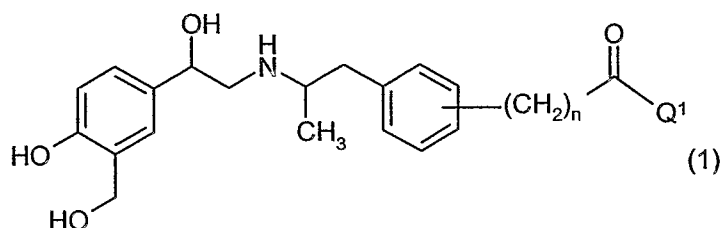


(2-HYDROXY-2-(4-HYDROXY-3-HYDROXYMETHYLPHENYL)-ETHYLAMINO)-PROPYLPHENYL
DERIVATIVES AS BETA2 AGONISTS

This invention relates to β_2 agonists of general formula:



in which n and Q^1 have the meanings indicated below,

- 5 and to processes for the preparation of, intermediates used in 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
5 include both short and long acting inhaled β_2 agonists. Short acting, rapid onset β_2 agonists are used for "rescue" bronchodilation, whereas, long-acting forms provide sustained relief and are used as maintenance therapy.

Bronchodilation is mediated via agonism of the β_2 adrenoceptor expressed on airway smooth muscle cells, which results in relaxation and
10 hence bronchodilation. Thus, as functional antagonists, β_2 agonists can prevent and reverse the effects of all bronchoconstrictor substances, including leukotriene D4 (LTD4), acetylcholine, bradykinin, prostaglandins, histamine and endothelins. Because β_2 receptors are so widely distributed in the airway, β_2 agonists may also affect other types of cells that play a role in asthma. For
15 example, it has been reported that β_2 agonists may stabilize mast cells. The inhibition of the release of bronchoconstrictor substances may be how β_2 agonists block the bronchoconstriction induced by allergens, exercise and cold air. Furthermore, β_2 agonists inhibit cholinergic neurotransmission in the human airway, which can result in reduced cholinergic-reflex bronchoconstriction.

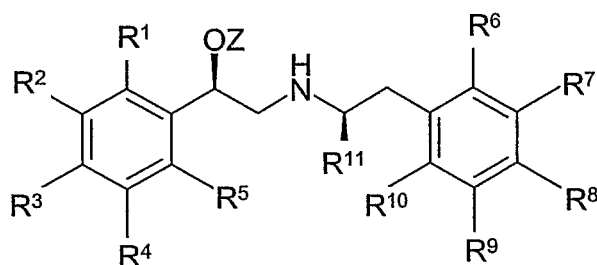
20 In addition to the airways, it has also been established that β_2 adrenoceptors are also expressed in other organs and tissues and thus β_2 agonists, such as those described in the present invention, may have application in the treatment of other diseases such as, but not limited to those of the nervous system, premature labor, congestive heart failure, depression,
25 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.

However, numerous β_2 agonists are limited in their use due to their low selectivity or adverse side-effects driven by high systemic exposure and mainly
30 mediated through action at β_2 adrenoreceptors expressed outside the airways

(muscle tremor, tachycardia, palpitations, restlessness). Therefore there is a need for improved agents in this class.

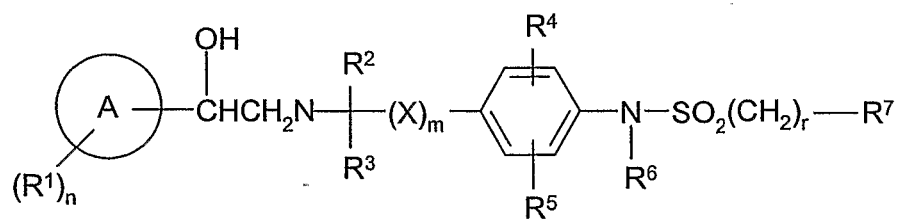
Accordingly, there is still a need for novel $\beta 2$ agonists that would have an appropriate pharmacological profile, for example in terms of potency, selectivity, duration of action and/or pharmacodynamic properties. In this context, the present invention relates to novel $\beta 2$ agonists.

EP 0654534 B1 and EP0939134 B1 disclose a process for the preparation of compounds of formula (XI):

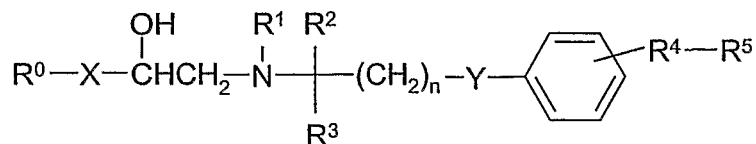


These compounds are disclosed as anti-obesity and anti-diabetic agents having specific $\beta 3$ activity.

US5,561,142 discloses selective $\beta 3$ agonists of formula

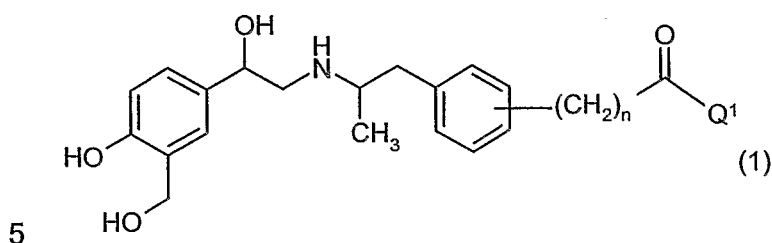


EP0236624 discloses compounds of formula

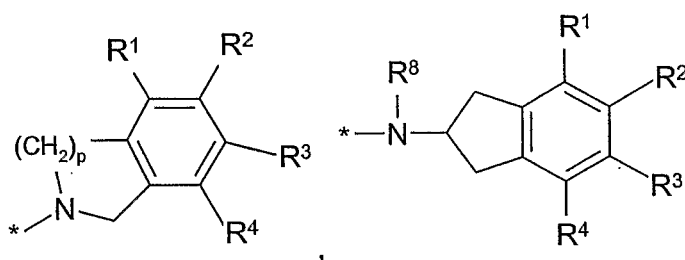


having anti-obesity and/or anti-hyperglycaemic activity coupled with good selectivity from cardiac side-effects.

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

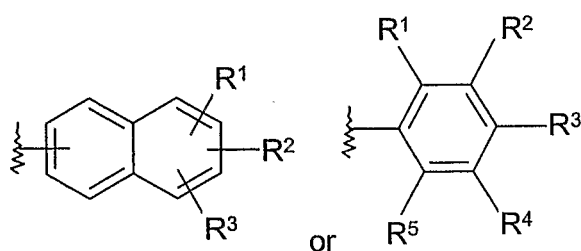


wherein the $(\text{CH}_2)_n\text{-C(=O)Q}^1$ group is in position meta or para, n is 1 or 2 and Q^1 is a group selected from:



and a group $\text{*N(R}^8\text{)-Q}^2\text{-A}$, wherein Q^2 is a single bond or a $\text{C}_1\text{-C}_4$ alkylene, R^8 is H or $\text{C}_1\text{-C}_4$ alkyl, p is 1 or 2, and A is pyridyl, or a group of formula

10



wherein R^1 , R^2 , R^3 , R^4 and R^5 are the same or different and are selected from H, $\text{C}_1\text{-C}_4$ alkyl, OR^6 , SR^6 , halo, CF_3 , OCF_3 , COOR^6 , $\text{SO}_2\text{NR}^6\text{R}^7$, CONR^6R^7 , NR^6R^7 , NHCOR^6 , wherein at least 2 of R^1 to R^5 are equal to H;

wherein R^6 and R^7 are the same or different and are selected from H or C_1-C_4 alkyl and the * represent the attachment point to the carbonyl group;

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

- 5 It has now been found that the compounds of formula (1) are agonists of the β_2 receptors, that are particularly useful for the treatment of β_2 -mediated diseases and/or conditions, and show good potency, in particular when administered via the inhalation route.

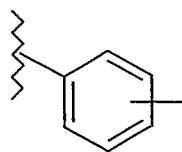
In the present invention, the term "potent" means that the compounds of
10 formula (1) show an agonist potency for the β_2 receptor, which is less than 10 nM as measured by the cell-based assay described herein.

Preferably, the compounds of the invention are selective agonists of the β_2 receptor receptors. Preferably, the compounds of the invention show an agonist
15 potency for the β_2 receptor, which is at least about 100-fold higher as for the β_3 receptor and at least about 500-fold higher as for the β_1 receptor.

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

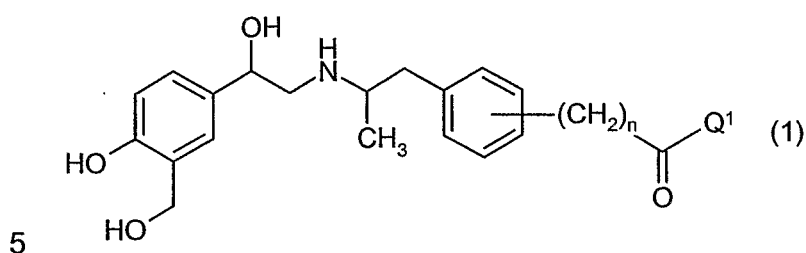
Finally, halo denotes a halogen atom selected from the group consisting
25 of fluoro, chloro, bromo and iodo in particular fluoro or chloro.

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



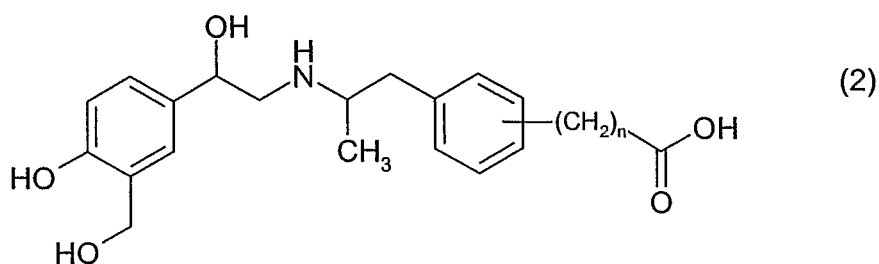
means that the phenyl can be substituted in the meta or para position.

The compounds of the formula (1)

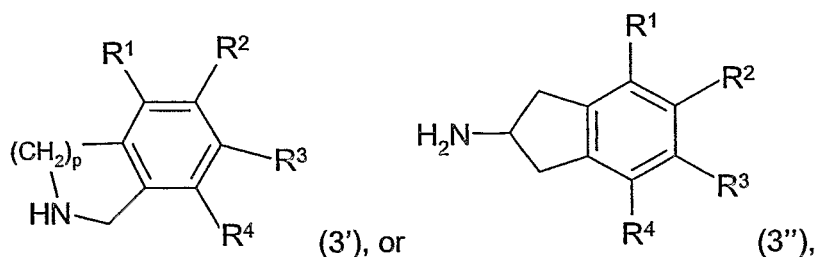


can be prepared using conventional procedures such as by the following illustrative methods in which Q^1 , Q^2 , A and n are as previously defined for the compounds of the formula (1) unless otherwise stated.

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



with an amine of formula $N(R^8)-Q^2-A$ (3),

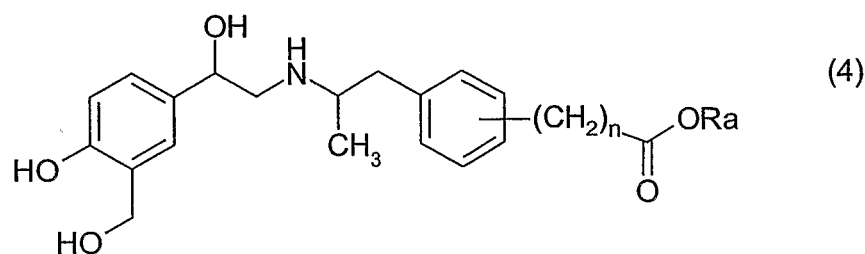


wherein R⁸, Q², A, p and R¹ to R⁵ are as previously defined for compounds of formula (1)

The coupling is generally carried out in an excess of said amine as an acid
 5 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
 10 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.

Said amine (3), (3') or (3'') is either commercially available or may be
 15 prepared by conventional methods well known to the one skilled in the art (e.g. reduction, oxidation, alkylation, protection, deprotection etc...) from commercially available material.

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

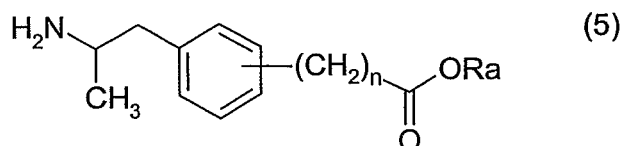


20

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

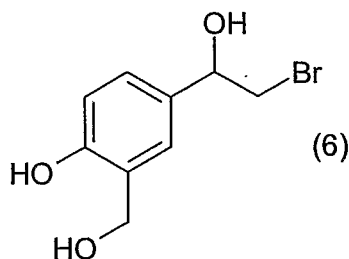
well-known to the one skilled in the art to prepare an acid from an ester, without modifying the rest of the molecule. For example, the ester may be hydrolysed by treatment with aqueous acid or base (e.g. hydrogen chloride, potassium hydroxide, sodium hydroxide or lithium hydroxide), optionally in the presence of
5 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 reaction of an amine of formula (5) :



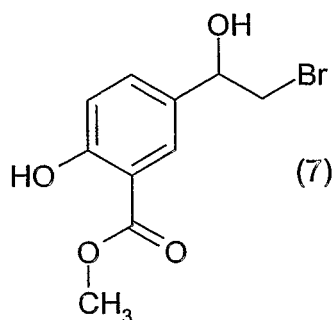
10

wherein Ra and n are as previously defined, with a bromide of formula (6) :



In a typical procedure, the amine of formula (5) is reacted with a bromide of formula (6) optionally in the presence of a solvent or mixture of solvents (e.g. dimethyl sulfoxide, toluene, *N,N*-dimethylformamide, acetonitrile), optionally in
15 the presence of a suitable base (e.g. triethylamine, diisopropylethylamine, potassium carbonate) at a temperature comprised between 80°C and 120°C, for 12 to 48 hours.

The bromide of formula (6) may be prepared from the ester of formula
20 (7) :

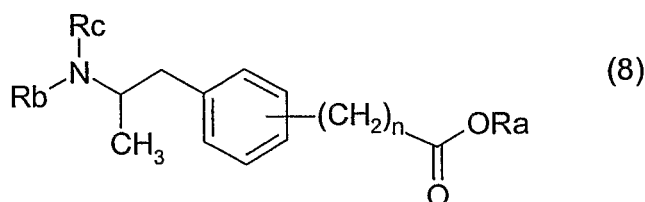


according to any method well-known to the one skilled in the art to prepare an alcohol from an ester, without modifying the rest of the molecule.

In a typical procedure, the ester of formula (7) is reduced with borane dimethylsulfide complex in tetrahydrofuran at a reflux for a period of 2 hours.

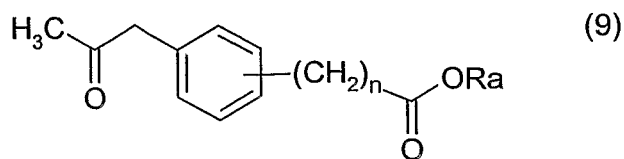
The alcohol of formula (7) may be prepared as either the (*R*) or (*S*) enantiomer according to methods well described in the literature (Tetrahedron Letters 1994, 35(50), 9375).

The amine of formula (5) may be prepared as either the (*R*) or (*S*) enantiomer from the corresponding protected amine of formula (8):



wherein R_a and n are as previously defined and R_b and R_c represent any suitable substituents so that HNR_bR_c is a chiral amine (for example, R_b may be hydrogen and R_c may be α -methylbenzyl), provided that the bonds between N and R_b and N and R_c 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.

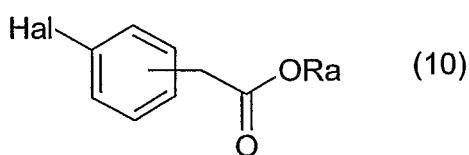
The amine of formula (8) may be prepared as a single diastereomer by reaction of an amine of formula HNR_bR_c with a ketone of formula (9):



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
 5 reduced by a suitable reducing agent (e.g. sodium cyanoborohydride of formula NaCNBH_3 or sodium triacetoxyborohydride of formula $\text{Na}(\text{OAc})_3\text{BH}$) 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
 10 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
 15 diastereomer.

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

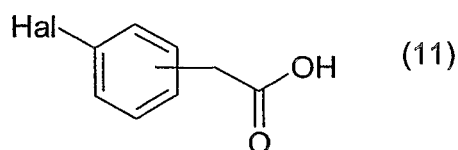


wherein Ra is as previously defined and Hal represents an halogen atom, which
 20 includes, but is not limited to bromo and iodo, with an enolate or enolate equivalent.

In a typical procedure, the aryl halide of formula (10) is reacted with a tin enolate generated in-situ by treatment of isoprenyl 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.

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

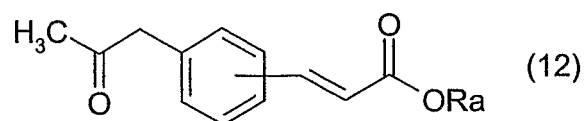


- wherein Hal is as previously defined,
according to any method well-known to the one skilled in the art to prepare an
10 ester from an acid, without modifying the rest of the molecule.

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.

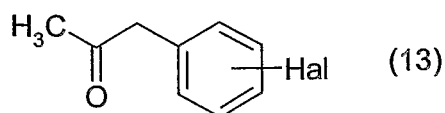
- 15 The acid of formula (11) is a commercial product.

The ketone of formula (9) where $n=2$ may be prepared by reduction of an alkene of formula (12) :



- In a typical procedure, a solution of the olefin of formula (12) in a suitable
20 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 room temperature and 60°C for 8-24 hours.

The alkene of formula (12) may be prepared by a palladium mediated coupling of an activated olefin with an aryl halide of formula (13):



5 In a typical procedure, the aryl halide (13) is coupled with a vinyl ester (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
10 suitable solvent (e.g. acetonitrile, *N,N*-dimethylformamide, toluene), optionally in the presence of a base such as triethylamine at a temperature between 40°C and 110°C for 8 to 24 hours.

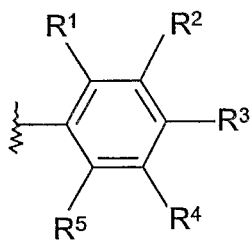
The ketone of formula (13) is a commercial product.

For some of the steps of the here above described process of preparation of
15 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 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
20 Publication, 1981) or by P. J. Kocienski (*Protecting groups*, Georg Thieme Verlag, 1994), can be used.

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
25 procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the examples and preparations hereto.

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.

- 5 Compounds of formula (1) wherein n is 1 or 2, Q¹ is a group *-NH-Q²-A, wherein Q² is C₁-C₄ alkylene and A is group of formula



wherein R¹, R², R³, R⁴ and R⁵ are as defined above, are particularly preferred.

- 10 Preferably n is 1.

Preferably, Q² is selected from -CH₂-, -(CH₂)₂-, -(CH₂)₃- and -CH(CH₃)-.

More preferably, Q² is -CH₂-.

Preferably, R¹, R², R³, R⁴ and R⁵ are the same or different and are selected from H, C₁-C₄ alkyl, OR⁶, Cl, F, CF₃, OCF₃, COOR⁶, SO₂NR⁶R⁷, provided at

- 15 least 2 of R¹ to R⁵ are equal to H,

wherein R⁶ and R⁷ are the same or different and are selected from H or C₁-C₄ alkyl.

Preferably, R¹, R², R³, R⁴ and R⁵ are the same or different and are selected from H, CH₃, OH, OCH₃, OCH₂CH₃, Cl, F, CF₃, OCF₃, COOH, SO₂NH₂,

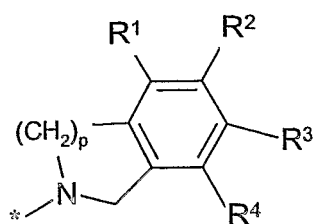
- 20 provided at least 2 of R¹ to R⁵ are equal to H.

Preferably, R¹, R², R³, R⁴ and R⁵ are the same or different and are selected from H, CH₃, OH, OCH₃, OCH₂CH₃, Cl, F, CF₃, OCF₃, COOH, SO₂NH₂, provided at least 3 of R¹ to R⁵ are equal to H.

Preferably, R¹, R², R³, R⁴ and R⁵ are selected from Cl, provided at least 3 of R¹ to R⁵ are equal to H.

- 25

Other preferred compounds are those wherein n is 1 or 2 and Q¹ is

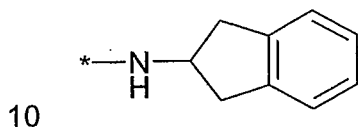


wherein p is 1 or 2, R^1 , R^2 , R^3 and R^4 are the same or different and are selected from H, C_1 - C_4 alkyl, OR^6 , SR^6 , halo, CF_3 , OCF_3 , $COOR^6$, $SO_2NR^6R^7$, $CONR^6R^7$, NR^6R^7 , $NHCOR^6$, provided at least 2 of R^1 to R^4 are equal to H;

- 5 wherein R^6 and R^7 are the same or different and are selected from H or C_1 - C_4 alkyl.

Preferably, R^1 , R^2 , R^3 , and R^4 are the same or different and are selected from H and OR^6 , provided at least 2 of R^1 to R^4 are equal to H.

Other preferred compounds are those wherein n is 1 or 2 and Q^1 is



Other preferred compounds are those wherein n is 1 or 2 and Q^1 is a group $*-NH-Q^2-A$, wherein Q^2 is C_1 - C_4 alkylene and A is pyridin-2-yl.

Other preferred compounds are those wherein n is 1 or 2 and Q^1 is a group $*-NH-Q^2-A$, wherein Q^2 is C_1 - C_4 alkylene and A is naphthyl.

15

Particularly preferred are the compounds of the formula (1) as described in the Examples section hereafter, i.e. :

- 20 *N*-(2,6-Dimethoxybenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;
- N*-(2-Ethoxybenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;

- N*-(2-Hydroxybenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;
2-(3-((2*R*)-2-[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-indan-2-yl-acetamide;
- 5 *N*-(3,4-Dichlorobenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;
N-[4-(Aminosulfonyl)benzyl]-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;
2-(3-((2*R*)-2-[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(pyridin-2-ylmethyl)-acetamide;
- 10 4-((2-(3-((2*R*)-2-[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetylamino)-methyl)-benzamide;
N-(3,4-Dimethoxybenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;
- 15 2-(3-((2*R*)-2-[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(4-trifluoromethoxybenzyl)-acetamide;
N-(2-Chloro, 6-fluorobenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;
N-(3,4-Dimethylbenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;
- 20 *N*-[2-Fluoro-5-(trifluoromethyl)benzyl]-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;
N-(2,6-Dichlorobenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;
- 25 2-(3-((2*R*)-2-[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(2-phenylethyl)acetamide;
N-Benzyl-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;
N-(3,5-Dichlorobenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;
- 30 *N*-(4-Chlorobenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;

- 4-{{[2-(3-{{(2*R*)-2-[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl)-acetyl]-amino)-methyl]-benzoic acid;
2-{3-[(2*R*)-2-{{(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}-*N*-[(1*R*)-1-phenylethyl]acetamide;
- 5 4-{{(1*R*)-2-[(1*R*)-2-{3-[2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]phenyl}-1-methylethyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol;
4-{{(1*R*)-2-[(1*R*)-2-{3-[2-(7-Ethoxy-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]phenyl}-1-methylethyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol;
- 10 *N*-[2-(4-Chlorophenyl)ethyl]-2-{3-[(2*R*)-2-{{(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}acetamide;
N-[2-(4-Ethylphenyl)ethyl]-2-{3-[(2*R*)-2-{{(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}acetamide;
- 15 *N*-(1,1-Dimethyl-2-phenylethyl)-2-{3-[(2*R*)-2-{{(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}acetamide;
N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-{3-[(2*R*)-2-{{(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}acetamide;
N-(3,4-Difluorobenzyl)-2-{3-[(2*R*)-2-{{(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}acetamide;
- 20 4-{{(1*R*)-2-[(1*R*)-2-{3-[2-(1,3-Dihydro-2*H*-isoindol-2-yl)-2-oxoethyl]phenyl}-1-methylethyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol;
2-{3-[(2*R*)-2-{{(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}-*N*-phenylacetamide;
- 25 2-{3-[(2*R*)-2-{{(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}-*N*-(1-naphthylmethyl)acetamide;
N-(3,4-Dichlorobenzyl)-2-{3-[(2*R*)-2-{{(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}-*N*-methylacetamide;
- 30 2-{3-[(2*R*)-2-{{(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}-*N*-(2-pyridin-2-ylethyl)acetamide;

- 2-{3-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}-*N*-[(2*R*)-2-phenylpropyl]acetamide;
- N*-Benzyl-2-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}-*N*-methylacetamide;
- 5 *N*-[3-(4-Fluorophenyl)propyl]-2-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}acetamide;
- N*-(2,6-Dichlorobenzyl)-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl}-propanamide;
- 10 *N*-(2,6-Dimethoxybenzyl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}propanamide;
- N*-(2-Ethoxybenzyl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}propanamide;
- N*-(3,4-Dimethylbenzyl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}propanamide;
- 15 *N*-(2,3-Dihydro-1*H*-inden-2-yl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}propanamide;
- 4-{[(1*R*)-2-[[[(1*R*)-2-{3-[3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-3-oxopropyl]phenyl]-1-methylethyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol};
- 20 *N*-(2-Chloro-6-fluorobenzyl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}propanamide;
- N*-(2-Chlorobenzyl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}propanamide;
- 3-{3-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}-*N*-(pyridin-2-ylmethyl)propanamide;
- 25 *N*-(2-Chlorobenzyl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}propanamide;
- 3-{3-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}-*N*-(pyridin-2-ylmethyl)propanamide;
- 30

- N*-Benzyl-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl}phenyl}propanamide;
3-{3-[(2*R*)-2-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl}phenyl}-*N*-(2-phenylethyl)propanamide;
5 3-{3-[(2*R*)-2-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl}phenyl}-*N*-(3-phenylpropyl)propanamide;
4-{(1*R*)-2-[(1*R*)-2-{3-[3-(1,3-Dihydro-2*H*-isoindol-2-yl)-3-oxopropyl]phenyl}-1-methylethyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol;
10 *N*-[2-Fluoro-5-(trifluoromethyl)benzyl]-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl}phenyl}propanamide;
N-(2-Hydroxybenzyl)-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl}phenyl}propanamide;
15 3-{3-[(2*R*)-2-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl}phenyl}-*N*-phenylpropanamide;
N-Benzyl-2-(4-{(2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl-amino]propyl}phenyl)acetamide;
2-(4-{(2*R*)-2-[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl-amino]propyl}phenyl)-*N*-(3-phenyl-propyl)acetamide;
20 2-(4-{(2*R*)-2-[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl-amino]propyl}phenyl)-*N*-indan-2-yl-acetamide;
1-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-2-(4-{(2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino]propyl}phenyl)ethanone;
25 *N*-(2-Hydroxybenzyl)-2-(4-{(2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]propyl}phenyl)-acetamide;
N-(3-Chlorobenzyl)-2-(4-{(2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]propyl}phenyl)-acetamide;
N-(4-Chlorobenzyl)-2-(4-{(2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]propyl}phenyl)-acetamide;
30 2-(4-{(2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino]-propyl}phenyl)-*N*-(2-methoxybenzyl)-acetamide;

2-(4-((2R)-2-((2R)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino)propyl)phenyl)-N-(3-methoxybenzyl)acetamide;

2-(4-((2R)-2-((2R)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino)propyl)phenyl)-N-(4-methoxybenzyl)-acetamide;

5 N-(2,6-Dimethoxybenzyl)-2-(4-((2R)-2-((2R)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino)propyl)phenyl)-acetamide,

2-(4-((2R)-2-((2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino)propyl)phenyl)-N-(pyridin-2-ylmethyl)acetamide,

10 N-[2-Fluoro-5-(trifluoromethyl)benzyl]-2-{4-[(2R)-2-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl}phenyl}acetamide, and,
2-{4-[(2R)-2-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl}phenyl)-N-(2-phenylethyl)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 position meta are generally preferred.

15 The compounds of formula (1) may also be optionally transformed into pharmaceutically acceptable salts. In particular, these pharmaceutically acceptable salts of the compounds of the formula (1) include the acid addition and the base salts (including disalts) thereof.

Suitable acid addition salts are formed from acids which form non-toxic
20 salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzone, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, hydrogen phosphate, isethionate,
25 D- and L-lactate, malate, maleate, malonate, mesylate, methylsulphate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen, phosphate/phosphate dihydrogen, saccharate, stearate, succinate, D- and L-tartrate, 1-hydroxy-2-naphthoate and tosylate salts.

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

5

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

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

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

- 15 (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 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
20 (iii) by converting one salt of the compound of formula (1) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

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

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex
30 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.

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-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 Haleblan (August 1975).

10

Hereinafter all references to compounds of formula (1) include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

15 The compounds of the invention include compounds of formula (1) as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula (1).

20

As indicated, so-called 'pro-drugs' of the compounds of formula (1) are also 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 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
25
30 Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by 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, 5 1985).

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 10 hydrogen of the carboxylic acid functionality of the compound of formula (1) is replaced by (C₁-C₈)alkyl;

(ii) where the compound of formula (1) contains an alcohol functionality (-OH), an ether thereof, for example, a compound wherein the hydrogen 15 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 amino functionality (-NH₂ or -NHR where R ≠ H), an amide thereof, for 20 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

- 5 (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 ($-\text{OR} \rightarrow -\text{OH}$);
- 10 (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 $-\text{NHR}^2$);
- (iv) where the compound of formula (1) contains a secondary amino group, a primary derivative thereof ($-\text{NHR}^1 \rightarrow -\text{NH}_2$);
- 15 (v) where the compound of formula (1) contains a phenyl moiety, a phenol derivative thereof ($-\text{Ph} \rightarrow -\text{PhOH}$); and
- 20 (I).(vi) where the compound of formula (1) contains an amide group, a 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 are possible. Where the compound contains, for example, a keto or 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 more than one type of isomerism.

25

30

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
5 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
10 those skilled in the art, for example, chromatography and fractional crystallisation.

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

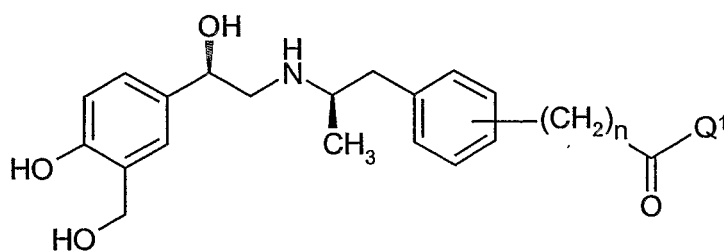
Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case
20 where the compound of formula (1) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric 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.

25

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

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).

- 5 According to one aspect of the present invention, the (*R,R*)-stereoisomer of the formula below is generally preferred:



wherein n and Q^1 are as defined above for compounds of formula (1).

- 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.

- 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 .

- 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 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 preferred in some circumstances.

5

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.

- 10 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.

15

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.

- 20 The compounds of formula (1), their pharmaceutically acceptable salts 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
- 25 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.

- 30 The compounds of formula (1) and their pharmaceutically acceptable salts and derived forms as mentioned above can be administered according to the invention to animals, preferably to mammals, and in particular to humans,

as pharmaceuticals for therapy and/or prophylaxis. They can be administered per se, in mixtures with one another or in the form of pharmaceutical preparations which as active constituent contain an efficacious dose of at least one compounds of formula (1), its pharmaceutically acceptable salts and/or
5 derived forms, in addition to customary pharmaceutically innocuous excipients and/or additives.

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms may be freeze-dried, spray-dried, or evaporatively dried to
10 provide a solid plug, powder, or film of crystalline or amorphous material. Microwave or radio frequency drying may be used for this purpose.

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms may be administered alone or in combination with other drugs
15 and will generally 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 of the invention. The choice of excipient will to a large extent depend on the particular mode of administration.

20

ORAL ADMINISTRATION

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the
25 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
30 (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).

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

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

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

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

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

15

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

20

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 comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

25

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

30

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), 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.

5

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 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.

30

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.

5

PARENTERAL ADMINISTRATION

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for
10 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.

15

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
20 conjunction with a suitable vehicle such as sterile, pyrogen-free water.

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

25

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.

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

compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA poly(*D*-lactic-co-glycolic) acid (PGLA) microspheres.

5

TOPICAL ADMINISTRATION

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
10 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
15 be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).

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

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

25

INHALED/INTRANASAL ADMINISTRATION

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
30 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 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
5 cyclodextrin.

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

Prior to use in a dry powder or suspension formulation, the drug product is
15 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.

20 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
25 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
30 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.

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

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

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with
15 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.

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

RECTAL/INTRAVAGINAL ADMINISTRATION

25 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.

30

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.

5 OCULAR/AURAL ADMINISTRATION

- 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
- 10 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,
- 15 hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.
- 20 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.

OTHER TECHNOLOGIES

25

- 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
- 30 the aforementioned modes of administration.

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

KIT-OF-PARTS

10

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

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

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.

30

DOSAGE

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
5 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
10 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
15 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)
20 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 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
25 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 substantially the same time to said patient,
- 15 • 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 significant time interval between each administration, whereupon said components are released at substantially different times to said patient; and
- 20 • sequential 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 in a controlled manner whereupon they are concurrently, consecutively, and/or overlappingly administered at the same and/or different times by said patient,
- 25 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 :

- (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,
- 5 (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,
- 10 (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,
- 15 (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,
- 20 (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,
- 25 (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 or syk kinase,
- (x) Agents that can be classed as mucolytics or anti-tussive, and
- 30 (y) Antibiotics.

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

- 5 - glucocorticosteroids, in particular inhaled glucocorticosteroids with reduced systemic side effects, including prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide, and mometasone furoate, or
- 10 - 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 preferred.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment. The description, which follows, 15 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 20 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 25 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, 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 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, 15 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 streptococcal bronchitis and vesicular bronchitis, 25
- acute lung injury, 30

- 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
5 bronchiectasis and follicular bronchiectasis.

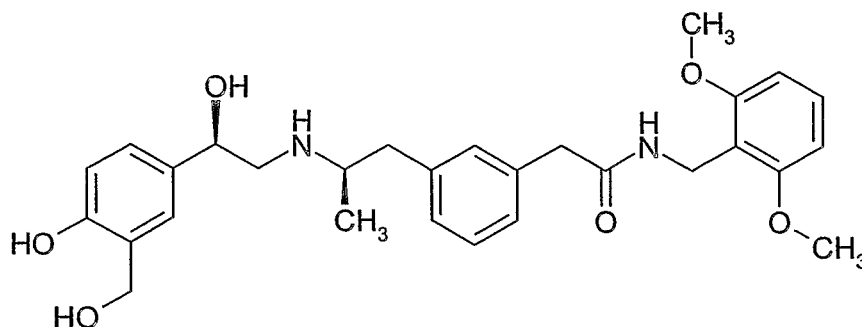
A still further aspect of the present invention also relates to the use of the compounds of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for the manufacture of a drug having a $\beta 2$ agonist activity. In particular, the present inventions concerns the use of the
10 compounds of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for the manufacture of a drug for the treatment of $\beta 2$ -mediated diseases and/or conditions, in particular the diseases and/or conditions listed above.

As a consequence, the present invention provides a particularly interesting method of treatment of a mammal, including a human being, including treating said mammal 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
15 method of treatment of a mammal, including a human being, to treat a $\beta 2$ -mediated diseases and/or conditions, in particular the diseases and/or conditions listed above, including treating said mammal with an effective amount of a compound of formula (1), its pharmaceutically acceptable salts and/or derived forms.

25

The following examples illustrate the preparation of the compounds of the formula (1):

Example 1: *N*-(2,6-Dimethoxybenzyl)-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide



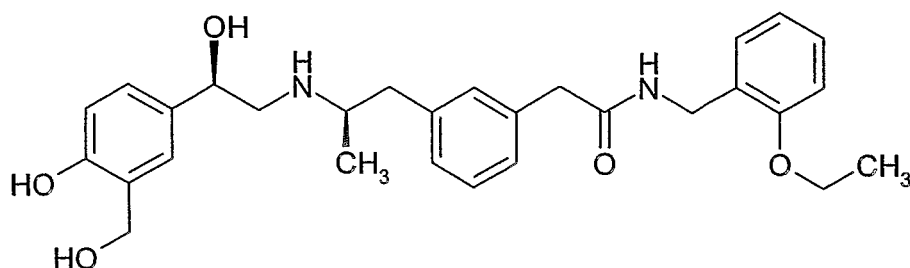
A solution of 2-(3-((2*R*)-2-((2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-*N*-(2,6-dimethoxybenzyl)-acetamide (Preparation 1) (125mg, 0.20mmol) in methanol (6ml) was treated with acetic acid (6ml) and ammonium fluoride (74mg, 2.0mmol) and the reaction heated to 40°C for 16 hours. The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (95:5:0.5 changing to 93:7:0.7, by volume) to give the title compound as a white solid after trituration with diethyl ether (59mg).

¹H NMR (400MHz, CD₃OD): δ = 7.24-7.15 (3H, m), 7.09-7.07 (1H, m), 7.02-6.97 (3H, m), 6.70-6.68 (1H, d), 6.61-6.59 (2H, d), 4.61 (2H, s), 4.61-4.58 (1H, m), 4.41 (2H, s), 3.75 (6H, s), 3.43 (2H, s), 2.92-2.84 (2H, m), 2.71-2.67 (2H, m), 2.57-2.52 (1H, dd), 1.05-1.03 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 509, [M-H]⁻ 507.

CHN analysis: found C 67.00%, H 7.48%, N 5.11%; C₂₉H₃₆N₂O₆+0.2Et₂O+0.6H₂O requires C 67.00%, H 7.40%, N 5.24%.

Example 2: *N*-(2-Ethoxybenzyl)-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide



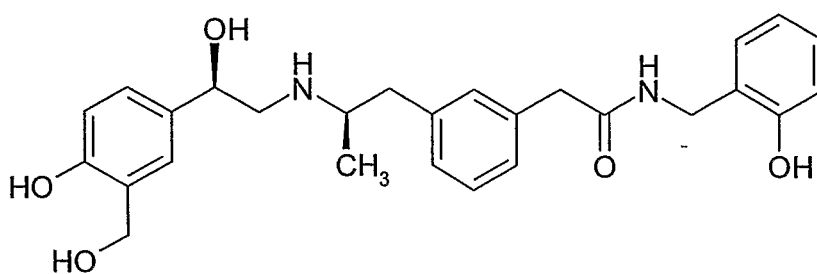
Prepared from 2-(3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(2-ethoxy benzyl)-acetamide (Preparation 2) according to the method for example 1 to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.22-7.18 (3H, m), 7.13-7.11 (2H, d), 7.07 (1H, s), 7.03-7.01 (2H, d), 6.90-6.88 (1H, d), 6.85-6.81 (1H, t), 6.71-6.69 (1H, d), 4.65-4.59 (1H, m), 4.62 (2H, s), 4.35 (2H, s), 4.03-3.98 (2H, q), 3.50 (2H, s), 2.99-2.85 (2H, m), 2.77-2.70 (2H, m), 2.59-2.54 (1H, dd), 1.34-1.31 (3H, t), 1.07-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 493, [M-H]⁻ 491.

CHN analysis : found C 69.25%, H 7.59%, N 5.31%; C₂₉H₃₆N₂O₅+0.15Et₂O+0.55H₂O requires C 69.22%, H 7.57%, N 5.45%.

Example 3: *N*-(2-Hydroxybenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide



Prepared from 2-(3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(2-hydroxy benzyl)-acetamide (Preparation 3) according to the method for example 1, using water

instead of acetic acid as the co-solvent, to give the title compound as a white foam.

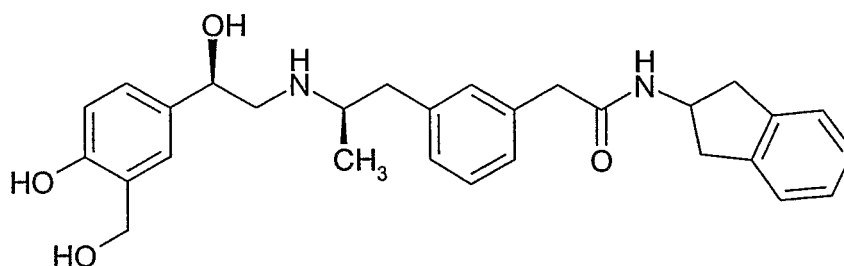
¹H NMR (400MHz, CD₃OD): δ = 7.23 (1H, s), 7.19-7.17 (1H, d), 7.12-7.00 (6H, m), 6.77-6.73 (2H, t), 6.71-6.69 (1H, d), 4.65-4.60 (1H, m), 4.62 (2H, s), 4.32 (2H, s), 3.50 (2H, s), 3.00-2.86 (2H, m), 2.75-2.70 (2H, m), 2.60-2.55 (1H, m), 1.07-1.06 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 465, [M+Na]⁺ 487, [M-H]⁻ 463.

CHN analysis : found C 67.46%, H 7.03%, N 5.66%; C₂₇H₃₂N₂O₅+0.9H₂O requires C 67.45%, H 7.09%, N 5.83%.

10

Example 4: 2-(3-((2R)-2-[(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-N-indan-2-yl-acetamide



Prepared from 2-(3-((2R)-2-[(2R)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-N-indan-2-yl-acetamide (Preparation 4) according to the method for example 3 to give the title compound as a white foam.

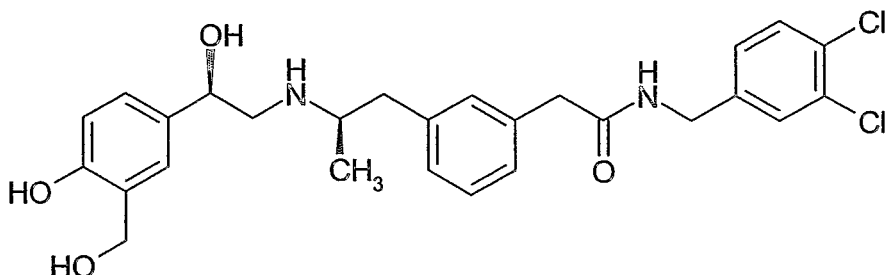
¹H NMR (400MHz, CD₃OD): δ = 7.22-7.16 (4H, m), 7.14-7.09 (3H, m), 7.05 (1H, s), 7.03-6.99 (2H, t), 6.70-6.68 (1H, d), 4.63-4.60 (1H, t), 4.61 (2H, s), 4.57-4.53 (1H, m), 3.43 (2H, s), 3.25-3.20 (2H, dd), 2.98-2.93 (1H, q), 2.90-2.85 (1H, dd), 2.84-2.79 (2H, dd), 2.74-2.69 (2H, m), 2.60-2.55 (1H, dd), 1.08-1.07 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 475, [M-H]⁻ 473.

CHN analysis : found C 72.29%, H 7.28%, N 5.79%; C₂₉H₃₄N₂O₄+0.4H₂O requires C 72.29%, H 7.28%, N 5.81%.

25

Example 5: *N*-(3,4-Dichlorobenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide



Prepared from 2-(3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(3,4-dichloro benzyl)-acetamide (Preparation 5) according to the method for example 3 to give the title compound as a white foam.

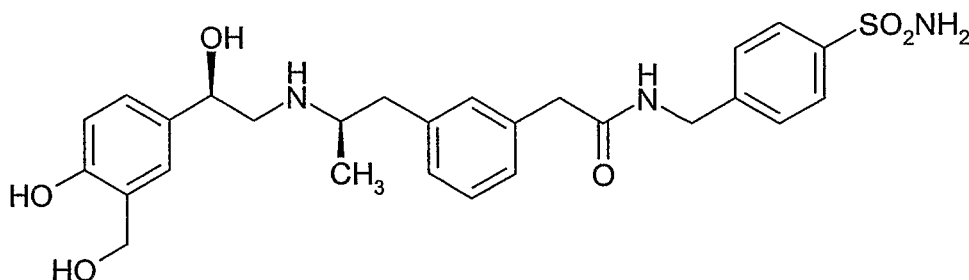
¹H NMR (400MHz, CD₃OD): δ = 7.41-7.38 (1H, d), 7.33 (1H, d), 7.21-7.17 (2H, m), 7.13-7.11 (2H, d), 7.06 (1H, s), 7.01-6.99 (2H, m), 6.69-6.67 (1H, d), 4.60 (2H, s), 4.60-4.57 (1H, m), 4.30 (2H, s), 3.50 (2H, s), 2.96-2.91 (1H, m), 2.88-2.83 (1H, dd), 2.73-2.68 (2H, m), 2.60-2.57 (1H, dd), 1.06-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 517 / 519, [M-H]⁻ 515 / 517.

CHN analysis : found C 61.95%, H 5.93%, N 5.37%; C₂₇H₃₀Cl₂N₂O₄+0.35H₂O requires C 61.92%, H 5.91%, N 5.35%.

15

Example 6: *N*-[4-(Aminosulfonyl)benzyl]-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide



Prepared from 2-(3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-[4-(aminosulfonyl)

20

benzyl]-acetamide (Preparation 6) according to the method for example 3 to give the title compound as a white foam.

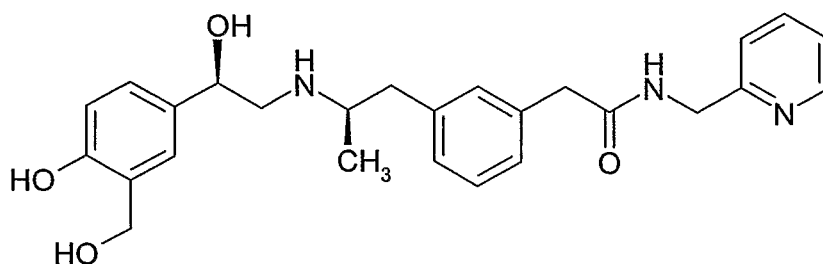
^1H NMR (400MHz, CD_3OD): δ = 7.82-7.79 (2H, d), 7.38-7.36 (2H, d), 7.25-7.13 (3H, m), 7.09 (1H, s), 7.05-7.03 (2H, d), 6.72-6.70 (1H, d), 4.65-4.62 (1H, m),
 5 4.62 (2H, s), 4.42 (2H, s), 3.53 (2H, s), 3.04-2.98 (1H, m), 2.93-2.86 (1H, m), 2.80-2.75 (2H, m), 2.63-2.57 (1H, m), 1.09-1.08 (3H, d) ppm.

LRMS (electrospray): m/z $[\text{M}+\text{H}]^+$ 528, $[\text{M}+\text{Na}]^+$ 550, $[\text{M}-\text{H}]^-$ 526.

CHN analysis : found C 59.44%, H 6.44%, N 7.65%; $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_6\text{S}+1.0\text{H}_2\text{O}$ requires C 59.43%, H 6.47%, N 7.70%.

10

Example 7: 2-(3-((2R)-2-[(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-N-(pyridin-2-ylmethyl)-acetamide



Prepared from 2-(3-((2R)-2-[(2R)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-N-(pyridin-2-ylmethyl)-
 15 acetamide (Preparation 7) according to the method for example 3 to give the title compound as a white foam.

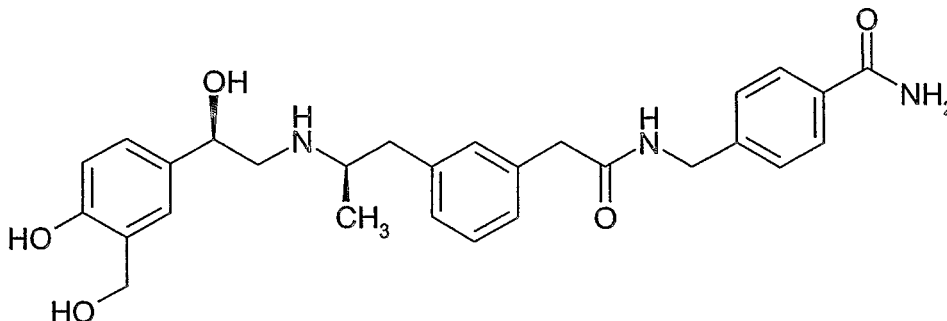
^1H NMR (400MHz, CD_3OD): δ = 8.44-8.42 (1H, d), 7.75-7.71 (1H, t), 7.28-7.14 (5H, m), 7.11 (1H, s), 7.04-7.01 (2H, t), 6.70-6.68 (1H, d), 4.63-4.60 (1H, m),
 20 4.62 (2H, s), 4.47 (2H, s), 3.57 (2H, s), 3.03-2.95 (1H, m), 2.91-2.86 (1H, dd), 2.77-2.72 (2H, m), 2.64-2.59 (1H, dd), 1.11-1.09 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 450, $[\text{M}+\text{Na}]^+$ 472, $[\text{M}-\text{H}]^-$ 448.

CHN analysis : found C 67.06%, H 6.94%, N 8.96%; $\text{C}_{26}\text{H}_{31}\text{N}_3\text{O}_4+0.9\text{H}_2\text{O}$ requires C 67.05%, H 7.10%, N 9.02%.

25

Example 8: 4-((2-(3-((2R)-2-[(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetylamino)-methyl)-benzamide



Prepared from 4-((2-(3-((2R)-2-[(2R)-2-[[*tert*-butyl(dimethyl)silyl]oxy}-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetylamino)-methyl)-benzamide (Preparation 8) according to the method for example 3 to give the title compound as a white foam.

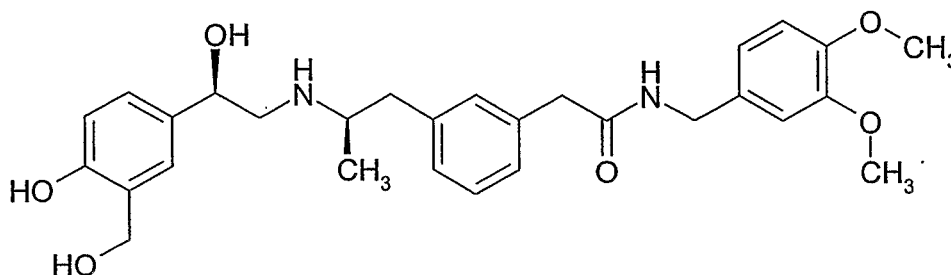
^1H NMR (400MHz, CD_3OD): δ = 7.80-7.78 (2H, d), 7.31-7.29 (2H, d), 7.21-7.12 (3H, m), 7.09 (1H, s), 7.03-7.01 (2H, d), 6.70-6.68 (1H, d), 4.61-4.59 (1H, m), 4.61 (2H, s), 4.40 (2H, s), 3.52 (2H, s), 2.98-2.94 (1H, m), 2.90-2.85 (1H, m), 2.74-2.70 (2H, m), 2.61-2.56 (1H, dd), 1.08-1.06 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 492, $[\text{M}+\text{Na}]^+$ 514, $[\text{M}-\text{H}]^-$ 490.

CHN analysis : found C 65.27%, H 6.73%, N 8.20%; $\text{C}_{28}\text{H}_{33}\text{N}_3\text{O}_5+1.3\text{H}_2\text{O}$ requires C 65.30%, H 6.97%, N 8.16%.

15

Example 9: *N*-(3,4-Dimethoxybenzyl)-2-(3-((2R)-2-[(2R)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide



Prepared from 2-(3-((2R)-2-[(2R)-2-[[*tert*-butyl(dimethyl)silyl]oxy}-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(3,4-dimethoxy benzyl)-

20

acetamide (Preparation 9) according to the method for example 3 to give the title compound as a white foam.

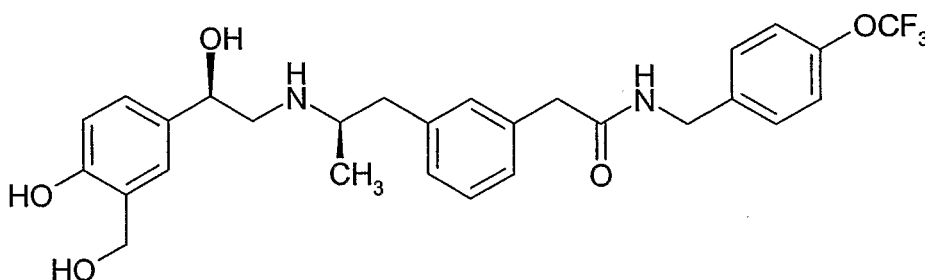
^1H NMR (400MHz, CD_3OD): δ = 7.21-7.13 (3H, m), 7.08 (1H, s), 7.02-7.00 (2H, d), 6.86-6.77 (3H, m), 6.70-6.68 (1H, d), 4.65-4.59 (1H, m), 4.61 (2H, s), 4.28
5 (2H, s), 3.78 (3H, s), 3.71 (3H, s), 3.49 (2H, s), 2.96-2.84 (2H, m), 2.73-2.66 (2H, m), 2.59-2.54 (1H, dd), 1.07-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 509, $[\text{M}+\text{Na}]^+$ 531, $[\text{M}-\text{H}]^-$ 507.

CHN analysis : found C 66.69%, H 7.44%, N 5.14%; $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_6+0.2\text{Et}_2\text{O}+0.75\text{H}_2\text{O}$ requires C 66.66%, H 7.41%, N 5.22%.

10

Example 10: 2-(3-((2R)-2-[(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-N-(4-trifluoromethoxybenzyl)-acetamide



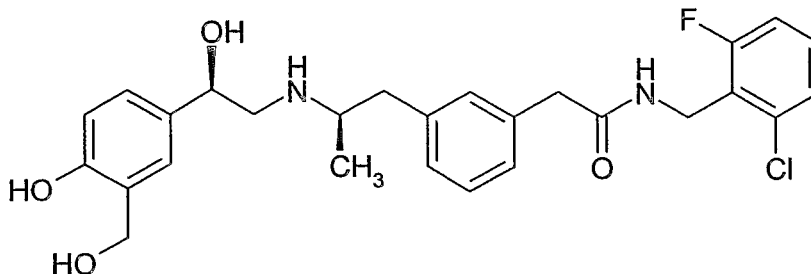
15 Prepared from 2-(3-((2R)-2-[(2R)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-N-(4-trifluoromethoxybenzyl)-acetamide (Preparation 10) using the method for example 3 to give the title compound as a white foam.

^1H NMR (400MHz, CD_3OD): δ = 7.32-7.30 (2H, d), 7.22-7.12 (5H, m), 7.08 (1H, s), 7.03-7.01 (2H, d), 6.70-6.68 (1H, d), 4.62-4.59 (1H, m), 4.61 (2H, s), 4.36
20 (2H, s), 3.51 (2H, s), 3.00-2.93 (1H, m), 2.90-2.85 (1H, dd), 2.73-2.69 (2H, m), 2.61-2.56 (1H, dd), 1.08-1.06 (3H, d) ppm.

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

CHN analysis : found C 62.12%, H 5.98%, N 5.15%; $\text{C}_{28}\text{H}_{31}\text{F}_3\text{N}_2\text{O}_5+0.5\text{H}_2\text{O}$
25 requires C 62.10%, H 5.96%, N 5.17%.

Example 11 : *N*-(2-Chloro, 6-fluorobenzyl)-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide



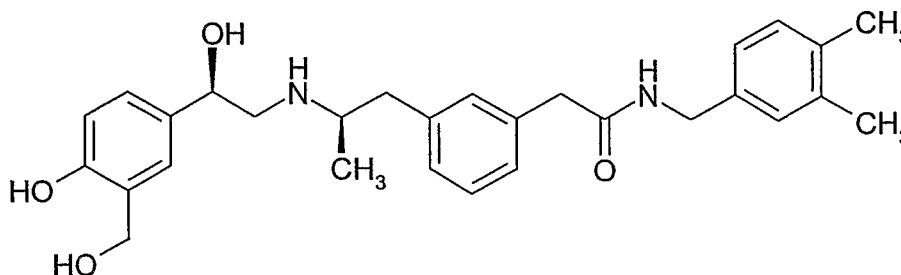
- 5 Prepared from 2-(3-((2*R*)-2-((2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy}-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)- *N*-(2-chloro, 6-fluorobenzyl)-acetamide (Preparation 11) using the method for example 3 to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.33-7.28 (1H, m), 7.25-7.22 (2H, m), 7.18-7.15 (1H, t), 7.09-6.97 (5H, m), 6.70-6.68 (1H, d), 4.63-4.60 (1H, m), 4.61 (2H, s), 4.53 (2H, s), 3.45 (2H, s), 2.97-2.91 (1H, m), 2.90-2.85 (1H, dd), 2.74-2.69 (2H, m), 2.57-2.52 (1H, dd), 1.06-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 501 / 503, [M-H]⁻ 499 / 501.

CHN analysis : found C 62.90%, H 6.06%, N 5.34%; C₂₇H₃₀ClF N₂O₄+0.8H₂O
15 requires C 62.92%, H 6.18%, N 5.44%.

Example 12: *N*-(3,4-Dimethylbenzyl)-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide



- 20 Prepared from 2-(3-((2*R*)-2-((2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy}-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-*N*-(3,4-dimethylbenzyl)-

acetamide (Preparation 12) using the method for example 3 to give the title compound as a white foam.

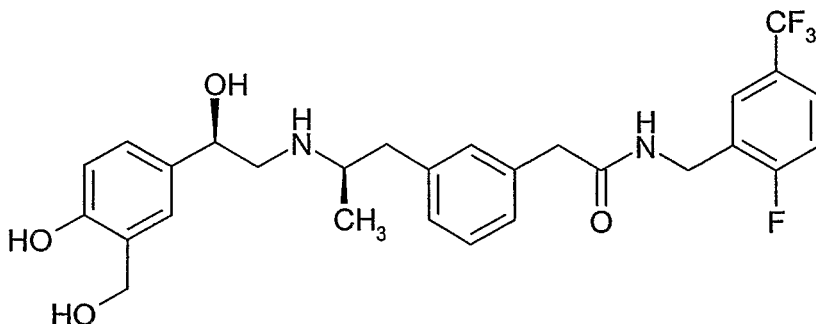
^1H NMR (400MHz, CD_3OD): δ = 7.21-7.12 (3H, m), 7.07 (1H, s), 7.05-7.00 (3H, m), 6.95-6.91 (2H, m), 6.70-6.68 (1H, d), 4.62-4.59 (1H, m), 4.61 (2H, s), 4.26 (2H, s), 3.49 (2H, s), 2.98-2.90 (1H, m), 2.90-2.85 (1H, dd), 2.74-2.69 (2H, m), 2.60-2.55 (1H, dd), 2.20 (3H, s), 2.19 (3H, s), 1.07-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 477, $[\text{M}-\text{H}]^-$ 475.

CHN analysis : found C 71.69, H 7.70, N 5.72; $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_4+0.5\text{H}_2\text{O}$ requires C 71.73%, H 7.68%, N 5.77%.

10

Example 13: *N*-[2-Fluoro-5-(trifluoromethyl)benzyl]-2-(3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl)-acetamide



15 Prepared from 2-(3-[(2*R*)-2-[(2*R*)-2-[(*tert*-butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl)-*N*-[2-fluoro-5-(trifluoromethyl)benzyl]-acetamide (Preparation 13) using the method for example 3 to give the title compound as a white foam.

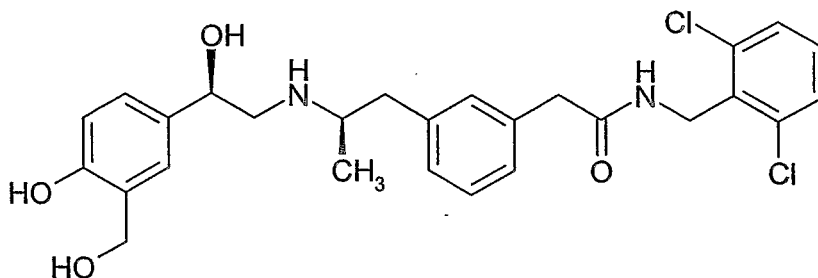
^1H NMR (400MHz, CD_3OD): δ = 7.61-7.57 (1H, m), 7.55-7.52 (1H, m), 7.28-7.18 (3H, m), 7.14-7.12 (1H, m), 7.07 (1H, s), 7.03-7.01 (2H, d), 6.70-6.68 (1H, d), 4.63-4.60 (1H, m), 4.61 (2H, s), 4.44 (2H, s), 3.52 (2H, s), 3.00-2.93 (1H, m), 2.91-2.86 (1H, dd), 2.76-2.70 (2H, m), 2.60-2.55 (1H, dd), 1.07-1.06 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 535, $[\text{M}-\text{H}]^-$ 533.

20

CHN analysis : found C 62.26%, H 5.81%, N 5.09%; $C_{28}H_{30}F_4N_2O_4 + 0.30H_2O$ requires C 62.28%, H 5.71%, N 5.19%.

Example 14: *N*-(2,6-Dichlorobenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide



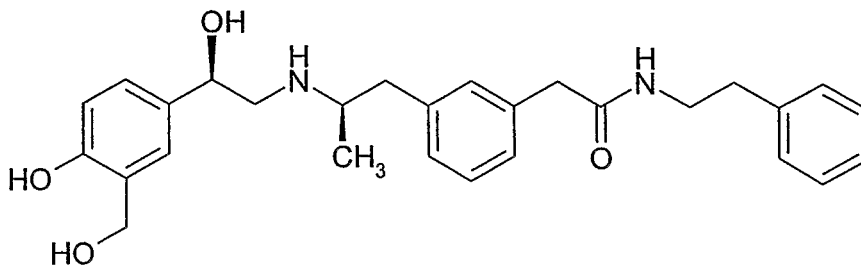
Prepared from 2-(3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(2,6-dichlorobenzyl)-acetamide (Preparation 14) using the method for example 3 to give the title compound as a white foam.

1H NMR (400MHz, CD_3OD): δ = 7.38-7.36 (2H, d), 7.27-6.97 (7H, m), 6.70-6.68 (1H, d), 4.69-4.55 (5H, m), 3.46 (2H, s), 3.00-2.83 (2H, m), 2.79-2.68 (2H, m), 2.61-2.50 (1H, m), 1.07-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 517 / 519, $[M+Na]^+$ 539 / 541, $[M-H]^-$ 515 / 517.

CHN analysis: found C 61.40%, H 6.13%, N 5.15%; $C_{27}H_{30}Cl_2N_2O_4 + 0.6H_2O$ requires C 61.39%, H 5.95%, N 5.30%.

Example 15: 2-(3-((2*R*)-2-[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(2-phenylethyl)acetamide



Prepared from 2-(3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(2-phenylethyl)acetamide (Preparation 15) using the method for example 3 to give the title compound as a white solid.

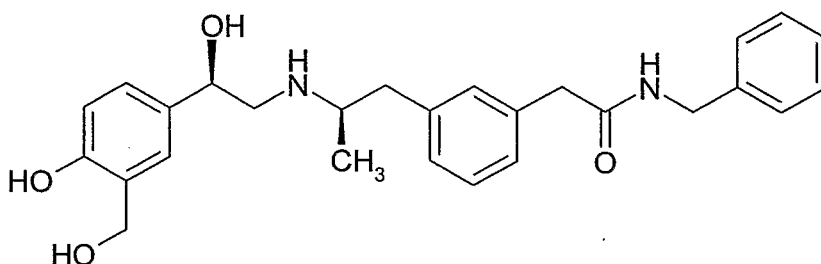
5 ^1H NMR (400MHz, CD_3OD): δ = 7.49-7.30 (8H, m), 7.26-7.22 (3H, m), 6.90-6.88 (1H, d), 4.81-4.78 (3H, m), 3.60-3.54 (4H, m), 3.16-3.00 (2H, m), 2.96-2.87 (4H, m), 2.80-2.75 (1H, dd), 1.28-1.26 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 463, $[\text{M}+\text{Na}]^+$ 485, $[\text{M}-\text{H}]^-$ 461.

CHN analysis : found C 69.89%, H 7.63%, N 5.98%; $\text{C}_{28}\text{H}_{34}\text{N}_2\text{O}_4+1.30\text{H}_2\text{O}$

10 requires C 69.20%, H 7.59%, N 5.76%.

Example 16: *N*-Benzyl-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide



15 Prepared from *N*-Benzyl-2-(3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide (Preparation 16) using the method for example 3 to give the title compound as a white foam.

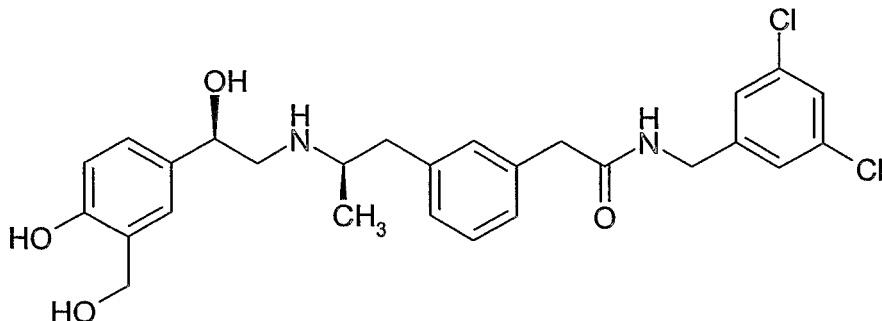
20 ^1H NMR (400MHz, CD_3OD): δ = 7.29-7.18 (7H, m), 7.14-7.12 (1H, m), 7.08 (1H, s), 7.05-6.99 (2H, m), 6.71-6.69 (1H, d), 4.64-4.62 (1H, m), 4.61 (2H, s), 4.34 (2H, s), 3.51 (2H, s), 3.02-2.93 (1H, m), 2.91-2.86 (1H, m), 2.76-2.72 (2H, dd), 2.61-2.56 (1H, dd), 1.08-1.07 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 449, $[\text{M}+\text{Na}]^+$ 471, $[\text{M}-\text{H}]^-$ 447.

CHN analysis : found C 69.02%, H 7.24%, N 5.95%; $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_4+1.15\text{H}_2\text{O}$

25 requires C 69.11%, H 7.37%, N 5.97%.

Example 17: *N*-(3,5-Dichlorobenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide



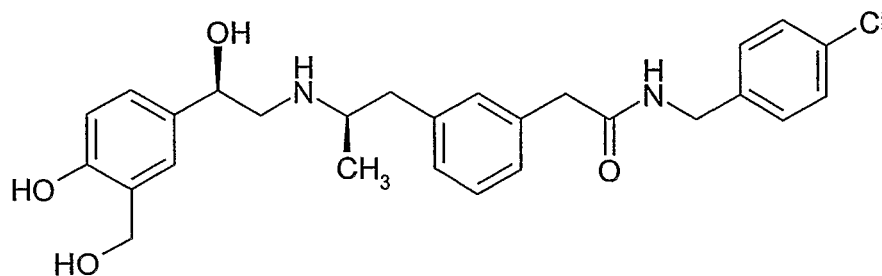
Prepared from 2-(3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(3,5-dichlorobenzyl)-acetamide (Preparation 17) using the method for example 3 to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.28-7.13 (6H, m), 7.08 (1H, s), 7.04-7.01 (2H, m), 6.71-6.69 (1H, d), 4.62 (2H, s), 4.62-4.59 (1H, m), 4.31 (2H, s), 3.52 (2H, s), 3.02-2.92 (1H, m), 2.90-2.85 (1H, m), 2.77-2.69 (2H, m), 2.62-2.57 (1H, dd), 1.08-1.06 (3H, d) ppm.

LRMS (electrospray): *m/z* [M+H]⁺ 517 / 519, [M+Na]⁺ 539 / 541, [M-H]⁻ 515 / 517.

CHN analysis : found C 60.61%, H 5.86%, N 5.14%; C₂₇H₃₀Cl₂N₂O₄+0.95H₂O requires C 60.67%, H 6.01%, N 5.24%.

Example 18: *N*-(4-Chlorobenzyl)-2-(3-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide



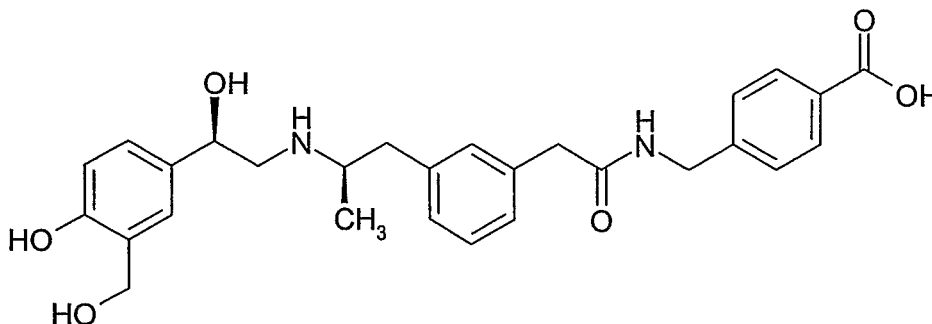
Prepared from 2-(3-((2*R*)-2-((2*R*)-2-((*tert*-butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(4-chlorobenzyl)-acetamide (Preparation 18) using the method for example 3 to give the title compound as a white foam.

5 ¹H NMR (400MHz, CD₃OD): δ = 7.28-7.18 (6H, m), 7.13-7.11 (1H, m), 7.06 (1H, s), 7.02-7.00 (2H, d), 6.70-6.68 (1H, d), 4.61 (2H, s), 4.61-4.58 (1H, m), 4.32 (2H, s), 3.50 (2H, s), 2.95-2.90 (1H, m), 2.89-2.84 (1H, dd), 2.72-2.67 (2H, m), 2.60-2.55 (1H, dd), 1.07-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 483 / 485, [M+Na]⁺ 505 / 507, [M-H]⁻ 481 /
10 483.

CHN analysis: found C 64.92%, H 6.46%, N 5.61%; C₂₇H₃₁ClN₂O₄+0.9H₂O requires C 64.96%, H 6.62%, N 5.61%.

**Example 19: 4-([2-(3-((2*R*)-2-((2*R*)-2-Hydroxy-2-(4-hydroxy-3-
15 hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetyl]-amino)-methyl}-benzoic acid**

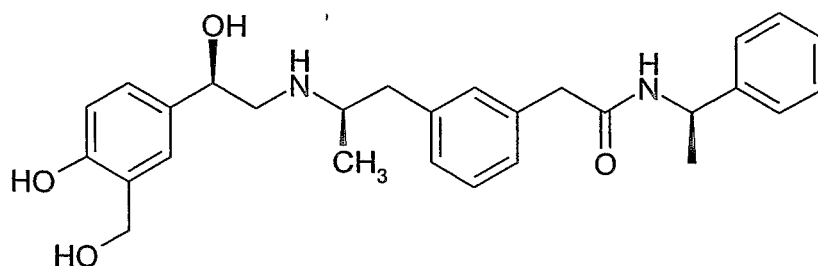


Prepared from 4-([2-(3-((2*R*)-2-((2*R*)-2-((*tert*-butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetyl]-amino)-methyl}-benzoic acid (Preparation 19) using the method for example 3 to give
20 the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.86-7.84 (2H, d), 7.33 (1H, s), 7.28-7.09 (7H, m), 6.78-6.76 (1H, d), 4.80 (1H, m, partially obscured by solvent), 4.65 (2H, s), 4.38 (2H, s), 3.54 (2H, s), 3.43-3.36 (1H, m), 3.13-3.05 (3H, m), 2.71-2.65 (1H, m),
25 1.16-1.14 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 493, $[M+Na]^+$ 515, $[M-H]^-$ 491.

Example 20: 2-{3-[(2*R*)-2-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-[(1*R*)-1-phenylethyl]acetamide



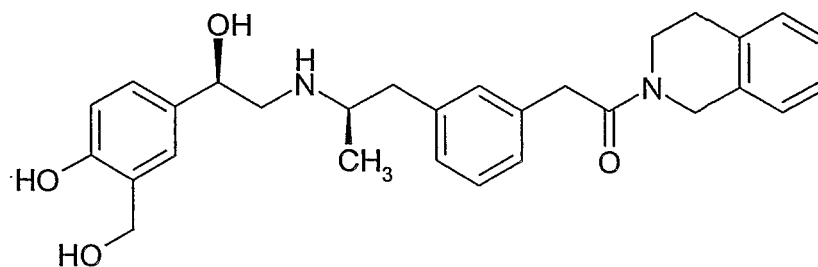
Prepared from 2-{3-[(2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-[(1*R*)-1-phenylethyl]acetamide (Preparation 21) according to the method for example 3 using dichloromethane:methanol: 880 ammonia (90:10:1 by volume) as the column eluent to give the title compound as a white foam.

^1H NMR (400MHz, CD_3OD): δ = 7.27-7.01 (11H, m), 6.73-6.71 (1H, d), 5.01-4.94 (1H, m), 4.69-4.63 (1H, m), 4.63 (2H, s), 3.49 (2H, s), 3.09-3.01 (1H, m), 2.98-2.89 (1H, m), 2.85-2.76 (2H, m), 2.64-2.56 (1H, m), 1.44-1.42 (3H, d) 1.09-1.08 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 463, $[M+Na]^+$ 485, $[M-H]^-$ 461.

CHN analysis : found C 69.24%, H 7.35%, N 5.73%; $\text{C}_{28}\text{H}_{34}\text{N}_2\text{O}_4 + 1.30\text{H}_2\text{O}$ requires C 69.20%, H 7.59%, N 5.76%.

Example 21: 4-[(1*R*)-2-[(1*R*)-2-{3-[2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]phenyl]-1-methylethyl]amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol



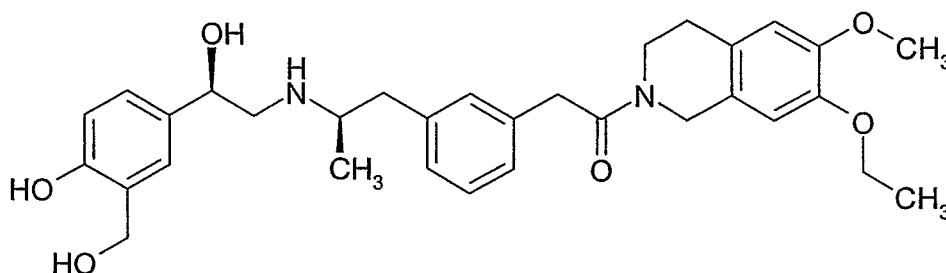
Prepared from 4-((1*R*)-1-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(((1*R*)-2-{3-[2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]phenyl]-1-methylethyl)amino]ethyl)-2-(hydroxymethyl)phenol (Preparation 22) according to the method for example 3 to give the title compound as a white foam.

- 5 ¹H NMR (400MHz, CD₃OD): δ = 7.24-6.94 (10H, m), 6.70-6.68 (1H, d), 4.69-4.67 (2H, m), 4.61 (2H, s), 4.61-4.58 (1H, m), 3.83-3.82 (2H, m), 3.81-3.70 (2H, m), 2.95-2.80 (3H, m), 2.74-2.62 (3H, m), 2.60-2.46 (1H, m), 1.05-0.97 (3H, m) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 475, [M+Na]⁺ 497, [M-H]⁻ 473.

- 10 CHN analysis : found C 71.47%, H 7.29%, N 5.71%; C₂₉H₃₄N₂O₄+0.70H₂O requires C 71.49%, H 7.32%, N 5.75%.

- Example 22:** 4-((1*R*)-2-(((1*R*)-2-{3-[2-(7-Ethoxy-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]phenyl]-1-methylethyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol



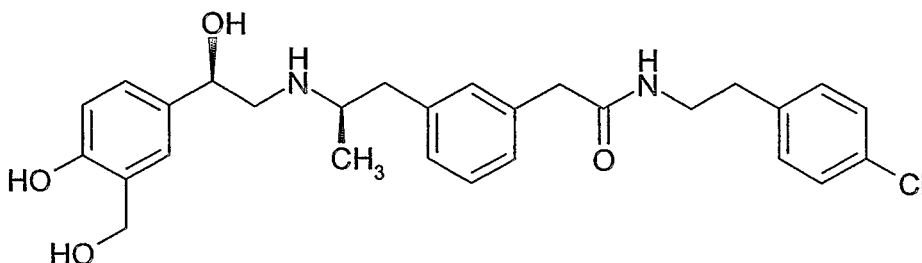
- Prepared from 4-((1*R*)-1-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(((1*R*)-2-{3-[2-(7-ethoxy-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]phenyl]-1-methylethyl)amino]ethyl)-2-(hydroxymethyl)phenol (Preparation 23) according to the method for example 3 to give the title compound as a white foam.

- 20 ¹H NMR (400MHz, CD₃OD): δ = 7.23-6.93 (6H, m), 6.70 (1H, s), 6.70-6.68 (1H, d), 6.65-6.56 (1H, m), 4.61-4.57 (5H, m), 4.02-3.92 (2H, m), 3.82 (2H, s), 3.76 (3H, s), 3.82-3.67 (2H, m), 2.98-2.44 (7H, m), 1.38-1.33 (3H, m), 1.06-0.96 (3H, m) ppm.

- 25 LRMS (electrospray) : m/z [M+H]⁺ 549, [M+Na]⁺ 571, [M-H]⁻ 547.

CHN analysis : found C 68.60%, H 7.47%, N 4.96%; C₃₂H₄₀N₂O₆+0.70H₂O requires C 68.48%, H 7.43%, N 4.99%.

Example 23: *N*-[2-(4-Chlorophenyl)ethyl]-2-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}acetamide



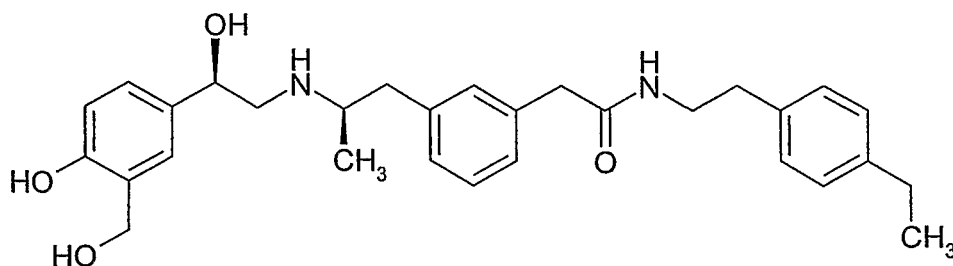
- 5 Prepared from 2-{3-[(2*R*)-2-[(2*R*)-2-[(*tert*-butyl(dimethyl)silyl]oxy)-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-[2-(4-chlorophenyl)ethyl]acetamide (Preparation 24) according to the method for example 3 to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.22-7.16 (4H, m), 7.09-7.01 (6H, m), 6.70-6.68 (1H, d), 4.62-4.59 (1H, m), 4.61 (2H, s), 3.39 (2H, s), 3.39-3.35 (2H, t), 3.00-2.92 (1H, m), 2.90-2.85 (1H, dd), 2.75-2.68 (4H, m), 2.61-2.56 (1H, dd), 1.09-1.07 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 497, [M+Na]⁺ 519, [M-H]⁻ 495.

CHN analysis : found C 66.68%, H 6.77%, N 5.66%; C₂₈H₃₃ClN₂O₄+0.40H₂O
15 requires C 66.70%, H 6.76%, N 5.56%.

Example 24: *N*-[2-(4-Ethylphenyl)ethyl]-2-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}acetamide



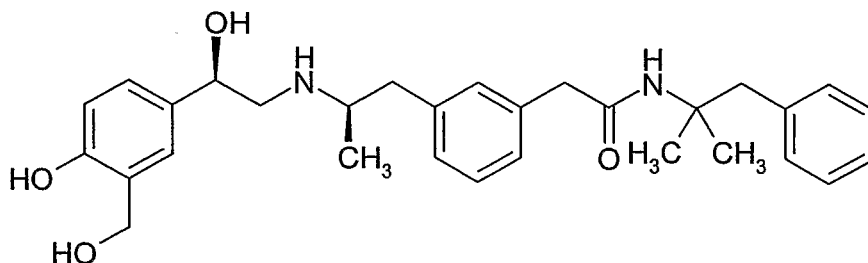
- 20 Prepared from 2-{3-[(2*R*)-2-[(2*R*)-2-[(*tert*-butyl(dimethyl)silyl]oxy)-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-[2-(4-ethylphenyl)ethyl]acetamide (Preparation 25) according to the method for example 3 to give the title compound as a white foam.

^1H NMR (400MHz, CD_3OD): δ = 7.22-7.16 (2H, m), 7.07-7.01 (8H, m), 6.70-6.68 (1H, d), 4.64-4.60 (1H, m), 4.61 (2H, s), 3.41 (2H, s), 3.37-3.34 (2H, t), 3.02-2.95 (1H, m), 2.91-2.86 (1H, dd), 2.75-2.68 (4H, m), 2.62-2.55 (3H, m), 1.20-1.16 (3H, t), 1.09-1.08 (3H, d) ppm.

5 LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 491, $[\text{M}+\text{Na}]^+$ 513, $[\text{M}-\text{H}]^-$ 489.

CHN analysis : found C 71.77%, H 7.84%, N 5.58%; $\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_4+0.60\text{H}_2\text{O}$ requires C 71.86%, H 7.88%, N 5.59%.

Example 25: *N*-(1,1-Dimethyl-2-phenylethyl)-2-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-
10 [4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}acetamide



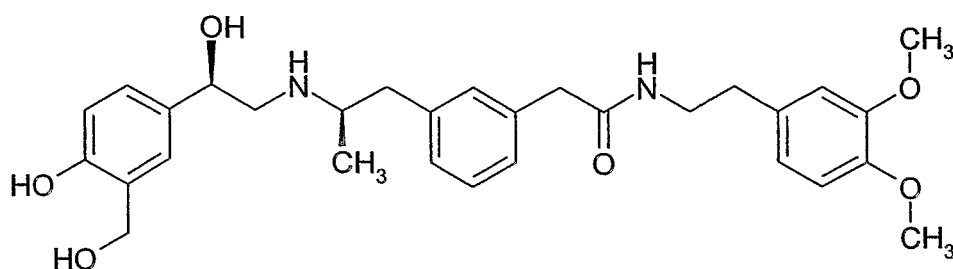
Prepared from 2-{3-[(2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-(1,1-dimethyl-2-phenylethyl)acetamide (Preparation 26) according to the method for example 3
15 to give the title compound as a white foam.

^1H NMR (400MHz, CD_3OD): δ = 7.24-7.20 (2H, m), 7.14-7.11 (4H, m), 7.07-7.02 (3H, m), 6.97-6.95 (2H, m), 6.71-6.69 (1H, d), 4.65-4.61 (1H, m), 4.61 (2H, s), 3.38 (2H, s), 3.01-2.95 (1H, m), 2.99 (2H, s), 2.92-2.87 (1H, dd), 2.79-2.73 (2H, m), 2.62-2.57 (1H, dd), 1.27 (3H, s), 1.26 (3H, s), 1.08-1.07 (3H, d) ppm.

20 LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 491, $[\text{M}+\text{Na}]^+$ 513, $[\text{M}-\text{H}]^-$ 489.

CHN analysis : found C 71.96%, H 7.81%, N 5.51%; $\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_4+0.60\text{H}_2\text{O}$ requires C 71.86%, H 7.88%, N 5.59%.

Example 26: *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}acetamide



Prepared from 2-{3-[(2*R*)-2-({(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-[2-(3,4-

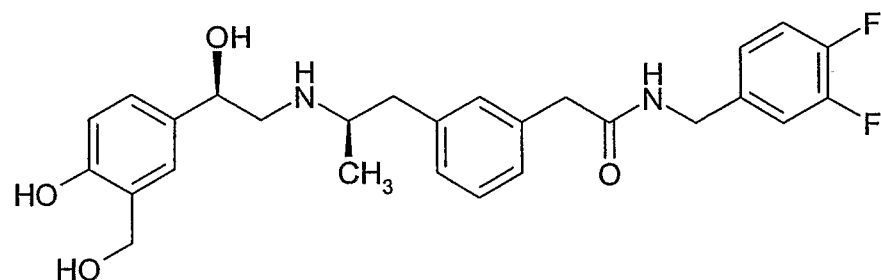
5 dimethoxyphenyl)ethyl]acetamide (Preparation 27) according to the method for

¹H NMR (400MHz, CD₃OD): δ = 7.21-7.15 (2H, m), 7.06-7.00 (4H, m), 6.82-6.77 (2H, m), 6.70-6.65 (2H, m), 4.64-4.59 (1H, m), 4.61 (2H, s), 3.78 (3H, s), 3.75 (3H, s), 3.41 (2H, s), 3.40-3.37 (2H, t), 2.98-2.91 (1H, m), 2.90-2.85 (1H, dd), 2.74-2.67 (4H, m), 2.60-2.55 (1H, dd), 1.08-1.07 (3H, d) ppm.

10 LRMS (electrospray) : m/z [M+H]⁺ 523, [M+Na]⁺ 545, [M-H]⁻ 521.

CHN analysis : found C 67.27%, H 7.73%, N 4.96%;
C₃₀H₃₈N₂O₆+0.70H₂O+0.20Et₂O requires C 67.25%, H 7.59%, N 5.09%.

Example 27: *N*-(3,4-Difluorobenzyl)-2-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-



Prepared from 2-{3-[(2*R*)-2-({(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-(3,4-

20 difluorobenzyl)acetamide (Preparation 28) according to the method for example

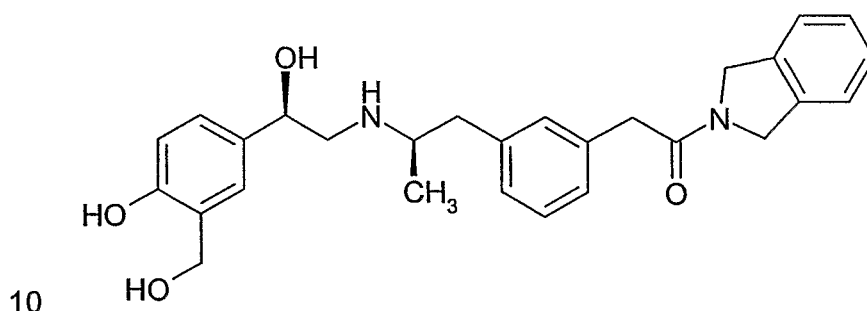
¹H NMR (400MHz, CD₃OD): δ = 7.21-7.15 (3H, m), 7.13-7.08 (3H, m), 7.06-7.00 (3H, m), 6.70-6.68 (1H, d), 4.61-4.57 (3H, m), 4.30 (2H, s), 3.50 (2H, s),

2.94-2.83 (2H, m), 2.71-2.66 (2H, m), 2.59-2.54 (1H, dd), 1.06-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 485, $[M+Na]^+$ 507, $[M-H]^-$ 483.

CHN analysis : found C 65.60%, H 6.32%, N 5.76%; $C_{27}H_{30}F_2N_2O_4+0.50H_2O$
 5 requires C 65.71%, H 6.33%, N 5.68%.

Example 28: 4-((1*R*)-2-(((1*R*)-2-{3-[2-(1,3-Dihydro-2*H*-isoindol-2-yl)-2-oxoethyl]phenyl}-1-methylethyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol



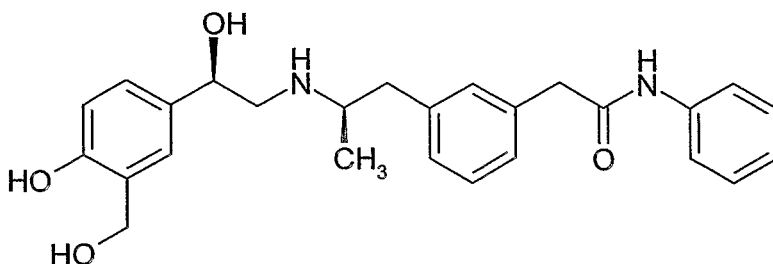
Prepared from 4-((1*R*)-1-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(((1*R*)-2-{3-[2-(1,3-dihydro-2*H*-isoindol-2-yl)-2-oxoethyl]phenyl}-1-methylethyl)amino]ethyl)-2-(hydroxymethyl)phenol (Preparation 29) according to the method for example 3 to give the title compound as a white foam.

15 1H NMR (400MHz, CD_3OD): δ = 7.29-7.27 (4H, m), 7.23-7.19 (2H, m), 7.15-7.13 (1H, d), 7.09 (1H, s), 7.02-6.96 (2H, m), 6.68-6.66 (1H, d), 4.74 (2H, s), 4.61-4.58 (3H, m), 3.77 (2H, s), 3.29 (2H, s), 2.96-2.83 (2H, m), 2.71-2.65 (2H, m), 2.62-2.57 (1H, dd), 1.07-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 461, $[M-H]^-$ 459.

20

Example 29: 2-{3-[(2*R*)-2-((2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}-*N*-phenylacetamide



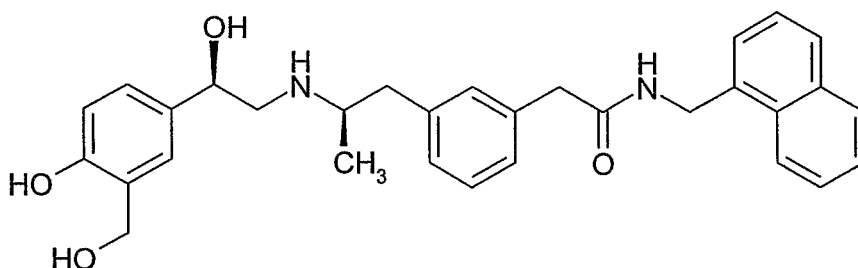
Prepared from 2-{3-[(2R)-2-({(2R)-2-[[*tert*-butyl(dimethyl)silyl]oxy)-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-phenylacetamide (Preparation 30) according to the method for example 3 to give the title compound as a white foam.

^1H NMR (400MHz, CD_3OD): δ = 7.53-7.51 (2H, d), 7.29-7.10 (6H, m), 7.08-6.99 (3H, m), 6.70-6.68 (1H, d), 4.66-4.58 (3H, m), 3.62 (2H, s), 3.01-2.85 (2H, m), 2.74-2.68 (2H, m), 2.62-2.57 (1H, dd), 1.08-1.06 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 435, $[\text{M}+\text{Na}]^+$ 457, $[\text{M}-\text{H}]^-$ 433.

10

Example 30: 2-{3-[(2R)-2-({(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-(1-naphthylmethyl)acetamide



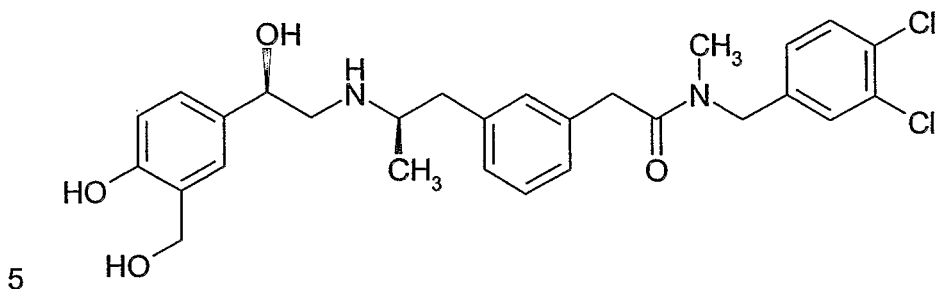
Prepared from 2-{3-[(2R)-2-({(2R)-2-[[*tert*-butyl(dimethyl)silyl]oxy)-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-(1-naphthylmethyl)acetamide (Preparation 31) according to the method for example 3 to give the title compound as a white foam.

^1H NMR (400MHz, CD_3OD): δ = 7.96-7.94 (1H, d), 7.86-7.83 ((1H, d), 7.79-7.76 (1H, dd), 7.48-7.42 (2H, m), 7.40-7.36 (2H, m), 7.20-7.09 (3H, m), 7.00-6.96 (3H, m), 6.70-6.68 (2H, d), 4.80 (2H, s), 4.61-4.55 (3H, m), 3.49 (2H, s), 2.83-2.78 (2H, m), 2.66-2.60 (2H, m), 2.50-2.45 (1H, dd), 1.00-0.99 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 499, $[\text{M}+\text{Na}]^+$ 521, $[\text{M}-\text{H}]^-$ 497.

20

Example 31: *N*-(3,4-Dichlorobenzyl)-2-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}-*N*-methylacetamide

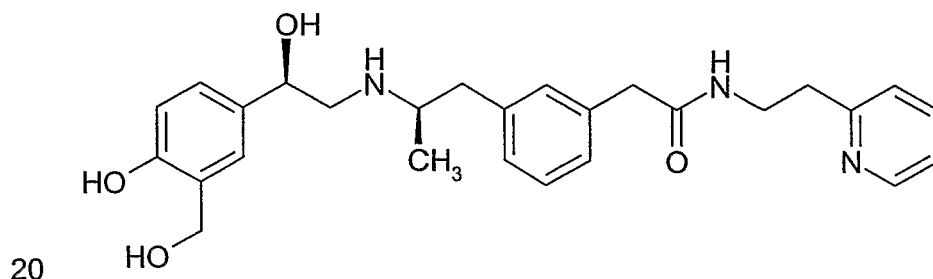


Prepared from (3-{(2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl}-phenyl)-acetic acid (Preparation 36) and the appropriate amine, using the amide coupling procedure of preparation 5 and the deprotection procedure of example 3 to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.44-7.36 (2H, m), 7.23-7.13 (2H, m), 7.10-7.04 (2H, m), 7.02-6.93 (3H, m), 6.70-6.67 (1H, d), 4.69-4.61 (5H, m), 3.78-3.76 (2H, d), 2.96 (2H, s), 2.93-2.83 (3H, m), 2.69-2.63 (2H, m), 2.60-2.49 (1H, m), 1.07-1.00 (3H, m) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 531, [M+Na]⁺ 553, [M-H]⁻ 529.

Example 32: 2-{3-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}-*N*-(2-pyridin-2-ylethyl)acetamide



Prepared from 2-{3-[(2*R*)-2-({(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}-*N*-(2-pyridin-2-

ylethyl)acetamide (Preparation 32) according to the method for example 3 to give the title compound as a white foam.

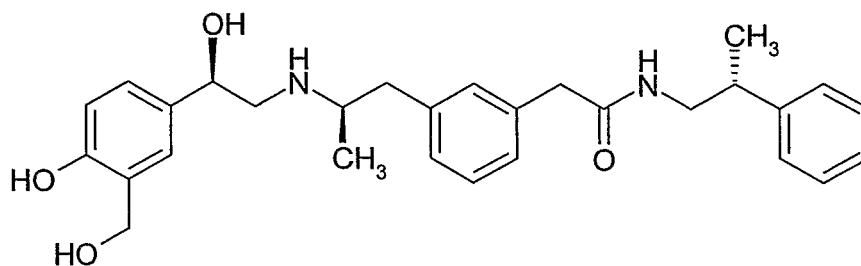
^1H NMR (400MHz, CD_3OD): δ = 8.40-8.39 (1H, d), 7.69-7.65 (1H, m), 7.24-7.16 (4H, m), 7.06-7.00 (4H, m), 6.70-6.68 (1H, d), 4.61-4.59 (3H, m), 3.53-3.50 (2H, t), 3.40 (2H, s), 2.96-2.84 (4H, m), 2.72-2.66 (2H, m), 2.60-2.55 (1H, m), 1.08-1.06 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 464, $[\text{M}+\text{Na}]^+$ 486, $[\text{M}-\text{H}]^-$ 462.

CHN analysis : found C 67.36%, H 7.21%, N 8.95%; $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_4+1.00\text{H}_2\text{O}$ requires C 67.34%, H 7.33%, N 8.73%.

10

Example 33: 2-{3-[(2R)-2-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-N-[(2R)-2-phenylpropyl]acetamide



15 Prepared from 2-{3-[(2R)-2-[(2R)-2-[(*tert*-butyl(dimethyl)silyl]oxy)-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-N-[(2R)-2-phenylpropyl]acetamide (Preparation 33) according to the method for example 3 to give the title compound as a white foam.

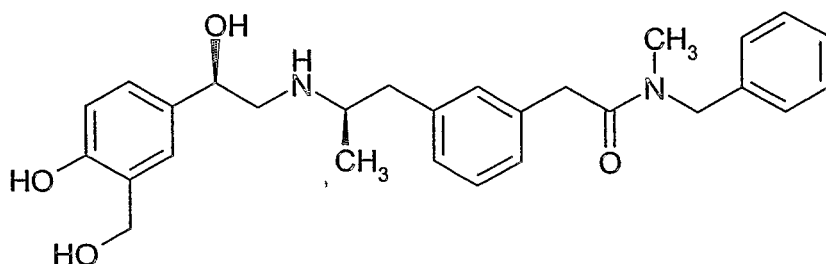
^1H NMR (400MHz, CD_3OD): δ = 7.31-7.21 (4H, m), 7.18-7.12 (3H, m), 7.03-6.97 (4H, m), 6.70-6.68 (1H, d), 4.61-4.57 ((3H, m), 3.37 (2H, s), 2.93-2.79 (4H, m), 2.71-2.64 (2H, m), 2.57-2.52 (1H, m), 1.26-1.24 (1H, m), 1.20-1.18 (3H, d), 1.07-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 477, $[\text{M}+\text{Na}]^+$ 499, $[\text{M}-\text{H}]^-$ 475.

CHN analysis : found C 71.73%, H 7.75%, N 6.12%; $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_4+0.50\text{H}_2\text{O}$ requires C 71.73%, H 7.68%, N 5.77%.

25

Example 34: *N*-Benzyl-2-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-methylacetamide



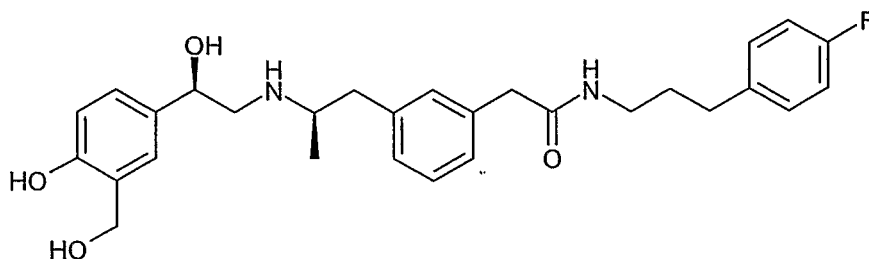
Prepared from *N*-benzyl-2-{3-[(2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-methylacetamide (Preparation 34) according to the method for example 3 to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.33-7.17 (6H, m), 7.11-7.06 (2H, m), 7.03-7.00 (3H, m), 6.71-6.69 (1H, d), 4.62-4.53 (5H, m), 3.78-3.76 (2H, m), 2.96-2.84 (5H, m), 2.75-2.67 (2H, m), 2.60-2.52 (1H, m), 1.03 (3H, m) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 463; [M+Na]⁺ 485, [M-H]⁻ 461.

CHN analysis : found C 70.58%, H 7.38%, N 5.78%; C₂₈H₃₄N₂O₄+0.75H₂O requires C 70.64%, H 7.52%, N 5.88%.

Example 35: *N*-[3-(4-Fluorophenyl)propyl]-2-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}acetamide



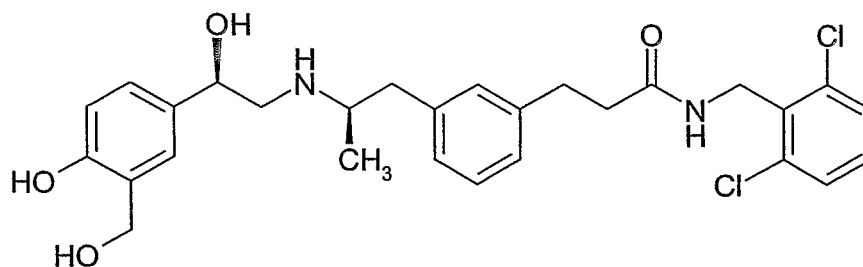
Prepared from 2-{3-[(2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-[3-(4-fluorophenyl)propyl]acetamide (Preparation 35) according to the method for example 3 to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD) δ : 7.25-7.22 (2H, m), 7.17-7.12 (4H, m), 7.06-6.96 (4H, m), 6.74 (1H, d), 4.67-4.62 (m, 3H), 3.49 (2H, s), 3.22-3.19 (2H, s), 2.99-

2.87 (2H, m), 2.75-2.70 (2H, m), 2.63-2.57 (3H, m), 1.81-1.76 (2H, m), 1.09 (3H, s) ppm.

MS (electrospray) : 495 $[M+H]^+$, 517 $[M+Na]^+$, 493 $[M-H]^-$

5 Example 36: *N*-(2,6-Dichlorobenzyl)-3-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-propanamide



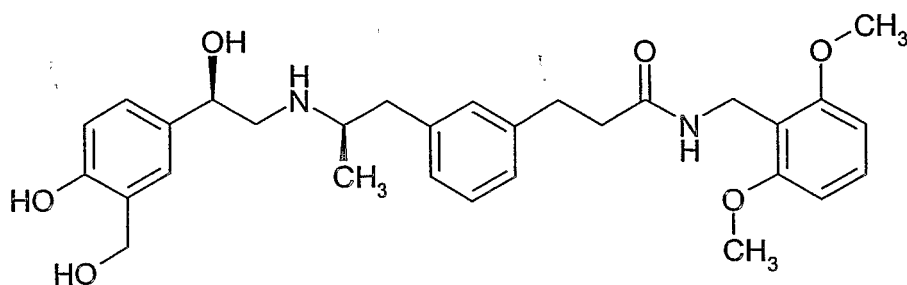
Prepared from 2-(3-((2*R*)-2-((2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-*N*-(2,6-dichlorobenzyl)-propanamide (Preparation 45) using the method for example 3 to give the title compounds as a white foam.

^1H NMR (400MHz, CD_3OD): δ = 7.39-7.37 (2H, d), 7.28-7.22 (2H, m), 7.15-7.11 (1H, t), 7.03-7.01 (2H, d), 6.98 (1H, s), 6.95-6.93 (1H, d), 6.71-6.69 (1H, d), 4.66-4.58 (5H, m), 3.05-2.09 (1H, m), 2.94-2.84 (3H, m), 2.79-2.71 (2H, m), 2.60-2.54 (1H, dd), 2.48-2.41 (2H, t), 1.09-1.08 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 531 / 533, $[M+Na]^+$ 553 / 555, $[M-H]^-$ 529 / 531.

CHN analysis: found C 60.34%, H 6.00%, N 4.89%; $\text{C}_{28}\text{H}_{32}\text{Cl}_2\text{N}_2\text{O}_4 + 1.45 \text{ H}_2\text{O}$ requires C 60.31%, H 6.31%, N 5.02%.

Example 37: *N*-(2,6-Dimethoxybenzyl)-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanamide

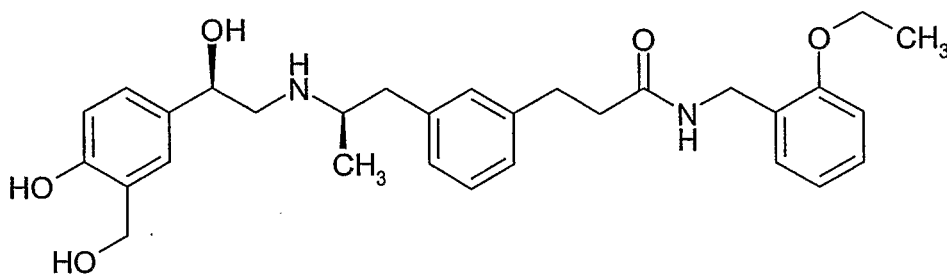


Prepared from 3-{3-[(2*R*)-2-({(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}-*N*-(2,6-dimethoxybenzyl)propanamide (Preparation 46) according to the method for
 5 example 1 using methanol:water (2.4:1 v/v) instead of acetic acid as solvent and using dichloromethane:methanol: 880 ammonia (97.5:2.5:0.25 by volume) as the column eluent to give the title compound as a white solid after trituration with diethyl ether.

¹H NMR (400MHz, CD₃OD): δ = 7.24-7.19 (2H, m), 7.13-7.09 (1H, t), 7.01-6.99
 10 (2H, d), 6.95-6.90 (2H, m), 6.70-6.68 (1H, d), 6.61-6.59 (2H, d), 4.65-4.60 (1H, m), 4.60 (2H, s), 4.38 (2H, s), 3.78 (6H, s), 2.97-2.81 (4H, m), 2.73-2.64 (2H, m), 2.57-2.52 (1H, dd), 2.43-2.39 (2H, t), 1.07-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 523, [M+Na]⁺ 545, [M-H]⁻ 521.

15 **Example 38: *N*-(2-Ethoxybenzyl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}propanamide**



Prepared from 3-{3-[(2*R*)-2-({(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}-*N*-(2-ethoxybenzyl)propanamide (Preparation 47) according to the method for
 20 example 1 using methanol:water (2.4:1 v/v) instead of acetic acid as solvent

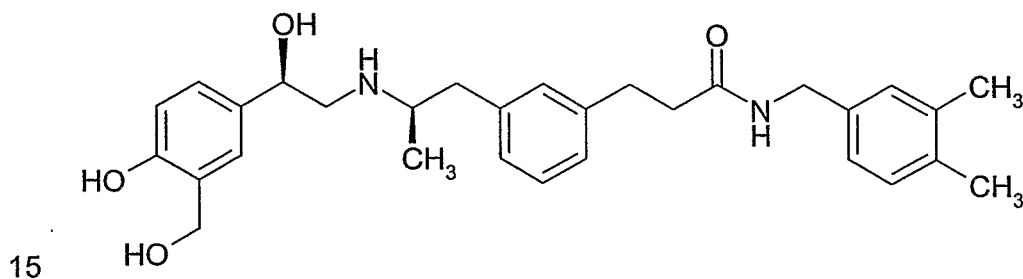
and using dichloromethane:methanol: 880 ammonia (94:6:0.6 by volume) as the column eluent to give the title compound as a white solid.

¹H NMR (400MHz, CD₃OD): δ = 7.24 (1H, s), 7.19-7.15 (2H, t), 7.07-6.98 (4H, m), 6.93-6.87 (2H, dd), 6.81-6.77 (1H, t), 6.72-6.70 (1H, d), 4.70-4.64 (1H, m),
 5 4.62 (2H, s), 4.31 (2H, s), 4.05-4.00 (2H, q), 3.10-3.04 (1H, m), 2.97-2.88 (3H, m), 2.83-2.74 (2H, m), 2.62-2.50 (3H, m), 1.39-1.36 (3H, t), 1.09-1.08 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 507, [M+Na]⁺ 529, [M-H]⁻ 505.

CHN analysis : found C 69.31%, H 7.53%, N 5.20%; C₃₀H₃₈N₂O₅+0.75H₂O
 10 requires C 69.27%, H 7.65%, N 5.39 %.

Example 39: N-(3,4-Dimethylbenzyl)-3-{3-[(2R)-2-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanamide



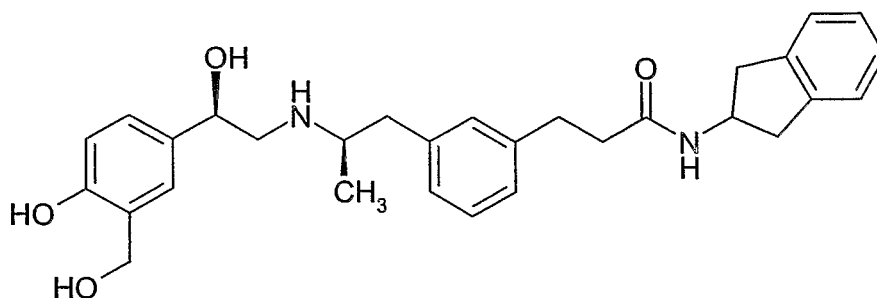
Prepared from 3-{3-[(2R)-2-[(2R)-2-[[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-N-(3,4-dimethylbenzyl)propanamide (Preparation 48) according to the method for
 20 example 1 using methanol:water (2.4:1 v/v) instead of acetic acid as solvent and using dichloromethane:methanol: 880 ammonia (94:6:0.6 by volume) as the column eluent to give the title compound as a white solid.

¹H NMR (400MHz, CD₃OD): δ = 7.21 (1H, s), 7.16-7.12 (1H, t), 7.04-6.92 (6H, m), 6.82-6.81 (1H, d), 6.70-6.68 (1H, d), 4.65-4.61 (1H, m), 4.61 (2H, s), 4.22 (2H, s), 2.97-2.85 (4H, m), 2.72-2.64 (2H, m), 2.57-2.52 (1H, dd), 2.51-2.47
 25 (2H, t), 2.20 (6H, s), 1.06-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 491, [M+Na]⁺ 513, [M-H]⁻ 489.

CHN analysis : found C 71.55%, H 7.71%, N 5.59%; $C_{30}H_{38}N_2O_4 + 0.70H_2O$ requires C 71.60%, H 7.89%, N 5.57 %.

Example 40: *N*-(2,3-Dihydro-1*H*-inden-2-yl)-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanamide



Prepared from 3-{3-[(2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-(2,3-dihydro-1*H*-inden-2-yl)propanamide (Preparation 49) according to the method for example 1 using
 10 methanol:water (2.4:1 v/v) instead of acetic acid as solvent and using dichloromethane:methanol: 880 ammonia (94:6:0.6 by volume) as the column eluent to give the title compound as a white solid.

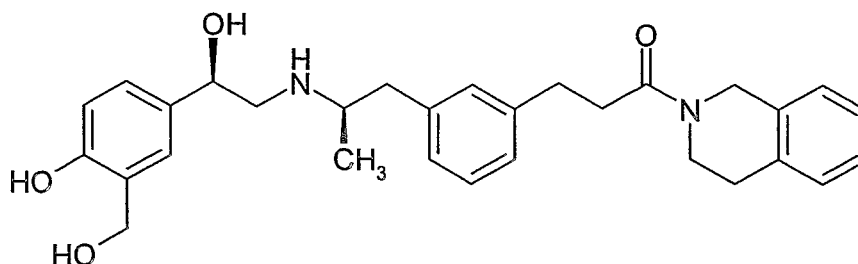
1H NMR (400MHz, CD_3OD): δ = 7.21-7.09 (6H, m), 7.02-6.92 (4H, m), 6.69-6.67 (1H, d), 4.65-4.56 (1H, m), 4.60 (2H, s), 4.53-4.50 (1H, t), 3.20-3.14 (2H, dd), 2.94-2.81 (4H, m), 2.76-2.64 (4H, m), 2.57-2.52 (1H, dd), 2.43-2.40 (2H, t),
 15 1.06-1.05 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 489, $[M+Na]^+$ 511, $[M-H]^-$ 487.

CHN analysis : found C 71.08%, H 7.35%, N 5.58%; $C_{30}H_{36}N_2O_4 + 1.05H_2O$ requires C 71.00%, H 7.57%, N 5.52 %.

20

Example 41: 4-[(1*R*)-2-[(1*R*)-2-{3-[3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-3-oxopropyl]phenyl}-1-methylethyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol



Prepared from 4-{{(1*R*)-1-[[*tert*-butyl(dimethyl)silyl]oxy}-2-[[{(1*R*)-2-{3-[3-(3,4-dihydroisoquinolin-2(1*H*)-yl)-3-oxopropyl]phenyl}-1-methylethyl)amino]ethyl}-2-(hydroxymethyl)phenol (Preparation 50) according to the method for example 1
 5 using methanol:water (2.4:1 v/v) instead of acetic acid as solvent and using dichloromethane:methanol: 880 ammonia (95:5:0.5 by volume) as the column eluent to give the title compound as a white solid.

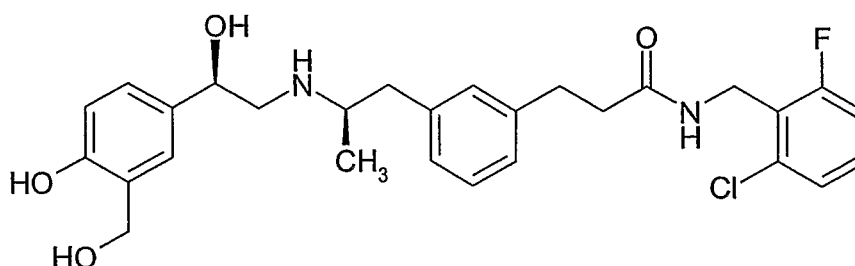
¹H NMR (400MHz, CD₃OD): δ = 7.22 (1H, s), 7.16-6.93 (8H, m), 6.87-6.85 (1H, bd), 6.71-6.68 (1H, m), 4.65-4.55 (2H, m), 4.63-4.60 (1H, m), 4.61 (2H, s), 3.75-
 10 3.60 (2H, m), 2.95-2.85 (4H, m), 2.80-2.60 (6H, m), 2.53-2.47 (1H, dd), 1.05-1.02 (3H, m) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 489, [M+Na]⁺ 511, [M-H]⁻ 487.

CHN analysis : found C 71.06%, H 7.27%, N 5.46%; C₃₀H₃₆N₂O₄+1.05H₂O requires C 71.00%, H 7.57%, N 5.52 %.

15

Example 42: *N*-(2-Chloro-6-fluorobenzyl)-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanamide



A solution of 3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanoic acid (Preparation
 20 60) (150mg, 0.29mmol), O-(1*H*-benzotrizol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (133mg, 0.35mmol), 2-fluoro-6-chlorobenzylamine (56mg, 0.35mmol) and triethylamine (0.12ml, 0.88mmol) were stirred at room

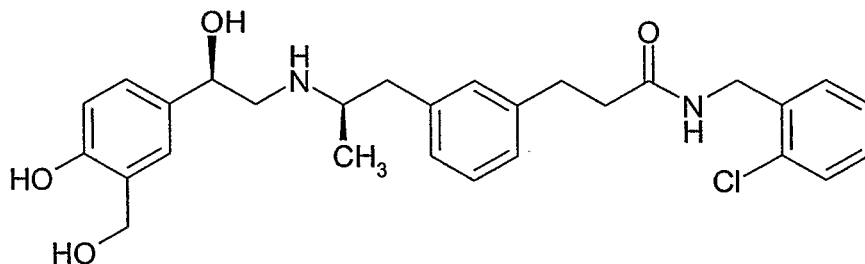
temperature for 16 hours in *N,N*-dimethylformamide (3ml). The solvent was removed *in vacuo* and the resulting brown oil was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol: 880 ammonia (98:2:0.2 followed by 94:6:0.6 by volume) to give the title compound as a white foam (30mg).

¹H NMR (400MHz, CD₃OD): δ = 7.32-7.20 (3H, m), 7.12-6.98 (4H, m), 6.95 (1H, s), 6.92-6.90 (1H, d), 6.70-6.68 (1H, d), 4.64-4.60 (3H, m), 4.49 (2H, s), 2.98-2.83 (4H, m), 2.75-2.66 (2H, m), 2.58-2.53 (1H, dd), 2.47-2.43 (2H, t), 1.08-1.07 (3H, d) ppm.

10 LRMS (electrospray) : m/z [M+H]⁺ 517, [M+Na]⁺ 537, [M-H]⁻ 513.

CHN analysis : found C 62.04%, H 6.11%, N 5.15%;
C₂₈H₃₂N₂O₄ClF+0.05H₂O+0.40CH₂Cl₂ requires C 62.03%, H 6.03%, N 5.09%.

Example 43: *N*-(2-Chlorobenzyl)-3-{3-[(2*R*)-2-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanamide



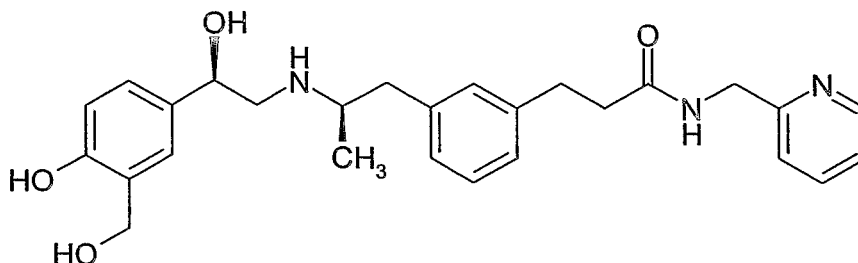
Prepared according to the procedure used for example 42 using 3-{3-[(2*R*)-2-((2*R*)-2-hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanoic acid (Preparation 20 60) and the appropriate amine to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.35-7.01 (10H, m), 6.76-6.74 (1H, d), 4.77-4.74 (1H, dd), 4.64 (2H, s), 4.39 (2H, s), 3.07-2.90 (6H, m), 2.67-2.55 (3H, m), 1.14-1.13 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 497, [M+Na]⁺ 519, [M-H]⁻ 495.

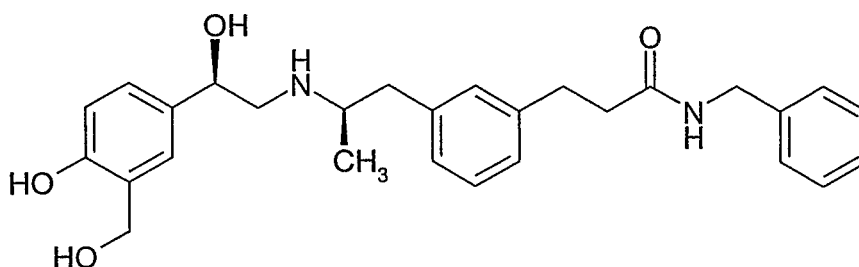
Example 44: 3-{3-[(2*R*)-2-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-(pyridin-2-ylmethyl)propanamide



- 5 Prepared according to the procedure used for example 42 using 3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanoic acid (Preparation 60) and the appropriate amine to give the title compound as a white foam.
- ¹H NMR (400MHz, CD₃OD): δ = 8.42-8.41 (1H, d), 7.71-7.67 (1H, m), 7.27-7.14 (3H, m), 7.06-6.96 (5H, m), 6.71-6.68 (1H, d), 4.63-4.59 (3H, m), 4.42 (2H, s), 2.96-2.85 (4H, m), 2.72-2.65 (2H, m), 2.59-2.53 (3H, m), 1.06-1.05 (3H, d) ppm.
- 10 LRMS (electrospray) : m/z [M+H]⁺ 464, [M+Na]⁺ 486, [M-H]⁻ 462.
- CHN analysis : found C 66.60%, H 6.97%, N 8.54%;
C₂₇H₃₃N₃O₄+0.05H₂O+0.35CH₂Cl₂ requires C 66.47%, H 6.89%, N 8.50%.

15

Example 45: *N*-Benzyl-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanamide



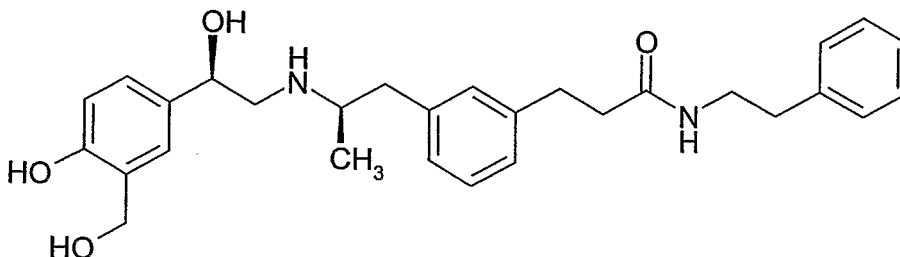
- Prepared according to the procedure used for example 42 using 3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanoic acid (Preparation 60) and the appropriate amine to give the title compound as a white foam.
- 20

^1H NMR (400MHz, CD_3OD): δ = 7.26-6.90 (11H, m), 6.70-6.68 (1H, d), 4.61-4.58 (3H, m), 4.30 (2H, s), 2.94-2.83 (4H, m), 2.70-2.63 (2H, m), 2.57-2.49 (3H, m), 1.06-1.04 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 463, $[\text{M}+\text{Na}]^+$ 485, $[\text{M}-\text{H}]^-$ 461.

- 5 CHN analysis : found C 68.16%, H 7.16%, N 5.66%;
 $\text{C}_{28}\text{H}_{34}\text{N}_2\text{O}_4 + 0.05\text{H}_2\text{O} + 0.25\text{CH}_2\text{Cl}_2$ requires C 68.11%, H 7.03%, N 5.58%.

Example 46: 3-{3-[(2*R*)-2-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-(2-phenylethyl)propanamide



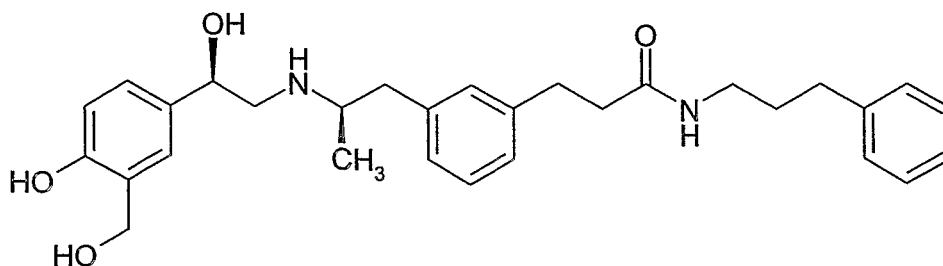
Prepared according to the procedure used for example 42 using 3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-

- (hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanoic acid (Preparation 15 60) and the appropriate amine to give the title compound as a white foam.

^1H NMR (400MHz, CD_3OD): δ = 7.26-7.22 (3H, m), 7.18-7.12 (4H, m), 7.03-7.01 (2H, d), 6.97-6.94 (2H, d), 6.71-6.69 (1H, d), 4.64-4.58 (3H, m), 3.36-3.30 (2H, m), 3.00-2.81 (4H, m), 2.75-2.68 (4H, m), 2.59-2.54 (1H, dd), 2.42-2.39 (2H, t), 1.08-1.06 (3H, d) ppm.

- 20 LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 477, $[\text{M}+\text{Na}]^+$ 499, $[\text{M}-\text{H}]^-$ 475.

Example 47: 3-{3-[(2*R*)-2-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-(3-phenylpropyl)propanamide

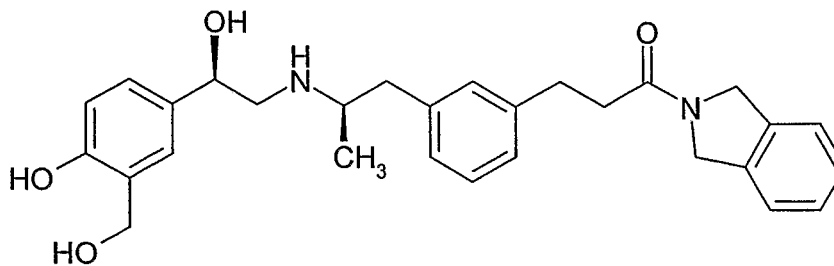


Prepared according to the procedure used for example 42 using 3-{3-[(2R)-2-
 ((2R)-2-hydroxy-2-[4-hydroxy-3-
 (hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}propanoic acid (Preparation
 5 60) and the appropriate amine to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.25-7.21 (3H, m), 7.15-7.11 (4H, m), 7.04-
 7.00 (2H, m), 6.97 (1H, s), 6.92-6.91 (1H, d), 6.71-6.69 (1H, d), 4.62-4.58 (3H,
 m), 3.14-3.11 (2H, t), 2.93-2.83 (4H, m), 2.70-2.62 (2H, m), 2.54-2.49 (3H, m),
 2.45-2.42 (2H, t), 1.73-1.66 (2H, m), 1.04-1.03 (3H, d) ppm.

10 LRMS (electrospray) : m/z [M+H]⁺ 491, [M+Na]⁺ 513, [M-H]⁻ 489.

Example 48: 4-{(1R)-2-[(1R)-2-{3-[3-(1,3-Dihydro-2H-isoindol-2-yl)-3-oxopropyl]phenyl}-1-methylethyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol



15

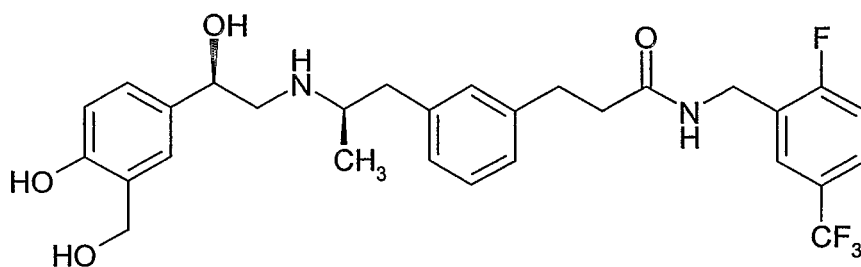
Prepared according to the procedure used for example 42 using 3-{3-[(2R)-2-
 ((2R)-2-hydroxy-2-[4-hydroxy-3-
 (hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}propanoic acid (Preparation
 60) and the appropriate amine to give the title compound as a pale grey foam.

20 ¹H NMR (400MHz, CD₃OD): δ = 7.30-7.21 (5H, m), 7.17-7.13 (1H, t), 7.10-7.08
 (1H, d), 7.03-6.99 (2H, m), 6.93-6.92 (1H, d), 6.70-6.68 (1H, d), 4.71-4.69 (4H,
 d), 4.65-4.58 (3H, m), 2.97-2.84 (4H, m), 2.74-2.65 (4H, m), 2.56-2.51 (1H, dd),
 1.02-1.01 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 475, $[M+Na]^+$ 497, $[M-H]^-$ 473.

CHN analysis : found C 70.10%, H 7.03%, N 5.66%; $C_{29}H_{34}N_2O_4 + 1.20H_2O$ requires C 70.19%, H 7.39%, N 5.65%.

5 Example 49: *N*-[2-Fluoro-5-(trifluoromethyl)benzyl]-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanamide



Prepared according to the procedure used for example 42 using 3-{3-[(2*R*)-2-
10 [(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanoic acid (Preparation 60) and the appropriate amine to give the title compound as a white foam.

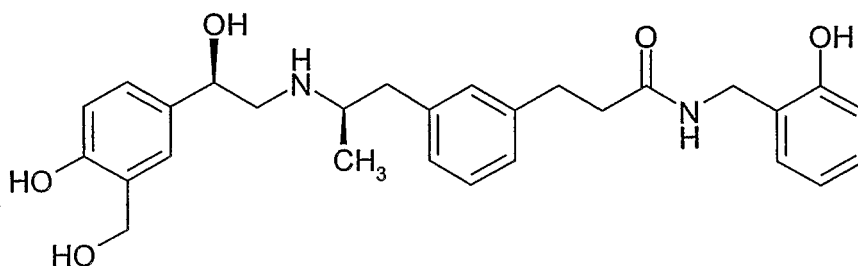
1H NMR (400MHz, CD_3OD): δ = 7.63-7.59 (2H, m), 7.28-7.21 (2H, m), 7.12-7.08 (1H, m), 7.02-6.91 (4H, m), 6.70-6.68 (1H, d), 4.63-4.58 (3H, m), 4.40 (2H, s), 2.96-2.84 (4H, m), 2.72-2.64 (2H, m), 2.57-2.48 (3H, m), 1.06-1.05 (3H, d)
15 ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 549, $[M+Na]^+$ 571, $[M-H]^-$ 547.

CHN analysis : found C 60.76%, H 5.79%, N 4.87%; $C_{29}H_{32}N_2O_4F_4 + 1.35H_2O$ requires C 60.80%, H 6.11%, N 4.89%.

20

Example 50: *N*-(2-Hydroxybenzyl)-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanamide



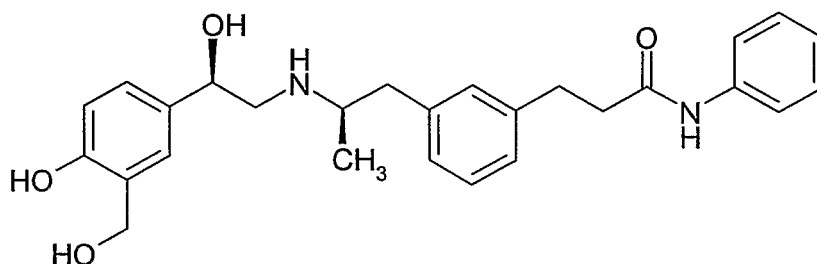
Prepared according to the procedure used for example 42 using 3-{3-[(2*R*)-2-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}propanoic acid (Preparation 60) and the appropriate amine to give the title compound as a white foam.

- 5 ¹H NMR (400MHz, CD₃OD): δ = 7.21 (1H, m), 7.12-6.99 (4H, m), 6.95-6.91 (3H, m), 6.77-6.68 (3H, m), 4.65-4.59 (3H, m), 4.27 (2H, s), 2.94-2.84 (4H, m), 2.70-2.61 (2H, m), 2.55-2.47 (3H, m), 1.05-1.04 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 479, [M+Na]⁺ 501, [M-H]⁻ 477.

- CHN analysis : found C 66.61%, H 6.91%, N 5.57%; C₂₈H₃₄N₂O₅+0.40 CH₂Cl₂
10 requires C 66.55%, H 6.84%, N 5.47%.

Example 51: 3-{3-[(2*R*)-2-((2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}-*N*-phenylpropanamide



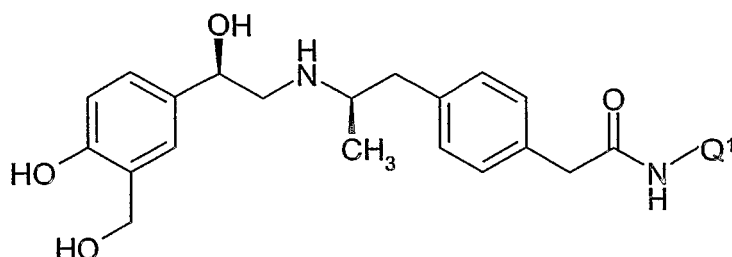
- 15 Prepared according to the procedure used for preparation 1 using 3-{3-[(2*R*)-2-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}propanoic acid (Preparation 60) and the appropriate amine, substituting dichloromethane instead of ethyl acetate as the extraction solvent to give the title compound as a white foam.

- 20 ¹H NMR (400MHz, CD₃OD): δ = 7.49-7.47 (2H, d), 7.28-7.21 (3H, m), 7.17-7.13 (1H, t), 7.08-7.00 (4H, m), 6.94-6.92 (1H, d), 6.71-6.69 (1H, d), 4.63-4.58 (3H, m), 2.97-2.84 (4H, m), 2.71-2.52 (5H, m), 1.04-1.02 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 449, [M+Na]⁺ 471, [M-H]⁻ 447.

25 Examples 52-63

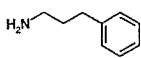
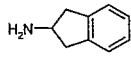
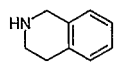
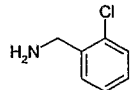
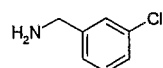
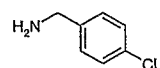
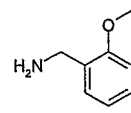
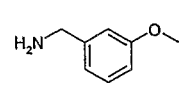
Examples 52 to 63 are of formula:

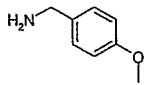
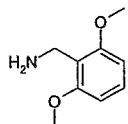
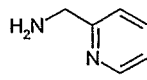


A solution of (4-{2-[2-(*tert*-butyldimethylsilanyloxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)ethylamino]propyl}phenyl)acetic acid (Preparation 61) (150mg, 0.32mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
 5 hydrochloride (67mg, 0.34mmol), 1-hydroxybenzotriazole monohydrate (54mg, 0.34mol) and diisopropylethylamine (82mg, 0.63mmol) were stirred in *N, N*-dimethylformamide (3ml) with the appropriate amine (0.34mmol) at room temperature for 18 hours. The solvent was removed *in vacuo* and the crude material taken up in a mixture of dichloromethane (5ml) and saturated
 10 potassium carbonate (3ml) and passed through a phase separating column. The organic layer was concentrated *in vacuo* and the material taken up in methanol (1ml) and treated with ammonium fluoride (117mg, 3.20mmol) in water (0.5ml) and the resulting mixture heated to 40°C for 20 hours

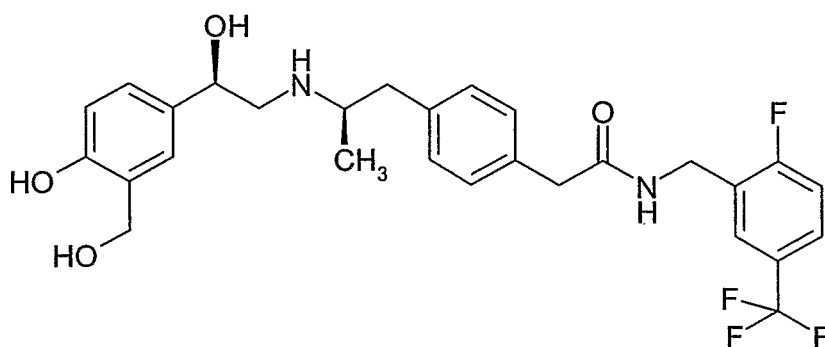
The solvent was removed *in vacuo* and dimethylsulfoxide (2ml) added and the
 15 mixture filtered before being purified by reverse phase chromatography (A - acetonitrile, B - H₂O buffered with 0.1% diethylamine : 0-1.90min 5% B, 1.90-2.00min 5-10% B, 2.00-10.50min 10-95% B, 10.50-13.80min 95% B) using a 150 x 21.2mm C8(2) column (0-3.00min 10-95% B).

Example number	Name	Amine used (intermediate (3), (3') or (3''))	HRMS [M+H] ⁺ calculated	HRMS [M+H] ⁺ found	Retention minutes
52	<i>N</i> -Benzyl-2-(4-((2 <i>R</i>)-2-((2 <i>R</i>)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl-amino)propyl)phenyl)acetamide		449.2442	449.2471	1.64

53	2-(4-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl-amino]propyl}phenyl)- <i>N</i> -(3-phenyl-propyl)acetamide		477.2755	477.2730	1.86
54	2-(4-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl-amino]propyl}phenyl)- <i>N</i> -indan-2-yl-acetamide		475.2598	475.2574	1.81
55	1-(3,4-Dihydro-1 <i>H</i> -isoquinolin-2-yl)-2-(4-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino]propyl}phenyl)ethanone		475.2598	475.2572	1.86
56	<i>N</i> -(2-Hydroxybenzyl)-2-(4-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]propyl}phenyl)-acetamide		483.2052	483.2029	1.79
57	<i>N</i> -(3-Chlorobenzyl)-2-(4-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]propyl}phenyl)-acetamide		483.2052	483.2028	1.83
58	<i>N</i> -(4-Chlorobenzyl)-2-(4-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]propyl}phenyl)-acetamide		483.2052	483.2028	1.83
59	2-(4-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino]-propyl}phenyl)- <i>N</i> -(2-methoxybenzyl)-acetamide		479.2547	479.2522	1.74
60	2-(4-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino]propyl}phenyl)- <i>N</i> -(3-methoxybenzyl)acetamide		479.2547	479.2523	1.68

61	2-(4-((2 <i>R</i>)-2-((2 <i>R</i>)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino)-propyl)phenyl)- <i>N</i> -(4-methoxybenzyl)-acetamide		479.2547	479.2524	1.66
62	<i>N</i> -(2,6-Dimethoxybenzyl)-2-(4-((2 <i>R</i>)-2-((2 <i>R</i>)-2-hydroxy-2-(4-hydroxy-3-hydroxy-methylphenyl)-ethylamino)propyl)phenyl)-acetamide		509.2653	509.2627	1.79
63	2-(4-((2 <i>R</i>)-2-((2 <i>R</i>)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethyl-amino)propyl)phenyl)- <i>N</i> -(pyridin-2-ylmethyl)acetamide		450.2394	450.2375	1.38

Example 64: *N*-[2-Fluoro-5-(trifluoromethyl)benzyl]-2-{4-[(2*R*)-2-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}acetamide



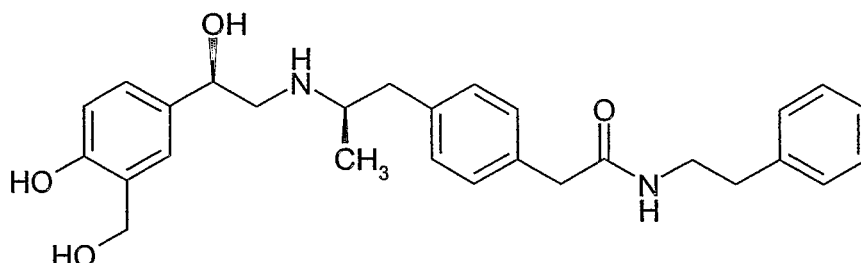
5

Prepared from 2-{4-[(2*R*)-2-((2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)propyl]phenyl}-*N*-[2-fluoro-5-(trifluoromethyl)benzyl]acetamide (Preparation 67) according to the method for example 3 to give the title compound as a white foam.

10 ^1H NMR (400MHz, CD_3OD): δ = 7.61-7.53 (2H, m), 7.35-6.98 (7H, m), 6.65 (1H, d), 4.60 (3H, m), 4.46 (2H, s), 3.55 (2H, s), 3.00-2.90 (2H, m), 2.75 (2H, m), 2.60 (1H, m), 1.05 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 535, $[\text{M}+\text{Na}]^+$ 557, $[\text{M}-\text{H}]^-$ 533.

Example 65: 2-{4-[(2*R*)-2-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl}-*N*-(2-phenylethyl)acetamide

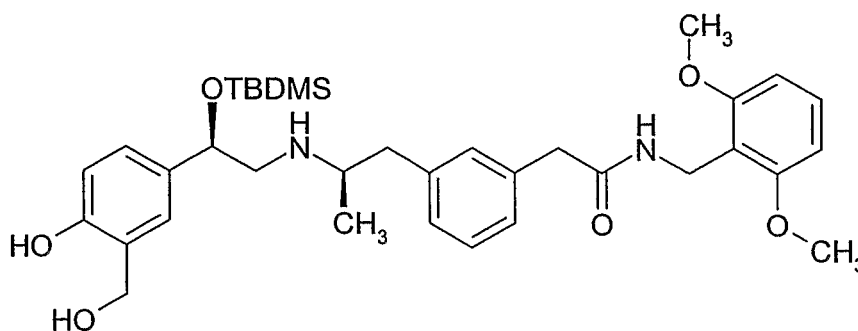


- 5 Prepared from 2-{4-[(2*R*)-2-[(2*R*)-2-[(*tert*-butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl}-*N*-(2-phenylethyl)acetamide (Preparation 68) according to the method for example 3 to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.26-7.00 (11H, m), 6.69 (1H, d), 4.60 (3H, m),
 10 3.40 (4H, m), 2.98 (2H, m), 2.70 (4H, m), 2.58 (1H, m), 1.07 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 463, [M+Na]⁺ 485, [M-H]⁻ 461.

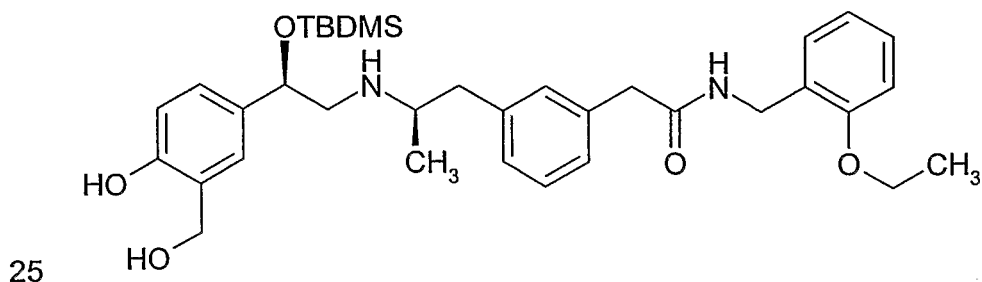
Preparation 1: 2-(3-[(2*R*)-2-[(2*R*)-2-[(*tert*-Butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl)-*N*-(2,6-dimethoxybenzyl)-acetamide



A solution of (3-[(2*R*)-2-[(2*R*)-2-[(*tert*-butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl)-acetic acid (Preparation 36)

- (150mg, 0.32mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (67mg, 0.35mmol), hydroxybenzotriazole monohydrate (47mg, 0.35mmol) in *N,N*-dimethylformamide (3ml) was treated with triethylamine (0.09ml, 0.63mmol) and 2,6-dimethoxybenzylamine (58mg, 0.35 mmol) and the
- 5 resulting suspension left to stir at room temperature under a nitrogen atmosphere for 18 hours. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate (10ml) and saturated aqueous sodium bicarbonate (10ml). The organic phase was separated, and the aqueous phase extracted with further ethyl acetate (2x10ml). The combined organic extracts
- 10 were washed with water (5ml), brine (5ml), dried (sodium sulphate) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol: 880 ammonia (95:5:0.5 by volume) to give the title compound as a pale yellow oil (128mg).
- 15 ¹H NMR (400MHz, CD₃OD): δ = 7.23-7.14 (3H, m), 7.09-7.07 (1H, d), 6.99-6.93 (3H, m), 6.69-6.67 (1H, d), 6.59-6.61 (2H, d), 4.70-4.67 (1H, m), 4.61 (2H, d), 4.41 (2H, s), 3.75 (6H, s), 3.42 (2H, s), 2.89-2.81 (2H, m), 2.67-2.60 (2H, m), 2.53-2.48 (1H, dd), 1.02-1.01 (3H, d), 0.84 (9H, s), 0.00 (3H, s), -0.19 (3H, s) ppm.
- 20 LRMS (electrospray) : m/z [M+H]⁺ 623, [M+Na]⁺ 645, [M-H]⁻ 621.

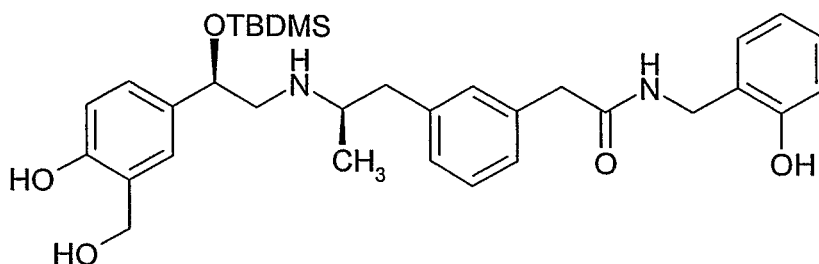
Preparation 2: 2-(3-((2*R*)-2-[(2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(2-ethoxybenzyl)-acetamide



Prepared according to the procedure used for preparation 1 using (3-((2*R*)-2-((2*R*)-2-((*tert*-butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white solid.

- 5 ¹H NMR (400MHz, CD₃OD): δ = 7.21-7.17 (3H, m), 7.14-7.12 (2H, d), 7.04 (1H, s), 7.00-6.98 (2H, d), 6.91-6.89 (1H, d), 6.85-6.81 (1H, t), 6.70-6.68 (1H, d), 4.72-4.68 (1H, t), 4.62-4.61 (2H, d), 4.35 (2H, s), 4.04-3.98 (2H, q), 3.50 (2H, s), 2.94-2.84 (2H, m), 2.72-2.62 (2H, m), 2.56-2.51 (1H, dd), 1.34-1.30 (3H, t), 1.04-1.02 (3H, d), 0.84 (9H, s), 0.00 (3H, s), -0.19 (3H, s) ppm.
- 10 LRMS (electrospray) : m/z [M+H]⁺ 607, [M+Na]⁺ 629, [M-H]⁻ 605.

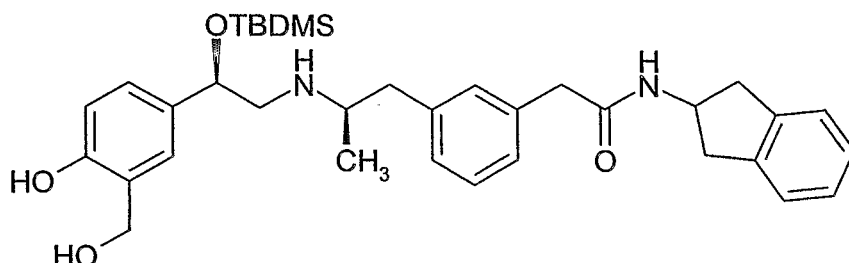
Preparation 3: 2-(3-((2*R*)-2-((2*R*)-2-((*tert*-Butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-*N*-(2-hydroxybenzyl)-acetamide



- 15 Prepared according to the procedure used for preparation 1 using (3-((2*R*)-2-((2*R*)-2-((*tert*-butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine, substituting dichloromethane as the reaction solvent to give the title compound as a white solid.
- 20

- ¹H NMR (400MHz, CD₃OD): δ = 7.19-7.02 (6H, m), 6.99-6.95 (2H, m), 6.75-6.70 (2H, m), 6.68-6.66 (1H, d), 4.71-4.67 (1H, t), 4.61 (2H, d), 4.32 (2H, s), 3.49 (2H, s), 2.91-2.84 (2H, m), 2.70-2.61 (2H, m), 2.55-2.50 (1H, dd), 1.04-1.03 (3H, d), 0.84 (9H, s), 0.01 (3H, s), -0.18 (3H, s) ppm.
- 25 LRMS (electrospray) : m/z [M+H]⁺ 579, [M+Na]⁺ 601, [M-H]⁻ 577.

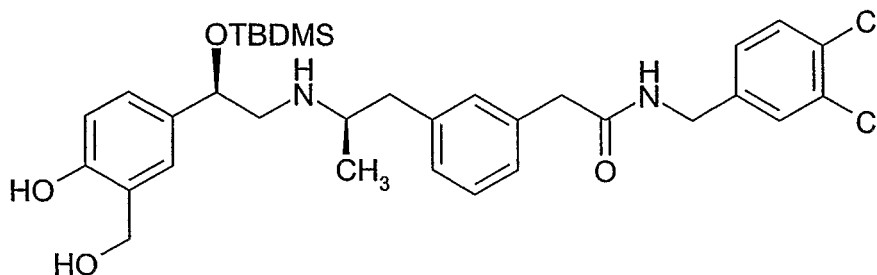
Preparation 4: 2-(3-((2R)-2-((2R)-2-((tert-Butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-N-indan-2-yl-acetamide



- 5 Prepared according to the procedure used for preparation 3 using (3-((2R)-2-((2R)-2-((tert-butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white solid.

¹H NMR (400MHz, CD₃OD): δ = 7.20-7.09 (7H, m), 7.02 (1H, s), 6.99-6.96 (2H, t), 6.69-6.67 (1H, d), 4.71-4.68 (1H, m), 4.61-4.60 (2H, d), 4.56-4.52 (1H, t) 3.42 (2H, s), 3.26-3.20 (2H, dd), 2.92-2.79 (4H, m), 2.69-2.62 (2H, m), 2.56-2.51 (1H, m), 1.05-1.03 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.20 (3H, s) ppm.
LRMS (electrospray) : m/z [M+H]⁺ 589, [M+Na]⁺ 611, [M-H]⁻ 587.

15 Preparation 5: 2-(3-((2R)-2-((2R)-2-((tert-Butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-N-(3,4-dichlorobenzyl)-acetamide



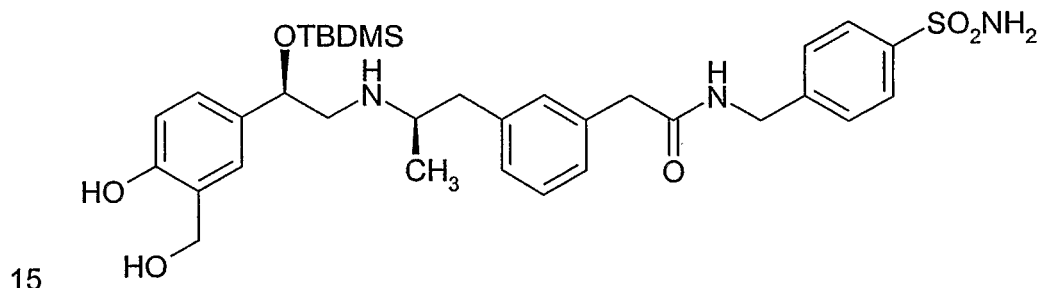
Prepared according to the procedure used for preparation 1 using (3-((2R)-2-
20 [(2R)-2-((tert-butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-

ethylamino]-propyl}-phenyl)-acetic acid (Preparation 36) and the appropriate amine substituting dichloromethane instead of ethyl acetate as the extraction solvent to give the title compound as a white solid.

¹H NMR (400MHz, CD₃OD): δ = 7.41-7.39 (1H, d), 7.34 (1H, s), 7.20-7.16 (2H, m), 7.14-7.10 (2H, t), 7.03 (1H, s), 7.00-6.96 (2H, d), 6.68-6.66 (1H, d), 4.70-4.67 (1H, t), 4.61-4.60 (2H, d), 4.30 (2H, s), 3.49 (2H, s), 2.92-2.84 (2H, m), 2.70-2.60 (2H, m), 2.56-2.51 (1H, dd), 1.03-1.01 (3H, d), 0.82 (9H, s), -0.01 (3H, s), -0.20 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 631 / 633, [M+Na]⁺ 653 / 655, [M-H]⁻ 629 / 631.

Preparation 6: 2-(3-((2R)-2-((2R)-2-[[*tert*-Butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-N-[4-(aminosulfonyl)benzyl]-acetamide

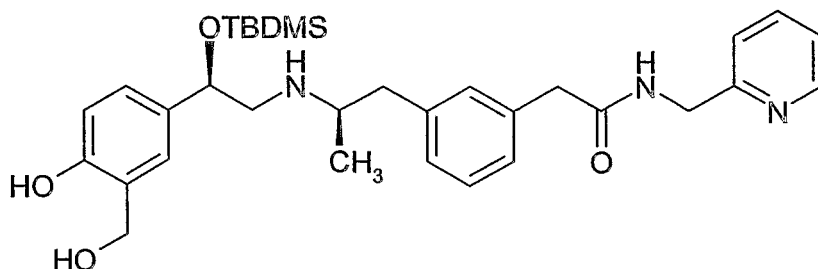


Prepared according to the procedure used for preparation 5 using (3-((2R)-2-((2R)-2-[[*tert*-butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.82-7.79 (2H, d), 7.38-7.36 (2H, d), 7.22-7.13 (3H, m), 7.05 (1H, s), 7.01-6.99 (2H, d), 6.70-6.67 (1H, d), 4.72-4.69 (1H, t), 4.62-4.61 (2H, d), 4.42 (2H, s), 3.51 (2H, s), 2.95-2.84 (2H, m), 2.71-2.63 (2H, m), 2.57-2.52 (1H, dd), 1.05-1.03 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.19 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 642, [M+Na]⁺ 664, [M-H]⁻ 640.

Preparation 7: 2-(3-((2R)-2-((2R)-2-((tert-Butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-N-(pyridin-2-ylmethyl)-acetamide



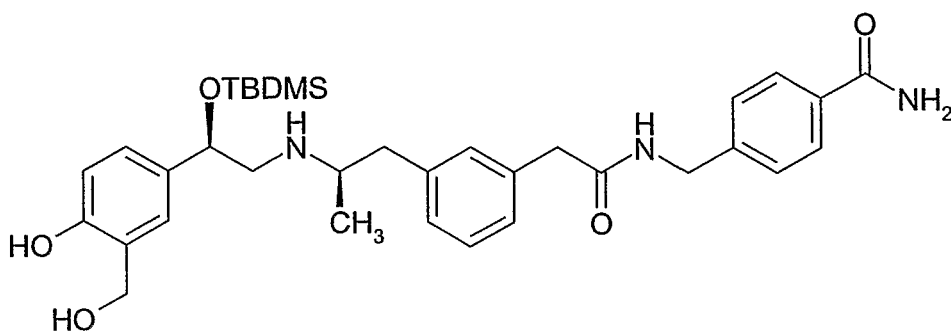
- 5 Prepared according to the procedure used for preparation 5 using (3-((2R)-2-((2R)-2-((tert-butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white solid.

¹H NMR (400MHz, CD₃OD): δ = 8.44-8.42 (1H, d), 7.74-7.70 (1H, t), 7.27-7.23 (2H, m), 7.20-7.13 (3H, m), 7.06 (1H, s), 6.99-6.97 (2H, m), 6.68-6.66 (1H, d), 4.71-4.67 (1H, t), 4.61 (2H, d), 4.46 (2H, s), 3.55 (2H, s), 2.93-2.85 (2H, m), 2.71-2.63 (2H, m), 2.58-2.53 (1H, dd), 1.06-1.04 (3H, d), 0.84 (9H, s), 0.01 (3H, s), -0.18 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 564, [M+Na]⁺ 586, [M-H]⁻ 562.

15

Preparation 8: 4-((2-(3-((2R)-2-((2R)-2-((tert-Butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetyl-amino)-methyl)-benzamide



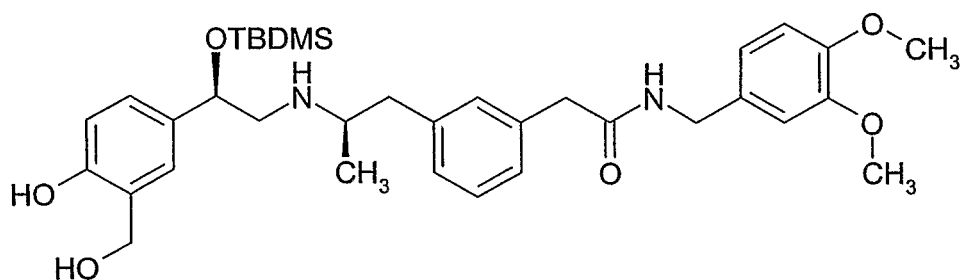
- 20 Prepared according to the procedure used for preparation 5 using (3-((2R)-2-((2R)-2-((tert-butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-

ethylamino]-propyl]-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white solid.

¹H NMR (400MHz, CD₃OD): δ = 7.79-7.77 (2H, d), 7.31-7.28 (2H, d), 7.20-7.11 (3H, m), 7.04 (1H, s), 6.99-6.97 (2H, m), 6.68-6.66 (1H, d), 4.71-4.69 (1H, t),
 5 4.61-4.60 (2H, d), 4.40 (2H, s), 3.51 (2H, s), 2.92-2.83 (2H, m), 2.70-2.61 (2H, m), 2.58-2.53 (1H, m), 1.06-1.04 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.18 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 606, [M+Na]⁺ 628, [M-H]⁻ 604.

10 **Preparation 9: 2-(3-((2R)-2-((2R)-2-([*tert*-Butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-N-(3,4-dimethoxybenzyl)-acetamide**

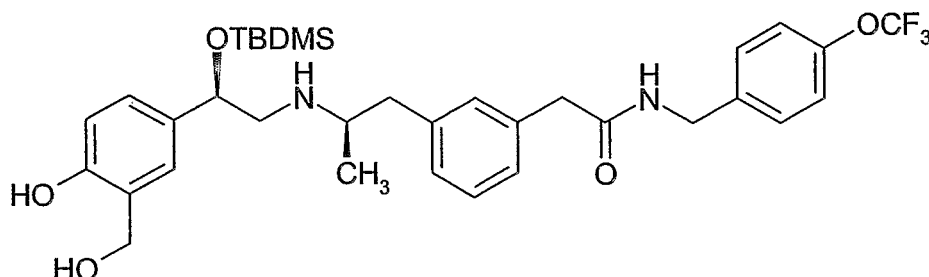


Prepared according to the procedure used for preparation 1 using (3-((2R)-2-
 15 [(2R)-2-([*tert*-butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white solid.

¹H NMR (400MHz, CD₃OD): δ = 7.20-7.13 (3H, m), 7.05 (1H, s), 7.00-6.98 (2H, d), 6.86-6.84 (1H, d), 6.79-6.77 (2H, m), 6.70-6.68 (1H, d), 4.72-4.68 (1H, m),
 20 4.62-4.61 (2H, d), 4.29 (2H, s), 3.78 (3H, s), 3.71 (3H, s), 3.48 (2H, s), 2.94-2.83 (2H, m), 2.70-2.60 (2H, m), 2.57-2.51 (1H, m), 1.04-1.03 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.19 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 623, [M+Na]⁺ 645, [M-H]⁻ 621.

Preparation 10: 2-(3-((2R)-2-[(2R)-2-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-N-(4-trifluoromethoxybenzyl)-acetamide

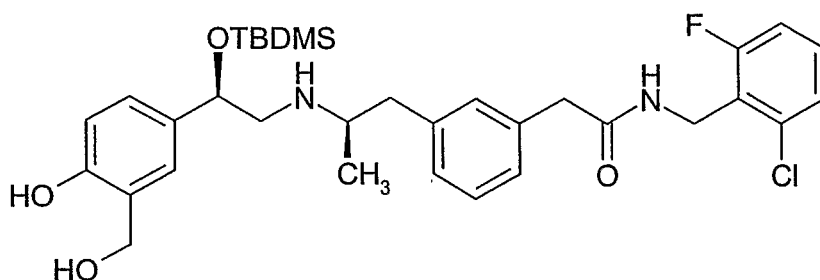


- 5 Prepared according to the procedure used for preparation 5 using 3-((2R)-2-[(2R)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white solid.

¹H NMR (400MHz, CD₃OD): δ = 7.32-7.30 (2H, d), 7.21-7.12 (5H, m), 7.05 (1H, s), 7.00-6.97 (2H, m), 6.69-6.67 (1H, d), 4.71-4.68 (1H, t), 4.60 (2H, d), 4.36 (2H, s), 3.49 (2H, s), 2.93-2.85 (2H, m), 2.70-2.60 (2H, m), 2.57-2.52 (1H, dd), 1.04-1.03 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.20 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 647, [M-H]⁻ 645.

- 15 **Preparation 11: 2-(3-((2R)-2-[(2R)-2-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-N-(2-chloro, 6-fluorobenzyl)-acetamide**

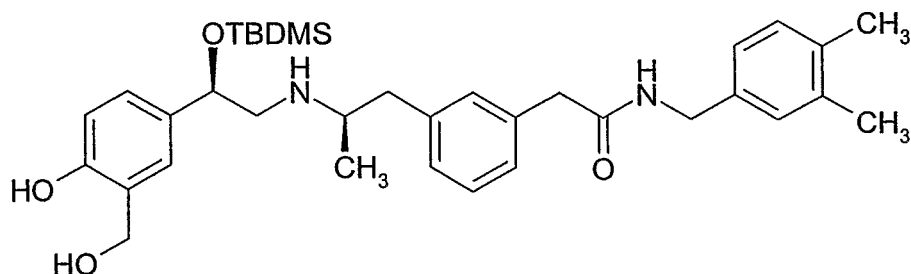


- 20 Prepared according to the procedure used for preparation 5 using 3-((2R)-2-[(2R)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white solid.

^1H NMR (400MHz, CD_3OD): δ = 7.33-7.14 (4H, m), 7.10-7.06 (2H, m), 7.02-6.95 (3H, m), 6.69-6.67 (1H, d), 4.72-4.68 (1H, t), 4.61-4.60 (2H, s), 4.52 (2H, s), 3.44 (2H, s), 2.93-2.85 (2H, m), 2.71-2.61 (2H, m), 2.54-2.49 (1H, dd), 1.04-1.02 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.19 (3H, s) ppm.

5 LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 615 / 617, $[\text{M}+\text{Na}]^+$ 637 / 639, $[\text{M}-\text{H}]^-$ 613 / 615.

Preparation 12: 2-(3-((2*R*)-2-[(2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(3,4-dimethylbenzyl)-acetamide

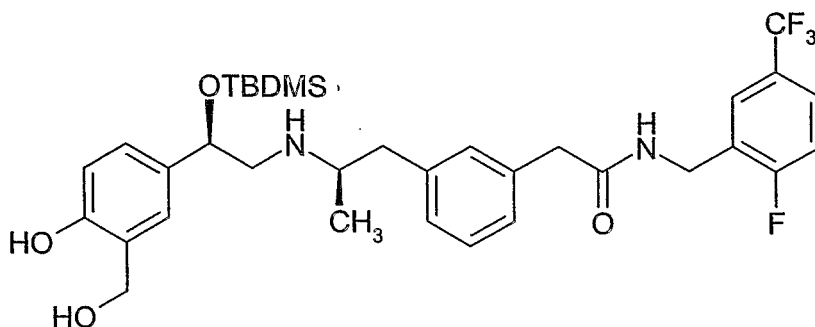


Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white solid.

^1H NMR (400MHz, CD_3OD): δ = 7.19-7.11 (3H, m), 7.04-6.90 (6H, m), 6.68-6.66 (1H, d), 4.70-4.67 (1H, t), 4.61-4.60 (2H, d), 4.26 (2H, s), 3.47 (2H, s), 2.91-2.84 (2H, m), 2.69-2.60 (2H, m), 2.55-2.50 (1H, dd), 2.20 (3H, s), 2.18 (3H, s), 1.03-1.02 (3H, d), 0.82 (9H, s), -0.01 (3H, s), -0.20 (3H, s) ppm.

20 LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 591, $[\text{M}-\text{H}]^-$ 589.

Preparation 13: 2-(3-((2*R*)-2-((2*R*)-2-((*tert*-Butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-*N*-[2-fluoro-5-(trifluoromethyl)benzyl]-acetamide



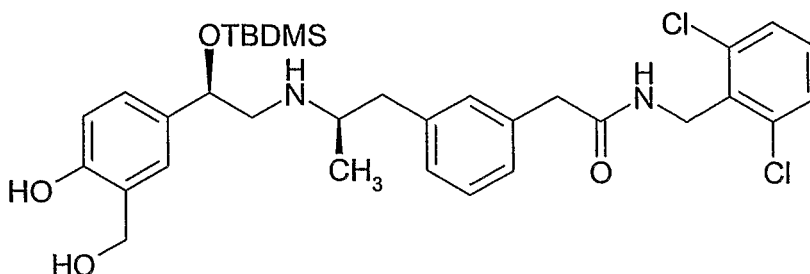
- 5 Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-((2*R*)-2-((*tert*-butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white solid.

¹H NMR (400MHz, CD₃OD): δ = 7.61-7.58 (1H, m), 7.55-7.53 (1H, d), 7.28-7.12 (4H, m), 7.05 (1H, s), 7.02-6.97 (2H, m), 6.69-6.67 (1H, d), 4.72-4.69 (1H, t), 4.61 (2H, d), 4.45 (2H, s), 3.51 (2H, s), 2.93-2.84 (2H, m), 2.74-2.60 (2H, m), 2.57-2.51 (1H, dd), 1.04-1.03 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.20 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 649, [M-H]⁻ 647.

15

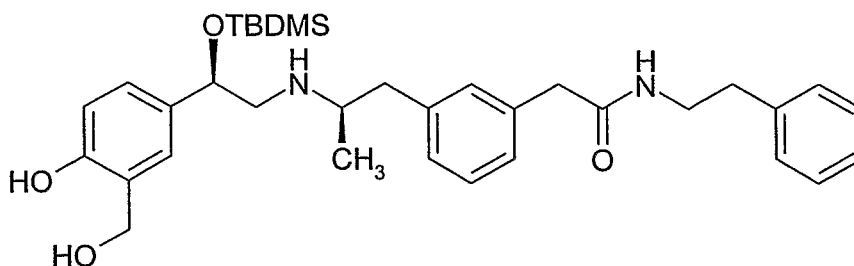
Preparation 14: 2-(3-((2*R*)-2-((2*R*)-2-((*tert*-Butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-*N*-(2,6-dichlorobenzyl)-acetamide



Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white solid.

- 5 ¹H NMR (400MHz, CD₃OD): δ = 7.35-7.33 (2H, m), 7.25-7.21 (1H, m), 7.17 (1H, s), 7.14-7.10 (1H, m), 7.07-7.05 (1H, m), 7.00 (1H, s), 6.97-6.91 (2H, m), 6.66-6.64 (1H, d), 4.68-4.65 (1H, t), 4.61 (2H, s), 4.58-4.57 (2H, d), 3.42 (2H, s), 2.89-2.82 (2H, m), 2.67-2.60 (2H, m), 2.51-2.47 (1H, dd), 1.00-0.99 (3H, d), 0.80 (9H, s), -0.04 (3H, s), -0.23 (3H, s) ppm.
- 10 LRMS (electrospray) : m/z [M+H]⁺ 631 / 633, [M+Na]⁺ 653 / 655, [M-H]⁻ 629 / 631.

Preparation 15: 2-(3-((2*R*)-2-[(2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(2-phenylethyl)acetamide

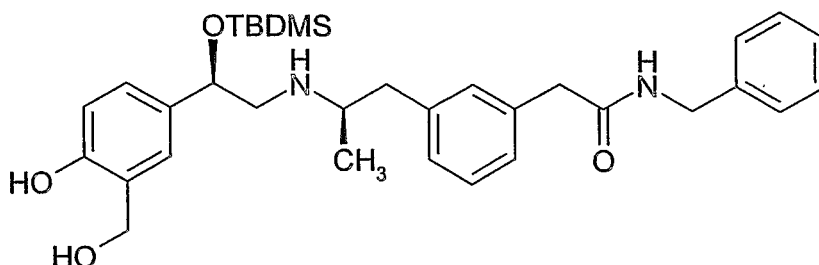


- Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a brown oil.
- 20

¹H NMR (400MHz, CD₃OD): δ = 7.31-7.11 (7H, m), 7.07-7.05 (1H, d), 6.99-6.97 (3H, m), 6.68-6.66 (1H, d), 4.70-4.67 (1H, t), 4.61-4.60 (2H, d), 3.41-3.37 (2H, m), 3.34 (2H, s), 2.95-2.84 (2H, m), 2.81-2.73 (2H, m), 2.68-2.61 (2H, m), 2.56-2.51 (1H, dd), 1.05-1.03 (3H, d), 0.82 (9H, s), -0.01 (3H, s), -0.20 (3H, s) ppm.

- 25 LRMS (electrospray) : m/z [M+H]⁺ 577, [M+Na]⁺ 599, [M-H]⁻ 575.

Preparation 16: *N*-Benzyl-2-(3-((2*R*)-2-((2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide

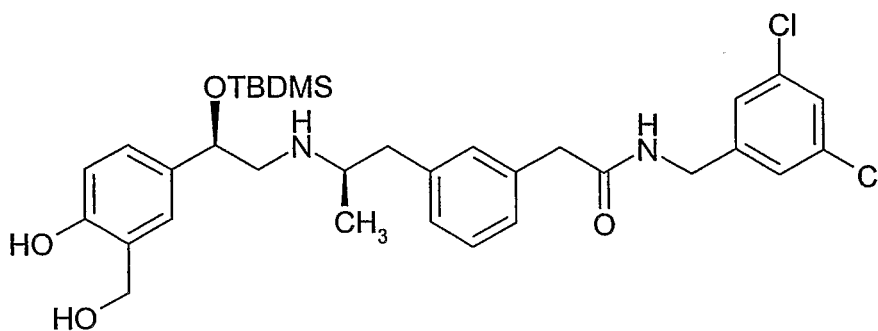


- 5 Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-((2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a colourless oil.

¹H NMR (400MHz, CD₃OD): δ = 7.35-7.12 (8H, m), 7.04 (1H, s), 6.99-6.97 (2H, d), 6.69-6.67 (1H, d), 4.70-4.67 (1H, t), 4.61-4.60 (2H, d), 4.35 (2H, s), 3.49 (2H, s), 2.90-2.83 (2H, m), 2.69-2.61 (2H, m), 2.55-2.50 (1H, dd), 1.04-1.02 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.20 (3H, s) ppm.

LRMS (electrospray) : m/z [M+Na]⁺ 585, [M-H]⁻ 561.

- 15 **Preparation 17: 2-(3-((2*R*)-2-((2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-*N*-(3,5-dichlorobenzyl)-acetamide**

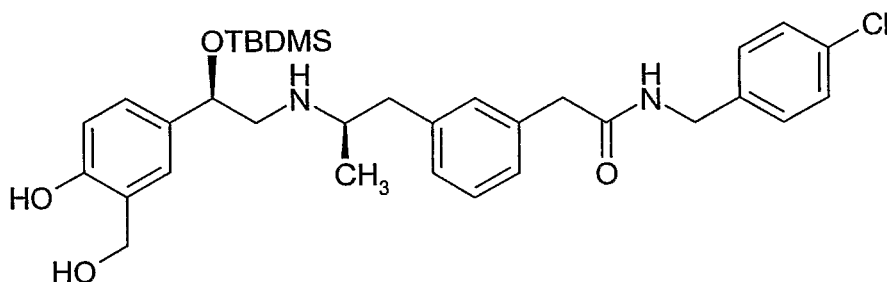


- 20 Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-((2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-

ethylamino]-propyl}-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a colourless oil.

^1H NMR (400MHz, CD_3OD): δ = 7.33-7.28 (2H, m), 7.22-7.12 (4H, m), 7.05 (1H, s), 7.01-6.98 (2H, m), 6.69-6.67 (1H, d), 4.71-4.68 (1H, t), 4.62-4.61 (2H, d),
 5 4.32 (2H, s), 3.51 (2H, s), 2.91-2.84 (2H, m), 2.71-2.61 (2H, m), 2.57-2.52 (1H, dd), 1.04-1.03 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.19 (3H, s) ppm.
 LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 631 / 633, $[\text{M}+\text{Na}]^+$ 653 / 655, $[\text{M}-\text{H}]^-$ 629 / 631.

10 Preparation 18: 2-(3-{(2R)-2-[(2R)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl}-phenyl)-N-(4-chlorobenzyl)-acetamide

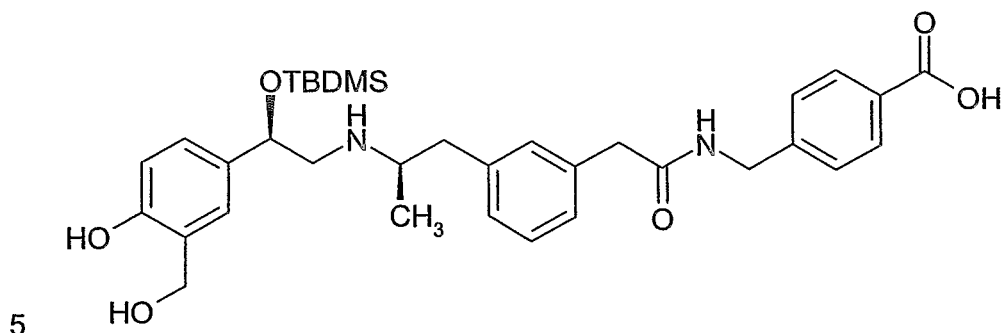


Prepared according to the procedure used for preparation 5 using (3-{(2R)-2-
 15 [(2R)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl}-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a colourless oil.

^1H NMR (400MHz, CD_3OD): δ = 7.31 (1H, s), 7.28-7.25 (1H, d), 7.21-7.16 (4H, m), 7.13-7.11 (1H, m), 7.03 (1H, s), 6.99-6.97 (2H, d), 6.69-6.67 (1H, d), 4.70-
 20 4.67 (1H, t), 4.62-4.62 (2H, d), 4.32 (2H, s), 3.48 (2H, s), 2.88-2.83 (2H, m), 2.68-2.60 (2H, m), 2.55-2.50 (1H, dd), 1.03-1.02 (2H, d), 0.83 (9H, s), -0.01 (3H, s), -0.20 (3H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 597 / 599, $[\text{M}+\text{Na}]^+$ 619 / 621, $[\text{M}-\text{H}]^-$ 595 / 597.

Preparation 19: 4-{([2-(3-{(2*R*)-2-[(2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl)-acetyl]-amino)-methyl}-benzoic acid



Prepared according to the procedure used for preparation 36, using methyl 4-
 {[2-(3-{(2*R*)-2-[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(4-hydroxy-3-
 hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl)-acetyl]-amino)-methyl}-
 benzoate (Preparation 20), to give the title compound as a white solid which
 10 was used without further purification.

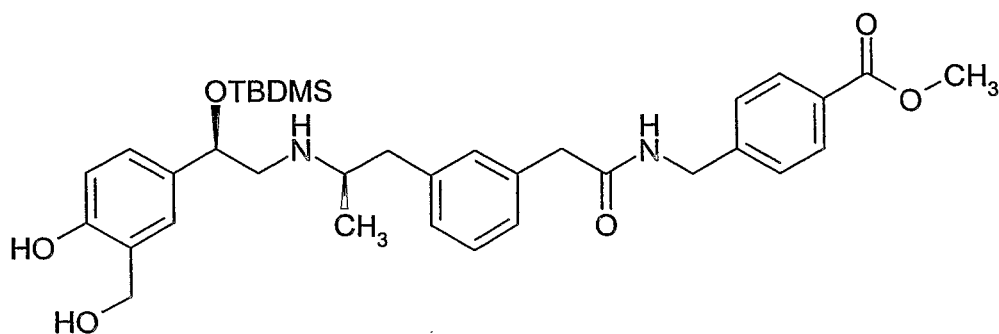
¹H NMR (400MHz, CD₃OD): δ = 7.89-7.87 (2H, d), 7.34-7.20 (5H, m), 7.15-7.09
 (3H, m), 6.80-6.78 (1H, d), 5.00-4.97 (1H, m), 4.67-4.66 (2H, d), 4.40 (2H, s),
 3.55 (2H, s), 3.45-3.38 (1H, m), 3.28-3.23 (1H, dd), 3.15-3.11 (1H, dd), 3.03-
 2.98 (1H, dd), 2.72-2.66 (1H, dd), 1.17-1.16 (3H, d), 0.86 (9H, s), 0.07 (3H, s), -
 15 0.12 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 607, [M+Na]⁺ 629, [M-H]⁻ 605.

CHN analysis : found C 62.04%, H 7.50% N 3.79%;

C₃₄H₄₆N₂O₆Si+0.5MeOH+2.6H₂O requires C 61.97%, H 7.87%, N 4.19%.

20 **Preparation 20: Methyl-4-{([2-(3-{(2*R*)-2-[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl)-acetyl]-amino)-methyl}-benzoate**

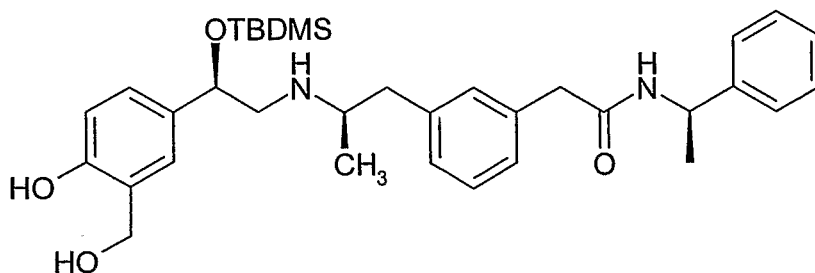


Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-
 [(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-
 ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate
 5 amine to give the title compound as an orange oil.

¹H NMR (400MHz, CD₃OD): δ = 7.93-7.91 (2H, d), 7.33-7.31 (2H, d), 7.21-7.13
 (3H, m), 7.05 (1H, s), 7.00-6.97 (2H, m), 6.69-6.67 (1H, d), 4.70-4.67 (1H, m),
 4.62-4.61 (2H, d), 4.42 (2H, s), 3.87 (3H, s), 3.52 (2H, s), 2.91-2.84 (2H, m),
 2.69-2.60 (2H, m), 2.56-2.51 (1H, dd), 1.04-1.02 (3H, d), 0.84 (9H, s), 0.01 (3H,
 10 s), -0.19 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 621.

**Preparation 21: 2-{3-[(2*R*)-2-[(2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-[4-
 hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl}-*N*-[(1*R*)-1-
 15 phenylethyl]acetamide**



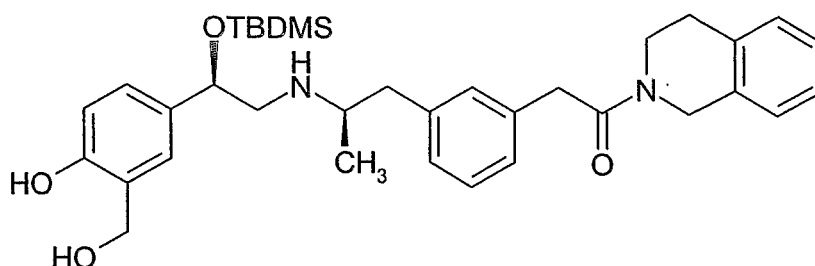
Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-
 [(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-
 ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate
 20 amine to give the title compound as a white solid.

¹H NMR (400MHz, CD₃OD): δ = 7.27-7.26 (4H, d), 7.21-7.09 (4H, m), 7.01-6.95
 (3H, m), 6.69-6.67 (1H, d), 5.00-4.95 (1H, q), 4.70-4.67 (1H, dd), 4.62-4.61 (2H,

d), 3.46 (2H, s), 2.88-2.83 (2H, m), 2.69-2.61 (2H, m), 2.53-2.48 (1H, dd), 1.44-1.42 (3H, d), 1.02-1.01 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.19 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 577, $[M+Na]^+$ 599, $[M-H]^-$ 575.

5 Preparation 22: 4-((1*R*)-1-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-(((1*R*)-2-{3-[2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]phenyl}-1-methylethyl)amino]ethyl)-2-(hydroxymethyl)phenol

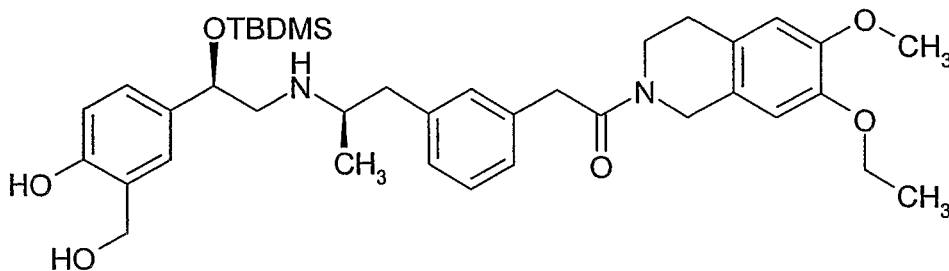


Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-
10 [(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white foam.

1H NMR (400MHz, CD_3OD): δ = 7.23-7.07 (7H, m), 7.03-6.92 (3H, m), 6.68-6.66 (1H, d), 4.70-4.66 (3H, m), 4.61 (2H, s), 3.82 (2H, s), 3.81-3.70 (2H, m),
15 2.90-2.81 (3H, m), 2.71-2.43 (4H, m), 1.02-0.94 (3H, m), 0.82 (9H, s), -0.01 (3H, s), -0.20 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 589, $[M+Na]^+$ 611, $[M-H]^-$ 587.

Preparation 23: 4-((1*R*)-1-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-(((1*R*)-2-{3-[2-(7-ethoxy-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]phenyl}-1-methylethyl)amino]ethyl)-2-(hydroxymethyl)phenol



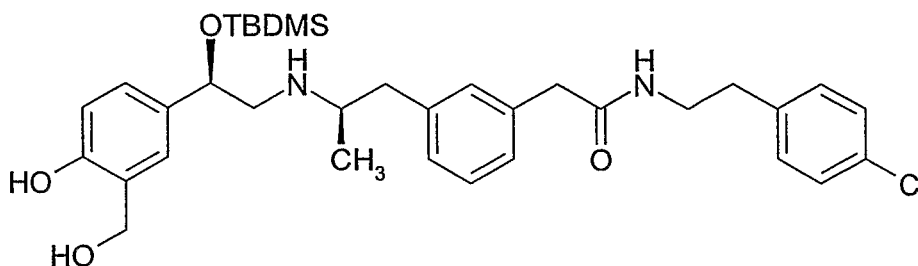
Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-((2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white foam.

- 5 ¹H NMR (400MHz, CD₃OD): δ = 7.23-6.91 (6H, m), 6.71-6.55 (3H, m), 4.69-4.64 (1H, m), 4.61 (2H, s), 4.61-4.56 (2H, m), 4.03-3.93 (2H, m), 3.81 (2H, s), 3.76 (3H, s), 3.79-3.66 (2H, m), 2.90-2.40 (7H, m), 1.38-1.33 (3H, m), 1.02-0.94 (3H, m), 0.82 (9H, s), -0.01 (3H, s), -0.21 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 663, [M-H]⁻ 661.

10

Preparation 24: 2-{3-[(2*R*)-2-((2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy)-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-[2-(4-chlorophenyl)ethyl]acetamide

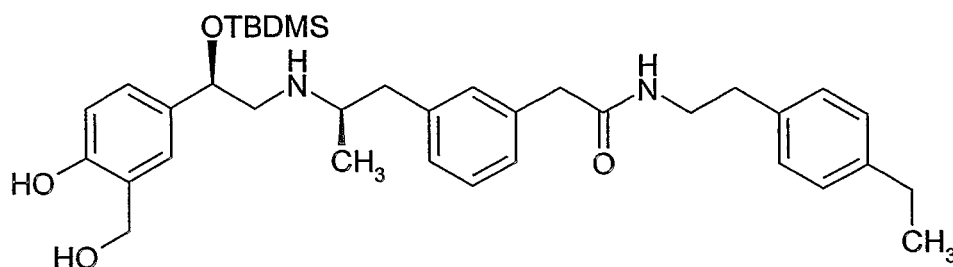


- 15 Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-((2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white foam.

- 20 ¹H NMR (400MHz, CD₃OD): δ = 7.21-7.15 (4H, m), 7.09-7.03 (3H, m), 7.00-6.97 (3H, m), 6.69-6.66 (1H, d), 4.71-4.68 (1H, t), 4.60 (2H, d), 3.38 (2H, s), 3.40-3.36 (2H, t), 2.93-2.85 (2H, m), 2.75-2.72 (2H, t), 2.69-2.62 (2H, m), 2.57-2.52 (1H, dd), 1.06-1.04 (3H, d), 0.82 (9H, s), -0.01 (3H, s), -0.20 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 611, [M-H]⁻ 609.

- 25 **Preparation 25: 2-{3-[(2*R*)-2-((2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy)-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-[2-(4-ethylphenyl)ethyl]acetamide**

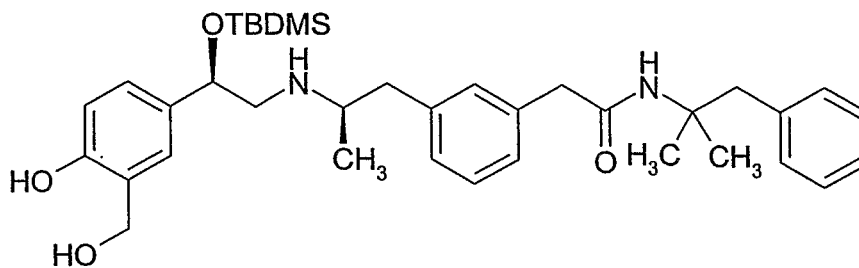


Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-
 5 [(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-
 ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate

¹H NMR (400MHz, CD₃OD): δ = 7.18 (1H, s), 7.16-7.14 (1H, d), 7.06-6.95 (8H, m), 6.67-6.65 (1H, d), 4.69-4.66 (1H, t), 4.60-4.59 (2H, d), 3.39 (2H, s), 3.37-3.34 (2H, t), 2.92-2.84 (2H, m), 2.72-2.68 (2H, t), 2.66-2.51 (5H, m), 1.19-1.16 (3H, t), 1.05-1.03 (3H, d), 0.81 (9H, s), -0.02 (3H, s), -0.21 (3H, s) ppm.

10 LRMS (electrospray) : m/z [M+H]⁺ 605, [M-H]⁻ 603.

Preparation 26: 2-{3-[(2*R*)-2-((2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy)-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-(1,1-dimethyl-2-phenylethyl)acetamide

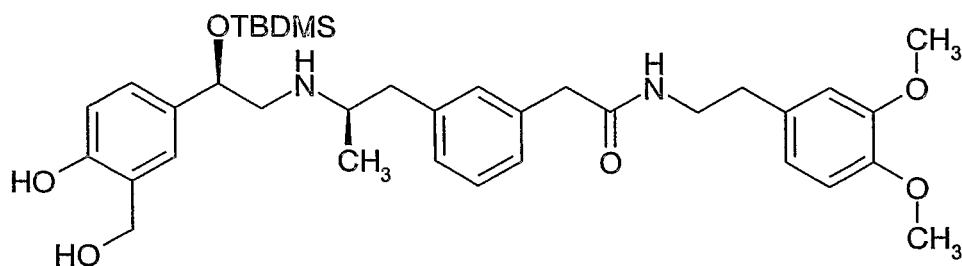


15 Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-
 [(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-
 ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate
 amine to give the title compound as a white foam.

20 ¹H NMR (400MHz, CD₃OD): δ = 7.22-7.18 (2H, m), 7.14-7.11 (4H, m), 7.03-6.95 (5H, m), 6.69-6.67 (1H, d), 4.71-4.68 (1H, q), 4.61 (2H, d), 3.37 (2H, s), 2.99 (2H, s), 2.92-2.84 (2H, m), 2.72-2.62 (2H, m), 2.57-2.52 (1H, dd), 1.26 (6H, s), 1.04-1.03 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.20 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 605, $[M-H]^-$ 603.

Preparation 27: 2-{3-[(2*R*)-2-({(2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide

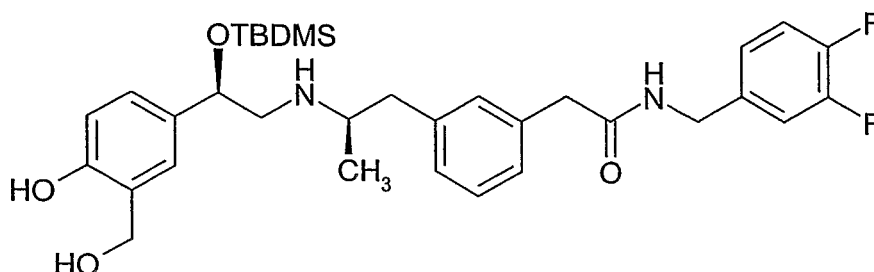


Prepared according to the procedure used for preparation 1 using (3-[(2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy}-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white foam.

^1H NMR (400MHz, CD_3OD): δ = 7.19-7.14 (2H, m), 7.05-7.04 (1H, d), 7.01-6.98 (3H, m), 6.82-6.77 (2H, m), 6.69-6.66 (2H, m), 4.71-4.69 (1H, m), 4.62-4.61 (2H, d), 3.78 (3H, s), 3.76 (3H, s), 3.41 (2H, s), 3.41-3.37 (2H, t), 2.95-2.86 (2H, m), 2.73-2.69 (2H, t), 2.67-2.62 (2H, m), 2.57-2.52 (1H, dd), 1.06-1.04 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.19 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 637, $[M-H]^-$ 635.

Preparation 28: 2-{3-[(2*R*)-2-({(2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-(3,4-difluorobenzyl)acetamide



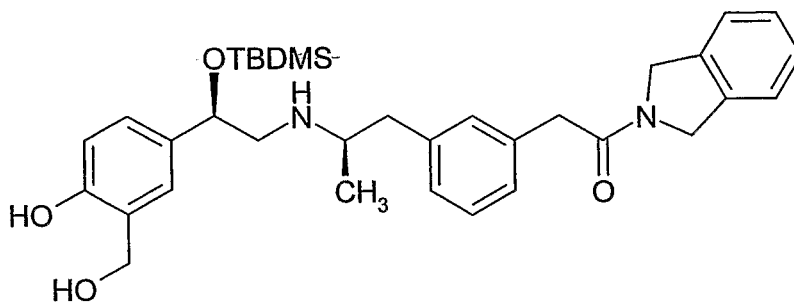
Prepared according to the procedure used for preparation 5 using (3-[(2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy}-2-(4-hydroxy-3-hydroxymethyl-phenyl)-

ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.20-7.07 (5H, m), 7.04-6.97 (4H, m), 6.97-6.69 (1H, d), 4.70-4.67 (1H, dd), 4.62-4.61 (2H, d), 4.31 (2H, s), 3.49 (2H, s),
 5 2.90-2.83 (2H, m), 2.69-2.60 (2H, m), 2.55-2.50 (1H, m), 1.03-1.02 (3H, d), 0.83
 (9H, s), -0.01 (3H, s), -0.20 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 599, [M-H]⁻ 597.

**Preparation 29: 4-((1*R*)-1-([*tert*-Butyl(dimethyl)silyl]oxy)-2-(((1*R*)-2-{3-[2-
 10 (1,3-dihydro-2*H*-isoindol-2-yl)-2-oxoethyl]phenyl}-1-methylethyl)amino]ethyl)-2-(hydroxymethyl)phenol**

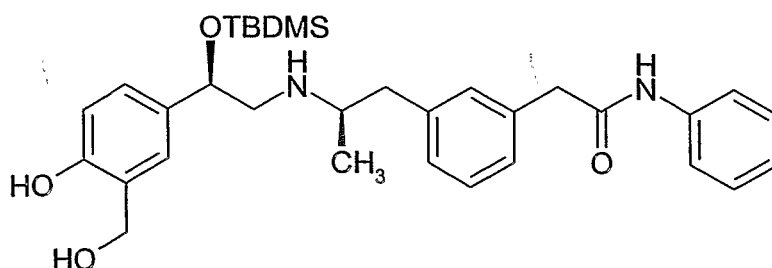


Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-
 [(2*R*)-2-([*tert*-butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-
 15 ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate
 amine to give the title compound as a yellow oil.

¹H NMR (400MHz, CD₃OD): δ = 7.26-7.13 (7H, m), 7.07 (1H, s), 6.99-6.97 (1H,
 d), 6.94-6.91 (1H, dd), 6.66-6.64 (1H, d), 4.74 (2H, s), 4.67-4.64 (1H, t), 4.61
 (2H, d), 3.76 (2H, s), 3.34 (2H, s), 2.93-2.82 (2H, m), 2.67-2.55 (3H, m), 1.06-
 20 1.04 (3H, d), 0.80 (9H, s), -0.03 (3H, s), -0.21 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 575, [M+Na]⁺ 597, [M-H]⁻ 573.

**Preparation 30: 2-{3-[(2*R*)-2-((2*R*)-2-([*tert*-Butyl(dimethyl)silyl]oxy)-2-[4-
 hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl]phenyl}-*N*-
 25 phenylacetamide**

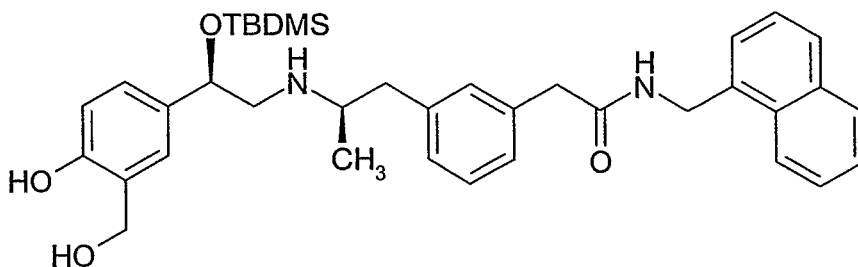


- Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-
 [(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-
 ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate
 5 amine to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.53-7.51 (2H, d), 7.28-7.24 (2H, m), 7.18 (3H, s), 7.11-7.03 (2H, m), 6.98-6.94 (1H, m), 6.68-6.66 (1H, d), 4.69-4.66 (1H, m), 4.62-4.61 (2H, d), 3.62 (2H, s), 2.94-2.85 (2H, m), 2.70-2.55 (3H, m), 1.07-1.05 (3H, d), 0.81 (9H, s), -0.02 (3H, s), -0.21 (3H, s) ppm.

- 10 LRMS (electrospray) : m/z [M+H]⁺ 549, [M+Na]⁺ 571, [M-H]⁻ 547.

Preparation 31: 2-{3-[(2*R*)-2-((2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-N-(1-naphthylmethyl)acetamide



15

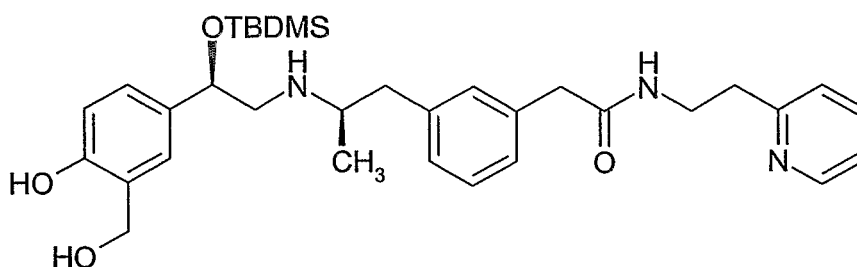
Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-
 [(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-
 ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate
 amine to give the title compound as a white foam.

- 20 ¹H NMR (400MHz, CD₃OD): δ = 7.96-7.94 (1H, d), 7.85-7.82 (1H, d), 7.78-7.75 (1H, d), 7.55-7.35 (4H, m), 7.19-7.09 (3H, m), 6.98-6.93 (3H, m), 6.70-6.68 (1H, d), 4.79 (2H, s), 4.68-4.58 (3H, m), 3.47 (2H, s), 2.82-2.72 (2H, m), 2.60-2.54

(2H, m), 2.45-2.40 (1H, m), 0.96-0.95 (3H, d), 0.83 (9H, s), -0.01 (3H, s), -0.20 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 613, [M+Na]⁺ 635, [M-H]⁻ 611.

5 Preparation 32: 2-{3-[(2R)-2-({(2R)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-N-(2-pyridin-2-ylethyl)acetamide

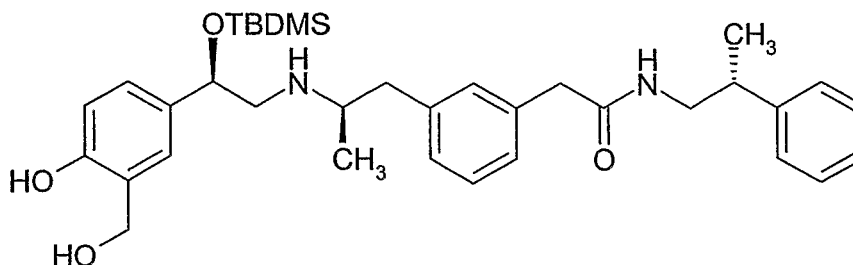


Prepared according to the procedure used for preparation 5 using 3-[(2R)-2-
 10 [(2R)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 8.41-8.39 (1H, d), 7.68-7.64 (1H, m), 7.23-7.14
 (4H, m), 7.06-7.04 (1H, d), 6.98-6.96 (3H, d), 6.69-6.67 (1H, d), 3.53-3.50 (1H,
 15 t), 3.39 (2H, s), 2.94-2.84 (4H, m), 2.67-2.61 (2H, m), 2.55-2.50 (1H, m), 1.04-
 1.03 (3H, d), 0.82 (9H, s), -0.01 (3H, s), -0.20 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 578, [M+Na]⁺ 600, [M-H]⁻ 576.

20 Preparation 33: 2-{3-[(2R)-2-({(2R)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-N-[(2R)-2-phenylpropyl]acetamide

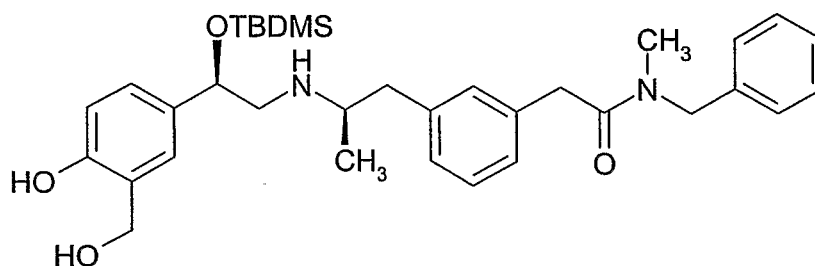


Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-((2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a white foam.

- 5 ¹H NMR (400MHz, CD₃OD): δ = 7.24-7.11 (7H, m), 7.00-6.94 (4H, m), 6.68-6.66 (1H, d), 4.69-4.66 (1H, m), 4.61-4.60 (2H, d), 3.31-3.28 (3H, m), 2.93-2.83 (3H, m), 2.78 (1H, s), 2.66-2.60 (2H, m), 2.53-2.48 (1H, m), 1.19-1.17 (3H, d), 1.03-1.01 (3H, d), 0.82 (9H, s), -0.02 (3H, s), -0.21 (3H, s) ppm.
LRMS (electrospray) : m/z [M+H]⁺ 591, [M+Na]⁺ 613, [M-H]⁻ 589.

10

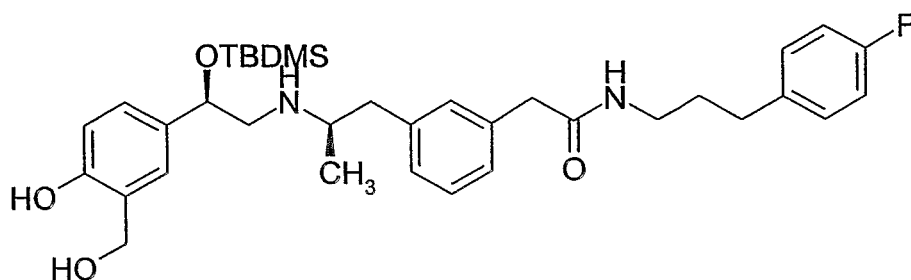
Preparation 34: N-Benzyl-2-{3-[(2*R*)-2-((2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-N-methylacetamide



- 15 Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-((2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate amine to give the title compound as a colourless oil.

- ¹H NMR (400MHz, CD₃OD): δ = 7.52-7.36 (6H, m), 7.30-7.25 (2H, m), 7.19-7.16 (3H, m), 6.89-6.87 (1H, d), 4.90-4.87 (1H, m), 4.83-4.73 (4H, m), 3.97-3.95 (2H, d), 3.11-3.03 (5H, m), 2.88-2.79 (2H, m), 2.75-2.70 (1H, m), 1.23-1.20 (3H, m), 0.79 (9H, s), -0.05 (3H, s), -0.23 (3H, s) ppm.
LRMS (electrospray) : m/z [M+H]⁺ 577, [M+Na]⁺ 599, [M-H]⁻ 575.

- 25 **Preparation 35: 2-{3-[(2*R*)-2-((2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-N-[3-(4-fluorophenyl)propyl]acetamide**



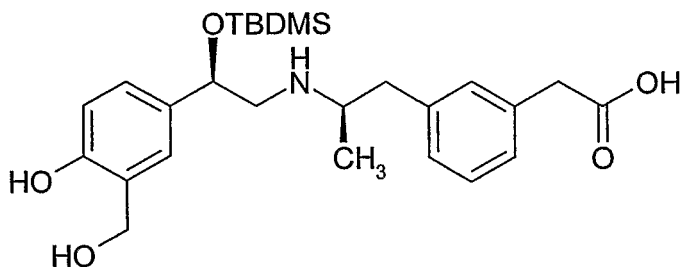
Prepared according to the procedure used for preparation 5 using (3-((2*R*)-2-
 [(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-
 ethylamino]-propyl)-phenyl)-acetic acid (Preparation 36) and the appropriate
 5 amine to give the title compound as a white foam.

¹HNMR (400MHz, CD₃OD) δ : 7.22-6.92 (10H, m), 6.69 (1H, d), 4.71-4.66 (1H, m), 4.62 (2H, s), 3.44 (2H, s), 3.20-3.16 (2H, m), 2.94-2.52 (7H, m), 1.80-1.73 (2H, m), 1.03 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.19 (3H, s) ppm.

LRMS (electrospray) : 609 [M+H]⁺, 631 [M+Na]⁺

10

Preparation 36: (3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetic acid



A solution of methyl (3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-
 15 hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetate
 (Preparation 37) (7.04g, 14.4mmol) in tetrahydrofuran (40ml) was treated with
 lithium hydroxide (28.9ml of a 1M aqueous solution, 28.9mmol) and the
 reaction left to stir at room temperature for 16 hours. Hydrochloric acid (28.9ml
 of a 1M aqueous solution, 28.9mmol) was added and then the tetrahydrofuran
 20 was removed *in vacuo*. The remaining aqueous layer was decanted and the
 residue washed with further water (10ml). The residue was redissolved in

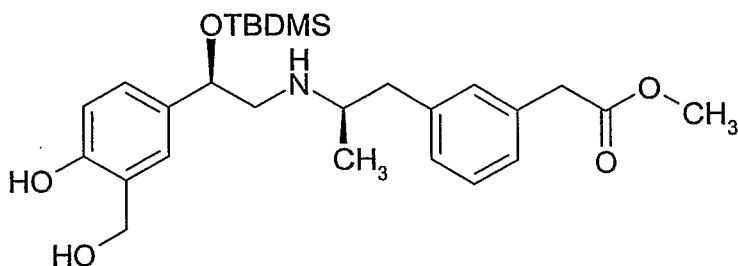
methanol (30ml) and the solvent removed *in vacuo* to give the title compound as a colorless foam (5.95g) which was used without further purification.

¹H NMR (400MHz, CD₃OD): δ = 7.32 (1H, s), 7.25-7.18 (2H, m), 7.13 (1H, s), 7.12-7.10 (1H, d), 7.02-7.01 (1H, d), 6.79-6.77 (1H, d), 4.98-4.95 (1H, m), 4.65-4.64 (2H, d), 3.48 (2H, s), 3.48-3.43 (1H, m), 3.28-3.23 (1H, dd), 3.13-3.09 (1H, dd), 2.98-2.93 (1H, dd), 2.77-2.72 (1H, dd), 1.23-1.21 (3H, d), 0.86 (9H, s), 0.06 (3H, s), -0.13 (3H, s) ppm.

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

CHN analysis : found C 64.15%, H 8.25%, N 2.84%; C₂₆H₃₉NO₅Si+0.7H₂O requires C 64.22%, H 8.37%, N 2.88%.

Preparation 37: Methyl-(3-((2*R*)-2-((2*R*)-2-([*tert*-butyl(dimethyl)silyl]oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetate

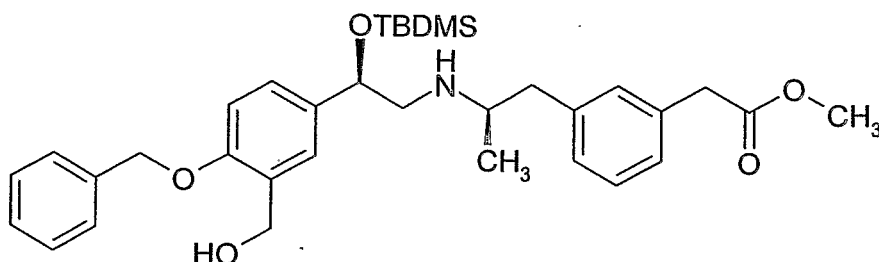


A suspension of methyl (3-((2*R*)-2-((2*R*)-2-([*tert*-butyl(dimethyl)silyl]oxy)-2-(4-benzyloxy)-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetate (Preparation 38) (5.27g, 9.12mmol) and 10% palladium on carbon (1.00g) in ethanol (50ml) was stirred under an atmosphere of hydrogen (60psi) at room temperature for 16 hours. The catalyst was filtered off through arbocel and the filtrate concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (96:4:0.4 changing to 95:5:0.5, by volume) to give the title compound as a pale yellow oil (1.99g) which was used without further purification.

¹H NMR (400MHz, CD₃OD): δ = 7.21-7.17 (2H, m), 7.11-7.09 (1H, d), 7.03-6.98 (3H, m), 6.69-6.67 (1H, d), 4.71-4.68 (1H, t), 4.62-4.61 (2H, d), 3.67 (3H, s), 3.59 (2H, s), 2.96-2.86 (2H, m), 2.69-2.55 (3H, m), 1.07-1.05 (3H, d), 0.82 (9H, s), -0.01 (3H, s), -0.20 (3H, s) ppm.

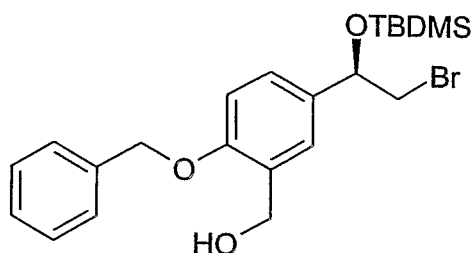
LRMS (electrospray) : m/z $[M+H]^+$ 488, $[M+Na]^+$ 510, $[M-H]^-$ 486

Preparation 38: Methyl-(3-((2*R*)-2-((2*R*)-2-((*tert*-butyl(dimethyl)silyl)oxy)-2-(4-(benzyloxy)-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetate



- A solution of [2-(benzyloxy)-5-((1*R*)-2-bromo-1-((*tert*-butyl(dimethyl)silyl)oxy)ethyl) phenyl]methanol (Preparation 39) (12.5g, 27.7mmol) and the amine from preparation 27 (11.5g, 55.4mmol) in dichloromethane (130ml) was heated to 90°C, allowing the dichloromethane to evaporate. The resulting melt was left at 90°C for a further 16 hours. The reaction mixture was cooled to room temperature and purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (98:2:0.2 changing to 97:3:0.3, by volume) to give the title compound (12.1g) as a colourless oil.
- ¹H NMR (400MHz, CD₃OD): δ = 7.47-7.45 (2H, m), 7.39-7.29 (4H, m), 7.19-7.15 (1H, t), 7.13-7.07 (2H, m), 7.03 (1H, s), 7.01-6.99 (1H, d), 6.93-6.91 (1H, d), 5.12 (2H, s), 4.76-4.73 (1H, t), 4.67-4.66 (2H, d), 3.66 (3H, s), 3.58 (2H, s), 2.95-2.80 (2H, m), 2.68-2.55 (3H, m), 1.06-1.05 (3H, d), 0.83 (9H, s), 0.00 (3H, s), -0.19 (3H, s) ppm.
- LRMS (electrospray) : m/z $[M+H]^+$ 578, $[M+Na]^+$ 600.

Preparation 39: [2-(Benzyloxy)-5-((1*R*)-2-bromo-1-((*tert*-butyl(dimethyl)silyl)oxy)ethyl) phenyl]methanol

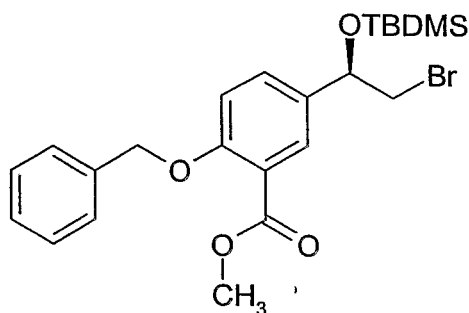


Borane dimethylsulfide complex (42.4ml of 10M solution in tetrahydrofuran, 424mmol) was added dropwise to a solution methyl-2-(benzyloxy)-5-((1R)-2-bromo-1-[[*tert*-butyl(dimethyl)silyl]oxy]ethyl)benzoate (Preparation 40) (91.0g, 189mmol) in tetrahydrofuran (1600ml). The resulting mixture was then heated to reflux for 2 hours and then cooled to 0°C before quenching with methanol (270ml). The mixture was left to stir at room temperature for 16 hours and then the solvent removed *in vacuo*. The residue was partitioned between dichloromethane (500ml) and water (500ml). The aqueous phase was separated and extracted with dichloromethane (500ml) and the combined organic extracts washed with brine (500ml), dried (magnesium sulfate) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with cyclohexane:ethyl acetate (100:0 changing to 80:20, by volume) to give the title compound (68.7g) as a colourless oil.

¹H NMR (400MHz, CDCl₃): δ = 7.42-7.36 (5H, m), 7.29-7.25 (3H, m), 6.94 (1H, d), 5.12 (2H, s), 4.84-4.81 (1H, m), 4.74 (2H, s), 3.48-3.40 (2H, m), 0.90 (9H, s), 0.11 (3H, s), -0.07 (3H, s) ppm.

LRMS (electrospray) : m/z [M+Na]⁺ 473 / 475.

Preparation 40: Methyl-2-(benzyloxy)-5-((1R)-2-bromo-1-[[*tert*-butyl(dimethyl)silyl]oxy]ethyl)benzoate

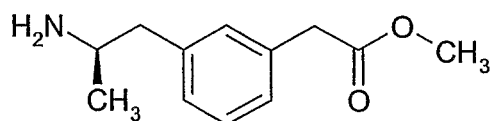


A solution of methyl 2-(benzyloxy)-5-[(1*R*)-2-bromo-1-hydroxyethyl]benzoate (71.0g, 195mmol), imidazole (18.5g, 272mmol), *tert*-butyldimethylsilyl chloride (32.2g, 214mmol) and 4-(*N,N*-dimethylamino)pyridine (440mg, 3.60mmol) in
 5 *N,N*-dimethylformamide (270ml) was left to stir at room temperature under a nitrogen atmosphere for a period of 24 hours. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate (500ml) and water (500ml). The organic phase was separated and washed with 2N aqueous hydrochloric acid (2x500ml), saturated aqueous sodium bicarbonate (2x500ml),
 10 brine (500ml), dried (magnesium sulfate) and the solvent removed *in vacuo* to give the title compound as a colourless oil (91.0g).

¹H NMR (400MHz, CDCl₃): δ = 7.81 (1H, bs), 7.51-7.30 (6H, m), 7.01 (1H, d), 5.19 (2H, s), 4.85-4.82 (1H, m), 3.91 (3H, s), 3.48-3.39 (2H, m), 0.90 (9H, s), 0.11 (3H, s), -0.08 (3H, s) ppm.

15 LRMS (electrospray) : m/z [M+Na]⁺ 501 / 503.

Preparation 41: Methyl-{3-[(2*R*)-2-aminopropyl]phenyl}acetate

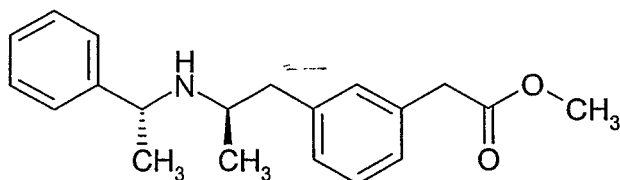


A solution of methyl-[3-((2*R*)-2-[(1*R*)-1-phenyl-ethyl]-amino)-propyl]-phenyl]-
 20 acetate hydrochloride (Preparation 42) (7.69g, 22.0mmol) and ammonium formate (6.94g, 110mmol) was heated to 75°C in the presence of 20% palladium hydroxide-on-charcoal (Pd(OH)₂/C, 2.00g). After 90 minutes the reaction 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).

- 5 ^1H NMR (400MHz, CD_3OD): 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 $[\text{M}+\text{H}]^+$ 208, $[\text{M}+\text{Na}]^+$ 230.

Preparation 42: Methyl-[3-((2*R*)-2-[(1*R*)-1-phenyl-ethyl]-amino)-propyl]-phenyl]-acetate hydrochloride
10



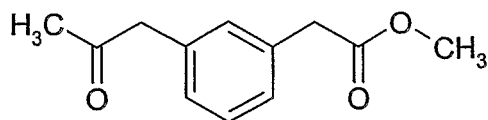
- A solution of methyl-[3-(2-oxopropyl)phenyl]acetate (Preparation 43) (8.50g, 41.2mmol), (*R*)- α -methyl benzylamine (4.8ml, 37.2mmol), sodium triacetoxyborohydride (11.6g, 56.0mmol) and acetic acid (2.2ml, 38.0mmol) in
15 dichloromethane (400ml) was stirred at room temperature for 48 hours. The reaction 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
20 reduced *in vacuo*. Purification by flash column chromatography eluting with dichloromethane:methanol: 880 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, 40.0mmol) followed by three successive crystallisations
25 (diisopropylether/methanol) gave the title compound as a white crystalline solid (5.68g).

^1H NMR (400MHz, CD_3OD): 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.

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

5 Preparation 43: Methyl-[3-(2-oxopropyl)phenyl]acetate

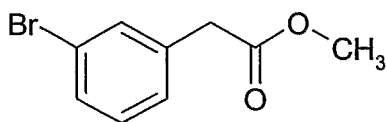


Tributyltin methoxide (28.3 ml, 98.0mmol), methyl-(3-bromophenyl)acetate (Preparation 44) (15.0g, 65.0mmol), isopropenyl acetate (10.8ml, 98.0mmol), palladium(II)acetate (750mg, 3.30mmol) and tri-*ortho*-tolylphosphine (2.00g, 6.5mmol) were stirred together in toluene (75ml) at 100°C under nitrogen for 5 hours. After cooling the reaction was diluted with ethyl acetate (150ml) and 4M aqueous potassium fluoride solution (90ml) and stirred for 15 minutes. The mixture was filtered through arbocel and the organic phase separated and reduced *in vacuo*. The residue was purified by flash column chromatography silica gel eluting with a solvent 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 (12.6g).

¹H NMR (400MHz, CDCl₃): 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 [M+NH₄]⁺ 224, [M+Na]⁺ 229.

Preparation 44: Methyl-(3-bromophenyl)acetate



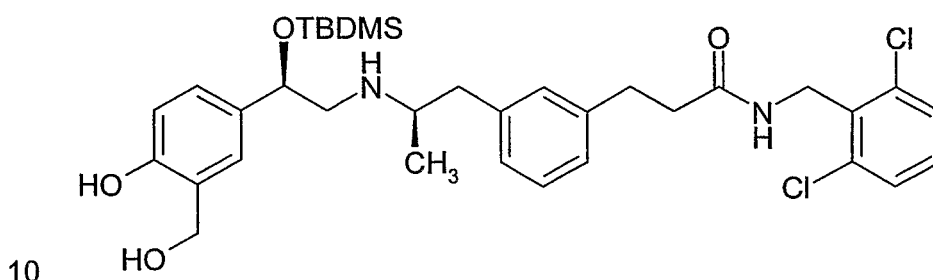
Acetyl chloride (0.70ml, 9.30mmol) was slowly added to a solution of (3-bromophenyl)-acetic acid (20.0g, 93mmol) in methanol (500ml) at 0°C under nitrogen and the reaction was allowed to warm gradually to room temperature over a period of 5 hours. The solvent was removed *in vacuo* and the residual oil was

dissolved in dichloromethane, dried (sodium sulfate) and concentrated *in vacuo* to give the title compound as a colourless oil (20.6g).

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

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

Preparation 45: 3-{3-[(2*R*)-2-[(2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl}-*N*-(2,6-dichlorobenzyl)propanamide



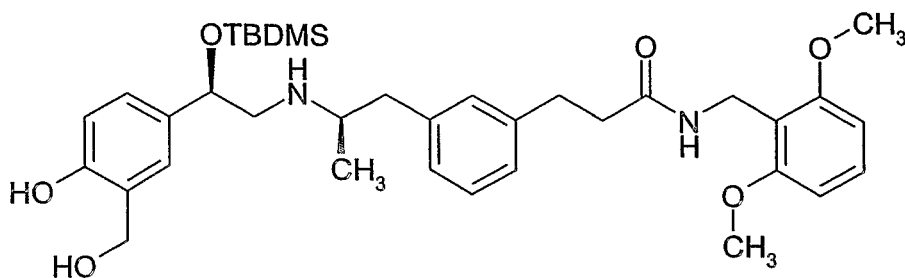
Prepared using the method for preparation 5 using 3-(3-[(2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl)-propanoic acid (Preparation 51) and the appropriate amine to give the title compound as a white solid.

15 ^1H NMR (400MHz, CD_3OD): δ = 7.39-7.37 (2H, d), 7.28-7.24 (1H, m), 7.20-7.19 (1H, d), 7.14-7.10 (1H, t), 7.03-6.97 (2H, m), 6.94-6.90 (2H, m), 6.69-6.67 (1H, d), 4.73-4.69 (1H, t), 4.64-4.56 (4H, m), 2.95-2.84 (4H, m), 2.69-2.63 (2H, m), 2.56-2.50 (1H, m), 2.48-2.44 (2H, t), 1.06-1.04 (3H, d), 0.82 (9H, s), -0.01 (3H, s), -0.19 (3H, s) ppm.

20 LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 645 / 647, $[\text{M}+\text{Na}]^+$ 667 / 669, $[\text{M}-\text{H}]^-$ 643 / 645.

Preparation 46: 3-{3-[(2*R*)-2-[(2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl}-*N*-(2,6-dimethoxybenzyl)propanamide

25

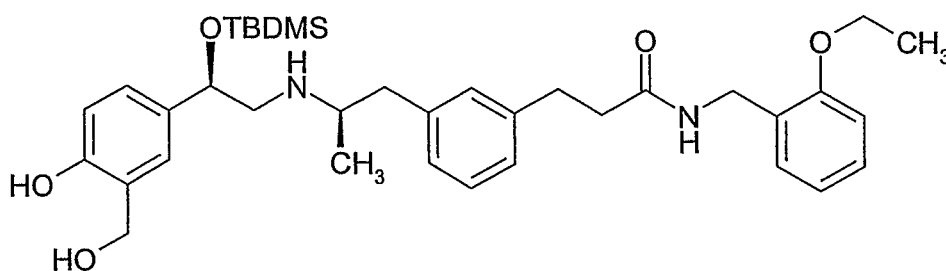


Prepared according to the procedure used for preparation 1 using 3-(3-((2*R*)-2-
 [(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-
 ethylamino]-propyl)-phenyl)-propanoic acid (Preparation 51) and the
 5 appropriate amine, substituting dichloromethane instead of ethyl acetate as the
 extraction solvent to give the title compound as a yellow foam.

¹H NMR (400MHz, CD₃OD): δ = 7.20-7.15 (2H, m), 7.09-7.06 (1H, t), 6.98-6.93
 (2H, m), 6.89-6.86 (2H, m), 6.66-6.64 (1H, d), 6.57-6.55 (2H, d), 4.70-4.67 (1H,
 t), 4.57-4.56 (2H, d), 4.34 (2H, s), 3.74 (6H, s), 2.94-2.86 (2H, m), 2.81-2.77
 10 (2H, t), 2.67-2.59 (2H, m), 2.52-2.46 (1H, dd), 2.39-2.35 (2H, t), 1.02-1.00 (3H,
 d), 0.78 (9H, s), -0.04 (3H, s), -0.23 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 637, [M+Na]⁺ 659, [M-H]⁻ 635.

**Preparation 47: 3-{3-[(2*R*)-2-((2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy)-2-[4-
 15 hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-(2-
 ethoxybenzyl)propanamide**



Prepared according to the procedure used for preparation 1 using 3-(3-((2*R*)-2-
 [(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-
 20 ethylamino]-propyl)-phenyl)-propanoic acid (Preparation 51) and the
 appropriate amine, substituting dichloromethane instead of ethyl acetate as the

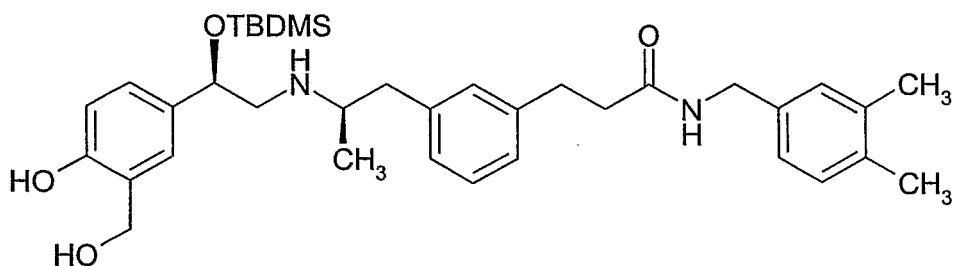
extraction solvent, and dichloromethane:methanol: 880 ammonia (98:2:0.2 by volume) instead of (95:5:0.5 by volume) as column eluent to give the title compound as a colourless oil.

¹H NMR (400MHz, CD₃OD): δ = 7.17-7.07 (3H, m), 7.00-6.98 (1H, d), 6.94-6.88 (4H, m), 6.84-6.82 (1H, d), 6.76-6.72 (1H, t), 6.64-6.62 (1H, d), 4.67-4.64 (1H, t), 4.57-4.56 (2H, d), 4.28 (2H, s), 4.01-3.96 (2H, q), 2.90-2.82 (4H, m), 2.63-2.57 (2H, m), 2.51-2.45 (3H, m), 1.37-1.33 (3H, t), 1.01-0.99 (3H, d), 0.79 (9H, s), -0.04 (3H, s), -0.23 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 621, [M-H]⁻ 620.

10

Preparation 48: 3-{3-[(2*R*)-2-({(2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-(3,4-dimethylbenzyl)propanamide

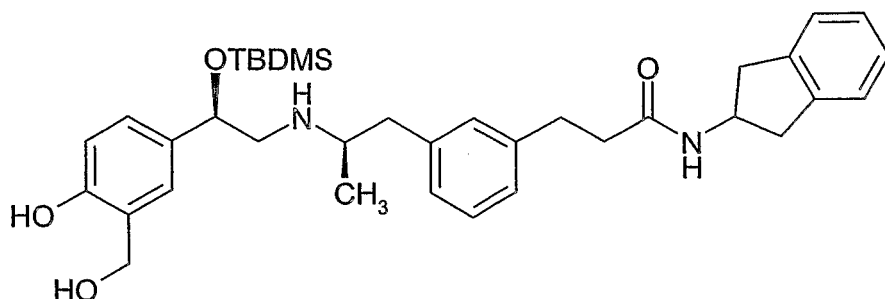


15 Prepared according to the procedure used for preparation 1 using 3-(3-[(2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy}-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl)-propanoic acid (Preparation 51) and the appropriate amine, substituting dichloromethane instead of ethyl acetate as the extraction solvent, and dichloromethane:methanol: 880 ammonia (98:2:0.2 by volume) instead of (95:5:0.5 by volume) as column eluent to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.19-7.18 (1H, d), 7.15-7.11 (1H, t), 7.04-6.92 (6H, m), 6.84-6.82 (1H, d), 6.68-6.66 (1H, d), 4.70-4.67 (1H, t), 4.61-4.60 (2H, d), 4.23 (2H, s), 2.90-2.84 (4H, m), 2.64-2.59 (2H, m), 2.53-2.46 (3H, m), 2.20 (6H, s), 1.03-1.02 (3H, d), 0.82 (9H, s), -0.01 (3H, s), -0.20 (3H, s) ppm.

25 LRMS (electrospray) : m/z [M+H]⁺ 605, [M+Na]⁺ 627, [M-H]⁻ 603.

Preparation 49: 3-{3-[(2*R*)-2-[(2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl}-*N*-(2,3-dihydro-1*H*-inden-2-yl)propanamide

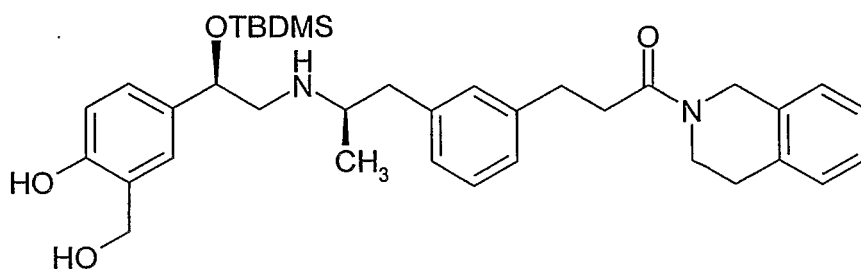


- 5 Prepared according to the procedure used for preparation 1 3-(3-{(2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl)-propanoic acid (Preparation 51) and the appropriate amine, substituting dichloromethane instead of ethyl acetate as the extraction, and dichloromethane:methanol: 880 ammonia (97:3:0.3 by volume) instead of (95:5:0.5 by volume) as column eluent to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.19-7.09 (6H, m), 7.02-6.90 (4H, m), 6.68-6.66 (1H, d), 4.70-4.67 (1H, dd), 4.60 (2H, s), 4.56-4.49 (1H, m), 3.21-3.15 (2H, dd), 2.91-2.81 (4H, m), 2.73-2.68 (2H, dd), 2.65-2.60 (2H, dd), 2.54-2.49 (1H, dd), 2.43-2.40 (2H, t), 1.04-1.02 (3H, d), 0.82 (9H, s), -0.01 (3H, s), -0.20 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 603, [M+Na]⁺ 625, [M-H]⁻ 601.

Preparation 50: 4-{(1*R*)-1-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-[(1*R*)-2-{3-[3-(3,4-dihydroisoquinolin-2(1*H*)-yl)-3-oxopropyl]phenyl]-1-methylethyl]amino]ethyl}-2-(hydroxymethyl)phenol

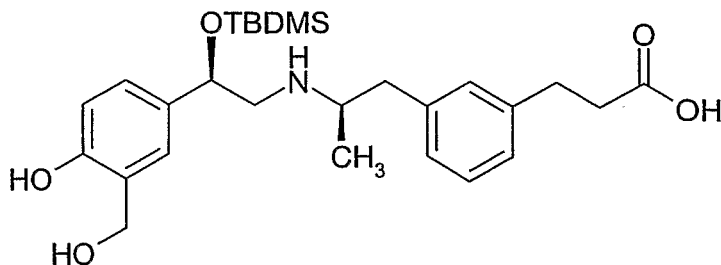


Prepared according to the procedure used for preparation 1 using 3-(3-((2*R*)-2-
 [(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-phenyl)-
 ethylamino]-propyl)-phenyl)-propanoic acid (Preparation 51) and the
 appropriate amine, substituting dichloromethane instead of ethyl acetate as the
 5 extraction solvent, and dichloromethane:methanol: 880 ammonia (96:4:0.4 by
 volume) instead of (95:5:0.5 by volume) as column eluent to give the title
 compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.19 (1H, s), 7.16-7.01 (5H, m), 6.99-6.90 (3H,
 m), 6.84-6.82 (1H, d), 6.70-6.67 (1H, m), 4.71-4.68 (1H, dd), 4.65+4.54 (2H, m),
 10 4.62-4.60 (2H, m), 3.76-3.60 (2H, m), 2.93-2.85 (4H, m), 2.80-2.69 (4H, m),
 2.66-2.53 (2H, m), 2.50-2.45 (1H, dd), 1.03-1.00 (3H, m), 0.82 (9H, s), -0.01
 (3H, s), -0.19 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 603, [M+Na]⁺ 625, [M-H]⁻ 601.

15 **Preparation 51: 3-(3-((2*R*)-2-[(2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-(4-
 hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-propanoic
 acid**



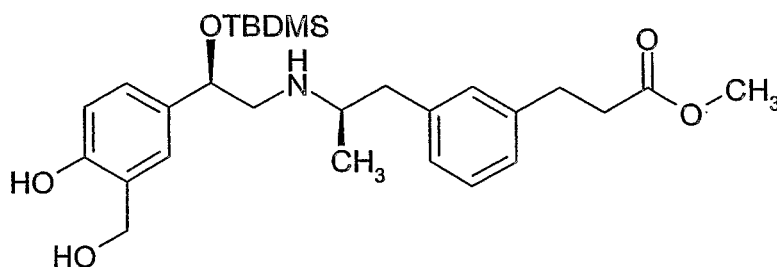
Prepared according to the procedure used for preparation 36, using methyl-3-
 20 (3-((2*R*)-2-[(2*R*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(4-hydroxy-3-hydroxymethyl-
 phenyl)-ethylamino]-propyl)-phenyl)-propanoate (Preparation 52) to give the
 title compound as a brown solid.

¹H NMR (400MHz, CD₃OD): δ = 7.27 (1H, s), 7.19-7.14 (1H, t), 7.09-7.02 (3H,
 m), 6.95-6.93 (1H, d), 6.75-6.73 (1H, d), 4.92-4.90 (1H, m), 4.61-4.60 (2H, d),
 25 3.37-3.32 (1H, m), 3.20-3.15 (1H, m), 3.04-3.00 (1H, dd), 2.91-2.83 (3H, m),
 2.68-2.62 (1H, m), 2.45-2.40 (2H, t), 1.15-1.14 (3H, d), 0.81 (9H, s), -0.01 (3H,
 s), -0.18 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 488, $[M+Na]^+$ 510, $[M-H]^-$ 486.

Preparation 52: Methyl-3-(3-((2*R*)-2-((2*R*)-2-((*tert*-butyl(dimethyl)silyl)oxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-

5 propanoate

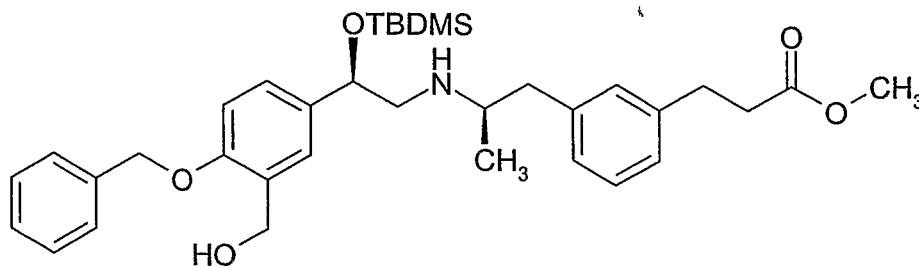


Prepared according to the procedure used for preparation 37, using methyl-3-(3-((2*R*)-2-((2*R*)-2-((*tert*-Butyl(dimethyl)silyl)oxy)-2-(4-[benzyloxy]-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-propanoate (Preparation 53) to give the title compound as a brown oil.

^1H NMR (400MHz, CD_3OD): δ = 7.08-7.15 (2H, m), 6.99-6.88 (4H, m), 6.65-6.62 (1H, d), 4.67-4.64 (1H, m), 4.58-4.57 (2H, d), 3.59 (3H, s), 2.90-2.80 (4H, m), 2.61-2.49 (5H, m), 1.01-1.00 (3H, d), 0.78 (9H, s), -0.06 (3H, s), -0.24 (3H, s) ppm.

15 LRMS (electrospray) : m/z $[M+H]^+$ 502, $[M+Na]^+$ 524, $[M-H]^-$ 500.

Preparation 53: Methyl-3-(3-((2*R*)-2-((2*R*)-2-((*tert*-Butyl(dimethyl)silyl)oxy)-2-(4-[benzyloxy]-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-propanoate



20

Prepared according to the procedure used for preparation 38 using methyl-3-((2*R*)-2-aminopropyl)phenyl]propanoate (Preparation 54) and [2-(benzyloxy)-5-

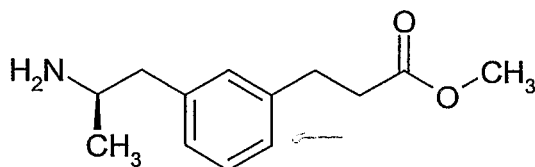
((1*R*)-2-bromo-1-[[*tert*-butyl(dimethyl)silyl]oxy]ethyl)phenyl]methanol

(Preparation 39) to give the title compound as a brown oil.

¹H NMR (400MHz, CD₃OD): δ = 7.43-7.24 (6H, m), 7.11-7.04 (2H, m), 6.69-6.95 (1H, d), 6.91-6.86 (3H, m), 5.07 (2H, s), 4.71-4.66 (1H, m), 4.63-4.62 (2H, d), 3.58 (3H, s), 2.89-2.79 (4H, m), 2.63-2.47 (5H, m), 1.02-1.00 (3H, d), 0.78 (9H, s), -0.05 (3H, s), -0.23 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 592, [M+Na]⁺ 614.

Preparation 54: Methyl-3-[(2*R*)-2-aminopropyl]phenyl]propanoate



10

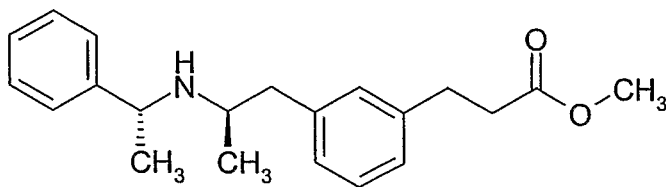
Prepared according to the procedure used for preparation 41, using methyl-[3-((2*R*)-2-[(1*R*)-1-phenyl-ethyl]-amino)-propyl]-phenyl]-propanoate hydrochloride (Preparation 55) to give the title compound as a brown oil.

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 55: Methyl-[3-((2*R*)-2-[(1*R*)-1-phenyl-ethyl]-amino)-propyl]-phenyl]-propanoate hydrochloride

20

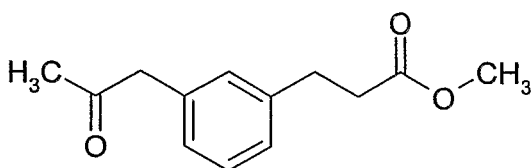


Prepared according to the procedure used for preparation 52, using methyl-3-[3-(2-oxopropyl)phenyl]propanoate (Preparation 56) to give the title compound as a white crystalline solid.

^1H NMR (400MHz, CD_3OD): 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.

5 LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 326.

Preparation 56: Methyl-3-[3-(2-oxopropyl)phenyl]propanoate



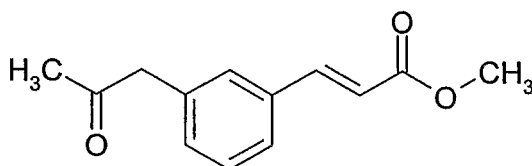
Prepared according to the procedure used for preparation 37 using methyl (2E)-
10 3-[3-(2-oxopropyl)phenyl]acrylate (Preparation 57) to give the title compound as an orange oil.

^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.

15

Preparation 57: Methyl (2E)-3-[3-(2-oxopropyl)phenyl]acrylate



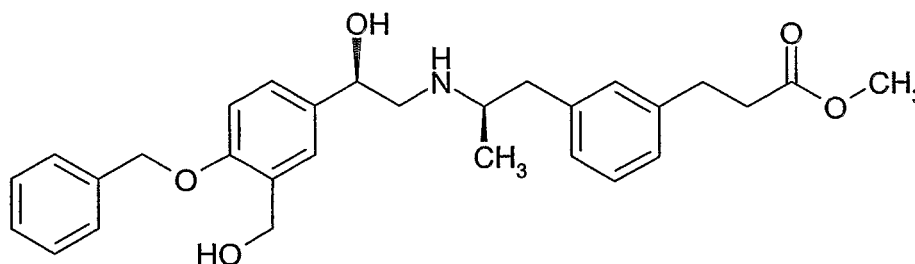
A solution of 3-bromophenylacetone (50.0g, 235mmol), methyl acrylate (40.4g, 469mmol), palladium(II)acetate (7.9g, 35.2mmol), tri-*ortho*-tolylphosphine
20 (21.4g, 70.4mmol) and triethylamine (82ml) in acetonitrile (900ml) was heated at reflux under a nitrogen atmosphere for a period of 16 hours. The 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
25 (54.3g).

^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.

5

Preparation 58: Methyl-3-{3-[(2R)-2-[(2R)-2-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]-2-hydroxyethyl]amino)propyl]phenyl}propanoate



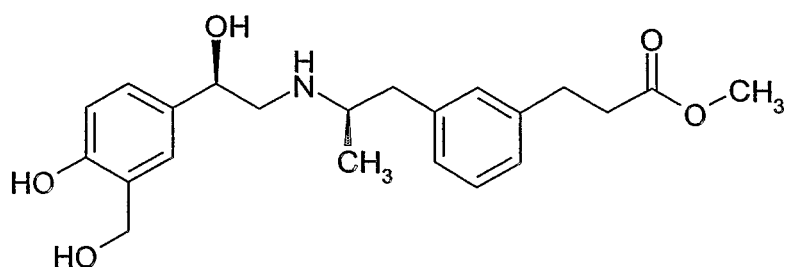
Ammonium fluoride (2.80g, 75.5mmol) was added in one portion to a solution of methyl-3-(3-{(2R)-2-[(2R)-2-[(*tert*-Butyl(dimethyl)silyl]oxy)-2-(4-[benzyloxy]-3-hydroxymethyl-phenyl)-ethylamino]-propyl}-phenyl)-propanoate (Preparation 53) (4.47g, 7.55mmol) in water (20ml) and methanol (30ml) at room temperature. The reaction was heated at 40°C for 18 hours and then allowed to cool to room temperature. The methanol was removed *in vacuo* and the resulting aqueous extracted with dichloromethane (3x75ml), the combined organics were washed with water (25ml), dried (sodium sulfate) and the solvent removed *in vacuo* to yield an orange foam. This was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol: 880 ammonia (95:5:0.5 by volume) to give the title compound as a yellow oil (3.21g).

^1H NMR (400MHz, CD_3OD): δ = 7.46-7.44 (2H, d), 7.38-7.28 (4H, m), 7.15-7.11 (2H, m), 7.00-6.90 (4H, m), 5.12 (s, 2H), 4.67-4.63 (3H, m), 3.62 (3H, s), 2.96-2.84 (4H, m), 2.74-2.66 (2H, m), 2.61-2.55 (3H, m), 1.09-1.07 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 478, $[\text{M}+\text{Na}]^+$ 500.

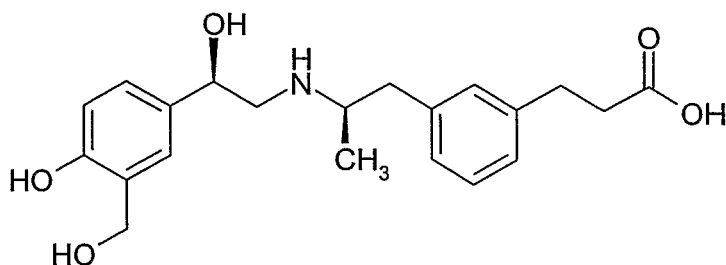
25

Preparation 59: Methyl-3-{3-[(2R)-2-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}propanoate



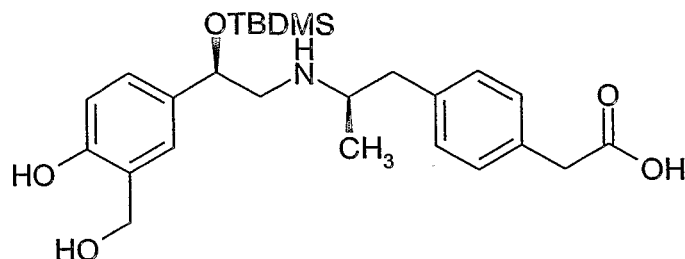
- Prepared according to the procedure used for preparation 37 using methyl-3-{3-[(2R)-2-({(2R)-2-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]-2-hydroxyethyl}amino)propyl]phenyl}propanoate (Preparation 58), substituting dichloromethane:methanol: 880 ammonia (95:5:0.5 changing to 90:10:1 by volume) as column eluent to give the title compound as a colourless oil.
- ^1H NMR (400MHz, CD_3OD): δ = 7.21 (1H, m), 7.16-7.13 (1H, t), 7.02-7.00 (2H, m), 6.97-6.93 (2H, m), 6.70-6.68 (1H, d), 3.63-3.60 (3H, m), 3.34 (3H, s), 2.95-2.84 (4H, m), 2.72-2.65 (2H, m), 2.61-2.53 (3H, m), 1.07-1.05 (3H, d) ppm.
- LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 388, $[\text{M}+\text{Na}]^+$ 410, $[\text{M}-\text{H}]^-$ 386.

Preparation 60: 3-{3-[(2R)-2-({(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}propanoic acid



- Prepared according to the procedure used for preparation 36 using methyl-3-{3-[(2R)-2-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}propanoate to give the title compound as a white foam.
- ^1H NMR (400MHz, CD_3OD): δ = 7.17-7.13 (3H, m), 7.35-7.33 (1H, m), 7.24-7.20 (1H, m), 7.07-7.03 (2H, d), 6.79-6.77 (1H, d), 4.87 (1H, s), 4.65 (2H, s), 3.52-3.47 (1H, m), 3.16-3.06 (3H, m), 2.91-2.87 (2H, t), 2.77-2.71 (1H, m), 2.48-2.44 (2H, t), 1.23-1.21 (3H, d) ppm.
- LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 374, $[\text{M}-\text{H}]^-$ 372.

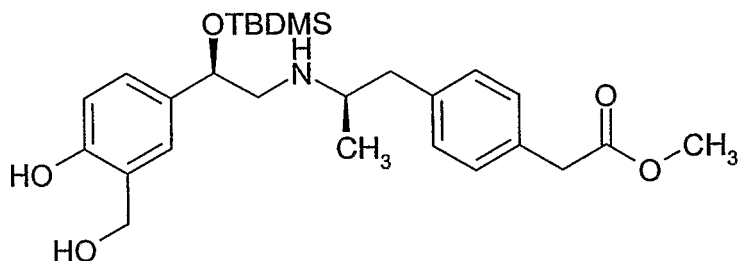
Preparation 61: (4-{2-[2-(*tert*-Butyldimethylsilanyloxy)-2-(4-hydroxy-3-hydroxymethyl-phenyl)ethylamino]propyl}phenyl)acetic acid



- 5 Prepared according to the procedure used for preparation 36, using methyl-(4-{2(2*R*)-[(2*R*)-2-(*tert*-butyldimethylsilanyloxy)-2-(4-hydroxy-3-hydroxymethylphenyl)ethylamino]propyl}phenyl)acetate (Preparation 62) to give the title compound as a brown solid.

¹H NMR (400 MHz, CD₃OD) : δ 7.15 (2H, d), 6.92 (2H, m), 7.00 (1H, d), 6.83 (1H, m), 6.64 (2H, bd), 4.67 (1H, s), 4.60 (2H, m), 3.43 (2H, m), 2.71-2.92 (3H, m), 2.55 (2H, m), 1.04 (3H, m), 0.83 (9H, s), 0.00 (3H, s), -0.18 (3H, s).
LRMS (electrospray) : m/z [M-H]⁺ 472.

Preparation 62 : Methyl-(4-{2(2*R*)-[(2*R*)-2-(*tert*-butyldimethylsilanyloxy)-2-(4-hydroxy-3-hydroxymethylphenyl)ethylamino]propyl}phenyl)acetate



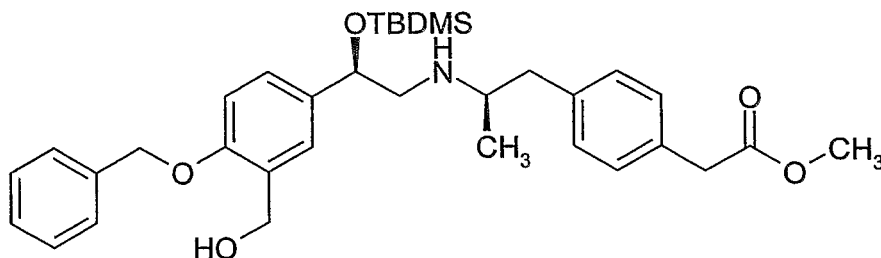
- Prepared according to the procedure used for preparation 37, using methyl-(4-{2(2*R*)-[(2*R*)-2-(4-benzyloxy-3-hydroxymethyl-phenyl)-2-(*tert*-butyldimethylsilanyloxy)ethylamino]propyl}phenyl)acetate (Preparation 63) to
20 give the title compound as a yellow coloured foam.

¹H NMR (400 MHz, CDCl₃) : δ 7.14 (2H, d), 7.04 (1H, d), 7.02 (1H, d), 7.00 (1H, d), 6.90 (1H, d), 6.70 (1H, d), 4.76 (1H, s), 4.73 (2H, s), 3.71 (3H, s), 3.59 (2H,

s), 2.92 (2H, m), 2.73 (1H, m), 2.66 (2H, m), 1.12 (3H, m), 0.81 (9H, s), -0.02 (3H, s), -0.19 (3H, s).

LRMS (electrospray) : m/z $[M+H]^+$ 488, $[M+Na]^+$ 510.

5 Preparation 63: Methyl-(4-((2R)-2-[(2R)-2-(4-benzyloxy-3-hydroxymethyl-phenyl)-2-(*tert*-butyldimethylsilyloxy)ethylamino]propyl]phenyl)acetate

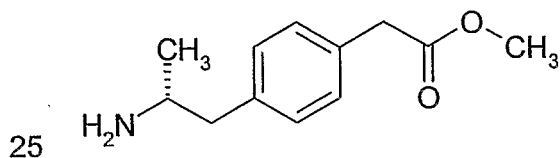


Methyl-{4-[(2R)-2-amino-propyl]phenyl}acetate (Preparation 64) (7.00g, 33.8mmol),
 [2-(benzyloxy)-5-((1R)-2-bromo-1-{*tert*-butyl(dimethyl)silyl]oxy}ethyl)phenyl]methanol (Preparation 39) (15.2g, 33.8mmol) and diisopropylethylamine (4.36 g, 33.8mmol) were heated in diemthylsulfoxide (50ml) at 90 °C under nitrogen for 16 hours. The mixture was cooled and diluted with ethyl acetate (250ml) and basified with 1M aqueous sodium hydroxide. The aqueous was extracted with ethyl acetate (250 ml) and the combined organics washed with brine (3x200 ml) and dried (magnesium sulfate). The crude material was purified by chromatography (90:10 dichloromethane:methanol) to furnish an orange coloured oil (9.86g).

^1H NMR (400 MHz, CDCl_3) : δ 7.32-7.43 (5H, m), 7.13 (1H, d), 7.17 (1H, m), 7.15 (2H, d), 7.07 (2H, d), 6.88 (1H, d), 5.10 (2H, s), 4.73 (1H, m), 4.70 (2H, d), 3.67 (3H, s), 3.57 (2H, s), 2.68-2.91 (4H, m), 2.48 (1H, m), 2.37 (1H, m), 1.01 (3H, d), 0.84 (9H, s), 0.00 (3H, s), -0.18 (3H, s).

LRMS (electrospray) : m/z $[M+H]^+$ 578, $[M+Na]^+$ 600.

Preparation 64: Methyl-{4-[(2R)-2-amino-propyl]phenyl}acetate

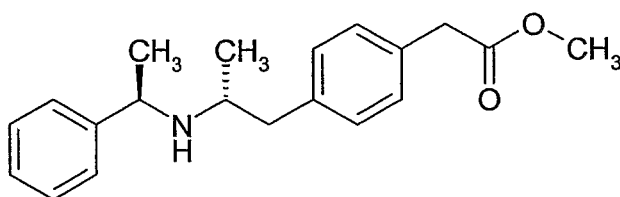


Prepared according to the procedure used for preparation 41, using methyl-(4-
 {(2*R*)-2-[(1*R*)-1-phenylethylamino]propyl}phenyl)acetate hydrochloride
 (Preparation 65) to give the title compound as white crystals.

¹H NMR (400 MHz, CDCl₃) : δ 7.22 (2H, d), 7.17 (2H, d), 3.69 (3H, s), 3.60 (2H,
 5 s), 3.35 (1H, m), 2.79 (1H, m), 1.24 (3H, d).

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

Preparation 65: Methyl-(4-[(2*R*)-2-[(1*R*)-1-phenylethylamino]propyl]phenyl)acetate hydrochloride



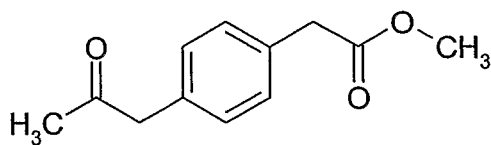
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Prepared according to the procedure used for preparation 42, using methyl-[4-(2-oxo-propyl)phenyl]acetate (Preparation 66) to give the title compound as white crystals.

¹H NMR (400 MHz, CD₃OD) : δ 7.53 (5H, m), 7.21 (2H, d), 7.06 (2H, d), 4.61
 15 (1H, q), 3.66 (3H, s), 3.62 (2H, s), 3.30 (2H, m), 3.18 (1H, m), 2.63 (1H, dd),
 1.70 (3H, d), 1.18 (3H, d).

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

Preparation 66: Methyl-[4-(2-oxo-propyl)phenyl]acetate

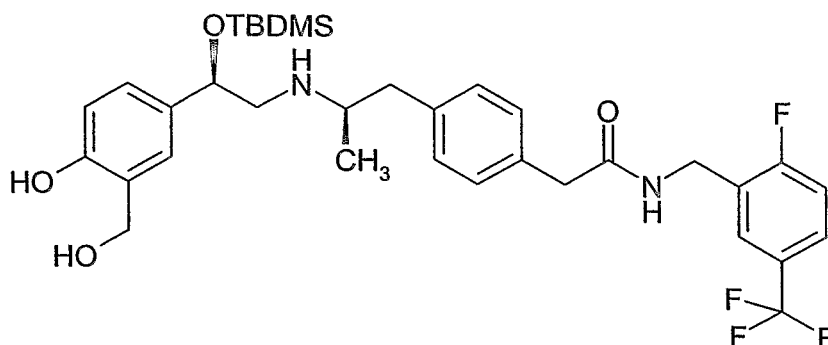


20

Prepared according to the procedure used for preparation 43, using methyl-4-bromophenylacetate to give the title compound as a clear oil.

LRMS (electrospray) : m/z [M+Na]⁺ 229, [M-H]⁻ 205.

Preparation 67: 2-{4-[(2*R*)-2-({(2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-[2-fluoro-5-(trifluoromethyl)benzyl]acetamide

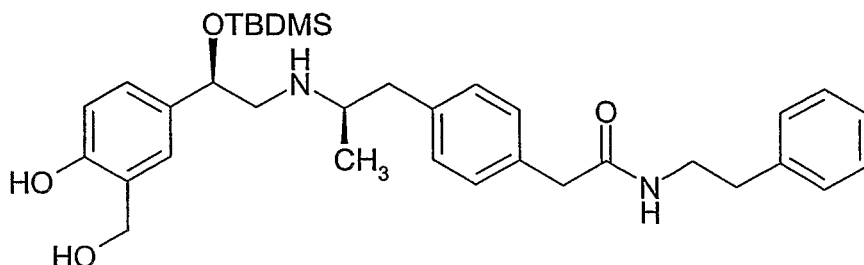


- 5 Prepared according to the procedure used for preparation 3 using 4-{2-[2-(*tert*-butyldimethylsilyloxy)-2-(4-hydroxy-3hydroxymethyl-phenyl)ethylamino]propyl}phenyl)acetic acid (Preparation 61) and the appropriate amine to give the title compound as a white foam.

¹H NMR (400MHz, CD₃OD): δ = 7.55 (2H, m), 7.31-6.82 (7H, m), 6.62 (1H, d),
 10 6.05 (1H, m), 4.75 (2H, s), 4.61 (2H, t), 4.55 (2H, d), 3.68 (2H, s), 2.95 (1H, m),
 2.83 (1H, m), 2.56 (3H, m), 1.05 (3H, d), 0.90 (9H, s), 0.00 (3H, s), -0.20 (3H, s)
 ppm.

LRMS (electrospray) : m/z [M+H]⁺ 649.

- 15 **Preparation 68: 2-{4-[(2*R*)-2-({(2*R*)-2-[[*tert*-Butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)propyl]phenyl}-*N*-(2-phenylethyl)acetamide**



Prepared according to the procedure used for preparation 3 using (4-{2-[2-(*tert*-butyldimethylsilyloxy)-2-(4-hydroxy-3hydroxymethyl-phenyl)ethylamino]propyl}phenyl)acetic acid (Preparation 61) and the appropriate amine to give the title compound as a white foam.

- 5 ^1H NMR (400MHz, CD_3OD): δ = 7.31-6.85 (11H, m), 6.62 (1H, d), 5.63 (1H, m), 4.75 (2H, s), 4.66 (1H, t), 3.55 (2H, m), 3.48 (2H, s), 2.88 (7H, m), 1.05 (3H, d), 0.90 (9H, s), 0.00 (3H, s), -0.20 (3H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 577, $[\text{M}+\text{Na}]^+$ 599, $[\text{M}-\text{H}]^-$ 575.

10 Abbreviations

TBDMS = *tert*-butyl(dimethyl)silyl

In vitro activity of the compounds of formula (1)

- 15 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.

Guinea-pig trachea

- Male, Dunkin-Hartley guinea pigs (475-525g) are killed by CO_2 asphyxiation and exsanguination from the femoral artery and the trachea is isolated. Four
20 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 opened by cutting the cartilage opposite the trachealis muscle, then transverse sections, 3-4 cartilage rings wide, are cut. The resulting strip preparations are
25 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 μM Indomethacin (Sigma I7378), 10 μM Guanethidine (Sigma G8520) and 10 μM Atenolol (Sigma A7655), heated at 37°C and gassed with 95% O_2 /5% CO_2 , before applying an
30 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 isometric transducers coupled to a data-collection system (custom-designed at Pfizer). Following the tensioning equilibration, the tissues are subjected to
5 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 cholinergic nerves in the trachea results in monophasic contractions of the smooth muscle and twitch height is recorded. The organ baths are constantly
10 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 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
15 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 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
20 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, bolus addition to the bath using half log increments in concentration. The concentration range used is 1^{e-9} to 1^{e-6} M. At the end of the isoprenaline
25 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 percentage inhibition of the EFS response. Data for beta-2 agonist are normalised by expressing inhibition as a percentage of the maximal inhibition
30 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

the present invention are then expressed as relative potency to isoprenaline defined by the ratio (EC₅₀ beta-2 agonist)/(EC₅₀ Isoprenaline).

Confirmation of beta-2 mediated functional activity

Beta-2 agonist activity of test compounds is confirmed using the protocol
5 above, however, prior to constructing the curve to beta-2 agonist according to 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.

- 10 It has thus been found that the compounds of formula (1) according to the present invention that have been tested show a relative potency to Isoprenaline which is comprised between 0.002 and 2.0.

According to another alternative, the agonist potency for the β_2 receptor of the compounds of the formula (1) may also be determined by the measure of
15 the concentration of compound according to the present invention required to produce half maximal effect (EC₅₀) for the β_2 receptor.

Compound Preparation

10 mM/100% DMSO (dimethylsulfoxide) stock of compound is diluted to required top dose in 4 % DMSO. This top dose is used to construct a 10-point
20 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

CHO (Chinese Hamster Ovary) cells recombinantly expressing the human β_2
25 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),

500 µg/ml geneticin (Sigma, G7034) and 10 µg/ml puromycin (Sigma, P8833). Cells were seeded to give about 90 % confluency for testing.

Assay Method

25 µl / well each dose of compound was transferred into a cAMP- Flashplate® (NEN, SMP004B), with 1% DMSO as basal controls and 100 nM Isoprenaline as max controls. This was diluted 1:2 by the addition of 25 µl / 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_hB2. Compounds were incubated with 50 µl / well cells for 1 hour. Cells were then lysed by the addition of 100 µl / well detection buffer (NEN, SMP004B) containing 0.18 µCi / ml ¹²⁵I-cAMP (NEN, NEX-130) and plates were incubated at room temperature for a further 2 hours. The amount of ¹²⁵I-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.

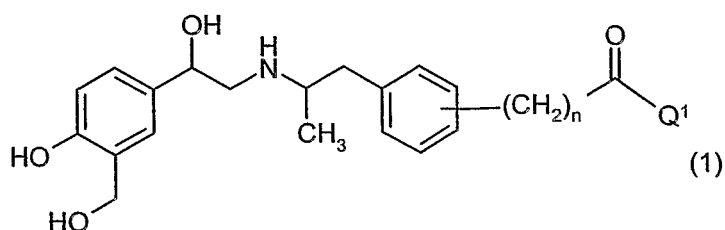
It has thus been found that the compounds of formula (1) according to the present invention that are illustrated in examples 1 to 65 above show a β₂ cAMP EC₅₀ between 0.006 nM and 0.467 nM.

The results below illustrate the activity of the compounds of formula (1):

Example Number	Cell based cAMP β ₂ activity (nM)
1	0.017
3	0.007
4	0.012
5	0.024
6	0.007
7	0.028
8	0.010
10	0.114
12	0.009
13	0.013
15	0.056

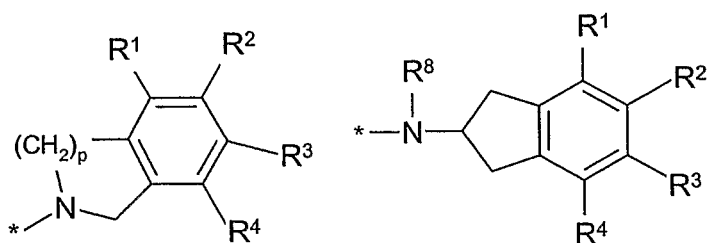
CLAIMS

1. A compound of formula (1):



wherein the $(\text{CH}_2)_n\text{-C}(=\text{O})\text{Q}^1$ group is in position meta or para, n is 1 or 2 and

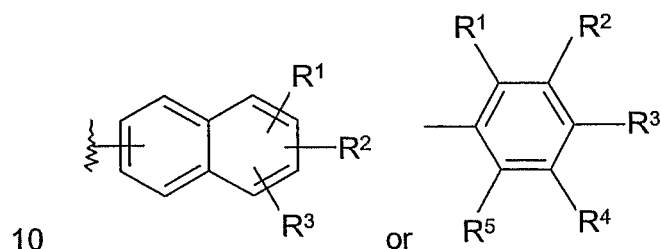
5 Q^1 is a group selected from:



wherein at least 2 of R^1 to

R^4 are equal to H, and,

a group $\text{*-(R}^8\text{)-Q}^2\text{-A}$, wherein Q^2 is a single bond or a $\text{C}_1\text{-C}_4$ alkylene, R^8 is H or a $\text{C}_1\text{-C}_4$ alkyl, p is 1 or 2, and A is pyridyl or a group of formula



10

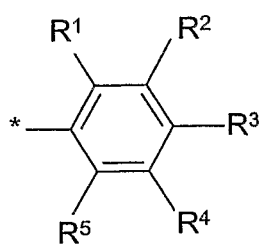
wherein at least 2 of R^1 to R^5 are equal to H,

wherein R^1 , R^2 , R^3 , R^4 and R^5 are the same or different and are selected from H, $\text{C}_1\text{-C}_4$ alkyl, OR^6 , SR^6 , halo, CF_3 , OCF_3 , COOR^6 , $\text{SO}_2\text{NR}^6\text{R}^7$, CONR^6R^7 , NR^6R^7 , NHCOR^6 ,

wherein R^6 and R^7 are the same or different and are selected from H or C₁-C₄ alkyl and the * represent the attachment point to the carbonyl group,

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

- 5 2. A compound according to claim 1 wherein n is 1 or 2 and Q^1 is *-NH- Q^2 -A wherein Q^2 is C₁-C₄ alkylene and A is a group of formula



wherein R^1 , R^2 , R^3 , R^4 and R^5 are as defined in claim 1.

3. A compound according to claim 2 wherein R^1 , R^2 , R^3 , R^4 and R^5 are the same or different and are selected from H, C₁-C₄ alkyl, OR⁶, Cl, F, CF₃, OCF₃,
 10 COOR⁶, SO₂NR⁶R⁷, provided at least 2 of R^1 to R^5 are equal to H,

wherein R^6 and R^7 are the same or different and are selected from H or C₁-C₄ alkyl.

4. A compound according to claim 3 wherein R^1 , R^2 , R^3 , R^4 and R^5 are the same or different and are selected from H, CH₃, OH, OCH₃, OCH₂CH₃, Cl, F,
 15 CF₃, OCF₃, COOH, SO₂NH₂, provided at least 2 of R^1 to R^5 are equal to H.

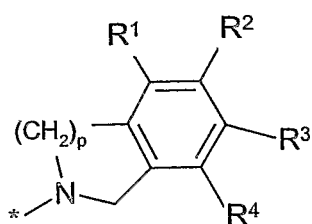
5. A compound according to claim 4 wherein R^1 , R^2 , R^3 , R^4 and R^5 are the same or different and are selected from H, CH₃, OH, OCH₃, OCH₂CH₃, Cl, F, CF₃, OCF₃, COOH, SO₂NH₂, provided at least 3 of R^1 to R^5 are equal to H.

6. A compound according to claim 1 wherein Q^1 is a group *-NH- Q^2 -A, wherein
 20 Q^2 is C₁-C₄ alkylene and A is pyridin-2-yl.

7. A compound according to any one of claims 1 to 6 wherein Q^2 is selected from -CH₂-, -(CH₂)₂-, -(CH₂)₃- and -CH(CH₃)-.

8. A compound according to any one of claims 1 to 6 wherein Q^2 is -CH₂-.

9. A compound according to claim 1 wherein n is 1 or 2 and Q¹ is

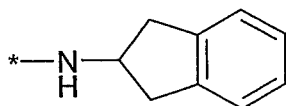


wherein p is 1 or 2, R¹, R², R³ and R⁴ are the same or different and are selected from H, C₁-C₄ alkyl, OR⁶, SR⁶, halo, CF₃, OCF₃, COOR⁶, SO₂NR⁶R⁷, CONR⁶R⁷, NR⁶R⁷, NHCOR⁶, provided at least 2 of R¹ to R⁴ are equal to H;

wherein R⁶ and R⁷ are the same or different and are selected from H or C₁-C₄ alkyl.

10. A compound according to claim 9 wherein R¹, R², R³ and R⁴ are the same or different and are selected from H and OR⁷, provided at least 2 of R¹ to R⁴ are equal to H.

11. A compound according to claim 1 wherein Q¹ is



12. A compound according to any one of claims 1 to 11 wherein n is 1.

13. A compound according to any one of claims 1 to 11 wherein n is 2.

14. The (R,R)-stereoisomer of a compound according to any one of claims 1 to 13.

15. A compound according to any one of claims 1 to 14 wherein the (CH₂)_n-C(=O)Q¹ group is in position meta.

16. A compound according to claim 1 selected from the group consisting of
N-(2,6-Dimethoxybenzyl)-2-(3-((2R)-2-[(2R)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl)-phenyl)-acetamide;

- N*-(2-Ethoxybenzyl)-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide;
- N*-(2-Hydroxybenzyl)-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide;
- 5 2-(3-((2*R*)-2-((2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-*N*-indan-2-yl-acetamide;
- N*-(3,4-Dichlorobenzyl)-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide;
- N*-[4-(Aminosulfonyl)benzyl]-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide;
- 10 2-(3-((2*R*)-2-((2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-*N*-(pyridin-2-ylmethyl)-acetamide;
- 4-((2-(3-((2*R*)-2-((2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetylamino)-methyl)-benzamide;
- 15 *N*-(3,4-Dimethoxybenzyl)-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide;
- 2-(3-((2*R*)-2-((2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-*N*-(4-trifluoromethoxybenzyl)-acetamide;
- N*-(2-Chloro, 6-fluorobenzyl)-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide;
- 20 *N*-(3,4-Dimethylbenzyl)-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide;
- N*-[2-Fluoro-5-(trifluoromethyl)benzyl]-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide;
- 25 *N*-(2,6-Dichlorobenzyl)-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide;
- 2-(3-((2*R*)-2-((2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-*N*-(2-phenylethyl)acetamide;
- N*-Benzyl-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide;
- 30 *N*-(3,5-Dichlorobenzyl)-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide;

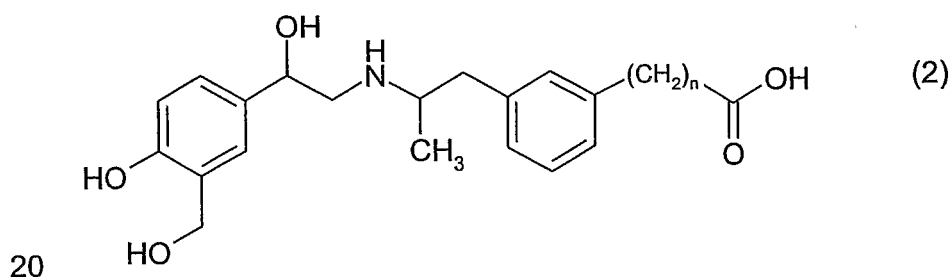
- N*-(4-Chlorobenzyl)-2-(3-((2*R*)-2-((2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetamide;
- 4-([2-(3-((2*R*)-2-((2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino)-propyl)-phenyl)-acetyl]-amino)-methyl)-benzoic acid;
- 5 2-{3-[(2*R*)-2-((2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl}phenyl)-*N*-[(1*R*)-1-phenylethyl]acetamide;
- 4-[(1*R*)-2-(((1*R*)-2-{3-[2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]phenyl}-1-methylethyl)amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol;
- 10 4-[(1*R*)-2-(((1*R*)-2-{3-[2-(7-Ethoxy-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]phenyl}-1-methylethyl)amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol;
- N*-[2-(4-Chlorophenyl)ethyl]-2-{3-[(2*R*)-2-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl}phenyl]acetamide;
- 15 *N*-[2-(4-Ethylphenyl)ethyl]-2-{3-[(2*R*)-2-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl}phenyl]acetamide;
- N*-(1,1-Dimethyl-2-phenylethyl)-2-{3-[(2*R*)-2-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl}phenyl]acetamide;
- N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-{3-[(2*R*)-2-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl}phenyl]acetamide;
- 20 *N*-(3,4-Difluorobenzyl)-2-{3-[(2*R*)-2-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl}phenyl]acetamide;
- 4-[(1*R*)-2-(((1*R*)-2-{3-[2-(1,3-Dihydro-2*H*-isoindol-2-yl)-2-oxoethyl]phenyl}-1-methylethyl)amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol;
- 25 2-{3-[(2*R*)-2-((2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl}phenyl)-*N*-phenylacetamide;
- 2-{3-[(2*R*)-2-((2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl}phenyl)-*N*-(1-naphthylmethyl)acetamide;
- 30 *N*-(3,4-Dichlorobenzyl)-2-{3-[(2*R*)-2-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl}phenyl)-*N*-methylacetamide;

- 2-{3-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}-*N*-(2-pyridin-2-ylethyl)acetamide;
- 2-{3-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}-*N*-[(2*R*)-2-phenylpropyl]acetamide;
- 5 *N*-Benzyl-2-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}-*N*-methylacetamide;
- N*-[3-(4-Fluorophenyl)propyl]-2-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}acetamide;
- 10 *N*-(2,6-Dichlorobenzyl)-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl]-phenyl}-propanamide;
- N*-(2,6-Dimethoxybenzyl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}propanamide;
- 15 *N*-(2-Ethoxybenzyl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}propanamide;
- N*-(3,4-Dimethylbenzyl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}propanamide;
- N*-(2,3-Dihydro-1*H*-inden-2-yl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}propanamide;
- 20 4-{[(1*R*)-2-[(1*R*)-2-{3-[3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-3-oxopropyl]phenyl]-1-methylethyl]amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol;
- N*-(2-Chloro-6-fluorobenzyl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}propanamide;
- 25 *N*-(2-Chlorobenzyl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}propanamide;
- 3-{3-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}-*N*-(pyridin-2-ylmethyl)propanamide;
- 30 *N*-(2-Chlorobenzyl)-3-{3-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]phenyl}propanamide;

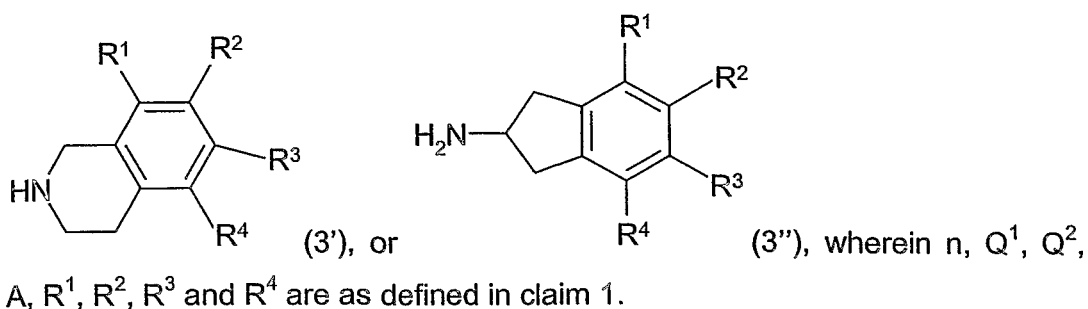
- 3-{3-[(2*R*)-2-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl}-*N*-(pyridin-2-ylmethyl)propanamide;
- N*-Benzyl-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl}propanamide;
- 5 3-{3-[(2*R*)-2-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl}-*N*-(2-phenylethyl)propanamide;
- 3-{3-[(2*R*)-2-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl}-*N*-(3-phenylpropyl)propanamide;
- 10 4-[(1*R*)-2-[(1*R*)-2-{3-[3-(1,3-Dihydro-2*H*-isoindol-2-yl)-3-oxopropyl]phenyl}-1-methylethyl]amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol;
- N*-[2-Fluoro-5-(trifluoromethyl)benzyl]-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl}propanamide;
- 15 *N*-(2-Hydroxybenzyl)-3-{3-[(2*R*)-2-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl}propanamide;
- 3-{3-[(2*R*)-2-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl}-*N*-phenylpropanamide;
- 20 *N*-Benzyl-2-(4-{(2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl-amino]propyl]phenyl)acetamide;
- 2-(4-{(2*R*)-2-[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl-amino]propyl]phenyl)-*N*-(3-phenyl-propyl)acetamide;
- 2-(4-{(2*R*)-2-[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl-amino]propyl]phenyl)-*N*-indan-2-yl-acetamide;
- 25 1-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-2-(4-{(2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino]propyl]phenyl)ethanone;
- N*-(2-Hydroxybenzyl)-2-(4-{(2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]propyl]phenyl)-acetamide;
- 30 *N*-(3-Chlorobenzyl)-2-(4-{(2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]propyl]phenyl)-acetamide;

- N-(4-Chlorobenzyl)-2-(4-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino]propyl)phenyl)-acetamide;
 2-(4-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino]-propyl)phenyl)-*N*-(2-methoxybenzyl)-acetamide;
 5 2-(4-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino]propyl)phenyl)-*N*-(3-methoxybenzyl)acetamide;
 2-(4-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethylamino]-propyl)phenyl)-*N*-(4-methoxybenzyl)-acetamide;
N-(2,6-Dimethoxybenzyl)-2-(4-((2*R*)-2-[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy-
 10 methylphenyl)-ethylamino]propyl)phenyl)-acetamide,
 2-(4-((2*R*)-2-[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)-ethyl-amino]propyl)phenyl)-*N*-(pyridin-2-ylmethyl)acetamide,
N-[2-Fluoro-5-(trifluoromethyl)benzyl]-2-{4-[(2*R*)-2-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl}phenyl}acetamide, and,
 15 2-{4-[(2*R*)-2-((2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]propyl}phenyl}-*N*-(2-phenylethyl)acetamide.

17. A process for the preparation of a compound of formula (1) as described in claim 1 or a pharmaceutically acceptable salt or derived form thereof comprising the step of coupling an acid of formula (2):



with an amine of formula $\text{NH}_2\text{-Q}^2\text{-A}$ (3),



18. A pharmaceutical composition including a compound of formula (1) as described in claim 1 or a pharmaceutically acceptable salt or derived form thereof, together with customary pharmaceutically innocuous excipients and/or additives.

19. A compound of formula (1) as described in claim 1 or a pharmaceutically acceptable salt, derived form or composition thereof, for use as a medicament.

20. A compound of formula (1) as described in claim 1 or a pharmaceutically acceptable salt, derived form or composition thereof, for use in the treatment of diseases, disorders, and conditions in which the β_2 receptor is involved.

21. A compound of formula (1) as described in claim 1 or a pharmaceutically acceptable salt, derived form or composition 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.
22. The use of a compound of formula (1) as described in claim 1 or of a pharmaceutically acceptable salt, derived form or composition thereof, for the manufacture of a drug having a β_2 agonist activity.

23. The use of a compound of formula (1) as described in claim 1 or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a drug for the treatment of diseases, disorders, and conditions selected from the group as described in claim 21.
- 5 24. 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 formula (1) as described in claim 1 or with a pharmaceutically acceptable salt, derived form or composition thereof.
- 10 25. A method according to claim 24 where the disease, disorder or condition is selected from the group as described in claim 21.