



(86) Date de dépôt PCT/PCT Filing Date: 2004/06/01
(87) Date publication PCT/PCT Publication Date: 2004/12/16
(85) Entrée phase nationale/National Entry: 2005/11/30
(86) N° demande PCT/PCT Application No.: IB 2004/001850
(87) N° publication PCT/PCT Publication No.: 2004/108676
(30) Priorité/Priority: 2003/06/04 (0312832.9) GB

(51) Cl.Int./Int.Cl. *C07D 213/73* (2006.01),
C07D 401/14 (2006.01), *A61P 11/00* (2006.01),
A61K 31/44 (2006.01)

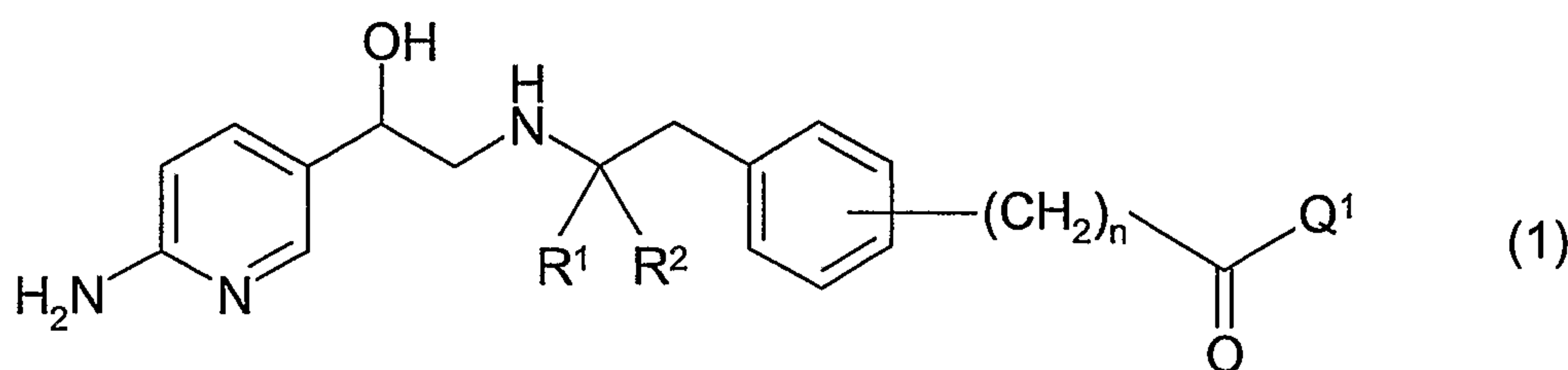
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(54) Titre : DERIVES DE 2-(6-AMINO-PYRIDINE-3-YL)-2-HYDROXYETHYLAMINE UTILISES COMME AGONISTES DES
RECEPTEURS BETA 2-ADRENERGIQUES

(54) Title: 2-(6-AMINO-PYRIDIN-3-YL)-2-HYDROXYETHYLAMINE DERIVATIVES AS BETA 2-ADRENOCEPTORS
AGONISTS



(57) **Abrégé/Abstract:**

The invention relates to compounds of formula (1) and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives. The compounds according to the present invention are useful in numerous diseases, disorders and conditions, in particular inflammatory, allergic and respiratory diseases, disorders and conditions.



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

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
16 December 2004 (16.12.2004)

PCT

(10) International Publication Number
WO 2004/108676 A1

(51) International Patent Classification⁷: **C07D 213/73**,
401/14, A61K 31/44, A61P 11/00

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(21) International Application Number:
PCT/IB2004/001850

(22) International Filing Date: 1 June 2004 (01.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0312832.9 4 June 2003 (04.06.2003) GB

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

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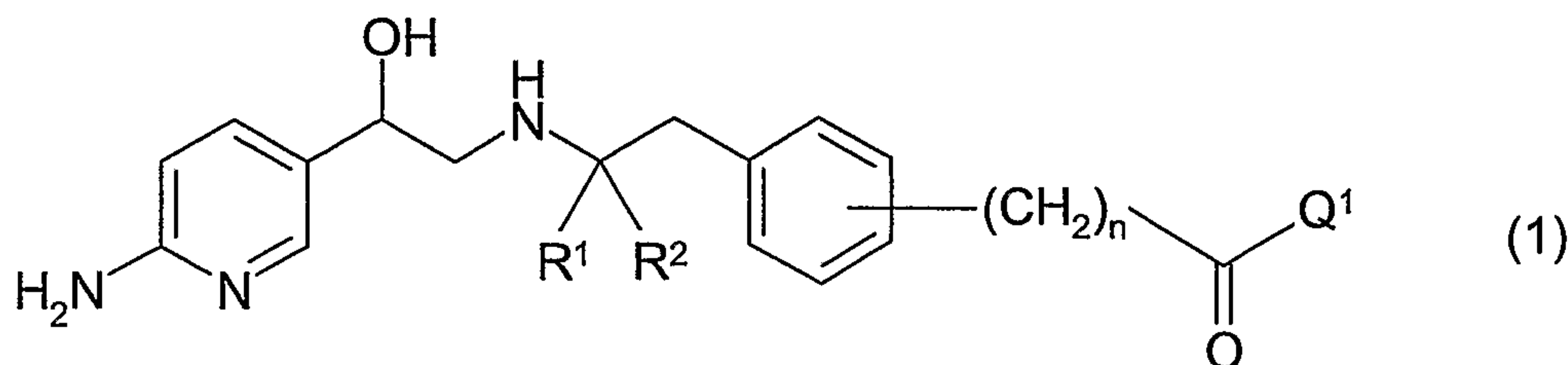
(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: 2-(6-AMINO-PYRIDIN-3-YL)-2-HYDROXYETHYLAMINE DERIVATIVES AS BETA 2-ADRENOCEPTORS AG-
ONISTS

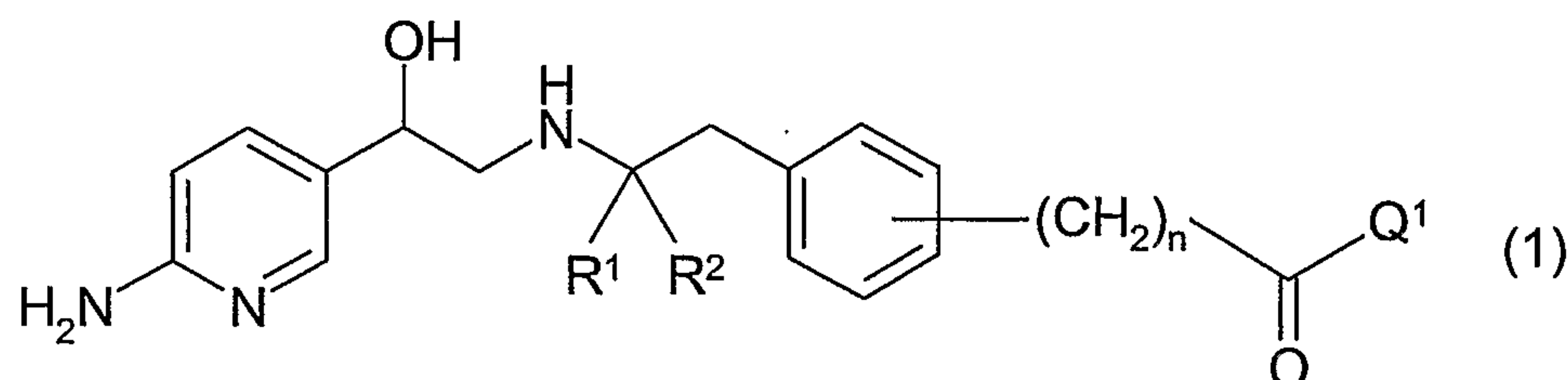


(57) Abstract: The invention relates to compounds of formula (1) and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives. The compounds according to the present invention are useful in numerous diseases, disorders and conditions, in particular inflammatory, allergic and respiratory diseases, disorders and conditions.

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2- (6-AMINO-PYRIDIN-3-YL) -2-HYDROXYETHYLAMINE DERIVATIVES AS BETA 2-ADRENOCEPTORS AGONISTS

This invention relates to β 2 agonists of general formula (1):



- 5 in which R^1 , R^2 , n and Q^1 have the meanings indicated below,
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
10 subfamilies with the β sub-family being composed of at least 3 receptor sub-
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
15 receptors are mainly expressed in fat tissues (therefore β 3 agonists could
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
20 extensively reviewed in the literature (for reference see Barnes, P.J. Chest,
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 $\beta 2$ 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 $\beta 2$ agonists. Short acting, rapid onset $\beta 2$ 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 $\beta 2$ adrenoceptor expressed on airway smooth muscle cells, which results in relaxation and
10 hence bronchodilation. Thus, as functional antagonists, $\beta 2$ agonists can prevent and reverse the effects of all bronchoconstrictor substances, including leukotriene D4 (LTD4), acetylcholine, bradykinin, prostaglandins, histamine and endothelins. Because $\beta 2$ receptors are so widely distributed in the airway, $\beta 2$ agonists may also affect other types of cells that play a role in asthma. For
15 example, it has been reported that $\beta 2$ agonists may stabilize mast cells. The inhibition of the release of bronchoconstrictor substances may be how $\beta 2$ agonists block the bronchoconstriction induced by allergens, exercise and cold air. Furthermore, $\beta 2$ agonists inhibit cholinergic neurotransmission in the human airway, which can result in reduced cholinergic-reflex bronchoconstriction.

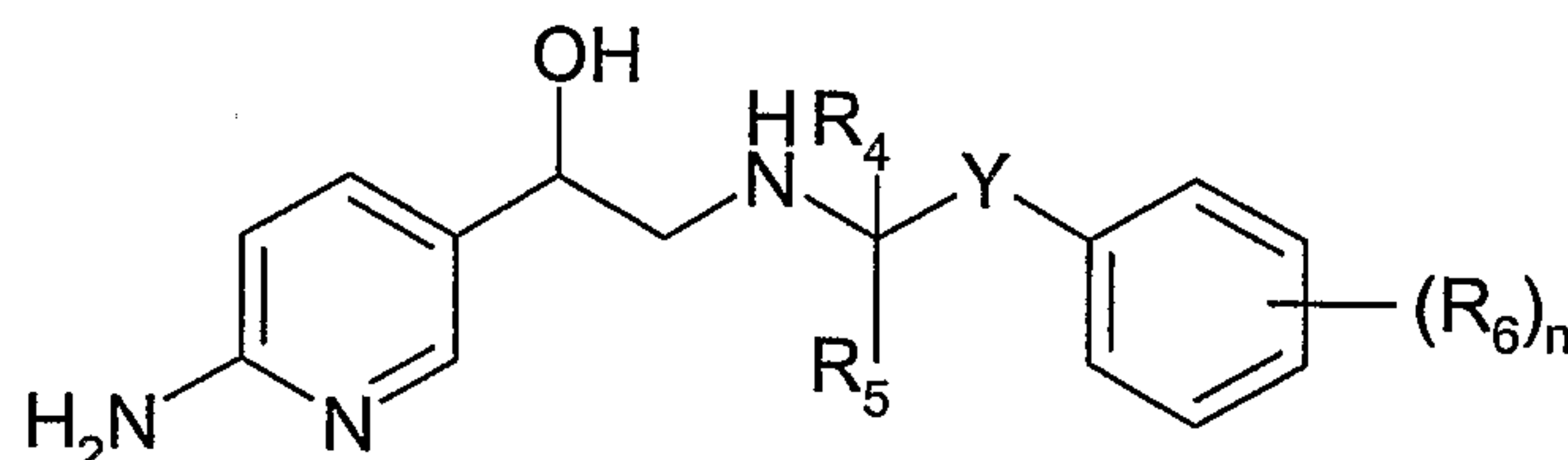
20 In addition to the airways, it has also been established that $\beta 2$ adrenoceptors are also expressed in other organs and tissues and thus $\beta 2$ agonists, such as those described in the present invention, may have application in the treatment of other diseases such as, but not limited to those 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 $\beta 2$ 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 $\beta 2$ adrenoreceptors expressed outside the airways

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

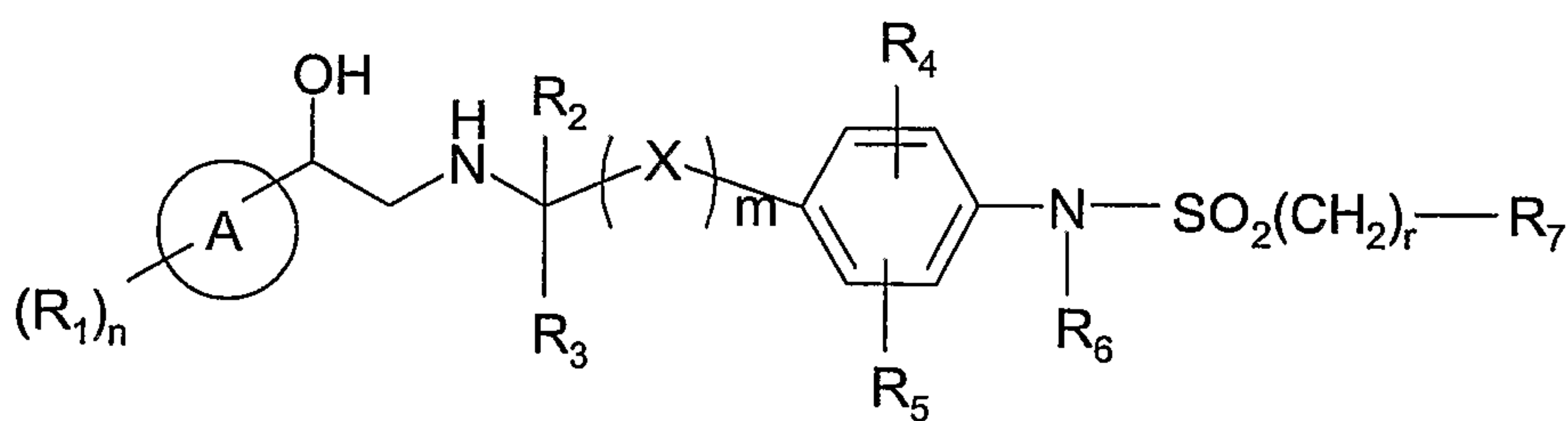
Accordingly, there is still a need for novel $\beta 2$ agonists that would have an appropriate pharmacological profile, for example in terms of potency, selectivity
5 and/or pharmacodynamic properties. In this context, the present invention relates to novel $\beta 2$ agonists.

Various 2-amino-pyridine derivatives have already been synthesised. For example, the US patent US 4,358,455 discloses compounds having a random activity either as beta-adrenergic stimulants or as beta-adrenergic blockers, of
10 formula :



wherein R_4 and R_5 are independently selected from H and (C_1-C_3) alkyl; Y may namely be a methylene group, R_6 is selected from H, OH, alkoxy, methylenedioxy, halo or alkyl; and n is equal to 1 or 2.

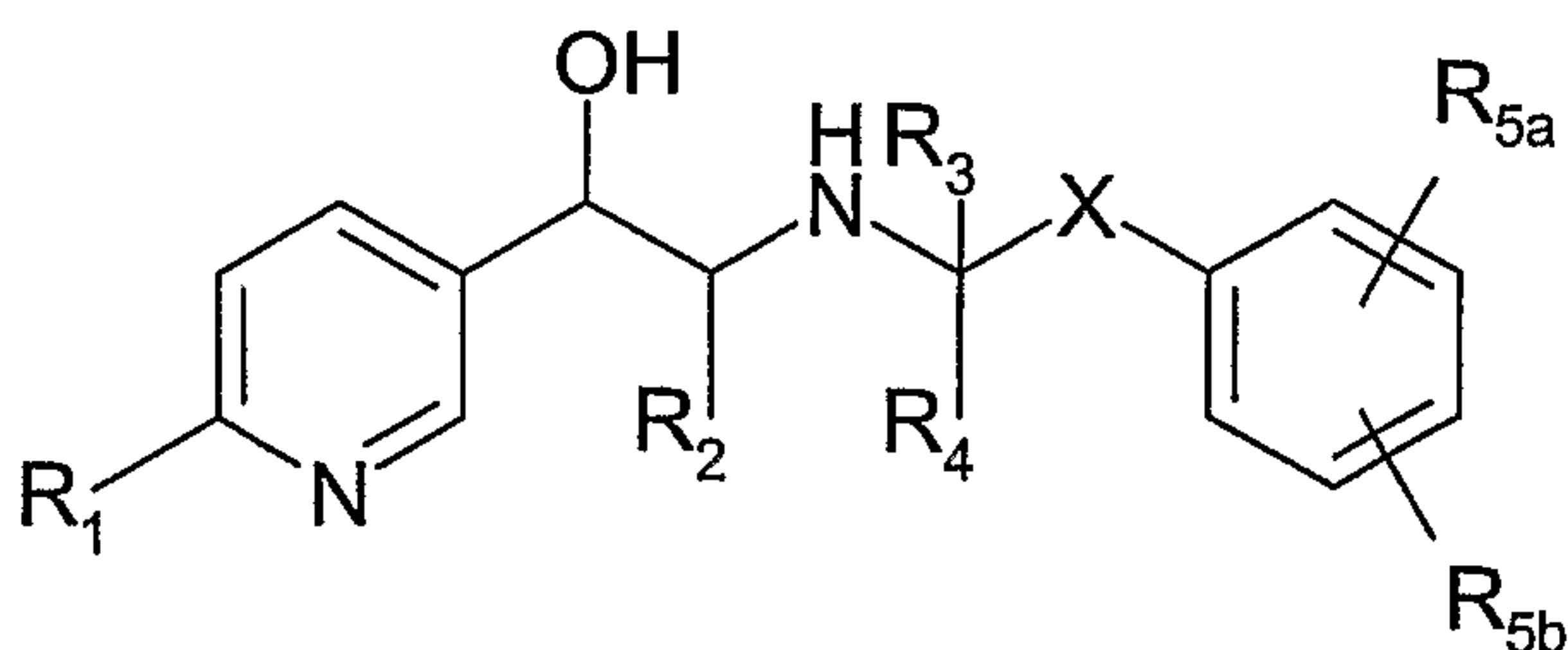
15 Another example concerns the patent application WO 95/29259 that discloses selective $\beta 3$ agonists (with little $\beta 1$ and $\beta 2$ activity) of formula :



wherein A may be a 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from O, S and N; R_1 may be amino and n may be equal to 1; R_2 , R_3
20 may be independently H or (C_1-C_{10}) alkyl; m is 0 or 1, and X may be a methylene group; R_4 , R_5 may be H; R_6 is H or (C_1-C_{10}) alkyl; r is 0 to 3 and R_7

may be a phenyl 0 to 5 times substituted by numerous substituents (OH, oxo, Hal, CN etc...).

Other 2-amino-pyridine derivatives are also disclosed in US 5,714,506 as selective β_3 agonists. They are more specifically of formula :

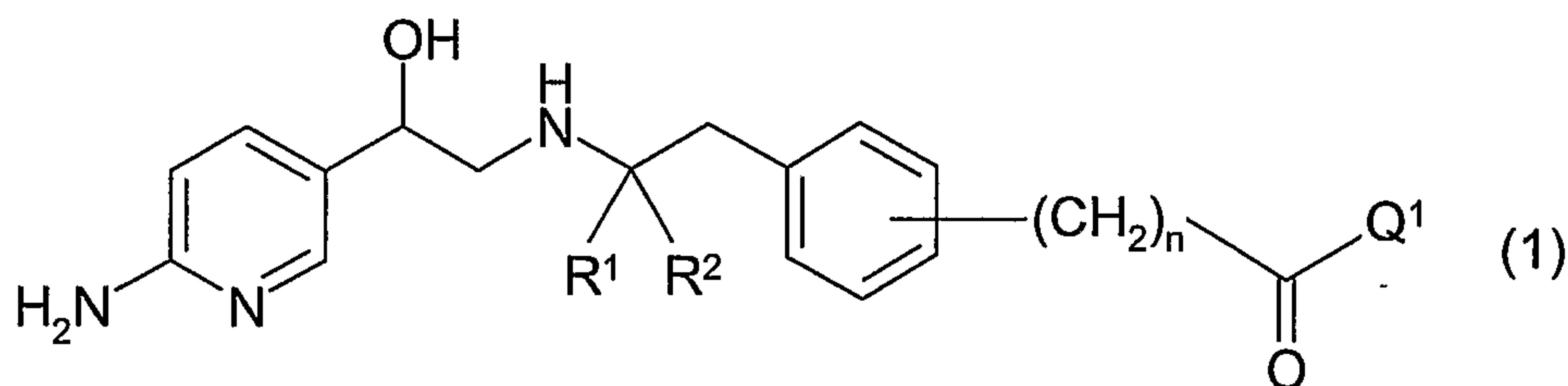


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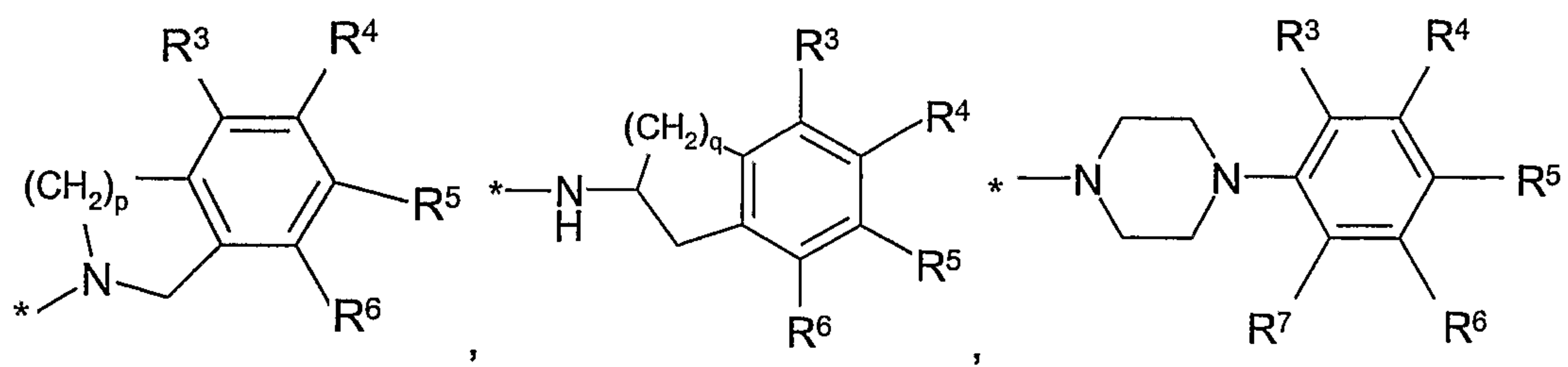
wherein R_1 may be amino; R_2 is H or (C_1-C_6) alkyl; R_3 and R_4 may be independently H or (C_1-C_{12}) alkyl; X may be a $-(CH_2)_n-$ group with n selected from 1, 2 and 3; and R_{5a} and R_{5b} may be chosen from $-CONR_2R_2$, $-O-CH_2-CONR_2R_2$, aryl, $-CH_2$ -alkoxy, $-CH_2-CONR_2R_2$ wherein R_2 is H or (C_1-C_6) alkyl.

10 However, none of the 2-amino-pyridine derivatives synthesised so far have shown a selective β_2 agonist activity, allowing them to be used as efficient drugs in the treatment of the β_2 -mediated diseases and/or conditions, in particular allergic and non-allergic airways diseases or other diseases such as those previously cited.

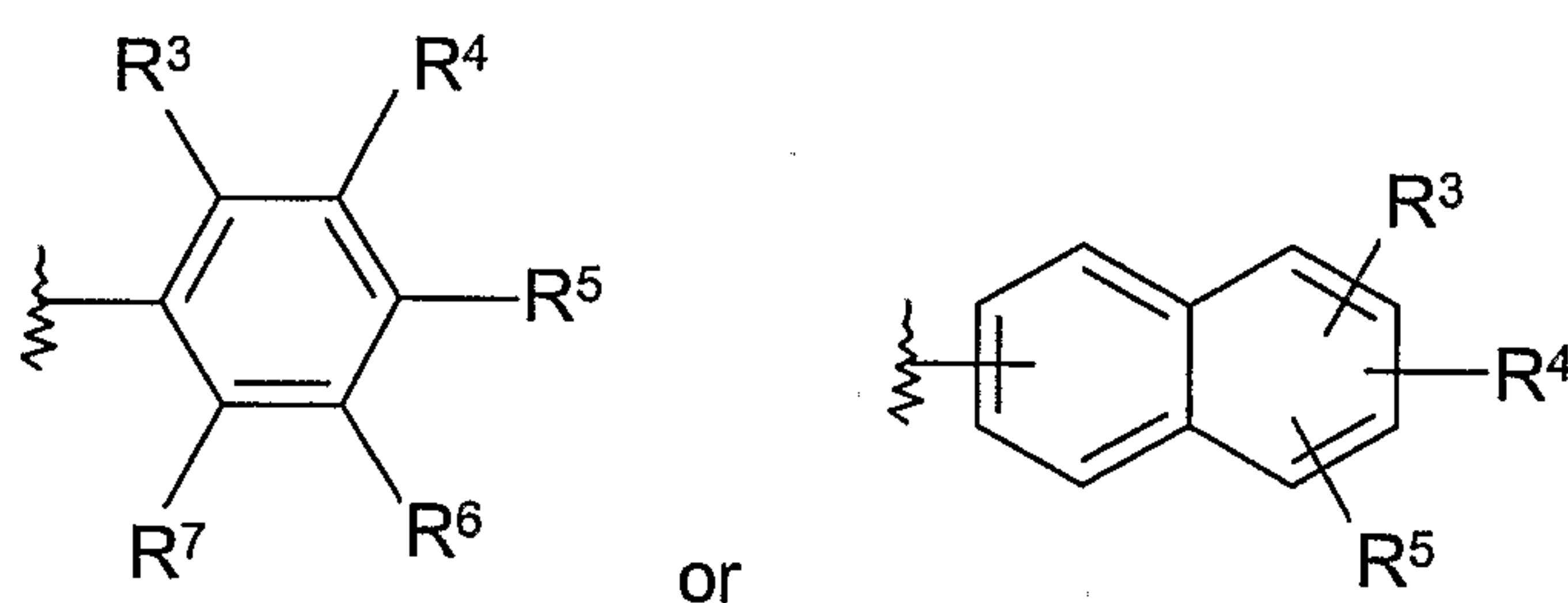
15 The invention relates to the compounds of general formula (1):



wherein the $(CH_2)_n-C(=O)Q^1$ group is in the meta or para position, R^1 and R^2 are independently selected from H and C_1-C_4 alkyl, n is 0, 1 or 2 and Q^1 is a group selected from:



and a group $^*\text{-NR-Q}^2\text{-A}$, wherein p is 1, 2 or 3, q is 1 or 2, Q^2 is a direct bond or a $\text{C}_1\text{-C}_4$ alkylene optionally substituted by OH, R is H, $\text{C}_1\text{-C}_4$ alkyl or phenyl optionally substituted by OH, and A is $\text{C}_3\text{-C}_7$ cycloalkyl, said cycloalkyl being
 5 optionally bridged by one or more carbon atoms, preferably 1 or 2 carbon atoms, tetrahydropyranyl, piperidiny, tetrahydrothiopyranyl, pyridyl or a group selected from :



wherein R^3 , R^4 , R^5 , R^6 and R^7 are the same or different and are each
 10 independently selected from H, $\text{C}_1\text{-C}_4$ alkyl, OR^9 , SR^9 , halo, CF_3 , OCF_3 , $(\text{CH}_2)_m\text{COOR}^9$, $\text{SO}_2\text{NR}^8\text{R}^9$, CONR^8R^9 , NR^8R^9 , NHCOR^8 , $\text{SO}_2(\text{C}_1\text{-C}_4)\text{alkyl}$ and phenyl optionally substituted by hydroxy or hydroxy($\text{C}_1\text{-C}_4$)alkyl;

wherein m is an integer selected from 0, 1, and 2 and R^8 and R^9 are the same or different and are independently selected from H or $\text{C}_1\text{-C}_4$ alkyl and the *
 15 represent the attachment point to the carbonyl group;

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

The compounds of the invention are selective agonists of the β_2 receptors, that are particularly useful for the treatment of β_2 -mediated diseases and/or

conditions, by showing excellent potency, in particular when administered via the inhalation route.

Preferably, the term "selective" means that the compounds of formula (1) show an agonist potency for the $\beta 2$ receptor, which is at least about 50-fold
5 higher as for the $\beta 3$ receptor and at least about 500-fold higher as for the $\beta 1$ receptor.

Preferably, the compounds of formula (1) show an agonist potency for the $\beta 2$ receptor, which is less than 10 nM as measured by the cell-based assay described herein.

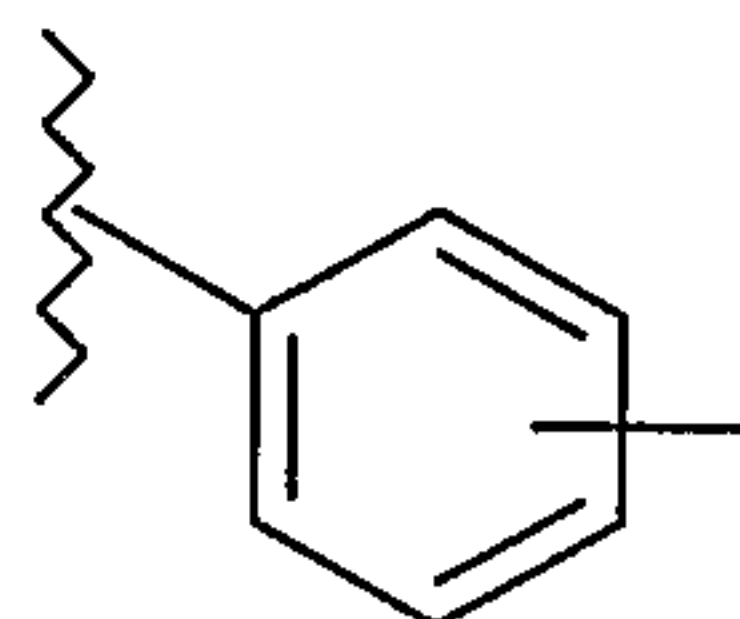
10 In the here above general formula (1), C_1-C_4 alkyl and C_1-C_4 alkylene denote a straight-chain or-branched group containing 1, 2, 3 or 4 carbon atoms. This also applies if they carry substituents or occur as substituents of other radicals, for example in hydroxy(C_1-C_4)alkyl, O-(C_1-C_4)alkyl radicals, S-(C_1-C_4)alkyl radicals etc... . Examples of suitable (C_1-C_4)alkyl radicals are methyl,
15 ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl.... hydroxy(C_1-C_4)alkyl radicals are alkyl radicals substituted by a hydroxy (OH) substituent. According to a preferred embodiment of said invention, such radicals contain one hydroxy substituent that can be located at any position on the alkyl radical. Examples of suitable hydroxy(C_1-C_4)alkyl radicals are hydroxymethyl, 1-
20 hydroxyethyl, 2-hydroxyethyl etc...

The term " C_3-C_7 cycloalkyl", includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A preferred cycloalkyl group is cyclohexyl.

The C_3-C_7 cycloalkyl wherein 2 carbon atoms or more are optionally bridged by one or more carbon atoms include adamantanyl,
25 bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane.

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

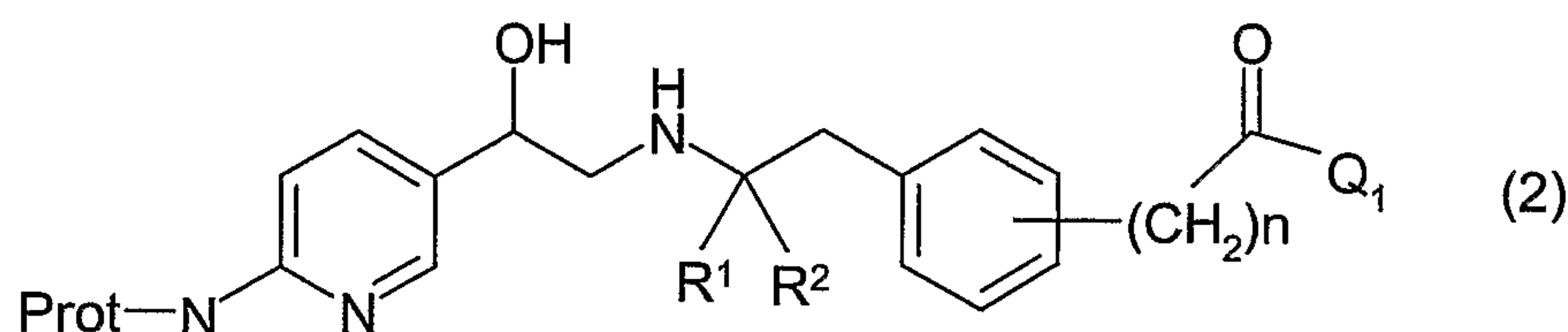
In the following, the free bond on the phenyl group such as in the structure below :



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

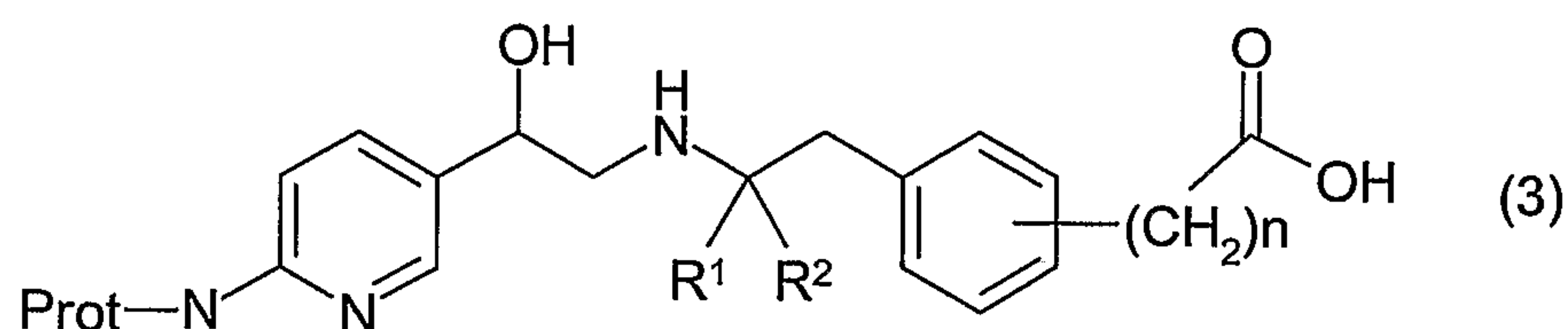
- 5 The 2-amino-pyridine derivatives of the formula (1) can be prepared using conventional procedures such as by the following illustrative methods in which R^1 , R^2 , Q^1 and n are as previously defined for the 2-amino-pyridine derivatives of the formula (1) unless otherwise stated.

10 The 2-amino-pyridine derivatives of the formula (1) may be prepared by removal of the protecting group(s) "Prot" from the compound of formula (2) :

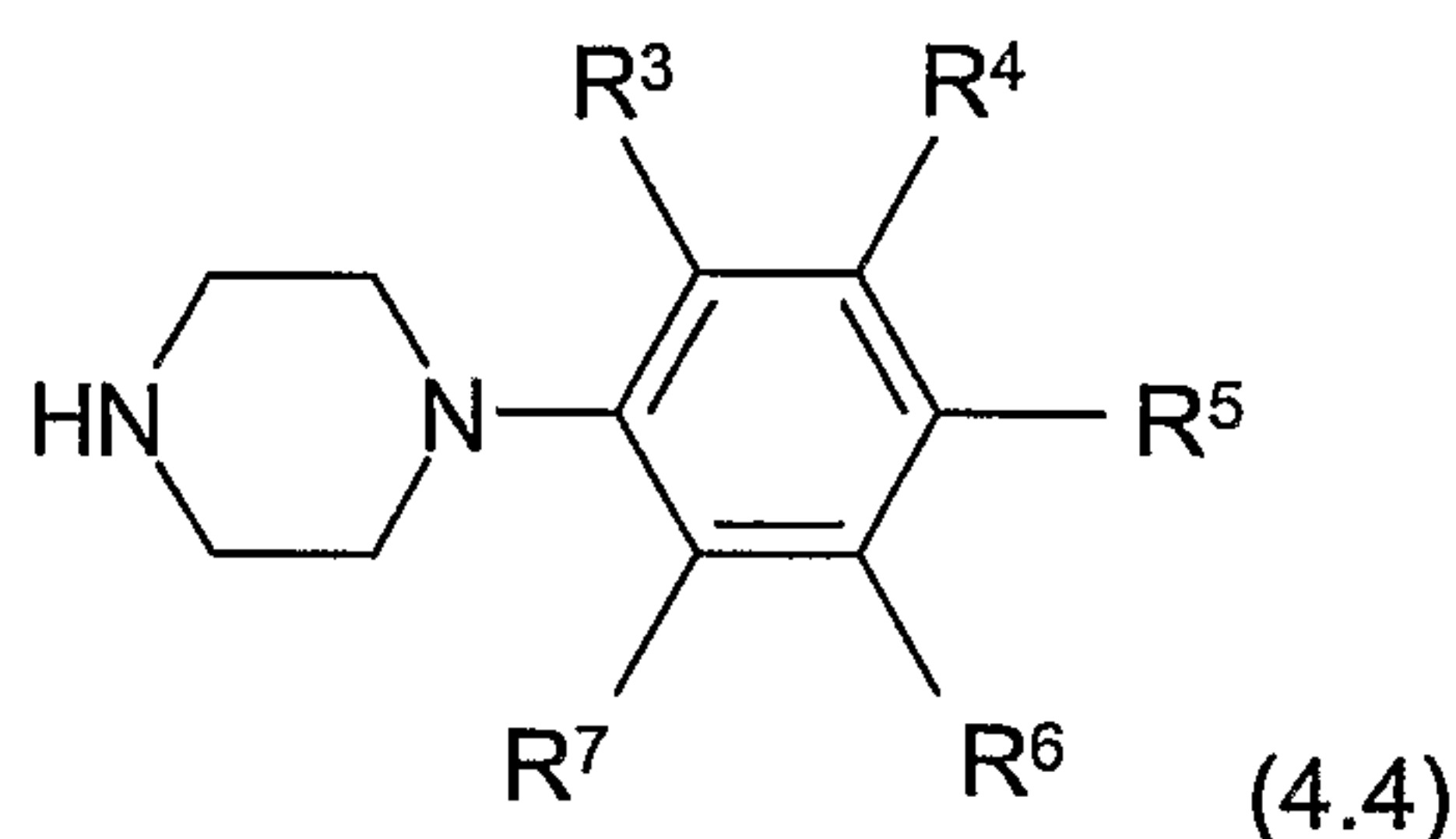
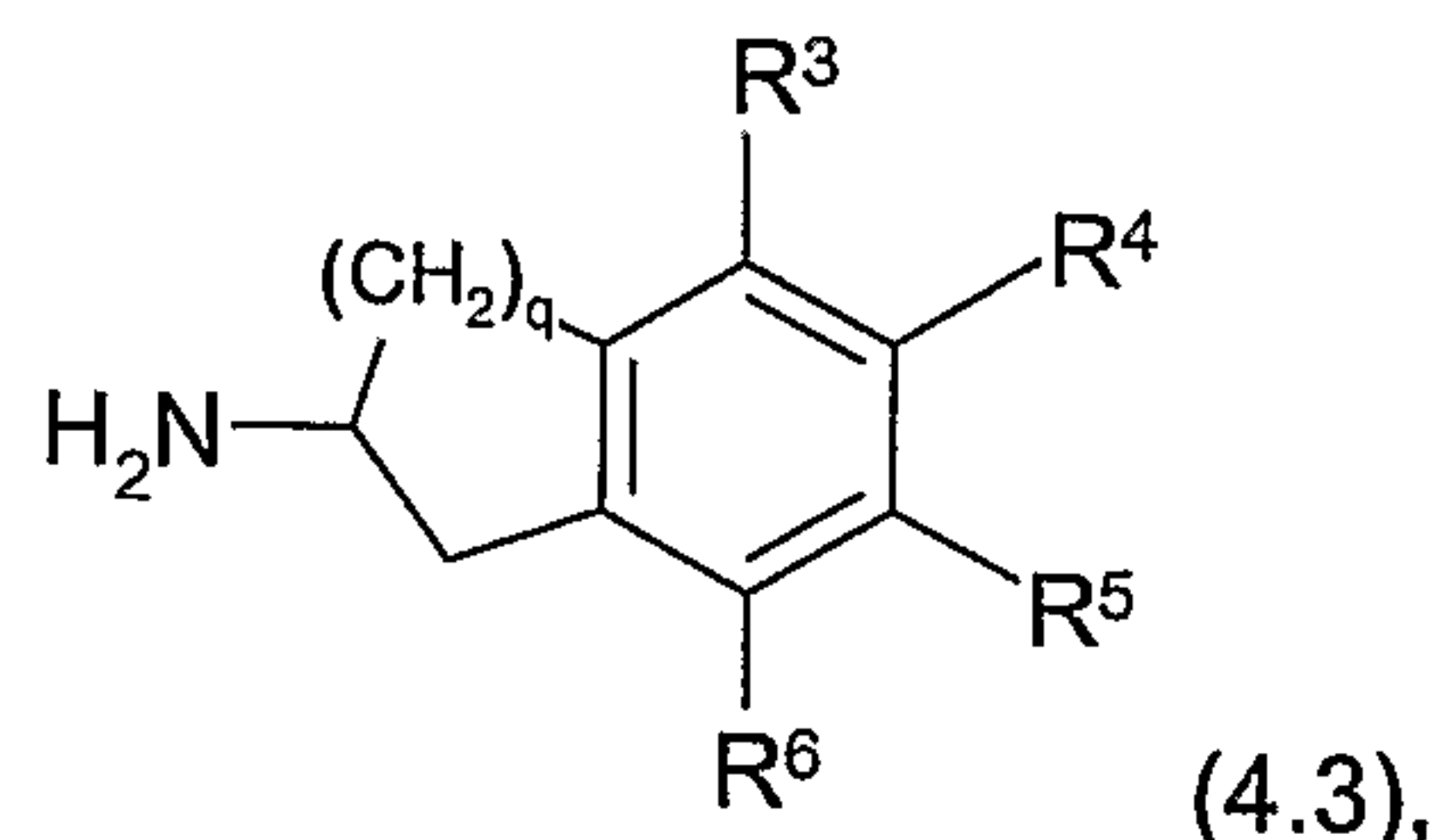
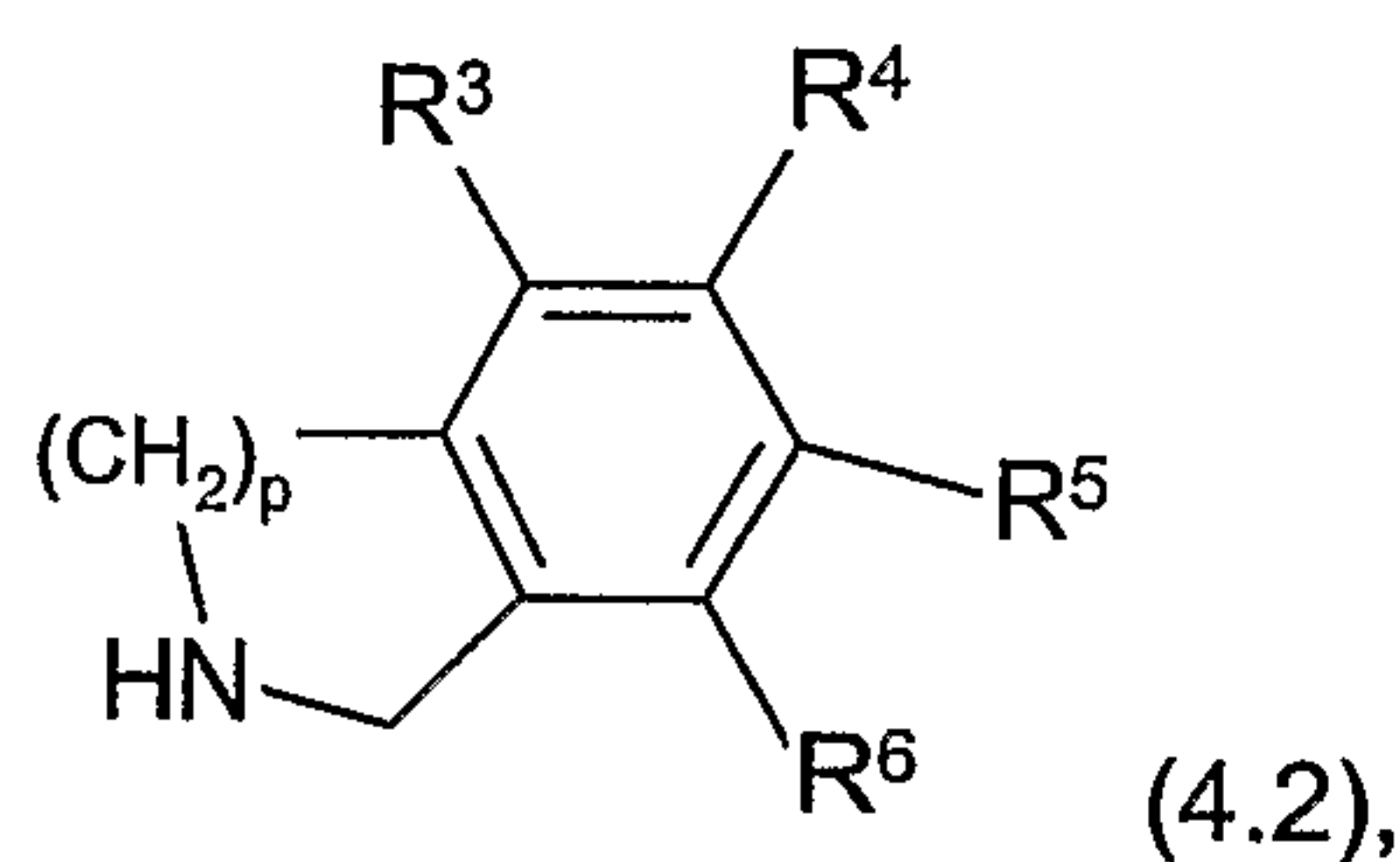


wherein R^1 , R^2 , Q^1 and n are as previously described for the 2-amino-pyridine derivatives of formula (1) and Prot is a suitable protecting group (or 2 suitable protecting groups) for the amino-pyridine, which include but is not limited to *tert*-butoxycarbonyl, acyl or 2,5-dimethyl pyrrole,
 15 by methods well known to those skilled in the art such as standard methodology for cleaving nitrogen protecting groups as found in textbooks (e.g. T.W. GREENE, *Protective Groups in Organic Synthesis*, A. Wiley-Interscience Publication, 1981).

20 The compound of formula (2) may be prepared by coupling an acid of formula (3) :



wherein Prot, R¹, R² and n are as previously defined,
with an amine of formula NRH-Q²-A (4.1),



5

, or

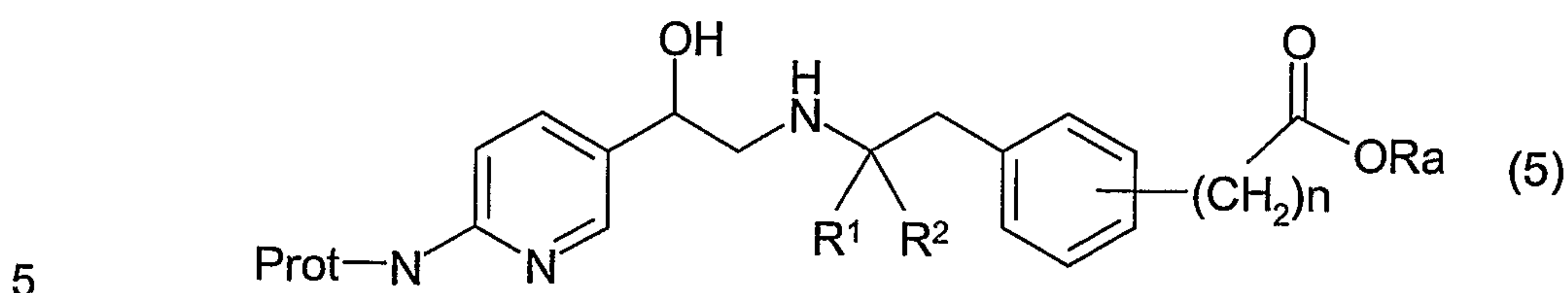
wherein p, q, R³, R⁴, R⁵, R⁶ and R⁷ are as previously defined.

The coupling of the acid (3) to the amine (4.1), (4.2), (4.3) or (4.4) is generally carried out in an excess of said amine, 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 *N,N*-diisopropylethylamine). The reaction may be undertaken in a suitable solvent such as pyridine, *N,N*-dimethylformamide, tetrahydrofuran, dimethylsulfoxide, dichloromethane or ethyl acetate, and at temperature comprised between 10°C and 40°C (room temperature).

Said (4.1), (4.2), (4.3) or (4.4), is either commercially available or may be prepared by conventional methods well-known to the one skilled in the art (e.g.

acylation, sulfonylation, reduction, oxidation, alkylation, protection, deprotection etc...) from commercially available material.

The acid of formula (3) may be prepared from the corresponding ester of formula (5) :

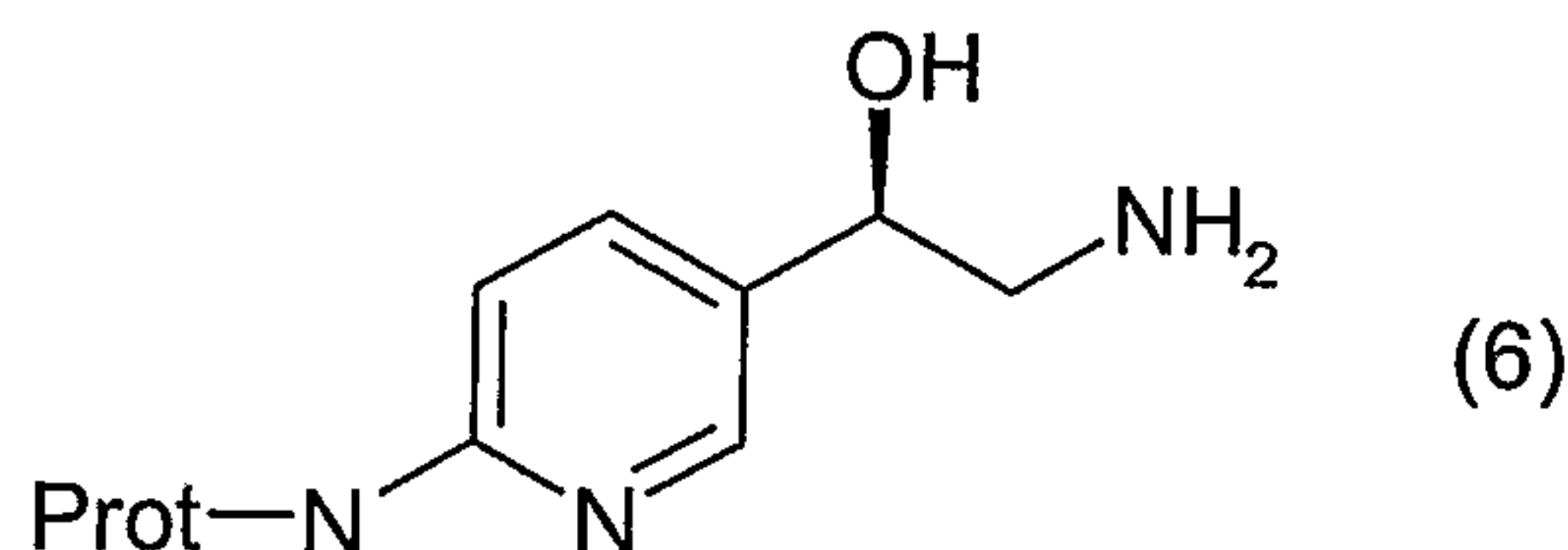


wherein Prot, R^1 , R^2 , Ra and n are as previously defined according to any method well-known to the one skilled in the art to prepare an acid from an ester.

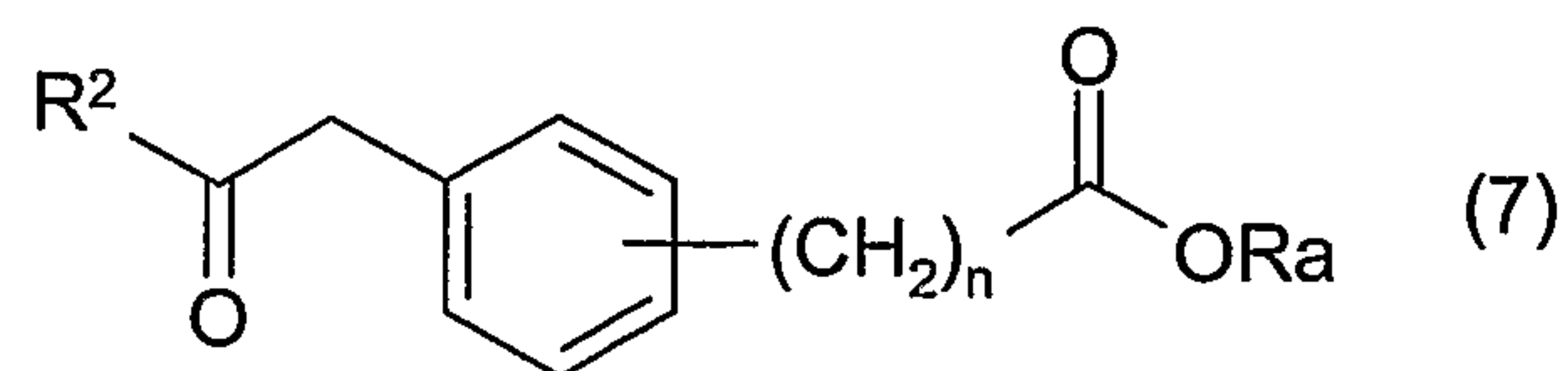
10 In a typical procedure, the hydrolysis of the ester to give an acid is undertaken according to any method well known to the man skilled in the art to prepare an acid from an ester, without modifying the rest of the molecule. For example, the ester may be hydrolysed by treatment with aqueous acid or base (e.g. hydrogen chloride, potassium hydroxide, sodium hydroxide or lithium hydroxide), optionally in the presence of a co-solvent (e.g. tetrahydrofuran/1,4-dioxan), at a temperature comprised between 20°C and 100°C, for a period of 15 to 40 hours.

The ester of formula (5) may be prepared according to different routes depending on the choice of R^1 and R^2 .

20 If R^1 is hydrogen, R^2 is (C₁-C₄)alkyl and n is different from 0, then the ester of formula (5) may be prepared by reaction of an amine of formula (6) :



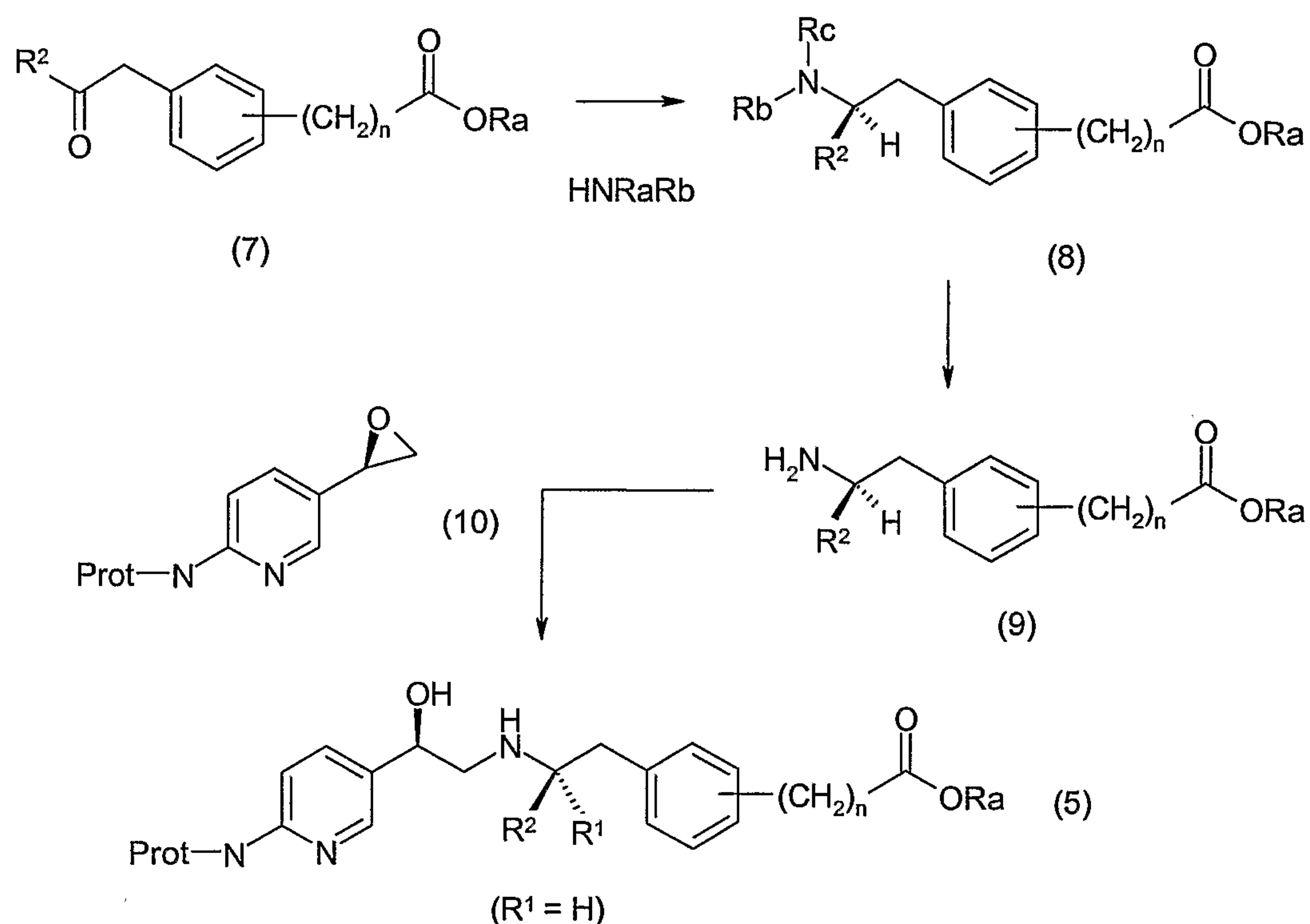
with an excess of a ketone of formula (7) :



wherein Prot, R², Ra and n are as previously defined, to form an intermediate compound, which is reduced by a suitable reducing agent (e.g. sodium cyanoborohydride of formula NaCN(BH)₃ or sodium triacetoxymorohydride of formula Na(OAc)₃BH), optionally in the presence of acetic acid. The reaction is generally performed in a suitable solvent such as tetrahydrofuran or dichloromethane, at a temperature comprised between 20°C and 80°C for 3 to 72 hours, giving the compound of formula (5) as a mixture of diastereomers.. According to another alternative, the reduction may be carried out in the presence of a drying agent such as molecular sieves or magnesium sulfate.

The amine of formula (6) may be prepared starting from a 2-amino-5-bromo-pyridine as described in EP 1 078 924 or WO 99/32475.

Alternatively, the ester of formula (5) may be prepared according to scheme 1 as follows :



wherein n , Ra and Prot are as previously defined, and Rb and Rc represent any suitable substituents so that HNRbRc is a chiral amine (for example, Rb may be hydrogen and Rc may be a α -methylbenzyl group) and the bonds between N and Rb and N and Rc can be easily cleaved to give the free amine of formula (9).

In a typical procedure, the ketone of formula (7) is reacted with a suitable chiral non-racemic amine HNRbRc (e.g. α -methylbenzylamine or any other commercially available chiral non-racemic amine) to form a chiral intermediate, which is reduced by a suitable reducing agent (e.g. sodium cyanoborohydride of formula $\text{NaCN}(\text{BH})_3$ or sodium triacetatoxyborohydride of formula $\text{Na}(\text{OAc})_3\text{BH}$) optionally in the presence of sodium acetate or acetic acid, and also optionally in the presence of a drying agent (e.g. molecular sieves, magnesium sulfate) as previously described. 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 the diastereomerically pure product

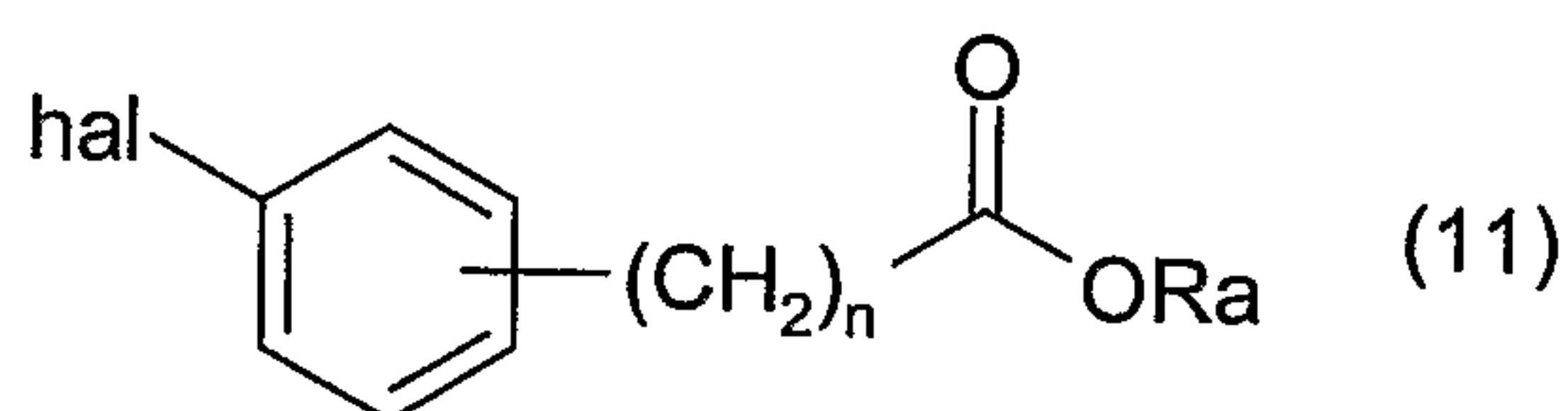
of formula (8), or its enantiomer, if the opposite enantiomer of the amine HNR^bR^c is used.

The protected amine of formula (8) is then cleaved to give the corresponding free amine of formula (9) using standard methodology for
 5 cleaving nitrogen protecting groups, such as that found in the text book (see for example T.W. Greene, *Protective Groups in Organic Synthesis*, A. Wiley-Interscience Publication, 1981). When a α -methylbenzylamine is used, then the cleavage may be performed using ammonium formate and palladium hydroxide on carbon of formula Pd(OH)₂/C as catalyst.

10 Said amine of formula (9) is then reacted with an epoxide of formula (10) in a suitable solvent or mixture of solvents (e.g. dimethyl sulfoxide/toluene), at a temperature comprised between 20°C and 80°C and optionally in the presence of a catalyst for 8 to 40 hours, to give the ester of formula (5).

The epoxide of formula (10) may be prepared starting from starting from
 15 a 2-amino-5-bromo-pyridine as described in EP 1 078 924 or WO 99/32475.

The ketone of formula (7) described above may be prepared by enolate arylation of an aryl halide of formula (11) :

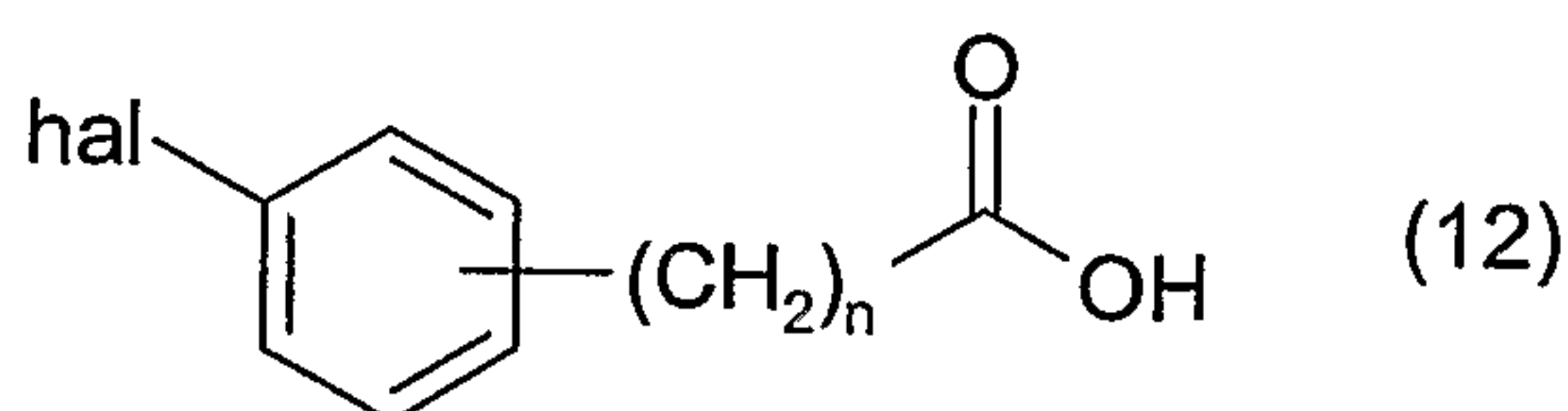


wherein Ra and n are as previously defined and halo represents an halogen
 20 atom, which includes, but is not limited to, fluoro, chloro and bromo.

In a typical procedure, the aryl halide of formula (11) is reacted with a tin enolate generated *in situ* by treatment of a vinyl acetate (e.g. isoprenyl acetate with tri-n-butyltin methoxide of formula Bu₃SnOMe) in the presence of a suitable palladium catalyst (palladium acetate/ tri-*ortho*-tolylphosphine of formula
 25 Pd(OAc)₂/P(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.

The aryl halide of formula (11) may be prepared by esterification of the corresponding acid of formula (12) :



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

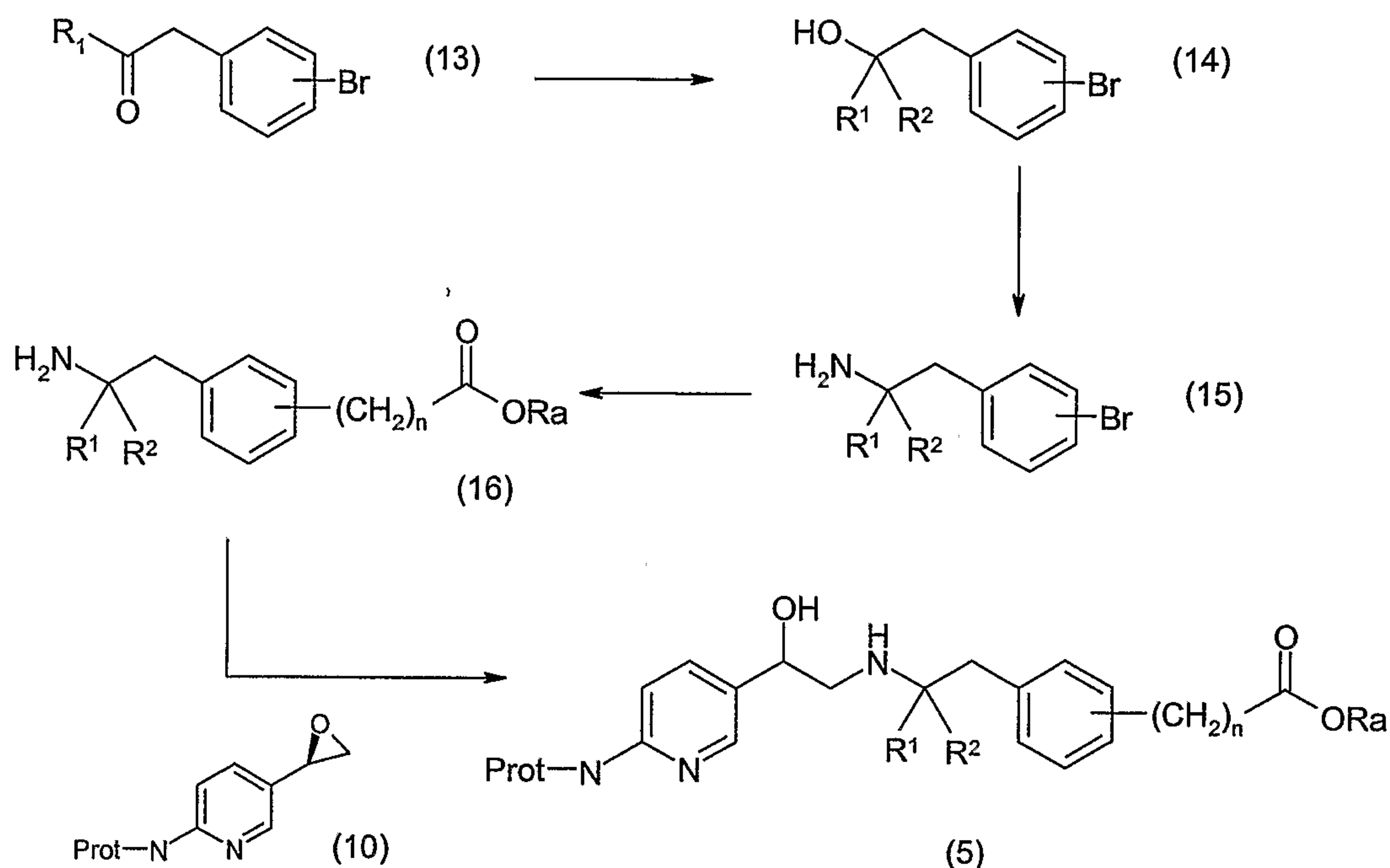
10 In a typical procedure, the acid of formula (12) is reacted with an alcoholic solvent of formula RaOH, wherein Ra is as previously defined, in the presence of an acid such as hydrogen chloride at a temperature between 10°C and 40°C (room temperature) for 8 to 16 hours.

15 According to another alternative, the acid of formula (12) is reacted with a bromoalkyl of formula RaBr in the presence of a suitable base such as cesium carbonate, in a suitable organic solvent (e.g. *N,N*-dimethylformamide, tetrahydrofuran) at a temperature and for a time as here above mentioned.

The acid of formula (12) is either a commercial product or it may be prepared by conventional procedures well-known to the man skilled in the art.

20 If R₁ and R₂ are both different from hydrogen and n is different from 0, then the ester of formula (5) may be prepared according to scheme 2 as follows:

Scheme 2



wherein R^1 , R^2 , R_a and $Prot'$ are as previously defined.

In a typical procedure, the halo ketone of formula (13) is reacted with an
5 "activated" alkyl (organometallic alkyl such as R^2MgBr , R^2MgCl or R^2Li) to give
the corresponding tertiary alcohol of formula (14). This organometallic addition
is generally undertaken in a suitable solvent such as tetrahydrofuran, ether,
cyclohexane or 1,4-dioxane, at a temperature comprised between 10°C and
40°C (room temperature) for 1 to 24 hours

10 Said tertiary alcohol of formula (14) is then treated with an alkyl nitrile (e.g. acetonitrile, chloroacetonitrile) in the presence of an acid (e.g. sulphuric acid, acetic acid) to give a protected intermediate which in turn cleaved using standard methodology for cleaving nitrogen protecting group such as those mentioned in textbooks, to give the amine of formula (15).

15 The amine of formula (15) is then converted to the boronic acid ester by treatment with a suitable boron source (e.g. pinacolborane, bis(pinacolato)diboron) in the presence of a suitable palladium catalyst (e.g.

palladium(II)acetate/ tri-*ortho*-tolylphosphine of formula $\text{Pd}(\text{OAc})_2/\text{P}(\text{o-tol})_3$ or (diphenylphosphino) ferrocenyl palladium(II)chloride of formula dppfPdCl_2). The reaction is generally undertaken in a suitable solvent such as dimethyl sulfoxide or toluene, optionally in the presence of a base (e.g. potassium acetate), at a temperature comprised between 60°C and 110°C for a period of 4 to 24 hours. The intermediate boronic acid ester is then coupled with ethylbromoacetate in the presence of a suitable palladium catalyst (e.g. tetrakis(triphenylphosphine) palladium(0) of formula $\text{Pd}(\text{PPh}_3)_4$, palladium(II)acetate/tri-*ortho*-tolylphosphine of formula $\text{Pd}(\text{OAc})_2/\text{P}(\text{o-tol})_3$ or (diphenylphosphino)ferrocenyl palladium(II)chloride of formula dppfPdCl_2) to give the compound of formula (16).

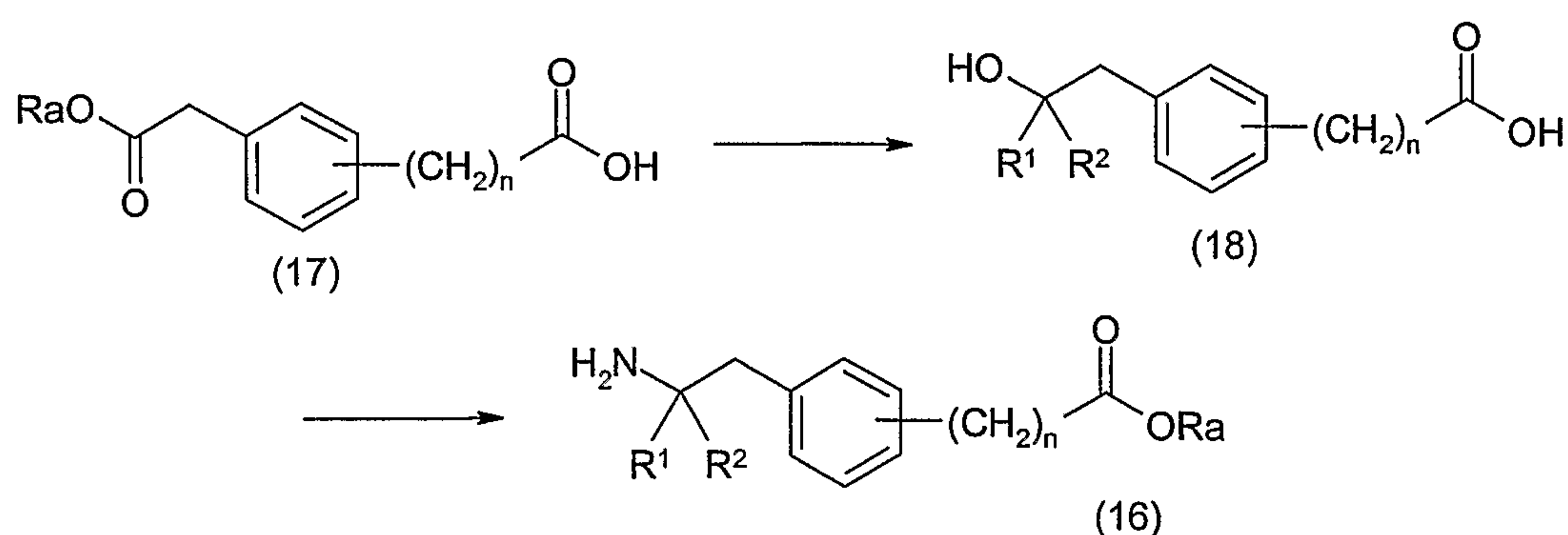
The compound of formula (5) is finally obtained by reaction of the compound of formula (16) with the epoxide of formula (10) as previously described.

The compound of formula (13) is either commercial or it may be easily prepared from commercial compounds by conventional procedures well known to the one skilled in the art.

Alternatively the amine of formula (16) may be prepared according to scheme 3 as follows:

20

Scheme 3



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

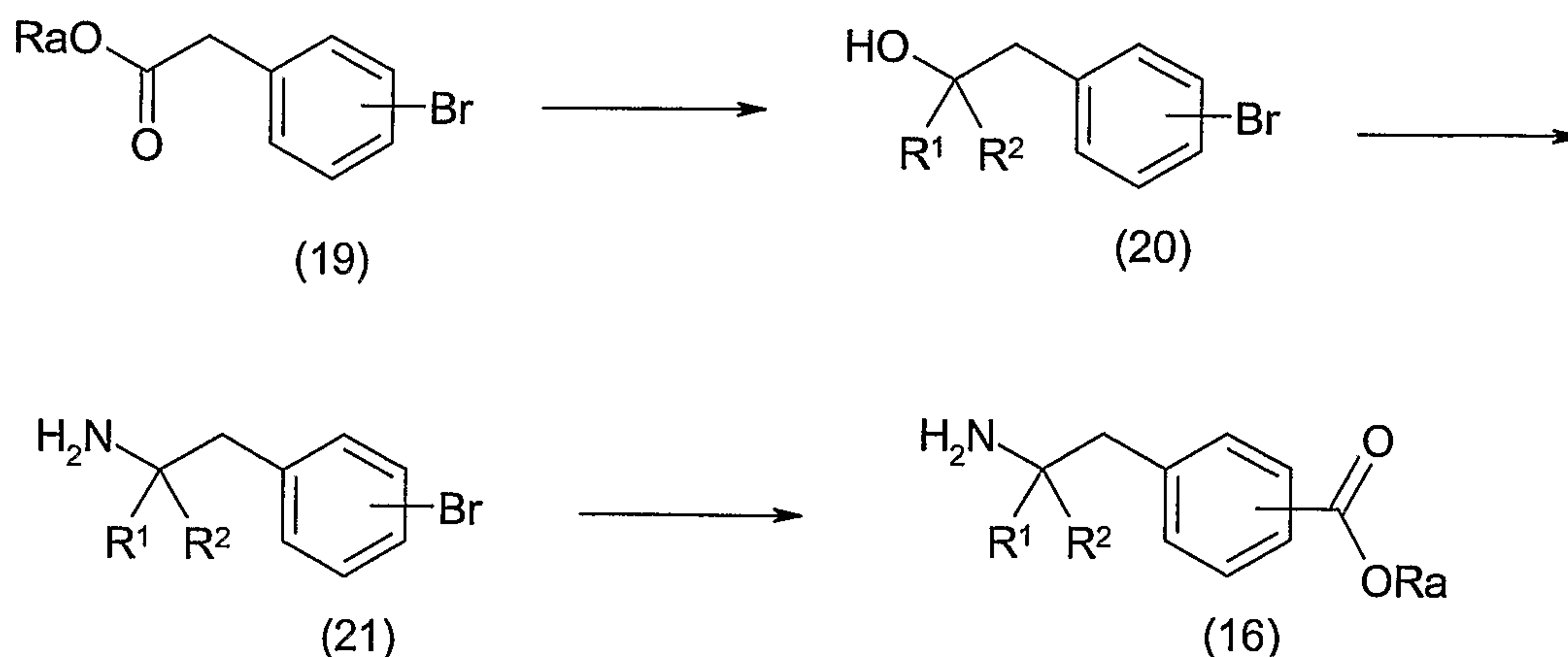
In a typical procedure, the ester of formula (17) is reacted with an "activated" alkyl (organometallic alkyl such as R^2MgBr , R^2MgCl or R^2Li) to give the corresponding tertiary alcohol of formula (18) using the method described above.

- 5 Said tertiary alcohol of formula (17) is then treated with an alkyl nitrile (e.g. acetonitrile, chloroacetonitrile) in the presence of an acid (e.g. sulphuric acid, acetic acid) to give a protected intermediate which is in turn cleaved using standard methodology for cleaving nitrogen protecting group such as those mentioned in textbooks. The resulting aminoacid is then esterified using the
10 method described herein to give the amine of formula (16).

The compound of formula (17) is either commercial or it may be easily prepared from commercial compounds by conventional procedures well known to the one skilled in the art.

- If n is equal to 0, then the amine of formula (16) may be prepared according to
15 the following scheme:

Scheme 4



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

- In a typical procedure, the ester of formula (19) is reacted with an
20 "activated" alkyl (organometallic alkyl such as R^2MgBr , R^2MgCl or R^2Li) to give

the corresponding tertiary alcohol of formula (20) using the method described above.

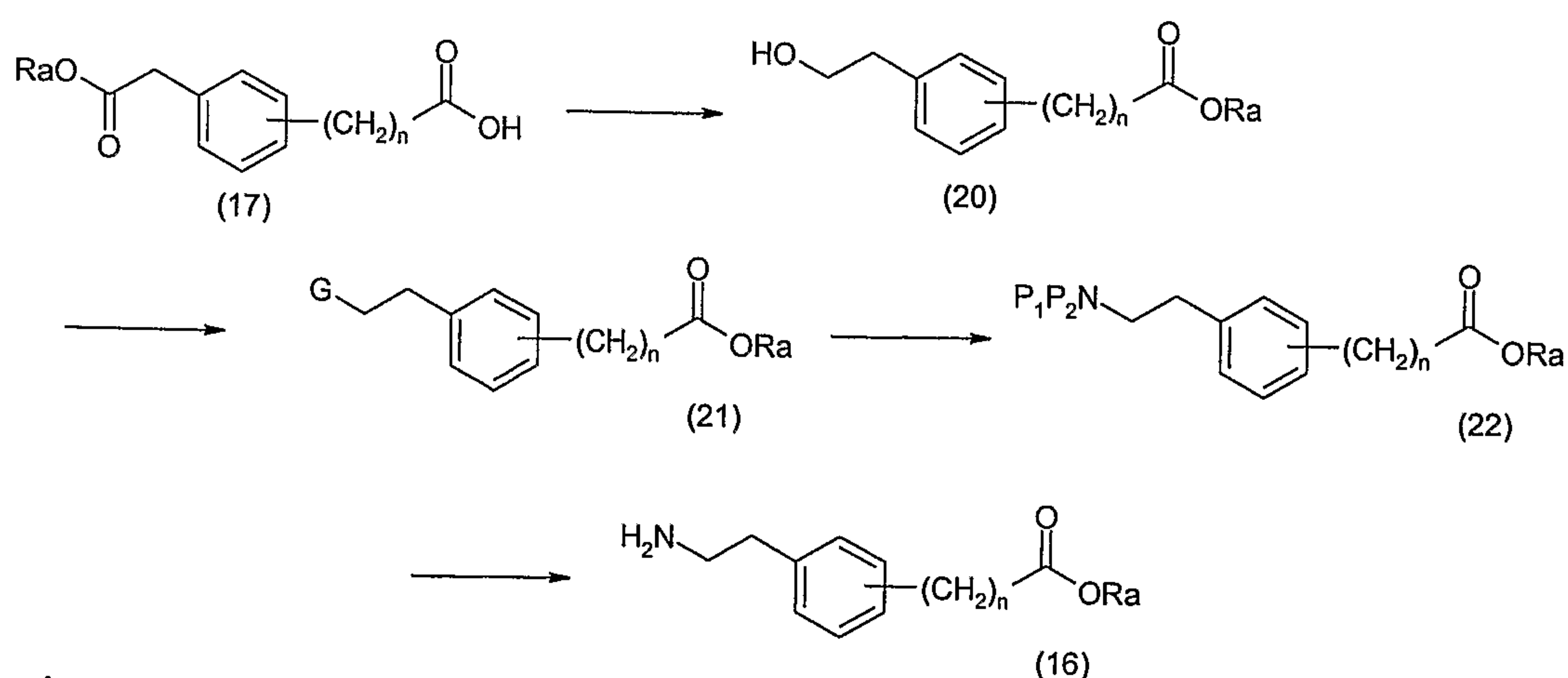
Said tertiary alcohol of formula (20) is then treated with an alkyl nitrile (e.g. acetonitrile, chloroacetonitrile) in the presence of an acid (e.g. sulphuric acid, acetic acid) to give a protected intermediate which is in turn cleaved using standard methodology for cleaving nitrogen protecting group such as those mentioned in textbooks to give the bromo amine (21).

The resulting bromo amine (21) is treated with a suitable palladium catalyst (e.g. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) under an atmosphere of carbon monoxide using RaOH as solvent (e.g. MeOH, EtOH) at elevated temperature (100°C) and pressure (100psi) to give the ester of formula (16).

The compound of formula (19) is either commercial or it may be easily prepared from commercial compounds by conventional procedures well known to the one skilled in the art.

Alternatively, where both R^1 and R^2 are H, the amine of formula (16) may be prepared according to scheme 5 as follows:

Scheme 5



wherein Ra is as previously defined.

In a typical procedure, the ester of formula (17) is reduced with an a reducing agent (such as LiAlH_3) to give the corresponding primary alcohol of formula (20) using the method described above.

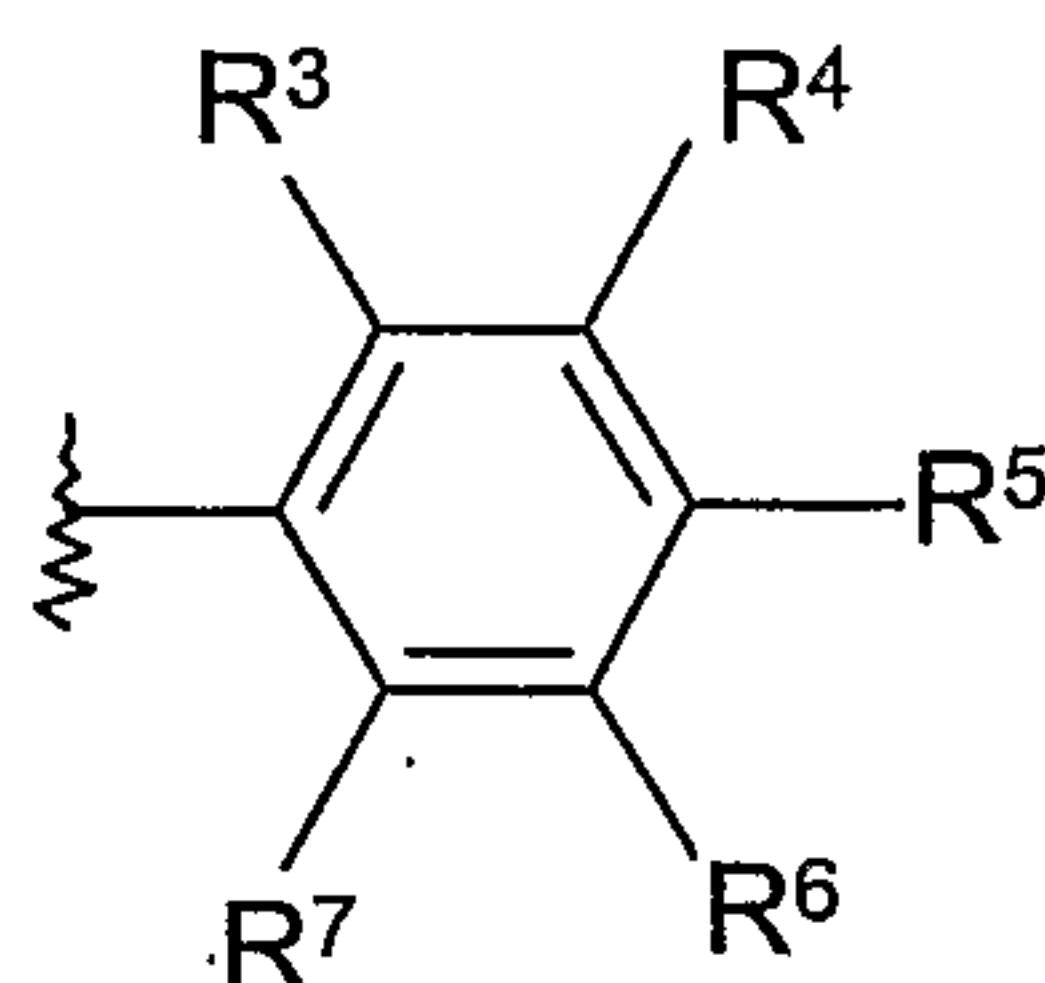
Said tertiary alcohol of formula (20) is then treated to yield an activating
5 group (G) (halogen, mesylate, tosylate) using standard methodology for alcohol activation such as those mentioned in textbooks. The resulting activating group is then displaced by a nitrogen containing group (such as azide, phthalamide) using standard methodology for nucleophilic displacements such as those mentioned in textbooks. The amine is then liberated by hydrolysis (hydroxide,
10 hydrazine) or reduction (hydrogenation, reducing agents such as LiAlH_4) of the nitrogen containing group to give the amine of formula (16).

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
15 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.

For some of the steps of the here above described process of preparation of the 2-amino-pyridine derivatives of formula (1), it can be
20 necessary to protect the 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 Publication, 1981) or by
25 McOMIE (*Protective Groups in Organic Chemistry*, Plenum Press, 1973), can be used.

Also, the 2-amino-pyridine derivatives 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.

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



wherein R³, R⁴, R⁵, R⁶ and R⁷ are as defined above, are particularly preferred.

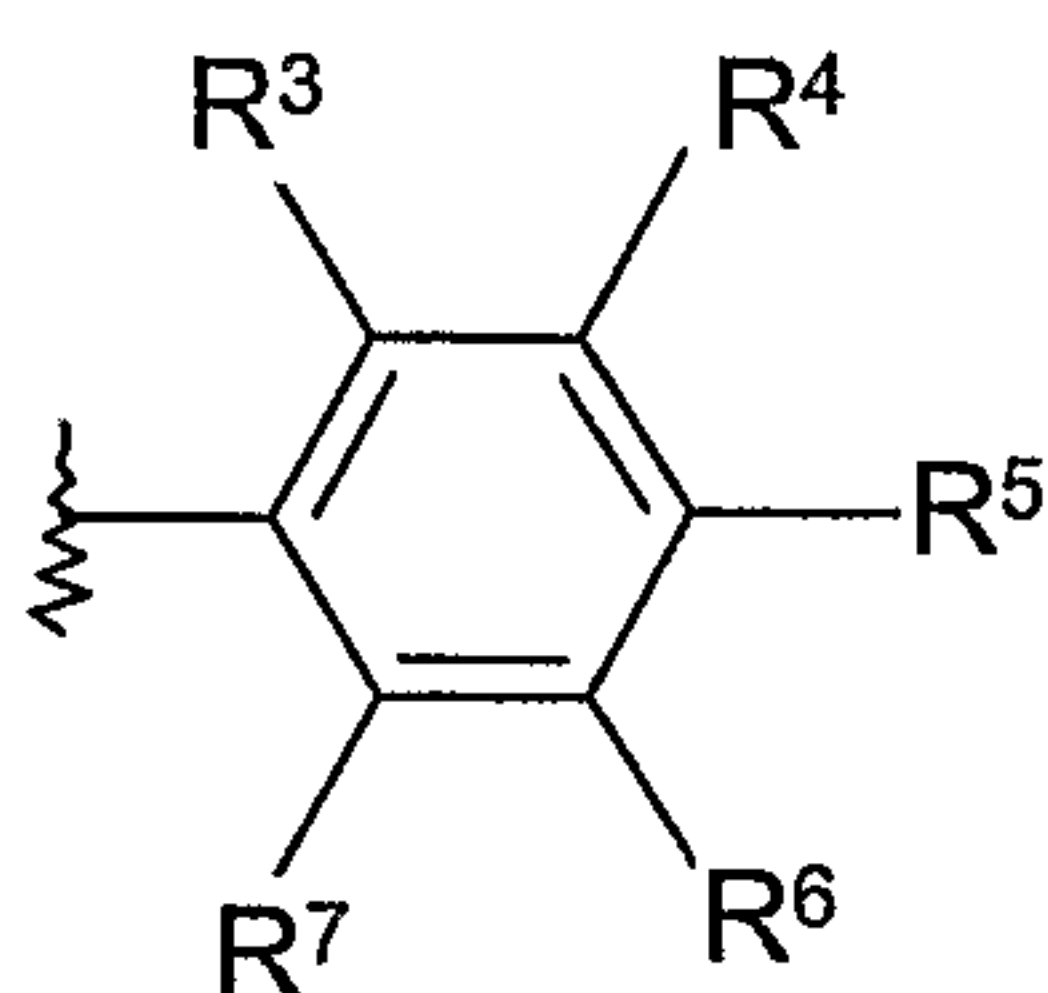
5 The following substituents are generally preferred:

- R¹ is H and R² is C₁-C₄ alkyl, more preferably CH₃ or R¹ and R² are the same or different and are selected from C₁-C₄ alkyl, more preferably R¹ and R² are both CH₃ and/or,

- n is 1 and/or,

10 - Q² is selected from -CH₂-, -(CH₂)₂-, -(CH₂)₃- and -CH(CH₃)-, more preferably Q² is -CH₂-, and/or

- A is a group of formula :

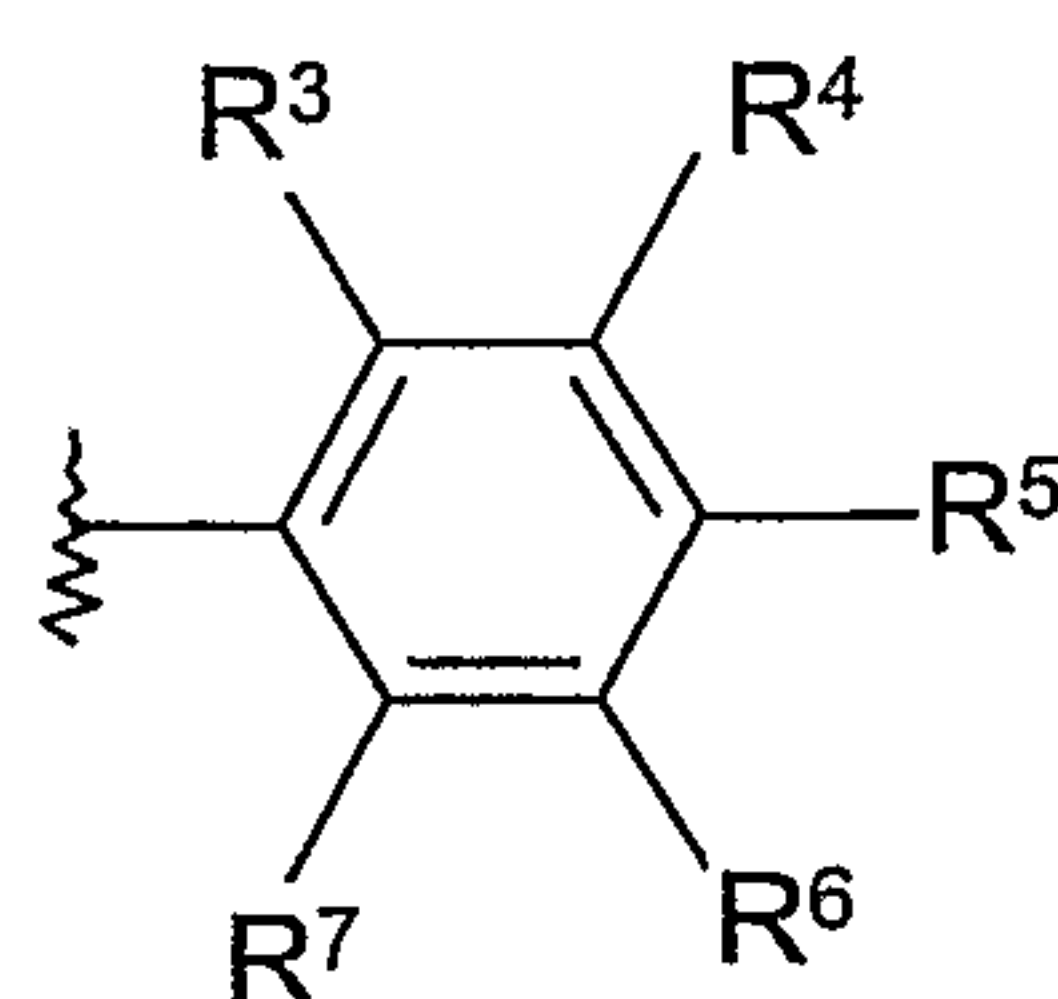


wherein R³, R⁴, R⁵, R⁶ and R⁷ are the same or different and are selected from

15 H, C₁-C₄ alkyl, OR⁹, Cl, F, CF₃, OCF₃, COOR⁹, C(=O)NR⁸R⁹, SO₂NR⁸R⁹, provided at least 2 of R³ to R⁷ are equal to H,

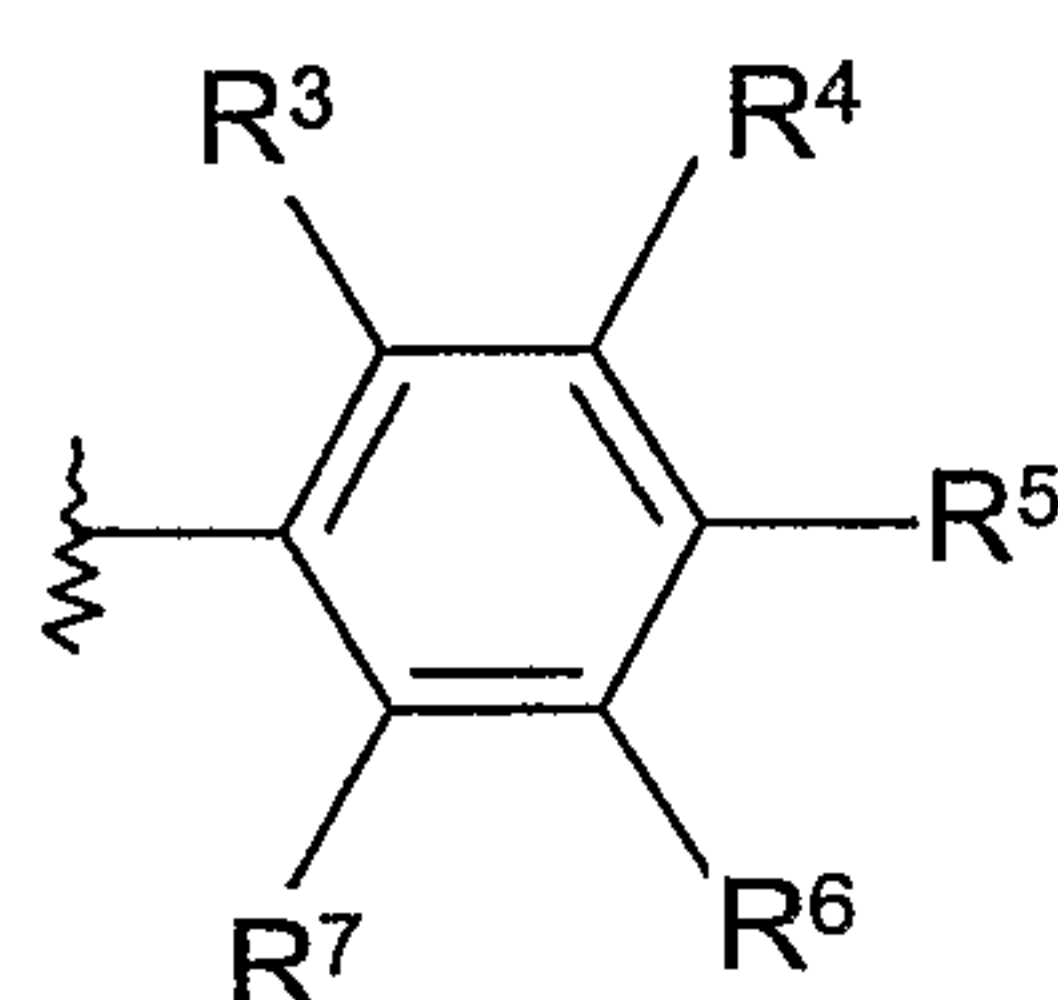
wherein R⁸ and R⁹ are the same or different and are selected from H or C₁-C₄ alkyl.

Preferably, A is a group of formula :



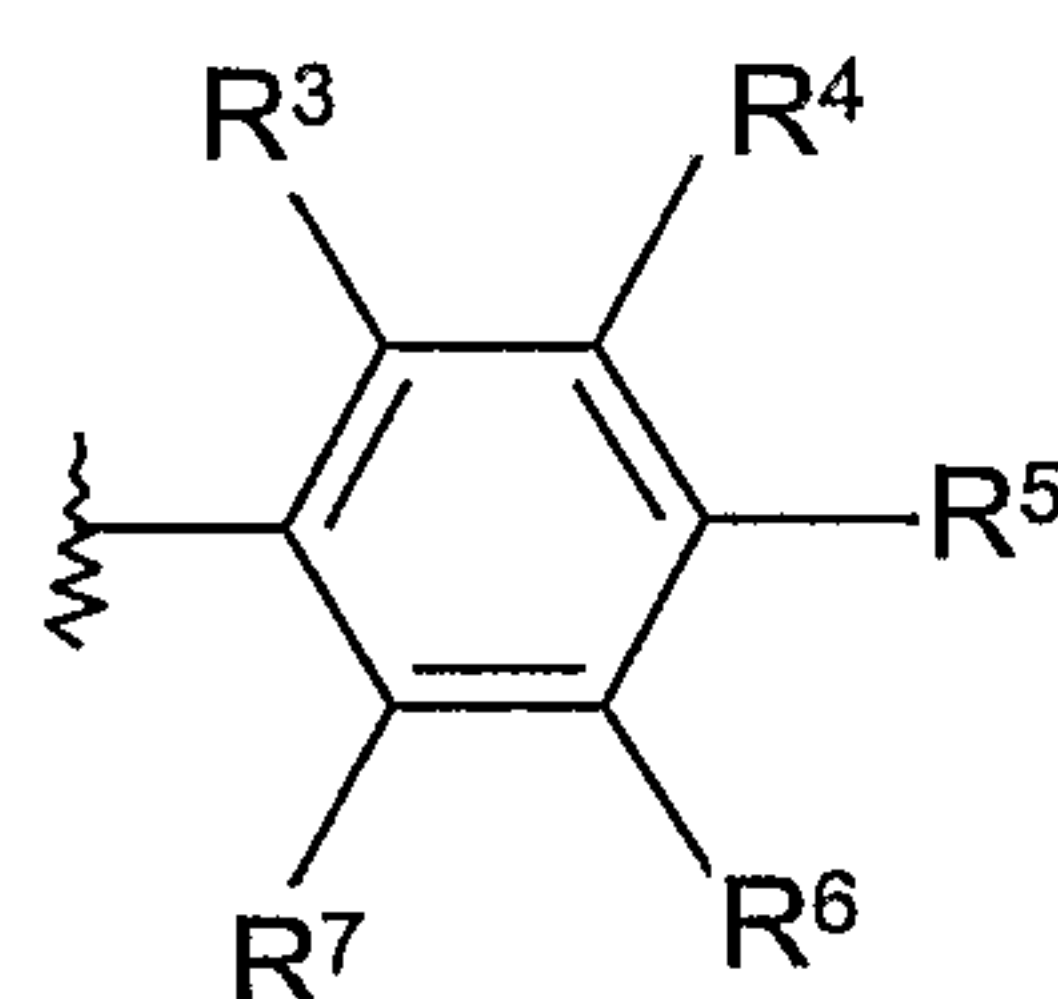
wherein R³, R⁴, R⁵, R⁶ and R⁷ are the same or different and are selected from H, CH₃, OH, OCH₃, OCH₂CH₃, Cl, F, CF₃, OCF₃, COOH, SO₂NH₂, provided at least 2 of R³ to R⁷ are equal to H.

5 Preferably, A is a group of formula :



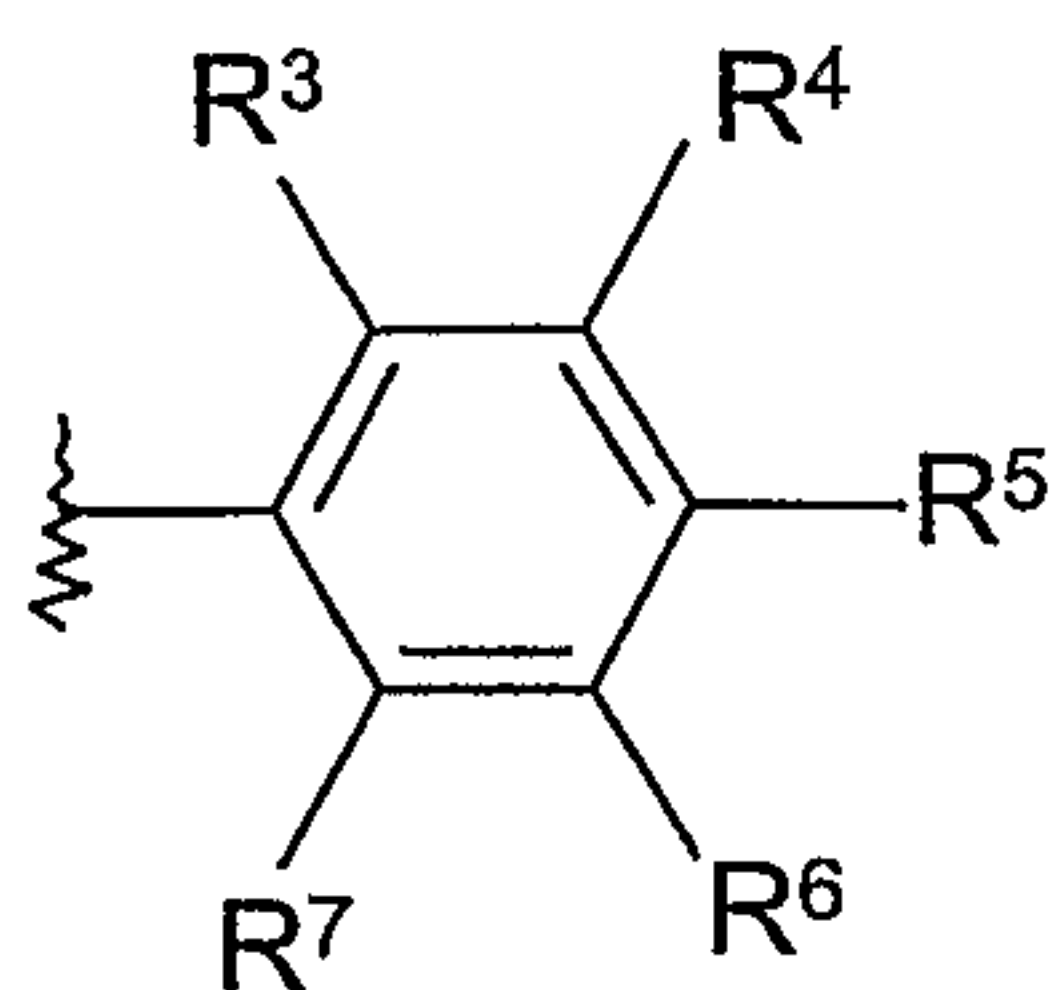
wherein R³, R⁴, R⁵, R⁶ and R⁷ are the same or different and are selected from H, CH₃, OH, OCH₃, OCH₂CH₃, Cl, F, CF₃, OCF₃, COOH, SO₂NH₂, provided at least 3 of R³ to R⁷ are equal to H.

10 Preferably A is a group of formula :



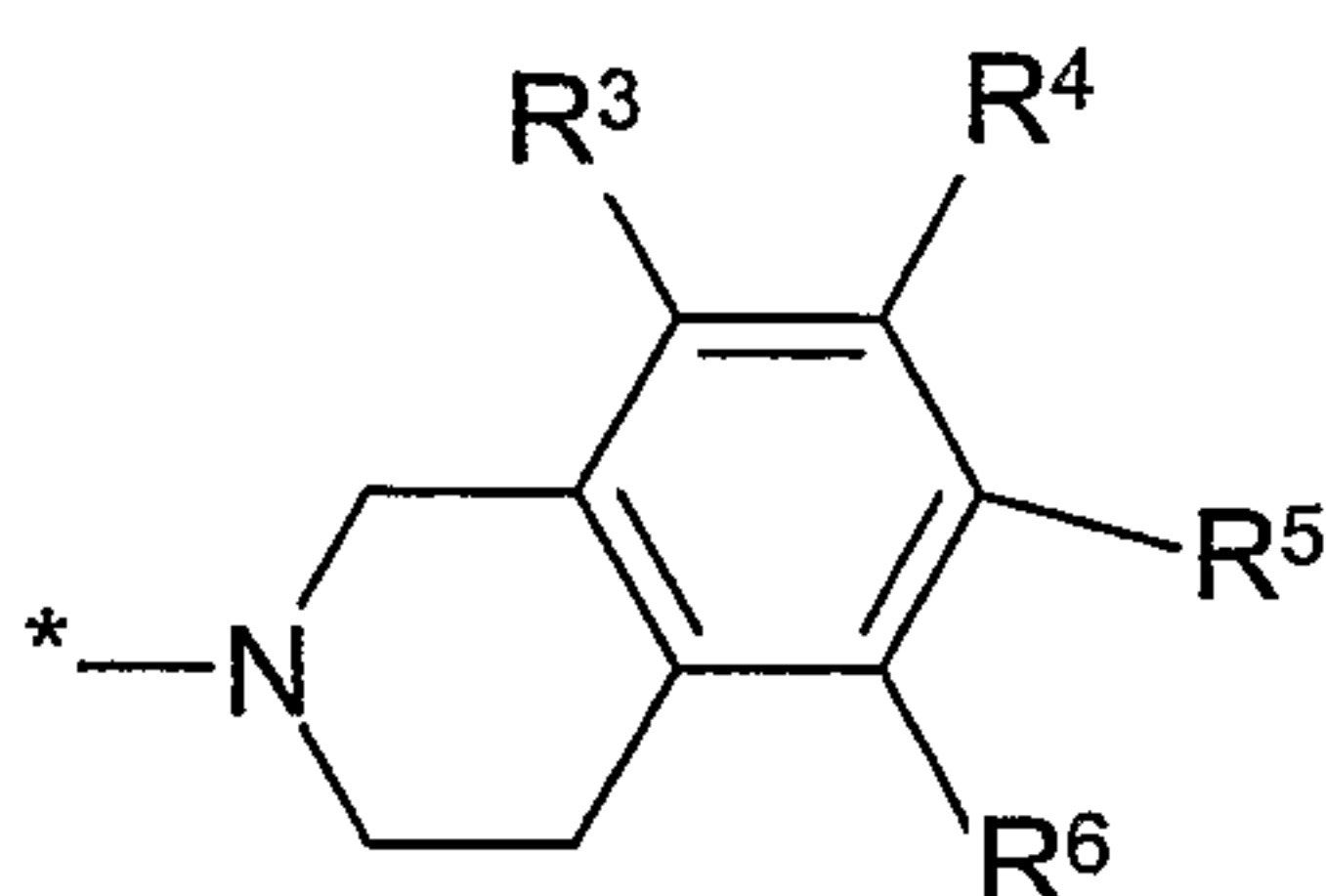
wherein R³, R⁴, R⁵, R⁶ and R⁷ are selected from H, CH₃, OH, Cl, OCH₂CH₃, provided at least 3 of R³ to R⁷ are equal to H.

Preferably A is a group of formula :



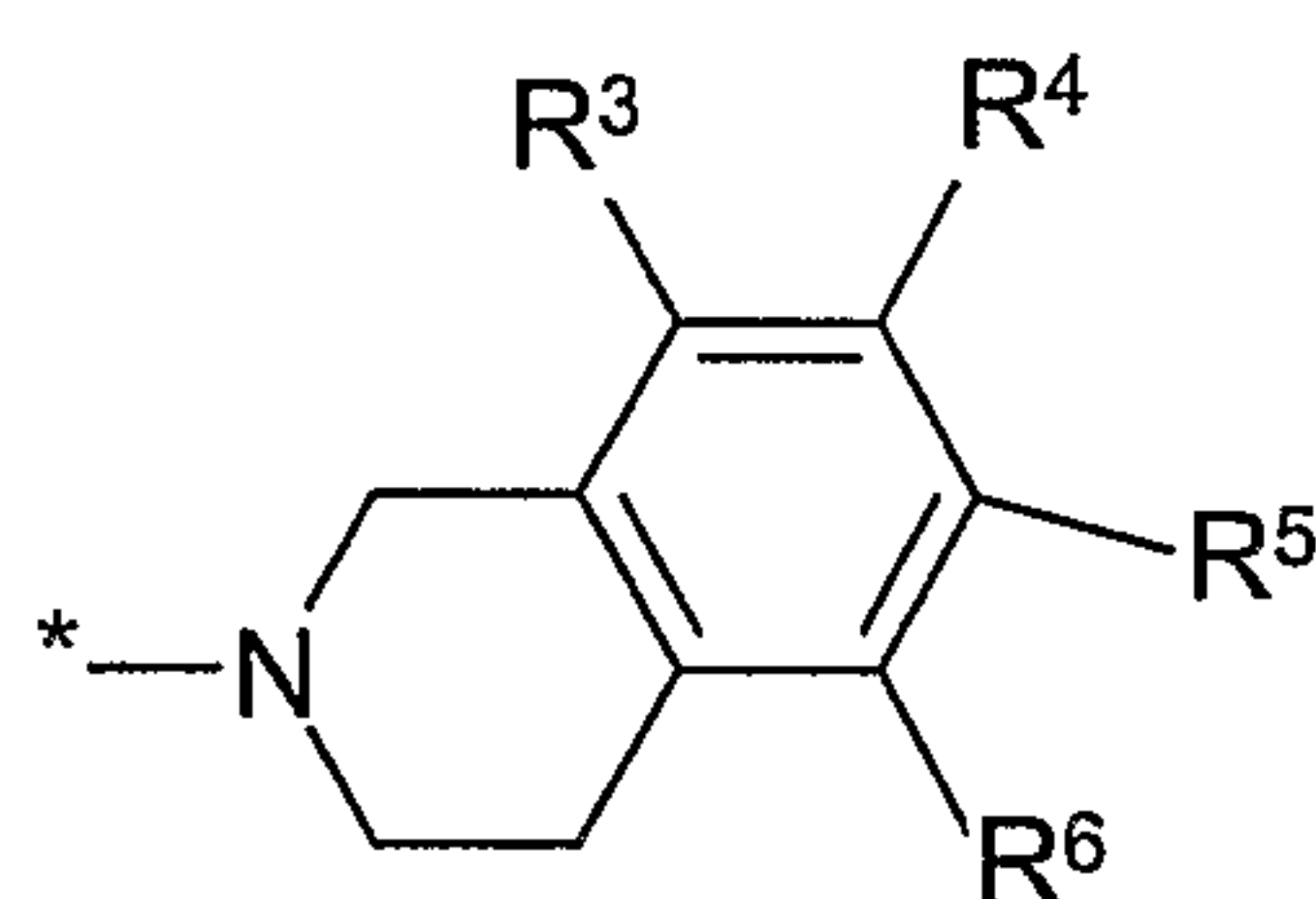
wherein at least one of R³, R⁴, R⁵, R⁶ and R⁷ is other than hydrogen.

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



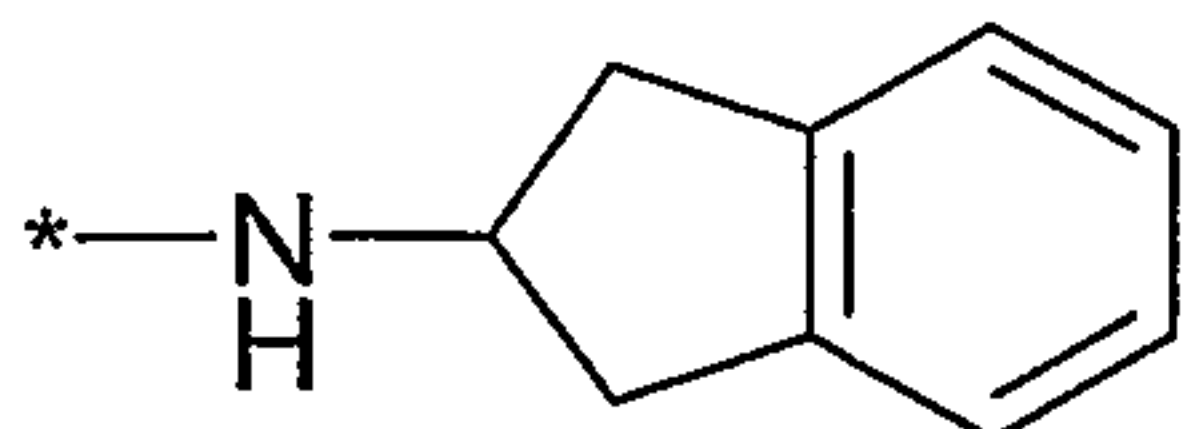
- 5 wherein R³, R⁴, R⁵ and R⁶ are the same or different and are selected from H, C₁-C₄ alkyl, OR⁹, SR⁹, halo, CF₃, OCF₃, COOR⁹, SO₂NR⁸R⁹, CONR⁸R⁹, NR⁸R⁹, NHCOR⁹, provided at least 2 of R³ to R⁶ are equal to H, wherein R⁸ and R⁹ are the same or different and are selected from H or C₁-C₄ alkyl.

- 10 Preferably, Q¹ is



wherein R³, R⁴, R⁵ and R⁶ are the same or different and are selected from H and OR⁹, provided at least 2 of R³ to R⁶ are equal to H; wherein R⁹ is selected from H or C₁-C₄ alkyl.

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



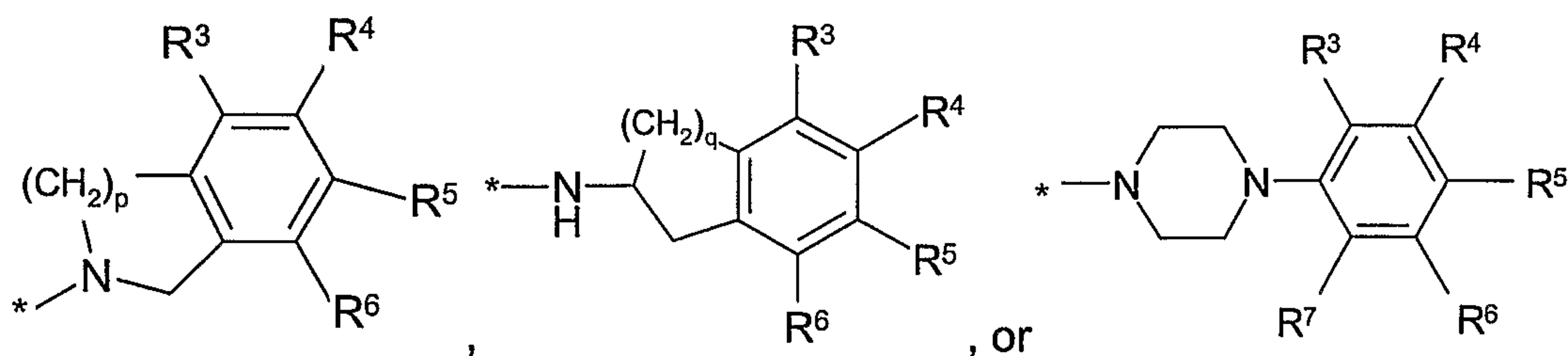
Other preferred compounds are those wherein n is 1 or 2 and Q¹ is a group *-NH-Q²-A, wherein Q² is a C₁-C₄ alkylene and A is a pyridin-2-yl.

5 Other preferred compounds are those wherein n is 1 or 2 and Q¹ is a group *-NH-Q²-A, wherein Q² is a C₁-C₄ alkylene and A is naphthyl.

Other preferred compounds are those wherein n is 1 or 2 and Q¹ is a group *-NH-Q²-A, wherein Q² is a C₁-C₄ alkylene and A is C₃-C₇ cycloalkyl, said cycloalkyl being optionally bridged by one or more carbon atoms. Preferably A
10 is cyclohexyl, cycloheptyl or adamantanyl.

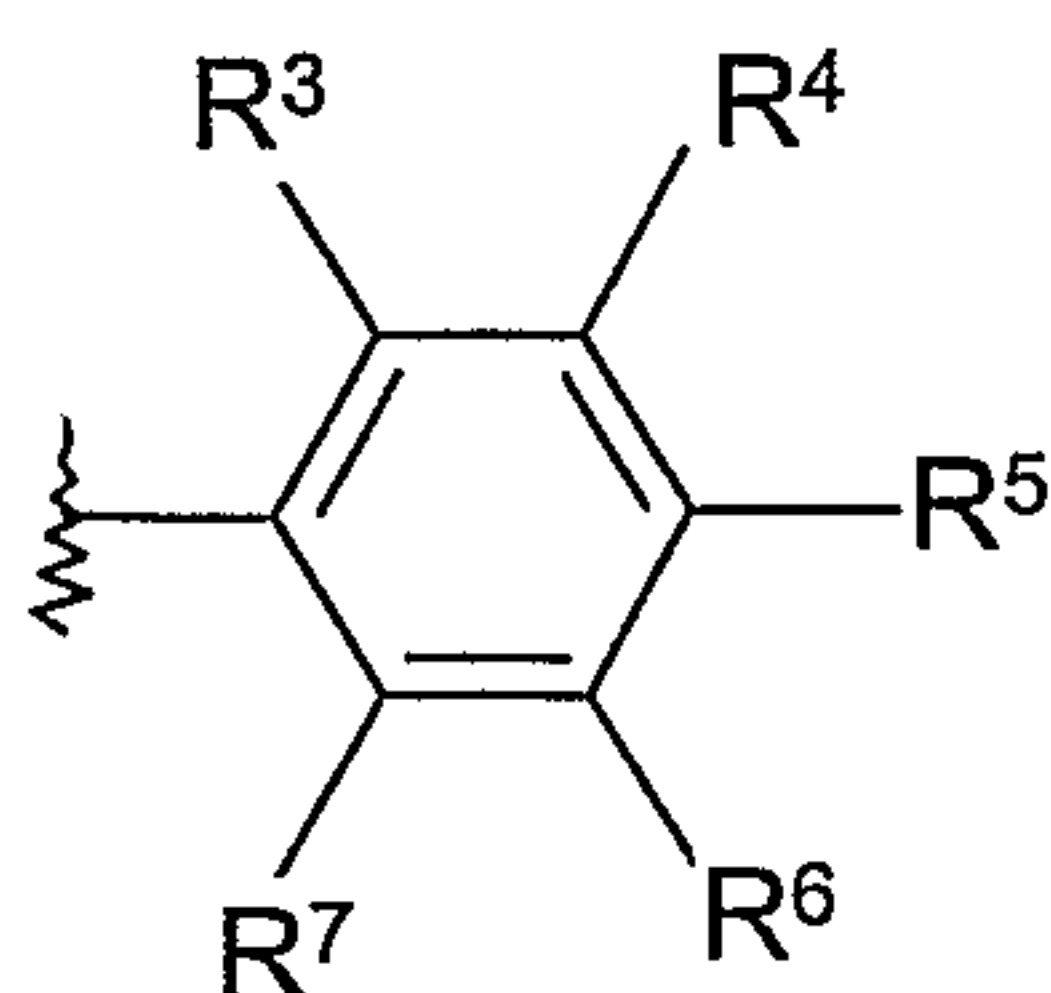
Other preferred compounds are those wherein n is 1 or 2 and Q¹ is a group *-NH-Q²-A, wherein Q² is a C₁-C₄ alkylene and A is naphthyl substituted with OH.

Other preferred compounds are those of formula (1) wherein n is 0 or 1
15 and Q¹ is a group of formula :



wherein p is 2 or 3, q is 2, R³, R⁴, R⁵, R⁶ and R⁷ are the same or different and are selected from H and OH, provided that at least one of R³, R⁴, R⁵, R⁶ and R⁷ is OH.

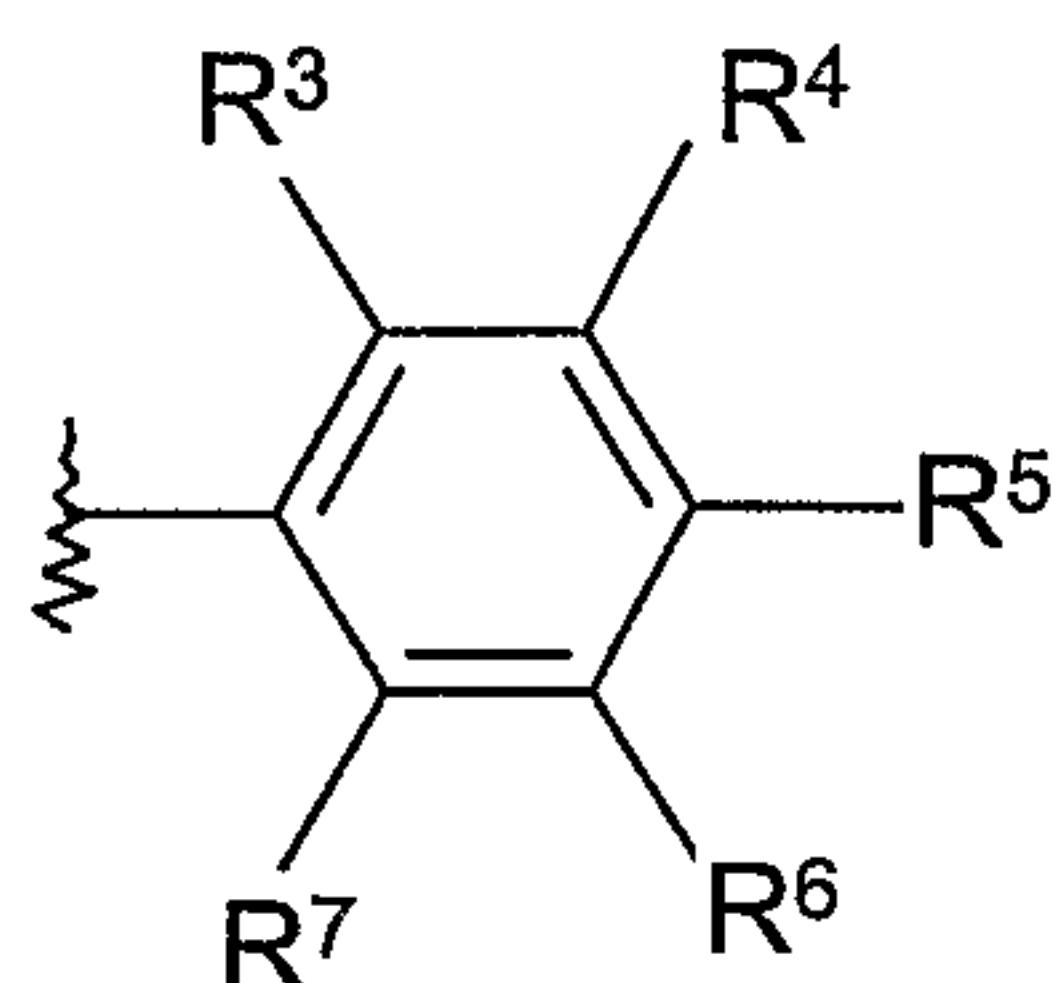
20 Other preferred compounds are those of formula (1) wherein n is 0 or 1, R¹ is H or C₁-C₄ alkyl, R² is C₁-C₄ alkyl, and Q¹ is a group *-NR-Q²-A wherein A is of formula:



wherein R, R³, R⁴, R⁵, R⁶ and R⁷ are as previously defined.

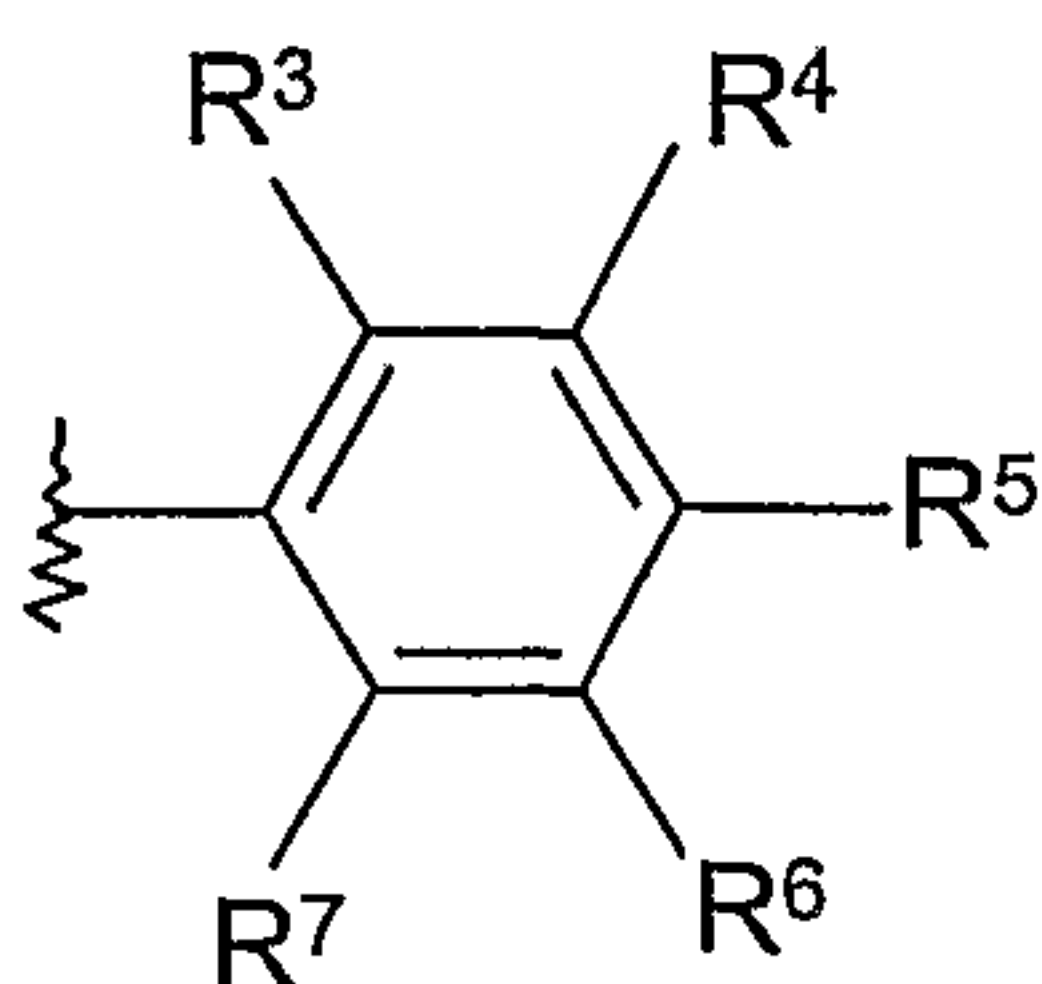
The following substituents are generally preferred:

- R¹ is H and R² is C₁-C₄ alkyl, more preferably CH₃ or R¹ and R² are the same
- 5 or different and are selected from C₁-C₄ alkyl, more preferably R¹ and R² are both CH₃ and/or,
- R is selected from H, CH₃, CH₂CH₃ and phenyl substituted by OH, and/or
- Q² is a direct bond or is selected from -CH₂-, -(CH₂)₂-, -(CH₂)₄-, -CH₂-C(CH₃)₂-, and -CH₂-CH(OH)-, and/or
- 10 - A is a group of formula :



- wherein R³, R⁴, R⁵, R⁶ and R⁷ are the same or different and are selected from H, C₁-C₄ alkyl, OR⁹, Cl, F, CF₃, COOR⁹, SO₂(C₁-C₄)alkyl, and phenyl substituted by OH or hydroxy(C₁-C₄)alkyl, provided at least 2 of R³ to R⁷ are
- 15 equal to H,
- wherein R⁸ and R⁹ are the same or different and are selected from H or C₁-C₄ alkyl.

Preferably, A is of formula



wherein R^3 , R^4 , R^5 , R^6 and R^7 are the same or different and are selected from H, CH_3 , $C(CH_3)_3$, OH, OCH_3 , OCH_2CH_3 , Cl, F, CF_3 , $COOCH_3$, $SO_2-CH_2CH_3$, and phenyl substituted by OH or by $-CH_2-OH$, provided at least 2 of R^3 to R^7 are equal to H.

- 5 Particularly preferred are the compounds of the formula (1) as described in the Examples section hereafter, i.e. :
- 2-(3-{(2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-benzyl-acetamide,
- 2-(3-{(2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(2-methoxy-benzyl)-acetamide,
- 10 2-(3-{(2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(2-ethoxy-benzyl)-acetamide,
- 2-(3-{(2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(3-phenyl-propyl)-acetamide,
- 15 2-(3-{(2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-phenethyl-acetamide,
- 2-(3-{(2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(3,4-dimethyl-benzyl)-acetamide,
- 2-(3-{(2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-indan-2-yl-acetamide,
- 20 2-(3-{(2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(3,4-dichloro-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(4-hydroxy-3-methoxy-benzyl)-acetamide,
- 25 2-(4-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(3-methoxy-benzyl)-acetamide,
- 2-(4-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(2,6-dimethoxy-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(4-sulfamoyl-benzyl)-acetamide,
- 30

- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(2-ethoxy-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-indan-2-yl-acetamide,
- 5 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-benzyl-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-phenethyl-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(3-phenyl-propyl)-acetamide,
- 10 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(3,5-dichloro-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(3,4-dimethyl-benzyl)-acetamide,
- 15 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(3,4-dichloro-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(2-fluoro-5-trifluoromethyl-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(3-trifluoromethoxy-benzyl)-acetamide,
- 20 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(3-fluoro-4-trifluoromethyl-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(3,4,5-trimethoxy-benzyl)-acetamide,
- 25 -(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(4-trifluoromethoxy-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(4-fluoro-2-trifluoromethyl-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(5-fluoro-2-trifluoromethyl-benzyl)-acetamide,
- 30 2-(3-{(2*R*)-2-[2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}phenyl)-*N*-(4'-hydroxybiphenyl-3-ylmethyl)acetamide,

- 2-(3-((2*R*)-2-[2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl)phenyl)-*N*-(4'-hydroxybiphenyl-4-ylmethyl)acetamide,
- 2-(3-((2*R*)-2-[(2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]propyl)phenyl)-*N*-(4'-hydroxy-biphenyl-3-ylmethyl)acetamide,
- 5 2-(3-((2*R*)-2-[(2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]propyl)phenyl)-*N*-(4-hydroxynaphthalen-1-ylmethyl)acetamide,
- 3-{2-[(2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}-*N*-(4'-hydroxybiphenyl-3-ylmethyl)benzamide,
- 3-((2*R*)-2-[2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl)-*N*-[2-10 (4-hydroxy-phenyl)-2-methyl-propyl]-benzamide,
- 3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}-*N*-[2-(4-hydroxy-2,5-dimethylphenyl)ethyl]benzamide,
- 3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}-*N*-[2-(4-hydroxy-2,3-dimethylphenyl)ethyl]benzamide,
- 15 3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}-*N*-[2-(4-hydroxy-2-methylphenyl)ethyl]benzamide,
- 3-((2*R*)-2-[(2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]propyl)-*N*-[2-(4-hydroxy-2,5-dimethylphenyl)ethyl]benzamide,
- 3-((2*R*)-2-[(2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]propyl)-*N*-[2-(4-20 hydroxy-2,3-dimethylphenyl)ethyl]benzamide,
- 3-((2*R*)-2-[(2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]propyl)-*N*-[2-(4-hydroxy-2-methylphenyl)ethyl]benzamide,
- 2-[3-(2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(3-hydroxy-4-methoxy-phenyl)acetamide,
- 25 2-[3-(2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(3-hydroxy-phenyl)acetamide,
- 2-[3-(2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(2-chloro-4-hydroxy-phenyl)acetamide,
- 2-[3-(2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(4-hydroxy-3-methoxy-benzyl)acetamide,
- 30 2-[3-(2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[5-(ethylsulfonyl)-2-hydroxyphenyl]acetamide,

- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(2-hydroxy-5-methyl-phenyl)acetamide,
2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(5-chloro-2-hydroxy-benzyl)acetamide,
5 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(4-hydroxy-1,1'-biph-enyl-3-yl)acetamide,
2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[2-hydroxy-2-(3-hydroxyphenyl)ethyl]-*N*-methyl-acetamide,
2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-
10 propyl)phenyl]-*N*-ethyl-*N*-(3-hydroxy-phenyl)acetamide,
2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[2-(3-ethoxy-4-hydroxyphenyl)ethyl]acetamide,
2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-{[4'-(hydroxymeth-yl)-1,1'-biphenyl-3-yl]methyl}acetamide,
15 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(2,4-dichloro-6-hydroxybenzyl)acetamide,
2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[(3-fluoro-4'-hydroxy-1,1'-biphenyl-4-yl)meth-yl]acetamide,
2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-
20 propyl)phenyl]-*N*-[(4'-hydroxy-3-methyl-1,1'-biphenyl-4-yl)methyl]acetamide,
2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(2-chloro-5-hydroxy-benzyl)-*N*-ethylacetamide,
2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[(2'-hydroxy-1,1'-biphenyl-2-yl)methyl]acetamide,
25 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[3-hydroxy-5-(trifluoro-methyl)benzyl]-*N*-methylacetamide,
2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(3-chloro-5-hydroxy-benzyl)-*N*-ethylacetamide,
2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-
30 propyl)phenyl]-*N*-(3-chloro-5-hydroxy-benzyl)acetamide,
2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(4-hydroxy-3,5-dimethylbenzyl)acetamide,

- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[2-(2-hydroxyphen-yl)ethyl]acetamide,
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-benzyl-*N*-(4-hydroxyphenyl)acetamide,
- 5 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[2-(4-hydroxyphenyl)-ethyl]acetamide,
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(4-hydroxybenzyl)acetamide,
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-
- 10 propyl)phenyl]-*N*-(2-hydroxybenzyl)acetamide,
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(3-hydroxybenzyl)acetamide,
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[2-(3-hydroxyphenyl)-ethyl]acetamide,
- 15 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[2-(4-hydroxy-3-meth-oxyphenyl)ethyl]acetamide,
- methyl 4-([3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]acetyl)amino)-3-hydroxybenzoate,
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-
- 20 propyl)phenyl]-*N*-(5-tert-butyl-2-hydroxy-phenyl)acetamide,
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(3-hydroxy-4-methyl-phenyl)acetamide,
- 2-[3-((*(2R)*)-2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyeth-yl]amino}propyl)phenyl]-*N*-[2-(4-hydroxyphenyl)ethyl]acetamide,
- 25 2-[3-((*(2R)*)-2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(4-hydroxybenzyl)acetamide,
- 2-[3-((*(2R)*)-2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(2-hydroxybenzyl)acetamide,
- 2-[3-((*(2R)*)-2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxy-
- 30 ethyl]amino}propyl)phenyl]-*N*-(3-hydroxybenzyl)acetamide,
- 2-[3-((*(2R)*)-2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[2-(3-hydroxyphenyl)ethyl]acetamide,

- 2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[2-(4-hydroxy-3-methoxyphenyl)ethyl]acetamide,
2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(5-tert-butyl-2-hydroxy-phenyl)acetamide,
5 2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(3-hydroxy-4-methyl-phenyl)acetamide,
2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(3-hydroxy-4-methoxy-phenyl)acetamide,
2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(4-hydroxy-3-methoxy-benzyl)acetamide,
10 2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[5-(ethylsulfonyl)-2-hydroxyphenyl]acetamide,
2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(2-hydroxy-5-methyl-phenyl)acetamide,
15 2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(3-hydroxy-2-methyl-phenyl)acetamide,
2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(5-chloro-2-hydroxybenzyl)-acetamide,
2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[2-hydroxy-2-(3-hydroxyphenyl)ethyl]-*N*-methyl-
20 acetamide,
2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[2-(3-ethoxy-4-hydroxy-phenyl)ethyl]acetamide,
2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[2-(3-hydroxy-4-methoxy-phenyl)ethyl]acetamide,
25 2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-ethyl-*N*-[2-(4-hydroxyphen-yl)ethyl]acetamide,
2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(2-chloro-4-hydroxybenzyl)-*N*-ethylacetamide,
30 2-[3-((2*R*)-2-[[*(2R)*-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(5-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide,

- 2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(4-hydroxyphenyl)acetamide,
2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[4-(4-hydroxyphenyl)butyl]acetamide,
5 2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[(4'-hydroxy-1,1'-biphenyl-4-yl)methyl]acetamide,
2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[4'-(hydroxymethyl)-1,1'-biphenyl-3-yl]methyl]acetamide,
10 2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(2,4-dichloro-6-hydroxy-benzyl)acetamide,
2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[(3-fluoro-4'-hydroxy-1,1'-biphenyl-4-yl)methyl]acetamide,
15 2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[(4'-hydroxy-3-methyl-1,1'-biphenyl-4-yl)methyl]acetamide,
2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(2-chloro-5-hydroxybenzyl)-*N*-ethylacetamide,
20 2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[(2'-hydroxy-1,1'-biphenyl-2-yl)methyl]acetamide,
2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[3-hydroxy-5-(trifluoro-methyl)benzyl]-*N*-methylacetamide,
25 2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(3-chloro-5-hydroxybenzyl)-*N*-ethylacetamide,
2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(3-chloro-5-hydroxy-benzyl)acetamide,
2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(4-hydroxy-3,5-dimethylbenzyl)acetamide,
30 2-[3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(3,5-dichloro-2-hydroxy-benzyl)acetamide,

- 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-[2-(4-hydroxyphenyl)ethyl]benzamide,
- 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-(4-hydroxybenzyl)benzamide,
- 5 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-(2-hydroxybenzyl)benzamide,
- 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-[2-(3-hydroxyphenyl)ethyl]benzamide,
- 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-
- 10 [2-(4-hydroxy-3-methoxyphenyl)ethyl]benzamide,
- 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-(3-hydroxy-4-methyl-phenyl)benzamide,
- 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-[2-(4-hydroxy-3,5-dimethoxyphenyl)ethyl]benzamide,
- 15 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-(3-hydroxy-4-methoxyphenyl)benzamide,
- 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-(3-hydroxyphenyl)benzamide,
- 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-
- 20 (4-hydroxy-3-methoxybenzyl)benzamide,
- 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-[5-(ethylsulfonyl)-2-hydroxyphenyl]benzamide,
- 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-(3-hydroxy-2-methyl-phenyl)benzamide,
- 25 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-(5-chloro-2-hydroxy-benzyl)benzamide,
- 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-(4-hydroxy-1,1'-biphenyl-3-yl)benzamide,
- 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-
- 30 [2-hydroxy-2-(3-hydroxyphenyl)ethyl]-*N*-methylbenzamide,
- 3-(2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)-*N*-(2-hydroxybenzyl)-*N*-methylbenzamide,

- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-
(3,5-dichloro-2-hydroxybenzyl)benzamide,
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-
[2-(2-hydroxyphenyl)ethyl]benzamide,
- 5 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-
[2-(3-ethoxy-4-hydroxyphenyl)ethyl]benzamide,
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-
[2-(3-hydroxy-4-methoxyphenyl)ethyl]benzamide,
- 2-[3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-
10 benzoyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepin-8-ol,
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-
[(4'-hydroxy-3-methyl-1,1'-biphenyl-4-yl)methyl]-benzamide,
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-
[(3'-hydroxy-1,1'-biphenyl-2-yl)-methyl]benzamide,
- 15 3-((2*R*)-2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(5-
chloro-2-hydroxy-benzyl)benzamide,
- 3-((2*R*)-2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[2-
hydroxy-2-(3-hydroxyphenyl)ethyl]-*N*-methylbenzamide,
- 3-((2*R*)-2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(2-
20 hydroxybenzyl)-*N*-methylbenzamide,
- 3-((2*R*)-2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[2-(3-
ethoxy-4-hydroxyphenyl)ethyl]benzamide,
- 3-((2*R*)-2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[2-(3-
hydroxy-4-methoxyphenyl)ethyl]benzamide,
- 25 2-[3-((2*R*)-2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-
amino}propyl)benzoyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepin-8-ol,
- 3-((2*R*)-2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-ethyl-
N-[2-(4-hydroxyphenyl)ethyl]benzamide,
- 3-((2*R*)-2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(2-
30 chloro-4-hydroxy-benzyl)-*N*-ethylbenzamide,
- 3-((2*R*)-2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(5-
hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide,

- 2-{4-[3-((2*R*)-2-[(2*R*)-2-(6-amino-pyridin-3-yl)-2-hydroxyethyl]amino}propyl)benzoyl]piperazin-1-yl}phenol,
 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(4-hydroxyphenyl)benzamide,
 5 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[4-(4-hydroxyphen-yl)butyl]benzamide,
 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[(4'-hydroxy-1,1'-biphenyl-4-yl)methyl]benzamide,
 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[(4'-
 10 (hydroxymethyl)-1,1'-biphenyl-3-yl)methyl]benzamide,
 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(2,4-dichloro-6-hydroxybenzyl)benzamide,
 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[(3-fluoro-4'-hydroxy-1,1'-biphenyl-4-yl)methyl]benzamide,
 15 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[(4'-hydroxy-3-methyl-1,1'-biphenyl-4-yl)methyl]benzamide,
 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(2-chloro-5-hydroxy-benzyl)-*N*-ethylbenzamide,
 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[(2'-
 20 hydroxy-1,1'-biphenyl-2-yl)methyl]benzamide,
 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[(4'-hydroxy-1,1'-biphenyl-2-yl)methyl]benzamide,
 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[3-hydroxy-5-(trifluoro-methyl)benzyl]-*N*-methylbenzamide,
 25 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3-chloro-5-hydroxy-benzyl)-*N*-ethylbenzamide,
 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3-chloro-5-hydroxy-benzyl)benzamide,
 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[(4'-
 30 hydroxy-1,1'-biphenyl-3-yl)methyl]benzamide,
 3-((2*R*)-2-[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(4-hydroxy-3,5-dimethylbenzyl)benzamide,

- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3,5-dichloro-2-hydroxybenzyl)benzamide,
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[2-(2-hydroxyphenyl)-ethyl]benzamide,
- 5 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3-hydroxy-4-methoxy-phenyl)benzamide,
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3-hydroxyphenyl)benzamide,
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(4-10 hydroxy-3-methoxy-benzyl)benzamide,
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[5-(ethylsulfonyl)-2-hydroxyphenyl]benzamide,
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(2-hydroxy-5-methyl-phenyl)benzamide,
- 15 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3-hydroxy-2-methyl-phenyl)benzamide,
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[2-(4-hydroxyphen-yl)ethyl]benzamide,
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(4-20 hydroxybenzyl)benzamide,
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(2-hydroxybenzyl)benzamide,
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3-hydroxybenzyl)benzamide, and
- 25 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[2-(3-hydroxyphen-yl)ethyl]benzamide.

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

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

Suitable acid addition salts are formed from acids which form non-toxic salts.

5 Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzenate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, 10 maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

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

Hemisalts of acids and bases may also be formed, for example, hemisulphate 20 and hemicalcium salts.

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

25

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

- 30 (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

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

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation
10 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
15 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,
20 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
25 ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblan (August 1975).

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

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
5 (1).

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,
10 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
15 Drug Design', Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (1)
20 with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H. Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include:

25

(i) where the compound of formula (1) contains a carboxylic acid functionality (-COOH), an ester thereof, for example, a compound wherein the hydrogen of the carboxylic acid functionality of the compound of formula (1) is replaced by (C₁-C₈)alkyl;

30

(ii) where the compound of formula (1) contains an alcohol functionality (-OH), an ether thereof, for example, a compound wherein the hydrogen

of the alcohol functionality of the compound of formula (1) is replaced by (C₁-C₆)alkanoyloxymethyl; and

- 5 (iii) where the compound of formula (1) contains a primary or secondary amino functionality (-NH₂ or -NHR where R ≠ H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound of formula (1) is/are replaced by (C₁-C₁₀)alkanoyl.
- 10 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
15 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
- 20 (i) where the compound of formula (1) contains a methyl group, an hydroxymethyl derivative thereof (-CH₃ → -CH₂OH);
- (ii) where the compound of formula (1) contains an alkoxy group, an hydroxy derivative thereof (-OR → -OH);
- 25 (iii) where the compound of formula (1) contains a tertiary amino group, a secondary amino derivative thereof (-NR¹R² → -NHR¹ or -NHR²);
- (iv) where the compound of formula (1) contains a secondary amino group, a
30 primary derivative thereof (-NHR¹ → -NH₂);

(v) where the compound of formula (1) contains a phenyl moiety, a phenol derivative thereof (-Ph → -PhOH); and

(vi) where the compound of formula (1) contains an amide group, a
5 carboxylic acid derivative thereof (-CONH₂ → 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
10 are possible. Where structural isomers are interconvertible *via* a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula (1) containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit
15 more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (1), including compounds exhibiting more than one type of isomerism, and mixtures
20 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
25 those skilled in the art, for example, chromatography and fractional crystallisation.

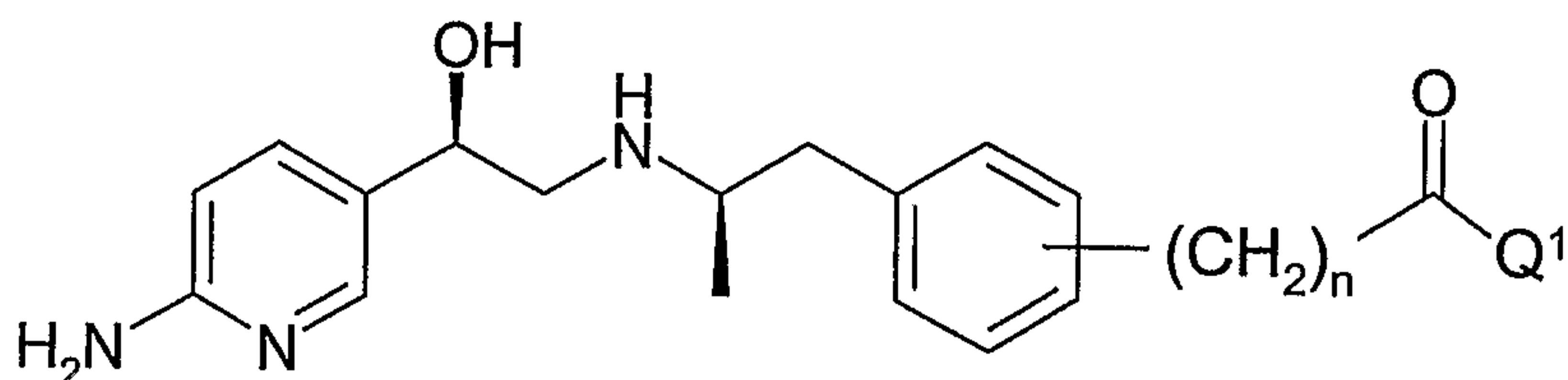
Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of
30 the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (1) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting
5 diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be
10 obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the
15 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).

20 According to one aspect of the present invention, the (*R,R*)-stereoisomer of the formula below, wherein *n* and *Q*¹ are as defined above, is generally preferred:



_____The present invention includes all pharmaceutically acceptable
25 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 ,
5 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
10 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
15 therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

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

Isotopically-labeled compounds of formula (1) can generally be prepared by conventional techniques known to those skilled in the art or by processes
25 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.

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

The compounds of formula (1), their pharmaceutically acceptable salts 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, 5 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 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 10 in gastric and peptic ulceration.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or 15 radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a 20 formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage 25 form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation 30 may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).

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

5

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

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

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

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

- Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.
- Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.
- Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet.
- Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.
- Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant.
- Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may

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

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

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellaable thin film dosage forms which may be rapidly
10 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.

15 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
20 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 %.

25

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.

30

Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper.

This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

5 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.

10 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.

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

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

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

The solubility of compounds of formula (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.

- 5 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
10 release of the active compound. Examples of such formulations include drug-coated stents and poly(*dl*-lactic-co-glycolic)acid (PGLA) microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this
15 purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may
20 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
25 (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.

30

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for

example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce
5 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 cyclodextrin.

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

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

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to
25 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 /-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

30

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

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
5 polyethylene glycol.

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

10

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

15

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 0.001mg to 10mg of the compound of formula (1). The overall
20 daily dose will typically be in the range 0.001mg to 40mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

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

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

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

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

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

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

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion
30 complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and

gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Inasmuch as it may 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.

10

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.

15

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.

20

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 0.001mg to 5000mg depending, of course, on the mode of administration. For example, an intravenous daily dose may only require from 0.001mg to 40mg. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein.

25

30

These dosages are based on an average human subject having a weight of about 65kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

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

According to another embodiment of the present invention, the compounds of the formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, can also be used as a combination with one or
10 more additional therapeutic agents to be co-administered to a patient to obtain some particularly desired therapeutic end result such as the treatment of pathophysiologically-relevant disease processes including, but not limited to (i) bronchoconstriction, (ii) inflammation, (iii) allergy, (iv) tissue destruction, (v) signs and symptoms such as breathlessness, cough. The second and more
15 additional therapeutic agents may also be a compound of the formula (1), or a pharmaceutically acceptable salt, derived forms or compositions thereof, or one or more β 2 agonists known in the art. More typically, the second and more therapeutic agents will be selected from a different class of therapeutic agents.

As used herein, the terms "co-administration", "co-administered" and "in
20 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:

- simultaneous administration of such combination of compound(s) of formula (1) and therapeutic agent(s) to a patient in need of treatment,
25 when such components are formulated together into a single dosage form which releases said components at substantially the same time to said patient,
- substantially simultaneous administration of such combination of compound(s) of formula (1) and therapeutic agent(s) to a patient in need
30 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,

- 5 • 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;
10 and
- 15 • 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,

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,
25 and LTE₄,
- (c) Histamine receptor antagonists including H1 and H3 antagonists,
- (d) α_1 - and α_2 -adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use,
- (e) muscarinic M3 receptor antagonists or anticholinergic agents,
- 30 (f) PDE inhibitors, e.g. PDE3, PDE4 and PDE5 inhibitors,

- (g) Theophylline,
- (h) Sodium cromoglycate,
- (i) COX inhibitors both non-selective and selective COX-1 or COX-2 inhibitors (NSAIDs),
- 5 (j) Oral and inhaled glucocorticosteroids,
- (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,
- 10 (o) Immunosuppressive agents,
- (p) Inhibitors of matrix metalloproteases (MMPs),
- (q) Tachykinin NK₁, NK₂ and NK₃ receptor antagonists,
- (r) Elastase inhibitors,
- (s) Adenosine A2a receptor agonists,
- 15 (t) Inhibitors of urokinase,
- (u) Compounds that act on dopamine receptors, e.g. D2 agonists,
- (v) Modulators of the NF κ B pathway, e.g. IKK inhibitors,
- (w) modulators of cytokine signalling pathways such as p38 MAP kinase or syk kinase,
- 20 (x) Agents that can be classed as mucolytics or anti-tussive, and
- (y) Antibiotics.

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

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

are further preferred.

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 further preferred.

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

20 The compounds of formula (1) have the ability to interact with the β_2 receptor and thereby have a wide range of therapeutic applications, as described further below, because of the essential role which the β_2 receptor plays in the physiology of all mammals.

25 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 β_2 receptor is involved. More specifically, the present invention also concerns the compounds of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for use in the

treatment of diseases, disorders, and conditions selected from the group consisting of :

- asthma of whatever type, etiology, or pathogenesis, in particular asthma that is a member selected from the group consisting of atopic asthma, non-atopic asthma, allergic asthma, atopic bronchial IgE-mediated asthma, bronchial asthma, essential asthma, true asthma, intrinsic asthma caused by pathophysiologic disturbances, extrinsic asthma caused by environmental factors, essential asthma of unknown or inapparent cause, non-atopic asthma, bronchitic asthma, emphysematous asthma, exercise-induced asthma, allergen induced asthma, cold air induced asthma, occupational asthma, infective asthma caused by bacterial, fungal, protozoal, or viral infection, non-allergic asthma, incipient asthma, wheezy infant syndrome and bronchiolitis, 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
- 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 20

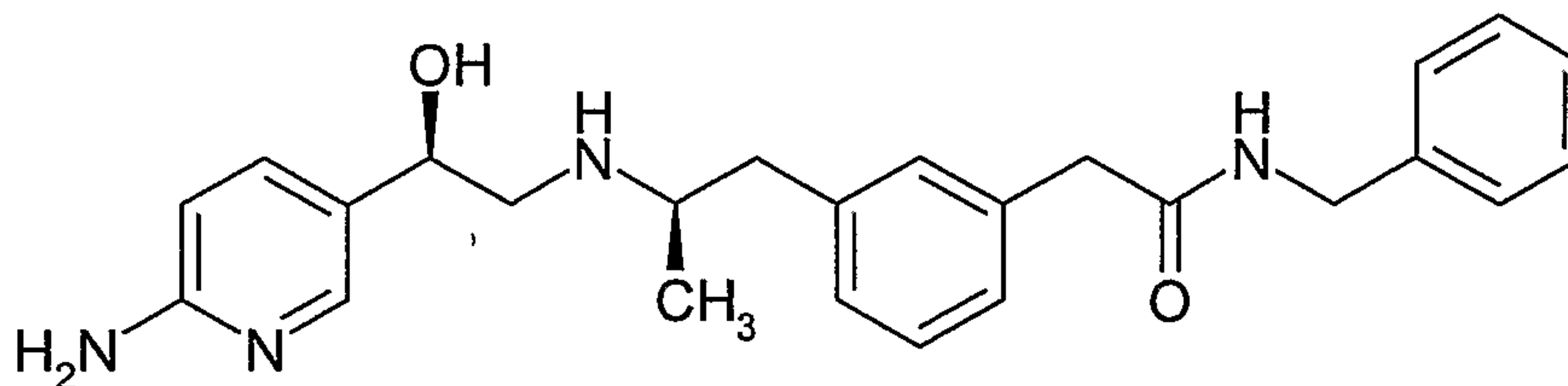
asthmatic bronchitis, productive bronchitis, staphylococcus or streptococcal bronchitis and vesicular bronchitis,

- acute lung injury,
 - bronchiectasis of whatever type, etiology, or pathogenesis, in particular
5 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.
- 10 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 compounds of formula (1), or pharmaceutically acceptable salts, derived forms
15 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 to treat a mammal, including a human being, with an
20 effective amount of a compound of formula (1), or a pharmaceutically acceptable salt, derived form or composition thereof. More precisely, the present invention provides a particularly interesting method for the treatment of a $\beta 2$ -mediated diseases and/or conditions in a mammal, including a human being, in particular the diseases and/or conditions listed above, comprising
25 administering said mammal with an effective amount of a compound of formula (1), its pharmaceutically acceptable salts and/or derived forms.

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

Example 1 : 2-(3-((2R)-2-[(2R)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl)-phenyl)-N-benzyl-acetamide

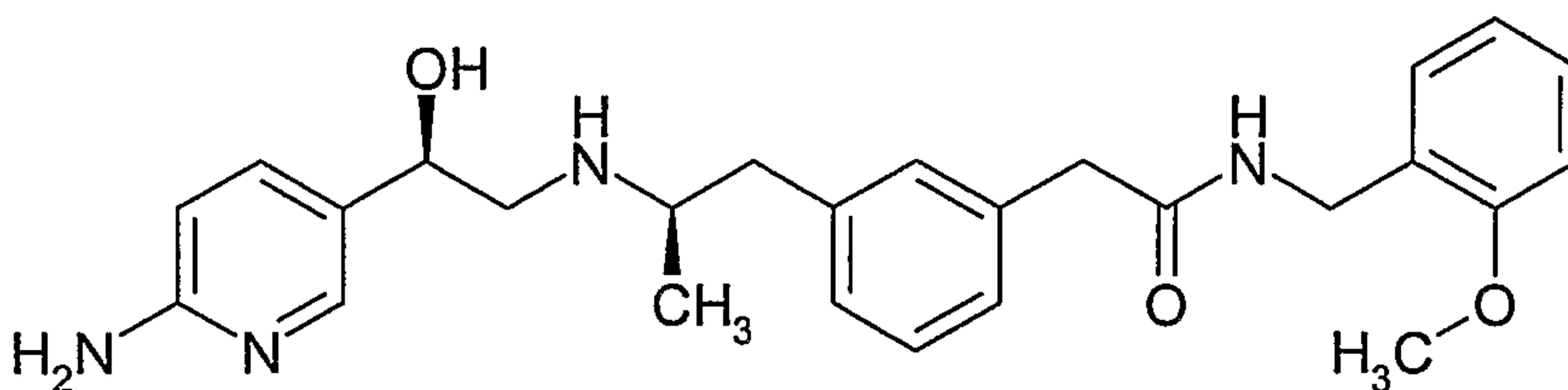


A solution of *N*-Benzyl-2-[3-((2R)-2-[(2R)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino]-propyl)-phenyl]-acetamide (preparation 1, 148mg, 0.30mmol) in ethanol (5ml) was treated with hydroxylamine hydrochloride (103mg, 1.48mmol) and the resulting mixture heated to 85C for 48 hours. The reaction was cooled to room temperature and passed through a Strong Cation Exchange column eluting with methanol followed by 2N ammonia in methanol to elute the product. Further purification by flash column chromatography eluting with dichloromethane:methanol: 880 ammonia (97:3:0.5 changing to 90:10:1 by volume) gave the title compound as a pale yellow solid (36mg).

¹H NMR (400MHz, CD₃OD): δ = 7.78 (1H, s), 7.37 (1H, d), 7.27-7.00 (9H, m), 6.51 (1H, s), 4.53 (1H, s), 4.35 (2H, s), 3.51 (2H, s), 2.90-2.82 (2H, m), 2.66-2.58 (3H, m), 1.07 (3H, d) ppm.

LRMS (APCI) : m/z [M+H]⁺ 419.

Example 2 : 2-(3-((2R)-2-[(2R)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl)-phenyl)-N-(2-methoxy-benzyl)-acetamide



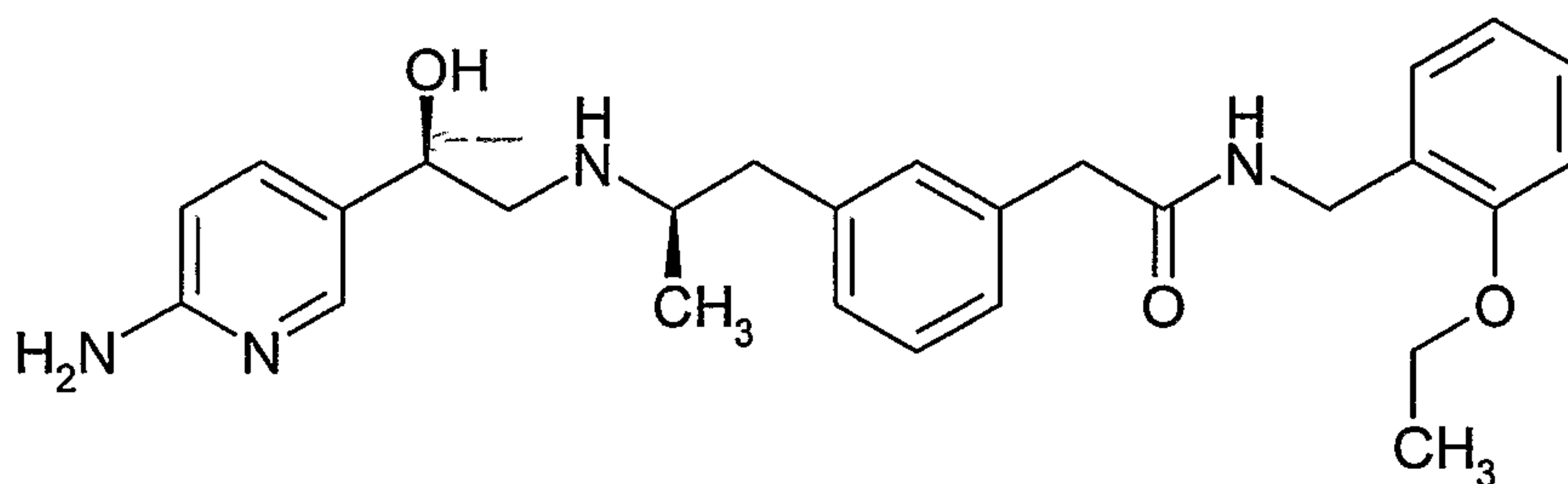
Prepared from 2-[3-((2R)-2-[(2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino]-propyl)-phenyl]-N-(2-methoxy-benzyl)-acetamide

(preparation 2) according to the method for example 1 to give the title compound as a pale yellow foam.

¹H NMR (400MHz, CD₃OD): δ = 7.77 (1H, s), 7.36 (1H, d), 7.23-6.84 (8H, m), 6.50 (1H, d), 4.52 (1H, m), 4.34 (2H, s), 3.78 (3H, s), 3.50 (2H, s), 2.88-2.81
5 (2H, m), 2.66-2.57 (3H, m), 1.06 (3H, d) ppm.

LRMS (APCI) : m/z [M+H]⁺ 449.

Example 3 : 2-(3-((2R)-2-((2R)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino)-propyl)-phenyl)-N-(2-ethoxy-benzyl)-acetamide

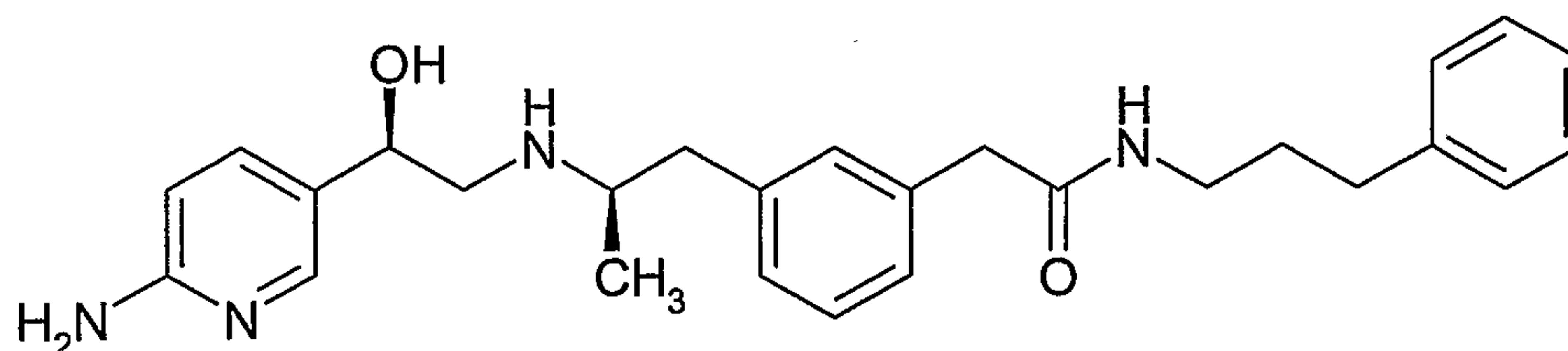


10 Prepared from 2-[3-((2R)-2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-N-(2-ethoxy-benzyl)-acetamide
(preparation 3) according to the method for example 1 to give the title compound as a pale yellow foam.

¹H NMR (400MHz, CD₃OD): δ = 7.78 (1H, s), 7.37 (1H, d), 7.21-7.00 (6H, m),
15 6.90 (1H, d), 6.83 (1H, t), 6.50 (1H, s), 4.52 (1H, m), 4.35 (2H, s), 3.99 (2H, m), 3.51 (2H, s), 2.89-2.81 (2H, m), 2.70-2.54 (3H, m), 1.34 (3H, d), 1.06 (3H, d) ppm.

LRMS (APCI) : m/z [M+H]⁺ 463.

Example 4 : 2-(3-((2R)-2-((2R)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino)-propyl)-phenyl)-N-(3-phenyl-propyl)-acetamide
20

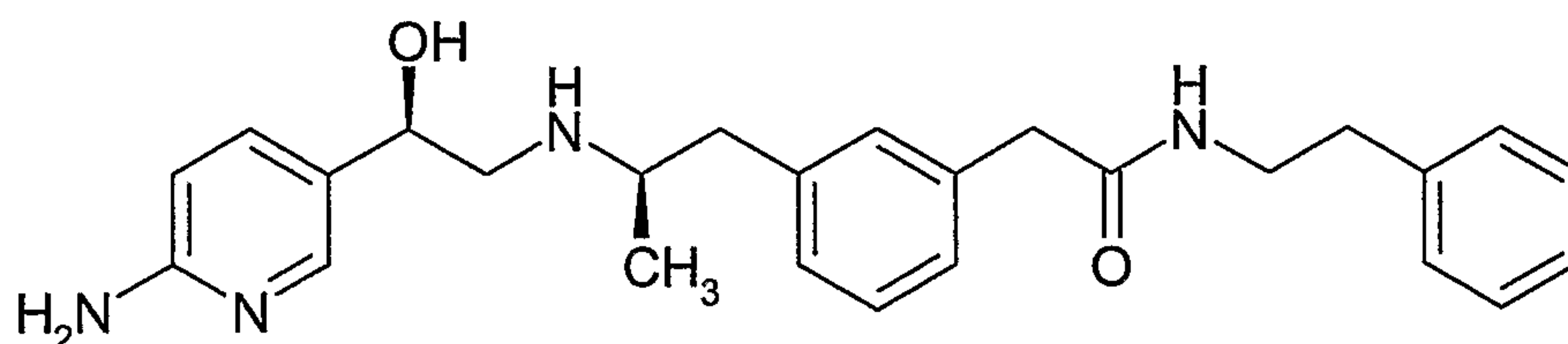


Prepared from 2-[3-((2R)-2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-N-(3-phenyl-propyl)-acetamide (preparation 4) according to the method for example 1 to give the title compound as a pale yellow foam.

^1H NMR (400MHz, CD_3OD): δ = 7.79 (1H, s), 7.38 (1H, d), 7.24 (3H, m), 7.14 (5H, m), 7.01 (1H, d), 6.49 (1H, d), 4.51 (1H, m), 3.46 (2H, s), 3.20 (2H, t), 2.92-2.81 (2H, m), 2.68-2.55 (5H, m), 1.79 (2H, m), 1.06 (3H, d) ppm.

LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 447.

10 Example 5 : 2-(3-((2R)-2-((2R)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino)-propyl)-phenyl)-N-phenethyl-acetamide

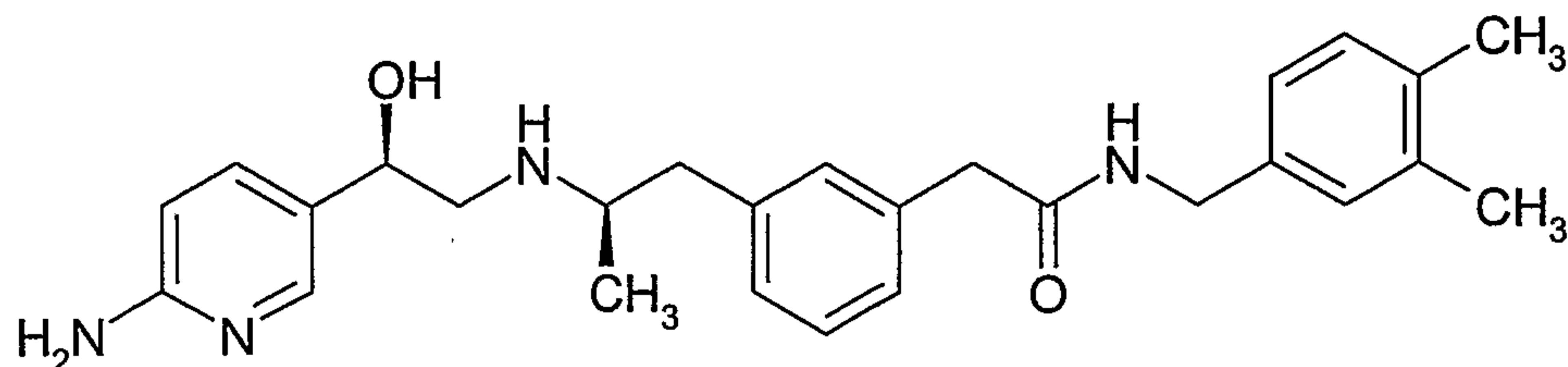


Prepared from 2-[3-((2R)-2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-N-phenethyl-acetamide (preparation 5) according to the method for example 1 to give the title compound as a pale yellow foam.

^1H NMR (400MHz, CD_3OD): δ = 7.79 (1H, s), 7.38 (1H, d), 7.28-7.01 (9H, m), 6.49 (1H, d), 4.53 (1H, m), 3.42-3.37 (4H, m), 2.92-2.87 (2H, m), 2.77-2.73 (2H, m), 2.67-2.59 (3H, m), 1.08 (3H, d) ppm.

LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 433.

Example 6: 2-(3-((2*R*)-2-((2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino)-propyl)-phenyl)-*N*-(3,4-dimethyl-benzyl)-acetamide

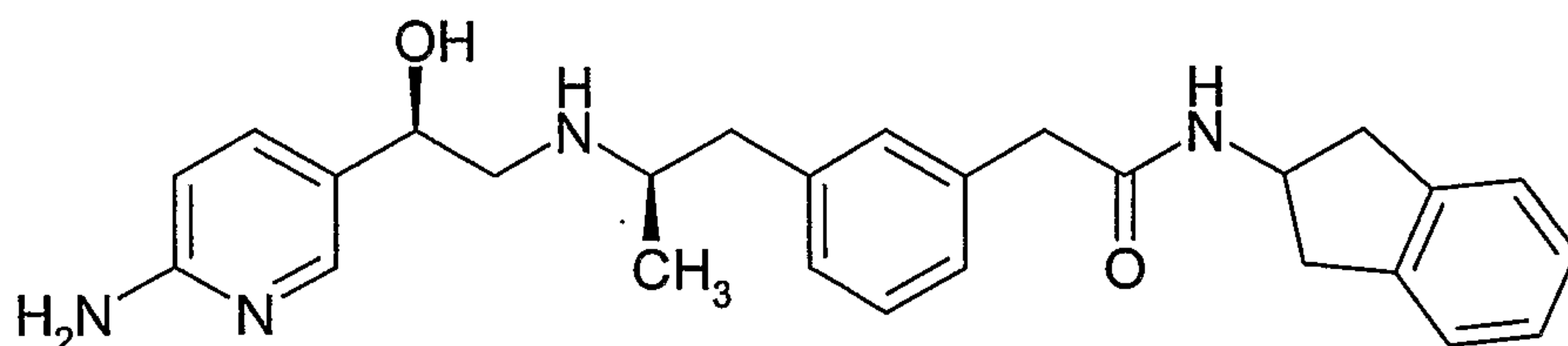


Prepared from *N*-(3,4-Dimethyl-benzyl)-2-[3-((2*R*)-2-((2*R*)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-acetamide (preparation 6) according to the method for example 1 to give the title compound as a pale yellow foam.

¹H NMR (400MHz, CD₃OD): δ = 7.77 (1H, s), 7.35 (1H, d), 7.19-6.96 (7H, m), 6.50 (1H, d), 4.50 (1H, m), 4.27 (2H, s), 3.50 (2H, s), 2.89-2.81 (2H, m), 2.67-2.55 (3H, m), 2.18 (6H, s), 1.06 (3H, d) ppm.

LRMS (APCI) : m/z [M+H]⁺ 419.

Example 7 : 2-(3-((2*R*)-2-((2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino)-propyl)-phenyl)-*N*-indan-2-yl-acetamide

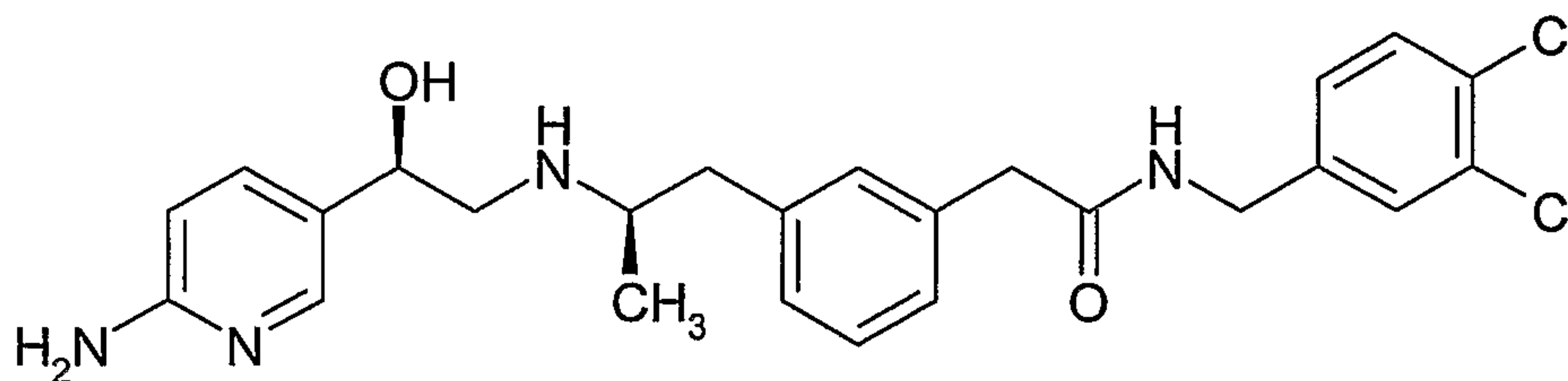


Prepared from 2-[3-((2*R*)-2-((2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-*N*-indan-2-yl-acetamide (preparation 7) according to the method for example 1 to give the title compound as a pale yellow foam.

¹H NMR (400MHz, CD₃OD): δ = 7.78 (1H, s), 7.37 (1H, d), 7.20-6.99 (8H, m), 6.51 (1H, s), 4.54 (2H, m), 3.43 (2H, s), 3.23 (2H, m), 2.89-2.79 (4H, m), 2.69-2.56 (3H, m), 1.07 (3H, d) ppm.

LRMS (APCI) : m/z $[M+H]^+$ 444.

Example 8 : 2-(3-((2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl)-phenyl)-*N*-(3,4-dichloro-benzyl)-acetamide

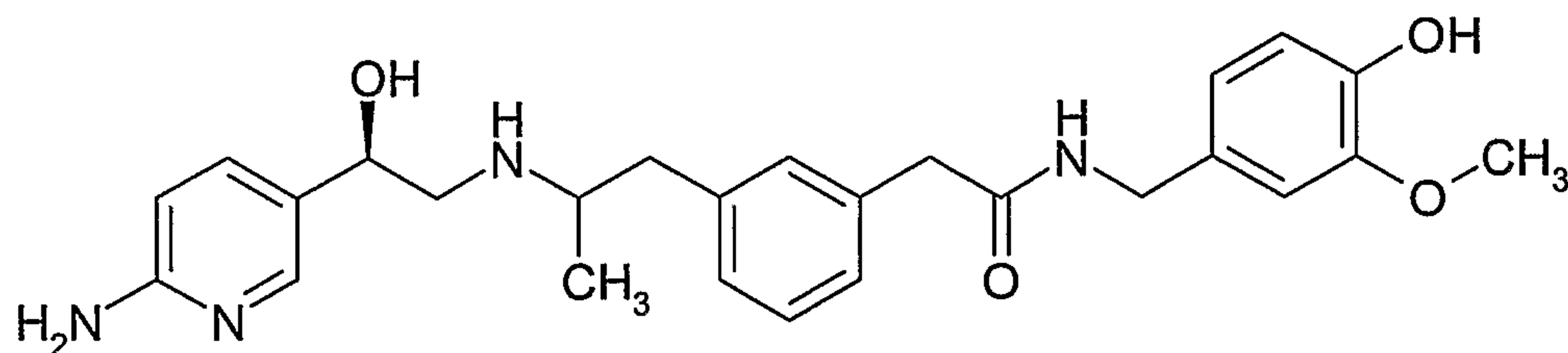


- 5 Prepared from *N*-(3,4-Dichloro-benzyl)-2-[3-((2*R*)-2-[(2*R*)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino]-propyl)-phenyl]-acetamide (preparation 8) according to the method for example 1 to give the title compound as a pale yellow foam.

¹H NMR (400MHz, CD₃OD): δ = 7.78 (1H, s), 7.41-7.35 (3H, m), 7.22-7.02 (5H, m), 6.51 (1H, s), 4.50 (1H, m), 4.31 (2H, s), 3.52 (2H, s), 2.92-2.82 (2H, m), 2.70-2.56 (3H, m), 1.06 (3H, d) ppm.

LRMS (APCI) : m/z $[M+H]^+$ 487 / 489.

Example 9: 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(4-hydroxy-3-methoxy-benzyl)-acetamide



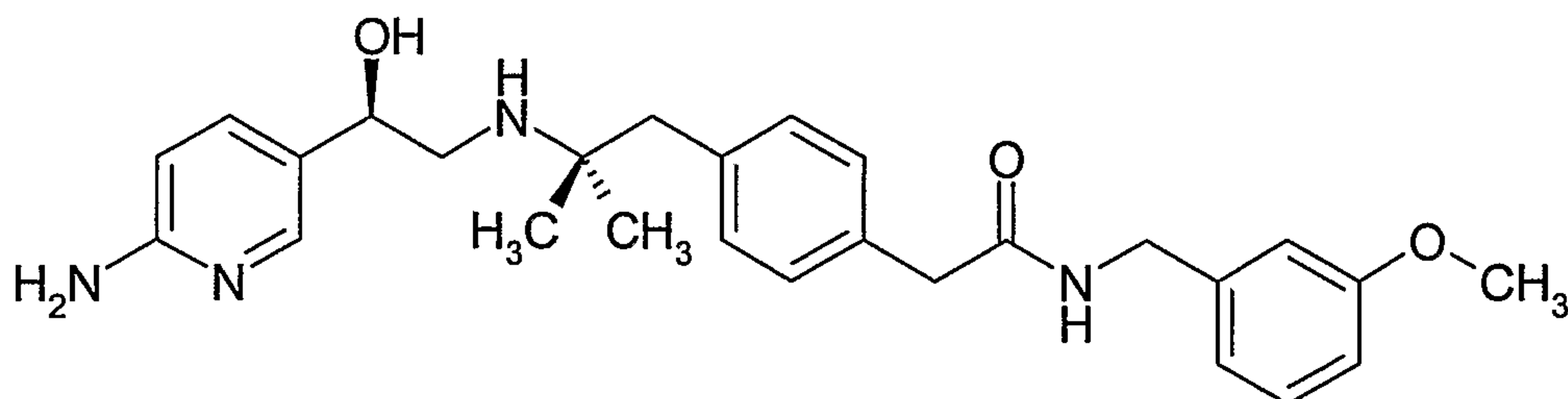
15

Prepared from 2-[3-(2-[(2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino]-propyl)-phenyl]-*N*-(4-hydroxy-3-methoxy-benzyl)-acetamide (preparation 9) according to the method for example 1 to give the title compound as a pale yellow foam.

^1H NMR (400MHz, CD_3OD): δ = 7.80 (1H, m), 7.39 (1H, m), 7.25-7.00 (4H, m), 6.77 (1H, bs), 6.69 (2H, m), 6.52 (1H, m), 4.55 (1H, m), 4.26 (2H, s), 3.73 (3H, s), 3.51 (2H, d), 2.90-2.58 (5H, m), 1.05 (3H, m) ppm.

LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 465, $[\text{M}+\text{Na}]^+$ 487, $[\text{M}-\text{H}]^-$ 463.

5 Example 10 : 2-(4-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(3-methoxy-benzyl)-acetamide

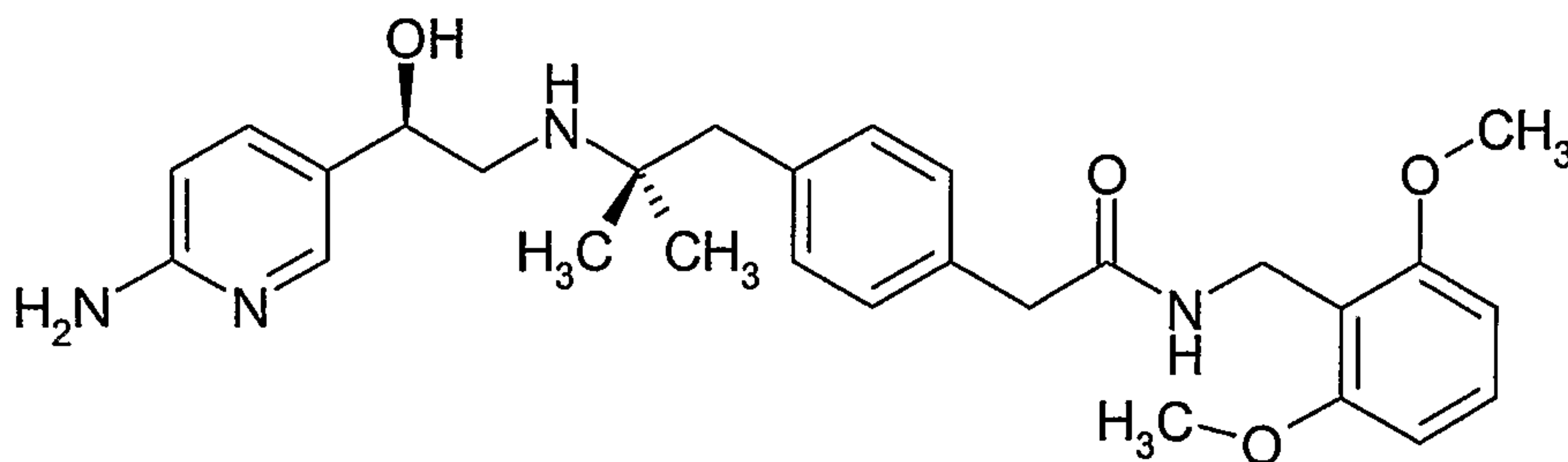


Prepared from 2-[4-(2-{(2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino}-2-methyl-propyl)-phenyl]-*N*-(3-methoxy-benzyl)-acetamide (preparation 10) according to the method for example 1 to give the title compound as a pale yellow foam.

^1H NMR (400MHz, CD_3OD): δ = 7.87 (1H, s), 7.47 (1H, d), 7.20 (3H, m), 7.11 (2H, d), 6.77 (3H, m), 6.55 (1H, d), 4.56 (1H, m), 4.33 (2H, s), 3.71 (3H, s), 3.52 (2H, s), 2.86 (1H, m), 2.70 (3H, m), 1.06 (3H, s), 1.05 (3H, s) ppm.

15 LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 463.

Example 11 : 2-(4-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(2,6-dimethoxy-benzyl)-acetamide

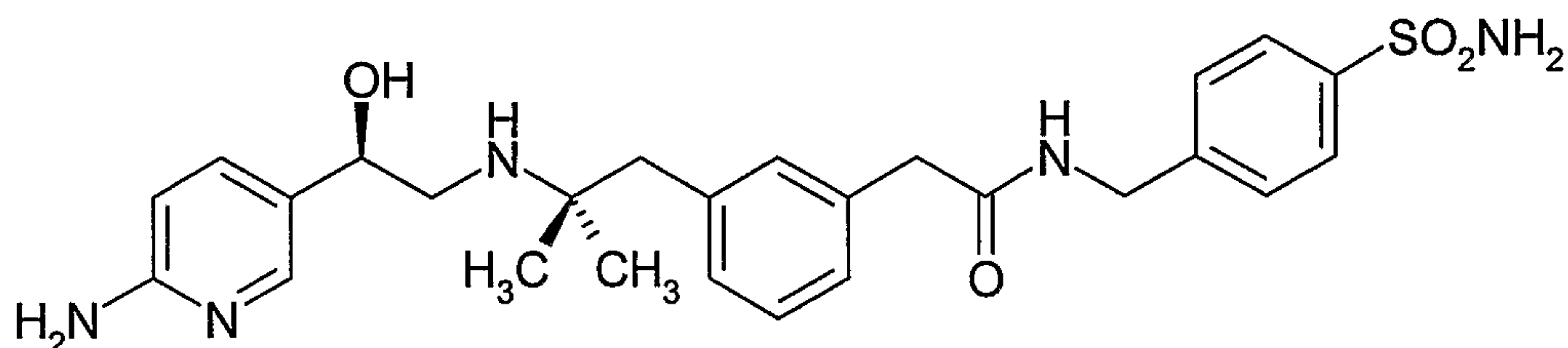


Prepared from *N*-(2,6-Dimethoxy-benzyl)-2-[4-(2-((2*R*)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-acetamide (preparation 11) according to the method for example 1 to give the title compound as a pale yellow foam.

- 5 ^1H NMR (400MHz, CD_3OD): δ = 7.86 (1H, s), 7.46 (1H, d), 7.28-7.08 (5H, m), 6.60 (2H, d), 6.54 (1H, d), 4.56 (1H, m), 4.42 (2H, s), 3.76 (6H, s), 3.45 (2H, s), 2.87 (1H, m), 2.70 (3H, m), 1.06 (3H, s), 1.05 (3H, s) ppm.

LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 493.

Example 12 : 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(4-sulfamoyl-benzyl)-acetamide

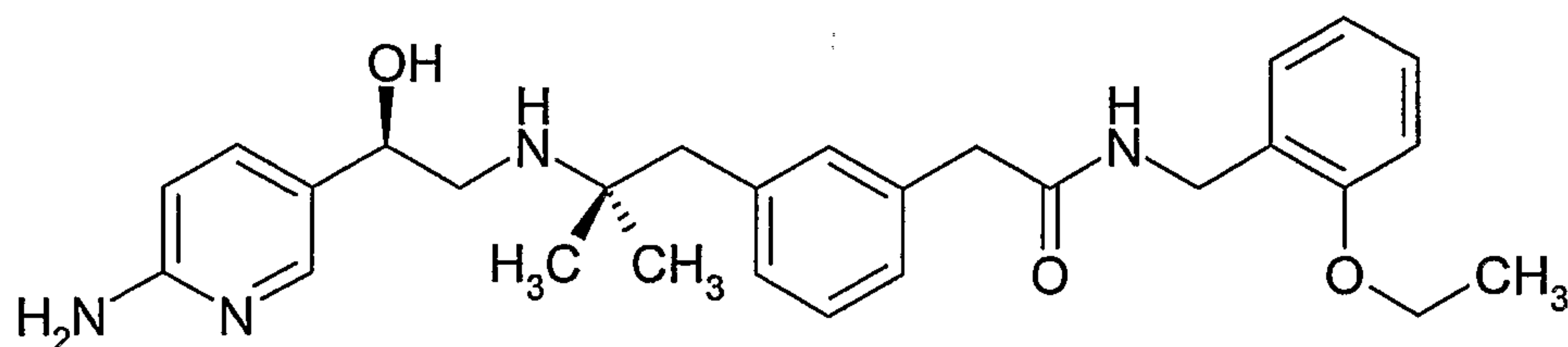


- Prepared from 2-[3-(2-((2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-*N*-(4-sulfamoyl-benzyl)-acetamide (preparation 12) according to the method for example 1 to give the title compound as a pale yellow foam.

^1H NMR (400MHz, CD_3OD): δ = 7.85 (1H, s), 7.79 (2H, d), 7.48 (1H, d), 7.38 (2H, d), 7.25-7.10 (3H, m), 7.05 (1H, s), 6.58 (1H, d), 4.58 (1H, m), 4.40 (2H, s), 3.55 (2H, s), 2.82 (1H, m), 2.75-2.60 (3H, m), 1.05 (3H, s), 1.04 (3H, s) ppm.

LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 512.

Example 13 : 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(2-ethoxy-benzyl)-acetamide

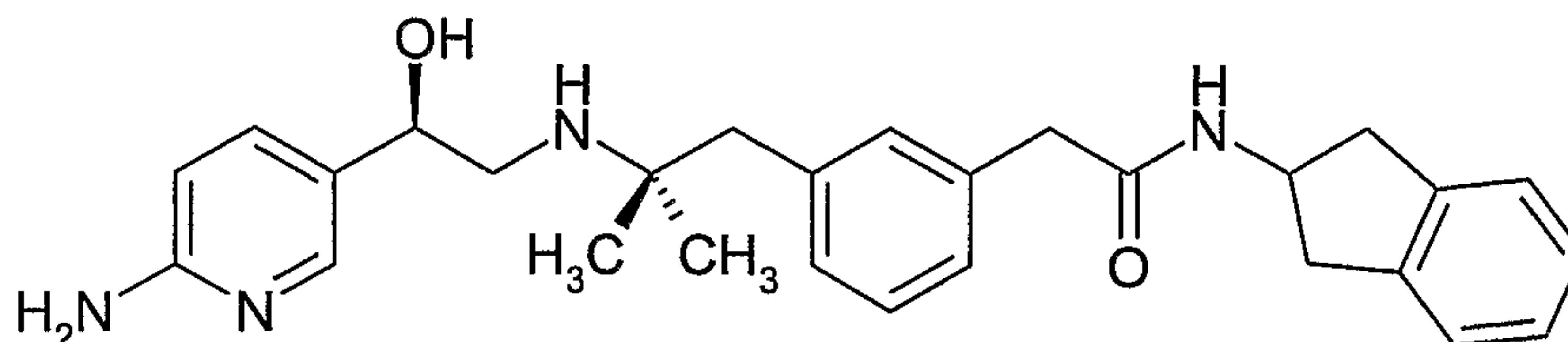


Prepared from 2-[3-(2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-N-(2-ethoxy-benzyl)-acetamide (preparation 13) according to the method for example 1 to give the title compound as a pale yellow foam.

^1H NMR (400MHz, CD_3OD): δ = 7.87 (1H, s), 7.48 (1H, d), 7.21-7.04 (6H, m), 6.87 (1H, d), 6.83 (1H, t), 6.57 (1H, d), 4.57 (1H, m), 4.36 (2H, s), 4.01 (2H, q), 3.52 (2H, s), 2.88-2.83 (1H, m), 2.74-2.64 (3H, m), 1.32 (3H, t), 1.03 (3H, s), 1.02 (3H, s) ppm.

10 LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 477.

Example 14 : 2-(3-{2-[(2R)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-indan-2-yl-acetamide

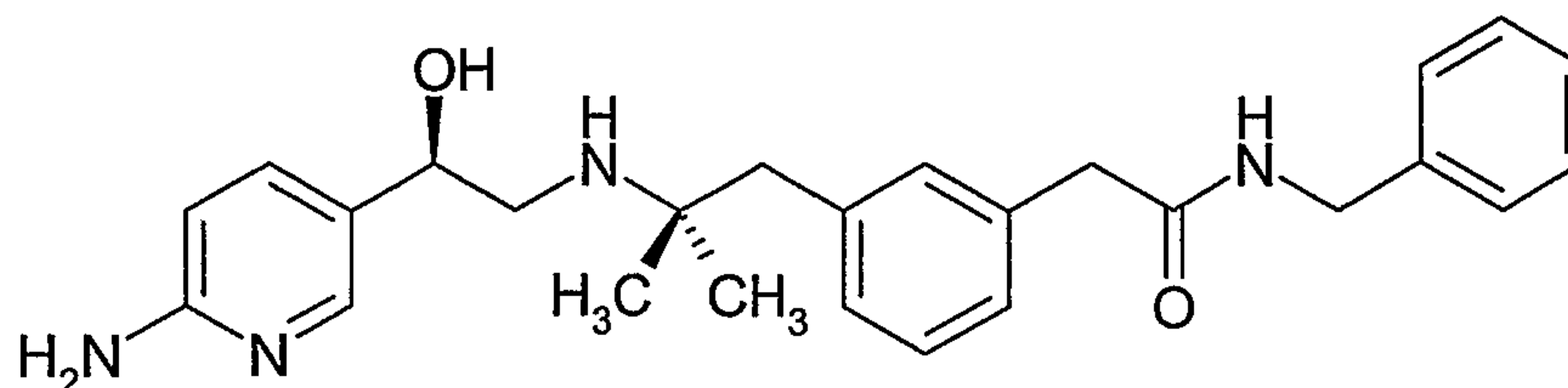


Prepared from 2-[3-(2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-N-indan-2-yl-acetamide (preparation 14) according to the method for example 1 to give the title compound as a pale yellow foam.

^1H NMR (400MHz, CD_3OD): δ = 7.90 (1H, s), 7.48 (1H, d), 7.22-7.11 (7H, m), 7.04 (1H, d), 6.57 (1H, d), 4.56 (2H, m), 3.45 (2H, s), 3.24-3.20 (2H, m), 2.86-2.67 (6H, m), 1.07 (3H, s), 1.06 (3H, s) ppm.

LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 459.

Example 15 : 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-benzyl-acetamide

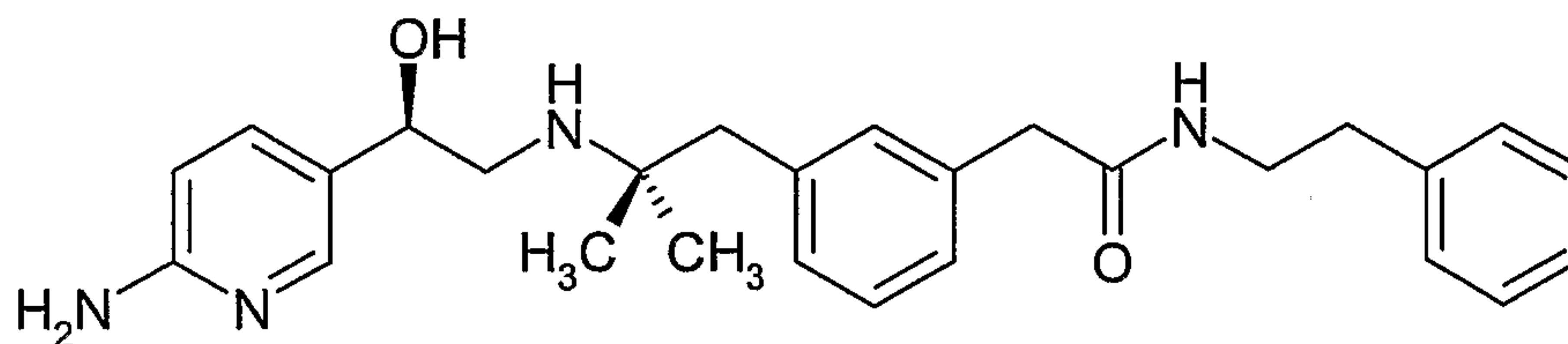


Prepared from *N*-Benzyl-2-[3-(2-{(2*R*)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino}-2-methyl-propyl)-phenyl]-acetamide (preparation 15) according to the method for example 1 to give the title compound as a colourless foam.

¹H NMR (400MHz, CD₃OD): δ = 7.87 (1H, m), 7.48 (1H, dd), 7.28-7.13 (8H, m), 7.05 (1H, d), 6.57 (1H, d), 4.59-4.56 (1H, m), 4.36 (2H, s), 3.54 (2H, s), 2.90-2.85 (1H, m), 2.77-2.67 (3H, m), 1.08 (3H, s), 1.05 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 433, [M+Na]⁺ 455, [M-H]⁻ 431.

Example 16 : 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-phenethyl-acetamide

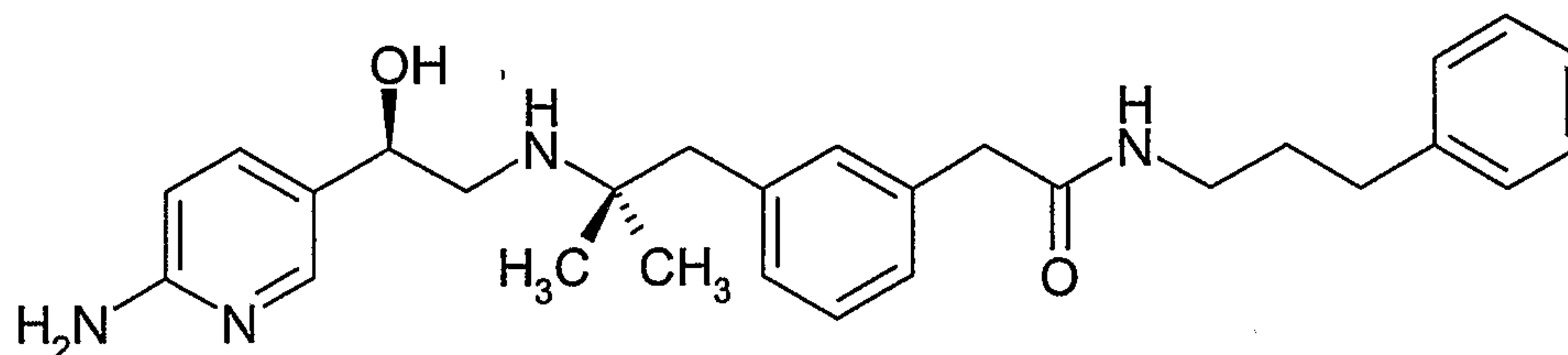


Prepared from 2-[3-(2-{(2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino}-2-methyl-propyl)-phenyl]-*N*-phenethyl-acetamide (preparation 16) according to the method for example 1 to give the title compound as a colourless foam.

¹H NMR (400MHz, CD₃OD): δ = 7.91-7.89 (1H, m), 7.51-7.49 (1H, m), 7.24-7.05 (9H, m), 6.58 (1H, d), 4.60-4.57 (1H, m), 3.44 (2H, s), 3.42-3.38 (2H, m), 2.90-2.85 (1H, m), 2.77-2.66 (6H, m), 1.08 (3H, s), 1.05 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 447, $[M+Na]^+$ 469, $[M-H]^-$ 445.

Example 17 : 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(3-phenyl-propyl)-acetamide

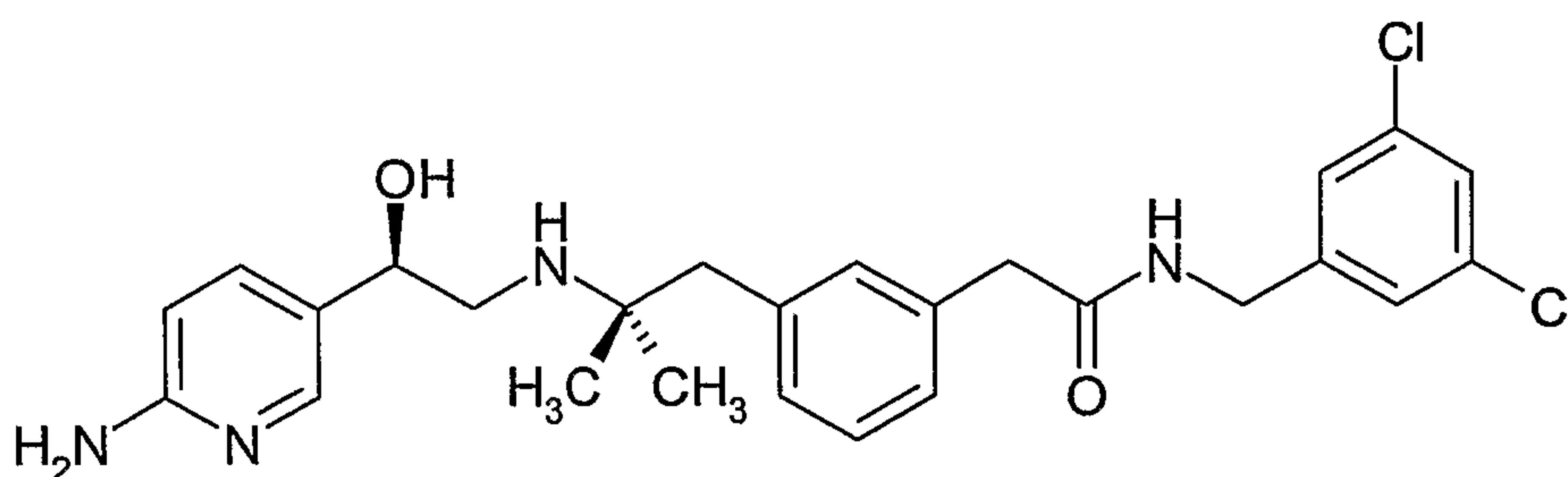


- 5 Prepared from 2-[3-(2-{(2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino}-2-methyl-propyl)-phenyl]-*N*-(3-phenyl-propyl)-acetamide (preparation 17) according to the method for example 1 to give the title compound as a colourless foam.

^1H NMR (400MHz, CD_3OD): δ = 7.88 (1H, s), 7.49-7.47 (1H, m), 7.24-7.11 (8H, m), 7.06-7.04 (1H, m), 6.56 (1H, d), 4.58-4.55 (1H, m), 3.47 (2H, s), 3.18 (2H, t), 2.88-2.83 (1H, m), 2.75-2.65 (3H, m), 2.59-2.55 (2H, m), 1.81-1.74 (2H, m), 1.06 (3H, s), 1.03 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 461, $[M+Na]^+$ 483, $[M-H]^-$ 459.

Example 18 : 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(3,5-dichloro-benzyl)-acetamide



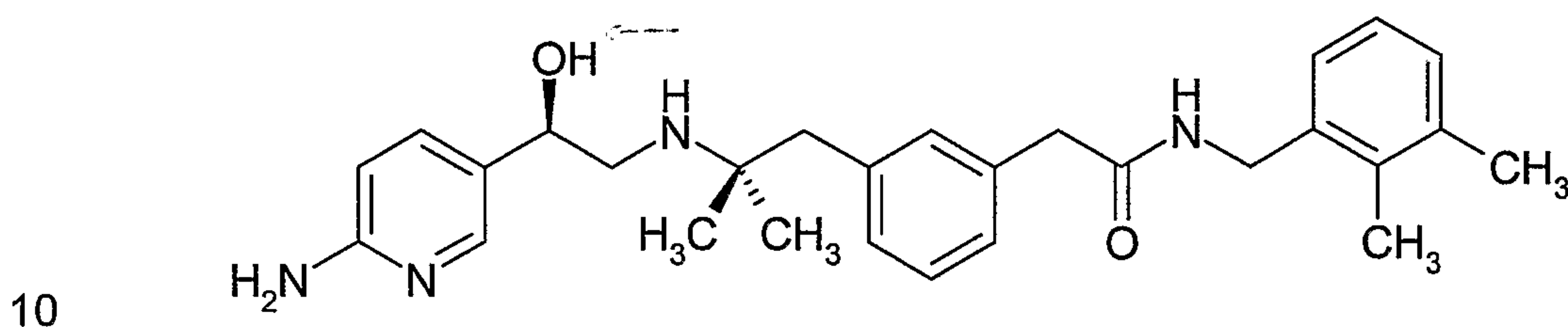
Prepared from *N*-(3,5-Dichloro-benzyl)-2-[3-(2-{(2*R*)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino}-2-methyl-propyl)-phenyl]-acetamide

(preparation 18) according to the method for example 1 to give the title compound as a colourless foam.

¹H NMR (400MHz, CD₃OD): δ = 7.87 (1H, s), 7.49-7.47 (1H, m), 7.26-7.12 (7H, m), 6.56 (1H, d), 4.59-4.56 (1H, m), 4.32 (2H, s), 3.55 (2H, s), 2.90-2.85 (2H, m), 2.77-2.66 (2H, m), 1.07 (3H, s), 1.04 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 501 / 503, [M+Na]⁺ 523 / 525, [M-H]⁻ 499 / 501.

Example 19 : 2-(3-{2-[(2R)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(3,4-dimethyl-benzyl)-acetamide

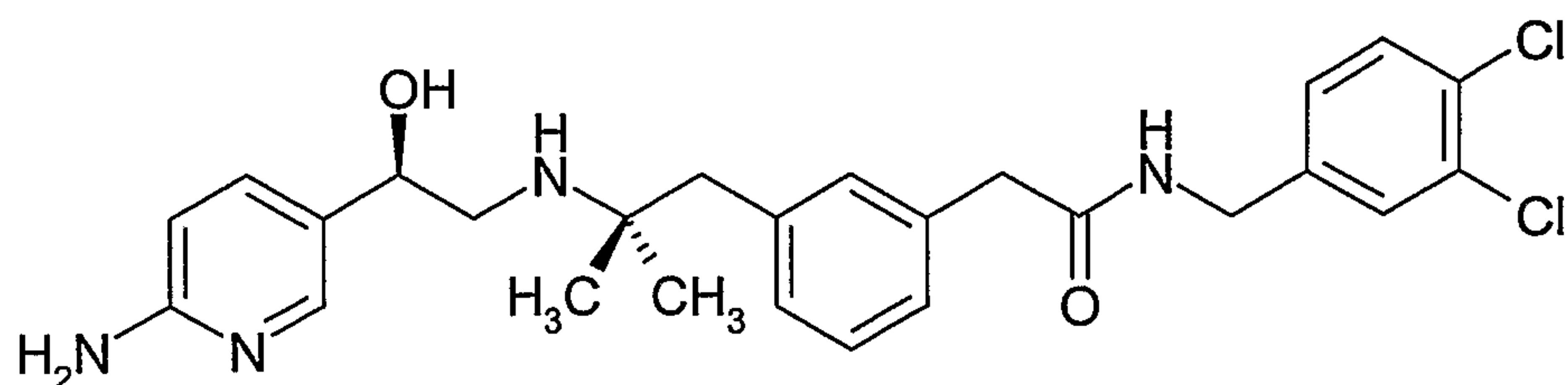


Prepared from *N*-(3,4-Dimethyl-benzyl)-2-[3-(2-{(2R)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino}-2-methyl-propyl)-phenyl]-acetamide (preparation 19) according to the method for example 1 to give the title compound as a colourless foam.

15 ¹H NMR (400MHz, CD₃OD): δ = 7.87 (1H, s), 7.49-7.47 (1H, m), 7.22-7.13 (3H, m), 7.05-6.95 (4H, m), 6.56 (1H, d), 4.58-4.55 (1H, m), 4.36 (2H, s), 3.51 (2H, s), 2.89-2.84 (1H, m), 2.75-2.65 (3H, m), 2.26 (3H, s), 2.14 (3H, s), 1.06 (3H, s), 1.04 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 461, [M+Na]⁺ 483, [M-H]⁻ 459.

20 **Example 20 : 2-(3-{2-[(2R)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-N-(3,4-dichloro-benzyl)-acetamide**

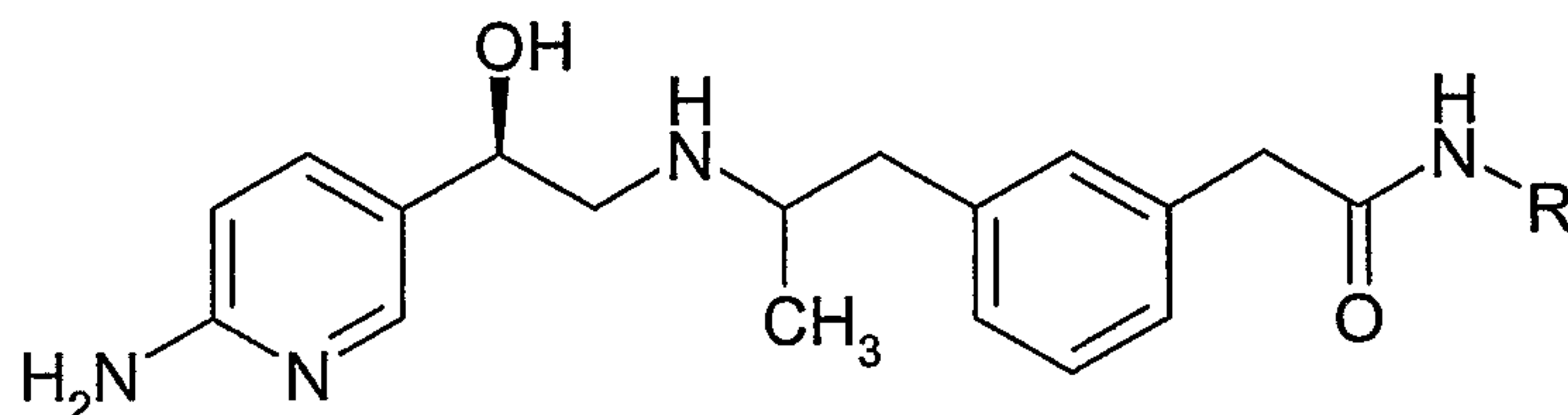


Prepared from *N*-(3,4-Dichloro-benzyl)-2-[3-(2-((2*R*)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-acetamide (preparation 20) according to the method for example 1 to give the title compound as a colourless foam.

¹H NMR (400MHz, CD₃OD): δ = 7.88 (1H, s), 7.49-7.47 (1H, m), 7.39 (1H, d), 7.33 (1H, m), 7.24-7.11 (4H, m), 7.07-7.05 (1H, m), 6.56 (1H, d), 4.59-4.57 (1H, m), 4.32 (2H, s), 3.54 (2H, s), 2.90-2.85 (1H, m), 2.76-2.66 (3H, m), 1.06 (3H, s), 1.04 (3H, s) ppm.

10 LRMS (electrospray) : m/z $[M+H]^+$ 501 / 503, $[M+Na]^+$ 523 / 525, $[M-H]^-$ 499 / 501.

Examples 21-27 (R as defined in table 1)



Prepared using the method for preparation 1 using the acid from preparation 30
15 and the appropriate amine to give amides, which were subjected to the
conditions for example 1 without purification. Purification by HPLC :

Column: Phenomenex Luna C18, 10um, 150x10mm id, ambient temperature

Eluent A: 0.05% diethylamine in water Eluent B: Acetonitrile

Sample solvent: 90% dimethyl sulfoxide in water.

Gilson LC Pump Gradient Timetable Gilson 119 uv detector / Collect 225 (nm)

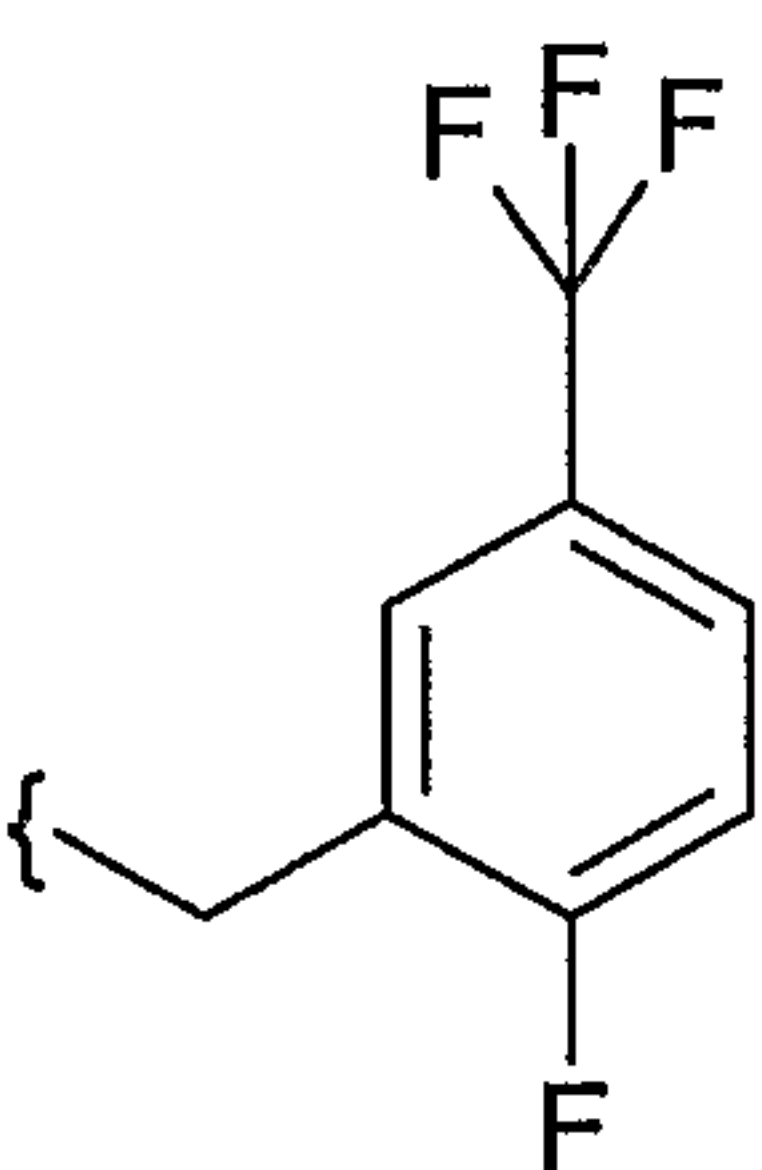
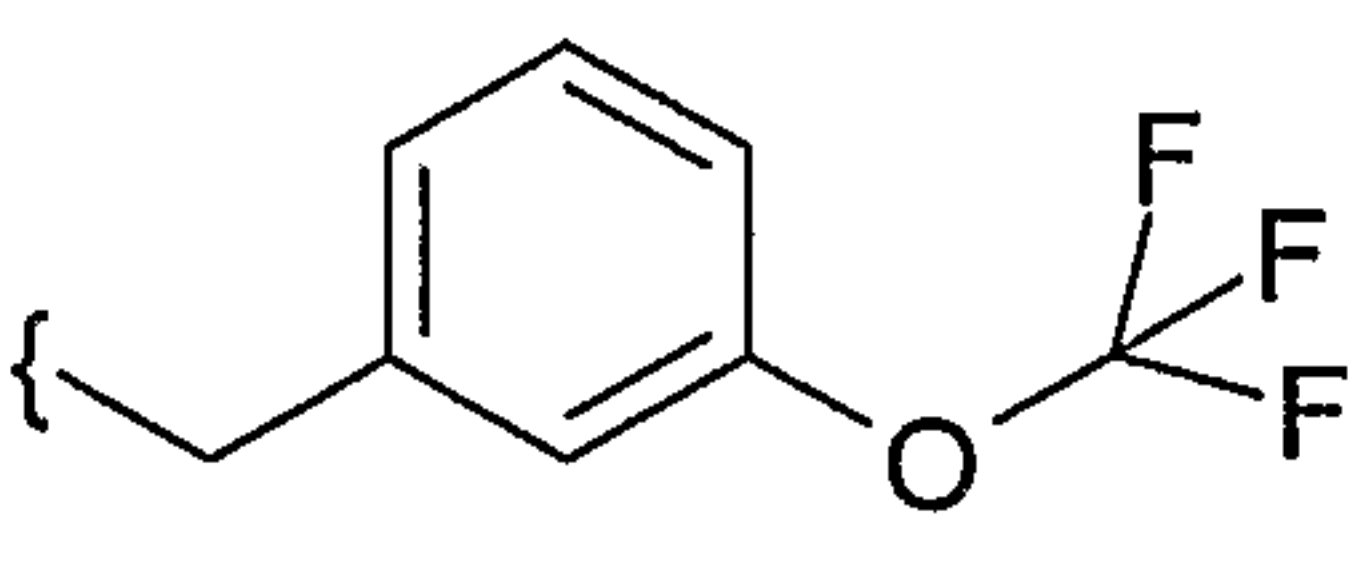
	Time	A%	B%	Flow (ml/min)
	0.00	80.0	20.0	6.000
5	0.20	80.0	20.0	6.000
	7.00	5.0	95.0	6.000
	9.00	5.0	95.0	6.000
	9.10	80.0	20.0	6.000
	10.50	80.0	20.0	6.000

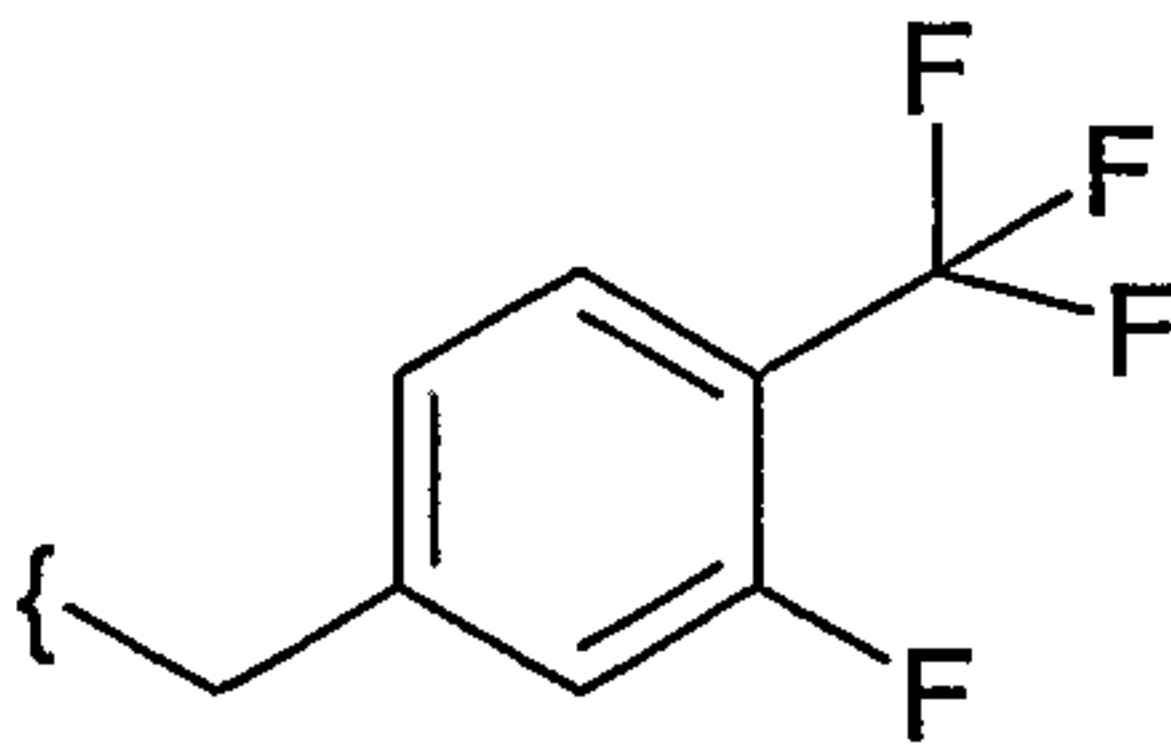
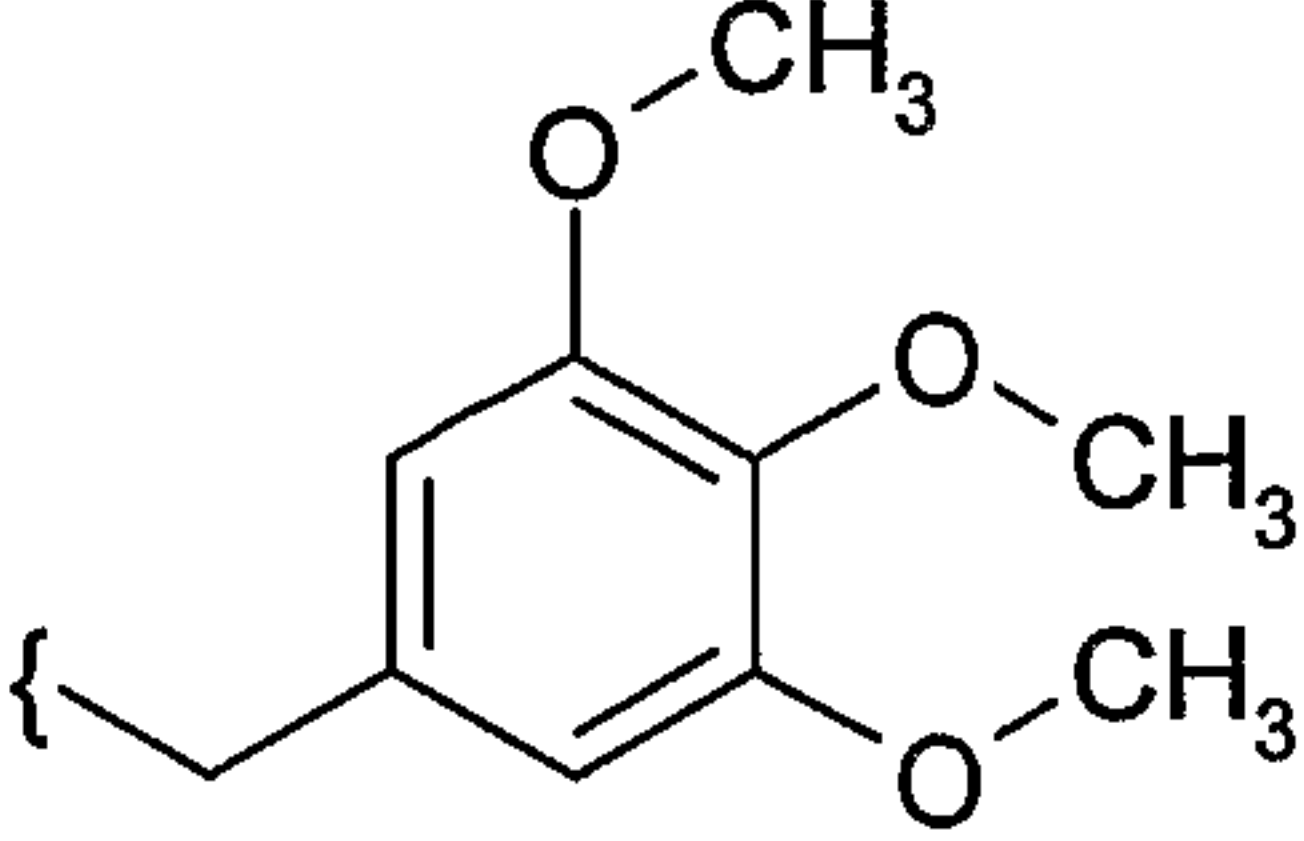
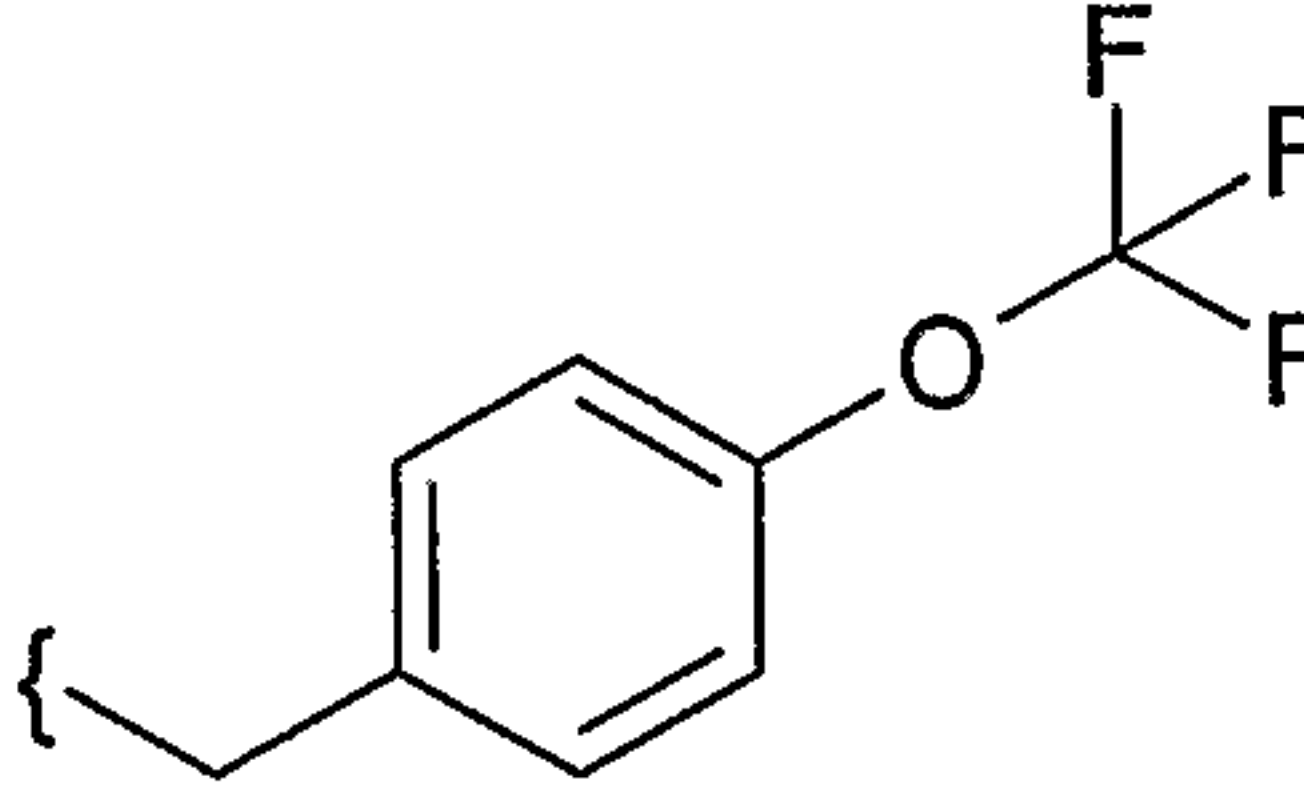
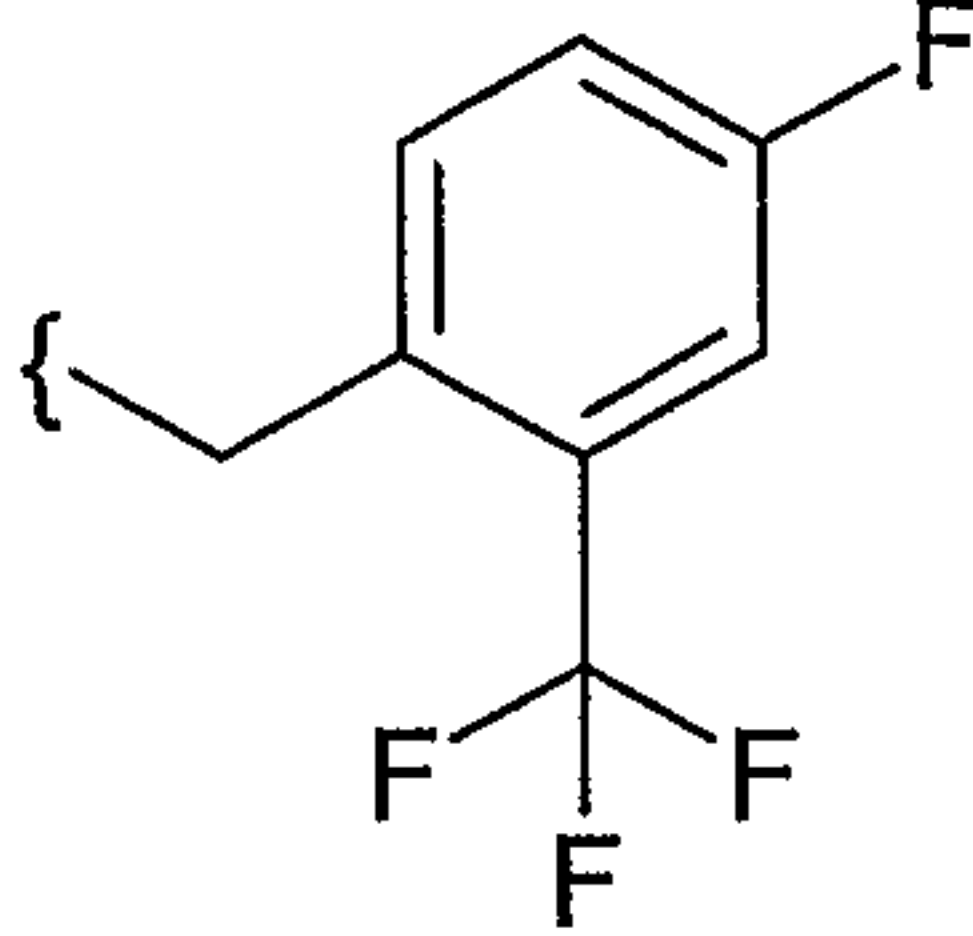
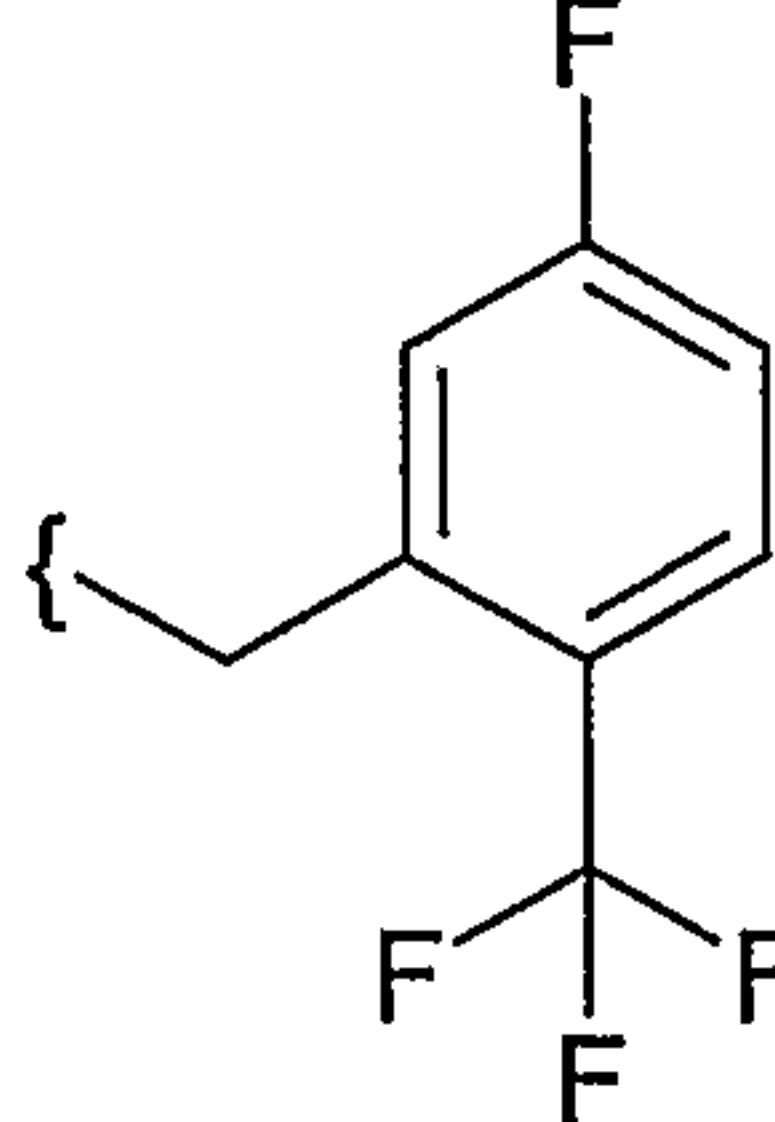
10 Dual sensitivity 200 / Peak sensitivity 60 / Peak width 0.3 min.

Gilson Autosampler Injection Vol(ul) - 550.00

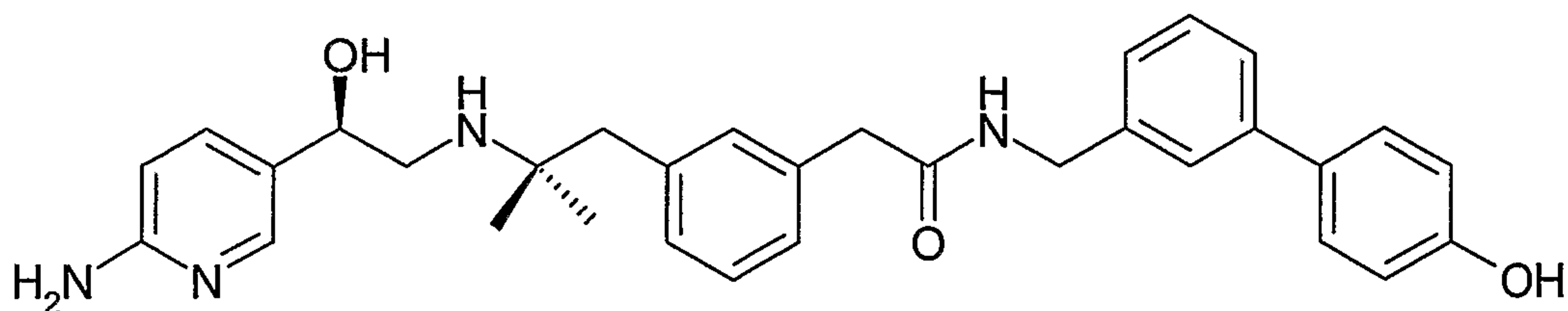
gave the title compounds.

Table 1

Example	R	Retention time (min)	LRMS (electrospray)	
			[M+H] ⁺	[M-H] ⁻
21		5.91	505	503
22		5.97	503	501

23		5.9	505	503
24		4.76	509	507
25		5.95	503	501
26		5.84	505	503
27		5.79	505	503

Example 28 : 2-(3-((2R)-2-[2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl)phenyl)-N-(4'-hydroxybiphenyl-3-ylmethyl)acetamide

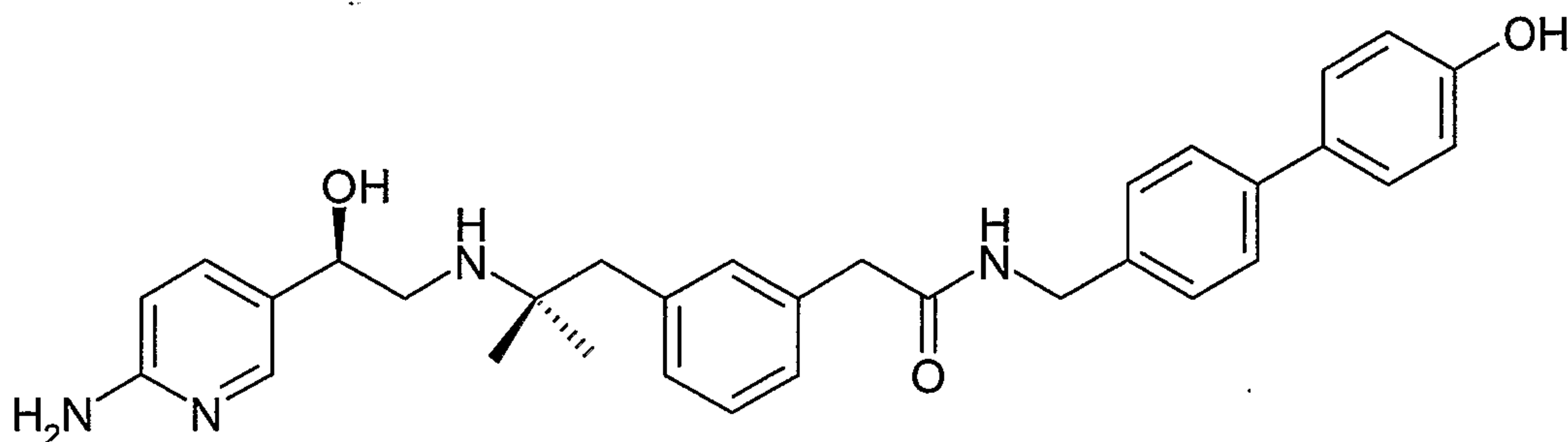


Prepared according to the method described for example 1 using the amide from preparation 48 to give the title compound as a light brown solid.

¹H NMR (400MHz, CD₃OD): δ = 7.86 (1H, m), 7.45 (1H, dd), 7.27-7.40 (5H, m),
 5 7.17-7.24 (2H, m), 7.11-7.13 (2H, m), 7.03-7.05 (1H, m), 6.79-6.83 (2H, m),
 6.54 (1H, d), 4.53 (1H, dd), 4.41 (2H, s), 3.54 (2H, s), 2.80 (1H, dd), 2.59-2.70
 (3H, m), 1.01 (3H, s), 0.98 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 525, [M+Na]⁺ 547.

**Example 29 : 2-(3-((2R)-2-[2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]-2-
 10 methylpropyl)phenyl)-N-(4'-hydroxybiphenyl-4-ylmethyl)acetamide**

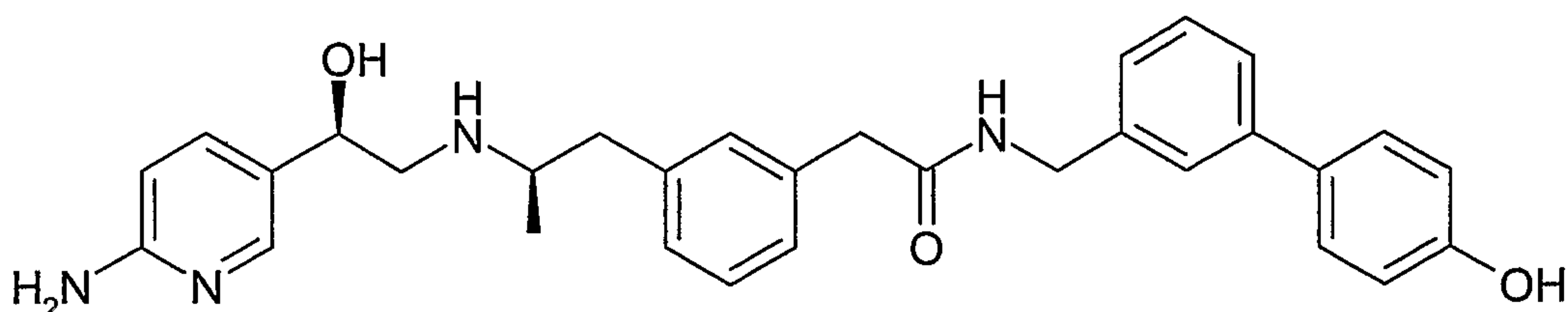


Prepared according to the method described for example 1 using the amide from preparation 49 to give the title compound as a pink foam.

¹H NMR (400MHz, CD₃OD): δ = 7.87 (1H, d), 7.39-7.48 (5H, m), 7.14-7.26 (5H,
 15 m), 7.05-7.07 (1H, m), 6.81-6.85 (2H, m), 6.55 (1H, d), 4.54 (1H, dd), 4.37 (2H,
 s), 3.54 (2H, s), 2.83-2.88 (1H, m), 2.65-2.76 (3H, m), 1.05 (3H, s), 1.02 (3H, s)
 ppm.

LRMS (electrospray) : m/z [M+H]⁺ 525, [M+Na]⁺ 547.

Example 30 : 2-(3-{(2*R*)-2-[(2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]propyl}phenyl)-*N*-(4'-hydroxy-biphenyl-3-ylmethyl)acetamide

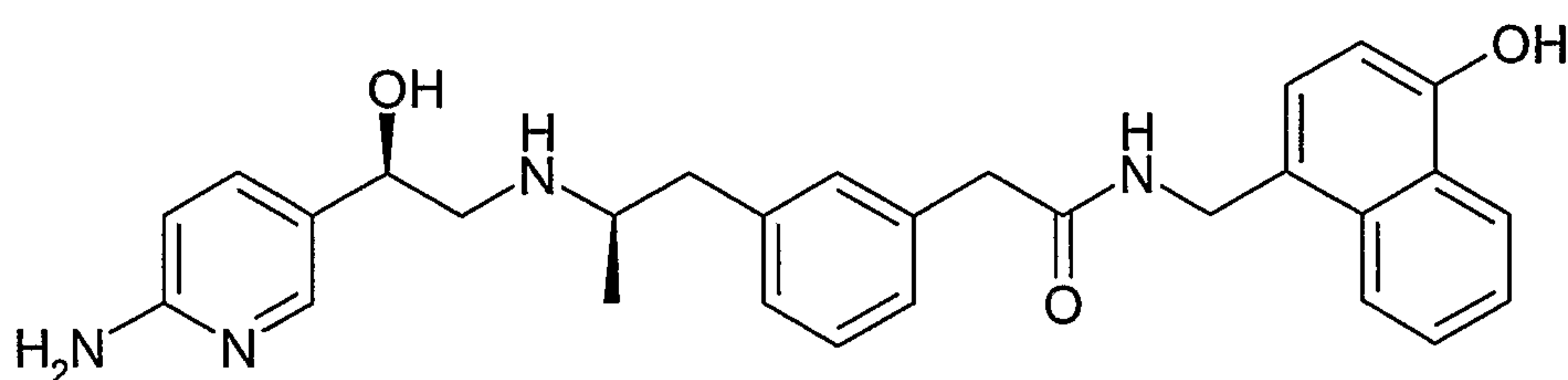


5 Prepared according to the method described for example 1 using the amide from preparation 50 to give the title compound as a colourless foam.

¹H NMR (400MHz, CD₃OD): δ = 7.76 (1H, d), 7.27-7.41 (6H, m), 7.09-7.22 (4H, m), 7.00-7.03 (1H, m), 6.79-6.83 (2H, m), 6.47 (1H, d), 4.48 (1H, dd), 4.40 (2H, s), 3.53 (2H, s), 2.79-2.88 (2H, m), 2.59 (2H, dd), 2.50-2.55 (1H, m), 1.00 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 511, [M+Na]⁺ 533.

Example 31 : 2-(3-{(2*R*)-2-[(2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]propyl}phenyl)-*N*-(4-hydroxynaphthalen-1-ylmethyl)acetamide



15

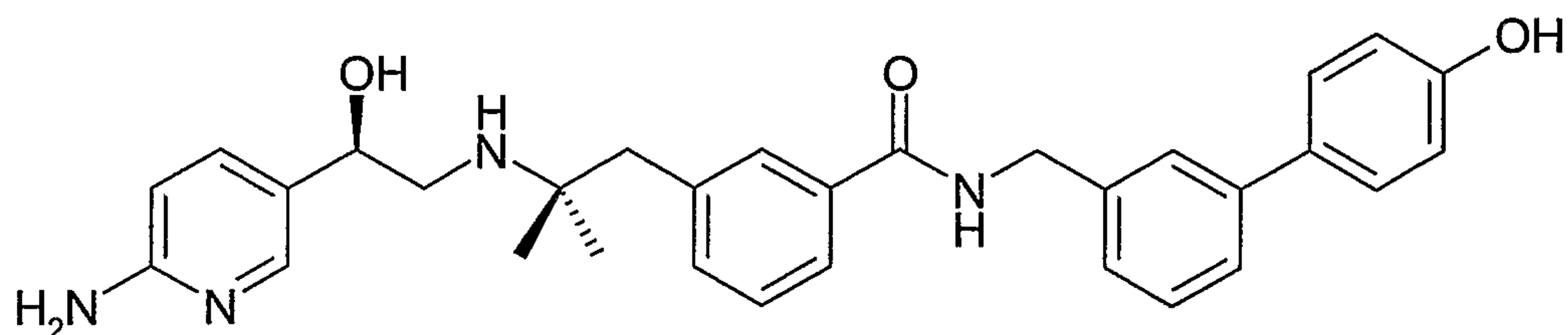
Prepared according to the method described for example 1 using the amide from preparation 57 to give the title compound as a light brown solid.

¹H NMR (400MHz, CD₃OD): δ = 8.17-8.20 (1H, m), 7.81-7.83 (1H, m), 7.71 (1H, d), 7.36-7.38 (2H, m), 7.7.28 (1H, dd), 7.18 (1H, d), 7.09-7.13 (2H, m), 6.92-

6.94 (2H, m), 6.68 (1H, d), 6.43 (1H, d), 4.65 (2H, d), 4.44 (1H, dd), 3.43 (2H, s), 2.71-2.79 (2H, m), 2.53-2.58 (2H, m), 2.43-2.48 (1H, m), 0.95 (3H, d) ppm.

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

Example 32 : 3-{2-[(2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}-*N*-(4'-hydroxybiphenyl-3-ylmethyl)benzamide

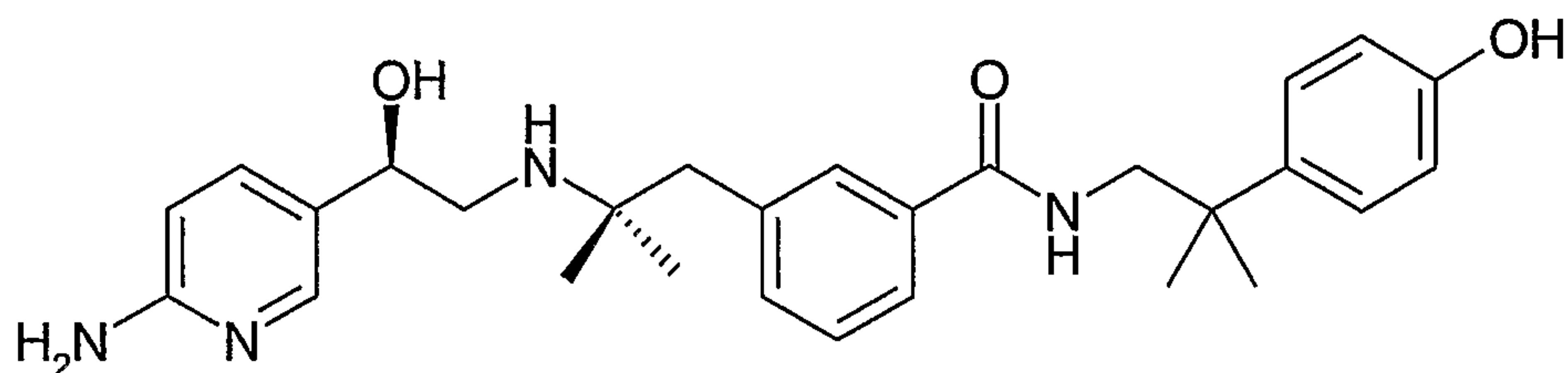


Prepared according to the method described for example 1 using the amide from preparation 52 to give the title compound as an off-white solid.

^1H NMR (400MHz, CD_3OD): δ = 7.86 (1H, d), 7.71-7.75 (2H, m), 7.53 (1H, bs), 7.33-7.46 (7H, m), 7.25-7.27 (1H, d), 6.81-6.85 (2H, m), 6.49 (1H, d), 4.57 (1H, dd), 4.56 (2H, dd), 2.87-2.95 (2H, m), 2.69-2.74 (2H, m), 1.11 (3H, s), 1.05 (3H, s) ppm.

LRMS (APCI) : m/z $[M+H]^+$ 511, $[M+Na]^+$ 533.

Example 33 : 3-{(2*R*)-2-[2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-*N*-[2-(4-hydroxy-phenyl)-2-methyl-propyl]-benzamide

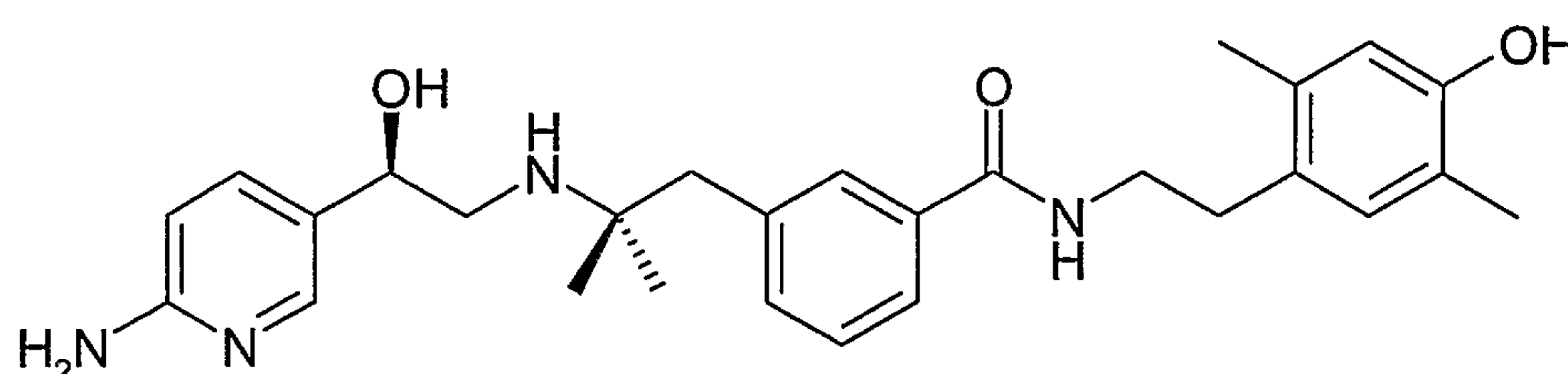


Prepared according to the method described for example 1 using the amide from preparation 53 to give the title compound as a light brown solid.

^1H NMR (400MHz, CD_3OD): δ = 7.87 (1H, d), 7.53-7.55 (1H, m), 7.48-7.51 (2H, m), 7.32-7.33 (2H, m), 7.24 (2H, dd), 6.72 (2H, dd), 6.56 (1H, d), 4.55 (1H, dd), 3.51 (2H, s), 2.80-2.92 (2H, m), 2.70-2.74 (2H, m), 1.33 (6H, s), 1.08 (3H, s), 1.04 (3H, s) ppm.

5 LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 477.

Example 34 : 3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}-*N*-[2-(4-hydroxy-2,5-dimethylphenyl)ethyl]benzamide

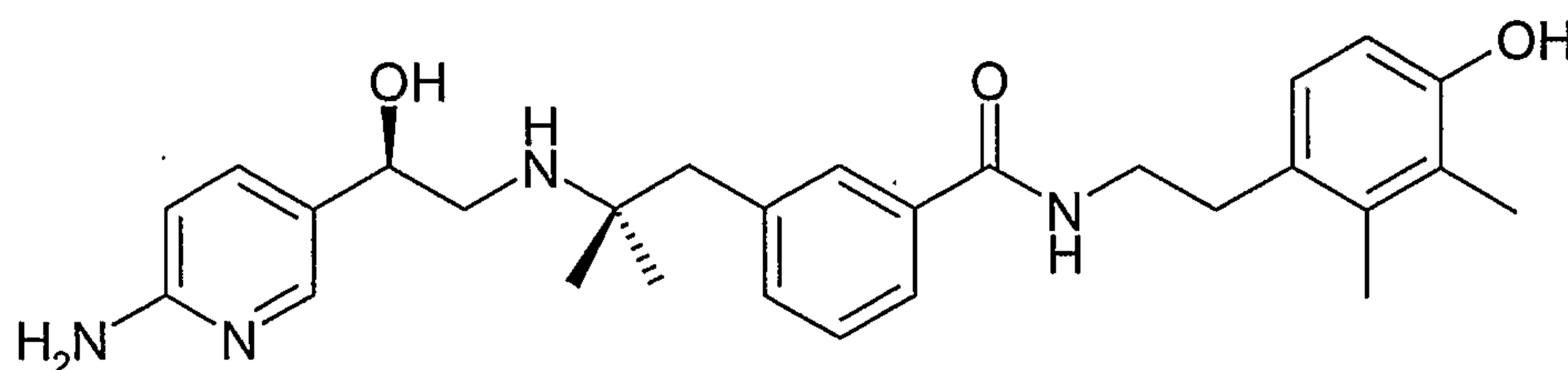


Prepared according to the method described for example 1 using the amide
10 from preparation 54 to give the title compound as a colourless solid.

^1H NMR (400MHz, CD_3OD): δ = 7.89 (1H, d), 7.62-7.67 (2H, m), 7.83-7.89 (2H, m), 6.83 (1H, s), 6.57 (1H, d), 6.53 (1H, s), 4.57 (1H, dd), 3.44-3.48 (2H, m), 2.87-2.97 (2H, m), 2.70-2.80 (4H, m), 2.21 (3H, s), 2.08 (3H, s), 1.11 (3H, s), 1.04 (3H, s) ppm.

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

Example 35 : 3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}-*N*-[2-(4-hydroxy-2,3-dimethylphenyl)ethyl]benzamide

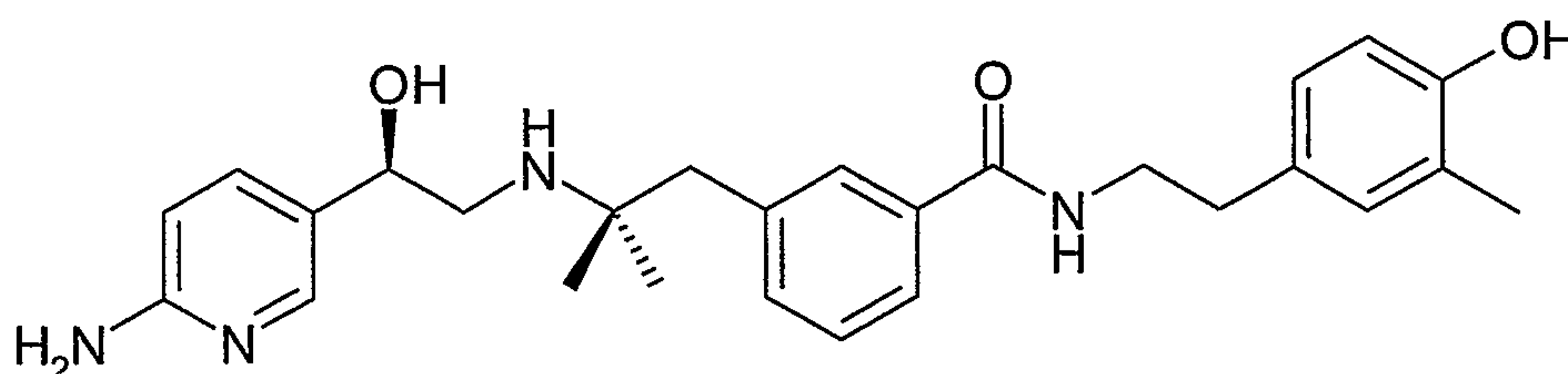


Prepared according to the method described for example 1 using the amide
20 from preparation 55 to give the title compound as a colourless solid.

^1H NMR (400MHz, CD_3OD): δ = 1.05 (3H, s), 1.12 (3H, s), 2.12 (3H, s), 2.23 (3H, s), 2.70-2.75 (2H, m), 2.83-2.99 (4H, m), 2.45-2.48 (2H, m), 4.68-4.51 (1H, m), 6.53-6.59 (2H, m), 6.80 (1H, d), 7.33-7.41 (2H, m), 7.51 (1H, dd), 7.62-7.67 (2H, m), 7.90 (1H, d) ppm.

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

Example 36 : 3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}-*N*-[2-(4-hydroxy-2-methylphenyl)ethyl]benzamide

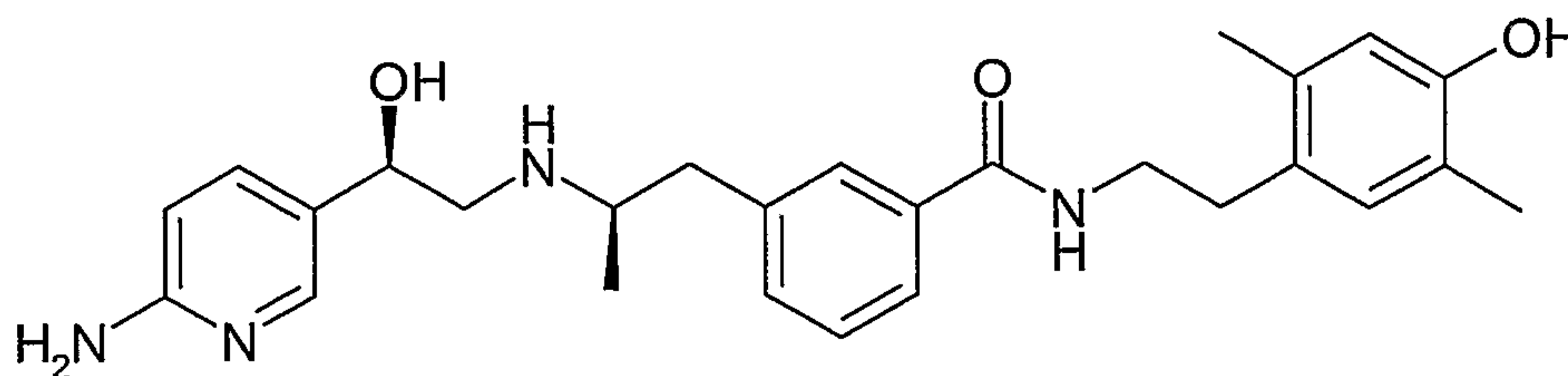


Prepared according to the method described for example 1 using the amide
10 from preparation 56 to give the title compound as a beige coloured foam.

^1H NMR (400MHz, CD_3OD): δ = 1.06 (3H, s), 1.13 (3H, s), 2.14 (3H, s), 2.72-2.79 (4H, m), 2.87-2.98 (2H, m), 3.46-3.64 (2H, m), 4.69 (1H, dd), 6.57 (1H, d), 6.64 (1H, d), 6.85 (1H, dd), 6.93 (1H, d), 7.33-7.39 (2H, m), 7.60 (1H, dd), 7.61 (1H, bs), 7.63 (1H, dt), 7.89 (1H, d) ppm.

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

Example 37 : 3-{2-[(2*R*)-2-[(2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]propyl]-*N*-[2-(4-hydroxy-2,5-dimethylphenyl)ethyl]benzamide

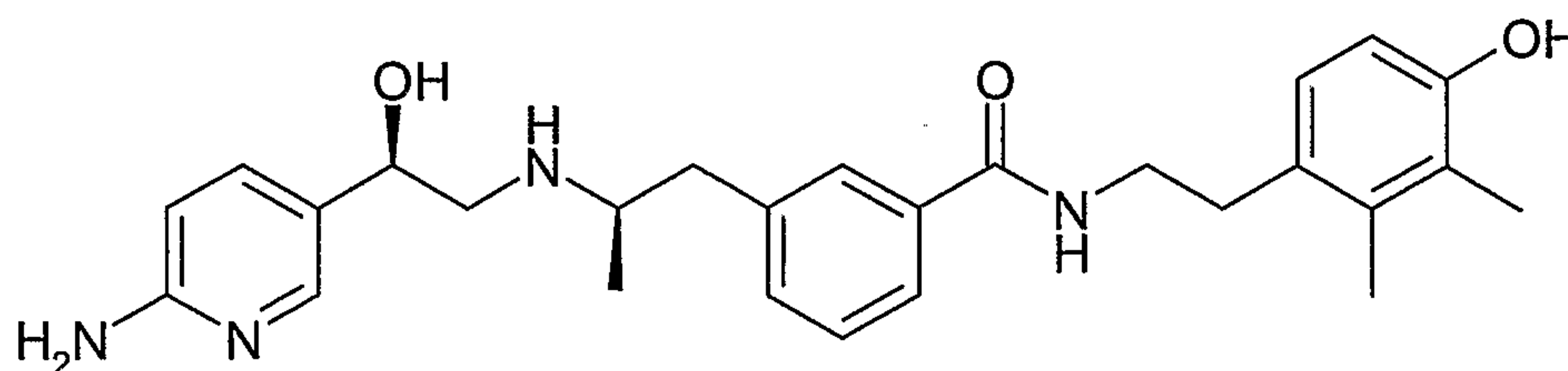


Prepared according to the method described for example 1 using the amide from preparation 57 to give the title compound as an off-white solid.

¹H NMR (400MHz, CD₃OD): δ = 7.80 (1H, d), 7.60-7.62 (1H, m), 7.57-7.58 (1H, m), 7.39 (1H, dd), 7.29-7.36 (2H, m), 6.55 (1H, s), 6.50 (1H, d), 4.54 (1H, dd),
5 3.46-3.50 (2H, m), 2.96 (1H, q), 2.78-2.90 (4H, m), 2.61-2.72 (2H, m), 2.24 (3H, s), 2.09 (3H, s), 1.07 (3H, d) ppm.

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

Example 38 : 3-((2*R*)-2-((2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino)propyl)-*N*-[2-(4-hydroxy-2,3-
10 **dimethylphenyl)ethyl]benzamide**

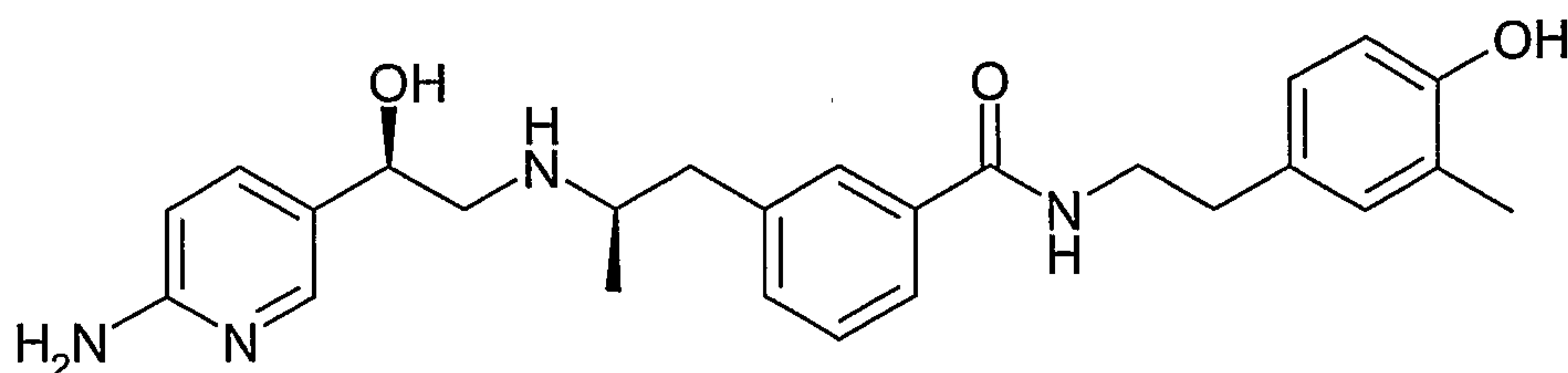


Prepared according to the method described for example 1 using the amide from preparation 58 to give the title compound as a pale pink foam.

¹H NMR (400MHz, CD₃OD): δ = 1.08 (3H, d), 2.13 (3H, s), 2.26 (3H, s), 2.61
15 (1H, dd), 2.70 (1H, dd), 2.79-2.81 (4H, m), 2.98 (1H, q), 3.46-3.49 (2H, s), 4.55 (1H, dd), 6.50 (1H, d), 6.54 (1H, d), 6.81 (1H, d), 7.29-7.86 (2H, m), 7.89 (1H, dd), 7.58 (1H, bs), 7.60 (1H, dt), 7.80 (1H, d) ppm.

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

Example 39 : 3-((2*R*)-2-((2*R*)-2-(6-Aminopyridin-3-yl)-2-
20 **hydroxyethylamino)propyl)-*N*-[2-(4-hydroxy-2-methylphenyl)ethyl]benzamide**



Prepared according to the method described for example 1 using the amide from preparation 59 to give the title compound as a beige coloured foam.

^1H NMR (400MHz, CD_3OD): δ = 1.08 (3H, d), 2.15 (6H, s), 2.62 (1H, dd), 2.70-2.92 (5H, m), 2.98 (1H, q), 3.51 (2H, t), 4.55 (1H, dd), 6.50 (1H, d), 6.65 (1H, d), 6.86 (1H, dd), 6.95 (1H, d), 7.28-7.36 (2H, m), 7.39 (1H, dd), 7.56 (1H, bs), 7.59 (1H, dt), 7.80 (1H, d) ppm.

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

Examples 40 to 169 were prepared using the following procedure :

- 10 The acid (150 μl of a 0.2 M solution) in anhydrous dimethylacetamide/3.75 % triethylamine was added to each well of a 96 well polypropylene plate (2 ml volume per well). 225 μl of 0.2 M solutions of the amines in anhydrous dimethylacetamide/3.75 % triethylamine were added to each well, followed by 225 μl of a freshly prepared 0.25 M solution of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate in dimethylacetamide was manually added to each well. The plates were sealed with a Teflon sheet and a rubber gasket and tightly clamped between two aluminium blocks and shaken and heated at 60 $^\circ\text{C}$ for 3 days, then the plate was opened and evaporated to dryness.
- 20 Methanol (200 μl) was added to each well and the plate re-sealed and shaken for 30 min until all residues were dissolved. The plates were re-opened and hydroxylamine hydrochloride (200 μl of a 1.0 M solution) in anhydrous ethanol was added manually to each well. The plate was sealed with a Teflon sheet and a rubber gasket and tightly clamped between two aluminium blocks and shaken and heated to 80 $^\circ\text{C}$ for 16 h, then evaporated to dryness.
- 25

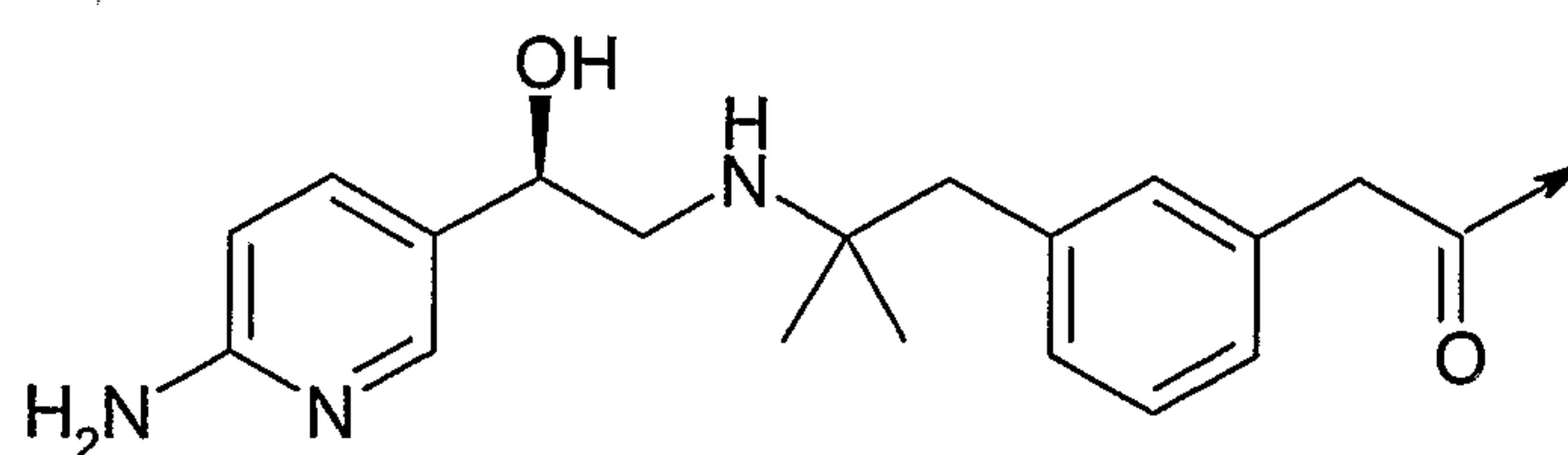
Dimethylsulfoxide (300 μ l) was added to each well and the plate sealed and shaken for 30 min until all residues were dissolved. The plate was opened, water (150 μ l) was manually added and the plate sealed and manually shaken for 1 min.

- 5 Preparative reversed phase chromatography was performed on a Phenomenex Luna C18, 10 μ m HPLC column (150 x 10 mm i.d.) at room temperature. The column flow rate was 8 ml / min. The mobile phase used was a binary acetonitrile / water buffered with 0.05 % (v/v) diethylamine. Initial chromatographic conditions were set to 0 % acetonitrile. Sample separation
- 10 was achieved by increasing the acetonitrile concentration to 70 % over 11.60 minutes with a hold of an additional 0.5 minutes before re-conditioning the column at 0% acetonitrile for a further 2.5 minutes. Fractions were collected by UV trigger based upon 225 nm and 254 nm wavelengths, the Dual sensitivity was set to 200, Peak sensitivity 30, and Peak width 0.3 min.

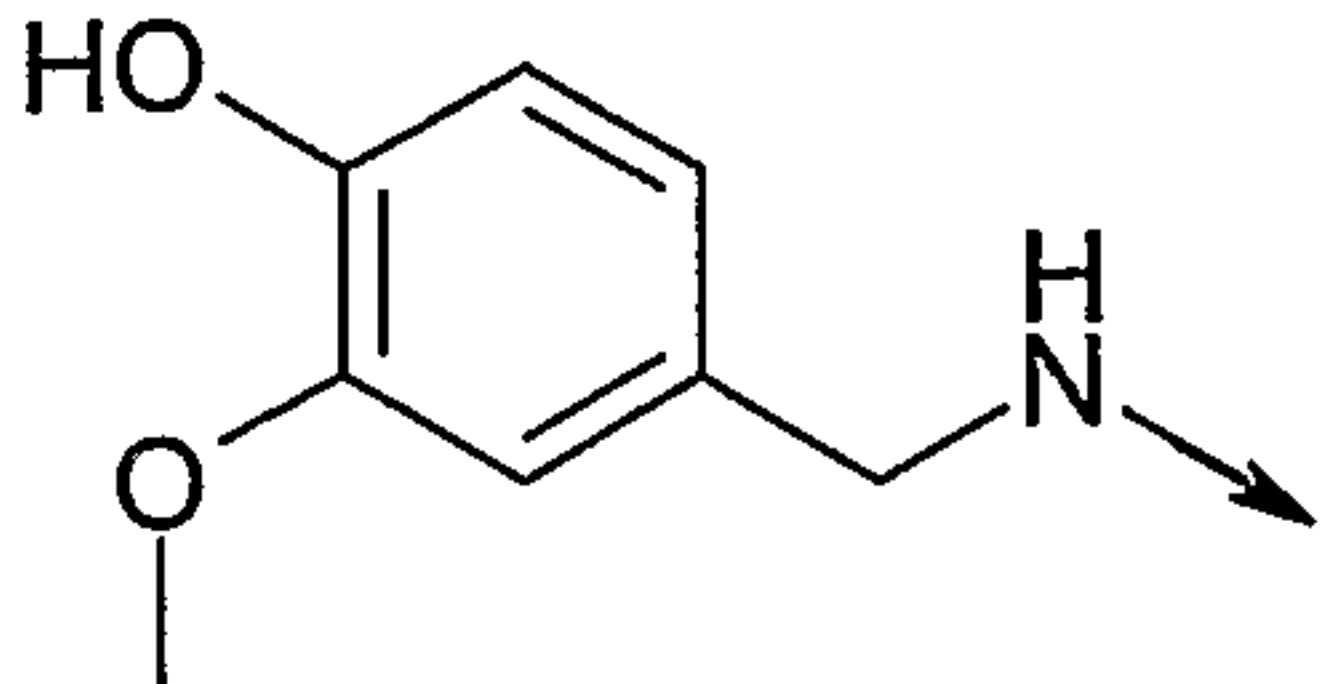
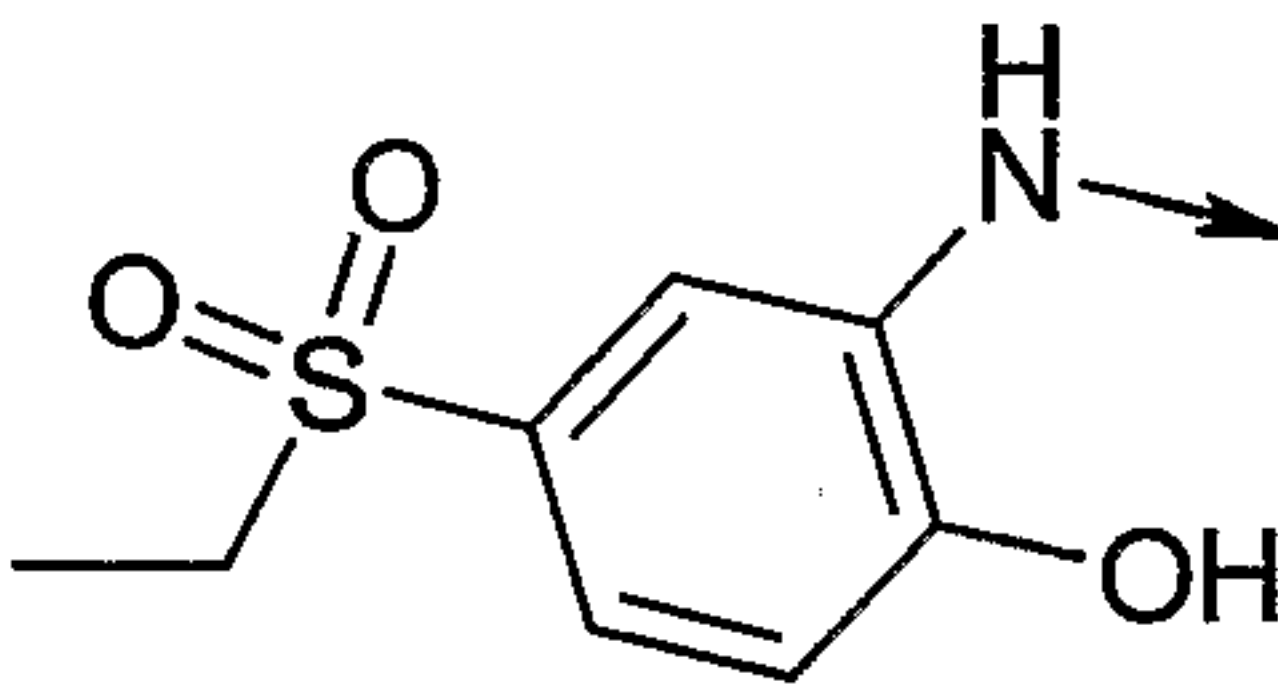
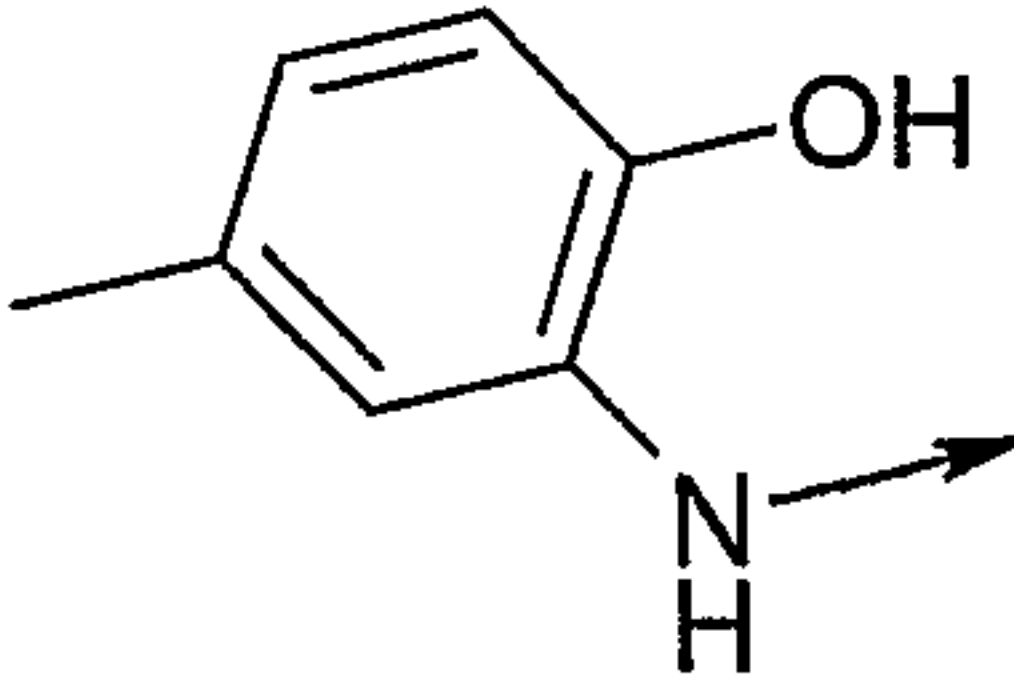
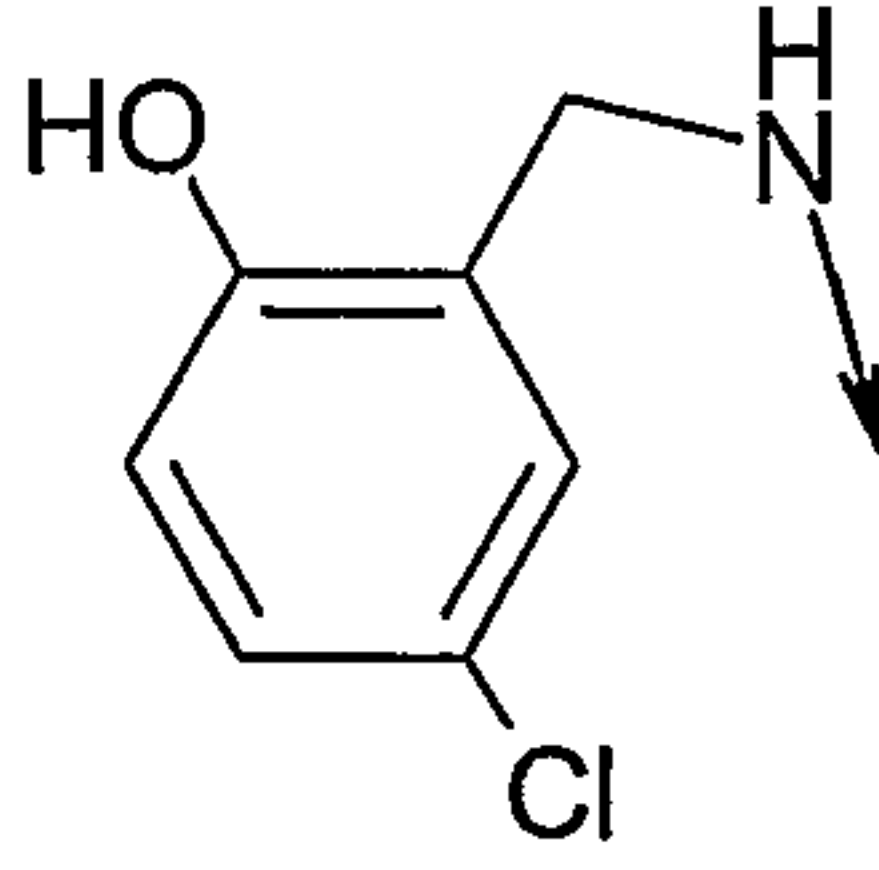
15 **QC Analysis.**

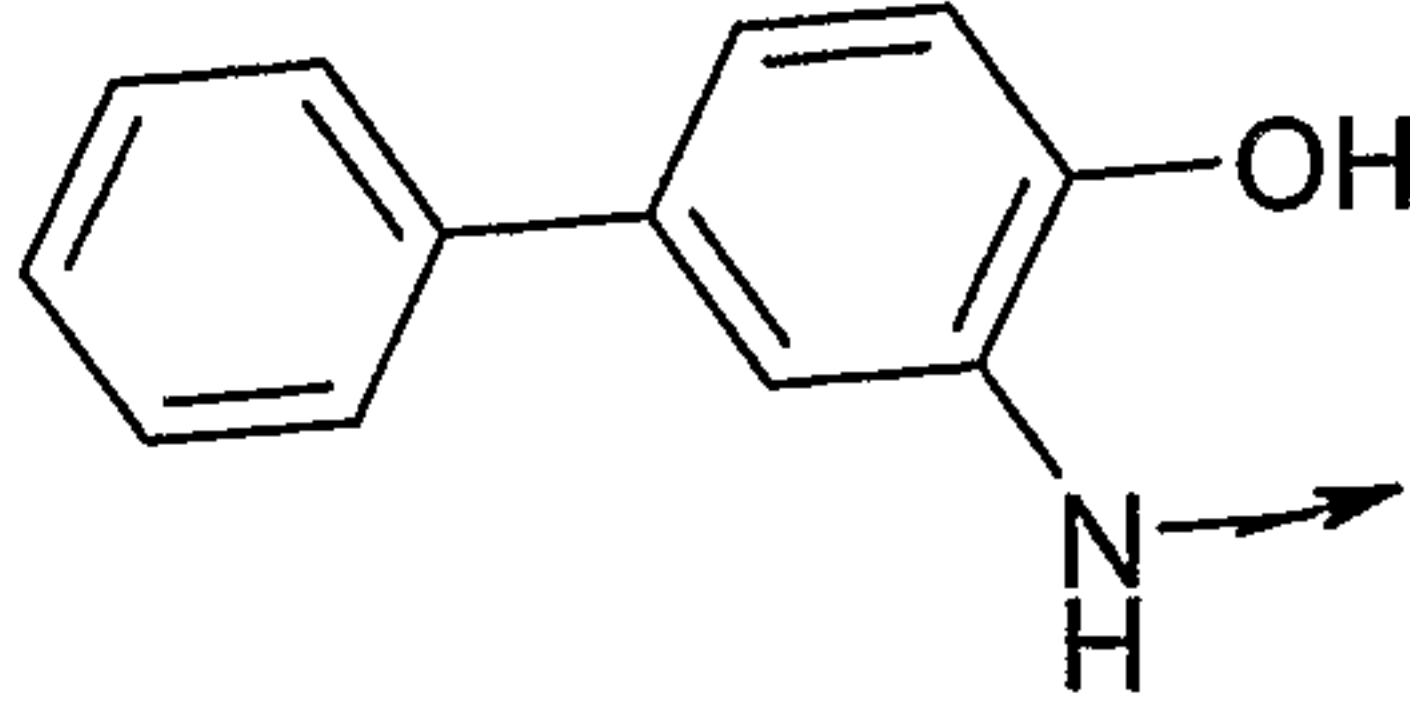
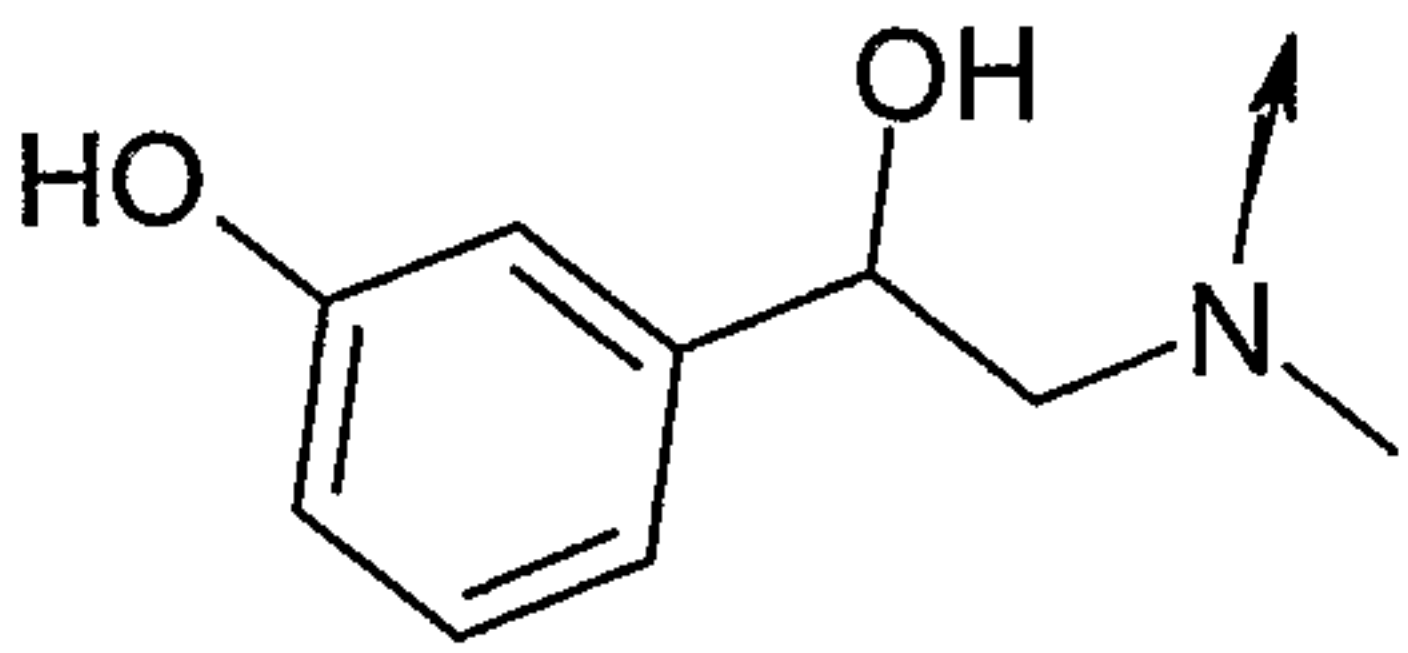
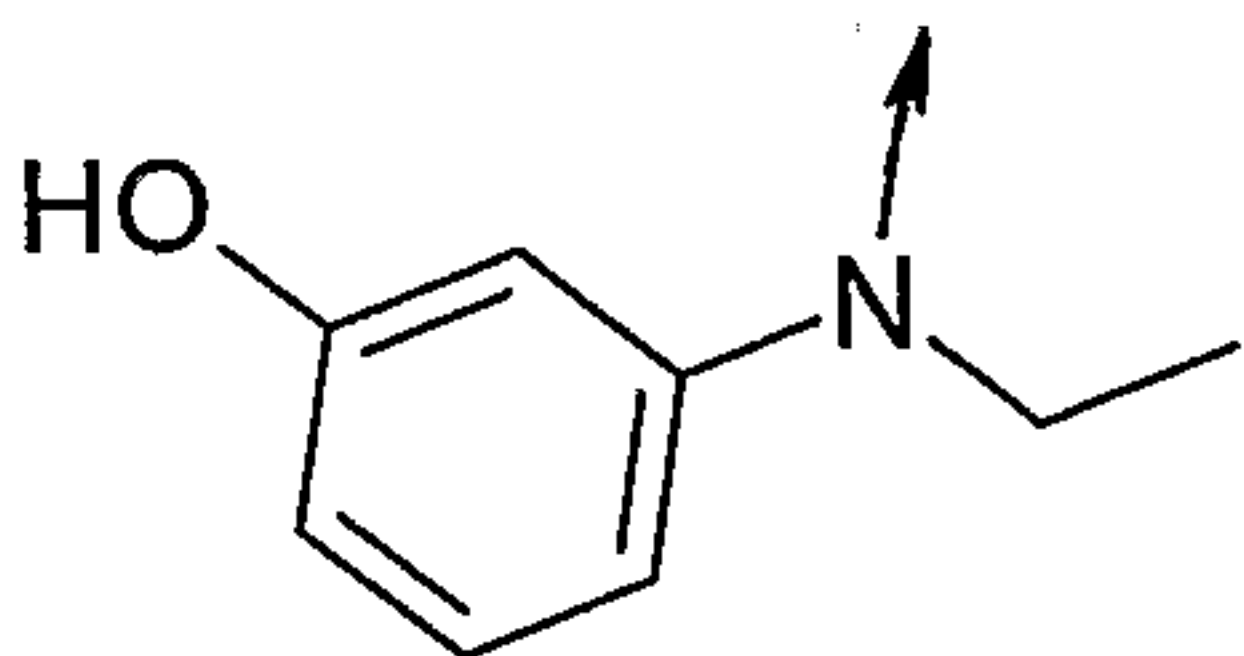
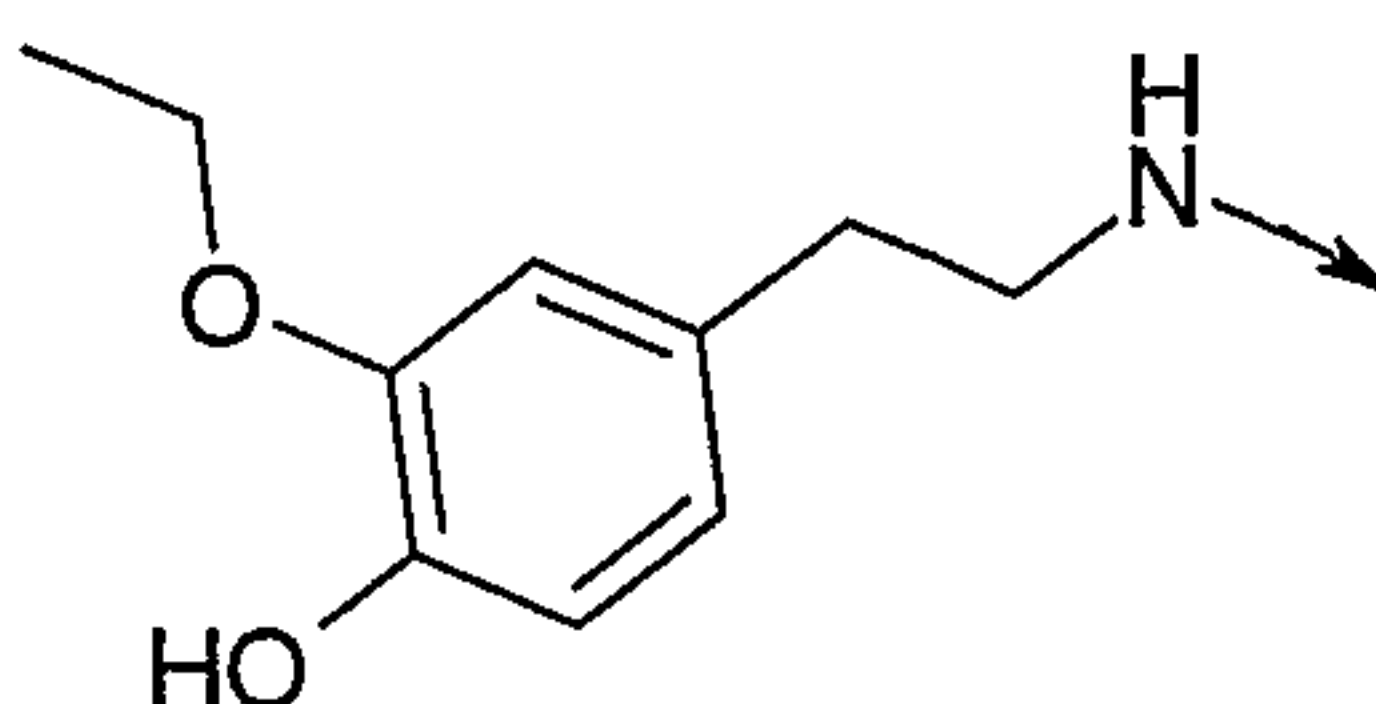
All purified compounds were analysed by LC-MS analysis prior to registration. Two methods of detection were used, UV (DIAD) and ELSD.

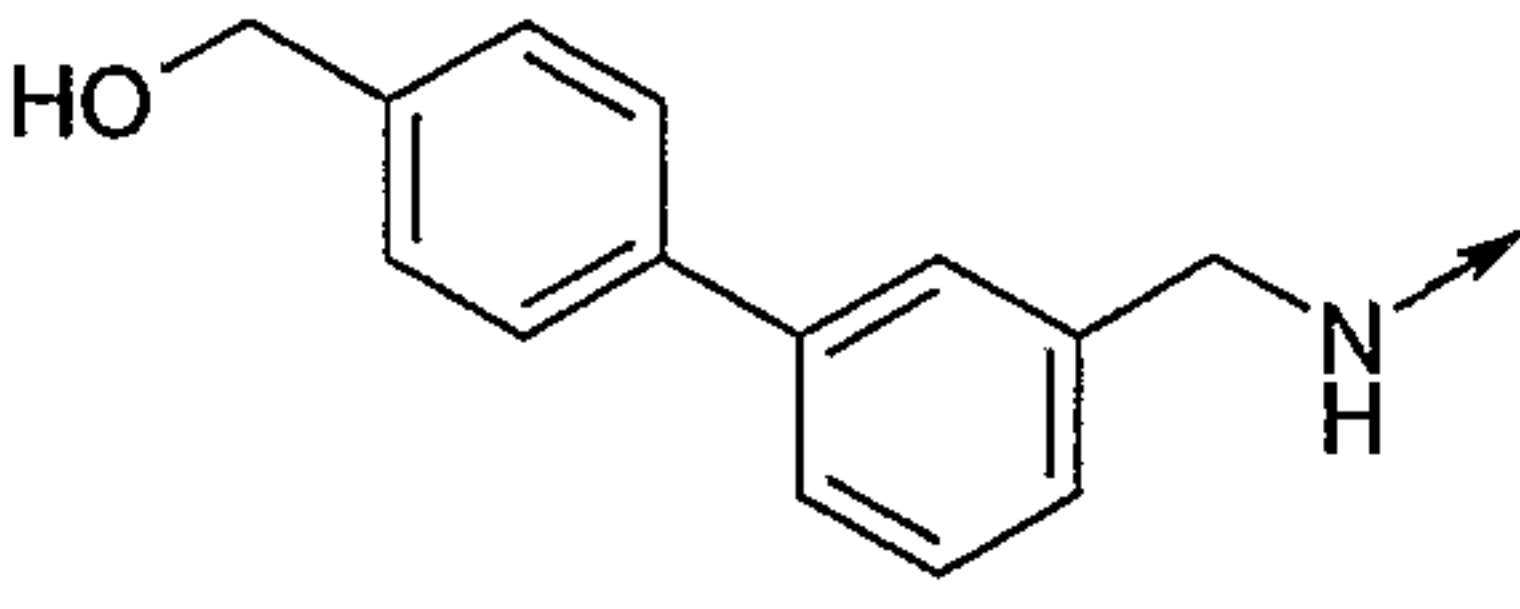
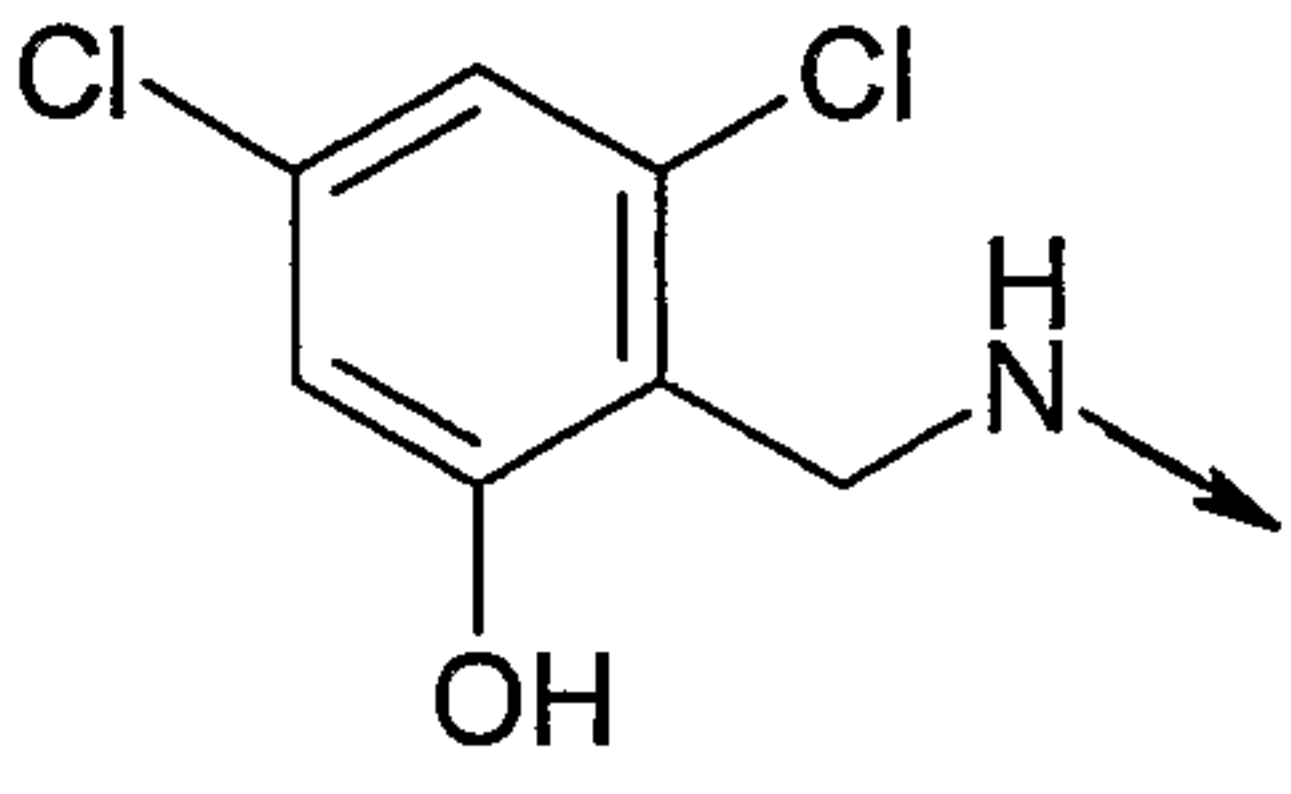
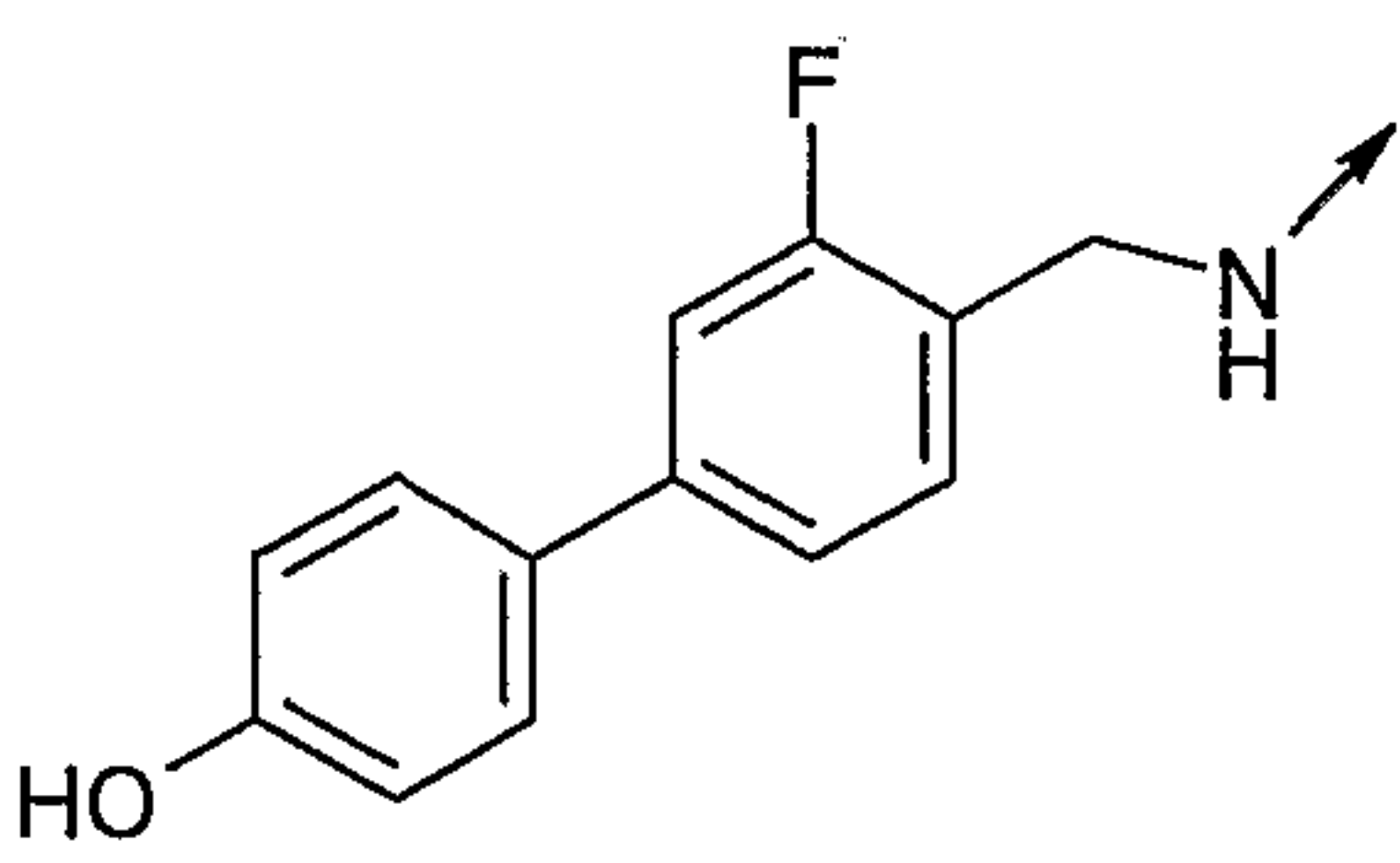
- Analytical reversed phase chromatography was performed on Phenomenex Luna C18, 5 μ m, HPLC column (30 x 4.6 mm id.) at room temperature using a
- 20 Waters 1525 binary LC Pump. The column flow rate was 2.5 ml / min. The mobile phase used was a binary acetonitrile / water buffered with 0.05 % (v/v) ammonium acetate. Initial chromatographic conditions were set to 5 % acetonitrile. The gradient timetable was achieved by increasing the acetonitrile concentration to 95 % over 3 minutes with a hold of an additional 0.5 minutes
- 25 before re-conditioning the column at 5% acetonitrile for a further 1.0 minute. A Waters 2488 dual wavelength detector was used detecting dual wavelengths of 225 nm and 254 nm.

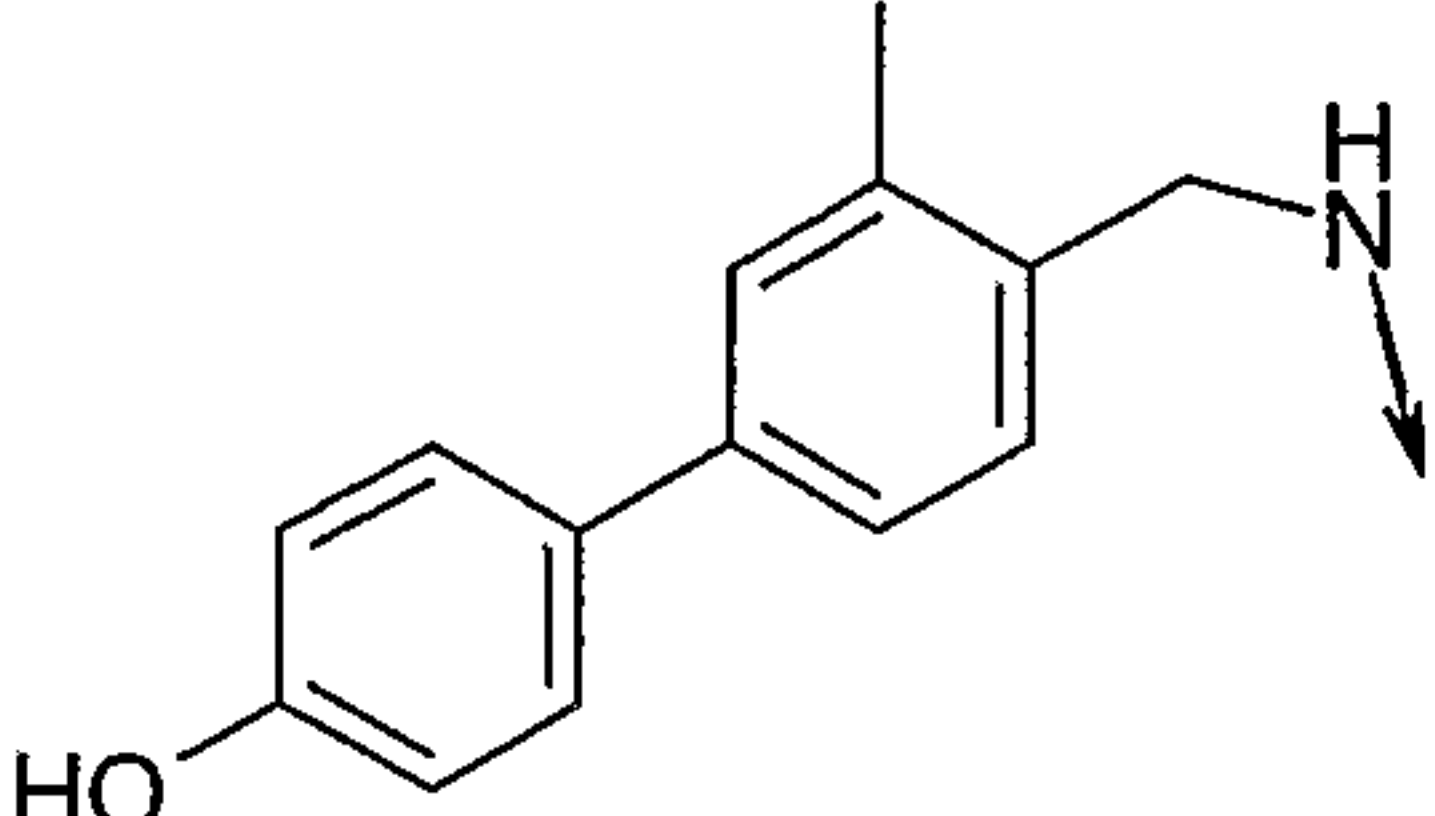
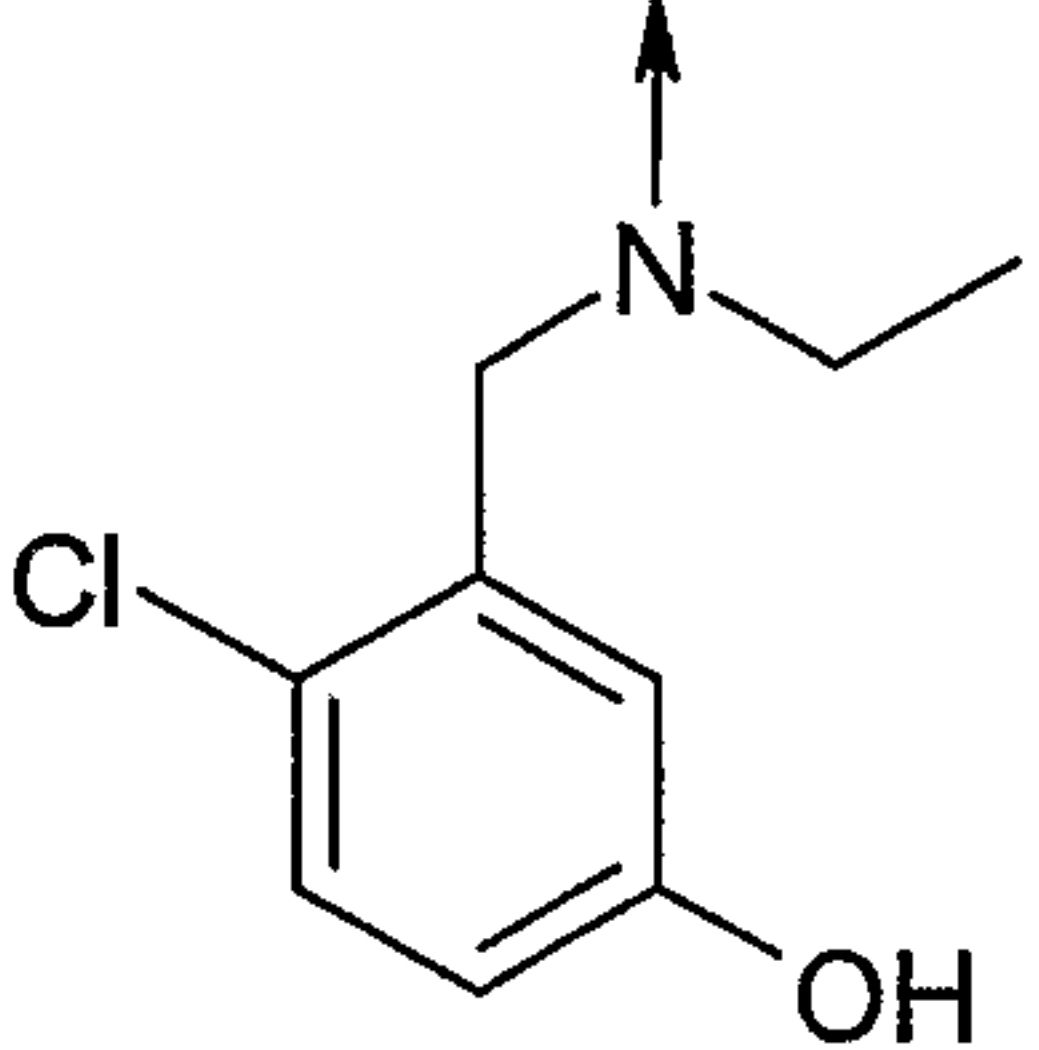
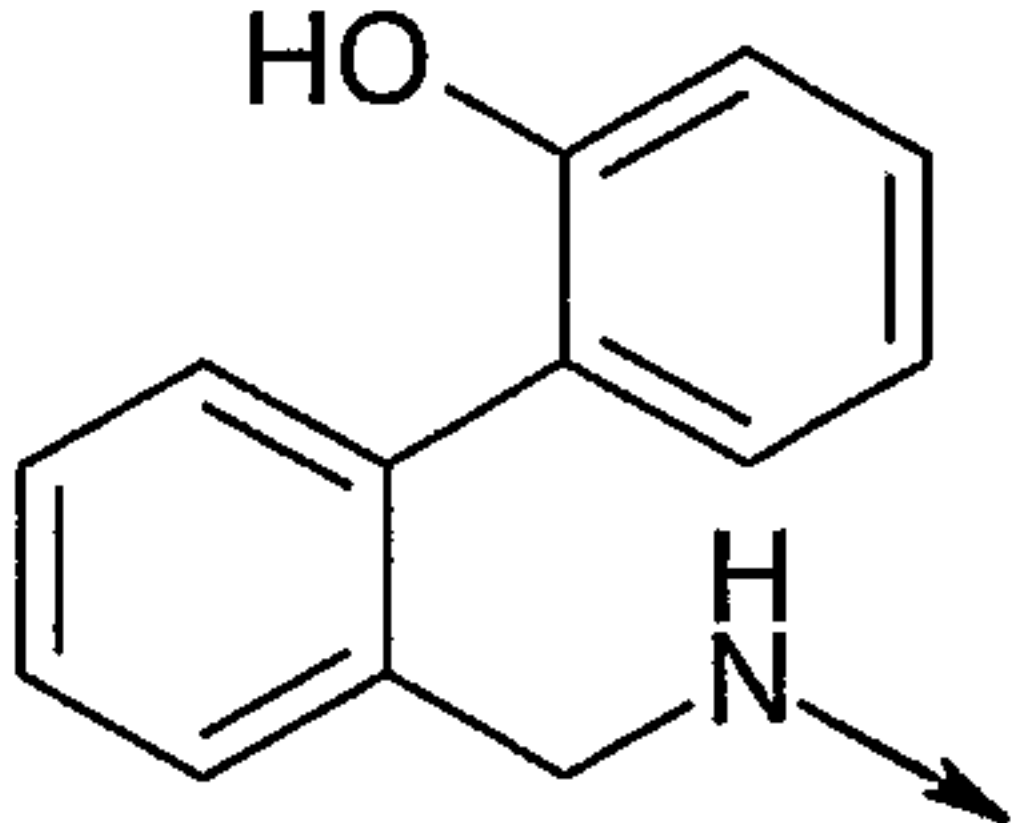


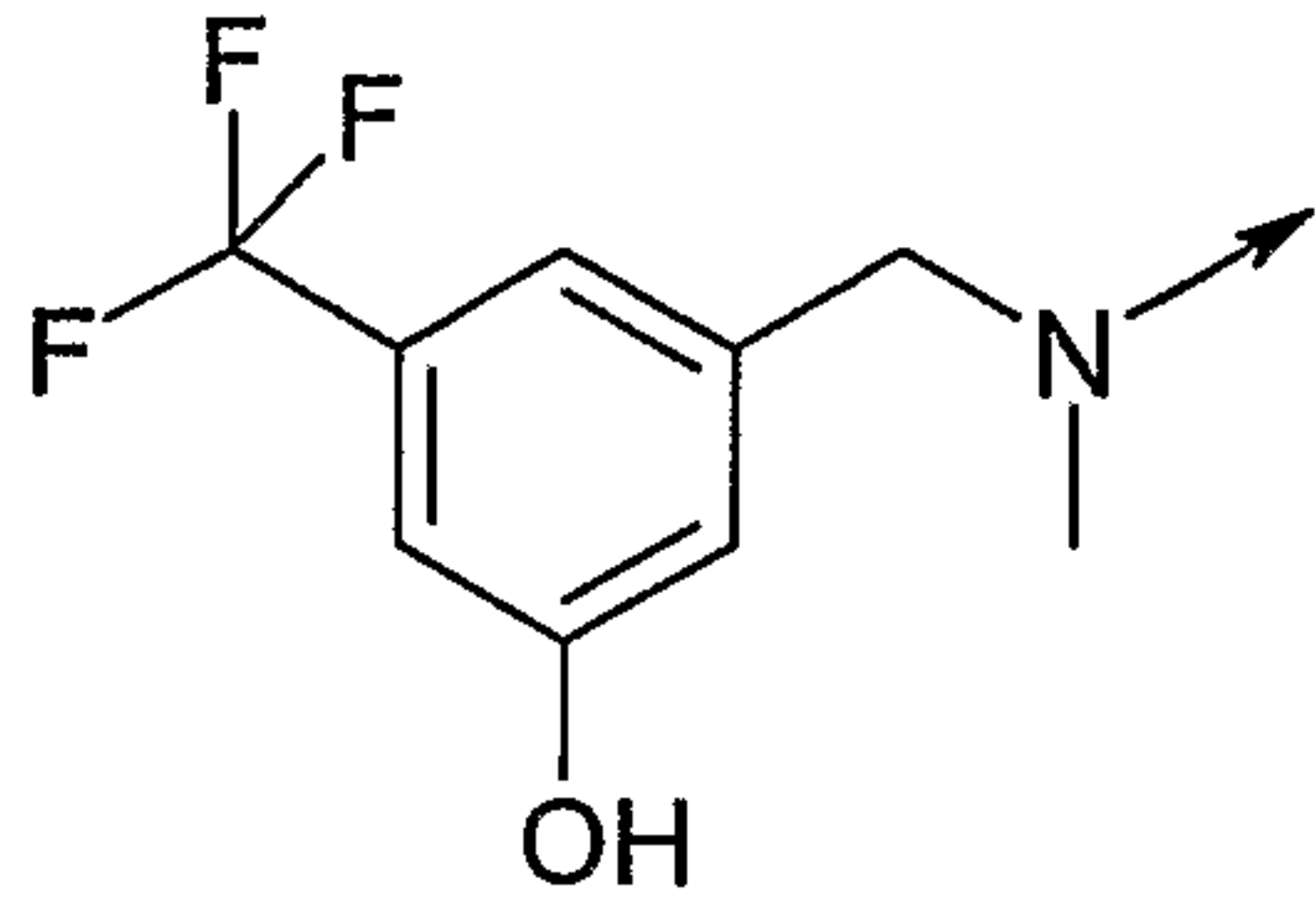
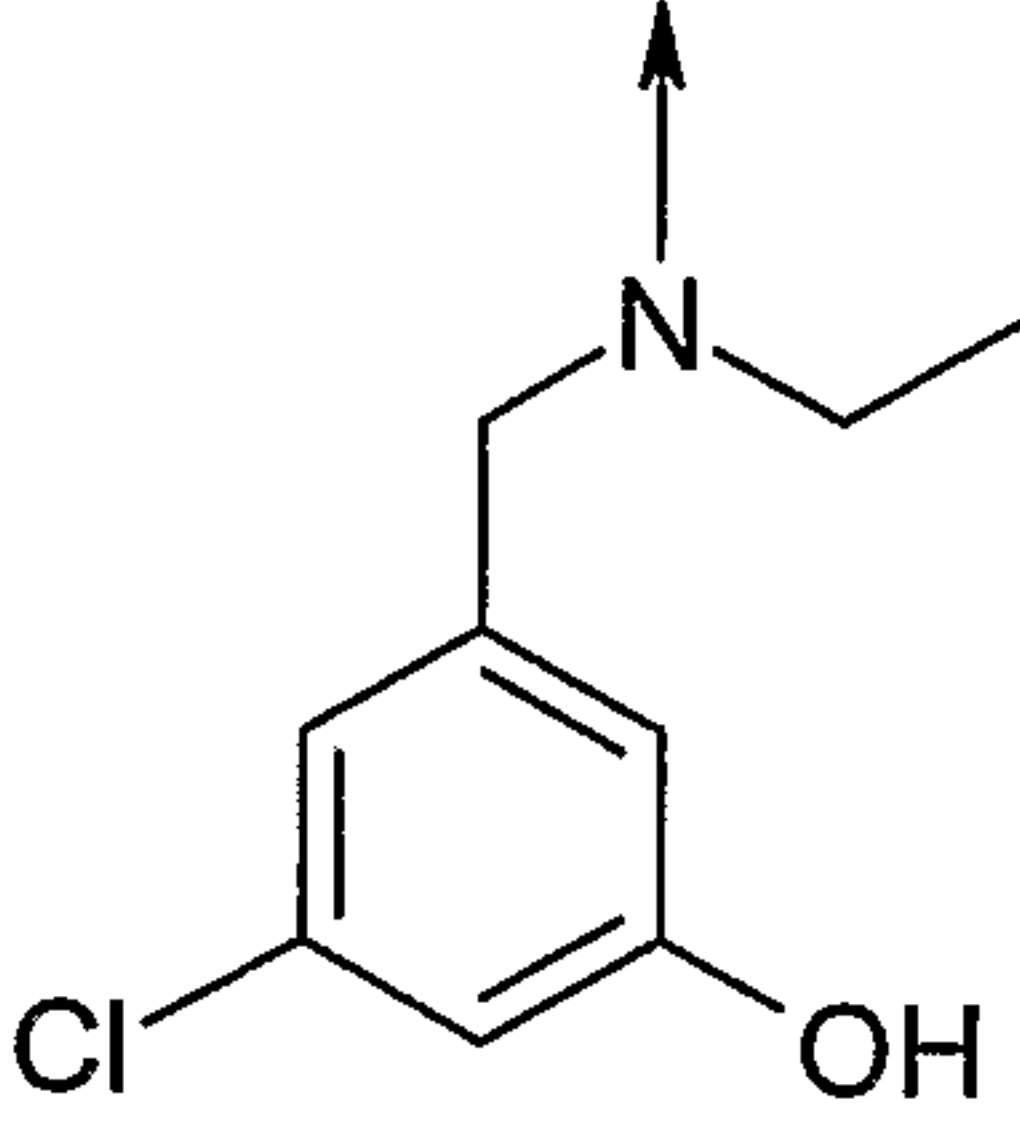
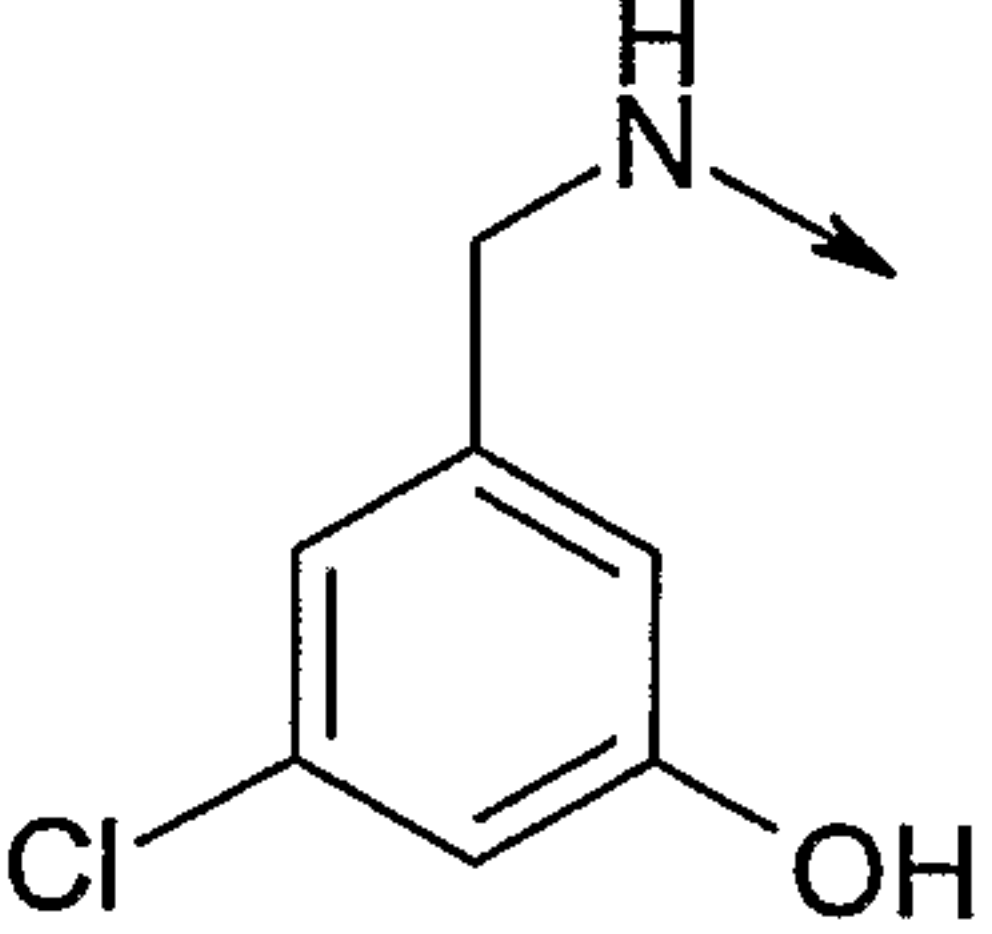
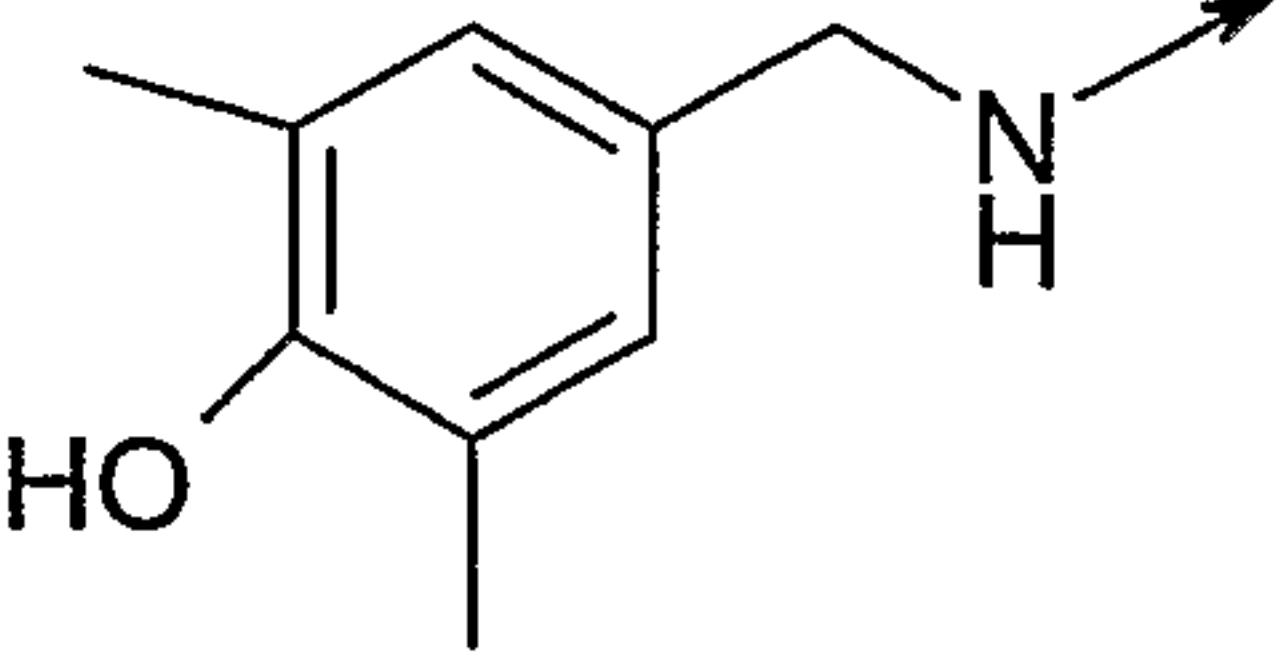
Ex	Name	Mass	Detector	Rt	
40	2-[3-(2-[[<i>(2R)</i>]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -(3-hydroxy-4-methoxyphenyl)acetamide	464.24	ELSD	1.35	
41	2-[3-(2-[[<i>(2R)</i>]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -(3-hydroxyphenyl)acetamide	434.23	ELSD	1.3	
42	2-[3-(2-[[<i>(2R)</i>]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -(2-chloro-4-hydroxyphenyl)acetamide	468.19	ELSD	1.46	

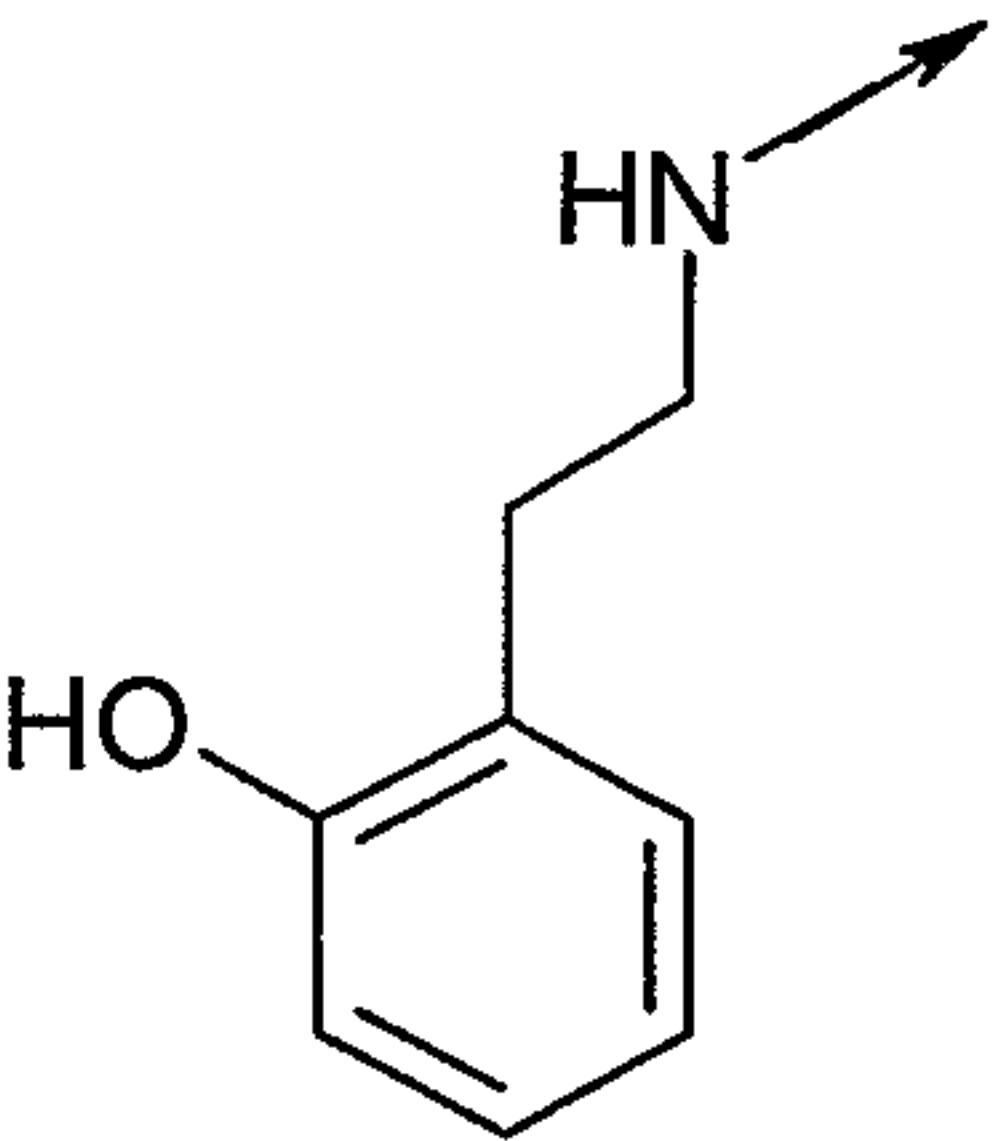
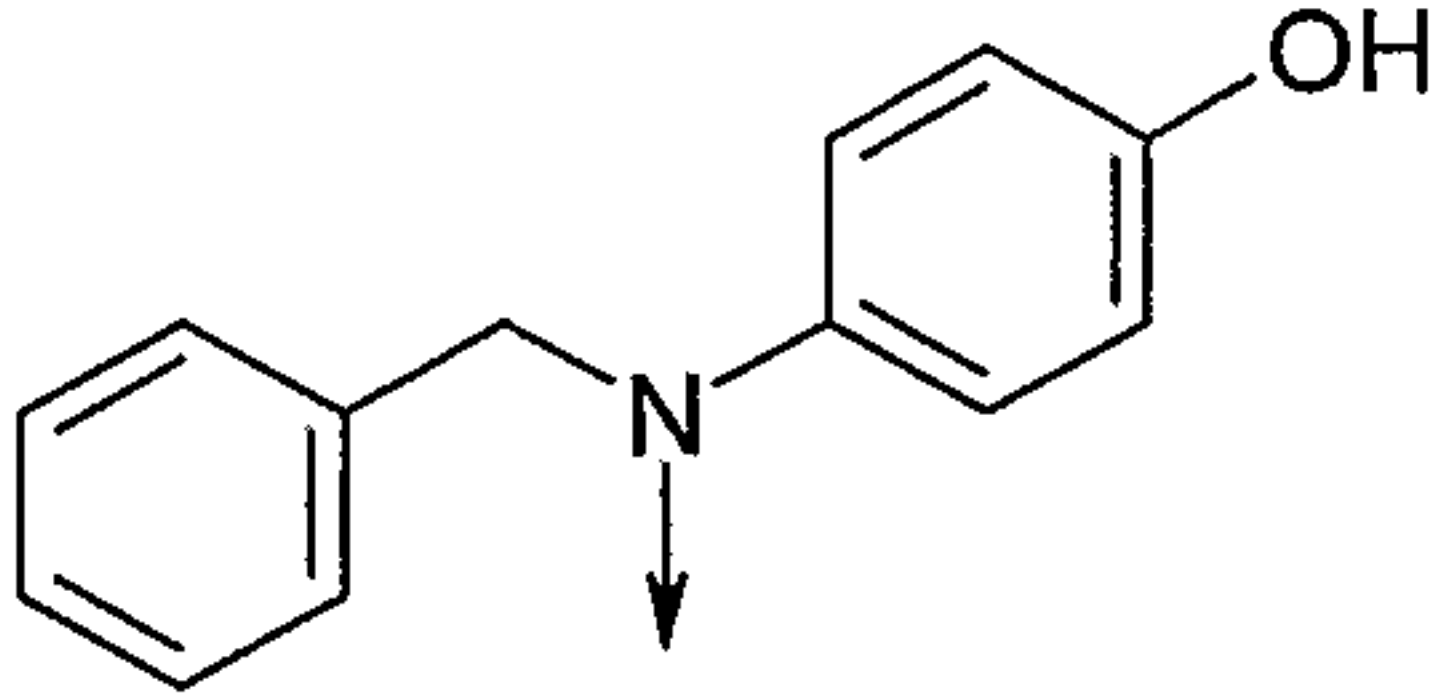
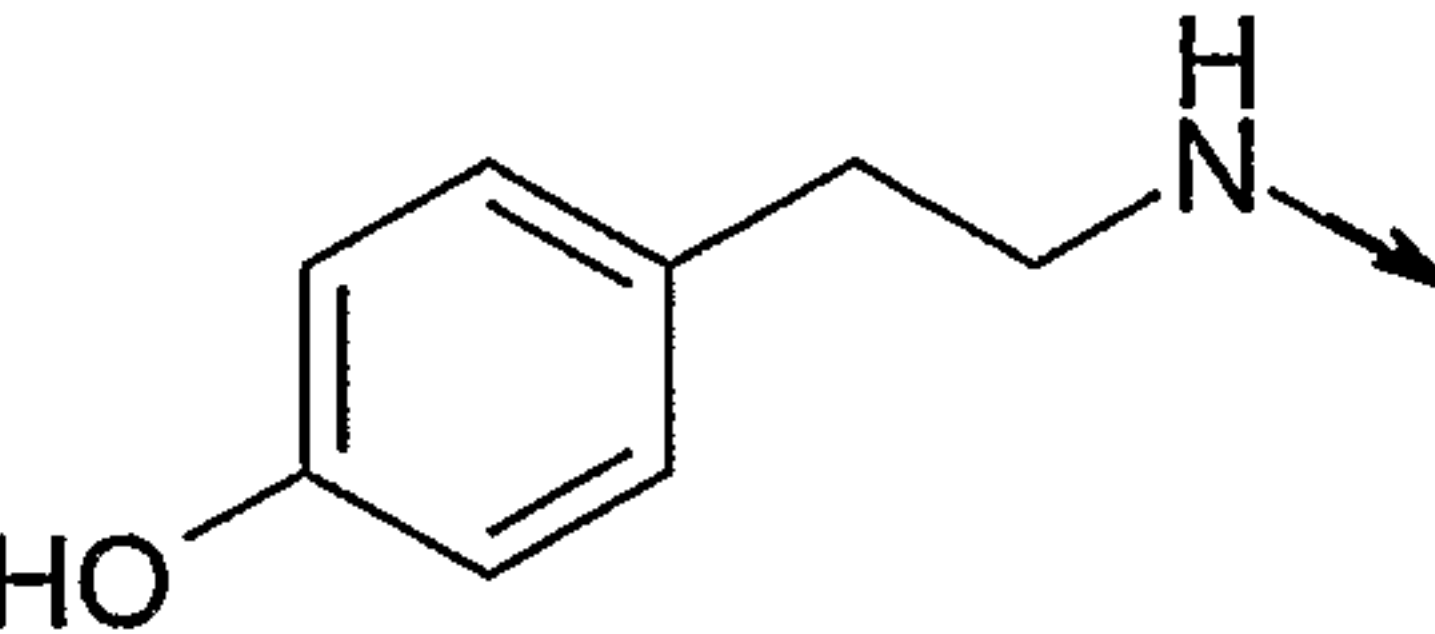
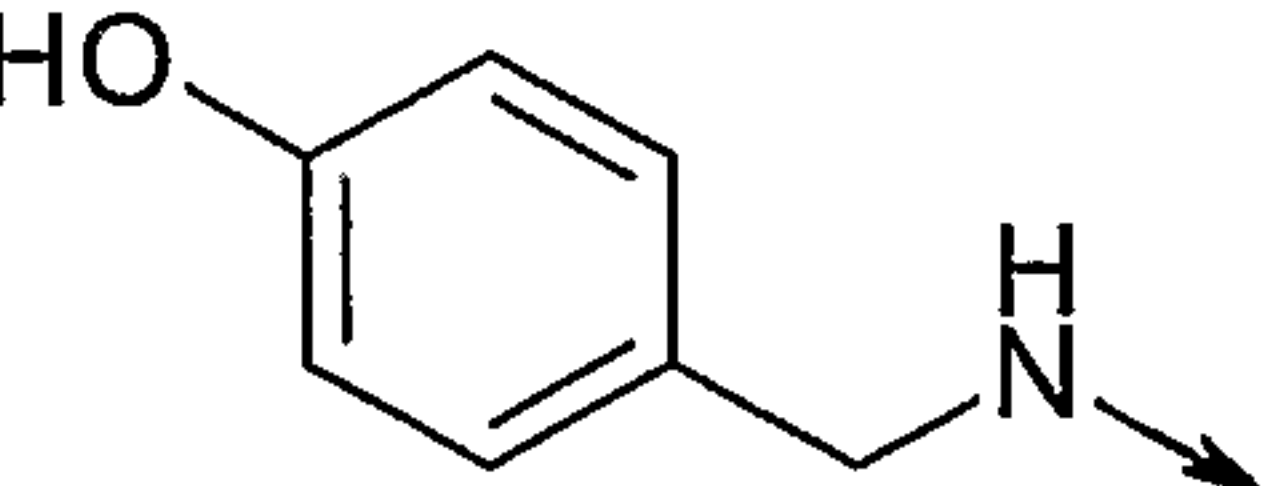
43	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)phenyl]- <i>N</i> -(4-hydroxy-3-methoxy-benzyl)acetamide	478.26	ELSD	1.25	
44	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)phenyl]- <i>N</i> -[5-(ethylsulfonyl)-2-hydroxyphenyl]acetamide	526.22	ELSD	1.25	
45	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)phenyl]- <i>N</i> -(2-hydroxy-5-methyl-phenyl)acetamide	448.25	DAD: 225	1.52	
46	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)phenyl]- <i>N</i> -(5-chloro-2-hydroxy-benzyl)acetamide	482.21	ELSD	1.55	

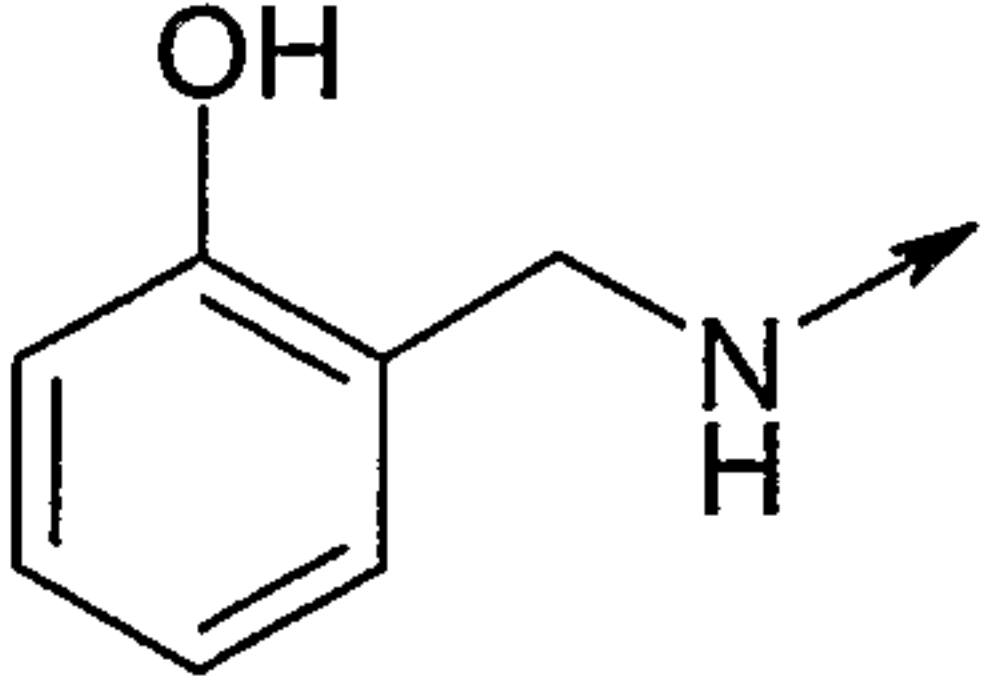
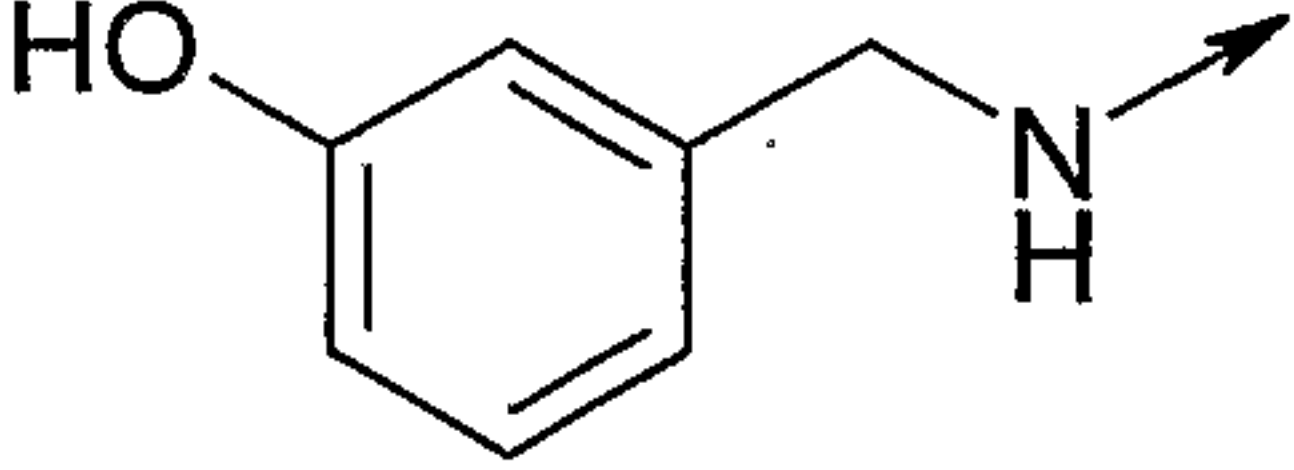
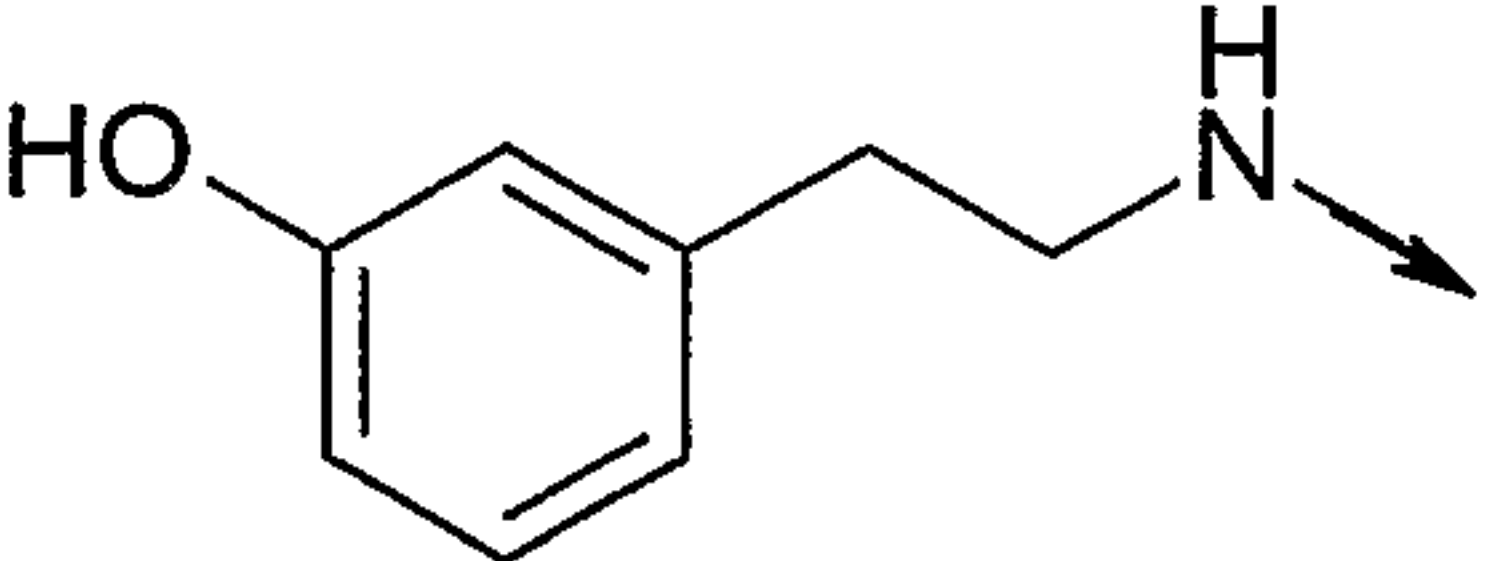
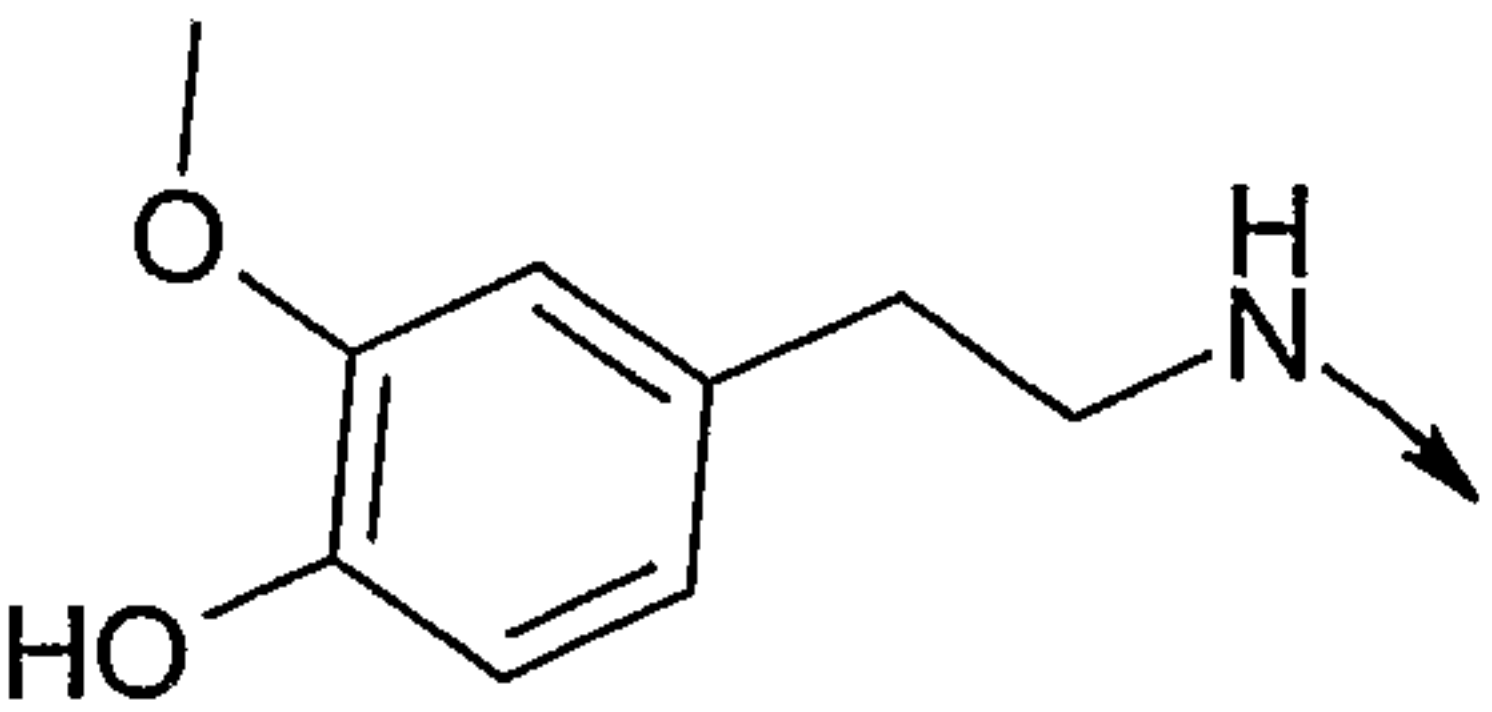
47	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -(4-hydroxy-1,1'-biphenyl-3-yl)acetamide	510.26	ELSD	1.89	
48	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -[2-hydroxy-2-(3-hydroxyphenyl)ethyl]- <i>N</i> -methylacetamide	492.27	ELSD	1.25	
49	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -ethyl- <i>N</i> -(3-hydroxyphenyl)acetamide	462.26	DAD: 255	1.45	
50	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -[2-(3-ethoxy-4-	506.29	ELSD	1.4	

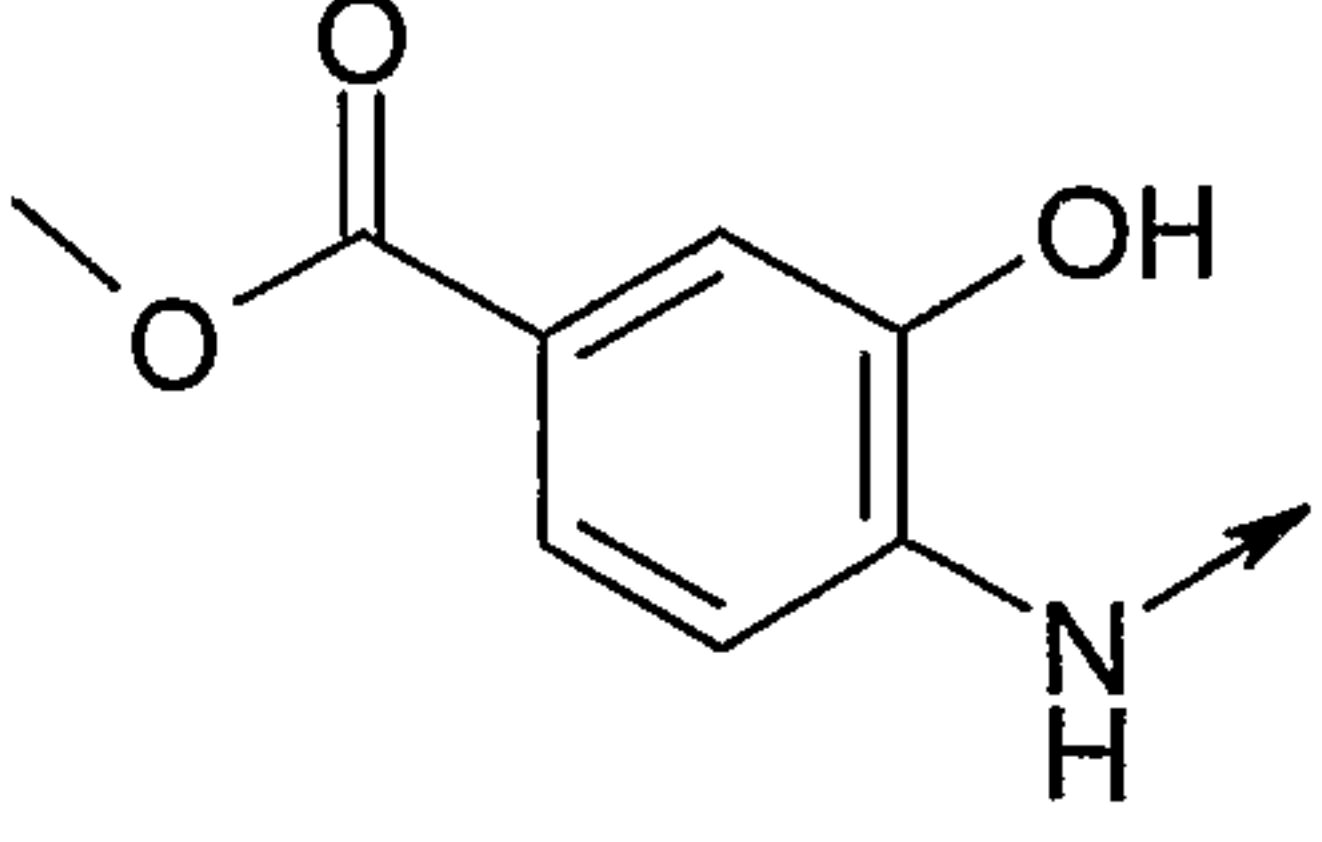
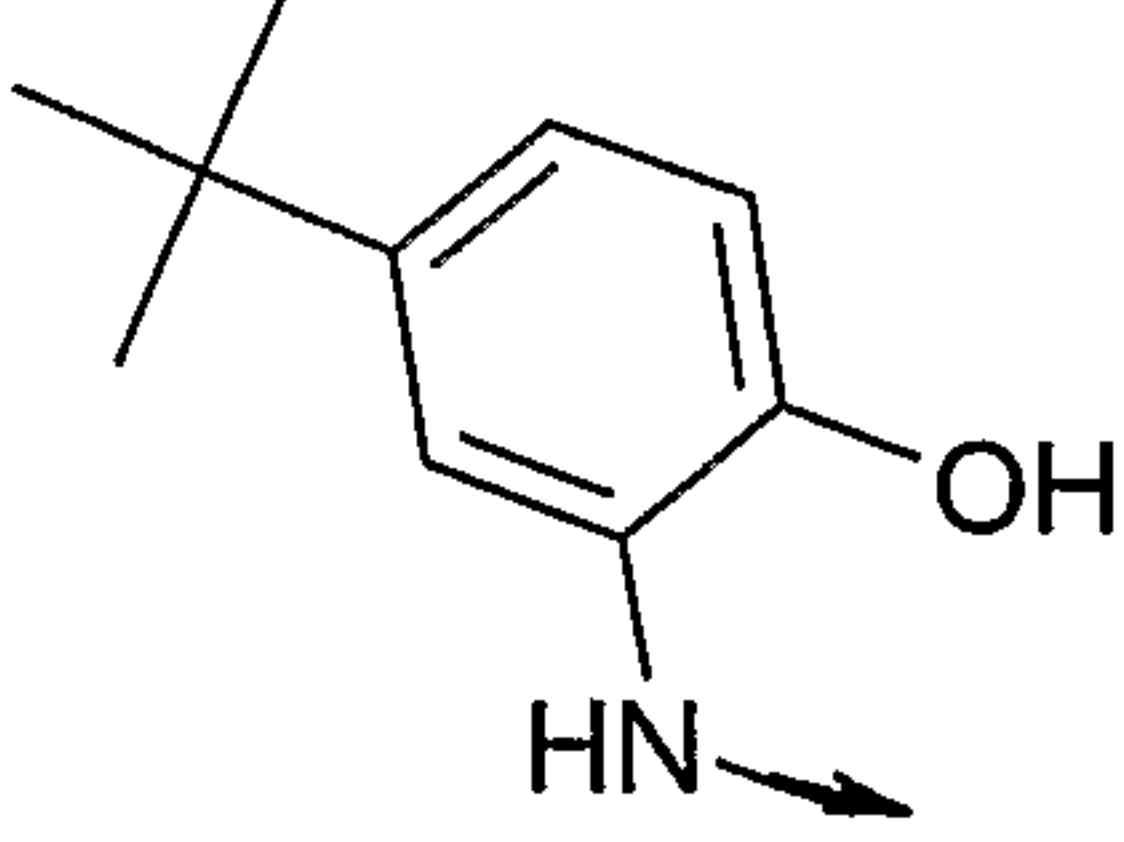
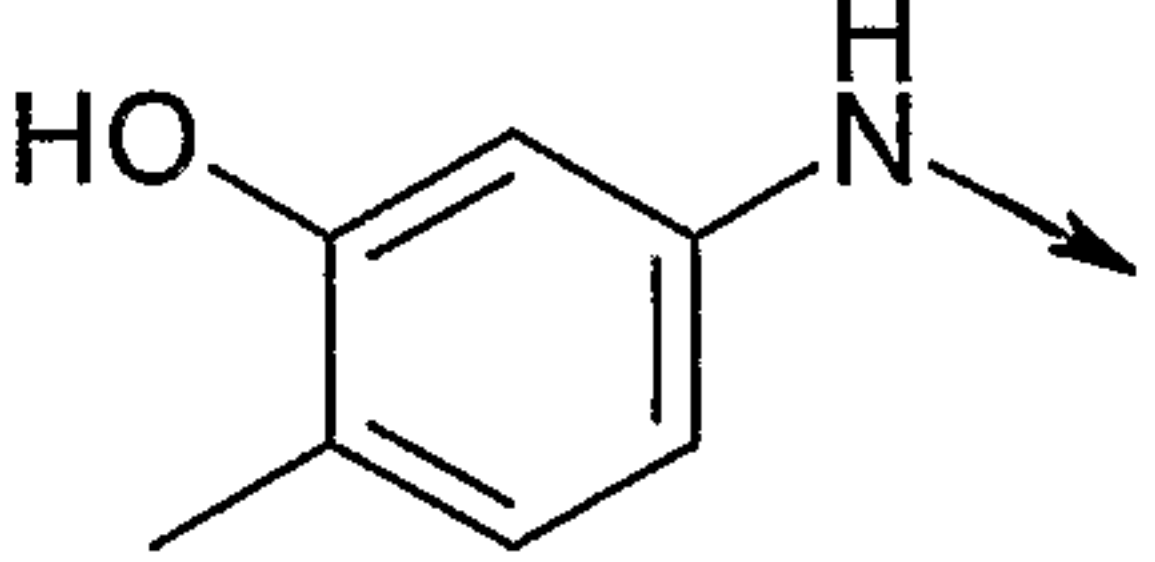
	hydroxyphenyl)ethyl]acetamide				
51	2-[3-(2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]=amino}-2-methylpropyl)phenyl]- <i>N</i> -{[4'-(hydroxymethyl)-1,1'-biphenyl-3-yl]methyl}acetamide	538.29	ELSD	1.49	
52	2-[3-(2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)phenyl]- <i>N</i> -(2,4-dichloro-6-hydroxybenzyl)acetamide	516.17	DAD: 255	1.9	
53	2-[3-(2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)phenyl]- <i>N</i> -[(3-fluoro-4'-hydroxy-1,1'-biphenyl-4-yl)methyl]acetamide	542.27	ELSD	1.59	

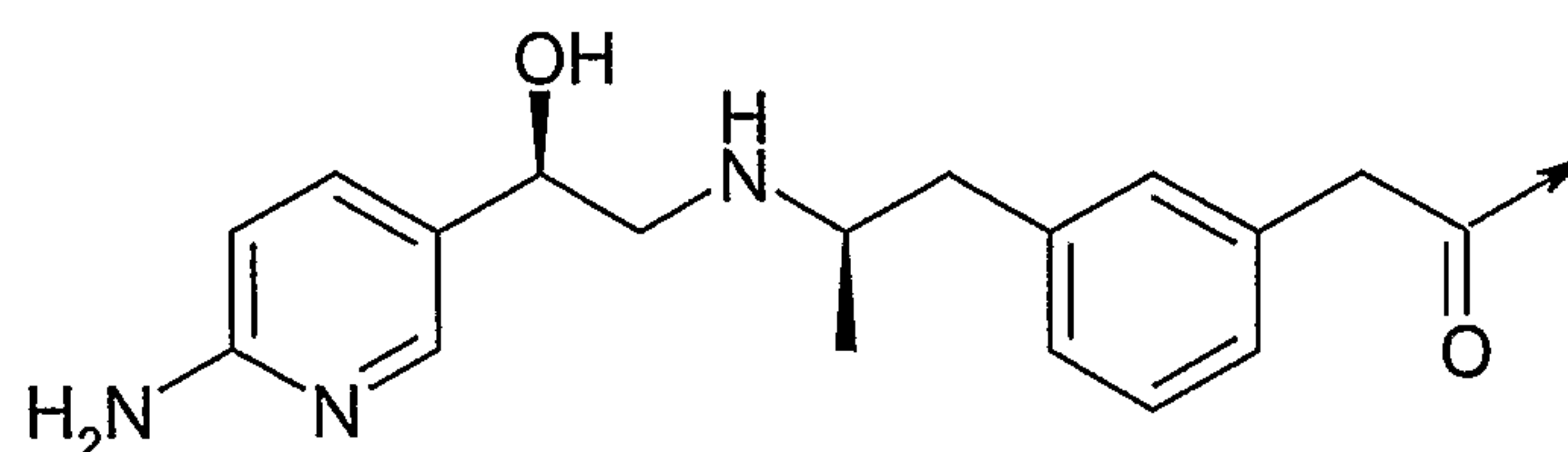
54	2-[3-(2-([(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methylpropyl)phenyl]- <i>N</i> -[(4'-hydroxy-3-methyl-1,1'-biphenyl-4-yl)methyl]acetamide	538.29	ELSD	1.7	
55	2-[3-(2-([(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methylpropyl)phenyl]- <i>N</i> -(2-chloro-5-hydroxybenzyl)- <i>N</i> -ethylacetamide	510.24	DAD: 255	1.67	
56	2-[3-(2-([(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methylpropyl)phenyl]- <i>N</i> -[(2'-hydroxy-1,1'-biphenyl-2-yl)methyl]acetamide	524.28	ELSD	1.73	

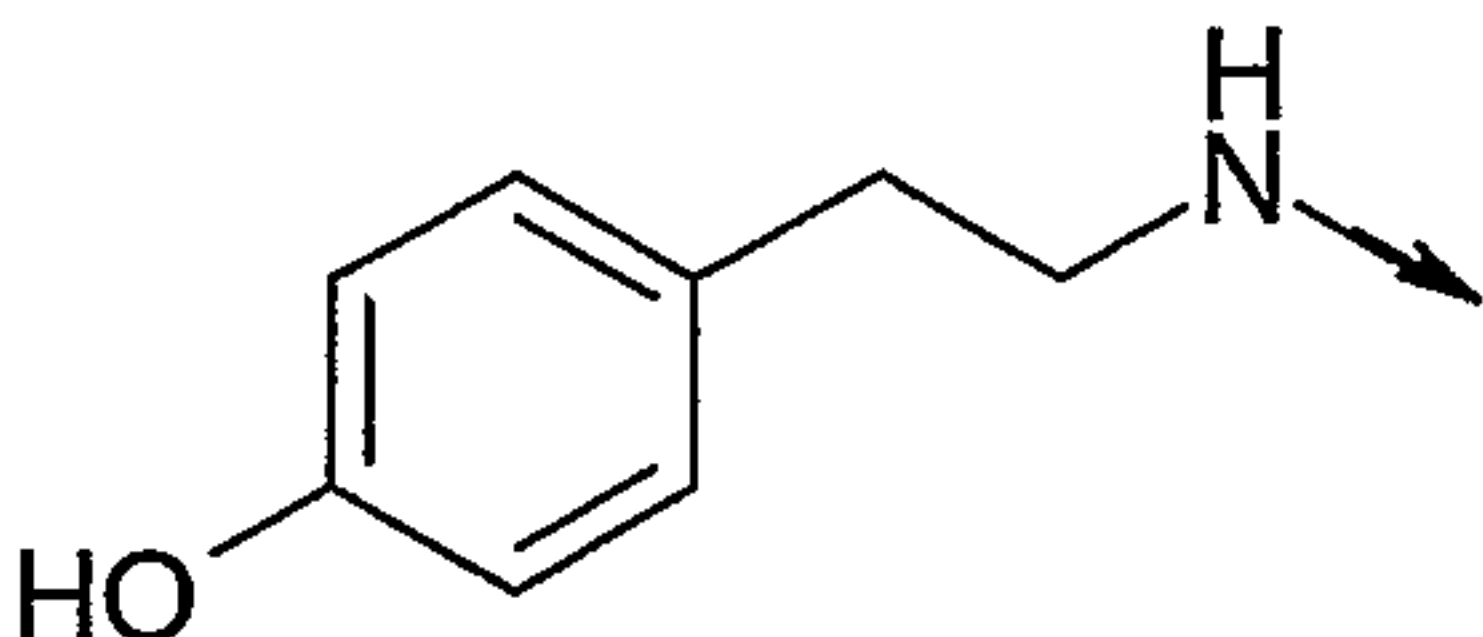
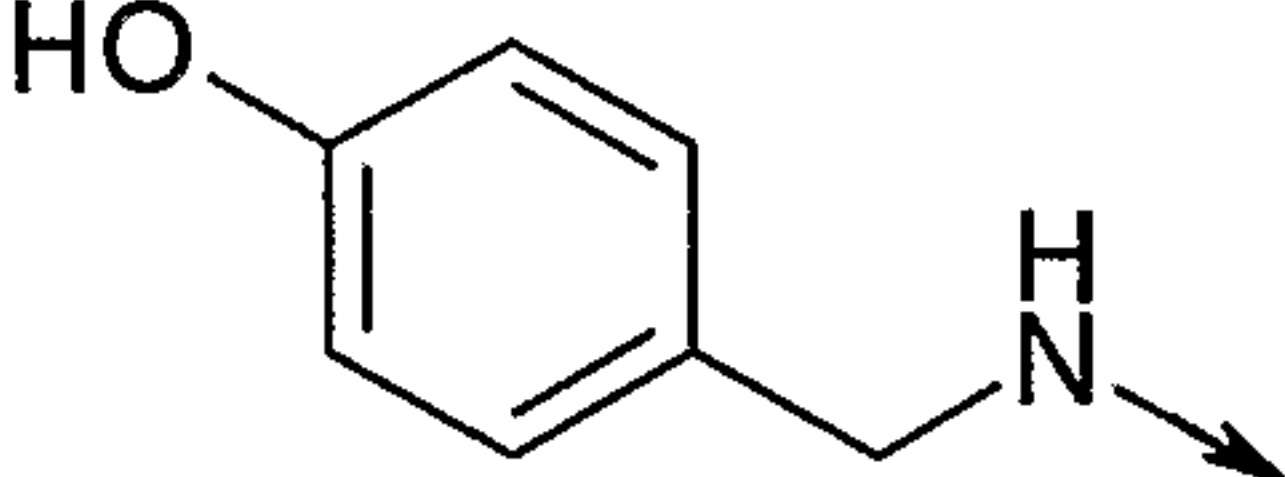
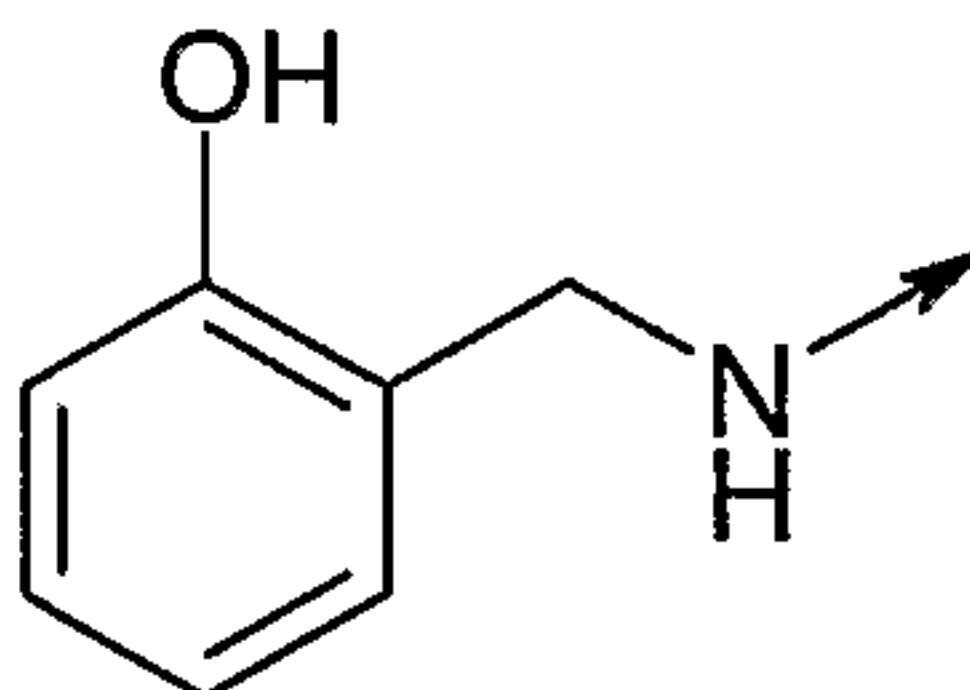
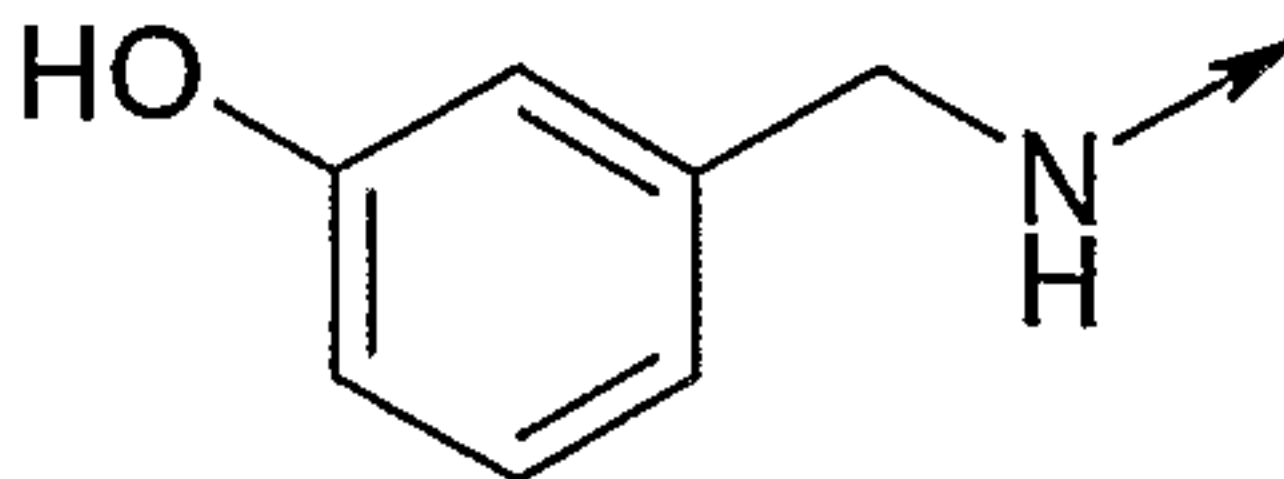
57	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -[3-hydroxy-5-(trifluoromethyl)benzyl]- <i>N</i> -methylacetamide	530.25	ELSD	1.77	
58	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -(3-chloro-5-hydroxybenzyl)- <i>N</i> -ethylacetamide	510.24	ELSD	1.65	
59	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -(3-chloro-5-hydroxybenzyl)acetamide	482.21	ELSD	1.52	
60	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -(4-hydroxy-3,5-	476.28	ELSD	1.49	

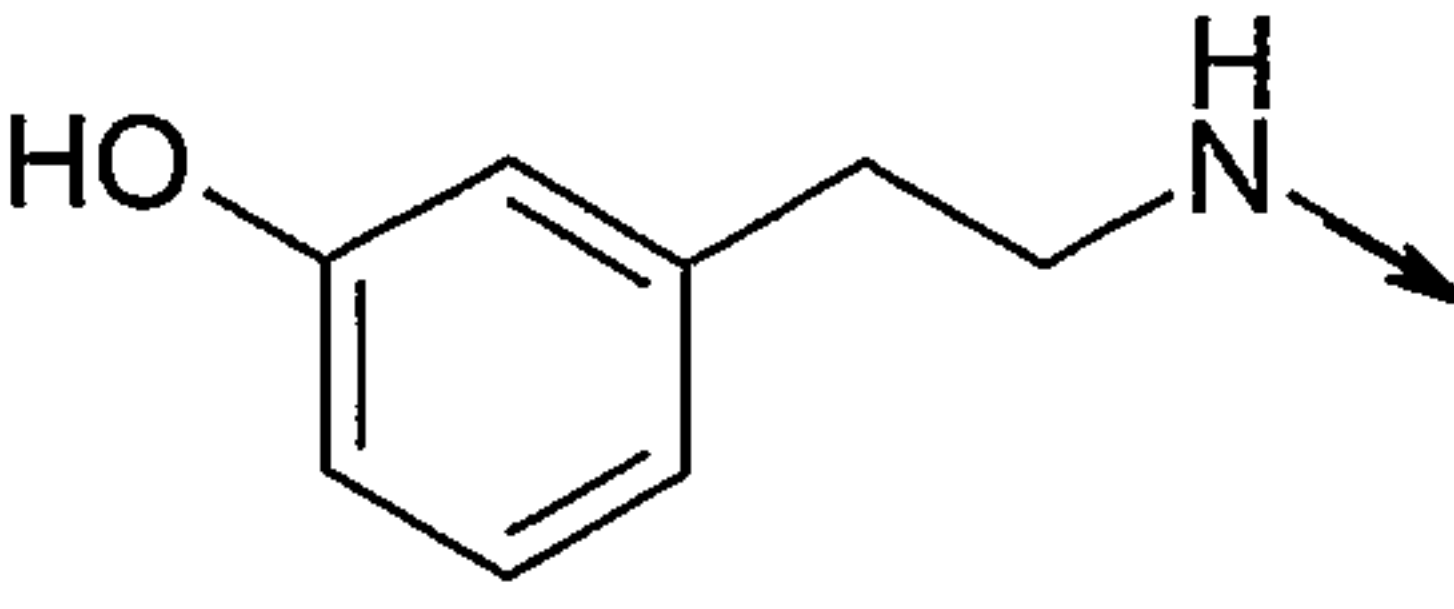
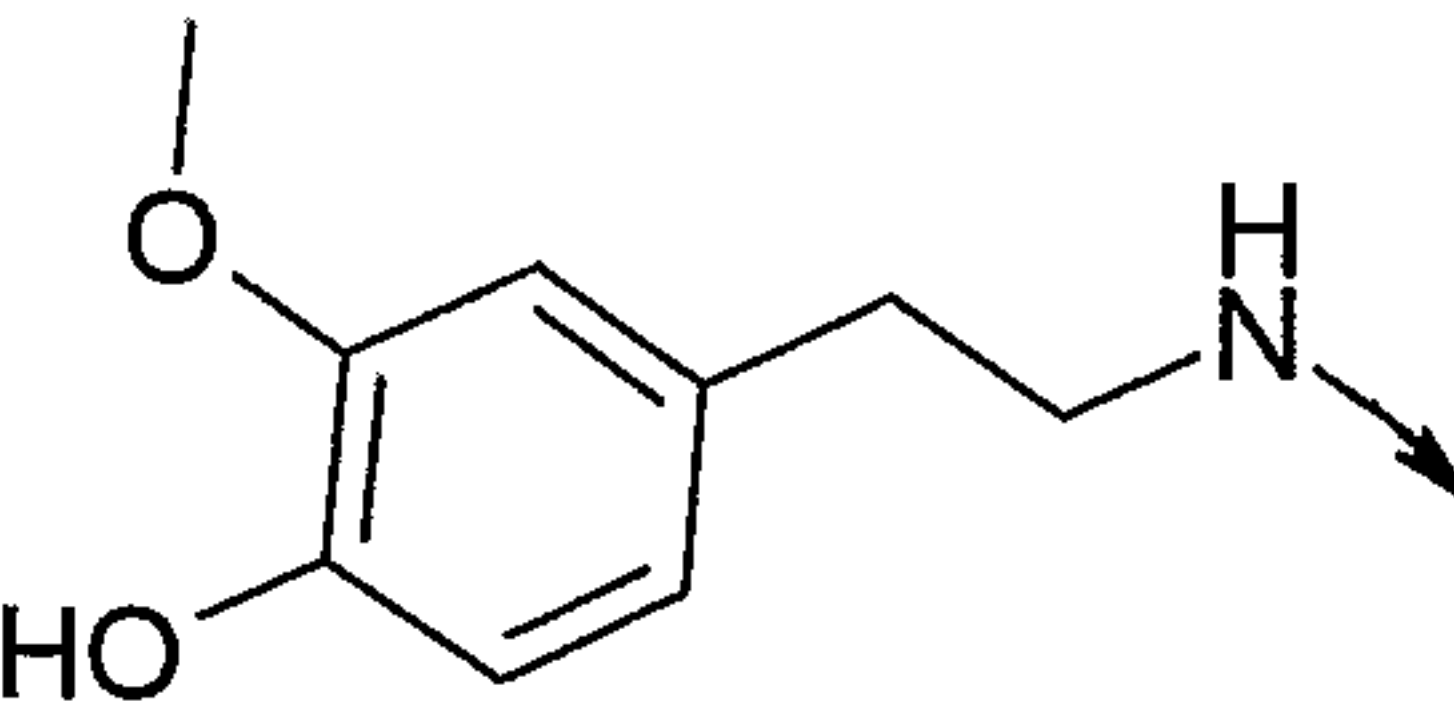
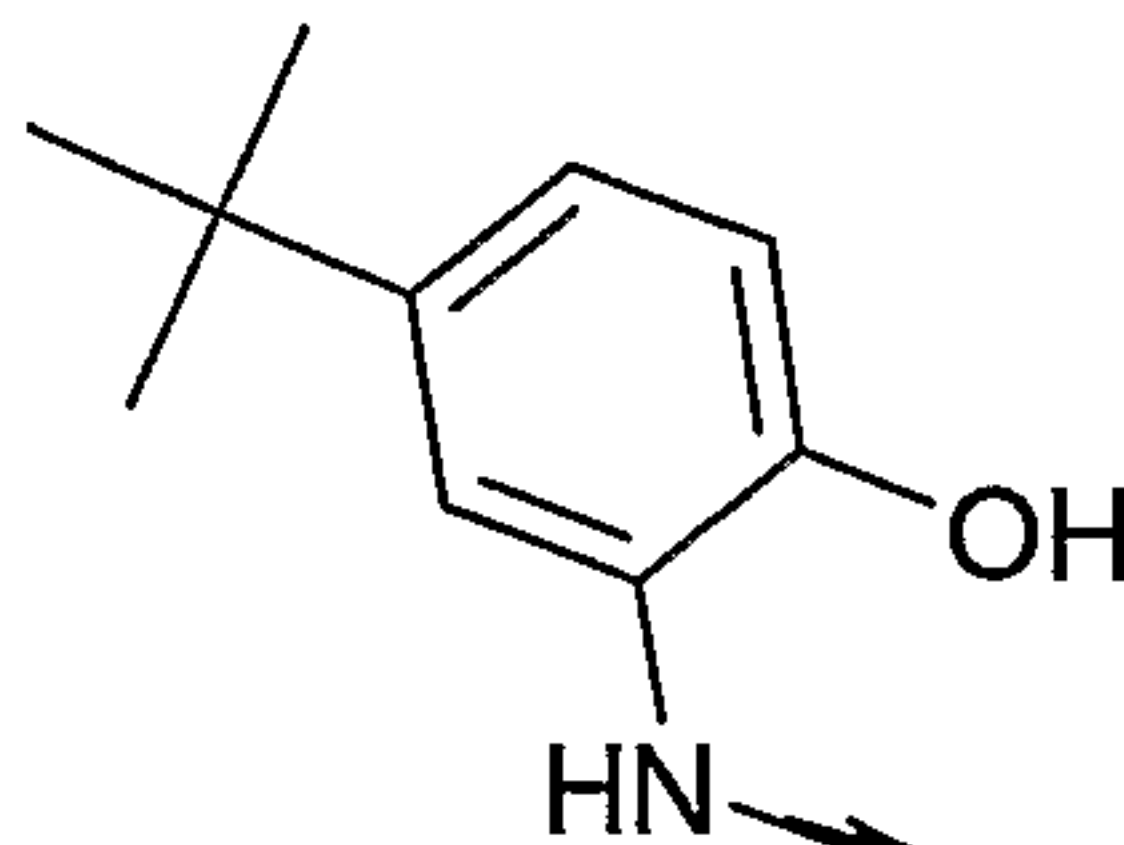
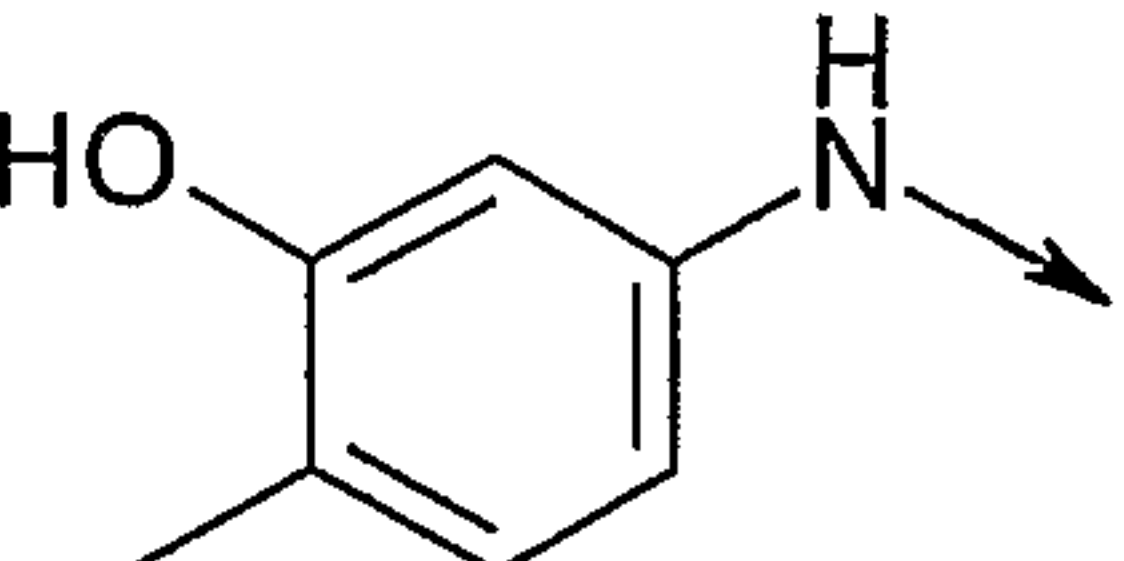
	dimethylbenzyl)acetamide				
61	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -[2-(2-hydroxyphenyl)ethyl]acetamide	462.26	ELSD	1.46	
62	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -benzyl- <i>N</i> -(4-hydroxyphenyl)acetamide	524.3	ELSD	1.75	
63	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -[2-(4-hydroxyphenyl)ethyl]acetamide	462.3	ELSD	1.26	
64	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)phenyl]- <i>N</i> -(4-	448.3	ELSD	1.33	

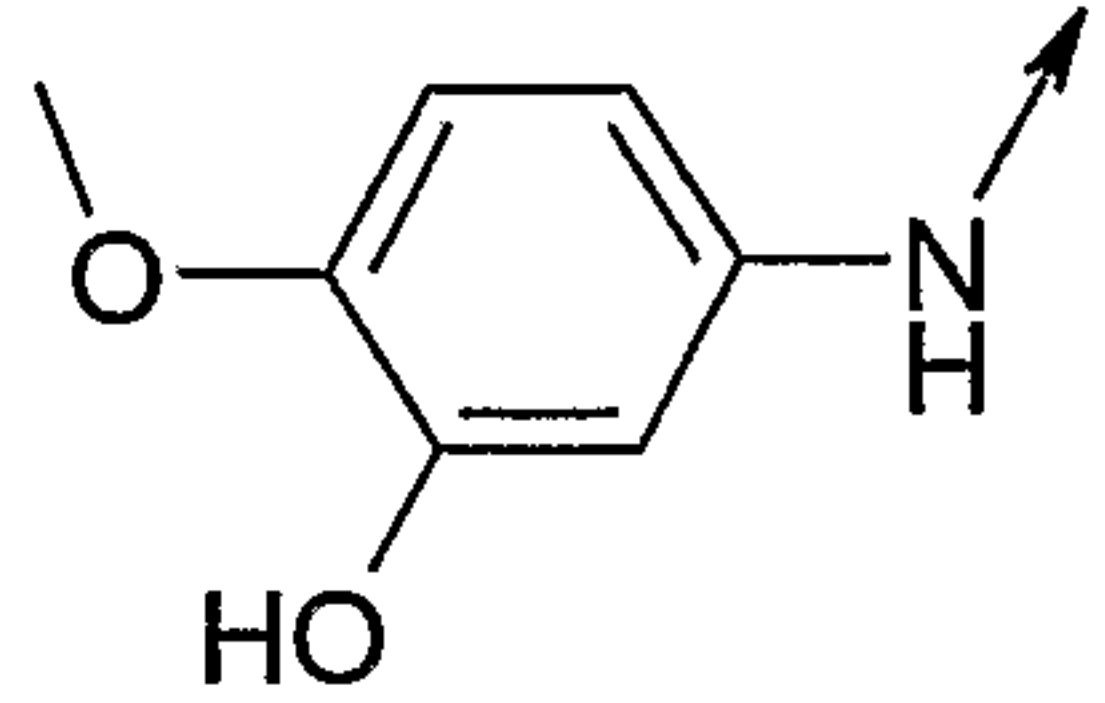
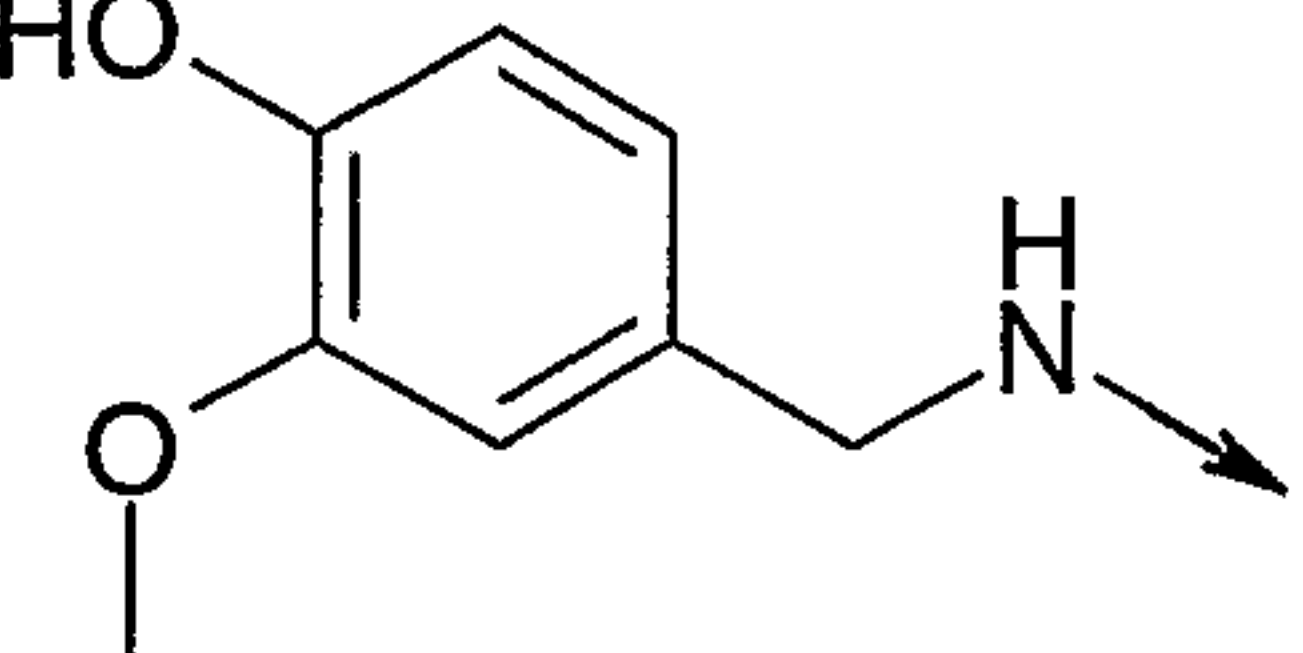
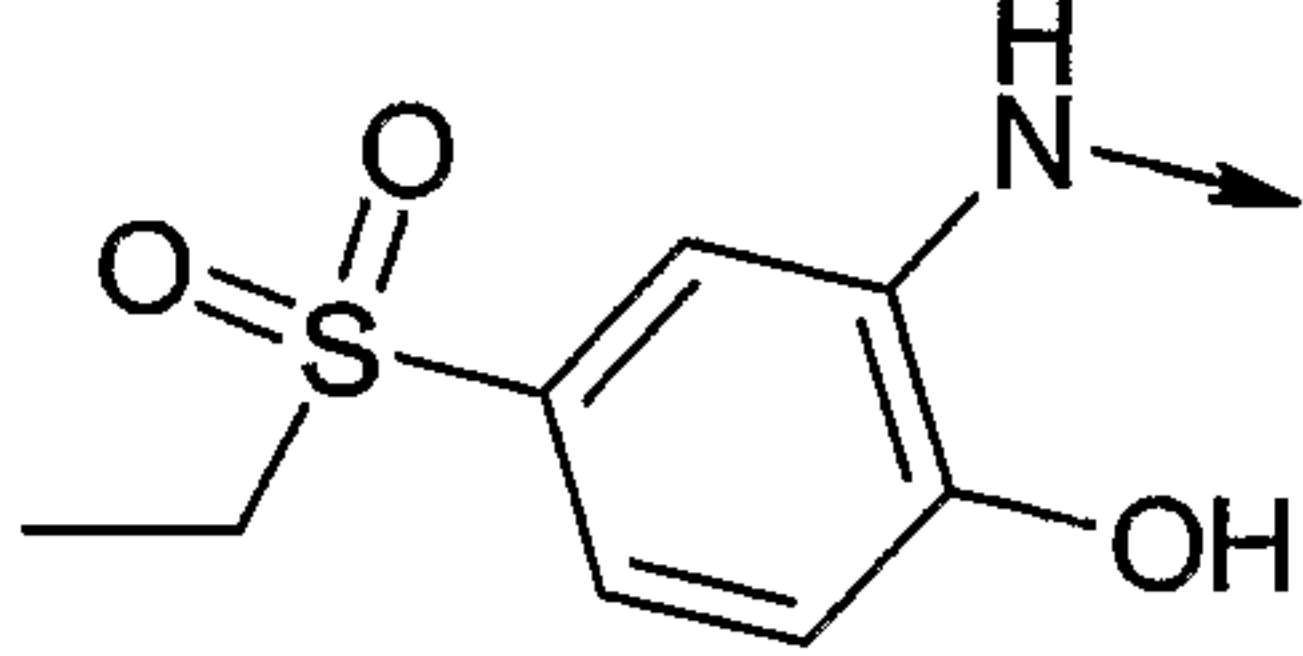
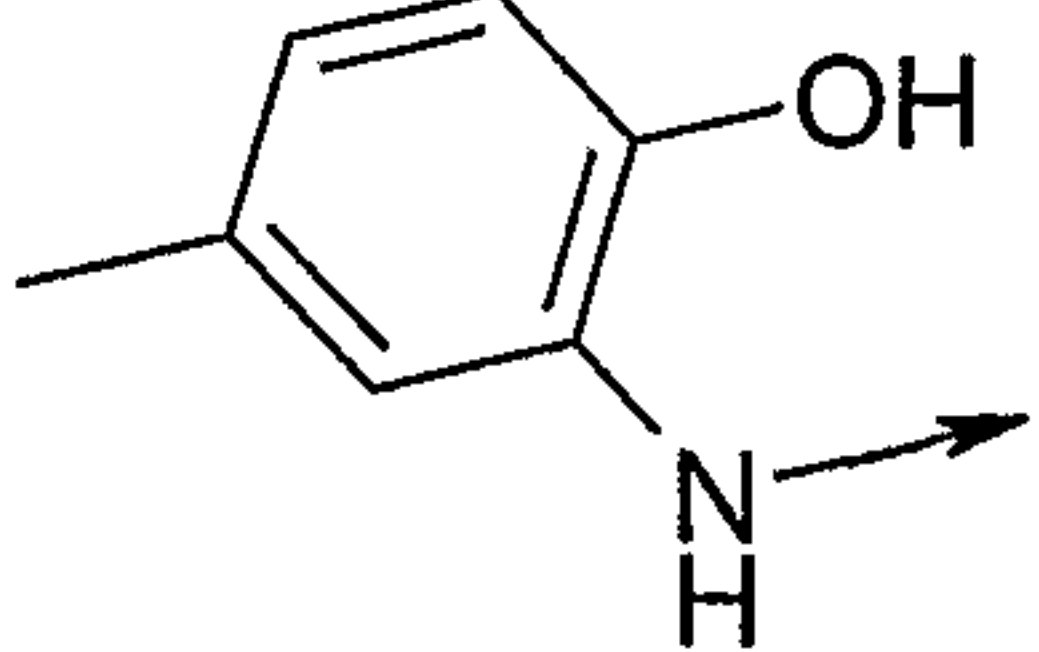
	hydroxybenzyl)acet amide				
65	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)phenyl]- <i>N</i> -(2-hydroxybenzyl)acet amide	448.3	ELSD	1.38	
66	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)phenyl]- <i>N</i> -(3-hydroxybenzyl)acet amide	448.3	ELSD	1.33	
67	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)phenyl]- <i>N</i> -[2-(3-hydroxyphenyl)-ethyl]acetamide	462.3	ELSD	1.41	
68	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methyl-propyl)phenyl]- <i>N</i> -[2-(4-hydroxy-3-meth-	492.3	ELSD	1.29	

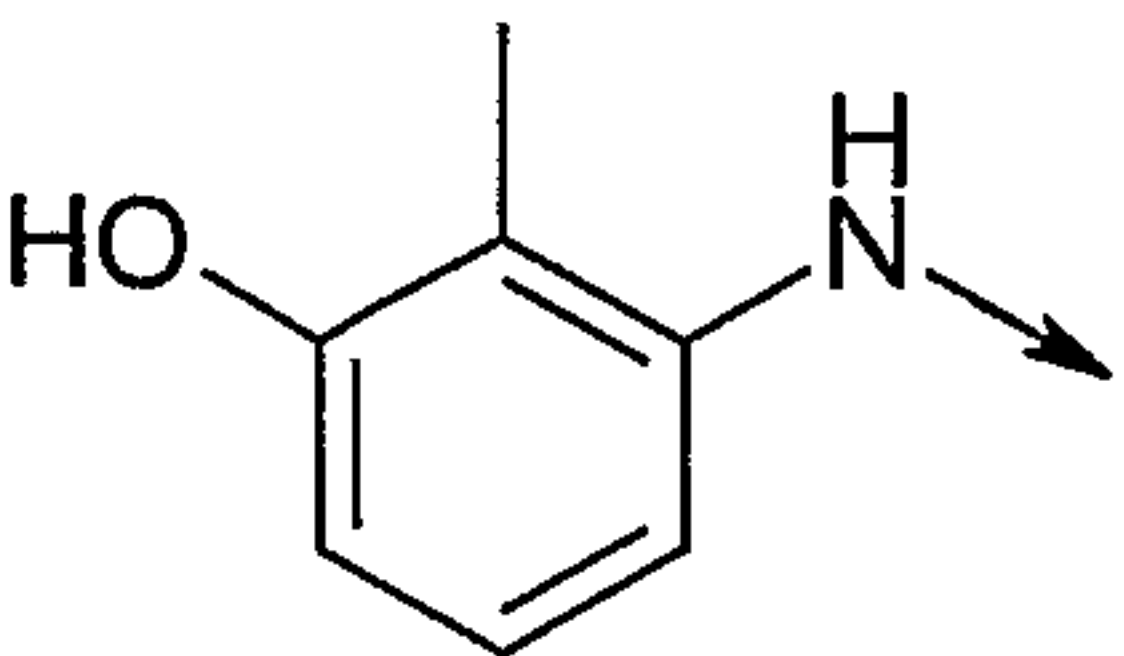
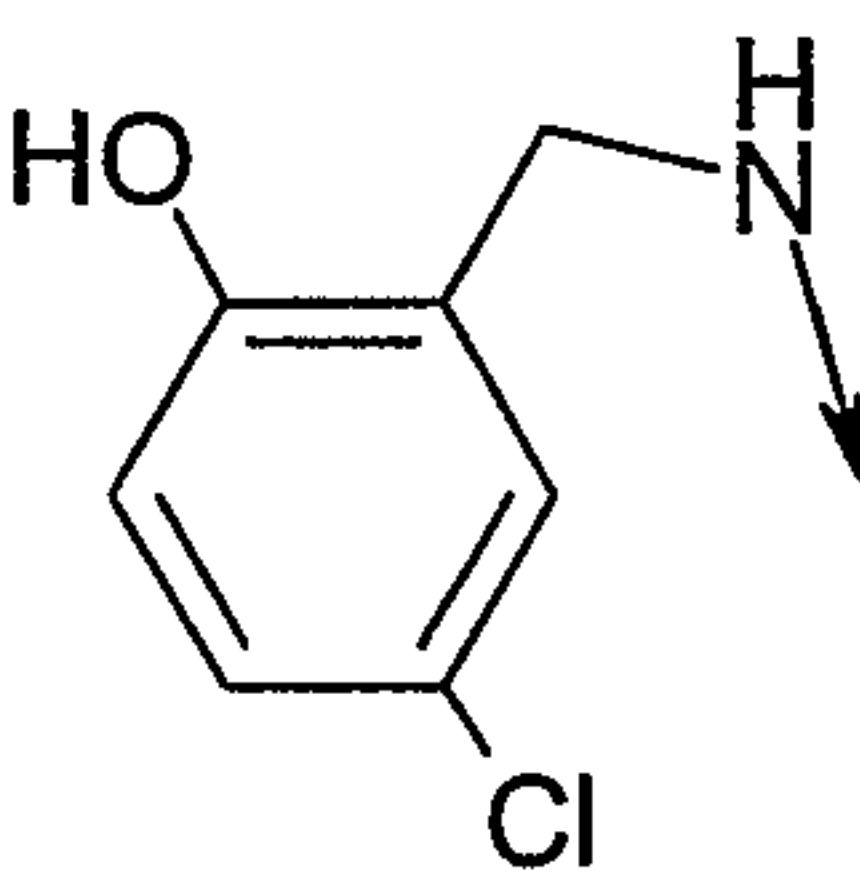
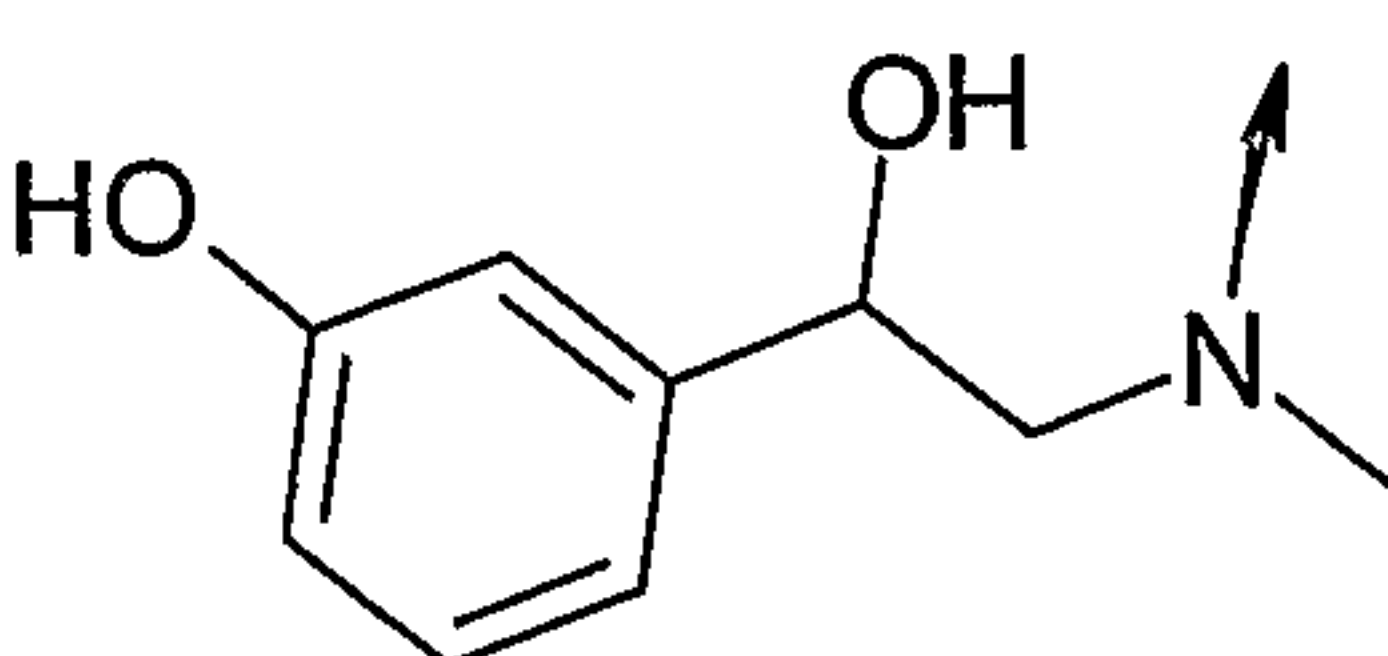
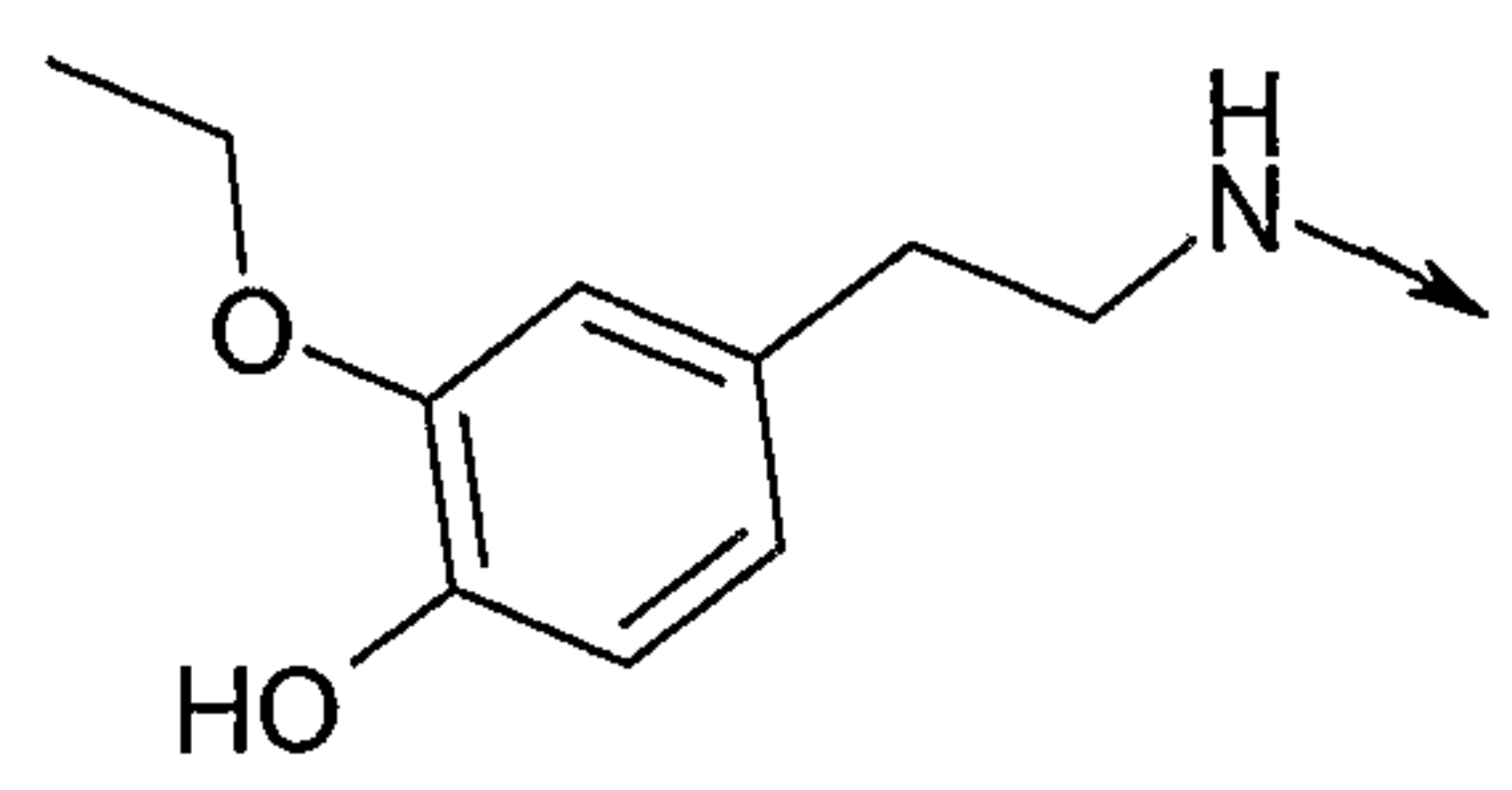
	oxyphenyl)ethyl]acetamide				
69	methyl 4-({[3-(2- {[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)- 2-hydroxyethyl]- amino}-2-methyl- propyl)phenyl]acetyl }amino)-3- hydroxybenzoate	492.2	ELSD	1.57	
70	2-[3-(2-({[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)- 2-hydroxyethyl]- amino}-2-methyl- propyl)phenyl]- <i>N</i> -(5- tert-butyl-2-hydroxy- phenyl)acetamide	490.3	ELSD	1.85	
71	2-[3-(2-({[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)- 2-hydroxyethyl]- amino}-2-methyl- propyl)phenyl]- <i>N</i> -(3- hydroxy-4-methyl- phenyl)acetamide	448.3	ELSD	1.54	



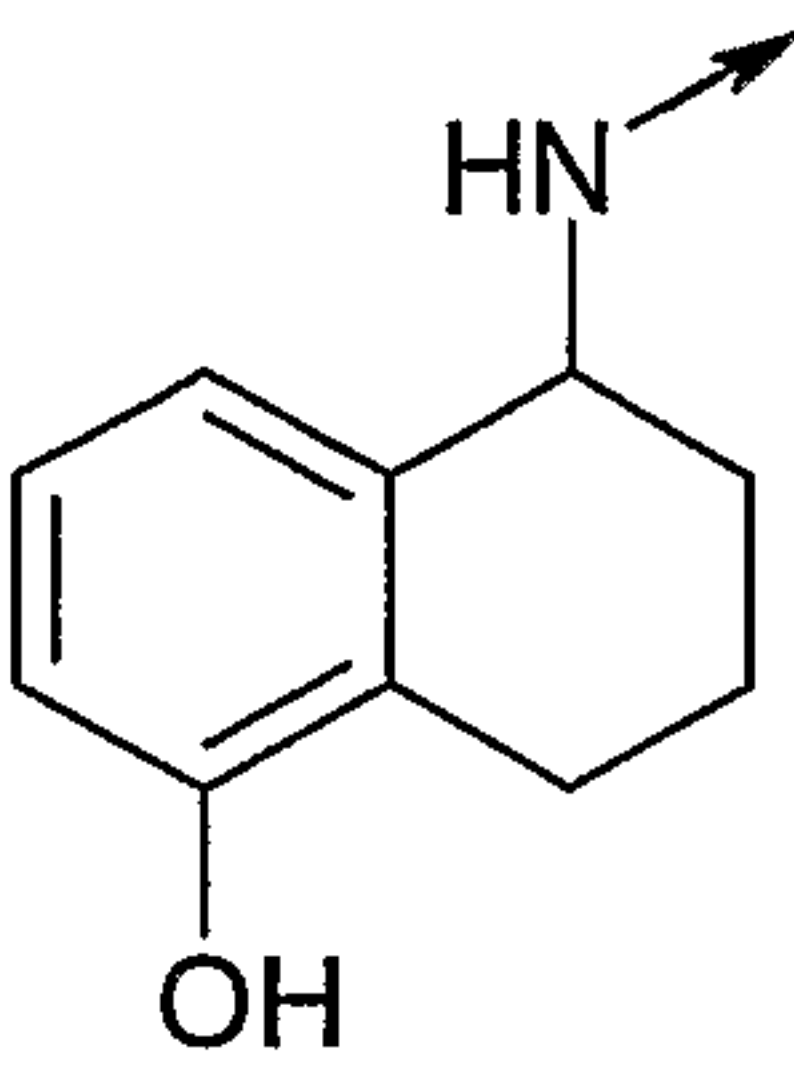
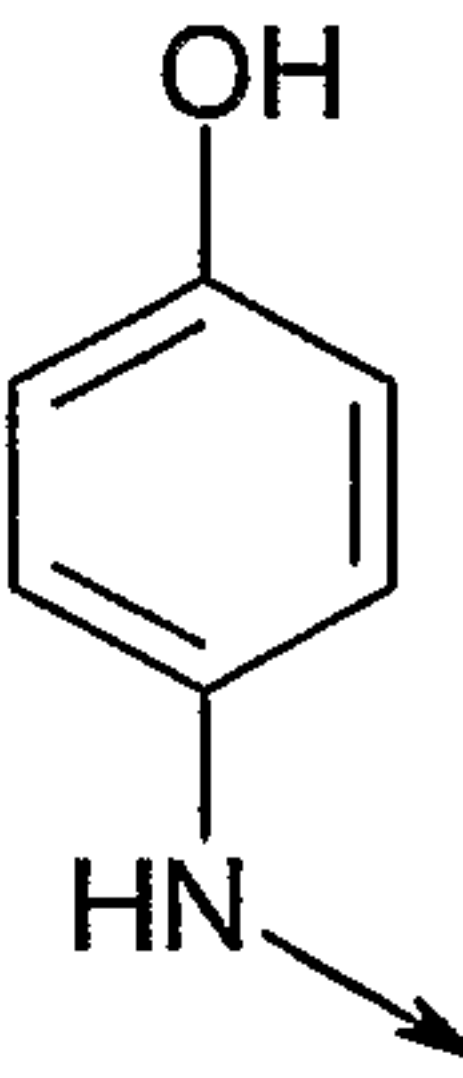
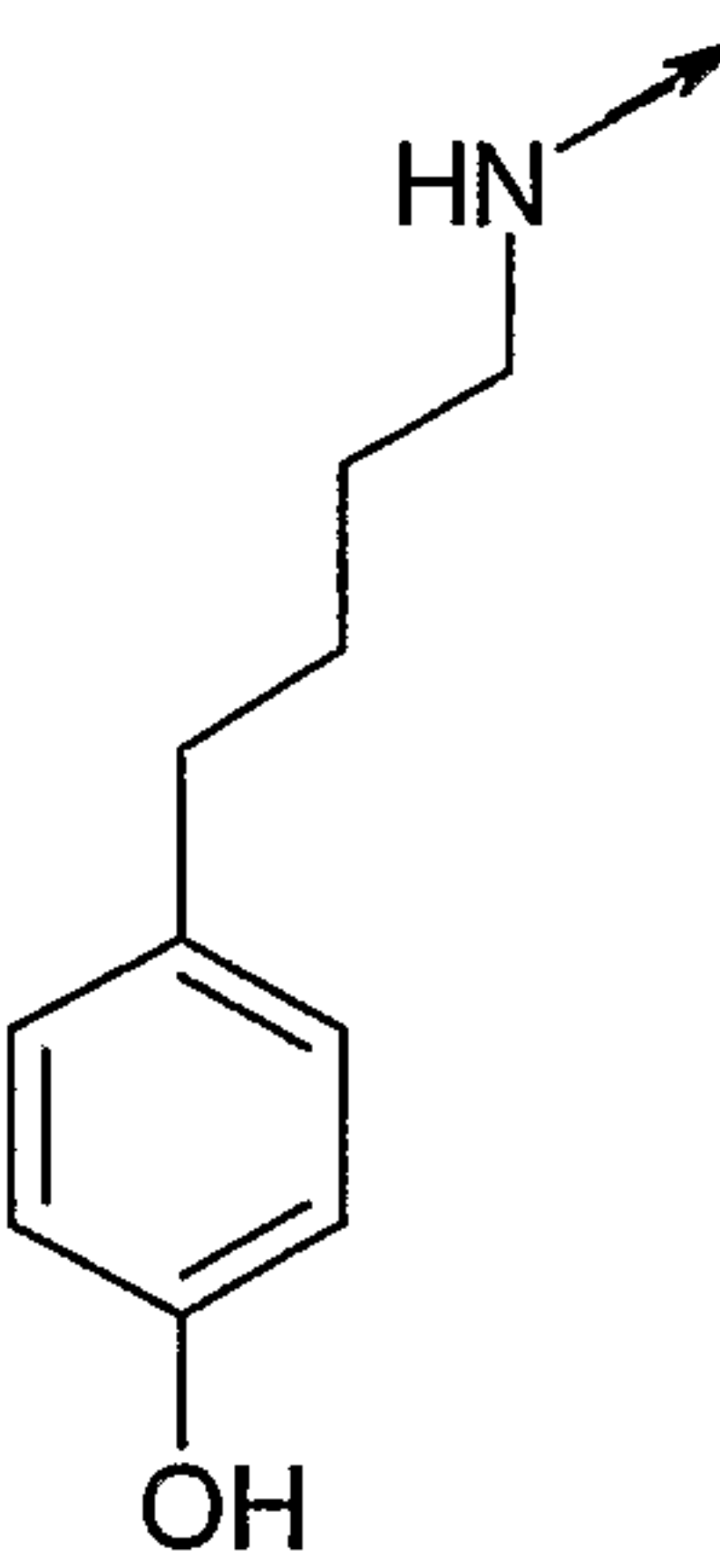
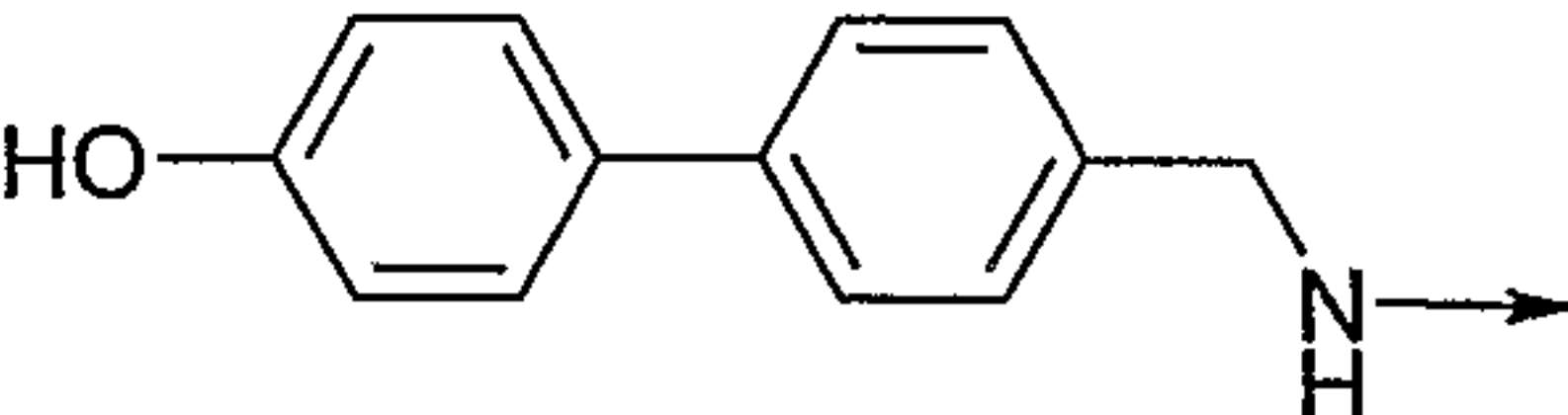
Ex	Name	Mass	Detector	Rt	
72	2-[3-((2 <i>R</i>)-2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]- <i>N</i> -[2-(4-hydroxyphenyl)ethyl]acetamide	448.25	ELSD	1.3	
73	2-[3-((2 <i>R</i>)-2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]- <i>N</i> -(4-hydroxybenzyl)acetamide	434.23	ELSD	1.16	
74	2-[3-((2 <i>R</i>)-2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]- <i>N</i> -(2-hydroxybenzyl)acetamide	434.23	DAD: 225	1.35	
75	2-[3-((2 <i>R</i>)-2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]- <i>N</i> -(3-hydroxybenzyl)acet	434.23	ELSD	1.23	

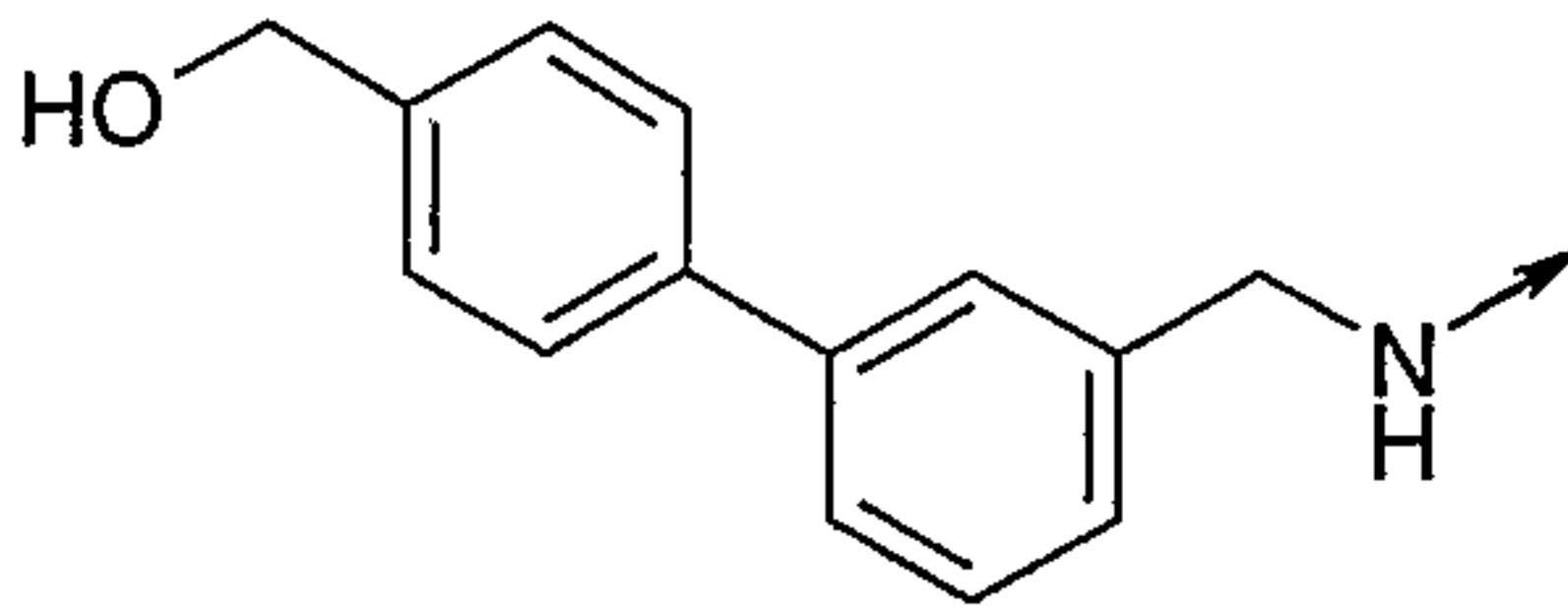
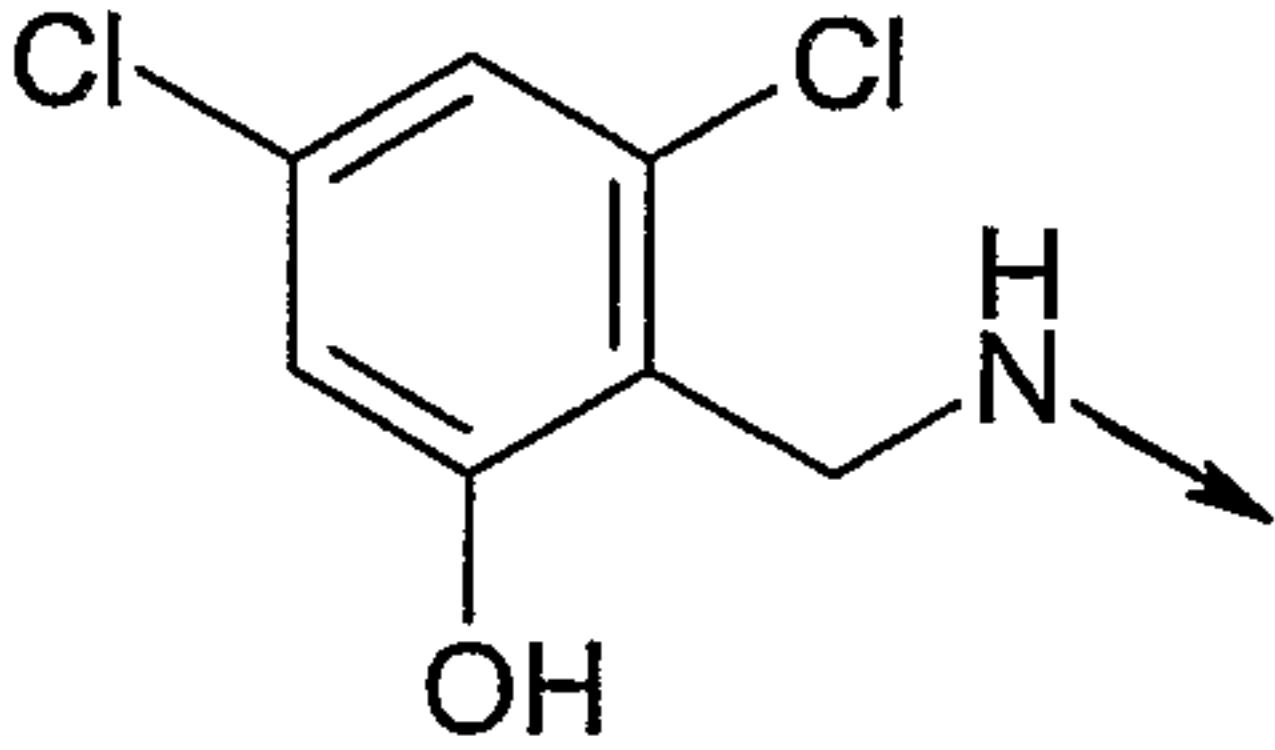
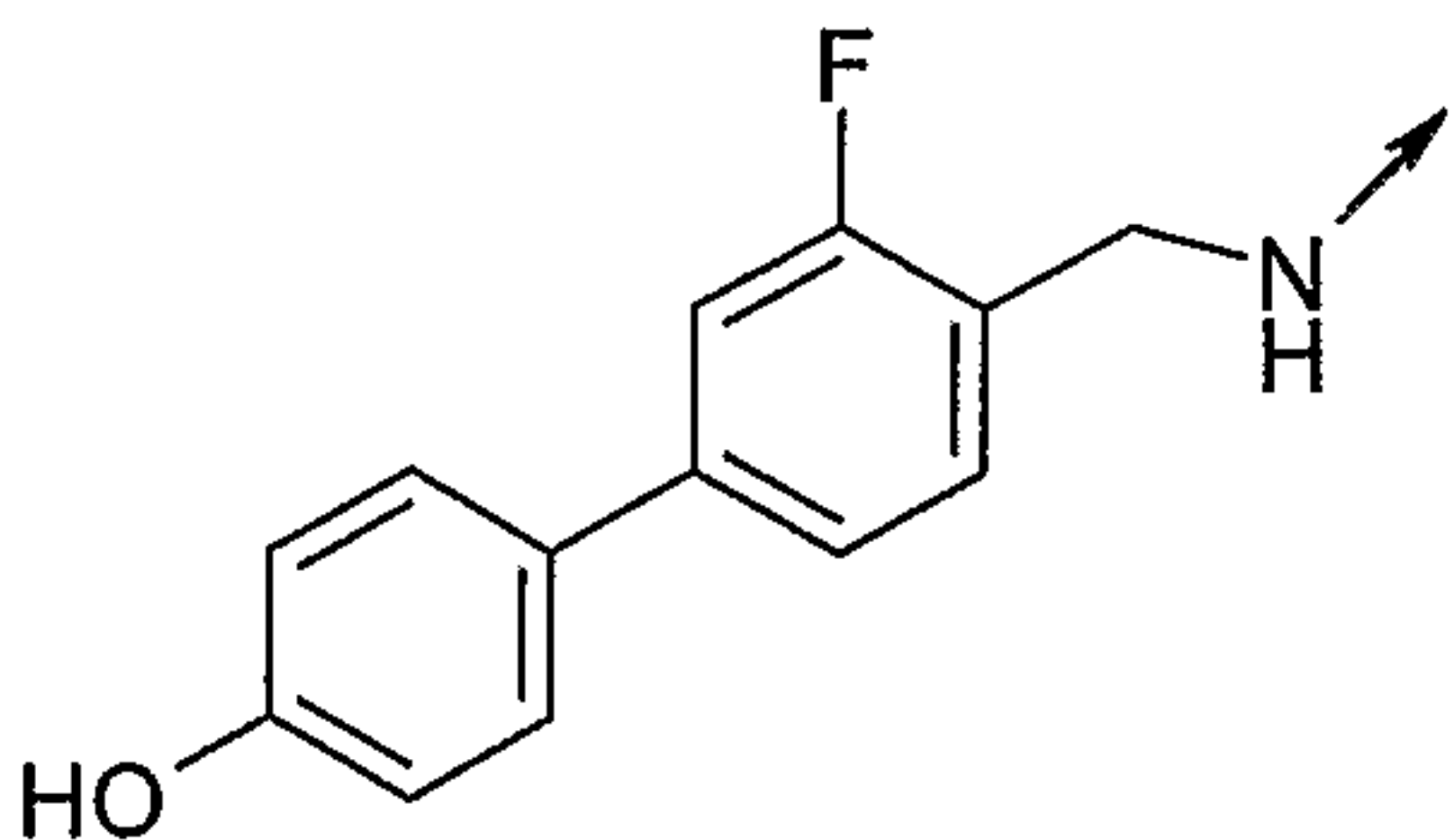
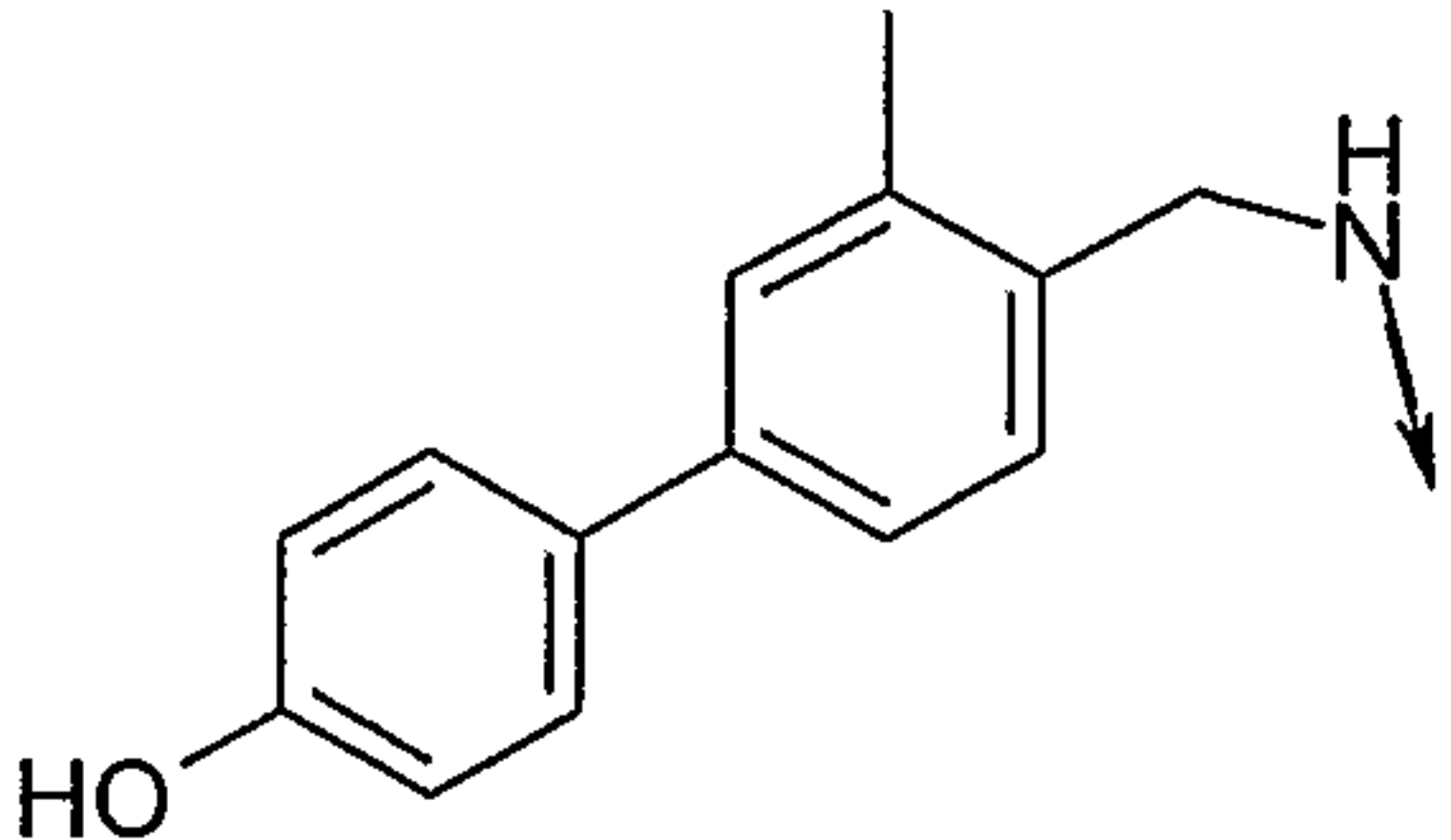
	amide				
76	2-[3-((2 <i>R</i>)-2-[[2- 2-(6-aminopyridin- 3-yl)-2-hydroxy- ethyl]amino}propyl) phenyl]- <i>N</i> -[2-(3- hydroxyphenyl)ethyl]acetamide	448.25	ELSD	1.34	
77	2-[3-((2 <i>R</i>)-2-[[2- 2-(6-aminopyridin- 3-yl)-2-hydroxy- ethyl]amino}propyl) phenyl]- <i>N</i> -[2-(4- hydroxy-3- methoxyphenyl)ethy l]acetamide	478.26	ELSD	1.24	
78	2-[3-((2 <i>R</i>)-2-[[2- 2-(6-aminopyridin- 3-yl)-2-hydroxy- ethyl]amino}propyl) phenyl]- <i>N</i> -(5-tert- butyl-2-hydroxy- phenyl)acetamide	476.28	ELSD	1.82	
79	2-[3-((2 <i>R</i>)-2-[[2- 2-(6-aminopyridin- 3-yl)-2-hydroxy- ethyl]amino}propyl) phenyl]- <i>N</i> -(3- hydroxy-4-methyl-	434.23	DAD: 255	1.52	

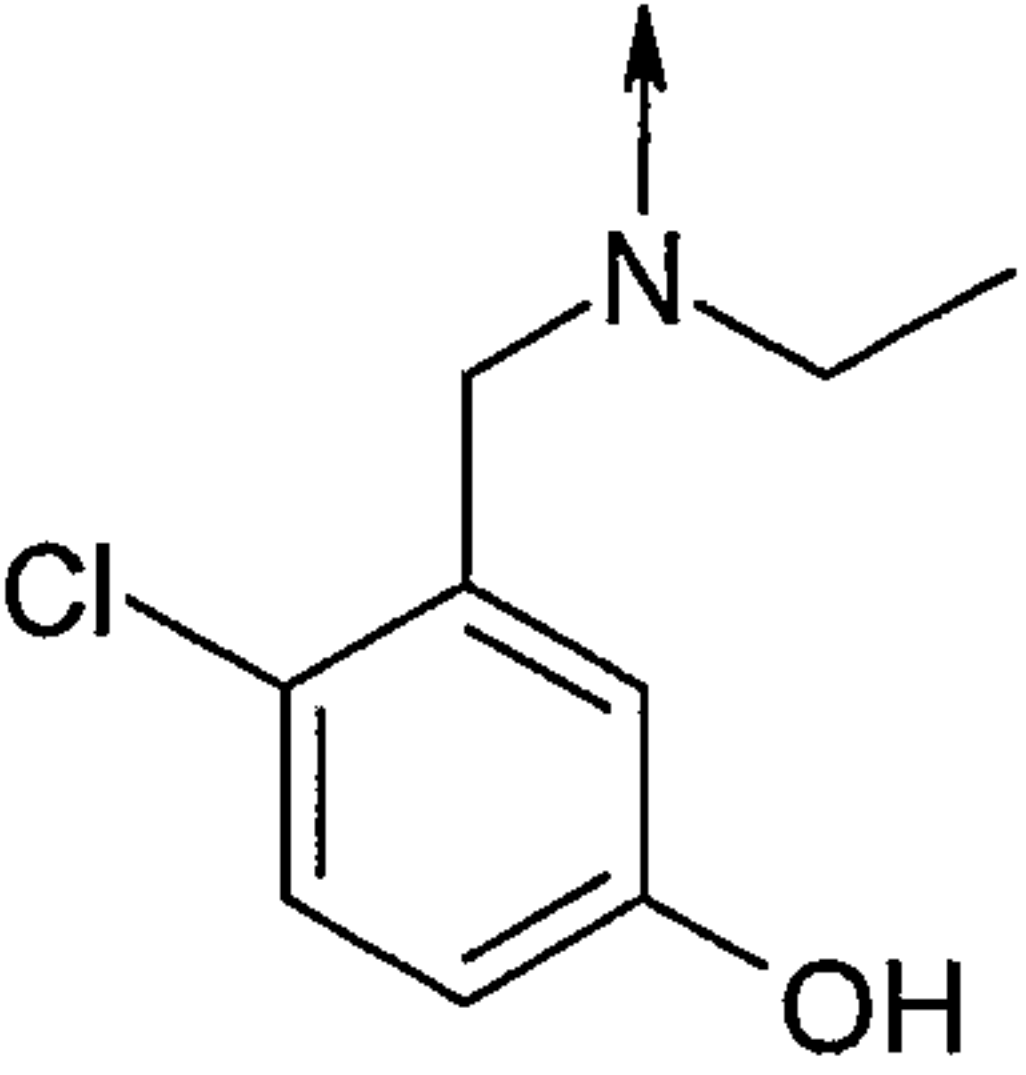
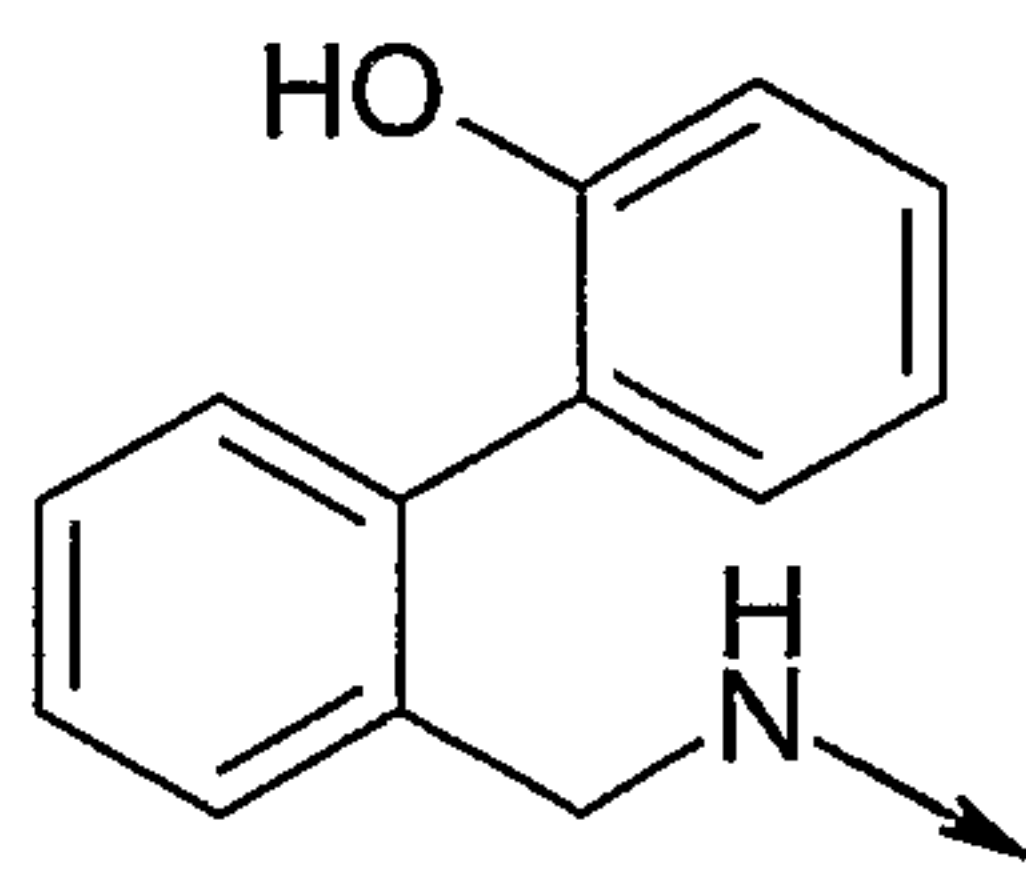
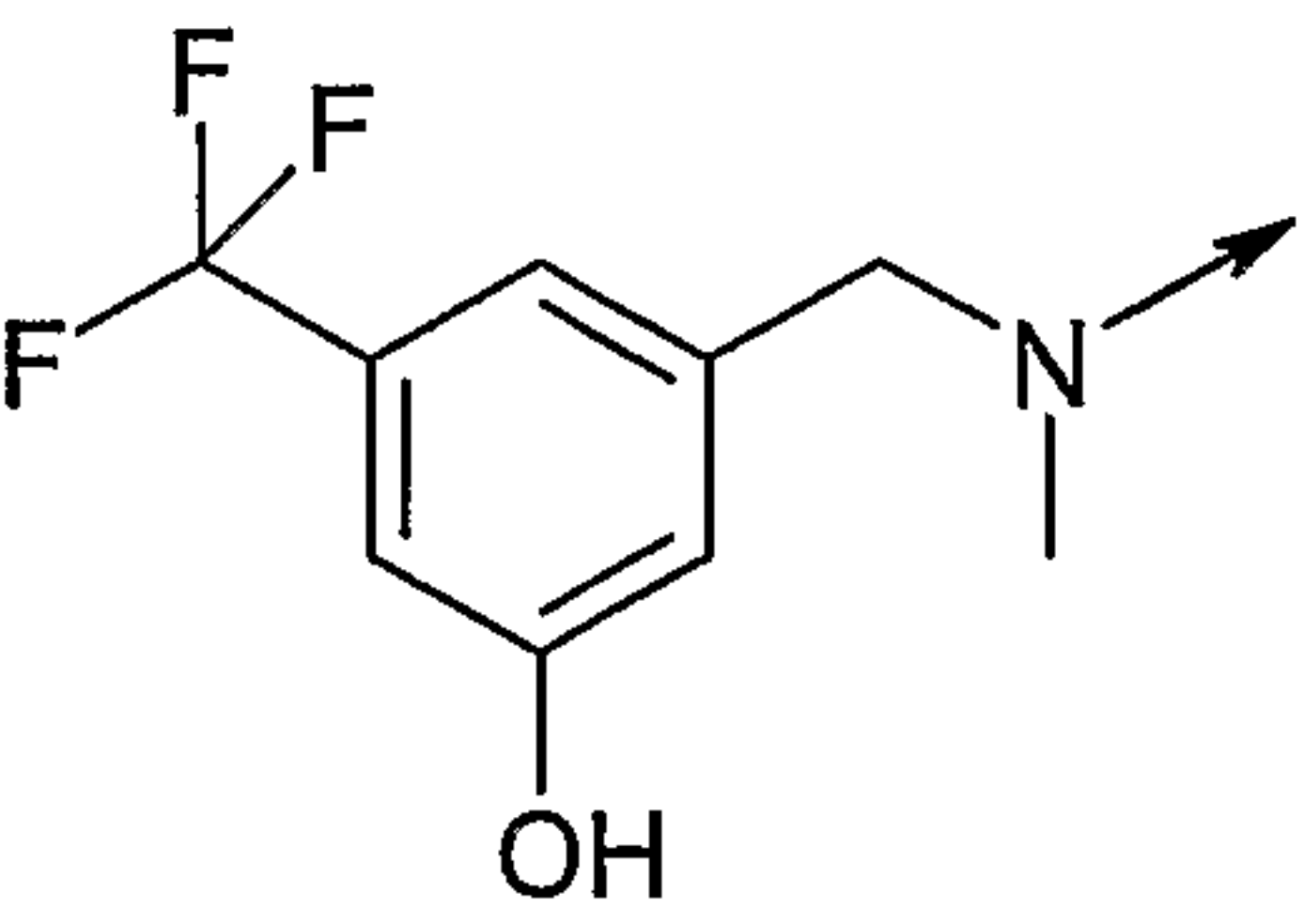
	phenyl)acetamide				
80	2-[3-((2 <i>R</i>)-2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]- <i>N</i> -(3-hydroxy-4-methoxyphenyl)acetamide	450.23	ELSD	1.25	
81	2-[3-((2 <i>R</i>)-2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]- <i>N</i> -(4-hydroxy-3-methoxybenzyl)acetamide	464.24	ELSD	1.3	
82	2-[3-((2 <i>R</i>)-2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]- <i>N</i> -[5-(ethylsulfonyl)-2-hydroxyphenyl]acetamide	512.21	ELSD	1.22	
83	2-[3-((2 <i>R</i>)-2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]- <i>N</i> -(2-hydroxy-5-methyl-	434.23	ELSD	1.47	

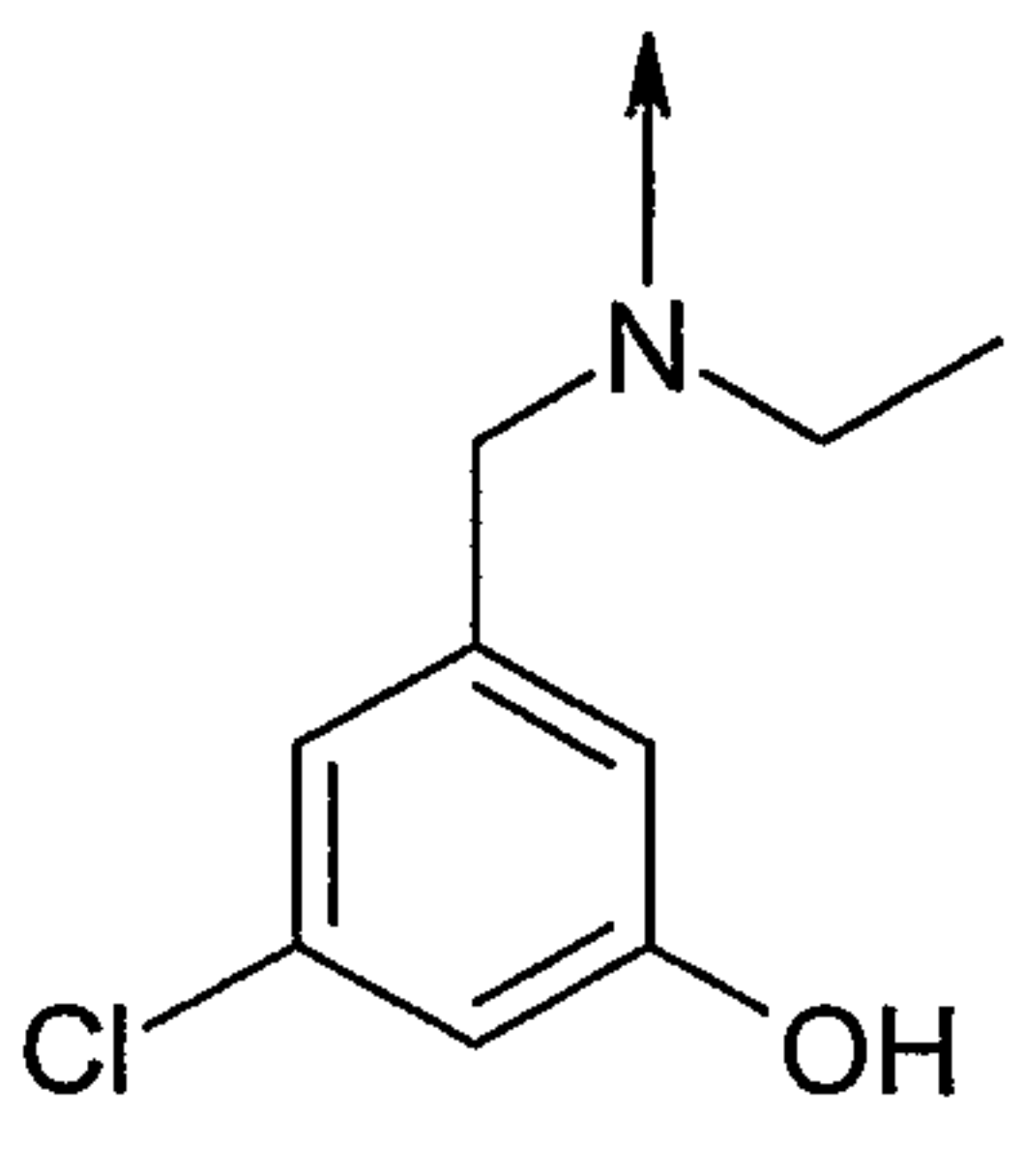
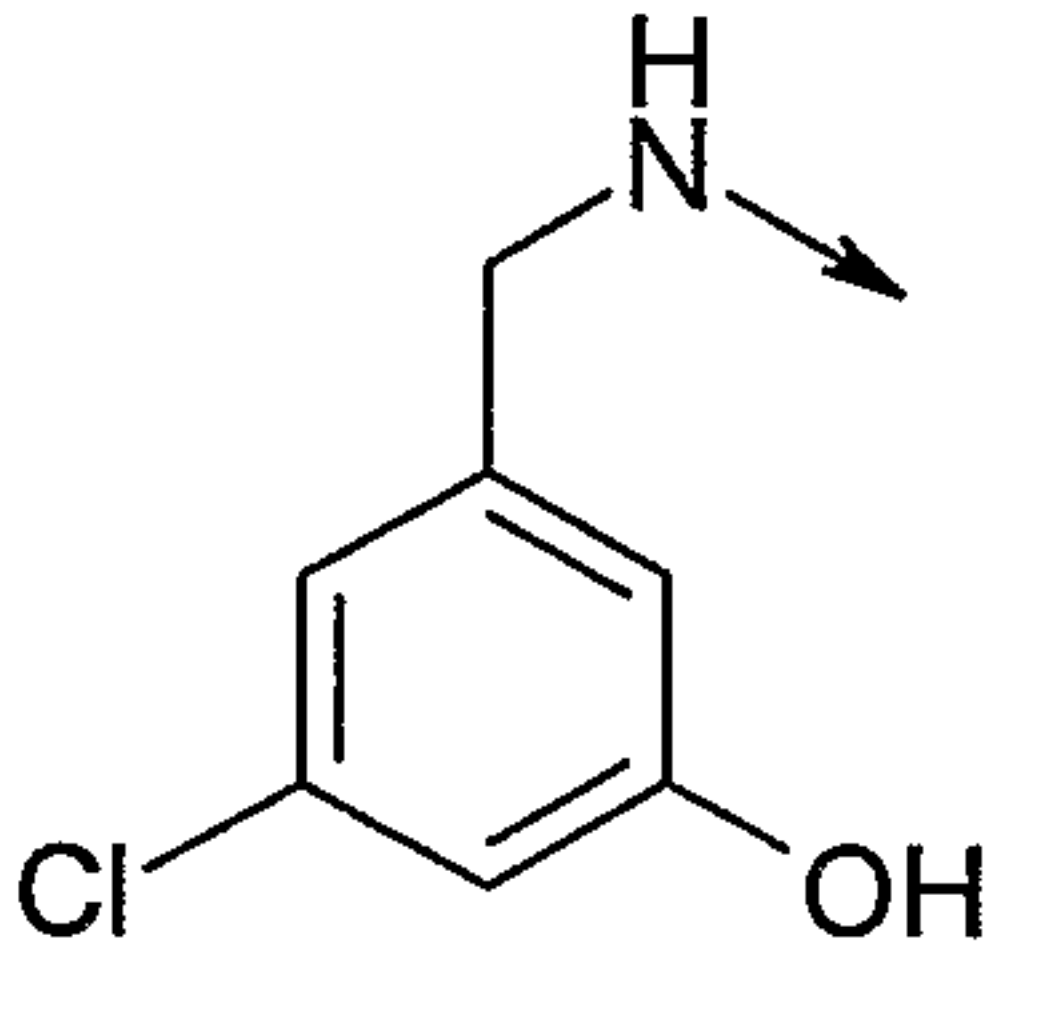
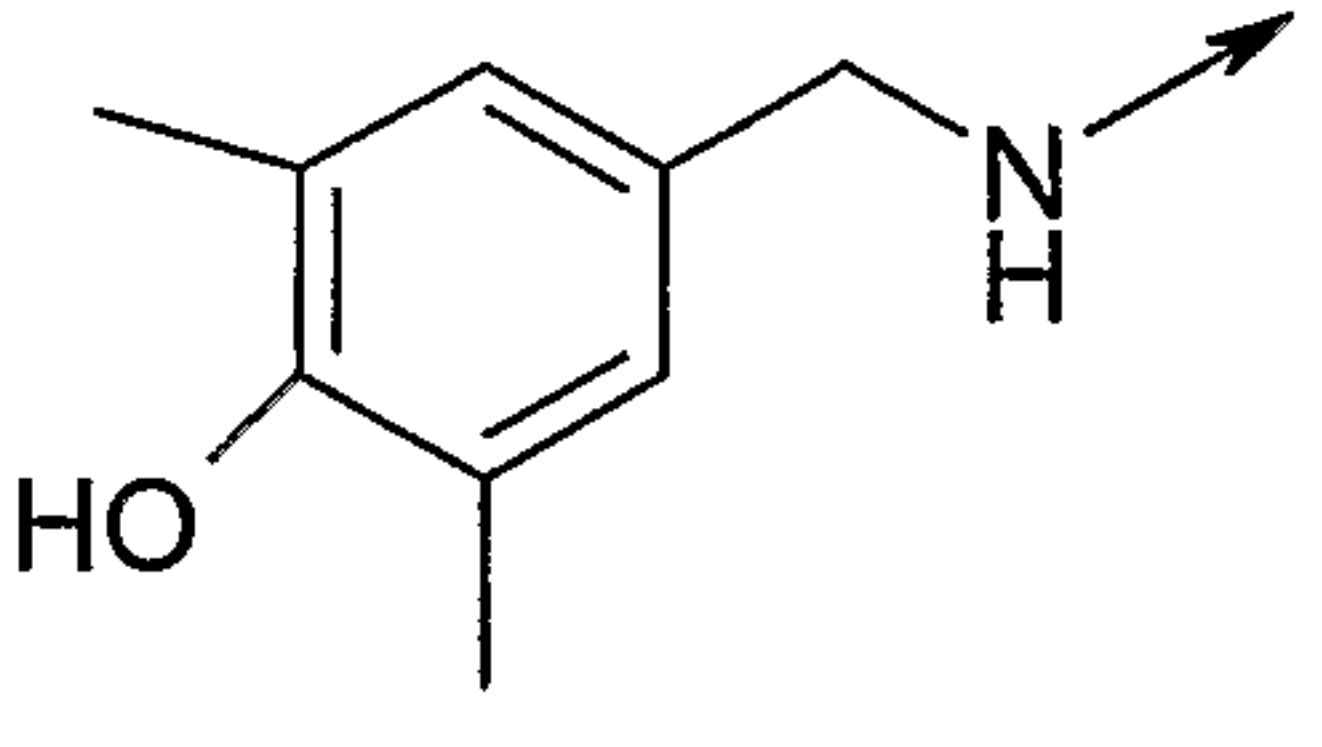
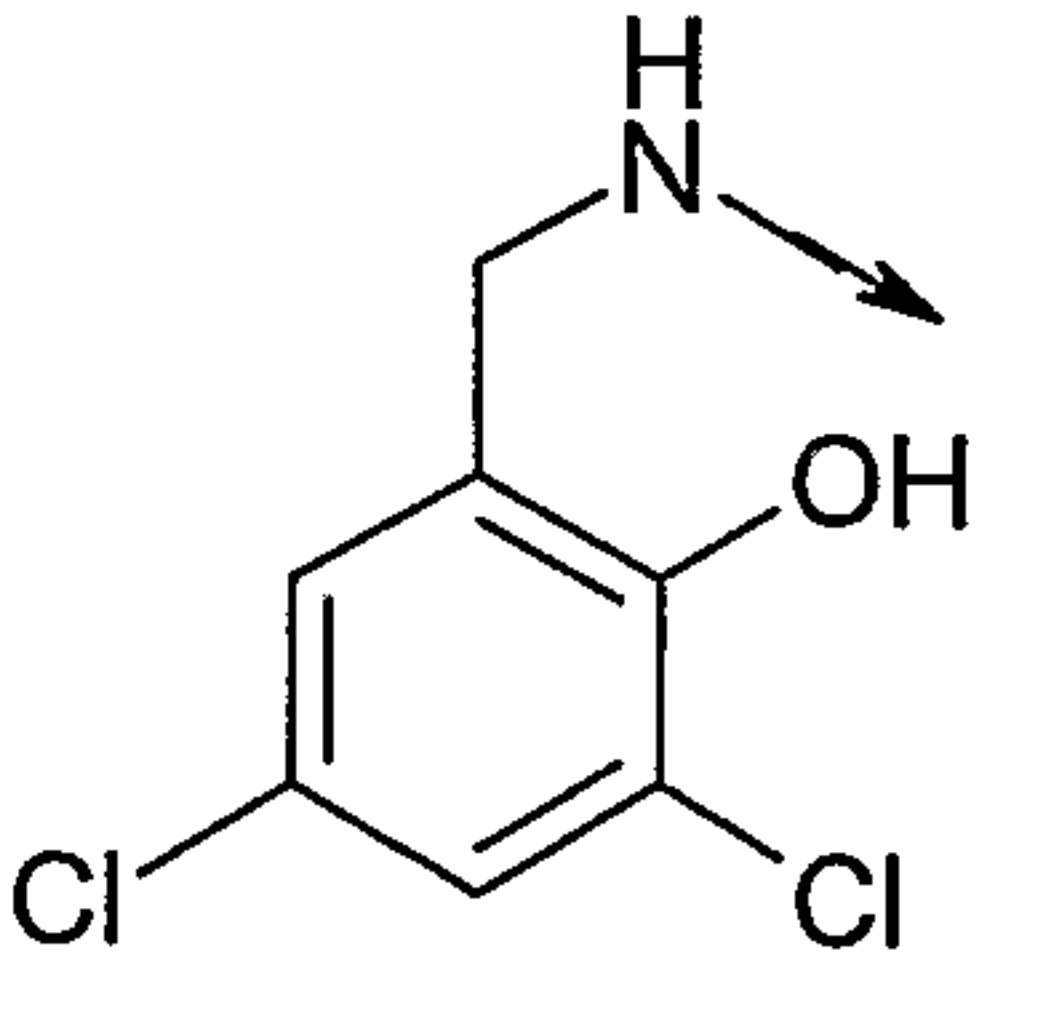
	phenyl)acetamide				
84	2-[3-((2 <i>R</i>)-2-[[2- 2-(6-aminopyridin- 3-yl)-2-hydroxy- ethyl]amino}propyl) phenyl]- <i>N</i> -(3- hydroxy-2-methyl- phenyl)acetamide	434.23	DAD: 225	1.24	
85	2-[3-((2 <i>R</i>)-2-[[2- 2-(6-aminopyridin- 3-yl)-2-hydroxy- ethyl]amino}propyl) phenyl]- <i>N</i> -(5-chloro- 2-hydroxybenzyl)- acetamide	468.19	ELSD	1.5	
86	2-[3-((2 <i>R</i>)-2-[[2- 2-(6-aminopyridin- 3-yl)-2-hydroxy- ethyl]amino}propyl) phenyl]- <i>N</i> -[2- hydroxy-2-(3- hydroxyphenyl)ethyl]- <i>N</i> -methyl- acetamide	478.26	ELSD	1.26	
87	2-[3-((2 <i>R</i>)-2-[[2- 2-(6-aminopyridin- 3-yl)-2-hydroxy- ethyl]amino}propyl) phenyl]- <i>N</i> -[2-(3-	492.27	DAD: 225	1.35	

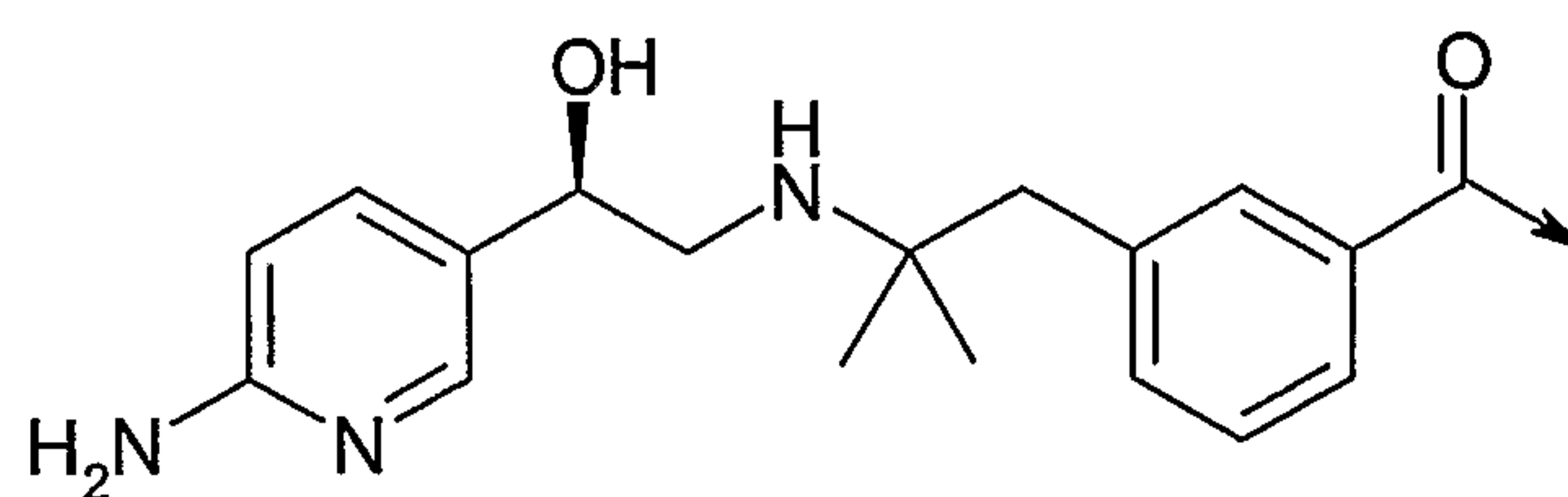
	ethoxy-4-hydroxy-phenyl)ethyl]acetamide				
88	2-[3-((2 <i>R</i>)-2-[[2- <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]- <i>N</i> -[2-(3-hydroxy-4-methoxyphenyl)ethyl]acetamide	478.26	ELSD	1.29	
89	2-[3-((2 <i>R</i>)-2-[[2- <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]- <i>N</i> -ethyl- <i>N</i> -[2-(4-hydroxyphenyl)ethyl]acetamide	476.28	ELSD	1.52	
90	2-[3-((2 <i>R</i>)-2-[[2- <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]- <i>N</i> -(2-chloro-4-hydroxybenzyl)- <i>N</i> -ethylacetamide	496.22	ELSD	1.56	

91	2-[3-((2 <i>R</i>)-2-[[2- 2-(6-aminopyridin- 3-yl)-2-hydroxy- ethyl]amino}propyl) phenyl]- <i>N</i> -(5- hydroxy-1,2,3,4- tetrahydronaphthalen-1-yl)acetamide	474.26	ELSD	1.36	
92	2-[3-((2 <i>R</i>)-2-[[2- 2-(6-aminopyridin- 3-yl)-2-hydroxy- ethyl]amino}propyl) phenyl]- <i>N</i> -(4- hydroxyphenyl)acet amide	420.22	ELSD	1.19	
93	2-[3-((2 <i>R</i>)-2-[[2- 2-(6-aminopyridin- 3-yl)-2-hydroxy- ethyl]amino}propyl) phenyl]- <i>N</i> -[4-(4- hydroxyphenyl)butyl]acetamide	476.28	DAD: 255	1.42	
94	2-[3-((2 <i>R</i>)-2-[[2- 2-(6-aminopyridin- 3-yl)-2-hydroxy- ethyl]amino}propyl) phenyl]- <i>N</i> -[(4'- hydroxy-1,1'-	510.26	ELSD	1.51	

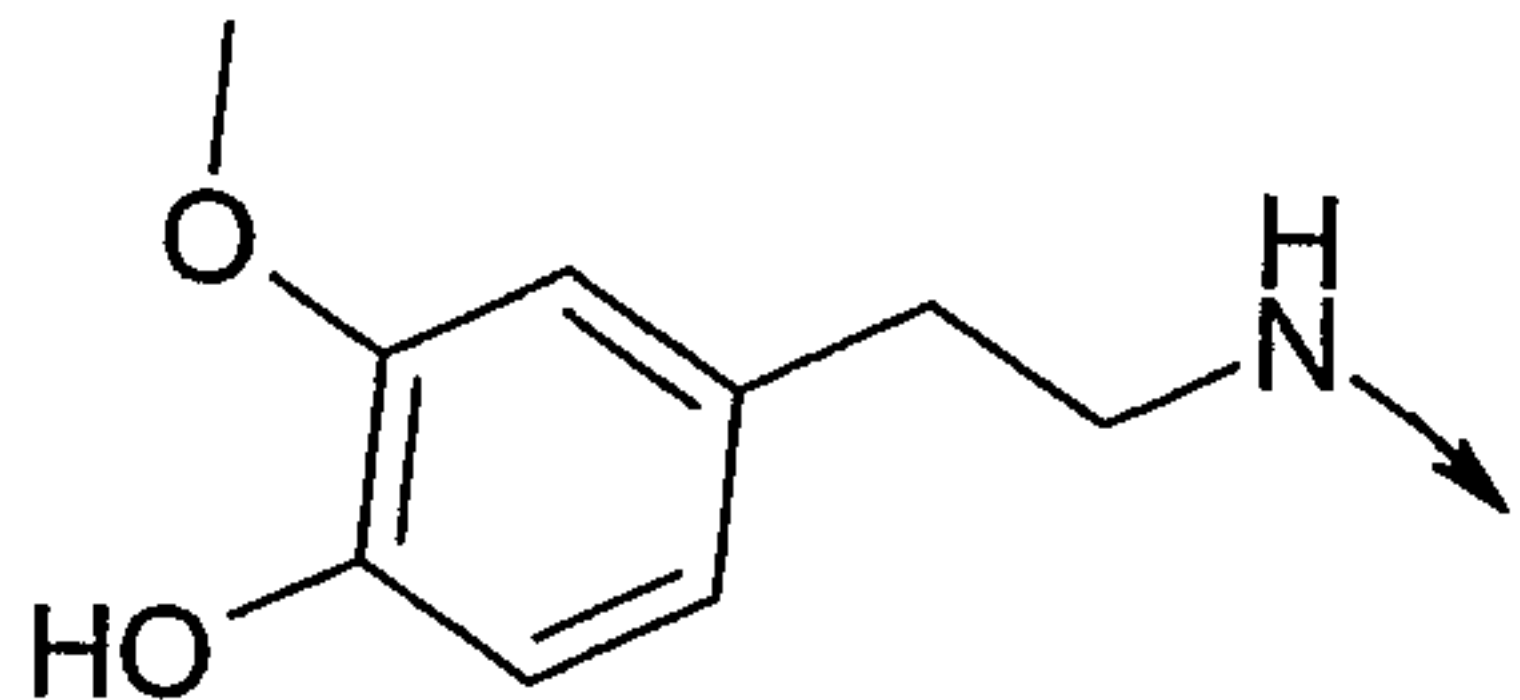
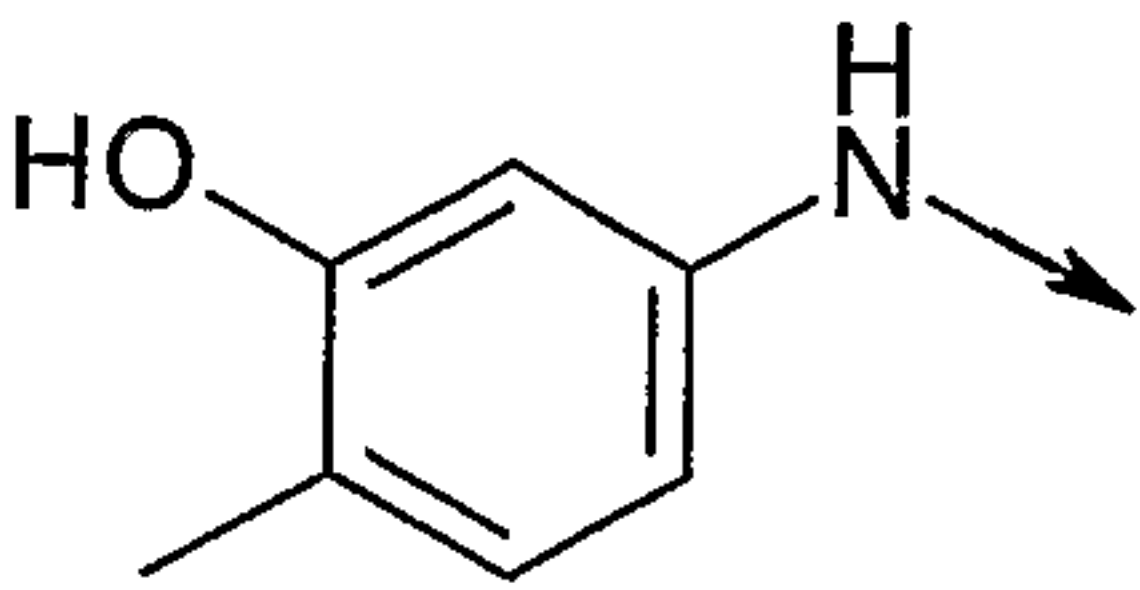
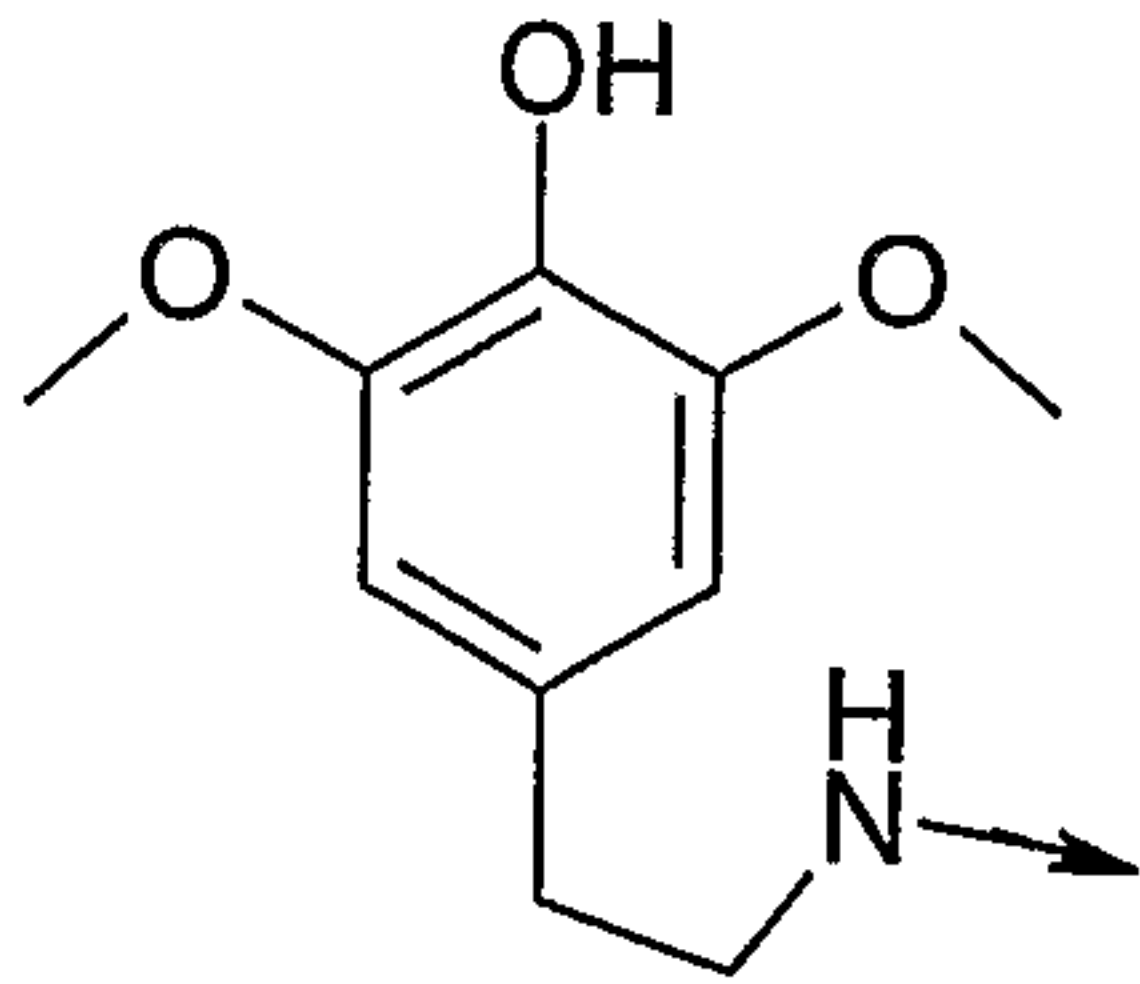
	biphenyl-4-yl)methyl]acetamide				
95	2-[3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]- <i>N</i> -[4'-(hydroxymethyl)-1,1'-biphenyl-3-yl]methyl}acetamide	524.28	ELSD	1.53	
96	2-[3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]- <i>N</i> -(2,4-dichloro-6-hydroxybenzyl)acetamide	502.15	ELSD	1.74	
97	2-[3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]- <i>N</i> -[(3-fluoro-4'-hydroxy-1,1'-biphenyl-4-yl)methyl]acetamide	528.25	ELSD	1.64	
98	2-[3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]- <i>N</i> -[4'-methyl-1,1'-biphenyl-3-yl]methyl}acetamide	524.28	ELSD	1.59	

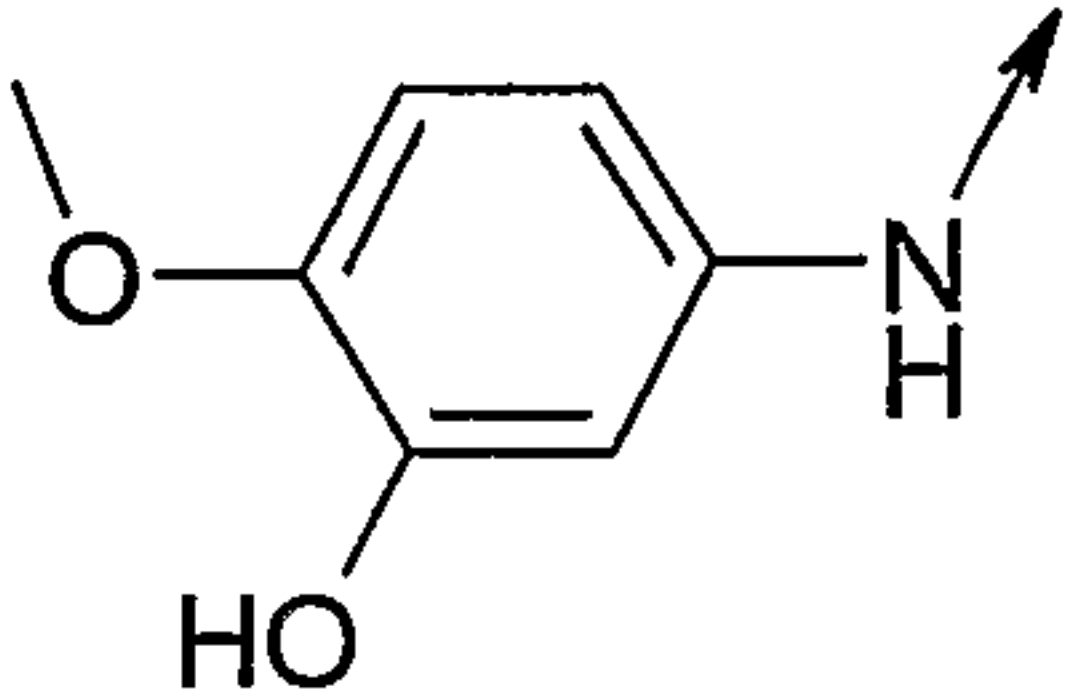
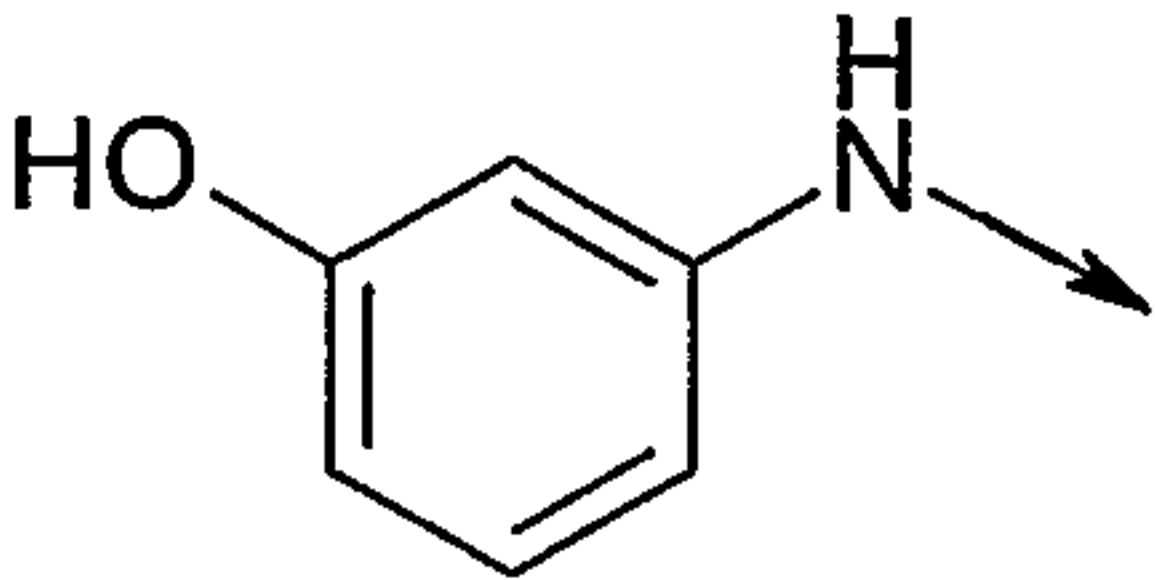
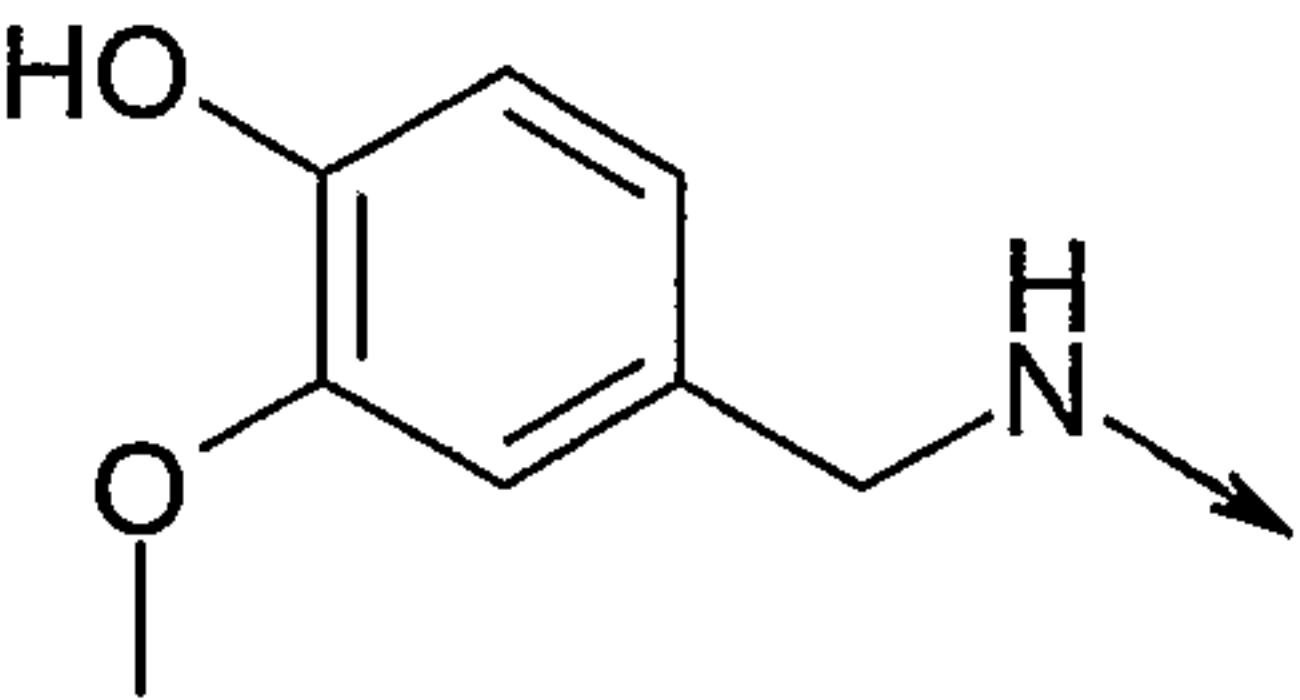
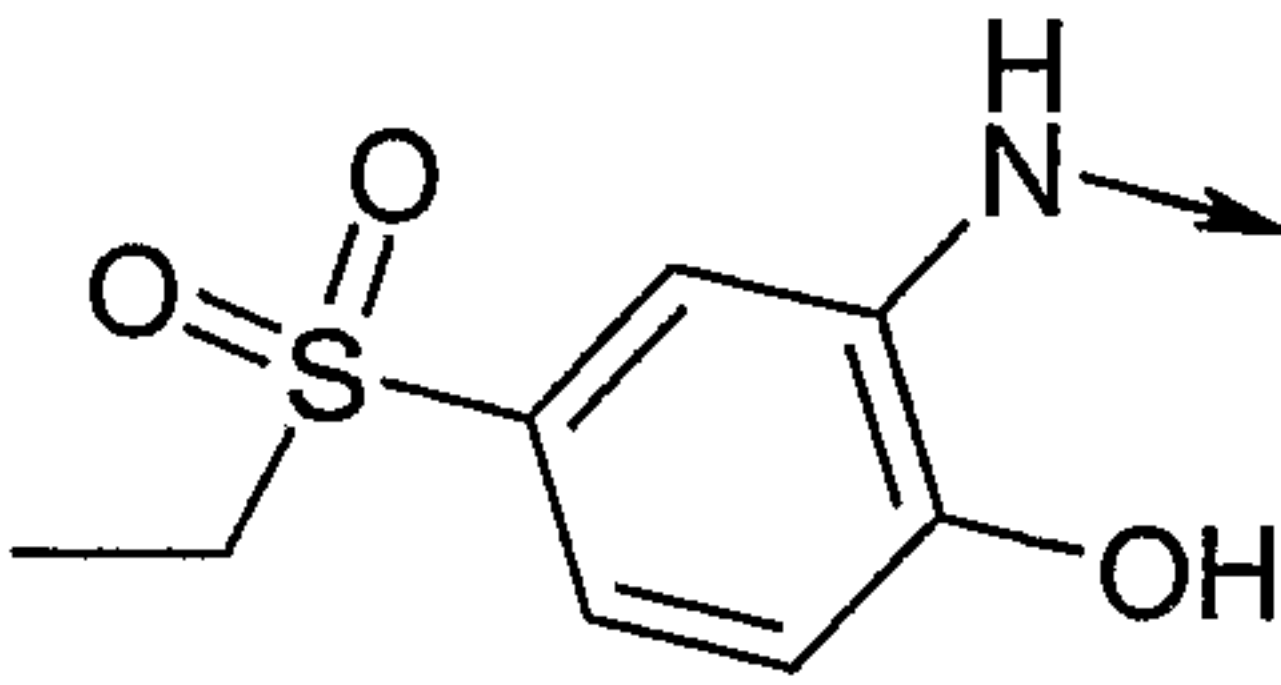
	phenyl]-N-[(4'-hydroxy-3-methyl-1,1'-biphenyl-4-yl)methyl]acetamide				
99	2-[3-((2R)-2-[(2R)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]-N-(2-chloro-5-hydroxybenzyl)-N-ethylacetamide	496.22	ELSD	1.7	
100	2-[3-((2R)-2-[(2R)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]-N-[(2'-hydroxy-1,1'-biphenyl-2-yl)methyl]acetamide	510.26	ELSD	1.61	
101	2-[3-((2R)-2-[(2R)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]-N-[3-hydroxy-5-(trifluoromethyl)benzyl]-N-methylacetamide	516.23	ELSD	1.69	

102	2-[3-((2 <i>R</i>)-2-[[2- <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]- <i>N</i> -(3-chloro-5-hydroxybenzyl)- <i>N</i> -ethylacetamide	496.22	ELSD	1.6	
103	2-[3-((2 <i>R</i>)-2-[[2- <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]- <i>N</i> -(3-chloro-5-hydroxybenzyl)acetamide	468.2	ELSD	1.4	
104	2-[3-((2 <i>R</i>)-2-[[2- <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]- <i>N</i> -(4-hydroxy-3,5-dimethylbenzyl)acetamide	462.3	ELSD	1.35	
105	2-[3-((2 <i>R</i>)-2-[[2- <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]- <i>N</i> -(3,5-dichloro-2-hydroxybenzyl)acetamide	502.2	ELSD	1.76	

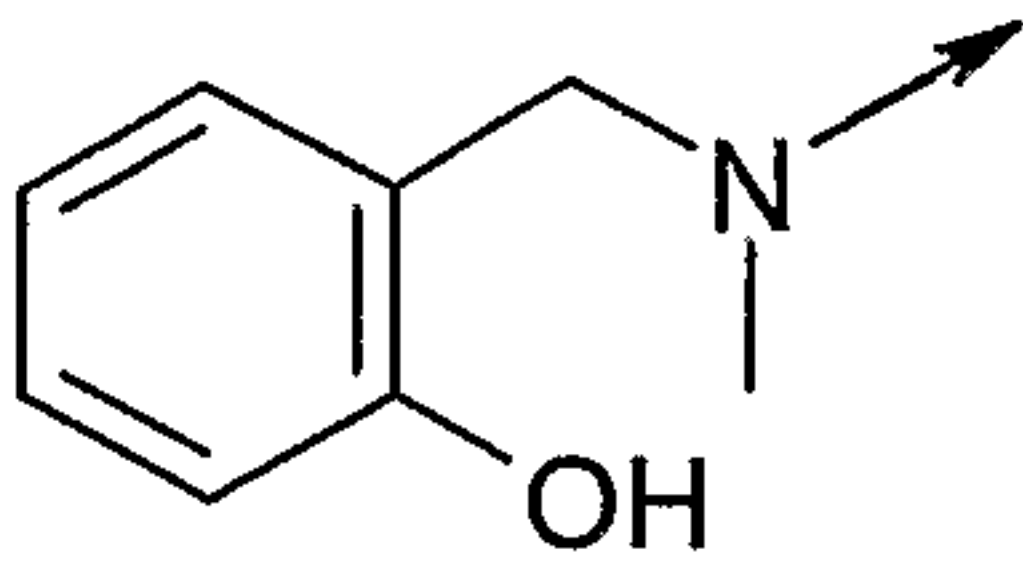
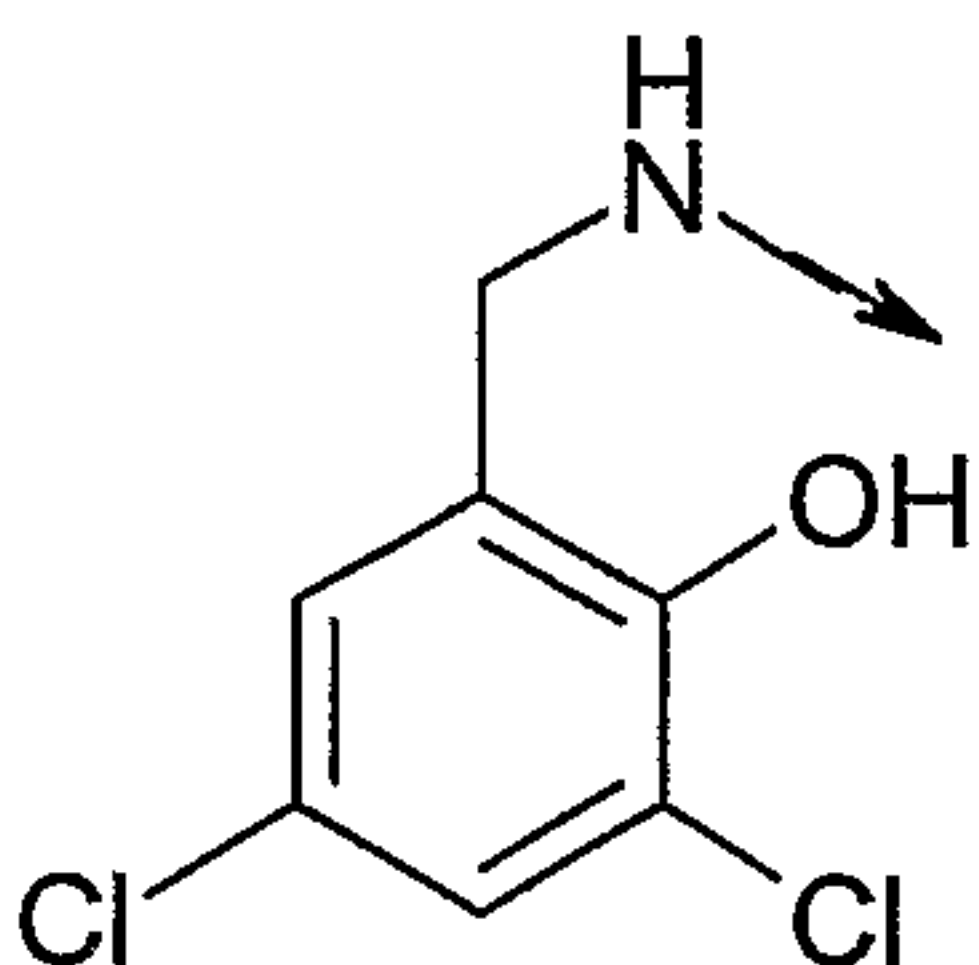
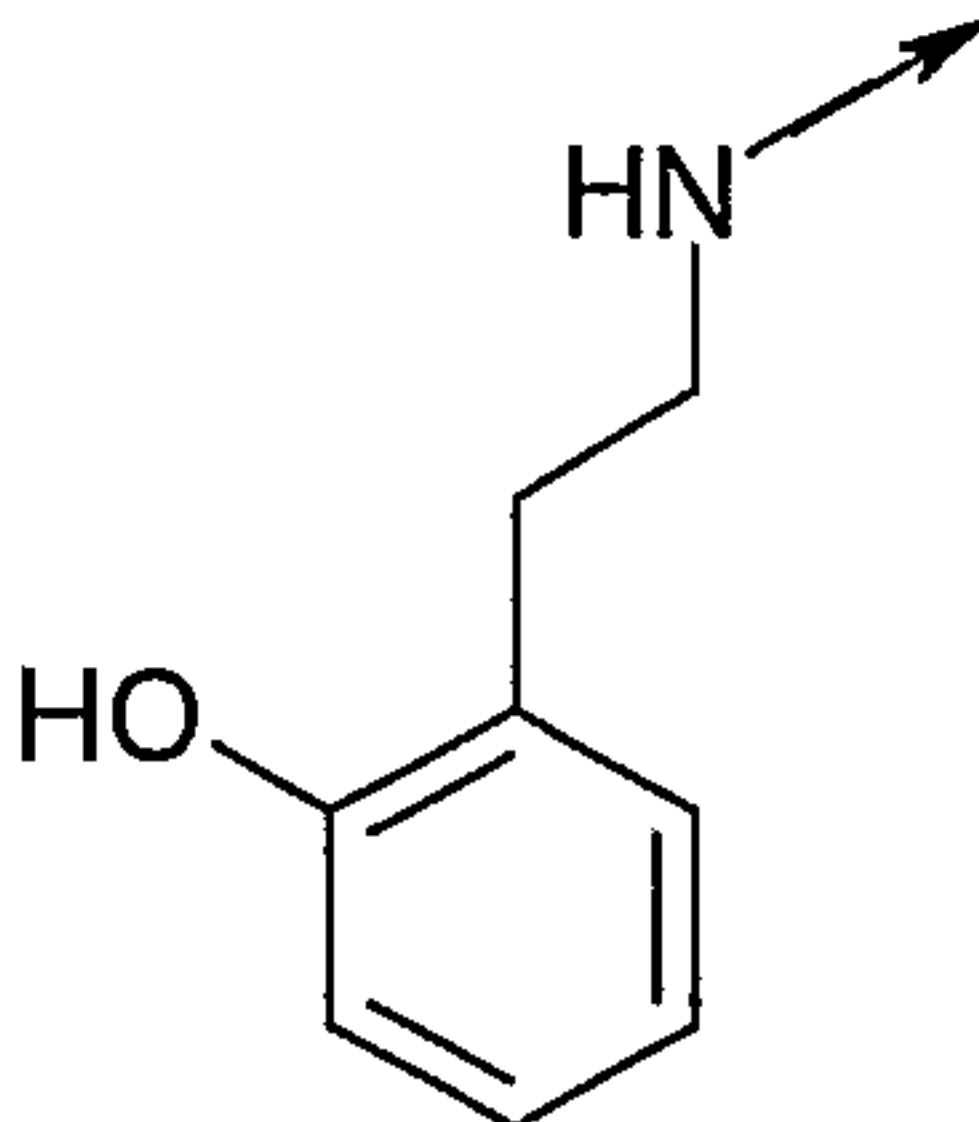


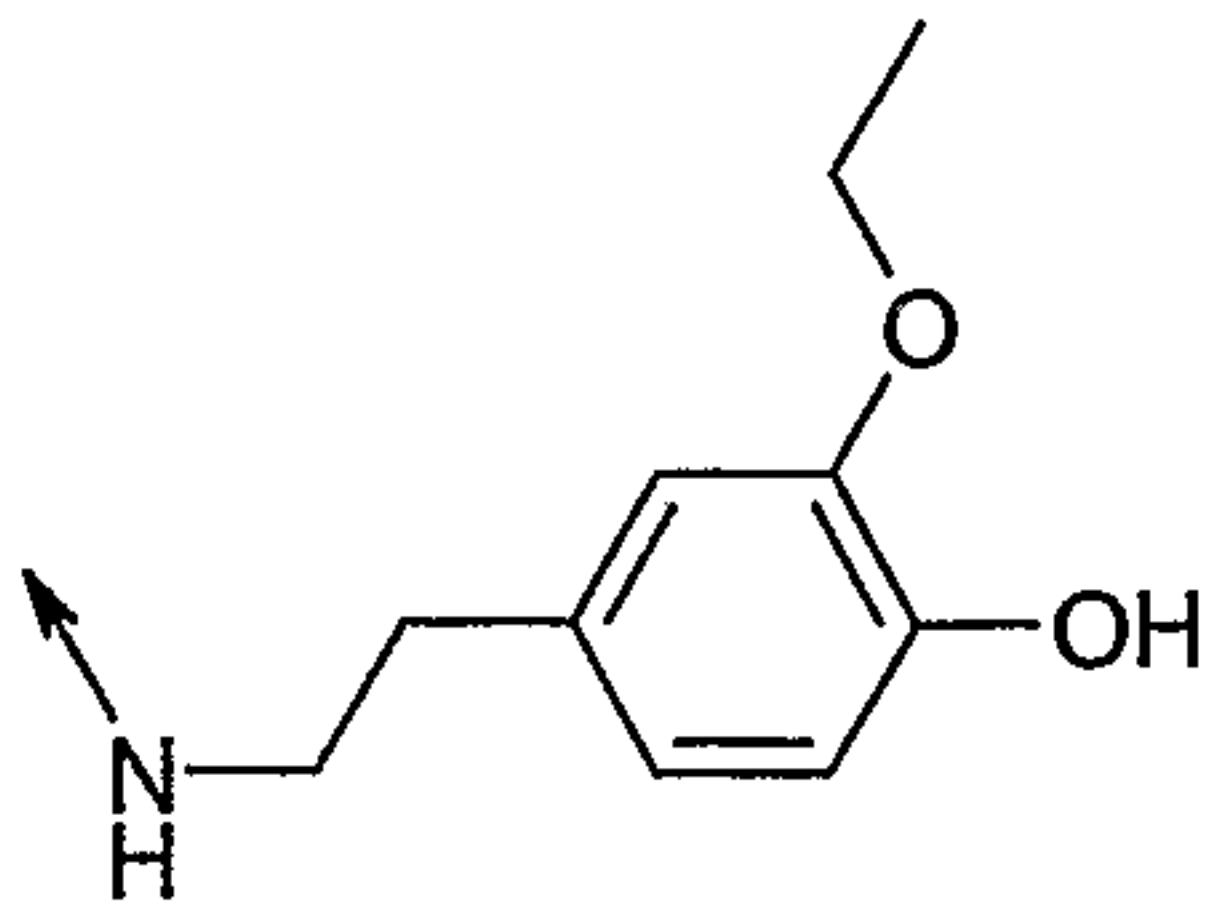
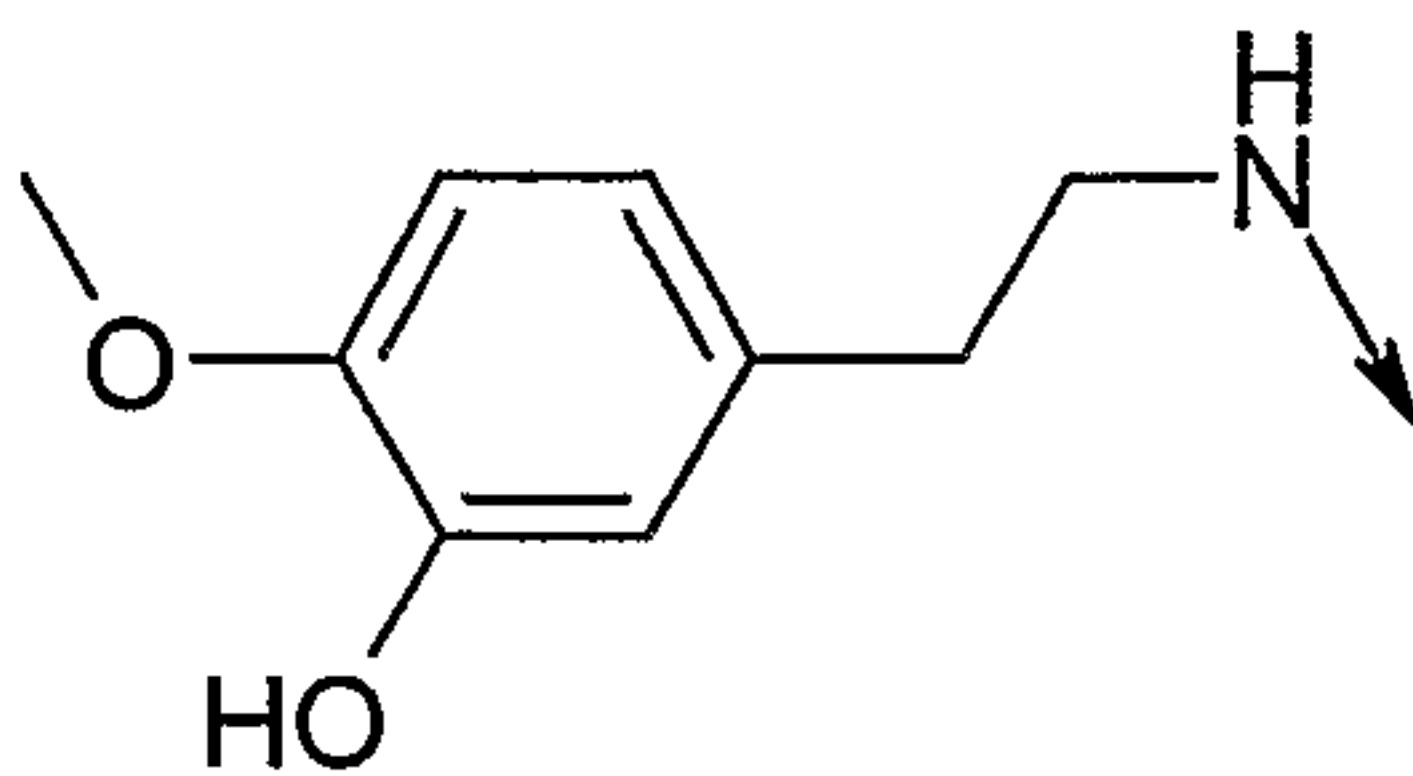
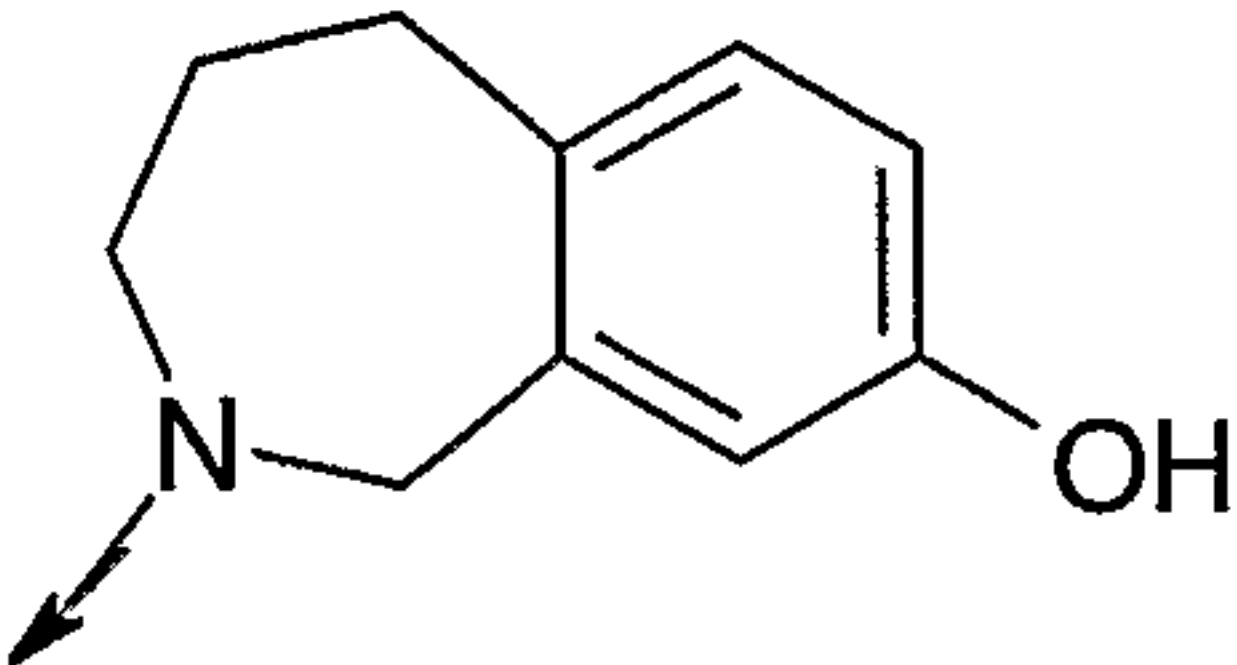
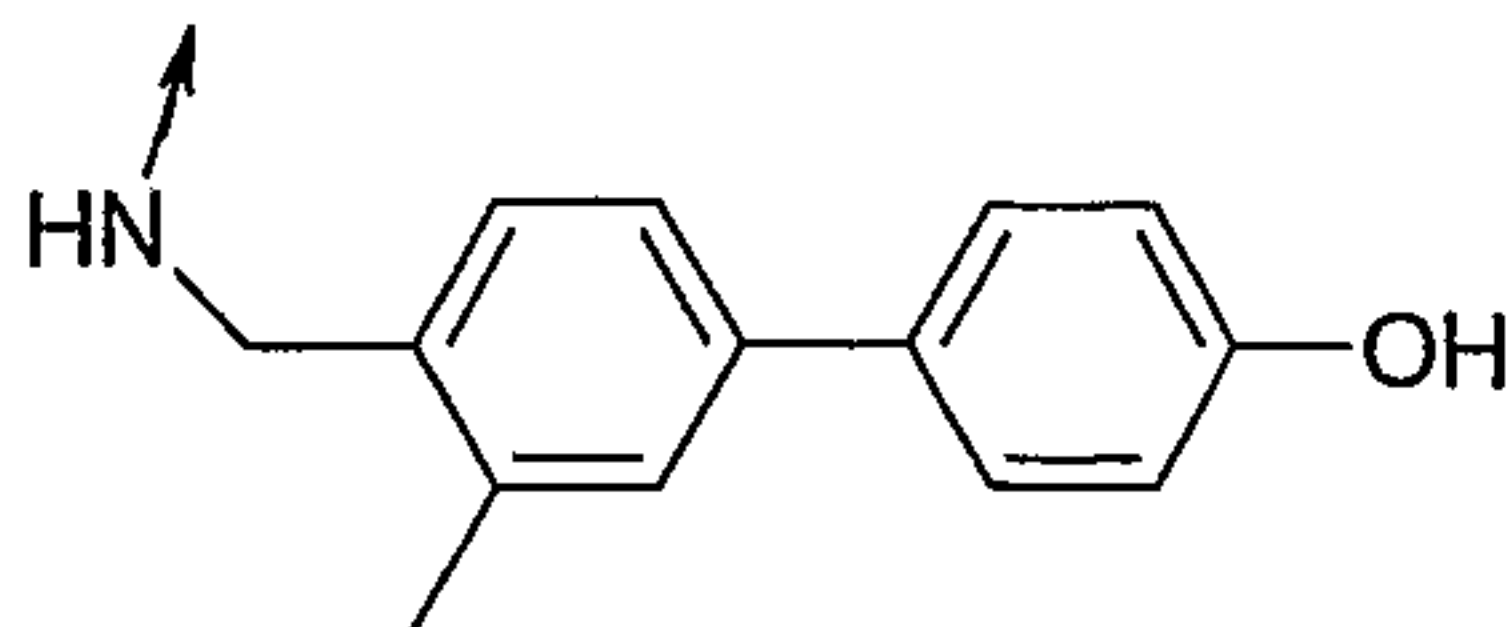
Ex	Name	Mass	Detector	Rt	
106	3-(2-([(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)- <i>N</i> -[2-(4-hydroxyphenyl)ethyl]benzamide	448.25	ELSD	1.26	
107	3-(2-([(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)- <i>N</i> -(4-hydroxybenzyl)benzamide	434.23	ELSD	1.34	
108	3-(2-([(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)- <i>N</i> -(2-hydroxybenzyl)benzamide	434.23	ELSD	1.43	
109	3-(2-([(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-	448.25	ELSD	1.32	

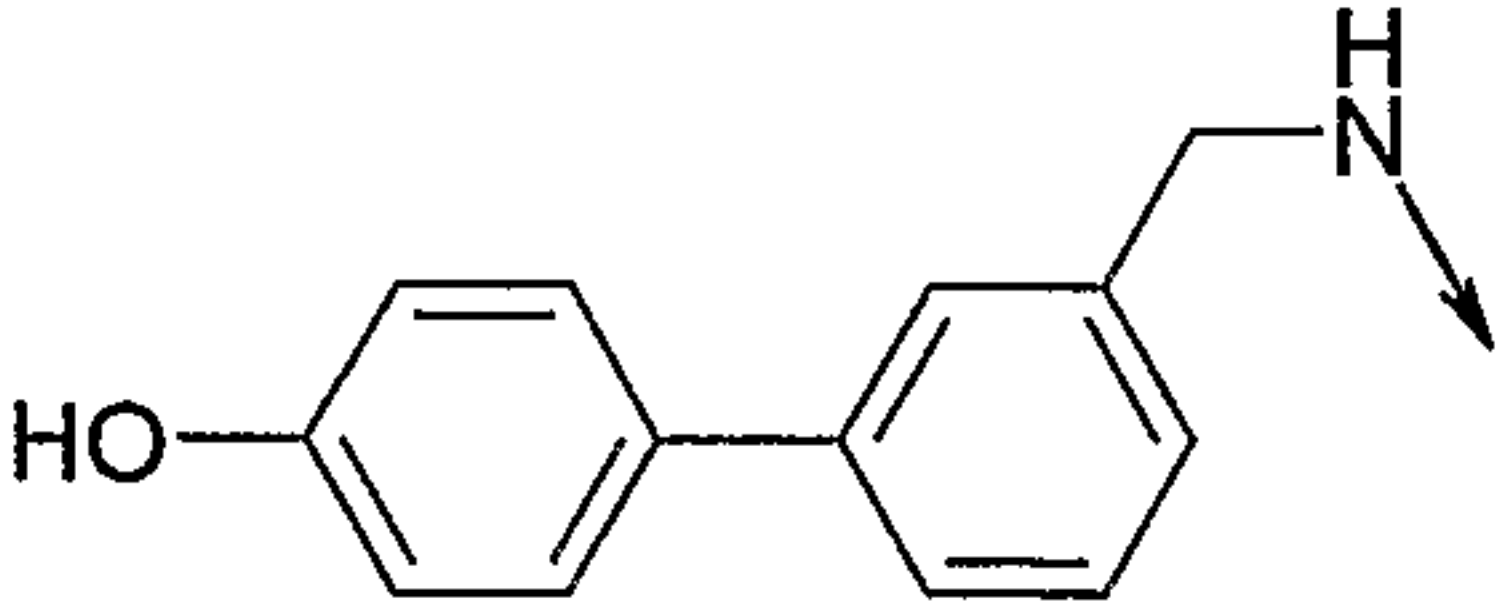
	amino}-2-methyl-propyl)- <i>N</i> -[2-(3-hydroxyphenyl)ethyl]benzamide				
110	3-(2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)- <i>N</i> -[2-(4-hydroxy-3-methoxyphenyl)ethyl]benzamide	478.26	ELSD	1.4	
111	3-(2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)- <i>N</i> -(3-hydroxy-4-methylphenyl)benzamide	434.23	ELSD	1.44	
112	3-(2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)- <i>N</i> -[2-(4-hydroxy-3,5-dimethoxyphenyl)ethyl]benzamide	508.27	ELSD	1.34	

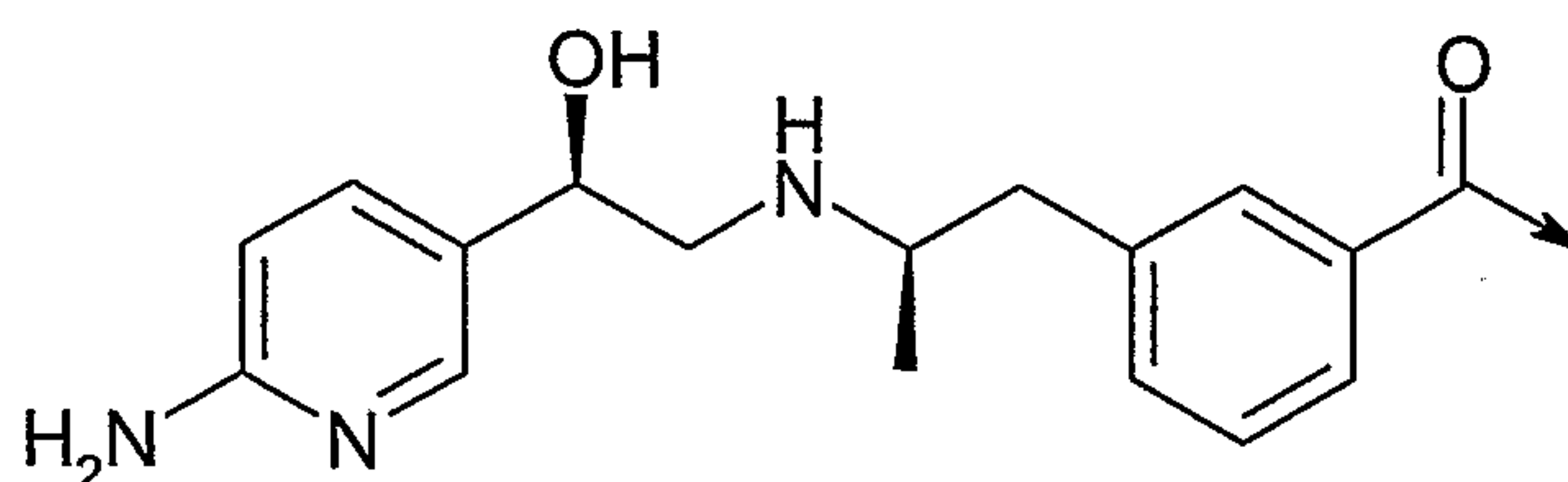
113	3-(2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)- <i>N</i> -(3-hydroxy-4-methoxyphenyl)benzamide	450.23	ELSD	1.27	
114	3-(2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)- <i>N</i> -(3-hydroxyphenyl)benzamide	420.22	ELSD	1.4	
115	3-(2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)- <i>N</i> -(4-hydroxy-3-methoxybenzyl)benzamide	464.24	ELSD	1.25	
116	3-(2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)- <i>N</i> -[5-(ethylsulfonyl)-2-	512.21	ELSD	1.24	

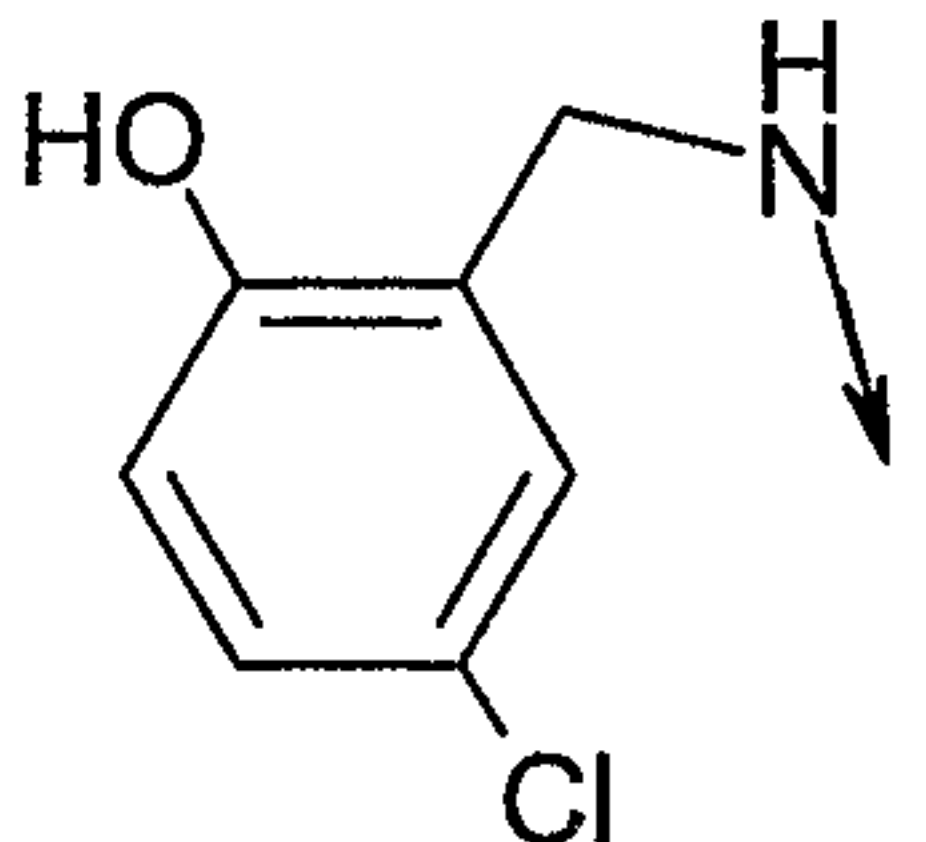
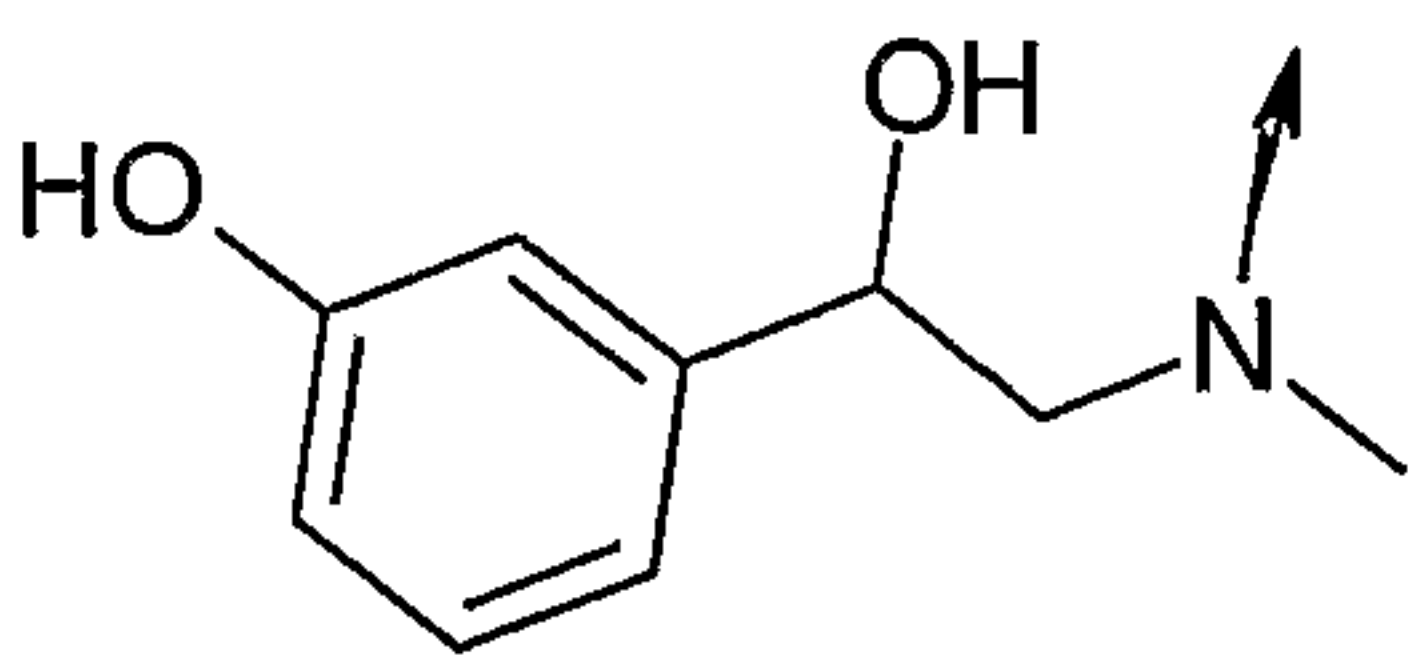
	hydroxyphenyl]benzamide				
117	3-(2-([(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methylpropyl)- <i>N</i> -(3-hydroxy-2-methylphenyl)benzamide	434.23	ELSD	1.26	
118	3-(2-([(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methylpropyl)- <i>N</i> -(5-chloro-2-hydroxybenzyl)benzamide	468.19	ELSD	1.69	
119	3-(2-([(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methylpropyl)- <i>N</i> -(4-hydroxy-1,1'-biphenyl-3-yl)benzamide	496.25	ELSD	1.84	
120	3-(2-([(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methylpropyl)- <i>N</i> -[2-	478.26	ELSD	1.29	

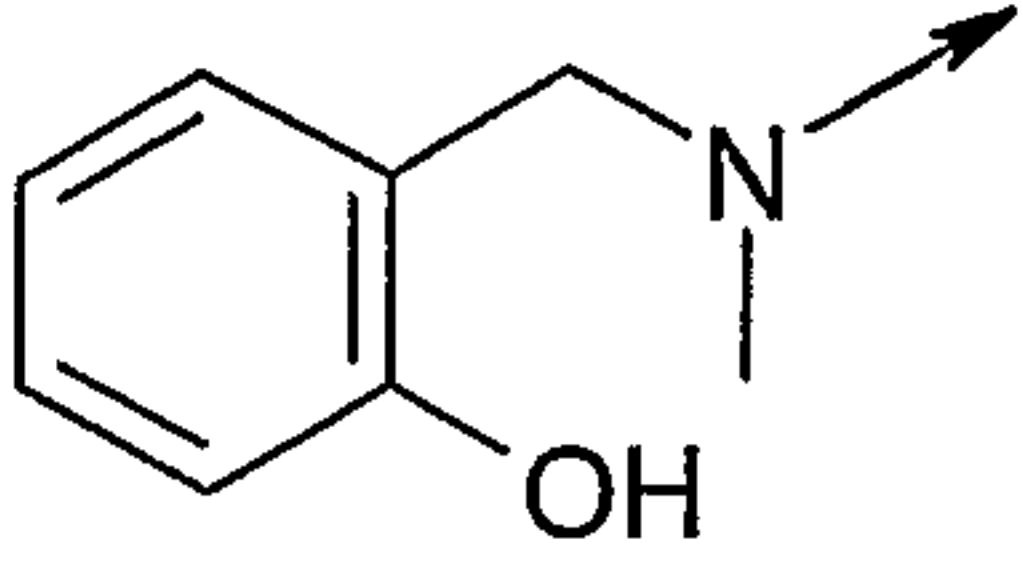
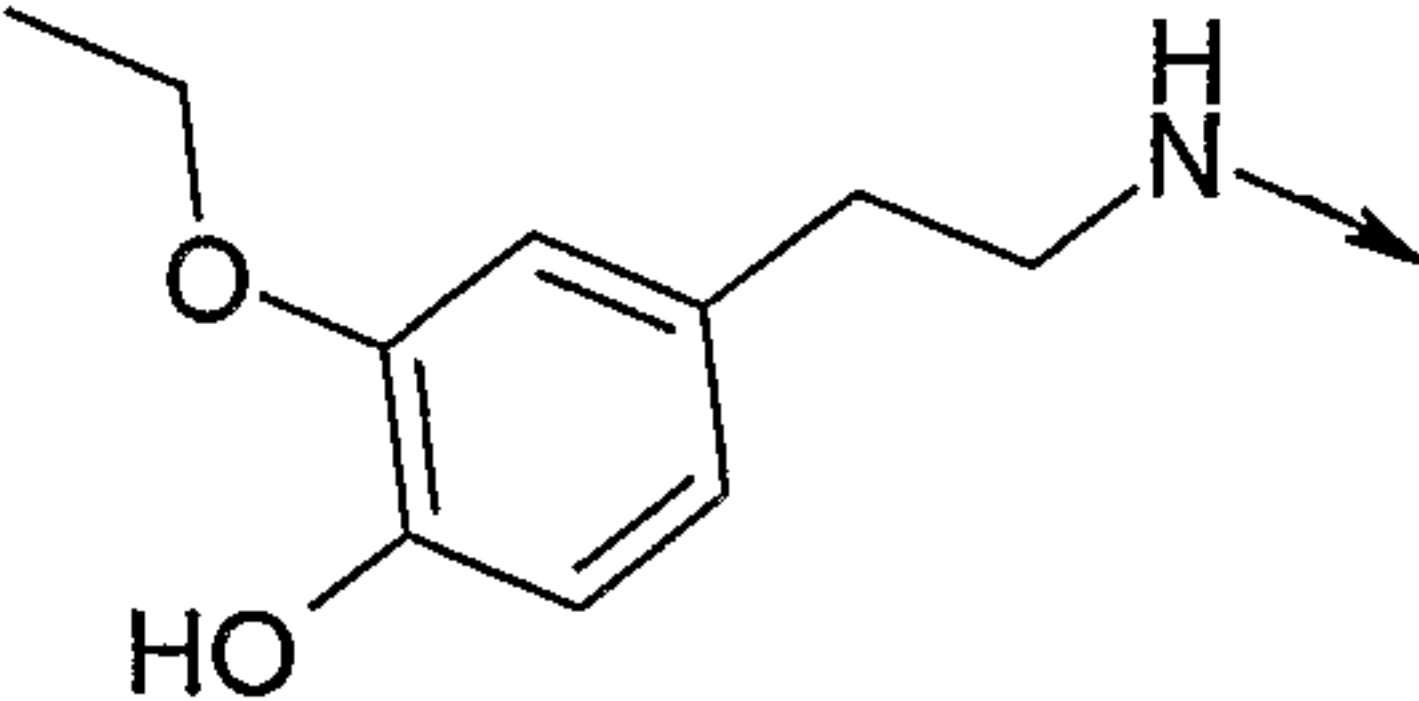
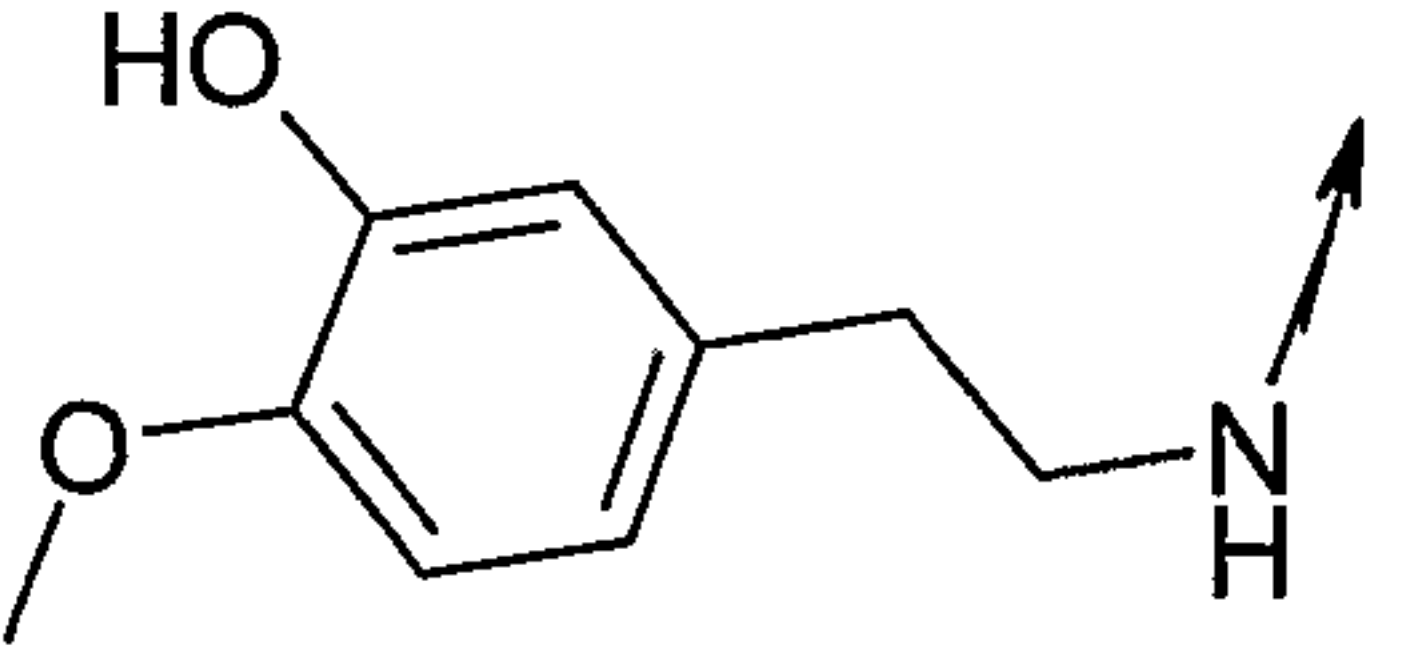
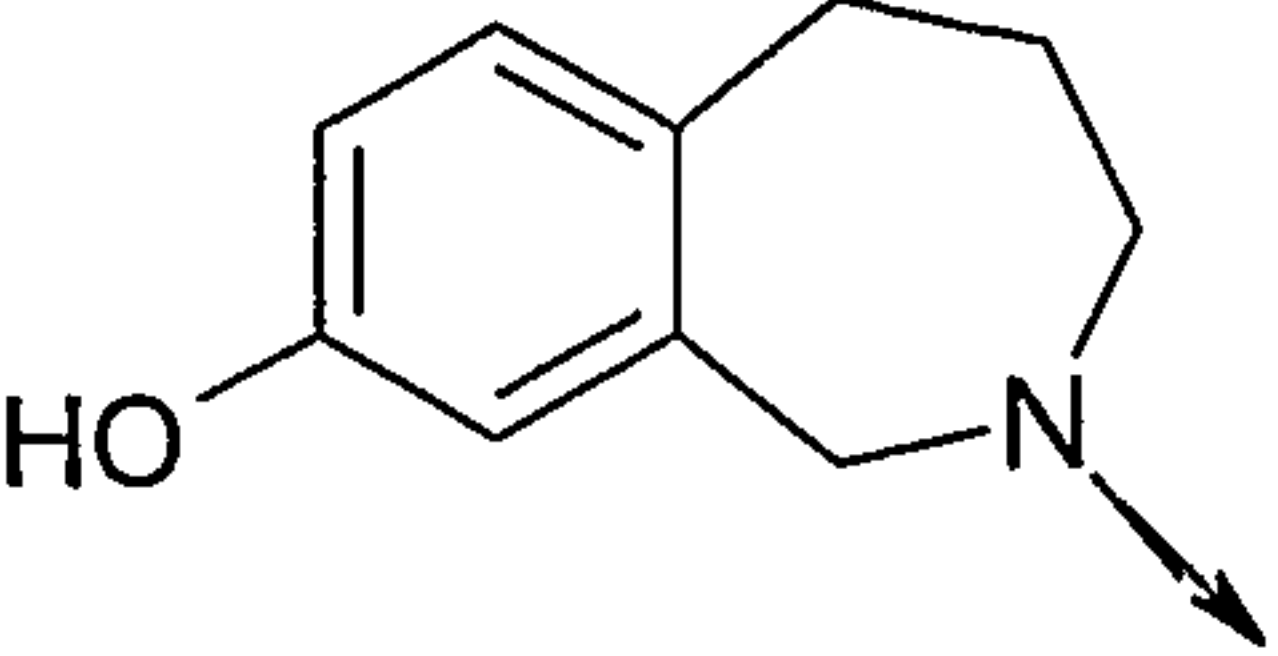
	hydroxy-2-(3-hydroxyphenyl)ethyl]-N-methylbenzamide				
121	3-(2-{[(2R)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)-N-(2-hydroxybenzyl)-N-methylbenzamide	448.25	ELSD	1.43	
122	3-(2-{[(2R)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)-N-(3,5-dichloro-2-hydroxybenzyl)benzamide	502.15	DAD: 225	1.82	
123	3-(2-{[(2R)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)-N-[2-(2-hydroxyphenyl)ethyl]benzamide	448.25	ELSD	1.41	

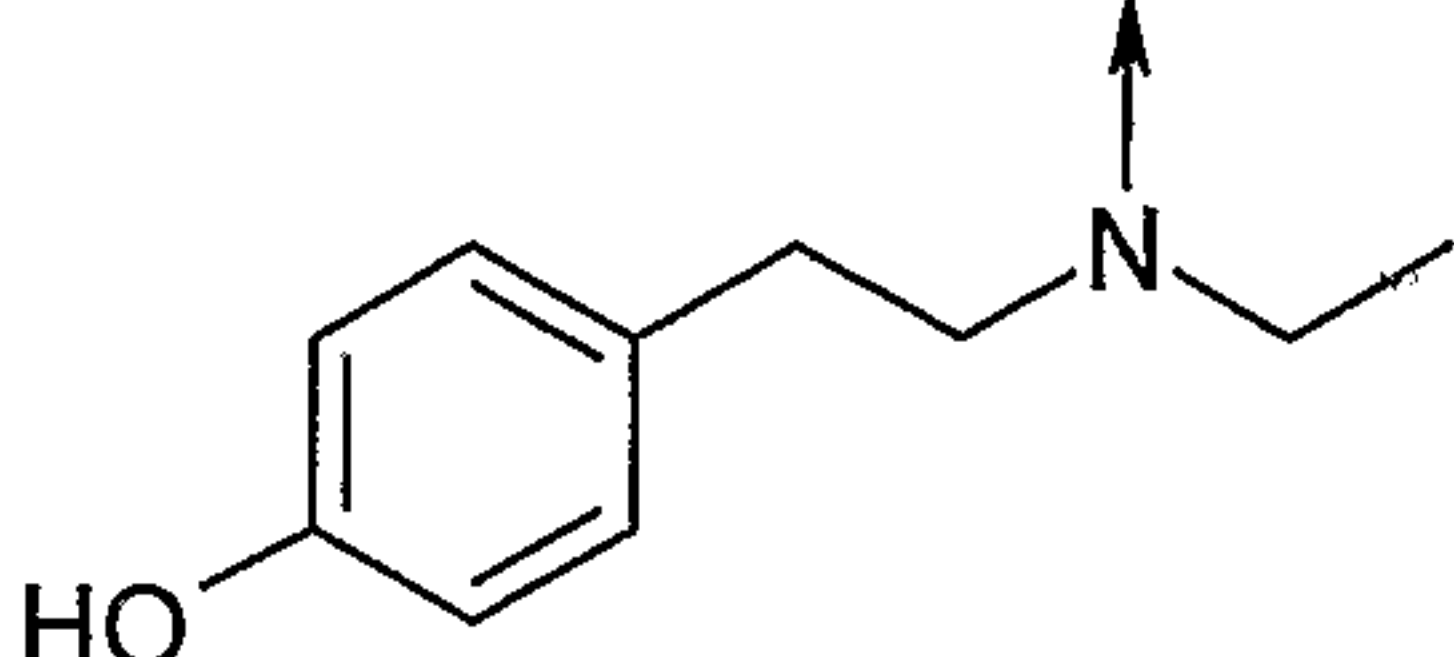
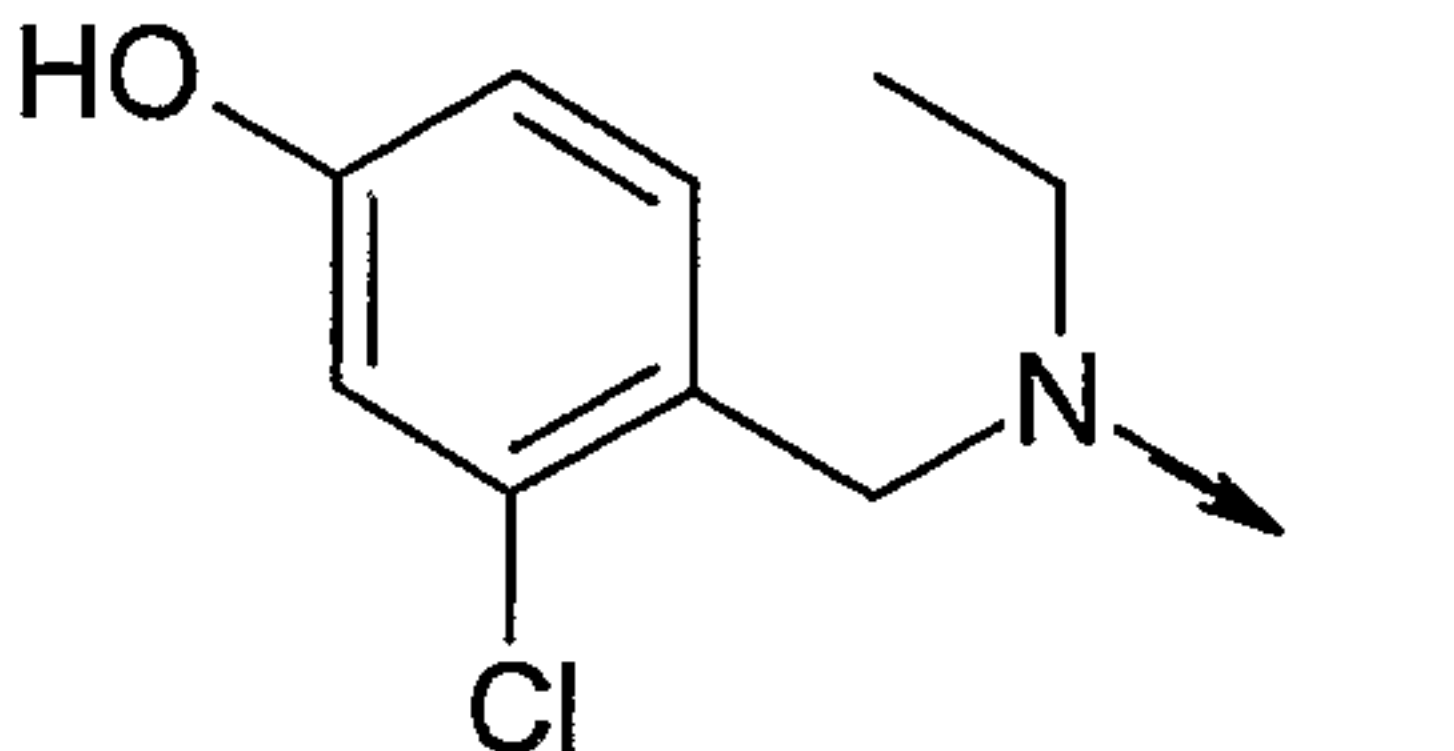
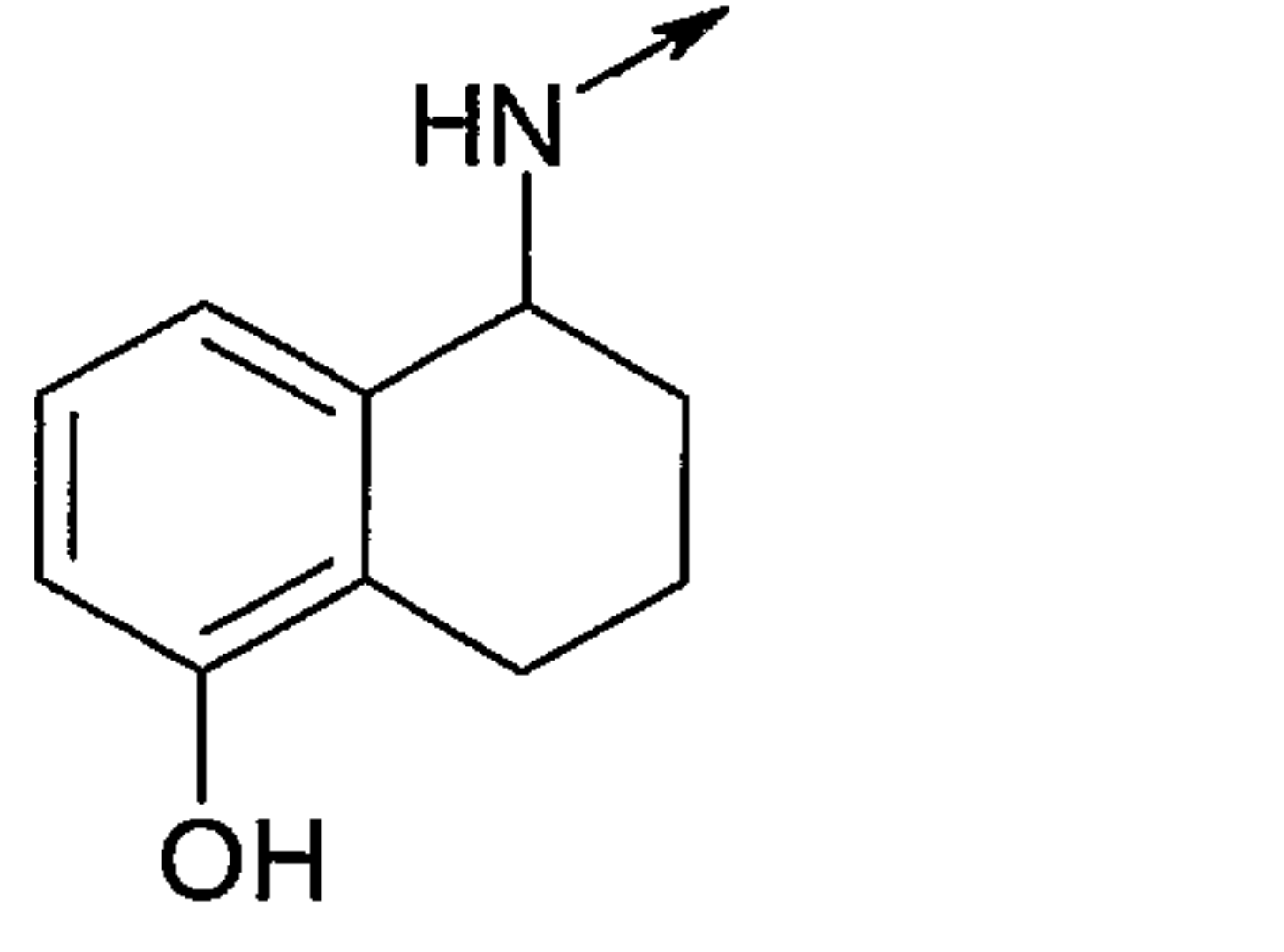
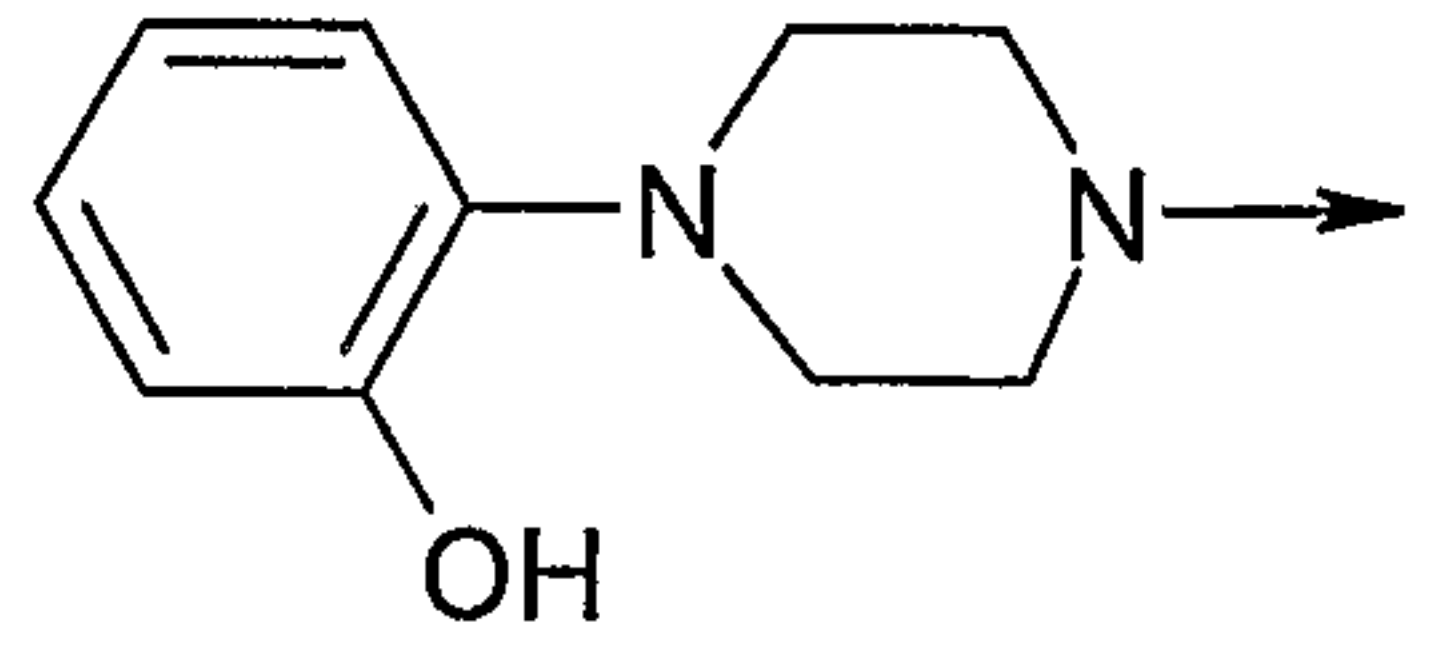
124	3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)- <i>N</i> -[2-(3-ethoxy-4-hydroxyphenyl)ethyl]benzamide	492.27	ELSD	1.34	
125	3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)- <i>N</i> -[2-(3-hydroxy-4-methoxyphenyl)ethyl]benzamide	478.26	ELSD	1.09	
126	2-[3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)-benzoyl]-2,3,4,5-tetrahydro-1 <i>H</i> -2-benzazepin-8-ol	474.26	ELSD	1.28	
127	3-(2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]-2-methylpropyl)- <i>N</i> -[(4'-	524.28	ELSD	1.48	

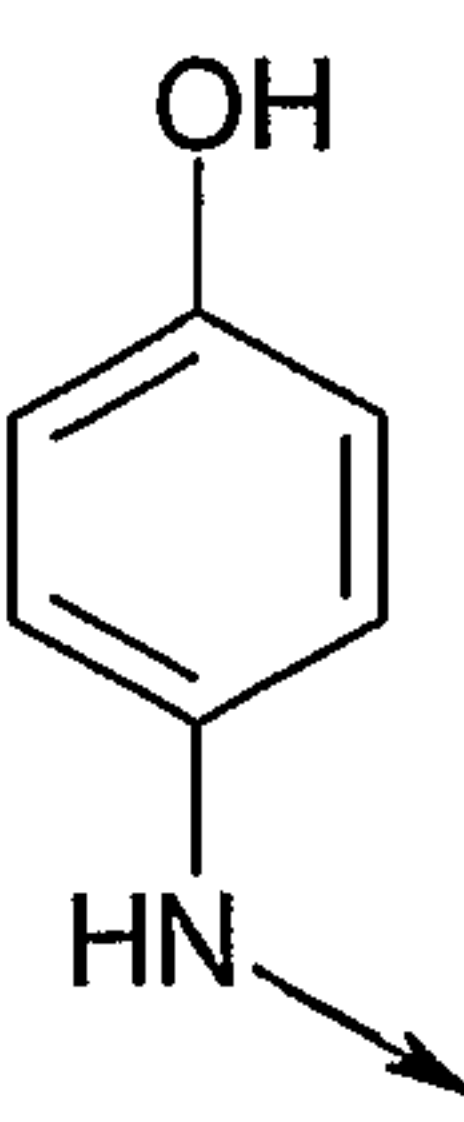
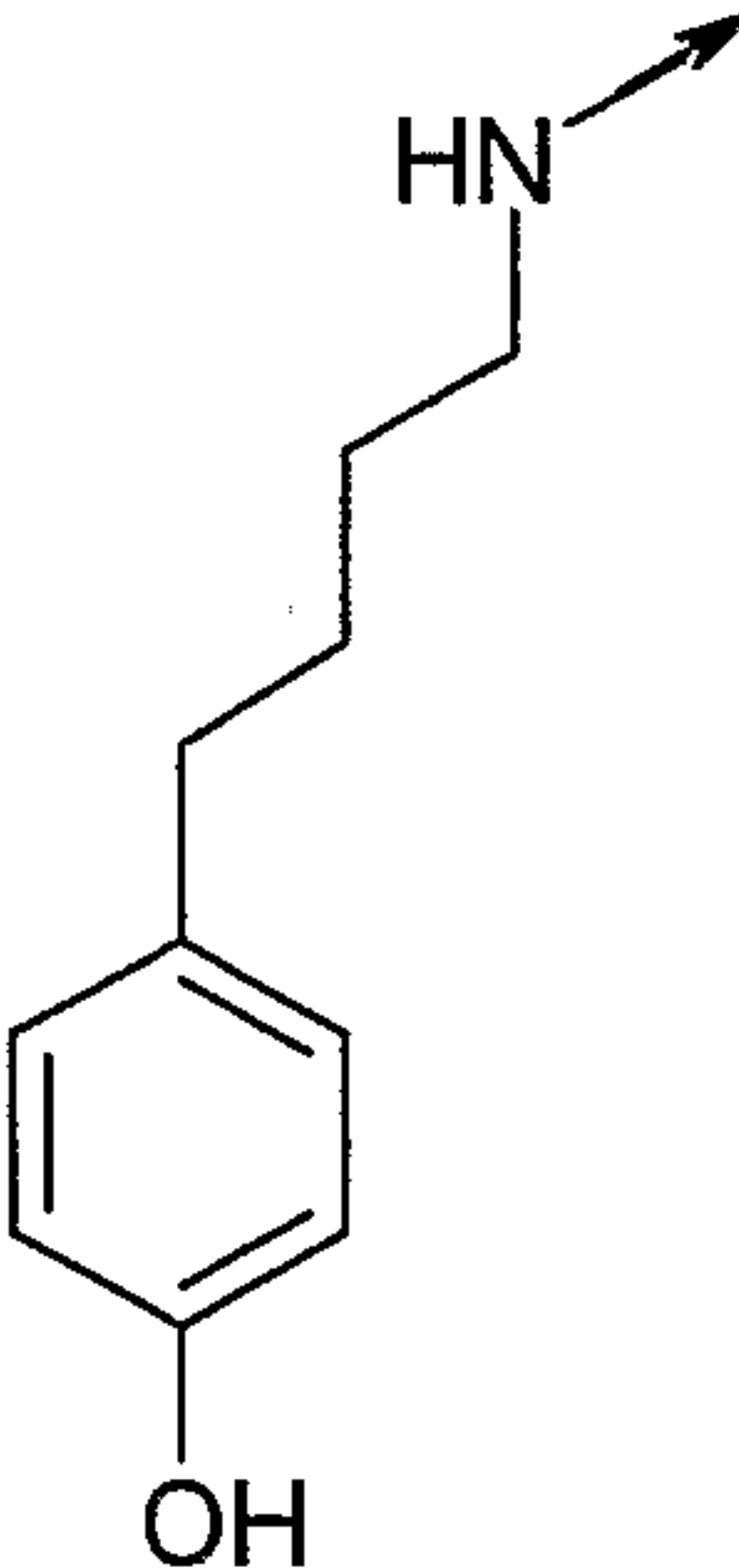
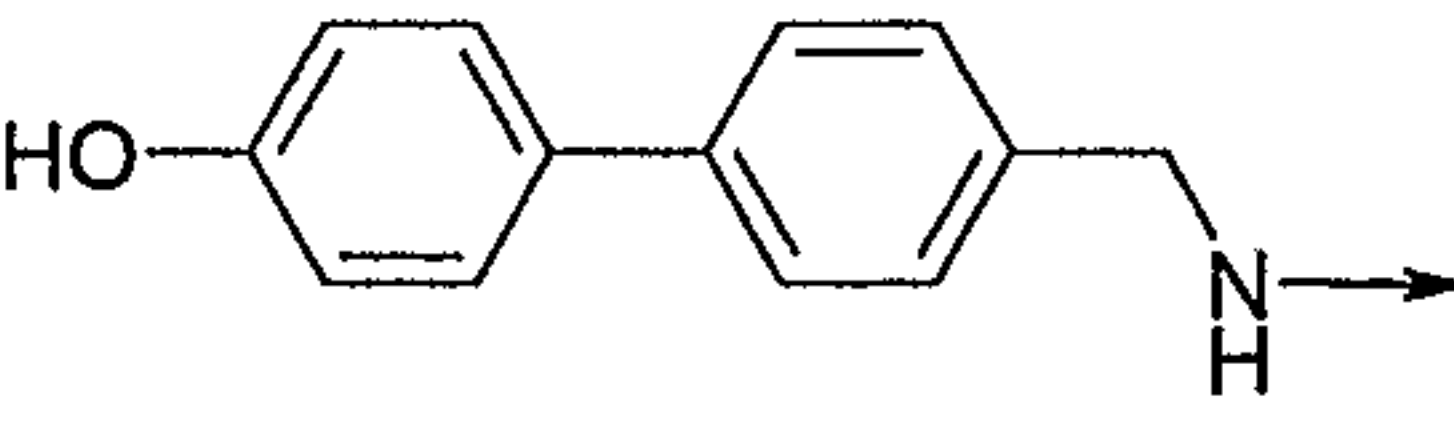
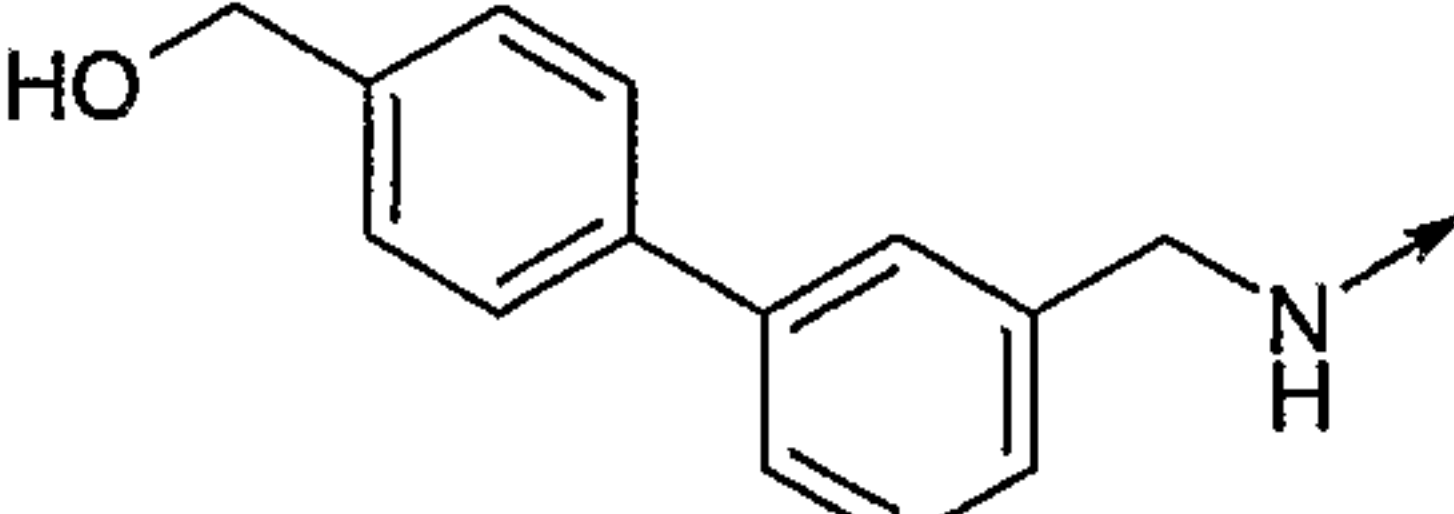
	hydroxy-3-methyl-1,1'-biphenyl-4-yl)methyl]-benzamide				
128	3-(2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)- <i>N</i> -[(3'-hydroxy-1,1'-biphenyl-2-yl)-methyl]benzamide	510.26	ELSD	1.25	

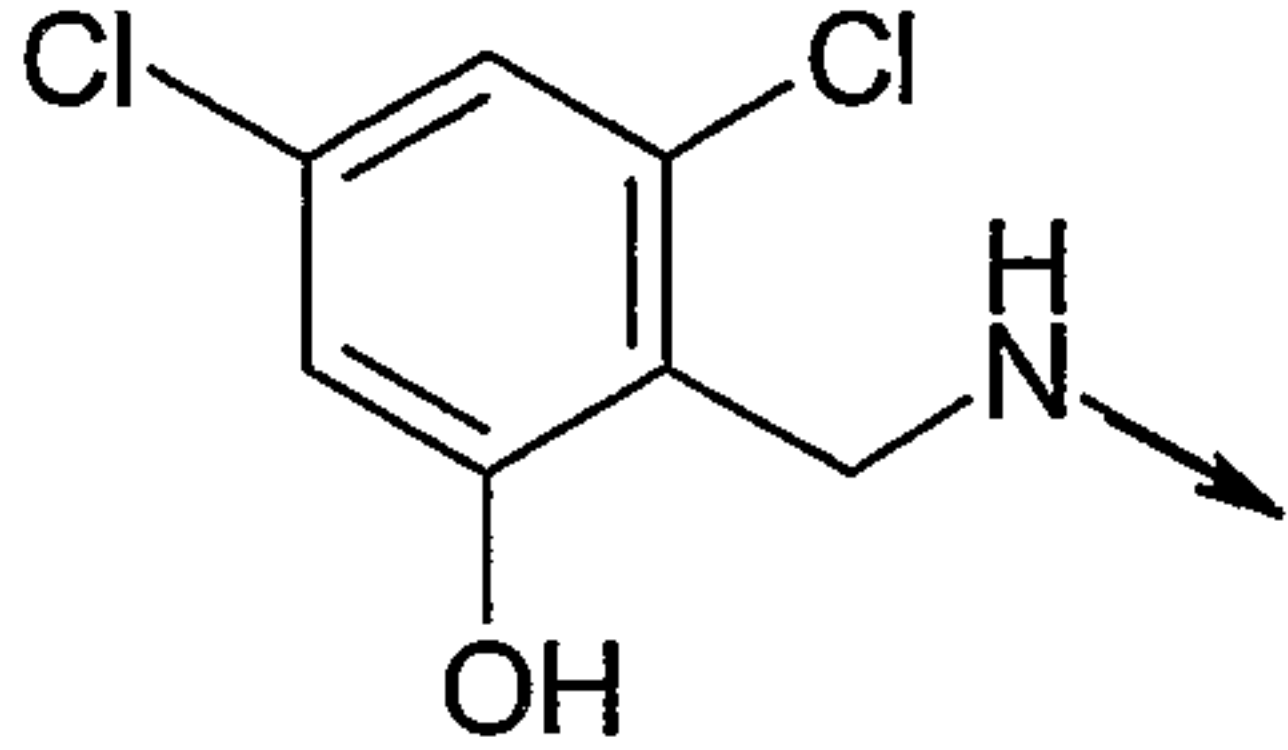
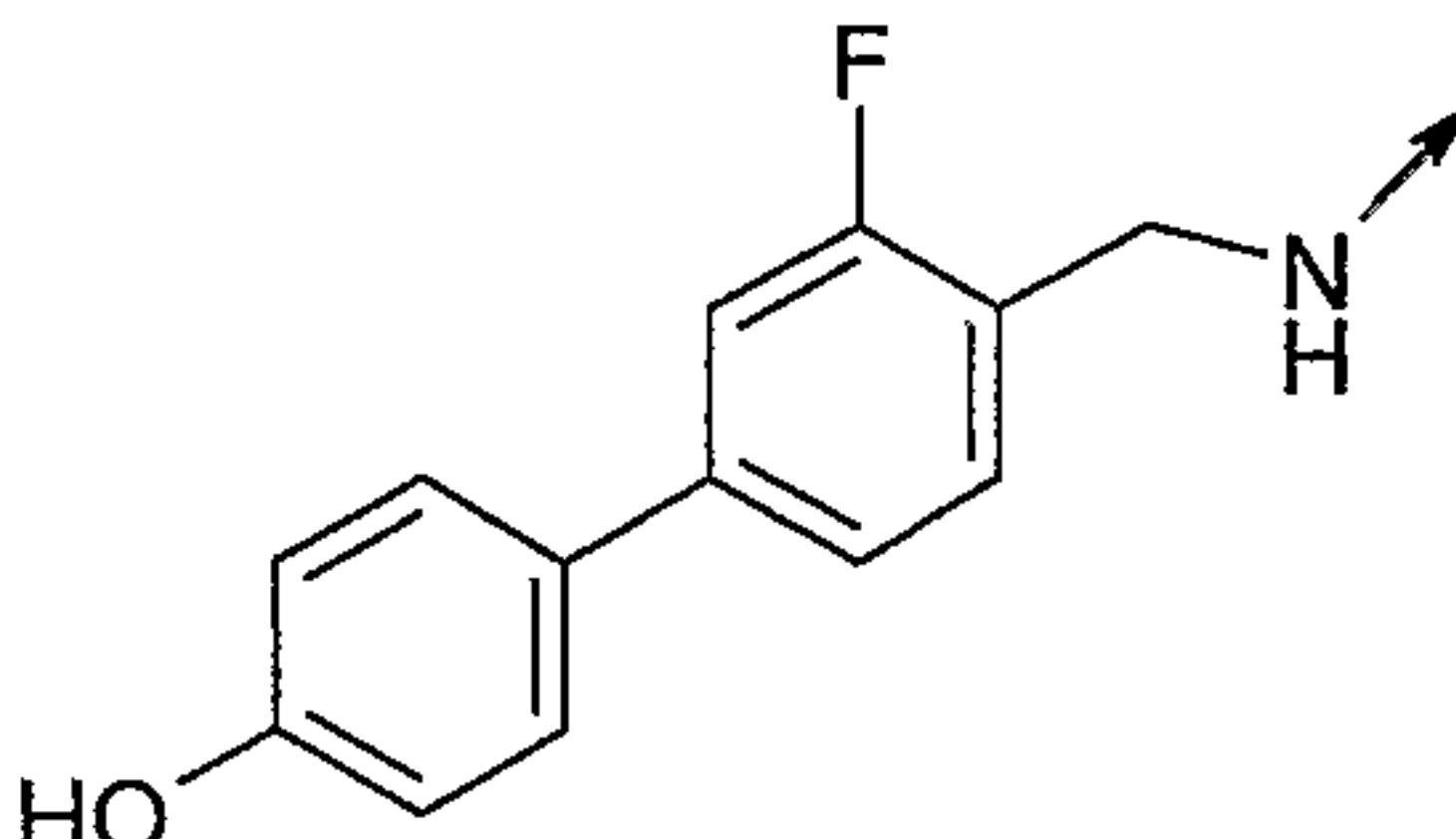
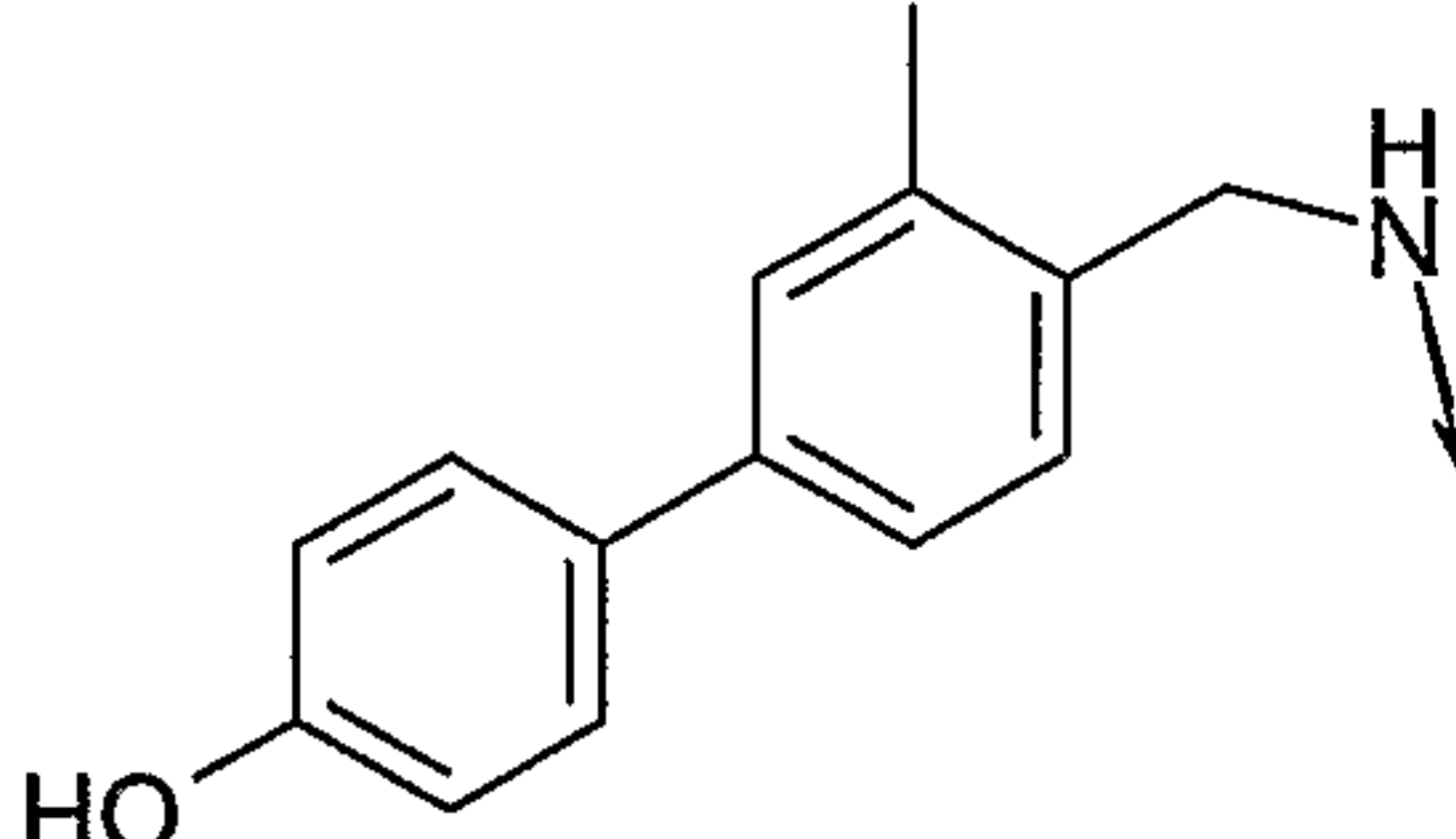
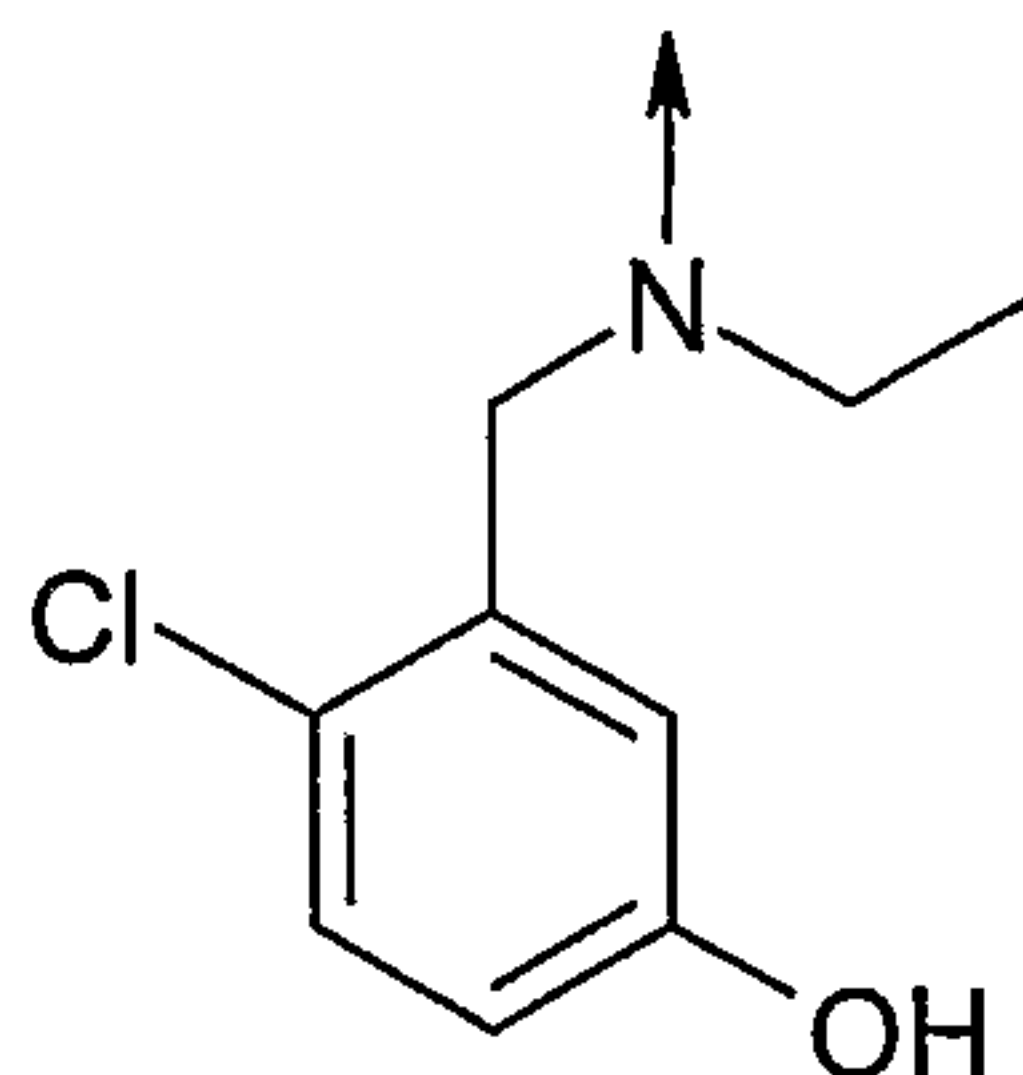


Ex	Name	Mass	Detector	Rt.	
129	3-((2 <i>R</i>)-2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(5-chloro-2-hydroxy-benzyl)benzamide	454.2	ELSD	1.63	
130	3-((2 <i>R</i>)-2-{[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -[2-hydroxy-2-(3-hydroxyphenyl)ethyl]	464.2	ELSD	1.25	

	-N-methylbenzamide				
131	3-((2R)-2-[(2R)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-N-(2-hydroxybenzyl)-N-methylbenzamide	434.2	ELSD	1.4	
132	3-((2R)-2-[(2R)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-N-[2-(3-ethoxy-4-hydroxyphenyl)ethyl] benzamide	478.3	ELSD	1.36	
133	3-((2R)-2-[(2R)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-N-[2-(3-hydroxy-4-methoxyphenyl)ethyl] benzamide	464.2	ELSD	1.39	
134	2-[3-((2R)-2-[(2R)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)benzoyl]-2,3,4,5-tetrahydro-1H-2-benzazepin-8-ol	460.3	ELSD	1.39	

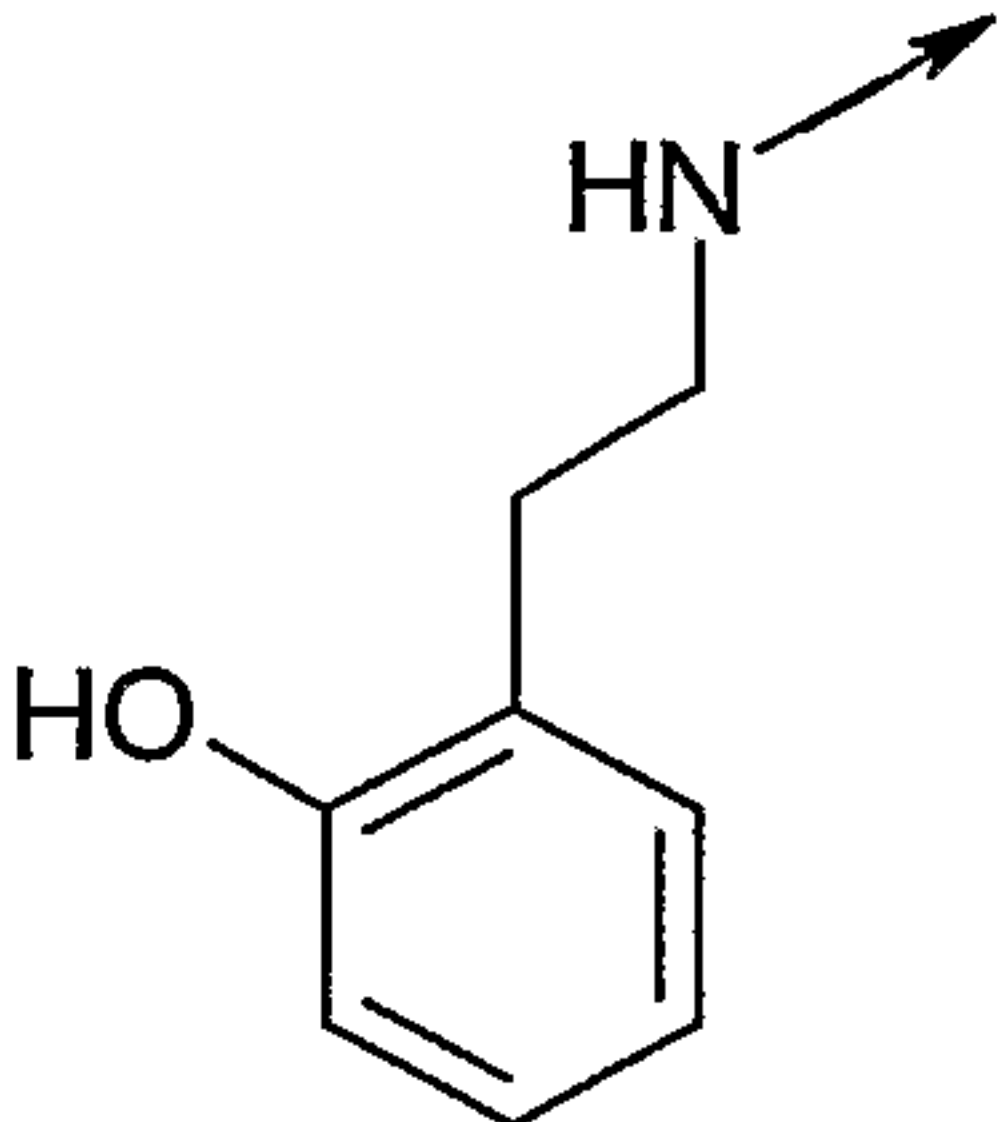
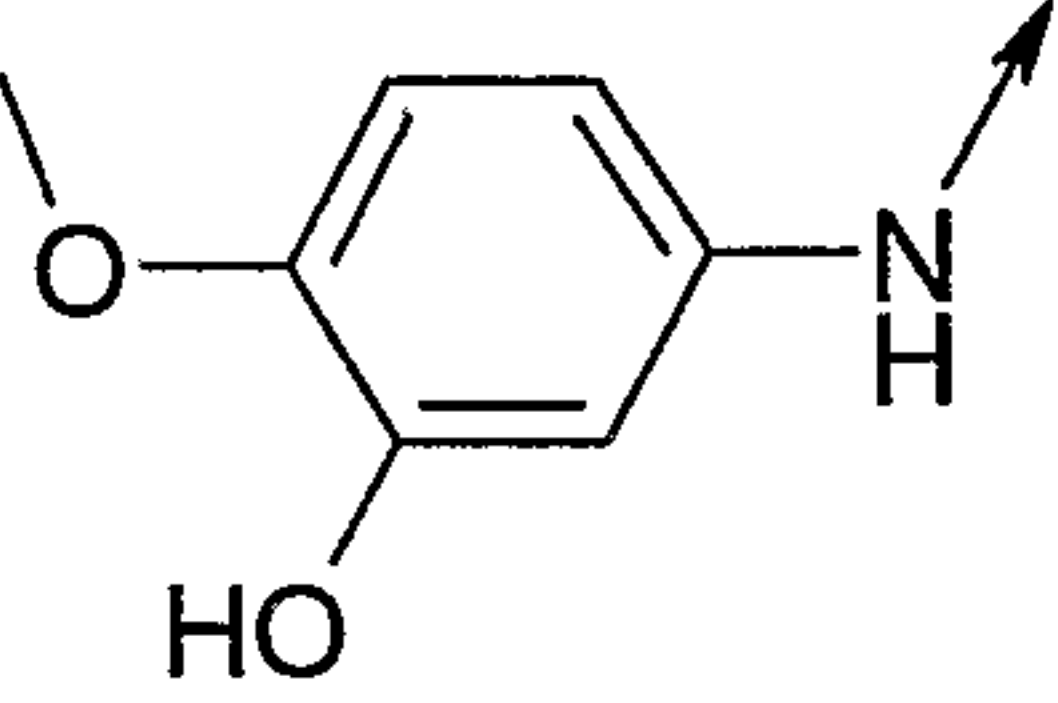
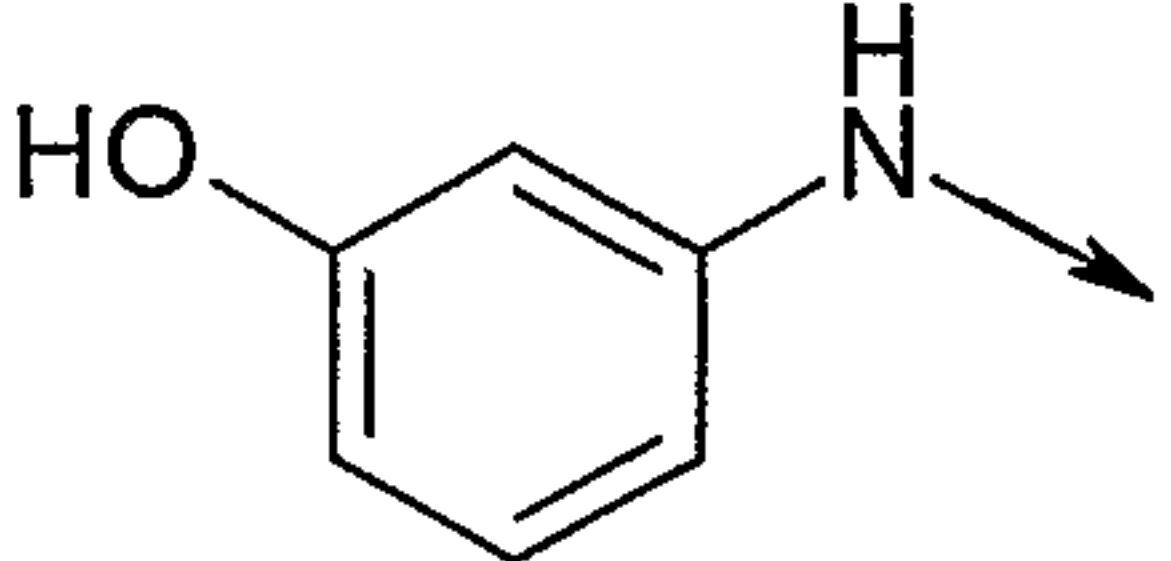
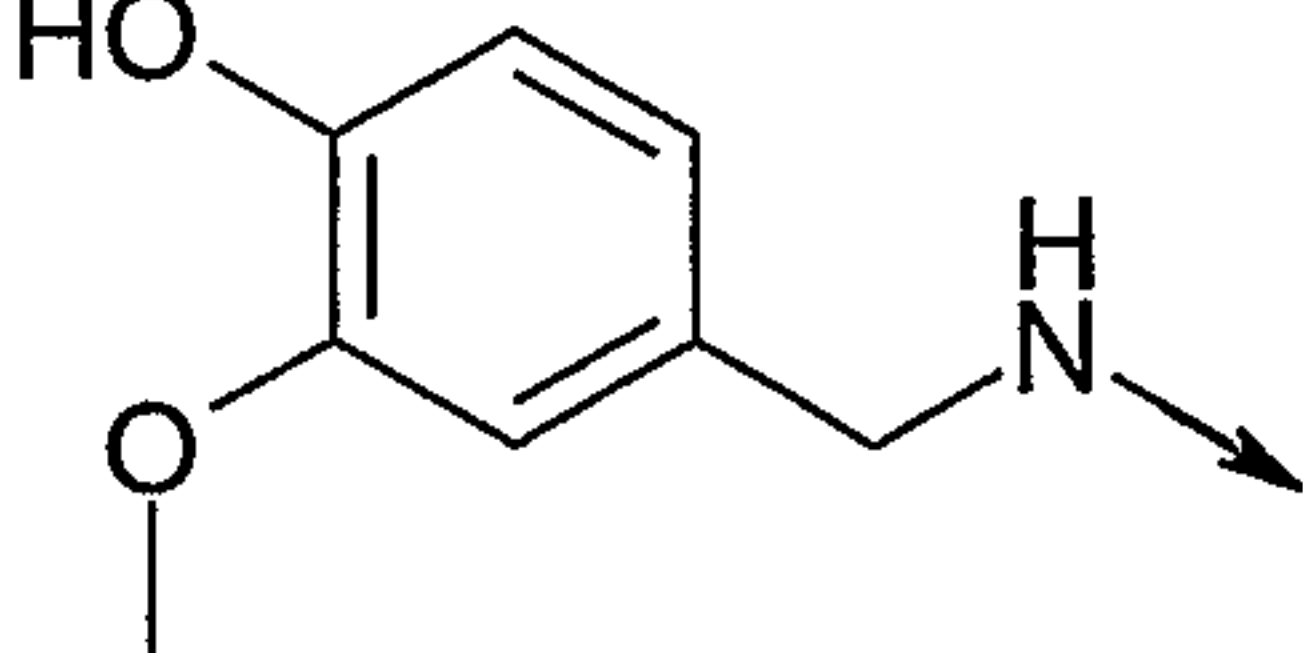
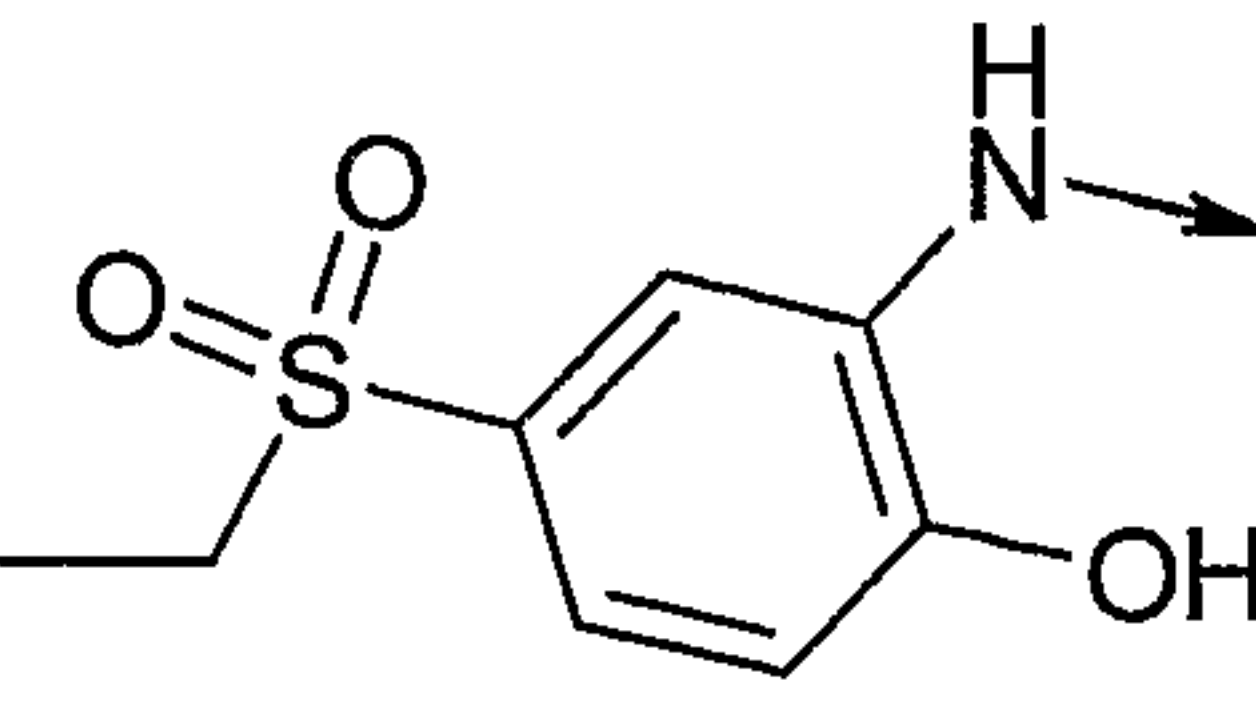
135	3-((2 <i>R</i>)-2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -ethyl- <i>N</i> -[2-(4-hydroxyphenyl)ethyl]benzamide	462.3	ELSD	1.45	
136	3-((2 <i>R</i>)-2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(2-chloro-4-hydroxybenzyl)- <i>N</i> -ethylbenzamide	482.2	ELSD	1.49	
137	3-((2 <i>R</i>)-2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(5-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	460.3	ELSD	1.48	
138	2-{4-[3-((2 <i>R</i>)-2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)benzoyl]piperazin-1-yl}phenol	475.3	ELSD	1.46	

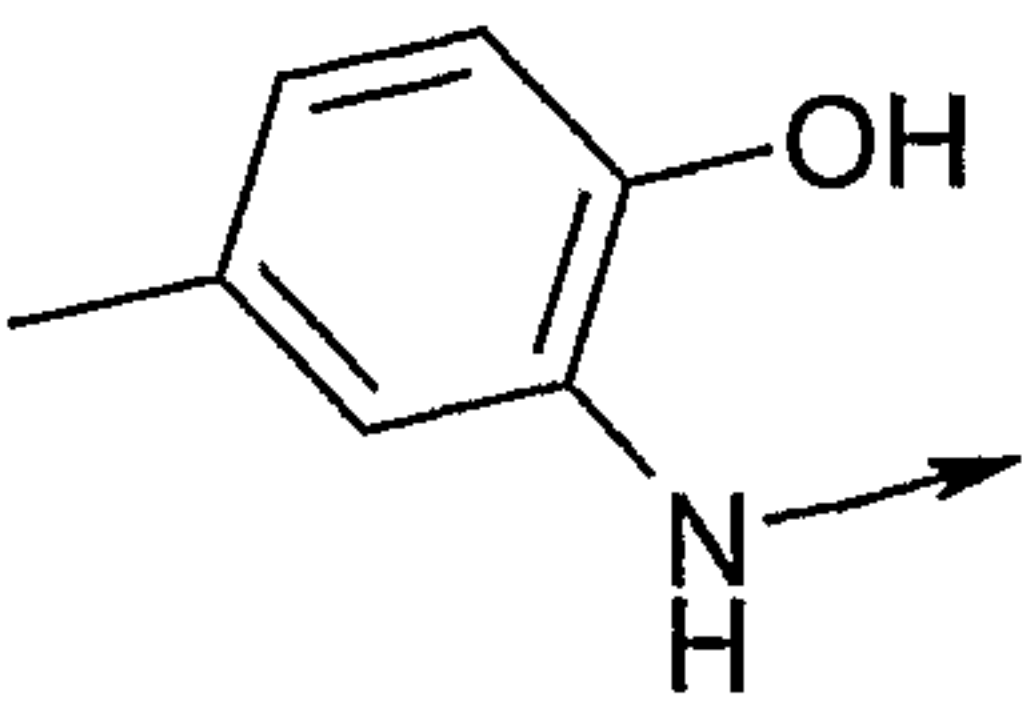
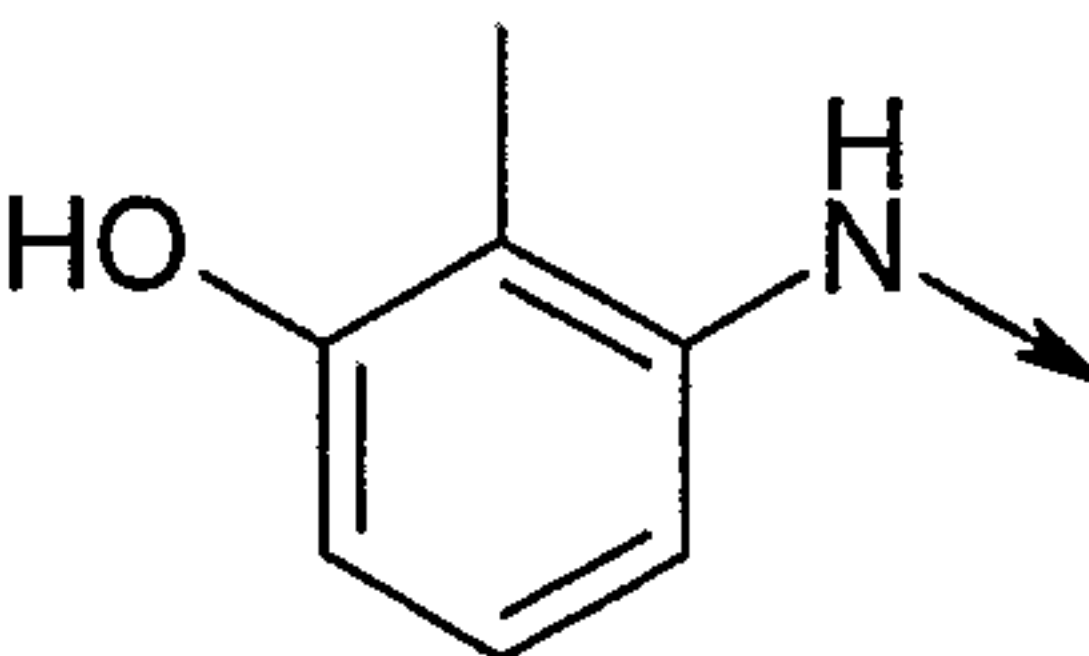
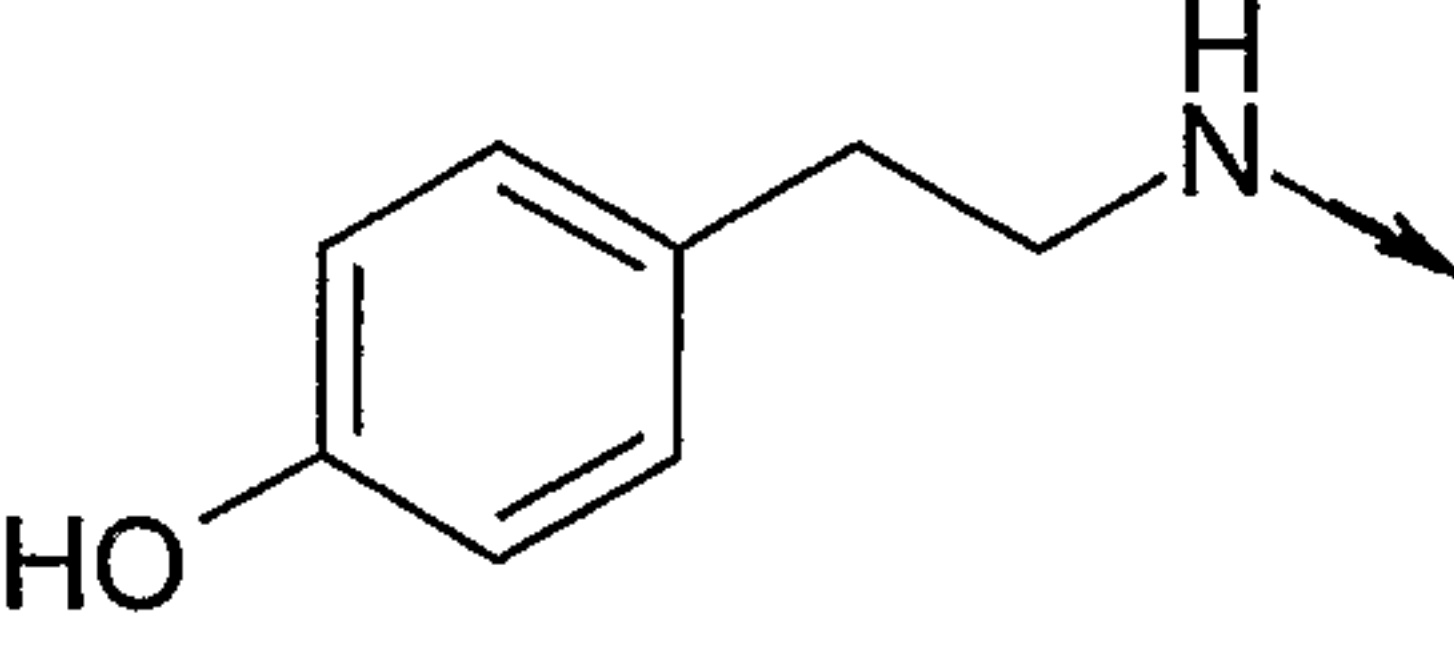
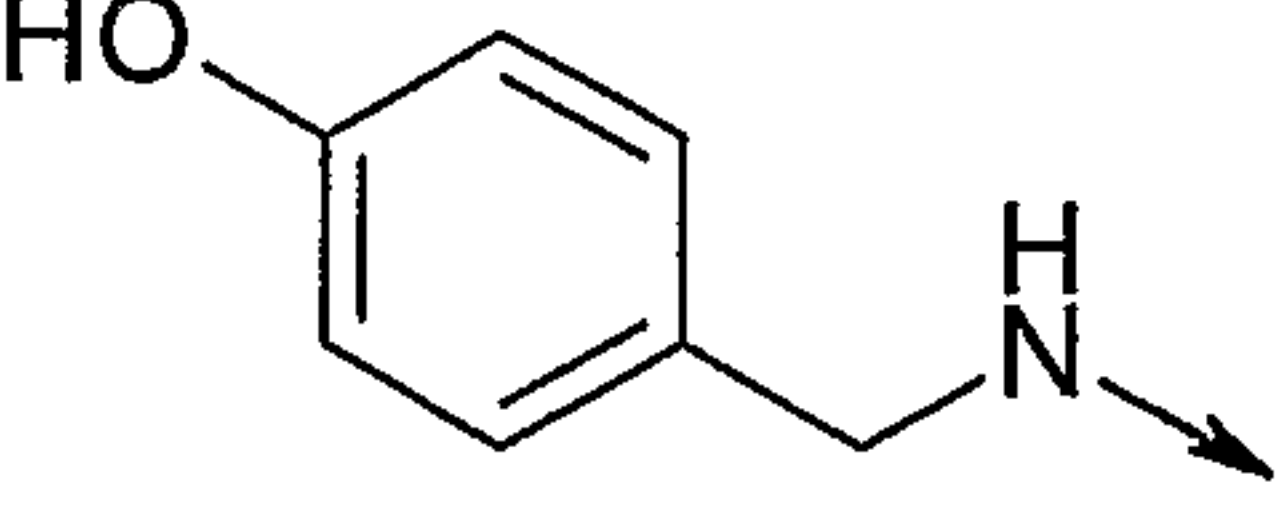
139	3-((2 <i>R</i>)-2-[[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]propyl)- <i>N</i> -(4-hydroxyphenyl)benzamide	406.2	ELSD	1.24	
140	3-((2 <i>R</i>)-2-[[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]propyl)- <i>N</i> -[4-(4-hydroxyphenyl)butyl]benzamide	462.3	ELSD	1.44	
141	3-((2 <i>R</i>)-2-[[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]propyl)- <i>N</i> -[(4'-hydroxy-1,1'-biphenyl-4-yl)methyl]benzamide	496.3	ELSD	1.54	
142	3-((2 <i>R</i>)-2-[[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino]propyl)- <i>N</i> -{[4'-(hydroxymethyl)-1,1'-biphenyl-3-yl]methyl}benzamide	510.3	ELSD	1.54	

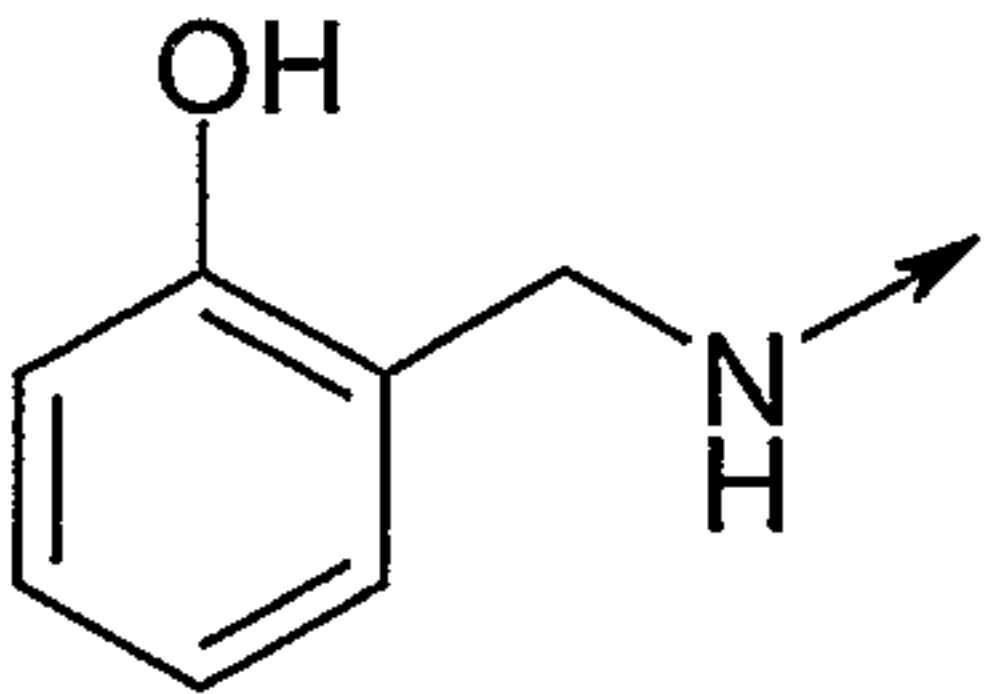
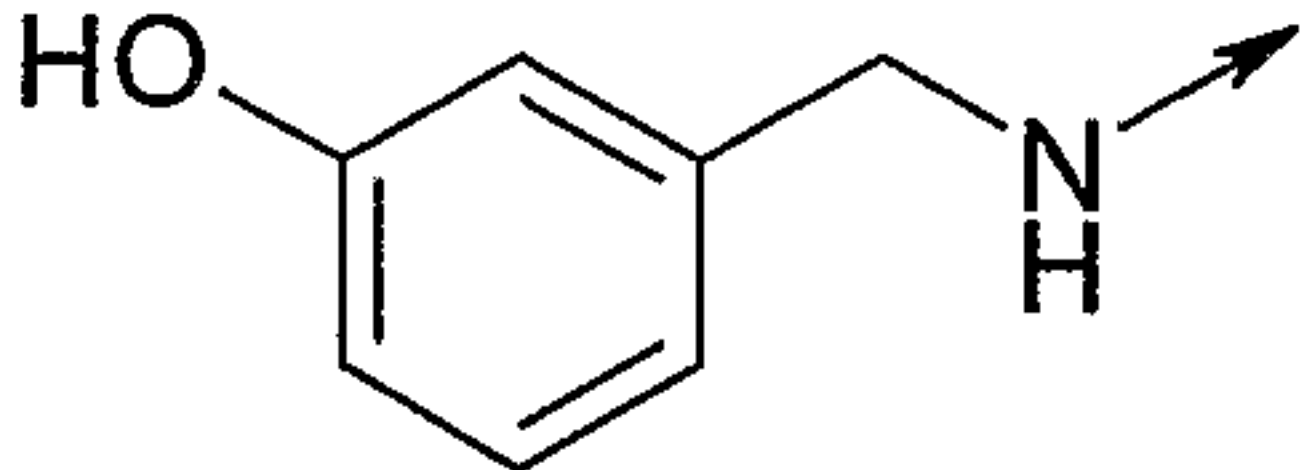
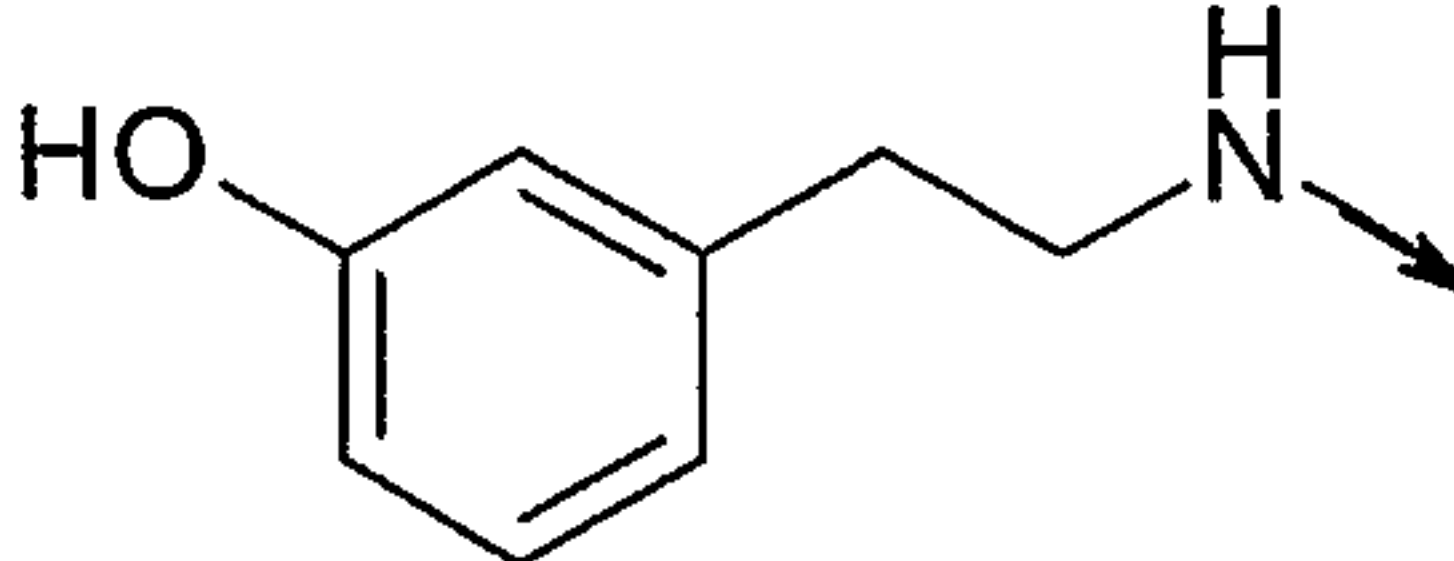
143	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(2,4-dichloro-6-hydroxybenzyl)benzamide	488.1	ELSD	1.79	
144	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -[(3-fluoro-4'-hydroxy-1,1'-biphenyl-4-yl)methyl]benzamide	514.2	ELSD	1.69	
145	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -[(4'-hydroxy-3-methyl-1,1'-biphenyl-4-yl)methyl]benzamide	510.3	ELSD	1.61	
146	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(2-chloro-5-hydroxybenzyl)- <i>N</i> -ethylbenzamide	482.2	ELSD	1.63	

147	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -[(2'-hydroxy-1,1'-biphenyl-2-yl)methyl]benzamide	496.3	ELSD	1.64	
148	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -[(4'-hydroxy-1,1'-biphenyl-2-yl)methyl]benzamide	496.3	ELSD	1.59	
149	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -[3-hydroxy-5-(trifluoromethyl)benzyl]- <i>N</i> -methylbenzamide	502.2	ELSD	1.65	
150	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(3-chloro-5-hydroxybenzyl)- <i>N</i> -ethylbenzamide	482.2	ELSD	1.55	

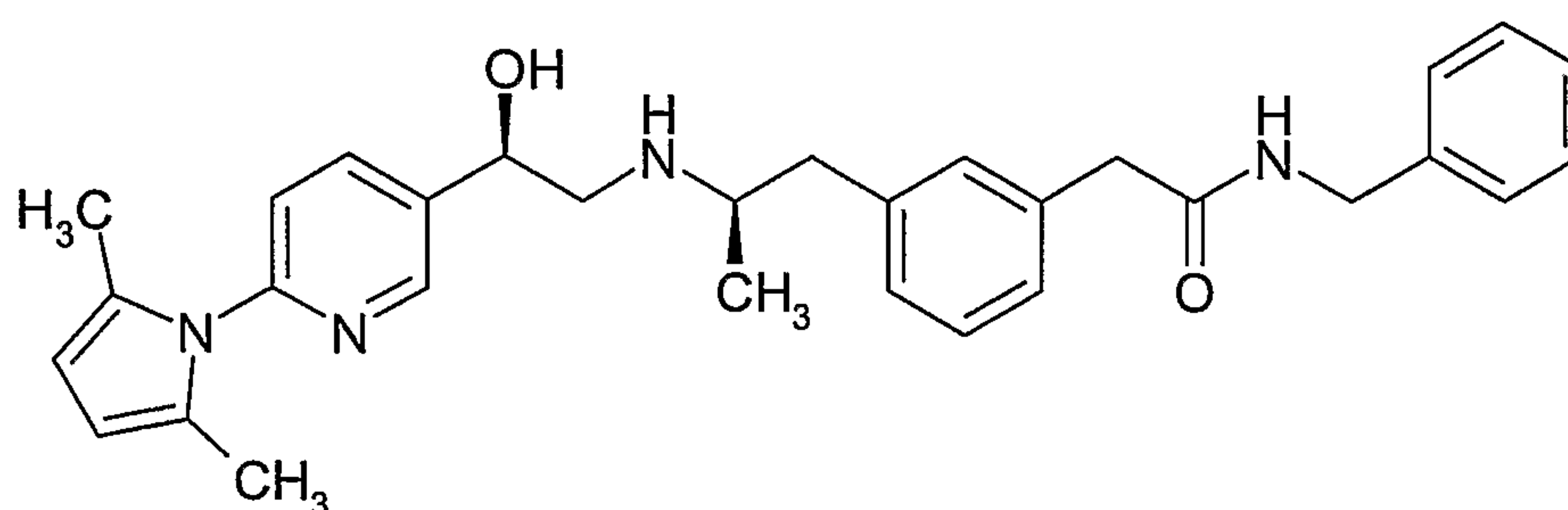
151	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(3-chloro-5-hydroxybenzyl)benzamide	454.2	ELSD	1.44	
152	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -[(4'-hydroxy-1,1'-biphenyl-3-yl)methyl]benzamide	496.3	ELSD	1.63	
153	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(4-hydroxy-3,5-dimethylbenzyl)benzamide	448.3	ELSD	1.35	
154	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(3,5-dichloro-2-hydroxybenzyl)benzamide	488.1	ELSD	1.88	

155	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -[2-(2-hydroxyphenyl)-ethyl]benzamide	434.2	ELSD	1.37	
156	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(3-hydroxy-4-methoxyphenyl)benzamide	436.21	ELSD	1.23	
157	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(3-hydroxyphenyl)benzamide	406.2	ELSD	1.31	
158	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(4-hydroxy-3-methoxybenzyl)benzamide	450.23	ELSD	1.31	
159	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -[5-(ethylsulfonyl)-2-	498.19	ELSD	1.17	

	hydroxyphenyl]benzamide				
160	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(2-hydroxy-5-methylphenyl)benzamide	420.22	ELSD	1.57	
161	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(3-hydroxy-2-methylphenyl)benzamide	420.22	ELSD	1.2	
162	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -[2-(4-hydroxyphenyl)ethyl]benzamide	434.23	ELSD	1.25	
163	3-((2 <i>R</i>)-2-[(2 <i>R</i>)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(4-hydroxybenzyl)benzamide	420.22	ELSD	1.18	

165	3-((2 <i>R</i>)-2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(2-hydroxybenzyl)benzamide	420.22	ELSD	1.49	
168	3-((2 <i>R</i>)-2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -(3-hydroxybenzyl)benzamide	420.22	ELSD	1.23	
169	3-((2 <i>R</i>)-2-[[<i>(2R)</i> -2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)- <i>N</i> -[2-(3-hydroxyphenyl)ethyl]benzamide	434.23	ELSD	1.34	

Preparation 1 : *N*-Benzyl-2-[3-((2*R*)-2-[(2*R*)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino}-propyl)-phenyl]-acetamide



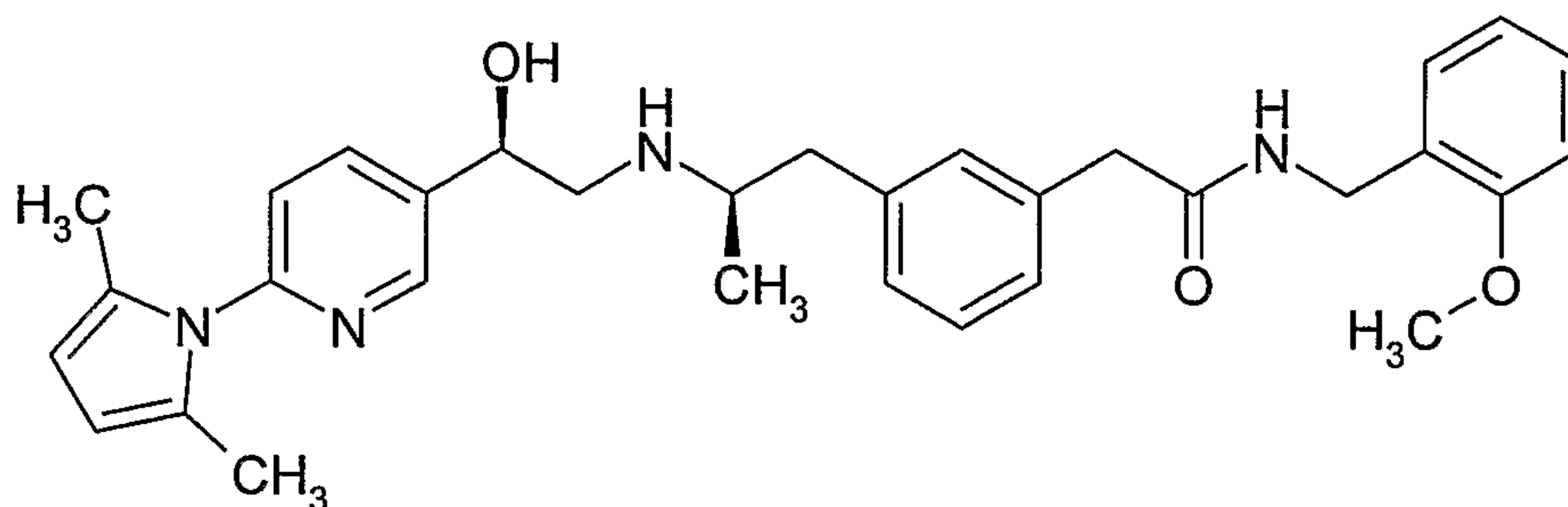
A solution of the acid from preparation 21 (200mg, 0.41mmol), *O*-benzotriazol-
 5 1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (114mg, 0.48mmol),

triethylamine (1.0 ml, 7.17 mmol) and benzylamine (52mg, 0.48mmol) in *N,N*-dimethylformamide (3ml) was stirred at room temperature for 40 hours under a nitrogen atmosphere. The reaction mixture was diluted with water (3ml) and extracted with ethyl acetate (2 x 10ml). The combined organic extracts were
 5 dried (sodium sulfate) and reduced *in vacuo*. Purification by flash column chromatography eluting with dichloromethane:methanol: ammonia (100:0:0 changing to 94:6:0.5 by volume) gave the title compound as a pale yellow oil (148mg).

¹H NMR (400MHz, CD₃OD): δ = 8.52 (1H, s), 7.96 (1H, d), 7.30-7.09 (10H, m),
 10 5.82 (2H, s), 4.86 (1H, m), 4.34 (2H, s), 3.53 (2H, s), 3.01 (1H, m), 2.88 (2H, m), 2.80 (1H, m), 2.61 (1H, m), 2.03 (6H, s), 1.08 (3H, d) ppm.

LRMS (APCI) : m/z [M+H]⁺ 497.

Preparation 2 : 2-[3-((2*R*)-2-((2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-*N*-(2-methoxy-benzyl)-acetamide



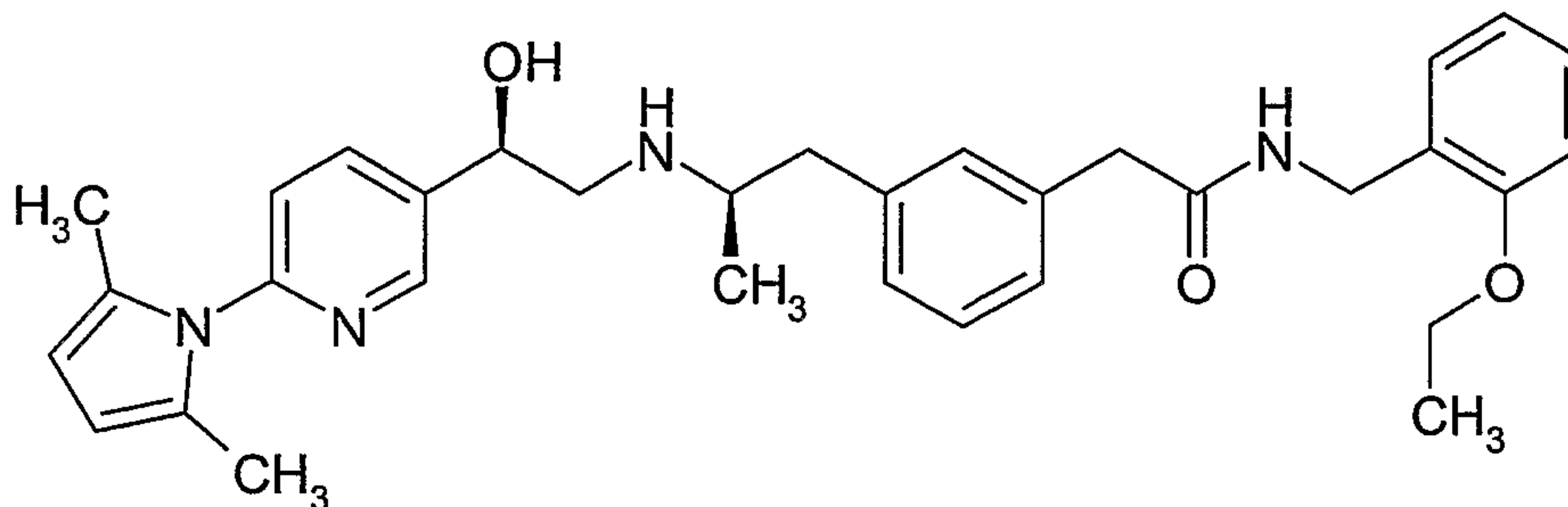
15

Prepared according to the method described for preparation 1 using the appropriate amine to give the title compound as a pale yellow oil.

¹H NMR (400MHz, CD₃OD): δ = 8.51 (1H, s), 7.92 (1H, d), 7.29-6.83 (9H, m),
 5.81 (2H, s), 4.81 (1H, m), 4.34 (2H, s), 3.77 (3H, s), 3.52 (2H, s), 2.95 (1H, s),
 20 2.85 (2H, m), 2.74 (1H, m), 2.59 (1H, m), 2.03 (6H, s), 1.06 (3H, d) ppm.

LRMS (APCI) : m/z [M+H]⁺ 527.

Preparation 3 : 2-[3-((2*R*)-2-((2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-*N*-(2-ethoxy-benzyl)-acetamide

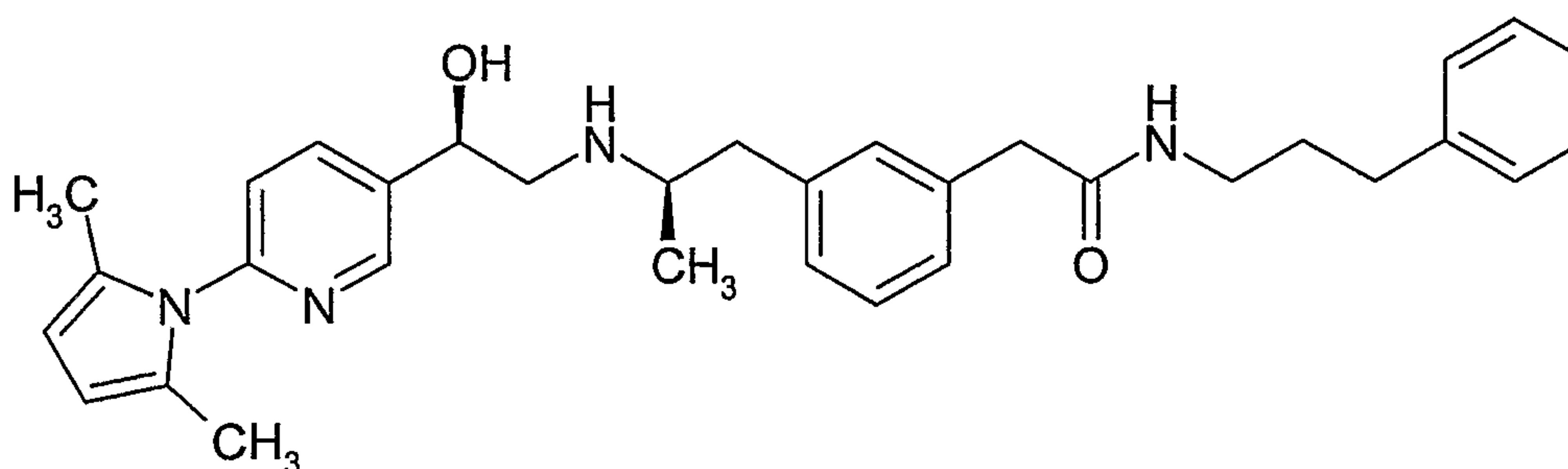


Prepared according to the method described for preparation 1 using the appropriate amine to give the title compound as a pale yellow oil.

^1H NMR (400MHz, CD_3OD): δ = 8.50 (1H, s), 7.94 (1H, d), 7.29-6.80 (9H, m), 5.82 (2H, s), 4.83 (1H, m), 4.35 (2H, s), 3.99 (2H, q), 3.52 (2H, s), 2.96 (1H, m), 2.85 (2H, m), 2.76 (1H, m), 2.55 (1H, m), 2.03 (6H, s), 1.33 (3H, t), 1.06 (3H, d) ppm.

10 LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 541.

Preparation 4 : 2-[3-((2*R*)-2-((2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-*N*-(3-phenyl-propyl)-acetamide

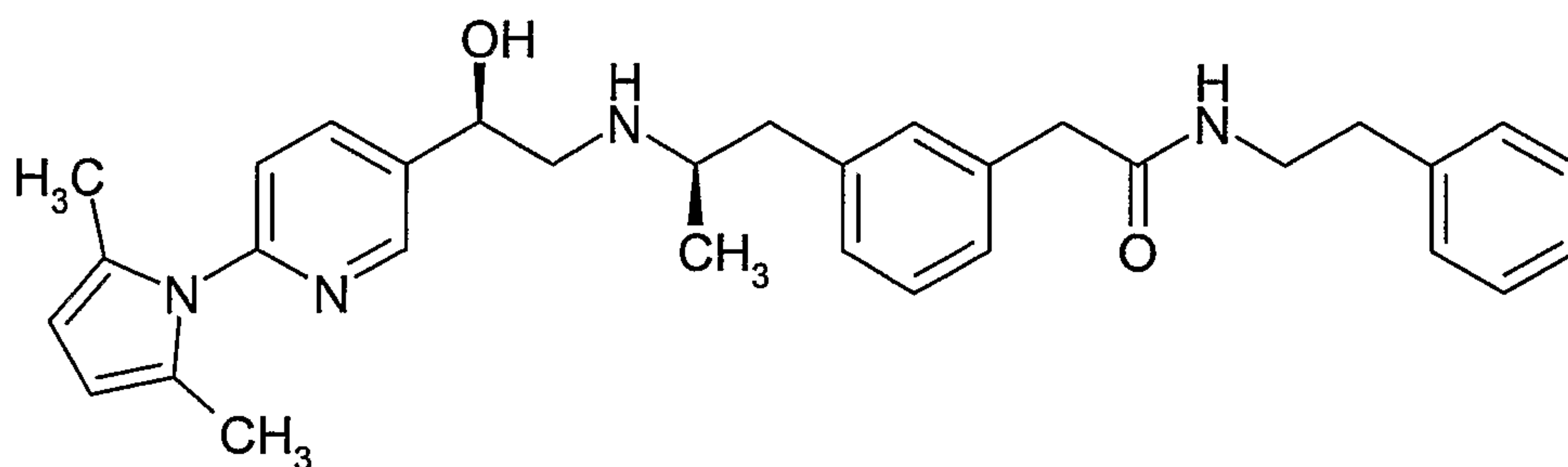


Prepared according to the method described for preparation 1 using the appropriate amine to give the title compound as a pale yellow oil.

^1H NMR (400MHz, CD_3OD): δ = 8.52 (1H, s), 7.94 (1H, d), 7.28-7.08 (10H, m), 5.82 (2H, s), 4.82 (1H, m), 3.47 (2H, s), 3.19 (2H, m), 3.00 (1H, m), 2.86-2.77 (3H, m), 2.60-2.54 (3H, m), 2.03 (6H, s), 1.77 (2H, m), 1.05 (3H, d) ppm.

LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 525.

5 Preparation 5 : 2-[3-((2R)-2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-N-phenethyl-acetamide

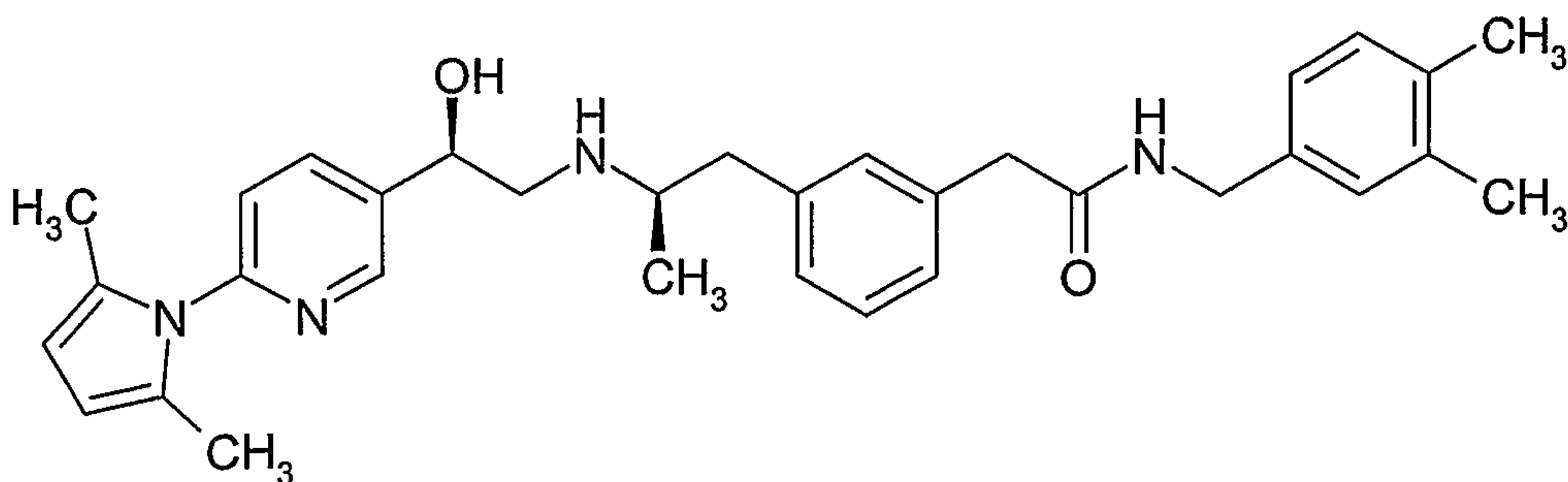


Prepared according to the method described for preparation 1 using the appropriate amine to give the title compound as a pale yellow oil.

10 ^1H NMR (400MHz, CD_3OD): δ = 8.51 (1H, d), 7.95 (1H, d), 7.29-7.08 (10H, m), 5.81 (2H, s), 4.83 (1H, m), 3.44 (2H, s), 2.99 (1H, m), 2.85 (3H, m), 2.77 (4H, m), 2.60 (1H, m), 2.04 (6H, s), 1.08 (3H, d) ppm.

LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 511.

15 Preparation 6: N-(3,4-Dimethyl-benzyl)-2-[3-((2R)-2-((2R)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-acetamide

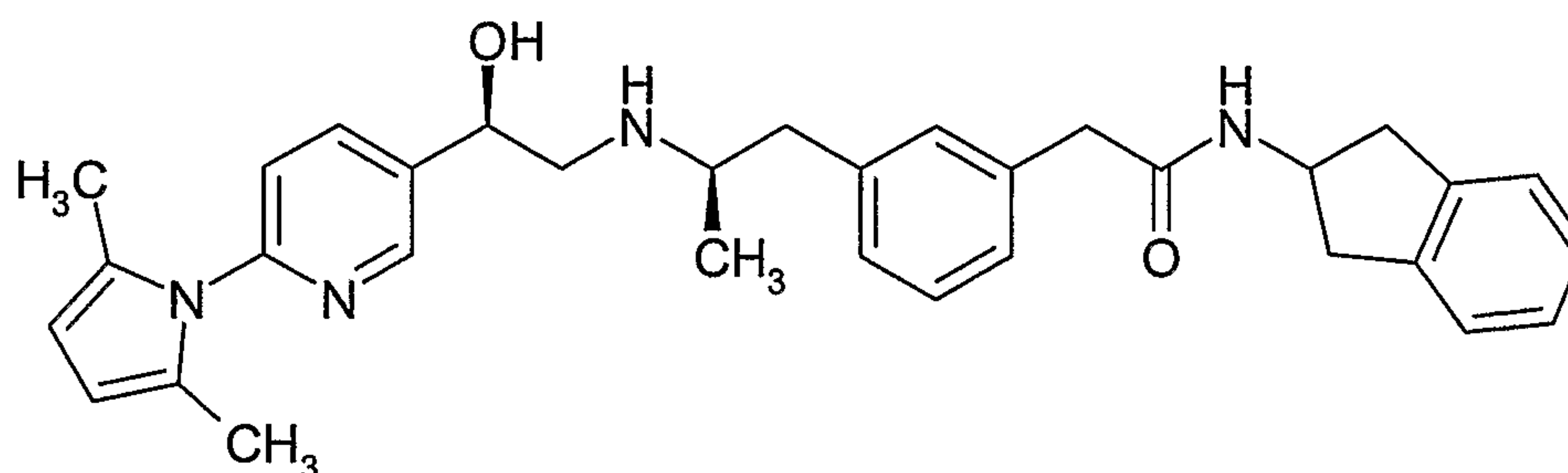


Prepared according to the method for preparation 1 using the appropriate amine to give the title compound as a pale yellow oil.

¹H NMR (400MHz, CD₃OD): δ = 8.55 (1H, s), 7.95 (1H, d), 7.32-6.90 (8H, m), 5.81 (2H, s), 4.90 (1H, m), 4.25 (2H, s), 3.52 (2H, s), 3.18 (1H, m), 3.00 (2H, m), 2.88 (1H, m), 2.65 (1H, m), 2.18 (6H, s), 2.02 (6H, s), 1.06 (3H, d) ppm.

LRMS (APCI) : m/z [M+H]⁺ 525.

Preparation 7 : 2-[3-((2R)-2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-N-indan-2-yl-acetamide

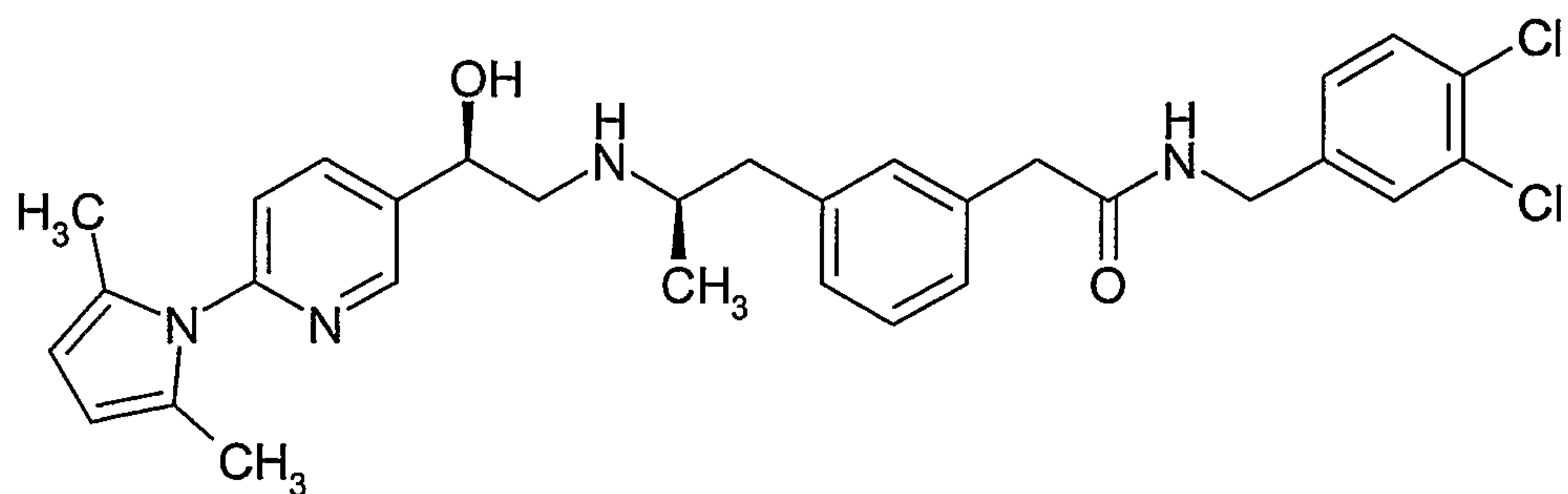


10 Prepared according to the method described for preparation 1 using the appropriate amine to give the title compound as a pale yellow oil.

¹H NMR (400MHz, CD₃OD): δ = 8.57 (1H, s), 8.00 (1H, d), 7.33-7.10 (9H, m), 5.82 (2H, s), 4.94 (1H, m), 4.55 (1H, m), 3.47 (2H, s), 3.31-2.66 (9H, m), 2.04 (6H, s), 1.17 (3H, d) ppm.

15 LRMS (APCI) : m/z [M+H]⁺ 523.

Preparation 8 : N-(3,4-Dichloro-benzyl)-2-[3-((2R)-2-((2R)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-acetamide

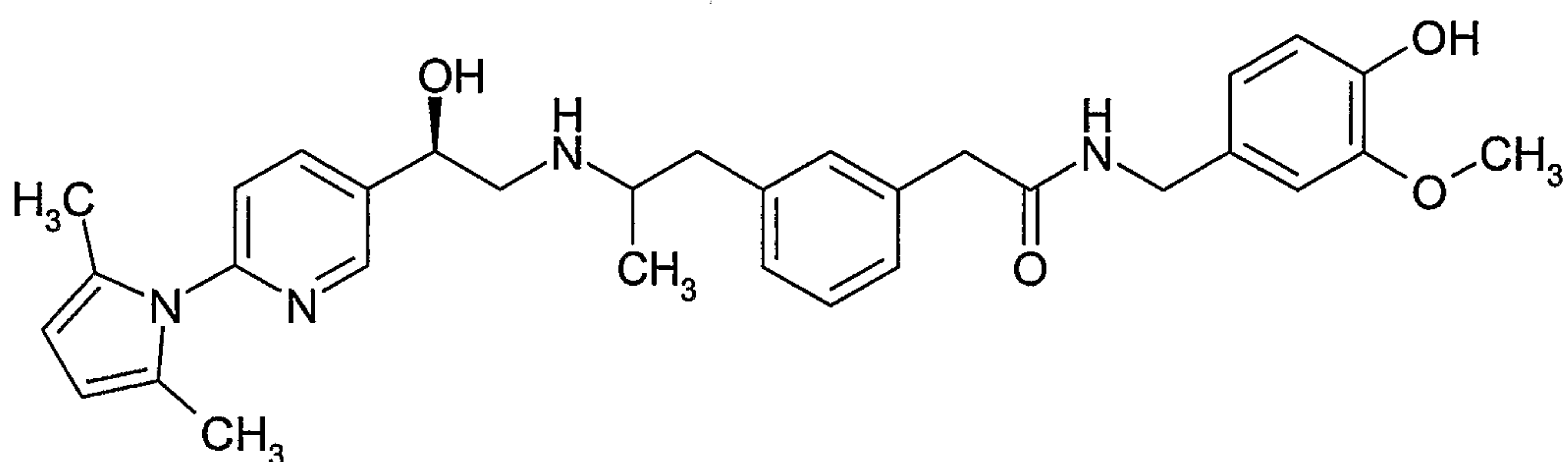


Prepared according to the method described for preparation 1 using 3,4-dichlorobenzylamine as the amine to give the title compound as a pale yellow oil.

- 5 ¹H NMR (400MHz, CD₃OD): δ = 8.56 (1H, s), 8.01 (1H, d), 7.59-7.13 (8H, m), 5.82 (2H, s), 4.92 (1H, m), 4.32 (2H, s), 3.55 (2H, s), 3.20 (1H, m), 3.05 (2H, m), 2.91 (1H, m), 2.70 (1H, m), 2.04 (6H, s), 1.15 (3H, d) ppm.

LRMS (APCI) : m/z $[M+H]^+$ 541 / 543.

Preparation 9 : 2-[3-(2-((2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-*N*-(4-hydroxy-3-methoxy-benzyl)-acetamide



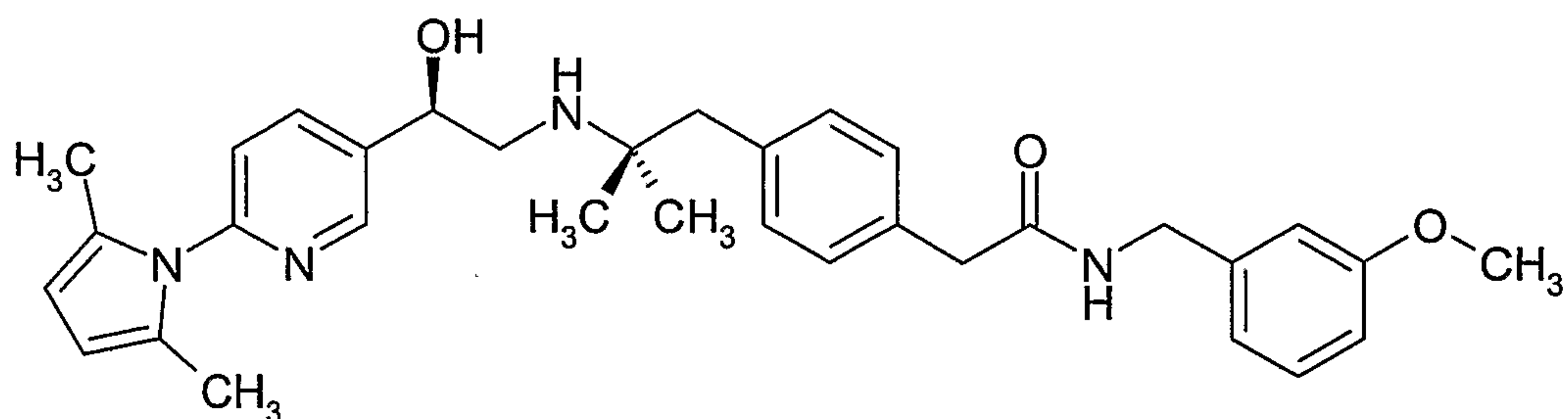
Prepared according to the method described for preparation 1 using the acid from preparation 30 and the appropriate amine to give the title compound as a
15 pale yellow oil.

¹H NMR (400MHz, CDCl₃): δ = 8.47 (1H, m), 7.78-7.75 (1H, m), 7.28-7.24 (1H, m), 7.17-7.08 (3H, m), 6.86-6.61 (4H, m), 6.01-5.94 (3H, m), 4.72-4.57 (1H, m),

4.34-4.25 (2H, m), 3.80 (3H, m), 3.58-3.56 (2H, m), 3.10-2.57 (5H, m), 2.09 (6H, s), 1.13 (3H, t) ppm.

LRMS (APCI) : m/z $[M+H]^+$ 543, $[M+Na]^+$ 565, $[M-H]^-$ 541.

Preparation 10 : 2-[4-(2-((2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-*N*-(3-methoxy-benzyl)-acetamide

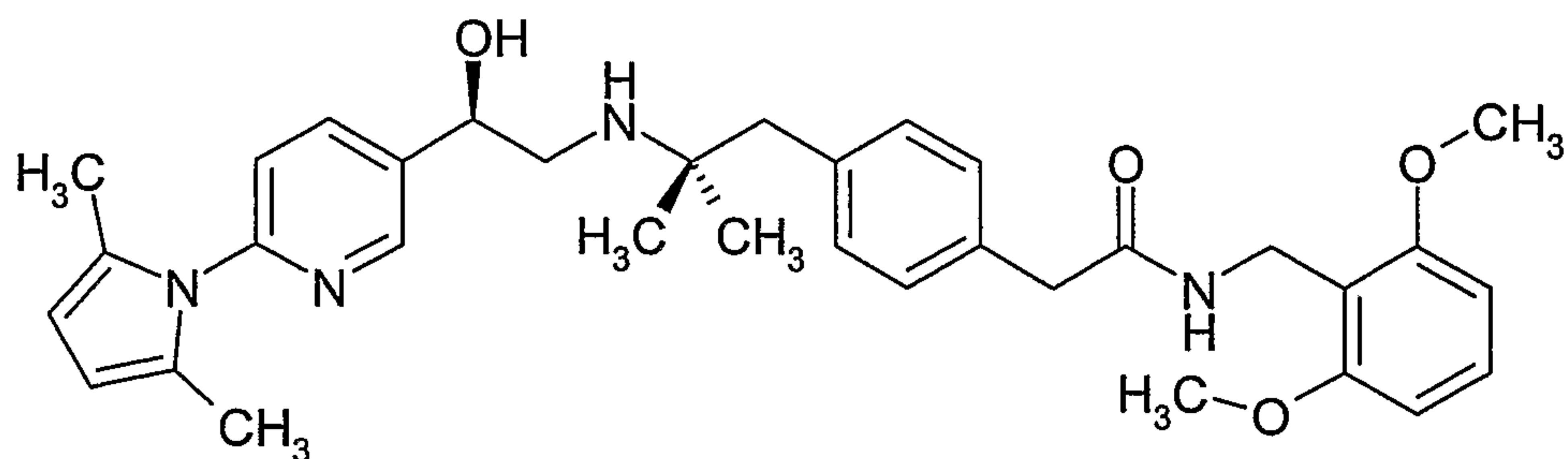


Prepared according to the method for preparation 1 using the acid from preparation 36 and the appropriate amine to give the title compound as a pale yellow foam.

^1H NMR (400MHz, CDCl_3): δ = 8.58 (1H, s), 7.82 (1H, d), 7.20 (4H, m), 7.18 (2H, m), 6.78 (2H, m), 6.72 (1H, s), 5.98 (1H, bs), 5.85 (2H, s), 4.62 (1H, dd), 4.38 (2H, d), 3.72 (3H, s), 3.58 (2H, s), 3.00 (1H, dd), 2.65 (3H, m), 2.08 (6H, s), 1.11 (3H, s), 1.10 (3H, s) ppm.

LRMS (APCI) : m/z $[M+H]^+$ 541.

Preparation 11 : *N*-(2,6-Dimethoxy-benzyl)-2-[4-(2-((2*R*)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-acetamide

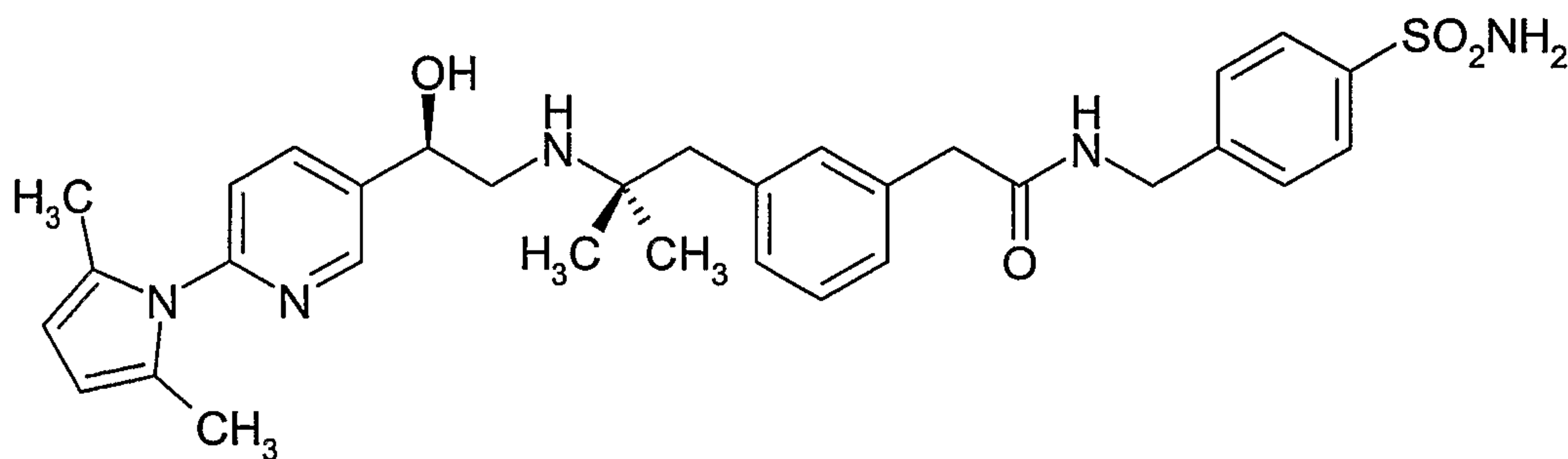


Prepared according to the method for preparation 1 using the acid from preparation 36 and the appropriate amine to give the title compound as a pale yellow solid.

- 5 ^1H NMR (400MHz, CDCl_3): δ = 8.58 (1H, s), 7.90 (1H, d), 7.20-7.10 (6H, m), 6.50 (2H, d), 6.00 (1H, s), 5.90 (2H, s), 4.70 (1H, dd), 4.50 (2H, d), 3.73 (6H, s), 3.50 (2H, s), 3.05 (1H, dd), 2.72 (3H, m), 2.10 (6H, s), 1.11 (3H, s), 1.10 (3H, s) ppm.

LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 571.

- 10 **Preparation 12 : 2-[3-(2-((2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-*N*-(4-sulfamoyl-benzyl)-acetamide**



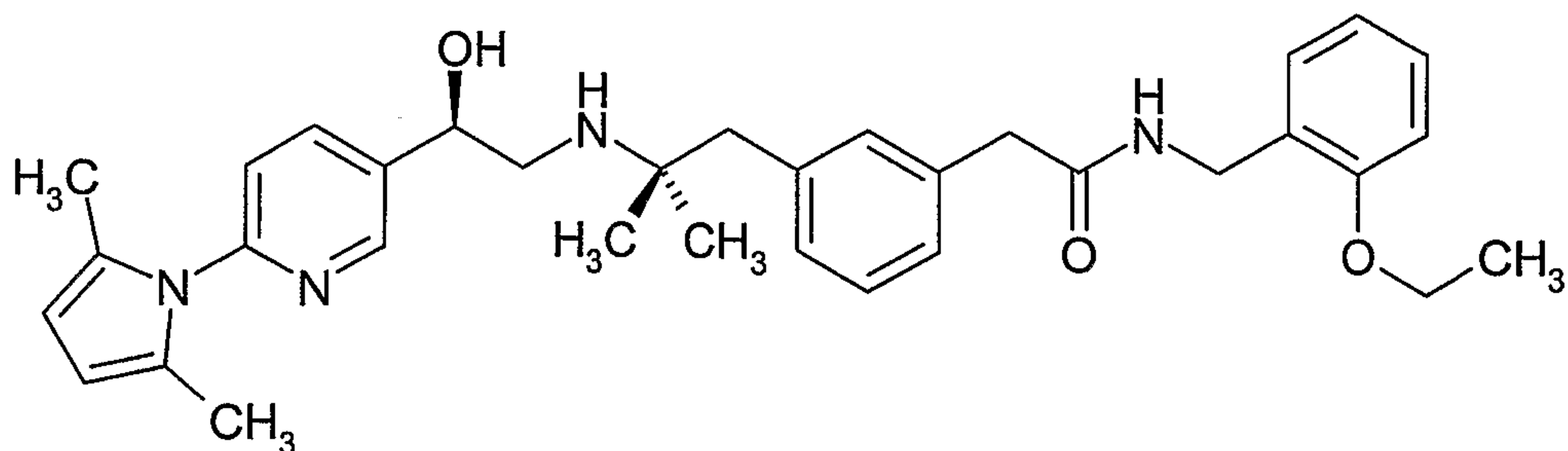
- 15 Prepared according to the method for preparation 1 using the acid from preparation 34 and the appropriate amine to give the title compound as a pale yellow solid.

^1H NMR (400MHz, CD_3OD): δ = 8.58 (1H, s), 8.03 (1H, d), 7.79 (2H, d), 7.37 (2H, d), 7.31 (1H, d), 7.23 (1H, d), 7.18 (2H, m), 7.13 (1H, d), 5.82 (2H, s), 4.81

(1H, partially obscured by solvent), 4.42 (2H, s), 3.56 (2H, s), 2.91-2.88 (2H, m), 2.78-2.66 (2H, m), 2.04 (6H, s), 1.07 (3H, s), 1.04 (3H, s) ppm.

LRMS (APCI) : m/z $[M+H]^+$ 590, $[M-H]^-$ 588.

Preparation 13 : 2-[3-(2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-N-(2-ethoxy-benzyl)-acetamide

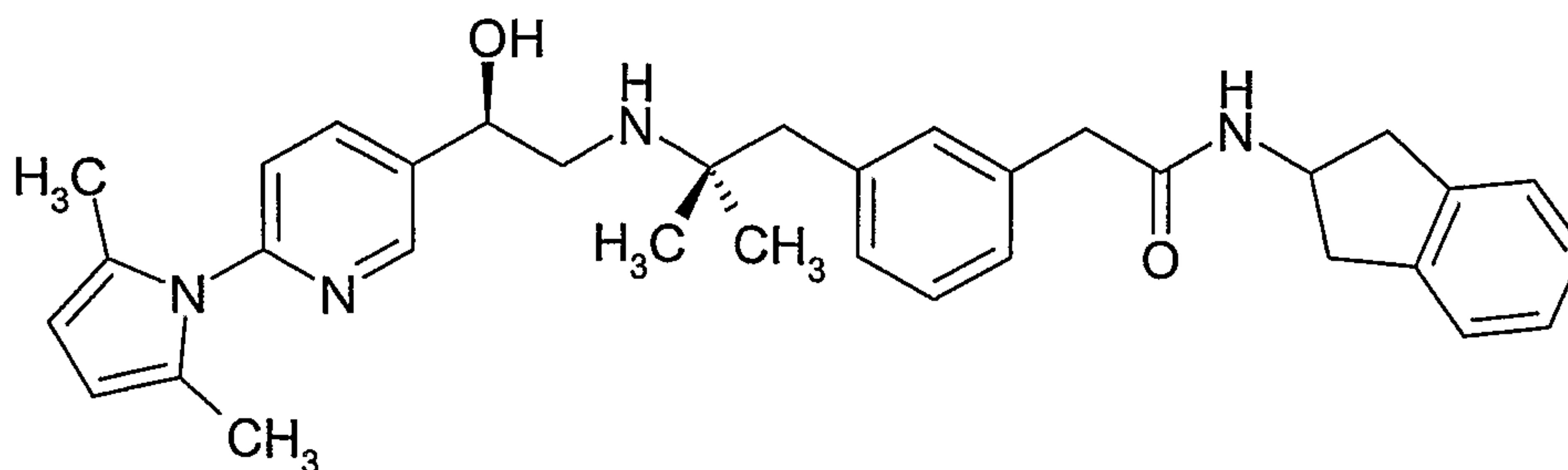


Prepared according to the method for preparation 1 using the acid from preparation 34 and the appropriate amine to give the title compound as a pale yellow solid.

^1H NMR (400MHz, CD_3OD): δ = 8.58 (1H, s), 8.02 (1H, d), 7.30 (1H, d), 7.25-7.10 (5H, m), 6.91-6.80 (3H, m), 5.80 (2H, s), 4.92 (1H, partially obscured by solvent), 4.38 (2H, s), 4.02 (2H, q), 3.55 (2H, s), 2.90-2.82 (2H, m), 2.78-2.65 (2H, m), 2.03 (6H, s), 1.03 (3H, t), 1.05 (3H, s), 1.04 (3H, s) ppm.

LRMS (APCI) : m/z $[M+H]^+$ 555.

Preparation 14 : 2-[3-(2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-N-indan-2-yl-acetamide

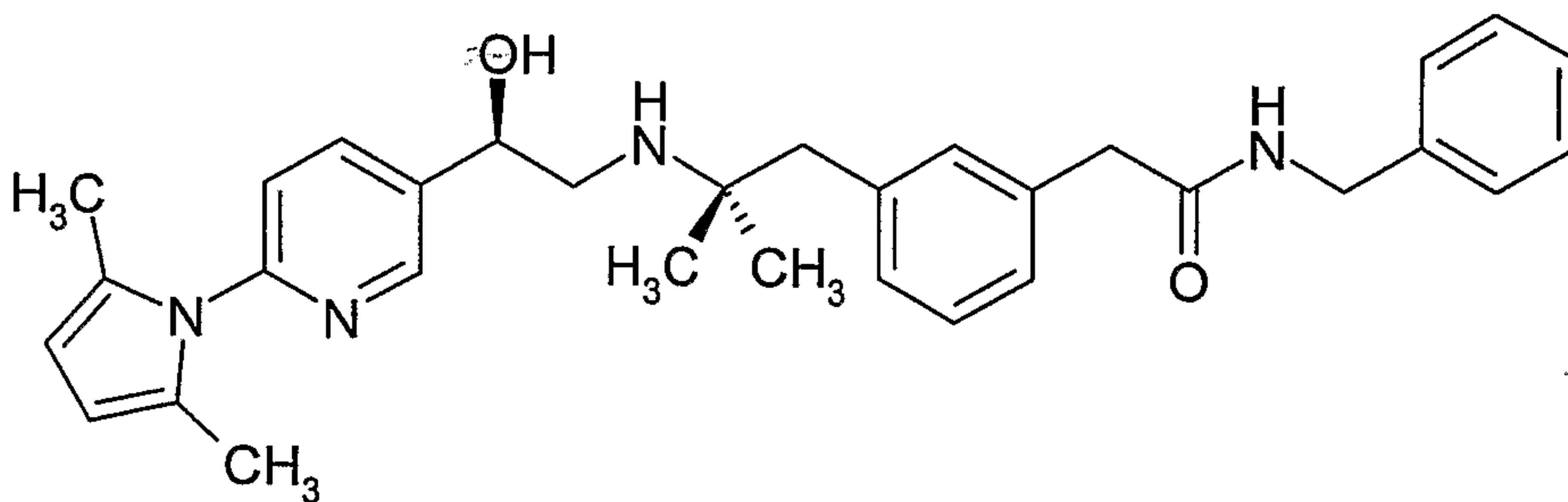


Prepared according to the method described for preparation 1 using the acid from preparation 34 and the appropriate amine to give the title compound as a pale yellow oil.

¹H NMR (400MHz, CD₃OD): δ = 8.58 (1H, s), 8.05 (1H, d), 7.30 (1H, d), 7.25-7.08 (8H, m), 5.81 (2H, s), 4.55 (1H, m), 3.47 (2H, s), 3.25 (1H, d), 3.20 (1H, d), 2.98-2.90 (7H, m), 2.00 (6H, s), 1.10 (3H, s), 1.09 (3H, s) ppm.

LRMS (APCI) : m/z [M+H]⁺ 537.

Preparation 15: N-Benzyl-2-[3-(2-((2R)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-acetamide



10

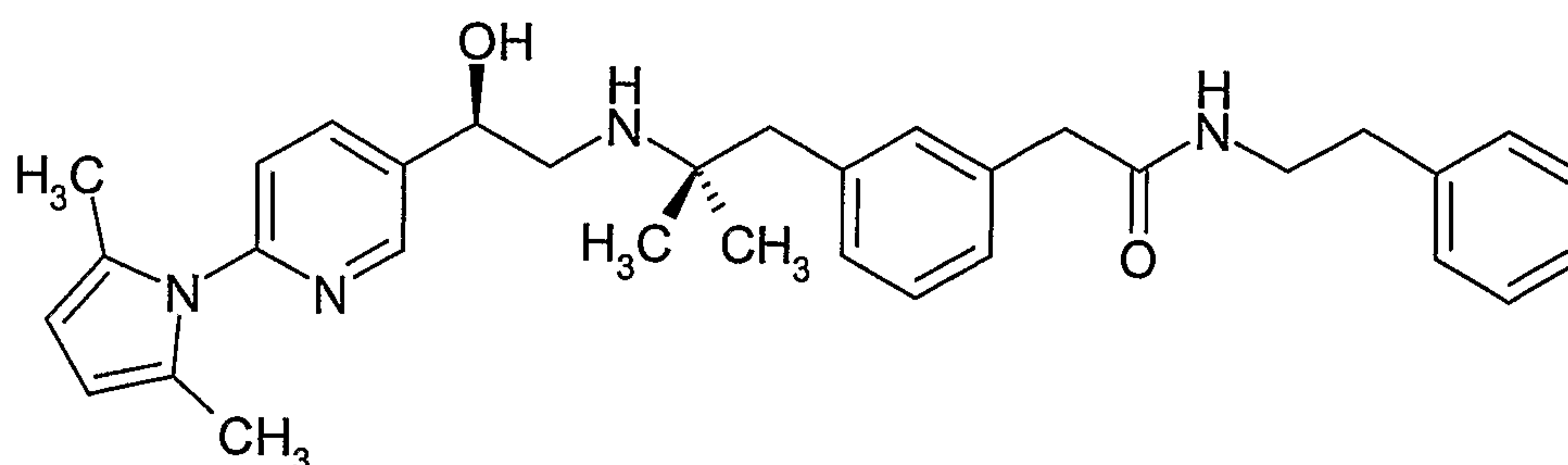
Prepared according to the method described for preparation 1 using the acid from preparation 34 and the appropriate amine to give the title compound as a pale yellow oil.

¹H NMR (400MHz, CD₃OD): δ = 8.58 (1H, s), 8.03-8.00 (1H, m), 7.31-7.10 (10H, m), 5.82 (2H, s), 4.82 (1H, m, partially obscured by solvent), 4.35 (2H, s), 3.54 (2H, s), 2.94-2.84 (2H, m), 2.77-2.66 (2H, dd), 2.04 (6H, s), 1.07 (3H, s), 1.04 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 511, [M+Na]⁺ 533, [M-H]⁻ 509.

Preparation 16 : 2-[3-(2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-N-phenethyl-acetamide

20

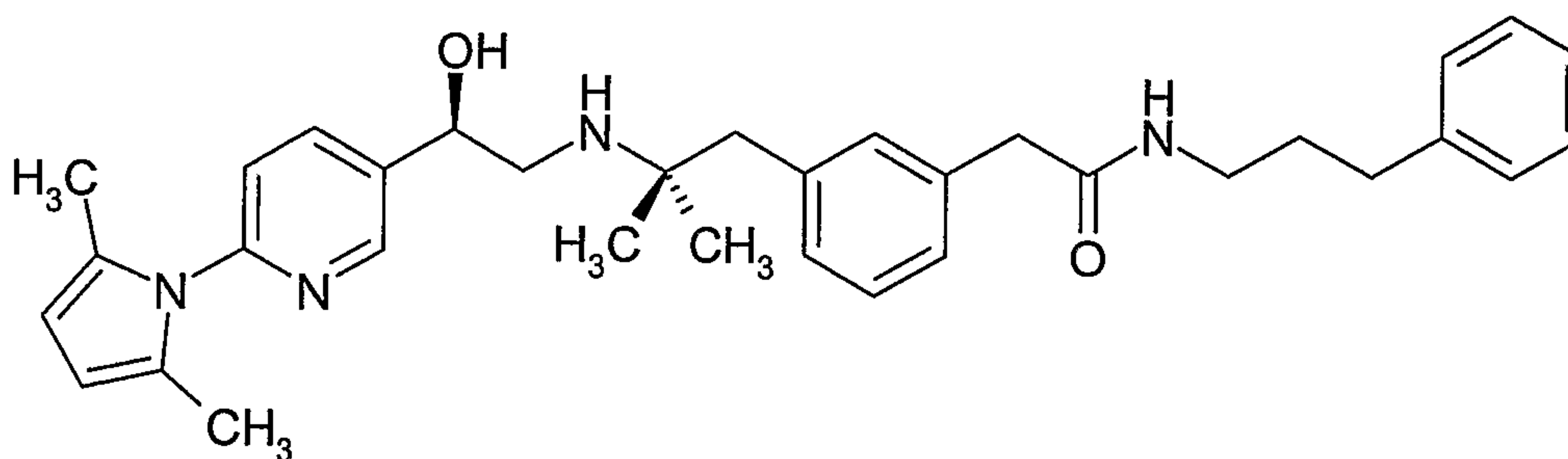


Prepared according to the method described for preparation 1 using the acid from preparation 34 and the appropriate amine to give the title compound as a pale yellow oil.

- 5 ^1H NMR (400MHz, CD_3OD): δ = 8.58 (1H, s), 8.03-8.01 (1H, m), 7.30 (1H, d), 7.24-7.09 (9H, m), 5.82 (2H, s), 4.85 (1H, m, obscured by solvent), 3.45 (2H, s), 3.41-3.38 (2H, m), 2.94-2.86 (2H, m), 2.78-2.66 (4H, m), 2.04 (6H, s), 1.08 (3H, s), 1.05 (3H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 525, $[\text{M}+\text{Na}]^+$ 547, $[\text{M}-\text{H}]^-$ 523.

- 10 **Preparation 17 : 2-[3-(2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-N-(3-phenyl-propyl)-acetamide**



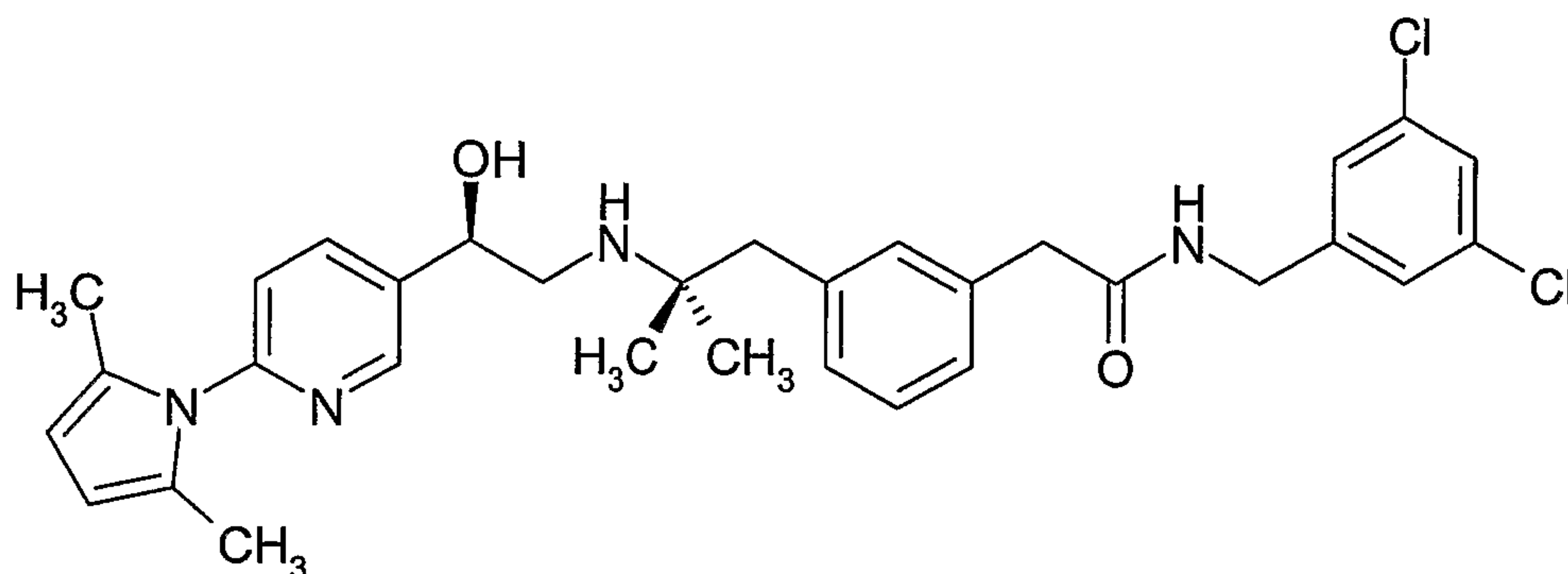
- 15 Prepared according to the method described for preparation 1 using the acid from preparation 34 and the appropriate amine to give the title compound as a pale yellow oil.

^1H NMR (400MHz, CD_3OD): δ = 8.58 (1H, s), 8.02-8.00 (1H, m), 7.31-7.11 (10H, m), 5.82 (2H, s), 4.82 (1H, partially obscured by solvent), 3.49 (2H, s),

3.20-3.17 (2H, m), 2.94-2.85 (2H, m), 2.79-2.67 (2H, m), 2.59-2.55 (2H, m), 2.04 (6H, s), 1.81-1.74 (2H, m), 1.08 (3H, s), 1.05 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 539, $[M+Na]^+$ 561, $[M-H]^-$ 537.

Preparation 18 : *N*-(3,5-Dichloro-benzyl)-2-[3-(2-((2*R*)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-acetamide

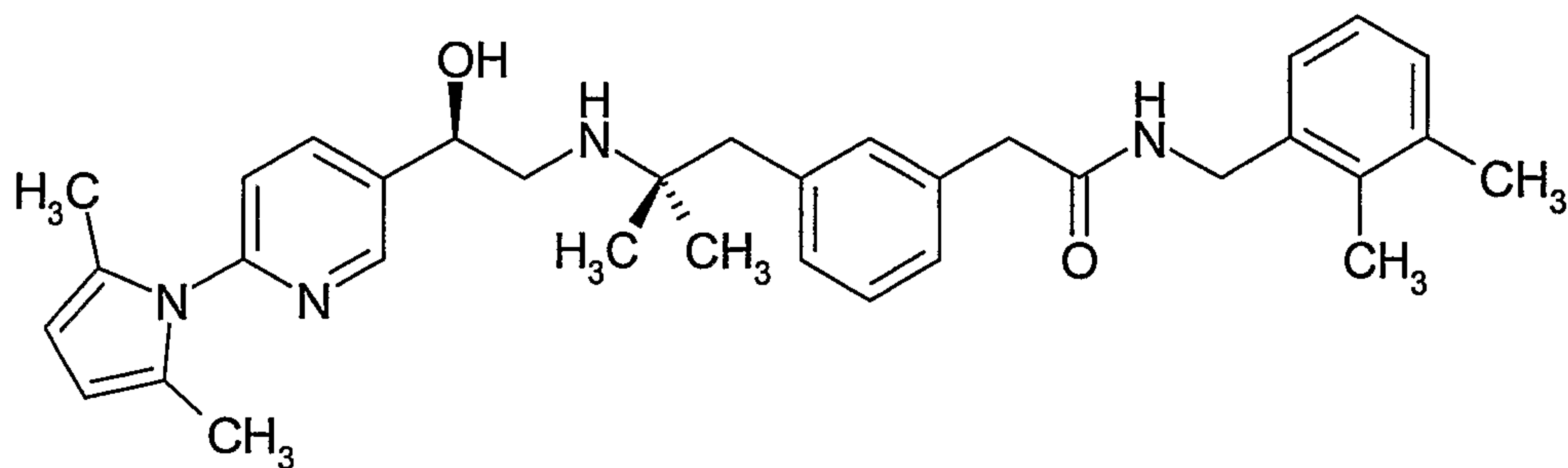


Prepared according to the method described for preparation 1 using the acid from preparation 34 and the appropriate amine to give the title compound as a pale yellow oil.

^1H NMR (400MHz, CD_3OD): δ = 8.59 (1H, s), 8.03-8.01 (1H, m), 7.32-7.11 (8H, m), 5.82 (2H, s), 4.83 (1H, m, partially obscured by solvent), 4.32 (2H, s), 3.56 (2H, s), 2.95-2.84 (2H, m), 2.79-2.67 (2H, dd), 2.04 (6H, s), 1.07 (3H, s), 1.04 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 579 / 581, $[M+Na]^+$ 601 / 603, $[M-H]^-$ 577 / 579.

Preparation 19 : *N*-(2,3-Dimethyl-benzyl)-2-[3-(2-((2*R*)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-acetamide

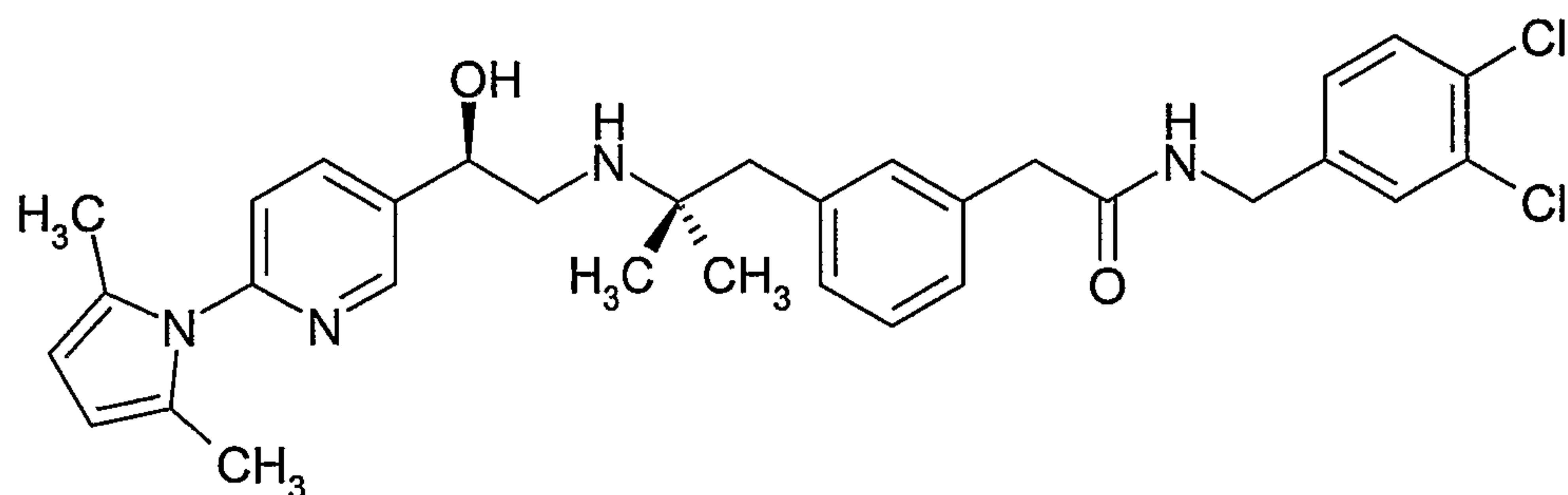


Prepared according to the method described for preparation 1 using the acid from preparation 34 and the appropriate amine to give the title compound as a pale yellow oil.

- 5 ^1H NMR (400MHz, CD_3OD): δ = 8.61 (1H, s), 8.05-8.03 (1H, m), 7.32-6.95 (8H, m), 5.83 (2H, s), 4.95-4.92 (1H, m), 4.36 (2H, s), 3.53 (2H, s), 3.05-3.03 (2H, m), 2.86-2.76 (2H, dd), 2.24 (3H, s), 2.13 (3H, s), 2.04 (6H, s), 1.15 (3H, s), 1.13 (3H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 539, $[\text{M}+\text{Na}]^+$ 561, $[\text{M}-\text{H}]^-$ 537.

- 10 **Preparation 20** : *N*-(3,4-Dichloro-benzyl)-2-[3-(2-((2*R*)-2-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-acetamide



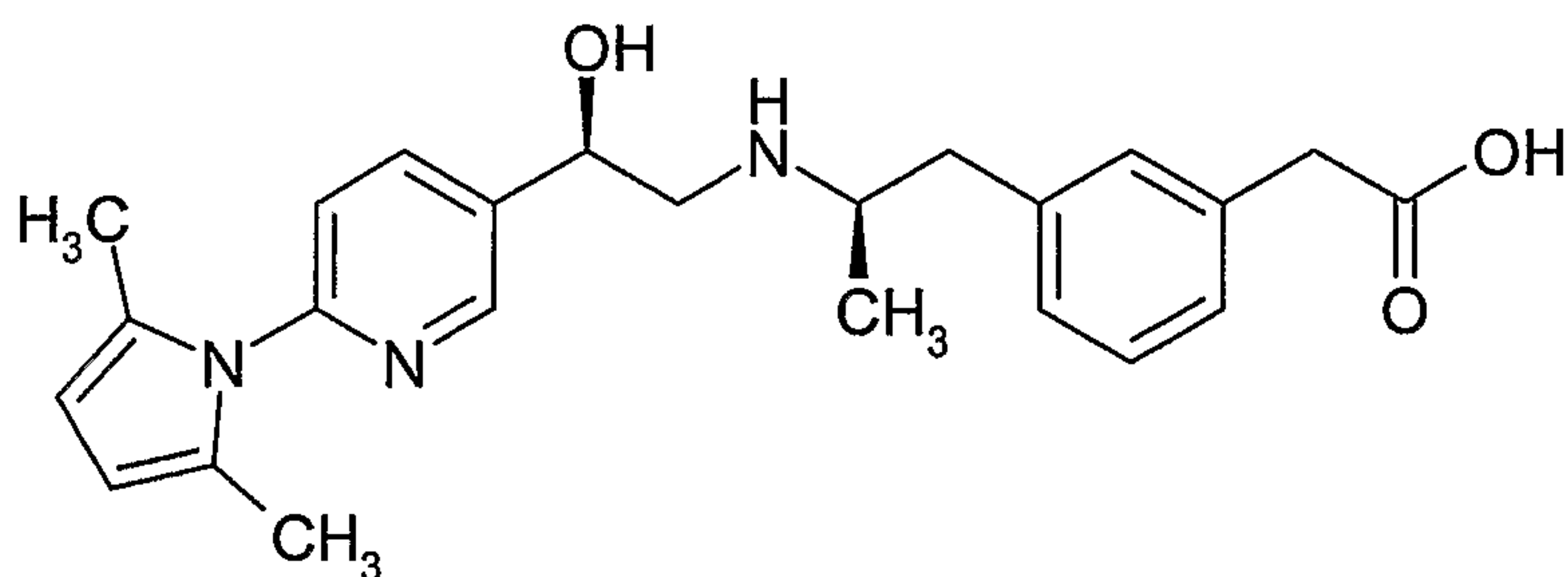
- 15 Prepared according to the method described for preparation 1 using the acid from preparation 34 and the appropriate amine to give the title compound as a pale yellow oil.

^1H NMR (400MHz, CD_3OD): δ = 8.58 (1H, s), 8.03-8.01 (1H, m), 7.46-7.11 (8H, m), 5.82 (2H, s), 4.82 (1H, m, partially obscured by solvent), 4.32 (2H, s), 3.55

(2H, s), 2.94-2.84 (2H, m), 2.78-2.66 (2H, dd), 2.04 (6H, s), 1.06 (3H, s), 1.03 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 579 / 581, $[M+Na]^+$ 601 / 603, $[M-H]^-$ 577 / 579.

5 Preparation 21 : [3-((2R)-2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-acetic acid

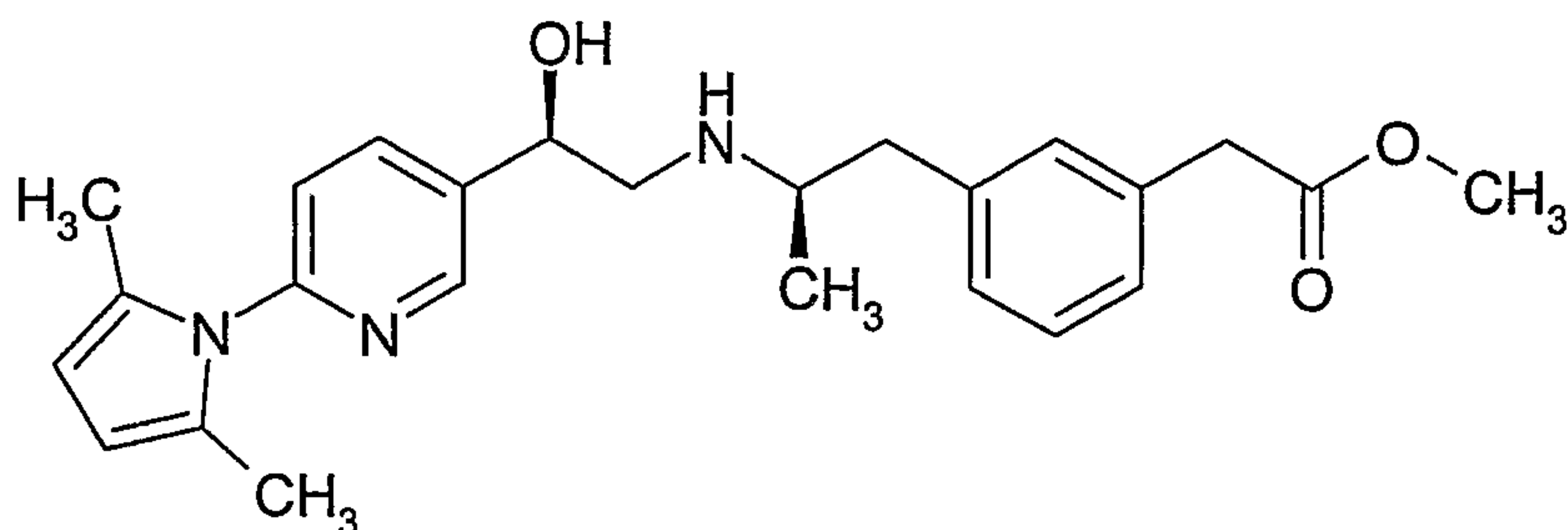


A solution of the ester from preparation 22 (5.45g, 12.93mmol) in tetrahydrofuran (80ml) was treated with 1N lithium hydroxide (26ml, 26mmol) and the resulting mixture left to stir at room temperature for 16 hours. 1N hydrogen chloride (26ml, 26mmol) was added, and the solvent was removed *in vacuo*. The residue was azeotropically dried with toluene and then purified by flash column chromatography eluting with dichloromethane:methanol: 880 ammonia (90:10:1 changing to 80:20:3 by volume) to give the title compound as a colourless solid (3.7g).

^1H NMR (400MHz, DMSO-d_6): δ = 8.54 (1H, bs), 7.92-7.90 (1H, m), 7.33 (1H, d), 7.16 (1H, d), 7.07-7.00 (3H, m), 5.77 (2H, s), 4.77-4.74 (1H, m), 3.47 (2H, s), 2.91-2.75 (4H, m), 2.43-2.38 (1H, m), 2.01 (6H, s), 0.92 (3H, d) ppm.

LRMS (APCI) : m/z $[M+H]^+$ 408.

20 Preparation 22 : [3-((2R)-2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-acetic acid methyl ester

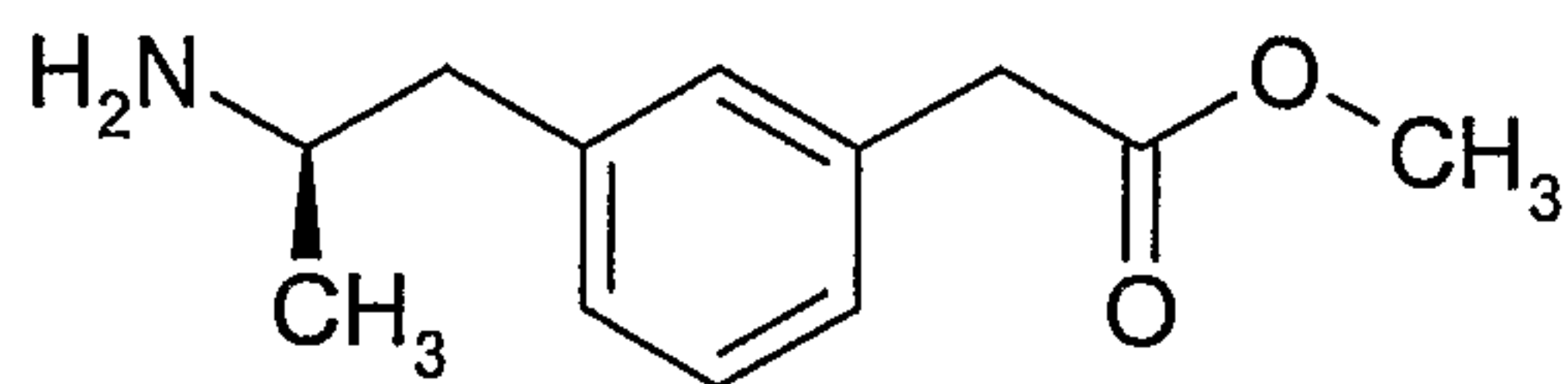


A solution of the epoxide from preparation 27 (5.43g of 66% b/w crude material, 3.58g, 16.7mmol) and the amine from preparation 23 (4.15g, 20.02mmol) in dimethyl sulfoxide (50ml) was heated at 85°C under nitrogen for a period of 16
 5 hours. The reaction mixture was cooled to room temperature and loaded directly onto a Strong Cation Exchange column. The column was eluted with methanol (300ml) and then the product eluted with 2M ammonia in methanol (100ml). The solvent was removed *in vacuo* and the residue purified by flash column chromatography eluting with dichloromethane:methanol:880 ammonia
 10 (100 changing to 98:2:0.2 by volume) to give the title compound as a pale orange oil (5.45g).

¹H NMR (400MHz, CD₃OD): δ = 8.54 (1H, bs), 7.79 (1H, dd), 7.31-7.22 (2H, m), 7.15-7.10 (3H, m), 5.82 (2H, s), 4.91-4.81 (1H, m, partially obscured by solvent), 3.67 (3H, s), 3.63 (2H, s), 3.04-2.96 (1H, m), 2.88 (2H, d), 2.81-2.74 (1H, m),
 15 2.66-2.58 (1H, m), 2.04 (6H, s), 1.09 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 422, [M+Na]⁺ 444, [M-H]⁻ 420.

Preparation 23 : [3-((2*R*)-2-Amino-propyl)-phenyl]-acetic acid methyl ester hydrochloride



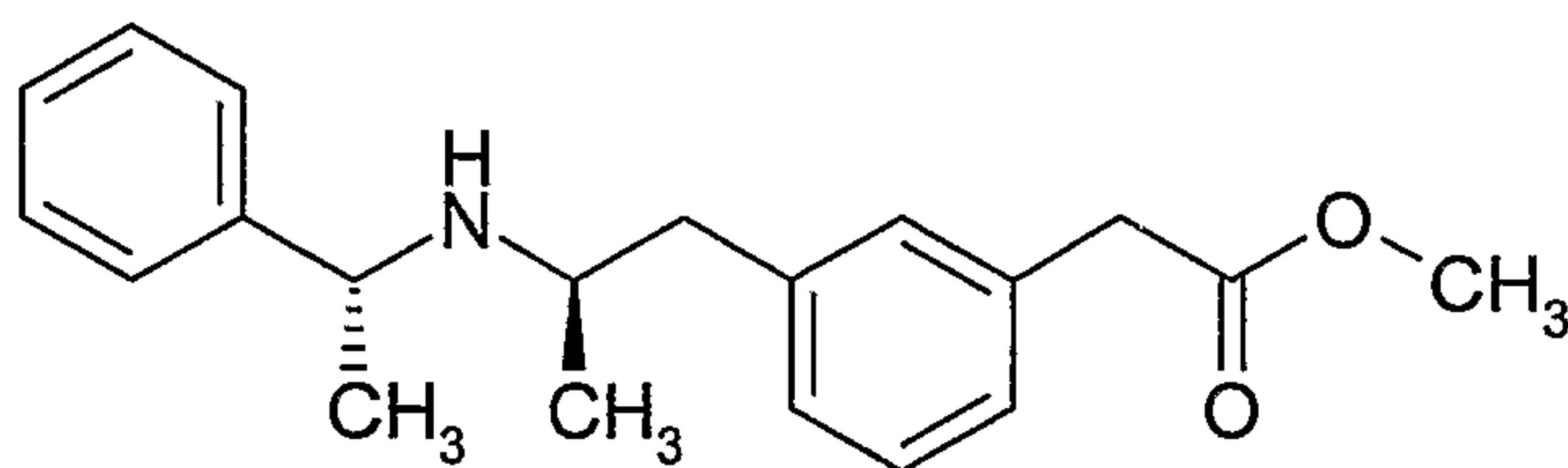
20 A solution of the amine from preparation 24 (7.69g, 22mmol) and ammonium formate (6.94 g, 110 mmol) was heated to 75°C in the presence of 20% of palladium hydroxide-on-charcoal (2.00g). After 90 minutes the reaction mixture

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 with dichloromethane (100ml) and the combined
5 organic extracts dried (magnesium sulfate) and reduced *in vacuo* to give the title compound as a colourless oil (4.78g).

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

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

10 **Preparation 24 : {3-[(2*R*)-2-((1*R*)-1-Phenyl-ethylamino)-propyl]-phenyl}-acetic acid methyl ester**

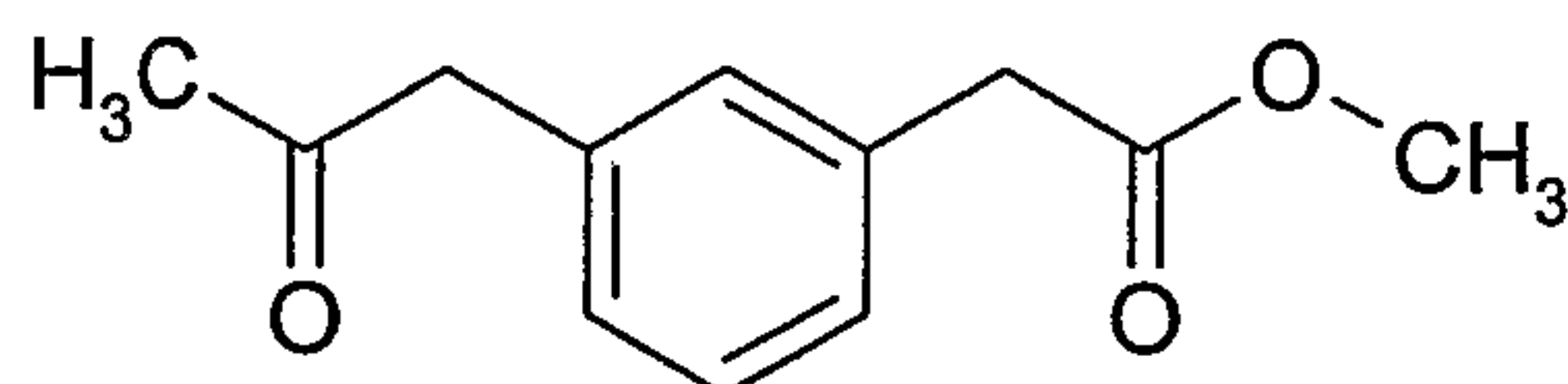


A solution of the ketone from preparation 25 (8.5g, 41.2mmol), (*R*)-α-methyl benzylamine (4.8ml, 37.2mmol), sodium triacetoxyborohydride (11.6g, 56mmol)
15 and acetic acid (2.2ml, 38mmol) in dichloromethane (400ml) was stirred at room temperature for 48 hours. The reaction mixture was quenched by addition 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
20 were dried (magnesium sulfate) and reduced *in vacuo*. Purification by flash column chromatography eluting with dichloromethane:methanol:880 ammonia (99:1:0.1 changing 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 excess 1M hydrogen chloride in methanol followed by three successive crystallisations
25 (diisopropylether/methanol) gave the title compound as a colourless 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.

5 LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 312, $[\text{M}+\text{Na}]^+$ 334.

Preparation 25 : [3-(2-Oxo-propyl)-phenyl]-acetic acid methyl ester

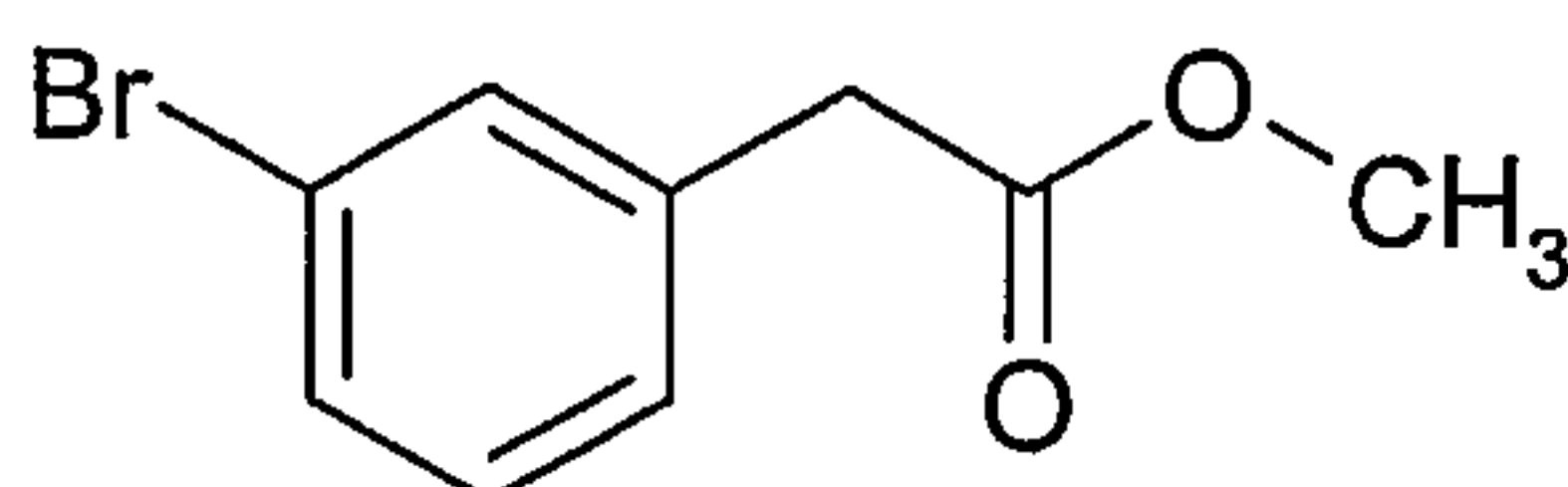


A solution of the bromide from preparation 26 (15.0g, 65.0mmol), tributyltin methoxide (28.3ml, 98mmol), isopropenyl acetate (10.8ml, 98.0mmol),
10 palladium(II) acetate (750mg, 3.30mmol) and tri-*ortho*-tolylphosphine (2.0g, 6.5 mmol) were stirred together in toluene (75ml) at 100°C under nitrogen for 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
15 reduced *in vacuo*. The residue was purified by flash column chromatography silica gel eluting with a solvent gradient of diethyl ether:pentane:dichloromethane (0:100:0 changing to 25:75:0 then to 0:0:100, by volume) to give the title compound as a pale yellow oil (12.6g).

^1H NMR (400MHz, CDCl_3): δ = 7.30 (1H, t), 7.19 (1H, d), 7.13-7.10 (2H, m),
20 3.69 (5H, s), 3.61 (2H, s), 2.15 (3H, s) ppm.

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

Preparation 26 : (3-Bromo-phenyl)-acetic acid methyl ester

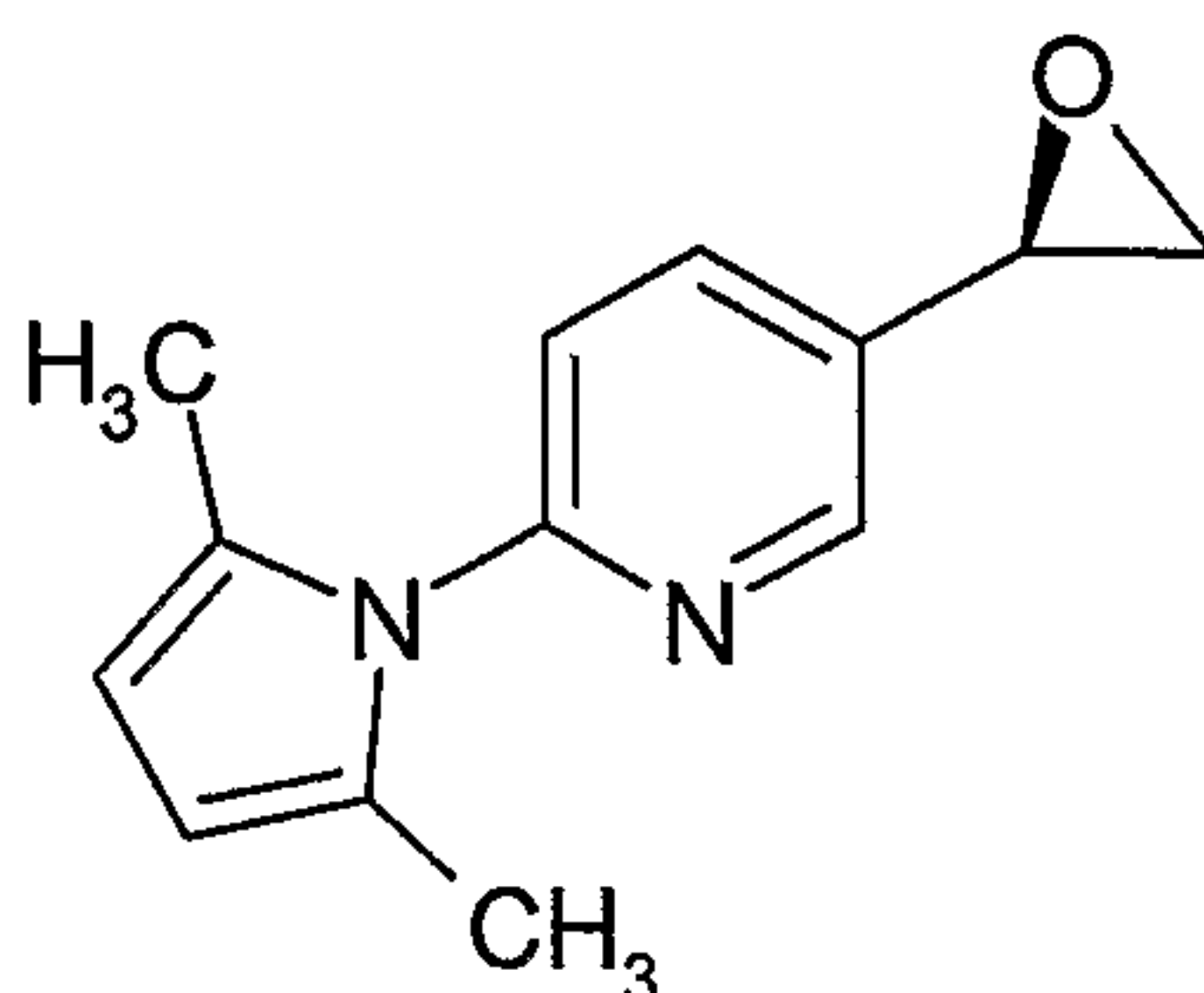


Acetyl chloride (0.7ml, 9.3mmol) was slowly added to a solution of (3-bromo-phenyl)-acetic acid (20.0g, 93mmol) in methanol (500ml) at 0°C under nitrogen and the reaction was allowed to warm gradually to room temperature over a period of 5 hours. The solvent was removed *in vacuo* and the residue dissolved
5 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.

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

10 **Preparation 27 : 2-(2,5-Dimethyl-pyrrol-1-yl)-5-[(2*R*)-oxiranyl]pyridine**



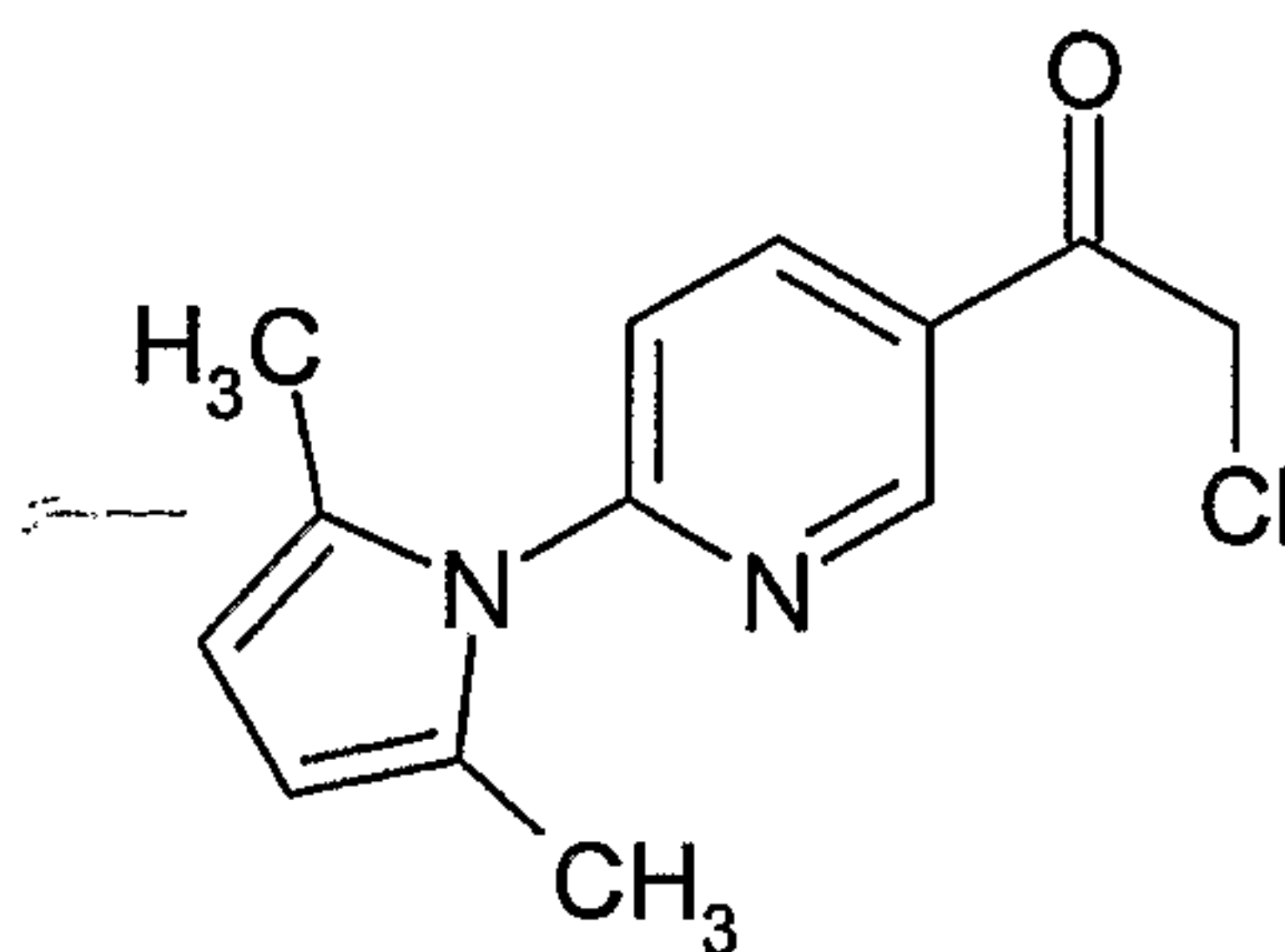
A solution of the chloride from preparation 28 (12.0g, 48.1mmol) in tetrahydrofuran (20ml) was slowly added to a solution of (-)-*B*-chlorodiisopinocampheylborane (20.1g, 62.5mmol) in *tert*-butyl-methylether
15 (15ml) and tetrahydrofuran (30ml) at -30°C under nitrogen. The reaction was stirred for 6 hours at -30°C and then sodium perborate tetrahydrate (7.4g, 48.1mmol) followed by *tert*-butyl-methylether (50ml) were added. The reaction was stirred at room temperature for 18 hours, treated with 2M aqueous sodium hydroxide (190ml) and stirred for a further 6 hours. The organic phase was
20 separated and the aqueous phase extracted with further *tert*-butyl- methylether (50ml). The combined organic extracts were washed with 1M aqueous sodium hydroxide (50ml), saturated aqueous sodium chloride (50ml), dried (sodium sulfate) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with pentane:dichloromethane (80:2

changing to 100:0, by volume) to give the crude epoxide (65% b/w, 11.0 g), which was used without further purification.

^1H NMR (400MHz, CDCl_3): δ = 8.58 (1H, bs), 7.68-7.66 (1H, dd), 7.22-7.20 (1H, d), 3.97-3.96 (1H, m), 3.26-3.24 (1H, m), 2.91-2.89 (1H, m), 2.12 (6H, s) ppm.

5 LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 215, $[\text{M}+\text{Na}]^+$, 237.

Preparation 28 : 2-Chloro-1-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-ethanone

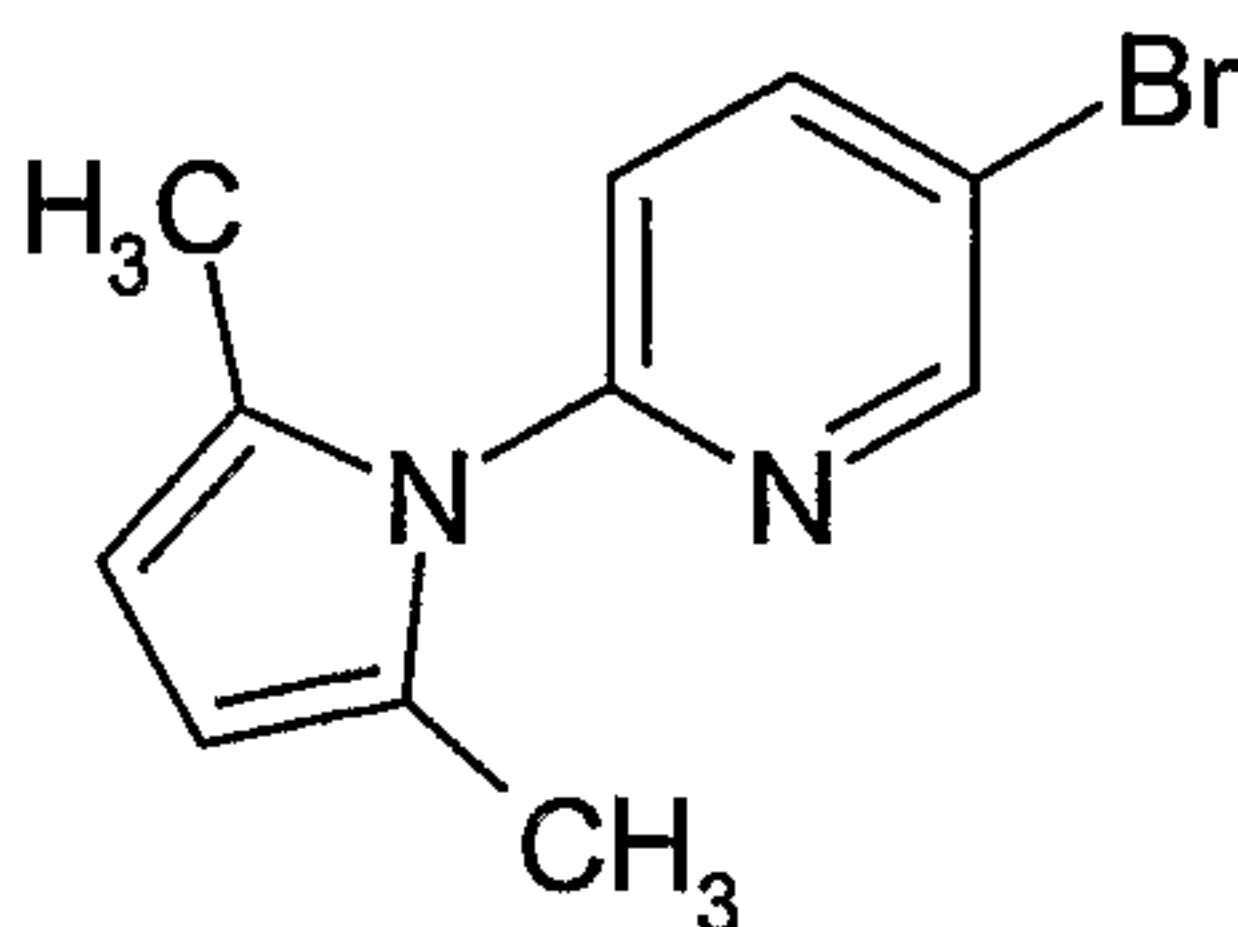


A solution of 2.5 M *n*-butyl lithium in hexanes (35ml, 87.6mmol) was added to a
10 solution of the bromide from preparation 29 (20.0g, 79.7mmol) in *tert*-butyl
methylether (300ml) at -78°C under nitrogen over 10 minutes. The reaction
was stirred for a further 10 minutes and 2-chloro-N-methoxy-N-methyl-
acetamide (12.1g, 87.6mmol) in *tert*-butyl-methylether (40ml) was added slowly.
The reaction was stirred at -78°C for 20 minutes and then 1M hydrochloric acid
15 (200ml) was added. The mixture was allowed to warm to room temperature,
stirred for 2 hours and the organic phase separated. The aqueous phase was
extracted with *tert*-butyl methylether and the combined organic extracts were
washed with water (100ml), saturated aqueous sodium chloride (100ml) and 1M
sodium hydroxide (100ml). The organic phase was dried (sodium sulfate),
20 concentrated *in vacuo* and the residual oil purified by flash column
chromatography on silica gel eluting with pentane:dichloromethane:methanol
(75:25:0 changing to 0:99:1, by volume). The residue was recrystallised from
pentane:dichloromethane to give the title compound as a yellow solid.

^1H NMR (400MHz, CDCl_3): δ = 9.11 (1H, s), 8.34-8.33 (1H, d), 7.32-7.30 (1H, d), 5.91 (2H, s), 4.66 (2H, s), 2.17 (6H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}-\text{H}]^+$ 247.

Preparation 29 : 5-Bromo-2-(2,5-dimethyl-pyrrol-1-yl)-pyridine



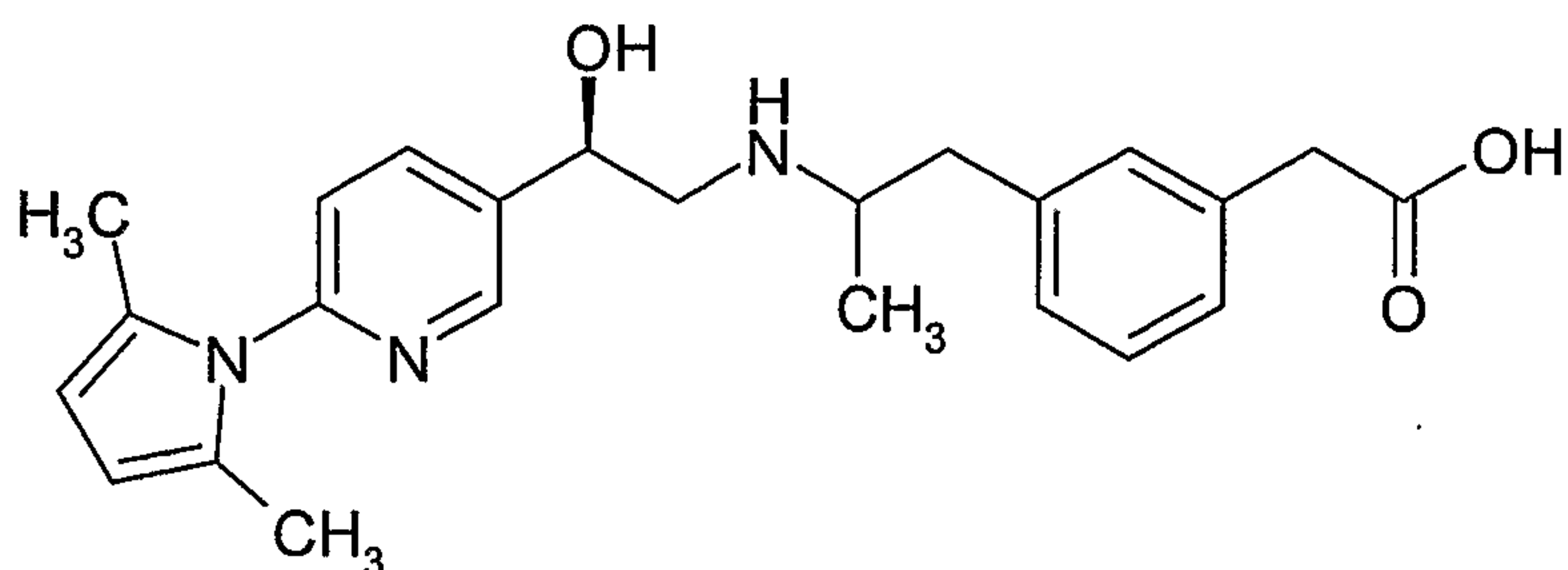
5

2,5-hexanedione (46.2g, 0.41mol) was added to a suspension of 2-amino-5-bromopyridine (50.0g, 0.29mol) and the reaction heated to reflux for 24 hours under Dean and Stark conditions. *para*-Toluene sulfonic acid (100mg) was added and the reaction was refluxed for a further 18 hours. 8 ml of water were removed, so the reaction was cooled to room temperature, washed with water (100ml) and passed through a plug of silica gel, eluting with toluene. The eluent was concentrated *in vacuo* and the residue dissolved in pentane:dichloromethane (1:1 by volume) and passed through a plug of silica gel, eluting with pentane:dichloromethane (1:1 by volume). The eluent was concentrated *in vacuo* to give a red liquid, which solidified on standing. The solid was recrystallised (isopropanol) to give the title compound as a pale yellow solid (54.4g).

^1H NMR (400MHz, CDCl_3): δ = 8.66 (1H, s), 7.93-7.92 (1H, d), 7.13-7.11 (1H, d), 5.91 (2H, s), 2.13 (6H, s) ppm.

20 LRMS (thermospray) : m/z $[\text{M}+\text{H}]^+$ 252.

Preparation 30 : [3-(2-((2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-acetic acid

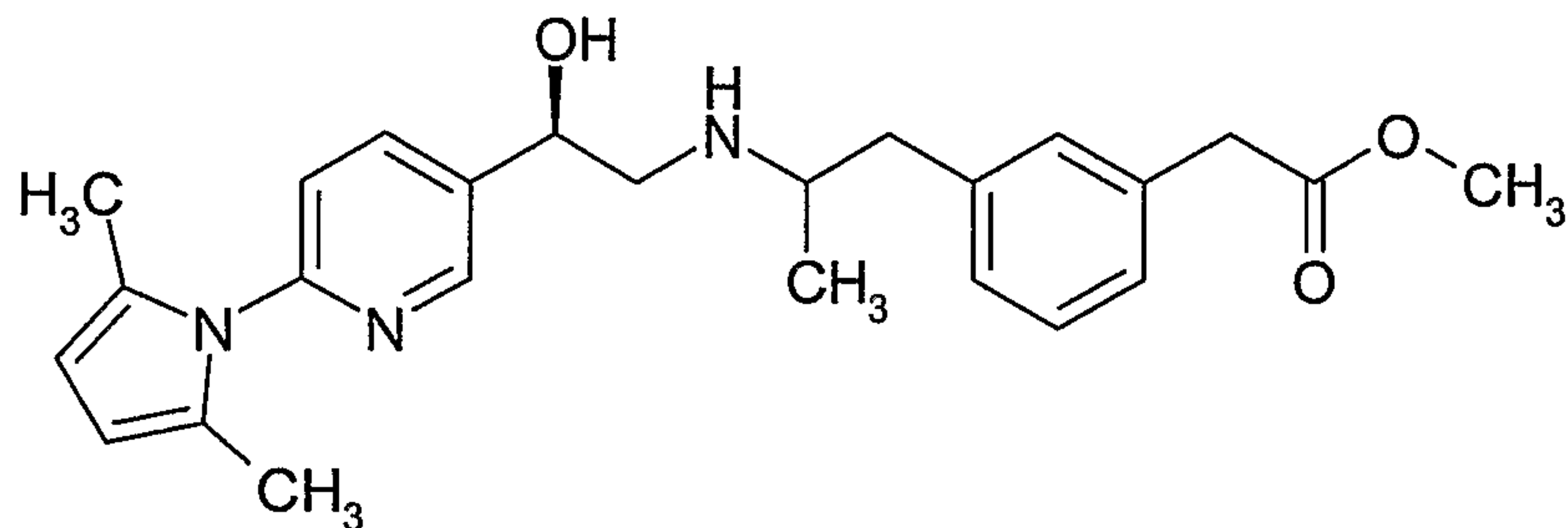


Prepared using the method for preparation 21 using the ester from preparation 31 to give the title compound as a colourless solid which was used without further purification.

- 5 ^1H NMR (400MHz, DMSO-d_6): δ = 8.55 (1H, s), 7.93 (1H, t), 7.35 (1H, d), 7.18-7.15 (1H, m), 7.10-7.03 (3H, m), 5.77 (2H, s), 4.87-4.80 (1H, m), 3.48 (2H, s), 3.01-2.89 (4H, m), 2.50-2.40 (1H, m, partially masked by solvent), 2.01 (6H, s), 0.96 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 408.

- 10 **Preparation 31** : [3-(2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-propyl)-phenyl]-acetic acid methyl ester



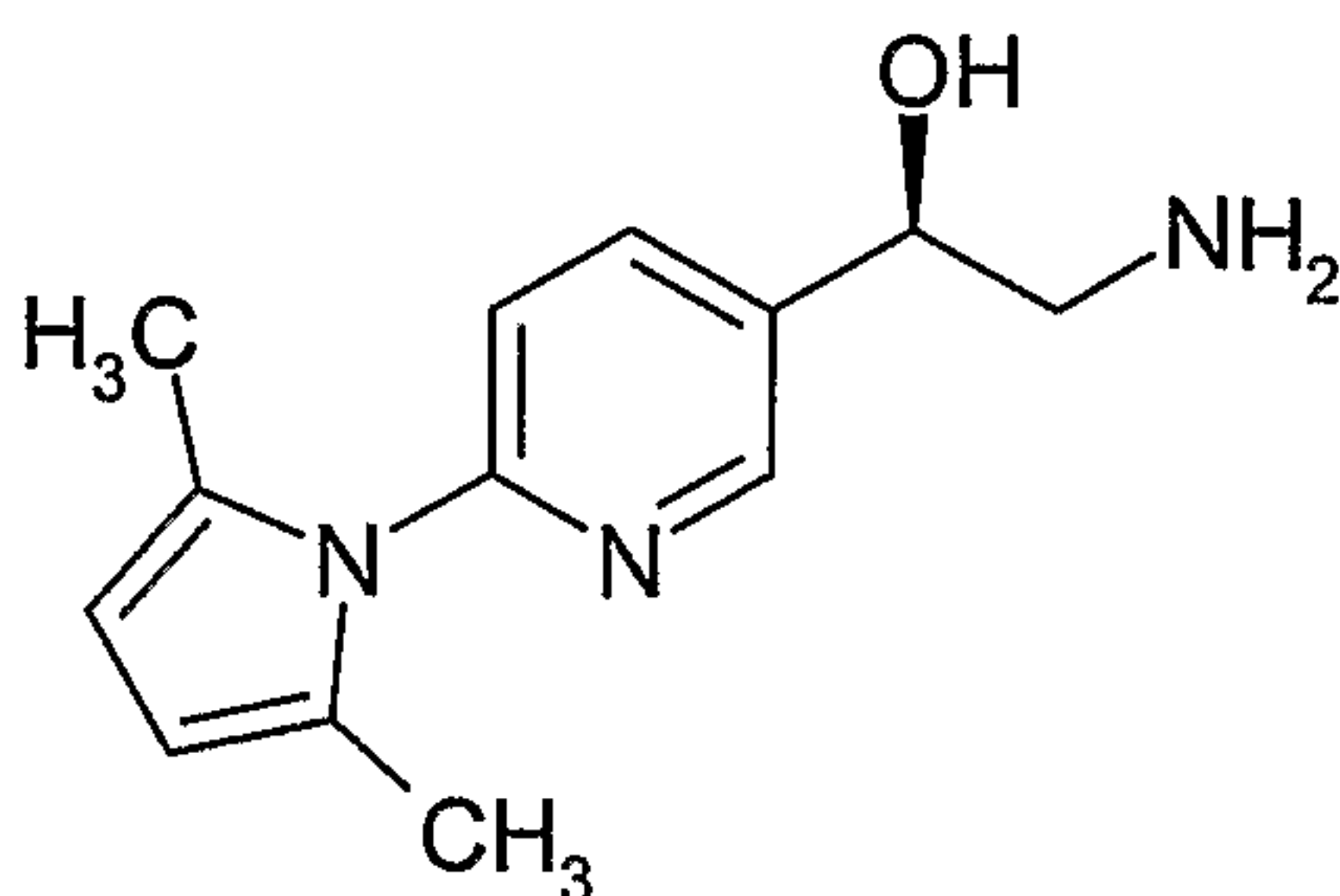
- 15 A solution of the amine from preparation 32 (2.0g, 8.65mmol), the ketone from preparation 25 (2.14g, 10.0mmol), acetic acid (0.5 ml, 8.65 mmol) and sodium triacetoxyborohydride (2.75g, 13.0mmol) were stirred in dichloromethane (25ml) under nitrogen at room temperature for 18 hours. The mixture was washed with water (25ml) and the aqueous phase extracted with further dichloromethane (2 x 10ml). The combined organic extracts were dried (magnesium sulfate), reduced *in vacuo* and the residue purified by flash column chromatography on

silica gel eluting with dichloromethane:methanol:880 ammonia (98:2:0 changing to 95:5:0 then 95:5:0.5, by volume) to give the title compound (1:1 mixture of diastereoisomers) as a pale yellow oil (3.65g).

¹H NMR (400MHz, CDCl₃): δ = 8.56 (1H, s), 7.87-7.84 (1H, m), 7.30-7.26 (1H, m, partially masked by solvent), 7.20-7.09 (4H, m), 5.88 (2H, s), 4.97-4.87 (1H, m), 3.69 (3H, s), 3.62 (2H, s), 3.18-3.03 (2H, m), 2.94-2.74 (3H, m), 2.10 (6H, s), 1.22 (3H, d) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 422.

Preparation 32 : (1*R*)-2-Amino-1-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-3-yl]-ethanol

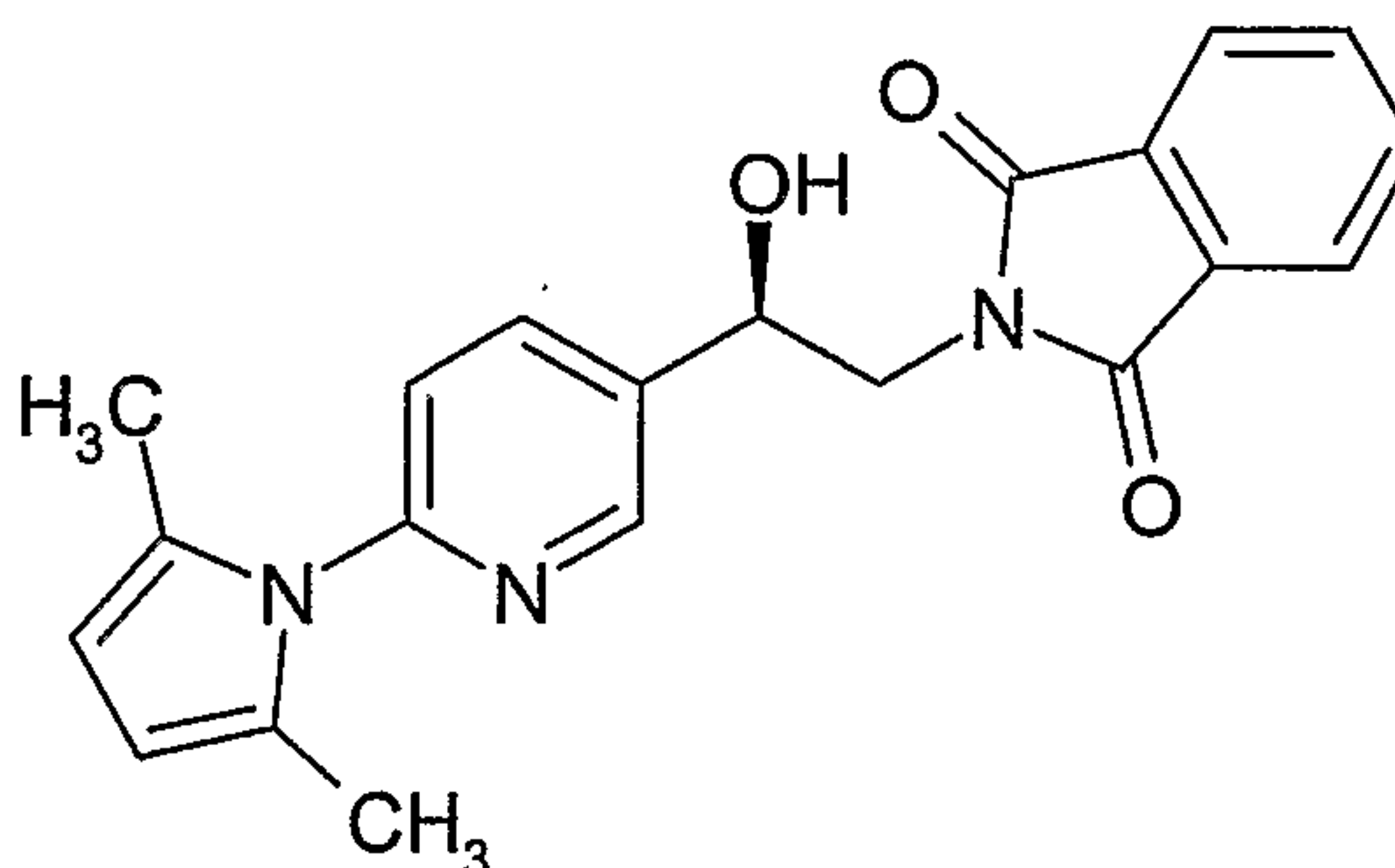


A solution of the phthalimide from preparation 33 (4.85g, 13.4mmol) in 8M methylamine in ethanol (50 ml) was stirred under a nitrogen atmosphere at room temperature for 18 hours. The reaction was concentrated under reduced pressure and the residue dissolved in methanol. This solution was passed through a Strong Cation Exchange resin cartridge eluting with methanol and then 2N ammonia in methanol to elute the product. The eluent was concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (95:5:0 changing to 90:10:1, by volume) to give the title compound as a pale yellow solid (1.6g).

¹H NMR (400MHz, CDCl₃): δ = 8.17 (1H, s), 7.85 (1H, d), 7.21 (1H, d), 5.89 (2H, s), 4.69 (1H, t), 3.15-3.11 (1H, dd), 2.85-2.80 (1H, dd), 2.11 (6H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 232, $[M+Na]^+$, 254.

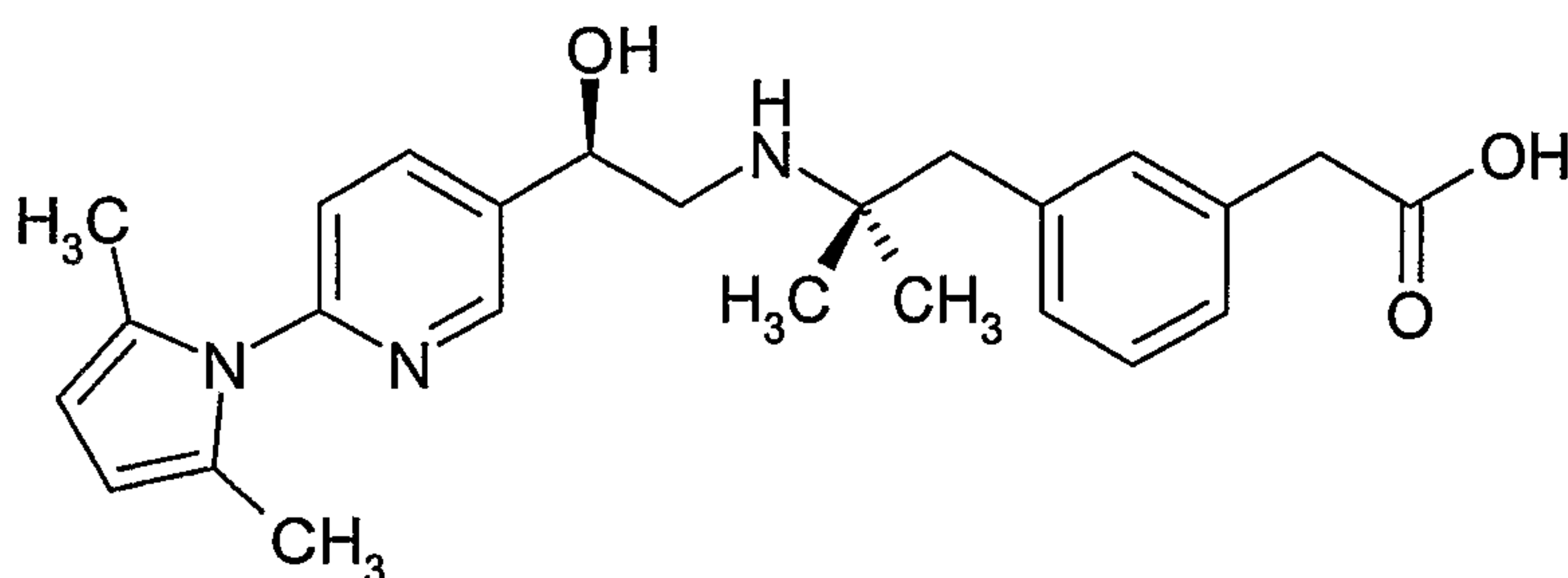
Preparation 33 : 2-[(2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethyl]-isoindole-1,3-dione



- 5 A solution of the crude epoxide from preparation 27 (30.0g of 65% b/w epoxide, 19.50g, 91.0mmol), phthalimide (12.51g, 85.0mmol) and potassium phthalimide (2.78g, 15.0mmol) in *N,N*-dimethylformamide (200ml) was heated at 90°C under nitrogen for 6 hours. After cooling the reaction was stirred at room temperature for 18 hours, concentrated *in vacuo* and the residue partitioned
- 10 between dichloromethane (600ml) and water (400ml). The organic phase was separated and the aqueous phase extracted with further dichloromethane (200ml). The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo*. Crystallisation from ethyl acetate (300ml) gave the title compound as a pale yellow crystalline solid (22.1 g).
- 15 ^1H NMR (400MHz, DMSO- d_6): δ = 8.42 (1H, s), 7.90 (1H, d), 7.80 (4H, d), 7.30 (1H, d), 5.90 (1H, s), 5.80 (2H, s), 5.00 (1H, brs), 3.82 (1H, m), 3.75 (1H, m), 1.95 (6H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 362.

- Preparation 34 : [3-(2-[(2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino]-2-methyl-propyl)-phenyl]-acetic acid**
- 20

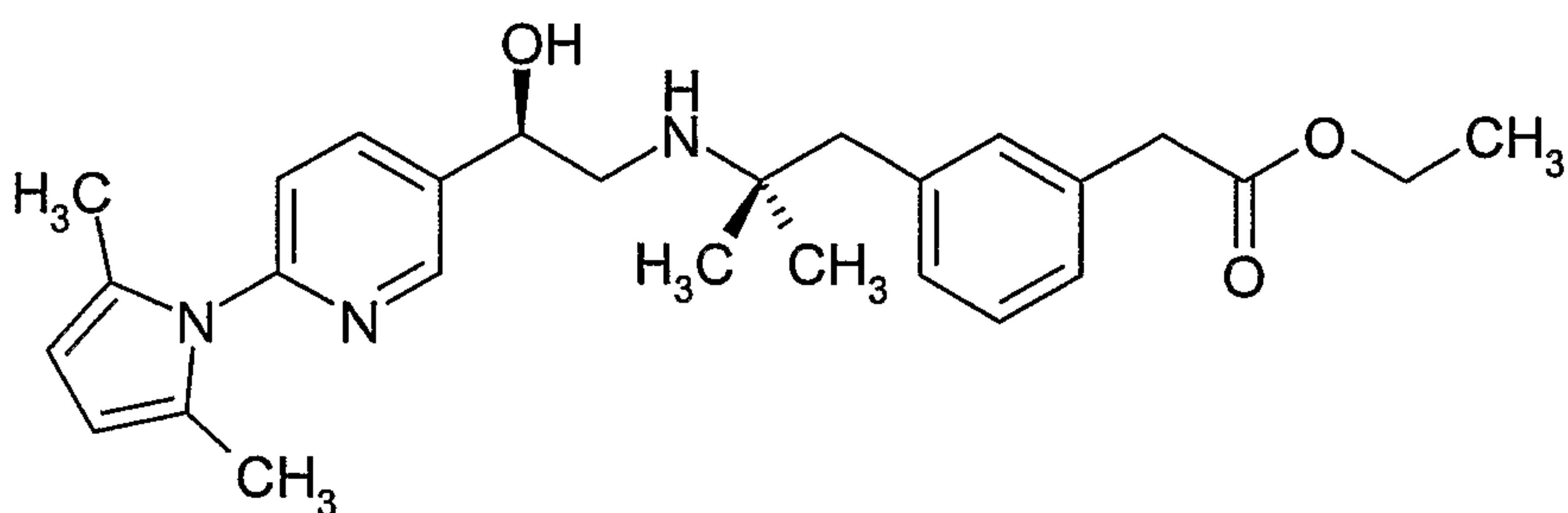


Prepared according to the method described for preparation 21 using the ester from preparation 35 to give the title compound as a colourless solid.

¹H NMR (400MHz, CD₃OD): δ = 8.66 (1H, s), 8.13-8.10 (1H, m), 7.39 (1H, d),
 5 7.31-7.23 (3H, m), 7.14-7.12 (1H, m), 5.83 (2H, s), 5.11-5.07 (1H, m), 3.55 (2H, s), 3.42-3.23 (2H, m), 3.04-2.97 (2H, m), 2.05 (6H, s), 1.37 (3H, s), 1.36 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 422, [M+Na]⁺ 444, [M-H]⁻ 420.

Preparation 35 : [3-(2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-acetic acid ethyl ester
 10

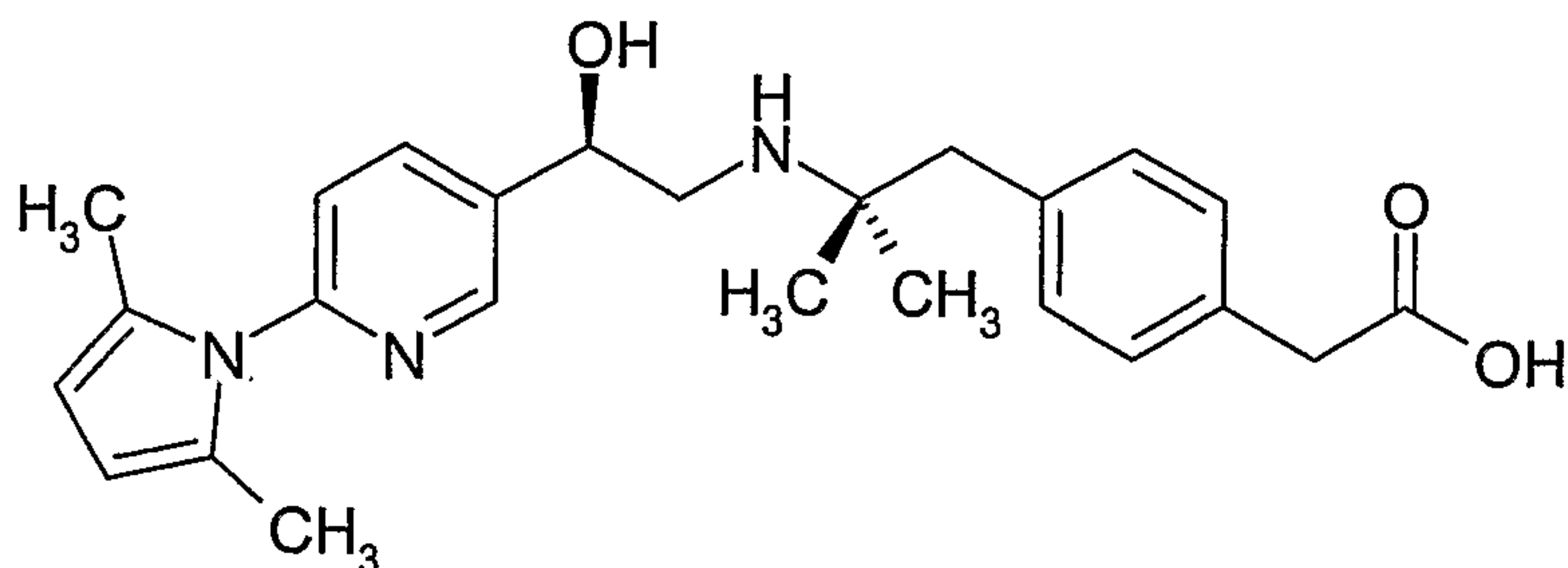


Prepared according to the method described for preparation 22 using the epoxide from preparation 27 and the amine from preparation 45 to give the title compound as a pale yellow oil.

15 ¹H NMR (400MHz, CD₃OD): δ = 8.58 (1H, s), 8.04-8.01 (1H, m), 7.32 (1H, d), 7.24 (1H, t), 7.17-7.11 (3H, m), 5.82 (2H, s), 4.13 (2H, q), 3.62 (2H, s), 2.95-2.85 (2H, m), 2.80-2.67 (2H, dd), 2.04 (6H, s), 1.22 (3H, t), 1.09 (3H, s), 1.06 (3H, s) ppm.

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

Preparation 36 : [4-(2-((2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-acetic acid

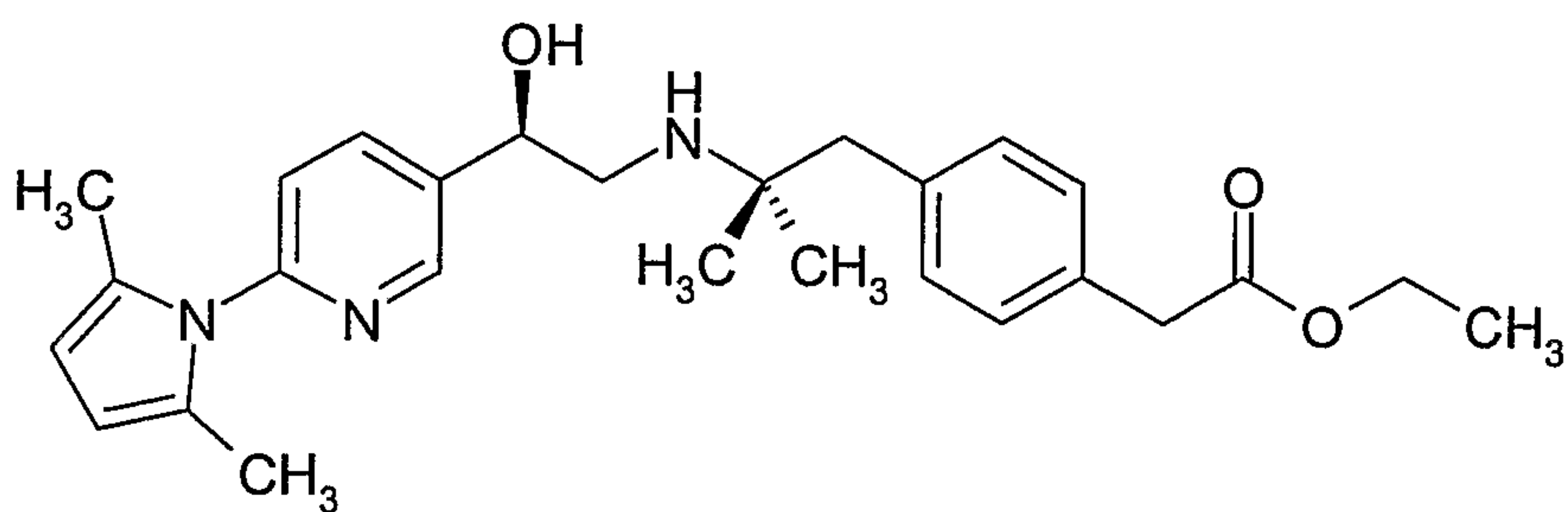


- 5 Prepared according to the method described for preparation 21 using the ester from preparation 37 to give the title compound as a pale yellow solid.

^1H NMR (400MHz, DMSO-d_6): δ = 8.56 (1H, s), 7.93 (1H, d), 7.32 (1H, d), 7.14-7.06 (4H, m), 5.77 (2H, s), 4.72 (1H, m), 3.46 (2H, s), 2.83-2.82 (2H, m), 2.60 (2H, s), 2.01 (6H, s), 0.95 (3H, s), 0.93 (3H, s) ppm.

- 10 LRMS (electrospray) : m/z $[M+H]^+$ 422, $[M-H]^-$ 420.

Preparation 37 : [4-(2-((2*R*)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-3-yl]-2-hydroxy-ethylamino)-2-methyl-propyl)-phenyl]-acetic acid methyl ester

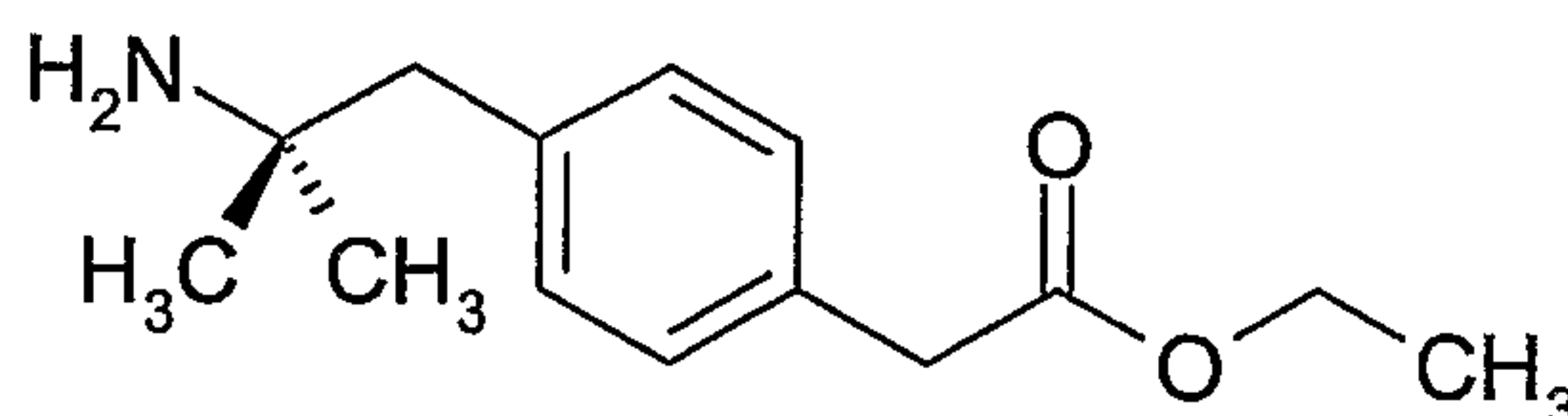


- 15 Prepared according to the method described for preparation 22 using the epoxide from preparation 27 and the amine from preparation 38 to give the title compound as a pale yellow oil.

^1H NMR (400MHz, CDCl_3): δ = 8.58 (1H, s), 7.82 (1H, d), 7.20 (3H, m), 7.15 (2H, m), 5.80 (2H, s), 4.70 (1H, m), 4.17 (2H, q), 3.59 (2H, s), 3.05 (1H, m), 2.75-2.65 (3H, m), 2.10 (6H, s), 1.25 (3H, t), 1.18 (3H, s), 1.17 (3H, s) ppm.

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

5 Preparation 38 : [4-(2-Amino-2-methyl-propyl)-phenyl]-acetic acid ethyl ester

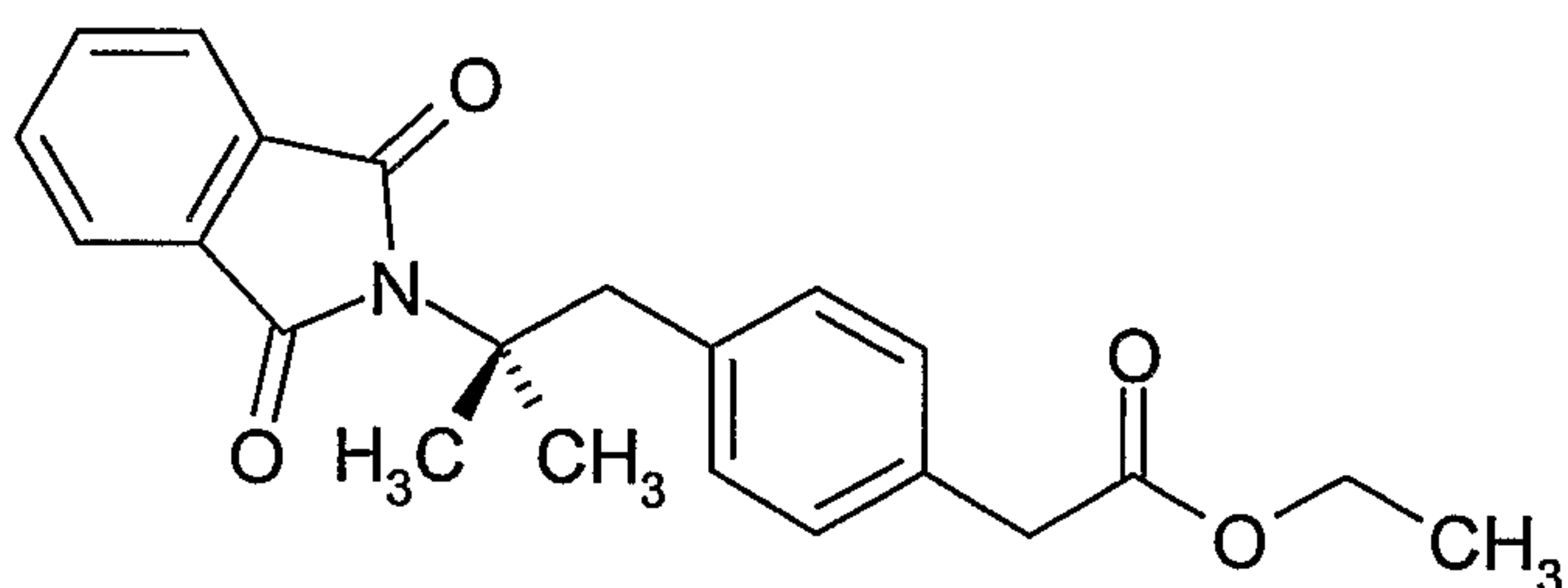


A solution of the ester from preparation 39 (1.99g, 5.44mmol) was treated with a solution of methylamine in ethanol (10ml of 8M solution, 80mmol) and the resulting solution left to stir at room temperature. After 3 hours the solvent was removed *in vacuo* and the residue triturated with methanol to give *N*-[1,1-dimethyl-2-(4-methylcarbamoylmethyl-phenyl)-ethyl]-*N'*-methyl-phthalimide as a colourless solid. The solid was treated with hydrochloric acid (100ml of 6N solution) and heated to 100°C for 48 hours. The solvent was removed *in vacuo* and the crude amino-acid residue treated with a mixture of ethanol (50ml) and concentrated sulphuric acid (2ml) at room temperature for 16 hours. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (100ml) and saturated aqueous potassium carbonate (100ml). The organic phase was separated, dried (sodium sulfate) and the solvent removed *in vacuo* to give the title compound as apale yellow oil (760mg, 59%).

^1H NMR (400MHz, CDCl_3): δ = 7.22 (2H, d), 7.15 (2H, d), 4.17 (2H, q), 3.60 (2H, s), 2.61 (2H, s), 1.25 (3H, t), 1.10 (6H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 236.

Preparation 39 : {4-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-methyl-propyl]-phenyl}-acetic acid ethyl ester

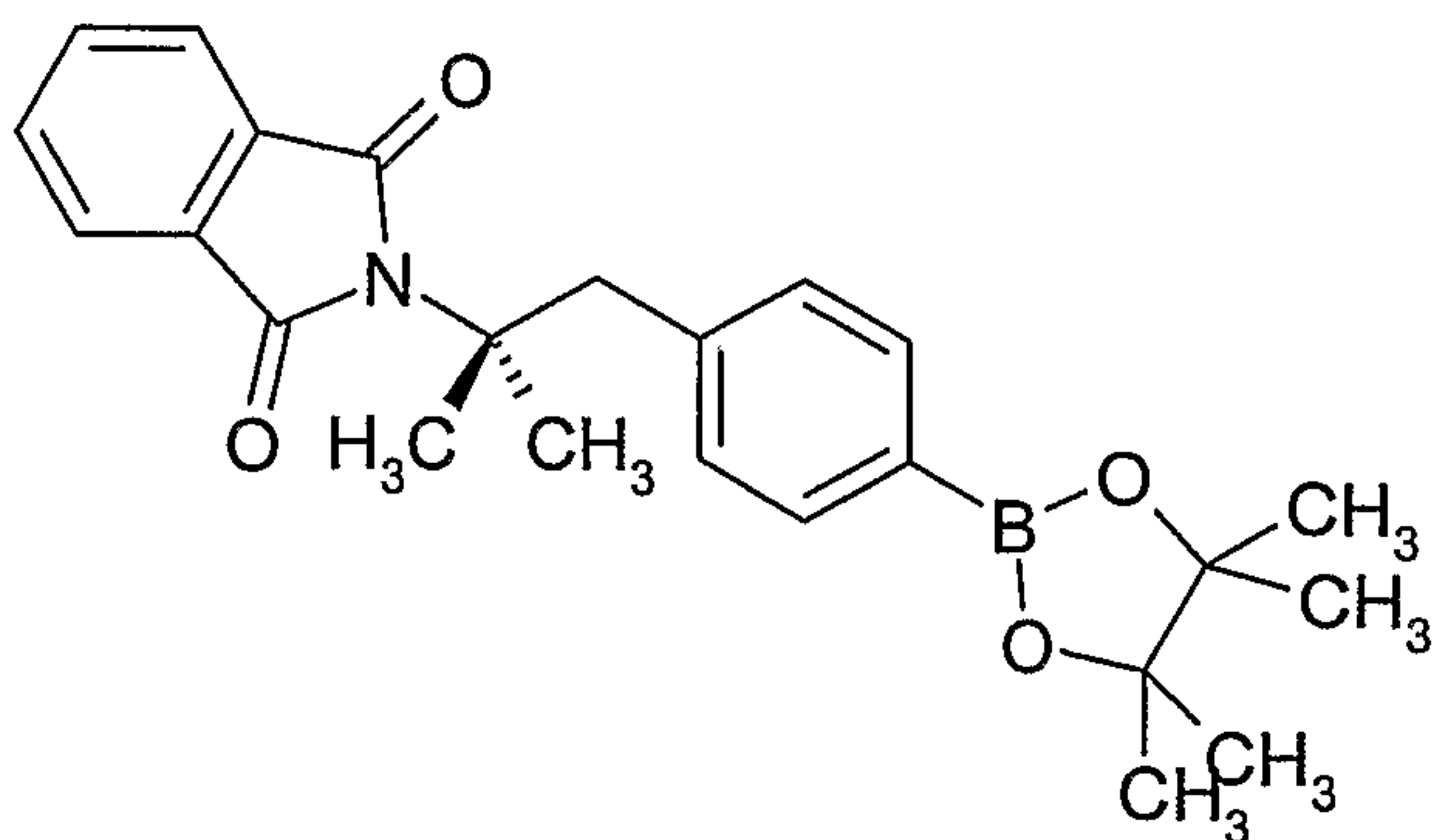


A solution of the boronic acid ester from preparation 40 (3.32g, 8.19mmol) in tetrahydrofuran (35ml) was treated with ethyl bromoacetate (0.75ml, 6.8mmol), palladium(II)acetate (46mg, 0.20mmol), tri-ortho-tolylphosphine (187mg, 0.61mmol), and potassium phosphate (7.24g, 34mmol) and the resulting suspension stirred at room temperature under a nitrogen atmosphere for 16 hours. The reaction mixture was diluted with dichloromethane (150ml), washed with water (100ml), saturated aqueous sodium chloride (100ml), dried (sodium sulfate) and reduced *in vacuo* to give the title compound as an orange oil (1.85g, 74%).

^1H NMR (400MHz, CDCl_3): δ = 7.77 (2H, m), 7.70 (2H, m), 7.12 (2H, d), (7.06 (2H, d), 4.12 (2H, q), 3.54 (2H, s), 3.26 (2H, s), 1.75 (6H, s), 1.23 (3H, t) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 366, $[\text{M}+\text{Na}]^+$ 388.

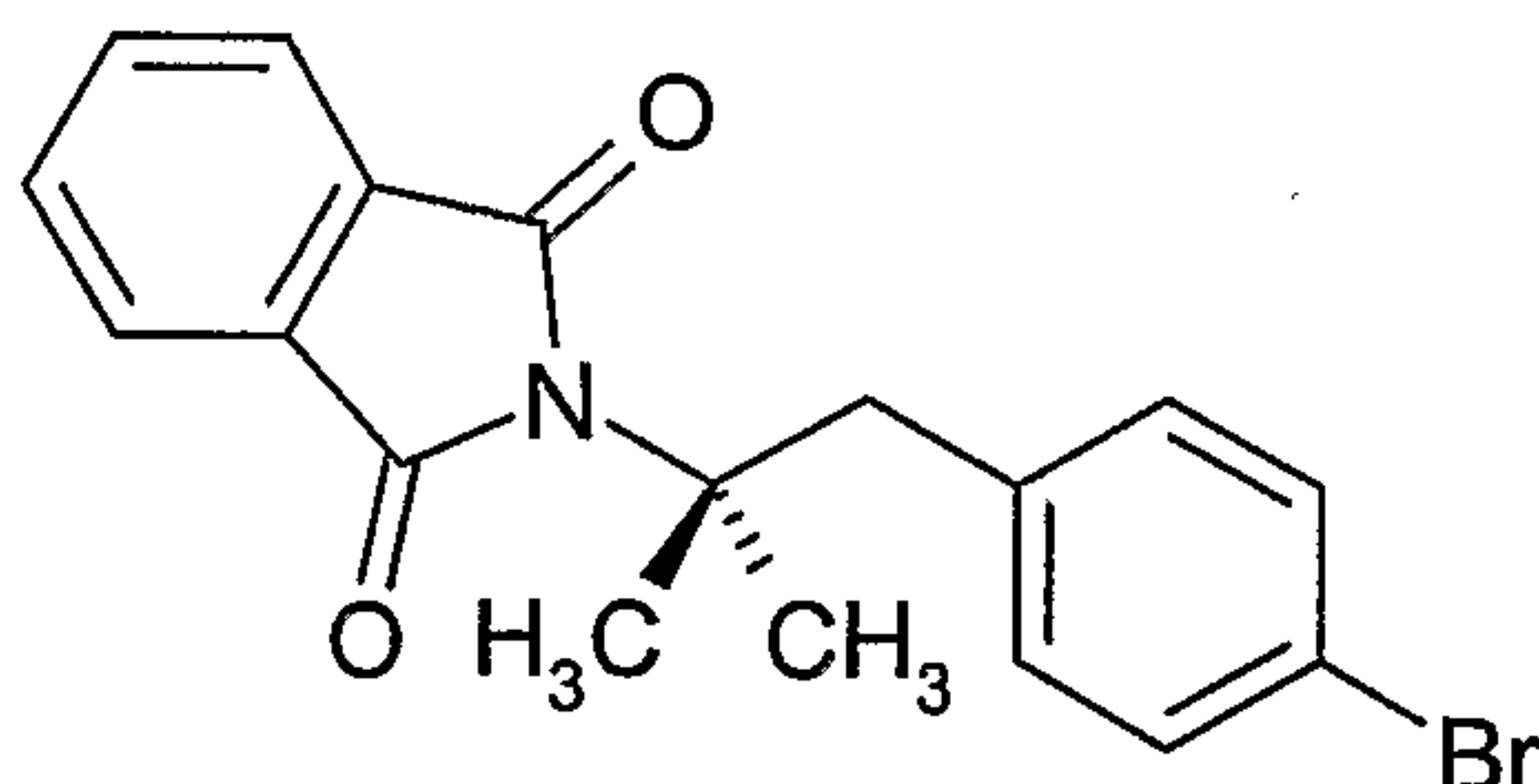
Preparation 40: 2-{1,1-Dimethyl-2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-ethyl}-isoindole-1,3-dione



A solution of the bromide from preparation 41 (6.88g, 19mmol), potassium acetate (5.65g, 57mmol), bis(pinacolato)diboron (5.85g, 23mmol) and [1,1'-

- bis(diphenylphosphino)ferrocene]palladium(II)chloride (0.80g, 0.98mmol) in dimethylsulfoxide (100ml) was heated at 80°C under a nitrogen atmosphere for 16 hours. The reaction mixture was cooled to room temperature, diluted with water (300ml) and extracted with ethyl acetate (3 x 100ml). The combined
5 organic extracts were washed with water (100ml) saturated aqueous sodium chloride (100ml), dried (sodium sulfate) and reduced *in vacuo*. Purification by flash column chromatography on silica gel eluting with pentane:dichloromethane (60:40 changing to 0:100, by volume) to give the title compound as a colourless oil (5.58g, 72%).
- 10 ¹H NMR (400MHz, CDCl₃): δ = 7.73 (2H, m), 7.68 (2H, m), 7.60 (2H, d), 7.08 (2H, d), 3.27 (2H, s), 1.74 (6H, s), 1.30 (12H, s) ppm.

Preparation 41 : 2-[2-(4-Bromo-phenyl)-1,1-dimethyl-ethyl]-isoindole-1,3-dione

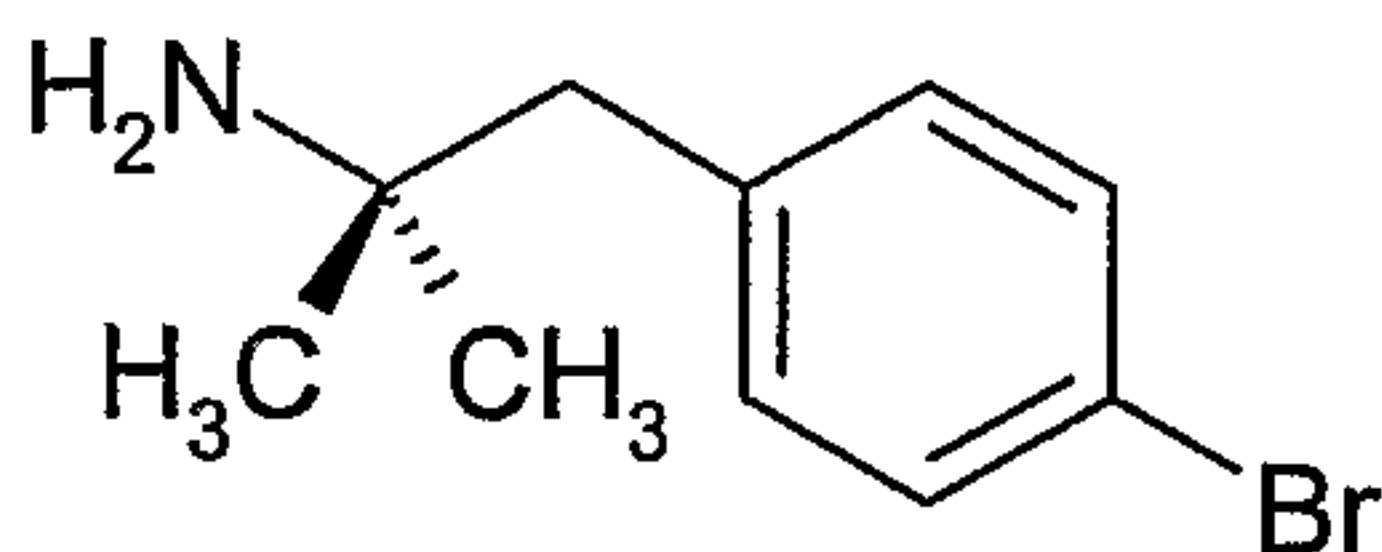


- 15 A solution of the amine from preparation 42 (5.13g, 22mmol), carboethoxyphthalimide (5.91g, 27mmol) and triethylamine (7.52ml, 54mmol) in toluene (80ml) was heated at 110°C under a nitrogen atmosphere for 16 hours. The reaction mixture was cooled to room temperature and the solvent reduced *in vacuo*. The residue was partitioned between dichloromethane (100ml) and
20 saturated sodium bicarbonate (100ml). The organic phase was separated, dried (sodium sulfate) and reduced *in vacuo*. Purification by flash column chromatography on silica gel eluting with pentane:dichloromethane (60:40 changing to 0:100, by volume) gave the title compound as a colourless oil (5.14g, 64%).

^1H NMR (400MHz, CDCl_3): δ = 7.78 (2H, m), 7.65 (2H, m), 7.25 (2H, d), 6.98 (2H, d), 3.20 (2H, s), 1.75 (6H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 359, $[\text{M}+\text{NH}_4]^+$ 376.

Preparation 42 : 2-(4-Bromo-phenyl)-1,1-dimethyl-ethylamine



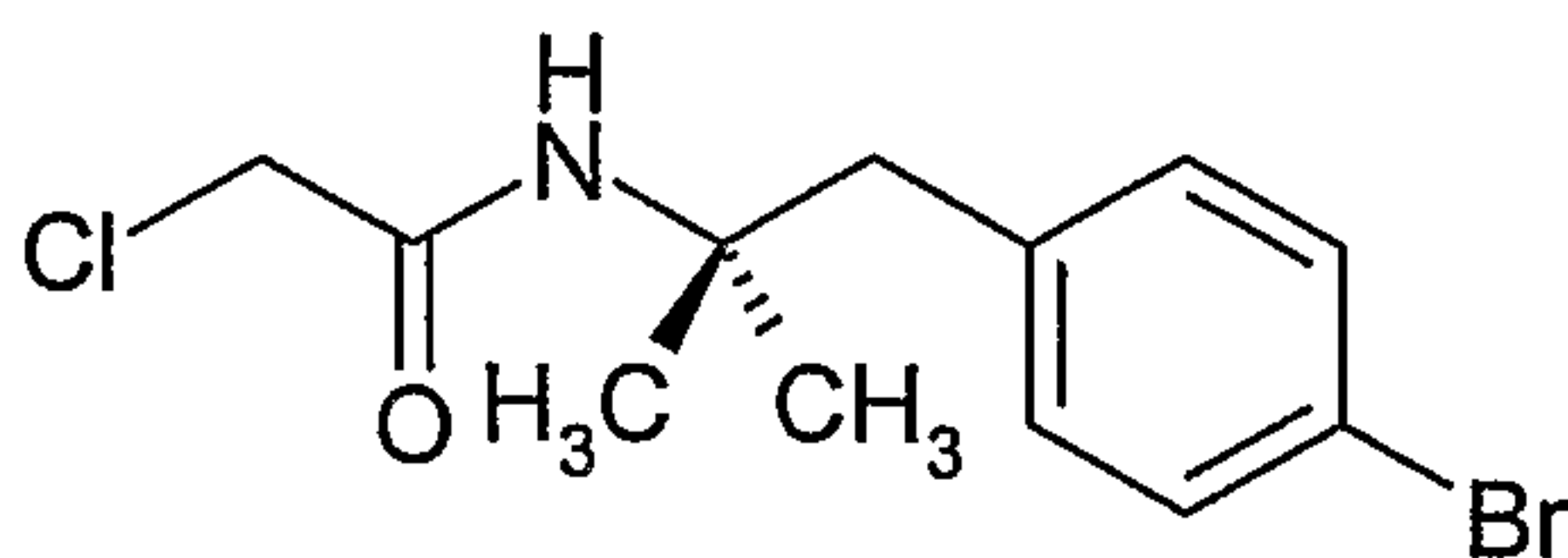
5

A solution of the amide from preparation 43 (19.0g, 62mmol), thiourea (5.70g, 75mmol) and acetic acid (30ml) in ethanol (150ml) was heated to reflux under a nitrogen atmosphere for 16 hours. The reaction mixture was cooled to room temperature and filtered washing the solid precipitate with ethanol (50ml). The
 10 filtrate was reduced *in vacuo* and the residue partitioned between dichloromethane (500ml) and 1M aqueous sodium hydroxide (300ml). The organic phase was separated and the aqueous extracted with dichloromethane (500ml). The combined organic extracts were washed with saturated aqueous sodium chloride (200ml), dried (sodium sulfate) and the solvent removed *in*
 15 *vacuo* to give the title compound as a dark orange oil (12.58g, 88%).

^1H NMR (400MHz, CDCl_3): δ = 7.41 (2H, d), 7.05 (2H, d), 2.60 (2H, s), 1.08 (6H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 228 / 230.

**Preparation 43 : N-[2-(4-Bromo-phenyl)-1,1-dimethyl-ethyl]-2-chloro-
 20 acetamide**

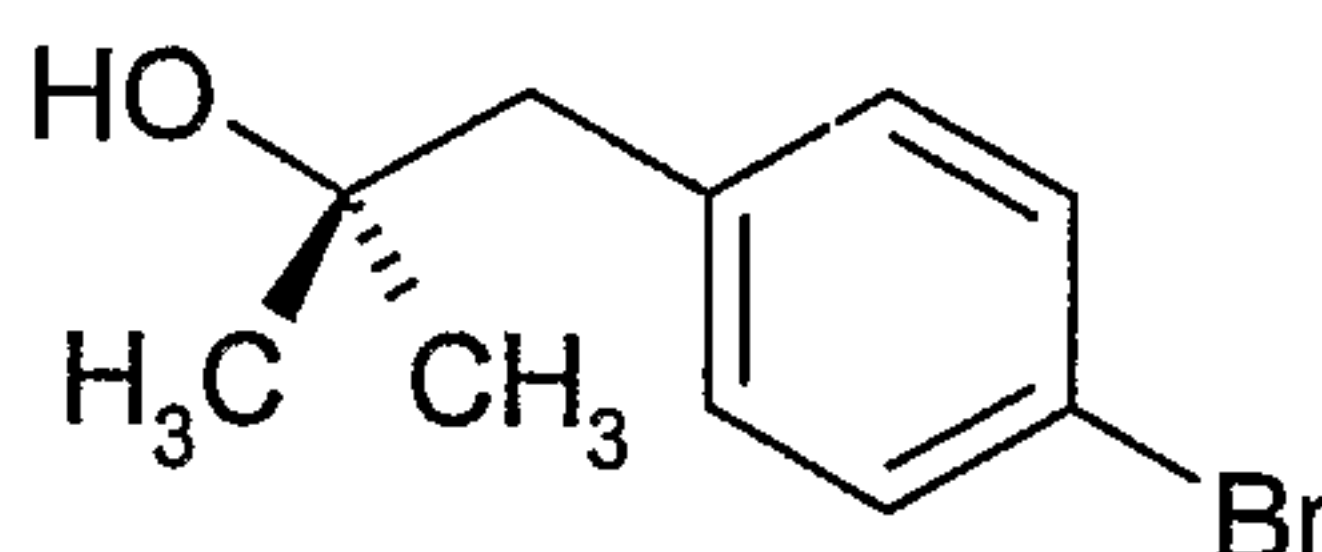


2-Chloroacetonitrile (8.8ml, 140mmol) was added to a solution of the alcohol from preparation 44 (16.0g, 70mmol), in acetic acid (33 ml). The resulting solution was cooled to 0°C and treated with concentrated sulphuric acid (33ml) maintaining an internal temperature < 10°C. The reaction mixture was then
5 allowed to warm gradually to room temperature. After 4 hours the reaction mixture was poured onto ice and basified with solid sodium carbonate. The solution was extracted with ethyl acetate (2 x 500ml) and the combined organic extracts dried (sodium sulfate) and reduced *in vacuo* to give the title compound as a colourless solid (19.0g, 89%).

10 ^1H NMR (400MHz, CDCl_3): δ = 7.41 (2H, d), 7.00 (2H, d), 6.18 (1H, s), 3.95 (2H, s), 3.02 (2H, s), 1.35 (6H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 304 / 306.

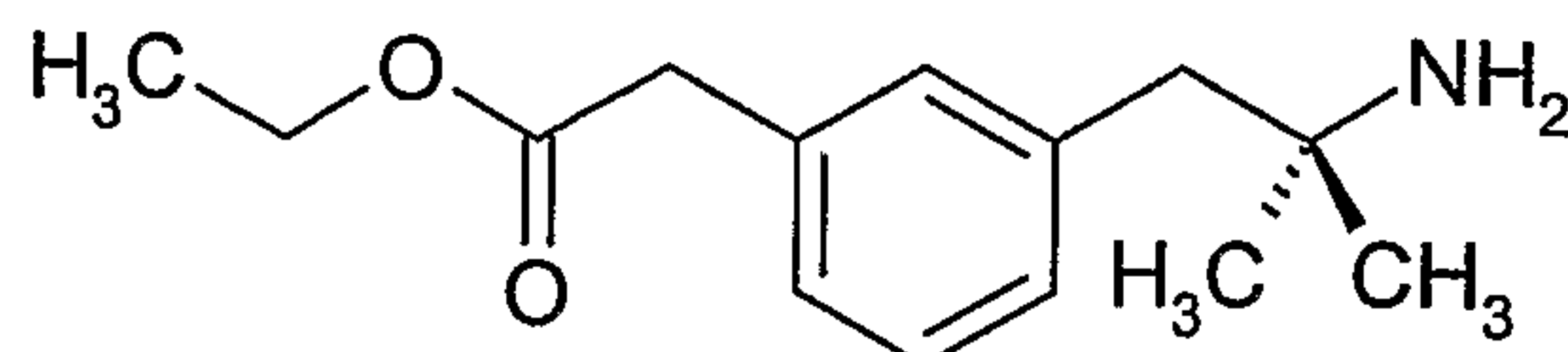
Preparation 44 : 1-(4-Bromo-phenyl)-2-methyl-propan-2-ol



15 A solution of 4-bromophenylacetone (6.85g, 32mmol) in diethyl-ether (100ml) was cooled to 0°C and treated with methylmagnesium bromide (23.5ml of a 3M solution in diethyl-ether, 70mmol). The reaction mixture was allowed to warm gradually to room temperature. After 2 hours the reaction was quenched by addition of saturated aqueous ammonium chloride (200ml). The organic phase
20 was separated and washed with saturated sodium chloride (100ml), dried (sodium sulfate) and reduced *in vacuo*. Purification by flash column chromatography on silica gel eluting with pentane:dichloromethane (60:40 changing to 0:100, by volume) gave the title compound as a colourless oil (6.23g, 84%).

25 ^1H NMR (400MHz, CDCl_3): δ = 7.42 (2H, d), 7.10 (2H, d), 2.70 (2H, s), 1.22 (6H, s) ppm.

Preparation 45 : [3-(2-Amino-2-methyl-propyl)-phenyl]-acetic acid ethyl ester

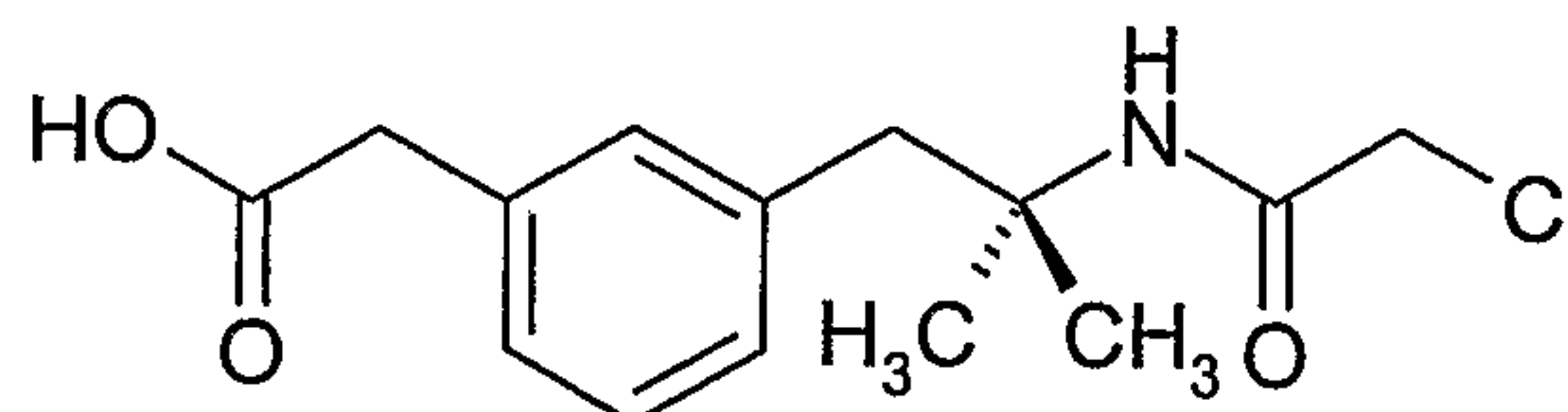


A solution of the amide from preparation 46 (5.1g, 18mmol), thiourea (1.6g, 21mmol) and acetic acid (18ml) in ethanol (80ml) was heated to reflux under a nitrogen atmosphere for 16 hours. The reaction mixture was cooled and filtered. The filtrate was reduced *in vacuo*, the residue dissolved in ethanol (150ml), saturated with hydrogen chloride gas and the resulting solution heated to reflux for 16 hours. The solvent was reduced *in vacuo* and the residue partitioned between ethyl acetate (200ml) and 5% aqueous sodium carbonate (200ml). The organic extract was washed with saturated sodium chloride (100ml), dried (sodium sulfate) and reduced *in vacuo*. The residue was purified by strong cation exchange resin, eluting with methanol and then 2N ammonia in methanol to elute the product. The eluent was concentrated *in vacuo* giving the title compound as a yellow oil (2.68g, 63%).

^1H NMR (400MHz, CDCl_3): δ = 7.29-7.04 (4H, m), 4.08 (2H, q), 3.64 (2H, s), 2.57 (2H, s), 1.18 (3H, t), 0.99 (6H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 236, $[\text{M}+\text{NH}_4]^+$ 258.

Preparation 46 : {3-[2-(2-Chloro-acetyl-amino)-2-methyl-propyl]-phenyl}-acetic acid



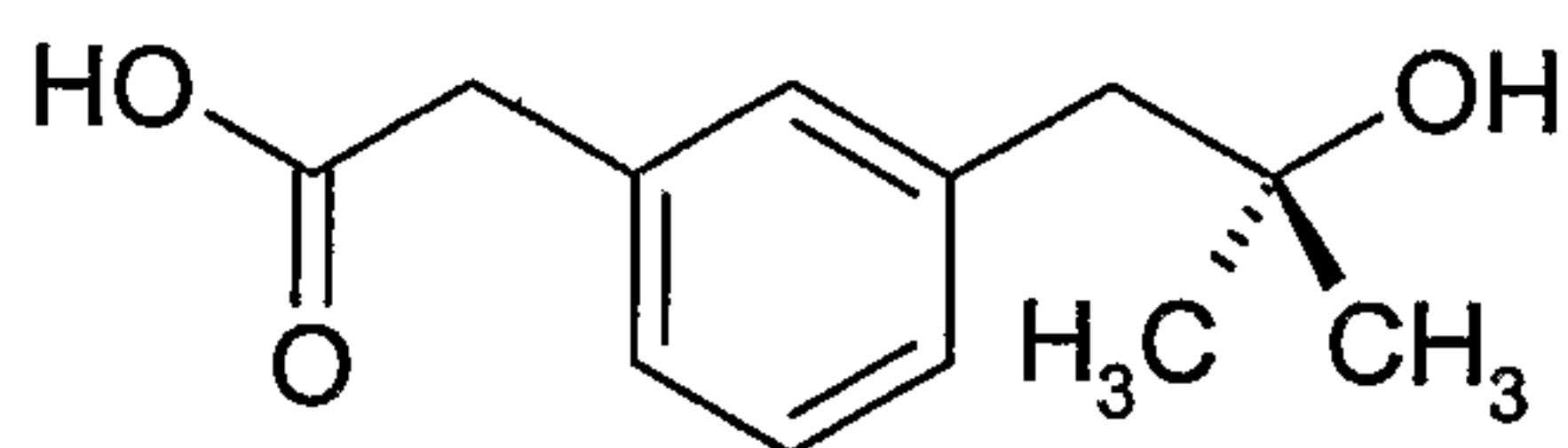
Prepared using the method for preparation 43 using the alcohol from preparation 47 as starting material to give the title compound as a colourless solid.

^1H NMR (400MHz, CDCl_3): δ = 7.31-7.06 (4H, m), 6.19 (1H, bs), 3.95 (2H, s), 3.62 (2H, s), 3.02 (2H, s), 1.36 (6H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}-\text{H}]^-$ 282 / 284.

Preparation 47 : [3-(2-Hydroxy-2-methyl-propyl)-phenyl]-acetic acid

5



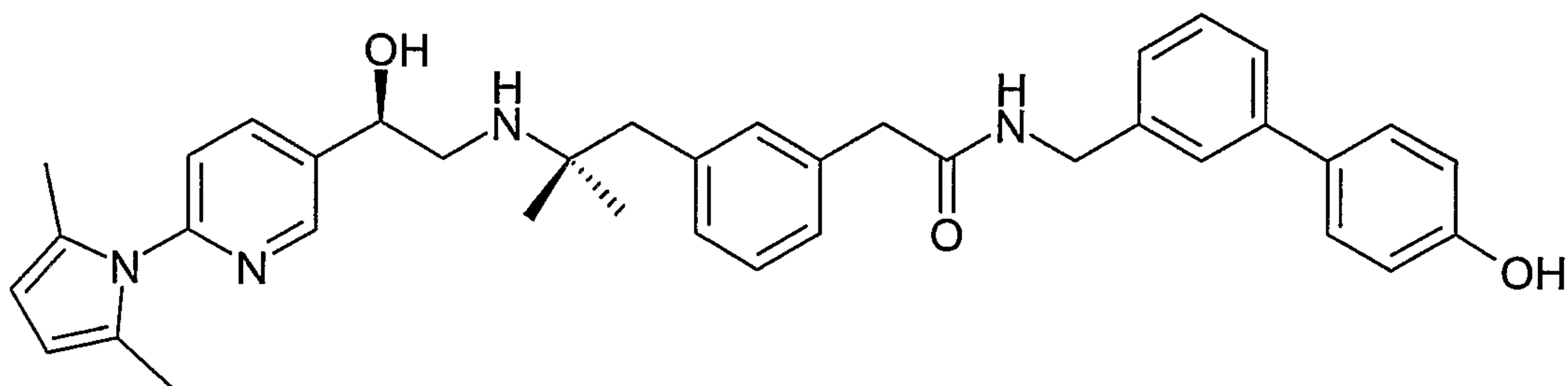
Prepared according to the method for preparation 44 using (3-ethoxycarbonylmethyl-phenyl)-acetic acid as starting material to give the title compound as a pale yellow oil.

10 ^1H NMR (400MHz, CDCl_3): δ = 7.30-7.12 (4H, m), 3.63 (2H, s), 2.75 (2H, s), 1.22 (6H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 209.

Preparation 48 : 2-[3-(2-((2R)-2-[6-(2,5-Dimethylpyrrol-1-yl)pyridin-3-yl]-2-hydrox-ethylamino)-2-methylpropyl)phenyl]-N-(4'-hydroxybiphenyl-3-ylmethyl)acetamide

15

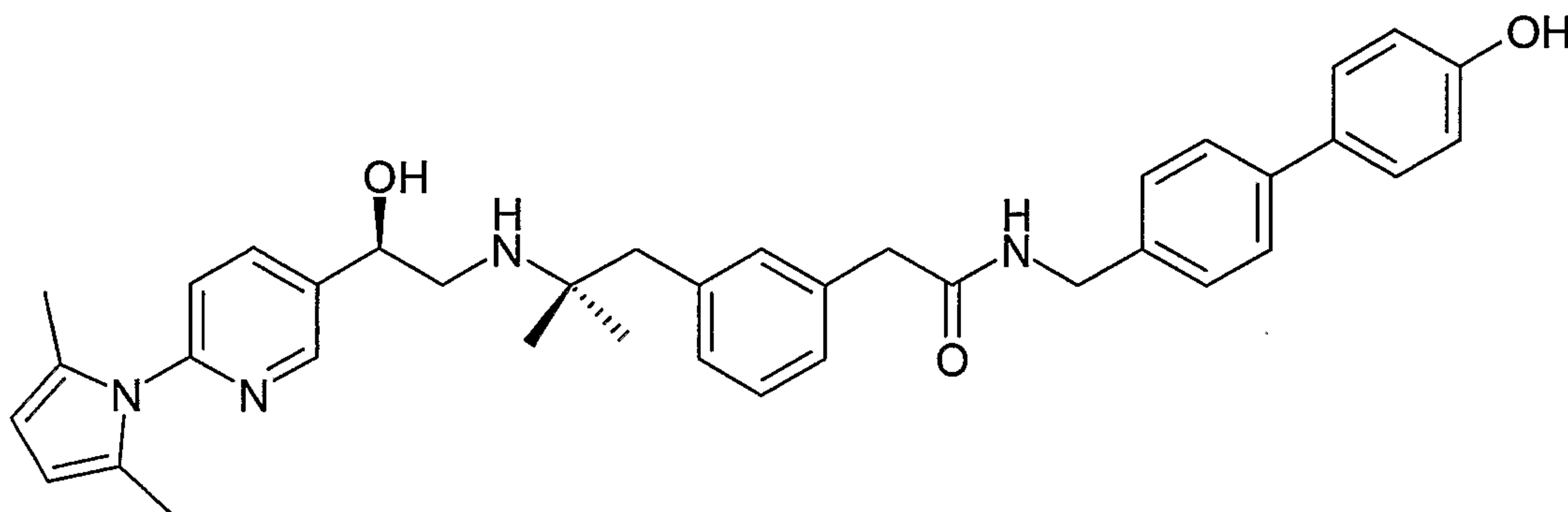


Prepared according to the method described for preparation 1 using the acid from preparation 34 and the amine from preparation 73 to give the title compound as an amber coloured oil.

^1H NMR (400MHz, CD_3OD): δ = 8.54 (1H, d), 7.97 (1H, d), 7.35-7.38 (2H, m), 7.27-7.32 (2H, m), 7.24-7.25 (2H, m), 7.17-7.22 (3H, m), 7.08-7.12 (2H, m), 6.78-6.80 (2H, m), 5.81 (2H, s), 4.78 (1H, dd), 4.40 (2H, s), 3.55 (2H, s), 2.80-2.90 (2H, m), 2.60 (2H, dd), 2.03 (6H, s), 1.03 (3H, s), 1.00 (3H, s) ppm.

5 LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 603, $[\text{M}+\text{Na}]^+$ 625.

Preparation 49 : 2-[3-(2-((2*R*)-2-[6-(2,5-Dimethylpyrrol-1-yl)pyridin-3-yl]-2-hydroxy-ethylamino)-2-methylpropyl)phenyl]-*N*-(4'-hydroxybiphenyl-4-ylmethyl)acetamide

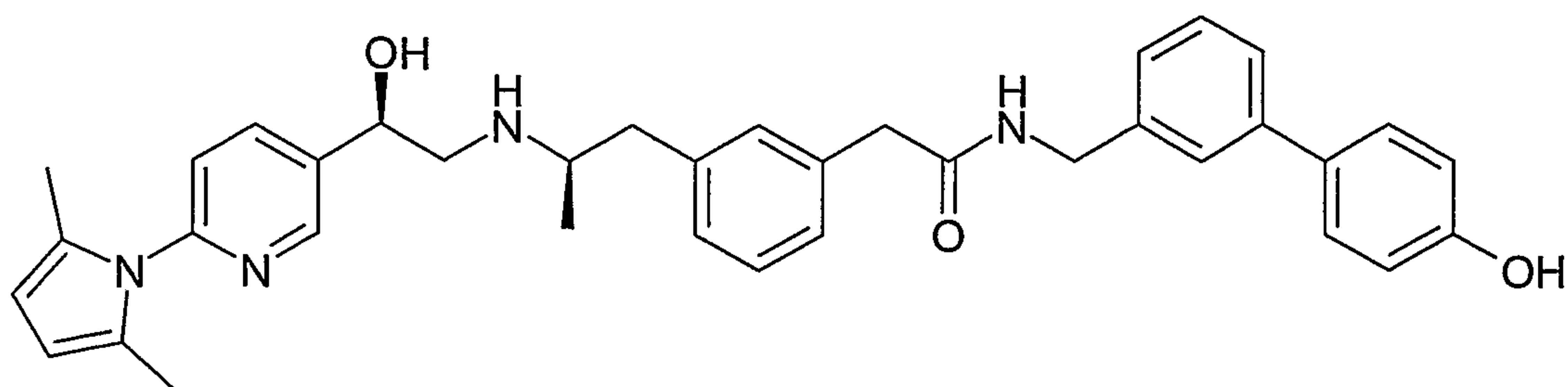


10 Prepared according to the method described for preparation 1 using the acid from preparation 34 and the amine from preparation 82 to give the title compound as an amber coloured oil.

^1H NMR (400MHz, CD_3OD): δ = 8.56 (1H, d), 7.98 (1H, dd), 7.39-7.47 (4H, m), 7.23-7.31 (4H, m), 7.18-7.19 (2H, m), 7.11-7.13 (1H, m), 6.81-6.84 (2H, m),
15 5.82 (2H, s), 4.80 (1H, dd), 4.88 (2H, s), 3.65 (2H, s), 2.83-2.95 (2H, m), 2.66 (2H, dd), 2.03 (6H, s), 1.06 (3H, s), 1.03 (3H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 603, $[\text{M}+\text{Na}]^+$ 625.

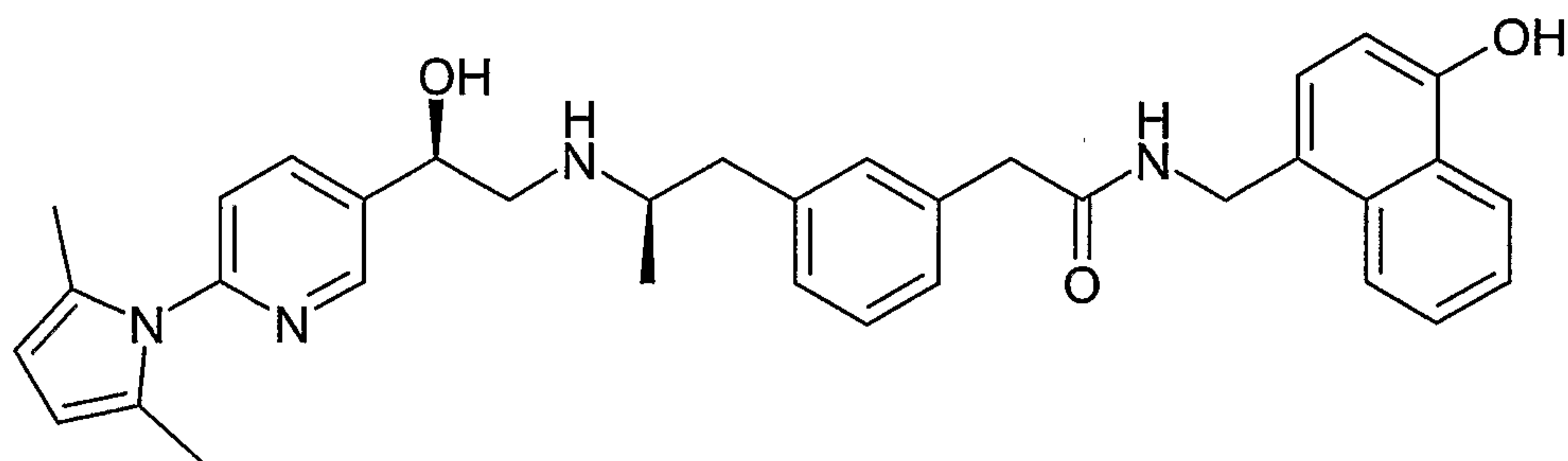
Preparation 50 : 2-[3-((2*R*)-2-((2*R*)-2-[6-(2,5-Dimethylpyrrol-1-yl)pyridin-3-yl]-2-hydroxyethylamino)propyl)-phenyl]-*N*-(4'-hydroxybiphenyl-3-ylmethyl)acetamide
20



Prepared according to the method described for preparation 1 using the acid from preparation 21 and the amine from preparation 73 to give the title compound as an amber coloured oil.

- 5 ^1H NMR (400MHz, CD_3OD): δ = 8.49 (1H, d), 7.90 (1H, dd), 7.38-7.40 (1H, m), 7.31-7.35 (3H, m), 7.22-7.29 (3H, m), 7.17-7.19 (2H, m), 7.06-7.13 (2H, m), 6.80-6.82 (2H, m), 5.81 (2H, s), 4.78 (1H, dd), 4.40 (2H, s), 3.55 (2H, s), 2.92 (1H, dd), 2.81-2.83 (2H, m), 2.70 (1H, dd), 2.52-2.57 (1H, m), 2.02 (6H, s), 1.02 (3H, s) ppm.
- 10 LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 589, $[\text{M}+\text{Na}]^+$ 611.

Preparation 51 : 2-[3-((2R)-2-((2R)-2-[6-(2,5-Dimethylpyrrol-1-yl)pyridin-3-yl]-2-hydroxyethylamino}propyl)phenyl]-N-(4-hydroxynaphthalen-1-ylmethyl)acetamide

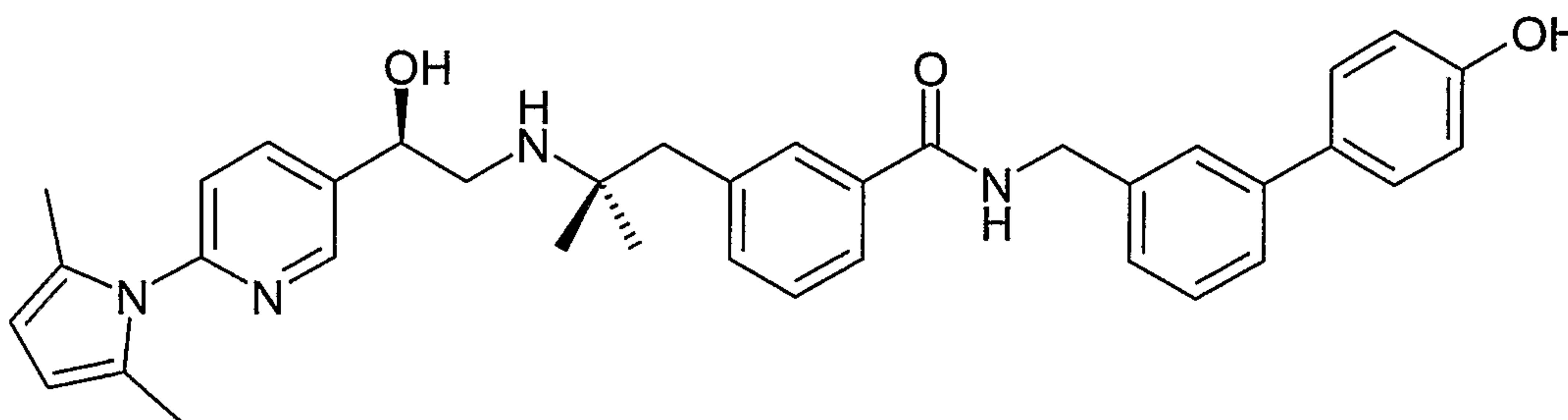


- 15 Prepared according to the method described for preparation 1 using the acid from preparation 21 and the amine from preparation 79 to give the title compound as a light brown foam.

^1H NMR (400MHz, CD_3OD): δ = 8.47 (1H, d), 8.20-8.23 (1H, m), 7.91 (1H, dd), 7.84-7.86 (1H, m), 7.05-7.12 (2H, m), 6.71 (1H, d), 5.81 (2H, s), 4.79 (1H, dd), 4.70 (2H, s), 2.68-2.91 (6H, m), 2.02 (6H, s), 1.01 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 563, $[\text{M}+\text{Na}]^+$ 585.

5 **Preparation 52 : 3-(2-((2R)-2-[6-(2,5-Dimethylpyrrol-1-yl)pyridin-3-yl]-2-hydroxyethylamino)-2-methylpropyl)-N-(4'-hydroxybiphenyl-3-ylmethyl)benzamide**

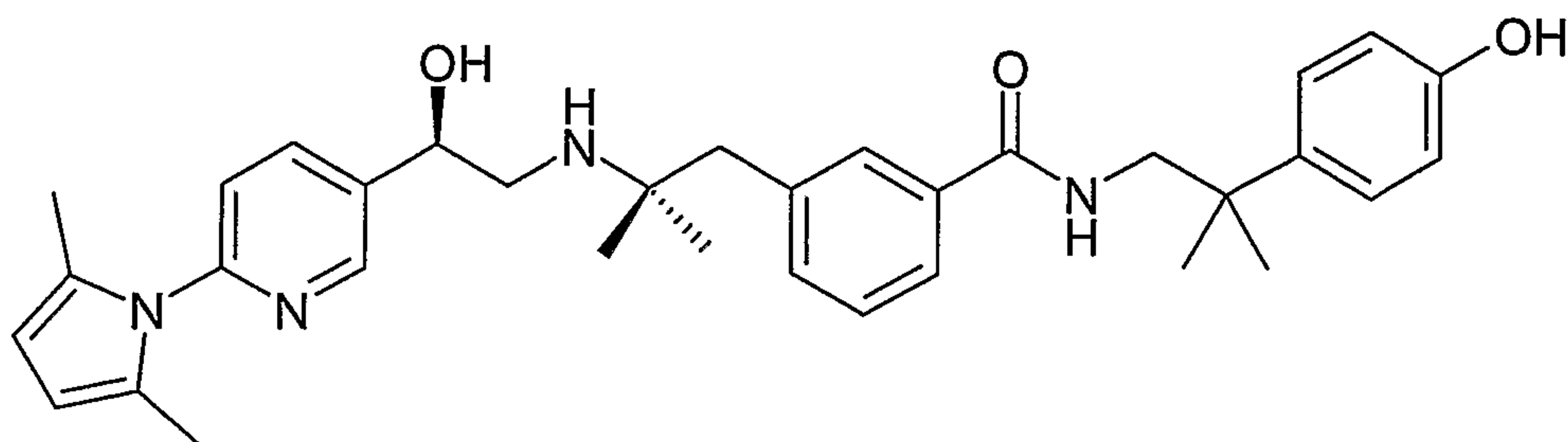


Prepared according to the method described for preparation 1 using the acid
10 from preparation 60 and the amine from preparation 73 to give the title compound as a colourless solid.

^1H NMR (400MHz, CD_3OD): δ = 8.59 (1H, d), 8.00 (1H, dd), 7.77-7.80 (2H, m), 7.53-7.56 (1H, m), 7.40-7.45 (5H, m), 7.33 (1H, t), 7.24-7.28 (2H, m), 6.80-6.84 (2H, m), 5.82 (2H, s), 4.95 (1H, t), 4.58 (2H, dd), 3.12 (2H, d), 2.89 (2H, dd),
15 2.02 (6H, s), 1.2 (3H, s), 1.19 (3H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 589, $[\text{M}+\text{Na}]^+$ 611.

Preparation 53 : 3-(2-((2R)-2-[6-(2,5-Dimethylpyrrol-1-yl)pyridin-3-yl]-2-hydroxy-ethylamino)-2-methylpropyl)-N-[2-(4-hydroxyphenyl)-2-methylpropyl]benzamide

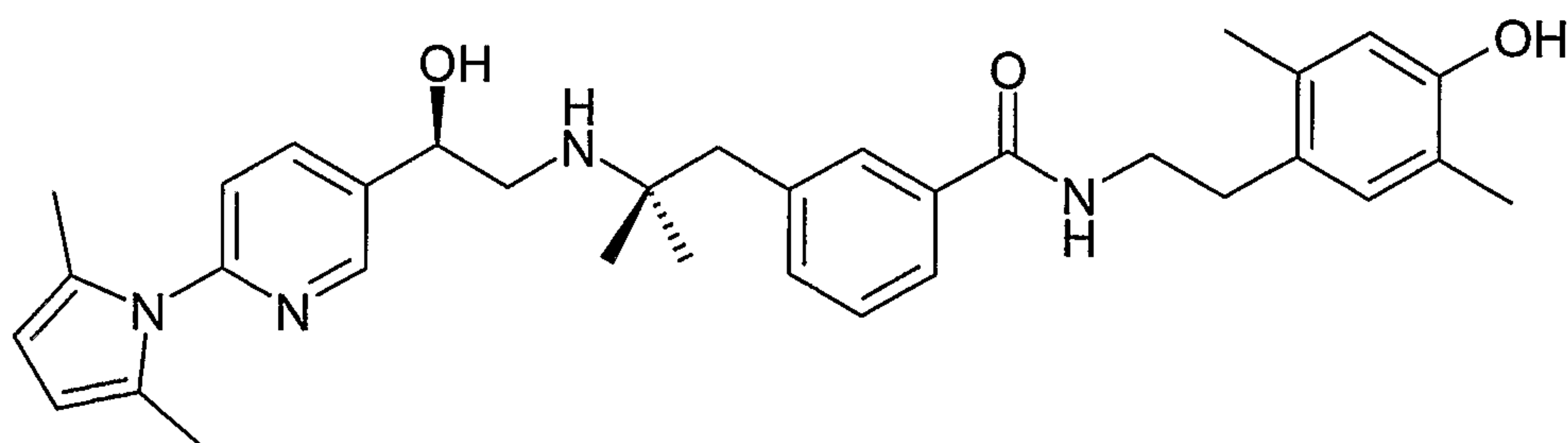


Prepared according to the method described for preparation 1 using the acid from preparation 60 and the amine from preparation 76 to give the title compound as a light brown foam.

- 5 ^1H NMR (400MHz, CD_3OD): δ = 8.65 (1H, d), 8.10 (1H, dd), 7.57–7.61 (2H, m), 7.38–7.44 (3H, m), 7.24–7.28 (2H, m), 6.72–6.76 (2H, m), 5.83 (2H, s), 5.03 (1H, dd), 3.52 (2H, s), 3.22–3.28 (2H, m), 3.02 (2H, s), 2.05 (6H, s), 1.84 (6H, s), 1.28 (3H, s), 1.31 (3H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 555, $[\text{M}+\text{Na}]^+$ 577.

- 10 **Preparation 54 : 3-(2-((2R)-2-[6-(2,5-Dimethyl-pyrrol-1-yl)pyridin-3-yl]-2-hydroxyethyl-amino)-2-methylpropyl)-N-[2-(4-hydroxy-2,5-dimethylphenyl)ethyl]benzamide**



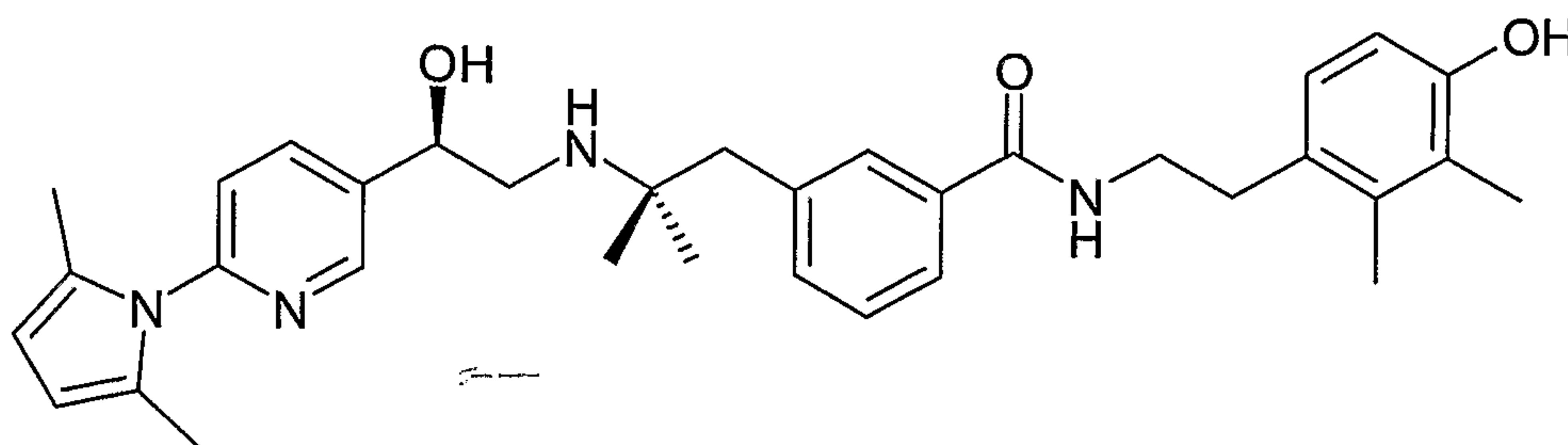
- 15 Prepared according to the method described for preparation 1 using the acid from preparation 60 and the amine from preparation 86 to give the title compound as a colourless solid.

^1H NMR (400MHz, CD_3OD): δ = 8.59 (1H, d), 8.62 (1H, dd), 7.65–7.68 (2H, m), 7.38–7.40 (2H, m), 7.32 (1H, d), 6.84 (1H, s), 6.54 (1H, s), 5.81 (2H, s), 3.45

(2H, s), 3.45 (2H, dt), 2.96 (1H, dd), 2.88-2.91 (2H, m), 2.73-2.81 (3H, m), 2.23 (3H, s), 2.08 (3H, s), 2.03 (3H, s), 1.12 (3H, s), 1.06 (3H, s) ppm.

LRMS (electrospray) : m/z [M+H]⁺ 555, [M+Na]⁺ 577.

Preparation 55 : 3-(2-((2*R*)-2-[6-(2,5-Dimethylpyrrol-1-yl)pyridin-3-yl]-2-hydroxy-ethylamino)-2-methylpropyl)-*N*-[2-(4-hydroxy-2,3-dimethylphenyl)ethyl]benzamide

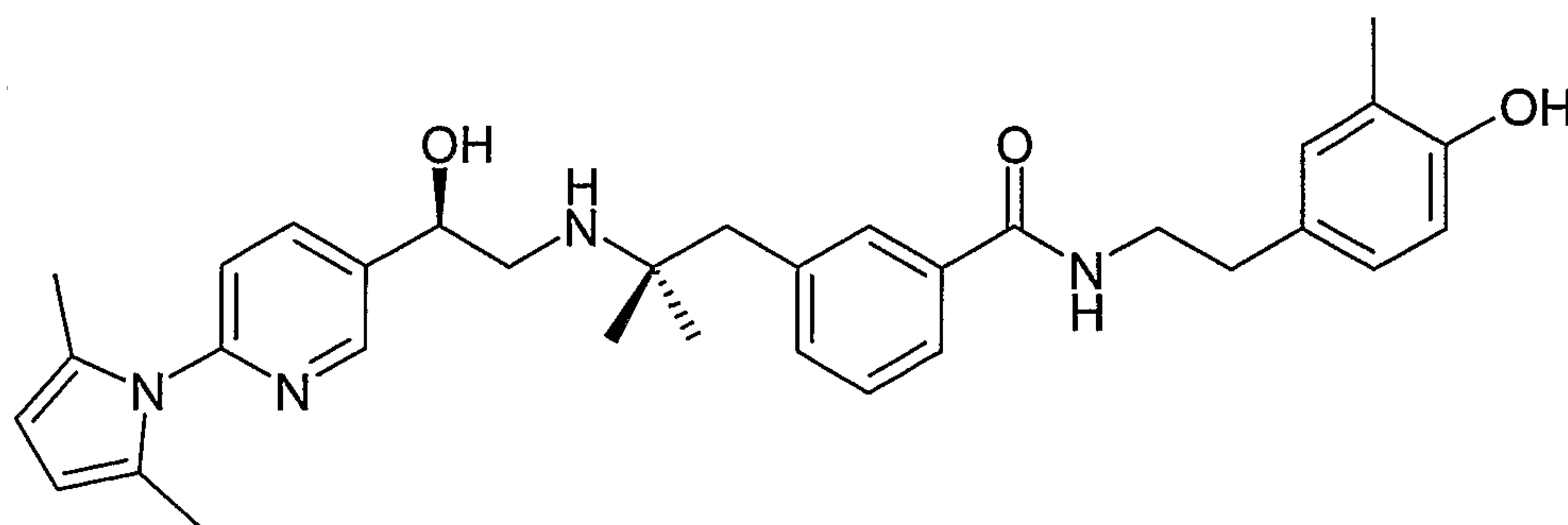


Prepared according to the method described for preparation 1 using the acid from preparation 60 and the amine from preparation 87 to give the title compound as a straw coloured foam.

¹H NMR (400MHz, CD₃OD): δ = 1.06 (3H, s), 1.13 (3H, s), 2.04 (6H, s), 2.11 (3H, s), 2.24 (3H, s), 2.73 (1H, d), 2.83-2.92 (4H, m), 2.97-3.02 (1H, m), 3.46-3.49 (2H, m), 4.84 (1H, m, partially obscured by solvent peak), 2.82 (2H, s), 6.53 (1H, d), 6.80 (1H, d), 7.82 (1H, d), 7.38-7.41 (2H, m), 7.65-7.68 (2H, m), 8.03 (1H, dd), 8.59 (1H, s) ppm.

LRMS (APCI) : m/z [M+H]⁺ 555.

Preparation 56 : 3-(2-((2*R*)-2-[6-(2,5-Dimethylpyrrol-1-yl)pyridin-3-yl]-2-hydroxy-ethylamino)-2-methylpropyl)-*N*-[2-(4-hydroxy-3-methylphenyl)ethyl]benzamide

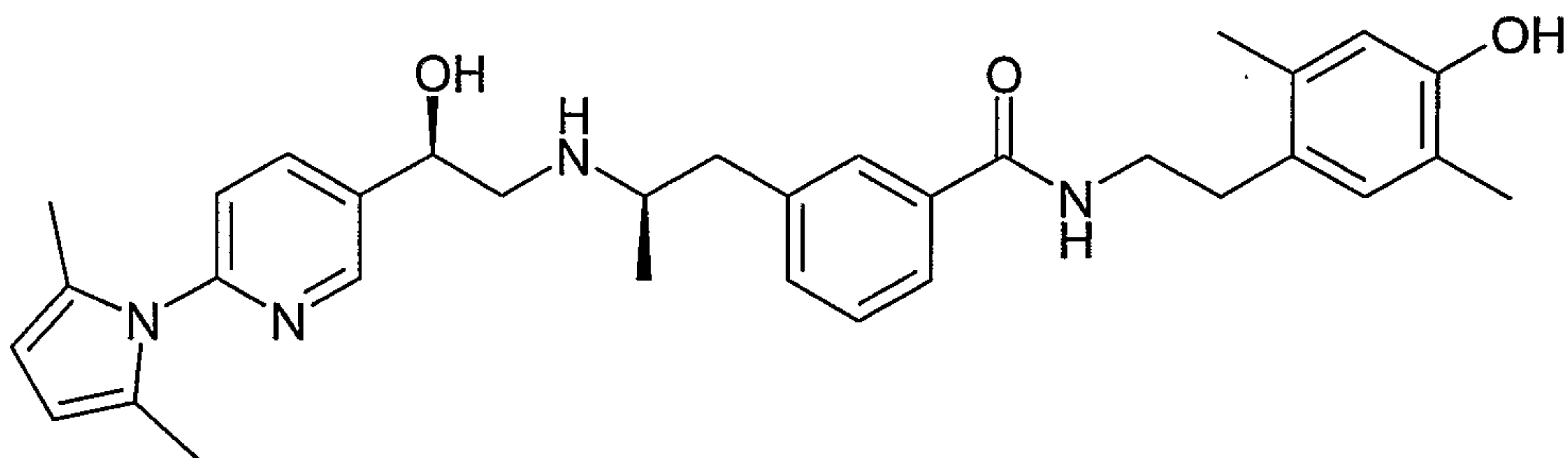


Prepared according to the method described for preparation 1 using the acid from preparation 60 and the amine from preparation 86 to give the title compound as a beige foam.

- 5 ^1H NMR (400MHz, CDCl_3): δ = 1.04 (3H, s), 1.12 (3H, s), 2.12 (9H, s), 2.62 (1H, d), 2.73-2.87 (4H, m), 2.95 (1H, d), 3.52-3.58 (1H, m), 3.74-3.81 (1H, m), 4.64 (1H, d), 5.89 (2H, s), 6.48 (1H, bs), 6.63 (1H, d), 6.86 (1H, d), 6.95 (1H, s), 7.20 (1H, d), 7.33 (1H, t), 7.48 (1H, s), 7.60 (1H, d), 7.81 (1H, d), 8.53 (1H, s) ppm.

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

- 10 **Preparation 57 : 3-((2R)-2-((2R)-2-[6-(2,5-Dimethylpyrrol-1-yl)-pyridin-3-yl]-2-hydroxyethylamino)propyl)-N-[2-(4-hydroxy-2,5-dimethylphenyl)ethyl]benzamide**

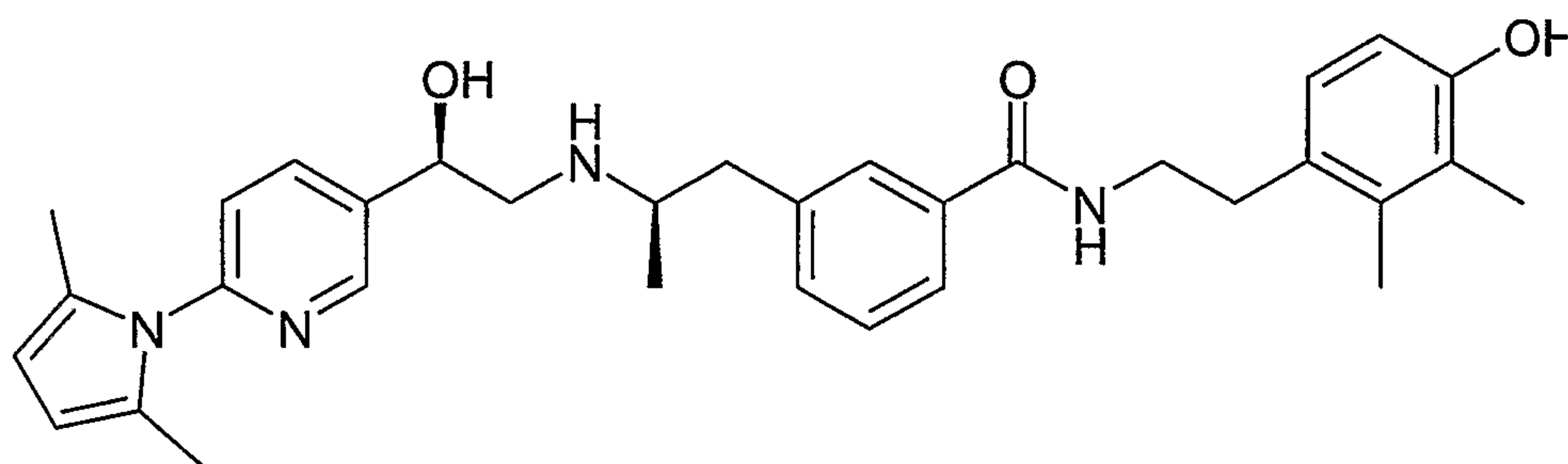


- 15 Prepared according to the method described for preparation 1 using the acid from preparation 68 and the amine from preparation 86 to give the title compound as a colourless solid.

^1H NMR (400MHz, CD_3OD): δ = 8.53 (1H, d), 7.96 (1H, dd), 7.87-7.88 (2H, m), 7.60-7.63 (2H, m), 7.29 (1H, d), 6.85 (1H, s), 6.54 (1H, s), 5.81 (2H, s), 4.84-4.85 (1H, m), 3.45 (2H, t), 3.02 (1H, dd), 2.86-2.92 (3H, m), 2.77-2.81 (2H, m), 2.626-2.67 (1H, m), 2.23 (3H, s), 2.09 (3H, s), 2.03 (6H, s), 1.08 (3H, d) ppm.

5 LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 541, $[\text{M}+\text{Na}]^+$ 563.

Preparation 58 : 3-((2*R*)-2-((2*R*)-2-[6-(2,5-Dimethylpyrrol-1-yl)-pyridin-3-yl]-2-hydroxyethylamino)propyl)-*N*-[2-(4-hydroxy-2,3-dimethylphenyl)ethyl]benzamide



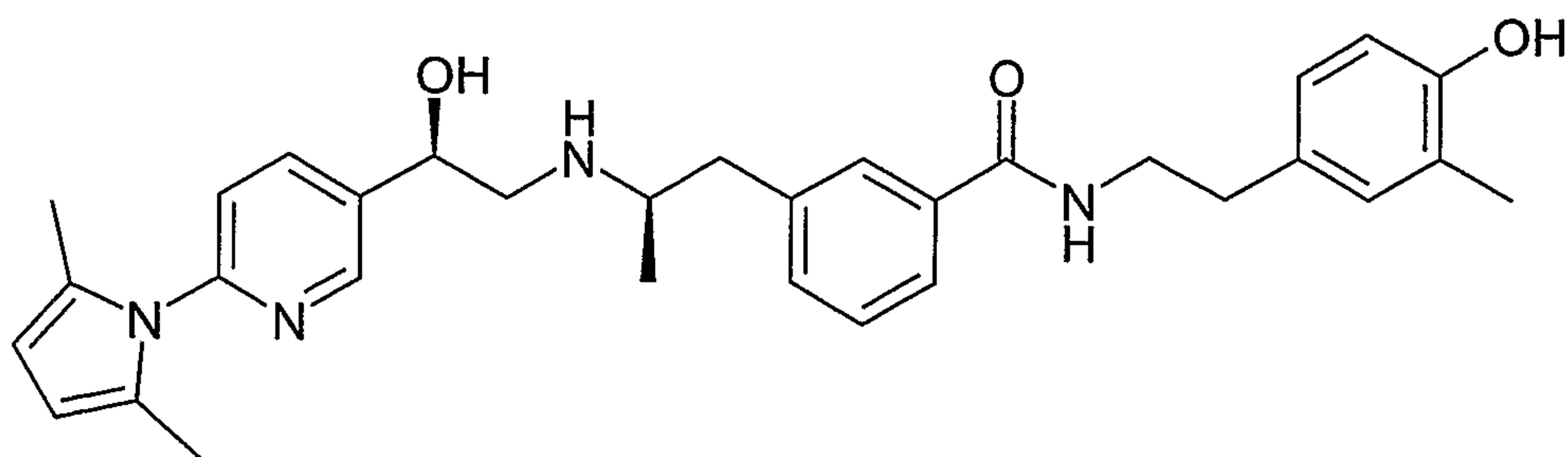
10 Prepared according to the method described for preparation 1 using the acid from preparation 68 and the amine from preparation 87 to give the title compound as a straw coloured foam.

^1H NMR (400MHz, CD_3OD): δ = 1.09 (3H, s), 1.10 (3H, s), 2.03 (6H, s), 2.12 (3H, s), 2.25 (3H, s), 2.62 (1H, dd), 2.83-2.94 (5H, m), 3.02-3.07 (1H, m), 3.45-3.48 (2H, m), 4.85 (1H, m, partially obscured by solvent peak), 5.81 (2H, s), 6.53 (1H, d), 6.80 (1H, d), 7.29 (1H, d), 7.86-7.89 (2H, m), 7.60-7.64 (2H, m), 7.96 (1H, dd), 8.52 (1H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 541, $[\text{M}+\text{Na}]^+$ 563.

Preparation 59 : 3-((2*R*)-2-((2*R*)-2-[6-(2,5-Dimethylpyrrol-1-yl)-pyridin-3-yl]-2-hydroxyethylamino)propyl)-*N*-[2-(4-hydroxy-3-methylphenyl)ethyl]benzamide

20

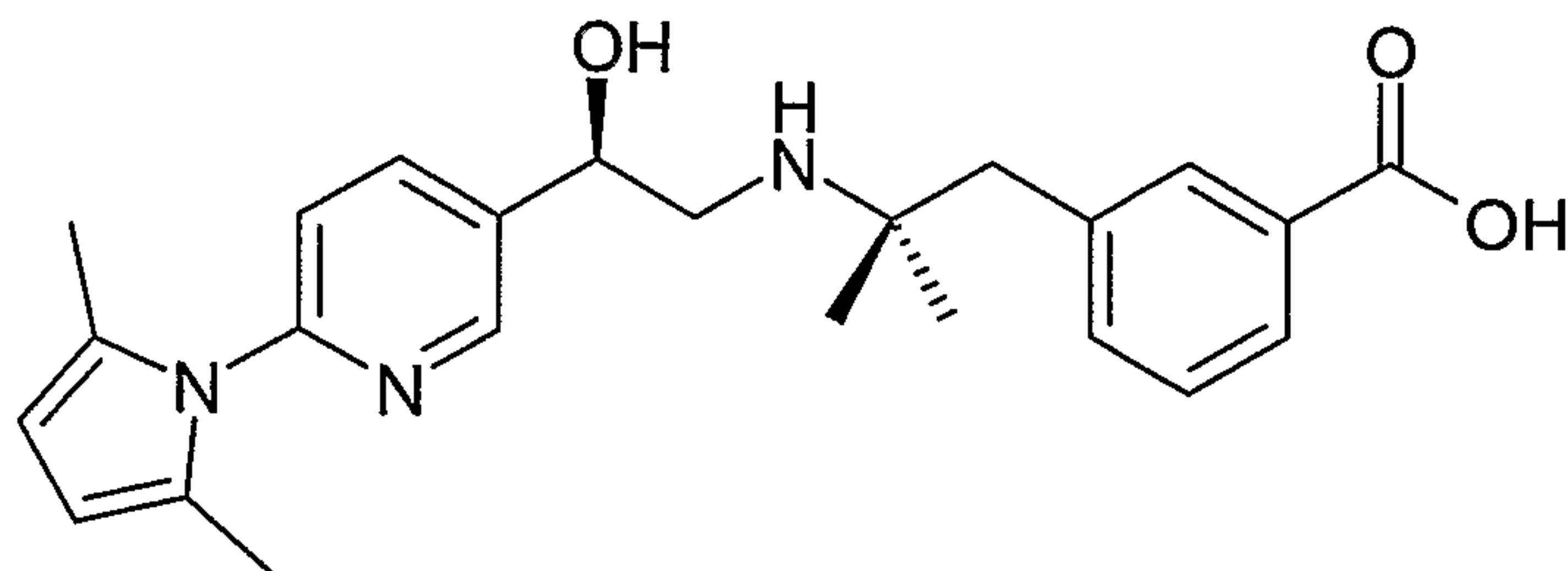


Prepared according to the method described for preparation 1 using the acid from preparation 68 and the amine from preparation 88 to give the title compound as a light beige foam.

- 5 ^1H NMR (400MHz, CD_3OD): δ = 1.12 (3H, d), 2.09 (6H, s), 2.20 (3H, s), 2.67-2.73 (3H, m), 2.79 (2H, t), 2.94-3.02 (2H, m), 3.59-3.70 (2H, m), 4.59 (1H, dd), , 5.88 (1H, s), 6.21 (1H, t), 6.67 (1H, d), 6.88 (1H, dd), 6.97 (1H, d), 7.18 (1H, d), 7.28-7.36 (2H, m), 7.49-7.52 (2H, m), 7.80 (1H, dd), 7.48 (1H, d) ppm.

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

- 10 **Preparation 60** : 3-(2-((2*R*)-2-[6-(2,5-Dimethylpyrrol-1-yl)pyridin-3-yl]-2-hydroxyethylamino)-2-methylpropyl)benzoic acid

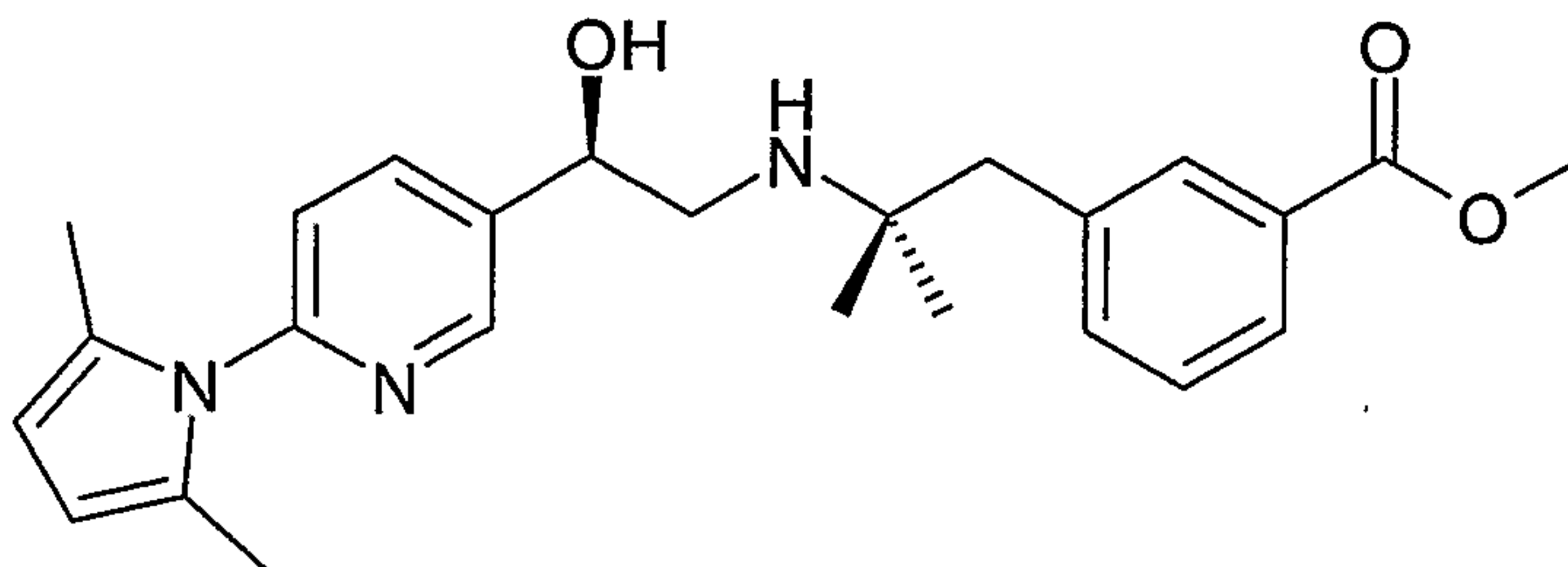


Prepared according to the method described for preparation 21 using preparation 61 to give the title compound as a cream coloured powder.

- 15 ^1H NMR (400MHz, CD_3OD): δ = 8.67 (1H, d), 8.13 (1H, d), 7.94 (1H, d), 7.87-7.92 (2H, m), 7.40-7.47 (3H, m), 5.83 (2H, s), 5.08 (1H, dd), 3.43 (1H, dd), 3.32 (1H, dd), 3.10 (2H, d), 2.06 (6H, s), 1.35 (6H, s) ppm.

LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 408, $[\text{M}-\text{H}]^-$ 406.

Preparation 61 : 3-(2-((2R)-2-[6-(2,5-Dimethylpyrrol-1-yl)pyridin-3-yl]-2-hydroxyethylamino)-2-methylpropyl)-benzoic acid methyl ester

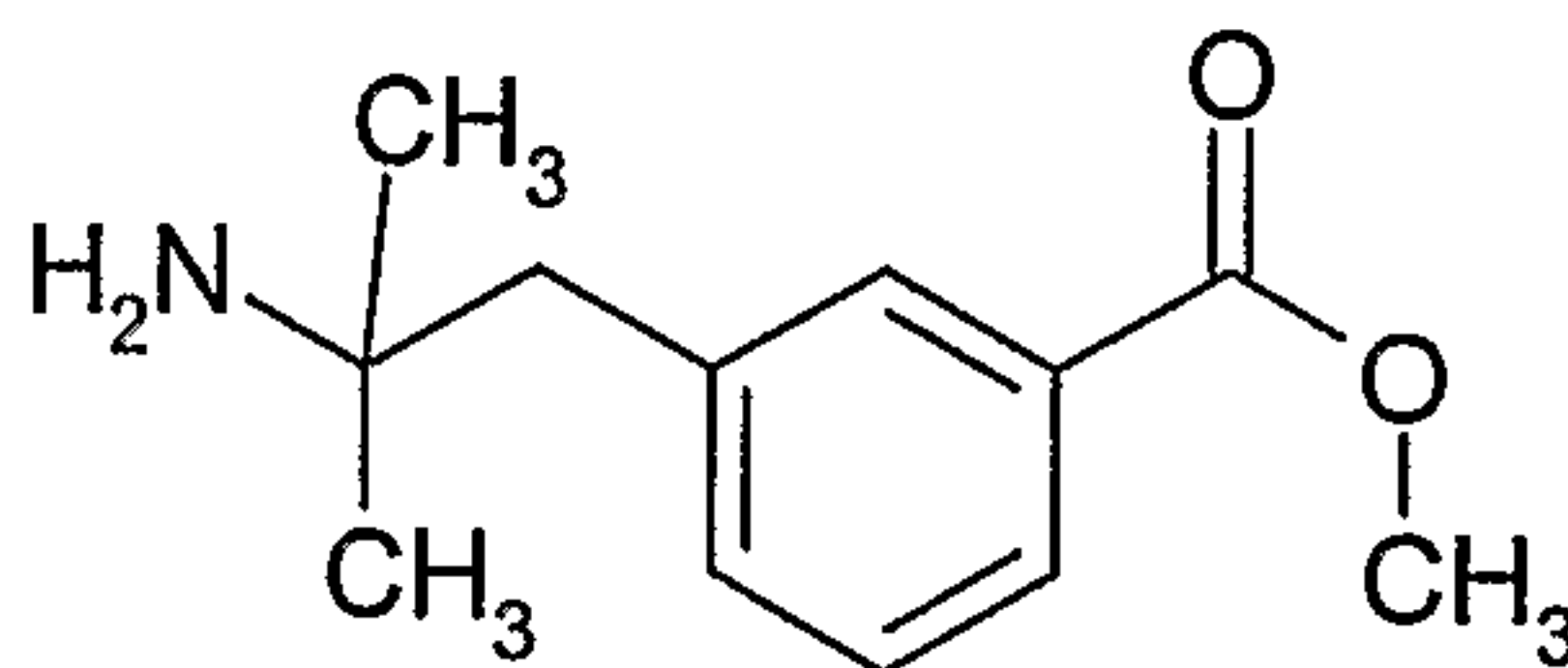


Prepared according to the method described for preparation 22 using the amine 5 from preparation 62 and the epoxide from preparation 27 to give the title compound as a brown oil.

^1H NMR (400MHz, CD_3OD): δ = 8.57 (1H, d), 7.86-7.93 (3H, m), 7.36-7.38 (2H, m), 7.20 (1H, d), 5.89 (2H, s), 4.65 (1H, d), 3.91 (3H, s), 3.05 (1H, d), 2.76 (2H, d), 2.67 (1H, dd), 2.11 (6H, s), 1.11 (6H, s) ppm.

10 LRMS (APCI) : m/z $[\text{M}+\text{H}]^+$ 422.

Preparation 62 : 3-(2-amino-2-methylpropyl)benzoic acid methyl ester

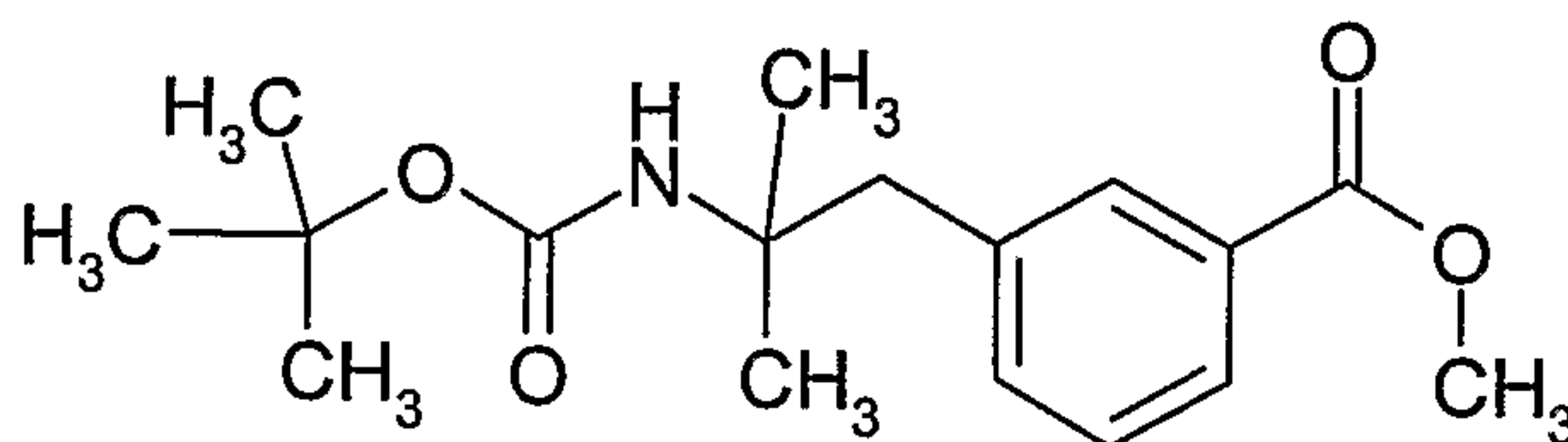


A solution of preparation 63 (1.6g, 5.2mmol) in dichloromethane (160ml) at 0°C was treated with trifluoroacetic acid (13.6ml) and left to warm to room temperature over 2 hours. The solvent was removed *in vacuo* and the product purified by cation exchange chromatography (methanol followed by 2M ammonia in methanol) to yield the title compound as an amber oil (1.06g).

^1H NMR (400MHz, CDCl_3) δ = 7.90-7.88 (1H, m), 7.84 (1H, s), 7.36-7.35 (2H, m), 3.90 (3H, s), 2.71 (2H, s), 1.67 (2H, bs), 1.12 (6H, s).

20 LRMS (electrospray) m/z 208 $[\text{M}+\text{H}]^+$

Preparation 63 : 3-(2-*tert*-butoxycarbonylamino-2-methylpropyl)benzoic acid methyl ester

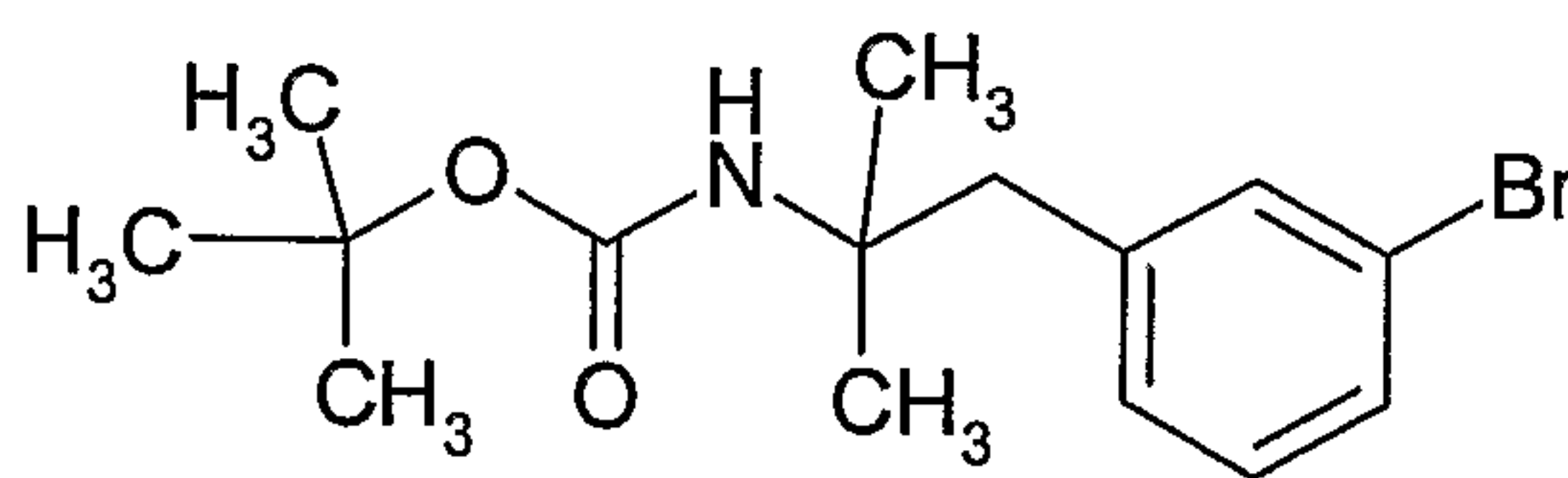


A solution of preparation 64 (7.0g, 21mmol), [1,1'-
 5 *bis*(diphenylphosphino)ferrocene]dichloropalladium(II) (1.74g, 2.1mmol) and triethylamine (5.94ml, 43mmol) in methanol (250ml) was heated to 100°C under 100psi carbon monoxide for 12 hours. The reaction mixture was filtered through arbocel and the filtrate concentrated *in vacuo* and purified by flash column chromatography on silica gel eluting with dichloromethane:pentane (50:50 by
 10 volume) to afford the title compound as a yellow solid (3.76g).

^1H NMR (400MHz, CDCl_3) δ = 7.92-7.90 (1H, m), 7.82 (1H, s), 7.35-7.34 (2H, m), 4.24 (1H, bs), 3.90 (3H, s), 3.05 (2H, s), 1.48 (9H, s), 1.26 (6H, s).

LRMS (electrospray) m/z 208 $[\text{M}+\text{H}-\text{BOC}]^+$

**Preparation 64: [2-(3-bromophenyl)-1,1-dimethylethyl]carbamic acid *tert*-
 15 butyl ester**



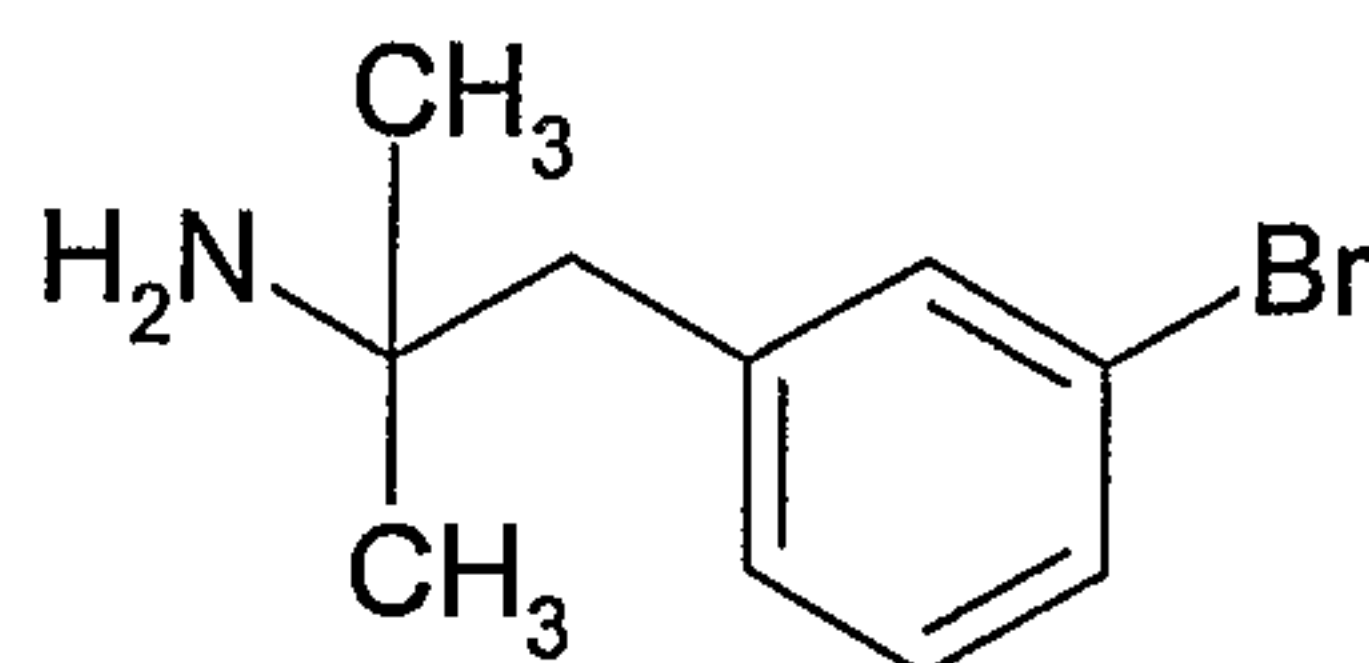
Preparation 65 (5.0g, 22mmol) was treated with di-*tert*-butyl dicarbonate (5.26g, 24mmol) in dichloromethane (50ml) and stirred for 20 hours. The reaction mixture was washed with water (50ml) and the combined organics dried
 20 (sodium sulfate) and the solvent removed *in vacuo*. The crude material was purified using a cation exchange column (methanol followed by 2M ammonia in methanol), followed by purification by flash column chromatography on silica

gel eluting with dichloromethane to afford the title compound as a brown oil (7.23g).

^1H NMR (400MHz, CDCl_3) δ = 7.35 (1H, d), 7.30 (1H, s), 7.15-7.11 (1H, t), 7.05 (1H, d), 4.24 (1H, bs), 2.97 (2H, s), 1.50 (9H, s), 1.27 (6H, s).

5 LRMS (electrospray) m/z 350 $[\text{M}+\text{NH}_4]^+$

Preparation 65: 2-(3-bromophenyl)-1,1-dimethylethylamine

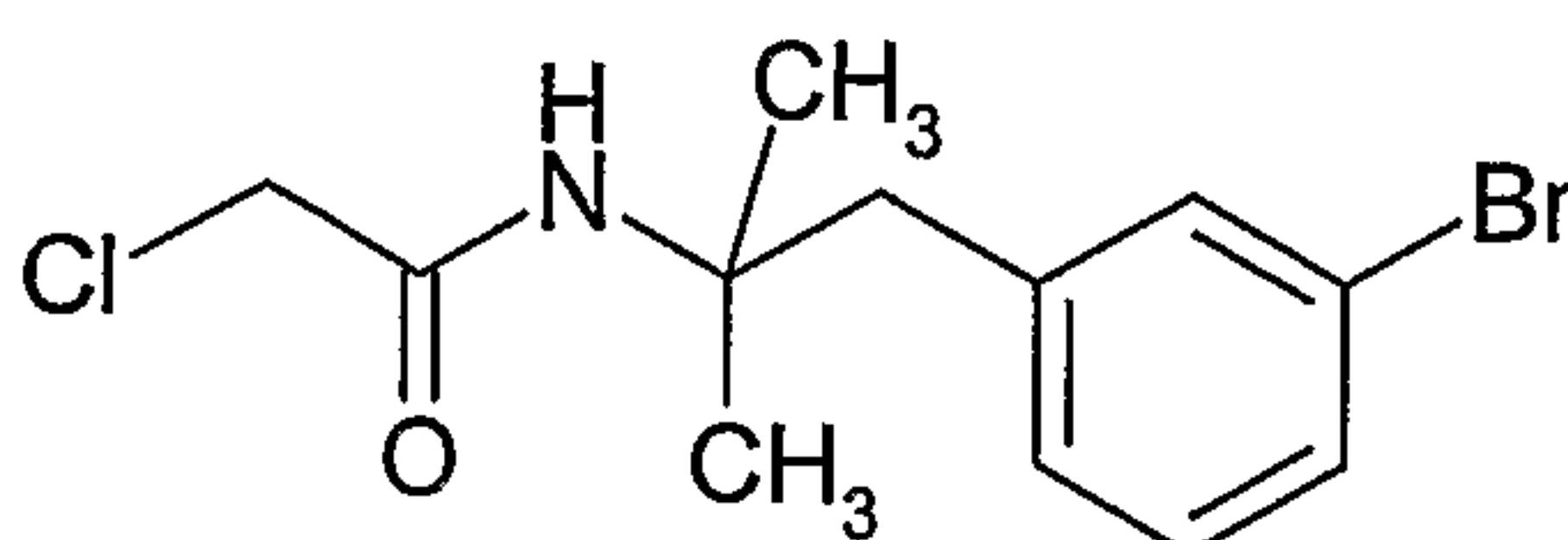


A solution of preparation 66 (32.0g, 105mmol), thiourea (9.60g, 126mmol) and acetic acid (50ml) in ethanol (250ml) was heated to reflux overnight. The reaction mixture was cooled to room temperature and filtered, the filtrate was concentrated *in vacuo* and basified using aqueous sodium hydroxide solution (1M, 450ml). The product was extracted with dichloromethane (2×500ml) and the combined organics washed with brine (50ml), dried (sodium sulfate) and the solvent removed *in vacuo* to afford the title compound as a black oil (23g).

15 ^1H NMR (400MHz, CDCl_3) δ = 7.36-7.32 (2H, m), 7.16-7.08 (2H, m), 2.62 (2H, s), 1.84 (2H, bs), 1.12 (6H, s).

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

Preparation 66: N-[2-(3-bromophenyl)-1,1-dimethylethyl]-2-chloroacetamide



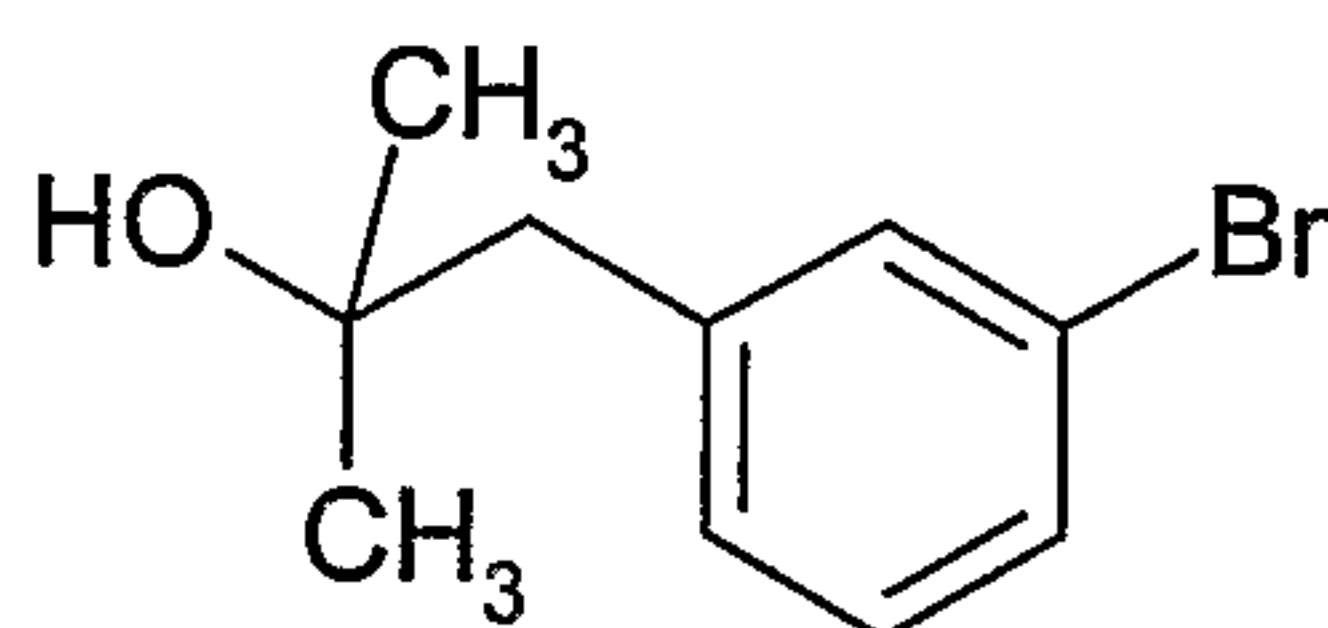
Chloroacetonitrile (6.63ml, 105mmol) was added to a stirred solution of preparation 67 (12.0g, 52.0mmol) in acetic acid (25ml) at room temperature. The resulting solution was cooled to 0°C and concentrated sulfuric acid (25ml) was added keeping the temperature <10°C. The resulting solution was left to stir for 1 hour and then poured onto ice and basified by the addition of solid potassium carbonate. The product was extracted with ethyl acetate (2×500ml), the organics combined and washed with water (50ml), dried (sodium sulfate) and the solvent removed *in vacuo* to afford the title compound as an orange solid (16.08 g).

10 ^1H NMR (400MHz, CDCl_3) δ = 7.39-7.32 (1H, d), 7.26 (1H, s), 7.1-7.13 (1H, t), 7.08-7.03 (1H, d), 6.17 (1H, bs), 3.94 (2H, s), 3.02 (2H, s), 1.37 (6H, s).

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

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

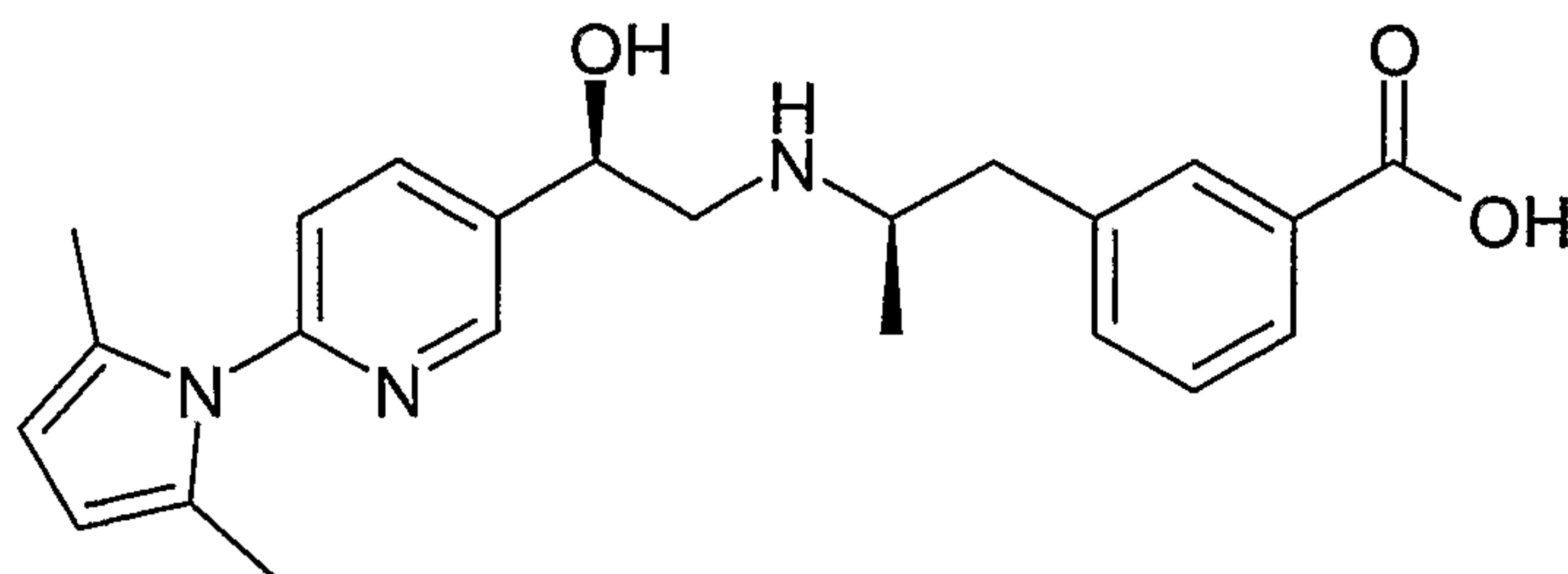
15 **Preparation 67: 1-(3-bromophenyl)-2-methylpropan-2-ol**



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

25 ^1H NMR (400MHz, CDCl_3) δ = 7.40 (2H, m), 7.15 (2H, m), 2.74 (2H, s), 1.42 (1H, bs), 1.22 (6H, s).

Preparation 68 : 3-((2*R*)-2-((2*R*)-2-[6-(2,5-Dimethylpyrrol-1-yl)pyridin-3-yl]-2-hydroxyethylamino)propyl)benzoic acid

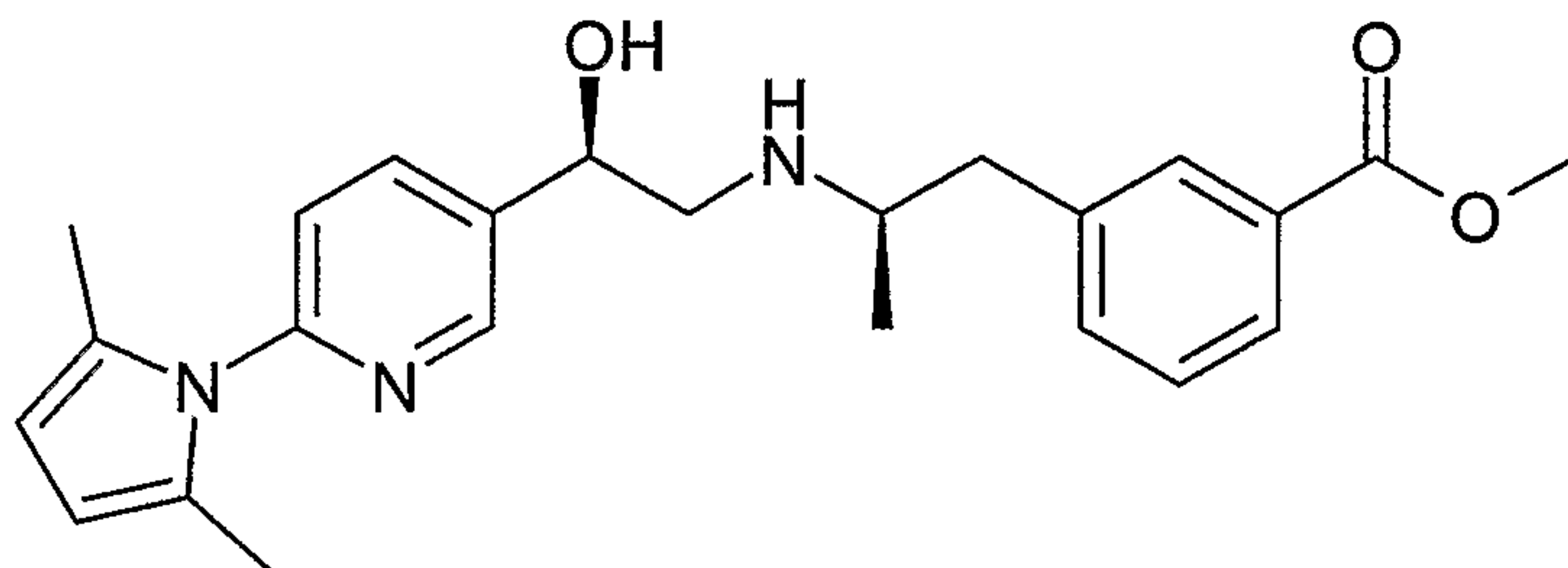


Prepared according to the method described for preparation 21 using
5 preparation 69 to give the title compound as an orange solid.

^1H NMR (400MHz, CD_3OD): δ = 8.84 (1H, d), 8.08 (1H, dd), 7.87-7.89 (2H, m), 7.37-7.40 (3H, m), 5.82 (2H, s), 5.11 (1H, dd), 3.57-3.63 (1H, m), 3.34-3.39 (2H, m), 3.23-3.28 (1H, m), 2.81 (1H, dd), 2.05 (6H, s), 1.26 (3H, d) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{H}]^+$ 394, $[\text{M}-\text{H}]^-$ 392.

10 Preparation 69 : 3-((2*R*)-2-((2*R*)-2-[6-(2,5-Dimethylpyrrol-1-yl)pyridin-3-yl]-2-hydroxyethylamino)propyl)benzoic acid methyl ester

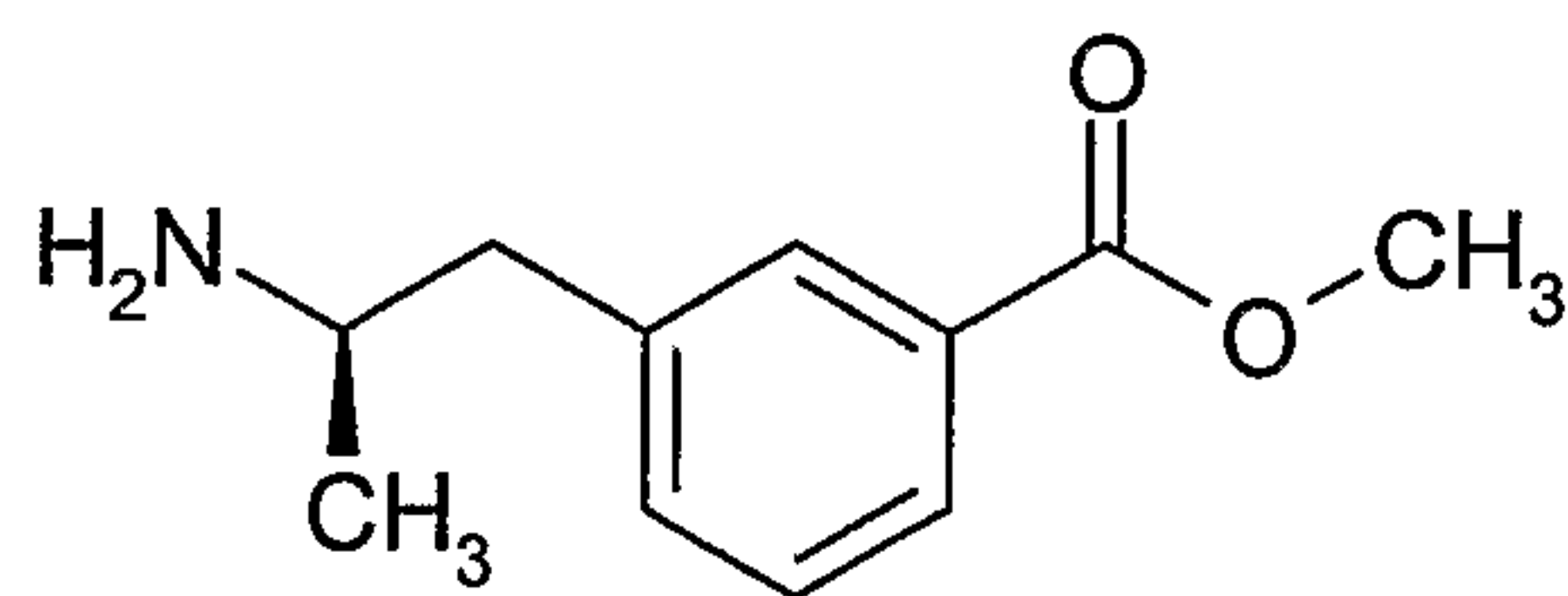


Prepared according to the method described for preparation 22 using the amine
from preparation 70 and the epoxide from preparation 27 to give the title
15 compound as a brown oil.

^1H NMR (400MHz, CD_3OD): δ = 8.53 (1H, d), 7.95 (1H, dd), 7.84-7.87 (2H, m), 7.45-7.48 (1H, m), 7.38-7.42 (1H, m), 7.28 (1H, d), 5.81 (2H, s), 4.83-4.85 (1H, m), 3.88 (3H, s), 2.99 (1H, q), 2.86-2.91 (3H, m), 2.63 (1H, dd), 2.03 (6H, s), 1.07 (3H, d) ppm.

LRMS (APCI) : m/z $[M+H]^+$ 408.

Preparation 70 : methyl {3-[(2*R*)-2-aminopropyl]phenyl}acetate

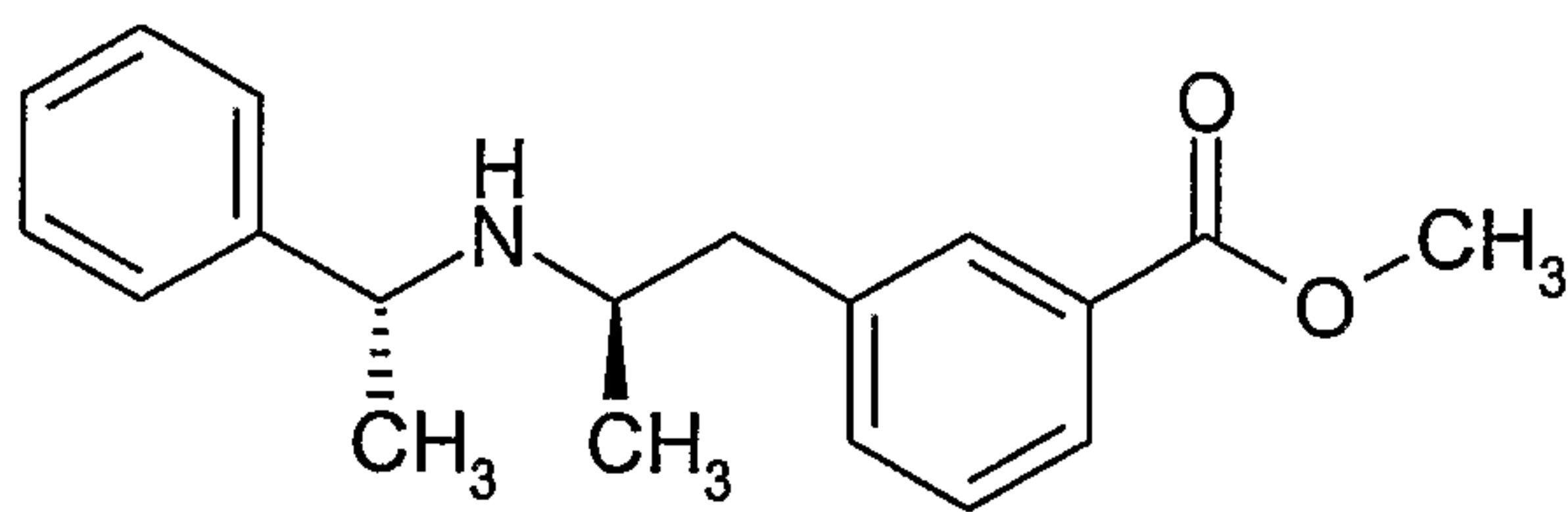


A solution of preparation 71 (13.65g, 40.9mmol) and ammonium formate
 5 (12.9g, 204mmol) in ethanol (200ml) was heated at reflux in the presence of
 20% of palladium hydroxide on charcoal ($Pd(OH)_2/C$, 1.36g). After 3 hours the
 reaction mixture was cooled to room temperature, filtered through arbocel and
 the filtrate concentrated *in vacuo*. The residue was partitioned between
 dichloromethane (200ml) and 880 ammonia (100ml) and the organic phase
 10 separated. The aqueous phase was extracted with further dichloromethane
 (3x100ml) and the combined organic extracts washed with brine (100ml), dried
 (sodium sulfate) and reduced *in vacuo* to give the title compound (8.48g) as a
 pale yellow oil.

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

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

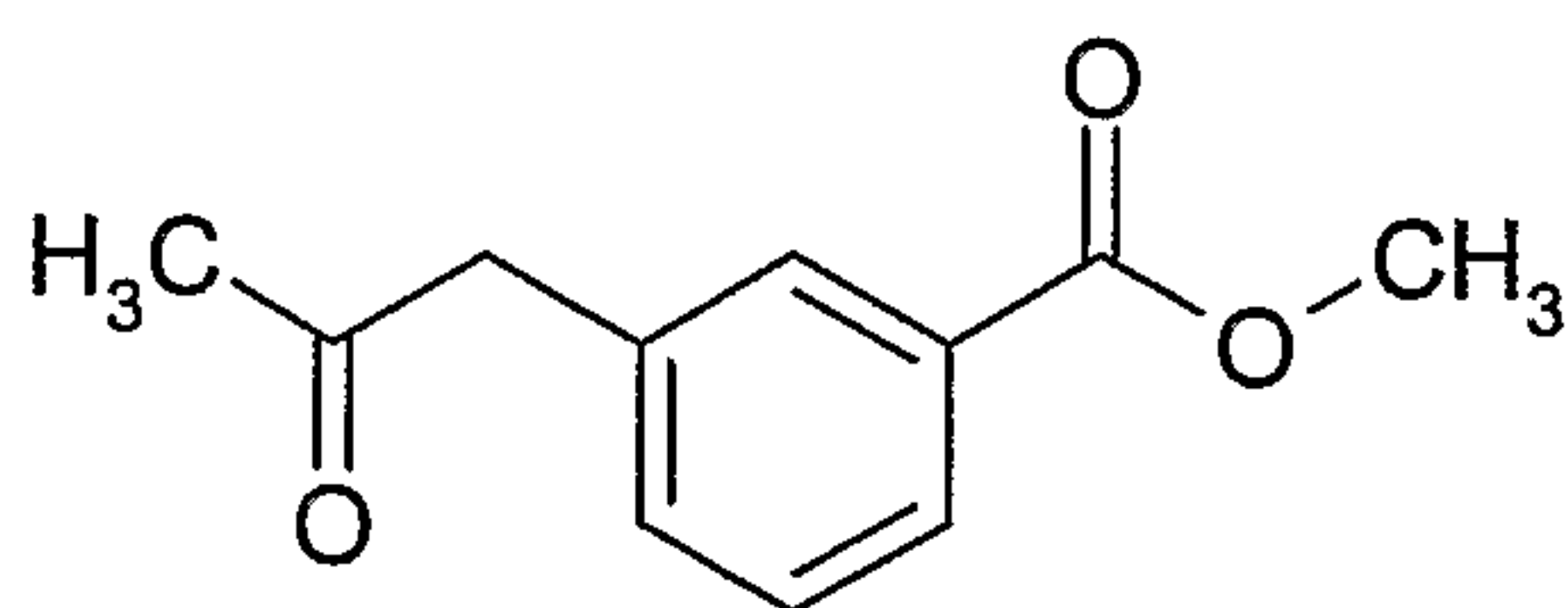
Preparation 71 : methyl [3-((2*R*)-2-[(1*R*)-1-phenyl-ethyl]-amino)-propyl]-phenyl]-acetate hydrochloride



A solution of preparation 72 (45.3g, 236mmol), (*R*)- α -methylbenzylamine (27.6ml, 214mmol), sodium triacetoxyborohydride (68.1g, 321mmol) and acetic acid (14.7ml, 257mmol) in dichloromethane (1500ml) was stirred at room temperature for 18 hours. The reaction mixture was quenched by addition of
5 saturated aqueous sodium bicarbonate (600ml) and allowed to stir until effervescence ceased. The organic phase was separated and the aqueous phase extracted with further dichloromethane (2x100ml). The combined organic extracts were washed with brine (100ml), dried (sodium sulfate), filtered through Celite and reduced *in vacuo*. The oil was dissolved in methanol (200ml), treated
10 with 1M hydrogen chloride in methanol (300ml) and reduced *in vacuo* to give a 4:1 mixture of diastereomers (*R,R* major) as an off-white, hydrochloride salt. Two successive crystallisations (diisopropylether/methanol) gave the title compound (27.3g) as a colourless crystalline solid.

¹H NMR (400MHz, CD₃OD): δ = 7.92-7.90 (1H, d), 7.75 (1H, s), 7.55-7.49 (5H, m), 7.45-7.42 (1H, dd), 7.35-7.33 (1H, d), 4.68-4.63 (1H, q), 3.90 (3H, s), 3.43-3.38 (1H, dd), 3.25-3.19 (1H, m), 2.71-2.65 (1H, dd), 1.71-1.69 (3H, d), 1.17-1.16, (3H, d) ppm.

Preparation 72 : methyl [3-(2-oxopropyl)phenyl]acetate



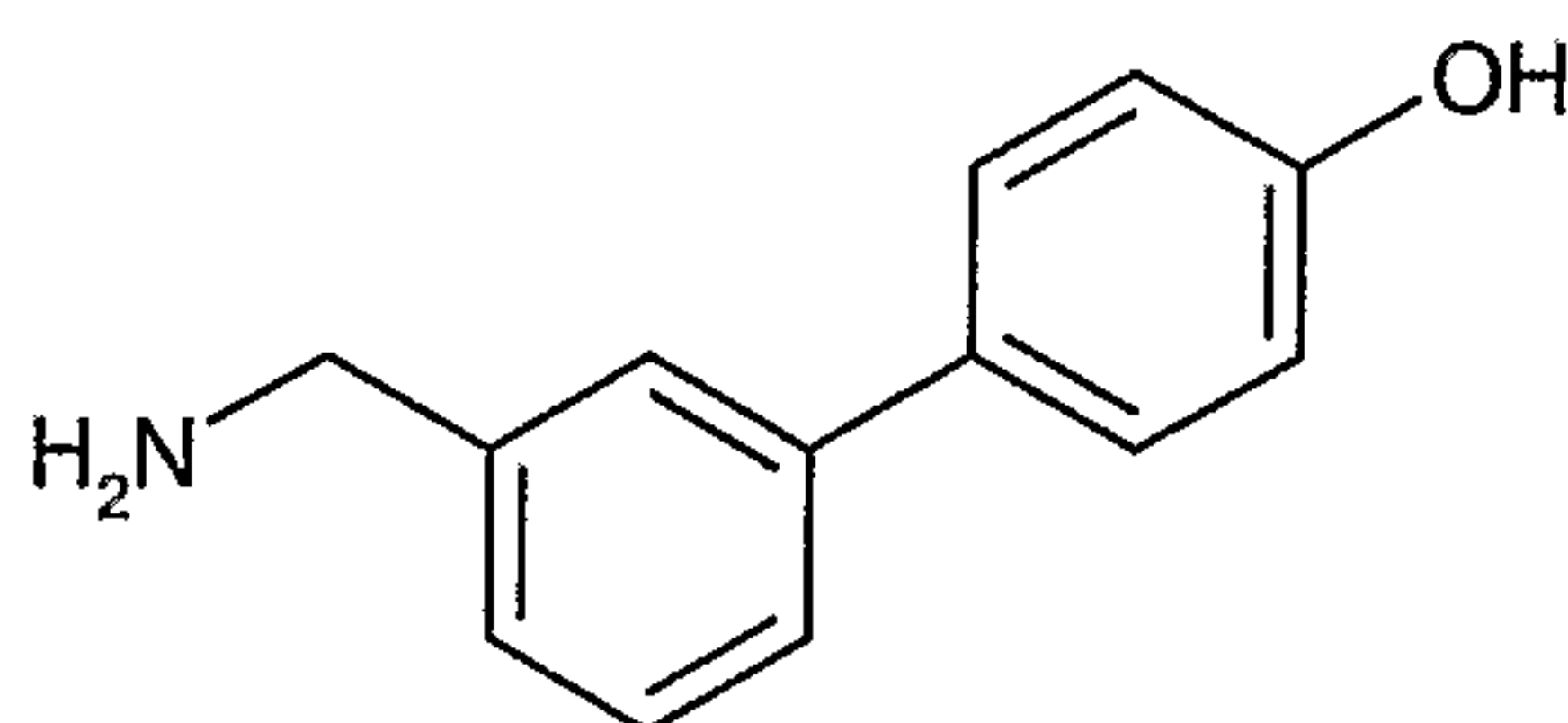
20 Tributyltin methoxide (80.3ml, 279mmol), methyl 3-bromobenzoate (53.5g, 249mmol), isopropenyl acetate (39.4ml, 358mmol), palladium(II)acetate (2.6g, 11.6mmol) and tri-*o*-tolylphosphine (7.1g, 23.2mmol) were stirred together in toluene (350ml) at 100°C under nitrogen for 18 hours. After cooling, the reaction was treated with 4M aqueous potassium fluoride solution (560ml) and
25 stirred for 2 hours. The resulting mixture was diluted with further toluene (200ml) and filtered through Celite, washing the filter pad with ethyl acetate. The organic phase was separated, dried (sodium sulfate) and reduced *in*

vacuo. The residue was purified by flash column chromatography on silica gel eluting with ethylacetate:pentane (10:90, changing to 20:80, by volume) to give the title compound (45.3g) as an orange oil.

^1H NMR (400MHz, CDCl_3): δ = 7.95-7.93 (1H, d), 7.87 (1H, s), 7.43-7.37 (2H, m), 3.91 (3H, s), 3.75 (2H, s), 2.18 (3H, s) ppm.

LRMS (electrospray) : m/z $[\text{M}+\text{Na}]^+$ 215, $[\text{M}-\text{H}]^-$ 191.

Preparation 73 : 3'-(Aminomethyl)biphenyl-4-ol

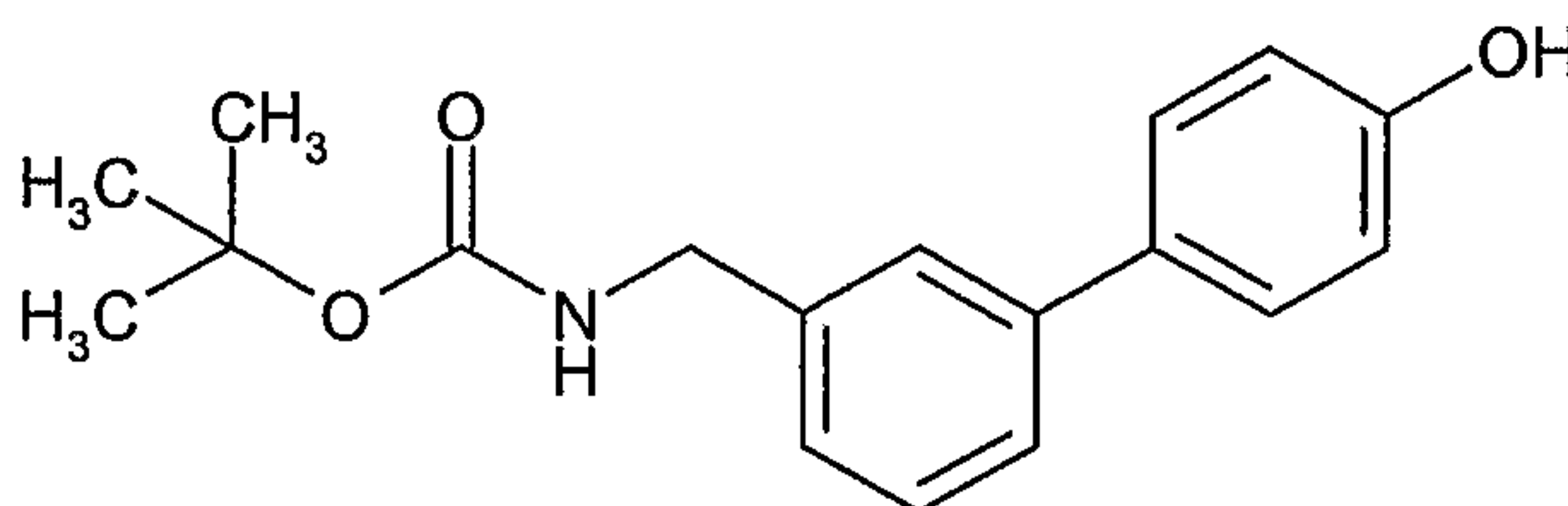


The phenol from preparation 74 (0.73g, 2.43mmol) was treated with 4M HCl in dioxan (6ml, 24.3mmol) and the resulting solution allowed to stir at room temperature for 3 hours. The solvent was removed *in vacuo* to give the title compound as a colourless solid.

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

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

Preparation 74 : *tert*-Butyl [(4'-hydroxybiphenyl-3-yl)methyl]carbamate



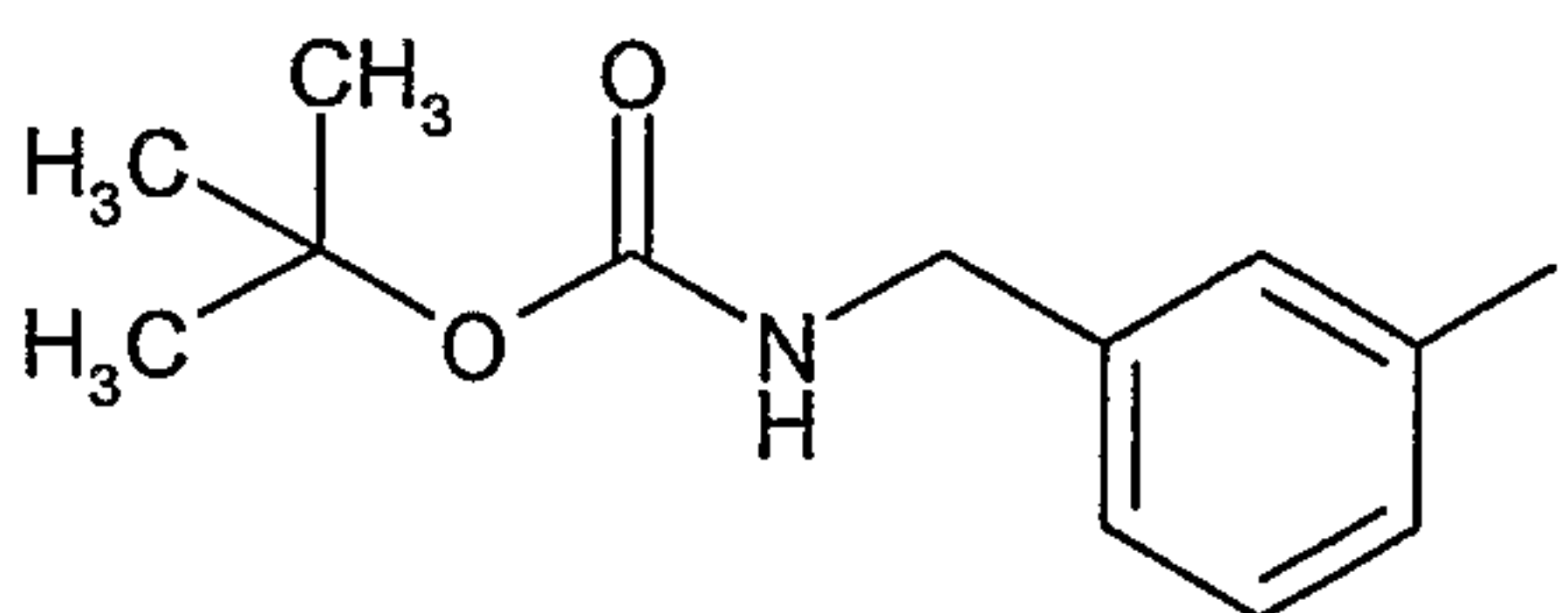
A solution of the iodide from preparation 75 (0.75g, 2.25mmol), 4-hydroxy phenylboronic acid (0.62g, 4.50mmol), 1,1'-bis(diphenylphosphino)ferrocenyl palladium(II)chloride (0.11g, 0.14mmol), in *N,N*-dimethylformamide (14ml) was

treated with 2M aq. sodium carbonate (4ml) and the resulting mixture heated at 80°C under a nitrogen atmosphere for 16 hours. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with ethyl acetate:pentane (1:3) to give the title compound as a
 5 pale pink crystalline solid (0.73g).

¹HNMR (400MHz, CDCl₃) δ : 7.43-7.45 (m, 4H), 7.37 (dd, 1H), 7.21 (d, 1H), 6.89 (d, 2H), 4.87-4.94 (bs, 1H), 4.33-4.41 (m, 2H), 1.47 (s, 9H) ppm.

MS (electrospray) m/z 298 [M-H]⁻, 322 [M+Na]⁺

Preparation 75 : *tert*-Butyl (3-iodobenzyl)carbamate



10

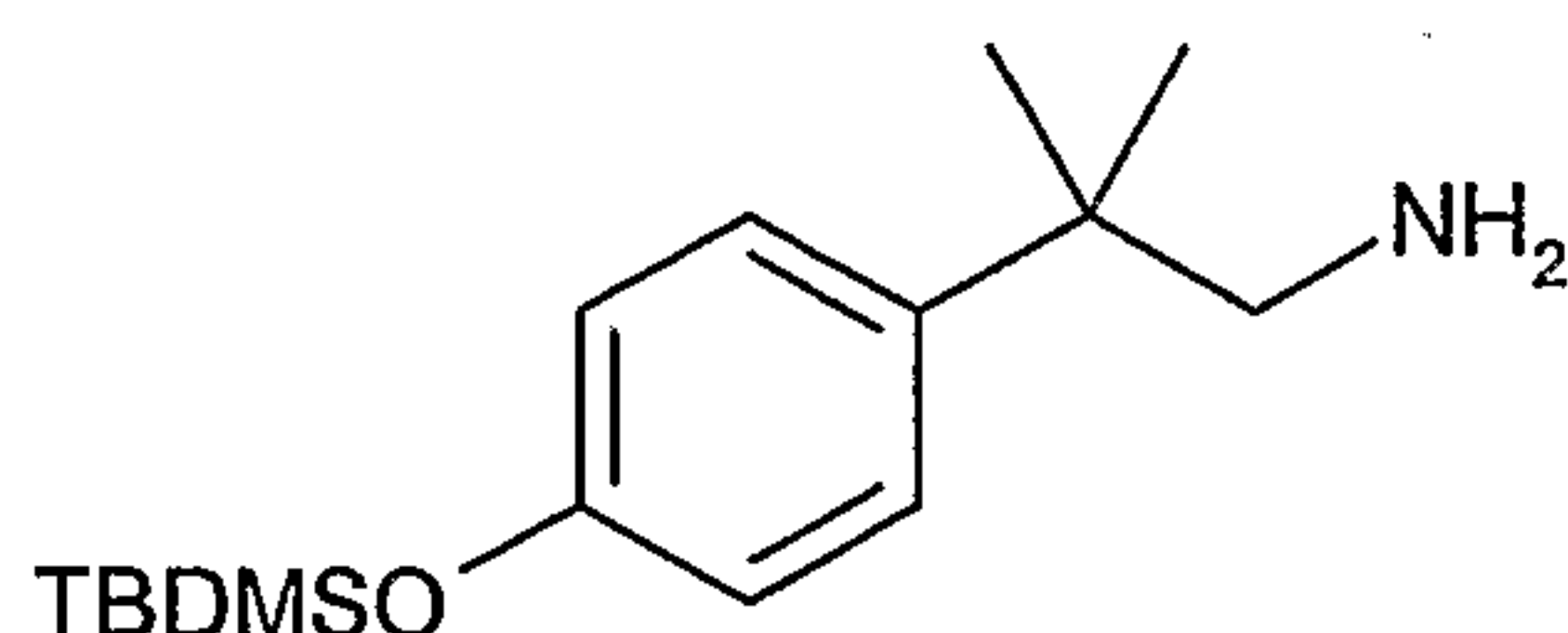
A suspension of 3-iodobenzylamine hydrochloride (4.95g, 18.4mmol) in dichloromethane (100ml) was treated with triethylamine (3.1ml, 22mmol) and di-*t*-butyl dicarbonate (4.40g, 20mmol) and the resulting solution left to stir at room temperature under a nitrogen atmosphere for 1.5 hours. The reaction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

¹HNMR (400MHz, CDCl₃) δ :

7.63 (s, 1H), 7.60 (d, 1H), 7.25 (d, 1H), 7.06 (dd, 1H), 4.79-4.89 (bs, 1H), 4.21-
 20 4.30 (m, 2H), 1.46 (s, 9H) ppm.

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

Preparation 76 : [2-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-2-methylpropyl]amine

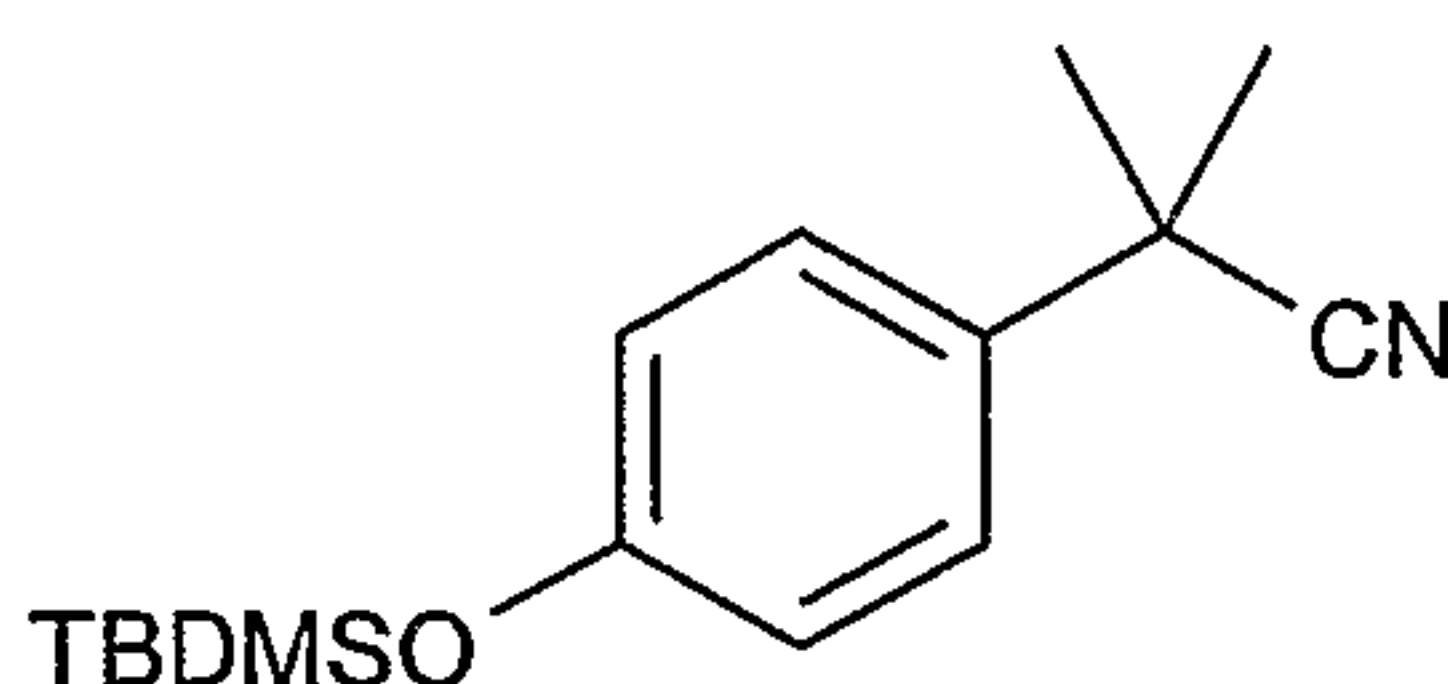


A solution of the nitrile from preparation 77 (0.75g, 2.7mmol) in diethyl ether (5ml) was added dropwise to a cold (0°C) solution of lithium aluminium hydride in diethyl ether (2.98ml of a 1M solution). The resulting solution was stirred at
 5 0°C for 3 hours and then quenched by addition of water (0.1ml), 2N aqueous sodium chloride (0.1ml), and further water (0.3ml). The resulting suspension was filtered and the filtrate concentrated *in vacuo*. Purification by column chromatography on silica gel eluting with dichloromethane:methanol :0.880 ammonia (97:3:0.5 changing to 93:7:0.5) gave the title compound as a
 10 colourless oil (0.52g).

¹HNMR (400MHz, CDCl₃) δ : 7.16 (d, 2H), 6.78 (d, 2H), 2.73 (s, 2H), 1.25 (s, 6H), 1.00 (bs, 2H), 0.97 (s, 9H), 0.18 (s, 6H) ppm.

MS (APCI) m/z 280 [M+H]⁺

Preparation 77 : 2-(4-[[*tert*-Butyl(dimethyl)silyl]oxy]phenyl)-2-methyl
 15 **propanenitrile**



A solution of the nitrile from preparation 78 (5.62g, 22.7mmol), methyl iodide (3.11ml, 50mmol), and 18-crown-6 (1.5g, 5.6mmol) in dry tetrahydrofuran (300ml) was cooled to -78°C under a nitrogen atmosphere. Potassium tert-
 20 butoxide (50ml of a 1M solution in tetrahydrofuran, 50 mmol) was added dropwise over 20 minutes and the reaction mixture then allowed to warm gradually to room temperature. After 2 hours the reaction was re-cooled to -78°C and quenched by addition of sat. aq. ammonium chloride (200ml) and

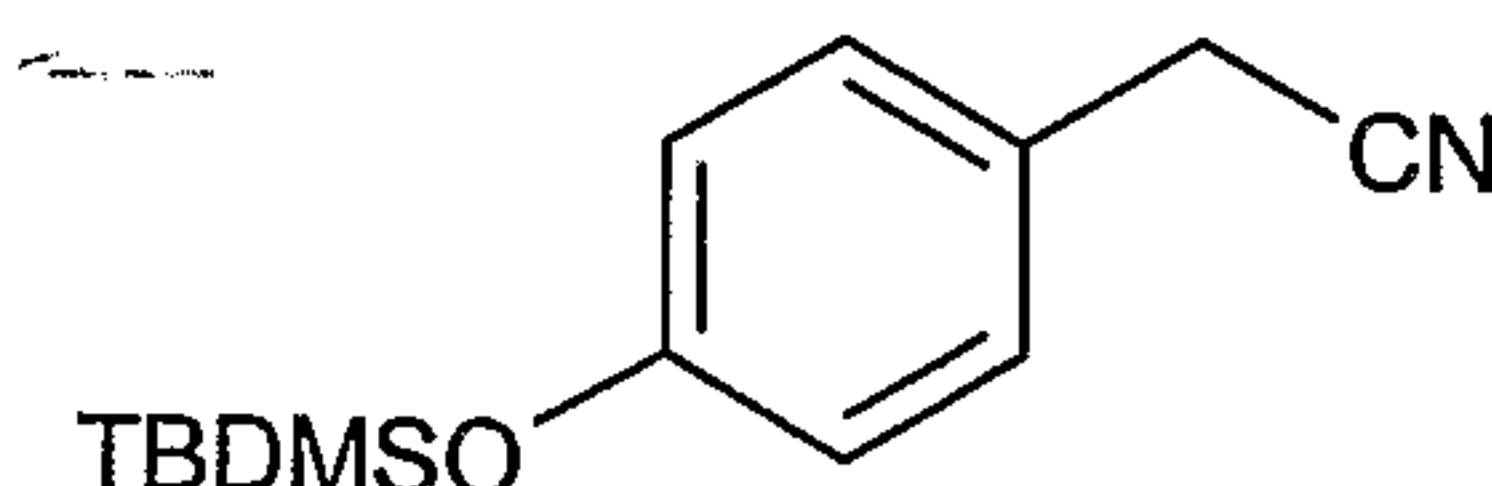
allowed to warm to room temperature. The resulting solution was extracted with ethyl acetate (300ml x 2), the combined organics were dried (sodium sulfate) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel eluting with ethyl acetate:pentane (0:100 changing to 10:90) gave the
 5 title compound as a colourless oil (4.75 g).

^1H NMR (400MHz, CDCl_3) δ : 7.30 (d, 2H), 6.82 (d, 2H), 1.68 (s, 6H), 0.97 (s, 9H), 0.19 (s, 6H) ppm.

MS (APCI) m/z 293 $[\text{M}+\text{NH}_4]^+$

Preparation 78 : (4- $\{[tert\text{-Butyl(dimethyl)silyl]oxy}\}$ phenyl)acetonitrile

10

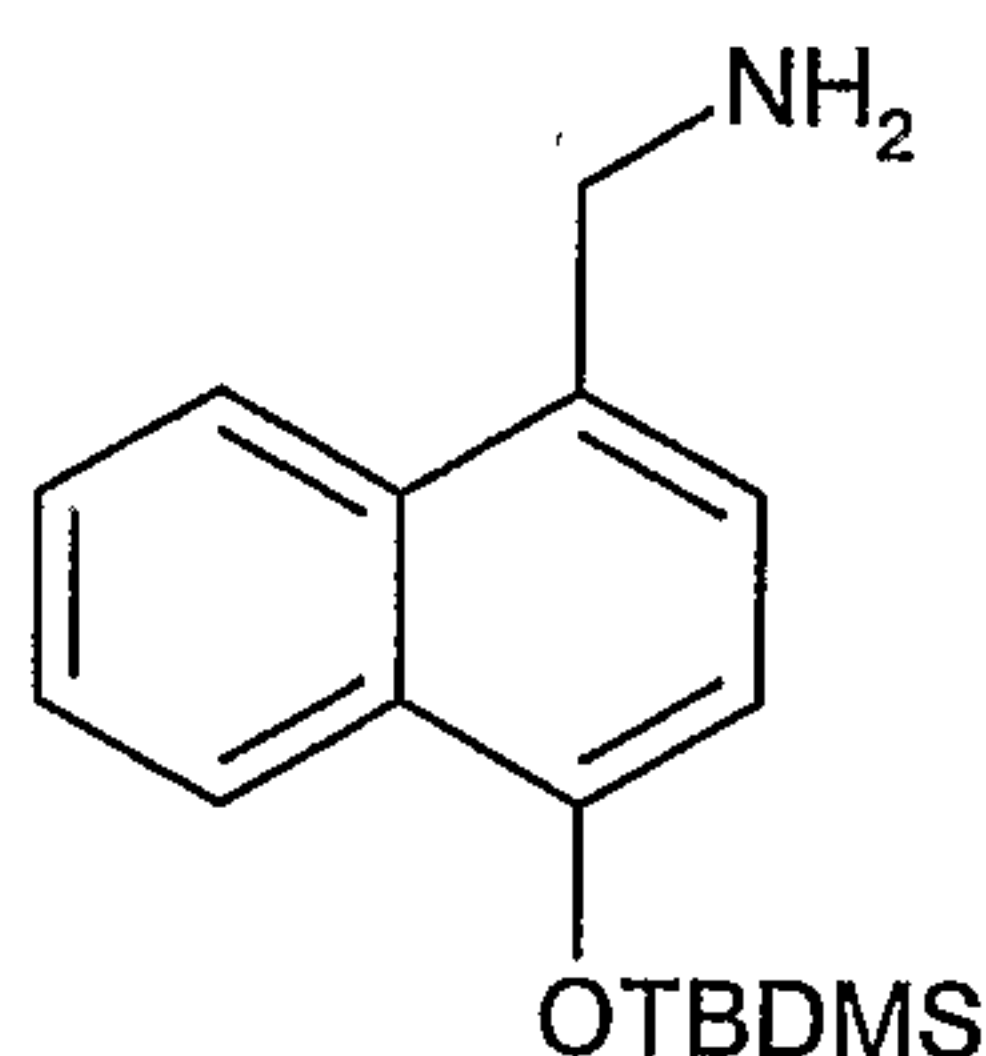


A solution of (4-hydroxyphenyl)acetonitrile (6.01g, 45.1mmol) in *N,N*-dimethylformamide (60ml) was treated with imidazole (3.81g, 58.6mmol), *tert*-butyldimethylsilylchloride (7.49g, 49.6mmol) and *N,N*-dimethylaminopyridine (20mg) and the resulting solution left to stir at room temperature under a
 15 nitrogen atmosphere for 16 hours. The reaction mixture was diluted with water (200ml) and extracted with ethyl acetate (200ml x 2). The combined organic extracts were washed with sat. aq. sodium chloride (200ml), dried (sodium sulfate) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel eluting with ethyl acetate:pentane (0:100 changing
 20 to 10:90) gave the title compound as a pale yellow oil (9.44g).

^1H NMR (400MHz, CDCl_3) δ : 7.17 (d, 2H), 6.82 (d, 2H), 3.66 (s, 2H), 0.97 (s, 9H), 0.19 (s, 6H) ppm.

MS (APCI) m/z 265 $[\text{M}+\text{NH}_4]^+$

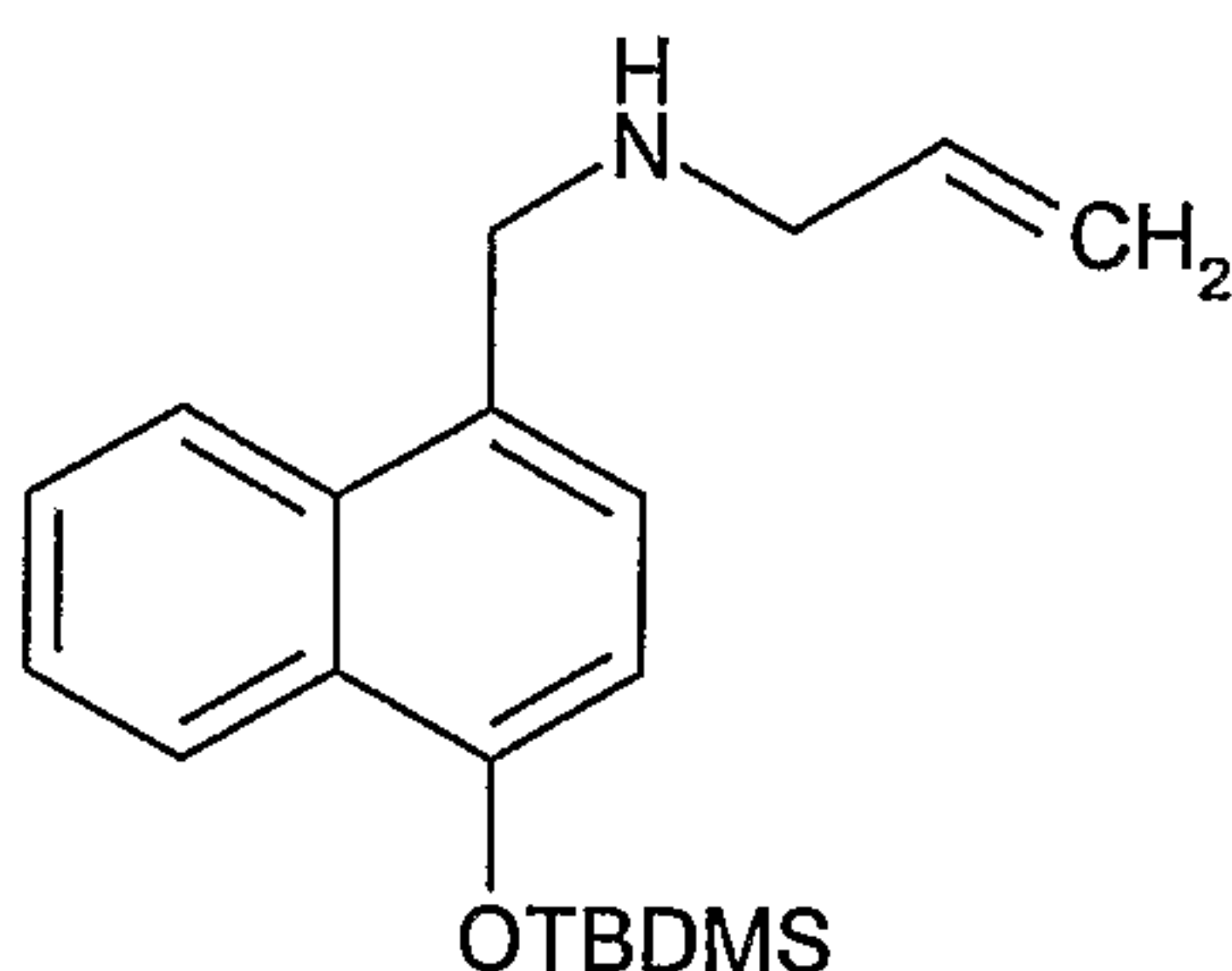
Preparation 79 : [(4- $\{[tert\text{-Butyl(dimethyl)silyl]oxy}\}$ -1-naphthyl)methyl]amine
 25



Preparation 80 (250 mg, 0.76 mmol) and dimethylbarbituric acid (581 mg, 3.72 mmol) were heated to reflux in dichloromethane (30 ml) for 15 min. *Tetrakis*(triphenylphosphine)palladium(0) (88 mg, 76 μ mol) was added and the
 5 resulting mixture heated to reflux for 20 h. The solvent was removed and the material dissolved in ethyl acetate (30 ml), washed with sodium hydroxide (1M, 3x 30 ml). The aqueous was extracted with ethyl acetate (30 ml). The combined organics were passed through a strong cation exchange resin column (methanol to 1M ammonia in methanol) to afford a brown oil (162 mg).

10 ^1H NMR (400MHz, CDCl_3) δ : 8.25 (d, 1H), 8.00 (d, 1H), 7.46-7.55 (m, 4H), 7.27 (t, 1H), 6.80 (d, 1H), 4.24 (s, 2H), 2.31 (bs, 2H), 1.09 (s, 9H), 0.28 (s, 6H).

Preparation 80 : *N*-[(4-[(*tert*-butyl(dimethyl)silyl]oxy)-1-naphthyl)methyl]prop-2-en-1-amine



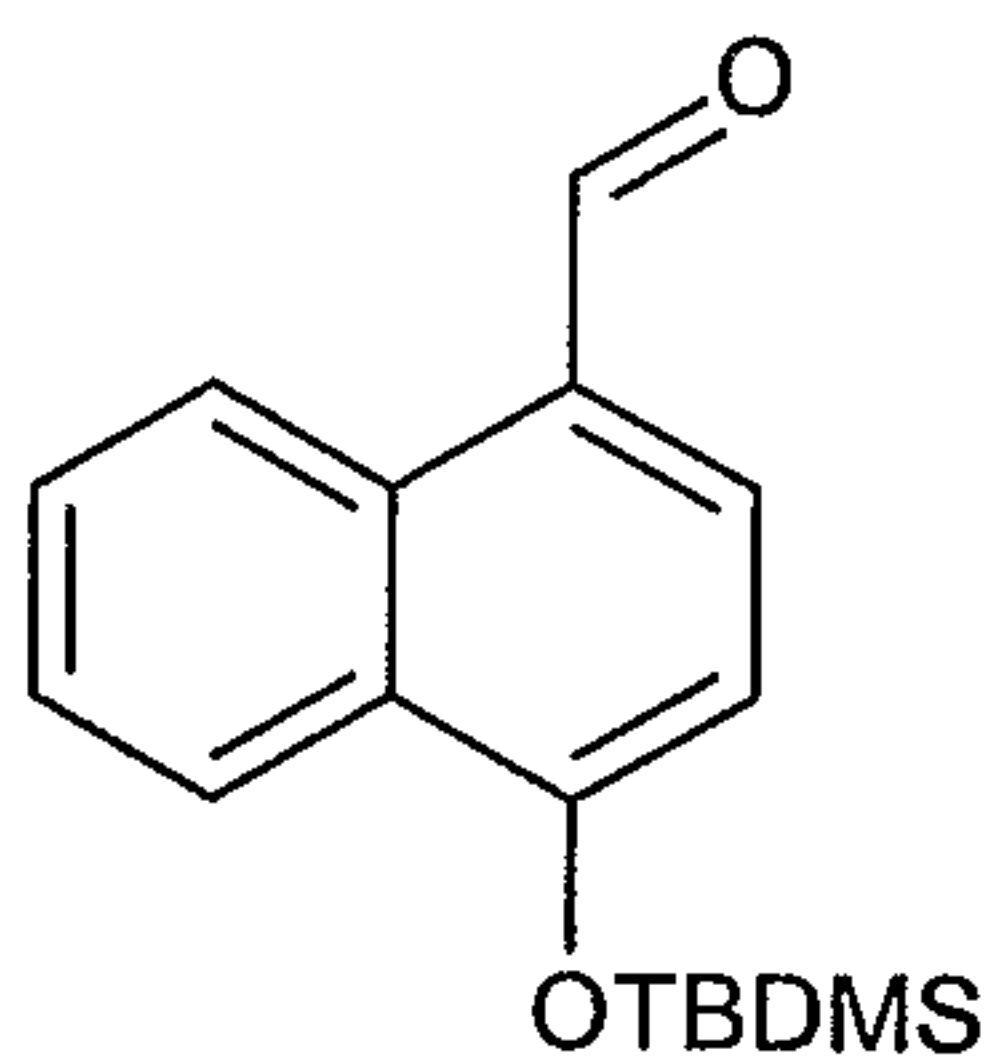
15 Preparation 81 (1.00 g, 3.5 mmol), allylamine (219 mg, 3.85 mmol) and acetic acid (2 drops) were dissolved in dichloromethane (10 ml) and stirred for 15 min. Sodium triacetoxyborohydride (1.11 g, 5.25 mmol) was added and the resulting mixture allowed to stir for 4 days. Sodium hydrogen carbonate (10 ml) was added and the mixture stirred for a further 90 min. The mixture was separated
 20 and the aqueous phase re-extracted with dichloromethane (10 ml), and the

combined organics washed with brine (20 ml) and dried (MgSO_4). The material was purified by chromatography (0-10 % methanol in dichloromethane +1 % ammonia), the material was further purified by chromatography (0-25 % ethyl acetate in pentane) to yield a dark yellow oil (250 mg)

- 5 ^1H NMR (400MHz, CDCl_3) δ : 8.25 (d, 1H), 8.07 (d, 1H), 7.47-7.57 (m, 2H), 7.32 (d, 1H), 6.82 (d, 1H), 5.95-6.05 (m, 1H), 5.25 (dd, 1H), 5.16 (dd, 1H), 4.17 (s, 2H), 3.39 (d, 2H), 1.97 (bs, 1H), 1.11 (s, 9H), 0.30 (s, 6H) ppm.

MS (electrospray) m/z 328 $[\text{M}+\text{H}]^+$, 655 $[2\text{M}+\text{H}]^+$

Preparation 81 : 4-[[*tert*-Butyl(dimethyl)silyl]oxy]-1-naphthaldehyde

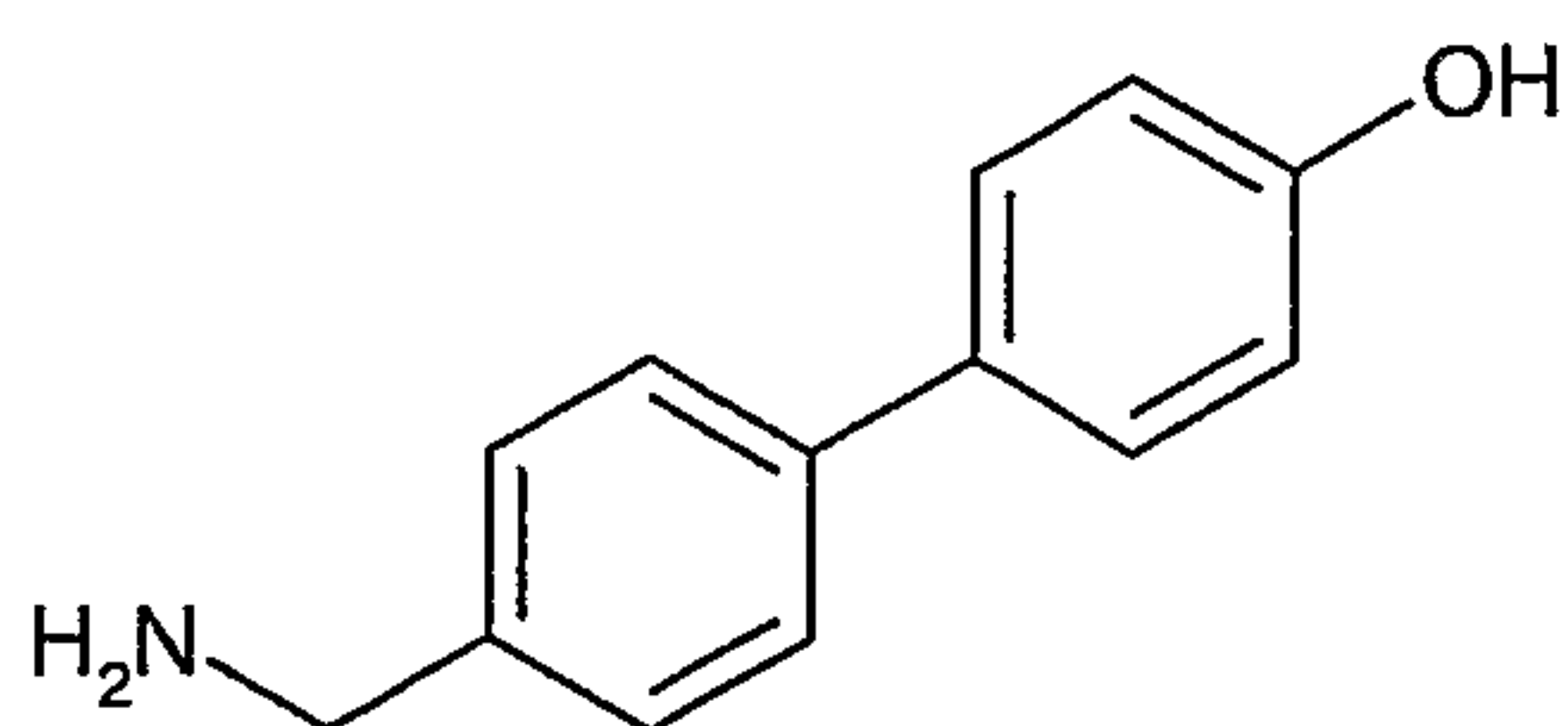


10

- 4-Hydroxynaphthalene-1-carbaldehyde (2.00 g, 11.63 mmol), *tert*-butyldimethylsilyl chloride (1.93 g, 12.80 mmol), imidazole (983 mg, 15.12 mmol) and *N,N*-dimethylaminopyridine (4 mg) in *N,N*-dimethylformamide (20 ml) were stirred at RT for 20 h. The solvent was removed and the mixture
 15 suspended in ethyl acetate (20 ml) and washed with water (20 ml). The aqueous phase was extracted with ethyl acetate (20 ml) and the combined organics washed with brine (2x 20 ml) and dried (MgSO_4). The solvent was removed leaving the product as a brown oil which solidified on standing.

- ^1H NMR (400MHz, CDCl_3) δ : 10.21 (s, 1H), 9.30 (dd, 1H), 8.27 (dd, 1H), 7.86
 20 (d, 1H), 7.68 (dd, 1H), 7.56 (dd, 1H), 6.94 (d, 1H), 1.10 (s, 9H), 0.36 (s, 6H).

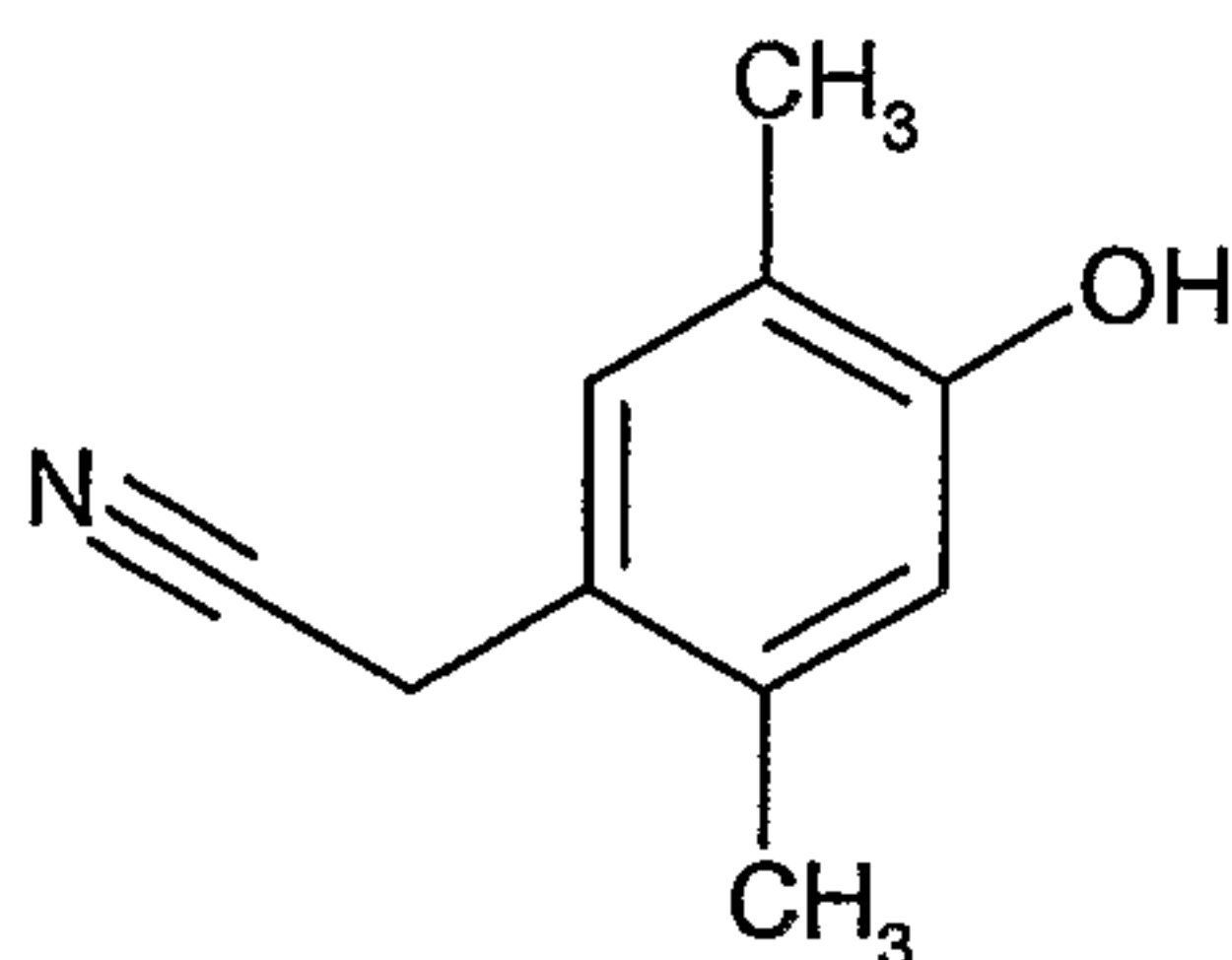
Preparation 82 : 4'-(Aminomethyl)biphenyl-4-ol hydrochloride



A solution of 4'-hydroxybiphenyl-4-carbonitrile (10.0 g, 51.22 mmol) in tetrahydrofuran (500 ml) was treated with a solution of diborane (1M in tetrahydrofuran, 102 ml, 102 mmol) and the resulting solution heated to reflux
5 under nitrogen for 6 h. After cooling to RT the mixture was treated with hydrochloric acid (6N, 200 ml) and heated to reflux for 30 min. The solvents were removed and dissolved in methanol, then added onto a strong cation exchange column (methanol then 1M ammonia in methanol) to yield a cream solid. The solid was taken up in 1M hydrochloric acid in methanol and after
10 removal of the solvent a yellow solid was obtained (3.8 g)

¹HNMR (400MHz, CD₃OD) δ : 7.62 (d, 2H), 7.44-7.46 (m, 4H), 6.83 (d, 2H), 4.15 (s, 2H) ppm.

Preparation 83 : (4-Hydroxy-2,5-dimethylphenyl)acetonitrile



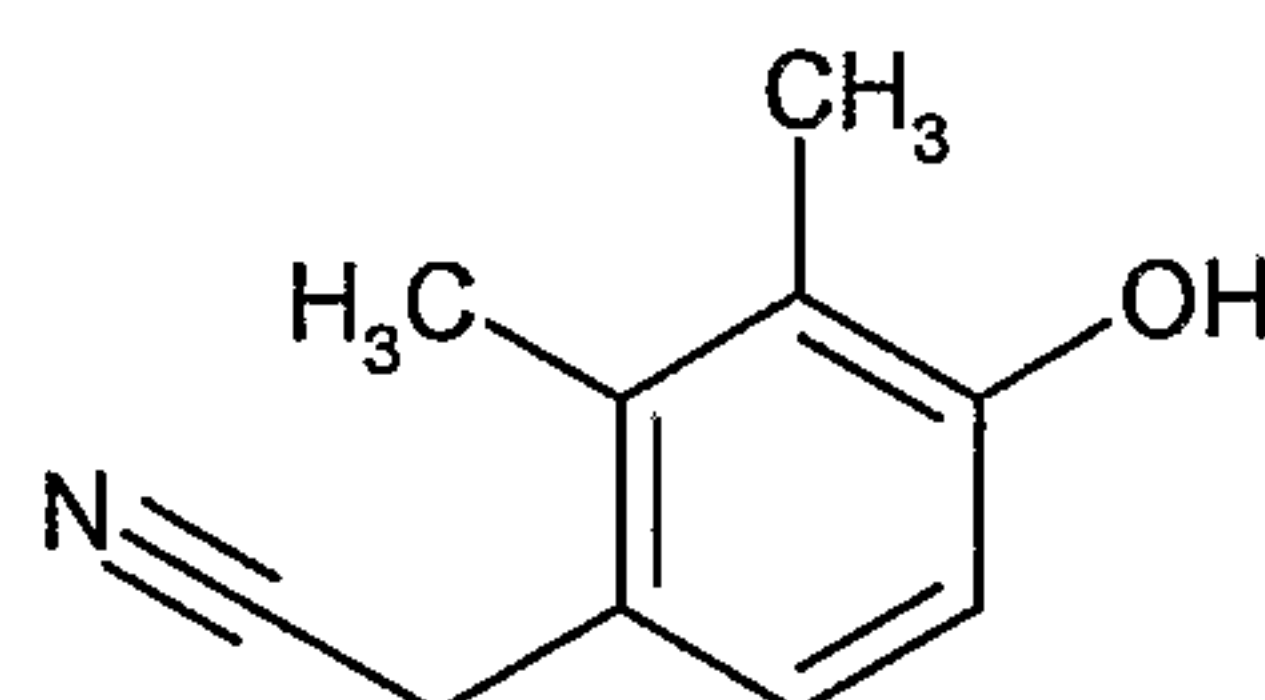
15 A solution of (4-methoxy-2,5-dimethylphenyl)acetonitrile (0.5g, 2.9mmol) in dichloromethane (10ml) was cooled to -80°C and treated with a solution of boron tribromide in dichloromethane (14.3ml of a 1M solution, 14.3mmol). The reaction mixture was stirred at -80°C for a further 30 minutes and then gradually allowed to warm to room temperature over a period of 2 hours. The reaction
20 mixture was quenched with saturated aqueous sodium bicarbonate (20ml) and the organic phase separated. The organic phase was washed with saturated aqueous sodium chloride (20ml), dried (sodium sulfate) and the solvent

removed *in vacuo* to give a pale brown solid. Purification by column chromatography on silica gel eluting with ethyl acetate:pentane (1:4 changing to 1:2) gave the title compound as a colourless solid (0.28g).

¹HNMR(400MHz, CD₃OD) δ : 2.13 (s, 3H), 2.23 (s, 3H), 3.66 (s, 2H), 6.60 (s, 1H), 6.98 (s, 1H) ppm.

MS (electrospray) m/z 160 [M-H]⁻

Preparation 84 : (4-Hydroxy-2,3-dimethylphenyl)acetonitrile

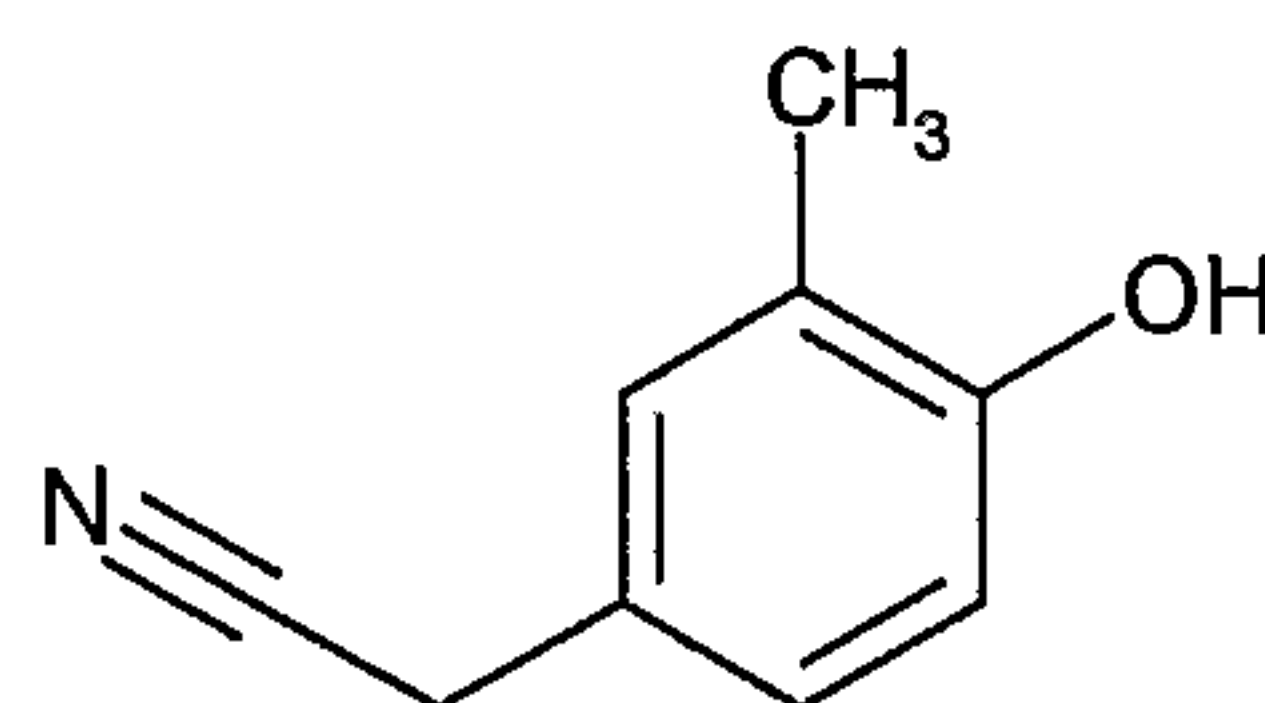


Prepared from (4-methoxy-2,3-dimethylphenyl)acetonitrile using the method from preparation 83 to give the title compound as a pale yellow solid.

¹HNMR(400MHz, CDCl₃) δ : 2.20 (s, 3H), 2.24 (s, 3H), 3.62 (s, 2H), 4.91 (bs, 1H), 6.64 (d, 1H), 7.03 (d, 1H) ppm.

MS (electrospray) m/z 160 [M-H]⁻

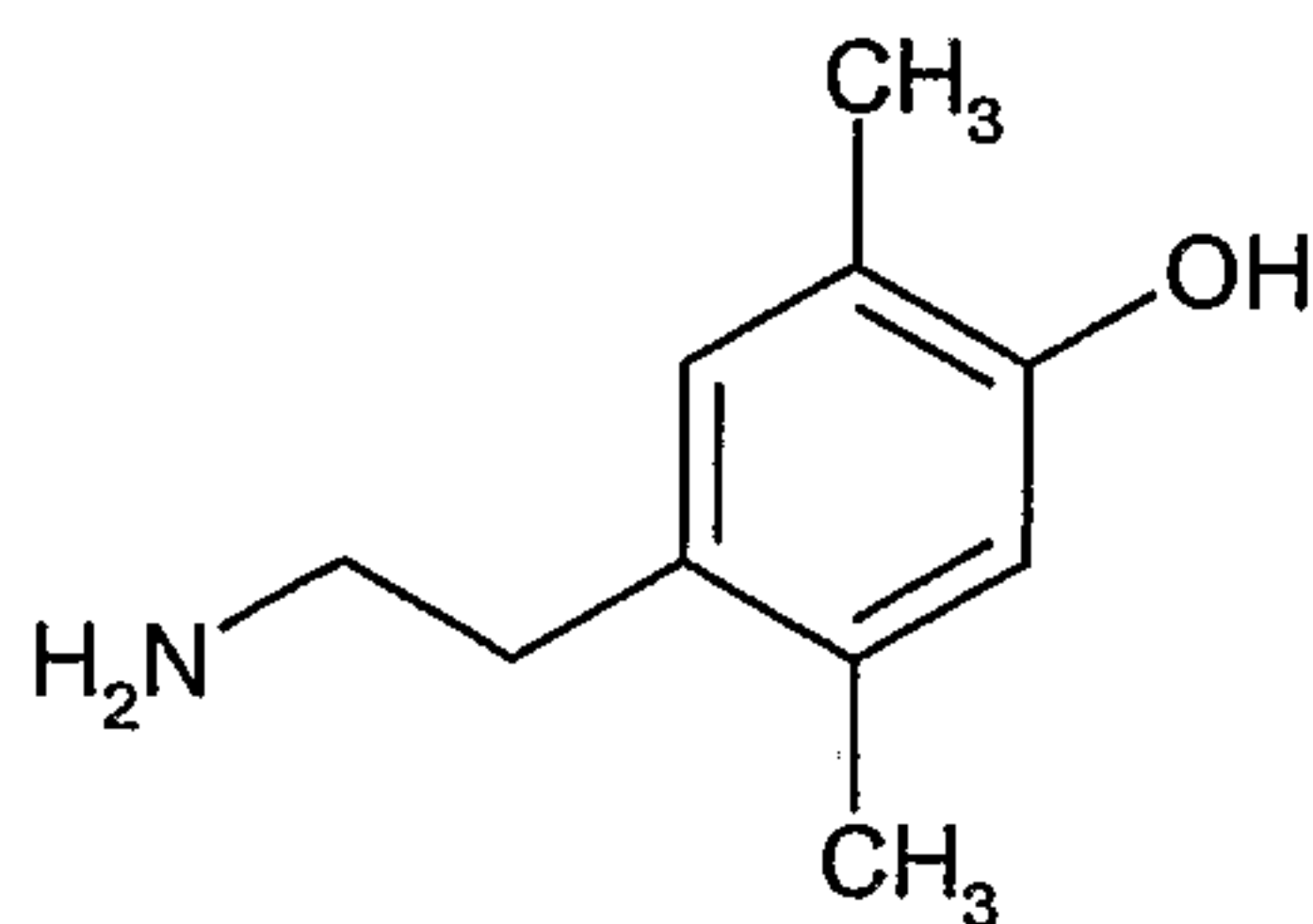
Preparation 85 : (4-Hydroxy-3-methylphenyl)acetonitrile



Prepared from (4-methoxy-3-methylphenyl)acetonitrile using the method from preparation 83 to give the title compound as a pale yellow solid.

¹HNMR(400MHz, CDCl₃) δ : 2.25 (s, 3H), 3.65 (s, 2H), 4.98 (bs, 1H), 6.76 (d, 1H), 7.01 (d, 1H), 7.07 (s, 1H) ppm.

MS (electrospray) m/z 146 [M-H]⁻

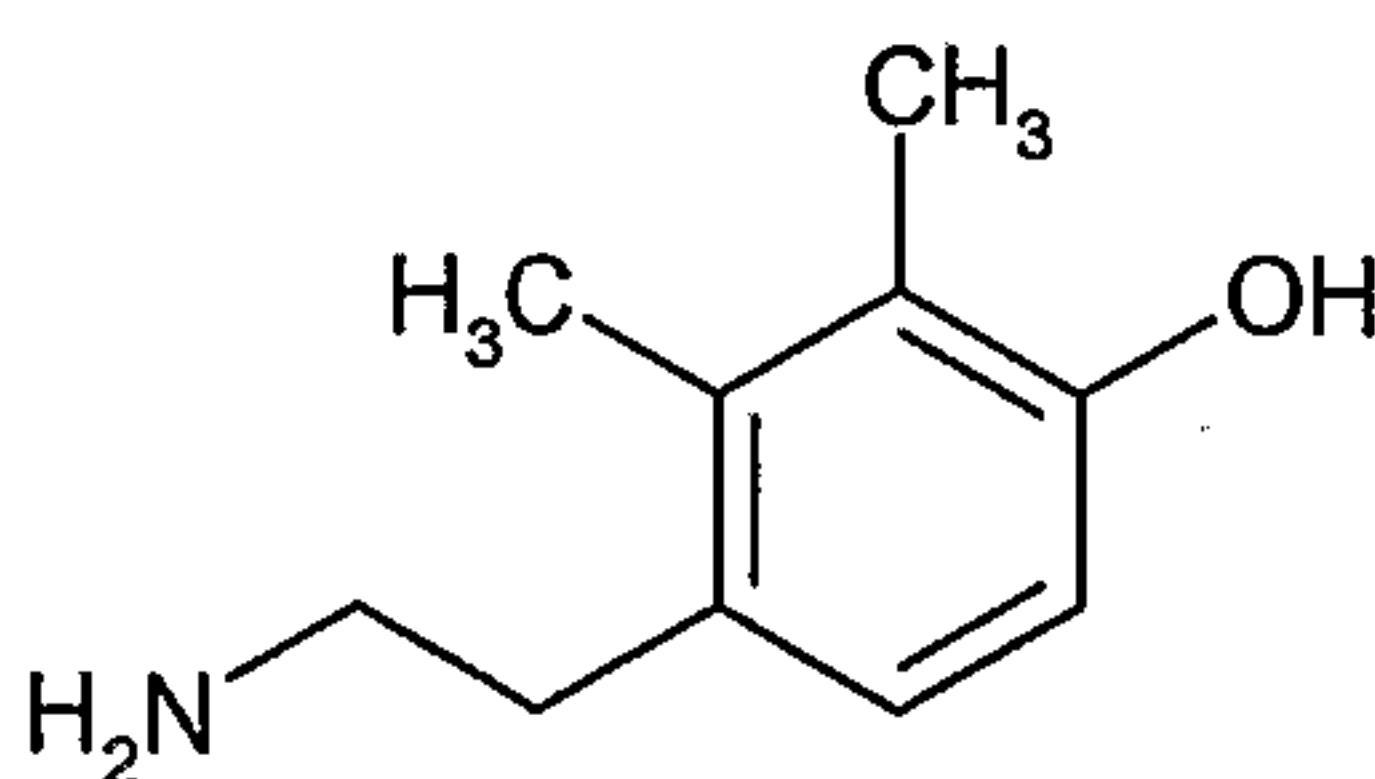
Preparation 86 : 4-(2-Aminoethyl)-2,5-dimethylphenol

A solution of the nitrile from preparation 83 (0.28g, 1.74mmol) in ethanol (15ml) was hydrogenated at 60psi over Raney Nickel (0.1g, 50% w/w) for 16 hours.

- 5 The reaction mixture was filtered and the solvent removed in vacuo. The residue was purified by strong cation exchange resin eluting non-basic impurities with methanol and then 1M ammonia in methanol to give the title compound as a colourless oil.

¹HNMR(400MHz, CD₃OD) δ : 2.11 (s, 3H), 2.19 (s, 3H), 2.63-2.67 (m, 2H),
10 2.72-2.76 (m, 2H), 6.54 (s, 1H), 6.81 (s, 1H) ppm.

MS (electrospray) m/z 166 [M+H]⁺

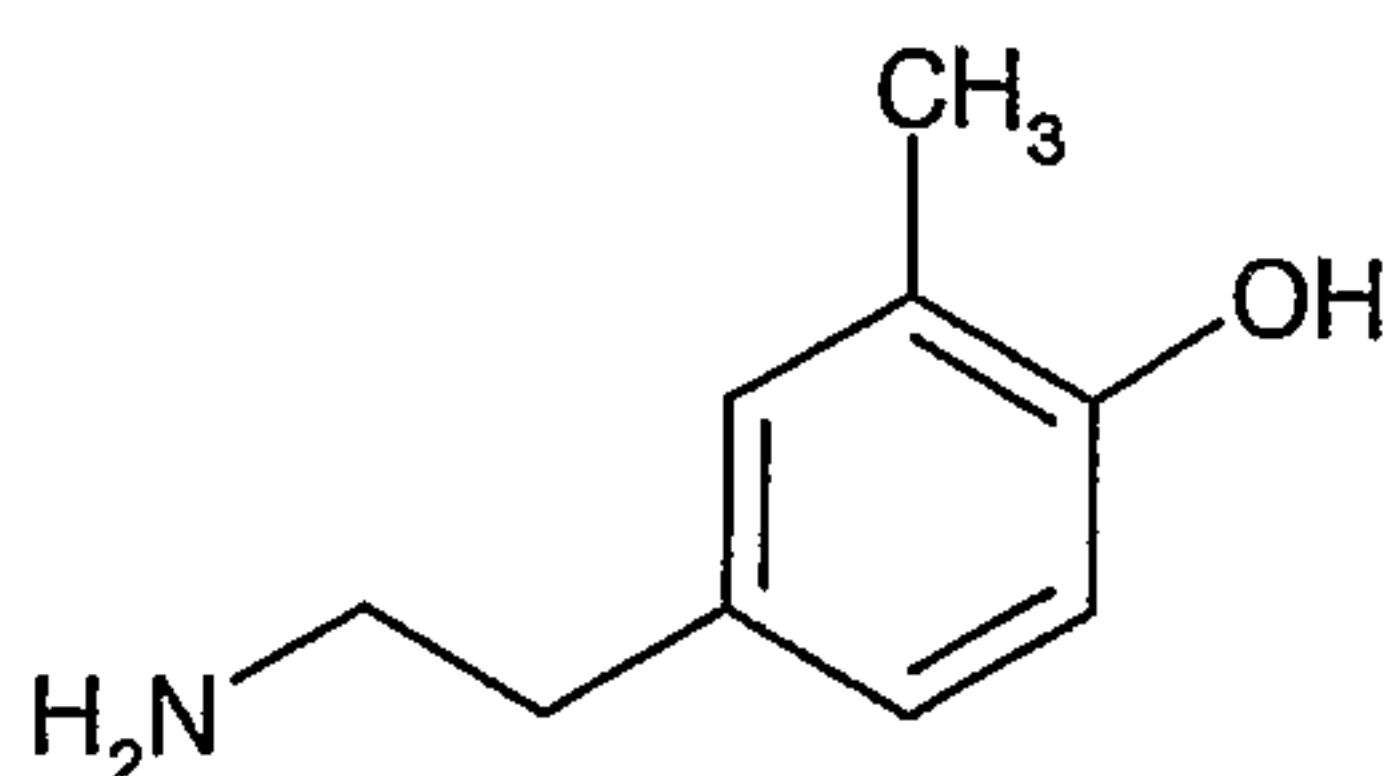
Preparation 87 : 4-(2-Aminoethyl)-2,3-dimethylphenol

- Prepared from the nitrile of preparation 84 using the method of preparation 86
15 to give the title compound as a colourless oil.

¹HNMR(400MHz, CD₃OD) δ : 2.12 (s, 3H), 2.19 (s, 3H), 2.68-2.75 (m, 4H), 6.55 (d, 1H), 6.78 (d, 1H) ppm.

MS (electrospray) m/z 166 [M+H]⁺

Preparation 88 : 4-(2-Aminoethyl)-2-methylphenol



Prepared from the nitrile of preparation 85 using the method of preparation 86 to give the title compound as a colourless oil.

¹HNMR(400MHz, CD₃OD) δ : 2.15 (s, 3H), 2.60-2.64 (m, 2H), 2.79-2.83 (m, 5 2H), 6.66 (d, 1H), 6.82 (d, 1H), 6.90 (s, 1H) ppm.

MS (electrospray) m/z 152 [M+H]⁺

In vitro activity of the compounds of formula (1)

The ability of the compounds of the formula (1) to act as potent β₂ agonists therefore mediating smooth muscle relaxation may be determined by 10 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 CO₂ asphyxiation and exsanguination from the femoral artery and the trachea is isolated. Four 15 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 suspended in 5 ml organ baths using cotton threads tied through the upper and 20 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% O₂/5% CO₂, before applying an initial tension of 1 g. The preparations are allowed to equilibrate for a further 30- 25 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 electrical field stimulation (EFS) using the following parameters : 10 s trains
5 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 perfused with the above-described Krebs Ringer buffer by means of a
10 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 reached for the wash-out period.

15 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 response. The isoprenaline is then washed out over a period of 40 minutes.
20 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 10^{-9} to 10^{-6} M. At the end of the isoprenaline curve the preparations are washed again for 40 minutes before commencing a
25 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 induced by isoprenaline in Curve 1. The EC_{50} value for beta-2 agonist
30 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 (EC_{50} beta-2 agonist)/(EC_{50} Isoprenaline).

Confirmation of beta-2 mediated functional activity

Beta-2 agonist activity of test compounds is confirmed using the protocol
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 0.01 and 10.0.

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 (EC_{50}) 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.

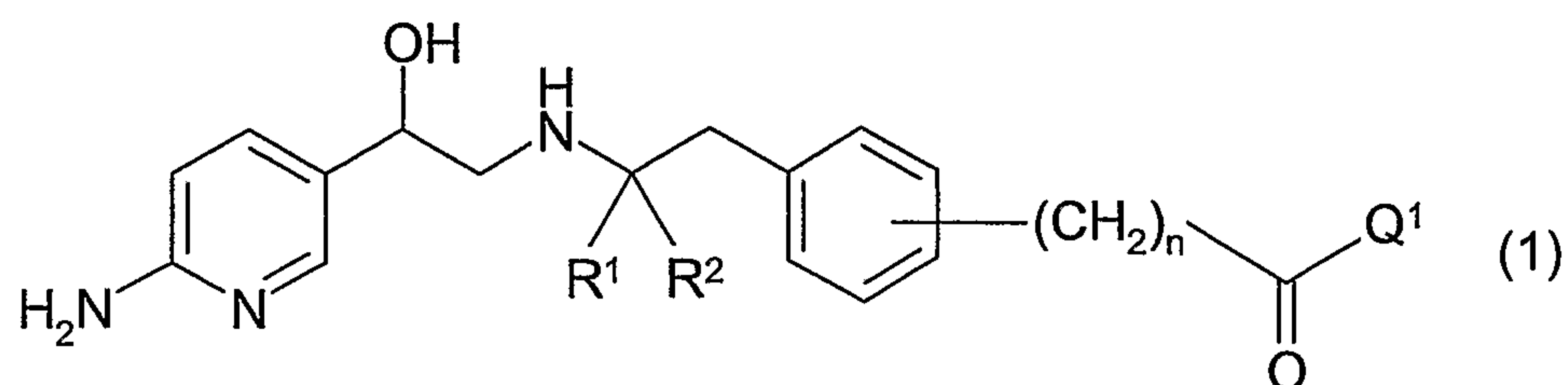
Assay Method

- 5 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
- 10 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),
- 15 normal counting efficiency for 1 minute. Dose-response data was expressed as % Isoprenaline activity and fitted using a four parameter sigmoid fit.

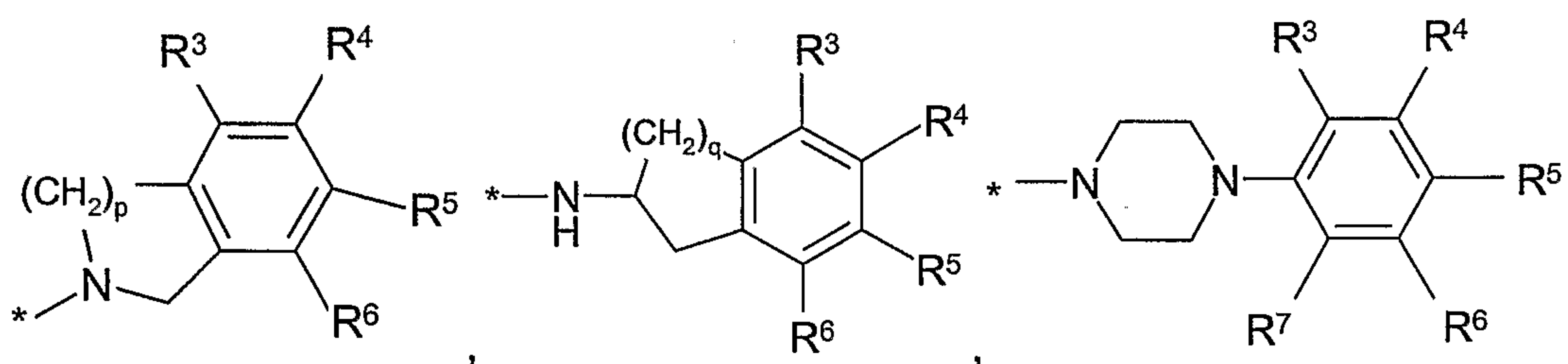
The compounds according to examples 1 to 27 show a β₂ cAMP EC₅₀ between 0.01 nM and 4 nM.

CLAIMS

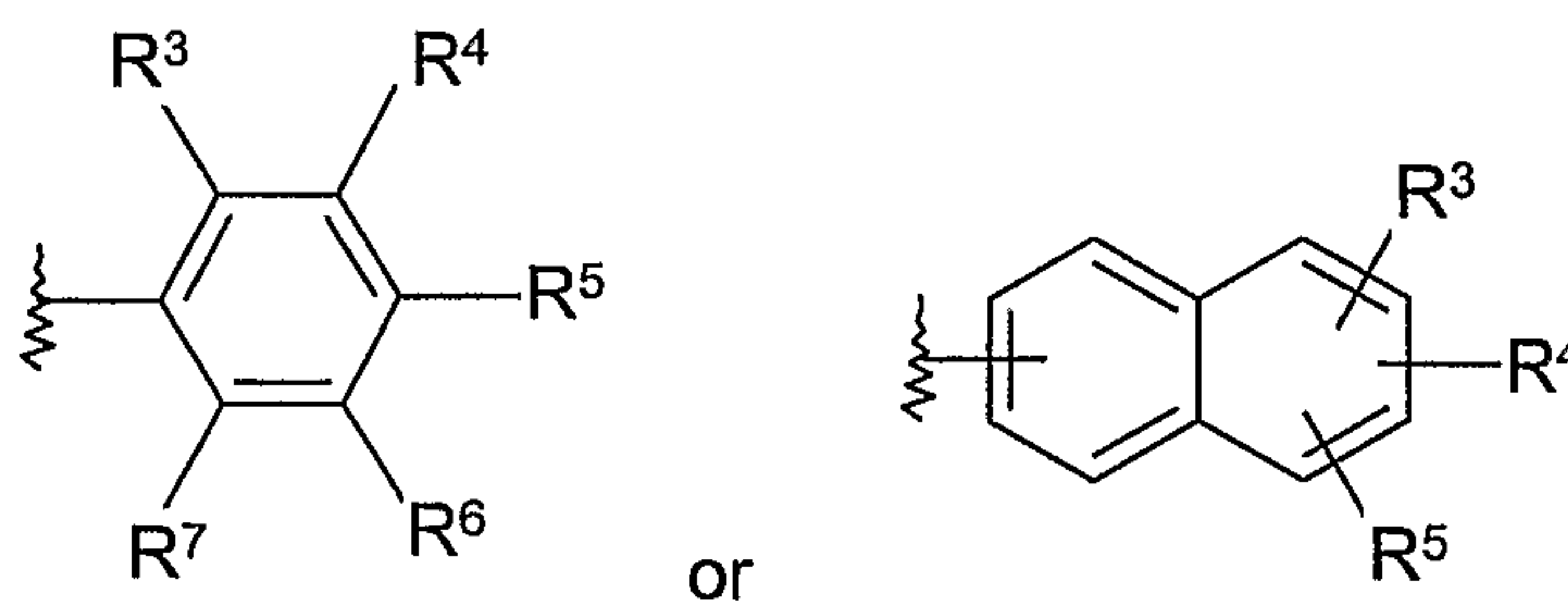
1. A compound of the formula:



wherein the $(\text{CH}_2)_n\text{-C(=O)Q}^1$ group is in the meta or para position, R^1 and R^2 are independently selected from H and $\text{C}_1\text{-C}_4$ alkyl, n is 0, 1 or 2 and Q^1 is a group selected from:



and a group $\text{*NR-Q}^2\text{-A}$, wherein p is 1, 2 or 3, q is 1 or 2, Q^2 is a direct bond or a $\text{C}_1\text{-C}_4$ alkylene optionally substituted by OH, R is H, $\text{C}_1\text{-C}_4$ alkyl or phenyl optionally substituted by OH, and A is $\text{C}_3\text{-C}_7$ cycloalkyl, said cycloalkyl being optionally bridged by one or more carbon atoms, tetrahydropyranyl, piperidiny, tetrahydrothiopyranyl, pyridyl or a group selected from :



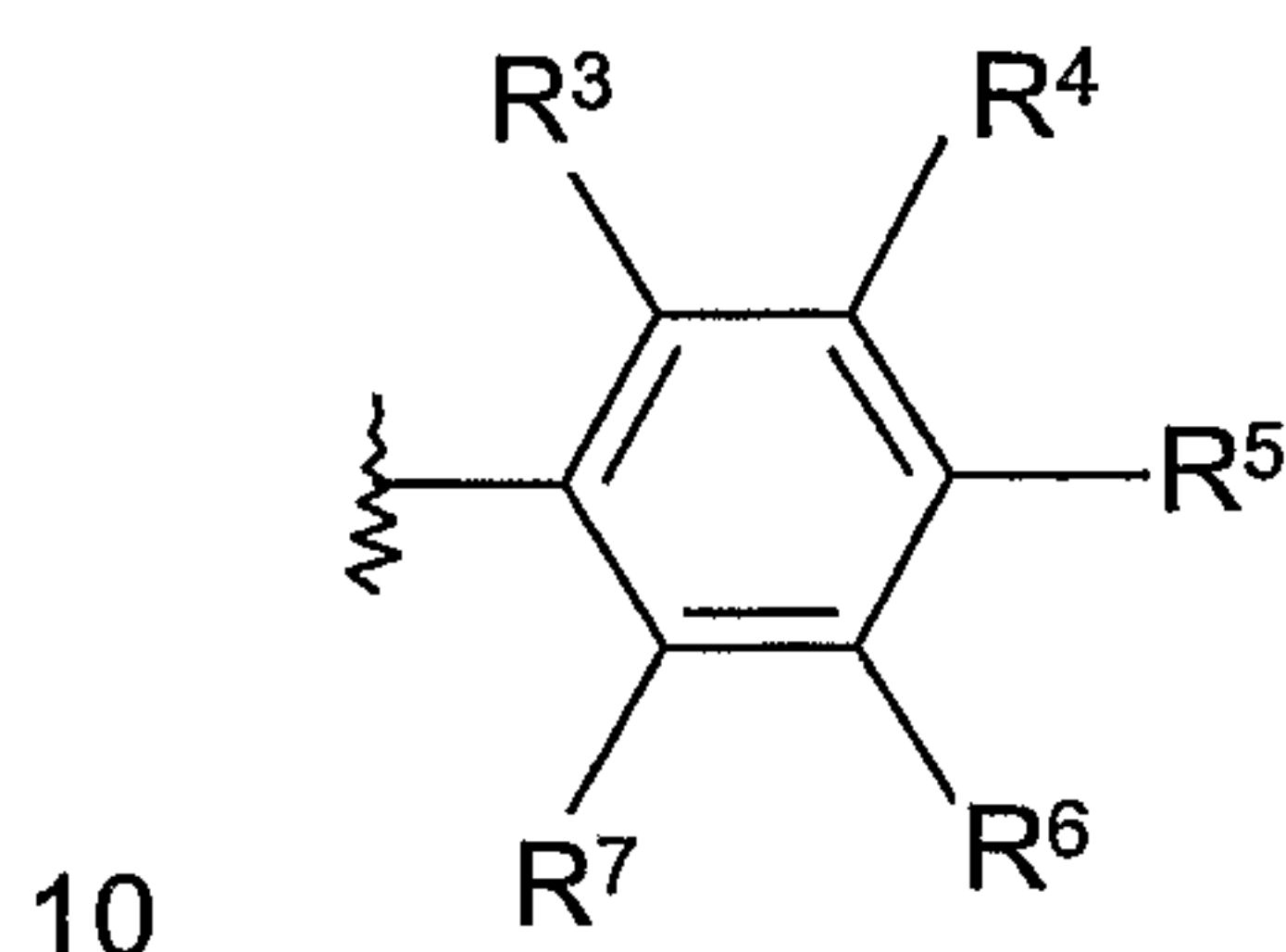
wherein R^3 , R^4 , R^5 , R^6 and R^7 are the same or different and are each independently selected from H, $\text{C}_1\text{-C}_4$ alkyl, OR^9 , SR^9 , halo, CF_3 , OCF_3 ,

$(\text{CH}_2)_m\text{COOR}^9$, $\text{SO}_2\text{NR}^8\text{R}^9$, CONR^8R^9 , NR^8R^9 , NHCOR^8 , $\text{SO}_2(\text{C}_1\text{-C}_4)\text{alkyl}$ and phenyl optionally substituted by hydroxy or hydroxy($\text{C}_1\text{-C}_4$)alkyl;

wherein m is an integer selected from 0, 1, and 2 and R^8 and R^9 are the same or different and are independently selected from H or $\text{C}_1\text{-C}_4$ alkyl and the *
5 represent the attachment point to the carbonyl group;

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

2. A compound according to claim 1 wherein n is 1 or 2 and Q^1 is $^*\text{-NH-Q}^2\text{-A}$ wherein Q^2 is a $\text{C}_1\text{-C}_4$ alkylene and A is a group



wherein R^3 , R^4 , R^5 , R^6 and R^7 are as defined in claim 1.

3. A compound according to claim 2 wherein R^3 , R^4 , R^5 , R^6 and R^7 are the same or different and are selected from H, $\text{C}_1\text{-C}_4$ alkyl, OR^9 , Cl, F, CF_3 , OCF_3 , COOR^9 , $\text{SO}_2\text{NR}^9\text{R}^{10}$, provided at least 2 of R^3 to R^7 are equal to H,
15 wherein R^8 and R^9 are the same or different and are selected from H or $\text{C}_1\text{-C}_4$ alkyl.

4. A compound according to claim 3 wherein R^3 , R^4 , R^5 , R^6 and R^7 are the same or different and are selected from H, CH_3 , OH, OCH_3 , OCH_2CH_3 , Cl, F, CF_3 , OCF_3 , COOH , SO_2NH_2 , provided at least 2 of R^3 to R^7 are equal to H.

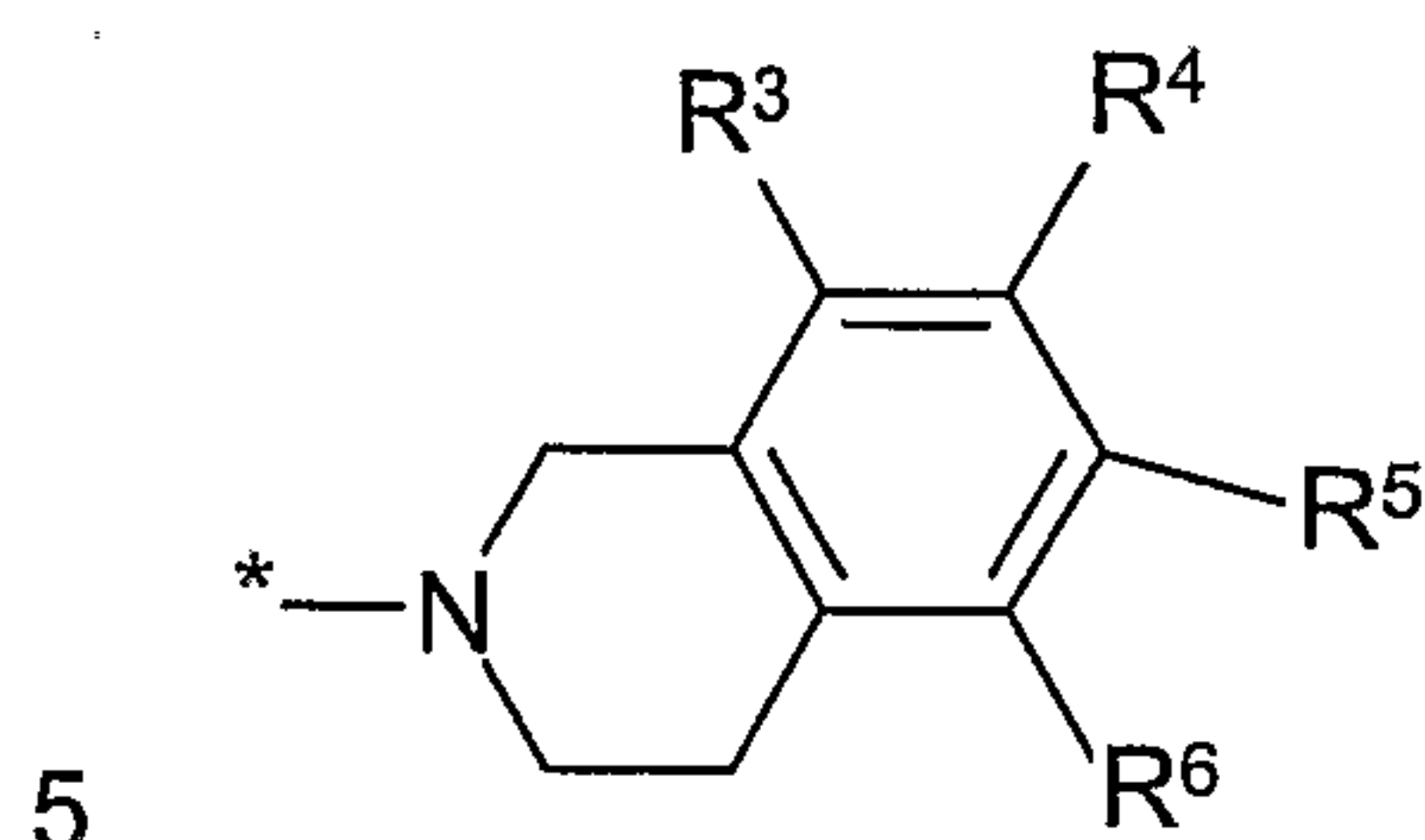
20 5. A compound according to claim 4 wherein R^1 , R^2 , R^3 , R^4 and R^5 are the same or different and are selected from H, CH_3 , OH, OCH_3 , OCH_2CH_3 , Cl, F, CF_3 , OCF_3 , COOH , SO_2NH_2 , provided at least 3 of R^3 to R^7 are equal to H.

6. A compound according to claim 1 wherein Q^1 is a group $^*\text{-NH-Q}^2\text{-A}$, wherein Q^2 is a $\text{C}_1\text{-C}_4$ alkylene and A is a pyridin-2-yl.

7. A compound according to any one of claims 1 to 6 wherein Q^2 is selected from $-\text{CH}_2-$, $-(\text{CH}_2)_2-$, $-(\text{CH}_2)_3-$ and $-\text{CH}(\text{CH}_3)-$.

8. A compound according to any one of claims 1 to 6 wherein Q^2 is $-\text{CH}_2-$.

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



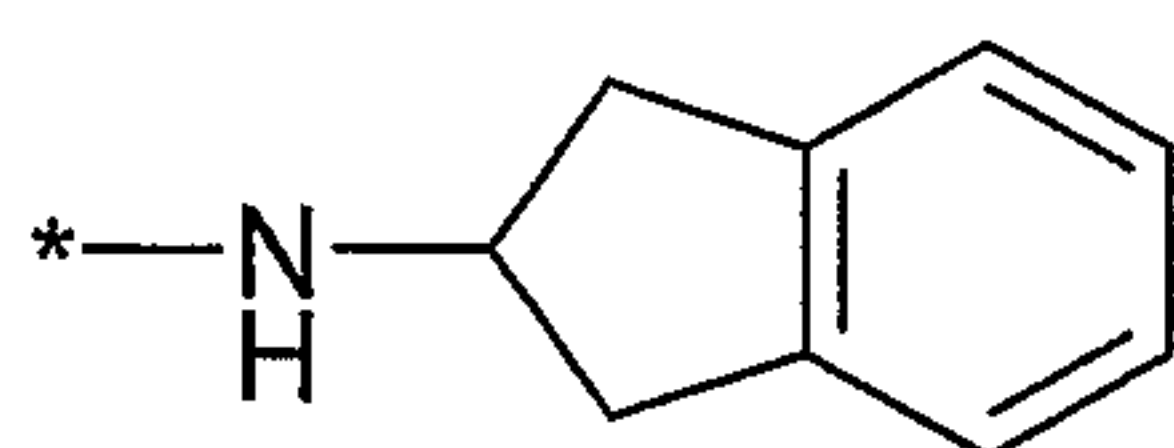
wherein R^3 , R^4 , R^5 and R^6 are the same or different and are selected from H, C_1 - C_4 alkyl, OR^9 , SR^9 , halo, CF_3 , OCF_3 , COOR^9 , $\text{SO}_2\text{NR}^8\text{R}^9$, CONR^8R^9 , NR^8R^9 , NHCOR^8 , provided at least 2 of R^3 to R^6 are equal to H;

10 wherein R^8 and R^9 are the same or different and are selected from H or C_1 - C_4 alkyl.

10. A compound according to claim 9 wherein R^3 , R^4 , R^5 and R^6 are the same or different and are selected from H and OR^9 , provided at least 2 of R^3 to R^6 are equal to H;

wherein R^9 is selected from H or C_1 - C_4 alkyl.

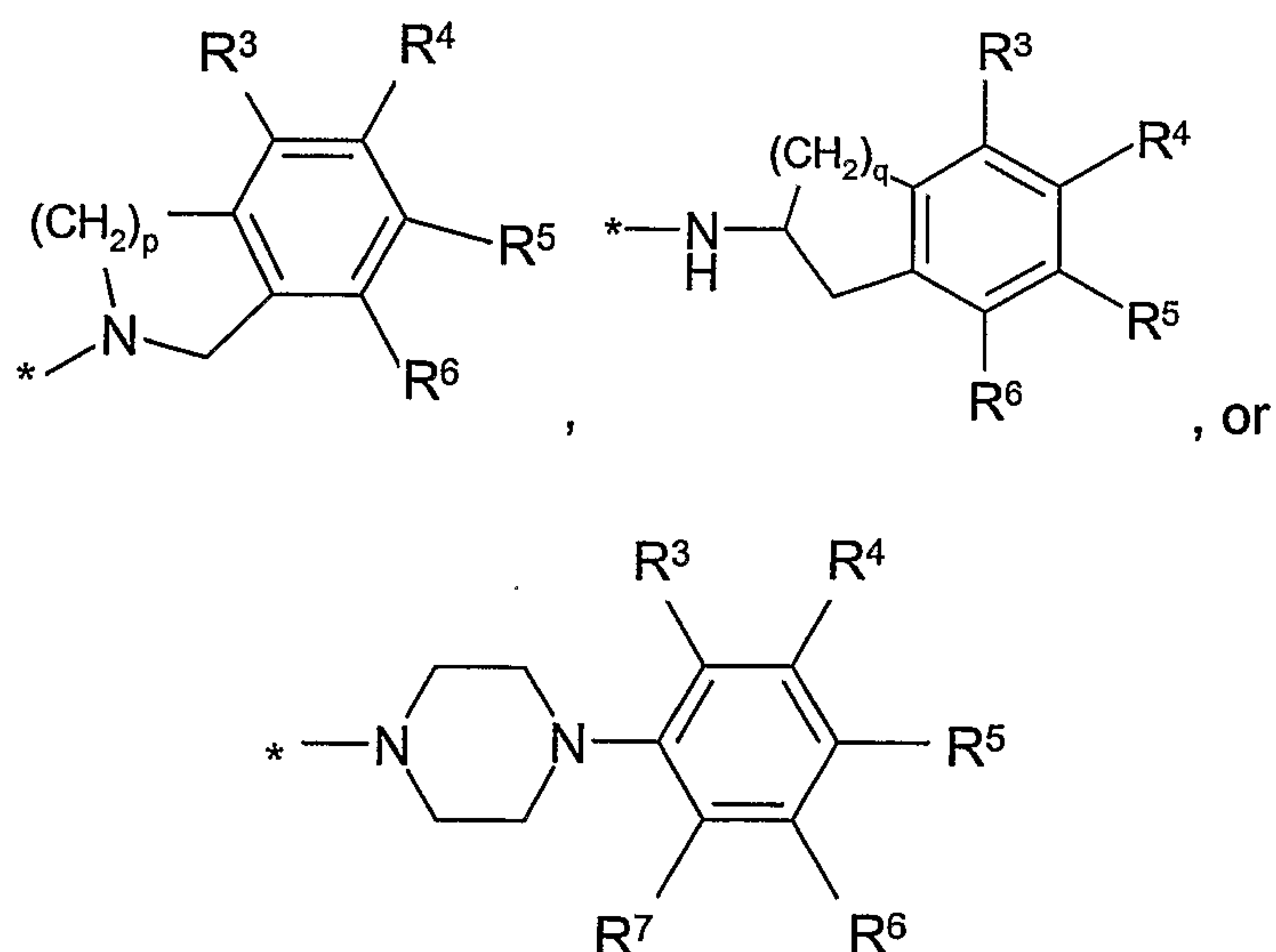
15 11. A compound according to claim 1 wherein Q^1 is



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

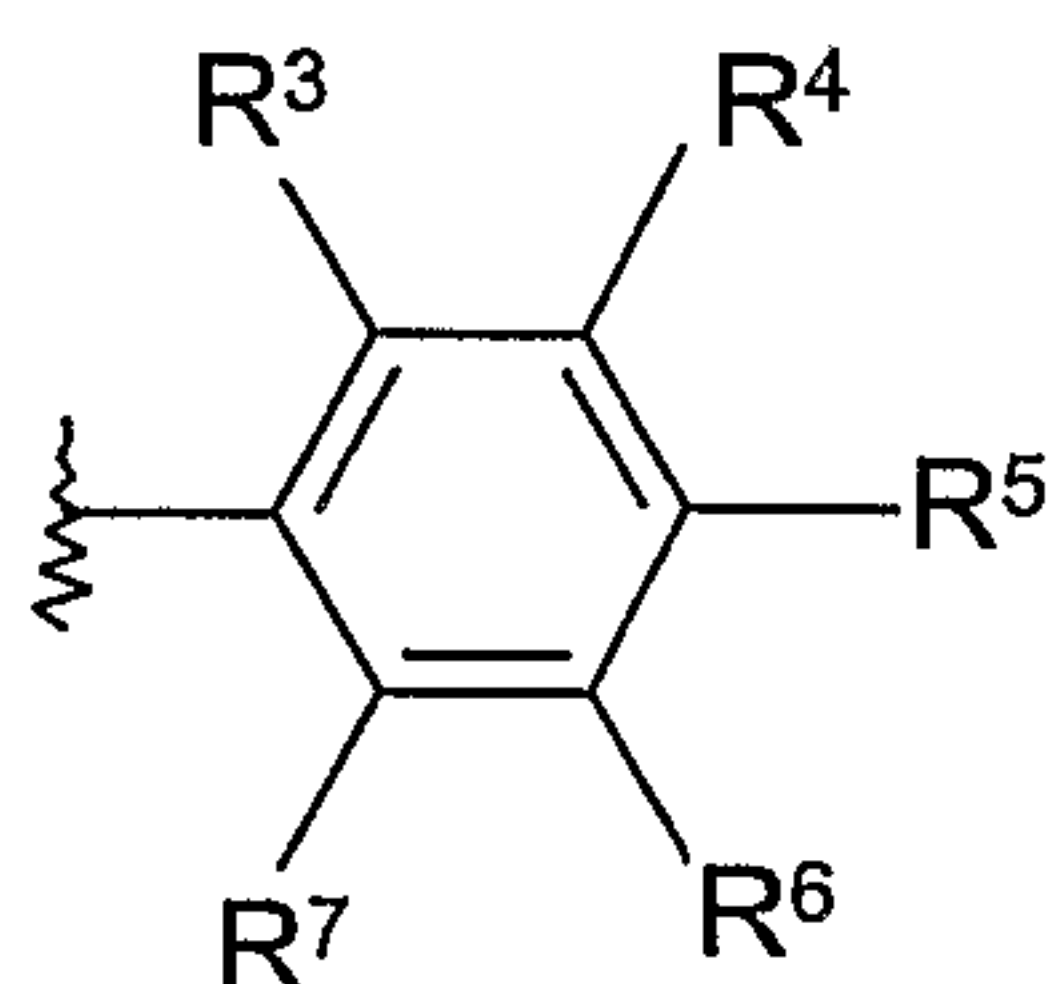
13. A compound according to any one of claims 1 to 12 wherein R^1 is H and R^2 is CH_3 or R^1 and R^2 are CH_3 .

20 14. A compound according to claim 1 wherein n is 0 or 1 and Q^1 is a group of formula:



wherein p is 2 or 3, q is 2 and R^3 , R^4 , R^5 , R^6 and R^7 are the same or different and are selected from H and OH, provided that at least one of R^3 , R^4 , R^5 , R^6 and R^7 is OH.

15. A compound according to claim 1 wherein n is 0 or 1, R^1 is H or C_1 - C_4 alkyl, R^2 is C_1 - C_4 alkyl, and Q^1 is a group $*-NR-Q^2-A$ wherein A is of formula:



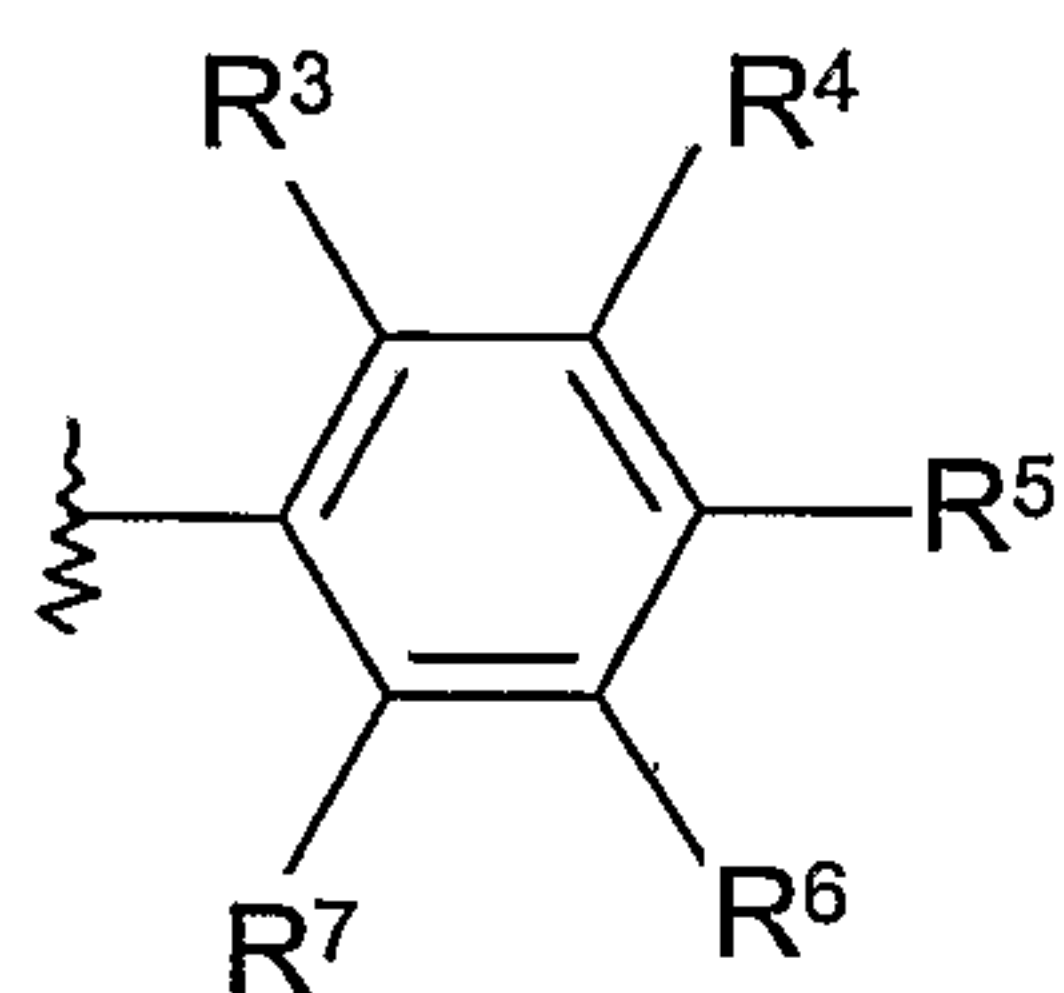
wherein R , R^3 , R^4 , R^5 , R^6 and R^7 are as defined in claim 1.

16. A compound according to claim 15 wherein R^1 is H and R^2 is CH_3 or R^1 and R^2 are both CH_3 .

17. A compound according to any one of claims 15 and 16 wherein R is selected from H, CH_3 , CH_2CH_3 and phenyl substituted by OH.

18. A compound according to any one of claims 15 to 17 wherein Q^2 is a direct bond or is selected from $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_4-$, $-CH_2-C(CH_3)_2-$, and $-CH_2-CH(OH)-$.

19. A compound according to any one of claims 15 to 18 wherein A is a group of formula :



wherein R³, R⁴, R⁵, R⁶ and R⁷ are the same or different and are selected from H, C₁-C₄ alkyl, OR⁹, Cl, F, CF₃, COOR⁹, SO₂(C₁-C₄)alkyl, and phenyl substituted by OH or hydroxy(C₁-C₄)alkyl, provided at least 2 of R³ to R⁷ are equal to H, and R⁸ and R⁹ are the same or different and are selected from H or C₁-C₄ alkyl.

20. A compound according to claim 19 wherein R³, R⁴, R⁵, R⁶ and R⁷ are the same or different and are selected from H, CH₃, C(CH₃)₃, OH, OCH₃, OCH₂CH₃, Cl, F, CF₃, COOCH₃, SO₂-CH₂CH₃, and phenyl substituted by OH or by -CH₂-OH, provided at least 2 of R³ to R⁷ are equal to H.

21. The (*R,R*)-stereoisomer of a compound according to any one of claims 1 to 20.

22. A compound according to any one of claims 1 to 21 wherein the (CH₂)_n-C(=O)Q¹ group is in the meta position.

23. A compound according to claim 1 selected from the group consisting of :

2-(3-((2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl)-phenyl)-*N*-benzyl-acetamide,

2-(3-((2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl)-phenyl)-*N*-(2-methoxy-benzyl)-acetamide,

2-(3-((2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl)-phenyl)-*N*-(2-ethoxy-benzyl)-acetamide,

2-(3-((2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl)-phenyl)-*N*-(3-phenyl-propyl)-acetamide,

- 2-(3-{{(2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-phenethyl-acetamide,
- 2-(3-{{(2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(3,4-dimethyl-benzyl)-acetamide,
- 5 2-(3-{{(2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-indan-2-yl-acetamide,
- 2-(3-{{(2*R*)-2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(3,4-dichloro-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-
- 10 (4-hydroxy-3-methoxy-benzyl)-acetamide,
- 2-(4-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(3-methoxy-benzyl)-acetamide,
- 2-(4-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(2,6-dimethoxy-benzyl)-acetamide,
- 15 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(4-sulfamoyl-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(2-ethoxy-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-
- 20 phenyl)-*N*-indan-2-yl-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-benzyl-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-phenethyl-acetamide,
- 25 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(3-phenyl-propyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(3,5-dichloro-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-
- 30 phenyl)-*N*-(3,4-dimethyl-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenyl)-*N*-(3,4-dichloro-benzyl)-acetamide,

- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(2-fluoro-5-trifluoromethyl-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(3-trifluoromethoxy-benzyl)-acetamide,
- 5 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(3-fluoro-4-trifluoromethyl-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(3,4,5-trimethoxy-benzyl)-acetamide,
- (3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-
- 10 (4-trifluoromethoxy-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(4-fluoro-2-trifluoromethyl-benzyl)-acetamide,
- 2-(3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-propyl}-phenyl)-*N*-(5-fluoro-2-trifluoromethyl-benzyl)-acetamide,
- 15 2-(3-{(2*R*)-2-[2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}phenyl)-*N*-(4'-hydroxybiphenyl-3-ylmethyl)acetamide
- 2-(3-{(2*R*)-2-[2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}phenyl)-*N*-(4'-hydroxybiphenyl-4-ylmethyl)acetamide
- 2-(3-{(2*R*)-2-[(2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]propyl}phenyl)-
- 20 *N*-(4'-hydroxy-biphenyl-3-ylmethyl)acetamide
- 2-(3-{(2*R*)-2-[(2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]propyl}phenyl)-*N*-(4-hydroxynaphthalen-1-ylmethyl)acetamide
- 3-{2-[(2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}-*N*-(4'-hydroxybiphenyl-3-ylmethyl)benzamide
- 25 3-{(2*R*)-2-[2-(6-Amino-pyridin-3-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-*N*-[2-(4-hydroxy-phenyl)-2-methyl-propyl]-benzamide
- 3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}-*N*-[2-(4-hydroxy-2,5-dimethylphenyl)ethyl]benzamide
- 3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}-*N*-[2-
- 30 (4-hydroxy-2,3-dimethylphenyl)ethyl]benzamide
- 3-{2-[(2*R*)-2-(6-Amino-pyridin-3-yl)-2-hydroxyethylamino]-2-methylpropyl}-*N*-[2-(4-hydroxy-2-methylphenyl)ethyl]benzamide

- 3-((2*R*)-2-((2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino)propyl)-*N*-[2-(4-hydroxy-2,5-dimethylphenyl)ethyl]benzamide
- 3-((2*R*)-2-((2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino)propyl)-*N*-[2-(4-hydroxy-2,3-dimethylphenyl)ethyl]benzamide
- 5 3-((2*R*)-2-((2*R*)-2-(6-Aminopyridin-3-yl)-2-hydroxyethylamino)propyl)-*N*-[2-(4-hydroxy-2-methylphenyl)ethyl]benzamide
- 2-[3-(2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl)-amino)-2-methylpropyl)phenyl]-*N*-(3-hydroxy-4-methoxy-phenyl)acetamide
- 2-[3-(2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl)-amino)-2-methylpropyl)phenyl]-*N*-(3-hydroxy-phenyl)acetamide
- 10 2-[3-(2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl)-amino)-2-methylpropyl)phenyl]-*N*-(2-chloro-4-hydroxy-phenyl)acetamide
- 2-[3-(2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl)-amino)-2-methylpropyl)phenyl]-*N*-(4-hydroxy-3-methoxy-benzyl)acetamide
- 15 2-[3-(2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl)-amino)-2-methylpropyl)phenyl]-*N*-[5-(ethylsulfonyl)-2-hydroxyphenyl]acetamide
- 2-[3-(2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl)-amino)-2-methylpropyl)phenyl]-*N*-(2-hydroxy-5-methyl-phenyl)acetamide
- 2-[3-(2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl)-amino)-2-methylpropyl)phenyl]-*N*-(5-chloro-2-hydroxy-benzyl)acetamide
- 20 2-[3-(2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl)-amino)-2-methylpropyl)phenyl]-*N*-(4-hydroxy-1,1'-biph-enyl-3-yl)acetamide
- 2-[3-(2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl)-amino)-2-methylpropyl)phenyl]-*N*-[2-hydroxy-2-(3-hydroxyphenyl)ethyl]-*N*-methyl-acetamide
- 25 2-[3-(2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl)-amino)-2-methylpropyl)phenyl]-*N*-ethyl-*N*-(3-hydroxy-phenyl)acetamide
- 2-[3-(2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl)-amino)-2-methylpropyl)phenyl]-*N*-[2-(3-ethoxy-4-hydroxyphenyl)ethyl]acetamide
- 2-[3-(2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl)-amino)-2-methylpropyl)phenyl]-*N*-{[4'-(hydroxymeth-yl)-1,1'-biphenyl-3-yl]methyl}acetamide
- 30 2-[3-(2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl)-amino)-2-methylpropyl)phenyl]-*N*-(2,4-dichloro-6-hydroxybenzyl)acetamide

- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[(3-fluoro-4'-hydroxy-1,1'-biphenyl-4-yl)methyl]acetamide
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[(4'-hydroxy-3-methyl-1,1'-biphenyl-4-yl)methyl]acetamide
- 5 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(2-chloro-5-hydroxy-benzyl)-*N*-ethylacetamide
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[(2'-hydroxy-1,1'-biphenyl-2-yl)methyl]acetamide
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[3-hydroxy-5-(trifluoro-methyl)benzyl]-*N*-methylacetamide
- 10 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(3-chloro-5-hydroxy-benzyl)-*N*-ethylacetamide
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(3-chloro-5-hydroxy-benzyl)acetamide
- 15 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(4-hydroxy-3,5-dimethylbenzyl)acetamide
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[2-(2-hydroxyphen-yl)ethyl]acetamide
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-benzyl-*N*-(4-hydroxyphenyl)acetamide
- 20 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[2-(4-hydroxyphenyl)-ethyl]acetamide
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(4-hydroxybenzyl)acetamide
- 25 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(2-hydroxybenzyl)acetamide
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-(3-hydroxybenzyl)acetamide
- 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[2-(3-hydroxyphenyl)-ethyl]acetamide
- 30 2-[3-(2-[[*(2R)*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)phenyl]-*N*-[2-(4-hydroxy-3-meth-oxyphenyl)ethyl]acetamide

- methyl 4-({[3-(2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)phenyl]acetyl}amino)-3-hydroxybenzoate
- 2-[3-(2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)phenyl]-*N*-(5-tert-butyl-2-hydroxy-phenyl)acetamide
- 5 2-[3-(2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)phenyl]-*N*-(3-hydroxy-4-methyl-phenyl)acetamide
- 2-[3-((2*R*)-2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]amino}propyl)phenyl]-*N*-[2-(4-hydroxyphenyl)ethyl]acetamide
- 2-[3-((2*R*)-2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-
- 10 ethyl]amino}propyl)phenyl]-*N*-(4-hydroxybenzyl)acetamide
- 2-[3-((2*R*)-2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-
- ethyl]amino}propyl)phenyl]-*N*-(2-hydroxybenzyl)acetamide
- 2-[3-((2*R*)-2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-
- ethyl]amino}propyl)phenyl]-*N*-(3-hydroxybenzyl)acetamide
- 15 2-[3-((2*R*)-2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-
- ethyl]amino}propyl)phenyl]-*N*-[2-(3-hydroxyphenyl)ethyl]acetamide
- 2-[3-((2*R*)-2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-
- ethyl]amino}propyl)phenyl]-*N*-[2-(4-hydroxy-3-methoxyphenyl)ethyl]acetamide
- 2-[3-((2*R*)-2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-
- 20 ethyl]amino}propyl)phenyl]-*N*-(5-tert-butyl-2-hydroxy-phenyl)acetamide
- 2-[3-((2*R*)-2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-
- ethyl]amino}propyl)phenyl]-*N*-(3-hydroxy-4-methyl-phenyl)acetamide
- 2-[3-((2*R*)-2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-
- ethyl]amino}propyl)phenyl]-*N*-(3-hydroxy-4-methoxy-phenyl)acetamide
- 25 2-[3-((2*R*)-2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-
- ethyl]amino}propyl)phenyl]-*N*-(4-hydroxy-3-methoxy-benzyl)acetamide
- 2-[3-((2*R*)-2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-
- ethyl]amino}propyl)phenyl]-*N*-[5-(ethylsulfonyl)-2-hydroxyphenyl]acetamide
- 2-[3-((2*R*)-2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-
- 30 ethyl]amino}propyl)phenyl]-*N*-(2-hydroxy-5-methyl-phenyl)acetamide
- 2-[3-((2*R*)-2-{{(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-
- ethyl]amino}propyl)phenyl]-*N*-(3-hydroxy-2-methyl-phenyl)acetamide

- 2-[3-((2*R*)-2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl)amino)propyl)phenyl]-*N*-(5-chloro-2-hydroxybenzyl)-acetamide
- 2-[3-((2*R*)-2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl)amino)propyl)phenyl]-*N*-[2-hydroxy-2-(3-hydroxyphenyl)ethyl]-*N*-methyl-
5 acetamide
- 2-[3-((2*R*)-2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl)amino)propyl)phenyl]-*N*-[2-(3-ethoxy-4-hydroxy-phenyl)ethyl]acetamide
- 2-[3-((2*R*)-2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl)amino)propyl)phenyl]-*N*-[2-(3-hydroxy-4-methoxy-phenyl)ethyl]acetamide
- 10 2-[3-((2*R*)-2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl)amino)propyl)phenyl]-*N*-ethyl-*N*-[2-(4-hydroxyphenyl)ethyl]acetamide
- 2-[3-((2*R*)-2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl)amino)propyl)phenyl]-*N*-(2-chloro-4-hydroxybenzyl)-*N*-ethylacetamide
- 2-[3-((2*R*)-2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl)amino)propyl)phenyl]-*N*-(5-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide
15
- 2-[3-((2*R*)-2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl)amino)propyl)phenyl]-*N*-(4-hydroxyphenyl)acetamide
- 2-[3-((2*R*)-2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl)amino)propyl)phenyl]-*N*-[4-(4-hydroxyphenyl)butyl]acetamide
20
- 2-[3-((2*R*)-2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl)amino)propyl)phenyl]-*N*-[(4'-hydroxy-1,1'-biphenyl-4-yl)methyl]acetamide
- 2-[3-((2*R*)-2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl)amino)propyl)phenyl]-*N*-{[4'-(hydroxymethyl)-1,1'-biphenyl-3-yl]methyl}acetamide
25
- 2-[3-((2*R*)-2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl)amino)propyl)phenyl]-*N*-(2,4-dichloro-6-hydroxy-benzyl)acetamide
- 2-[3-((2*R*)-2-((2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl)amino)propyl)phenyl]-*N*-[(3-fluoro-4'-hydroxy-1,1'-biphenyl-4-yl)methyl]acetamide
30

- 2-[3-((2*R*)-2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[(4'-hydroxy-3-methyl-1,1'-biphenyl-4-yl)methyl]acetamide
- 2-[3-((2*R*)-2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(2-chloro-5-hydroxybenzyl)-*N*-ethylacetamide
- 5 2-[3-((2*R*)-2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[(2'-hydroxy-1,1'-biphenyl-2-yl)methyl]acetamide
- 2-[3-((2*R*)-2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-[3-hydroxy-5-(trifluoro-methyl)benzyl]-*N*-methylacetamide
- 10 2-[3-((2*R*)-2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(3-chloro-5-hydroxybenzyl)-*N*-ethylacetamide
- 2-[3-((2*R*)-2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(3-chloro-5-hydroxy-benzyl)acetamide
- 15 2-[3-((2*R*)-2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(4-hydroxy-3,5-dimeth-ylbenzyl)acetamide
- 2-[3-((2*R*)-2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxy-ethyl]amino}propyl)phenyl]-*N*-(3,5-dichloro-2-hydroxy-benzyl)acetamide
- 3-(2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)-*N*-[2-(4-hydroxyphenyl)ethyl]benzamide
- 20 3-(2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)-*N*-(4-hydroxybenzyl)benzamide
- 3-(2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)-*N*-(2-hydroxybenzyl)benzamide
- 25 3-(2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)-*N*-[2-(3-hydroxyphenyl)ethyl]benzamide
- 3-(2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)-*N*-[2-(4-hydroxy-3-meth-oxyphenyl)ethyl]benzamide
- 3-(2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)-*N*-(3-hydroxy-4-methyl-phenyl)benzamide
- 30 3-(2-[[2*R*]-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino)-2-methyl-propyl)-*N*-[2-(4-hydroxy-3,5-dimethoxyphenyl)ethyl]benzamide

- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-(3-hydroxy-4-methoxyphenyl)benzamide
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-(3-hydroxyphenyl)benzamide
- 5 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-(4-hydroxy-3-methoxybenzyl)benzamide
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-[5-(ethylsulfonyl)-2-hydroxyphenyl]benzamide
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-
- 10 (3-hydroxy-2-methyl-phenyl)benzamide
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-(5-chloro-2-hydroxy-benzyl)benzamide
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-(4-hydroxy-1,1'-biphenyl-3-yl)benzamide
- 15 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-[2-hydroxy-2-(3-hydroxyphenyl)ethyl]-*N*-methylbenzamide
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-(2-hydroxybenzyl)-*N*-methylbenzamide
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-
- 20 (3,5-dichloro-2-hydroxybenzyl)benzamide
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-[2-(2-hydroxyphenyl)ethyl]benzamide
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-[2-(3-ethoxy-4-hydroxyphenyl)ethyl]benzamide
- 25 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-[2-(3-hydroxy-4-methoxyphenyl)ethyl]benzamide
- 2-[3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-benzoyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepin-8-ol
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-
- 30 [(4'-hydroxy-3-methyl-1,1'-biphenyl-4-yl)methyl]-benzamide
- 3-(2-{[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}-2-methyl-propyl)-*N*-[(3'-hydroxy-1,1'-biphenyl-2-yl)-methyl]benzamide

- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(5-chloro-2-hydroxy-benzyl)benzamide
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[2-hydroxy-2-(3-hydroxyphenyl)ethyl]-*N*-methylbenzamide
- 5 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(2-hydroxybenzyl)-*N*-methylbenzamide
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[2-(3-ethoxy-4-hydroxyphenyl)ethyl]benzamide
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[2-(3-10 hydroxy-4-methoxyphenyl)ethyl]benzamide
- 2-[3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)benzoyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepin-8-ol
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-ethyl-*N*-[2-(4-hydroxyphenyl)ethyl]benzamide
- 15 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(2-chloro-4-hydroxy-benzyl)-*N*-ethylbenzamide
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(5-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide
- 2-{4-[3-((2*R*)-2-[[(2*R*)-2-(6-amino-pyridin-3-yl)-2-20 hydroxyethyl]amino}propyl)benzoyl]piperazin-1-yl}phenol
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(4-hydroxyphenyl)benzamide
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[4-(4-hydroxyphen-yl)butyl]benzamide
- 25 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[(4'-hydroxy-1,1'-biphenyl-4-yl)methyl]benzamide
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[{4'-(hydroxymethyl)-1,1'-biphenyl-3-yl)methyl}benzamide
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(2,4-30 dichloro-6-hydroxybenzyl)benzamide
- 3-((2*R*)-2-[[(2*R*)-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[(3-fluoro-4'-hydroxy-1,1'-biphenyl-4-yl)methyl]benzamide

- 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[(4'-hydroxy-3-methyl-1,1'-biphenyl-4-yl)methyl]benzamide
- 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(2-chloro-5-hydroxy-benzyl)-*N*-ethylbenzamide
- 5 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[(2'-hydroxy-1,1'-biphenyl-2-yl)methyl]benzamide
- 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[(4'-hydroxy-1,1'-biphenyl-2-yl)methyl]benzamide
- 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[3-10 hydroxy-5-(trifluoro-methyl)benzyl]-*N*-methylbenzamide
- 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3-chloro-5-hydroxy-benzyl)-*N*-ethylbenzamide
- 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3-chloro-5-hydroxy-benzyl)benzamide
- 15 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[(4'-hydroxy-1,1'-biphenyl-3-yl)methyl]benzamide
- 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(4-hydroxy-3,5-dimethylbenzyl)benzamide
- 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3,5-20 dichloro-2-hydroxybenzyl)benzamide
- 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[2-(2-hydroxyphenyl)-ethyl]benzamide
- 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3-hydroxy-4-methoxy-phenyl)benzamide
- 25 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3-hydroxyphenyl)benzamide
- 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(4-hydroxy-3-methoxy-benzyl)benzamide
- 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[5-30 (ethylsulfonyl)-2-hydroxyphenyl]benzamide
- 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(2-hydroxy-5-methyl-phenyl)benzamide

3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3-hydroxy-2-methyl-phenyl)benzamide

3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[2-(4-hydroxyphen-yl)ethyl]benzamide

5 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(4-hydroxybenzyl)benzamide

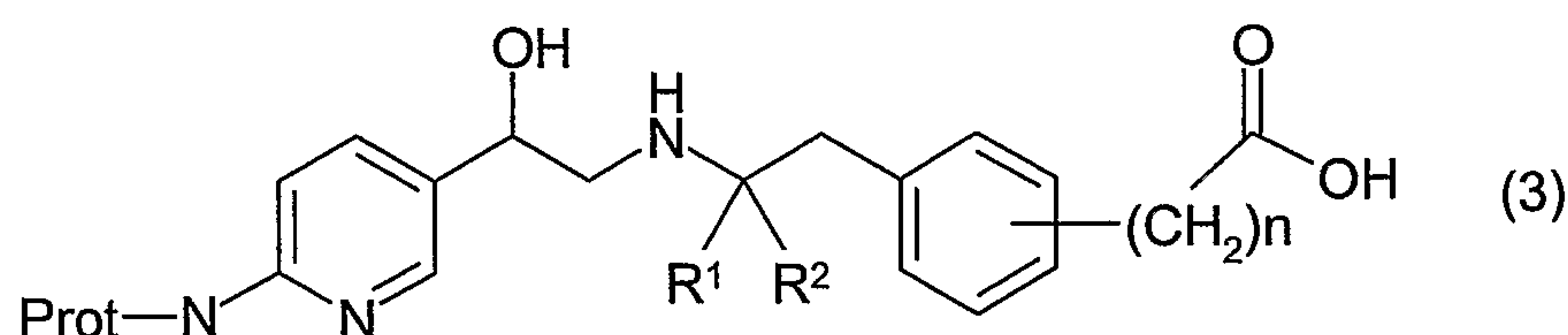
3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(2-hydroxybenzyl)benzamide

10 3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-(3-hydroxybenzyl)benzamide and

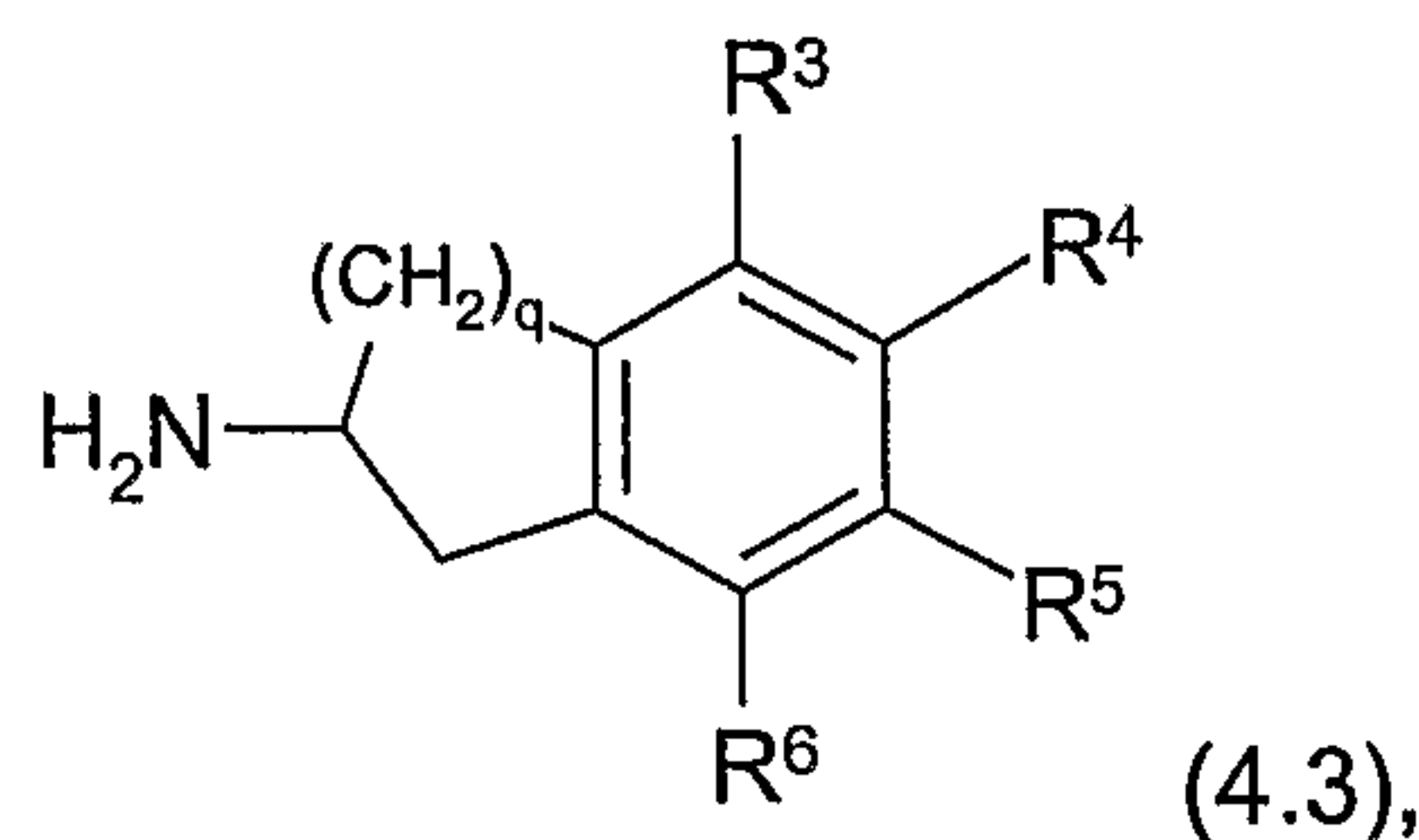
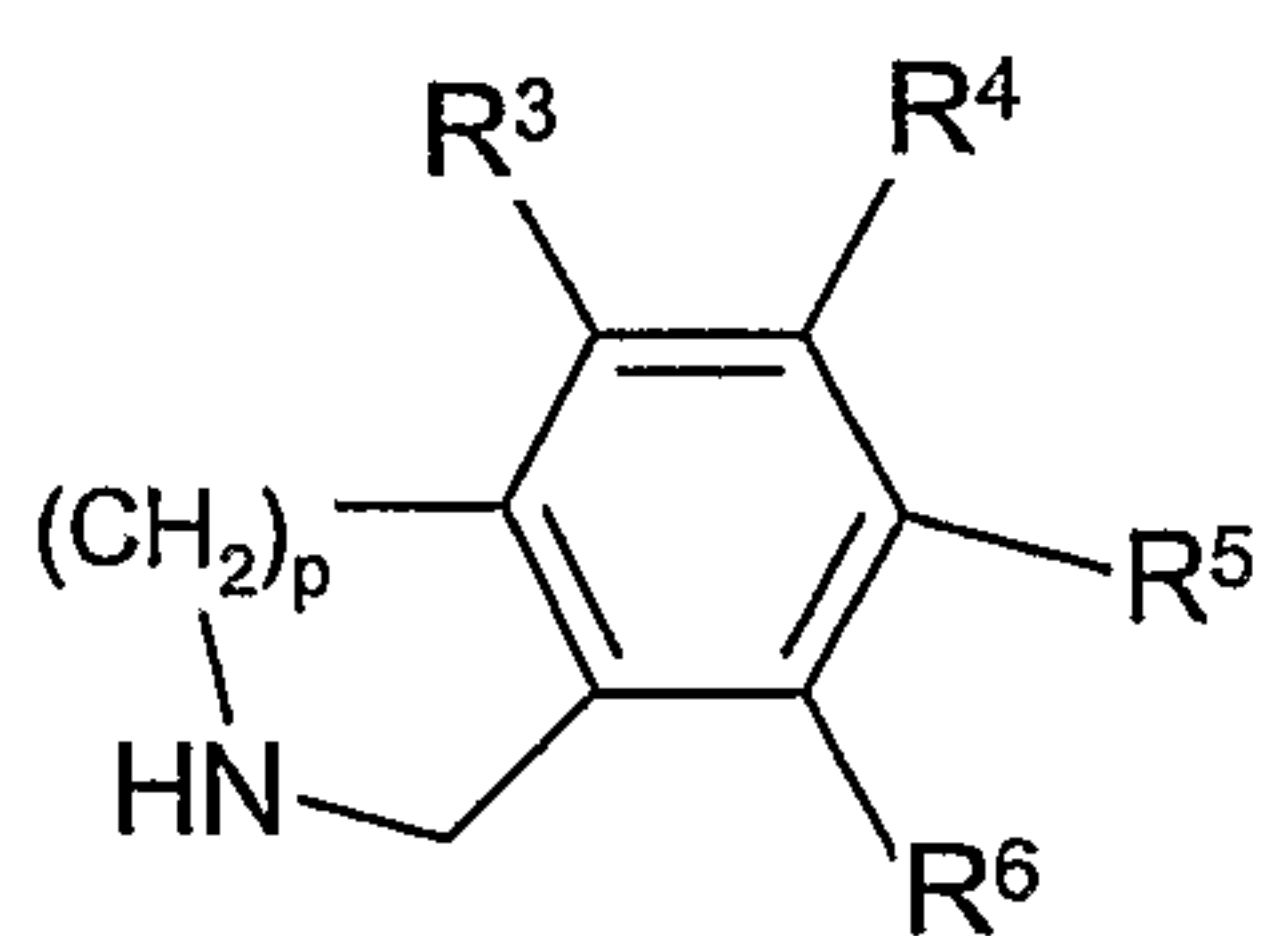
3-((2*R*)-2-[[*(2R)*-2-(6-aminopyridin-3-yl)-2-hydroxyethyl]-amino}propyl)-*N*-[2-(3-hydroxyphen-yl)ethyl]benzamide.

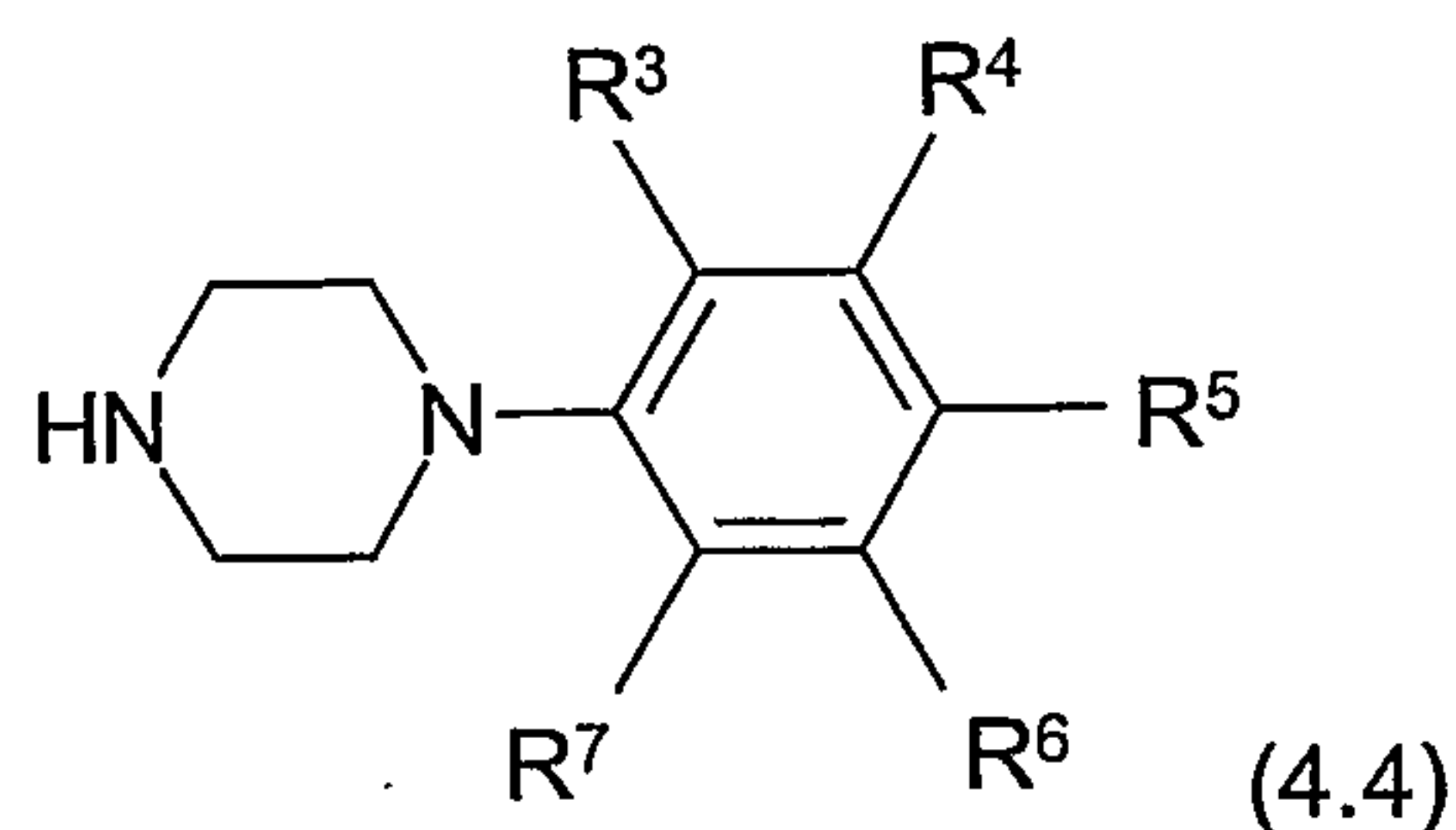
24. A process for the preparation of a compound of the formula (1) as described in any one of claims 1 to 23 or a pharmaceutically acceptable salt or
15 derived form thereof characterized in that it comprises the following step of

(a) coupling an acid of formula (3) :



wherein Prot is a protecting group and R^1 , R^2 and n are as defined in claim 1, with an amine of formula $NRH-Q^2-A$ (4.1),

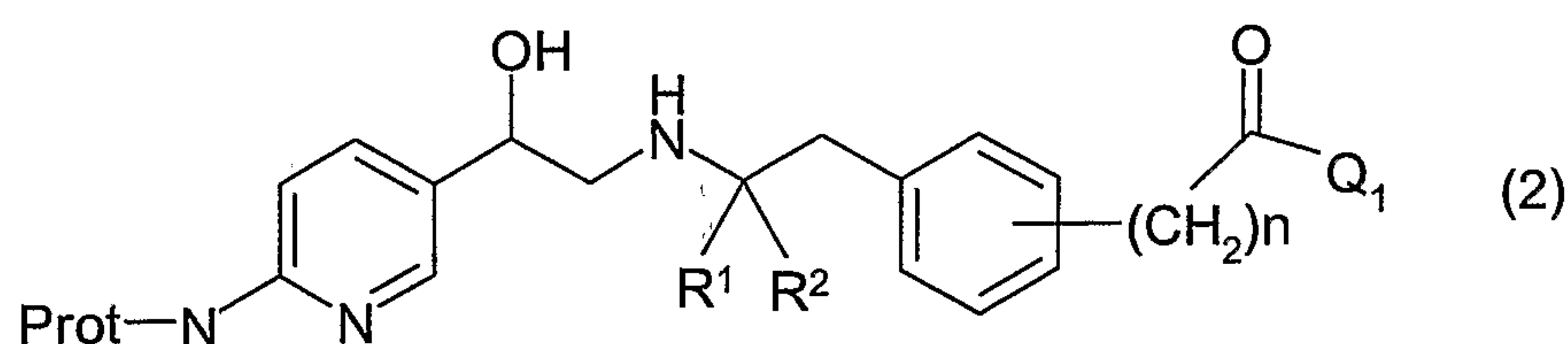




, or

wherein p, q, R³, R⁴, R⁵, R⁶ and R⁷ are as defined in claim 1, and

(b) removing the protecting group "Prot" from the compound of formula (2),



5 to obtain the 2-amino-pyridine derivative of formula (1),

(3) isolating said compound of formula (1).

25. A pharmaceutical composition including a compound of the formula (1) as described in any one of claims 1 to 23 or a pharmaceutically acceptable salt or derived form thereof, together with customary pharmaceutically innocuous
10 excipients and/or additives.

26. A compound of the formula (1) as described in any one of claims 1 to 23 or a pharmaceutically acceptable salt, derived form or composition thereof, for use as a medicament.

27. A compound of the formula (1) as described in any one of claims 1 to 23 or
15 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.

28. A compound of the formula (1) as described in any one of claims 1 to 23 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
5 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.

29. The use of a compound of the formula (1) as described in any one of claims
10 1 to 23 or of a pharmaceutically acceptable salt, derived form or composition thereof, for the manufacture of a drug having a β 2 agonist activity.

30. The use of a compound of the formula (1) as described in any one of claims
1 to 23 or of a pharmaceutically acceptable salt, solvate or composition thereof,
15 for the manufacture of a drug for the treatment of diseases, disorders, and conditions selected from the group as described in claim 28.

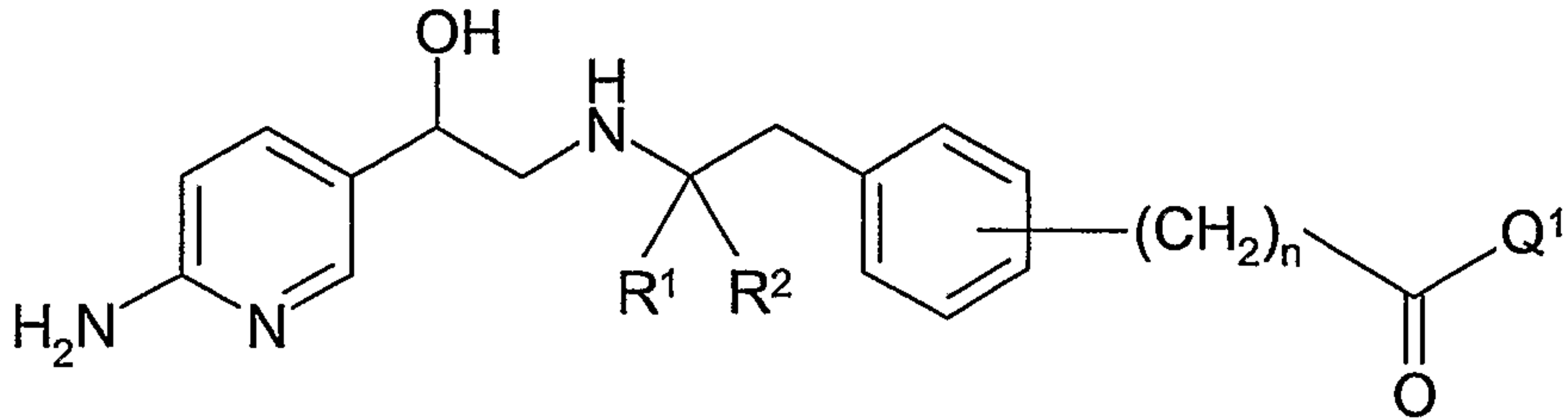
31. A method of treatment of a mammal, including a human being, with a β 2 agonist including treating said mammal with an effective amount of a compound of the formula (1) as described in any one of claims 1 to 23 or with a pharmaceutically acceptable salt, derived form or composition thereof.

20 32. A method according to claim 31 where the disease, disorder or condition is selected from the group as described in claim 28.

33. Combination of a compound according to any one of claims 1 to 23 with other therapeutic agents selected from :

- 25 (a) 5-Lipoxygenase (5-LO) inhibitors or 5-lipoxygenase activating protein (FLAP) antagonists,
- (b) Leukotriene antagonists (LTRAs) including antagonists of LTB₄, LTC₄, LTD₄, and LTE₄,
- (c) Histamine receptor antagonists including H1 and H3 antagonists,

- (d) α_1 - and α_2 -adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use,
- (e) muscarinic M3 receptor antagonists or anticholinergic agents,
- (f) PDE inhibitors, e.g. PDE3, PDE4 and PDE5 inhibitors,
- 5 (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,
- 10 (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,
- 15 (o) Immunosuppressive agents,
- (p) Inhibitors of matrix metalloproteases (MMPs),
- (q) Tachykinin NK₁, NK₂ and NK₃ receptor antagonists,
- (r) Elastase inhibitors,
- (s) Adenosine A2a receptor agonists,
- 20 (t) Inhibitors of urokinase,
- (u) Compounds that act on dopamine receptors, e.g. D2 agonists,
- (v) Modulators of the NF κ B pathway, e.g. IKK inhibitors,
- (w) Agents that can be classed as mucolytics or anti-tussive, and
- (x) Antibiotics.



(1)