}-benzamide;
- 15 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-sulfamoyl-benzyl)-acetamide;
- 4-{[2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetyl-amino]-methyl}-benzoic acid methyl ester;
- N-(1-Benzyl-piperidin-4-yl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- 20 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-phenethyl]-benzamide;
- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(5-fluoro-2-methyl-phenyl)-ethyl]-benzamide;
- 25 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-trifluoromethyl-phenyl)-ethyl]-benzamide;
- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-(2-naphthalen-1-yl-ethyl)-benzamide;
- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2,4,5-30 trimethyl-phenyl)-ethyl]-benzamide;
- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2,3-dimethyl-phenyl)-ethyl]-benzamide;

- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-hydroxy-3-chloro-phenyl)-ethyl]-benzamide;
3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(4-chloro-phenyl)-ethyl]-benzamide;
- 5 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-hydroxy-5-chloro-phenyl)-ethyl]-benzamide;
3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-chloro-4-fluoro-phenyl)-ethyl]-benzamide;
2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2-methyl-benzyl)-acetamide;
- 10 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(3-methyl-benzyl)-acetamide;
2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-methyl-benzyl)-acetamide;
- 15 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2-methoxy-benzyl)-acetamide
2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-methoxy-benzyl)-acetamide;
2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2,3-dimethyl-benzyl)-acetamide;
- 20 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(3,4-dimethyl-benzyl)-acetamide;
2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2-chloro-6-methyl-benzyl)-acetamide;
- 25 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(3-chloro-4-methyl-benzyl)-acetamide;
2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-[2-(6-methoxy-naphthalen-2-yl)-ethyl]-acetamide;
N-(2-Chlorobenzyl)-3-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]
- 30 propyl}phenyl)propionamide;
N-(2,6-Dichlorobenzyl)-3-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)propionamide;

- 1-(3,4-Dihydro-1H-isoquinolin-2-yl)-3-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)propan-1-one;
N-(2-Chloro-4-fluorobenzyl)-2-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)acetamide;
- 5 *N*-(4-Bromobenzyl)-2-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]-2-methylpropyl}phenyl)acetamide;
 2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]-2-methylpropyl}phenyl)-*N*-(3,4-dimethylphenyl)acetamide;
 2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)-*N*-(2,3-
- 10 dimethylbenzyl)acetamide;
 2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)-*N*-(4-fluorobenzyl)acetamide;
 2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)-1-(4-pyridin-2-yl)piperazin-1-yl)ethanone; and,
- 15 2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]-2-methylpropyl} phenyl)-*N*-(2-phenylpropyl)acetamide.

According to one aspect of the present invention, the compounds of formula (1) wherein the $(\text{CH}_2)_n\text{-C(=O)Q}^1$ group is in the meta position are generally

20 preferred.

Pharmaceutically acceptable salts of the compounds of formula (1) include the acid addition and base salts thereof.

- 25 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,
- 30 hydrobromide/bromide, hydroiodide/iodide, hydrogen phosphate, isethionate, D- and L-lactate, malate, maleate, malonate, mesylate, methylsulphate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate,

phosphate/hydrogen, phosphate/phosphate dihydrogen, pyroglutamate, saccharate, stearate, succinate, tannate, D- and L-tartrate, 1-hydroxy-2-naphthoate tosylate and xinafoate salts.

- 5 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
10 and hemicalcium salts.

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

15

Pharmaceutically acceptable salts of compounds of formula (1) may be prepared by one or more of three methods:

- (i) by reacting the compound of formula (1) with the desired acid or base;
- (ii) by removing an acid- or base-labile protecting group from a suitable
20 precursor of the compound of formula (1) 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 (1) to another by
25 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.

30

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex

comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

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

Hereinafter all references to compounds of formula (1) include references to

15 salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

The compounds of the invention include compounds of formula (1) as hereinbefore defined, including all polymorphs and crystal habits thereof,

20 prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula (1).

As indicated, so-called 'pro-drugs' of the compounds of formula (1) are also

25 within the scope of the invention. Thus certain derivatives of compounds of formula (1) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (1) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of

30 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
5 replacing appropriate functionalities present in the compounds of formula (1) 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).

10 Some examples of prodrugs in accordance with the invention include:

- (i) where the compound of formula (1) 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 (1) is replaced by (C₁-C₈)alkyl;
- 15 (ii) where the compound of formula (1) contains an alcohol functionality (-OH), an ether thereof, for example, a compound wherein the hydrogen of the alcohol functionality of the compound of formula (1) is replaced by (C₁-C₆)alkanoyloxymethyl; and
- (iii) where the compound of formula (1) contains a primary or secondary
20 amino functionality (-NH₂ 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 (1) is/are replaced by (C₁-C₁₀)alkanoyl.

25 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 (1) may themselves act as prodrugs of
30 other compounds of formula (1).

Also included within the scope of the invention are metabolites of compounds of formula (1), 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 (1) contains a methyl group, an hydroxymethyl derivative thereof ($-\text{CH}_3 \rightarrow -\text{CH}_2\text{OH}$);
- (ii) where the compound of formula (1) contains an alkoxy group, an hydroxy derivative thereof ($-\text{OR} \rightarrow -\text{OH}$);
- (iii) where the compound of formula (1) contains a tertiary amino group, a secondary amino derivative thereof ($-\text{NR}^1\text{R}^2 \rightarrow -\text{NHR}^1$ or $-\text{NHR}^2$);
- 10 (iv) where the compound of formula (1) contains a secondary amino group, a primary derivative thereof ($-\text{NHR}^1 \rightarrow -\text{NH}_2$);
- (v) where the compound of formula (1) contains a phenyl moiety, a phenol derivative thereof ($-\text{Ph} \rightarrow -\text{PhOH}$); and
- (vi) where the compound of formula (1) contains an amide group, a
15 carboxylic acid derivative thereof ($-\text{CONH}_2 \rightarrow \text{COOH}$).

Compounds of formula (1) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (1) contains an alkenyl or alkenylene group, geometric *cis/trans* (or *Z/E*) isomers
20 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 (1) 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
25 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 (1), including compounds exhibiting more than one type of isomerism, and mixtures
30 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.

5

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).

10

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 (1) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting

15 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

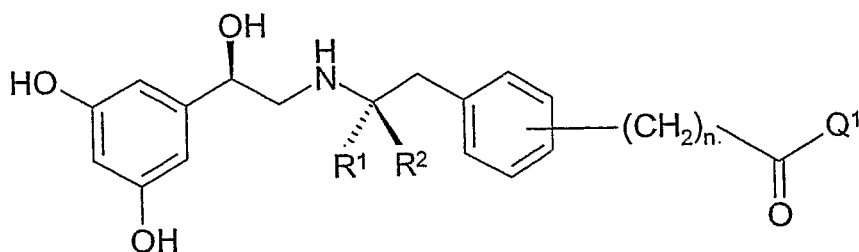
20 obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine,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

25 enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel (Wiley, New York, 1994).

30

According to one aspect of the present invention, the (R,R)-stereoisomer of the formula below, wherein R^1 is hydrogen and R^2 is C_1 - C_4 alkyl, preferably methyl, and n and Q^1 are as defined above, is generally preferred:



5 The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (1) 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.

10 Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^2H and ^3H , 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 .

15

Certain isotopically-labelled compounds of formula (1), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^3H , and carbon-14, *i.e.* ^{14}C , are particularly useful for this purpose in view of their ease of incorporation

20 and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^2H , 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

25 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.

- 5 Isotopically-labeled compounds of formula (1) 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 reagents in place of the non-labeled reagent previously employed.

10

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 (1), their pharmaceutically acceptable salts
15 and/or derived forms, are valuable pharmaceutically active compounds, which are suitable for the therapy and prophylaxis of numerous disorders in which the β_2 receptor is involved or in which agonism of this receptor may induce benefit, in particular the allergic and non-allergic airways diseases but also in the treatment of other diseases such as, but not limited to those of the nervous
20 system, premature labor, congestive heart failure, depression, inflammatory and allergic skin diseases, psoriasis, proliferative skin diseases, glaucoma and in conditions where there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

- Compounds of the invention intended for pharmaceutical use may be
25 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.

- 30 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, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules 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).

5 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,
10 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.

15

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
20 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
25 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.

30 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,
5 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
10 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 tableting. The final formulation may
15 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,
20 1980).

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellaable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula (1),
25 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 (1) 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
30

to 88 weight % of the solutes. Alternatively, the compound of formula (1) 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

and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

- 5 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.

10

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.

- 15 The solubility of compounds of formula (1) 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
20 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 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-
25 coated stents and poly(*dl*-lactic-coglycolic)acid (PGLA) microspheres.

- The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting
30 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).

- 5 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
10 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
15 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 or 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
20 as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. 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
25 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.

30

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.

- 5 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
10 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 1 μ g to 20mg of
15 the compound of the invention per actuation and the actuation volume may vary from 1 μ l to 100 μ l. A typical formulation may comprise a compound of formula (1), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

20

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.

- 25 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.
- 30 In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with

the invention are typically arranged to administer a metered dose or "puff" containing from 0.001mg to 10mg of the compound of formula (1). The overall daily dose will typically be in the range 0.001mg to 40mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of formula (1) are particularly suitable for an administration by inhalation

10 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.

15 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, 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, gelatin 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.

- 5 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.

10

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.

15

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

25

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (1) 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.

30

The kit of the invention is particularly suitable for administering different dosage forms, for example 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, an intravenous daily dose may only require from 0.001mg to 40mg. 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 65kg 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.

According to another embodiment of the present invention, the compounds of the formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, can also be used as a combination with one or more additional therapeutic agents to be co-administered to a patient to obtain some particularly desired therapeutic end result such as the treatment of pathophysiologically-relevant disease processes including, but not limited to (i) bronchoconstriction, (ii) inflammation, (iii) allergy, (iv) tissue destruction, (v) signs and symptoms such as breathlessness, cough. The second and more additional therapeutic agents may also be a compound of the formula (1), or a pharmaceutically acceptable salt, derived forms or compositions thereof, or one or more β_2 agonists known in the art. More typically, the second and more therapeutic agents will be selected from a different class of therapeutic agents.

As used herein, the terms "co-administration", "co-administered" and "in combination with", referring to the compounds of formula (1) and one or more other therapeutic agents, is intended to mean, and does refer to and include the following:

- 5 • simultaneous administration of such combination of compound(s) of formula (1) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components at substantially the same time to said patient,
- 10 • substantially simultaneous administration of such combination of compound(s) of formula (1) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at substantially the same time by said patient, whereupon said components are released at
15 substantially the same time to said patient,
- sequential administration of such combination compound(s) of formula (1) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at consecutive times by said patient with a
20 significant time interval between each administration, whereupon said components are released at substantially different times to said patient; and
- sequential administration of such combination of compound(s) of formula (1) and therapeutic agent(s) to a patient in need of treatment, when such
25 components are formulated together into a single dosage form which releases said components in a controlled manner whereupon they are concurrently, consecutively, and/or overlappingly administered at the same and/or different times by said patient,

where each part may be administered by either the same or different route.

Suitable examples of other therapeutic agents which may be used in combination with the compound(s) of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, include, but are by no means limited to :

- 5 (a) 5-Lipoxygenase (5-LO) inhibitors or 5-lipoxygenase activating protein (FLAP) antagonists,
- (b) Leukotriene antagonists (LTRAs) including antagonists of LTB₄, LTC₄, LTD₄, and LTE₄,
- (c) Histamine receptor antagonists including H1 and H3 antagonists,
- 10 (d) α_1 - and α_2 -adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use,
- (e) muscarinic M3 receptor antagonists or anticholinergic agents,
- (f) PDE inhibitors, e.g. PDE3, PDE4 and PDE5 inhibitors,
- (g) Theophylline,
- 15 (h) Sodium cromoglycate,
- (i) COX inhibitors both non-selective and selective COX-1 or COX-2 inhibitors (NSAIDs),
- (j) Oral and inhaled glucocorticosteroids, such as DAGR (dissociated agonists of the corticoid receptor),
- 20 (k) Monoclonal antibodies active against endogenous inflammatory entities,
- (l) Anti-tumor necrosis factor (anti-TNF- α) agents,
- (m) Adhesion molecule inhibitors including VLA-4 antagonists,
- (n) Kinin-B₁- and B₂-receptor antagonists,
- (o) Immunosuppressive agents,
- 25 (p) Inhibitors of matrix metalloproteases (MMPs),
- (q) Tachykinin NK₁, NK₂ and NK₃ receptor antagonists,
- (r) Elastase inhibitors,
- (s) Adenosine A2a receptor agonists,
- (t) Inhibitors of urokinase,
- 30 (u) Compounds that act on dopamine receptors, e.g. D2 agonists,
- (v) Modulators of the NF κ B pathway, e.g. IKK inhibitors,

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

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

(y) Antibiotics,

5 (z) HDAC inhibitors, and,

(aa) PI3 kinase inhibitors.

According to the present invention, combination of the compounds of formula (1) with :

- H3 antagonists,
- 10 - Muscarinic M3 receptor antagonists,
- PDE4 inhibitors,
- glucocorticosteroids,
- Adenosine A2a receptor agonists,
- Modulators of cytokine signalling pathways such as p38 MAP kinase or syk
- 15 kinase, or,
- Leukotriene antagonists (LTRAs) including antagonists of LTB₄, LTC₄, LTD₄, and LTE₄,
- are preferred.

According to the present invention, combination of the compounds of formula (1) 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
- 25 furoate, or
- muscarinic M3 receptor antagonists or anticholinergic agents including in particular ipratropium salts, namely bromide, tiotropium salts, namely bromide, oxitropium salts, namely bromide, perenzepine, and telenzepine,

are further preferred.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment. The description, which follows, concerns the therapeutic applications to which the compounds of formula (1) may be put.

The compounds of formula (1) have the ability to interact with the $\beta 2$ receptor and thereby have a wide range of therapeutic applications, as described further below, because of the essential role which the $\beta 2$ receptor plays in the physiology of all mammals.

Therefore, a further aspect of the present invention relates to the compounds of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for use in the treatment of diseases, disorders, and conditions in which the $\beta 2$ receptor is involved. More specifically, the present invention also concerns the compounds of formula (1), 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 :

- 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 bronchiolitis,

- 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,
- 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.

25 A still further aspect of the present invention also relates to the use of the compounds of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for the manufacture of a drug having a β_2 agonist activity. In particular, the present inventions concerns the use of the compounds of formula (1), or pharmaceutically acceptable salts, derived forms

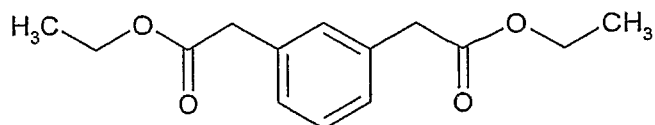
or compositions thereof, for the manufacture of a drug for the treatment of β 2-mediated diseases and/or conditions, in particular the diseases and/or conditions listed above.

As a consequence, the present invention provides a particularly
5 interesting method to treat a mammal, including a human being, with an effective amount of a compound of formula (1), or a pharmaceutically acceptable salt, derived form or composition thereof. More precisely, the present invention provides a particularly interesting method for the treatment of
10 a β 2-mediated diseases and/or conditions in a mammal, including a human being, in particular the diseases and/or conditions listed above, comprising administering said mammal with an effective amount of a compound of formula (1), its pharmaceutically acceptable salts and/or derived forms.
The following examples illustrate the preparation of the compounds of the formula (1):

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Preparation 1

Diethyl 2,2'-(1,3-phenylene)diacetate



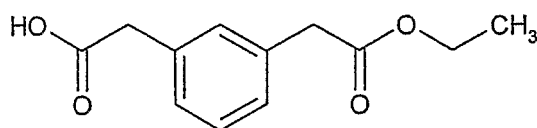
2,2'-(1,3-Phenylene)diacetic acid (10.0g, 51mmol) was dissolved in ethanol
20 (100mL) and the solution treated dropwise with catalytic acetyl chloride (2.5mL). The reaction mixture was stirred at reflux for 18 hours before being allowed to cool and concentrated under reduced pressure. The residue was taken up in ethyl acetate (100mL) and washed with sodium bicarbonate solution (3 x 50mL) and brine (3 x 50mL). The organic phase was dried over
25 magnesium sulphate and concentrated under reduced pressure. The residue was triturated with pentane to yield the title product, 11.8g.

^1H NMR (CDCl_3 , 400MHz) δ 1.31 (6H, t), 3.65 (4H, s), 4.20 (4H, q), 7.24-7.36 (4H, m).

LRMS : m/z ES^+ 251 $[\text{MH}]^+$

5 Preparation 2

[3-(2-Ethoxy-2-oxoethyl)phenyl]acetic acid



A solution of the diester from preparation 1 (44.3g, 177mmol) and 2,2'-(1,3-phenylene)diacetic acid (59.2g, 308mmol) in ethanol (24mL) and dioxan
10 (290mL) was treated dropwise with 12M hydrochloric acid (4.9mL, 58.8mmol). The reaction mixture was stirred and heated under reflux for 18 hours before being allowed to cool and concentrated to low volume. The reaction mixture was diluted with toluene (125mL) and the resulting slurry filtered. The filtrate was concentrated under reduced pressure and the residue taken up in water
15 and neutralised with sodium bicarbonate. The mixture was diluted with ethyl acetate (200mL) and the organic layer was separated and washed with sodium bicarbonate solution (5x30mL) and brine (50mL). The combined aqueous extracts were acidified to pH 3 with 6M hydrochloric acid and extracted with ether (3 x 30mL). The organics were combined, dried over magnesium sulphate
20 and concentrated under reduced pressure. The residue was triturated with pentane giving the title compound as a colourless solid 10.8g.

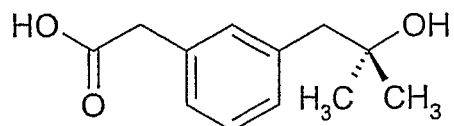
^1H NMR (CD_3OD , 400MHz) δ 1.25 (3H, t), 3.60 (2H, m), 3.63 (2H, m), 4.15 (2H, q), 7.18-7.32 (4H, m)

LRMS : m/z ES^+ 245 $[\text{MNa}]^+$

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Preparation 3

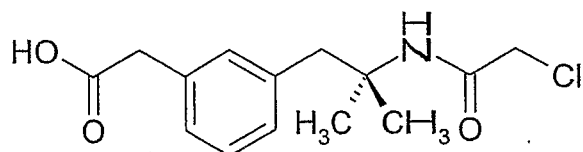
[3-(2-Hydroxy-2-methyl-propyl)-phenyl]-acetic acid



- A solution of the acid of preparation 2 (6.85g, 32mmol) in diethyl-ether (100mL) was cooled to 0°C and treated with a 3M solution of methylmagnesium bromide in ether (23.5mL, 70.0mmol). The reaction mixture was allowed to warm gradually to room temperature. After 2 hours the reaction was quenched by addition of saturated aqueous ammonium chloride solution (200mL). The organic phase was separated and washed with brine (100mL), dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography on silica gel eluting with pentane:dichloromethane (60:40 to 0:100) gave the title compound as a colourless oil, 6.23g.
- ¹H NMR (CDCl₃, 400MHz) δ 1.22 (6H, s), 2.75 (2H, s), 3.63 (2H, s), 7.12-7.30 (4H, m).
- LRMS: m/z ES⁺ 209 [MH]⁺

Preparation 4

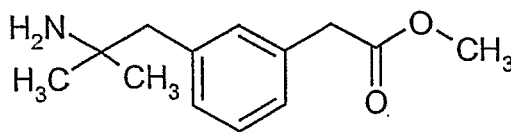
- {3-[2-(2-Chloro-acetyl-amino)-2-methyl-propyl]-phenyl}-acetic acid**



- 2-Chloroacetonitrile (8.8mL, 140mmol) was added to a solution of the alcohol from preparation 3 (16.0g, 70mmol), in acetic acid (33mL). The resulting solution was cooled to 0°C, treated with concentrated sulfuric acid (33mL), and the reaction mixture allowed to warm gradually to room temperature. After 4 hours the reaction mixture was poured onto ice and basified with solid sodium carbonate. The solution was extracted with ethyl acetate (2x500mL) and the combined organic extracts dried over magnesium sulphate and concentrated under reduced pressure to give the title product as a colourless solid, 19.0g.
- ¹H NMR (CDCl₃, 400MHz) δ 1.36 (6H, s), 3.02 (2H, s), 3.62 (2H, s), 3.95 (2H, s), 6.19 (1H, br s), 7.06-7.31 (4H, m)
- LRMS: m/z ES⁻ 282, 284 [M-H]⁻

Preparation 5

- Methyl [3-(2-amino-2-methylpropyl)phenyl]acetate**



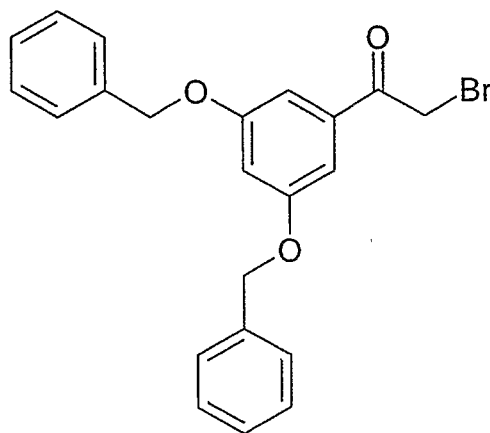
A solution of the amide from preparation 4 (5.1g, 18mmol), thiourea (1.6g, 21mmol) and acetic acid (18mL) in methanol (80mL) was heated to reflux under a nitrogen atmosphere for 16 hours. The reaction mixture was cooled and
5 filtered. The filtrate was concentrated under reduced pressure and the residue dissolved in methanol (150mL). The solution was saturated with hydrogen chloride gas and then heated to reflux for 16 hours. The solvent was reduced *in vacuo* and the residue partitioned between ethyl acetate (200mL) and 5% aqueous sodium carbonate (200mL). The organic extract was washed with
10 saturated sodium chloride (100mL), dried over sodium sulphate and reduced *in vacuo*. The residue was purified on strong cation exchange resin, eluting with methanol and then 2N ammonia in methanol to elute the product. The eluent was concentrated *in vacuo* to give the title compound as a yellow oil, 2.68g.

^1H NMR (CDCl_3 , 400MHz) δ 1.14 (6H, s), 2.68 (2H, s), 3.62 (2H, s), 3.69 (3H, s), 7.08-7.16 (3H, m), 7.23-7.27 (1H, m).

LRMS : m/z ES^+ 236 $[\text{MH}]^+$

Preparation 6

1-[3,5-bis(Benzyloxy)phenyl]-2-bromoethanone



20

To a stirred solution of 1-[3,5-bis(benzyloxy)phenyl]ethanone (5g, 15.04mmol) in tetrahydrofuran (60mL) and methanol (35mL) was added tetrabutylammonium tribromide (7.25g, 15.04mmol) in tetrahydrofuran (20mL)

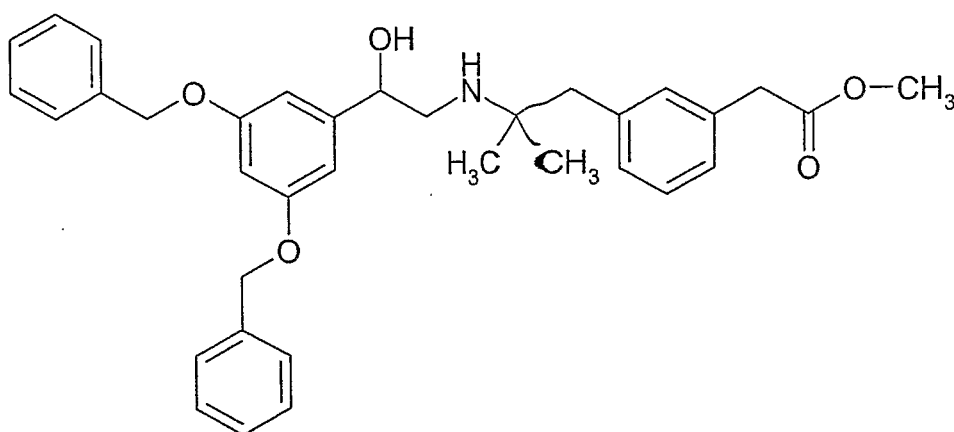
at room temperature. The reaction mixture was stirred for 24 hours and the solvent removed *in vacuo*. The residue was dissolved in ethyl acetate (100mL) and washed with water (2 x 50mL). The combined organic extracts were dried over magnesium sulfate and concentrated to afford the desired compound as a yellow oil in quantitative yield.

¹H NMR (400 MHz, CDCl₃) δ 4.38 (2H, s), 5.05 (4H, s), 6.81 (1H, s), 7.10-7.25 (2H, m), 7.30-7.42 (10H, m).

LRMS: m/z APCI⁺ 413 [MH⁺].

10 Preparation 7

Methyl {3-[2-({2-[3,5-bis(benzyloxy)]phenyl}-2-hydroxyethyl)amino)-2-methylpropyl]phenyl}acetate



A stirred solution of the compound of preparation 6 (4.7g, 11.4mmol), the compound of preparation 5 (2.53g, 11.4mmol) and N-ethyldiisopropylamine (2mL, 11.4mmol) in tetrahydrofuran (140mL) were heated under reflux for 24 hours. The reaction mixture was cooled to room temperature, sodium borohydride (647mg, 17.10mmol) was added and the mixture stirred for 5 hours at room temperature. The reaction was quenched by addition of methanol (5mL) and the solvent was evaporated *in vacuo*. The residual orange oil was partitioned between dichloromethane (60mL) and saturated sodium hydrogen carbonate solution (40mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 x 40mL). The organic extracts were combined and concentrated *in vacuo*. Purification by column

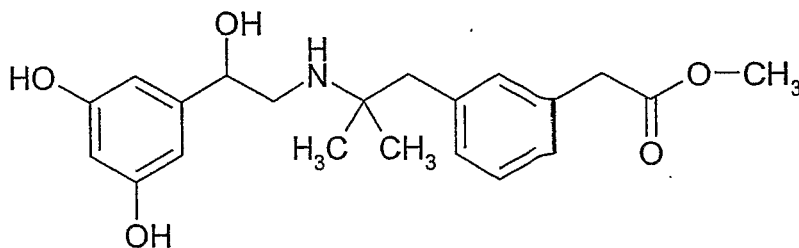
chromatography on silica gel using dichloromethane and then dichloromethane:methanol:0.88 ammonia (95:5:0.5) as eluent afforded the desired product, 4.50g (70%).

¹H NMR (400 MHz, CD₃OD) δ 1.01 (6H, d), 2.61 (4H, m), 3.58 (2H, s), 3.62 (3H, s), 4.61-4.64 (1H, dd), 5.03 (4H, s), 6.54-6.55 (1H, t), 6.63-6.64 (2H, d), 7.00-7.01 (1H, d), 7.08-7.10 (2H, d), 7.16-7.20 (1H, t), 7.25-7.28 (2H, m), 7.31-7.34 (4H, t), 7.38-7.40 (4H, d).

LRMS: m/z APCI⁺ 554 [MH⁺].

10 Preparation 8

Methyl [3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]acetate



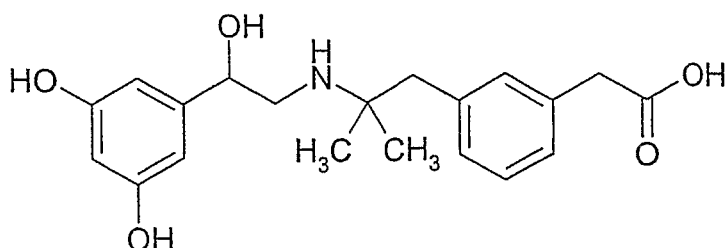
A mixture of the compound of preparation 7 (4.50g, 8.13mmol), ammonium formate (3.59 g, 113.86mmol) and palladium hydroxide on carbon (900mg) in ethanol (80mL) was heated under reflux for 24 hours. The reaction mixture was cooled to room temperature, filtered through Arbocel® and washed with methanol (3 x 20mL). The filtrate was concentrated *in vacuo* to give an orange oil as the desired product, 2.64g (87%).

¹H NMR (400 MHz, CD₃OD) δ 1.06 (3H, s), 1.07 (3H, s), 2.67-2.87 (4H, m), 3.62 (2H, s), 3.66 (3H, s), 4.56-4.59 (1H, q), 6.18-6.19 (1H, t), 6.34 (2H, d), 7.03-7.23 (4H, m).

LRMS: m/z APCI⁺ 374 [MH⁺].

25 Preparation 9

[3-(2-[[2-(3,5-Dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]acetic acid



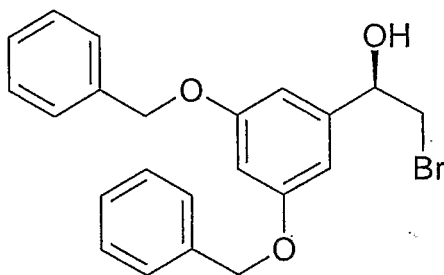
1M Lithium hydroxide solution (21.2 mL, 21.2 mmol) was added dropwise to a solution of the compound of preparation 8 (2.64g, 7.07mmol) in tetrahydrofuran (30mL) and the reaction mixture was stirred for 24 hours. A 1M solution of
 5 hydrochloric acid (21.2mL, 21.2mmol) was added and the solvent removed *in vacuo*. The crude residue obtained was azeotroped with methanol, and the product used subsequently without further purification.

¹H NMR (400 MHz, DMSO-d₆) δ 1.07 (6H, s), 2.74-2.87 (4H, m), 3.39 (2H, s), 4.63-4.61 (1H, d), 6.14-6.15 (1H, t), 6.24-6.25 (2H, d), 6.96-7.22 (4H, m).

10 LRMS: m/z APCI⁺ 357 [MH⁺].

Preparation 10

1-(3,5-Bis-benzyloxy-phenyl)-2-bromo-ethanol



15 Trimethylboroxine (0.58mL, 4.20mmol) in toluene (15mL) was added to (R)-2-(diphenylhydroxymethylpyrrolidine) (1.48g, 5.80mmol) and the reaction stirred under nitrogen for 15 minutes. The solution was concentrated to a volume of 5mL by distillation at 1 atmosphere and further toluene (10mL) was added. The distillation/redilution cycle was performed 3 times to furnish an orange solution
 20 (volume of toluene 10mL). This solution was added in one portion to a stirred solution of the compound of preparation 6 (5.00g, 12.2mmol) in tetrahydrofuran (72mL) at -8°C under nitrogen. To this mixture a solution of borane dimethylsulfide complex (1.60mL, 16.8mmol) in tetrahydrofuran (16mL) was

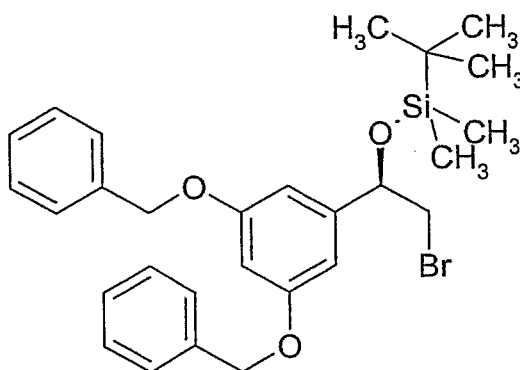
added by syringe pump over 90 minutes maintaining a temperature of -8°C . Once addition was complete methanol (16mL) was added by syringe pump over 45 minutes maintaining a temperature of 0°C and the reaction allowed to warm to room temperature over 12 hours. The solvent was removed *in vacuo* to give a yellow oil and methanol (80mL) added and removed *in vacuo*. Methanol (80mL) was added and removed *in vacuo* and the resulting yellow oil dissolved in dichloromethane (500mL), washed with 1M aqueous hydrochloric acid (96mL), water (2x120mL), dried (magnesium sulfate) and the solvent removed *in vacuo* to furnish the title compound as a cream solid, 4.73g.

^1H NMR (400MHz, CD_3OD) δ 3.52 (1H, m), 3.62 (1H, m), 4.82 (1H, dd), 5.09 (4H, s), 6.60 (1H, m), 6.69 (1H, s), 6.70 (1H, s), 7.33 (2H, m), 7.40 (4H, m), 7.45 (5H, m).

LRMS: m/z electrospray 413, 415 $[\text{M}+\text{H}^+]$.

15 Preparation 11

[1-(3,5-Bis-benzyloxy-phenyl)-2-bromo-ethoxy]-tert-butyl-dimethyl-silane



Tert-butyldimethylsilanetriflate (3.40mL, 7.45mmol) was added dropwise to a solution of the compound of preparation 10 (3.08g, 7.45mmol) and 2,6-lutidine (1.75mL, 15.0mmol) in dichloromethane (74mL) at 0°C , under nitrogen. The reaction was allowed to warm to room temperature over 12 hours and then washed with 1M aqueous hydrochloric acid (2x24mL), water (2x32mL), dried (magnesium sulfate) and the solvent removed *in vacuo* to give a yellow oil. This was purified by column chromatography on silica gel eluting with dichloromethane to furnish the title compound as a colourless oil, 3.51g.

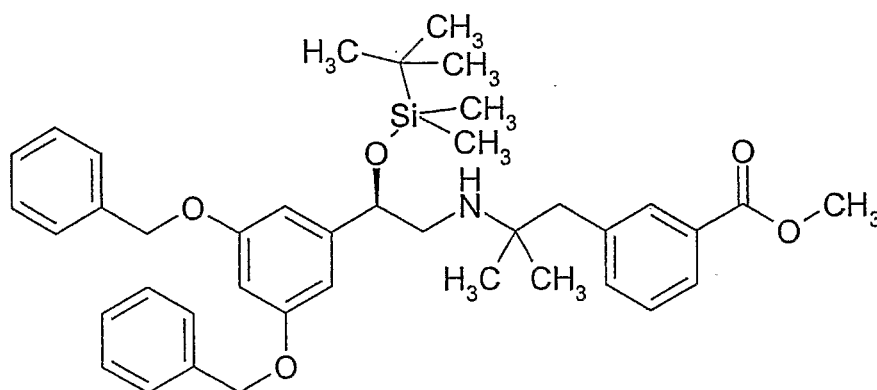
^1H NMR (400MHz, CD_3OD) δ -0.07 (3H, s), 0.13 (3H, s), 0.93 (9H, s), 3.52 (2H, m), 4.86 (1H, dd), 5.10 (4H, s), 6.60 (1H, m), 6.65 (1H, s), 6.66 (1H, s), 7.33 (2H, m), 7.40 (4H, m), 7.45 (4H, m).

LRMS: m/z electrospray 549 $[\text{M}+\text{Na}^+]$.

5

Preparation 12

3-{2-[2-(3,5-Bis-benzyloxy-phenyl)-2-(tert-butyl-dimethyl-silanyloxy)-ethylamino]-2-methyl-propyl}-benzoic acid methyl ester



- 10 A solution of the compound of preparation 11 (2.54g, 4.80mmol) and the compound of preparation 21 (2.00g, 9.60mmol) in dichloromethane (40mL) was heated to 75°C and the solvent allowed to evaporate off. The resulting melt was heated at 75°C for 4 days and then allowed to cool to room temperature. The residue was purified by column chromatography on silica gel eluting with
15 dichloromethane:methanol:880 ammonia (100:0:0 then 95:5:0.5) to furnish the title compound as a yellow oil, 2.00g.

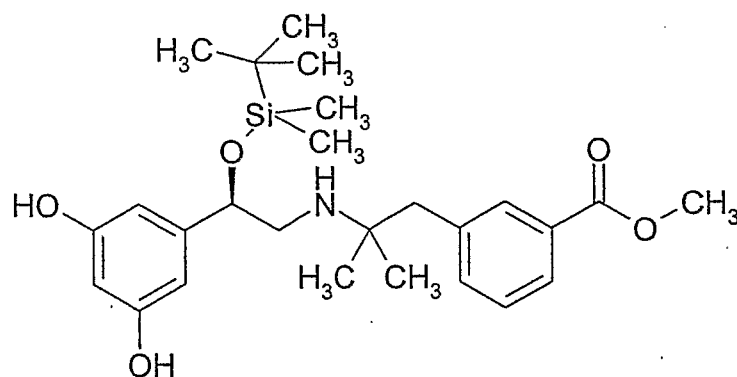
^1H NMR (400MHz, CD_3OD) δ -0.18 (3H, s), -0.04 (3H, s), 0.78 (9H, s), 1.11 (3H, s), 1.13 (3H, s), 2.70 (4H, m), 3.92 (3H, s), 4.70 (1H, dd), 5.12 (4H, s), 6.60 (1H, m), 6.62 (1H, s), 6.63 (1H, s), 7.32 (2H, m), 7.38 (6H, m), 7.45 (4H, m),
20 7.92 (2H, m).

LRMS: m/z electrospray 654 $[\text{M}+\text{H}^+]$.

Preparation 13

3-{2-[2-(tert-Butyl-dimethyl-silanyloxy)-2-(3,5-dihydroxy-phenyl)-ethylamino]-2-methyl-propyl}-benzoic acid methyl ester

25



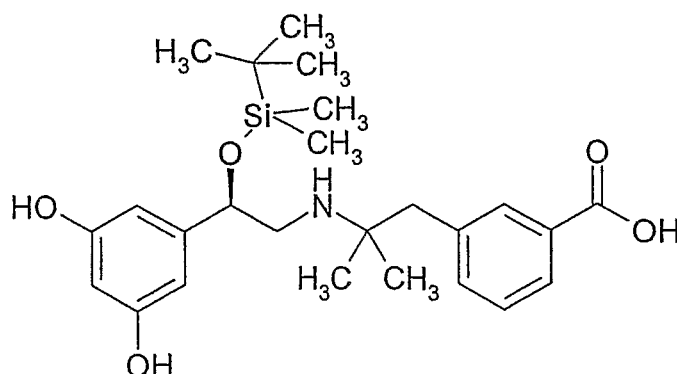
Palladium hydroxide (340mg) was added in one portion to a stirred solution of the compound of preparation 12 (1.97g, 3.00mmol) and ammonium formate (2.17g, 47.1mmol) in ethanol (31mL) at room temperature. The reaction was heated under reflux for 2 hours and allowed to cool to room temperature. The reaction was filtered through Arbocel® and the filtrate concentrated *in vacuo* to furnish the title compound as a white foam, 1.41g.

¹H NMR (400MHz, CD₃OD) δ -0.11 (3H, s), -0.00 (3H, s), 0.81 (9H, s), 1.13 (3H, s), 1.15 (3H, s), 2.70 (4H, m), 3.96 (3H, s), 4.63 (1H, dd), 6.22 (1H, m), 6.33 (1H, s), 6.34 (1H, s), 7.42 (2H, m), 7.92 (2H, m).

LRMS: m/z electrospray 474 [M+H⁺], 496 [MNa⁺], 472 [M-H⁻].

Preparation 14

3-{2-[2-(tert-Butyl-dimethyl-silanyloxy)-2-(3,5-dihydroxy-phenyl)-ethylamino]-2-methyl-propyl}-benzoic acid



1M aqueous lithium hydroxide (9.00mL, 9.00mmol) was added in one portion to a stirred solution of the compound of preparation 13 (1.39g, 2.93mmol) in tetrahydrofuran (30mL) at room temperature. The reaction was stirred at room temperature for 24 hours and 1M aqueous hydrochloric acid (9.00mL,

9.00mmol) was added in one portion. The solvent was removed *in vacuo* to furnish the title compound as a brown foam, 2.06g.

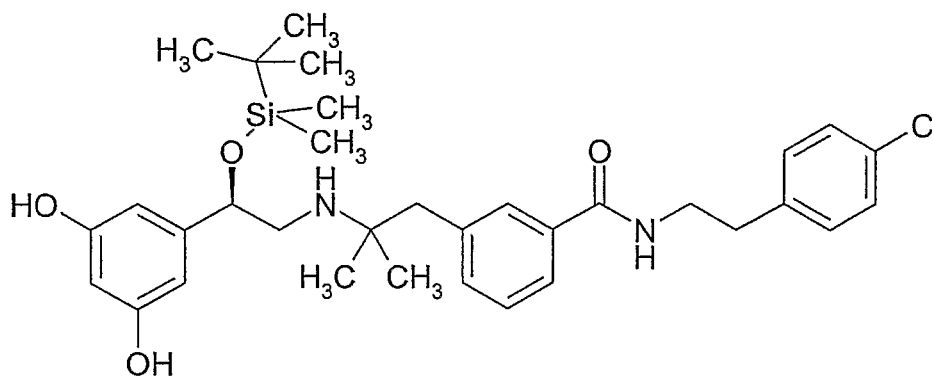
^1H NMR (400MHz, CD_3OD) δ -0.05 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.35 (3H, s), 1.37 (3H, s), 3.08 (2H, m), 3.25 (2H, m), 4.93 (1H, m), 6.29 (1H, m), 6.38 (1H, s), 6.39 (1H, s), 7.42 (2H, m), 7.92 (1H, m), 8.00 (1H, m).

LRMS: m/z electrospray 460 $[\text{M}+\text{H}^+]$.

Preparation 15

3-{2-[2-(tert-Butyl-dimethyl-silanyloxy)-2-(3,5-dihydroxy-phenyl)-

ethylamino]-2-methyl-propyl}-N-[2-(4-chloro-phenyl)-ethyl]-benzamide



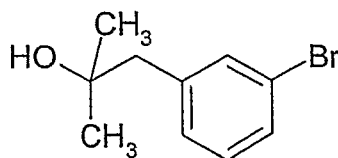
4-Chlorophenethylamine (967mg, 6.20mmol), triethylamine (1.00mL, 7.20mmol), hydroxybenzotriazole (567mg, 4.20mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (910mg, 4.70mmol) were added to a stirred solution of the compound of preparation 14 (2.06g, 3.50mmol) in *N,N*-dimethylformamide (35mL) at room temperature under nitrogen. The reaction was stirred for 12 hours and the solvent removed *in vacuo*, the residue was then azeotroped with toluene (20mL) and purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (100:0:0 then 95:5:0.5 then 90:10:1) and recolumned eluting with ethyl acetate:pentane:880 ammonia (0:100:0 changing to 80:20:5 in 10% steps) to furnish the title compound as a cream foam, 773mg.

^1H NMR (400MHz, CD_3OD) δ -0.10 (3H, s), 0.01 (3H, s), 0.84 (9H, s), 1.12 (3H, s), 1.14 (3H, s), 2.74 (4H, m), 3.94 (2H, m), 3.62 (2H, m), 4.66 (1H, dd), 6.22 (1H, m), 6.34 (1H, s), 6.35 (1H, s), 7.42 (6H, m), 7.67 (2H, m).

LRMS: m/z electrospray 597 [M+H⁺].

Preparation 16

1-(3-Bromophenyl)-2-methylpropan-2-ol



5

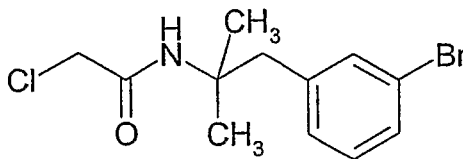
Methylmagnesium bromide (3M solution in diethylether, 51.6mL, 155mmol) was slowly added to a solution of 1-(3-bromo-phenyl)propan-2-one (15.0g, 70mmol) in dry diethylether (200mL) at 0°C. The resulting mixture was left for 3 hours, then cooled to 0°C and slowly quenched with saturated aqueous ammonium chloride solution. The organic phase was washed with brine and dried (sodium sulfate). The yellow oil was then purified by column chromatography on silica gel eluting with dichloromethane:pentane:methanol (90:5:5 by volume to afford a pale yellow oil (13.26 g).

¹H NMR (400MHz, CDCl₃) δ = 7.40 (2H, m), 7.15 (2H, m), 2.74 (2H, s), 1.42 (1H, bs), 1.22 (6H, s).

15

Preparation 17

N-[2-(3-Bromophenyl)-1,1-dimethylethyl]-2-chloroacetamide



20 Chloroacetonitrile (6.63mL, 105mmol) was added to a stirred solution of 1-(3-bromophenyl)-2-methylpropan-2-ol (Preparation 16) (12.0g, 52.0mmol) in acetic acid (25mL) at room temperature. The resulting solution was cooled to 0°C and concentrated sulfuric acid (25mL) was added keeping the temperature <10°C. The resulting solution was left to stir for 1 hour and then poured onto ice and basified by the addition of solid potassium carbonate. The product was extracted with ethyl acetate (2x500mL), the organics combined and washed

25

with water (50mL), dried (sodium sulfate) and the solvent removed *in vacuo* to afford the title compound as an orange solid (16.08g).

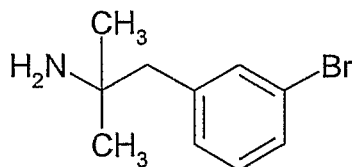
^1H NMR (400MHz, CDCl_3) δ = 7.39-7.32 (1H, d), 7.26 (1H, s), 7.1-7.13 (1H, t), 7.08-7.03 (1H, d), 6.17 (1H, bs), 3.94 (2H, s), 3.02 (2H, s), 1.37 (6H, s).

5 CHN for $\text{C}_{12}\text{H}_{15}\text{BrClNO}$ calc. (found): C 47.32 (47.26), H 4.96 (4.87), N 4.60 (4.65).

LRMS (electrospray) m/z 306 $[\text{M}+\text{H}]^+$

Preparation 18

10 2-(3-Bromophenyl)-1,1-dimethylethylamine



A solution of *N*-[2-(3-bromophenyl)-1,1-dimethylethyl]-2-chloroacetamide (Preparation 17) (32.0g, 105mmol), thiourea (9.60g, 126mmol) and acetic acid (50mL) in ethanol (250mL) was heated to reflux overnight. The reaction mixture

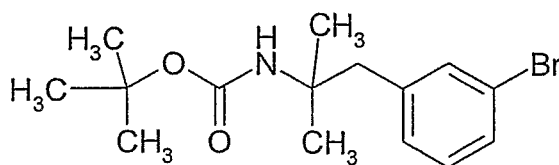
15 was cooled to room temperature and filtered, the filtrate was concentrated *in vacuo* and basified using aqueous sodium hydroxide solution (1M, 450mL). The product was extracted with dichloromethane (2×500mL) and the combined organics washed with brine (50mL), dried (sodium sulfate) and the solvent removed *in vacuo* to afford the title compound as a black oil (23g).

20 ^1H NMR (400MHz, CDCl_3) δ = 7.36-7.32 (2H, m), 7.16-7.08 (2H, m), 2.62 (2H, s), 1.84 (2H, bs), 1.12 (6H, s).

LRMS (electrospray) m/z 228 $[\text{M}+\text{H}]^+$

Preparation 19

25 [2-(3-Bromophenyl)-1,1-dimethylethyl]carbamic acid tert-butyl ester



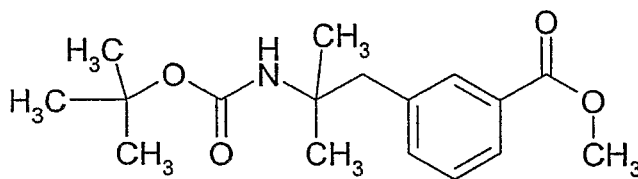
2-(3-Bromophenyl)-1,1-dimethylethylamine (Preparation 18) (5.0g, 22mmol) was treated with di-*tert*-butyl dicarbonate (5.26g, 24mmol) in dichloromethane (50mL) and stirred for 20 hours. The reaction mixture was washed with water (50mL) and the combined organics dried (sodium sulfate) and the solvent removed *in vacuo*. The crude material was purified using a cation exchange column (methanol followed by 2M ammonia in methanol), followed by purification by flash column chromatography on silica gel eluting with dichloromethane to afford the title compound as a brown oil (7.23g).

¹H NMR (400MHz, CDCl₃) δ = 7.35 (1H, d), 7.30 (1H, s), 7.15-7.11 (1H, t), 7.05 (1H, d), 4.24 (1H, bs), 2.97 (2H, s), 1.50 (9H, s), 1.27 (6H, s).

LRMS (electrospray) m/z 350 [M+NH₄]⁺

Preparation 20

3-(2-*tert*-Butoxycarbonylamino-2-methylpropyl)benzoic acid methyl ester



15

A solution of [2-(3-bromophenyl)-1,1-dimethylethyl]carbamic acid *tert*-butyl ester (Preparation 19) (7.0g, 21mmol), [1,1'-*bis*(diphenylphosphino)ferrocene]dichloropalladium(II) (1.74g, 2.1mmol) and triethylamine (5.94mL, 43mmol) in methanol (250mL) was heated to 100°C under 100psi carbon monoxide for 12 hours. The reaction mixture was filtered through Arbocel® and the filtrate concentrated *in vacuo* and purified by flash column chromatography on silica gel eluting with dichloromethane:pentane (50:50 by volume) to afford the title compound as a yellow solid (3.76g).

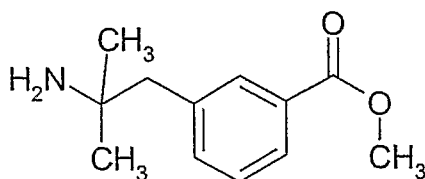
¹H NMR (400MHz, CDCl₃) δ = 7.92-7.90 (1H, m), 7.82 (1H, s), 7.35-7.34 (2H, m), 4.24 (1H, bs), 3.90 (3H, s), 3.05 (2H, s), 1.48 (9H, s), 1.26 (6H, s).

25

LRMS (electrospray) m/z 208 [M+H-BOC]⁺

Preparation 21

3-(2-Amino-2-methylpropyl)benzoic acid methyl ester



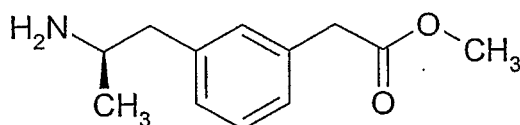
A solution of 3-(2-*tert*-butoxycarbonylamino-2-methylpropyl)benzoic acid methyl ester (Preparation 20) (1.6g, 5.2mmol) in dichloromethane (160mL) at 0°C was treated with trifluoroacetic acid (13.6mL) and left to warm to room temperature over 2 hours. The solvent was removed *in vacuo* and the product purified by cation exchange chromatography (methanol followed by 2M ammonia in methanol) to yield the title compound as an amber oil (1.06g).

¹H NMR (400MHz, CDCl₃) δ = 7.90-7.88 (1H, m), 7.84 (1H, s), 7.36-7.35 (2H, m), 3.90 (3H, s), 2.71 (2H, s), 1.67 (2H, bs), 1.12 (6H, s).

LRMS (electrospray) m/z 208 [M+H]⁺

Preparation 22

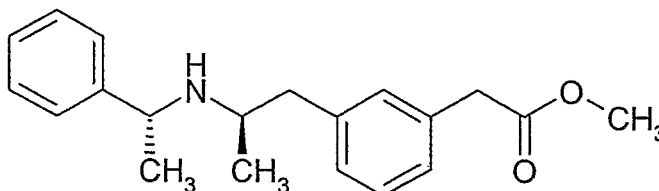
Methyl {3-[(2R)-2-aminopropyl]phenyl}acetate



A solution of methyl [3-((2R)-2-[(1R)-1-phenyl-ethyl]-amino)-propyl]-phenyl]-acetate hydrochloride (Preparation 23) (7.69g, 22mmol) and ammonium formate (6.94g, 110mmol) was heated to 75°C in the presence of 20% palladium hydroxide-on-charcoal (Pd(OH)₂/C, 2.00g). After 90 minutes the reaction mixture was cooled to room temperature, filtered through Arbocel® and the filtrate concentrated *in vacuo*. The residue was partitioned between dichloromethane (100mL) and 880 ammonia (100mL) and the organic phase separated. The aqueous phase was extracted dichloromethane (100mL) and the combined organic extracts dried (magnesium sulfate) and reduced *in vacuo* to give the title compound as a colourless oil (4.78g).

¹H NMR (400MHz, CD₃OD): δ = 7.27-7.23 (1H, t), 7.13-7.09 (3H, m), 3.67 (3H, s), 3.63 (2H, s), 3.12-3.05 (1H, m), 2.67-2.57 (2H, m), 1.06 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 208, [M+Na]⁺ 230.

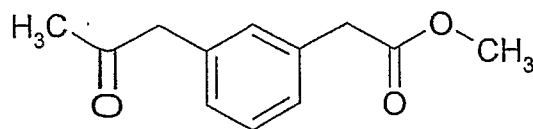
Preparation 23**Methyl [3-((2*R*)-2-[[*(1R)*-1-phenyl-ethyl]-amino]-propyl)-phenyl]-acetate hydrochloride**

5 A solution of methyl [3-(2-oxopropyl)phenyl]acetate (Preparation 24) (8.50g, 41.2mmol), (*R*)- α -methyl benzylamine (4.8mL, 37.2mmol), sodium triacetoxyborohydride (11.6g, 56mmol) and acetic acid (2.2mL, 38mmol) in dichloromethane (400mL) was stirred at room temperature for 48 hours. The
10 reaction mixture was quenched by addition of saturated aqueous sodium bicarbonate (200mL) and allowed to stir until effervescence ceased. The organic phase was separated and the aqueous phase extracted with dichloromethane (100mL). The combined organic extracts were dried (magnesium sulfate) and reduced *in vacuo*. Purification by flash column
15 chromatography eluting with dichloromethane:methanol: ammonia (99:1:0.1 to 95:5:0.5 by volume) gave a 4:1 mixture of diastereomers (*R,R* major) as a pale yellow oil (8.71g). Treatment with hydrogen chloride (40mL of a 1M solution in methanol, 40mmol) followed by three successive crystallisations (diisopropylether/ methanol) gave the title compound as a white crystalline solid
20 (5.68g).

¹H NMR (400MHz, CD₃OD): δ = 7.52-7.48 (5H, m), 7.28-7.25 (1H, m), 7.18-7.16 (1H, m), 7.02-6.99 (2H, m), 4.59 (1H, q), 3.62 (2H, s), 3.30 (3H, s), 3.30-3.25 (1H, m), 3.26-3.15 (1H, m), 2.66-2.60 (1H, m), 1.68 (3H, d), 1.18, (3H, d) ppm.

25 LRMS (electrospray): m/z [M+H]⁺ 312, [M+Na]⁺ 334.

Preparation 24**Methyl [3-(2-oxopropyl)phenyl]acetate**



Tributyltin methoxide (28.3 mL, 98 mmol), preparation 25 (15.0 g, 65 mmol), isopropenyl acetate (10.8 mL, 98 mmol), palladium(II)acetate (750 mg, 3.30 mmol) and tri-*ortho*-tolylphosphine (2.0 g, 6.5 mmol) were stirred together in
 5 toluene (75 mL) at 100°C under nitrogen for 5 hours. After cooling the reaction was diluted with ethyl acetate (150 mL) and 4M aqueous potassium fluoride solution (90 mL) and stirred for 15 minutes. The mixture was filtered through arbolcel and the organic phase separated and reduced *in vacuo*. The residue was purified by flash column chromatography silica gel eluting with a solvent
 10 gradient of diethyl ether:pentane (0:100 to 25:75, by volume) changing to dichloromethane to give the title compound as a pale yellow oil (12.6 g).

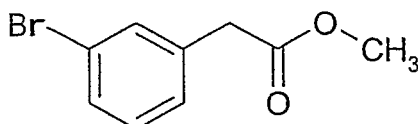
^1H NMR (400 MHz, CDCl_3): δ = 7.30 (1H, t), 7.19 (1H, d), 7.13-7.10 (2H, m), 3.69 (5H, s), 3.61 (2H, s), 2.15 (3H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{NH}_4]^+$ 224, $[\text{M}+\text{Na}]^+$ 229.

15

Preparation 25

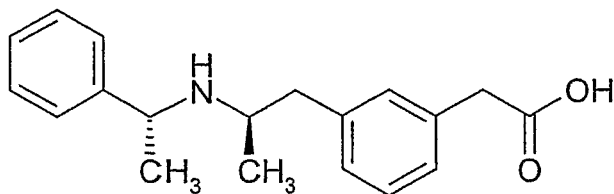
Methyl (3-bromophenyl)acetate



Acetyl chloride (0.7 mL, 9.3 mmol) was slowly added to a solution of (3-bromo-
 20 phenyl)-acetic acid (20.0 g, 93 mmol) in methanol (500 mL) at 0°C under nitrogen and the reaction was allowed to warm gradually to room temperature over a period of 5 hours. The solvent was removed *in vacuo* and the residual oil was redissolved in dichloromethane, dried (sodium sulfate) and concentrated *in vacuo* to give the title compound as a colourless oil (20.6 g).

25 ^1H NMR (400 MHz, CDCl_3): δ = 7.37-7.45 (2H, m), 7.24-7.17 (2H, m), 3.70 (3H, s), 3.59 (2H, s) ppm.

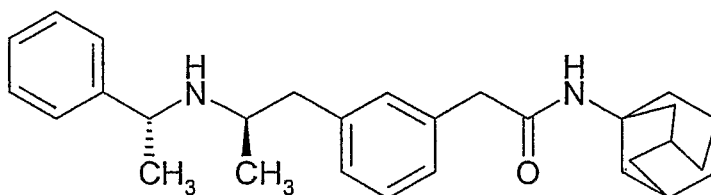
LRMS (electrospray) : m/z $[\text{M}+\text{Na}]^+$ 253.

Preparation 26**[3-((2R)-2-[[[(1R)-1-Phenyl-ethyl]-amino]-propyl]-phenyl)-acetic acid**

1M aqueous lithium hydroxide (90mL, 90mmol) was added in one portion to a stirred solution of the compound of preparation 23 (13.5g, 43.5mmol) in methanol (2000mL) at room temperature. The reaction was stirred at room temperature for 24 hours and 1M aqueous hydrochloric acid (90mL, 90mmol) was added in one portion. The solvent was removed *in vacuo* to reduce the volume to 80mL and the white precipitate removed by filtration and washed with water (20mL), 20% ethanol in water (100mL), dried to furnish the title compound as a white solid, 11.8g.

¹H NMR (400MHz, CD₃OD) δ 1.16 (3H, d), 1.62 (3H, d), 2.64 (1H, m), 3.20 (2H, m), 3.46 (2H, s), 4.42 (1H, q), 6.91 (1H, d), 7.08 (1H, s), 7.19 (1H, s), 7.20 (1H, m), 7.48 (5H, m).

LRMS: m/z electrospray 298 [M+H⁺], 296 [M-H].

Preparation 27**N-Adamantan-1-yl-2-{3-[2-(1-phenyl-ethylamino)-propyl]-phenyl}-acetamide**

To a stirred suspension of the compound of preparation 26 (297mg, 1.00mmol) in dichloromethane (4mL) at room temperature 1-adamantylamine (151mg, 1.00mmol) was added and the suspension stirred for 15 minutes. 2-Chloro-1,3-dimethylimidazolinium hexafluorophosphate (278mg, 1.00mmol) was added in one portion and the reaction stirred for 2 hours, after which time the reaction was homogeneous. The reaction was washed with water (5mL), dried (magnesium sulphate) and the solvent removed *in vacuo*. The residue was

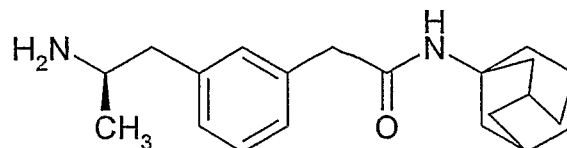
purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (98:2:0.2 then 95:5:0.5) to furnish the title compound as a pale yellow foam, 325mg.

^1H NMR (400MHz, CD_3OD) δ 0.89 (3H, d), 1.36 (3H, d), 1.75 (6H, m), 1.98 (6H, s), 2.04 (6H, s), 2.40 (1H, dd), 2.74 (1H, m), 3.00 (1H, dd), 3.36 (2H, s), 4.00 (1H, q), 6.90 (1H, d), 6.98 (1H, s), 7.08 (1H, d), 7.19 (1H, t), 7.22 (1H, m), 7.38 (4H, m).

LRMS: m/z electrospray 431 $[\text{M}+\text{H}]^+$.

10 Preparation 28

N-Adamantan-1-yl-2-[3-(2-amino-propyl)-phenyl]-acetamide



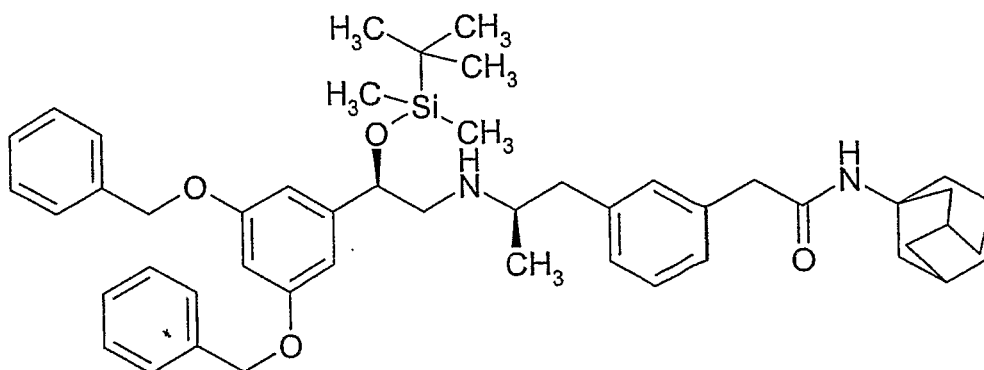
A solution the compound of preparation 27 (17.6g, 36mmol) and ammonium formate (22.7g, 360mmol) was heated to 70°C in the presence of 20% palladium hydroxide-on-charcoal ($\text{Pd}(\text{OH})_2/\text{C}$, 2.00g). After 60 minutes further catalyst (500mg) was added and the reaction heated for a further 4 hours. The reaction mixture was cooled to room temperature, filtered through Arbocel® and the filtrate concentrated *in vacuo*. The residue was partitioned between dichloromethane (300mL) and 10% 880 ammonia in water (150mL) and the organic phase separated dried (sodium sulfate) and reduced *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (95:5:0.5 then 90:10:1) to furnish the title compound as a white solid, 10.8g.

^1H NMR (400MHz, CD_3OD): δ 1.09 (3H, d), 1.68 (6H, m), 2.00 (6H, s), 2.03 (3H, s), 2.64 (2H, m), 3.14 (1H, q), 3.40 (2H, s), 7.14 (4H, m).

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 327.

Preparation 29

N-Adamantan-1-yl-2-(3-{2-[2-(3,5-bis-benzyloxy-phenyl)-2-(tert-butyl-dimethyl-silanyloxy)-ethylamino]-propyl}-phenyl)-acetamide



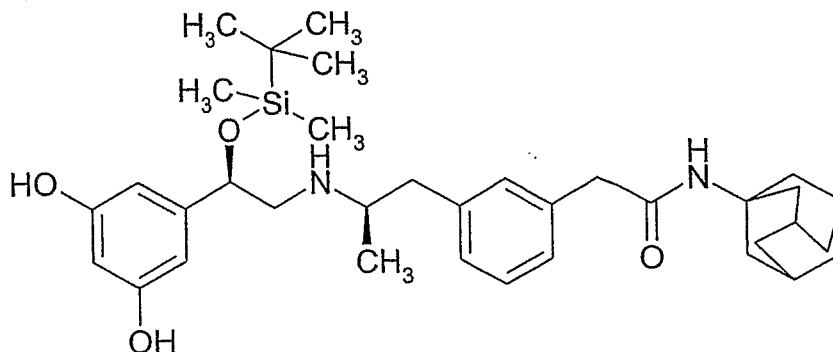
A solution of the compound of preparation 11 (263mg, 0.50mmol) and the compound of preparation 28 (326mg, 1.00mmol) in dichloromethane (1mL) was heated to 90°C and the solvent allowed to evaporate off. The resulting melt was heated at 90°C for 1 day and then allowed to cool to room temperature. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (98:2:0.2) to furnish the title compound as a clear oil, 168mg.

¹H NMR (400MHz, CD₃OD) δ -0.09 (3H, s), -0.02 (3H, s), 0.82 (9H, s), 1.03 (3H, d), 1.66 (6H, s), 1.99 (6H, s), 2.02 (3H, s), 2.59 (1H, m), 2.65 (2H, m), 2.85 (2H, m), 3.37 (2H, s), 4.86 (1H, m), 5.06 (4H, m), 6.54 (3H, m), 7.00 (14H, m).

LRMS: m/z electrospray 773 [M+H⁺].

Preparation 30

N-Adamantan-1-yl-2-(3-{2-[2-(tert-butyl-dimethyl-silanyloxy)-2-(3,5-dihydroxy-phenyl)-ethylamino]-propyl}-phenyl)-acetamide



A solution the compound of preparation 29 (160mg, 0.21mmol) and ammonium formate (150mg, 2.10mmol) was heated to 70°C in the presence of 20% palladium hydroxide-on-charcoal (Pd(OH)₂/C, 20mg). After 3 hours the reaction

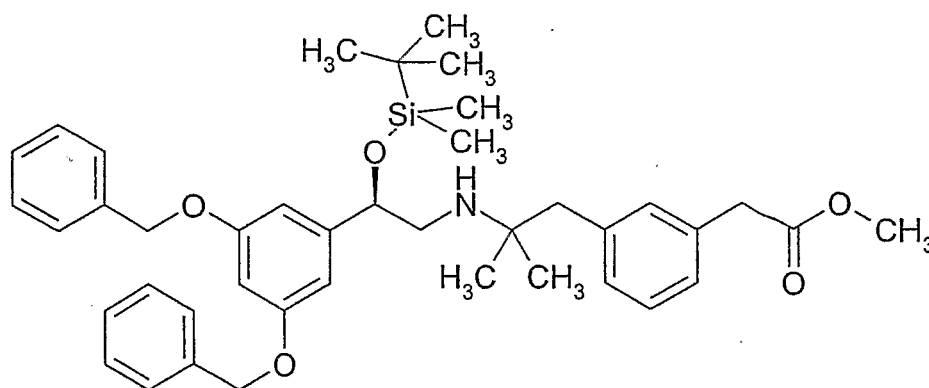
mixture was cooled to room temperature, filtered through Arbocel® and the filtrate concentrated *in vacuo*. The residue was partitioned between ethyl acetate (10mL) and 10% 880 ammonia in water (10mL) and the organic phase separated dried. The aqueous was extracted with dichloromethane (2x50mL) and the combined organics dried (sodium sulfate) and reduced *in vacuo* to furnish the title compound as a yellow foam, 160mg.

¹H NMR (400MHz, CD₃OD) δ -0.16 (3H, s), 0.01 (3H, s), 0.84 (9H, s), 1.03 (3H, d), 1.69 (6H, m), 2.01 (9H, m), 2.60 (3H, m), 2.91 (2H, m), 3.39 (2H, s), 4.60 (1H, m), 6.13 (1H, m), 6.20 (2H, m), 6.98 (1H, d), 7.05 (1H, s), 7.07 (1H, d), 7.18 (1H, t).

LRMS: m/z electrospray 593 [M+H⁺], 591 [M-H]⁻.

Preparation 31

(3-{2-[2-(3,5-Bis-benzyloxy-phenyl)-2-(tert-butyl-dimethyl-silanyloxy)-ethylamino]-2-methyl-propyl}-phenyl)-acetic acid methyl ester



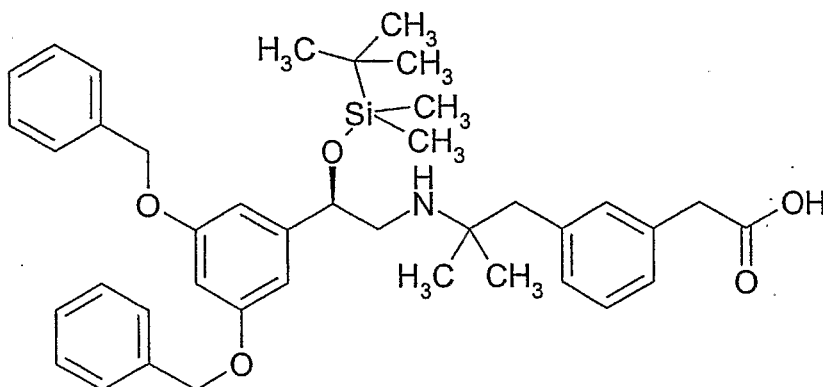
A solution of the compound of preparation 11 (5.30g, 10.0mmol) and the compound of preparation 5 (4.42g, 20.0mmol) were combined and heated to 92°C under nitrogen. The resulting melt was heated at 92°C for 24 hours and then allowed to cool to room temperature. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (98:2:0.2) to furnish the title compound as a golden oil, 5.38g.

¹H NMR (400MHz, CD₃OD) δ -0.20 (3H, s), -0.03 (3H, s), 0.79 (9H, s), 1.01–1.03 (6H, d), 2.58–2.82 (4H, m), 3.59 (2H, s), 3.63 (3H, s), 4.62–4.66 (1H, m), 4.84 (4H, s), 6.76 (3H, s), 7.15–7.65 (14H, m).

LRMS: m/z electrospray 668 [M+H⁺].

Preparation 32

(3-{2-[2-(3,5-Bis-benzyloxy-phenyl)-2-(tert-butyl-dimethyl-silanyloxy)-
5 ethylamino]-2-methyl-propyl}-phenyl)-acetic acid



1M aqueous lithium hydroxide (8.80mL, 8.80mmol) was added in one portion to a stirred solution of the compound of preparation 31 (5.30g, 7.95mmol) in tetrahydrofuran (150mL) at room temperature under nitrogen. The reaction was stirred at room temperature for 24 hours and 1M aqueous hydrochloric acid (8.80mL, 8.80mmol) was added in one portion. The majority of the solvent was removed *in vacuo* and the resulting mixture was partitioned between dichloromethane (200mL) and water (200mL). The organic layer was washed with brine (50mL), dried (sodium sulfate) and the solvent removed *in vacuo* to afford the title compound as a colourless foam (5.16g).

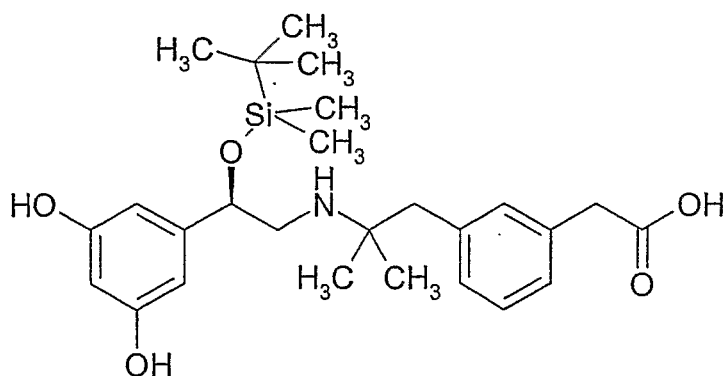
¹H NMR (400MHz, CD₃OD) δ -0.17 (3H, s), 0.02 (3H, s), 0.82 (9H, s), 1.26 (6H, s), 2.84-2.96 (2H, q), 3.18-3.19 (2H, d), 3.53 (2H, s), 4.87-4.92 (1H, t), 5.10 (4H, s), 6.60-6.63 (3H, m), 7.03-7.43 (14H, m)

LRMS: m/z electrospray 654 [M+H⁺].

20

Preparation 33

(3-{2-[2-(tert-Butyl-dimethyl-silanyloxy)-2-(3,5-dihydroxy-phenyl)-ethylamino]-2-methyl-propyl}-phenyl)-acetic acid



Palladium hydroxide (500mg) was added in one portion to a stirred solution of the compound of preparation 32 (5.10g, 7.81mmol) and ammonium formate (5.00g, 74.6mmol) in ethanol (250mL) at room temperature. The reaction was
 5 heated at 70°C for 3 hours. Further palladium hydroxide was then added (250mg) and the reaction heated at 70°C for a further 1.5 hours and allowed to cool to room temperature under nitrogen overnight. The reaction was filtered through Arbocel® and the filtrate concentrated *in vacuo*. The residue was triturated with water (50mL) and filtered to furnish the title compound as a white
 10 solid, 3.61g.

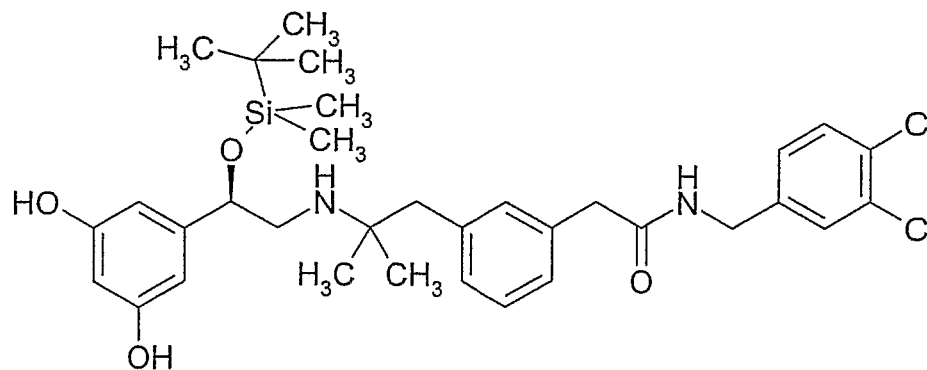
¹H NMR (400MHz, CD₃OD) δ -0.07 (3H, s), 0.03 (3H, s), 0.83 (9H, s), 1.34 (6H, s), 2.90-2.97 (2H, q), 3.18-3.19 (2H, s), 3.50-3.58 (2H, q), 4.85-4.95 (1H, m), 6.12 (1H, s), 6.35 (2H, s), 7.03-7.35 (4H, m).

LRMS: m/z electrospray 474 [M+H⁺].

15

Preparation 34

2-(3-{2-[2-(tert-Butyl-dimethyl-silanyloxy)-2-(3,5-dihydroxy-phenyl)-ethylamino]-2-methyl-propyl}-phenyl)-N-(3,4-dichloro-benzyl)-acetamide



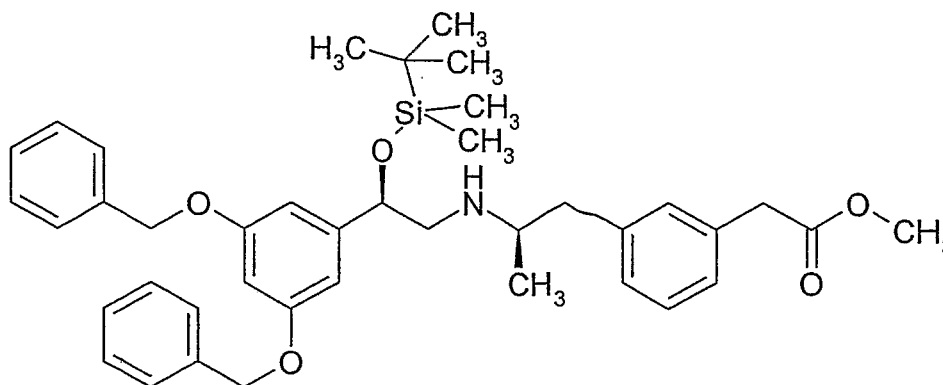
3,4-Dichlorobenzylamine (53mg, 0.301mmol), hydroxybenzotriazole (39mg, 0.289mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (57mg, 0.297mmol) were added to a stirred solution of the compound of preparation 33 (142mg, 0.300mmol) in *N,N*-dimethylformamide (2mL) at room temperature under nitrogen. The reaction was stirred for 18 hours and the solvent removed *in vacuo*, the residue was then was partitioned between dichloromethane (50mL) and saturated aqueous sodium hydrogen carbonate (50mL). The organic layer was dried (sodium sulfate) and the solvent removed *in vacuo* and purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (95:5:0.5) to furnish the title compound as a cream foam, 125mg.

^1H NMR (400MHz, CD_3OD) δ -0.16 (3H, s), 0.00 (3H, s), 0.82 (9H, s), 1.01-1.03 (6H, d), 2.60-2.86 (4H, m), 3.52 (2H, s), 4.31 (2H, s), 4.78-4.81 (1H, m), 6.18 (1H, s), 6.29 (2H, s), 7.02-7.24 (5H, m), 7.36-7.42 (2H, m).

LRMS: m/z electrospray 631 $[\text{M}+\text{H}^+]$.

Preparation 35

(3-{2-[2-(3,5-Bis-benzyloxy-phenyl)-2-(tert-butyl-dimethyl-silanyloxy)-ethylamino]-propyl}-phenyl)-acetic acid methyl ester



A solution of the compound of preparation 11 (5.00g, 9.45mmol) and the compound of preparation 22 (3.92g, 18.9mmol) in dichloromethane (50mL) was heated to 95°C and the solvent allowed to evaporate off. The resulting melt was heated at 95°C for 24 hours and then allowed to cool to room temperature. Diethylether (50mL) was added and the mixture was stirred for 5 minutes. The

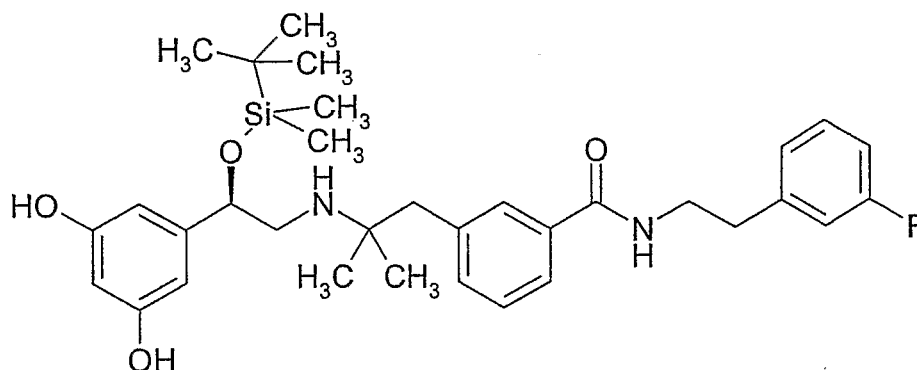
ether layer was separated from the gum and then the gum was extracted twice more with diethylether (2x50mL). The ether extracts were combined and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (100:0:0 to 95:5:0.5) to furnish the title compound as a pale yellow gum, 4.50g.

¹H NMR (400MHz, CD₃OD) δ -0.20 (3H, s), -0.05 (3H, s), 0.81 (9H, s), 1.01–1.03 (3H, d), 2.60 (3H, m), 2.86 (2H, m), 3.55 (2H, s), 3.63 (3H, s), 4.66 (1H, m), 4.85 (4H, m), 6.70 (3H, m), 6.73 (1H, m), 6.98 (2H, m), 7.06 (1H, m), 7.17 (1H, m), 7.10 (2H, m), 7.11–7.22 (7H, m).

LRMS: m/z electrospray 654 [M+H⁺].

Preparation 36

3-{2-[2-(tert-Butyl-dimethyl-silanyloxy)-2-(3,5-dihydroxy-phenyl)-ethylamino]-2-methyl-propyl}-N-[2-(3-fluoro-phenyl)-ethyl]-benzamide



15

2-Fluorophenylethylamine (95mg, 0.680mmol), hydroxybenzotriazole (100mg, 0.740mmol), triethylamine (0.10mL, 0.720mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (79mg, 0.410mmol) were added to a stirred solution of the compound of preparation 14 (151mg, 0.330mmol) in *N,N*-dimethylformamide (1mL) at room temperature under nitrogen. The reaction was stirred for 18 hours and the solvent removed *in vacuo* and purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (100:0:0 to 95:5:0.5 to 90:10:1) to furnish the title compound as a cream foam, 132mg.

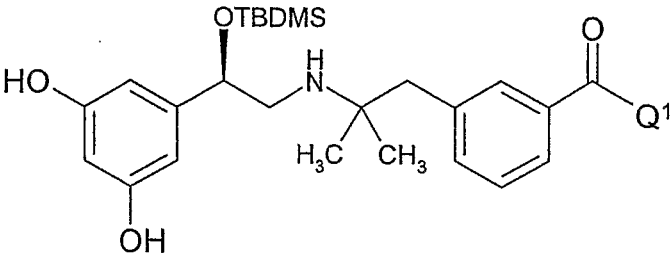
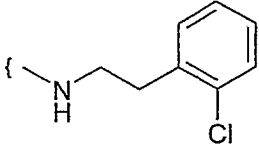
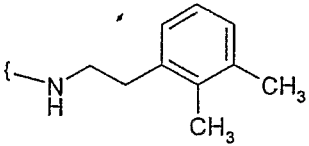
20

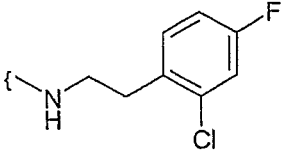
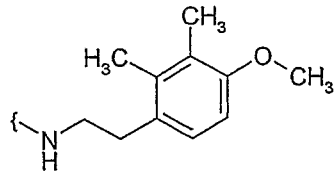
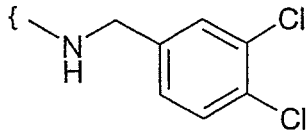
^1H NMR (400MHz, CD_3OD) δ -0.16 (3H, s), -0.02 (3H, s), 0.78 (9H, s), 1.12 (6H, d), 2.65-2.95 (6H, m), 3.61 (2H, s), 4.64 (1H, s), 6.18 (1H, s), 6.29 (2H, s), 6.93 (1H, m), 7.02 (1H, m), 7.06 (1H, m), 7.20-7.39 (3H, m), 7.64 (2H, m).

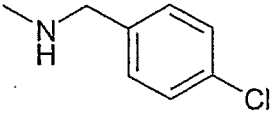
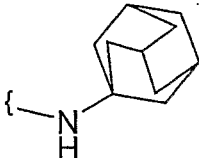
LRMS: m/z electrospray 581 $[\text{M}+\text{H}^+]$.

5

Preparation 37 to 43 were prepared from compounds of preparation 14 and the appropriate amine using the method disclosed for preparation 36:

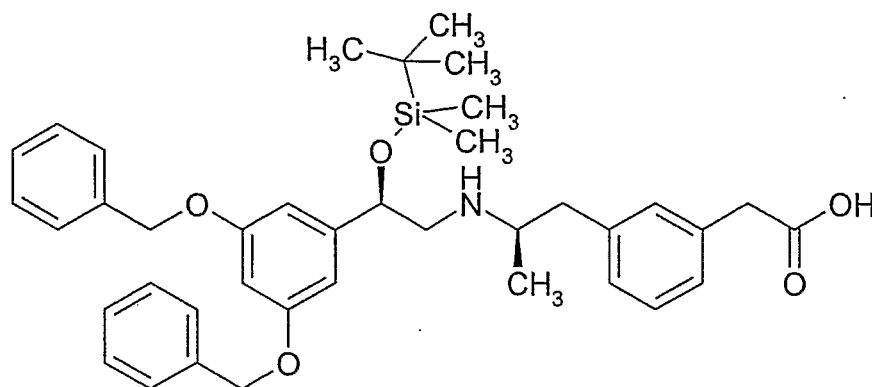
Preparations 37 to 43		
		
No	Q^1	Data
37		The compound was isolated as a brown oil ^1H NMR (400MHz, CD_3OD) δ -0.16 (3H, s), -0.02 (3H, s), 0.78 (9H, s), 1.08 (6H, d), 2.60-2.84 (4H, m), 3.08 (2H, m), 3.64 (2H, m), 4.61 (1H, m), 6.18 (1H, s), 6.29 (2H, s), 7.13-7.39 (6H, m), 7.63 (2H, m). LRMS: m/z electrospray 597 $[\text{M}+\text{H}^+]$.
38		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.16 (3H, s), -0.02 (3H, s), 0.80 (9H, s), 1.08 (6H, d), 2.27 (3H, s), 2.29 (3H, s), 2.60-2.89 (4H, m), 2.96 (2H, m), 3.55 (2H, m), 4.61 (1H, m), 6.18 (1H, s), 6.29 (2H, s), 6.93-7.03 (3H, m), 7.30-7.38 (2H, m), 7.65 (2H, m). LRMS: m/z electrospray 591 $[\text{M}+\text{H}^+]$.

39		The compound was isolated as an orange foam. ^1H NMR (400MHz, CD_3OD) δ -0.16 (3 H, s), -0.02 (3H, s), 0.80 (9H, s), 1.10 (6H, d), 2.60-2.89 (4H, m), 3.05 (2H, m), 3.62 (2H, m), 4.61 (1H, m), 6.18 (1H, s), 6.29 (2H, s), 7.00 (1H, m), 7.19 (1H, m), 7.27-7.38 (3H, m), 7.64 (2H, m). LRMS: m/z electrospray 615 $[\text{M}+\text{H}^+]$.
40		The compound was isolated as a pale orange solid. ^1H NMR (400MHz, CD_3OD) δ -0.16 (3 H, s), -0.02 (3H, s), 0.80 (9H, s), 1.10 (6H, d), 2.14 (3H, s), 2.27 (3H, s), 2.60-2.93 (6H, m), 3.49 (2H, m), 3.77 (3H, s), 4.61 (1H, m), 6.18 (1H, s), 6.29 (2H, s), 6.69 (1H, m), 6.98 (1H, m), 7.30-7.39 (2H, m), 7.65 (2H, m). LRMS: m/z electrospray 621 $[\text{M}+\text{H}^+]$.
41		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.16 (3 H, s), -0.02 (3H, s), 0.80 (9H, s), 1.13 (3H, s), 1.16 (3H, s), 2.68-2.72 (1H, m), 2.78-2.81 (1H, m), 2.85-2.90 (2H, m), 4.59 (2H, s), 4.62-4.65 (1H, m), 6.21 (1H, m), 6.33 (1H, m), 6.34 (1H, m), 7.33-7.35 (1H, m), 7.39-7.46 (2H, m), 7.50-7.53 (1H, m), 7.56 (1H, m), 7.78 (2H, m). LRMS: m/z electrospray 619 $[\text{M}+\text{H}^+]$.

42		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.12 (3H, s), -0.02 (3H, s), 0.80 (9H, s), 1.13 (3H, s), 1.16 (3H, s), 2.68-2.72 (1H, m), 2.78-2.88 (3H, m), 4.59 (2H, s), 4.62-4.65 (1H, m), 6.21 (1H, m), 6.34 (2H, m), 7.35-7.45 (6H, m), 7.77 (2H, m). LRMS: m/z electrospray 583 $[\text{M}+\text{H}^+]$.
43		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.09 (3H, s), -0.02 (3H, s), 0.85 (9H, s), 1.13 (3H, s), 1.16 (3H, s), 1.81 (6H, s), 2.15 (3H, s), 2.21 (6H, m), 2.68-2.90 (4H, m), 4.64-4.67 (1H, s), 6.21 (1H, m), 6.33 (1H, s), 6.34 (1H, s), 7.30-7.40 (2H, m), 7.64 (2H, m). LRMS: m/z electrospray 594 $[\text{M}+\text{H}^+]$.

Preparation 44

(3-{2-[2-(3,5-Bis-benzyloxy-phenyl)-2-(tert-butyl-dimethyl-silanyloxy)-ethylamino]-propyl}-phenyl)-acetic acid



5

1M aqueous lithium hydroxide (16.0mL, 16.0mmol) was added in one portion to a stirred solution of the compound of preparation 35 (4.75g, 7.26mmol) in tetrahydrofuran (20mL) at room temperature. The reaction was stirred at room temperature for 24 hours and 1M aqueous hydrochloric acid was added until pH reached 1 –2. Extracted with dichloromethane (1x200mL then 2x50mL) and the

10

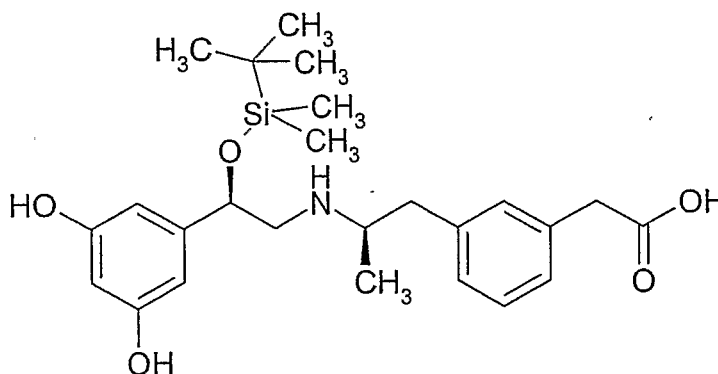
combined organic layers washed with brine (20mL), dried (magnesium sulphate) and the solvent removed *in vacuo* to furnish the title compound hydrochloride salt as an off-white foam, 4.80g.

¹H NMR (400MHz, CD₃OD) δ -0.12 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.23 (3H, d), 2.77 (1H, m), 3.03 (1H, m), 3.23 (1H, m), 3.45-3.60 (3H, m), 5.01 (1H, m), 5.10 (4H, s), 6.64 (2H, m), 6.68 (1H, m), 7.10 (1H, m), 7.15 (1H, s), 7.23 (1H, m), 7.27-7.43 (11H, m).

LRMS: m/z APCI 640 [M+H⁺].

10 Preparation 45

(3-{2-[2-(tert-Butyl-dimethyl-silanyloxy)-2-(3,5-dihydroxy-phenyl)-ethylamino]-propyl}-phenyl)-acetic acid

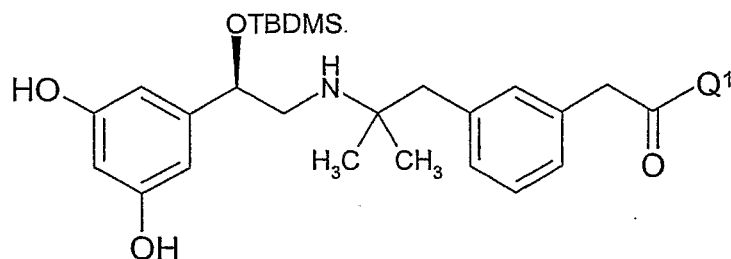


Palladium hydroxide (350mg) was added in one portion to a stirred solution of the compound of preparation 44 (3.50g, 5.48mmol) and ammonium formate (1.80g, 39.1mmol) in ethanol (250mL) at room temperature. The reaction was heated under reflux for 45 minutes and allowed to cool to room temperature. The reaction was filtered through Arbocel® and the filtrate concentrated *in vacuo* to furnish the title compound as a pale yellow solid, 2.30g.

¹H NMR (400MHz, CD₃OD) δ -0.06 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.25 (3H, d), 2.81 (1H, m), 2.96 (1H, m), 3.15 (1H, m), 3.25 (1H, m), 3.43-3.55 (3H, m), 4.89 (1H, m), 6.24 (1H, m), 6.33 (2H, m), 7.06 (1H, m), 7.17 (1H, s), 7.19-7.28 (2H, m).

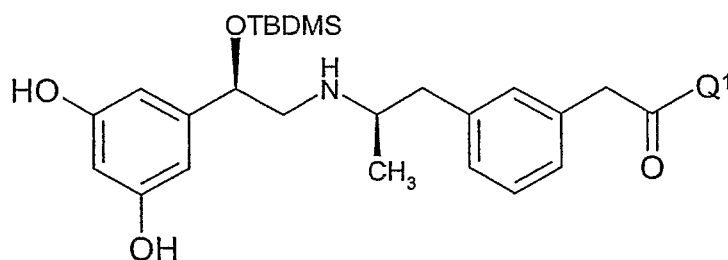
LRMS: m/z APCI 460 [M+H⁺].

Preparations 46 to 48, 55 to 65 and 73 to 76 were prepared from preparation 33 and the appropriate amine, using the method of preparation 34. These compounds are of generic formula



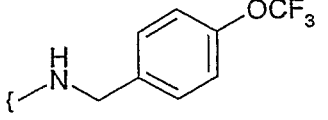
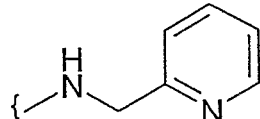
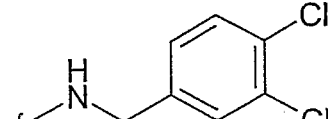
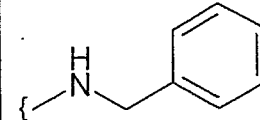
5 and are listed in the table below.

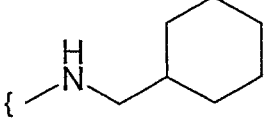
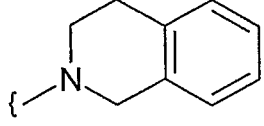
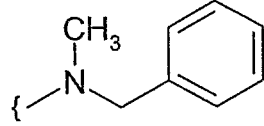
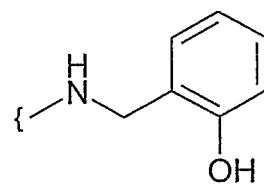
Preparations 49 to 54, 66 to 72 and 77 to 87 were prepared from preparation 45 and the appropriate amine, using the method of preparation 34. These compounds are of generic formula

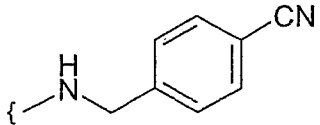
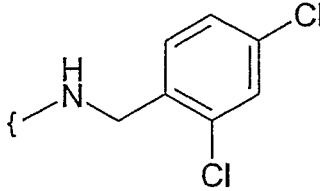
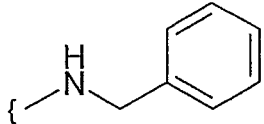
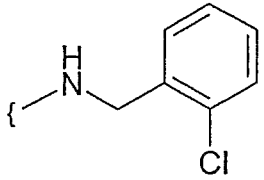


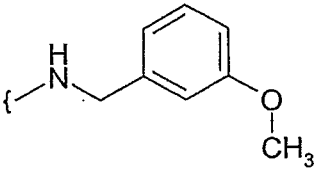
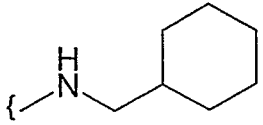
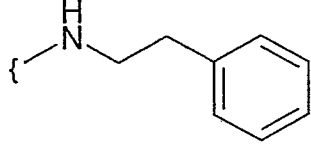
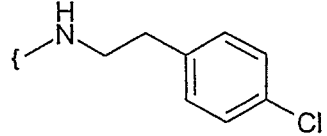
10 and are listed in the table below.

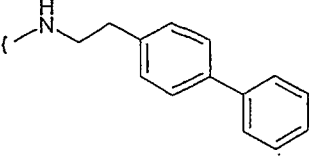
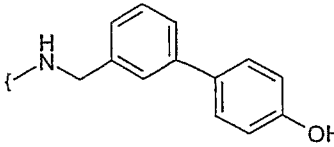
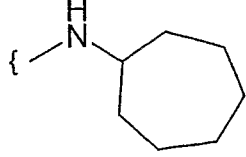
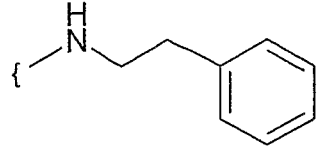
No	Q ¹	Data
46		The compound was isolated as a white solid. ¹H NMR (400MHz, CD₃OD) δ -0.14 (3H, s), 0.00 (3H, s), 0.80 (9H, s), 1.01-1.03 (6H, d), 2.62-2.84 (4H, m), 3.53 (2H, s), 4.34 (2H, s), 4.58-4.62 (1H, m), 6.18 (1H, s), 6.26 (2H, s), 7.01-7.27 (8H, m). LRMS: m/z electrospray 597 [M+H⁺].

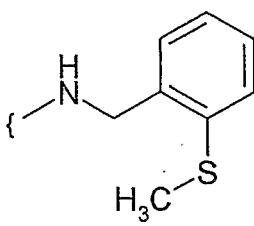
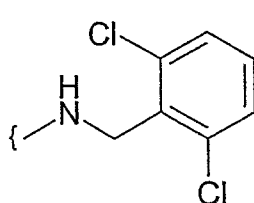
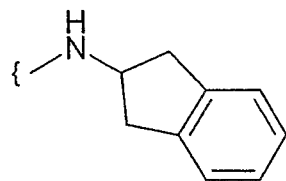
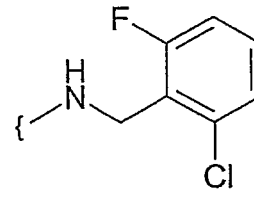
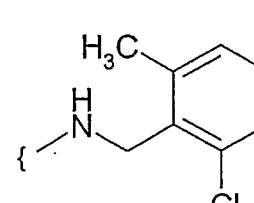
47		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.12 (3H, s), 0.00 (3H, s), 0.82 (9H, s), 1.01-1.03 (6H, d), 2.60-2.84 (4H, m), 3.54 (2H, s), 4.37 (2H, s), 4.58-4.62 (1H, m), 6.17 (1H, s), 6.28 (2H, s), 7.03 (1H, d), 7.08 (1H, s), 7.15-7.23 (4H, m), 7.32 (2H, d). LRMS: m/z electrospray 647 $[\text{M}+\text{H}^+]$.
48		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.13 (3H, s), 0.00 (3H, s), 0.82 (9H, s), 1.05-1.06 (6H, d), 2.65-2.83 (4H, m), 3.58 (2H, s), 4.47 (2H, s), 4.58-4.63 (1H, m), 6.17 (1H, s), 6.29 (2H, s), 7.06 (1H, d), 7.13 (1H, s), 7.18-7.30 (4H, m), 7.71-7.75 (1H, t), 8.44-8.45 (1H, d). LRMS: m/z electrospray 564 $[\text{M}+\text{H}^+]$.
49		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.18 (3H, s), 0.00 (3H, s), 0.81 (9H, s), 1.02 (3H, d), 2.60 (3H, m), 2.83 (2H, m), 3.51 (2H, s), 4.32 (2H, s), 4.58 (1H, m), 6.17 (1H, s), 6.22 (2H, d), 7.20 (6H, m), 7.40 (2H, m). LRMS: m/z APCI 617 $[\text{M}+\text{H}^+]$, 615 $[\text{M}-\text{H}]$.
50		^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.03 (3H, d), 2.58 (1H, m), 2.65 (2H, m), 2.83 (2H, m), 3.53 (2H, s), 4.36 (2H, s), 4.59 (1H, m), 6.16 (1H, m), 6.22 (2H, s), 6.98 (1H, m), 7.06 (1H, s), 7.13 (1H, m), 7.20 (6H, m). LRMS: m/z APCI 549 $[\text{M}+\text{H}^+]$, 547 $[\text{M}-\text{H}]$.

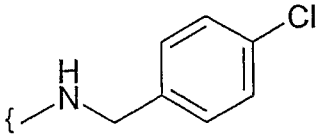
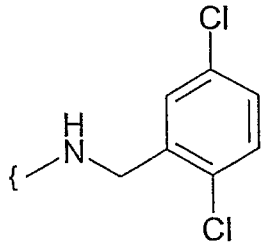
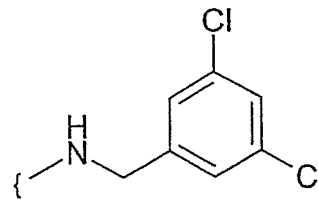
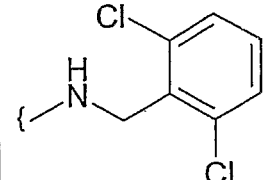
51	 <chem>NCC1CCCCC1</chem>	The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.01 (3H, s), 0.85 (11H, m), 1.06 (3H, d), 1.15 (3H, m), 1.42 (1H, m), 1.68 (5H, m), 2.55 (1H, m), 2.65 (2H, m), 2.88 (2H, m), 3.02 (2H, d), 3.46 (2H, s), 4.60 (1H, m), 6.15 (1H, m), 6.22 (2H, s), 6.98 (1H, m), 7.07 (1H, s), 7.10 (1H, m), 7.18 (1H, m). LRMS: m/z APCI 555 $[\text{M}+\text{H}^+]$, 553 $[\text{M}-\text{H}]$.
52	 <chem>NCC1CCC2=CC=CC=C2CC1</chem>	The compound was isolated as a pale yellow foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.03 (3H, m), 2.58 (7H, m), 3.73 (1H, m), 3.82 (3H, m), 4.57 (1H, m), 4.68 (2H, m), 6.16 (1H, m), 6.23 (2H, m), 7.10 (8H, m). LRMS: m/z APCI 575 $[\text{M}+\text{H}^+]$, 573 $[\text{M}-\text{H}]$.
53	 <chem>CN(C)CC1=CC=CC=C1</chem>	The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.02 (3H, m), 2.58 (3H, m), 2.83 (5H, m), 3.77 (2H, m), 4.58 (3H, m), 6.15 (1H, m), 6.22 (2H, m), 6.98 (2H, m), 7.07 (2H, m), 7.20 (5H, m). LRMS: m/z APCI 563 $[\text{M}+\text{H}^+]$, 561 $[\text{M}-\text{H}]$.
54	 <chem>NCC1=CC=C(C=C1)O</chem>	The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.01 (3H, s), 0.86 (9H, s), 1.03 (3H, d), 2.55 (1H, m), 2.64 (2H, m), 2.85 (2H, m), 3.53 (2H, s), 4.35 (2H, s), 4.59 (1H, m), 6.15 (1H, m), 6.22 (2H, s), 6.76 (2H, m), 6.98 (1H, m), 7.06 (4H, m), 7.18 (1H, m). LRMS: m/z APCI 565 $[\text{M}+\text{H}^+]$, 563 $[\text{M}-\text{H}]$.

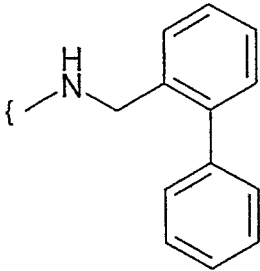
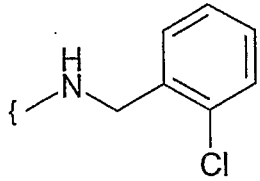
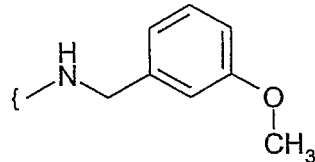
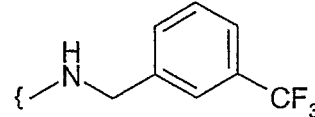
55		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.08 (3H, s), 0.04 (3H, s), 0.87 (9H, s), 1.10 (3H, s), 1.12 (3H, s), 2.65 (3H, m), 2.90 (1H, m), 3.59 (2H, s), 4.47 (2H, s), 4.64 (1H, m), 6.22 (1H, m), 6.34 (2H, s), 7.09 (1H, m), 7.15 (1H, s), 7.25 (2H, m), 7.42 (2H, d), 7.67 (2H, d). LRMS: m/z electrospray 588 $[\text{M}+\text{H}^+]$, 586 $[\text{M}-\text{H}]$.
56		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.08 (3H, s), 0.04 (3H, s), 0.87 (9H, s), 1.09 (3H, s), 1.11 (3H, s), 2.80 (4H, m), 3.59 (2H, s), 4.46 (2H, s), 4.64 (1H, m), 6.22 (1H, m), 6.34 (2H, s), 7.10 (1H, d), 7.14 (1H, s), 7.22 (1H, m), 7.27 (3H, m), 7.48 (1H, s). LRMS: m/z electrospray 633 $[\text{M}+\text{H}^+]$, 629 $[\text{M}-\text{H}]$.
57		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.10 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.06 (3H, s), 1.08 (3H, s), 2.65 (3H, m), 2.83 (1H, m), 3.53 (2H, s), 4.37 (2H, s), 4.59 (1H, m), 6.18 (1H, s), 6.28 (2H, s), 7.03 (1H, d), 7.11 (1H, s), 7.16 (1H, m), 7.27 (6H, m). LRMS: m/z electrospray 563 $[\text{M}+\text{H}^+]$.
58		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.10 (3H, s), 0.01 (3H, s), 0.84 (9H, s), 1.06 (3H, s), 1.08 (3H, s), 2.68 (3H, m), 2.84 (1H, m), 3.56 (2H, s), 4.43 (2H, s), 4.59 (1H, m), 6.18 (1H, m), 6.28 (2H, s), 7.07 (1H, d), 7.12 (1H, s), 7.20 (5H, m), 7.37 (1H, d). LRMS: m/z electrospray 597 $[\text{M}+\text{H}^+]$.

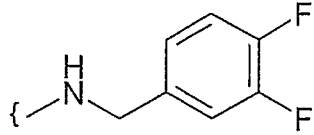
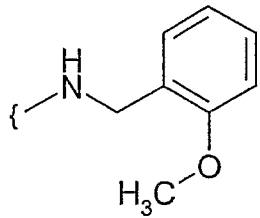
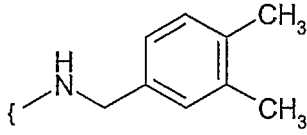
59		The compound was isolated as a colourless oil. LRMS: m/z electrospray 593 [M+H⁺].
60		The compound was isolated as a white foam. ¹H NMR (400MHz, CD₃OD) δ -0.08 (3H, s), 0.02 (3H, s), 0.84 (9H, s), 0.90 (2H, m), 1.06 (3H, s), 1.08 (3H, s), 1.18 (3H, m), 1.40 (1H, m), 1.68 (5H, m), 2.68 (3H, m), 2.83 (1H, m), 3.02 (2H, d), 3.47 (2H, s), 4.60 (1H, m), 6.17 (1H, t), 6.27 (2H, s), 7.04 (1H, d), 7.12 (1H, s), 7.15 (1H, d), 7.21 (1H, t). LRMS: m/z electrospray 569 [M+H⁺].
61		The compound was isolated as a white foam. ¹H NMR (400MHz, CD₃OD) δ -0.08 (3H, s), 0.01 (3H, s), 0.82 (9H, s), 1.08 (3H, s), 1.08 (3H, s), 2.68 (6H, m), 3.41 (2H, t), 3.44 (2H, s), 4.60 (1H, m), 6.17 (1H, m), 6.27 (2H, s), 7.14 (9H, m). LRMS: m/z electrospray 577 [M+H⁺].
62		The compound was isolated as a white foam. ¹H NMR (400MHz, CD₃OD) δ -0.08 (3H, s), 0.01 (3H, s), 0.82 (9H, s), 1.07 (3H, s), 1.08 (3H, s), 2.67 (3H, m), 2.73 (2H, m), 2.83 (1H, m), 3.42 (4H, m), 4.60 (1H, m), 6.08 (1H, s), 6.28 (2H, s), 7.05 (2H, d), 7.11 (3H, m), 7.20 (3H, m). LRMS: m/z electrospray 611 [M+H⁺].

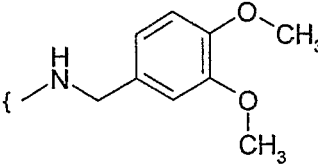
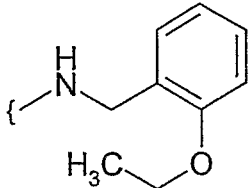
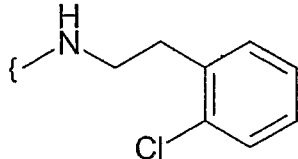
63		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.08 (3H, s), 0.01 (3H, s), 0.81 (9H, s), 1.04 (3H, s), 1.04 (3H, s), 2.64 (3H, m), 2.80 (3H, m), 2.83 (1H, m), 3.42 (4H, m), 4.60 (1H, m), 6.17 (1H, m), 6.28 (2H, s), 7.03 (2H, m), 7.11 (1H, d), 7.20 (3H, m), 7.28 (1H, m), 7.41 (2H, t), 7.48 (1H, d), 7.57 (3H, m). LRMS: m/z electrospray 653 $[\text{M}+\text{H}^+]$.
64		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.08 (3H, s), 0.01 (3H, s), 0.82 (9H, s), 1.01 (3H, s), 1.02 (3H, s), 2.60 (3H, m), 2.78 (1H, m), 3.56 (2H, s), 4.42 (2H, s), 4.58 (1H, m), 6.17 (1H, s), 6.27 (2H, s), 6.84 (2H, m), 7.04 (1H, d), 7.09 (1H, s), 7.20 (3H, m), 7.17 (1H, d), 7.30 (7H, m). LRMS: m/z electrospray 655 $[\text{M}+\text{H}^+]$, 653 $[\text{M}-\text{H}]$.
65		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.08 (3H, s), 0.01 (3H, s), 0.83 (9H, s), 1.07 (3H, s), 1.07 (3H, s), 1.55 (9H, m), 1.84 (2H, m), 2.68 (3H, m), 2.86 (1H, m), 3.43 (2H, s), 3.80 (1H, m), 4.60 (1H, m), 6.17 (1H, m), 6.28 (2H, s), 7.04 (1H, d), 7.09 (1H, s), 7.16 (1H, d), 7.22 (1H, t). LRMS: m/z electrospray 570 $[\text{M}+\text{H}^+]$, 568 $[\text{M}-\text{H}]$.
66		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.14 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.05 (3H, d), 2.55 (7H, m), 3.42 (4H, m), 4.59 (1H, m), 6.13 (1H, m), 6.23 (2H, s), 7.18 (9H, m). LRMS: m/z APCI 563 $[\text{M}+\text{H}^+]$.

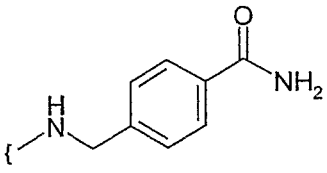
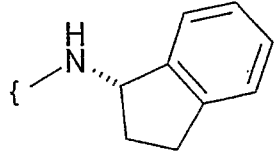
67		^1H NMR (400MHz, CD_3OD) δ -0.14 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.03 (3H, d), 2.43 (3H, s), 2.60 (5H, m), 3.52 (2H, s), 4.04 (2H, s), 4.59 (1H, m), 6.14 (1H, m), 6.24 (2H, s), 7.18 (8H, m). LRMS: m/z APCI 595 $[\text{M}+\text{H}^+]$.
68		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.14 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.03 (3H, d), 2.52 (1H, m), 2.66 (2H, m), 2.85 (2H, m), 3.48 (2H, s), 4.60 (1H, m), 4.66 (2H, s), 6.14 (1H, m), 6.24 (2H, s), 7.20 (7H, m). LRMS: m/z APCI 615 $[\text{M}+\text{H}^+]$.
69		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.14 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.04 (3H, d), 2.58 (3H, m), 2.85 (4H, m), 3.25 (2H, m), 3.48 (2H, s), 4.60 (2H, m), 6.15 (1H, m), 6.23 (2H, s), 7.10 (8H, m). LRMS: m/z APCI 575 $[\text{M}+\text{H}^+]$.
70		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.14 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.03 (3H, d), 2.52 (1H, m), 2.62 (2H, m), 2.85 (2H, m), 3.48 (2H, s), 4.52 (2H, m), 4.60 (1H, m), 6.18 (1H, s), 6.24 (2H, s), 7.20 (7H, m).
71		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.14 (3H, s), 0.01 (3H, s), 0.84 (9H, s), 1.03 (3H, d), 2.18 (3H, s), 2.52 (1H, m), 2.62 (2H, m), 2.85 (2H, m), 3.43 (2H, s), 4.52 (2H, m), 4.60 (1H, m), 6.18 (1H, s), 6.24 (2H, s), 7.20 (7H, m). LRMS: m/z APCI 597 $[\text{M}+\text{H}^+]$, 595 $[\text{M}-\text{H}^-]$.

72		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.18 (3H, s), 0.01 (3H, s), 0.84 (9H, s), 1.03 (3H, d), 2.60 (3H, m), 2.85 (2H, m), 3.48 (2H, s), 4.33 (2H, s), 4.57 (1H, m), 6.18 (1H, s), 6.24 (2H, s), 7.20 (8H, m). LRMS: m/z APCI 583 $[\text{M}+\text{H}^+]$, 581 $[\text{M}-\text{H}]$.
73		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.08 (3H, s), 0.05 (3H, s), 0.87 (9H, s), 1.10 (3H, s), 1.12 (3H, s), 2.78 (4H, m), 3.61 (2H, s), 4.47 (2H, s), 4.65 (1H, m), 6.22 (1H, m), 6.34 (2H, s), 7.11 (1H, d), 7.17 (1H, s), 7.28 (4H, m), 7.40 (1H, d). LRMS: m/z electrospray 631 $[\text{M}+\text{H}^+]$, 631 $[\text{M}-\text{H}]$.
74		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.08 (3H, s), 0.04 (3H, s), 0.87 (9H, s), 1.09 (3H, s), 1.11 (3H, s), 2.74 (3H, m), 2.88 (1H, m), 3.58 (2H, s), 4.37 (2H, s), 4.65 (1H, m), 6.22 (1H, m), 6.34 (2H, s), 7.11 (1H, m), 7.14 (1H, s), 7.21 (3H, m), 7.28 (1H, m), 7.33 (1H, t). LRMS: m/z electrospray 631 $[\text{M}+\text{H}^+]$, 629 $[\text{M}-\text{H}]$.
75		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.08 (3H, s), 0.04 (3H, s), 0.87 (9H, s), 1.08 (3H, s), 1.10 (3H, s), 2.74 (3H, m), 2.88 (1H, m), 3.53 (2H, s), 4.64 (1H, m), 4.71 (2H, s), 6.22 (1H, m), 6.34 (2H, s), 7.07 (1H, d), 7.13 (1H, s), 7.19 (1H, m), 7.25 (1H, m), 7.33 (1H, m), 7.43 (2H, d). LRMS: m/z electrospray 634 $[\text{M}+\text{H}^+]$, 630 $[\text{M}-\text{H}]$.

76		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.09 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 1.09 (3H, s), 1.11 (3H, s), 2.74 (4H, m), 3.51 (2H, s), 4.32 (2H, s), 4.64 (1H, m), 6.22 (1H, m), 6.34 (2H, s), 7.11 (2H, m), 7.18 (1H, d), 7.30 (10H, m). LRMS: m/z electrospray 639 $[\text{M}+\text{H}^+]$, 637 $[\text{M}-\text{H}]$.
77		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.03 (3H, d), 2.64 (5H, m), 3.54 (2H, s), 4.45 (2H, s), 4.59 (1H, m), 6.15 (1H, m), 6.23 (2H, s), 6.99 (1H, m), 7.08 (1H, m), 7.20 (6H, m). LRMS: m/z APCI 583 $[\text{M}+\text{H}^+]$.
78		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.13 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.03 (3H, d), 2.64 (5H, m), 3.51 (2H, s), 3.70 (3H, s), 4.33 (2H, s), 4.59 (1H, m), 6.15 (1H, m), 6.23 (2H, s), 6.80 (3H, m), 6.99 (1H, m), 7.06 (1H, m), 7.18 (3H, m). LRMS: m/z APCI 579 $[\text{M}+\text{H}^+]$.
79		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.02 (3H, s), 0.85 (9H, s), 1.03 (3H, d), 2.64 (3H, m), 2.86 (2H, m), 3.53 (2H, s), 4.43 (2H, s), 4.59 (1H, m), 6.14 (1H, m), 6.23 (2H, s), 6.91 (1H, m), 7.06 (1H, s), 7.15 (1H, m), 7.19 (1H, m), 7.48 (4H, m). LRMS: m/z APCI 617 $[\text{M}+\text{H}^+]$, 615 $[\text{M}-\text{H}]$.

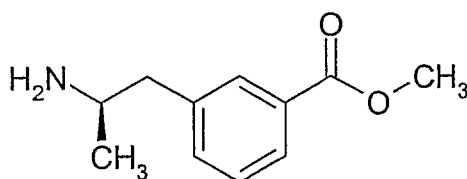
80		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.03 (3H, d), 2.60 (3H, m), 2.86 (2H, m), 3.52 (2H, s), 4.33 (2H, s), 4.58 (1H, m), 6.14 (1H, m), 6.23 (2H, s), 7.18 (7H, m). LRMS: m/z APCI 585 $[\text{M}+\text{H}^+]$, 583 $[\text{M}-\text{H}]$.
81		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.02 (3H, d), 2.53 (1H, m), 2.64 (2H, m), 2.84 (2H, m), 3.50 (2H, s), 3.78 (3H, s), 4.36 (2H, s), 4.59 (1H, m), 6.14 (1H, m), 6.23 (2H, s), 6.86 (1H, m), 6.93 (1H, m), 6.98 (1H, m), 7.06 (1H, s), 7.15 (4H, m). LRMS: m/z APCI 579 $[\text{M}+\text{H}^+]$, 577 $[\text{M}-\text{H}]$.
82		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.01 (3H, s), 0.86 (9H, s), 1.03 (3H, d), 2.18 (3H, s), 2.18 (3H, s), 2.55 (3H, m), 2.84 (2H, m), 3.48 (2H, s), 4.27 (2H, s), 4.58 (1H, m), 6.15 (1H, m), 6.23 (2H, s), 6.99 (5H, m), 7.13 (1H, m), 7.17 (1H, m). LRMS: m/z APCI 577 $[\text{M}+\text{H}^+]$, 575 $[\text{M}-\text{H}]$.

83		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.00 (3H, s), 0.85 (9H, s), 1.02 (3H, d), 2.55 (3H, m), 2.84 (2H, m), 3.48 (2H, s), 3.71 (3H, s), 3.77 (3H, s), 4.27 (2H, s), 4.58 (1H, m), 6.15 (1H, m), 6.22 (2H, s), 6.78 (2H, m), 6.85 (1H, m), 6.97 (1H, m), 7.06 (1H, s), 7.16 (2H, m). LRMS: m/z APCI 609 $[\text{M}+\text{H}^+]$, 608 $[\text{M}-\text{H}]$.
84		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.03 (3H, d), 1.34 (3H, t), 2.53 (1H, m), 2.64 (2H, m), 2.84 (2H, m), 3.52 (2H, s), 4.00 (2H, q), 4.38 (2H, s), 4.58 (1H, m), 6.15 (1H, m), 6.23 (2H, s), 6.83 (1H, m), 6.88 (1H, m), 6.98 (1H, m), 7.05 (1H, s), 7.13 (2H, m), 7.18 (2H, m). LRMS: m/z APCI 593 $[\text{M}+\text{H}^+]$, 591 $[\text{M}-\text{H}]$.
85		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.01 (3H, s), 0.86 (9H, s), 1.05 (3H, d), 2.58 (3H, m), 2.88 (5H, m), 3.41 (4H, m), 4.58 (1H, m), 6.14 (1H, m), 6.23 (2H, s), 7.00 (2H, m), 7.06 (1H, m), 7.18 (5H, m). LRMS: m/z APCI 597 $[\text{M}+\text{H}^+]$, 595 $[\text{M}-\text{H}]$.

86		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.01 (3H, s), 0.83 (9H, s), 1.03 (3H, d), 2.58 (1H, m), 2.69 (2H, m), 2.94 (2H, m), 3.59 (2H, s), 4.38 (2H, s), 4.58 (1H, m), 6.15 (1H, m), 6.23 (2H, s), 7.05 (1H, d), 7.10 (1H, s), 7.15 (1H, d), 7.20 (1H, m), 7.32 (2H, d), 7.80 (2H, d). LRMS: m/z APCI 592 $[\text{M}+\text{H}^+]$, 590 $[\text{M}-\text{H}]$.
87		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.03 (3H, d), 1.85 (1H, m), 2.52 (2H, m), 2.65 (2H, m), 2.83 (3H, m), 3.00 (1H, m), 3.50 (2H, m), 4.58 (1H, m), 5.37 (1H, m), 6.15 (1H, m), 6.23 (2H, s), 7.00 (1H, d), 7.10 (7H, m). LRMS: m/z APCI 575 $[\text{M}+\text{H}^+]$, 573 $[\text{M}-\text{H}]$.

Preparation 88

Methyl {3-[(2R)-2-aminopropyl]phenyl}acetate



- 5 A solution of methyl [3-((2R)-2-[(1R)-1-phenyl-ethyl]-amino)-propyl]-phenyl]-acetate (Preparation 89) (13.65g, 40.9mmol) and ammonium formate (12.9g, 204mmol) in ethanol (200ml) was heated at reflux in the presence of 20% of palladium hydroxide on charcoal ($\text{Pd}(\text{OH})_2/\text{C}$, 1.36g). After 3 hours the reaction mixture was cooled to room temperature, filtered through arbocel and the
- 10 filtrate concentrated *in vacuo*. The residue was partitioned between dichloromethane (200ml) and 880 ammonia (100ml) and the organic phase

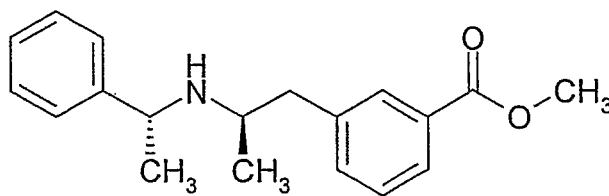
separated. The aqueous phase was extracted with further dichloromethane (3x100ml) and the combined organic extracts washed with brine (100ml), dried (sodium sulfate) and reduced *in vacuo* to give the title compound (8.48g) as a pale yellow oil.

- 5 ^1H NMR (400MHz, CDCl_3): δ = 7.90-7.87 (2H, m), 7.38-7.34 (2H, m), 3.90 (3H, s), 3.26-3.17 (1H, m), 2.78-2.73 (1H, dd), 2.64-2.59 (1H, dd), 1.14-1.12 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 194.

10 Preparation 89

Methyl [3-((2R)-2-[[[(1R)-1-phenyl-ethyl]-amino]-propyl]-phenyl]-acetate hydrochloride



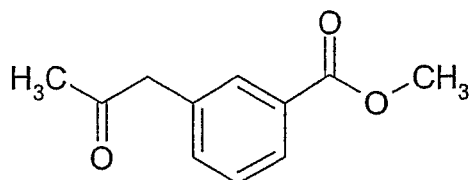
- A solution of methyl [3-(2-oxopropyl)phenyl]acetate (Preparation 90) (45.3g, 236mmol), (R)- α -methyl benzylamine (27.6ml, 214mmol), sodium triacetoxyborohydride (68.1g, 321mmol) and acetic acid (14.7ml, 257mmol) in dichloromethane (1500ml) was stirred at room temperature for 18 hours. The reaction mixture was quenched by addition of saturated aqueous sodium bicarbonate (600ml) and allowed to stir until effervescence ceased. The organic phase was separated and the aqueous phase extracted with further dichloromethane (2x100ml). The combined organic extracts were washed with brine (100ml), dried (sodium sulfate), filtered through celite and reduced *in vacuo*. The oil was dissolved in methanol (200ml), treated with 1M hydrogen chloride in methanol (300ml) and reduced *in vacuo* to give a 4:1 mixture of diastereomers (*R,R* major) as an off-white, hydrochloride salt. Two successive crystallisations (diisopropylether/methanol) gave the title compound (27.3g) as a colourless crystalline solid.

^1H NMR (400MHz, CD_3OD): δ = 7.92-7.90 (1H, d), 7.75 (1H, s), 7.55-7.49 (5H, m), 7.45-7.42 (1H, dd), 7.35-7.33 (1H, d), 4.68-4.63 (1H, q), 3.90 (3H, s), 3.43-

3.38 (1H, dd), 3.25-3.19 (1H, m), 2.71-2.65 (1H, dd), 1.71-1.69 (3H, d), 1.17-1.16, (3H, d) ppm.

Preparation 90

5 Methyl [3-(2-oxopropyl)phenyl]acetate



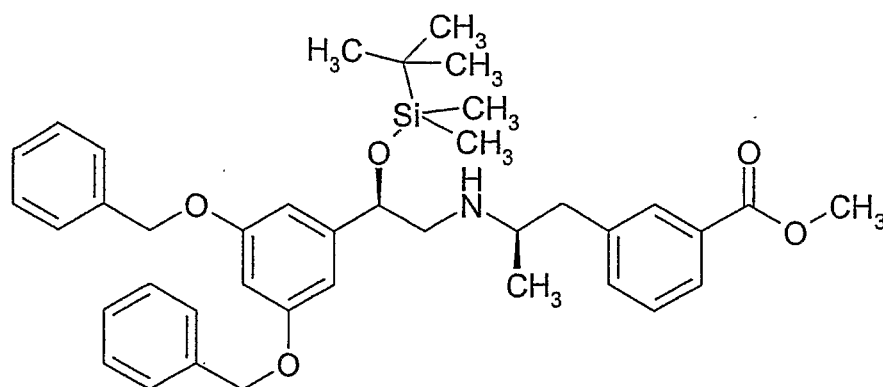
Tributyltin methoxide (80.3ml, 279mmol), methyl 3-bromobenzoate (53.5g, 249mmol), isopropenyl acetate (39.4ml, 358mmol), palladium(II)acetate (2.6g, 11.6mmol) and tri-*o*-tolylphosphine (7.1g, 23.2mmol) were stirred together in
 10 toluene (350ml) at 100°C under nitrogen for 18 hours. After cooling, the reaction was treated with 4M aqueous potassium fluoride solution (560ml) and stirred for 2 hours. The resulting mixture was diluted with further toluene (200ml) and filtered through celite, washing the filter pad with ethyl acetate. The organic phase was separated, dried (sodium sulfate) and reduced *in vacuo*.
 15 The residue was purified by flash column chromatography on silica gel eluting with ethylacetate:pentane (10:90, changing to 20:80, by volume) to give the title compound (45.3g) as an orange oil.

¹H NMR (400MHz, CDCl₃): δ = 7.95-7.93 (1H, d), 7.87 (1H, s), 7.43-7.37 (2H, m), 3.91 (3H, s), 3.75 (2H, s), 2.18 (3H, s) ppm.

20 LRMS (electrospray) : m/z [M+Na]⁺ 215, [M-H]⁻ 191.

Preparation 91

3-{2-[2-(3,5-Bis-benzyloxy-phenyl)-2-(tert-butyl-dimethyl-silanyloxy)-ethylamino]-propyl}-benzoic acid methyl ester



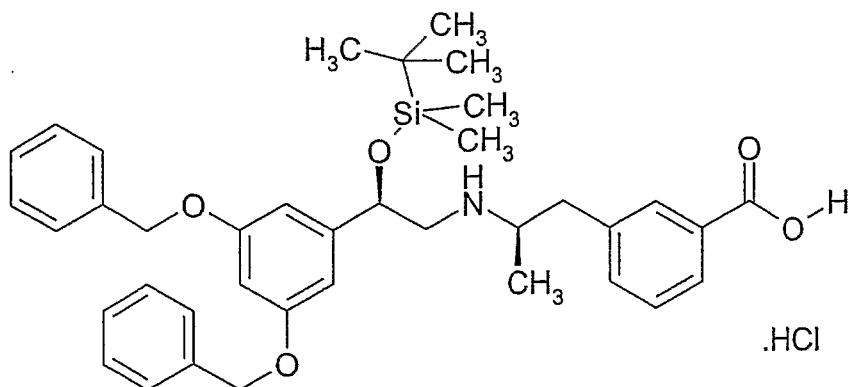
The compound of preparation 11 (7.10g, 13.5mmol) was added to a solution of the compound of preparation 88 (5.23g, 27.0mmol) in dichloromethane (50mL) and the solvent removed *in vacuo*. The mixture was heated at 95°C for 12 hours and cooled to room temperature. Diethyl ether (150mL) was added and the the reaction stirred for 1 hour, the resulting white precipitate was removed by filtration and the filtrate evaporated to furnish a yellow oil. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (100:0:0 then 95:5:0.5) to furnish the title compound as a yellow oil, 4.30g.

^1H NMR (400MHz, CD_3OD) δ -0.23 (3H, s), -0.06 (3H, s), 0.78 (9H, s), 1.06 (3H, d), 2.57 (1H, m), 2.66 (2H, m), 2.88 (2H, m), 3.83 (3H, s), 4.64 (1H, m), 4.85 (4H, s), 6.46 (2H, s), 6.49 (1H, m), 7.32 (12H, m), 7.78 (1H, s), 7.82 (1H, m).

LRMS: m/z APCI 640 $[\text{M}+\text{H}^+]$.

Preparation 92

3-{2-[2-(3,5-Bis-benzyloxy-phenyl)-2-(tert-butyl-dimethyl-silanyloxy)-ethylamino]-propyl}-benzoic acid hydrochloride



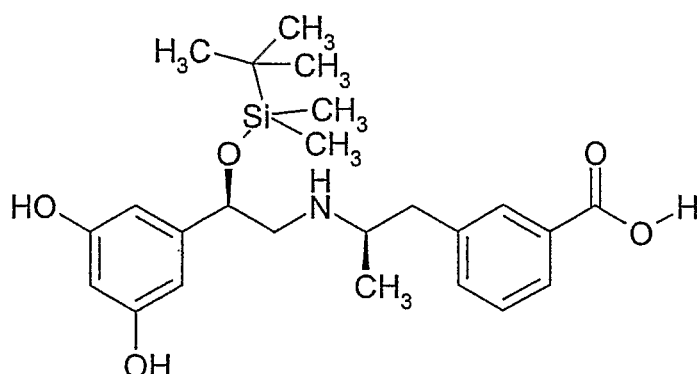
The compound of preparation 91 (5.35g, 8.37mmol) was stirred in tetrahydrofuran (20mL) and 1M aqueous lithium hydroxide (18.4mL, 18.4mmol) was added in one portion. The reaction was stirred for 12 hours and then heated at 40°C for 12 hours. Further 1M aqueous lithium hydroxide (36.8mL, 36.8mmol) and tetrahydrofuran (100mL) added in one portion and reaction heated at 40°C for 12 hours, reaction cooled and further 1M aqueous lithium hydroxide (36.8mL, 36.8mmol) added. The reaction was heated at 60°C for 5 hours and cooled to room temperature, the tetrahydrofuran was removed under reduced pressure and dioxane (50mL) added. The reaction was heated at 60°C for 1 hour, cooled to room temperature and the solvent removed *in vacuo*. The residue was acidified to pH1 with 1M aqueous hydrochloric acid and extracted with dichloromethane:methanol (97:3; v/v; 3x150mL), the combined organics were washed with brine (30mL), dried (magnesium sulphate) and the solvent removed *in vacuo* to furnish the title compound as a yellow foam, 5.00g.

¹H NMR (400MHz, CD₃OD) δ -0.13 (3H, s), 0.07 (3H, s), 0.86 (9H, s), 1.24 (3H, d), 2.83 (1H, m), 3.19 (1H, m), 3.30 (2H, m), 3.59 (1H, m), 5.05 (1H, m), 5.11 (4H, s), 6.64 (3H, m), 7.30 (10H, m), 7.47 (2H, m), 7.92 (1H, s), 7.97 (1H, m).

LRMS: m/z APCI 626 [M+H⁺].

Preparation 93

3-{2-[2-(tert-Butyl-dimethyl-silanyloxy)-2-(3,5-dihydroxy-phenyl)-ethylamino]-propyl}-benzoic acid

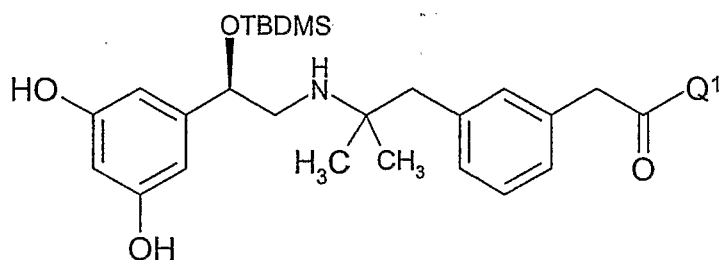


The compound of preparation 92 (4.97g, 7.95mmol) was dissolved in ethanol (300mL) and ammonium formate (2.75g, 60mmol) and palladium hydroxide (500mg) added in one portion. The reaction was heated under reflux for 1 hour, cooled to room temperature, filtered through Arbocel® and washed through with methanol (500mL). The filtrate was condensed *in vacuo* to furnish the title compound as an off white solid 3.60g.

¹H NMR (400MHz, CD₃OD) δ -0.06 (3H, s), 0.05 (3H, s), 0.86 (9H, s), 1.23 (3H, d), 2.83 (1H, m), 3.12 (2H, m), 3.25 (1H, m), 3.51 (1H, m), 4.90 (1H, m), 6.24 (1H, m), 6.35 (2H, s), 7.27 (2H, m), 7.83 (1H, m), 7.88 (1H, m).

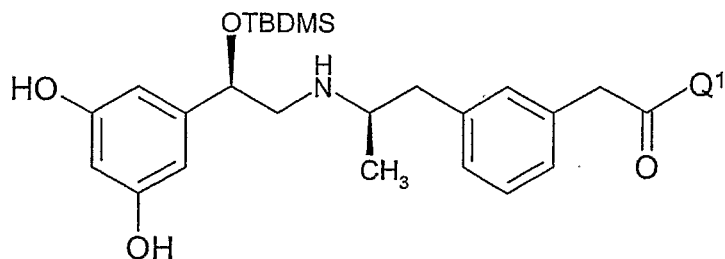
LRMS: m/z APCI 446 [M+H⁺].

Preparations 100 to 104 and 115 to 124 were prepared from preparation 33 and the appropriate amine, using the method of preparation 34. These compounds are of generic formula



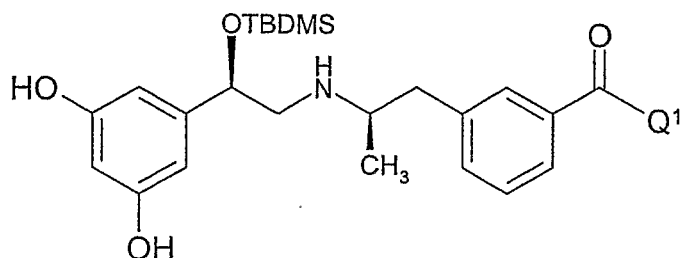
and are listed in the table below.

Preparations 96 to 99 were prepared from preparation 45 and the appropriate amine, using the method of preparation 34. These compounds are of generic formula



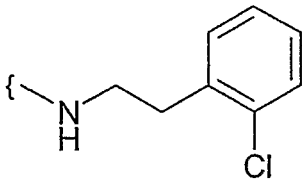
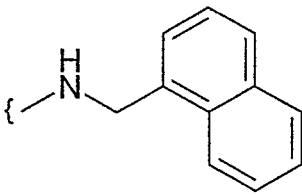
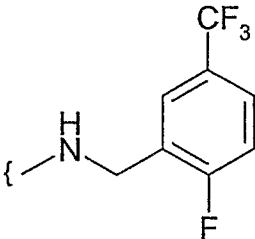
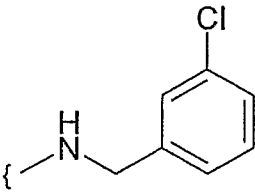
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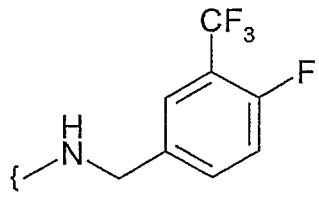
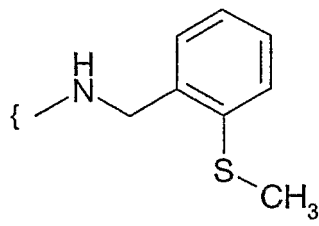
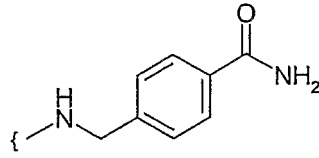
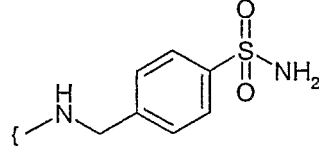
Preparations 94, 95 and 105 to 114 were prepared from preparation 93 and the
 5 appropriate amine, using the method of preparation 34. These compounds are
 of generic formula

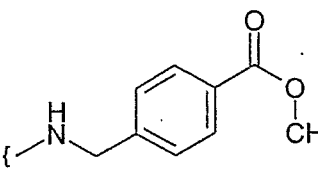
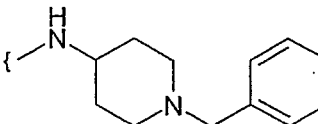
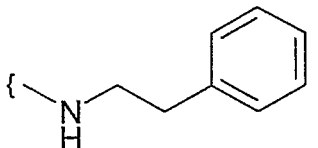


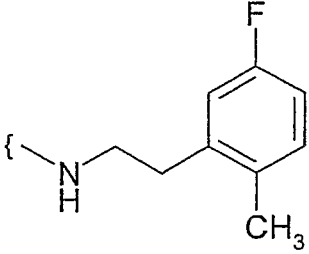
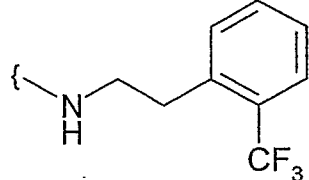
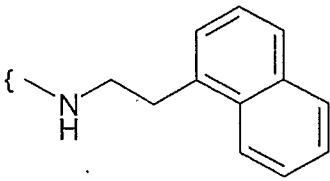
and are listed in the table below.

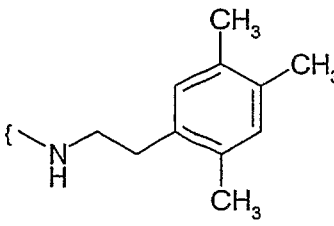
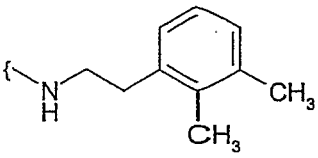
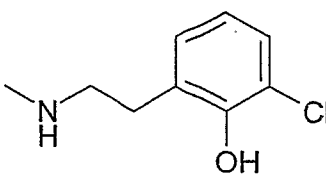
No	Q ¹	Data
94		The compound was isolated as a pale yellow solid. ¹H NMR (400MHz, CD₃OD) δ -0.15 (3H, s), -0.01 (3H, s), 0.85 (9H, s), 1.05 (3H, d), 2.73 (7H, m), 3.60 (2H, t), 4.60 (1H, m), 6.16 (1H, m), 6.25 (2H, s), 6.92 (1H, m), 7.05 (2H, m), 7.30 (3H, m), 7.60 (2H, m). LRMS: m/z APCI 567 [M+H⁺].

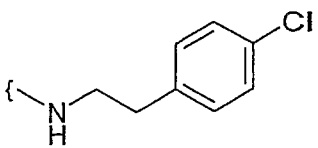
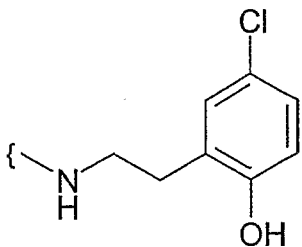
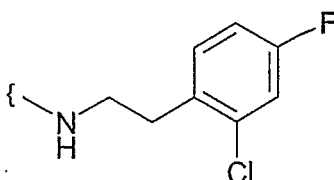
95		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), -0.01 (3H, s), 0.83 (9H, s), 1.05 (3H, d), 2.73 (5H, m), 3.07 (2H, m), 3.63 (2H, t), 4.60 (1H, m), 6.16 (1H, m), 6.25 (2H, s), 7.20 (6H, m), 7.60 (2H, m). LRMS: m/z APCI 583 $[\text{M}+\text{H}^+]$, 581 $[\text{M}-\text{H}]$.
96		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.22 (3H, s), 0.01 (3H, s), 0.90 (9H, s), 1.08 (3H, d), 2.58 (1H, m), 2.71 (2H, m), 2.88 (2H, m), 3.61 (2H, s), 4.65 (2H, s), 6.28 (1H, m), 6.38 (2H, s), 7.10 (2H, m), 7.35 (2H, m), 7.58 (3H, m), 7.91 (1H, d), 7.95 (1H, d), 8.08 (1H, d). LRMS: m/z APCI 599 $[\text{M}+\text{H}^+]$.
97		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.18 (3H, s), 0.00 (3H, s), 0.82 (9H, s), 1.04 (3H, d), 2.58 (1H, m), 2.71 (2H, m), 2.83 (2H, m), 3.51 (2H, s), 4.45 (2H, s), 4.58 (1H, m), 6.18 (1H, s), 6.23 (2H, s), 6.98 (1H, m), 7.05 (1H, s), 7.23 (3H, m), 7.58 (2H, m). LRMS: m/z APCI 635 $[\text{M}+\text{H}^+]$, 633 $[\text{M}-\text{H}]$.
98		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), 0.03 (3H, s), 0.82 (9H, s), 1.04 (3H, d), 2.58 (1H, m), 2.68 (2H, m), 2.83 (2H, m), 3.51 (2H, s), 4.38 (2H, s), 4.58 (1H, m), 6.18 (1H, s), 6.23 (2H, s), 6.98 (1H, d), 7.05 (1H, s), 7.23 (6H, m). LRMS: m/z APCI 583 $[\text{M}+\text{H}^+]$, 581 $[\text{M}-\text{H}]$.

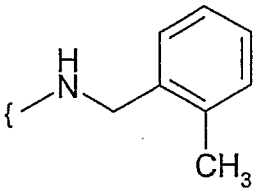
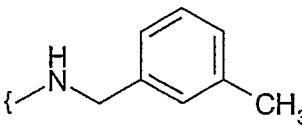
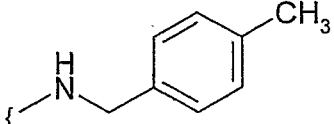
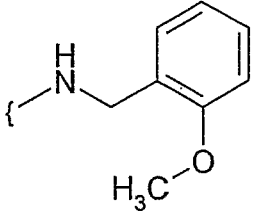
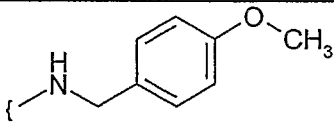
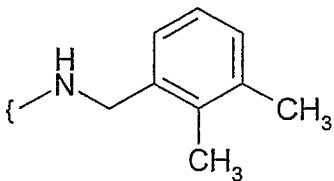
99		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.16 (3H, s), -0.03 (3H, s), 0.82 (9H, s), 1.04 (3H, d), 2.60 (3H, m), 2.83 (2H, m), 3.51 (2H, s), 4.38 (2H, s), 4.58 (1H, m), 6.18 (1H, s), 6.23 (2H, s), 6.98 (1H, d), 7.05 (1H, s), 7.09 (1H, d), 7.23 (2H, m), 7.51 (2H, m). LRMS: m/z APCI 635 $[\text{M}+\text{H}^+]$, 633 $[\text{M}-\text{H}]$.
100		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.08 (3H, s), 0.04 (3H, s), 0.87 (9H, s), 1.08 (3H, s), 1.10 (3H, s), 2.48 (3H, s), 2.74 (4H, m), 3.58 (2H, s), 4.47 (2H, s), 4.64 (1H, m), 6.22 (1H, m), 6.34 (2H, s), 7.11 (8H, m). LRMS: m/z electrospray 611 $[\text{M}+\text{H}^+]$, 608 $[\text{M}-\text{H}]$.
101		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.08 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 1.10 (3H, s), 1.12 (3H, s), 2.76 (4H, m), 3.59 (2H, s), 4.46 (2H, s), 4.64 (1H, m), 6.22 (1H, m), 6.34 (2H, s), 7.10 (1H, d), 7.16 (1H, s), 7.25 (2H, m), 7.34 (2H, d), 7.83 (2H, d). LRMS: m/z electrospray 607 $[\text{M}+\text{H}^+]$, 605 $[\text{M}-\text{H}]$.
102		The compound was isolated as a white solid. ^1H NMR (400MHz, CD_3OD) δ -0.08 (3H, s), 0.05 (3H, s), 0.87 (9H, s), 1.10 (3H, s), 1.12 (3H, s), 2.69 (3H, m), 2.90 (1H, m), 3.59 (2H, s), 4.47 (2H, s), 4.67 (1H, m), 6.22 (1H, m), 6.34 (2H, s), 7.10 (1H, d), 7.15 (1H, s), 7.22 (1H, m), 7.27 (1H, m), 7.41 (2H, d), 7.84 (2H, d). LRMS: m/z electrospray 643 $[\text{M}+\text{H}^+]$, 640 $[\text{M}-\text{H}]$.

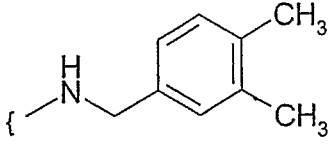
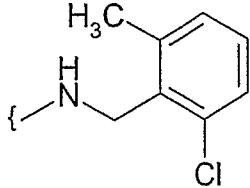
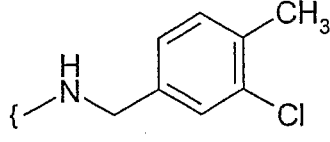
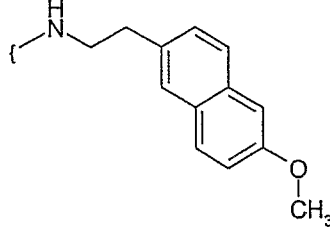
103		The compound was isolated as a white solid. ¹H NMR (400MHz, CD₃OD) δ -0.08 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 1.08 (3H, s), 1.11 (3H, s), 2.86 (4H, m), 3.59 (2H, s), 3.92 (3H, s), 4.47 (2H, s), 4.63 (1H, m), 6.22 (1H, m), 6.34 (2H, s), 7.10 (1H, d), 7.15 (1H, s), 7.22 (2H, m), 7.36 (2H, d), 7.96 (2H, d). LRMS: m/z electrospray 623 [M+H⁺], 620 [M-H].
104		The compound was isolated as a white solid. ¹H NMR (400MHz, CD₃OD) δ -0.09 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 1.10 (3H, s), 1.12 (3H, s), 1.55 (2H, m), 1.87 (2H, m), 2.15 (2H, m), 2.75 (3H, m), 2.86 (3H, m), 3.49 (2H, s), 3.56 (2H, s), 3.68 (1H, m), 4.63 (1H, m), 6.22 (1H, m), 6.34 (2H, s), 7.06 (1H, m), 7.14 (1H, s), 7.19 (1H, m), 7.25 (1H, m), 7.30 (1H, m), 7.35 (4H, m). LRMS: m/z electrospray 647 [M+H⁺], 645 [M-H].
105		The compound was isolated as a pale brown foam. ¹H NMR (400MHz, CD₃OD) δ -0.15 (3H, s), -0.01 (3H, s), 0.84 (9H, s), 1.06 (3H, d), 2.63 (2H, m), 2.76 (1H, m), 2.85 (1H, m), 2.90 (3H, m), 3.59 (2H, t), 4.61 (1H, m), 6.17 (1H, m), 6.25 (2H, s), 7.18 (1H, m), 7.25 (5H, m), 7.35 (1H, m), 7.60 (2H, m). LRMS: m/z APCI 549 [M+H⁺], 547 [M-H].

106		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), -0.01 (3H, s), 0.82 (9H, s), 1.05 (3H, d), 2.32 (3H, s), 2.63 (2H, m), 2.76 (1H, m), 2.85 (1H, m), 2.90 (3H, m), 3.57 (2H, t), 4.61 (1H, m), 6.17 (1H, m), 6.25 (2H, s), 6.81 (1H, m), 6.92 (1H, m), 7.13 (1H, m), 7.27 (1H, m), 7.36 (1H, m), 7.60 (2H, m). LRMS: m/z APCI 581 $[\text{M}+\text{H}^+]$, 579 $[\text{M}-\text{H}]$.
107		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), -0.01 (3H, s), 0.85 (9H, s), 1.06 (3H, d), 2.63 (2H, m), 2.77 (1H, m), 2.85 (1H, m), 2.95 (1H, m), 3.13 (2H, t), 3.63 (2H, t), 4.61 (1H, m), 6.16 (1H, m), 6.24 (2H, s), 7.28 (1H, m), 7.36 (2H, m), 7.51 (2H, m), 7.65 (3H, m).
108		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), -0.01 (3H, s), 0.85 (9H, s), 1.05 (3H, d), 2.63 (2H, m), 2.75 (1H, m), 2.85 (2H, m), 3.41 (2H, t), 3.52 (2H, t), 4.61 (1H, m), 6.17 (1H, m), 6.25 (2H, s), 7.27 (1H, m), 7.36 (3H, m), 7.48 (3H, m), 7.62 (1H, m), 7.75 (1H, m), 7.85 (1H, m), 8.26 (1H, m). LRMS: m/z APCI 599 $[\text{M}+\text{H}^+]$, 597 $[\text{M}-\text{H}]$.

109		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), -0.01 (3H, s), 0.84 (9H, s), 1.05 (3H, d), 2.17 (6H, s), 2.28 (3H, s), 2.63 (2H, m), 2.75 (4H, m), 2.95 (1H, m), 3.50 (2H, t), 4.61 (1H, m), 6.17 (1H, m), 6.24 (2H, s), 6.88 (1H, s), 6.93 (1H, s), 7.27 (1H, m), 7.36 (1H, m), 7.59 (1H, s), 7.62 (1H, m). LRMS: m/z APCI 591 $[\text{M}+\text{H}^+]$, 590 $[\text{M}-\text{H}]$.
110		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), -0.01 (3H, s), 0.84 (9H, s), 1.05 (3H, d), 2.27 (3H, s), 2.28 (3H, s), 2.63 (2H, m), 2.77 (1H, m), 2.84 (1H, m), 2.93 (3H, m), 3.53 (2H, t), 4.61 (1H, m), 6.17 (1H, m), 6.24 (2H, s), 7.00 (3H, m), 7.27 (1H, m), 7.36 (1H, m), 7.62 (2H, m). LRMS: m/z APCI 577 $[\text{M}+\text{H}^+]$, 575 $[\text{M}-\text{H}]$.
111		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), -0.01 (3H, s), 0.84 (9H, s), 1.06 (3H, d), 2.63 (2H, m), 2.77 (1H, m), 2.84 (1H, m), 2.93 (3H, m), 3.61 (2H, t), 4.61 (1H, m), 6.17 (1H, m), 6.23 (2H, s), 6.76 (1H, t), 7.07 (1H, m), 7.17 (1H, m), 7.27 (1H, m), 7.35 (1H, m), 7.58 (2H, m). LRMS: m/z APCI 599 $[\text{M}+\text{H}^+]$, 597 $[\text{M}-\text{H}]$.

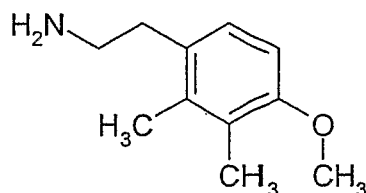
112		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), -0.01 (3H, s), 0.84 (9H, s), 1.05 (3H, d), 2.63 (2H, m), 2.76 (1H, m), 2.84 (4H, m), 3.58 (2H, t), 4.60 (1H, m), 6.16 (1H, m), 6.24 (2H, s), 7.27 (5H, m), 7.35 (1H, m), 7.56 (1H, s), 7.60 (1H, m). LRMS: m/z APCI 583 $[\text{M}+\text{H}^+]$, 581 $[\text{M}-\text{H}]$.
113		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), -0.01 (3H, s), 0.83 (9H, s), 1.06 (3H, d), 2.63 (2H, m), 2.77 (1H, m), 2.84 (4H, m), 3.58 (2H, t), 4.60 (1H, m), 6.17 (1H, m), 6.24 (2H, s), 6.74 (1H, m), 7.00 (1H, m), 7.10 (1H, m), 7.26 (1H, m), 7.35 (1H, m), 7.57 (1H, s), 7.61 (1H, m). LRMS: m/z APCI 599 $[\text{M}+\text{H}^+]$, 597 $[\text{M}-\text{H}]$.
114		The compound was isolated as a pale brown foam. ^1H NMR (400MHz, CD_3OD) δ -0.15 (3H, s), -0.02 (3H, s), 0.82 (9H, s), 1.04 (3H, d), 2.63 (2H, m), 2.77 (1H, m), 2.85 (1H, m), 2.94 (1H, m), 3.04 (2H, t), 3.62 (2H, t), 4.60 (1H, m), 6.17 (1H, m), 6.24 (2H, s), 6.98 (1H, m), 7.18 (1H, m), 7.27 (1H, m), 7.35 (2H, m), 7.59 (1H, m). LRMS: m/z APCI 601 $[\text{M}+\text{H}^+]$, 599 $[\text{M}-\text{H}]$.

115		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.09 (3H, s), 0.04 (3H, s), 0.78 (9H, s), 1.04 (3H, s), 1.05 (3H, s), 2.22 (3H, s), 2.74 (3H, m), 2.83 (1H, m), 3.56 (2H, s), 4.37 (2H, s), 4.55 (1H, m), 6.18 (1H, m), 6.36 (2H, s), 7.04 (1H, d), 7.12 (6H, m), 7.21 (1H, m). LRMS: m/z electrospray 577 $[\text{M}+\text{H}^+]$.
116		The compound was isolated as a white foam. LRMS: m/z electrospray 577 $[\text{M}+\text{H}^+]$.
117		The compound was isolated as a white foam. LRMS: m/z electrospray 577 $[\text{M}+\text{H}^+]$.
118		The compound was isolated as a white foam. ^1H NMR (400MHz, CD_3OD) δ -0.09 (3H, s), 0.04 (3H, s), 0.98 (9H, s), 1.04 (3H, s), 1.05 (3H, s), 2.68 (2H, t), 2.77 (1H, m), 2.83 (1H, m), 3.56 (2H, s), 3.79 (3H, s), 4.37 (2H, s), 4.55 (1H, m), 6.18 (1H, m), 6.37 (2H, s), 6.82 (1H, t), 6.92 (1H, d), 7.03 (1H, d), 7.12 (3H, m), 7.22 (2H, m). LRMS: m/z electrospray 593 $[\text{M}+\text{H}^+]$, 591 $[\text{M}-\text{H}]$.
119		The compound was isolated as a white foam. LRMS: m/z electrospray 594 $[\text{M}+\text{H}^+]$, 591 $[\text{M}-\text{H}]$.
120		The compound was isolated as a white foam. LRMS: m/z electrospray 591 $[\text{M}+\text{H}^+]$, 589 $[\text{M}-\text{H}]$.

121		The compound was isolated as a white foam. LRMS: m/z electrospray 591 [M+H ⁺], 589 [M-H].
122		The compound was isolated as a white foam. ¹ H NMR (400MHz, CD ₃ OD) δ -0.09 (3H, s), 0.04 (3H, s), 0.94 (9H, s), 1.04 (3H, s), 1.05 (3H, s), 2.37 (3H, s), 2.68 (3H, m), 2.83 (1H, m), 3.47 (2H, s), 4.53 (2H, s), 4.55 (1H, m), 6.18 (1H, m), 6.36 (2H, s), 7.04 (1H, d), 7.09 (1H, d), 7.18 (4H, m), 7.21 (1H, m). LRMS: m/z electrospray 611 [M+H ⁺], 609 [M-H].
123		The compound was isolated as a white foam. LRMS: m/z electrospray 611 [M+H ⁺], 609 [M-H].
124		The compound was isolated as a white foam. LRMS: m/z electrospray 658 [M+H ⁺].

Preparation 125

2-(4-Methoxy-2,3-dimethyl-phenyl)-ethylamine



- 5 A mixture of (4-methoxy-2,3-dimethyl-phenyl)-acetonitrile (200mg, 1.14mmol) and Raney[®] nickel (50mg) in 2M methanolic ammonia (10mL) was stirred under 60psi of hydrogen gas at room temperature for 18 hours. Tlc analysis showed that not all of the starting material had been consumed and so further Raney[®]

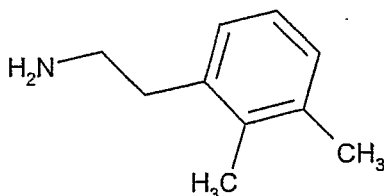
nickel (50mg) in 2M methanolic ammonia (10mL) was added. The reaction mixture was stirred under 60psi of hydrogen gas for an additional 18 hours at room temperature and was then filtered through Arbocel[®]. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 100:0:0 to 90:10:1 to afford the title product as a pale brown solid, 233mg.

¹H NMR (400MHz, CDCl₃) δ: 6.96 (1H, d), 6.66 (1H, d), 3.80 (3H, s), 2.96-2.84 (2H, m), 2.81-2.73 (2H, m), 2.22 (3H, s), 2.17 (3H, s), 1.63 (2H, s) ppm LRMS APCI m/z 180 [M+H]⁺

10

Preparation 126

2-(2,3-Dimethyl-phenyl)-ethylamine



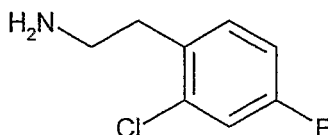
A mixture of 2,3-dimethylphenylacetonitrile (*J. Org Chem*, 51(26), 5157-60; 1986), (190mg, 1.31mmol) and Raney[®] nickel (100mg) in 2M methanolic ammonia (5mL) was stirred under 50psi of hydrogen gas for 4 days. The mixture was then filtered through Arbocel[®] and concentrated *in vacuo* to afford the title compound as a solid, 130mg.

¹H NMR (400MHz, CDCl₃) δ: 7.02-6.94 (3H, m), 2.26-2.13 (10H, m) ppm LRMS ESI m/z 150 [M+H]⁺

20

Preparation 127

2-(2-Chloro-4-fluoro-phenyl)-ethylamine



Sodium borohydride (1.73g, 45.51mmol) was added portionwise to a solution of 2-chloro-4-fluorophenylacetonitrile (1.04g, 6.15mmol) and cobalt (II) chloride hexahydrate (2.18g, 9.22mmol) in methanol (30mL) and the mixture was stirred

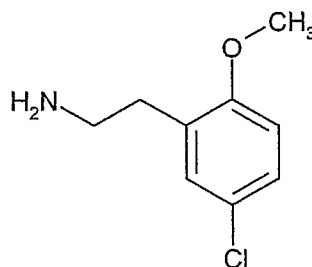
25

at room temperature for 3 hours. The suspension was then filtered through Celite[®], concentrated *in vacuo* and the residue was partitioned between 1M hydrochloric acid (40mL) and dichloromethane (40mL). The aqueous phase was separated, basified to pH 11 with 1M ammonia solution and extracted with dichloromethane (2x40mL). The combined organic solution was washed with brine (30mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 100:0:0 to 98:2:0.2, to afford the title compound as a yellow oil, 350mg.

10 ¹H NMR (400MHz, CDCl₃) δ: 7.30 (1H, dd), 7.17 (1H, dd), 6.99 (1H, m), 2.86 (4H, m) ppm
LRMS APCI m/z 174 [M+H]⁺

Preparation 128

15 2-(5-Chloro-2-methoxy-phenyl)-ethylamine



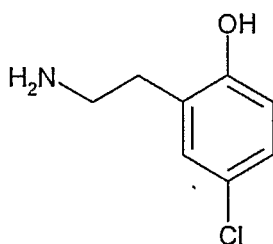
Chlorotrimethylsilane (2mL, 16mmol) was added dropwise to lithium borohydride (2M in tetrahydrofuran, 4mL, 8mmol). A solution of 2-methoxy-5-chlorophenylacetonitrile (312mg, 4mmol) in tetrahydrofuran (2mL) was then added at 0°C and the mixture was allowed to stir for 24 hours, whilst warming to room temperature. The mixture was then diluted with methanol (20mL) and concentrated *in vacuo*. The residue was taken up in 20% potassium hydroxide solution (20mL), extracted with dichloromethane (3x20mL) and the combined organic solution was dried over magnesium sulfate and concentrated *in vacuo*.

25 The residue was purified by column chromatography using an Isolute[®] SCX-2 cartridge, eluting with methanol followed by 1M ammonia in methanol, to give an oily residue. The oil was triturated with diethyl ether to afford the title compound, 485mg.

^1H NMR (400MHz, CDCl_3) δ : 7.11-7.00 (2H, m), 6.75-6.65 (1H, m) 3.72 (3H, s), 2.90-2.80 (2H, m), 2.70-2.60 (2H, m) ppm

Preparation 129

5 2-(5-Chloro-2-hydroxy-phenyl)-ethylamine



The amine of preparation 128 (66mg, 0.36mmol) was dissolved in 48% aqueous HBr and heated at 80°C with stirring for 12 hours. The reaction was cooled to room temperature and the solvent removed *in vacuo* to give a brown gum. This was dissolved in methanol (5mL) and purified by ion exchange column to furnish the title compound as a brown gum, 26mg.

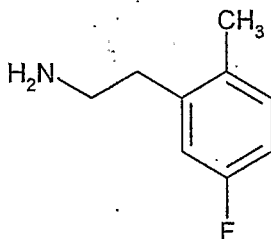
^1H NMR (400MHz, CDCl_3) δ : 2.70 (2H, t), 2.90 (2H, t), 6.70 (1H, d), 6.98 (1H, m), 7.02 (1H, s) ppm

LRMS APCI m/z 172 $[\text{M}+\text{H}]^+$

15

Preparation 130

2-(5-Fluoro-2-methyl-phenyl)-ethylamine

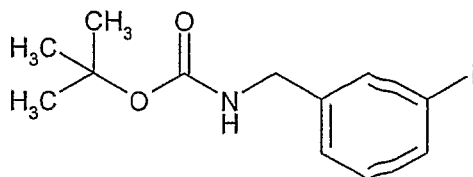


This compound was prepared using the method of preparation 128 and the appropriate nitrile.

^1H NMR (400MHz, CDCl_3) δ : 7.07 (1H, m), 6.83 (2H, m), 2.97 (2H, t), 2.78 (2H, m) 2.27 (3H, s) ppm

LRMS APCI m/z 154 $[\text{M}+\text{H}]^+$

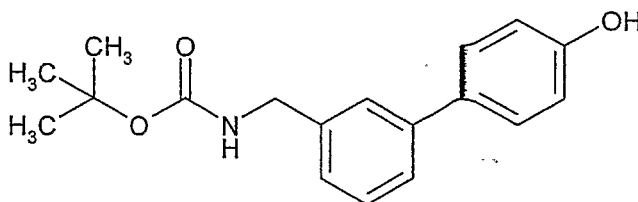
20

Preparation 131***tert*-butyl (3-iodobenzyl)carbamate**

A suspension of 3-iodobenzylamine hydrochloride (4.95g, 18.4mmol) in
 5 dichloromethane (100ml) was treated with triethylamine (3.1ml, 22mmol) and
 di-*t*-butyl dicarbonate (4.40g, 20mmol) and the resulting solution left to stir at
 room temperature under a nitrogen atmosphere for 1.5 hours. The reaction
 mixture was washed with 2M hydrochloric acid (30ml), water (30ml), dried
 (sodium sulfate), and the solvent removed *in vacuo* to give the title compound
 10 as a colourless solid (6.43g).

¹HNMR (400MHz, CDCl₃) δ : 1.46 (s, 9H), 4.21 -4.30 (m, 2H), 4.79-4.89 (bs,
 1H), 7.06 (dd, 1H), 7.25 (d, 1H), 7.60 (d, 1H), 7.63 (s, 1H) ppm.

MS (electrospray) m/z 332 [M-H]⁺, 356 [M+Na]⁺

15 Preparation 132***tert*-butyl [(4'-hydroxybiphenyl-3-yl)methyl]carbamate**

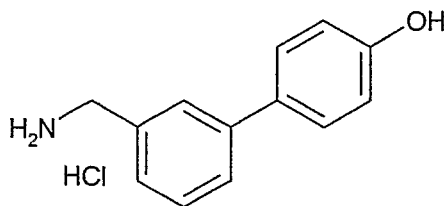
A solution of the iodide from preparation 131 (0.75g, 2.25mmol), 4-hydroxy
 phenylboronic acid (0.62g, 4.50mmol), 1,1'-Bis(diphenylphosphino)ferrocenyl
 20 palladium(II)chloride (0.11g, 0.14mmol), in *N,N*-dimethylformamide (14ml) was
 treated with 2M aq. sodium carbonate (4ml) and the resulting mixture heated at
 80°C under a nitrogen atmosphere for 16 hours. The solvent was removed
 under reduced pressure and the residue purified by column chromatography on
 silica gel eluting with ethyl acetate:pentane (1:3) to give the title compound as a
 25 pale pink crystalline solid (0.73g).

^1H NMR (400MHz, CDCl_3) δ : 1.47 (s, 9H), 4.33-4.41 (m), 4.87-4.94 (bs, 1H), 6.89 (d, 2H), 7.21 (d, 1H), 7.37 (dd, 1H), 7.43-7.45 (m, 4H) ppm.

MS (electrospray) m/z 298 $[\text{M}-\text{H}]^-$, 322 $[\text{M}+\text{Na}]^+$

5 Preparation 133

3'-(aminomethyl)biphenyl-4-ol hydrochloride



The phenol from preparation 132 (0.73g, 2.43mmol) was treated with 4M HCl in dioxan (6ml, 24.3mmol) and the resulting solution allowed to stir at room temperature for 3 hours. The solvent was removed *in vacuo* to give the title compound as a colourless solid.

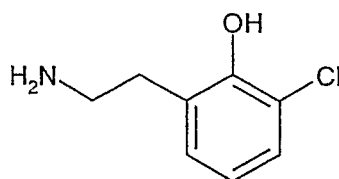
^1H NMR (400MHz, CD_3OD) δ : 4.17 (s, 2H), 6.87 (d, 2H), 7.34 (d, 1H), 7.45-7.50 (m, 3H), 7.61 (d, 1H), 7.65 (s, 1H) ppm.

MS (electrospray) m/z 198 $[\text{M}-\text{H}]^-$, 200 $[\text{M}+\text{H}]^+$

15

Preparation 134

2-(3-Chloro-2-hydroxy-phenyl)-ethylamine

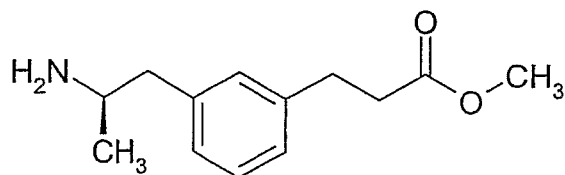


Prepared according to the procedure described in DE1959898.

20

Preparation 135

Methyl-3-[(2R)-2-aminopropyl]phenyl]propanoate



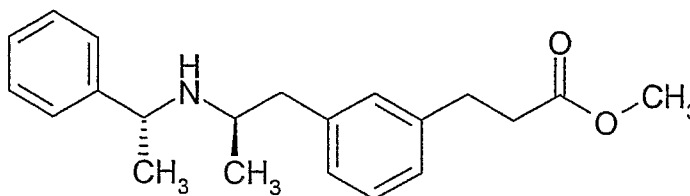
Prepared according to the procedure used for preparation 22, using methyl-3-((2*R*)-2-[(1*R*)-1-phenylethyl]amino}propyl)phenyl]propanoate hydrochloride (Preparation 136) to give the title compound as a brown oil.

¹H NMR (400MHz, CD₃OD): δ = 7.21-7.17 (1H, t), 7.03-7.01 (3H, m), 3.61 (3H, s), 3.11-3.03 (1H, m), 2.91-2.87 (2H, t), 2.64-2.54 (4H, m), 1.07-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 222.

Preparation 136

10 Methyl [3-((2*R*)-2-[(1*R*)-1-phenylethyl]amino}propyl)phenyl]propanoate hydrochloride



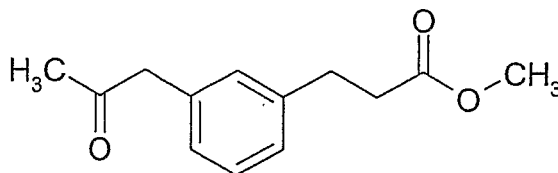
Prepared according to the procedure used for preparation 23, using methyl-3-[3-(2-oxopropyl)phenyl]propanoate (Preparation 137) to give the title compound as a white crystalline solid.

¹H NMR (400MHz, CD₃OD): δ = 7.54-7.47 (5H, m), 7.23-7.19 (1H, t), 7.12-7.10 (1H, d), 6.92-6.91 (2H, d), 4.64-4.59 (1H, q), 3.61 (3H, s), 3.34-3.29 (1H, m), 3.20-3.12 (1H, m), 2.89-2.85 (2H, t), 2.62-2.56 (3H, m), 1.71-1.69 (3H, d), 1.18-1.16 (3H, d) ppm.

20 LRMS (electrospray) : m/z [M+H]⁺ 326.

Preparation 137

Methyl-3-[3-(2-oxopropyl)phenyl]propanoate



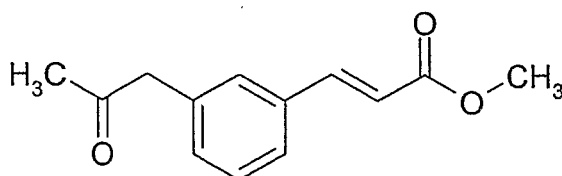
25 A suspension of methyl (2*E*)-3-[3-(2-oxopropyl)phenyl]acrylate (5.00g, Preparation 138) and 10% palladium on carbon (500mg) in ethanol (50ml) was

stirred under an atmosphere of hydrogen (60psi) at room temperature for 16 hours. The catalyst was filtered off through arbocel and the filtrate concentrated *in vacuo* to give the title compound as a pale yellow oil which was used without further purification.

- 5 ^1H NMR (400MHz, CD_3OD): δ = 7.27-7.23 (1H, q), 7.11-7.09 (1H, d), 7.05-7.04 (2H, d), 3.66 (5H, s), 2.96-2.92 (2H, t), 2.64-2.60 (2H, t), 2.14 (3H, s) ppm.
LRMS (electrospray) : m/z $[\text{M}+\text{Na}]^+$ 243, $[\text{M}-\text{H}]^-$ 219.

Preparation 138

10 Methyl (2E)-3-[3-(2-oxopropyl)phenyl]acrylate

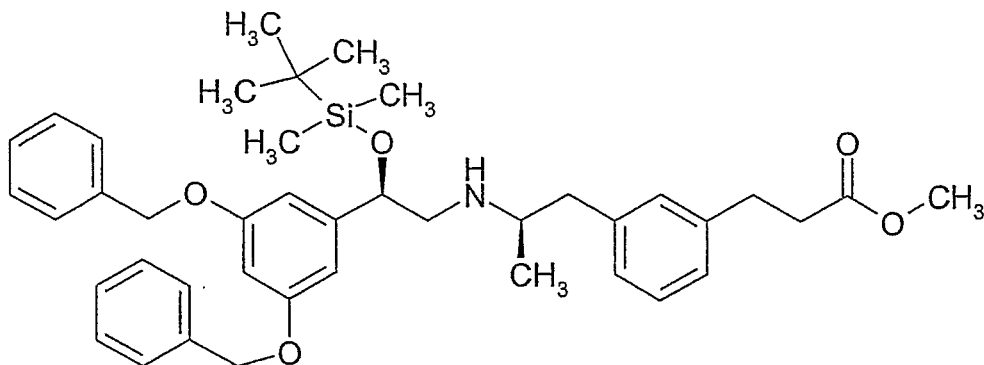


- A solution of 3-bromophenylacetone (50.0g, 235mmol), methyl acrylate (40.4g, 469mmol), palladium(II)acetate (7.9g, 35.2mmol), tri-*ortho*-tolylphosphine (21.4g, 70.4mmol) and triethylamine (82ml) in acetonitrile (900ml) was heated
15 at reflux under a nitrogen atmosphere for a period of 16 hours. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. Purification by flash column chromatography eluting with pentane:ethyl acetate (90:10 changing to 70:30 by volume) gave the title compound as an orange oil (54.3g).

- 20 ^1H NMR (400MHz, CD_3OD): δ = 7.66-7.62 (1H, d), 7.41-7.39 (1H, d), 7.34-7.31 (2H, t), 7.20-7.18 (1H, d), 6.43-6.39 (1H, d), 3.77 (3H, s), 3.70 (2H, s), 2.15 (3H, s) ppm.
LRMS (electrospray) : m/z $[\text{M}+\text{Na}]^+$ 241, $[\text{M}-\text{H}]^-$ 217.

25 Preparation 139

3-(3-{2-[2-(3,5-Bis-benzyloxy-phenyl)-2-(tert-butyl-dimethyl-silanyloxy)-ethylamino]-propyl}-phenyl)-propionic acid methyl ester

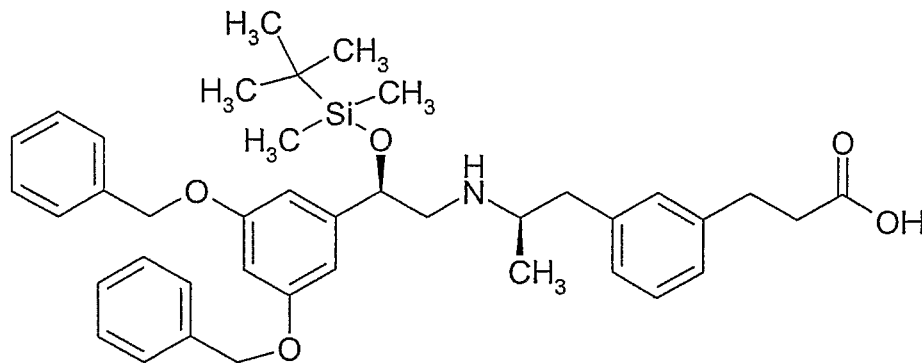


The bromide of preparation 11 (3.46g, 6.56mmol) and the amine of preparation 135 (2.90g, 13.1mmol) were combined in dichloromethane (50mL) and the solvent removed *in vacuo*. The resulting oil was heated at 90°C for 12 hours and cooled to room temperature, the orange oil was stirred in ether (200mL) for 5 minutes and the ethereal layer decanted off carefully. The remaining orange oil was stirred with ether (2x200mL) a further two times and the ether layers were combined and the solvent removed *in vacuo*. The resulting orange oil was purified by flash column chromatography eluting with dichloromethane:methanol:ammonia (100:0:0 then 96:4:0.4) to furnish the title compound as a golden oil (3.40g).

^1H NMR (400MHz, CD_3OD) δ : -0.20 (3H, s), -0.05 (3H, s), 0.82 (9H, s), 1.03 (3H, d), 2.52-2.65 (5H, m), 2.79-2.94 (4H, m), 3.60 (3H, s), 4.66 (1H, m), 5.04 (4H, m), 6.49 (2H, s), 6.53 (1H, m), 6.89-6.96 (2H, m), 6.99 (1H, m), 7.15 (1H, m), 7.23-7.44 (10H, m); LRMS APCI m/z 668 $[\text{M}+\text{H}]^+$

Preparation 140

3-(3-{2-[2-(3,5-Bis-benzyloxy-phenyl)-2-(tert-butyl-dimethyl-silanyloxy)-ethylamino]-propyl}-phenyl)-propionic acid hydrochloride

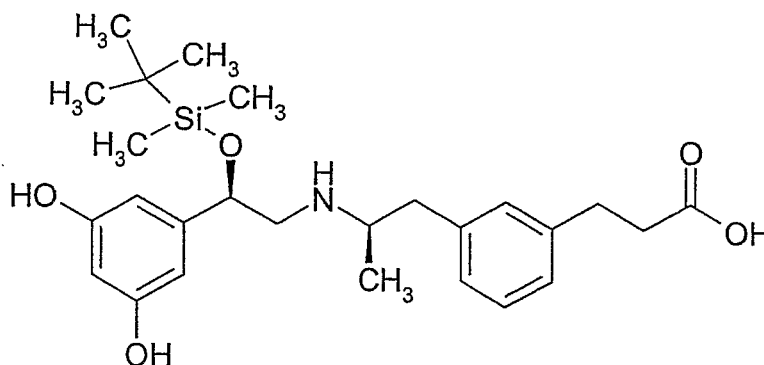


The ester of preparation 139 (3.40 g, 5.10 mmol) in tetrahydrofuran (15 mL) was treated with lithium hydroxide (1M, 11.2 mL, 11.21 mmol). Dioxane (50 mL) and water (10 mL) were added and the resulting solution stirred for 20 h. The solution was acidified to pH 1 with hydrochloric acid (1N) and extracted with dichloromethane (3x 150 mL). The organics were washed with brine (50 mL) and dried (magnesium sulfate). Filtration and evaporation of the solvent left a white foam (3.5 g, 91 %)

^1H NMR (400MHz, CD_3OD) δ : -0.13 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.03 (3H, d), 2.58 (2H, t), 2.75 (1H, m), 2.88 (2H, t), 3.06 (1H, m), 3.23 (1H, m), 3.34 (1H, m), 3.55 (1H, m), 5.04-5.16 (5H, m), 6.66 (3H, m), 7.06 (1H, m), 7.12 (1H, s), 7.18 (1H, m), 7.23-7.47 (11H, m); LRMS APCI m/z 655 $[\text{M}+\text{H}]^+$

Preparation 141

3-(3-{2-[2-(*tert*-Butyldimethylsilanyloxy)-2-(3,5-dihydroxyphenyl)ethylamino]propyl}phenyl)propionic acid

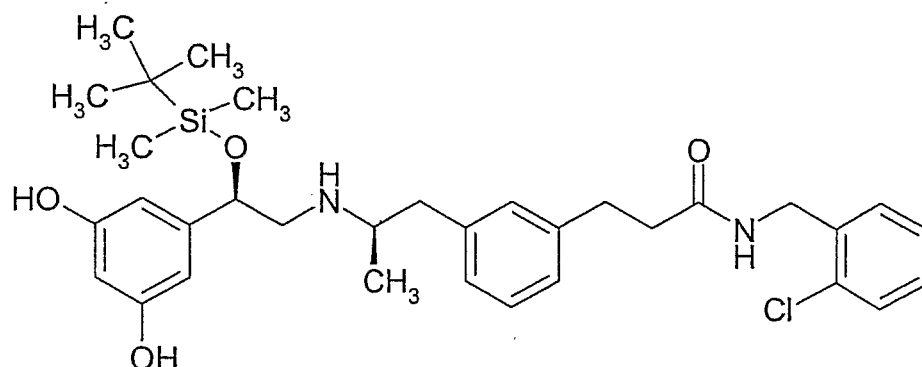


Prepared according to the procedure used for preparation 13, using 3-(3-{2-[2-(3,5-Bis-benzyloxy-phenyl)-2-(*tert*-butyl-dimethyl-silanyloxy)-ethylamino]-propyl}-phenyl)-propionic acid hydrochloride (Preparation 140) to give the title compound as a yellow solid.

^1H NMR (400MHz, CD_3OD) δ : -0.06 (3H, s), 0.08 (3H, s), 0.86 (9H, s), 1.22 (3H, d), 2.54 (2H, t), 2.74 (1H, m), 2.90 (2H, t), 3.15 (1H, m), 3.26 (1H, m), 3.45 (1H, m), 4.90 (1H, m), 6.26 (1H, m), 6.35 (2H, s), 7.02 (1H, m), 7.08 (1H, s), 7.16 (1H, m), 7.24 (1H, m); LRMS APCI m/z 474 $[\text{M}+\text{H}]^+$

Preparation 142

3-(3-{2-[2-(*tert*-Butyldimethylsilanyloxy)-2-(3,5-dihydroxyphenyl)ethylamino]propyl}phenyl)-*N*-(2-chlorobenzyl)propionamide

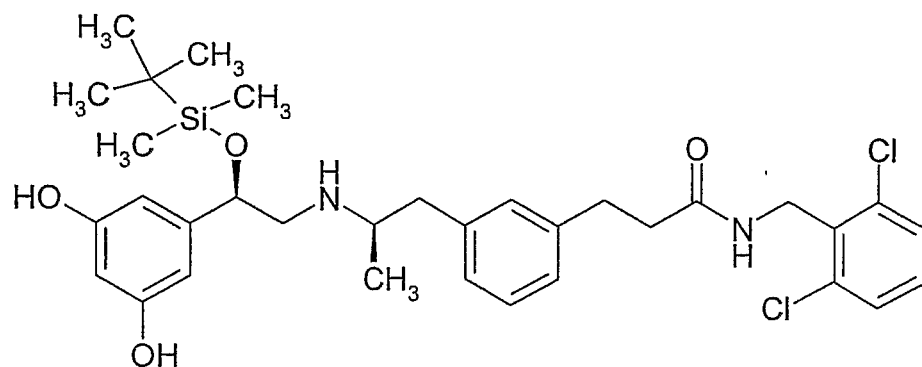


Prepared according to the procedure used for preparation 34, using
 5 Preparation 141, 2-chlorobenzylamine and N,N-dimethylacetamide replacing N,N-dimethylformamide.

^1H NMR (400MHz, CD_3OD) δ : -0.15 (3H, s), 0.01 (3H, s), 0.84 (9H, s), 1.03 (3H, d), 2.47-2.58 (3H, m), 2.60-2.70 (2H, m), 2.80-2.95 (4H, m), 4.41 (2H, m), 4.59 (1H, m), 6.16 (1H, m), 6.24 (2H, s), 6.95 (2H, m), 7.02-7.08 (2H, m), 7.13-7.25
 10 (3H, m), 7.36 (1H, m); LRMS APCI m/z 598 $[\text{M}+\text{H}]^+$

Preparation 143

3-(3-{2-[2-(*tert*-Butyldimethylsilanyloxy)-2-(3,5-dihydroxyphenyl)ethylamino]propyl}phenyl)-*N*-(2,6-dichlorobenzyl)propionamide



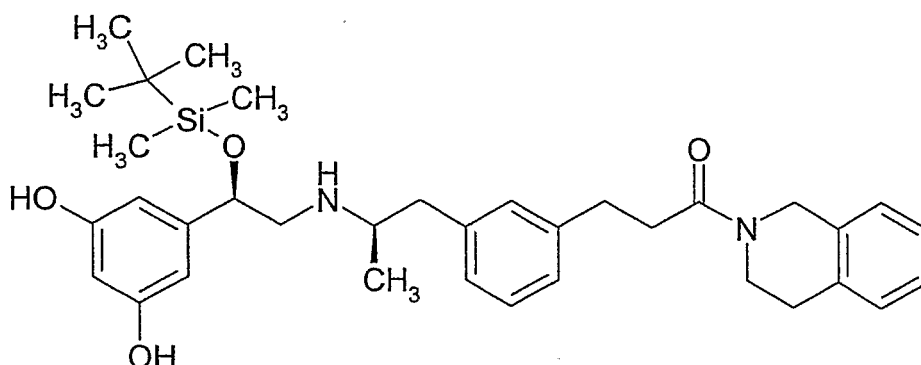
15 Prepared according to the procedure used for preparation 34, using Preparation 141, 2,6-dichlorobenzylamine and N,N-dimethylacetamide replacing N,N-dimethylformamide.

^1H NMR (400MHz, CD_3OD) δ : -0.15 (3H, s), 0.00 (3H, s), 0.85 (9H, s), 1.03 (3H, d), 2.44-2.57 (3H, m), 2.60-2.68 (2H, m), 2.80-2.90 (4H, m), 4.55-4.65 (3H, m),
 20

6.16 (1H, m), 6.24 (2H, s), 6.91 (1H, m), 6.94 (1H, m), 7.01 (1H, m), 7.12 (1H, m), 7.26 (1H, m), 7.37-7.41 (2H, m) ; LRMS APCI m/z 631 [M+H]⁺

Preparation 144

- 5 **3-(3-{2-[2-(*tert*-Butyldimethylsilanyloxy)-2-(3,5-dihydroxy-phenyl)ethylamino]propyl}phenyl)-1-(3,4-dihydro-1H-isoquinolin-2-yl)-propan-1-one**

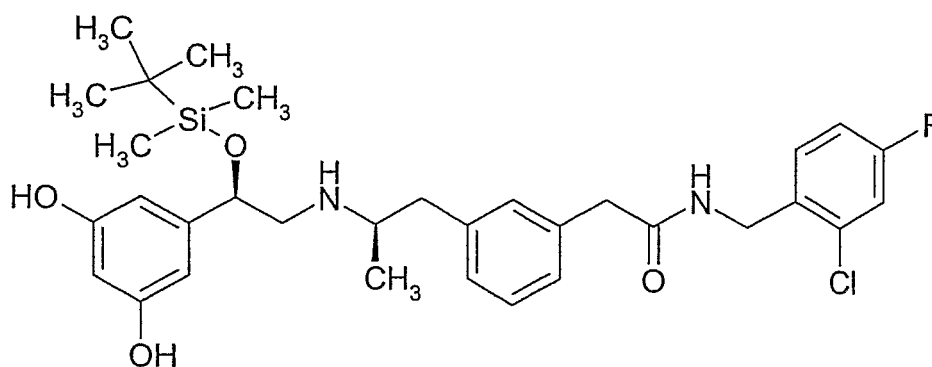


- Prepared according to the procedure used for preparation 34, using
10 Preparation 141, 1,2,3,4-tetrahydroisoquinoline and N,N-dimethylacetamide replacing N,N-dimethylformamide.

- ¹H NMR (400MHz, CD₃OD) δ: -0.15 (3H, s), -0.01 (3H, s), 0.85 (9H, s), 0.99 (3H, m), 2.42-2.64 (3H, m), 2.68-2.96 (8H, m), 3.63-3.76 (2H, m), 4.55-4.67 (3H, m), 6.16 (1H, m), 6.23 (2H, s), 6.81-7.21 (8H, m); LRMS APCI m/z 590
15 [M+H]⁺

Preparation 145

- 2-(3-{2-[2-(*tert*-Butyldimethylsilanyloxy)-2-(3,5-dihydroxy-phenyl)ethylamino]propyl}phenyl)-N-(2-chloro-4-fluorobenzyl)acetamide**

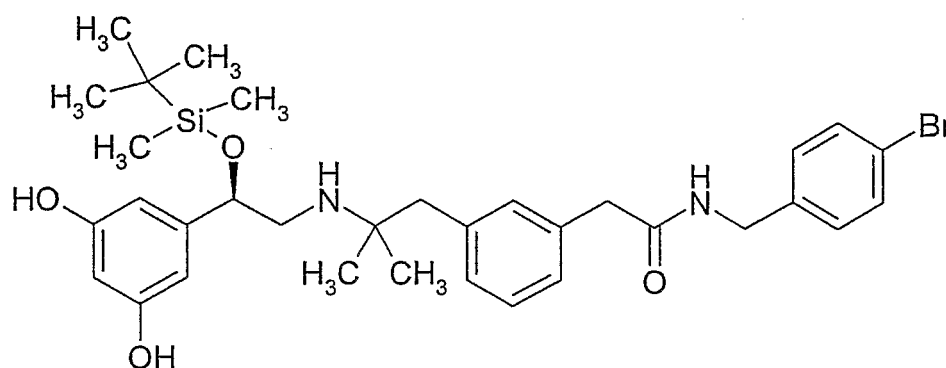


Prepared according to the procedure used for preparations 142, using the acid from Preparation 33 and 2-chloro-4-fluorobenzylamine.

^1H NMR (400MHz, CD_3OD) δ : -0.02 (3H, d), 0.00 (3H, s), 0.84 (9H, s), 1.04 (3H, d), 2.54-2.70 (3H, m), 2.86-2.93 (2H, m), 3.53 (2H, s), 4.41 (1H, s), 4.46 (1H, s), 4.60-4.63 (1H, m), 6.14-6.15 (1H, m), 6.22 (2H, d), 6.97-7.50 (7H, m), 7.64-7.69 (1H, m); LRMS APCI m/z 601 $[\text{M}+\text{H}]^+$.

Preparation 146

***N*-(4-Bromobenzyl)-2-(3-{2-[2-(*tert*-butyldimethylsilanyloxy)-2-(3,5-dihydroxyphenyl)ethylamino]-2-methylpropyl}phenyl)acetamide**

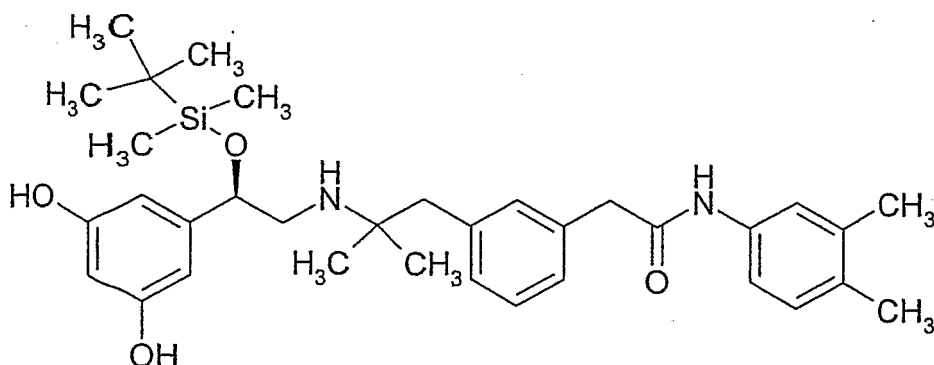


Prepared according to the procedure used for preparations 34, using the acid from Preparation 33 and 4-bromobenzylamine.

^1H NMR (400MHz, CD_3OD) δ : -0.23 (s, 3H), -0.04 (s, 3H), 0.82 (s, 9H), 1.07 (d, 6H), 2.63-2.77 (m, 3H), 2.84 (t, 1H), 3.56 (s, 2H), 4.31 (s, 2H), 4.57-4.63 (m, 1H), 6.18 (t, 1H), 6.36 (s, 2H), 7.08 (t, 2H), 7.12-7.18 (m, 3H), 7.21 (t, 1H), 7.42 (d, 2H).; LRMS ESI m/z 643 $[\text{M}+\text{H}]^+$.

Preparation 147

2-(3-{2-[2-(*tert*-Butyldimethylsilanyloxy)-2-(3,5-dihydroxyphenyl)ethylamino]-2-methylpropyl}phenyl)-*N*-(3,4-dimethylphenyl)acetamide

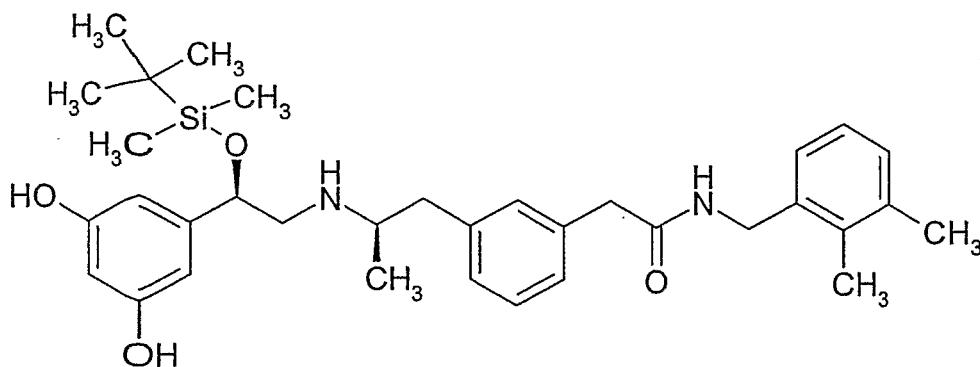


Prepared according to the procedure used for preparations 34, using the acid from Preparation 33 and 3,4-dimethylaniline.

^1H NMR (400MHz, CD_3OD) δ : -0.17 (s, 3H), -0.03 (s, 3H), 0.81 (s, 9H), 1.07 (d, 6H), 2.22 (d, 6H), 2.61-2.77 (m, 3H), 2.83 (t, 1H), 3.61 (s, 2H), 4.57-4.61 (m, 1H), 6.18 (s, 1H), 6.29 (s, 2H), 7.06 (t, 2H), 7.18 (s, 1H), 7.21-7.25 (m, 3H), 7.31 (s, 1H); LRMS ESI m/z 643 $[\text{M}+\text{H}]^+$.

Preparation 148

10 **2-(3-{2-[2-(*tert*-Butyldimethylsilyloxy)-2-(3,5-dihydroxyphenyl)ethylamino]propyl}phenyl)-*N*-(2,3-dimethylbenzyl)acetamide**

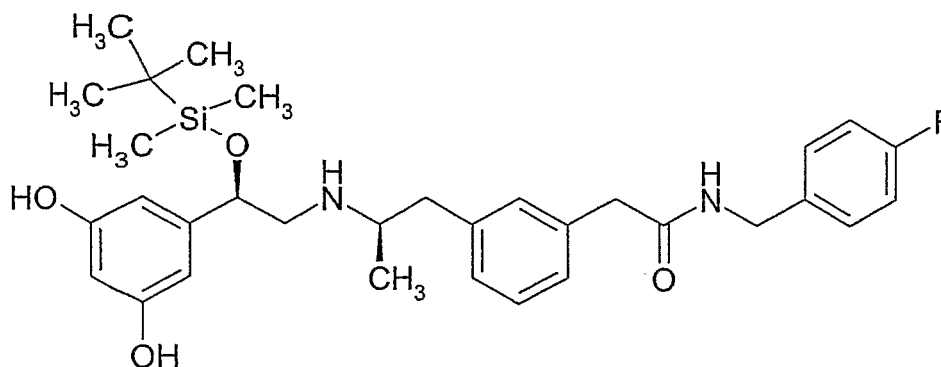


15 Prepared according to the procedure used for preparations 34, using the acid from Preparation 45 and 2,3-dimethylbenzylamine and *N,N*-dimethylacetamide replacing *N,N*-dimethylformamide.

^1H NMR (400MHz, CD_3OD) δ : -0.17 (3H, s), -0.04 (3H, s), 0.80 (9H, s), 0.97 (3H, d), 2.09 (3H, s), 2.21 (2.46-2.51 (1H, dd), 2.56-2.65 (2H, m), 2.76-2.84 (2H, m), 3.45 (2H, s), 4.32 (2H, s), 4.53 (1H, dd), 5.44 (2H, s), 6.09 (1H, t), 6.17 (1H, 1), 6.18 (1H, s), 6.93-7.17 (7H, m); LRMS APCI m/z 578 $[\text{M}+\text{H}]^+$.

Preparation 149

2-(3-{2-[2-(*tert*-Butyldimethylsilanyloxy)-2-(3,5-dihydroxyphenyl)ethylamino]propyl}phenyl)-*N*-(4-fluorobenzyl)acetamide



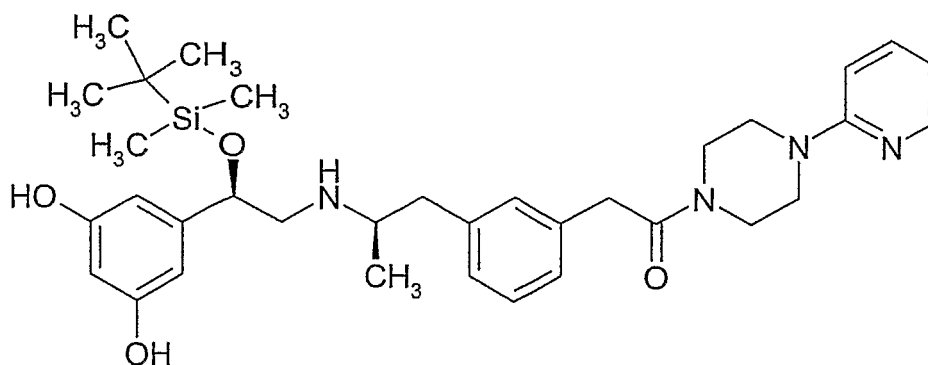
5

Prepared according to the procedure used for preparations 34, using the acid from Preparation 45 and 4-fluorobenzylamine and N,N-dimethylacetamide replacing N,N-dimethylformamide.

^1H NMR (400MHz, CD_3OD) δ : -0.17 (3H, s), -0.04 (3H, s), 0.80 (9H, s), 0.98 (3H, d), 2.47 (1H, dd), 2.55-2.64 (H, m), 2.77-2.84 (2H, m), 3.46 (2H, s), 4.28 (2H, s), 4.53 (1H, dd), 6.09-6.11 (1H, m), 6.17 (1H, s), 6.18 (1H, s), 6.91-7.02 (4H, m), 7.05-7.08 (1H, m), 7.13 (1H, t), 7.17-7.23 (2H, m); LRMS APCI m/z 567 $[\text{M}+\text{H}]^+$.

15 **Preparation 150**

2-(3-{2-[2-(*tert*-Butyldimethylsilanyloxy)-2-(3,5-dihydroxyphenyl)ethylamino]propyl}phenyl)-1-(4-pyridin-2-yl-piperazin-1-yl)ethanone



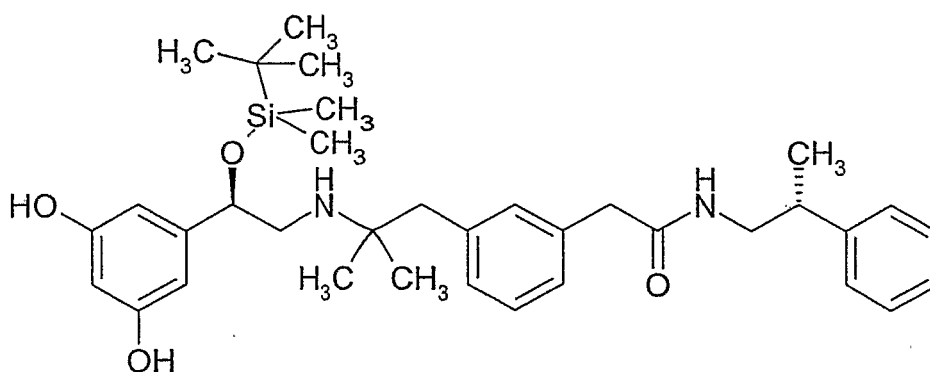
Prepared according to the procedure used for preparations 34, using the acid from Preparation 45 and 1-pyridin-2-ylpiperazine, and N,N-dimethylacetamide replacing N,N-dimethylformamide.

¹H NMR (400MHz, CD₃OD) δ: -0.12 (3H, s), 0.00 (3H, s), 0.80 (9H, s), 1.12 (3H, d), 2.66 (1H, dd), 2.88-2.93 (2H, m), 3.04-3.10 (1H, m), 3.15 (1H, dd), 3.32-3.43 (4H, m), 3.60-3.66 (4H, m), 3.73-3.79 (2H, m), 4.81-4.85 (1H, m), 6.18 (1H, t), 6.25 (1H, s), 6.26 (1H, s), 6.60-6.63 (1H, m), 6.72 (1H, d), 7.04-7.07 (2H, m), 7.12 (1H, d), 7.23 (1H, t), 7.46 (1H, dt), 8.00 (1H, d) ; LRMS APCI m/z 606 [M+H]⁺.

10

Preparation 151

2-(3-{2-[2-(*tert*-Butyldimethylsilyloxy)-2-(3,5-dihydroxyphenyl)ethylamino]-2-methylpropyl}phenyl)-N-(2-phenylpropyl)acetamide



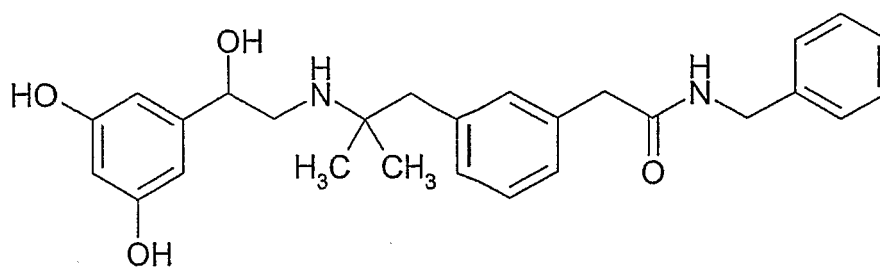
15 The title compound was prepared from the compound of preparation 33 and the appropriate amine using the method described for preparation 34 and was isolated as a white foam.

¹H NMR (400MHz, CD₃OD) δ -0.20 (3H, s), -0.07 (3H, s), 0.74 (9H, s), 1.02 (3H, d), 1.09 (3H, d), 2.62 (1H, dd), 2.79 (1H, dd), 2.88-2.97 (2H, m), 3.04 (1H, dd), 3.16-3.24 (1H, m), 3.27-3.88 (2H, m), 3.41 (2H, s), 4.74 (1H, dd), 6.19 (1H, t), 6.27 (1H, s), 6.28 (1H, s), 7.01-7.07 (2H, m), 7.13-7.27 (4H, m).

20 LRMS APCI m/z 578 [M+H]⁺.

Example 1

25 **N-Benzyl-2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]acetamide**

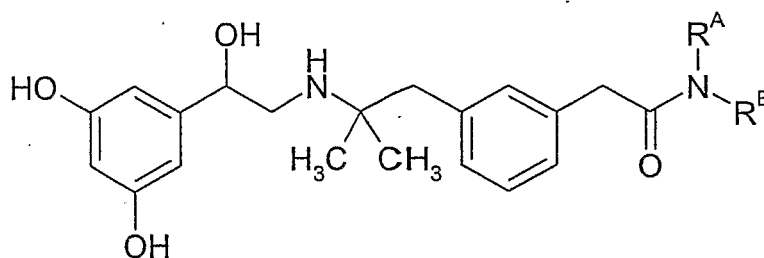


To a solution of the acid of preparation 9 (50mg, 0.10mmol) and benzylamine (14mg, 0.13mmol) in *N,N*-dimethylformamide (1mL) *O*-(1H-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (50mg, 0.13mmol) in *N,N*-dimethylformamide (3mL) was added and the reaction stirred for 12 hours. The solvent was removed *in vacuo* to give the crude residue. Purification by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (97.5:2.5:0.25-90:10:1) gave the desired product, 17mg (37%).

¹H NMR (400 MHz, CD₃OD) δ 1.02 (3H, s), 1.04 (3H, s), 2.84-2.64 (4H, m), 3.52 (2H, s), 4.35 (2H, s), 4.53-4.57 (1H, q), 6.18 (1H, s), 6.33 (2H, s), 7.02-7.04 (2H, d), 7.12-7.28 (7H, m).

LRMS: *m/z* APCI⁺ 449 [MH⁺].

Examples 2-11



15

A solution of the acid from preparation 9 (30μmol) in *N,N*-dimethylformamide (100μL) was added to the appropriate amine (HNR^AR^B) (30μmol) in *N,N*-dimethylformamide (100μL) and the reaction mixture was sealed and shaken. A solution of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (11.38mg, 30μmol) in *N,N*-dimethylformamide (200μL) was added, the reaction mixture sealed and shaken and allowed to stand at room temperature for 4 days. The reaction mixture was purified directly by

20

HPLC using a Phenomenex Luna C18 column (150x10mm, 10 μ m), at a flow rate of 8mL/min and detection at 225nm, using the following gradient system.

A-0.05% aqueous diethylamine

5 B-acetonitrile

Time (min)	%B
0-0.2	5
0.2-8	5-95
8-9.6	95

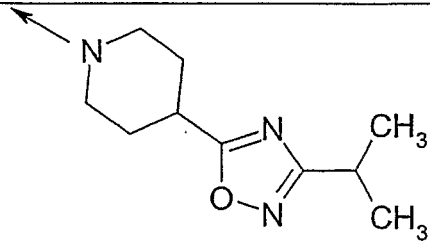
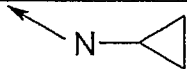
Each product was analysed using a Phenomenex Luna C18 (30 x 4.6mm, 5 μ m) column at a flow rate of 2.5mL/min using the gradient described in the table below.

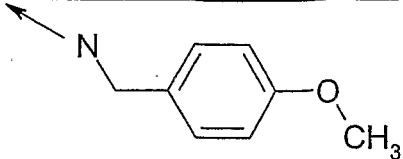
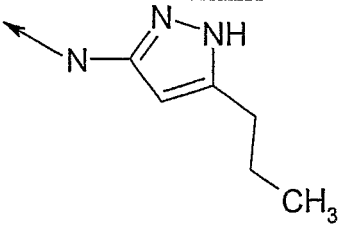
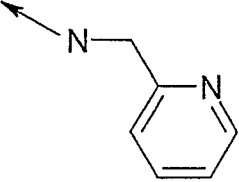
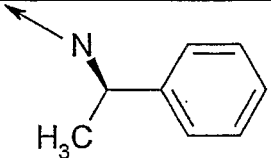
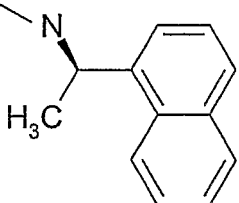
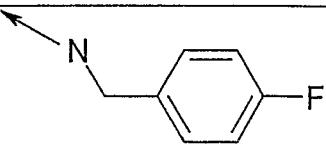
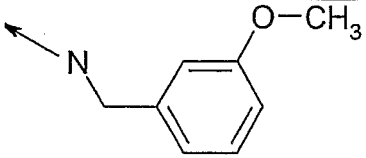
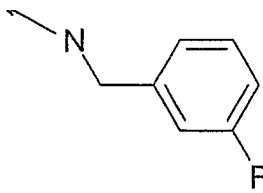
10

A-5% 6.5mM ammonium acetate in water:acetonitrile (95:5)

B-acetonitrile

Time (min)	%B
0	0
3	95
3.5	95

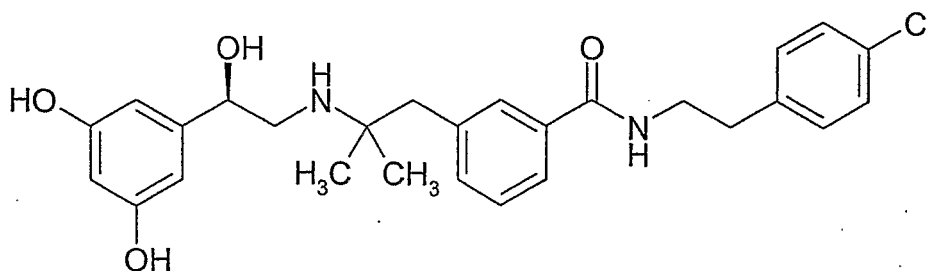
Example	-NR ^A R ^B	M ⁺	Retention time (min)
2		536.3	1.67
3		398.22	1.21

4		478.25	1.56
5 ^A		466.26	1.51
6		449.23	1.32
7		462.25	1.57
8		512.27	1.82
9		466.23	1.64
10		478.28	1.6
11		466.23	1.6

A = 3-amino-5-ethyl-1H-pyrazole prepared as described in WO 03/048133

Example 12

5 N-[2-(4-Chloro-phenyl)-ethyl]-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide



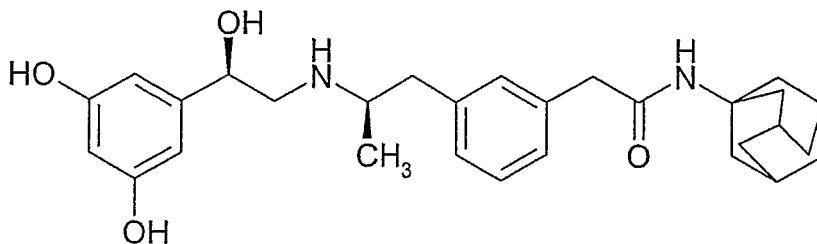
Ammonium fluoride (1.08g, 29.2mmol) was added in one portion to a stirred solution of the compound of preparation 15 (1.56g, 2.61mmol) in methanol (25mL) and water (18mL) at room temperature. The reaction was heated to 40°C for 48 hours, cooled to room temperature and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (100:0:0 then 95:5:0.5 then 90:10:1) to furnish the title compound as a brown solid, 885mg.

¹H NMR (400MHz, CD₃OD) δ 1.10 (3H, s), 1.16 (3H, s), 2.75 (6H, m), 3.62 (2H, m), 4.66 (1H, dd), 6.23 (1H, m), 6.40 (1H, s), 6.41 (1H, s), 7.33 (6H, m), 7.67 (2H, m).

LRMS: m/z APCI 484 [M+H⁺].

Example 13

20 N-Adamantan-1-yl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



Ammonium fluoride (100mg, 2.70mmol) was added in one portion to a stirred solution of the compound of preparation 30 (160mg, 0.27mmol) in methanol (2mL) and water (1mL) at room temperature. The reaction was heated to 40°C for 12 hours, cooled to room temperature and the solvent removed *in vacuo*.

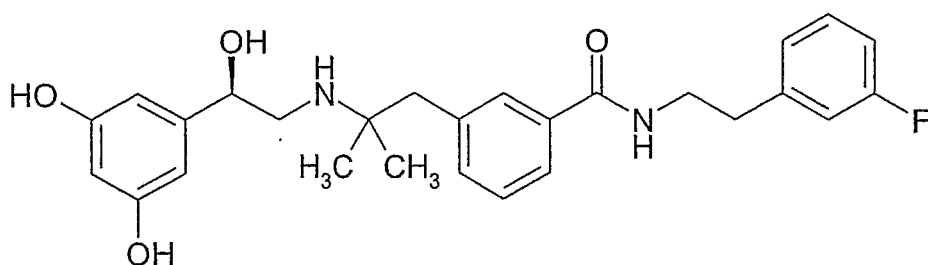
- 5 The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (93:7:0.7) to furnish the title compound as a white foam, 78mg.

¹H NMR (400MHz, CD₃OD) δ 1.07 (3H, d), 1.68 (6H, s), 2.01 (9H, m), 2.60 (4H, m), 2.91 (1H, m), 3.40 (2H, s), 4.50 (1H, m), 6.13 (1H, m), 6.23 (2H, s), 6.99
10 (1H, d), 7.08 (1H, s), 7.10 (1H, d), 7.18 (1H, t).

LRMS: m/z electrospray 479 [M+H⁺], 477 [M-H]⁻.

Example 14

- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-N-
15 [2-(3-fluoro-phenyl)-ethyl]-benzamide



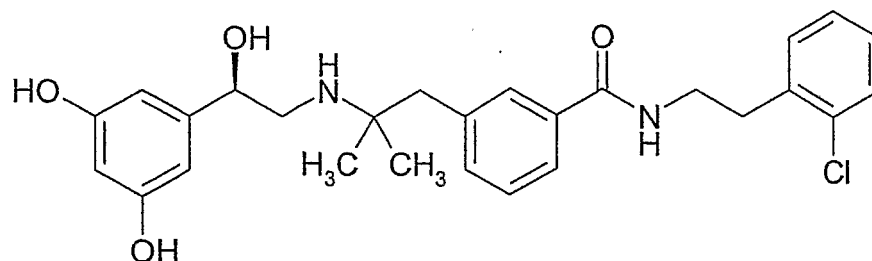
The title compound was prepared from the compound of preparation 36 using the method described for example 12 and was isolated as a white solid.

¹H NMR (400MHz, CD₃OD) δ 1.11 (3H, s), 1.15 (3H, s), 2.74-2.82 (2H, m),
20 2.90-3.00 (4H, m), 3.62-3.66 (2H, m), 4.61-4.66 (1H, m), 6.23-6.24 (1H, m),
6.39 (1H, s), 6.40 (1H, s), 6.94-6.98 (1H, m), 7.03-7.07 (1H, m), 7.10-7.12 (1H,
m), 7.29-7.43 (3H, m), 7.65-7.69 (2H, m).

LRMS: m/z APCI 467 [M+H⁺].

25 Example 15

N-[2-(2-Chloro-phenyl)-ethyl]-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide



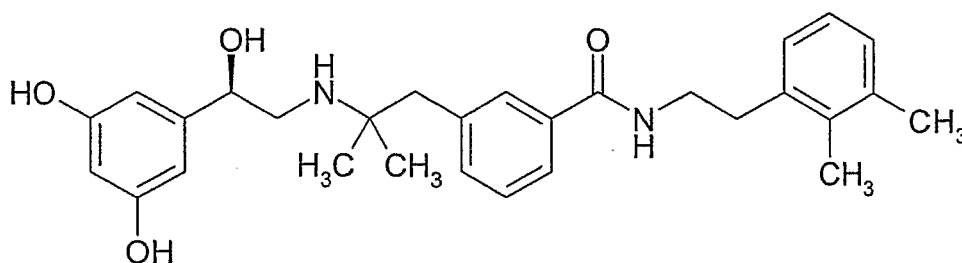
The title compound was prepared from the compound of preparation 37 using the method described for example 12 and was isolated as a white solid.

¹H NMR (400MHz, CD₃OD) δ 1.10 (3H, s), 1.15 (3H, s), 2.76-2.84 (2H, m),
5 2.88-2.96 (2H, m), 3.10-3.14 (2H, m), 3.66-3.70 (2H, m), 4.61-4.64 (1H, m),
6.22-6.24 (1H, m), 6.39 (1H, s), 6.40 (1H, s), 7.21-7.28 (2H, m), 7.35-7.42 (4H,
m), 7.66-7.69 (2H, m).

LRMS: m/z APCI 483 [M+H⁺].

10 Example 16

3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-N-[2-(2,3-dimethyl-phenyl)-ethyl]-benzamide



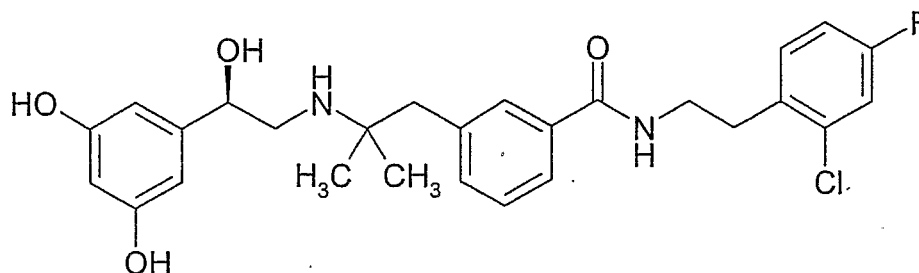
The title compound was prepared from the compound of preparation 38 using
15 the method described for example 12 and was isolated as a white solid.

¹H NMR (400MHz, CD₃OD) δ 1.14 (3H, s), 1.19 (3H, s), 2.30 (3H, s), 2.31 (3H,
s), 2.80-3.02 (6H, m), 3.56-3.59 (2H, m), 4.63-4.67 (1H, m), 6.24-6.25 (1H, m),
6.40 (1H, s), 6.41 (1H, s), 6.99-7.07 (3H, m), 7.38-7.45 (2H, m), 7.68-7.72 (2H,
m).

20 LRMS: m/z APCI 477 [M+H⁺].

Example 17

N-[2-(2-Chloro-4-fluoro-phenyl)-ethyl]-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide



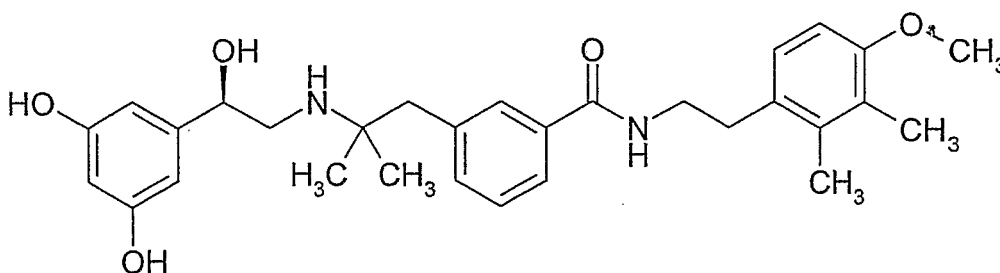
The title compound was prepared from the compound of preparation 39 using the method described for example 12 and was isolated as a white solid.

^1H NMR (400MHz, CD_3OD) δ 1.09 (3H, s), 1.15 (3H, s), 2.75-2.83 (2H, m), 2.88-2.96 (2H, m), 3.08-3.11 (2H, m), 3.64-3.68 (2H, m), 4.61-4.64 (1H, m), 6.22-6.23 (1H, m), 6.39 (1H, s), 6.40 (1H, s), 7.01-7.06 (1H, m), 7.21-7.24 (1H, m), 7.35-7.42 (3H, m), 7.65-7.68 (2H, m).

LRMS: m/z APCI 501 $[\text{M}+\text{H}^+]$.

Example 18

3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-N-[2-(4-methoxy-2,3-dimethyl-phenyl)-ethyl]-benzamide



15

The title compound was prepared from the compound of preparation 40 using the method described for example 12 and was isolated as a white solid.

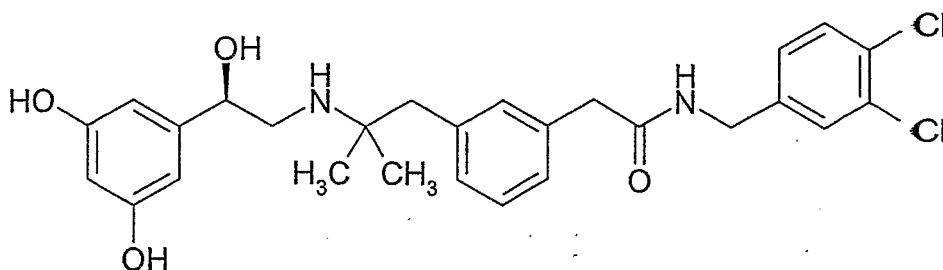
^1H NMR (400MHz, CD_3OD) δ 1.12 (3H, s), 1.18 (3H, s), 2.16 (3H, s), 2.30 (3H, s), 2.77-3.00 (6H, m), 3.52-3.56 (2H, m), 3.80 (3H, s), 4.62-4.65 (1H, m), 6.23-6.24 (1H, m), 6.40 (1H, s), 6.41 (1H, s), 6.72-6.74 (1H, d), 7.01-7.03 (1H, d), 7.37-7.44 (2H, m), 7.67 (1H, s), 7.70-7.72 (1H, m).

20

LRMS: m/z APCI 507 $[\text{M}+\text{H}^+]$.

Example 19

N-(3,4-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide



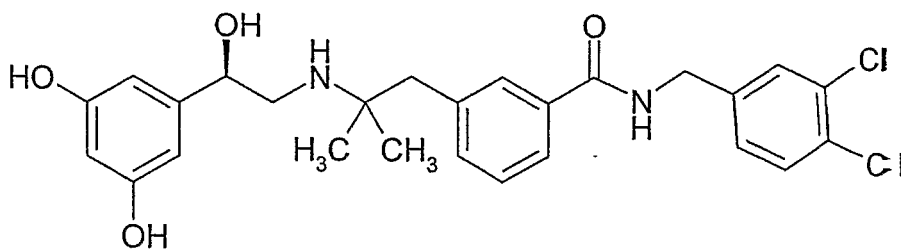
- 5 The title compound was prepared from the compound of preparation 34 using the method described for example 12 and was isolated as a white foam.

^1H NMR (400MHz, CD_3OD) δ 1.02 (3H, s), 1.04 (3H, s), 2.74 (4H, m), 3.56 (2H, s), 4.32 (2H, s), 4.54 (1H, m), 6.17 (1H, s), 6.36 (2H, s), 7.03 (1H, d), 7.15 (3H, m), 7.22 (1H, t), 7.36 (1H, d), 7.43 (1H, d).

- 10 LRMS: m/z electrospray 517 $[\text{M}+\text{H}^+]$.

Example 20

N-(3,4-Dichloro-benzyl)-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide



15

The title compound was prepared from the compound of preparation 41 using the method described for example 12 and was isolated as a white solid.

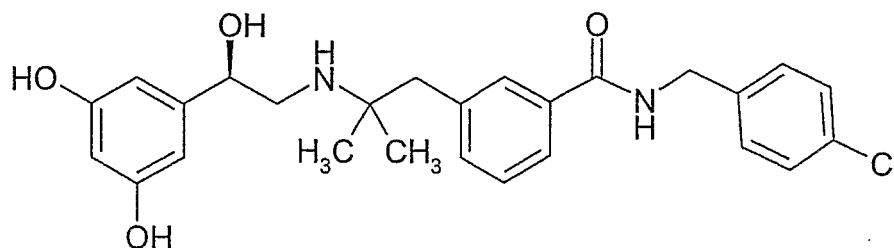
^1H NMR (400MHz, CD_3OD) δ 1.16 (3H, s), 1.20 (3H, s), 2.83-3.01 (4H, m), 4.59 (2H, s), 4.64-4.67 (1H, m), 6.23 (1H, m), 6.38 (1H, s), 6.39 (1H, s), 7.31-7.34 (1H, m), 7.41-7.55 (4H, s), 7.76-7.80 (2H, s).

20

LRMS: m/z APCI 503 $[\text{M}+\text{H}^+]$.

Example 21

N-(4-Chloro-benzyl)-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide



The title compound was prepared from the compound of preparation 42 using the method described for example 12 and was isolated as a white solid.

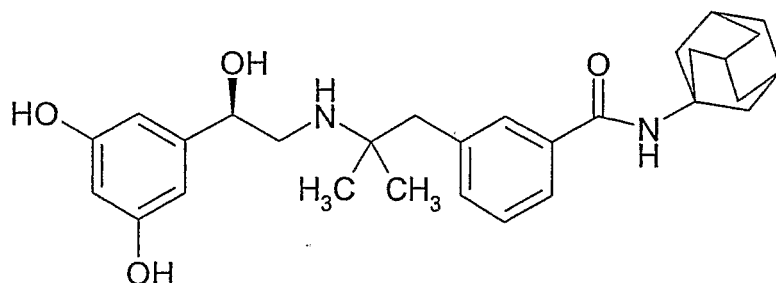
^1H NMR (400MHz, CD_3OD) δ 1.10 (3H, s), 1.15 (3H, s), 2.76-2.82 (2H, m), 2.90-2.96 (2H, m), 4.59 (2H, s), 4.60-4.63 (1H, m), 6.23 (1H, m), 6.37 (1H, s), 6.38 (1H, s), 7.34-7.45 (6H, m), 7.74-7.77 (2H, m).

LRMS: m/z APCI 469 $[\text{M}+\text{H}^+]$.

10

Example 22

N-Adamantan-1-yl-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide



The title compound was prepared from the compound of preparation 43 using the method described for example 12 and was isolated as a white solid.

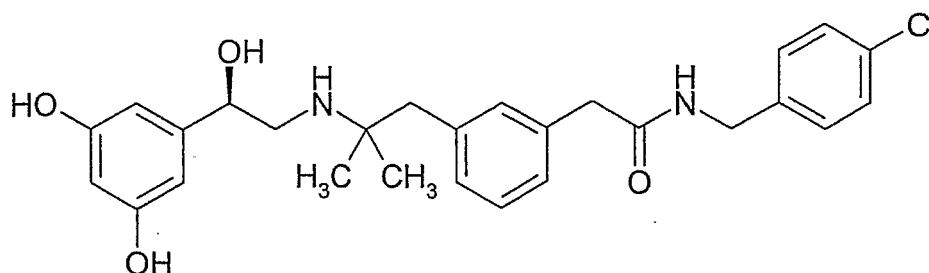
^1H NMR (400MHz, CD_3OD) δ 1.27 (3H, s), 1.28 (3H, s), 1.79-1.81 (6H, m), 2.14 (3H, m), 2.21-2.22 (6H, m), 2.95-3.09 (4H, m), 4.71-4.74 (1H, m), 6.26 (1H, m), 6.42 (1H, s), 6.42 (1H, s), 7.40-7.46 (2H, m), 7.65 (1H, s), 7.68-7.70 (1H, m).

LRMS: m/z APCI 480 $[\text{M}+\text{H}^+]$.

20

Example 23

N-(4-Chloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide



The title compound was prepared from the compound of preparation 46 using the method described for example 12 and was isolated as a white foam.

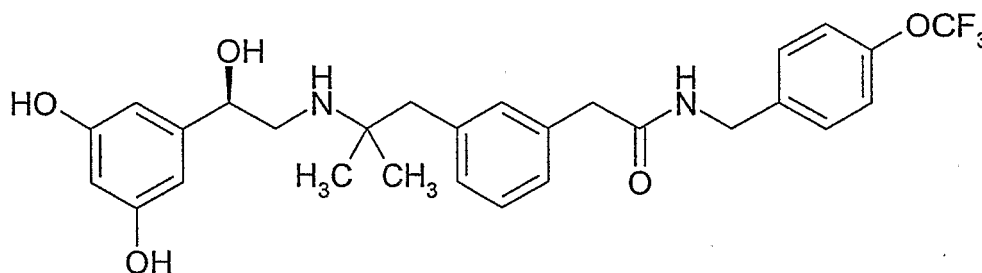
^1H NMR (400MHz, CD_3OD) δ 1.01 (3H, s), 1.04 (3H, s), 2.74 (4H, m), 3.53 (2H, s), 4.34 (2H, s), 4.54 (1H, m), 6.18 (1H, s), 6.34 (2H, s), 7.03 (1H, d), 7.11 (1H, s), 7.20 (6H, m).

LRMS: m/z electrospray 483 $[\text{M}+\text{H}^+]$.

10

Example 24

N-(4-Trifluoromethoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide



The title compound was prepared from the compound of preparation 47 using the method described for example 12 and was isolated as a white foam.

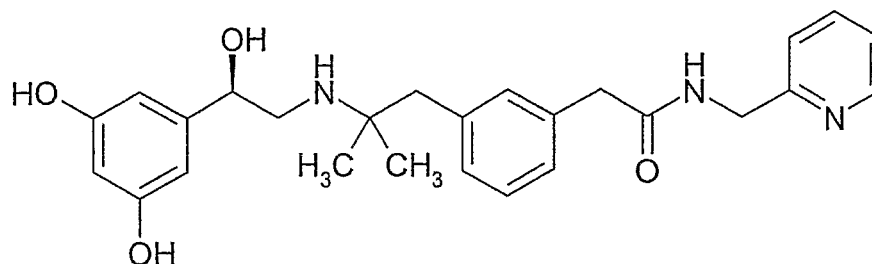
^1H NMR (400MHz, CD_3OD) δ 1.01 (3H, s), 1.03 (3H, s), 2.74 (4H, m), 3.53 (2H, s), 4.37 (2H, s), 4.54 (1H, m), 6.18 (1H, s), 6.34 (2H, s), 7.03 (1H, d), 7.20 (7H, m).

LRMS: m/z electrospray 533 $[\text{M}+\text{H}^+]$.

20

Example 25

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-pyridin-2-ylmethyl-acetamide



The title compound was prepared from the compound of preparation 48 using the method described for example 12 and was isolated as a white foam.

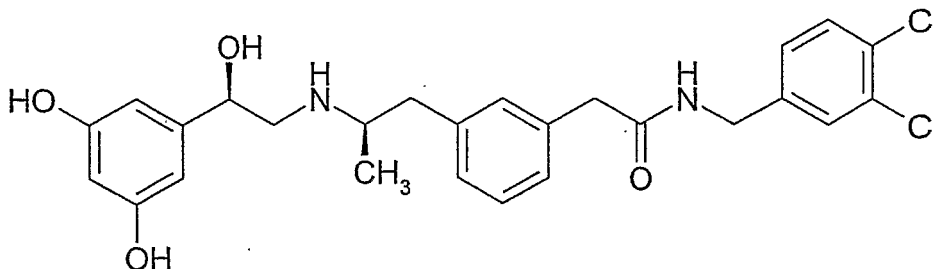
^1H NMR (400MHz, CD_3OD) δ 1.01 (3H, s), 1.03 (3H, s), 2.74 (4H, m), 3.59 (2H, s), 4.45 (2H, s), 4.54 (1H, m), 6.16 (1H, s), 6.35 (2H, s), 7.05 (1H, d), 7.20 (5H, m), 7.72 (1H, t), 8.42 (1H, d).

LRMS: m/z electrospray 450 $[\text{M}+\text{H}^+]$.

10

Example 26

N-(3,4-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



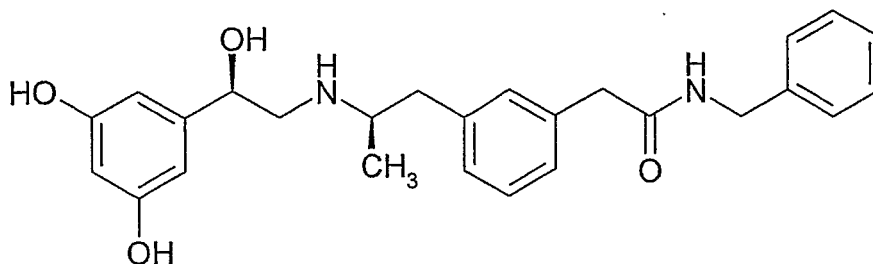
15 The title compound was prepared from the compound of preparation 49 using the method described for example 12 and was isolated as a white foam.

^1H NMR (400MHz, CD_3OD) δ 1.01 (3H, d), 2.58 (1H, m), 2.64 (2H, m), 2.78 (1H, m), 2.90 (1H, m), 3.56 (2H, s), 4.37 (2H, s), 4.54 (1H, m), 6.18 (1H, s), 6.25 (2H, s), 7.03 (5H, m), 7.38 (2H, m).

20 LRMS: m/z electrospray 503 $[\text{M}+\text{H}^+]$.

Example 27

N-(Benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



The title compound was prepared from the compound of preparation 50 using the method described for example 12 and was isolated as a brown foam.

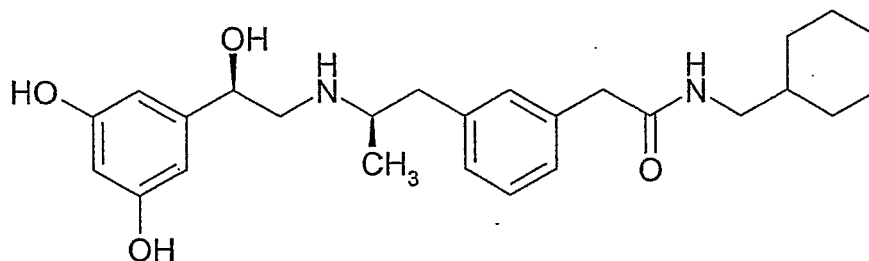
^1H NMR (400MHz, CD_3OD) δ 1.06 (3H, d), 2.57 (1H, m), 2.68 (2H, m), 2.81 (1H, m), 2.90 (1H, m), 3.53 (2H, s), 4.35 (2H, s), 4.52 (1H, m), 6.16 (1H, m), 6.25 (2H, s), 7.01 (1H, m), 7.08 (1H, s), 7.13 (1H, m), 7.20 (6H, m).

LRMS: m/z APCI 435 $[\text{M}+\text{H}^+]$, 433 $[\text{M}-\text{H}]$.

10

Example 28

N-Cyclohexylmethyl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



The title compound was prepared from the compound of preparation 51 using the method described for example 12 and was isolated as a brown foam.

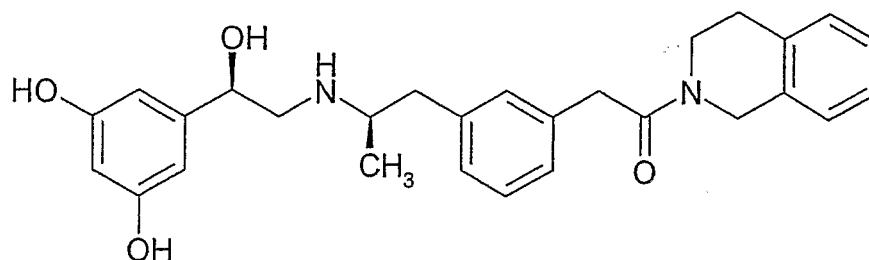
^1H NMR (400MHz, CD_3OD) δ 0.88 (2H, m), 1.06 (3H, d), 1.18 (3H, m), 1.42 (1H, m), 1.68 (5H, m), 2.58 (1H, m), 2.70 (2H, m), 2.81 (1H, m), 2.92 (1H, m), 2.99 (2H, d), 3.46 (2H, s), 4.53 (1H, m), 6.15 (1H, m), 6.25 (2H, s), 7.00 (1H, m), 7.08 (2H, m), 7.19 (1H, m).

20

LRMS: m/z APCI 441 $[\text{M}+\text{H}^+]$, 439 $[\text{M}-\text{H}]$.

Example 29

1-(3,4-Dihydro-1H-isoquinolin-2-yl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-ethanone



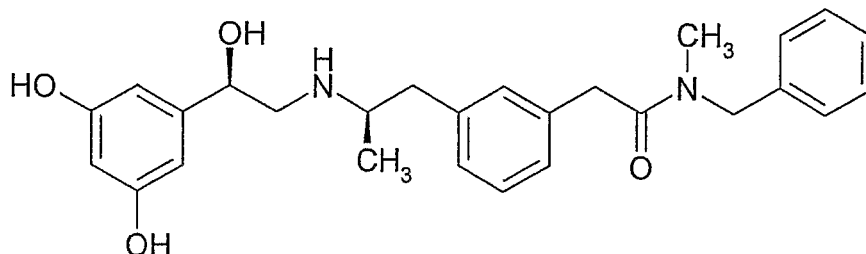
The title compound was prepared from the compound of preparation 52 using the method described for example 12 and was isolated as a brown foam.

^1H NMR (400MHz, CD_3OD) δ 1.00 (3H, m), 2.57 (7H, m), 3.70 (1H, m), 3.80 (3H, m), 4.50 (1H, m), 4.68 (2H, d), 6.16 (1H, m), 6.26 (2H, s), 7.01 (7H, m).

LRMS: m/z APCI 461 $[\text{M}+\text{H}^+]$, 459 $[\text{M}-\text{H}]$.

10 Example 30

N-Benzyl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-methyl-acetamide



The title compound was prepared from the compound of preparation 53 using the method described for example 12 and was isolated as a brown foam.

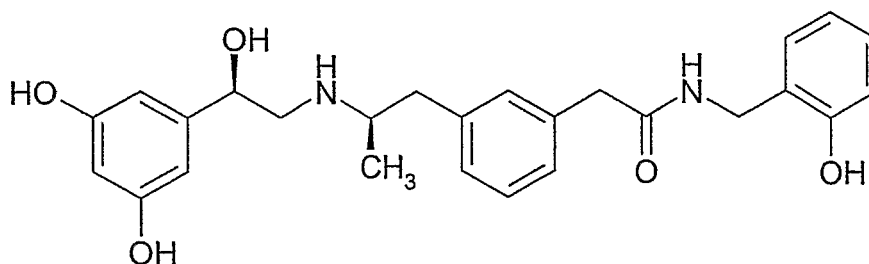
^1H NMR (400MHz, CD_3OD) δ 1.05 (3H, d), 2.62 (3H, m), 2.88 (5H, m), 3.78 (2H, m), 4.50 (1H, m), 4.58 (2H, m), 6.16 (1H, m), 6.26 (2H, s), 7.01 (2H, m), 7.07 (2H, m), 7.20 (5H, m).

LRMS: m/z APCI 449 $[\text{M}+\text{H}^+]$, 447 $[\text{M}-\text{H}]$.

20

Example 31

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(2-hydroxy-benzyl)-acetamide



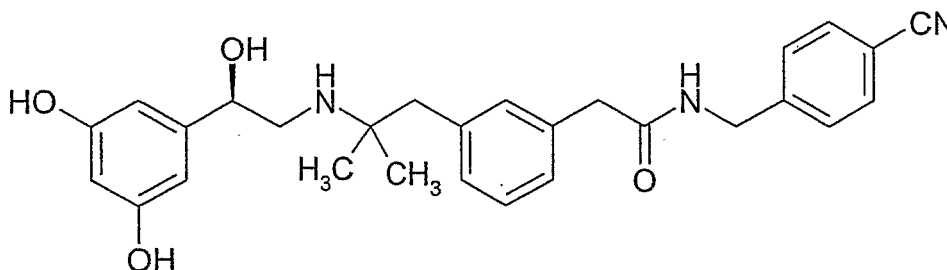
The title compound was prepared from the compound of preparation 54 using the method described for example 12 and was isolated as a brown foam.

^1H NMR (400MHz, CD_3OD) δ 1.05 (3H, d), 2.56 (1H, m), 2.68 (2H, m), 2.81 (2H, m), 3.52 (2H, s), 4.34 (2H, s), 4.53 (1H, m), 6.16 (1H, m), 6.25 (2H, s), 6.76 (2H, m), 7.00 (1H, m), 7.08 (4H, m), 7.18 (1H, m).

LRMS: m/z APCI 451 $[\text{M}+\text{H}^+]$, 449 $[\text{M}-\text{H}]$.

Example 32

10 **N-(4-Cyano-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide**



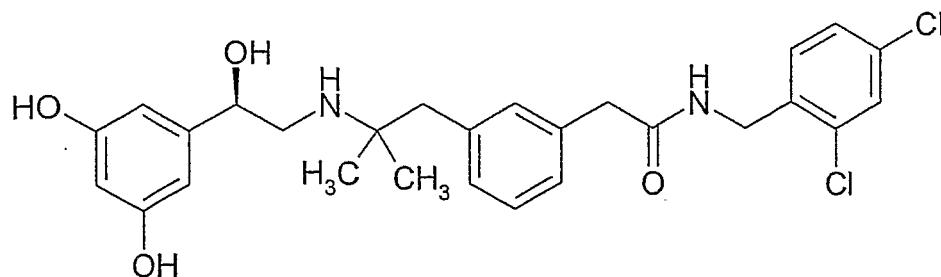
The title compound was prepared from the compound of preparation 55 using the method described for example 12 and was isolated as a white solid.

15 ^1H NMR (400MHz, CD_3OD) δ 1.13 (3H, s), 1.15 (3H, s), 2.85 (4H, m), 3.61 (2H, s), 4.47 (2H, s), 4.62 (1H, m), 6.23 (1H, m), 6.38 (2H, s), 7.11 (1H, d), 7.21 (2H, s), 7.28 (1H, m), 7.42 (2H, d), 7.67 (2H, d).

LRMS: m/z electrospray 474 $[\text{M}+\text{H}^+]$, 472 $[\text{M}-\text{H}]$.

20 Example 33

N-(2,4-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide



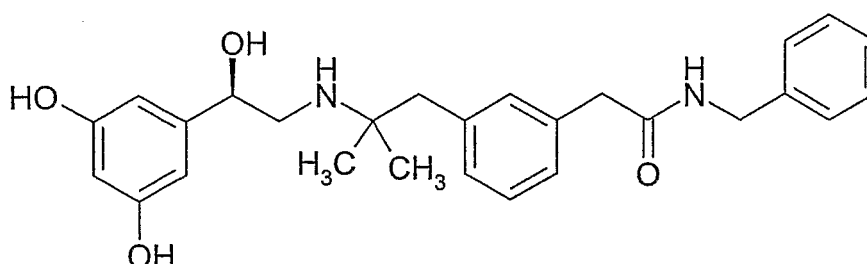
The title compound was prepared from the compound of preparation 56 using the method described for example 12 and was isolated as a white solid.

¹H NMR (400MHz, CD₃OD) δ 1.12 (3H, s), 1.13 (3H, s), 2.85 (4H, m), 3.60 (2H, s), 4.46 (2H, s), 4.62 (1H, m), 6.23 (1H, m), 6.38 (2H, s), 7.11 (1H, d), 7.20 (2H, m), 7.28 (3H, m), 7.47 (1H, s).

LRMS: m/z electrospray 517 [M+H⁺], 515 [M-H].

Example 34

10 N-(Benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide



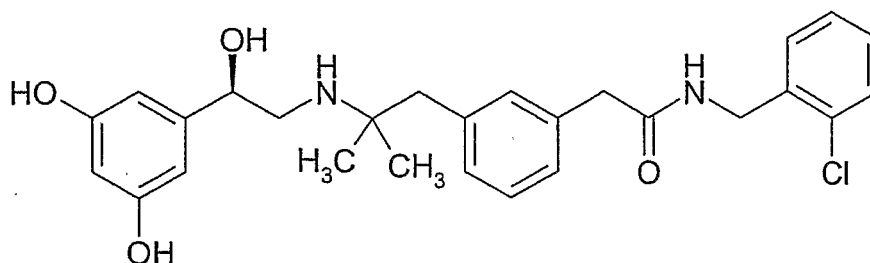
Triethylamine trihydrofluoride (42uL, 0.25mmol) was added in one portion to a stirred solution of the compound of preparation 57 (130mg, 0.23mmol) in methanol (4mL) at room temperature. The reaction was stirred for 12 hours and then the pH adjusted to pH 7 using trifluoroacetic acid. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (95:5:0.5 then 90:10:1) to furnish the title compound as a white foam, 80mg.

¹H NMR (400MHz, CD₃OD) δ 1.09 (3H, s), 1.10 (3H, s), 2.79 (4H, m), 3.53 (2H, s), 4.37 (2H, s), 4.55 (1H, m), 6.18 (1H, t), 6.33 (2H, s), 7.04 (1H, d), 7.13 (1H, s), 7.16 (1H, d), 7.25 (6H, m).

LRMS: m/z electrospray 449 [M+H⁺].

Example 35

N-(2-Chlorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide



5

The title compound was prepared from the compound of preparation 58 using the method described for example 34 and was isolated as a white foam.

^1H NMR (400MHz, CD_3OD) δ 1.06 (3H, s), 1.08 (3H, s), 2.70 (3H, m), 2.83 (1H, m), 3.57 (2H, s), 4.43 (2H, s), 4.56 (1H, m), 6.18 (1H, s), 6.34 (2H, s), 7.04 (1H, d), 7.18 (6H, m), 7.17 (1H, d).

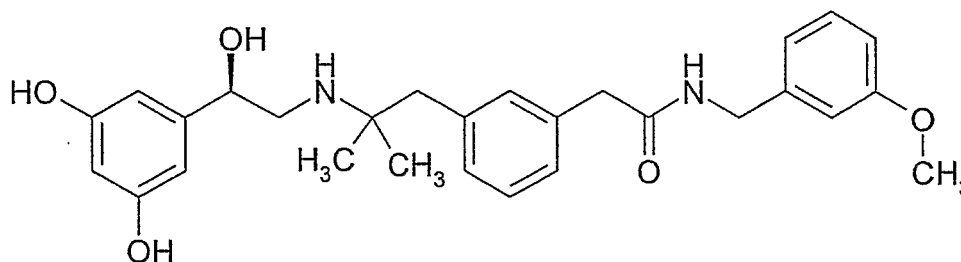
10

LRMS: m/z electrospray 483 $[\text{M}+\text{H}^+]$.

Example 36

N-(3-Methoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide

15



The title compound was prepared from the compound of preparation 59 using the method described for example 34 and was isolated as a white foam.

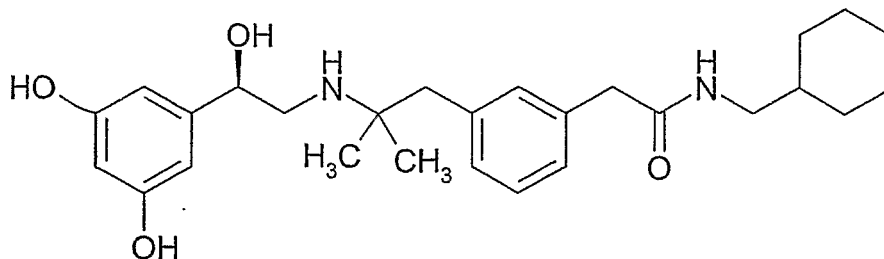
^1H NMR (400MHz, CD_3OD) δ 1.06 (3H, s), 1.08 (3H, s), 2.72 (4H, m), 3.53 (2H, s), 3.68 (3H, s), 4.33 (2H, s), 4.56 (1H, m), 6.18 (1H, m), 6.32 (2H, s), 6.78 (2H, m), 7.03 (1H, d), 7.18 (5H, m).

20

LRMS: m/z electrospray 479 $[\text{M}+\text{H}^+]$.

Example 37

N-(Cyclohexylmethyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide



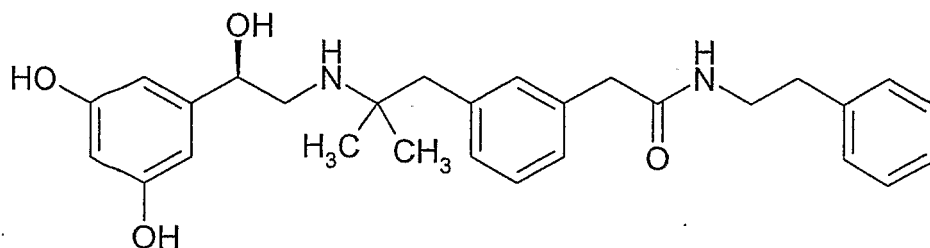
5 The title compound was prepared from the compound of preparation 60 using the method described for example 34 and was isolated as a white foam.

^1H NMR (400MHz, CD_3OD) δ 0.91 (2H, m), 1.06 (3H, s), 1.08 (3H, s), 1.18 (3H, m), 1.44 (1H, m), 1.70 (5H, m), 2.70 (3H, m), 2.84 (1H, m), 3.02 (2H, d), 3.46 (2H, s), 4.58 (1H, m), 6.17 (1H, t), 6.34 (2H, s), 7.07 (1H, d), 7.17 (2H, d), 7.22 (1H, t).

LRMS: m/z APCI 455 $[\text{M}+\text{H}^+]$.

Example 38

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-phenethyl-acetamide



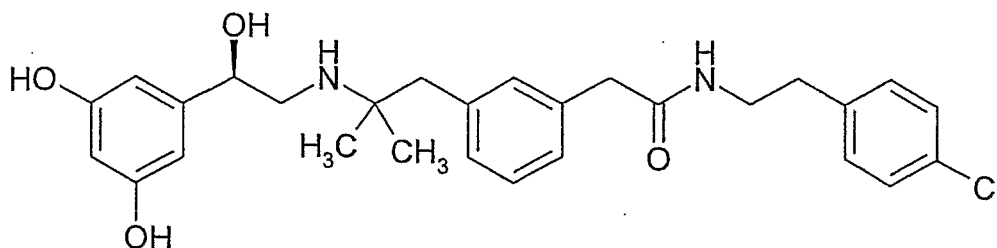
The title compound was prepared from the compound of preparation 61 using the method described for example 34 and was isolated as a white foam.

^1H NMR (400MHz, CD_3OD) δ 1.07 (3H, s), 1.08 (3H, s), 2.73 (6H, m), 3.42 (2H, m), 3.47 (2H, s), 4.55 (1H, m), 6.17 (1H, s), 6.33 (2H, s), 7.15 (8H, m).

LRMS: m/z electrospray 463 $[\text{M}+\text{H}^+]$, 461 $[\text{M}-\text{H}]$.

Example 39

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-chlorophenethyl)-acetamide



The title compound was prepared from the compound of preparation 62 using the method described for example 34 and was isolated as a white foam.

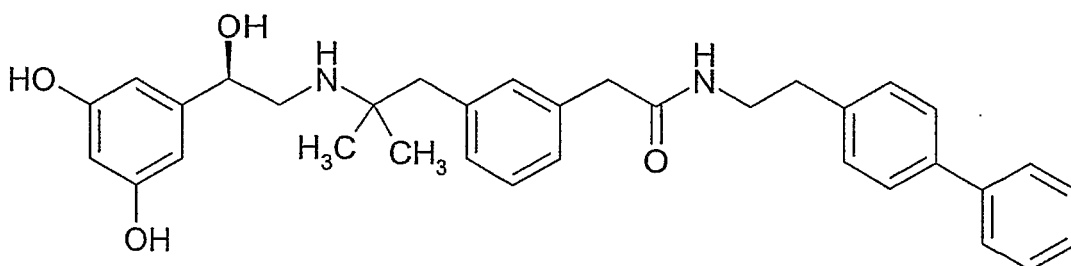
^1H NMR (400MHz, CD_3OD) δ 1.07 (3H, s), 1.08 (3H, s), 2.73 (6H, m), 3.43 (2H, m), 3.42 (2H, s), 4.55 (1H, m), 6.17 (1H, s), 6.36 (2H, s), 7.08 (5H, m), 7.21 (3H, m).

LRMS: m/z electrospray 497 $[\text{M}+\text{H}^+]$, 495 $[\text{M}-\text{H}]$.

10

Example 40

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-phenylphenethyl)-acetamide



The title compound was prepared from the compound of preparation 63 using the method described for example 34 and was isolated as a white foam.

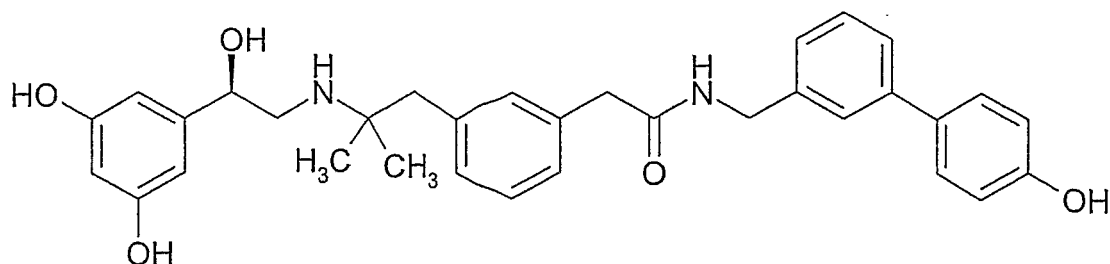
^1H NMR (400MHz, CD_3OD) δ 1.04 (3H, s), 1.05 (3H, s), 2.73 (6H, m), 3.43 (4H, m), 4.55 (1H, m), 6.18 (1H, m), 6.33 (2H, s), 7.08 (3H, m), 7.21 (3H, m), 7.31 (1H, t), 7.42 (2H, m), 7.51 (2H, d), 7.56 (2H, d).

LRMS: m/z electrospray 540 $[\text{M}+\text{H}^+]$.

20

Example 41

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4'-hydroxy-biphenyl-3-ylmethyl)-acetamide



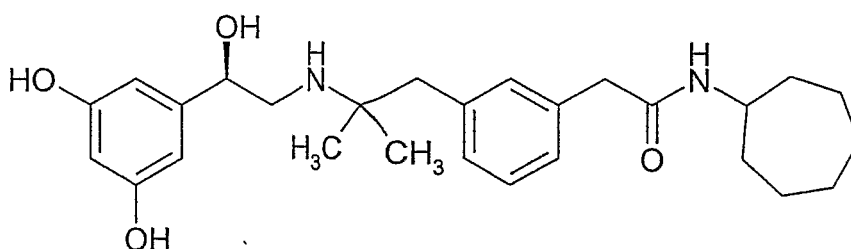
The title compound was prepared from the compound of preparation 64 using the method described for example 34 and was isolated as a white foam.

^1H NMR (400MHz, CD_3OD) δ 1.07 (3H, s), 1.08 (3H, s), 2.73 (2H, m), 2.85 (2H, m), 3.57 (2H, s), 4.42 (2H, s), 4.58 (1H, m), 6.19 (1H, m), 6.33 (2H, s), 6.83 (2H, d), 7.07 (1H, d), 7.13 (2H, d), 7.23 (2H, m), 7.38 (5H, m).

LRMS: m/z electrospray 541 $[\text{M}+\text{H}^+]$, 539 $[\text{M}-\text{H}]$.

Example 42

- 10 **N-Cycloheptyl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide**



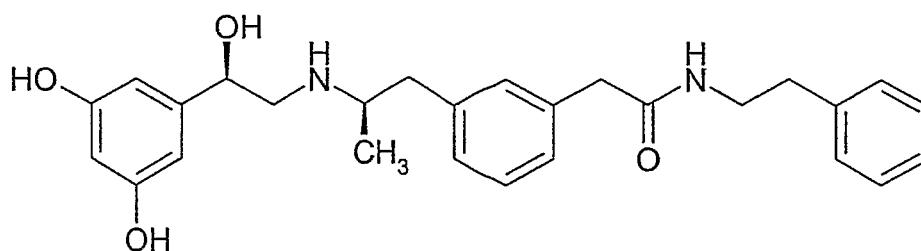
The title compound was prepared from the compound of preparation 65 using the method described for example 34 and was isolated as a white foam.

- 15 ^1H NMR (400MHz, CD_3OD) δ 1.07 (3H, s), 1.08 (3H, s), 1.58 (10H, m), 1.86 (2H, m), 2.73 (4H, m), 3.44 (2H, s), 3.80 (1H, m), 4.58 (1H, m), 6.18 (1H, m), 6.32 (2H, s), 7.05 (1H, d), 7.15 (2H, d), 7.23 (1H, t).

LRMS: m/z electrospray 455 $[\text{M}+\text{H}^+]$, 453 $[\text{M}-\text{H}]$.

20 Example 43

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-phenethyl-acetamide



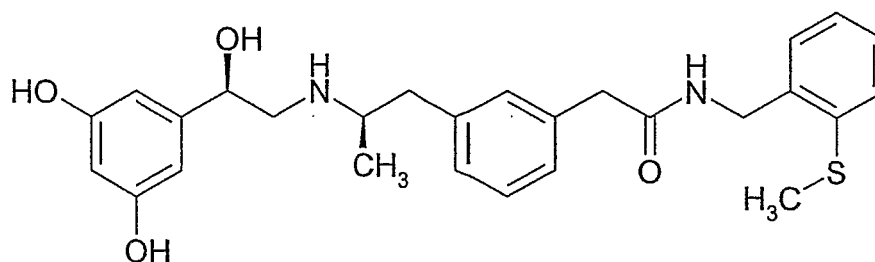
The title compound was prepared from the compound of preparation 66 using the method described for example 12 and was isolated as a white foam.

¹H NMR (400MHz, CD₃OD) δ 1.05 (3H, d), 2.78 (7H, m), 3.40 (4H, m), 4.52 (1H, m), 6.13 (1H, m), 6.24 (2H, s), 7.08 (9H, m).

LRMS: m/z APCI 447 [M-H].

Example 44

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(2-methylsulfanyl-benzyl)-acetamide

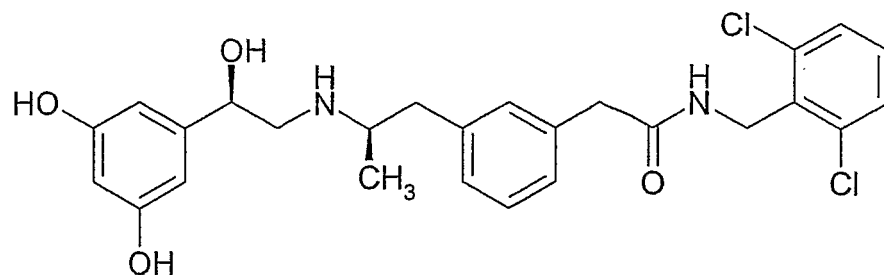


The title compound was prepared from the compound of preparation 67 using the method described for example 12 and was isolated as a white foam.

¹H NMR (400MHz, CD₃OD) δ 1.05 (3H, d), 2.44 (3H, s), 2.56 (1H, m), 2.75 (4H, m), 3.53 (2H, s), 4.44 (2H, s), 4.52 (1H, m), 6.13 (1H, m), 6.24 (2H, s), 7.10 (8H, m).

Example 45

N-(2,6-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



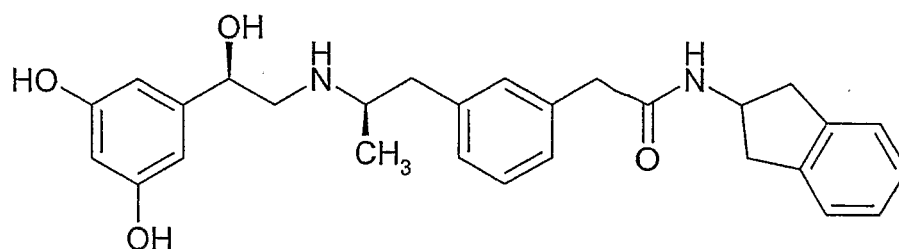
The title compound was prepared from the compound of preparation 68 using the method described for example 12 and was isolated as a white foam.

¹H NMR (400MHz, CD₃OD) δ 1.05 (3H, d), 2.54 (1H, m), 2.78 (5H, m), 3.48 (2H, s), 4.52 (1H, m), 4.66 (2H, s), 6.15 (1H, m), 6.25 (2H, s), 7.00 (1H, m), 7.08 (2H, m), 7.18 (1H, m), 7.27 (1H, m), 7.38 (2H, m).

LRMS: m/z APCI 503 [M+H⁺].

Example 46

10 **2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-indan-2-yl-acetamide**



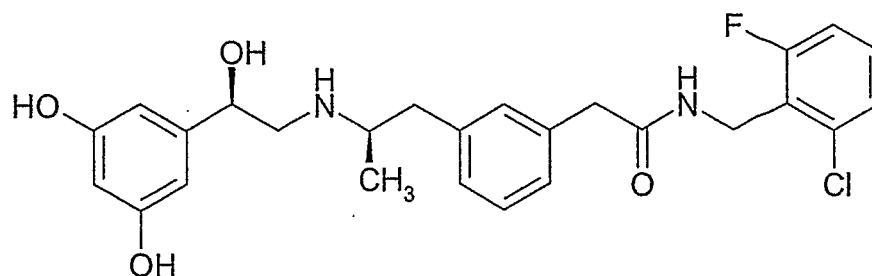
The title compound was prepared from the compound of preparation 69 using the method described for example 12 and was isolated as a white foam.

15 ¹H NMR (400MHz, CD₃OD) δ 1.05 (3H, d), 2.58 (1H, m), 2.78 (6H, m), 3.22 (2H, m), 3.45 (2H, s), 4.56 (2H, m), 6.15 (1H, m), 6.25 (2H, s), 7.00 (8H, m).

LRMS: m/z APCI 461 [M+H⁺].

Example 47

20 **N-(2-Chloro-6-fluorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide**



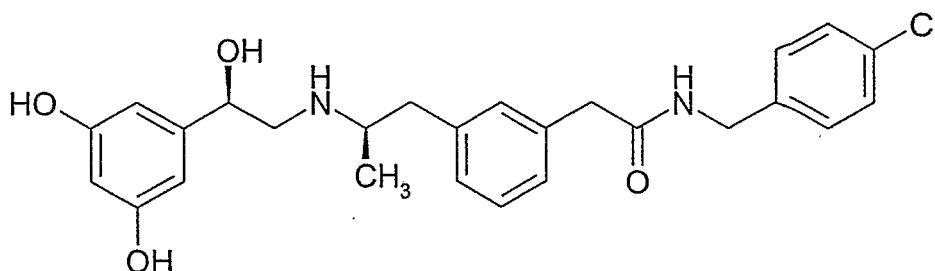
The title compound was prepared from the compound of preparation 70 using the method described for example 12 and was isolated as a white foam.

^1H NMR (400MHz, CD_3OD) δ 1.05 (3H, d), 2.54 (1H, m), 2.71 (2H, m), 2.83 (2H, m), 3.48 (2H, s), 4.57 (3H, m), 6.15 (1H, s), 6.25 (2H, s), 7.27 (7H, m).

LRMS: m/z APCI 487 $[\text{M}+\text{H}^+]$, 485 $[\text{M}-\text{H}]$.

Example 49

N-(4-Chlorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



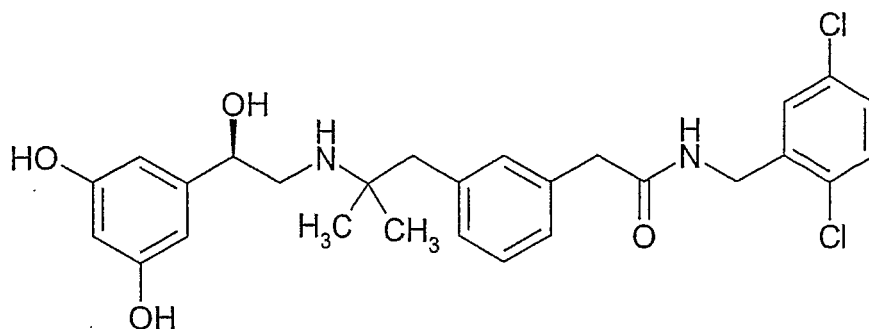
The title compound was prepared from the compound of preparation 72 using the method described for example 12 and was isolated as a white foam.

^1H NMR (400MHz, CD_3OD) δ 1.05 (3H, d), 2.58 (1H, m), 2.71 (2H, m), 2.83 (1H, m), 2.90 (1H, m), 3.48 (2H, s), 4.38 (2H, s), 4.57 (1H, m), 6.16 (1H, s), 6.25 (2H, s), 7.02 (1H, d), 7.09 (1H, s), 7.11 (1H, m), 7.20 (3H, m), 7.28 (2H, m).

LRMS: m/z APCI 469 $[\text{M}+\text{H}^+]$, 467 $[\text{M}-\text{H}]$.

20 Example 50

N-(2,5-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide



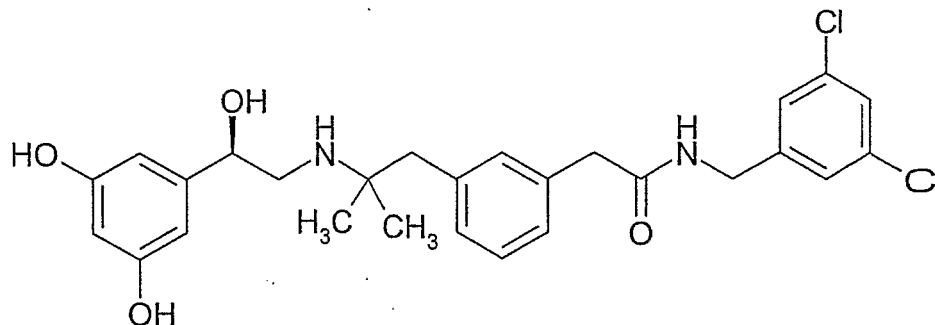
The title compound was prepared from the compound of preparation 73 using the method described for example 12 and was isolated as a white solid.

^1H NMR (400MHz, CD_3OD) δ 1.12 (3H, s), 1.13 (3H, s), 2.85 (4H, m), 3.62 (2H, s), 4.46 (2H, s), 4.62 (1H, m), 6.23 (1H, m), 6.38 (2H, s), 7.20 (6H, m), 7.39 (1H, d).

LRMS: m/z electrospray 517 $[\text{M}+\text{H}^+]$, 515 $[\text{M}-\text{H}]$.

Example 51

- 10 **N-(3,5-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide**



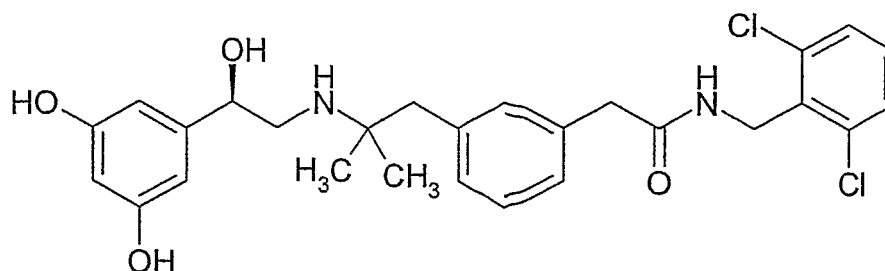
The title compound was prepared from the compound of preparation 74 using the method described for example 12 and was isolated as a white solid.

- 15 ^1H NMR (400MHz, CD_3OD) δ 1.11 (3H, s), 1.13 (3H, s), 2.85 (4H, m), 3.59 (2H, s), 4.37 (2H, s), 4.62 (1H, m), 6.23 (1H, m), 6.38 (2H, s), 7.01 (1H, m), 7.12 (1H, m), 7.17 (3H, m), 7.28 (1H, d), 7.32 (1H, m).

LRMS: m/z electrospray 517 $[\text{M}+\text{H}^+]$, 515 $[\text{M}-\text{H}]$.

- 20 **Example 52**

N-(2,6-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide



The title compound was prepared from the compound of preparation 75 using the method described for example 12 and was isolated as a white solid.

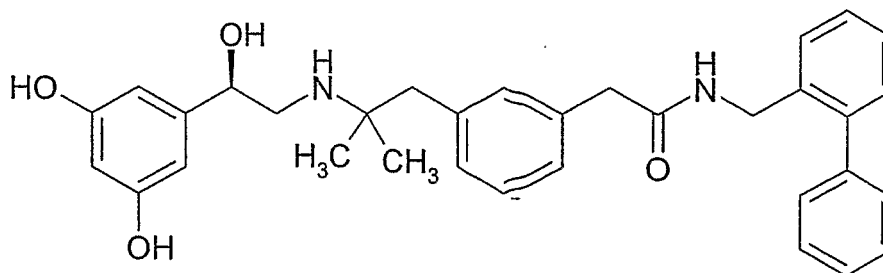
^1H NMR (400MHz, CD_3OD) δ 1.10 (3H, s), 1.11 (3H, s), 2.82 (4H, m), 3.54 (2H, s), 4.60 (1H, m), 4.71 (2H, s), 6.22 (1H, m), 6.38 (2H, s), 7.07 (1H, m), 7.18 (2H, m), 7.26 (1H, m), 7.31 (1H, m), 7.43 (1H, s), 7.45 (1H, m).

LRMS: m/z electrospray 520 $[\text{M}+\text{H}^+]$, 518 $[\text{M}-\text{H}]$.

10

Example 53

N-Biphenyl-2-ylmethyl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide



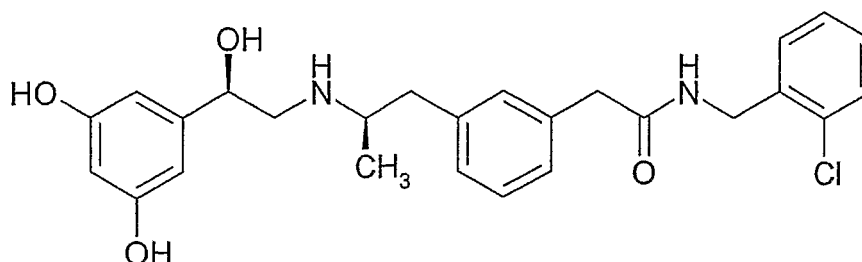
The title compound was prepared from the compound of preparation 76 using the method described for example 12 and was isolated as a white solid.

^1H NMR (400MHz, CD_3OD) δ 1.14 (3H, s), 1.15 (3H, s), 2.82 (2H, m), 2.93 (2H, m), 3.52 (2H, s), 4.32 (2H, s), 4.62 (1H, m), 6.23 (1H, m), 6.38 (2H, s), 7.11 (13H, m).

LRMS: m/z electrospray 527 $[\text{M}+\text{H}^+]$, 525 $[\text{M}-\text{H}]$.

Example 54

N-(2-Chlorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



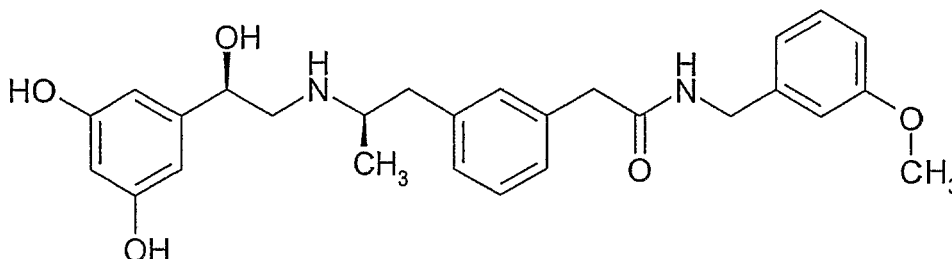
The title compound was prepared from the compound of preparation 77 using the method described for example 12 and was isolated as a white foam.

^1H NMR (400MHz, CD_3OD) δ 1.05 (3H, d), 2.56 (1H, m), 2.80 (4H, m), 3.55 (2H, s), 4.45 (2H, s), 4.52 (1H, m), 6.14 (1H, m), 6.25 (2H, s), 7.19 (8H, m).

LRMS: m/z APCI 469 $[\text{M}+\text{H}^+]$.

10 Example 55

N-(3-Methoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



The title compound was prepared from the compound of preparation 78 using the method described for example 12 and was isolated as a white foam.

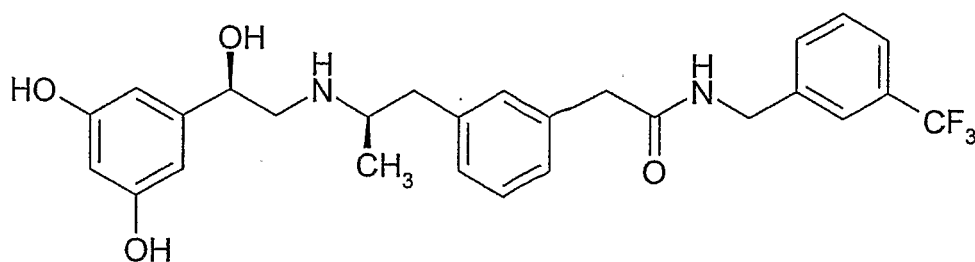
^1H NMR (400MHz, CD_3OD) δ 1.05 (3H, d), 2.60 (5H, m), 3.51 (2H, s), 3.69 (3H, s), 4.32 (2H, s), 4.51 (1H, m), 6.15 (1H, m), 6.25 (2H, s), 6.75 (3H, m), 7.02 (1H, m), 7.21 (4H, m).

LRMS: m/z APCI 465 $[\text{M}+\text{H}^+]$.

20

Example 56

N-(3-Trifluoromethylbenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



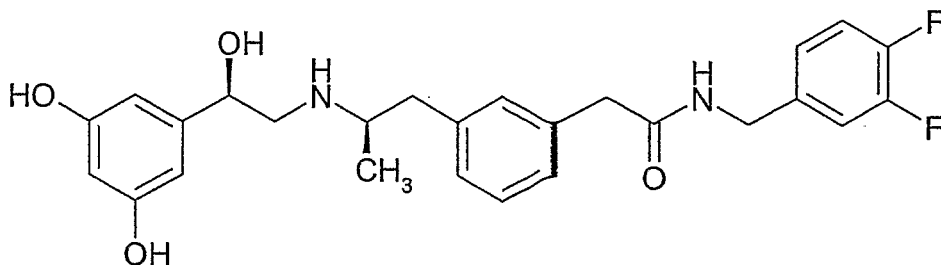
The title compound was prepared from the compound of preparation 79 using the method described for example 12 and was isolated as a pale brown foam.

^1H NMR (400MHz, CD_3OD) δ 1.05 (3H, d), 2.57 (1H, m), 2.66 (2H, m), 2.80 (1H, m), 2.90 (1H, m), 3.55 (2H, s), 4.43 (2H, s), 4.51 (1H, m), 6.16 (1H, m), 6.25 (2H, s), 7.03 (1H, m), 7.07 (1H, s), 7.14 (1H, m), 7.21 (1H, m), 7.47 (2H, m), 7.53 (2H, m).

LRMS: m/z APCI 503 $[\text{M}+\text{H}^+]$, 501 $[\text{M}-\text{H}]$.

10 Example 57

N-(3,4-Difluorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



The title compound was prepared from the compound of preparation 80 using the method described for example 12 and was isolated as a pale brown foam.

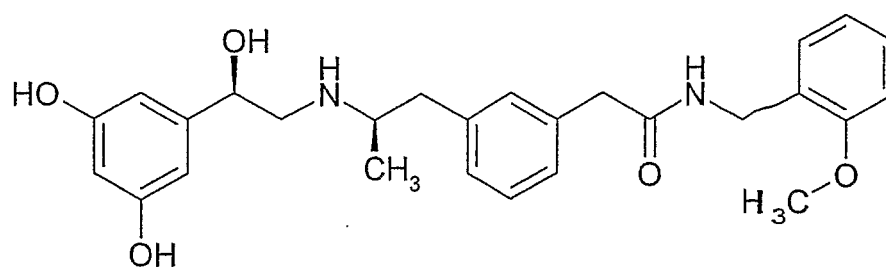
^1H NMR (400MHz, CD_3OD) δ 1.05 (3H, d), 2.58 (1H, m), 2.66 (2H, m), 2.80 (1H, m), 2.90 (1H, m), 3.53 (2H, s), 4.30 (2H, s), 4.52 (1H, m), 6.16 (1H, m), 6.24 (2H, s), 7.01 (2H, m), 7.15 (5H, m).

LRMS: m/z APCI 471 $[\text{M}+\text{H}^+]$, 469 $[\text{M}-\text{H}]$.

20

Example 58

N-(2-Methoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



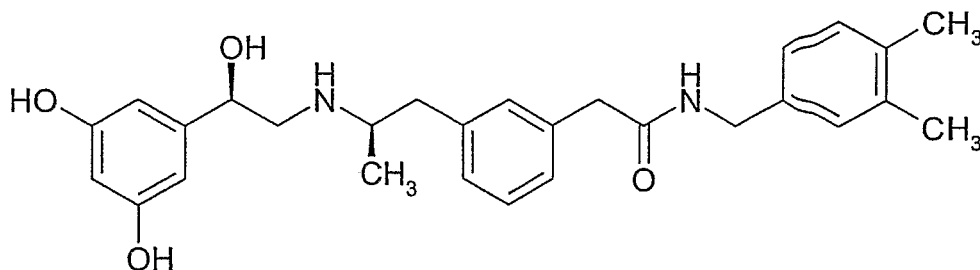
The title compound was prepared from the compound of preparation 81 using the method described for example 12 and was isolated as a pale brown foam.

¹H NMR (400MHz, CD₃OD) δ 1.05 (3H, d), 2.57 (1H, m), 2.68 (2H, m), 2.80 (1H, m), 2.87 (1H, m), 3.53 (2H, s), 3.78 (3H, s), 4.35 (2H, s), 4.52 (1H, m), 6.16 (1H, m), 6.23 (2H, s), 6.84 (1H, m), 6.91 (1H, m), 7.01 (1H, m), 7.07 (1H, s), 7.15 (2H, m), 7.21 (2H, m).

LRMS: m/z APCI 465 [M+H⁺], 463 [M-H⁻].

10. Example 59

N-(3,4-Dimethylbenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



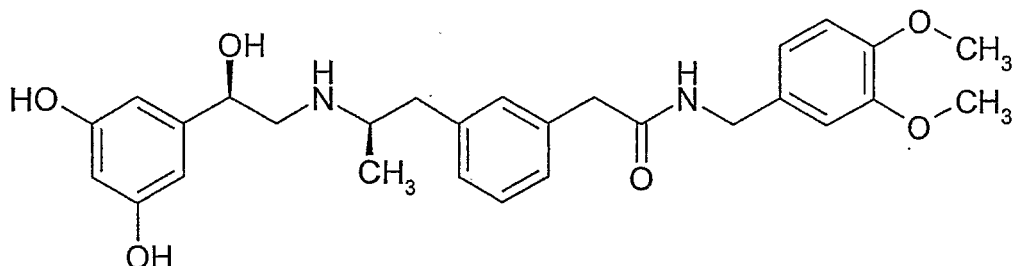
The title compound was prepared from the compound of preparation 82 using the method described for example 12 and was isolated as a pale brown foam.

¹H NMR (400MHz, CD₃OD) δ 1.04 (3H, d), 2.19 (3H, s), 2.19 (3H, s), 2.57 (1H, m), 2.66 (2H, m), 2.78 (1H, m), 2.88 (1H, m), 3.49 (2H, s), 4.26 (2H, s), 4.49 (1H, m), 6.16 (1H, m), 6.24 (2H, s), 6.93 (1H, m), 6.97 (1H, s), 7.01 (2H, m), 7.06 (1H, s), 7.13 (1H, m), 7.19 (1H, m).

LRMS: m/z APCI 463 [M+H⁺], 461 [M-H⁻].

Example 60

N-(3,4-Dimethoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



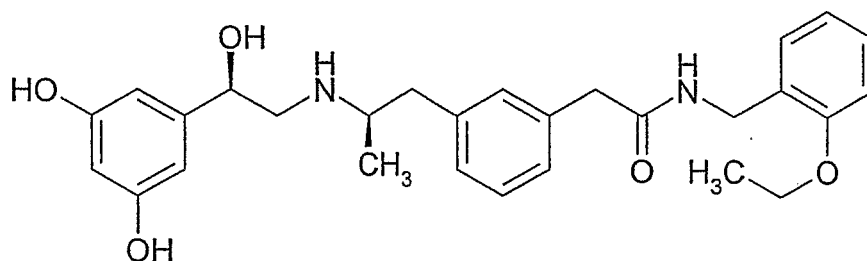
The title compound was prepared from the compound of preparation 83 using the method described for example 12 and was isolated as a pale brown foam.

^1H NMR (400MHz, CD_3OD) δ 1.04 (3H, d), 2.57 (1H, m), 2.66 (2H, m), 2.79 (1H, m), 2.88 (1H, m), 3.50 (2H, s), 3.72 (3H, s), 3.78 (3H, s), 4.28 (2H, s), 4.50 (1H, m), 6.16 (1H, m), 6.24 (2H, s), 6.78 (2H, m), 6.85 (1H, m), 7.01 (1H, m), 7.07 (1H, s), 7.14 (1H, m), 7.19 (1H, m).

LRMS: m/z APCI 495 $[\text{M}+\text{H}^+]$, 493 $[\text{M}-\text{H}]$.

Example 61

N-(2-Ethoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



15

The title compound was prepared from the compound of preparation 84 using the method described for example 12 and was isolated as a pale brown foam.

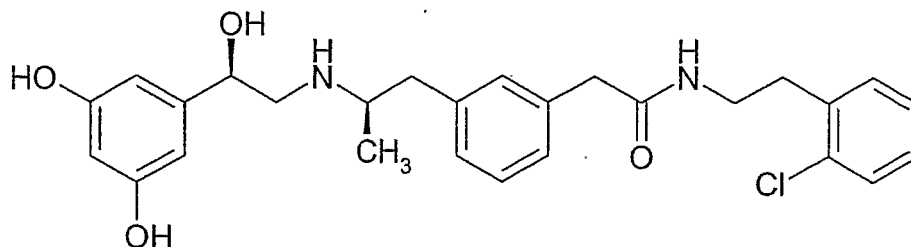
^1H NMR (400MHz, CD_3OD) δ 1.04 (3H, d), 1.35 (3H, t), 2.57 (1H, m), 2.68 (2H, m), 2.80 (1H, m), 2.88 (1H, m), 3.53 (2H, s), 4.00 (2H, q), 4.36 (2H, s), 4.50 (1H, m), 6.15 (1H, m), 6.25 (2H, s), 6.83 (1H, m), 6.88 (1H, m), 7.01 (1H, m), 7.07 (1H, s), 7.15 (2H, m), 7.19 (2H, m).

20

LRMS: m/z APCI 479 $[\text{M}+\text{H}^+]$, 477 $[\text{M}-\text{H}]$.

Example 62

N-[2-(2-Chloro-phenyl)-ethyl]-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide



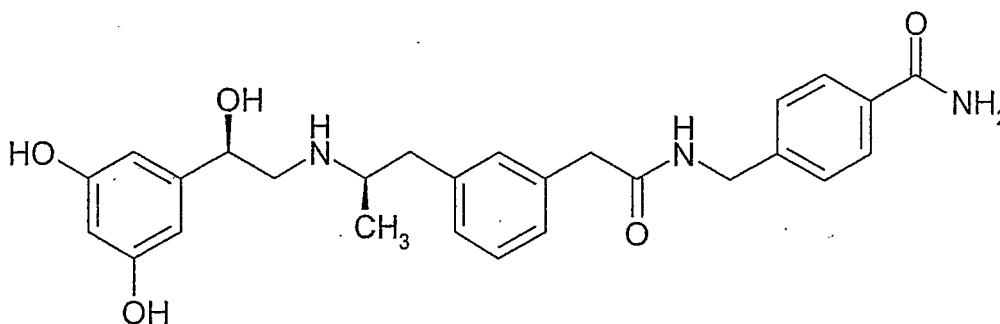
- 5 The title compound was prepared from the compound of preparation 85 using the method described for example 12 and was isolated as a pale brown foam.

¹H NMR (400MHz, CD₃OD) δ 1.06 (3H, d), 2.58 (1H, m), 2.67 (2H, m), 2.81 (1H, m), 2.88 (3H, m), 3.43 (4H, m), 4.53 (1H, m), 6.16 (1H, m), 6.24 (2H, s), 7.04 (3H, m), 7.20 (6H, m).

- 10 LRMS: m/z APCI 483 [M+H⁺], 481 [M-H].

Example 63

4-[[2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetyl-amino]-methyl]-benzamide



15

The title compound was prepared from the compound of preparation 86 using the method described for example 12 and was isolated as a white foam.

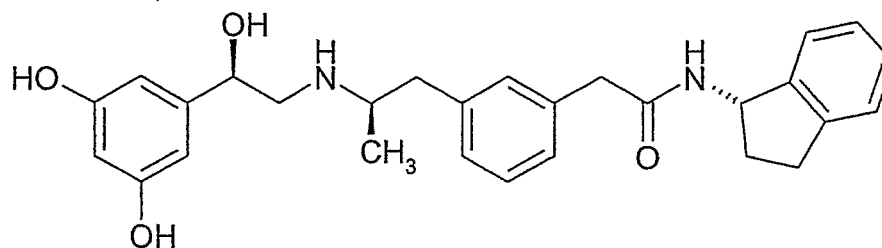
¹H NMR (400MHz, CD₃OD) δ 1.04 (3H, d), 2.57 (1H, m), 2.68 (2H, m), 2.80 (1H, m), 2.87 (1H, m), 3.58 (2H, s), 4.38 (2H, s), 4.51 (1H, m), 6.17 (1H, m), 6.25 (2H, s), 7.01 (1H, d), 7.07 (2H, m), 7.20 (1H, m), 7.29 (2H, d), 7.80 (2H, d).

20

LRMS: m/z APCI 478 [M+H⁺], 476 [M-H].

Example 64

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-indan-1-yl-acetamide



5 The title compound was prepared from the compound of preparation 87 using the method described for example 12 and was isolated as a pale brown foam.

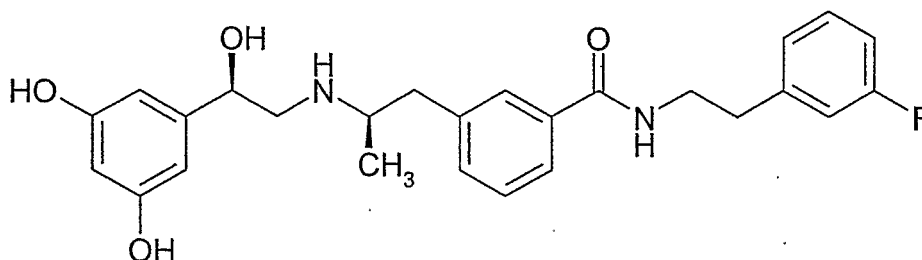
^1H NMR (400MHz, CD_3OD) δ 1.05 (3H, d), 1.81 (1H, m), 2.46 (1H, m), 2.57 (1H, m), 2.72 (2H, m), 2.87 (4H, m), 3.52 (2H, m), 4.53 (1H, m), 5.36 (1H, m), 6.16 (1H, m), 6.25 (2H, s), 7.01 (1H, m), 7.14 (7H, m).

LRMS: m/z APCI 461 $[\text{M}+\text{H}^+]$, 459 $[\text{M}-\text{H}]$.

10

Example 65

3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(3-fluoro-phenyl)-ethyl]-benzamide



15 The title compound was prepared from the compound of preparation 94 using the method described for example 12 and was isolated as a white foam.

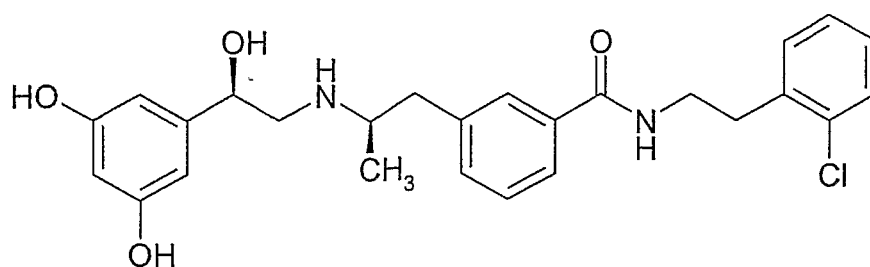
^1H NMR (400MHz, CD_3OD) δ 1.06 (3H, d), 2.80 (7H, m), 3.59 (2H, m), 4.55 (1H, m), 6.15 (1H, m), 6.26 (2H, s), 7.01 (3H, m), 7.30 (3H, m), 7.58 (2H, m).

LRMS: m/z APCI 453 $[\text{M}+\text{H}^+]$.

20

Example 66

3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-chloro-phenyl)-ethyl]-benzamide



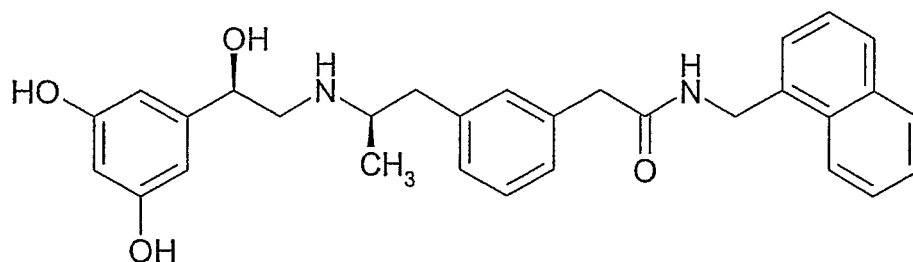
The title compound was prepared from the compound of preparation 95 using the method described for example 12 and was isolated as a white foam.

¹H NMR (400MHz, CD₃OD) δ 1.05 (3H, d), 2.81 (5H, m), 3.07 (2H, t), 3.63 (2H, t), 4.53 (1H, m), 6.15 (1H, m), 6.26 (2H, s), 7.20 (6H, m), 7.55 (2H, m).

LRMS: m/z APCI 469 [M+H⁺].

Example 67

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-naphthalen-1-ylmethyl-acetamide



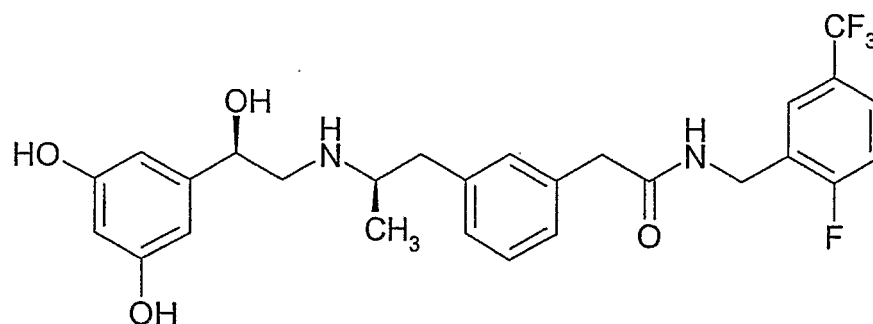
The title compound was prepared from the compound of preparation 96 using the method described for example 12 and was isolated as a white foam.

¹H NMR (400MHz, CD₃OD) δ 0.98 (3H, d), 2.47 (1H, m), 2.54 (2H, m), 2.78 (2H, m), 3.54 (2H, s), 4.51 (1H, m), 4.80 (2H, s), 6.17 (1H, s), 6.25 (2H, s), 6.98 (2H, m), 7.07 (2H, m), 7.40 (4H, m), 7.78 (1H, d), 7.84 (1H, d), 7.90 (1H, d).

LRMS: m/z APCI 485 [M+H⁺], 483 [M-H⁻].

Example 68

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(2-fluoro-5-trifluoromethyl-benzyl)-acetamide



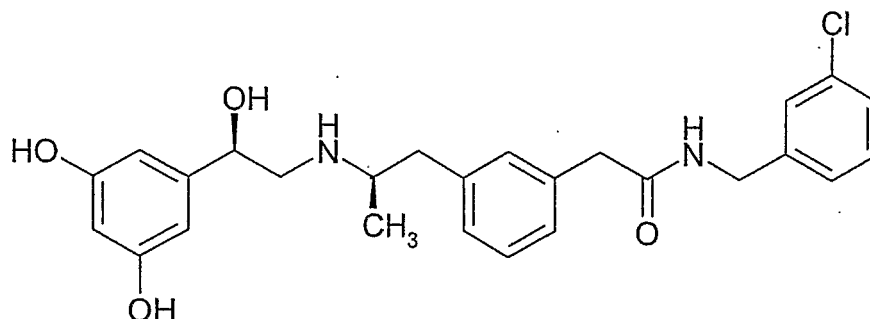
The title compound was prepared from the compound of preparation 97 using the method described for example 12 and was isolated as a white foam.

¹H NMR (400MHz, CD₃OD) δ 1.03 (3H, d), 2.47 (1H, m), 2.63 (2H, m), 2.78 (1H, m), 2.89 (1H, m), 3.54 (2H, s), 4.46 (2H, s), 4.58 (1H, m), 6.17 (1H, s), 6.22 (2H, s), 7.01 (1H, d), 7.08 (2H, m), 7.20 (2H, m), 7.58 (2H, m).

LRMS: m/z APCI 521 [M+H⁺], 519 [M-H].

Example 69

10 **2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(3-chlorobenzyl)-acetamide**



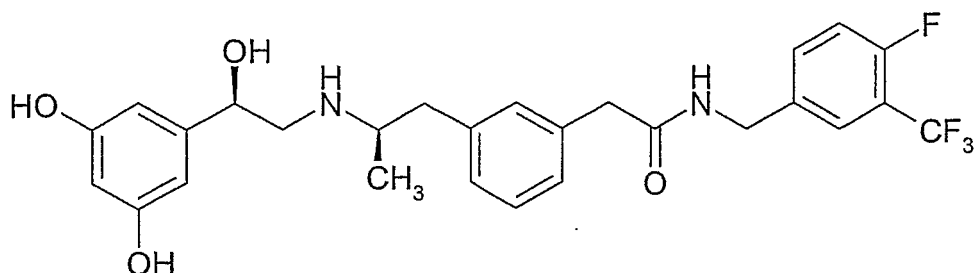
The title compound was prepared from the compound of preparation 98 using the method described for example 12 and was isolated as a white foam.

15 ¹H NMR (400MHz, CD₃OD) δ 1.03 (3H, d), 2.58 (1H, m), 2.63 (2H, m), 2.78 (1H, m), 2.85 (1H, m), 3.57 (2H, s), 4.38 (2H, s), 4.52 (1H, m), 6.17 (1H, s), 6.26 (2H, s), 7.01 (1H, d), 7.08 (1H, s), 7.20 (6H, m).

LRMS: m/z APCI 469 [M+H⁺], 467 [M-H].

20 **Example 70**

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-acetamide



The title compound was prepared from the compound of preparation 99 using the method described for example 12 and was isolated as a white foam.

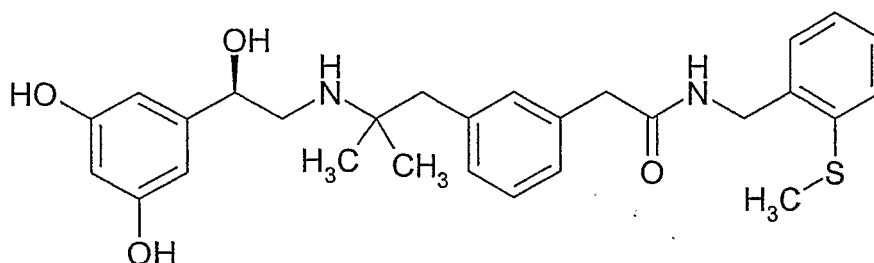
^1H NMR (400MHz, CD_3OD) δ 1.03 (3H, d), 2.58 (1H, m), 2.63 (2H, m), 2.78 (1H, m), 2.89 (1H, m), 3.52 (2H, s), 4.38 (2H, s), 4.52 (1H, m), 6.17 (1H, s), 6.26 (2H, s), 7.03 (1H, d), 7.08 (2H, m), 7.20 (2H, m), 7.51 (2H, m).

LRMS: m/z APCI 521 $[\text{M}+\text{H}^+]$, 519 $[\text{M}-\text{H}]$.

10

Example 71

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2-methylsulfanyl-benzyl)-acetamide



The title compound was prepared from the compound of preparation 100 using the method described for example 12 and was isolated as a white solid.

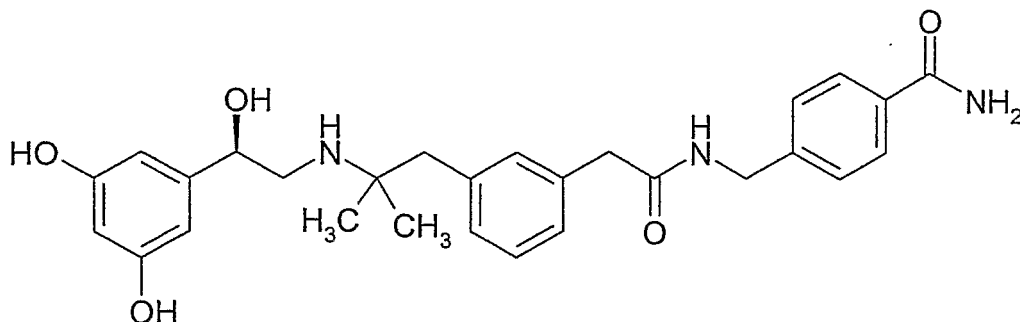
^1H NMR (400MHz, CD_3OD) δ 1.11 (3H, s), 1.12 (3H, s), 2.48 (3H, s), 2.85 (4H, m), 3.59 (2H, s), 4.47 (2H, s), 4.61 (1H, m), 6.23 (1H, m), 6.38 (2H, s), 7.07 (2H, m), 7.26 (6H, m).

LRMS: m/z electrospray 497 $[\text{M}+\text{H}^+]$, 494 $[\text{M}-\text{H}]$.

20

Example 72

4-[[2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetylamino]-methyl]-benzamide



The title compound was prepared from the compound of preparation 101 using the method described for example 12 and was isolated as a white solid.

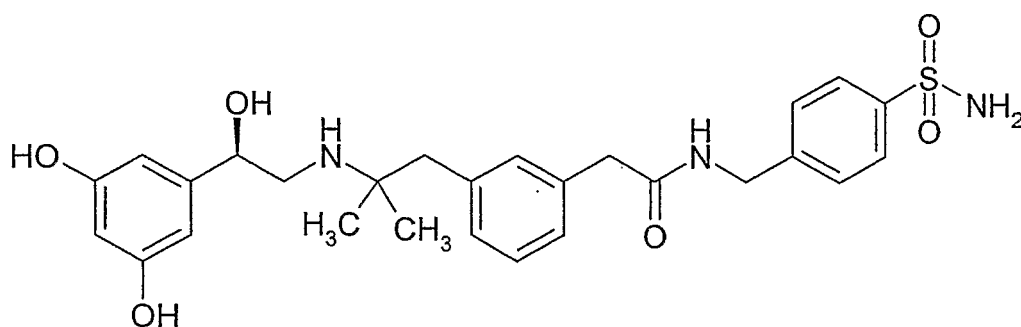
^1H NMR (400MHz, CD_3OD) δ 1.11 (3H, s), 1.12 (3H, s), 2.85 (4H, m), 3.60 (2H, s), 4.46 (2H, s), 4.61 (1H, m), 6.23 (1H, m), 6.38 (2H, s), 7.10 (1H, d), 7.22 (2H, m), 7.28 (1H, m), 7.34 (2H, d), 7.82 (2H, d).

LRMS: m/z electrospray 493 $[\text{M}+\text{H}^+]$, 491 $[\text{M}-\text{H}]$.

10

Example 73

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-sulfamoyl-benzyl)-acetamide



The title compound was prepared from the compound of preparation 102 using the method described for example 12 and was isolated as a white solid.

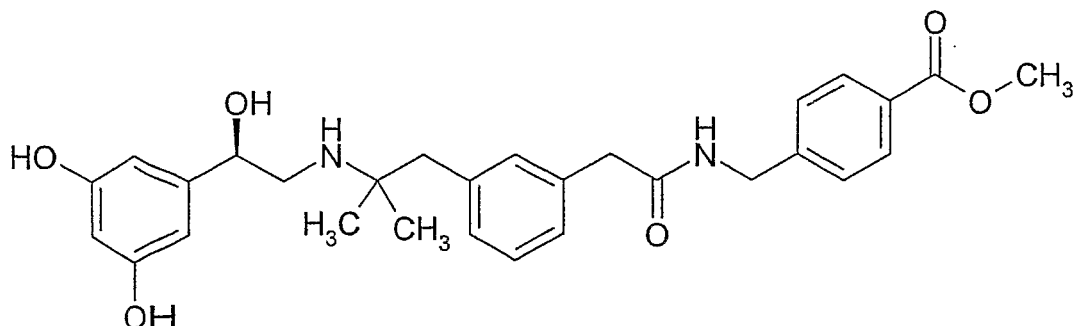
^1H NMR (400MHz, CD_3OD) δ 1.12 (3H, s), 1.13 (3H, s), 2.85 (4H, m), 3.60 (2H, s), 4.47 (2H, s), 4.61 (1H, m), 6.23 (1H, m), 6.38 (2H, s), 7.10 (1H, d), 7.22 (2H, m), 7.28 (1H, m), 7.40 (2H, d), 7.84 (2H, d).

LRMS: m/z electrospray 529 $[\text{M}+\text{H}^+]$, 527 $[\text{M}-\text{H}]$.

20

Example 74

4-[[2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetylamino]-methyl]-benzoic acid methyl ester



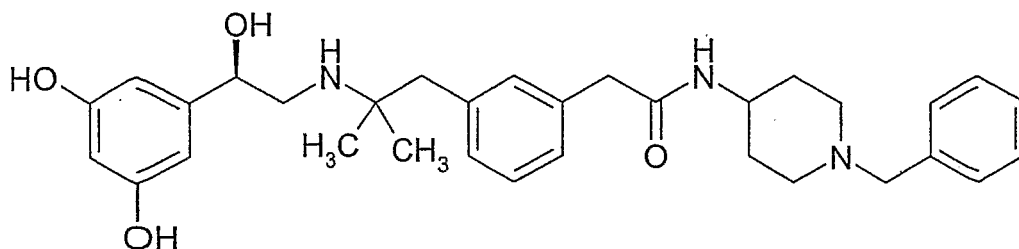
- 5 The title compound was prepared from the compound of preparation 103 using the method described for example 12 and was isolated as a white solid.

^1H NMR (400MHz, CD_3OD) δ 1.08 (3H, s), 1.10 (3H, s), 2.85 (4H, m), 3.60 (2H, s), 3.92 (3H, s), 4.47 (2H, s), 4.61 (1H, m), 6.22 (1H, m), 6.38 (2H, s), 7.09 (1H, d), 7.20 (2H, m), 7.28 (1H, m), 7.37 (2H, d), 7.95 (2H, d).

- 10 LRMS: m/z electrospray 508 $[\text{M}+\text{H}^+]$, 506 $[\text{M}-\text{H}]$.

Example 75

N-(1-Benzyl-piperidin-4-yl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide



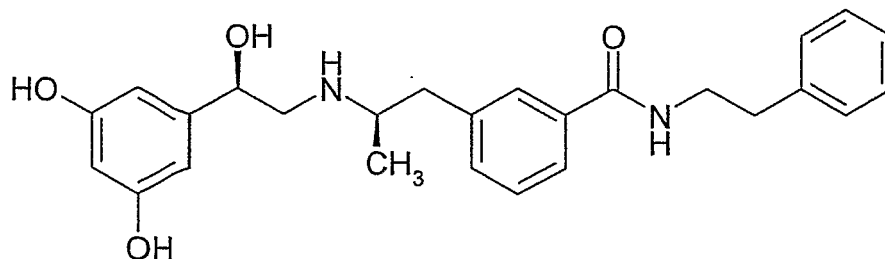
15

The title compound was prepared from the compound of preparation 104 using the method described for example 12 and was isolated as a white solid.

- ^1H NMR (400MHz, CD_3OD) δ 1.12 (3H, s), 1.13 (3H, s), 1.55 (2H, m), 1.87 (2H, m), 2.15 (2H, m), 2.80 (6H, m), 3.50 (2H, s), 3.55 (2H, s), 3.68 (1H, m), 4.61 (1H, m), 6.22 (1H, m), 6.37 (2H, s), 7.08 (1H, d), 7.18 (2H, m), 7.26 (2H, m), 7.35 (2H, s), 7.36 (2H, s).

20

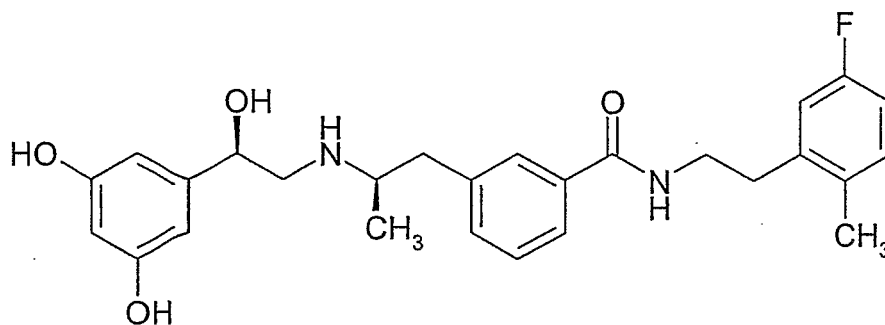
LRMS: m/z electrospray 533 $[\text{M}+\text{H}^+]$, 531 $[\text{M}-\text{H}]$.

Example 76**3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-phenethyl]-benzamide**

- 5 The title compound was prepared from the compound of preparation 105 using the method described for example 12 and was isolated as a white foam.

^1H NMR (400MHz, CD_3OD) δ 1.06 (3H, d), 2.62 (1H, m), 2.75 (1H, m), 2.80 (2H, m), 2.94 (3H, m), 3.58 (2H, t), 4.56 (1H, m), 6.16 (1H, m), 6.27 (2H, s), 7.18 (1H, m), 7.26 (6H, m), 7.57 (1H, s), 7.59 (1H, m).

- 10 LRMS: m/z APCI 435 $[\text{M}+\text{H}^+]$, 433 $[\text{M}-\text{H}]$.

Example 77**3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(5-fluoro-2-methyl-phenyl)-ethyl]-benzamide**

15

The title compound was prepared from the compound of preparation 106 using the method described for example 12 and was isolated as a white foam.

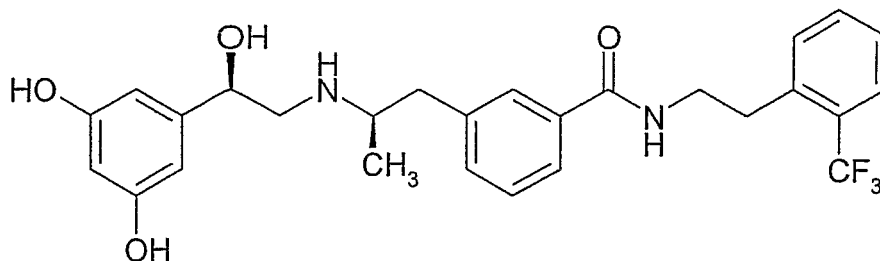
- ^1H NMR (400MHz, CD_3OD) δ 1.06 (3H, d), 2.33 (3H, s), 2.62 (1H, m), 2.76 (1H, m), 2.80 (2H, m), 2.94 (3H, m), 3.58 (2H, t), 4.55 (1H, m), 6.17 (1H, m), 6.26 (2H, s), 6.82 (1H, m), 6.93 (1H, m), 7.12 (1H, m), 7.35 (2H, m), 7.57 (1H, s), 7.61 (1H, m).

20

LRMS: m/z APCI 467 $[\text{M}+\text{H}^+]$, 465 $[\text{M}-\text{H}]$.

Example 78

3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-trifluoromethyl-phenyl)-ethyl]-benzamide



5

The title compound was prepared from the compound of preparation 107 using the method described for example 12 and was isolated as a white foam.

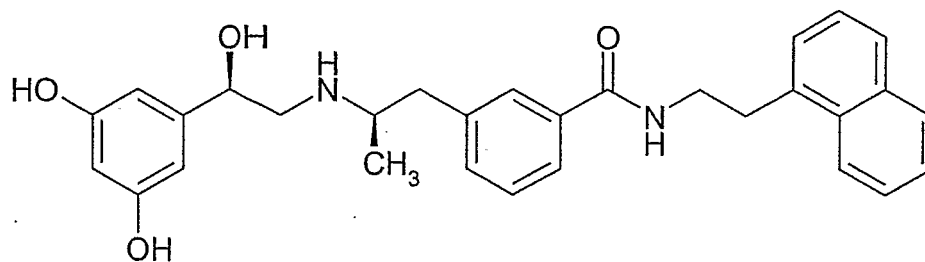
^1H NMR (400MHz, CD_3OD) δ 1.06 (3H, d), 2.62 (1H, m), 2.75 (1H, m), 2.82 (2H, m), 2.98 (1H, m), 3.12 (2H, t), 3.62 (2H, t), 4.56 (1H, m), 6.17 (1H, m),
10 6.26 (2H, s), 7.35 (3H, m), 7.50 (2H, m), 7.61 (3H, m).

LRMS: m/z APCI 503 $[\text{M}+\text{H}^+]$, 501 $[\text{M}-\text{H}]$.

Example 79

3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-(2-naphthalen-1-yl-ethyl)-benzamide

15



The title compound was prepared from the compound of preparation 108 using the method described for example 12 and was isolated as a white foam.

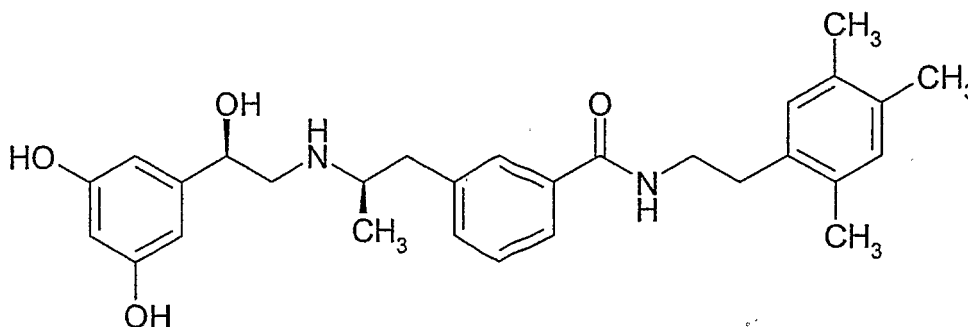
^1H NMR (400MHz, CD_3OD) δ 1.05 (3H, d), 2.60 (1H, m), 2.75 (3H, m), 2.96 (1H, m), 3.40 (2H, t), 3.70 (2H, t), 4.57 (1H, m), 6.17 (1H, m), 6.28 (2H, s), 7.35 (5H, m), 7.48 (3H, m), 7.59 (1H, m), 7.75 (1H, m), 7.84 (1H, m), 8.23 (1H, m).

20

LRMS: m/z APCI 485 $[\text{M}+\text{H}^+]$, 483 $[\text{M}-\text{H}]$.

Example 80

3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2,4,5-trimethyl-phenyl)-ethyl]-benzamide



5 The title compound was prepared from the compound of preparation 109 using the method described for example 12 and was isolated as a white foam.

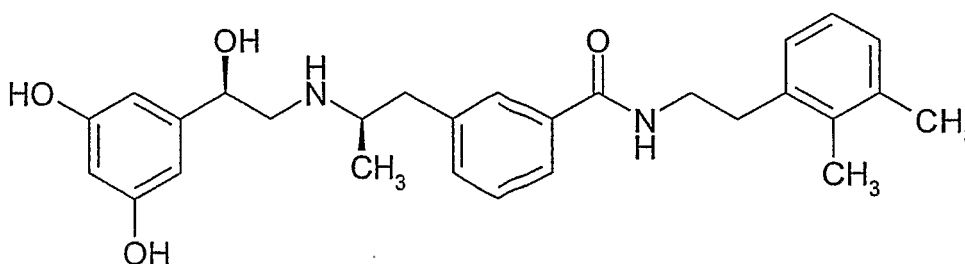
¹H NMR (400MHz, CD₃OD) δ 1.05 (3H, d), 2.17 (3H, s), 2.17 (6H, s), 2.27 (3H, s), 2.62 (1H, m), 2.75 (1H, m), 2.81 (4H, m), 2.98 (1H, m), 3.50 (2H, t), 4.55 (1H, m), 6.17 (1H, m), 6.26 (2H, s), 6.88 (1H, s), 6.91 (1H, s), 7.35 (2H, m).

10 7.38 (1H, s), 7.40 (1H, m).

LRMS: m/z APCI 477 [M+H⁺], 475 [M-H].

Example 81

3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2,3-
15 dimethyl-phenyl)-ethyl]-benzamide



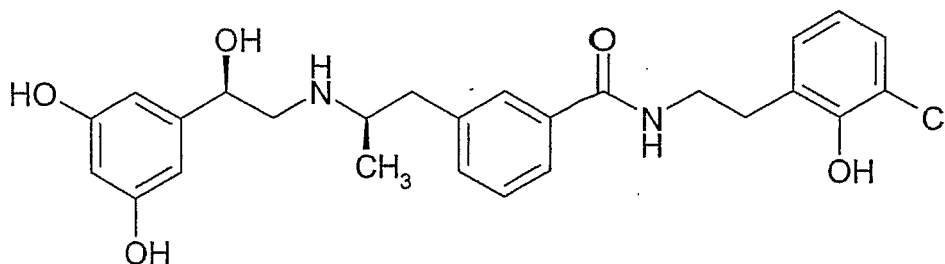
The title compound was prepared from the compound of preparation 110 using the method described for example 12 and was isolated as a white foam.

¹H NMR (400MHz, CD₃OD) δ 1.05 (3H, d), 2.26 (3H, s), 2.26 (3H, s), 2.62 (1H, m), 2.75 (1H, m), 2.81 (2H, m), 2.95 (3H, m), 3.54 (2H, t), 4.56 (1H, m), 6.17 (1H, m), 6.26 (2H, s), 6.98 (3H, m), 7.35 (2H, m), 7.38 (1H, s), 7.41 (1H, m).

LRMS: m/z APCI 463 [M+H⁺], 461 [M-H].

Example 82

3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-hydroxy-3-chloro-phenyl)-ethyl]-benzamide



5

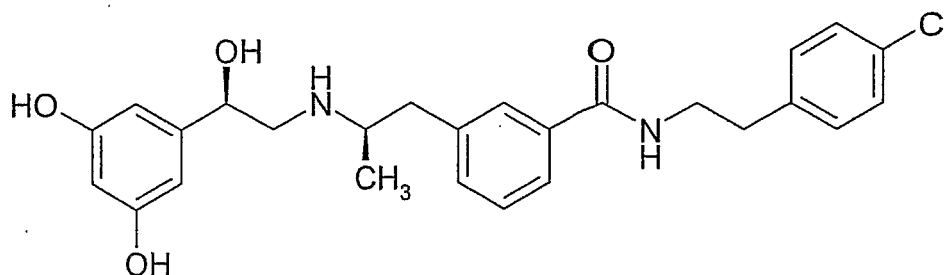
The title compound was prepared from the compound of preparation 111 using the method described for example 12 and was isolated as a white foam.

¹H NMR (400MHz, CD₃OD) δ 1.06 (3H, d), 2.62 (1H, m), 2.75 (1H, m), 2.81 (2H, m), 2.95 (3H, m), 3.60 (2H, t), 4.56 (1H, m), 6.17 (1H, m), 6.26 (2H, s),
10 6.74 (1H, m), 7.06 (1H, m), 7.17 (1H, m), 7.35 (2H, m), 7.57 (1H, s), 7.60 (1H, m).

LRMS: m/z APCI 485 [M+H⁺], 483 [M-H].

Example 83

15 **3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(4-chloro-phenyl)-ethyl]-benzamide**



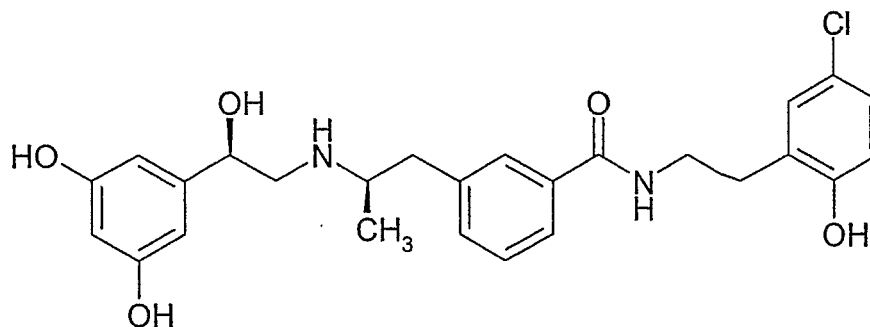
The title compound was prepared from the compound of preparation 112 using the method described for example 12 and was isolated as a white foam.

20 ¹H NMR (400MHz, CD₃OD) δ 1.05 (3H, d), 2.62 (1H, m), 2.75 (1H, m), 2.81 (2H, m), 2.95 (3H, m), 3.58 (2H, t), 4.56 (1H, m), 6.17 (1H, m), 6.26 (2H, s), 7.30 (6H, m), 7.58 (2H, m).

LRMS: m/z APCI 469 [M+H⁺], 467 [M-H].

Example 84

3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-hydroxy-5-chloro-phenyl)-ethyl]-benzamide



5

The title compound was prepared from the compound of preparation 113 using the method described for example 12 and was isolated as a white foam.

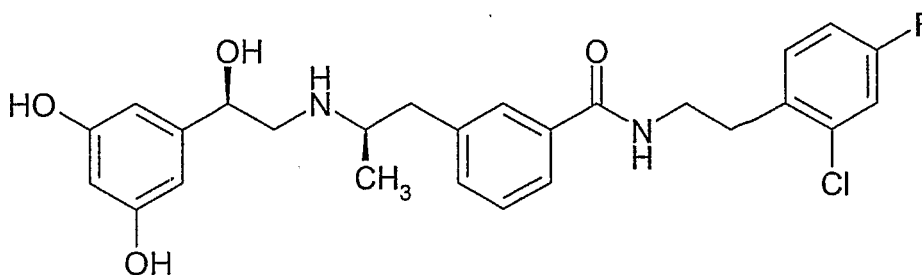
¹H NMR (400MHz, CD₃OD) δ 1.06 (3H, d), 2.63 (1H, m), 2.77 (1H, m), 2.86 (4H, m), 3.00 (1H, m), 3.58 (2H, t), 4.57 (1H, m), 6.17 (1H, m), 6.26 (2H, s), 6.78 (1H, m), 7.00 (1H, m), 7.09 (1H, m), 7.30 (2H, m), 7.57 (1H, s), 7.59 (1H, m).

10

LRMS: m/z APCI 485 [M+H⁺], 483 [M-H].

Example 85

3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-chloro-4-fluoro-phenyl)-ethyl]-benzamide



The title compound was prepared from the compound of preparation 114 using the method described for example 12 and was isolated as a white foam.

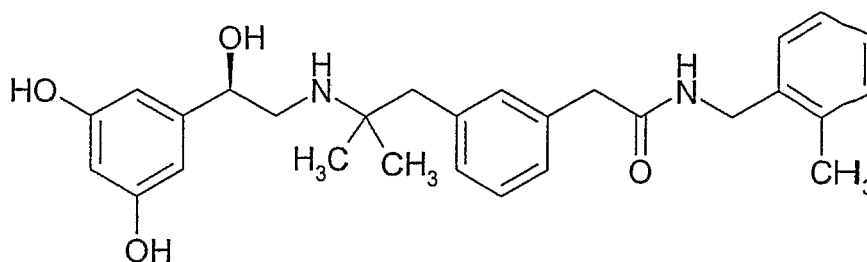
¹H NMR (400MHz, CD₃OD) δ 1.05 (3H, d), 2.62 (1H, m), 2.75 (1H, m), 2.83 (2H, m), 3.00 (1H, m), 3.05 (2H, t), 3.62 (2H, t), 4.56 (1H, m), 6.17 (1H, m), 6.26 (2H, s), 6.99 (1H, m), 7.19 (1H, m), 7.35 (3H, m), 7.60 (2H, m).

20

LRMS: m/z APCI 487 [M+H⁺], 485 [M-H].

Example 86

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2-methyl-benzyl)-acetamide



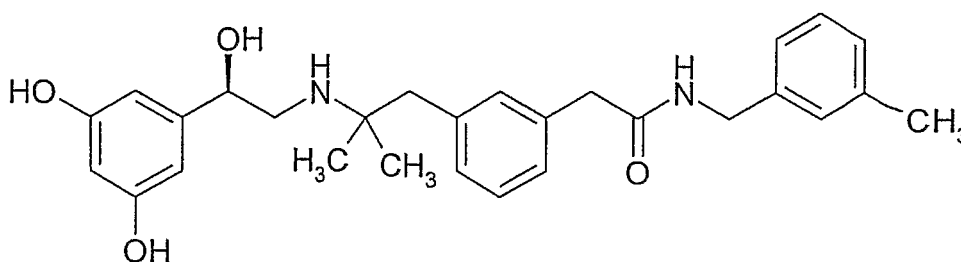
The title compound was prepared from the compound of preparation 115 using the method described for example 34 and was isolated as a white foam.

¹H NMR (400MHz, CD₃OD) δ 1.04 (3H, s), 1.05 (3H, s), 2.22 (3H, s), 2.73 (3H, m), 2.83 (1H, m), 3.56 (2H, s), 4.37 (2H, s), 4.55 (1H, m), 6.18 (1H, m), 6.36 (2H, s), 7.04 (1H, d), 7.10 (6H, m), 7.21 (1H, t).

LRMS: m/z electrospray 465 [M+H⁺], 462 [M-H].

Example 87

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(3-methyl-benzyl)-acetamide



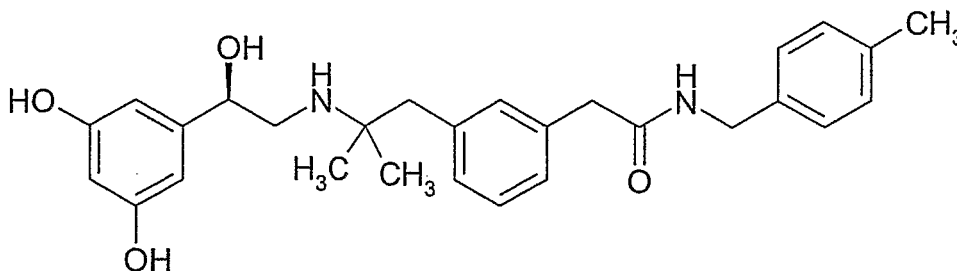
The title compound was prepared from the compound of preparation 116 using the method described for example 34 and was isolated as a white foam.

¹H NMR (400MHz, CD₃OD) δ 1.04 (3H, s), 1.05 (3H, s), 2.23 (3H, s), 2.73 (3H, m), 2.83 (1H, m), 3.56 (2H, s), 4.31 (2H, s), 4.55 (1H, m), 6.18 (1H, m), 6.36 (2H, s), 7.04 (4H, m), 7.15 (3H, m), 7.21 (1H, t).

LRMS: m/z electrospray 465 [M+H⁺], 462 [M-H].

Example 88

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-methyl-benzyl)-acetamide



5

The title compound was prepared from the compound of preparation 117 using the method described for example 34 and was isolated as a white foam.

^1H NMR (400MHz, CD_3OD) δ 1.04 (3H, s), 1.05 (3H, s), 2.27 (3H, s), 2.73 (3H, m), 2.83 (1H, m), 3.56 (2H, s), 4.28 (2H, s), 4.55 (1H, m), 6.18 (1H, m), 6.36 (2H, s), 7.04 (1H, d), 7.10 (5H, m), 7.17 (1H, d), 7.22 (1H, m).

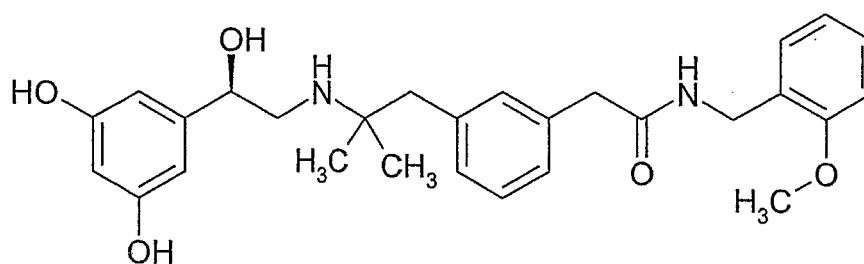
10

LRMS: m/z electrospray 465 $[\text{M}+\text{H}^+]$, 462 $[\text{M}-\text{H}]$.

Example 89

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2-methoxy-benzyl)-acetamide

15



The title compound was prepared from the compound of preparation 118 using the method described for example 34 and was isolated as a white foam.

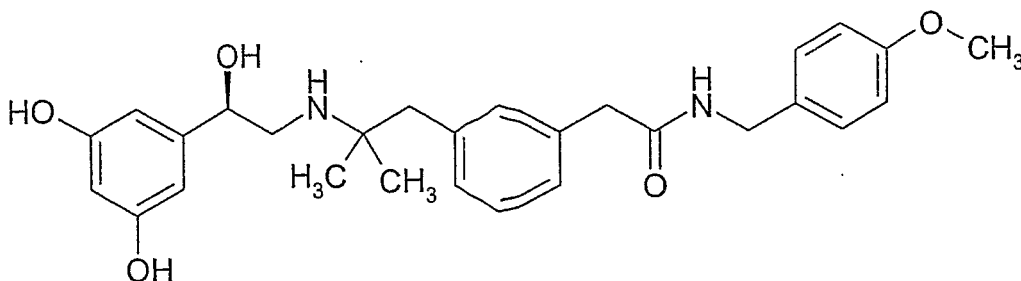
^1H NMR (400MHz, CD_3OD) δ 1.04 (3H, s), 1.05 (3H, s), 2.68 (2H, t), 2.77 (1H, m), 2.83 (1H, m), 3.56 (2H, s), 3.79 (3H, s), 4.37 (2H, s), 4.55 (1H, m), 6.18 (1H, m), 6.37 (2H, s), 6.82 (1H, m), 6.92 (1H, d), 7.03 (1H, d), 7.12 (3H, m), 7.22 (2H, m).

20

LRMS: m/z electrospray 480 $[\text{M}+\text{H}^+]$, 478 $[\text{M}-\text{H}]$.

Example 90

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-methoxy-benzyl)-acetamide



5

The title compound was prepared from the compound of preparation 119 using the method described for example 34 and was isolated as a white foam.

^1H NMR (400MHz, CD_3OD) δ 1.04 (3H, s), 1.05 (3H, s), 2.68 (3H, m), 2.83 (1H, m), 3.56 (2H, s), 3.77 (3H, s), 4.27 (2H, s), 4.55 (1H, m), 6.18 (1H, m), 6.36 (2H, s), 6.92 (2H, d), 7.04 (2H, d), 7.17 (4H, m), 7.21 (1H, m).

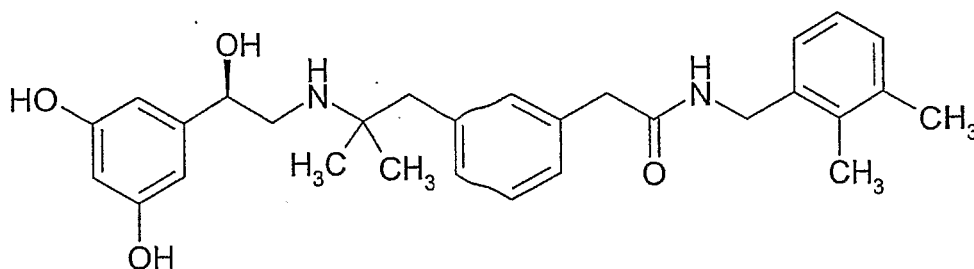
10

LRMS: m/z electrospray 481 $[\text{M}+\text{H}^+]$, 478 $[\text{M}-\text{H}]$.

Example 91

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2,3-dimethyl-benzyl)-acetamide

15



The title compound was prepared from the compound of preparation 120 using the method described for example 34 and was isolated as a white foam.

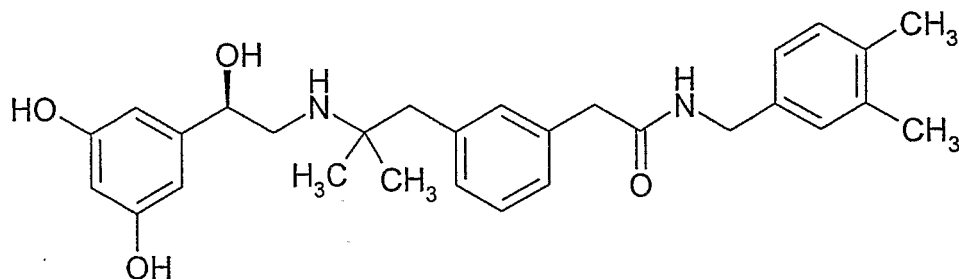
^1H NMR (400MHz, CD_3OD) δ 1.04 (3H, s), 1.05 (3H, s), 2.15 (3H, s), 2.24 (3H, s), 2.68 (3H, m), 2.83 (1H, m), 3.53 (2H, s), 4.37 (2H, s), 4.55 (1H, m), 6.18 (1H, m), 6.36 (2H, s), 7.02 (1H, d), 7.08 (3H, m), 7.11 (1H, m), 7.17 (1H, d), 7.21 (1H, m).

20

LRMS: m/z electrospray 478 $[\text{M}+\text{H}^+]$, 476 $[\text{M}-\text{H}]$.

Example 92

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(3,4-dimethyl-benzyl)-acetamide



5

The title compound was prepared from the compound of preparation 121 using the method described for example 34 and was isolated as a white foam.

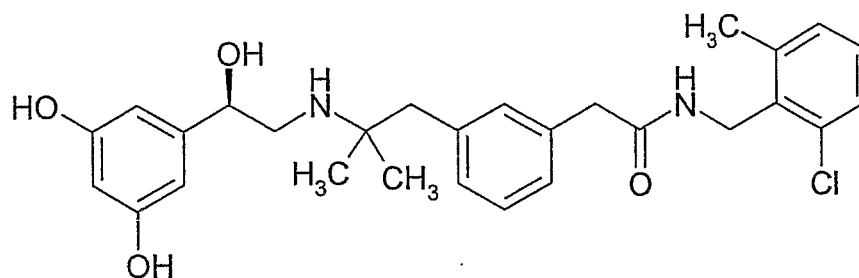
^1H NMR (400MHz, CD_3OD) δ 1.04 (3H, s), 1.05 (3H, s), 2.19 (3H, s), 2.19 (3H, s), 2.68 (3H, m), 2.83 (1H, m), 3.54 (2H, s), 4.27 (2H, s), 4.55 (1H, m), 6.18 (1H, m), 6.36 (2H, s), 6.96 (1H, d), 6.97 (1H, s), 7.06 (2H, m), 7.11 (1H, m), 7.18 (1H, m), 7.21 (1H, m).

10

LRMS: m/z electrospray 477 $[\text{M}+\text{H}^+]$, 475 $[\text{M}-\text{H}]$.

Example 93

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2-chloro-6-methyl-benzyl)-acetamide



The title compound was prepared from the compound of preparation 122 using the method described for example 34 and was isolated as a white foam.

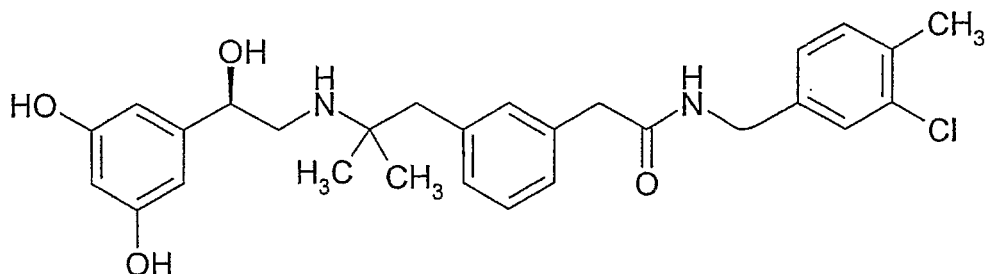
^1H NMR (400MHz, CD_3OD) δ 1.04 (3H, s), 1.05 (3H, s), 2.37 (3H, s), 2.68 (3H, m), 2.83 (1H, m), 3.47 (2H, s), 4.53 (2H, s), 4.55 (1H, m), 6.18 (1H, m), 6.36 (2H, s), 7.04 (1H, d), 7.09 (1H, m), 7.18 (4H, m), 7.21 (1H, m).

20

LRMS: m/z electrospray 497 $[\text{M}+\text{H}^+]$.

Example 94

2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(3-chloro-4-methyl-benzyl)-acetamide



5

The title compound was prepared from the compound of preparation 123 using the method described for example 34 and was isolated as a white foam.

^1H NMR (400MHz, CD_3OD) δ 1.04 (3H, s), 1.05 (3H, s), 2.31 (3H, s), 2.68 (3H, m), 2.83 (1H, m), 3.56 (2H, s), 4.28 (2H, s), 4.53 (1H, m), 6.18 (1H, m), 6.36 (2H, s), 7.04 (1H, d), 7.11 (1H, s), 7.18 (1H, m), 7.21 (4H, m).

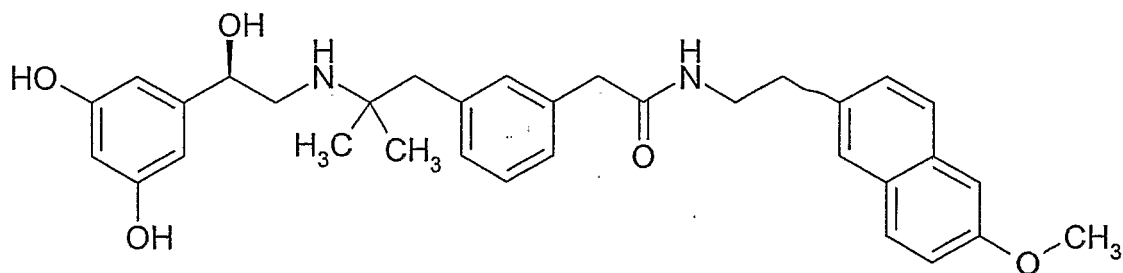
10

LRMS: m/z electrospray 497 $[\text{M}+\text{H}^+]$.

Example 95

2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]-2-methylpropyl}phenyl)-N-[2-(6-methoxynaphthalen-2-yl)ethyl]acetamide

15



The title compound was prepared from the compound of preparation 124 using the method described for example 34 and was isolated as a white foam.

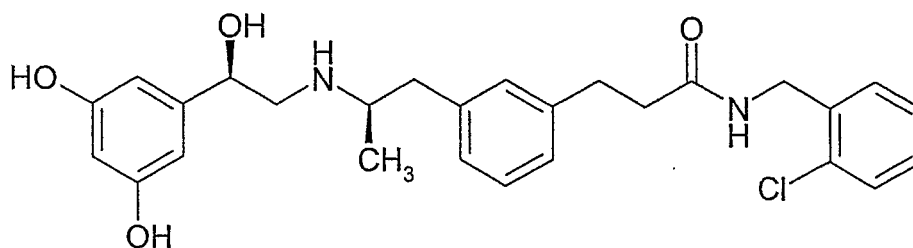
^1H NMR (400MHz, CD_3OD) δ 1.07 (3H, s), 1.07 (3H, s), 2.63 (2H, m), 2.81 (2H, m), 3.44 (2H, s), 3.51 (2H, m), 3.64 (2H, s), 3.87 (3H, s), 4.58 (1H, m), 6.18 (1H, m), 6.36 (2H, s), 7.04 (6H, m), 7.24 (1H, d), 7.47 (1H, s), 7.63 (2H, m).

20

LRMS: m/z electrospray 543 $[\text{M}+\text{H}^+]$.

Example 96

N-(2-Chlorobenzyl)-3-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)propionamide



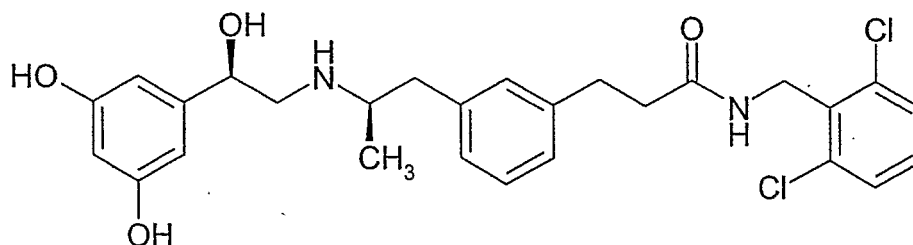
5 Prepared according to the procedure used for example 12, using preparation 142.

^1H NMR (400MHz, CD_3OD) 1.04 (3H, d), 2.50-2.72 (3H, m), 2.65-2.75 (2H, m), 2.76-2.85 (1H, m), 2.86-2.95 (3H, m), 4.40 (2H, s), 4.53 (1H, m), 6.16 (1H, m), 6.26 (2H, s), 6.94-7.08 (4H, m), 7.13-7.24 (3H, m), 7.35 (1H, m) ; LRMS APCI

10 m/z 483 $[\text{M}+\text{H}]^+$

Example 97

N-(2,6-Dichlorobenzyl)-3-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)propionamide



15

Prepared according to the procedure used for example 12, using preparation 143.

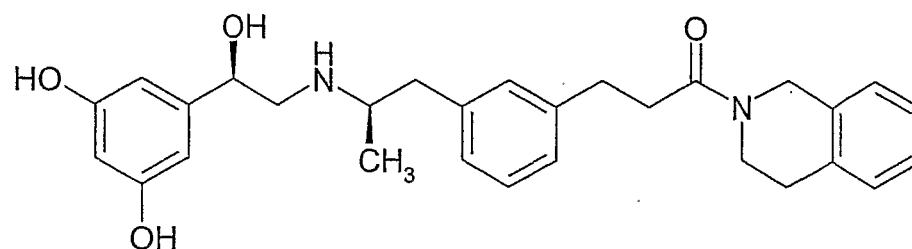
^1H NMR (400MHz, CD_3OD) δ : 1.04 (3H, d), 2.42-2.58 (3H, m), 2.62-2.75 (2H, m), 2.76-2.95 (4H, m), 4.53 (1H, m), 4.62 (2H, s), 6.16 (1H, m), 6.25 (2H, s), 6.92 (1H, m), 6.96 (1H, s), 7.01 (1H, m), 7.13 (1H, t), 7.26 (1H, t), 7.38 (2H, m) ;

20

LRMS APCI m/z 517 $[\text{M}+\text{H}]^+$

Example 98

1-(3,4-Dihydro-1H-isoquinolin-2-yl)-3-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)propan-1-one

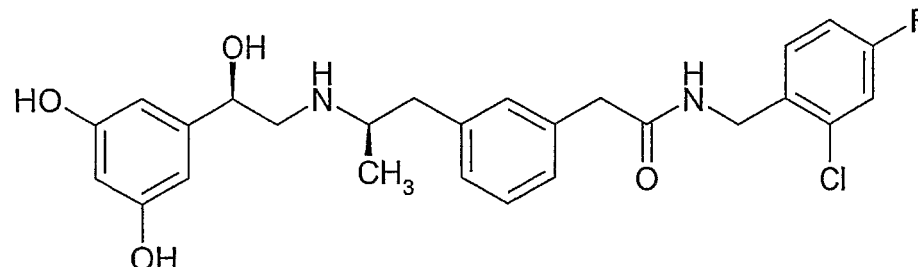


Prepared according to the procedure used for example 12, using preparation
5 144.

^1H NMR (400MHz, CD_3OD) δ : 1.03 (3H, d), 2.65-2.95 (11H, m), 3.62-3.75 (2H, m), 4.46-4.68 (3H, m), 6.16 (1H, m), 6.24 (2H, s), 6.84-7.19 (8H, m); LRMS APCI m/z 475 $[\text{M}+\text{H}]^+$

10 **Example 99**

N-(2-Chloro-4-fluorobenzyl)-2-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)acetamide



The title compound was prepared from the compound of preparation 145 using
15 the method described for example 34.

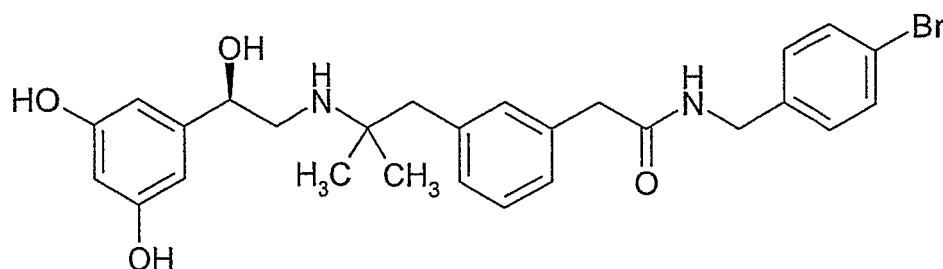
^1H NMR (400MHz, CD_3OD) δ 1.00 (3H, d), 2.60-2.65 (1H, m), 2.64-2.68 (2H, m), 2.83-2.93 (1H, m), 3.48 (2H, s), 4.86 (2H, s), 4.47-4.50 (1H, m), 6.11 (1H, s), 6.21 (2H, m), 6.99-7.83 (7H, m).

LRMS: m/z APCI 687 $[\text{M}+\text{H}]^+$.

20

Example 100

N-(4-Bromobenzyl)-2-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]-2-methylpropyl}phenyl)acetamide

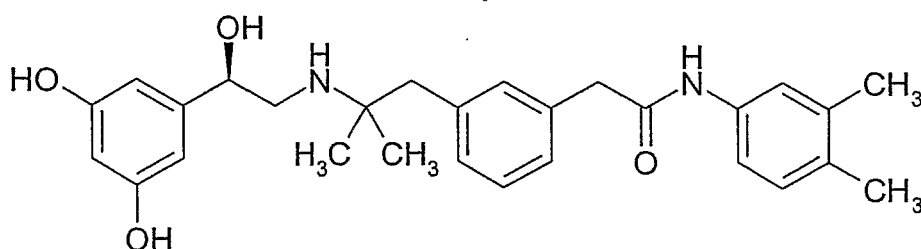


The title compound was prepared from the compound of preparation 146 using the method described for example 34.

¹H NMR (400MHz, CD₃OD) δ: 1.07 (d, 6H), 2.63-2.78 (m, 3H), 2.84 (t, 1H), 3.57 (s, 2H), 4.31 (s, 2H), 4.53-4.57 (m, 1H), 6.18 (s, 1H), 6.37 (s, 2H), 7.05 (d, 1H), 7.16 (t, 4H), 7.22 (t, 1H), 7.42 (d, 2H); LRMS APCI m/z 529 [M+H]⁺.

Example 101

2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]-2-methylpropyl}phenyl)-N-(3,4-dimethylphenyl)acetamide

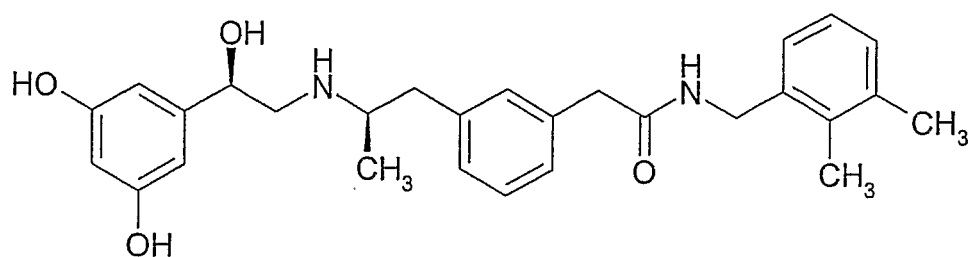


The title compound was prepared from the compound of preparation 147 using the method described for example 34.

¹H NMR (400MHz, CD₃OD) δ: 1.05 (d, 6H), 2.22 (d, 6H), 2.66-2.78 (m, 3H), 2.83 (t, 1H), 3.62 (s, 2H), 4.56-4.59 (m, 1H), 6.18 (s, 1H), 6.32 (s, 2H), 7.04 (t, 2H), 7.18-7.24 (m, 4H), 7.31 (s, 1H); LRMS APCI m/z 463 [M+H]⁺.

Example 102

2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)-N-(2,3-dimethylbenzyl)acetamide

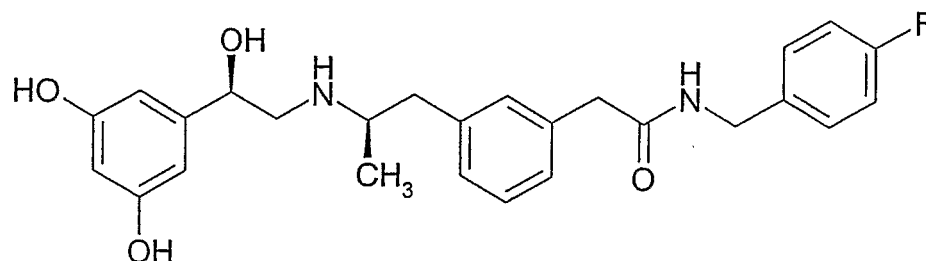


The title compound was prepared from the compound of preparation 148 using the method described for example 12.

¹H NMR (400MHz, CD₃OD) δ: 0.99 (3H, s), 2.20 (3H, s), 2.48 (1H, dd), 2.61-2.67 (2H, m), 2.72 (1H, dd), 2.80 (1H, dt), 3.45 (2H, s), 4.31 (2H, s), 4.44 (1H, dd), 6.09 (1H, t), 6.19 (1H, s), 6.20 (1H, s), 6.92-7.17 (7H, m); LRMS APCI m/z 462 [M+H]⁺.

Example 103

2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)-N-(4-fluorobenzyl)acetamide

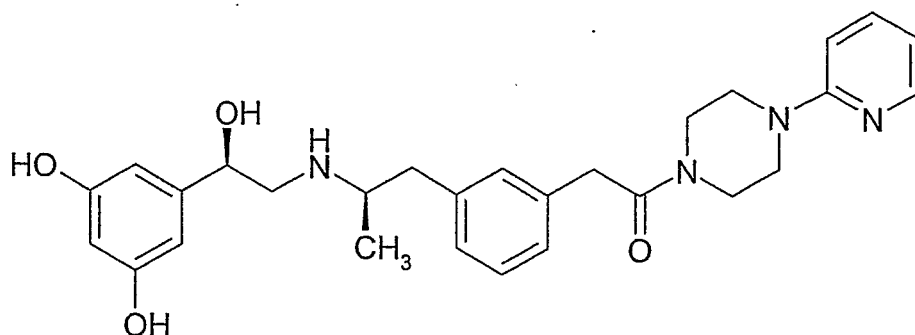


The title compound was prepared from the compound of preparation 149 using the method described for example 12.

¹H NMR (400MHz, CD₃OD) δ: 0.99 (3H, d), 2.49 (1H, dd), 2.60-2.66 (2H, m), 2.74 (1H, dd), 2.82-2.89 (1H, m), 3.46 (2H, s), 4.27 (2H, s), 4.46 (1H, dd), 6.12 (1H, t), 6.21 (1H, s), 6.22 (1H, s), 6.91-6.98 (3H, m), 7.02-7.07 (2H, m), 7.03-7.21 (3H, m); LRMS APCI m/z 451 [M+H]⁺.

Example 104

2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)-1-(4-pyridin-2-ylpiperazin-1-yl)ethanone

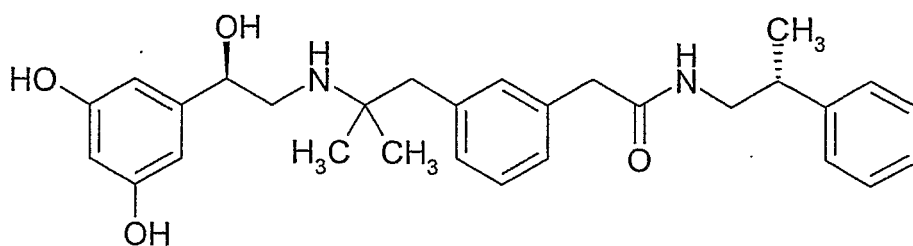


The title compound was prepared from the compound of preparation 150 using the method described for example 12.

¹H NMR (400MHz, CD₃OD) δ: 1.05 (3H, d), 2.59 (1H, dd), 2.78-2.93 (3H, m),
 5 3.08-3.15 (1H, m), 3.31 (2H, t), 3.41 (2H, t), 3.59 (2H, t), 3.66 (2H, t), 3.77 (2H, s), 4.55 (1H, dd), 6.13 (1H, t), 6.25 (1H, s), 6.26 (1H, s), 6.62-6.65 (1H, m), 6.73 (1H, d), 7.02-7.11 (3H, m), 7.20 (1H, t), 7.48 (1H, dt), 8.01 (1H, bd); LRMS APCI m/z 491 [M+H]⁺.

10 Example 105

2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]-2-methylpropyl} phenyl)-N-(2-phenylpropyl)acetamide



15 The title compound was prepared from the compound of preparation 151 using the method described for example 12.

¹H NMR (400MHZ, CD₃OD) δ: 0.92 (3H, D), 1.06 (3H, D), 2.40 (1H, DD), 2.53-2.59 (2H, M), 2.66 (1H, DD), 2.74-2.83 (2H, M), 3.14-3.24 (2H, M), 3.27 (2H, S), 4.38 (1H, DD), 6.02 (1H, T), 6.13 (1H, S), 6.13 (1H, S), 6.83-6.90 (2H, M), 6.98-
 20 7.07 (4H, M), 7.08-7.13 92H, M); LRMS APCI M/Z 463 [M+H]⁺.

The ability of the compounds of the formula (1) to act as potent β_2 agonists therefore mediating smooth muscle relaxation may be determined by the measure of the effect of beta-2 adrenergic receptor stimulation on electrical field stimulated-contraction of guinea pig trachea strips.

5 Guinea-pig trachea

Male, Dunkin-Hartley guinea pigs (475-525g) are killed by CO₂ asphyxiation and exsanguination from the femoral artery and the trachea is isolated. Four preparations are obtained from each animal, starting the dissection immediately below the larynx and taking 2.5 cm length of trachea. The piece of trachea is
10 opened by cutting the cartilage opposite the trachealis muscle, then transverse sections, 3-4 cartilage rings wide, are cut. The resulting strip preparations are suspended in 5 ml organ baths using cotton threads tied through the upper and lower cartilage bands. The strips are equilibrated, un-tensioned, for 20 minutes in a modified Krebs Ringer buffer (Sigma K0507) containing 3 μ M Indomethacin
15 (Sigma I7378), 10 μ M Guanethidine (Sigma G8520) and 10 μ M Atenolol (Sigma A7655), heated at 37°C and gassed with 95% O₂/5% CO₂, before applying an initial tension of 1 g. The preparations are allowed to equilibrate for a further 30-45 minutes, during which time they are re-tensioned (to 1 g) twice at 15-minute intervals. Changes in tension are recorded and monitored via standard
20 isometric transducers coupled to a data-collection system (custom-designed at Pfizer). Following the tensioning equilibration, the tissues are subjected to electrical field stimulation (EFS) using the following parameters : 10 s trains every 2 minutes, 0.1 ms pulse width, 10 Hz and just-maximal voltage (25 Volts) continuously throughout the length of the experiment. EFS of post-ganglionic
25 cholinergic nerves in the trachea results in monophasic contractions of the smooth muscle and twitch height is recorded. The organ baths are constantly perfused with the above-described Krebs Ringer buffer by means of a peristaltic pump system (pump flow rate 7.5 ml / minute) throughout the experiment, with the exception of when a beta-2 agonist according to the
30 present invention is added, the pump is then stopped for the time of the

cumulative dosing to the bath and started again after maximal response is reached for the wash-out period.

Experimental protocol for assessment of potency and efficacy

Following equilibration to EFS, the peristaltic pump is stopped and the
5 preparations 'primed' with a single dose of 300 nM isoprenaline (Sigma I5627)
to establish a maximal response in terms of inhibition of the contractile EFS
response. The isoprenaline is then washed out over a period of 40 minutes.
Following the priming and wash-out recovery, a standard curve to isoprenaline
is carried out on all tissues (Isoprenaline Curve 1) by means of cumulative,
10 bolus addition to the bath using half log increments in concentration. The
concentration range used is 10^{-9} to 10^{-6} M. At the end of the isoprenaline
curve the preparations are washed again for 40 minutes before commencing a
second curve, either to isoprenaline (as internal control) or a beta-2 agonist
according to the present invention. Beta-2 agonist responses are expressed as
15 percentage inhibition of the EFS response. Data for beta-2 agonist are
normalised by expressing inhibition as a percentage of the maximal inhibition
induced by isoprenaline in Curve 1. The EC_{50} value for beta-2 agonist
according to the present invention refers to the concentration of compound
required to produce half maximal effect. Data for beta-2 agonists according to
20 the present invention are then expressed as relative potency to isoprenaline
defined by the ratio (EC_{50} beta-2 agonist)/(EC_{50} Isoprenaline).

Confirmation of beta-2 mediated functional activity

Beta-2 agonist activity of test compounds is confirmed using the protocol
above, however, prior to constructing the curve to beta-2 agonist according to
25 the present invention, the preparations are pre-incubated (for a minimum of
45 minutes) with 300 nM ICI 118551 (a selective β_2 antagonist) which results in
the case of a beta-2 mediated effect in a rightward-shift of the test compound
dose response curve.

According to another alternative, the agonist potency for the β_2 receptor
30 of the compounds of the formula (1) may also be determined by the measure of

the concentration of compound according to the present invention required to produce half maximal effect (EC_{50}) for the β_2 receptor.

Compound Preparation

10 mM/100% DMSO (dimethylsulfoxide) stock of compound is diluted to
5 required top dose in 4 % DMSO. This top dose is used to construct a 10-point semi-log dilution curve, all in 4 % DMSO. Isoprenaline (Sigma, I-5627) was used as a standard in every experiment and for control wells on each plate. Data was expressed as % Isoprenaline response.

Cell Culture

10 CHO (Chinese Hamster Ovary) cells recombinantly expressing the human β_2 adrenergic receptor (from Kobilka et al., PNAS 84: 46-50, 1987 and Bouvier et al., Mol Pharmacol 33: 133-139 1988 CHO β_2) were grown in Dulbeccos MEM/ NUT MIX F12 (Gibco, 21331-020) supplemented with 10 % foetal bovine serum (Sigma, F4135, Lot 90K8404 Exp 09/04), 2 mM glutamine (Sigma, G7513),
15 500 μ g/ml geneticin (Sigma, G7034) and 10 μ g/ml puromycin (Sigma, P8833). Cells were seeded to give about 90 % confluency for testing.

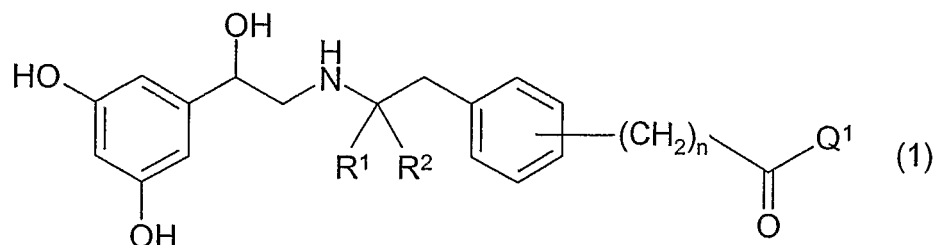
Assay Method

25 μ l / well each dose of compound was transferred into a cAMP- Flashplate® (NEN, SMP004B), with 1% DMSO as basal controls and 100 nM Isoprenaline
20 as max controls. This was diluted 1:2 by the addition of 25 μ l / well PBS. Cells were trypsinised (0.25% Sigma, T4049), washed with PBS (Gibco, 14040-174) and resuspended in stimulation buffer (NEN, SMP004B) to give 1×10^6 cells / ml CHO β_2 . Compounds were incubated with 50 μ l / well cells for 1 hour. Cells were then lysed by the addition of 100 μ l / well detection buffer (NEN,
25 SMP004B) containing 0.18 μ Ci / ml 125 I-cAMP (NEN, NEX-130) and plates were incubated at room temperature for a further 2 hours. The amount of 125 I-cAMP bound to the Flashplate® was quantified using a Topcount NXT (Packard), normal counting efficiency for 1 minute. Dose-response data was expressed as % Isoprenaline activity and fitted using a four parameter sigmoid fit.

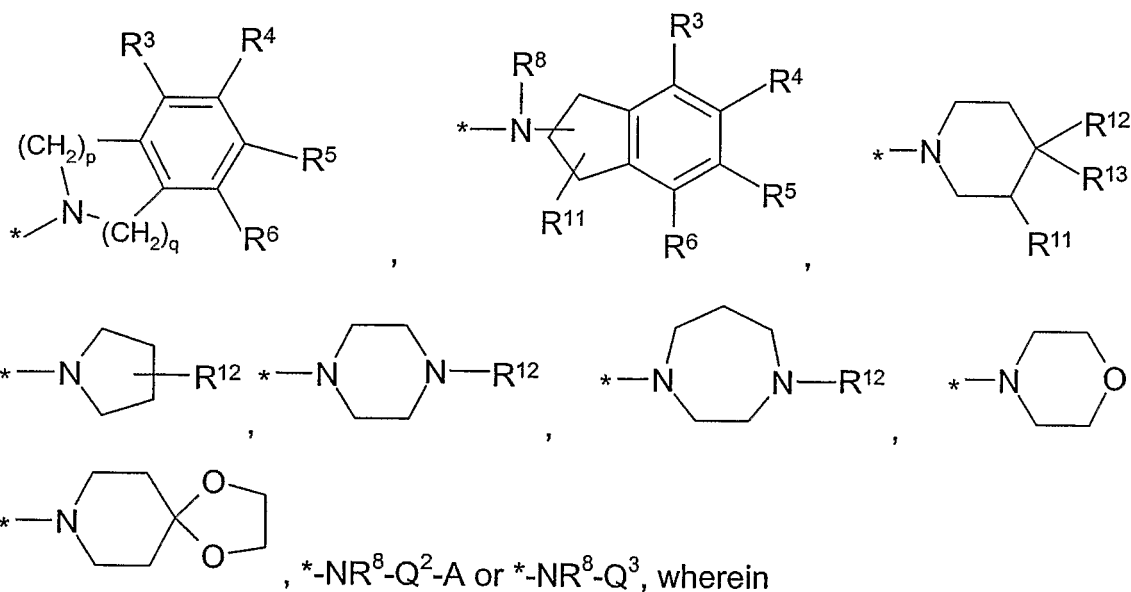
It has thus been found that the compounds of formula (1) according to the present invention that are illustrated in examples 1 to 105 show a $\beta 2$ cAMP EC_{50} below 30nM.

CLAIMS

1. A compound of general formula (1),

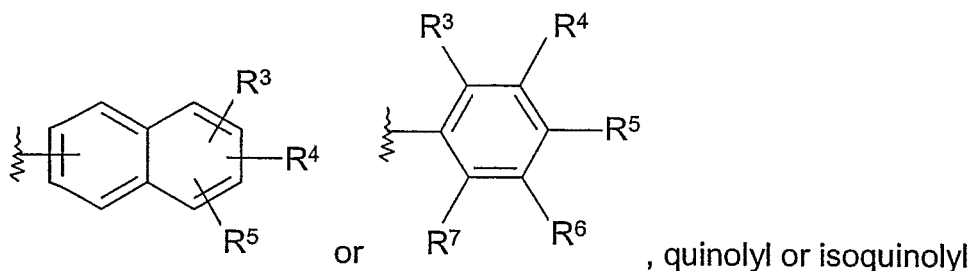


- 5 wherein the $(\text{CH}_2)_n\text{-C}(=\text{O})\text{Q}^1$ group is in the meta or para position,
 - R^1 and R^2 are independently selected from H and $\text{C}_1\text{-C}_4$ alkyl,
 - n is 0, 1 or 2 and
 - Q^1 is a group selected from,

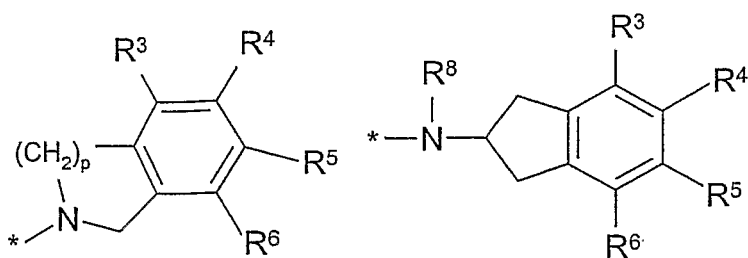


- p is 1 or 2 and q is 1 or 2,
 - Q^2 is a single bond or a $\text{C}_1\text{-C}_4$ alkylene optionally substituted with OH,
 - R^8 is H or $\text{C}_1\text{-C}_4$ alkyl and,
 15 - Q^3 is $\text{C}_1\text{-C}_6$ alkyl optionally substituted with NR^9R^{10} , OR^9 or phenoxy,
 - A is selected from:
 o $\text{C}_3\text{-C}_{10}$ cycloalkyl, said cycloalkyl being optionally bridged by or more carbon atoms, and being optionally substituted with one hydroxy group,

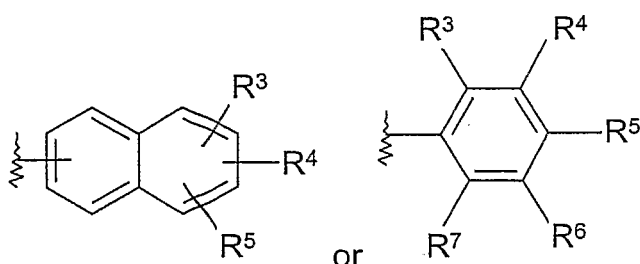
- a 5 to 6 membered heterocyclic group, optionally aromatic, containing one or two heteroatoms selected from O, N or S, optionally substituted by one or two substituents selected from C₁-C₄ alkyl, benzyl and cyclopropylmethyl or
- 5 ○ a group



- R³, R⁴, R⁵, R⁶ and R⁷ are the same or different and are selected from H, C₁-C₄ alkyl, OR⁹, SR⁹, SOR⁹, SO₂R⁹, halo, CN, CF₃, OCF₃, SO₂NR⁹R¹⁰, COOR⁹, CONR⁹R¹⁰, NR⁹R¹⁰, NHCOR¹⁰ and phenyl optionally substituted with OH;
- 10 - R⁹ and R¹⁰ are the same or different and are selected from H or C₁-C₄ alkyl,
- R¹¹ is selected from H or OH, and,
- R¹² and R¹³ are the same or different and are selected from H, C₁-C₄ alkyl optionally substituted with OR⁹, OR⁹, C(=O)NH₂, C(=O)CH₃, N(CH₃)C(=O)CH₃, C(=O)OR⁹, phenyl optionally substituted with halogen, pyridyl optionally
- 15 substituted with CN, oxadiazolyl optionally substituted with C₁-C₄ alkyl, and,
- * represents the attachment point to the carbonyl group;
- or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof.
- 20 2. A compound of general formula (1) according to claim 1, wherein the (CH₂)_n-C(=O)Q¹ group is in the meta or para position,
- R¹ and R² are independently selected from H and C₁-C₄ alkyl;
- n is 0, 1 or 2;
- Q¹ is a group selected from,

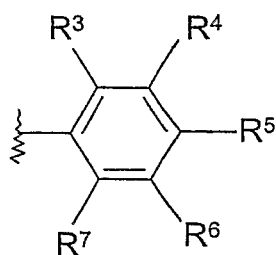


- and a group $^*\text{-NR}^8\text{-Q}^2\text{-A}$, wherein p is 1 or 2, Q^2 is a $\text{C}_1\text{-C}_4$ alkylene, R^8 is H or $\text{C}_1\text{-C}_4$ alkyl and A is pyridyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, said cycloalkyl being optionally bridged by 1, 2, 3 or 4 carbon atoms, tetrahydropyranyl, piperidinyl, 5 tetrahydrothiopyranyl or a group



- R^3 , R^4 , R^5 , R^6 and R^7 are the same or different and are selected from H, $\text{C}_1\text{-C}_4$ alkyl, OR^9 , SR^9 , SOR^9 , SO_2R^9 , halo, CN, CF_3 , OCF_3 , $\text{SO}_2\text{NR}^9\text{R}^{10}$, COOR^9 , $\text{CONR}^9\text{R}^{10}$, NR^9R^{10} , NHCOR^{10} and phenyl optionally substituted with OH;
10 - R^9 and R^{10} are the same or different and are selected from H or $\text{C}_1\text{-C}_4$ alkyl and the * represents the attachment point to the carbonyl group;
or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof.

3. A compound according to claim 1 or 2 wherein Q^1 is a group $^*\text{-NH-Q}^2\text{-A}$,
15 wherein A is cyclohexyl or adamantyl.
4. A compound according to claim 1 or 2 wherein A is naphthyl optionally substituted with OR^9 .
5. A compound according to claim 2 wherein Q^1 is a group $^*\text{-NH-Q}^2\text{-A}$, wherein A is a group

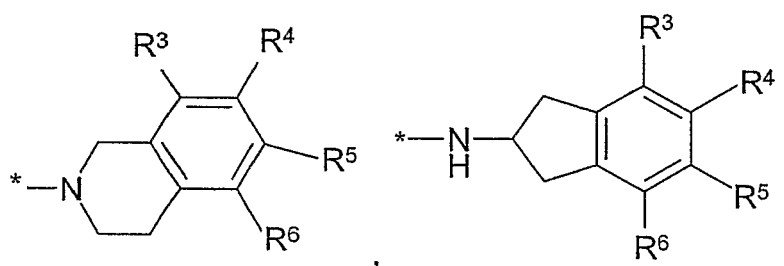


wherein R^3 , R^4 , R^5 , R^6 and R^7 are the same or different and are selected from H, C_1 - C_4 alkyl, OR^9 , SR^9 , halo, CN, CF_3 , OCF_3 , $SO_2NR^9R^{10}$, $COOR^9$, $CONR^9R^{10}$, NR^9R^{10} , $NHCOR^{10}$ and phenyl optionally substituted with OH,
 5 provided at least 2 of R^3 to R^7 are equal to H;

wherein R^9 and R^{10} are the same or different and are selected from H or C_1 - C_4 alkyl.

6. A compound according to any one of claims 1 to 5 wherein Q^2 is $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH(CH_3)-$, $-CH_2CH(CH_3)-$ or $C(CH_3)_2-$.

10 7. A compound according to claim 1 or 2 wherein Q^1 is



wherein R_3 , R_4 , R_5 and R_6 are H.

8. A compound according to any one of claims 1 to 7 wherein R^1 is H or CH_3 and R^2 is CH_3 .

15 9. A compound according to any one of claim 1 to 8 wherein n is 0 or 1.

10. The (R,R)-stereoisomer of a compound according to any one of claims 1 to 9.

11. A compound according to any one of claim 1 to 10 wherein the $(\text{CH}_2)_n\text{-C(=O)Q}^1$ group is in the meta position.
12. A compound according to claim 1 selected from the group consisting of
- 5 *N*-benzyl-2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]acetamide;
 - N*-cyclopropyl-2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]acetamide;
 - 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-[(1*R*,2*S*)-2-(hydroxymethyl)cyclohexyl]acetamide;
 - 10 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(3-morpholin-4-ylpropyl)acetamide;
 - 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(pyridin-2-ylmethyl)acetamide;
 - 15 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(2-morpholin-4-ylethyl)acetamide;
 - 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-isopropylacetamide;
 - N*-(4-chlorobenzyl)-2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]acetamide;
 - 20 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-[2-(dimethylamino)ethyl]acetamide;
 - N*-[2-(diethylamino)ethyl]-2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]acetamide;
 - 25 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-[3-(dimethylamino)propyl]acetamide;
 - 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-pentylacetamide;
 - 2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]-*N*-(2-pyrrolidin-1-ylethyl)acetamide;
 - 30 *N*-(2,4-dichlorobenzyl)-2-[3-(2-([2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino)-2-methylpropyl)phenyl]acetamide;

- N*-(3,4-dichlorobenzyl)-2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]acetamide;
- 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-(4-methoxybenzyl)acetamide;
- 5 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-(2-hydroxyethyl)acetamide;
- 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-propylacetamide;
- 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-(3-methoxypropyl)acetamide;
- 10 *N*-cyclobutyl-2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]acetamide;
- 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-[(1*R*)-1-(1-naphthyl)ethyl]acetamide;
- 15 *N*-2,3-dihydro-1*H*-inden-1-yl-2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]acetamide;
- 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-[2-(1-methylpyrrolidin-2-yl)ethyl]acetamide
- 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-(4-fluorobenzyl)acetamide;
- 20 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-(4-phenylbutyl)acetamide;
- 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-(3-methoxybenzyl)acetamide;
- 25 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-(3-ethoxypropyl)acetamide;
- 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-(3,4,5-trimethoxybenzyl)acetamide;
- 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-[4-(trifluoromethyl)benzyl]acetamide;
- 30 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-*N*-[2-(trifluoromethyl)benzyl]acetamide;

- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(3,5-dimethoxybenzyl)acetamide;
2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(2-phenoxyethyl)acetamide;
5 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[(1*S*)-2-hydroxy-1-methylethyl]acetamide;
2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]acetamide;
2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[(1*S*,2*S*)-1-(hydroxymethyl)-2-methylbutyl]acetamide;
10 *N*-[(1*R*)-1-benzyl-2-hydroxyethyl]-2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]acetamide;
2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[(1*R*)-1-(hydroxymethyl)propyl]acetamide;
15 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]acetamide;
N-[(1*S*)-2-cyclohexyl-1-(hydroxymethyl)ethyl]-2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]acetamide;
2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetamide;
20 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(2-propoxyethyl)acetamide;
2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(4-hydroxycyclohexyl)acetamide;
25 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(3-propoxypropyl)acetamide;
2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-ethyl-*N*-(2-hydroxyethyl)acetamide;
30 1-{[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]acetyl}piperidine-4-carboxamide;

- 5-{2-[(2-{3-[2-(4-acetylpiperazin-1-yl)-2-oxoethyl]phenyl}-1,1-dimethylethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 5-{2-[(2-{3-[2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]phenyl}-1,1-dimethylethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 5 *N*-benzyl-2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-methylacetamide;
- 5-(1-hydroxy-2-{[2-(3-{2-[4-(2-hydroxyethyl)piperazin-1-yl]-2-oxoethyl}phenyl)-1,1-dimethylethyl]amino}ethyl)benzene-1,3-diol;
- 5-(2-{[2-(3-{2-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-2-oxoethyl}phenyl)-1,1-dimethylethyl]amino}-1-hydroxyethyl)benzene-1,3-diol;
- 10 5-{2-[(1,1-dimethyl-2-{3-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]phenyl}ethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-methyl-*N*-(2-phenylethyl)acetamide;
- 15 5-{2-[(1,1-dimethyl-2-{3-[2-oxo-2-(4-pyridin-2-yl)piperazin-1-yl]ethyl]phenyl}ethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[3-(dimethylamino)propyl]-*N*-methylacetamide;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-(2-hydroxyethyl)-*N*-propylacetamide;
- 20 *N*-[2-(diethylamino)ethyl]-2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-methylacetamide;
- 5-{2-[(1,1-dimethyl-2-{3-[2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl]phenyl}ethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 25 5-{2-[(1,1-dimethyl-2-[3-(2-morpholin-4-yl-2-oxoethyl)phenyl]ethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 2-[3-(2-{[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-methyl-*N*-[(1*S*)-1-phenylethyl]acetamide;
- 5-{2-[(1,1-dimethyl-2-[3-(2-oxo-2-piperidin-1-ylethyl)phenyl]ethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
- 30 5-(1-hydroxy-2-{[2-(3-{2-[(3*R*)-3-hydroxypyrrolidin-1-yl]-2-oxoethyl}phenyl)-1,1-dimethylethyl]amino}ethyl)benzene-1,3-diol;

- 5-(1-hydroxy-2-{{2-(3-{2-[(3*R*)-3-hydroxypiperidin-1-yl]-2-oxoethyl}phenyl)-1,1-dimethylethyl}amino}ethyl)benzene-1,3-diol;
- 5-{{2-[(2-{3-[2-(4-acetyl-1,4-diazepan-1-yl)-2-oxoethyl]phenyl)-1,1-dimethylethyl}amino]-1-hydroxyethyl}benzene-1,3-diol;
- 5 5-(1-hydroxy-2-{{2-(3-{2-[4-(hydroxymethyl)piperidin-1-yl]-2-oxoethyl}phenyl)-1,1-dimethylethyl}amino}ethyl)benzene-1,3-diol;
- N*-(1-{{3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl)acetyl}pyrrolidin-3-yl)-*N*-methylacetamide;
- 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-
- 10 methylpropyl}phenyl]-*N*-(2-methoxyethyl)-*N*-propylacetamide;
- 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-ethyl-*N*-(2-methoxyethyl)acetamide;
- 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-[3-(dimethylamino)-2,2-dimethylpropyl]acetamide;
- 15 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-[3-fluoro-5-(trifluoromethyl)benzyl]acetamide;
- 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-[(1*S*)-1-(hydroxymethyl)-3-methylbutyl]acetamide;
- 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-
- 20 methylpropyl}phenyl]-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]acetamide;
- 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N,N*-diethylacetamide;
- 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-1*H*-pyrazol-5-ylacetamide;
- 25 2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]-*N*-(5-methyl-1*H*-pyrazol-3-yl)acetamide;
- N*-(cyclohexylmethyl)-2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]acetamide;
- ethyl 4-{{3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-
- 30 methylpropyl}phenyl)acetyl}piperazine-1-carboxylate;
- N*-(5-chloropyridin-2-yl)-2-[3-(2-{{2-(3,5-dihydroxyphenyl)-2-hydroxyethyl}amino)-2-methylpropyl}phenyl]acetamide;

- 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-N-(6-methylpyridin-2-yl)acetamide;
 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-N-(3-methylpyridin-2-yl)acetamide;
 5 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-N-isoquinolin-1-ylacetamide;
 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-N-(4,6-dimethylpyridin-2-yl)acetamide;
 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-N-(2-methoxybenzyl)acetamide;
 10 N-[(1S)-1-benzyl-2-hydroxyethyl]-2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]acetamide;
 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-N-(1-ethyl-1H-pyrazol-5-yl)acetamide;
 15 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-N-(1,3-dimethyl-1H-pyrazol-5-yl)acetamide;
 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-N-(3-fluorobenzyl)acetamide;
 1-[[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]acetyl]-L-prolinamide;
 20 5-{2-[(2-{3-[2-(5-amino-3-*tert*-butyl-1H-pyrazol-1-yl)-2-oxoethyl]phenyl}-1,1-dimethylethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
 2-[3-(2-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]-2-methylpropyl)phenyl]-N-[(1S)-1-phenylethyl]acetamide;
 25 5-{2-[(2-{3-[2-(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)-2-oxoethyl]phenyl}-1,1-dimethylethyl)amino]-1-hydroxyethyl}benzene-1,3-diol;
 N-[2-(4-Chloro-phenyl)-ethyl]-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide;
 N-Adamantan-1-yl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
 30 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-N-[2-(3-fluoro-phenyl)-ethyl]-benzamide;

- N-[2-(2-Chloro-phenyl)-ethyl]-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide;
3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-N-[2-(2,3-dimethyl-phenyl)-ethyl]-benzamide;
- 5 N-[2-(2-Chloro-4-fluoro-phenyl)-ethyl]-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide;
3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-N-[2-(4-methoxy-2,3-dimethyl-phenyl)-ethyl]-benzamide;
- 10 N-(3,4-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
N-(3,4-Dichloro-benzyl)-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide;
N-(4-Chloro-benzyl)-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide;
- 15 N-Adamantan-1-yl-3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-benzamide;
N-(4-Chloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
N-(4-Trifluoromethoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- 20 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-pyridin-2-ylmethyl-acetamide;
N-(3,4-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 25 N-(Benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
N-Cyclohexylmethyl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 30 1-(3,4-Dihydro-1H-isoquinolin-2-yl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-ethanone;
N-Benzyl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-methyl-acetamide;

- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(2-hydroxy-benzyl)-acetamide;
- N-(4-Cyano-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- 5 N-(2,4-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-(Benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-(2-Chlorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- 10 N-(3-Methoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-(Cyclohexylmethyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- 15 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-phenethyl-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-chlorophenethyl)-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-phenylphenethyl)-acetamide;
- 20 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4'-hydroxy-biphenyl-3-ylmethyl)-acetamide;
- N-Cycloheptyl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- 25 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-phenethyl-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(2-methylsulfanyl-benzyl)-acetamide;
- N-(2,6-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 30 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-indan-2-yl-acetamide;

- N-(2-Chloro-6-fluorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- N-(4-Chlorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 5 N-(2,5-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-(3,5-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-(2,6-Dichloro-benzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-
- 10 ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-Biphenyl-2-ylmethyl-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- N-(2-Chlorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 15 N-(3-Methoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- N-(3-Trifluoromethylbenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- N-(3,4-Difluorobenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-
- 20 propyl}-phenyl)-acetamide;
- N-(2-Methoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- N-(3,4-Dimethylbenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 25 N-(3,4-Dimethoxybenzyl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetamide;
- 4-{[2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-acetylamino]-methyl}-benzamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-
- 30 indan-1-yl-acetamide;
- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(3-fluoro-phenyl)-ethyl]-benzamide;

- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-chloro-phenyl)-ethyl]-benzamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-naphthalen-1-ylmethyl-acetamide;
- 5 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(2-fluoro-5-trifluoromethyl-benzyl)-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(3-chlorobenzyl)-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-phenyl)-N-(4-10 fluoro-3-trifluoromethyl-benzyl)-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2-methylsulfanyl-benzyl)-acetamide;
- 4-[[2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetylamino]-methyl]-benzamide;
- 15 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-sulfamoyl-benzyl)-acetamide;
- 4-[[2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-acetylamino]-methyl]-benzoic acid methyl ester;
- N-(1-Benzyl-piperidin-4-yl)-2-(3-{2-[2-(3,5-dihydroxy-phenyl)-2-hydroxy-20 ethylamino]-2-methyl-propyl}-phenyl)-acetamide;
- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-phenethyl]-benzamide;
- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(5-fluoro-2-methyl-phenyl)-ethyl]-benzamide;
- 25 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-trifluoromethyl-phenyl)-ethyl]-benzamide;
- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-(2-naphthalen-1-yl-ethyl)-benzamide;
- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2,4,5-30 trimethyl-phenyl)-ethyl]-benzamide;
- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2,3-dimethyl-phenyl)-ethyl]-benzamide;

- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-hydroxy-3-chloro-phenyl)-ethyl]-benzamide;
- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(4-chloro-phenyl)-ethyl]-benzamide;
- 5 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-hydroxy-5-chloro-phenyl)-ethyl]-benzamide;
- 3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-propyl}-N-[2-(2-chloro-4-fluoro-phenyl)-ethyl]-benzamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2-methyl-benzyl)-acetamide;
- 10 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(3-methyl-benzyl)-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-methyl-benzyl)-acetamide;
- 15 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2-methoxy-benzyl)-acetamide
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(4-methoxy-benzyl)-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2,3-dimethyl-benzyl)-acetamide;
- 20 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(3,4-dimethyl-benzyl)-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(2-chloro-6-methyl-benzyl)-acetamide;
- 25 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(3-chloro-4-methyl-benzyl)-acetamide;
- 2-(3-{2-[2-(3,5-Dihydroxy-phenyl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-[2-(6-methoxy-naphthalen-2-yl)-ethyl]-acetamide;
- N-(2-Chlorobenzyl)-3-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)propionamide;
- 30 N-(2,6-Dichlorobenzyl)-3-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)propionamide;

- 1-(3,4-Dihydro-1H-isoquinolin-2-yl)-3-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)propan-1-one;
N-(2-Chloro-4-fluorobenzyl)-2-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)acetamide;
- 5 *N*-(4-Bromobenzyl)-2-(3-{2-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]-2-methylpropyl}phenyl)acetamide;
 2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]-2-methylpropyl}phenyl)-*N*-(3,4-dimethylphenyl)acetamide;
 2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)-*N*-(2,3-
- 10 dimethylbenzyl)acetamide;
 2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)-*N*-(4-fluorobenzyl)acetamide;
 2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]propyl}phenyl)-1-(4-pyridin-2-ylpiperazin-1-yl)ethanone; and,
- 15 2-(3-{2-[2-(3,5-Dihydroxyphenyl)-2-hydroxyethylamino]-2-methylpropyl} phenyl)-*N*-(2-phenylpropyl)acetamide.
13. A pharmaceutical composition comprising at least an effective amount of a compound of the formula (1) as described in any one of claims 1 to 12 or a pharmaceutically acceptable salt or derived form thereof.
- 20 14. A compound of the formula (1) as described in any one of claims 1 to 12 or a pharmaceutically acceptable salt, derived form or composition thereof, for use as a medicament.
15. The use of a compound of the formula (1) as described in any one of claims 1 to 12 or of a pharmaceutically acceptable salt, solvate or composition thereof,
- 25 for the manufacture of a drug for the treatment of diseases, disorders, and conditions selected from the group consisting of :
- 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
- 30 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 bronchiolitis,
- 5
- chronic or acute bronchoconstriction, chronic bronchitis, small airways obstruction, and emphysema,
- 10
- 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
- 15
- 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,
- 20
- 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
- 25
- streptococcal bronchitis and vesicular bronchitis,
- 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.

16. A method of treatment of a mammal, including a human being, with a β 2 agonist including treating said mammal with an effective amount of a compound of the formula (1) as described in any one of claims 1 to 12 or with a pharmaceutically acceptable salt, derived form or composition thereof.
17. Combination of a compound according to any one of claims 1 to 15 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 LTB₄, LTC₄, LTD₄, and LTE₄,
 - (c) Histamine receptor antagonists including H1 and H3 antagonists,
 - (d) α ₁- and α ₂-adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use,
 - (e) muscarinic M3 receptor antagonists or anticholinergic agents,
 - (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, such as DAGR (dissociated agonists of the corticoid receptor),
 - (k) Monoclonal antibodies active against endogenous inflammatory entities,
 - (l) Anti-tumor necrosis factor (anti-TNF- α) agents,
 - (m) Adhesion molecule inhibitors including VLA-4 antagonists,
 - (n) Kinin-B₁- and B₂-receptor antagonists,
 - (o) Immunosuppressive agents,
 - (p) Inhibitors of matrix metalloproteases (MMPs),
 - (q) Tachykinin NK₁, NK₂ and NK₃ 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 NF κ B pathway, e.g. IKK inhibitors,
- 5 (w) modulators of cytokine signalling pathways such as p38 MAP kinase, syk kinase or JAK kinase inhibitor,
- (x) Agents that can be classed as mucolytics or anti-tussive, and
- (y) Antibiotics.