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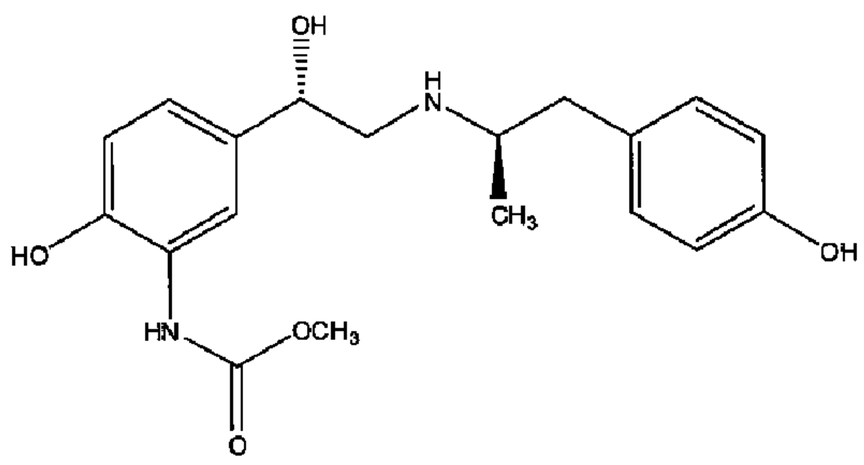
(54) Titre : STEREOISOMERE DU CARBAMATE
(54) Title: CARBAMATE STEREOISOMER



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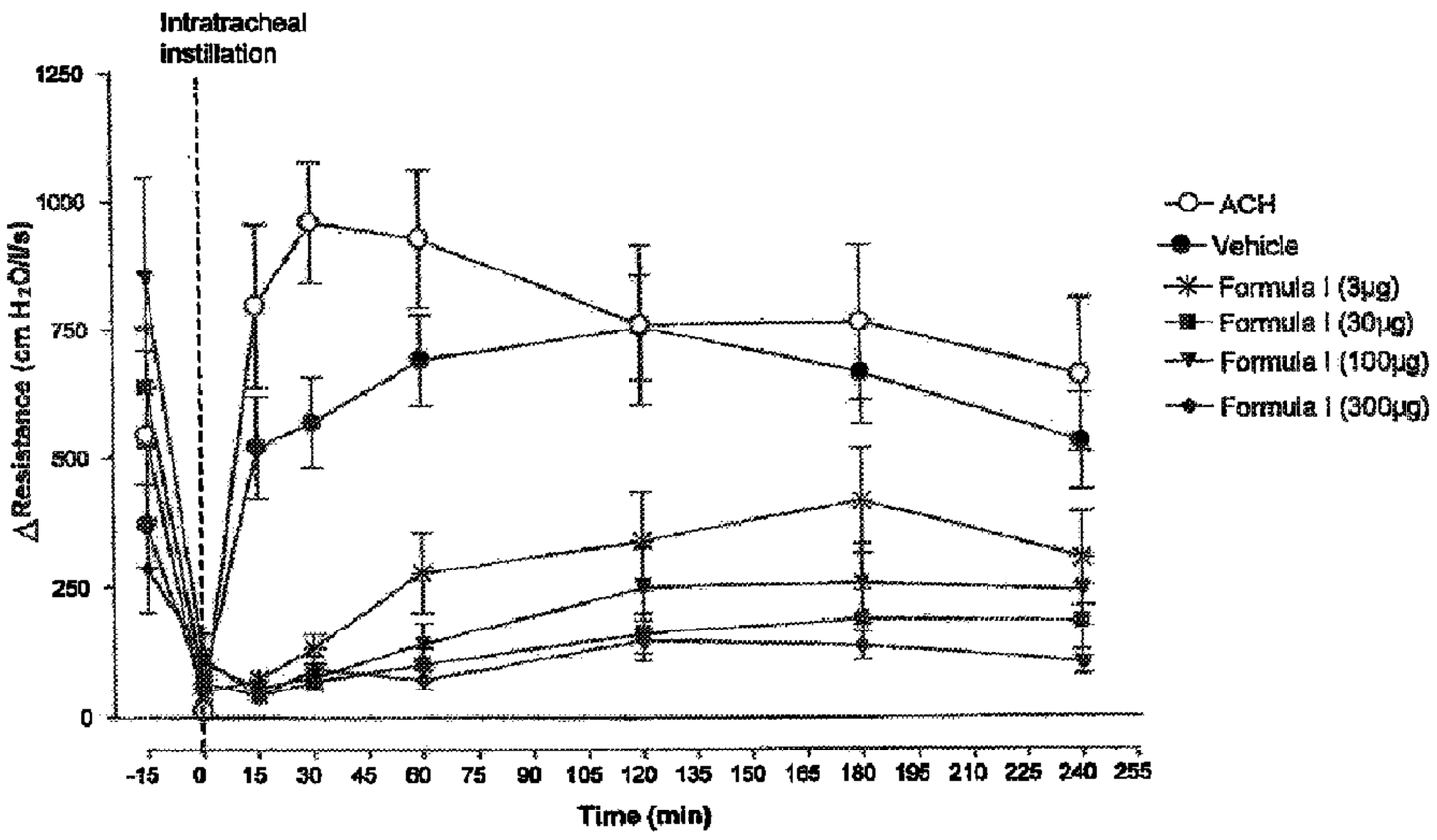

(57) Abrégé/Abstract:
The compound of formula (I) is a water-stable, long acting $ß_2$-selective adrenoceptor agonist useful as a bronchodilator in the treatment of bronchoconstriction associated with reversible obstructive airways diseases and the like.

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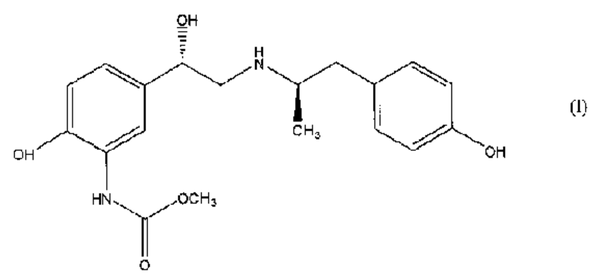

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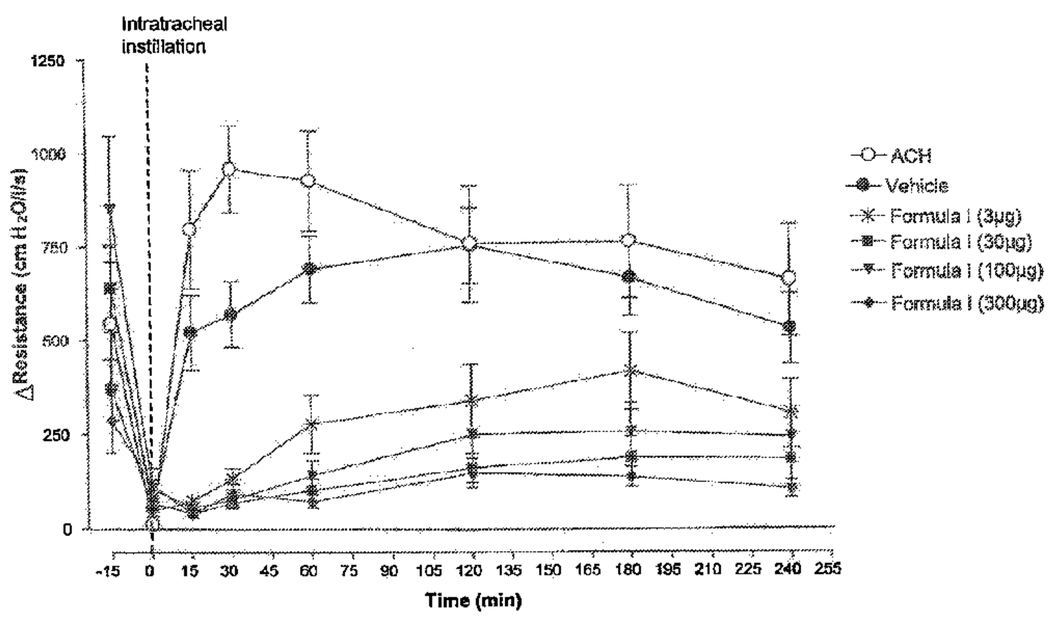

Figure 1

(57) **Abstract:** The compound of formula (I) is a water-stable, long acting $ß_2$-selective adrenoceptor agonist useful as a bronchodilator in the treatment of bronchoconstriction associated with reversible obstructive airways diseases and the like.

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CARBAMATE STEREOISOMER

Field of the Invention

[0002] The present invention relates to a novel carbamate stereoisomer, to a process for preparing the carbamate stereoisomer, to a pharmaceutical composition comprising the carbamate stereoisomer and to the use of the carbamate stereoisomer in therapy, in particular in the treatment of bronchoconstriction associated with reversible obstructive airways diseases including but not limited to asthma, cystic fibrosis and chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.

Background of the invention

[0003] Patients suffering from bronchoconstriction associated with reversible obstructive airways diseases are generally treated using a bronchodilator, to relax the bronchial smooth muscle.

[0004] Bronchodilators in use today generally fall into two classes, the β_2-selective adrenoceptor agonists, such as albuterol (salbutamol), salmeterol and formoterol, and the muscarinic receptor antagonists, such as ipratropium and tiatropium.

[0005] β_2-Selective adrenoceptor agonists may cause adverse effects, and these may in part be due to activation of the β_1-adrenoceptor. The selectivity of an agonist for the β_2-adrenoceptor receptor is therefore very important, because it limits the dose that can be given and so affects the magnitude of bronchodilations and the frequency of dosing.

[0006] A long duration of action is important to patients, not only to minimize the time spent taking the drug, but also to avoid having to take the drug during inconvenient times, for example at work, school or during the night. Some of the more recent β_2-selective adrenoceptor agonists, in particular salmeterol and formoterol, have a long duration of action,

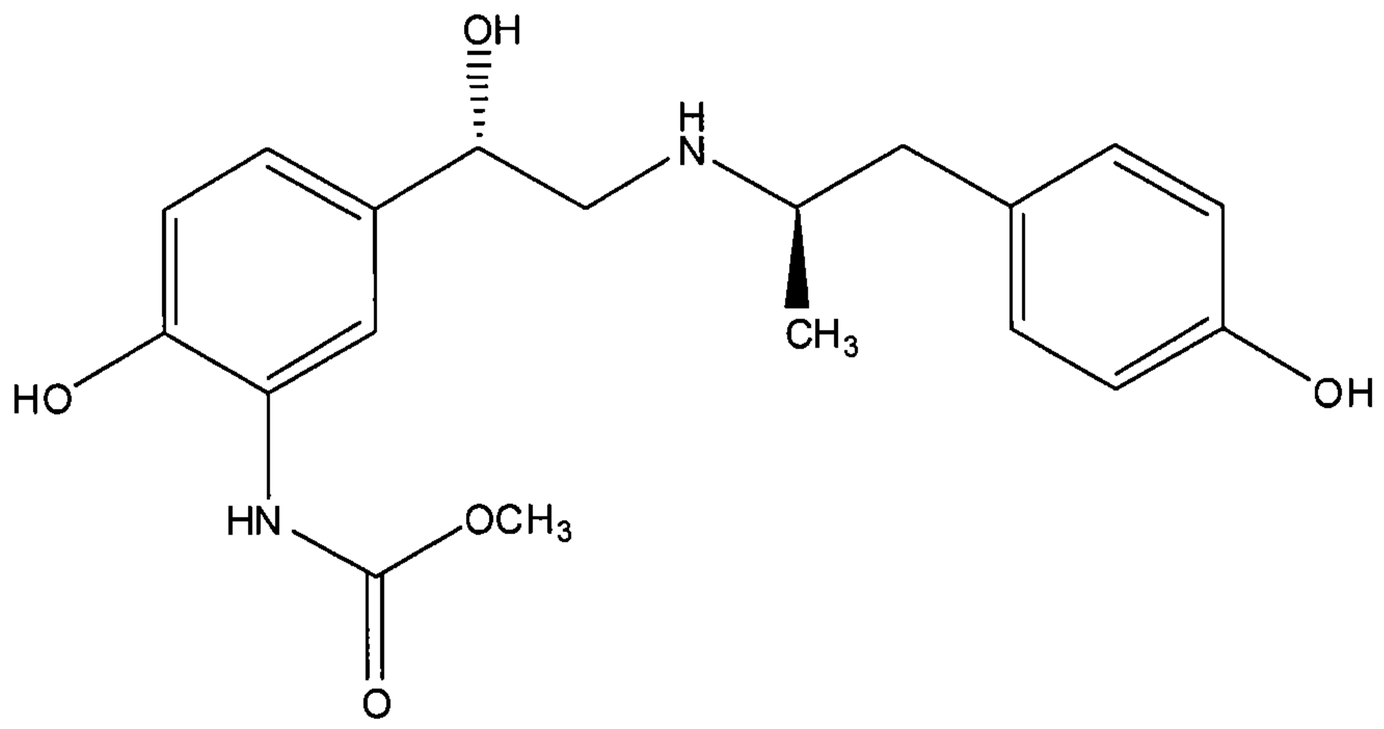
typically about 12 hours. Formoterol has a particular advantage that it also has a fast onset of action. However, formoterol is extremely potent, which makes it very difficult to formulate, especially for administration using a metered dose inhaler in a manner that results in uniform drug delivery via aerosol dose after dose (i.e., dose content uniformity). Furthermore, it is unstable in aqueous solution, which means that solutions for administration using a nebuliser have to be kept refrigerated for a majority of their post-manufacture shelf life.

[0007] Formoterol is one of a group of α-aminomethylbenzyl alcohol derivatives for which patent applications were filed during the early nineteen seventies, for example US 3,994,974. The invention of this compound built on earlier work by others, such as described in US 3,657,319 (equivalent to BE 765,986, cited in US 3,994,974). Perhaps because of the difficulties associated with formulating the compound, it took a long time to be commercialized. The compound contains two chiral centers, and hence is capable of existing and being isolated in four stereoisomeric forms. The compound was firstly commercialized as a racemic mixture of the active (R,R)- and inactive (S,S)- isomers, in a dry powder formulation, then more recently as the active (R,R)-isomer in a nebuliser solution. It is also known, for example from US 6,303,145, that the (S,R) isomer of formoterol is active. However, like the (R,R)-isomer, this compound is unstable at ambient temperature in aqueous solution and hence nebuliser solutions would need to be stored refrigerated.

Summary of the Invention

[0008] Surprisingly, it has now been found that by replacing the methoxy group in (S,R)-formoterol with a hydroxy group, and the formyl hydrogen atom with a methoxy group, an isomer having a particularly attractive combination of properties has been obtained.

[0009] According to one aspect, therefore, the present invention provides a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof.

[0010] The compound of formula (I) may also be referred to by the chemical name methyl [2-hydroxy-5-[(1S)-1-hydroxy-2-[[(1R)-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-phenyl] carbamate, which is indexed in Chemical Abstracts as carbamic acid, [2-hydroxy-5-[(1S)-1-hydroxy-2-[[(1R)-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-phenyl]-, methyl ester.

[0011] The isomer of formula (I) has been found to possess particularly advantageous properties. In particular, it possesses good, but not very high affinity for the β2-adrenoceptor, high selectivity for the β2- over the β1- adrenoceptor, a long duration of action and good stability in aqueous solution at ambient temperature.

Brief Description of the Drawing

[0012] The figure shows the effects of methyl [2-hydroxy-5-[(1S)-1-hydroxy-2-[[(1R)-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-phenyl] carbamate on acetylcholine effects on airway resistance.

Detailed Description of the Invention

[0013] It will be appreciated that the compound provided by the present invention is an isomer. This isomer may exist and be isolated in enantiomerically pure form, or in admixture with one or more of its other isomers. The present invention provides the isomer in any mixture of isomers other than a racemic mixture, which is described in Example 6 of US 3,657,319. In certain embodiments, the isomer is substantially free of the (R,R)- enantiomer,

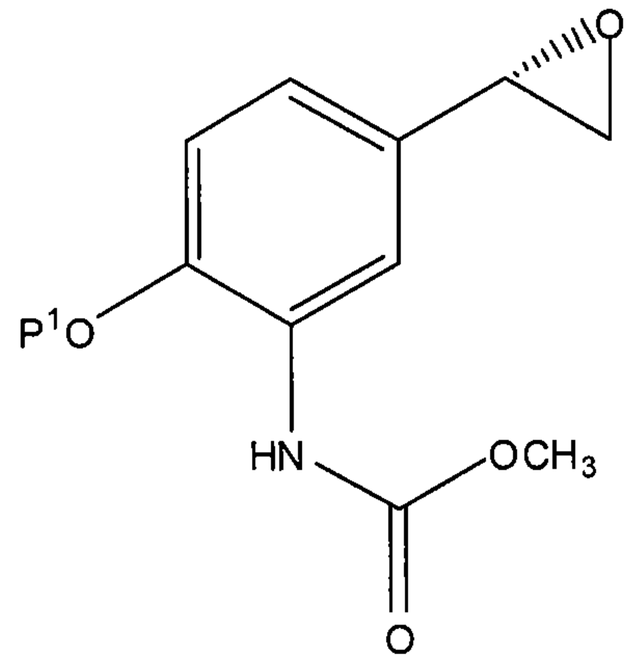
which can exhibit a different potency, resulting in significant variations in the potency of admixtures. It may exist as a 1:1 diastereomeric mixture with the (R,S)-isomer, but is most preferably enantiomerically pure (i.e. substantially free of all other isomers). For example, the isomer may comprise at least 50% by weight of all carbamic acid, [2-hydroxy-5-[1-hydroxy-2-[[(2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-, methyl ester present, preferably at least 75%, such as at least 90%, at least 95% or at least 99%.

[0014] As used herein, the term "pharmaceutically acceptable salt" refers to a salt prepared from a pharmaceutically acceptable, relatively non-toxic acid, including inorganic acids and organic acids. Suitable acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, carbonic, citric, dihydrogenphosphoric, ethenesulfonic, fumaric, galactunoric, gluconic, glucuronic, glutamic, hydrobromic, hydrochloric, hydriodic, isobutyric, isethionic, lactic, maleic, malic, malonic, mandelic, methanesulfonic, monohydrogencarbonic, monohydrogenphosphoric, monohydrogensulfuric, mucic, nitric, pamoic, pantothenic, phosphoric, phthalic, propionic, suberic, succinic, sulfuric, tartaric, toluenesulfonic, including *p*-toluenesulfonic *m*-toluenesulfonic and *o*-toluenesulfonic acids, and the like (see, *e.g.*, Berge *et al., J. Pharm. Sci.,* 66:1-19 (1977); Stahl and Wermuth, *Handbook of Pharmaceutical Salts*, Wiley VCH, (2002)). Also included are salts of other relatively non-toxic compounds that possess acidic character, including amino acids, such as arginine and the like, and other compounds, such as aspirin, ibuprofen, saccharin, and the like. Acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. As solids, salts can exist in crystalline or amorphous modifications. An example of an acid addition salt is the D-tartrate salt.

[0015] The compounds of the present invention may also be prepared in deuterated form, i.e., in which one or more hydrogen atoms, for example on the methoxycarbonyl group, are replaced with deuterium.

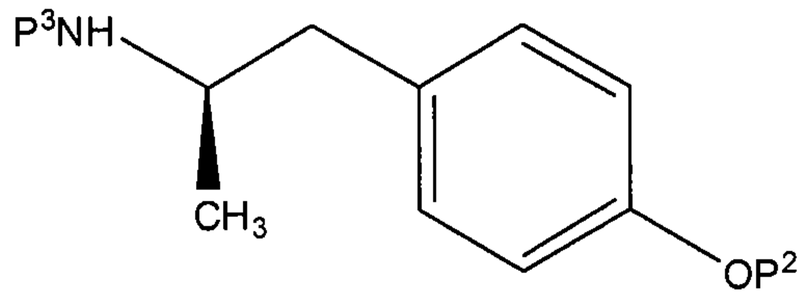
[0016] It is also contemplated that the methyl group in the methoxycarbonyl group in the compound of formula (I) may be replaced with a fluoromethyl group (i.e. a group in which one, two or three of the methyl hydrogen atoms is replaced with a fluorine atom). Such compounds may be prepared by a process analogous to that described herein for the preparation of the carbamate isomer.

[0017] The carbamate isomer and its pharmaceutically acceptable salts can be prepared by a process, which comprises reacting a compound of general formula (II)



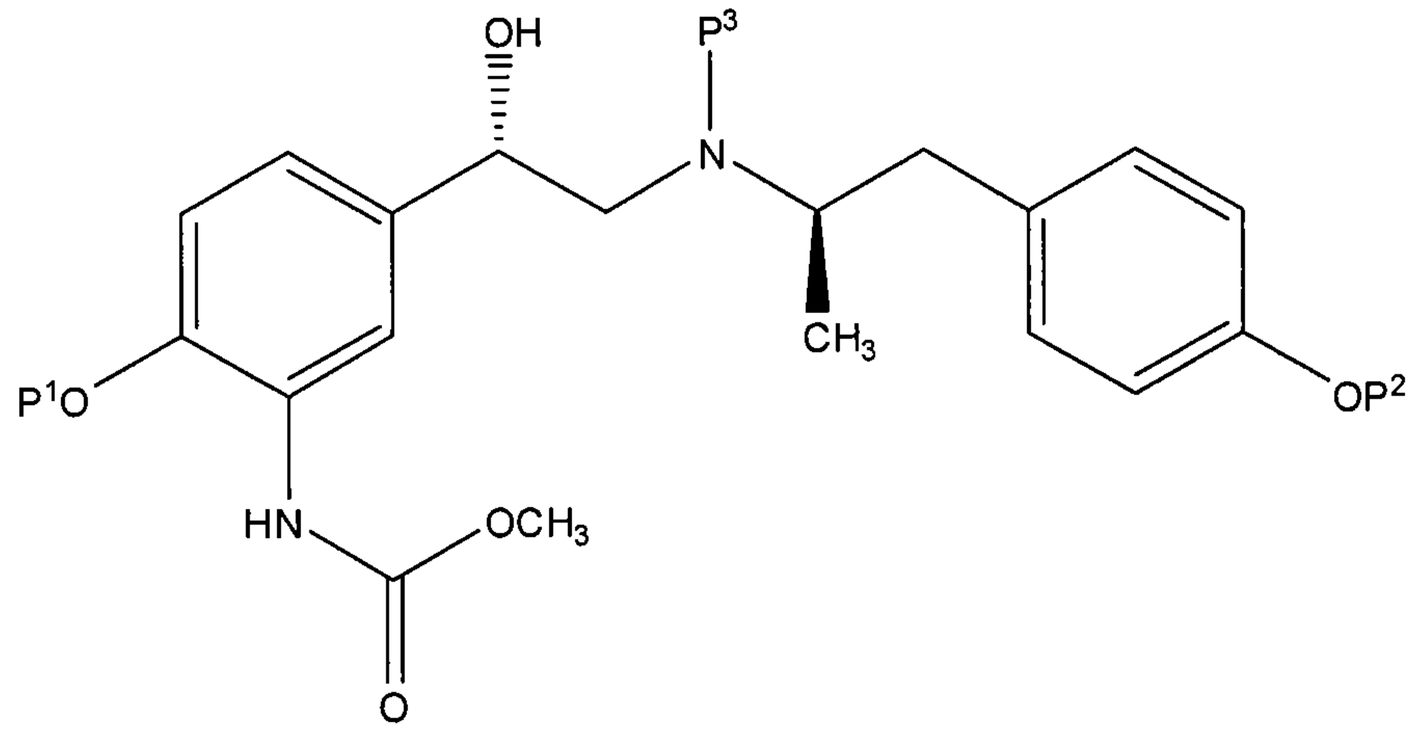
(II)

in which P^1 represents a hydrogen atom or a hydroxyl protecting group, with a compound of general formula (III)



(III)

in which P^2 represents a hydrogen atom or a hydroxyl protecting group and P^3 represents a benzylic amine protecting group, to afford a compound of general formula (IV)



(IV)

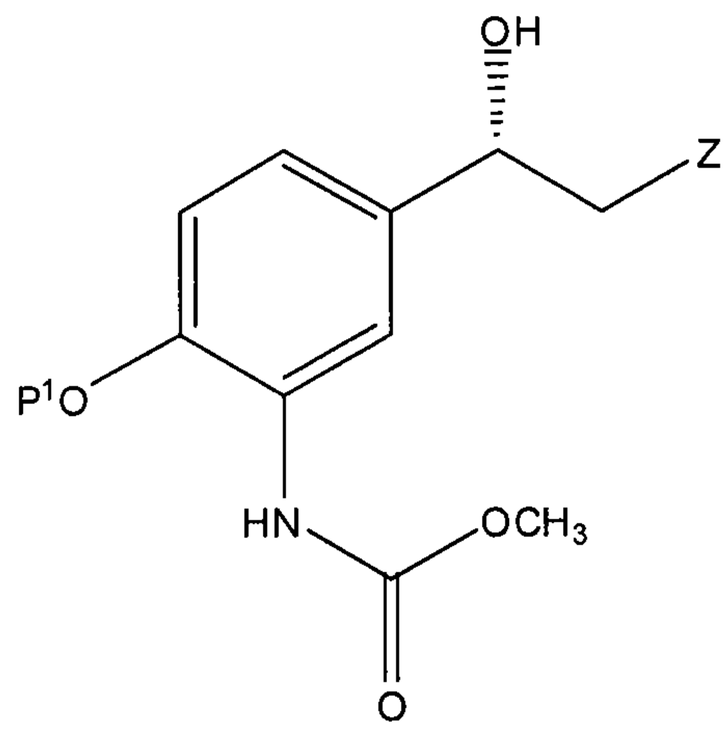
or a salt thereof, followed by removing any protecting groups P^1, P^2 and P^3 and, if desired, forming a pharmaceutically acceptable acid addition salt.

[0018] The protecting groups may be any suitable protecting group, for example as described in Green *et al.*, "Protective Groups in Organic Chemistry," (Wiley, 2nd ed. 1991). Examples of hydroxyl protecting groups include aralkyl groups, such as benzyl, and trialkylsilyl groups, such as t-butyl-dimethylsilyl (TBDMS). Examples of a benzylic amine protecting group are benzyl groups optionally substituted on the benzene ring by one or more, for example 1, 2 or 3 optional substituents, for example selected from halo, (1-4C) alkyl and (1-4C)alkoxy; for example unsubstituted benzyl.

[0019] The reaction between the compounds of formula (II) and (III) is conveniently performed by melting the two compounds together, for example by heating in the range of from 50 to 130 °C, such as about 75 °C.

[0020] Any protecting groups represented by P^1, P^2 and P^3 may be removed using a conventional procedure. For example, a benzyl group can be removed by catalytic hydrogenation in the presence of palladium on carbon, and a trialkylsilyl group by treatment with tetrabutylammonium fluoride.

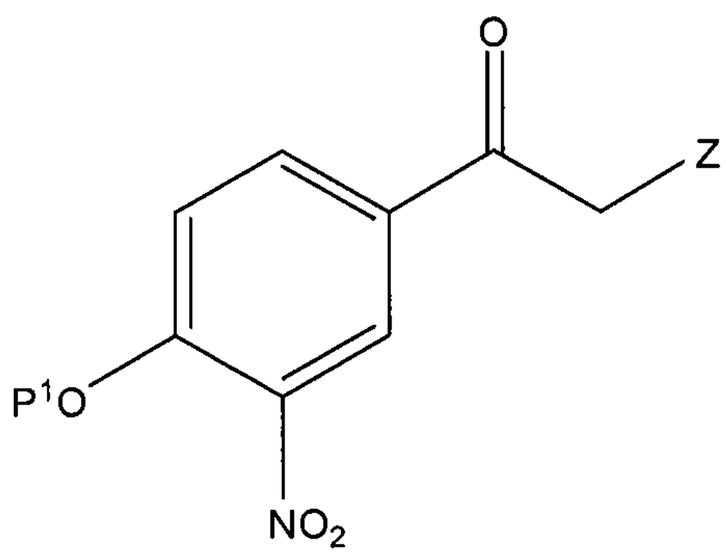
[0021] Compounds of formula (II) can be prepared by reacting a compound of formula (V)



(V)

in which Z represents a leaving atom or group, such as a bromine atom, with a base, for example an alkali metal carbonate such as potassium carbonate.

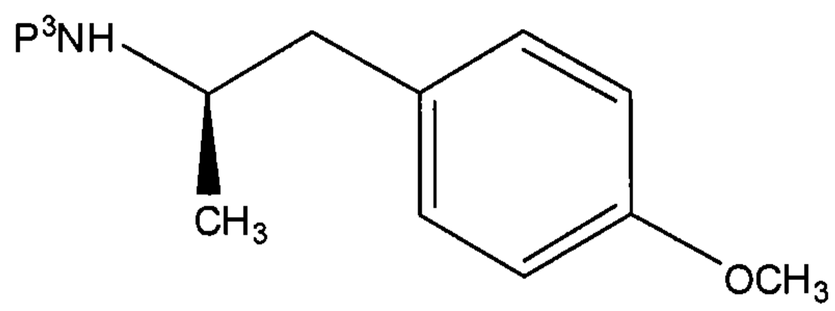
[0022] Compounds of formula (V) can be prepared by stereoselective reduction of a compound of formula (VI)



(VI)

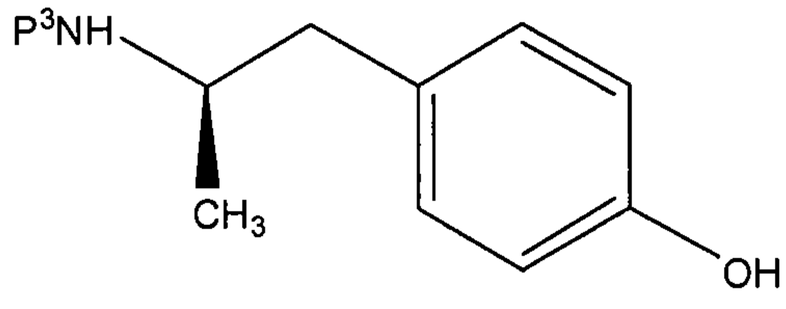
using, for example, borane in the presence of a chiral auxiliary, such as (1S,2R)-1-amino-2-indanol, followed by reduction of the nitro group to an amino group and acylation of the resultant amino group, for example using dimethyl carbonate.

[0023] Compounds of general formula (III) can be prepared by reacting a compound of general formula (VII)



(VII)

with boron tribromide, to afford a compound of formula (VIII)



(VIII)

The hydroxyl group may then be protected, for example by reaction with a trialkylsilyl halide, such as t-butyldimethylsilyl chloride.

[0024] It will be appreciated that the percentage by weight comprised by the compound of formula (I) of all carbamic acid, [2-hydroxy-5-[1-hydroxy-2-[[(2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-, methyl ester present in the final product of the process will depend upon the enantiomeric purity of the starting materials used and any enantiomeric purification steps taken, such as chiral liquid chromatography.

[0025] The intermediates of general formula (IV) are believed to be novel and are provided as a further aspect of the present invention.

[0026] According to another aspect, therefore, the present invention provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, as described herein, together with a pharmaceutically acceptable carrier.

[0027] The pharmaceutical composition according to the invention may be adapted for administration to patients by any convenient route, such as by oral, mucosal (e.g. nasal, sublingual, vaginal, buccal or rectal), parenteral or transdermal administration. It may be in the form of, for example, a solution, suspension, powder, tablet, aerosol formulation, lozenge, suppository, emulsion, hard or soft gelatin capsule or syrup. The compound of formula (I) may be dissolved in the carrier, diluted by the carrier or supported by the carrier. Thus the carrier may be a support for the compound of formula (I), such as a capsule, sachet, paper or other pharmaceutical container.

[0028] In one embodiment, the pharmaceutical composition is an aqueous solution adapted for administration using a nebuliser. The aqueous formulation may be isotonic and buffered at an optimal pH for stability. The aqueous formulation for nebulization could also be a suspension of nanoparticles or a micronized suspension of free base or an insoluble salt or a cyclodextrin adduct.

[0029] In another embodiment, the pharmaceutical composition is an aerosol formulation adapted for administration using a metered dose inhaler, the aerosol formulation comprising the acetamide isomer in crystalline form and a propellant or in solution with an appropriate propellant, combination of propellants or combination of propellant(s) and an acceptable co-solvent or other solubilizing agent.

[0030] The propellant may be any suitable propellant used in aerosol formulations, for example, a hydrofluoroalkane (HFA), such as 1,1,1,2-tetrafluoroethane (HFA134) or 1,1,1,2,3,3,3-heptafluoropropane (HFA227) or a combination of propellants. HFA134 is preferred. The propellant may comprise at least 90% by weight of the aerosol formulation, which may also include, *inter alia*, inert gases to aide in aerosol formation.

[0031] The aerosol formulation may further comprise a surfactant. The surfactant serves to stabilize and disperse the carbamate isomer in a suspension, and may also serve as a valve lubricant in the metered dose inhaler. It may be any suitable surfactant used in aerosol formulations. Examples of surfactants used in aerosol formulations are described in United States patent number 5,225,183. A preferred surfactant is oleic acid. The surfactant, when present, may generally be present in an amount of from 1:100 to 1:10 surfactant: carbamate isomer, preferably about 1:20.

[0032] The aerosol formulation may further comprise a co-solvent. A function of the co-solvent in the aerosol formulation is to facilitate dissolution of the surfactant, which may have poor solubility in the propellant. It may be any suitable carrier used in aerosol formulations. A co-solvent such as glycerol or ethanol may be used. A preferred co-solvent is ethanol, especially dehydrated ethanol. The content of ethanol may conveniently be up to 30% by weight of the aerosol formulation, such as from 2 to 6%.

[0033] Metered dose inhalers typically comprise a canister containing an aerosol formulation, a metering valve, a valve stem and an actuator which accepts the valve stem. In use, a patient depresses the canister into the actuator and inhales, causing a dose of the formulation to be administered and taken into the patient's lungs.

[0034] According to a further aspect, therefore, the present invention provides a metered dose inhaler comprising a canister containing an aerosol formulation as described herein, a metering valve and an actuator.

[0035] Preferably the interior surface of the canister is coated, for example with a protective polymer, or otherwise treated to minimize chemical or physical interaction between the formulation and the canister. The inhaler preferably has an aperture with a diameter in the range of from 0.2 to 0.60 mm.

[0036] In yet another embodiment, the pharmaceutical composition is in the form of a dry powder suitable for inhalation or insufflation. The composition may comprise carbamate isomer crystals alone (e.g. having a mass median aerodynamic diameter of from 1 to 10 microns, preferably from 2 to 7 microns), or carbamate isomer blended, co-precipitated, co-crystallized or spray dried together with a suitable pharmaceutically acceptable carrier or carriers. Suitable pharmaceutically acceptable carriers include, without limitation, solvates of

one or more natural or synthetic carbohydrates, such as a monosaccharides, disaccharides, trisaccharides, oligosaccharides, polysaccharides, polyols, amino acids and proteins, and/or in the form of their pharmaceutically acceptable esters, acetals, or salts (where such derivatives exist). The carrier is preferably lactose, more preferably lactose monohydrate. The dry powder composition may be presented in unit dosage form in, for example, capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator. The dry powder composition may be presented in multi dose form metered with the aid of an inhaler or insufflator, or pre-metered into discrete doses within the device for serial administrations.

[0037] Conveniently, dry powder formulations are administered using multidose dry powder inhalers.

[0038] The present invention therefore also provides a multidose dry powder inhaler, comprising a dry powder reservoir containing a dry powder aerosol formulation of carbamate isomer as described hereinabove, and a metering chamber.

[0039] The compound of formula (I) according to the present invention may be co-administered with one of more other active ingredients, for example selected from steroids, such as beclomethasone, triamcinolone, funisolide, mometasone, budesonide or fluticasone, muscarinic receptor antagonists, such as ipratropium, tiatropium, or glycopyrrolate. Accordingly, in one embodiment, the pharmaceutical composition in accordance with the present invention may further comprise a steroid and/or a muscarinic receptor antagonist and/or a controller agent or bronchodilator with a novel mechanism.

[0040] In another embodiment, the pharmaceutical composition in accordance with the present invention may further comprise anti-inflammatory agents such as inhibitors of tumor necrosis factor alpha (TNFα), dipeptidyl peptidase IV, and antibodies to pro-inflammatory interleukins such as IL4 and IL13.

[0041] In another embodiment, the pharmaceutical composition in accordance with the present invention may further comprise mucolytic agents such as cromoglycate, acetylcysteine, arginine, or 2-mercaptoethanesulphonate.

[0042] According to another aspect, the present invention provides a method of treating bronchoconstrictive disease, which comprises administering to a patient in need of treatment an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

[0043] The bronchoconstrictive disease may be, for example, chronic obstructive pulmonary disease (such as emphysema or bronchitis), cystic fibrosis, or asthma.

[0044] The patient may be a human or a non-human mammal, such as a dog, cat, horse, cow, sheep or pig. Preferably, the patient is a human.

[0045] The amount of compound administered will depend upon many factors, such as the species, weight and age of the patient, and the severity of the condition to be treated. For example, a dose administered to a human may contain from 75 to 5,000 μg of the carbamate isomer (calculated as the free base). The dose may be administered, for example, once or twice per day.

[0046] According to another aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in therapy.

[0047] According to yet another aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease.

[0048] According to a still further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier for the treatment of chronic obstructive pulmonary disease, or for use as a bronchodilator.

[0049] Although the foregoing invention has been described in some detail for purposes of illustration, it will be readily apparent to one skilled in the art that changes and modifications may be made without departing from the scope of the invention described herein.

Examples

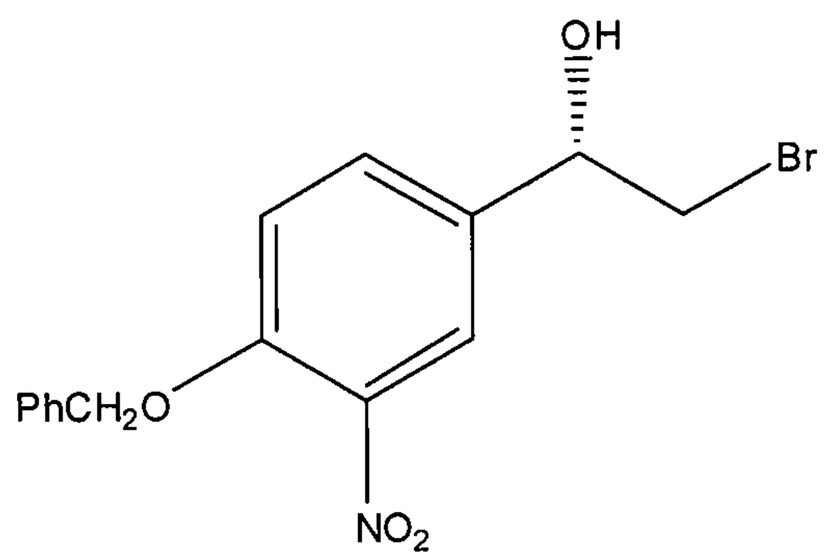
[0050] The following Examples illustrate the invention.

[0051] THF refers to tetrahydrofuran, EtOAc refers to ethyl acetate and Et_2O refers to diethyl ether.

[0052] **Example 1**

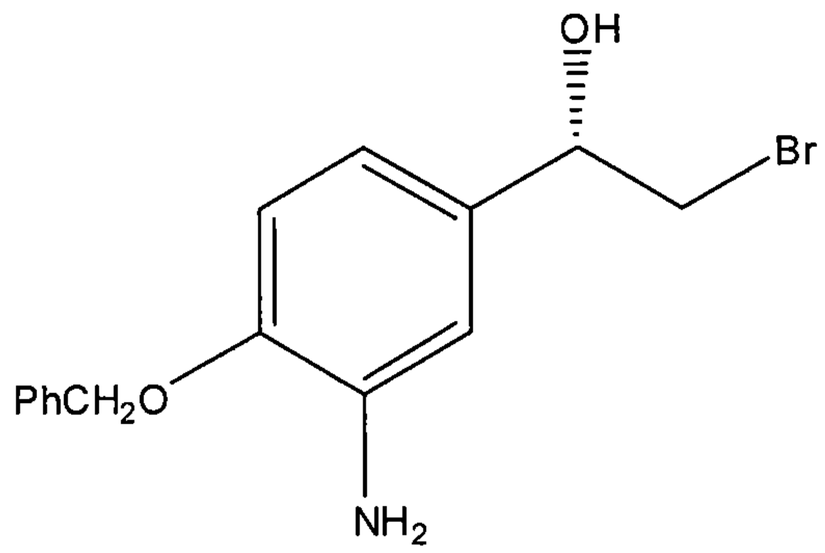
Carbamic acid, [2-hydroxy-5-[(1S)-1-hydroxy-2-[[(1R)-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-phenyl]-, methyl ester

[0053] **Step A) (1S)-1-(3-nitro-4-benzyloxyphenyl)-2-bromoethan-1-ol**



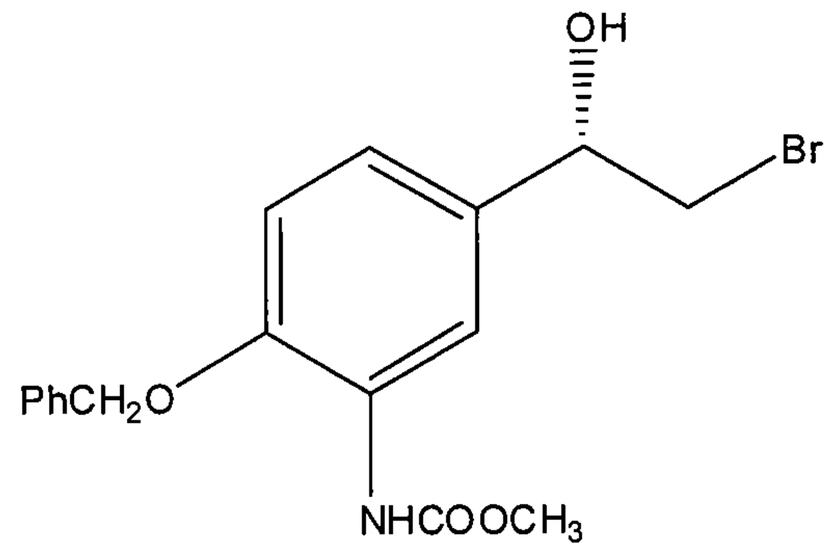
A cold (5°C) solution of (1S,2R)-1-amino-2-indanol (400 mg, 2.68 mmol) in THF (160 mL) was added dropwise to a cold (0°C) solution of borane-diethylaniline complex (7.0 g, 43 mmol) in THF (20 mL). After complete addition, the resulting solution was stirred at (0°C) for 30 min then 2-bromo-4'-benzyloxy-3'-nitroacetophenone (20.0 g, 57.1 mmol) was added in three portions over a 30 min period. The resulting solution was stirred at <5°C for 1 h, quenched by dropwise addition of acetone (17 mL) then allowed to warm to ambient temperature overnight. The reaction mixture was concentrated *in vacuo* to a residue, which was dissolved in toluene (100 mL) and washed in succession with 10% H_2SO_4 (2 x 45 mL), H_2O (2 x 45 mL) and sat. brine (1 x 40 mL). The organic layer was dried over $MgSO_4$, clarified then concentrated *in vacuo* to a volume of ~40 mL. Heptane (45 mL) was slowly added to give a thick slurry. The solid was collected on a filter and washed with heptane (2 x 5 mL). This material was dissolved in warm toluene (~50 mL), the solution was clarified then diluted with heptane (50 mL). The resulting mixture was stirred for 30 min, the solids were collected, washed with heptane (2 x 5 mL) then dried to constant weight *in vacuo* to give 18.9 g (94.0%) of the title compound.

[0054] Step B) (1S)-1-(3-amino-4-benzyloxyphenyl)-2-bromoethan-1-ol



A solution of the product of Step A) (18.7 g, 53.1 mmol) in toluene (40 mL) and THF (40 mL) was added to a Parr shaker bottle containing Pt_2O (370 mg). This mixture was shaken under H_2 (50 psi, 344.74 kpa) until the reaction was complete (18 h). The catalyst was removed by filtration, and the filtrate was concentrated to an oil. Column chromatography (1 kg silica gel packed in and eluted with CH_2Cl_2/MeOH, 19:1) gave 11.9 g (69.6%) of the title compound.

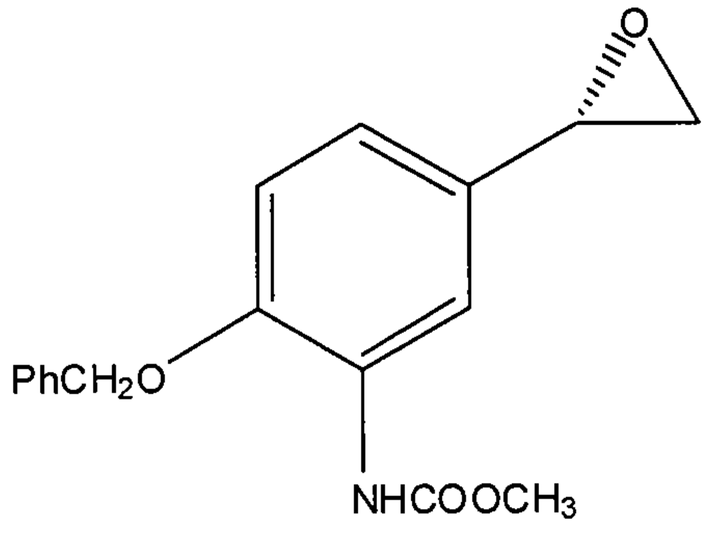
[0055] Step C) (1S)-1-(3-methoxycarbonylamino-4-benzyloxyphenyl)-2-bromoethan-1-ol



A solution of the product of Step B) (11.7 g, 36.3 mmol) in pyridine (117 mL) was stirred at ambient temperature for 15 min. Dimethyl dicarbonate (4.9 g, 37 mmol) was added in one portion, and the resulting solution was stirred at ambient temperature for 30 min followed by 4 h at 40°C. Additional dimethyl dicarbonate (1.3 g, 9.7 mmol) was added and stirring continued at 40°C for 2 h. The reaction solution was concentrated in vacuo to an oil that was partitioned between CH_2Cl_2 (470 mL) and 10% aq. HCl (120 mL). The aqueous layer was extracted with CH_2Cl_2 (1 x 120 mL). The combined organic layer was washed in succession with H_2O (1 x 350 mL) and brine (1 x 350 mL), dried over $MgSO_4$, clarified then concentrated in vacuo to a thick slurry. The mixture was diluted with hexanes (120 mL) and

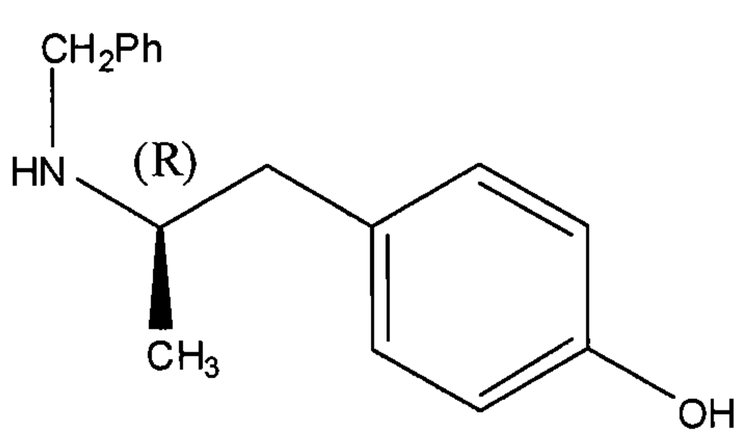
stirred for 30 min. The resulting solid was collected on a filter, washed with hexanes (2 x 60 mL) then dried to constant weight in vacuo to give ~10 g of a white solid. This material was further purified by trituration in Et_2O (60 mL). The solid was collected on a filter, washed with Et_2O (2 x 10 mL) then dried to constant weight in vacuo to give 8.5 g of a partially purified product. This material was further purified by silica gel chromatography (800 g column, packed in and eluted with CH_2Cl_2/MeOH, (19:1) to give 7.2 g (52%) of the title compound suitable for further transformation.

[0056] Step D) (1S)-1-(3-methoxycarbonylamino-4-benzyloxyphenyl)-epoxyethane



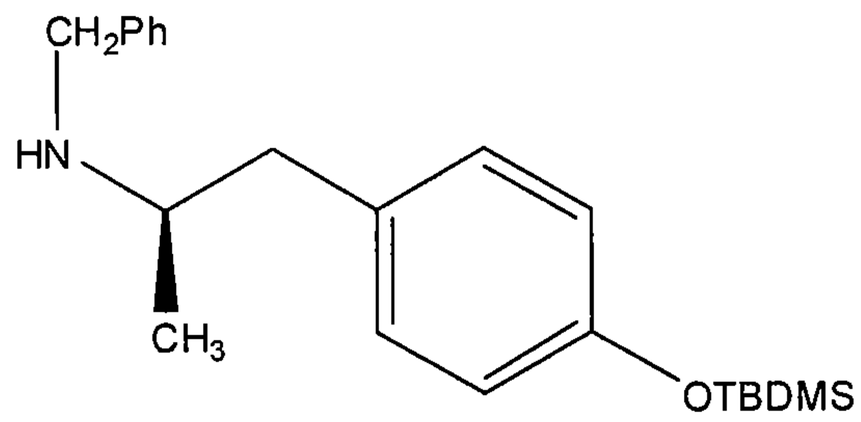
A suspension of the product of Step C) (3.5 g, 9.2 mmol) and potassium carbonate (1.7 g, 12 mmol) in methanol (30 mL) and THF (30 mL) was stirred at ambient temperature for 2.5 h, then concentrated in vacuo to a residue. The residue was triturated with CH_2Cl_2 (35 mL), and the resultant solid was discarded after washing with CH_2Cl_2 (2 x 8 mL). The combined CH_2Cl_2 extracts were concentrated to a residue that was triturated in hexanes/ether (1:9) (50 mL). The solid was collected on a filter, washed with hexanes (2 x 15 mL) then dried to constant weight in vacuo to give 1.4 g (51%) of the epoxide. An identical run using 3.7 g (9.7 mmol) of starting material was carried out to give 1.7 g (59%) of further product for a total of 3.1 g of the title epoxide suitable for further transformation.

[0057] Step E) [(1R)-N-Benzyl-2-(4-hydroxyphenyl)-1-methylethyl]-amine



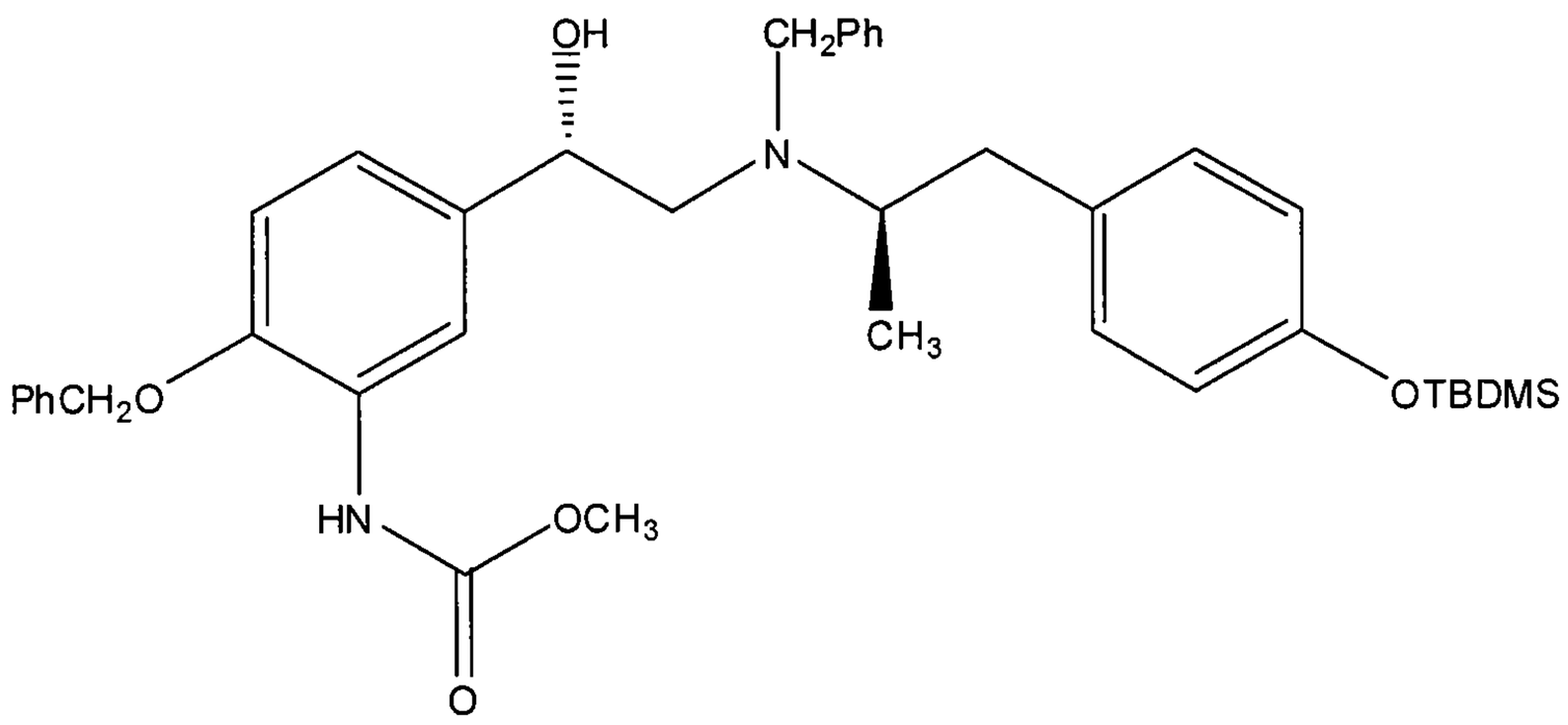
To a solution of [(1R)-N-Benzyl-2-(4-methoxyphenyl)-1-methylethyl]amine (5.30 g, 20.8 mmol) in CH_2Cl_2 (25 mL) was added a solution of BBr_3 in CH_2Cl_2 (25.0 mL, 1.0M, 25.0 mmol) slowly over 0.5 h. After the addition, the mixture was stirred at ambient temperature for 22 h. Water (125 mL) was added, followed by the addition of 2.5M aq. NaOH (15 mL) to pH 6. The mixture was extracted with EtOAc (4 x 200 mL), and the organic layer was dried (Na_2SO_4) and concentrated. The residue (3.9 g) was triturated with CH_2Cl_2 (120 mL) and then concentrated to dryness to give the title compound (3.8 g, 76%).

[0058] Step F) [(1R)-N-Benzyl-2-(4-t-butyldimethylsilyloxyphenyl)-1-methylethyl]amine



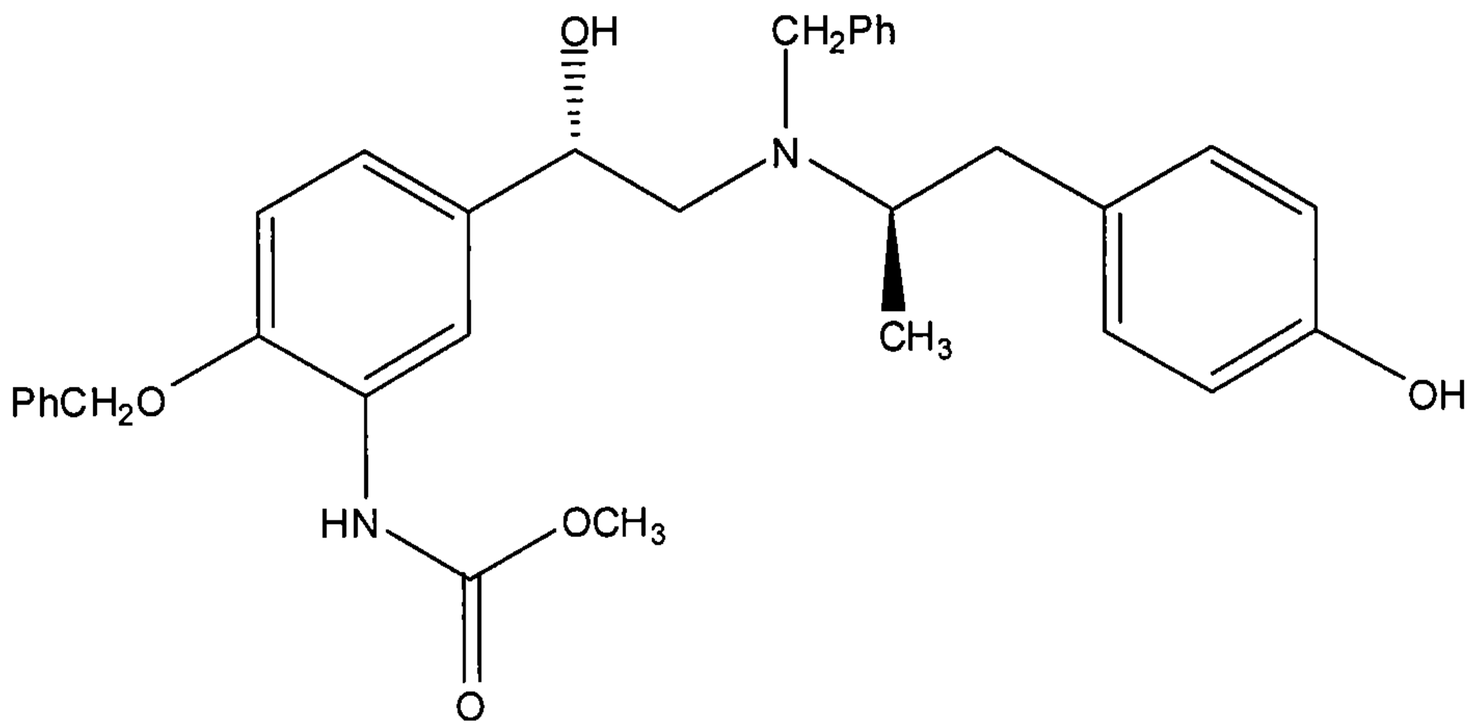
A solution of the product of Step E) (3.20 g, 13.3 mmol), tert-butyldimethylsilyl chloride (3.59 g, 23.8 mmol), and imidazole (2.86 g, 42.0 mmol) in DMF (30.0 mL) was stirred at ambient temperature for 18 h. The mixture was concentrated to dryness, and the residue was partitioned between EtOAc (200 mL) and sat. aq. $NaHCO_3$ (200 mL). The aqueous layer was separated and again extracted with EtOAc (100 mL). The combined organic layer was washed with brine (100 mL), dried with Na_2SO_4, filtered and concentrated to give an oil. The oil was chromatographed on silica gel (100 g, eluted with 1:1 EtOAc:hexanes) to give the title compound (4.0 g, 85%) as a tan oil.

[0059] Step G) Carbamic acid, [2-benzyloxy-5-[(1S)-1-hydroxy-2-[[(1R)-2-(4-t-butyldimethylsilyloxyphenyl)-1-methylethyl]-N-benzylamino]ethyl]phenyl]-, methyl ester



A mixture of the products of Step D) (1.26 g, 4.21 mmol) and Step F) (1.50 g, 4.22 mmol) was heated slowly to 75°C without any solvent. The resulting mixture was heated at this temperature for a total of three days at which time TLC evaluation (hexanes/EtOAc, 3:1) indicated complete loss of starting epoxide. After cooling to room temperature the rather complex reaction mixture was purified by chromatography two times on a column of silica gel (100 g) packed in and eluted with hexanes/EtOAc (3:1). A total of 2.9 g of the epoxide was reacted and purified in a similar manner to give 2.6 g (41%) of the title compound as a yellow oil. This material was suitable for further transformation.

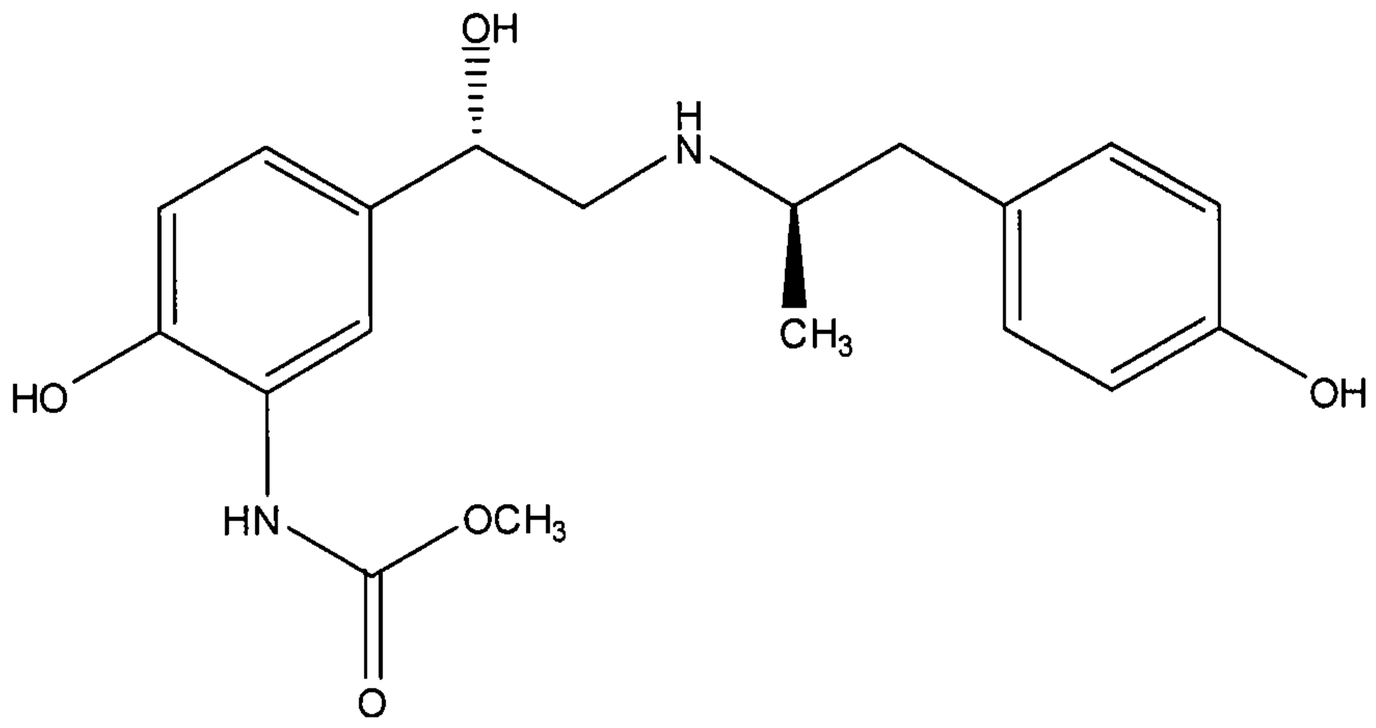
[0060] Step H) Carbamic acid, [2-benzyloxy-5-[(1S)-1-hydroxy-2-[[(1R)-2-(4-hydroxyphenyl)-1-methylethyl]-N-benzylamino]-ethyl]phenyl]-, methyl ester



To a solution of the product of Step G) (1.7 g, 2.6 mmol) in anhydrous THF (17 mL) cooled with an ice water bath was added tetrabutylammonium fluoride solution (5.3 mL of 1.0 M solution in THF, 5.3 mmol) while stirring under argon. The reaction mixture was stirred at

ambient temperature for 1 h, and TLC evaluation (EtOAc/hexanes, 1:1) indicated a complete reaction. The reaction mixture was diluted with EtOAc (200 mL) and washed twice with water (2 x 120 mL), then dried ($MgSO_4$), filtered, and concentrated to give crude product as a yellow oil. The crude material was purified by silica gel column chromatography (2 x 200 g columns), packed in and eluted with 1:1 EtOAc/hexanes [the crude product was loaded onto the column as a solution in CH_2Cl_2]. Fractions containing the purified product were combined and concentrated to give an oil. A total of 2.6 g of starting material was deblocked to give a total of 1.2 g (56%) of the title compound after purification.

[0061] Step I) Carbamic acid, [2-hydroxy-5-[(1S)-1-hydroxy-2-[[(1R)-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-, methyl ester



A mixture of the product of Step H) (300 mg, 0.555 mmol) 10% Pd/C (400 mg, dry material) and EtOH (30 mL) was hydrogenated (ambient temperature) at 50 psi (344.74 kpa) for 22 h. The catalyst was filtered off, and the filtrate was spin evaporated to afford the title compound as an oil (200 mg).

[0062] Step J) Carbamic acid, [2-hydroxy-5-[(1S)-1-hydroxy-2-[[(1R)-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-phenyl]-, methyl ester, (2S,3S)-2,3-dihydroxybutanedioate (1:1) (salt)

480 mg of product prepared by the method of Step I) was dissolved in 0.9 mL of i-PrOH. A solution of 151 mg (1.00 mmol) of D-tartaric acid in 0.3 mL of H_2O was added. The reaction mixture was stored at 5°C for 16 h. Crystallization did not occur. The mixture was subjected to spin evaporation to remove volatiles to produce a brown gum. Attempted triturations using acetone then iPrOH (10 mL each) were unsuccessful. This material (gum) was diluted with

isopropyl ether (15 mL). After stirring for 3 h, a light brown, free flowing solid was formed. The solid was collected on a funnel, washed with 5 mL of isopropyl ether then vacuum dried at room temperature for 60 h to constant weight to give 480 mg of the title compound. MS *m/z*:[M+H$^+$] 361. ^{1}H NMR spectrum consistent with the assigned structure.

[0063] β_1 and β_2 radioligand binding assays

The affinity of a test compound for adrenergic β_1 and β_2 receptors is investigated by evaluating the ability of the compound to displace specific binding of [^{125}I]-cyanopidolol or [^{3}H]-CGP-12177 at human recombinant β_1 and β_2 receptors, respectively (expressed in CHO cells). The IC_{50} is defined as the concentration that inhibits 50% of specific binding of the radioligand. The K_i is calculated from the IC_{50} and the known K_D of the radioligand (Cheng and Prusoff's equation).

[0064] In this test, the compound of Example 1 was found to afford a K_i of >10 μM with only 44% inhibition of specific binding at a concentration of 20 μM for the β_1 receptor and 0.99 μM for the β_2 receptor. The β_1/β_2 binding ratio was found to be >10.

[0065] By way of comparison, the values found for arformoterol and the (S,R) isomer of formoterol were 0.155 μM (β_1), 0.004 μM (β_2) and 41(β_1/β_2), and 2.50 μM (β_1), 0.075 μM (β_2) and 33(β_1/β_2), respectively.

[0066] Intrinsic activity assessment (β_2)

The intrinsic activity of a test compound is assessed by evaluating its ability to increase cAMP production from human recombinant β_2 receptors expressed in CHO cells. Data are expressed as % response relative to a procaterol-induced cAMP increase.

[0067] The compound of Example 1 was found to have an intrinsic activity of 79%.

[0068] By way of comparison, arformoterol and (S,R)-formoterol were found to have intrinsic activities of 98% and 91% respectively.

[0069] <u>β_1 and β_2 adrenergic activity (functional)</u>

Functional agonism at adrenergic β_1 receptors is demonstrated by a positive chronotropic effect in isolated right atria from Dunkin Hartley Guinea pigs. The concentration that gives 50% maximal effect is the EC_{50}.

[0070] Functional agonism at adrenergic β_2 receptors is demonstrated by relaxation of the spontaneous tone of isolated trachea from Dunkin Hartley Guinea pigs. The concentration that gives 50% maximal effect is the EC_{50}.

[0071] In these tests, an EC_{50} could not be determined for the compound of Example 1 for the β_1 functional assay as only a 20% increase in heart rate was seen at a concentration of 30 μM. However, the compound of Example 1 was found to have an EC_{50} of 62 nM for the β_2 receptor. The β_1/β_2 functional ratio was found to be >484.

[0072] By way of comparison, the values found for arformoterol were 3 nM (β_1), 0.041 nM (β_2) and 75.

[0073] **Stability in Aqueous Buffered Solutions**

***Solution Preparations*:** For each test compound, the following solutions are prepared.

- ***Solution A*** is prepared from ~ ***30 mg*** of the test compound in 150 mL of 0.005 M citrate buffer, pH 5.0 (~ 0.2 mg/mL).
- ***Solution B*** is prepared as follows: approximately 30 mL aliquot of Solution A is transferred to a separated container and the pH of the solution is adjusted to pH 3.0 with 1 N HCl (~ 0.2 mL).
- ***Solution C*** is prepared as follows: approximately 30 mL aliquot of Solution A is transferred to a separated container and the pH of the solution is adjusted to pH ~8.0 with 1 N NaOH (~ 0.2 mL).

Note: Because the volume of 1 N HCl or 1 N NaOH used for adjusting pH was negligible, the concentration of test compound in Solutions A, B and C were the same.

[0074] **Storage Scheme**

- As soon as the above solutions were prepared, aliquots of each solution were transferred into 11 vials, of which 9 vials are stored at -20°C, and one each is stored at 30°C and 40°C, respectively.
- At each interval listed below, two vials are removed from -20°C storage, and stored at 30°C and 40°C, respectively.
- The corresponding weeks under the storage condition (30°C or 40°C) are shown in the table below.

Week of Vial Removal	0	4	8	10	11	12
Weeks Under Storage Condition (30°C or 40°C)	12	8	4	2	1	0

[0075] On Week 12, the last vial stored at –20°C is removed and warmed up to the room temperature, which is the **Day 0 Solution**.

[0076] ***Sample Analysis:*** On Week 12, all solutions are assayed by an HPLC method using the Day 0 Solution at pH 5 as a standard solution. The test compounds were assayed by HPLC with UV detection (refer to **Table 1** for method conditions).

Table 1 HPLC Method Conditions			
Parameter	**Method Detail**		
Column	Atlantis dC18, 3µm 150 x 4.6 mm		
Mobile Phase A	Water/HCOOH 100/0.1, v/v		
Mobile Phase B	ACN/Water/HCOOH 30/70/0.1, v/v/v		
Column Temp	35°C		
Sampler Temp	5°C		
Injection Volume	5 µL		
Flow Rate	0.6 mL/min		
Wavelength	PDA 200-350 nm		
Run Time	50 min		
Gradient Table	**Time(min)**	**%A**	**%B**
	0	100	0
	8	100	0
	15	70	30
	45	5	95
	46	100	0
	50	100	0

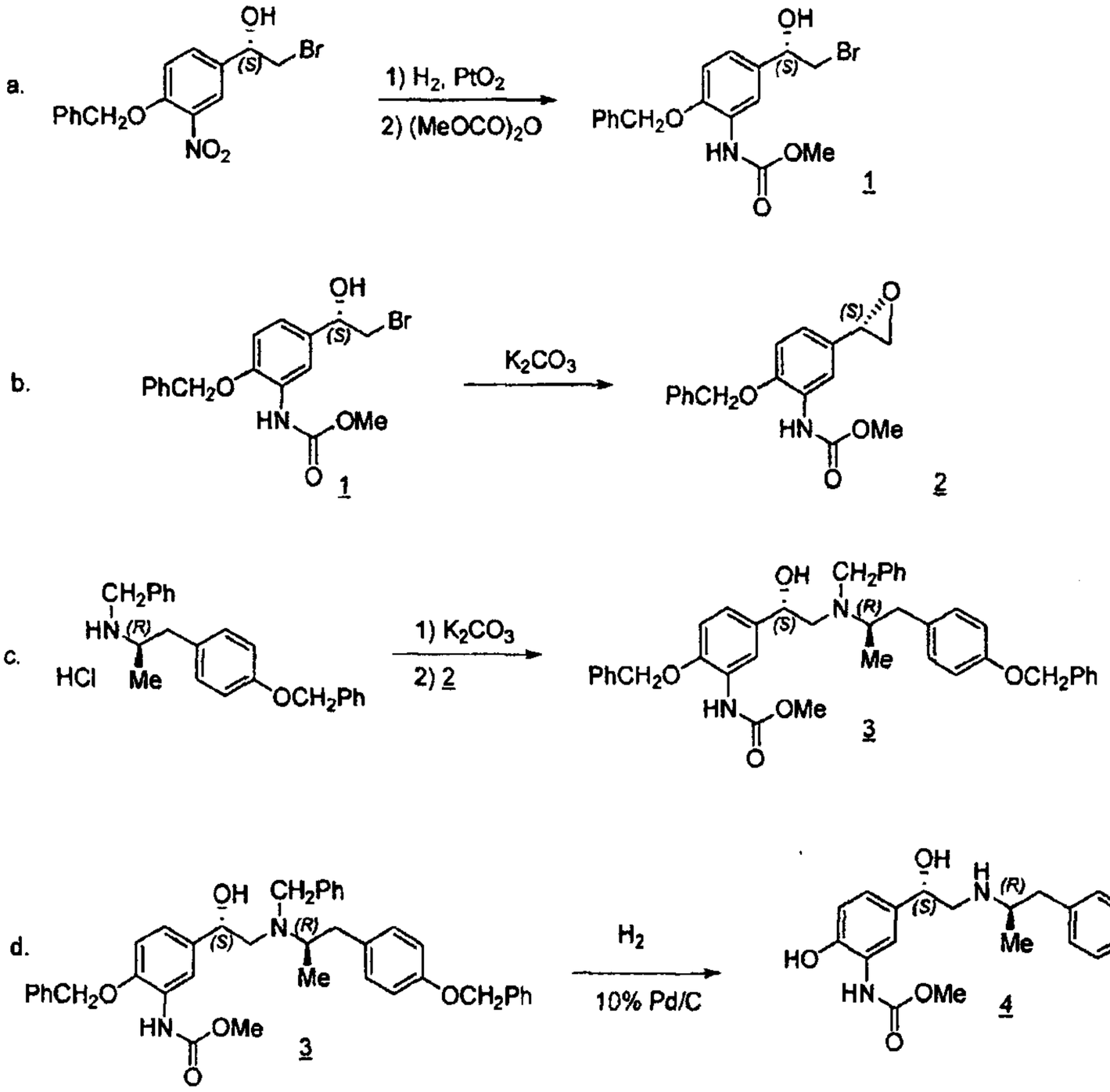
Table 2 Stability of Carbamic acid, [2-hydroxy-5-[(1S)-1-hydroxy-2-[[(1R)-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-phenyl]-, methyl ester Aqueous Solution (% of Initial Concentration (0.19847 mg/mL) in pH 5.0)						
Condition	pH 3.0		pH 5.0		~pH 8	
Time (wk)	30°C	40°C	30°C	40°C	30°C	40°C
0	98.31	98.31	100.20	100.20	97.78	97.78
1	99.95	98.87	99.68	100.40	69.33	30.18
2	99.12	100.33	101.08	101.07	50.77	8.85
4	100.91	105.71	101.59	102.09	27.72	0.52
8	101.16	106.72	105.28	104.88	6.96	0
12	101.54	106.51	106.61	106.74	1.24	0

[0077] Conclusion: At pH 3 or 5, the compound of Example 1 was found to be very stable for at least 12 weeks when stored at 30°C.

[0078] Example 2:

Alternative Preparation of Carbamic acid, [2-hydroxy-5-[(1S)-1-hydroxy-2-[[(1R)-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-phenyl]-, methyl ester.

[0080] Reaction Sequence 101



[0081] Preparation of Compound 1 in Reaction Sequence 101

A solution of (S)-2-bromo-1-(4-benzyloxy-3-nitrophenyl)-ethanol (83.6 g, 0.237 mol) in THF (150 mL) and toluene (150 mL) was added to a Parr shaker bottle containing PtO2 (1.08 g, Adam's catalyst). The mixture was shaken under H_2 (50 psi) until the reaction was complete (20 h). The catalyst was then removed by filtration through celite™ under an argon atmosphere, the cake was washed with THF (2 x 150 mL), and the filtrates were combined and stirred under an atmosphere of argon. Dimethyl dicarbonate (30.0 mL, d = 1.25, 0.280 mol) was added dropwise over 30 min. The mixture was then stirred for 6 h and then a second portion of dimethyl dicarbonate (10.0 mL, 0.0932 mol) was added. The mixture was stirred for a

further 15 h then H2O (750 mL) was added, and stirring was continued for 5 min. Dichloromethane (750 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 250 mL). The combined organics were then washed with water (2 x 750 mL), brine (2 x 250 mL) then dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated to a volume of (300 mL). Silica gel (200 g) was then added, and the mixture was concentrated to dryness. The solid was then loaded on to a column of SiO2 (2.8 kg) packed in CH_2Cl_2. The column was eluted with CH_2Cl_2 (3 L), 1% THF/CH_2Cl_2 (6 L), 2% THF/CH_2Cl_2 (9 L), 3% THF/CH_2Cl_2 (8 L), 3.5% THF/CH_2Cl_2 (2 L), 4% THF/CH_2Cl_2 (2 L), 5% THF/CH_2Cl_2 (4 L). The appropriate fractions as determined by TLC were combined and concentrated in vacuo to give a solid that was suspended in Et_2O (130 mL). The mixture was stirred for 4 h, and the solids were collected, washed with cold Et_2O (2 x 30 mL), then dried to a constant weight in vacuo to give 56.1 g (62.2%) of Compound 1. A total of 105 g of Compound 1 was made by this method.

[0082] **Preparation of Compound 2 in Reaction Sequence 101**

Compound 1 (28.0 g, 73.6 mmol) was dissolved in MeOH (235 mL) and THF (235 mL). Potassium carbonate (13.8 g, 99.9 mmol) was added, and the mixture was stirred at ambient temperature for 2.5 h. The mixture was concentrated in vacuo, then the residue was suspended in CH_2Cl_2 (275 mL) and stirred for 40 min. The solid was then removed by filtration and washed with CH_2Cl_2 (3 X 50 mL). The combined filtrates were then concentrated in vacuo, and the residue was suspended in Et_2O and stirred for 15 min. The undissolved solid was then removed by filtration and was washed with Et_2O (2 x 25 mL). The combined filtrates were then concentrated in vacuo, and the residue was suspended in hexane (150 mL) and was stirred for 30 min. The hexane was then decanted, and the solid was resuspended in hexane (150 mL) and was stirred for 30 min. The hexane was then decanted, and the solid was dried in vacuo at ambient temperature to a constant weight to give 19.8 g (89.9%) of Compound 2. A total of 71.1 g of Compound 2 was prepared by this method.

[0083] **Preparation of Compound 3 in Reaction Sequence 101**

(R)-1-(4-benzyloxyphenyl)-2-(benzylamino)propane hydrochloride (38.1 g, 0.104 mol) was added to a mixture of K_2CO_3 (134 g, 0.970 mol), H_2O (650 mL) and CH_2Cl_2 (650 mL). The mixture was stirred for 1 h then the layers were separated, and the aqueous layer was washed

with CH_2Cl_2 (2 x 300 mL). The combined organics were washed with water (2 x 500 mL), dried over Na_2SO_4, filtered and then concentrated in vacuo. The oil was then dried to constant weight in vacuo to give 32.9 g of the free base as a brown oil. Compound 2 (19.6 g, 65.5 mmol) was then mixed with the free base (31.1 g, 93.8 mmol)and then heated to 60°C. The resulting solution was heated at 60 ± 4°C for 20 h. The mixture was cooled, diluted with EtOAc (15 mL), hexanes (10 mL), and then loaded onto a column of SiO2 (1 kg) packed with 1:2 EtOAc/hexanes. The column was eluted with 1:2 EtOAc/hexanes (3.5 L), and the appropriate fractions as determined by TLC were combined and concentrated in vacuo. This gave 3.0 g of high purity material (96.7% HPLC) and 18.0 g (44%) of lower purity material which was then purified by column chromatography on A12O3 (1.2 kg). The column was packed with 1:2 EtOAc/hexanes and eluted with 1:2 EtOAc/hexanes (9 L). The appropriate fractions as determined by TLC were combined and concentrated in vacuo. This gave 4.7 g of high purity material (97.5%, HPLC) and 9.0 g of lower purity material. The different lots were combined with material of similar purity from other runs and further purified by column chromatography on Al_2O_3. In this way a total of 62.6 g of Compound 2 gave 36.9 g of Compound 3 with a purity of >98.6% (HPLC).

[0084] **Preparation of Compound 4 in Reaction Sequence 101**

Compound 3 (8.0 g, 12.7 mmol) was dissolved in a mixture of EtOH (160 mL) and EtOAc (15 mL). The solution was then added to a Parr shaker bottle containing 10% Pd/C (4.0 g), and the mixture was shaken under H_2 (50 psi) for 6 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo, then dried in vacuo to constant weight to give 4.2 g (92%) of Compound 4 as an off-white foam. This material was then combined with 11.0 g of similar material and dissolved in a mixture of EtOAc (40 mL) and EtOH (1 mL). Diethyl ether (600 mL) was then added in order to precipitate the product, and the resulting suspension was vigorously stirred for 2 h. The precipitated solid was then collected by filtration, washed with cold Et_2O (20 mL), then dried in vacuo at 25°C for 8 h. This process gave 11.4 g (75% recovery) of Compound 4 as an off-white solid, lot no. TR39-103-1 (95.1% HPLC purity). A further 4.4 g of Compound 4 was subjected to the above precipitation procedure to give 2.5 g of Compound 4 as an off-white solid, lot no. TR39-102-1 (94.3% HPLC purity). The mother liquors from the precipitation of lot TR39-102-1 were then concentrated to give 1.5 g of a yellow solid, lot No. TR39-102-2, that was enriched in the HPLC impurities.

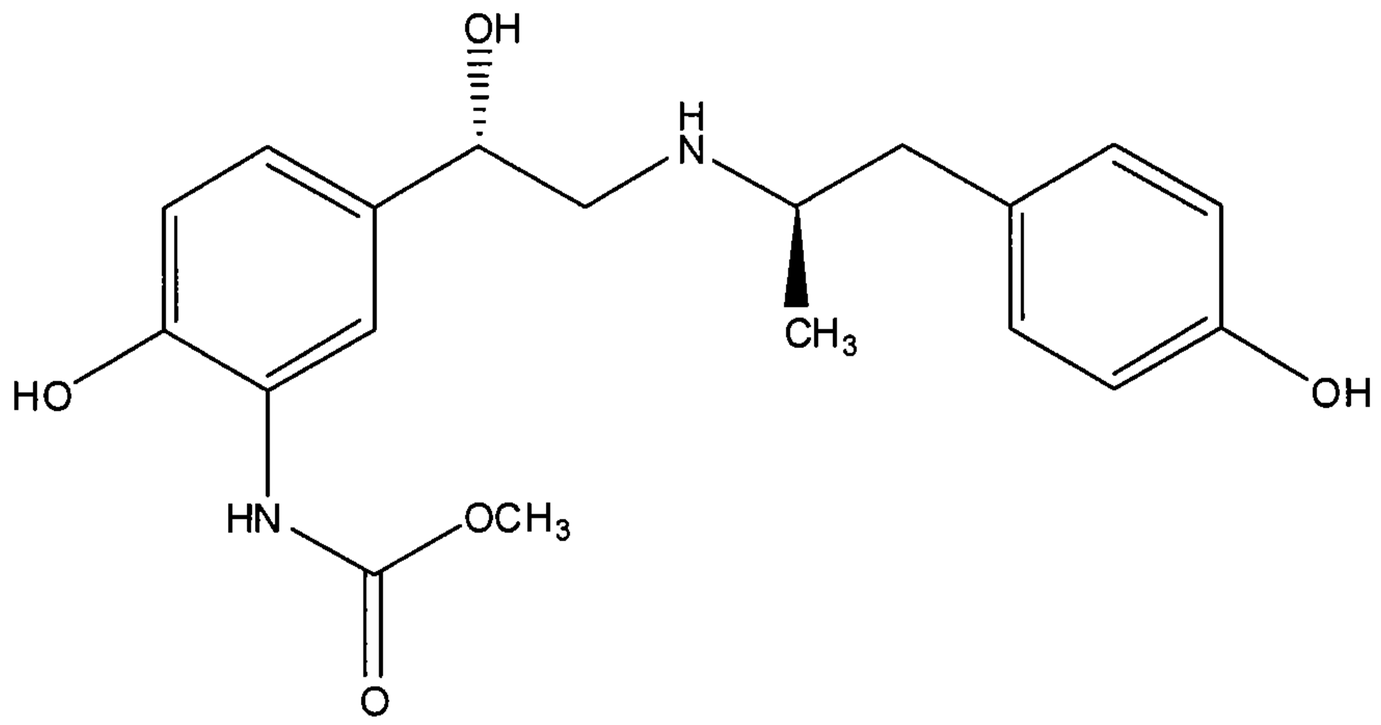
Source of Materials in Example 2

1.	(S)-2-bromo-(4-benzyloxy-3-nitrophenyl)ethanol	Sepracor Inc.
2.	Tetrahydrofuran	Aldrich Chemical Co.
3.	Platinum(IV) oxide	Aldrich Chemical Co.
4.	Toluene	Aldrich Chemical Co.
5.	Dimethyl dicarbonate	Aldrich Chemical Co.
6.	Dichloromethane	J.T. Baker Chemical Co.
7.	Magnesium sulfate	Fisher Scientific
8.	Silica gel	EMD Chemicals Inc.
9.	Diethyl ether	Fisher Scientific
10.	Methanol	Aldrich Chemical Co.
11.	Potassium carbonate	Aldrich Chemical Co.
12.	Hexanes	J.T. Baker Chemical Co.
13.	(R)-1-(4-benzyloxyphenyl)-2-(benzylamino)propane hydrochloride	Sepracor Inc.
14.	Sodium sulfate	J.T. Baker Chemical Co.
15.	Ethyl acetate	J.T. Baker Chemical Co.
16.	Aluminum oxide, neutral	Woelm Chemical Inc.
17.	10% Palladium on carbon	Aldrich Chemical Co.
18.	Ethyl alcohol	Aaper Chemical Co.
19.	Hydrogen gas	Mills Welding & Specialty Gases

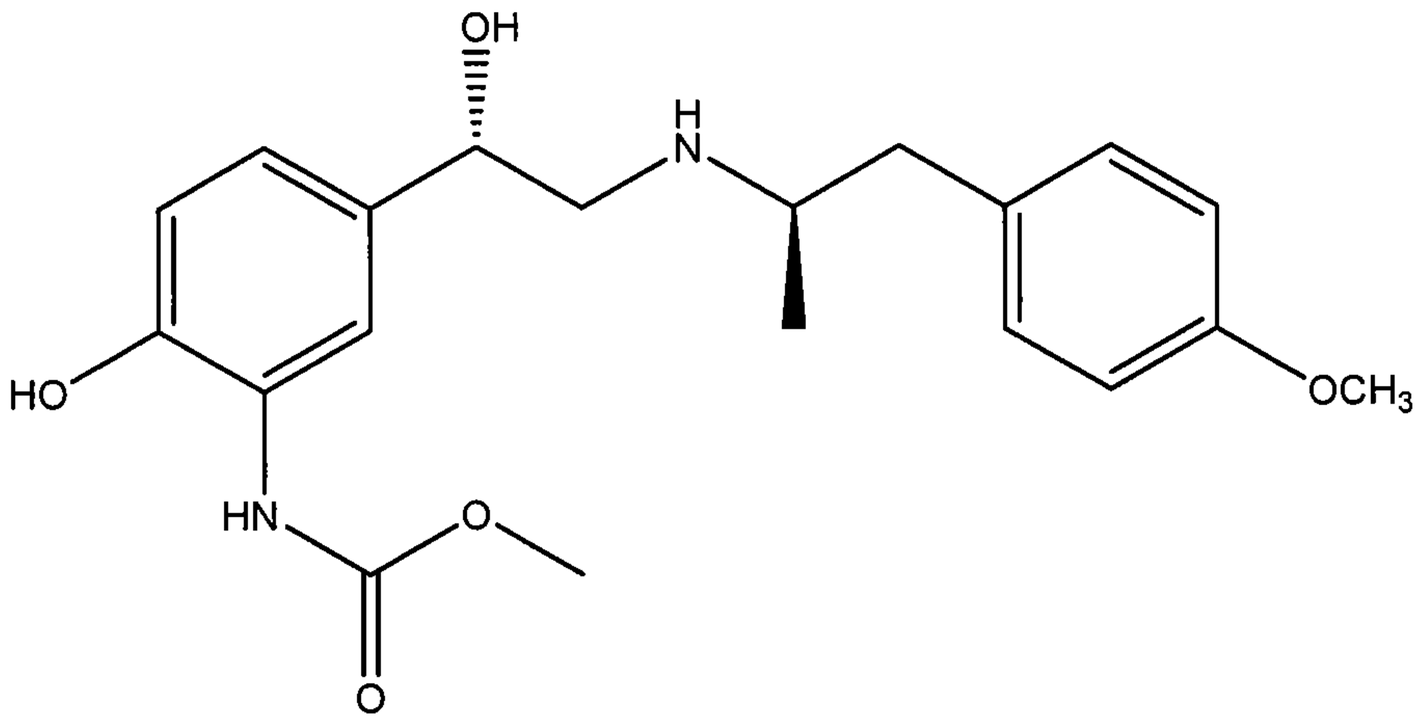
[0085] Table 3

Compound	K_i (μM)		β_1/β_2 Binding Ratio	Functional Activity EC_{50} (nM)		β_1/β_2 Functional Ratio	Intrinsic Activity cAMP (%)	Results of Secondary Screen % Inhibition of activity or specific binding at 3 μM				
	β_1	β_2		β_1	β_2			CYP2D6	α_{1A}	α_{1B}	α_{1D}	SERT
A	8.4	2.51	**3.3**	(0)	1900	**>16**	53	<50	**93**	**81**	**93**	**68**
Formula I	>10 (44%)	0.99	**>10**	(20)	62	**>484**	79	<50	**79**	**50**	**70**	<50
B	6.29	2.44	**2.6**	(0)	2500	**>12**	67	**54**	**90**	**73**	**83**	<50
Arformoterol	0.155	0.004	**41**	3	0.041	**75**	98	NT	NT	NT	NT	NT
Levalbuterol	1.54	0.24	**6.4**	177	747	**0.24**	17	NT	NT	NT	NT	NT
(*S,R*)-Formoterol	2.50	0.075	**33**	NT	NT	**NT**	91	NT	NT	NT	NT	NT

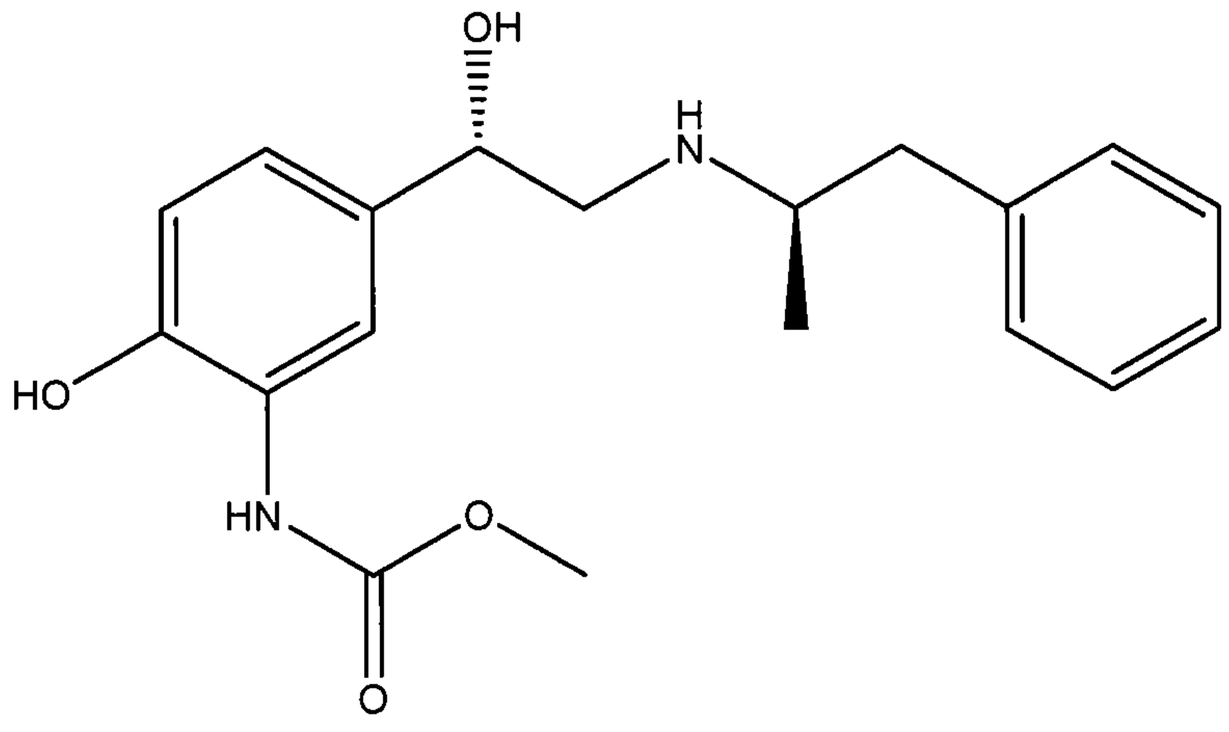
Compounds in Table 3



Formula I



Compound A

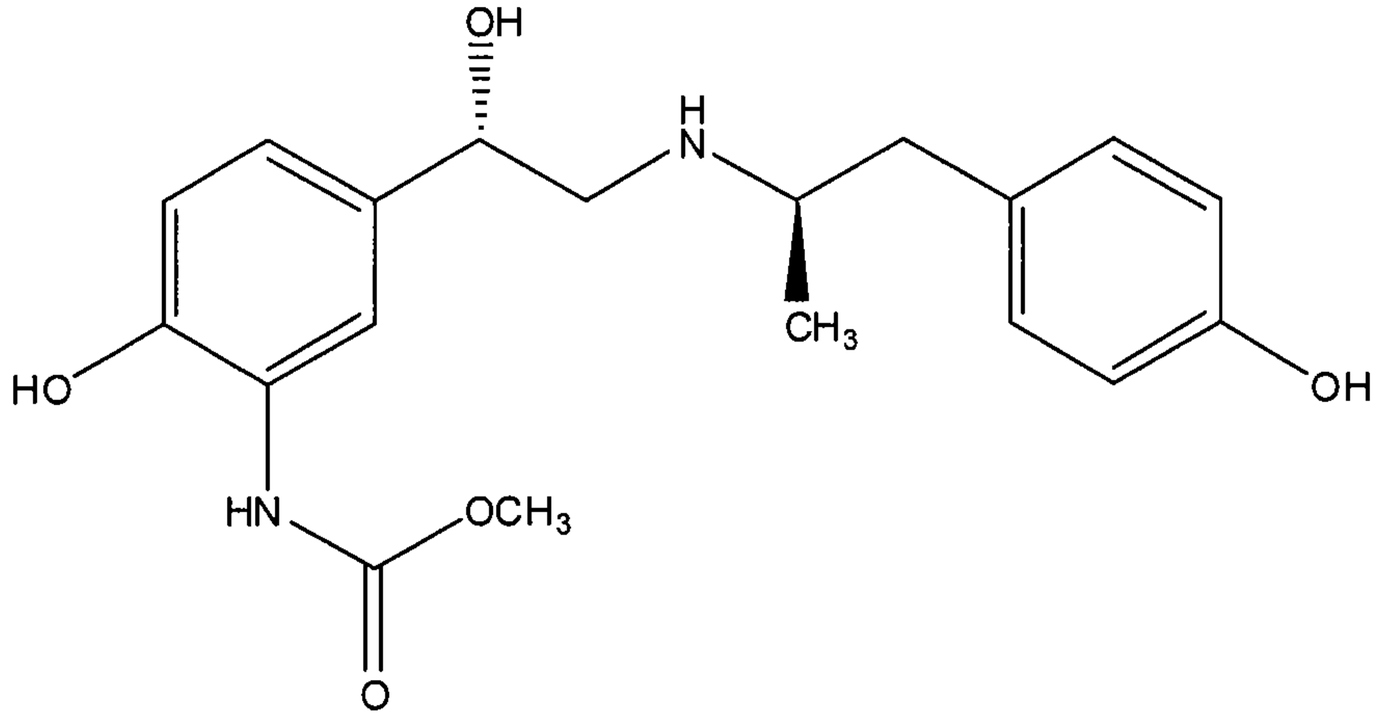


Compound B

In Table 3, K_i values were established using recombinant human transporters expressed in Rex16 cells (β1) or CHO cells (β2). The K_i for arformoterol at β2 was 3.76 nM. For compounds where K_i values are not provided, the percentage inhibition of specific binding at the highest concentration evaluated is in parentheses. The β_1 functional activity EC_{50} is the concentration that resulted in a 50% increase in atrial rate relative to 50 nM isoproterenol response in atria isolated from Dunkin Hartley Guinea pigs. The values in parentheses are the % increase in atrial rate at a concentration of 30 μM. compound A (35%), and compound B (31%) showed signs of β_1 antagonism at a 30 μM concentration. β_2 functional activity EC_{50} is the concentration that resulted in a 50% relaxation of spontaneous tone relative to a response induced by 15 nM isoproterenol in trachea isolated from Dunkin Hartley Guinea pigs. The intrinsic activity describes the increase in cAMP relative to the procaterol response in CHO cells expressing the human β2 adrenoceptor. In the table 3, α1 = α1 adrenoceptors, SERT = 5-HT transporter, and NT = not tested. In the results of secondary screen, compounds were evaluated for their ability to inhibit specific binding or activity

(CYP450s) in a panel of 72 assays. The targets listed are only those where a >50% specific binding or activity was determined.

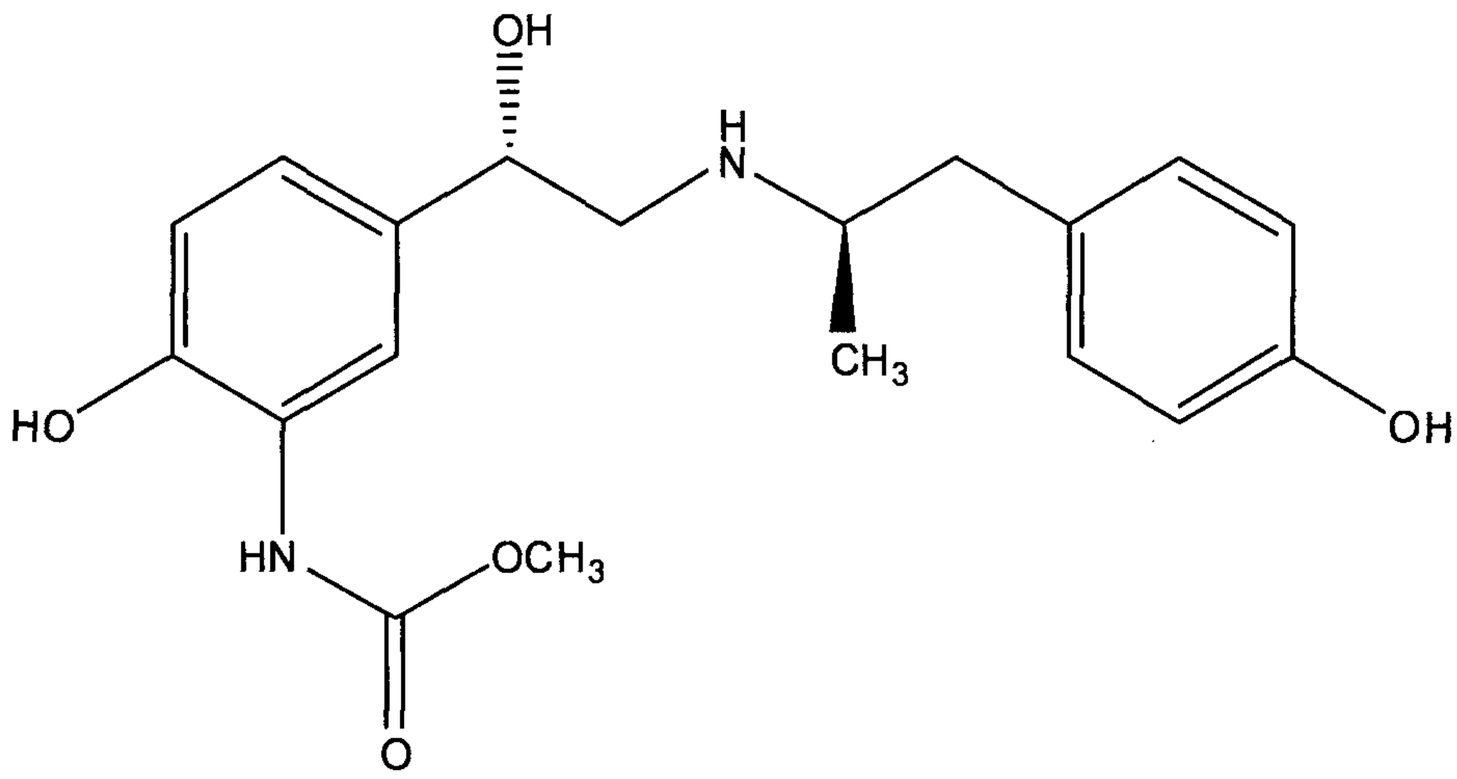
Figure 1 shows the effects of the compound of formula I, methyl [2-hydroxy-5-[(1S)-1-hydroxy-2-[[(1R)-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-phenyl] carbamate, compound of Formula 1



, on acetylcholine (Ach) induced effects on airway resistance. In Figure 1, it can be seen that that the compound of formula I, methyl [2-hydroxy-5-[(1S)-1-hydroxy-2-[[(1R)-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-phenyl] carbamate, is effective against bronchoconstriction.

What is claimed is:

1. A compound of formula (I)



(I)

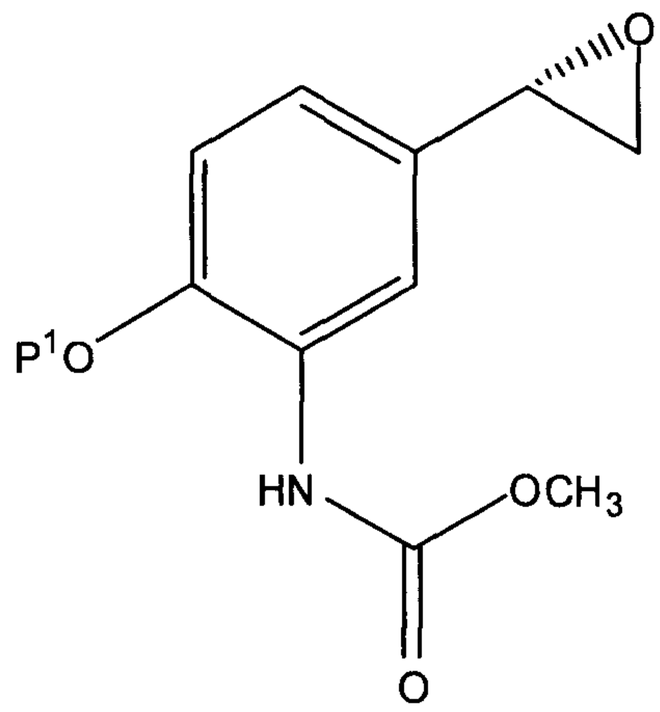
or a pharmaceutically acceptable salt thereof.

2. A mixture of isomers of methyl [2-hydroxy-5-[1-hydroxy-2-[[(2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-phenyl] carbamate, wherein the mixture comprises at least 90% by weight of the isomer

.

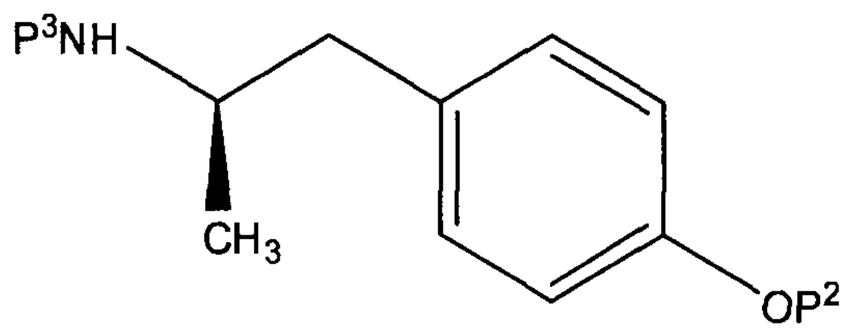
3. A compound as claimed in claim 1 or claim 2, which is in the form of a D-tartrate salt.

4. A process for the preparation of a compound as defined in any one of claims 1 to 3, which comprises reacting a compound of general formula (II)



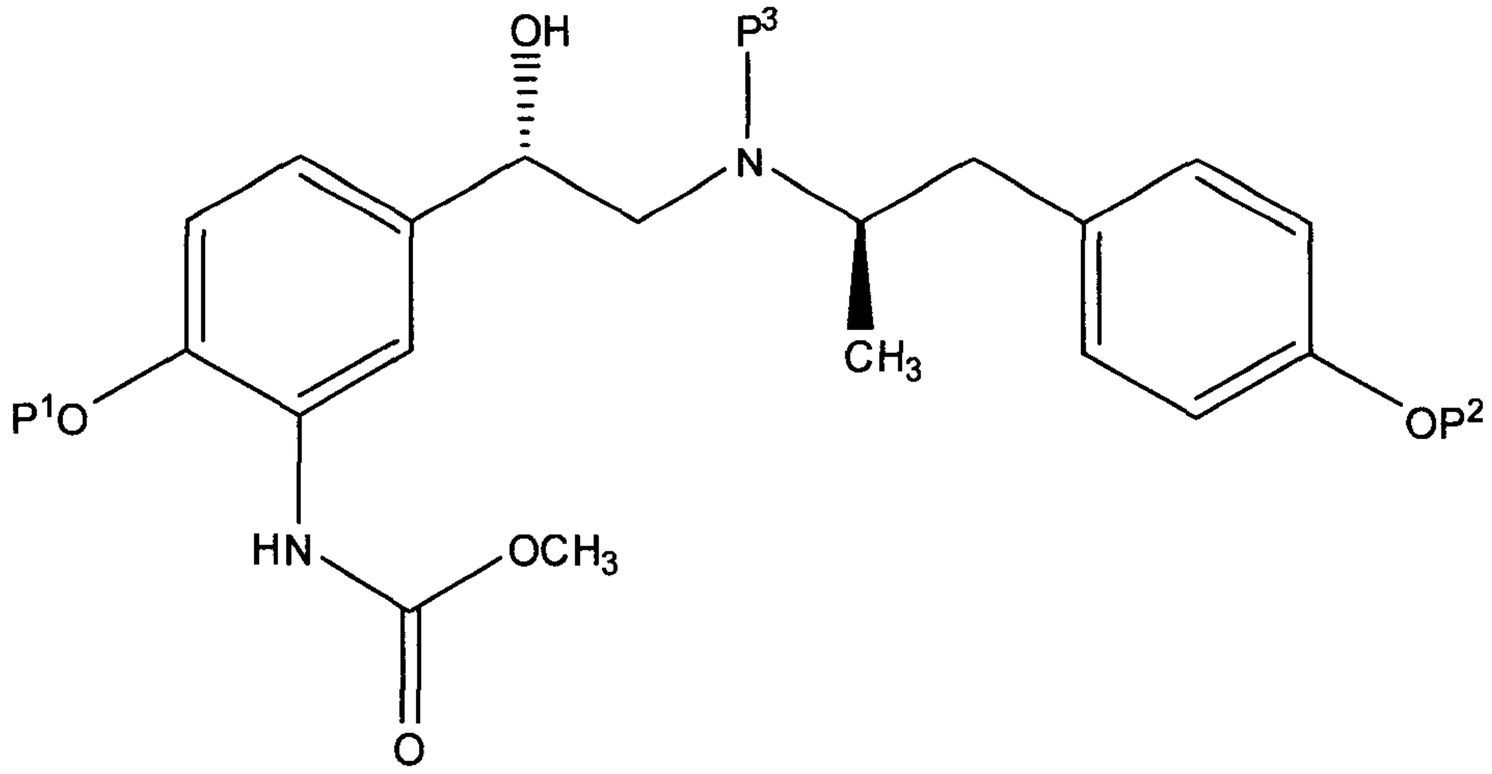
(II)

in which P^1 represents a hydrogen atom or a hydroxyl protecting group, with a compound of general formula (III)



(III)

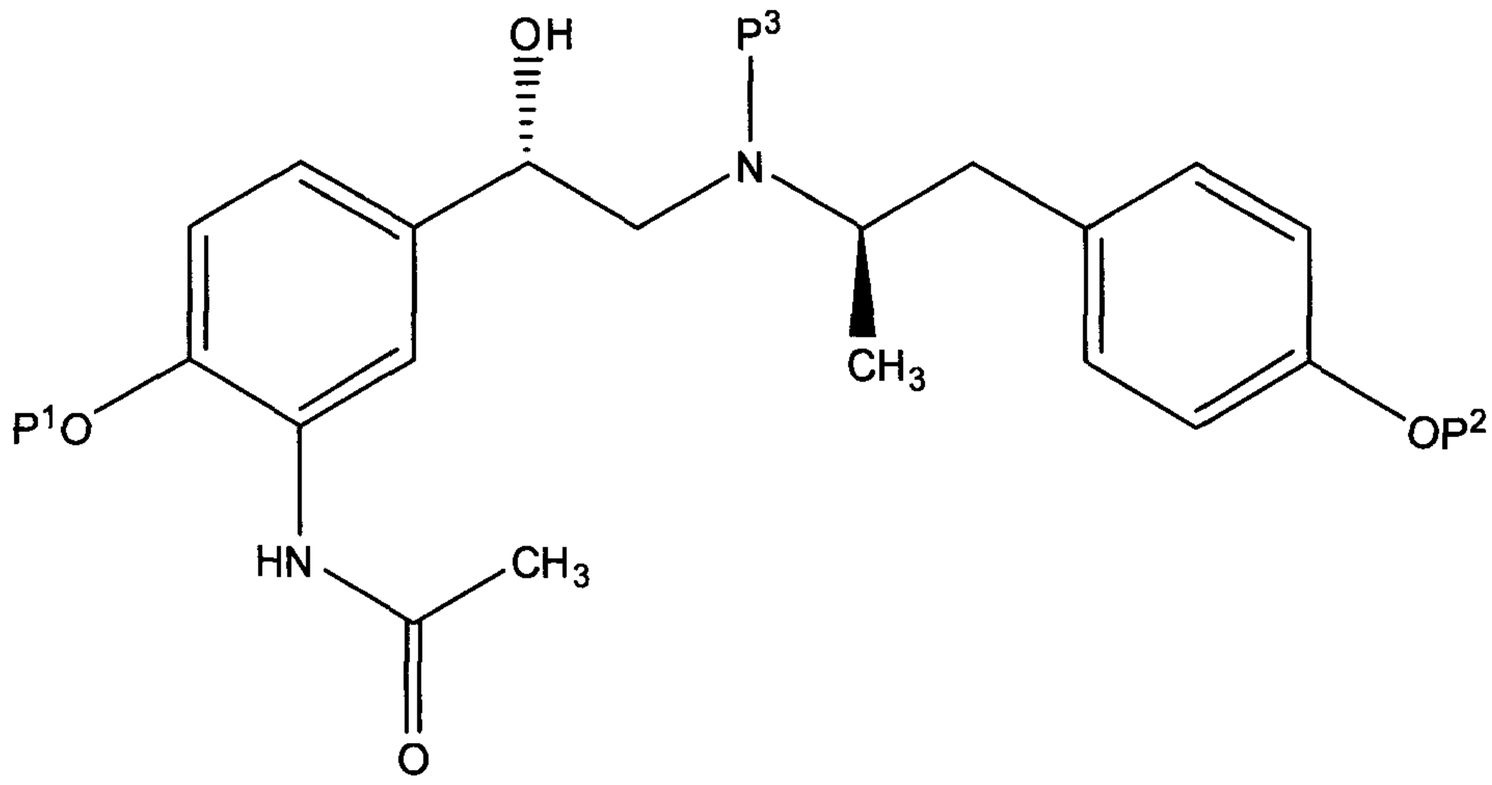
in which P^2 represents a hydrogen atom or a hydroxyl protecting group and P^3 represents a benzylic amine protecting group, to afford a compound of general formula (IV)



(IV)

or a salt thereof, followed by removing any protecting groups P^1, P^2 and P^3 and, if desired, forming a pharmaceutically acceptable acid addition salt.

5. A compound of general formula (IV)



(IV)

or a salt thereof, in which P^1 and P^2 each represents a hydrogen atom or a hydroxyl protecting group, and P^3 represents a hydrogen atom or a benzylic amine protecting group, provided that at least one of P^1, P^2 and P^3 represents a protecting group.

6. A pharmaceutical composition, which comprises a compound as claimed in any one of claims 1 to 3 and a pharmaceutically acceptable carrier.

7. A pharmaceutical composition as claimed in claim 6, which further comprises a steroid.

8. A pharmaceutical composition as claimed in claim 7, in which the steroid is beclomethasone, triamcinolone, funisolide, mometasone, budesonide or fluticasone.

9. A pharmaceutical composition as claimed in any one of claims 6 to 8, which further comprises a muscarinic receptor antagonist.

10. A pharmaceutical composition as claimed in claim 9, in which the muscarinic receptor antagonist is ipratropium or tiatropium.

11. A pharmaceutical composition as claimed in any one of claims 6 to 10 which further comprises an anticholinergic.

12. A pharmaceutical composition as claimed in claim 11, in which the anticholinergic is glycopyrralate.

13. A pharmaceutical composition as claimed in any one of claims 6 to 12 which further comprises a mucolytic.

14. A pharmaceutical composition as claimed in claim 13, in which the mucolytic is cromoglycate, acetylcysteine, arginine, or 2-mercaptoethanesulphonate.

15. A pharmaceutical composition as claimed in any one of claims 6 to 14 which further comprises an anti-inflammatory.

16. A pharmaceutical composition as claimed in claim 15, in which the anti-inflammatory agent is an inhibitor of tumor necrosis factor alpha or dipeptidyl peptidase IV, or antibodies to pro-inflammatory interleukins.

17. A use of an effective amount of a compound as claimed in claim 1, for treating bronchoconstriction associated with a reversible obstructive airways disease, in a patient in need of treatment.

18. A use of an effective amount of a compound as claimed in claim 1, for the preparation of a medicament for treating bronchoconstriction associated with a reversible obstructive airways disease, in a patient in need of treatment.

19. A pharmaceutical composition as claimed in claim 16, in which the antibodies to pro-inflammatory interleukins are IL4 or IL13.

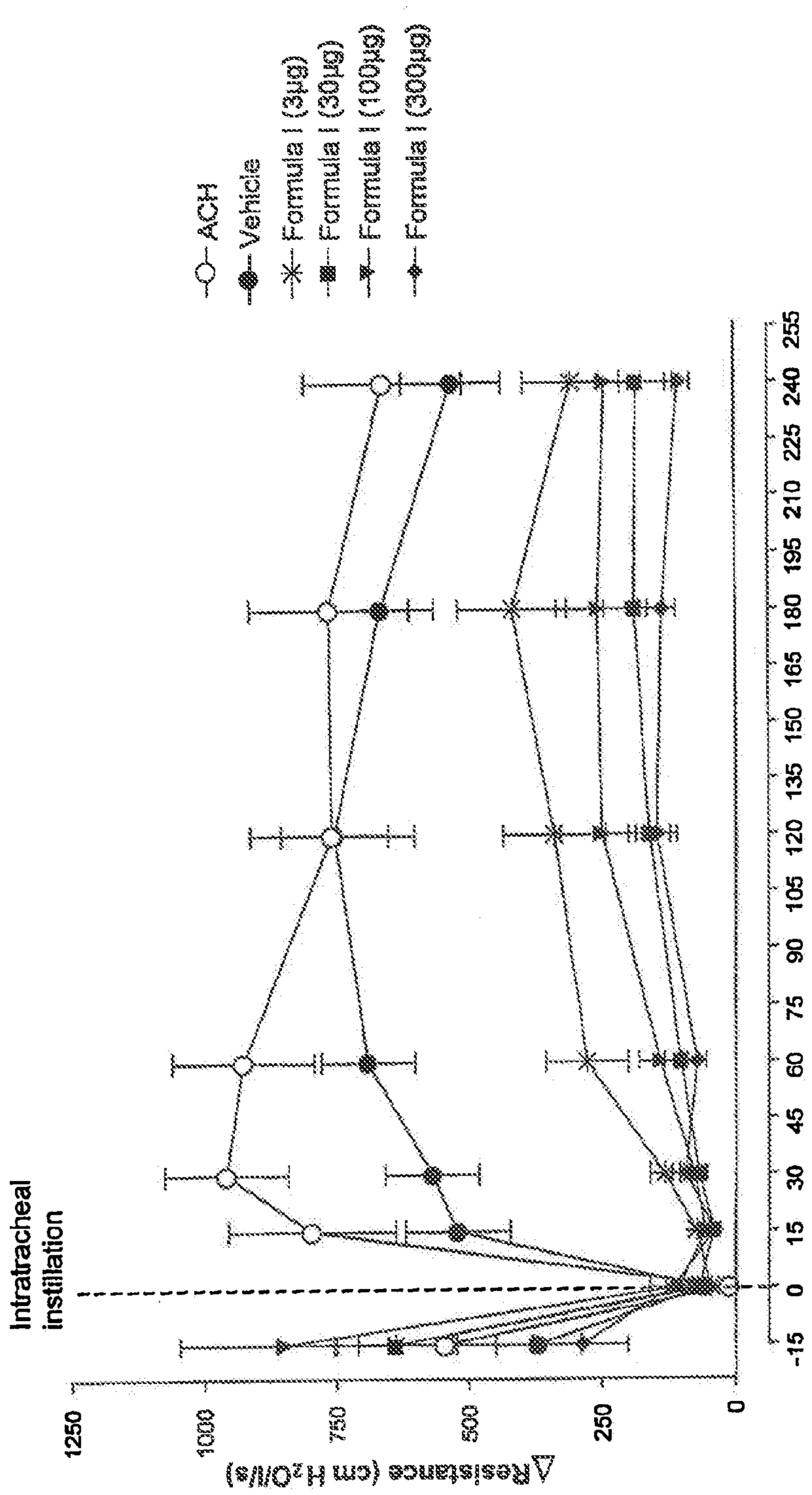
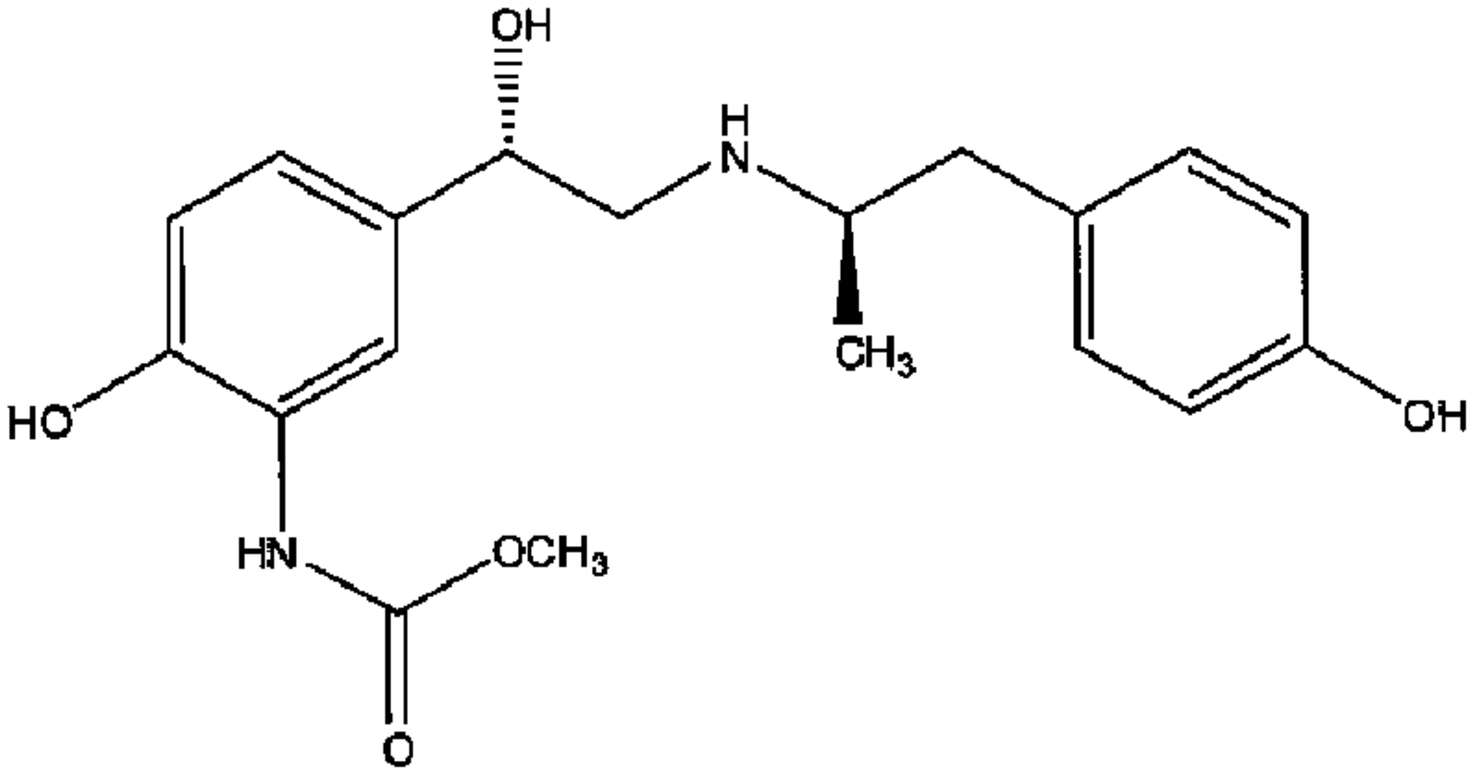
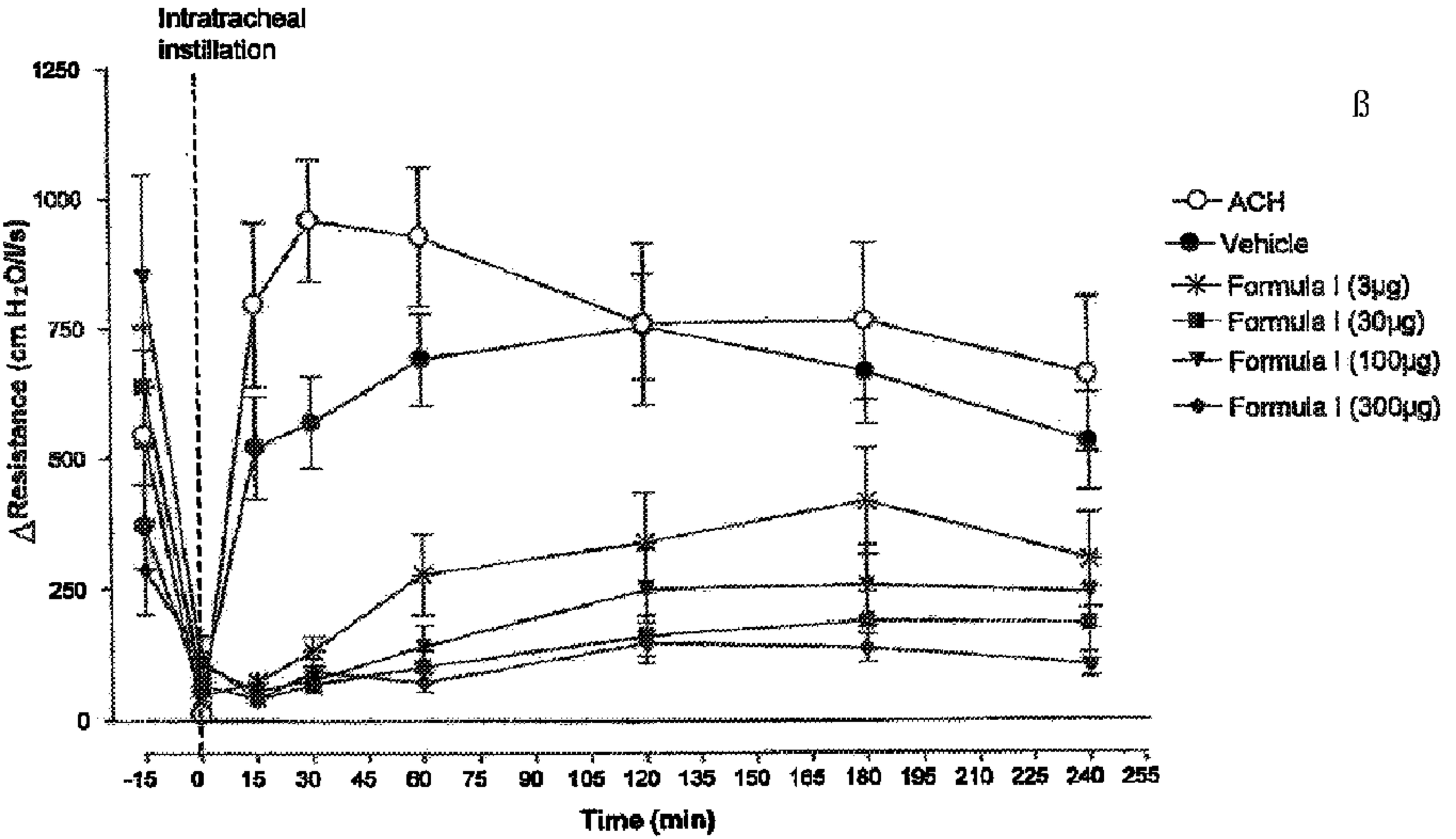

ACH
Vehicle
Formula I (3µg)
Formula I (30µg)
Formula I (100µg)
Formula I (300µg)
Intratracheal instillation
Time (min)
-15
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210
225
240
255
0
250
500
750
1000
1250
ΔResistance (cm H2O/l/s)

Figure 1


OH
H
N
CH3
HO
OH
HN
OCH3
O

(I)


Intratracheal instillation
1250
1000
750
500
250
0
Δ Resistance (cm H2O/l/s)
-15
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210
225
240
255
Time (min)
ACH
Vehicle
Formula I (3µg)
Formula I (30µg)
Formula I (100µg)
Formula I (300µg)

ß