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(54) Benævnelse: **ESTER PRO-DRUGS AF [3-(1-(1H-IMIDAZOL-4-YL)ETHYL)-2-METHYLPHENYL] METHANOL**

(56) Fremdragne publikationer:
WO-A1-95/14007
WO-A1-2006/036480
WO-A1-2009/089132
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TESTA B ET AL: "DESIGN OF INTRAMOLECULARLY ACTIVATED PRODRUGS", DRUG METABOLISM REVIEWS, MARCEL DEKKER, NEW YORK, NY, US, vol. 30, no. 4, 1 January 1998 (1998-01-01), pages 787-807, XP009009563, ISSN: 0360-2532

DESCRIPTION

BACKGROUND OF THE INVENTION

1. Field of the invention

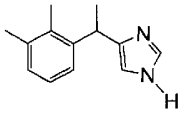
[0001] The invention relates to the field of pharmaceutical compounds, in particular ester pro-drugs of (S)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol. The invention further concerns pharmaceutical compositions containing the pro-drugs.

2. Summary of the related art

[0002] Three alpha-1 and three alpha-2 adrenergic receptors have been characterized by molecular and pharmacological methods. Activation of these alpha receptors evokes physiological responses with useful therapeutic applications.

[0003] 4-[1-(2,3-Dimethylphenyl)ethyl]-3*H*-imidazole, generically known as medetomidine, is an alpha 2 adrenergic agonist for use in the sedation of animals. The hydrochloride salt of the (*S*) enantiomer of medetomidine, generically known as dexmedetomidine, (*S*) 4-[1-(2,3-dimethylphenyl)ethyl]-3*H*-imidazole, is also indicated for use as a sedative or analgesic in cats and dogs.

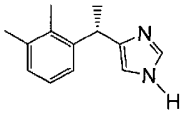
[0004] The metabolite of dexmedetomidine, (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, together with its racemic mixture compound, [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, are described in the literature in Journal of Chromatography, (1997), 762(1 + 2), 281-291 by Hui, Y.-H et al.



Medetomidine

4-(1-(2,3-dimethylphenyl) ethyl)-1*H*-imidazole

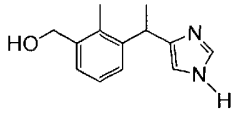
CAS 86347-14-0



Dexmedetomidine

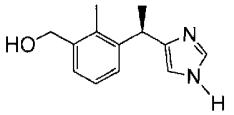
(*S*)-4-(1-(2,3-dimethylphenyl) ethyl)-1*H*-imidazole

CAS 189255-79-6



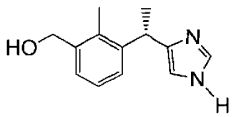
(3-(1-(1*H*-imidazol-4-yl)ethyl) -2-methylphenyl)methanol

CAS 128366-50-7



(*R*)-(3-(1-(1*H*-imidazol-4-yl)ethyl) -2-methylphenyl)methanol

CAS 1240244-32-9



(*S*)-(3-(1-(1*H*-imidazol-4-yl)ethyl) -2-methylphenyl)methanol

CAS 189255-79-6

[0005] [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl]methanol is described in "Synthesis of detomidine and medetomidine metabolites: 1,2,3-trisubstituted arenes with 4'(5')-imidazolylmethyl groups" in Journal of Heterocyclic Chemistry (1993), 30(6), 1645-1651 by Stoilov et al.

[0006] Kavanagh, et al. describe [3-(1-(1H-imidazol-4-yl)ethyl)-2-methylphenyl]methanol in "Synthesis of Possible Metabolites of Medetomidine {1-(2,3-dimethylphenyl)-1-[imidazol-4(5)-yl]ethane" in Journal of Chemical Research, Synopses (1993), (4), 152-3.

[0007] [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl)methanol] is described by Salonen, et al. in "Biotransformation of Medetomidine in the Rat" in Xenobiotica (1990), 20(5), 471-80.

[0008] PCT Int. Appl. WO 2010093930 A1 discloses [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl]methanol and its (*S*) and (*R*) enantiomers.

SUMMARY OF THE INVENTION

[0009] The present invention provides ester pro-drugs of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol and pharmaceutical compositions containing them. The pro-drugs can be used as pharmaceuticals. Upon hydrolytic and/or enzymatic cleavage of the ester functionality the parent compound, the active metabolite (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol is released to act as a selective modulator of the alpha 2 adrenergic receptors.

[0010] An aspect of the invention is a compound selected from the following compounds or a pharmaceutically acceptable salt thereof:

*i*so-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2,2-dimethyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

acetic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

benzoic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

3-phenyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-amino-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-(2-amino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-(2-amino-acetylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester; and

2-amino-3-phenyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester.

[0011] These novel compounds are useful for the treatment or prevention in mammals, including humans, of a range of conditions and diseases that are alleviated by alpha 2A, 2B, 2C activation, including but not limited to treating or preventing glaucoma, elevated intraocular pressure, ischemic neuropathy, optic neuropathy, pain such as visceral pain, corneal pain, headache pain, migraine, cancer pain, back pain, irritable bowel syndrome pain, muscle pain and pain associated with diabetic neuropathy, diabetic retinopathy and other retinal degenerative conditions, stroke, cognitive deficits, neuropsychiatric conditions, drug dependence and addiction, withdrawal symptoms, obsessive-compulsive disorders, obesity, insulin resistance, stress-related conditions, diarrhea, diuresis, nasal congestion, spasticity, attention deficit disorder, psychoses, anxiety, depression, autoimmune disease, Crohn's disease, gastritis, Alzheimer's, Parkinson's, ALS and other neurodegenerative diseases, dermatological conditions, skin erythema (redness) and inflammation, acne, age related macular degeneration, wet macular degeneration, dry macular degeneration, geographic atrophy, diabetic macular edema, tumors, wounds, inflammation and retinal vein occlusion, vision loss from conditions such as glaucoma, retinitis pigmentosa and neuritis secondary to multiple sclerosis, rosacea (dilation of the blood vessels just under the skin), sunburn, chronic sun damage, discreet erythemas, psoriasis, acne rosacea, menopause-associated hot flashes, hot flashes resulting from orchiectomyatopic dermatitis, photoaging, seborrheic dermatitis, allergic dermatitis, telangiectasia (dilations of previously existing small blood vessels) of the face, rhinophyma (hypertrophy of the nose with follicular dilation), red bulbous nose, acne-like skin eruptions (may ooze or crust), burning or stinging sensation of the face, irritated and bloodshot and watery eyes, erythema (redness) of the skin, cutaneous hyperactivity with dilation of blood vessels of the skin, Lyell's syndrome, Stevens-Johnson syndrome, erythema multiforme minor, erythema multiforme major and other inflammatory skin diseases.

[0012] Another aspect of the invention is a compound selected from the following compounds or a pharmaceutically acceptable salt thereof:

*i*so-butyric acid 3-[(*S*)-1-(1-*i*so-butyryl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2,2-dimethyl-propionic acid 3-{(S)-1-[1-(2,2-dimethyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester;

acetic acid 3-[(*S*)-1-(1-acetyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

benzoic acid 3-[(*S*)-1-(1-benzoyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

3-methyl-butyric acid 2-methyl-3-{(*S*)-1-[1-(3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-benzyl ester;

phenyl-propionic acid 2-methyl-3-{(*S*)-1-[1-(3-phenyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-benzyl ester;

2-*tert*-butoxycarbonylamino-3-methyl-butyric acid 3-{(*S*)-1-[1-(2-*tert*-butoxy carbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester;

2-*tert*-butoxycarbonylamino-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-(2-*tert*-butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-{(*S*)-1-[1-(2-*tert*-butoxycarbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester;

2-(2-*tert*-butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-(2-*tert*-butoxycarbonylamino-acetylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester; and

2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester.

DETAILED DESCRIPTION OF THE INVENTION

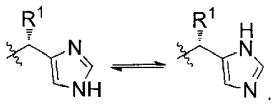
[0013] The present invention relates to novel compounds which are ester pro-drugs of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as alpha-2 agonists with therapeutic utility.

[0014] Upon hydrolytic or enzymatic cleavage of the ester functionality the parent compound, the active metabolite (*S*)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol is released to act as a selective modulator of the alpha 2 adrenergic receptors.

[0015] One aspect of the invention is a pharmaceutical composition comprising, consisting essentially of, or consisting of a therapeutically effective amount of an ester pro-drug of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, as defined above, including its enantiomers, diastereomers, hydrates, solvates, crystal forms, tautomers and pharmaceutically acceptable salts thereof.

[0016] "Prodrugs" are frequently referred to by the term "metabolically cleavable derivatives", which refers to compound forms which are rapidly transformed *in vivo* to the parent compound according to the invention, for example, by hydrolysis in blood. Thus, prodrugs are compounds bearing groups which are removed by biotransformation prior to exhibiting their pharmacological action. Such groups include moieties which are readily cleaved *in vivo* from the compound bearing it, which compound after cleavage remains or becomes pharmacologically active. Such metabolically cleavable groups form a class well known to practitioners of the art. They include, but are not limited to, such groups as alkanoyl (i.e. acetyl, propionyl, butyryl, and the like), unsubstituted and substituted carbocyclic aroyl (such as benzoyl, substituted benzoyl and 1- and 2-naphthoyl), alkoxycarbonyl (such as ethoxycarbonyl) and trialklysilyl (such as trimethyl- and triethylsilyl), monoesters formed with dicarboxylic acids (such as succinyl), phosphate, sulfate, sulfonate, sulfonyl, sulfinyl and the like. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. (T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery System", Vol. 14 of the A.C.S. Symposium Series; "Bioreversible Carriers in Drug Design", ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987).

[0017] As used herein, "tautomer" refers to the migration of protons between adjacent single and double bonds. The tautomerization process is reversible. Compounds described herein can undergo any possible tautomerization that is within the physical characteristics of the compound. The following is a tautomerization example that can occur in compounds described herein:



[0018] Intermediates of the invention are:

iso-butyric acid 3-[(*S*)-1-(1-*iso*-butyryl-1H-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2,2-dimethyl-propionic acid 3-{(*S*)-1-[1-(2,2-dimethyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester;

acetic acid 3-[(*S*)-1-(1-acetyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

benzoic acid 3-[(*S*)-1-(1-benzoyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester; 3-Methyl-butyric acid 2-methyl-3-{(*S*)-1-[1-(3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-benzyl ester;

phenyl-propionic acid 2-methyl-3-{(*S*)-1-[1-(3-phenyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-benzyl ester;

2-*tert*-butoxycarbonylamino-3-methyl-butyric acid 3-{(*S*)-1-[1-(2-*tert*-butoxy carbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester; 2-*tert*-butoxycarbonylamino-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-(2-*tert*-butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-{(*S*)-1-[1-(2-*tert*-butoxycarbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester;

2-(2-*tert*-butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-(2-*tert*-butoxycarbonylamino-acetylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester.

[0019] Compounds according to the present invention may exist in different polymorphic forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

[0020] Compounds of the present invention and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include, for example, hydrates, alcoholates and the like.

[0021] The term "pharmaceutically acceptable salts" refers to salts or complexes that retain the desired biological activity of the above identified compounds and exhibit minimal or no undesired toxicological effects. The "pharmaceutically acceptable salts" according to the invention include therapeutically active, non-toxic base or acid salt forms, which the compounds of the present invention are able to form.

[0022] The acid addition salt form of a compound of the present invention that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example but not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; or an organic acid such as for example but not limited to, as citric acid, acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene-sulfonic acid, napthalenedisulfonic, and polygalacturonic acid as well as base addition salts such as those formed with alkali- and alkaline earth metals such as sodium, potassium and calcium and the like (Handbook of Pharmaceutical Salts, P.Heinrich Stahl & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta- Zurich, 2002, 329-345).

[0023] The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include, but are not limiting to, the quaternary ammonium salt of the formula $-NY^{+}Z^{-}$, wherein Y is hydrogen, alkyl, or benzyl, and Z is a counterion, including but not limited to, chloride, bromide, iodide, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as fumarate, benzoate, succinate, acetate, glycolate, maleate, malate, fumarate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate).

[0024] In another embodiment of the invention, there are provided pharmaceutical compositions including at least one compound of the invention in a pharmaceutically acceptable carrier thereof. The phrase "pharmaceutically acceptable" means the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0025] Pharmaceutical compositions of the present invention can be used in the form of a solid, a solution, an emulsion, a dispersion, a patch, a micelle, a liposome, and the like, wherein the resulting composition contains one or more compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for enteral or parenteral applications. Invention compounds may be combined, for example, with the usual non-toxic, pharmaceutically

acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include but are not limited to, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition, auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. Invention compounds are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or disease condition.

[0026] Pharmaceutical compositions containing invention compounds may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets containing invention compounds in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the invention compounds are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the invention compounds are mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[0027] The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

[0028] The compounds of the invention can be used in a method of preventing or treating diseases that are alleviated by alpha 2A, 2B, 2C activation.

[0029] Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner. The patient will be administered the compound orally in any acceptable form, such as a tablet, liquid, capsule, powder and the like, or other routes may be desirable or necessary, particularly if the patient suffers from nausea. Such other routes may include, without exception, transdermal, parenteral, subcutaneous, intranasal, via an implant stent, intrathecal, intravitreal, topical to the eye, back to the eye, intramuscular, intravenous, and intrarectal modes of delivery. The actual amount of the compound to be administered in any given case will be determined by a physician taking into account the relevant circumstances, such as the severity of the condition, the age and weight of the patient, the patient's general physical condition, the cause of the condition, and the route of administration. Additionally, the formulations may be designed to delay release of the active compound over a given period of time, or to carefully control the amount of drug released at a given time during the course of therapy.

[0030] Ester pro-drugs of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol and their pharmaceutically-acceptable salts may be administered through different routes, including but not limited to topical eye drops, direct injection, application at the back of the eye or formulations that may further enhance the long duration of actions such as a slow releasing pellet, suspension, gel, or sustained delivery devices such as any suitable drug delivery system (DDS) known in the art. While topical administration is preferred, the compounds may also be used in an intraocular implant as described in U.S. Patent No.7,931,909. Such biocompatible intraocular implants include an ester pro-drug of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol and a polymer associated with the ester pro-drug to facilitate release thereof into an eye for an extended period of time.

[0031] Ophthalmic formulations of drug products are well known in the art and described in, for example, U.S. Patent Application Publication Nos. 20050059583, 20050277584 and 20070015691, and U.S. Patent Nos. 7,297,679; 5,474,979; and 6,582,718.

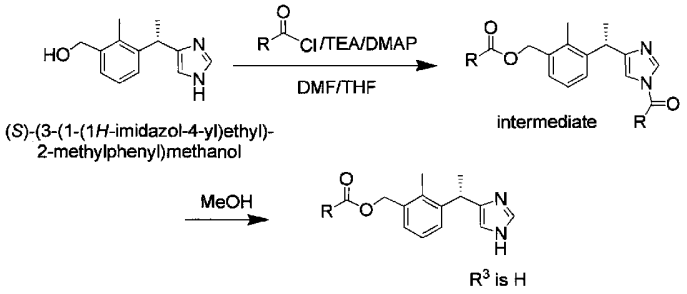
The ester pro-drugs of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol may be formulated with efficacy-enhancing components as disclosed in U.S. Patent No. 7,491,383 B2.

[0032] With respect to the present invention, reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically.

[0033] The synthetic scheme set forth below, illustrates how compounds according to the invention can be made. Those skilled in the art will be able to routinely modify and/or adapt the following scheme to synthesize any compounds of the invention.

General scheme for synthesizing ester prodrugs of (*S*)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol

[0034]



[0035] In a first step (*S*)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol (CAS 189255-79-6) can react with the desired acyl chloride, in the presence of *N,N*-dimethyl formamide (DMF), tetrahydrofuran (THF), triethylamine (TEA) and 4-dimethyl aminopyridine (DMAP). After a typical work-up by extraction, the residue can be purified by medium pressure liquid chromatography (MPLC) (0% to 40% ethyl acetate in hexanes) to yield the intermediate compound as a solid.

[0036] In a second step, the intermediate obtained in the first reaction, can react with methanol (MeOH). The residue can be purified by MPLC (50% ethyl acetate in hexanes then 5% 7N ammonia/ methanol /dichloromethane) to yield the desired compound as a solid.

[0037] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention claimed. As used herein, the use of the singular includes the plural unless specifically stated otherwise.

[0038] The present invention includes all pharmaceutically acceptable isotopically enriched compounds. Any compound of the invention may contain one or more isotopic atoms enriched or different than the natural ratio such as deuterium ^{2}H (or D) in place of protium ^{1}H (or H) or use of ^{13}C enriched material in place of ^{12}C and the like. Similar substitutions can be employed for N, O and S. The use of isotopes may assist in analytical as well as therapeutic aspects of the invention. For example, use of deuterium may increase the *in vivo* half-life by altering the metabolism (rate) of the compounds of the invention. These compounds can be prepared in accord with the preparations described by use of isotopically enriched reagents.

[0039] The following examples are for illustrative purposes only and are not intended, nor should they be construed as, limiting the invention in any manner.

[0040] The IUPAC names of the compounds mentioned in the examples were generated with ACD version 8.

[0041] Unless specified otherwise in the examples, characterization of the compounds is performed according to the following methods:

NMR spectra are recorded on 300 MHz Varian and acquired at room temperature. Chemical shifts are given in ppm referenced either to internal TMS or to the residual solvent signal.

[0042] All the reagents, solvents, catalysts for which the synthesis is not described are purchased from chemical vendors such as Sigma Aldrich, Fluka and Lancaster. However some known reaction intermediates, for which the CAS registry number is mentioned, were prepared in-house following known procedures.

[0043] Usually the compounds of the invention were purified by flash column chromatography.

[0044] The following abbreviations are used in the examples:

DCM
: dichloromethane

MeOH
: methanol

CD_3OD
: deuterated methanol

NH_3
: ammonia

Na_2SO_4
: sodium sulfate

DMF
: N,N-dimethylformamide

$MgSO_4$
: magnesium sulfate

EtOAc
: ethylacetate

i-PrOH
: *iso*-propanol

$CDCl_3$
: deuterated chloroform

MPLC
: medium pressure liquid chromatography

DMF
: dimethylformamide

TEA
: triethylamine

THF
: tetrahydrofuran

DMAP
: 4-dimethylaminopyridine

RT
: room temperature

Boc-L-Valine
: N-(*tert*-butoxycarbonyl)-L-valine

Boc-Glycine
: N-(*tert*-butoxycarbonyl)glycine

Boc-L-Phenylalanine
: N-(*tert*-butoxycarbonyl)-L-phenylalanine

HCl
: hydrochloric acid

H_2O
: water

EDCI
: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide

$NaHCO_3$
: sodium bicarbonate

Example 1

Intermediate 1

***iso*-Butyric acid 3-[(*S*)-1-(1-isobutyryl-1*H*-imidazol-4-yl)-ethyl] -2-methyl-benzyl ester**

[0045] To a solution of (S)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol (1.34g, 6.2mmol) in DMF (8ml) and THF (50ml), were added TEA (3.5ml, 24.8mmol), DMAP (780mg, 6.2mmol) and *iso*-butyryl chloride (2.18g, 20.5mmol). The resulting mixture was stirred at RT for 16 h, quenched with H_2O and extracted with ethyl acetate. The combined organic layers were washed with brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPLC (0% to 40% ethyl acetate in hexanes) to yield **Intermediate 1** as a solid.

[0046] ^{1}H-NMR (CD_3OD, δ ppm): 1.15 (d, J=7.03Hz, 6H), 1.26 (d, 6H, J=6.74Hz), 1.56 (d, J=7.03Hz, 3H), 2.34 (s, 3H), 2.58 (hept, J=7.03Hz, 1 H), 3.34(hept, J=7.74Hz, 1 H), 4.42(q, J=7.03Hz, 1H), 5.15(s, 2H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.31 (s, 1H), 8.35 (s, 1 H).

[0047] Intermediates 2-6 were prepared in a similar manner to the method described in **Example 1** starting with (*S*)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol.

[0048] The acyl chloride used in each case and the results are tabulated below in **Table 1.**

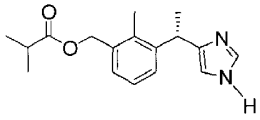
Table 1

Intermediate number	IUPAC name	Acyl chloride	^{1} NMR (Solvent; δ ppm)
2	**2,2-Dimethyl-propionic acid 3-{(*S*)-1-[1-(2,2-dimethyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester**	**Pivaloyl** chloride	(CD_3OD): 1.19 (s, 9H), 1.42 (s, 9H), 1.56 (d, J=7.03Hz, 3H), 2.34 (s, 3H), 4.42(q, J=7.03Hz, 1H), 5.15(s, 2H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.33 (s, 1H), 8.40 (s, 1H).
3	**Acetic acid 3-[(*S*)-1-(1-acetyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester**	Acetyl chloride	(CD_3OD): 1.55 (d, J=7.03Hz, 3H), 2.05 (s, 3H), 2.33 (s, 3H), 2.58 (s, 3H), 4.39(q, J=7.03Hz, 1H), 5.15(s, 2H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.30 (s, 1H), 8.29 (s, 1H).
4	**Benzoic acid 3-[(*S*)-1-(1-benzoyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester:**	Benzoyl chloride	(CD_3OD): 1.58 (d, J=7.03Hz, 3H), 2.43 (s, 3H), 4.46(q, J=7.03Hz, 1H), 5.41 (s, 2H), 7.11-7.18 (m, 2H), 7.27-7.35 (m, 2H), 7.42-7.50 (m, 2H), 7.50-7.63 (m, 3H), 7.65-7.71 (m, 1H), 7.79 (d, J=7.33Hz, 2H), 8.00 (d, J=7.33Hz, 2H), 8/09 (s, 1H).
5	**3-Methyl-butyric acid 2-methyl-3-{(*S*)-1-(1-(3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-benzyl ester**	Methylbutanoyl chloride	(CD_3OD): 0.91 (d, J=6.44Hz, 6H), 1.01 (d, J=6.44Hz, 6H), 1.54 (d, J=7.03Hz, 3H), 2.05 (hept, J=6.44Hz, 1H), 2.15-2.25 (m, 3H), 2.33 (s, 3H), 2.81 (d, J=7.03Hz, 3H), 4.42(q, J=7.03Hz, 1 H), 5.14(s, 2H), 7.07-7.19 (m, 3H), 7.28 (s, 1H), 8.32 (s, 1H).
6	**3-Phenyl-propionic acid 2-methyl-3-{(*S*)-1-[1-(3-phenyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-benzyl ester**	Phenylpropanoyl chloride	(CD_3OD): 1.52 (d, J=7.03Hz, 3H), 2.24 (s, 3H), 2.64 (t, J=7.61 Hz, 2H), 2.90 (t, J=7.61 Hz, 2H), 3.04 (t, J=7.61 Hz, 2H),3.24 (t, J=7.61 Hz, 2H), 4.34 (q, J=7.03Hz, 1H), 5.13 (s, 2H), 7.08-7.248 (m, 14H), 8.25 (s, 1H).

Example 2

Compound 1 *iso*-Butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0049]

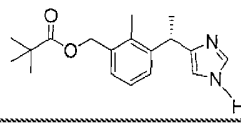
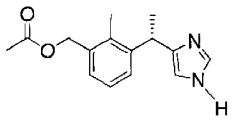
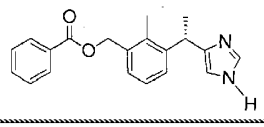
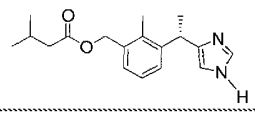


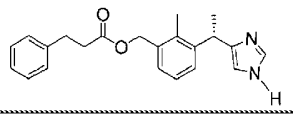
[0050] **Intermediate 1** was dissolved in MeOH (50ml) and the mixture was stirred at RT for 24 h and then concentrated under reduced pressure. The residue was purified by MPLC (50% ethyl acetate in hexanes then 5% 7N NH_3/ MeOH /DCM) to yield **Compound 1** as a solid.

[0051] ^{1}H-NMR (CD_3OD; δ ppm): 1.15 (d, J=7.03Hz, 6H), 1.54 (d, J=7.03Hz, 3H), 2.33 (s, 3H), 2.56 (hept, J=7.03Hz, 1 H), 4.42(q, J=7.03Hz, 1 H), 5.15(s, 2H), 6.70 (s, 1 H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.55 (s, 1H).

[0052] **Compounds 2-6** and of the invention were prepared according to the procedure described in **Example 2,** by reacting the corresponding intermediate with methanol. The results are tabulated below in **Table 2.**

Table 2

Comp. No.	IUPAC name	Inter. No.	^{1}NMR (Solvent, δ ppm)
2	**2,2-Dimethyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester**	2	(CD_3OD): 1.19 (s, 9H), 1.54 (d, J=7.03Hz, 3H), 2.33 (s, 3H), 4.42 (q, J=7.03Hz, 1H), 5.13 (s, 2H), 6.70 (s, 1H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.55 (s, 1H).
			
3	**Acetic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester**	3	(CD_3OD): 1.54 (d, J=7.03Hz, 3H), 2.04 (s, 3H), 2.33 (s, 3H), 4.42 (q, J=7.03Hz, 1H), 5.13 (s, 2H), 6.70 (s, 1H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.55 (s, 1H).
			
4	**Benzoic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester**	4	(CD_3OD): 1.54 (d, J=7.03Hz, 3H), 2.31 (s, 3H), 4.42(q, J=7.03Hz, 1H), 5.13 (s, 2H), 6.70 (s, 1H), 7.07-7.15 (m, 2H), 7.25-7.28 (m, 1H), 7.54-7.47 (m, 2H), 7.55-7.60 (m, 2H), 8.0 (d, J=7.33Hz, 2H).
			
5	**3-Methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl Ester**	5	(CD_3OD): 0.93 (d, J=7.03Hz, 6H), 1.54 (d, J=7.03Hz, 3H), 2.07 (hept, J=7.03Hz, 1H), 2.21 (d, J=7.03Hz, 2H), 2.33 (s, 3H), 4.42(q, J=7.03Hz, 1H), 5.15(s, 2H), 6.70 (s, 1H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.55 (s, 1H).
			

Comp. No.	IUPAC name	Inter. No.	^{1}NMR (Solvent, δ ppm)
6	**3-Phenyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl Ester**	6	(CD_3OD): 1.54 (d, J=7.03Hz, 3H), 2.23 (s, 3H), 2.65 (t, J=7.61Hz, 2H), 2.91 (t, J=7.61 Hz, 2H), 4.40 (q, J=7.03Hz, 1H), 5.13 (s, 2H), 6.70 (s, 1H), 7.08-7.24 (m, 8H), 7.55 (s, 1H).
			

Example 3

Intermediate 7

2-*tert*-Butoxycarbonylamino-3-methyl-butyric acid 3-{(*S*)-1-[1-(2-*tert*-butoxy carbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester

[0053] To a solution of (*S*)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol (216mg, 1.0mmol) in DMF (2ml) and THF (12ml) were added EDCI (671 mg, 3.5mmol), DMAP (427mg, 3.5mmol) and Boc-L-Valine (651 mg, 3.0mmol) . The mixture was stirred at RT for 16 h, quenched with H_2O and extracted with ethyl acetate. The combined organic layers were washed with H_2O, brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by a column chromatography (30% ethyl acetate in hexanes) to yield **Intermediate 7** as a white solid.

[0054] ^{1}H-NMR (CD_3OD; δ ppm): 0.85-1.01 (m, 12H), 1.20-1.48 (m, 18H), 1.56 (d, J=7.03Hz, 3H), 2.01-2.20(m, 2H), 2.35 (s, 3H), 4.03(m, 1 H), 4.42 (q, J=7.03Hz, 1 H), 4.60-4.65 (m, 1H), 5.15-5.29 (m, 2H), 7.10-7.20 (m, 2H), 7.20-7.25 (m, 1H), 7.33 (s, 1 H), 8.44 (s, 1 H).

Example 4

Intermediate 8

2-*tert*-Butoxycarbonylamino-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0055] The title compound was prepared from **Intermediate 7** (600mg, 0.98mmol) in 30ml of MeOH according to the procedure described in **Example 2.**

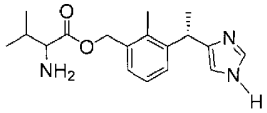
[0056] ^{1}H-NMR (CD_3OD; δ ppm): 0.85-0.95 (m, 6H), 1.42 (m, 9H), 1.54 (d, J=7.03Hz, 3H), 2.05 (m, 1 H), 2.33 (s, 3H), 4.00 (d, J=6.15Hz, 1 H), 4.40 (q, J=7.03Hz, 1 H), 5.15-5.28 (m, 2H), 6.67 (s, 1 H), 7.10-7.20 (m, 2H), 7.20-7.25 (m, 1 H), 7.55 (s, 1 H).

Example 5

Compound 7

2-Amino-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0057]



[0058] To **Intermediate 8** (390mg, 0.94mmol) was added 4N HCl in dioxane (8ml). The resulting solution was stirred at RT for 4 hrs, then quenched with H_2O, neutralized with aqueous saturated $NaHCO_3$ and extracted with 25% isopropyl alcohol in chloroform. The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by a column chromatography (5% 7N NH_3/MeOH in DCM) to yield **Compound 7** as a white solid.

[0059] ^{1}H-NMR (CD_3OD; δ ppm): 0.85 (d, J=6.74Hz, 3H), 0.91 (d, J=6.74Hz, 3H), 1.54 (d, J=7.03Hz, 3H), 1.96 (hept, J=6.74Hz, 1 H), 2.33 (s, 3H), 3.28 (d, J=6.74Hz, 2H), 4.42 (q, J=7.03Hz, 1 H), 5.20-5.25 (m, 2H), 6.67 (s, 1 H), 7.10-7.12 (m, 2H), 7.13-7.20 (m, 1H), 7.55 (s, 1 H).

Example 6

Intermediate 9

2-(2-*tert*-Butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-{(S)-1-[1-(2-*tert*-butoxycarbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester

[0060] The title compound was prepared from **Compound 7** (490mg, 1.55mmol), Boc-L-Valine (1.01 g, 4.67mmol), EDCl (1.04g, 5.42mmol) and DMAP (671mg, 5.5mmol) according to the procedure described in **Example 3.**

[0061] ^{1}H-NMR (CD_3OD; δ ppm): 0.85-0.92 (m, 12H), 1.43 (s, 9H), 1.55 (d, J=7.03Hz, 3H), 1.97 (m, 1H), 2.14 (hept, J=6.60Hz, 1H), 2.35 (s, 3H), 3.88 (d, J=7.30Hz,, 1H), 4.35 (d, J=6.90Hz, 1 H), 4.42(d, J=7.03Hz, 1 H), 5.18-5.25 (m, 2H), 6.67 (s, 1 H), 7.10-7.15 (m, 2H),7/17-7.20 (m, 1H), 7.55 (s, 1H).

Example 7

Intermediate 10

2-(2-*tert*-Butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0062] The title compound was prepared from **Intermediate 9** (750mg, 1.05mmol) in 30ml of MeOH according to the procedure described in **Example 2.**

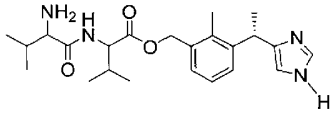
[0063] ^{1}H-NMR (CD_3OD; δ ppm): 0.89 (d,d , J=7.03Hz, 6H), 1.44 (s, 9H), 1.54 (d, J=7.33Hz, 3H), 2.14 (hept, J=6.74Hz, 1 H), 2.33 (s, 3H), 3.74 (s, 2H), 4.35-4.55 (m, 2H), 5.20 (s, 2H), 6.67 (s, 1H), 7.10-7.17 (m, 2H), 7.19-7.23 (m, 1 H), 7.56 (s, 1H).

Example 8

Compound 8

2-(2-Amino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0064]



[0065] The title compound was prepared from **Intermediate 10** (450mg, 0.87mmol) in 8ml of 4N HCl/Dioxane according to the procedure described in **Example 5.**

[0066] ^{1}H-NMR (CD_3OD; δ ppm): 0.85 (d, J=7.03Hz, 3H), 0.91 (d, J=6.74Hz, 3H), 0.92 (d, J=7.3Hz. 3H), 1.14 (d, J=6.2Hz, 3H), 1.54 (d, J=7.03Hz, 3H), 1.94 (hept, J=5.2Hz, 1 H), 2.14 (hept, J=6.2Hz, 1 H), 2.33 (s, 3H), 3.18 (d, J=5.2Hz, 1 H), 4.34 (d, J=6.2Hz, 1 H), 4.42(q, J=7.03Hz, 1 H), 5.21-5.26 (m, 2H), 6.67 (s, 1 H), 7.10-7.15 (m, 2H), 7.18-7.20 (m, 1H), 7.55 (s, 1 H).

Example 9

Intermediate 11

2-(2-*tert*-Butoxycarbonylamino-acetylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1H-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0067] The title compound was prepared from **Compound 8** (405mg, 1.28mmol), Boc-Glycine(675mg, 3.86mmol), EDCI(859mg, 4.48mmol) and DMAP(547mg, 4.48mmol) according to the procedure described in **Example 3.** The title compound was purified by column chromatography using 5% 7N NH_3/MeOH in DCM .

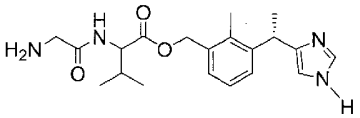
[0068] ^{1}H-NMR (CD_3OD; δ ppm): 0.89 (d, J=6.74Hz, 3H), 0.91 (d, J=6.74Hz, 3H), 1.55 (d, J=7.30Hz, 3H), 2.14 (hept, J=6.74Hz, 1 H), 2.33 (s, 3H), 4.37 (d, J=5.90Hz, 1 H), 4.42(q, J=7.03Hz, 1 H), 5.20-5.25 (m, 2H), 6.67 (s, 1 H), 7.10-7.12 (m, 2H), 7.13-7.20 (m, 1H), 7.55 (s, 1H).

Example 10

Compound 9

2-(2-Amino-acetylamino)-3-methyl-butyric acid 3-[(S)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0069]



[0070] The title compound was prepared from **Intermediate 11** (320mg, 0.68mmol) with 10ml of 4N HCl/Dioxane according the

procedure described in **Example 5.**

[0071] ^{1}H-NMR (CD_3OD; δ ppm): 0.89 (d, J=6.74Hz, 3H), 0.91 (d, J=6.74Hz, 3H), 2.14 (hept, J=6.74Hz, 1H), 2.33 (s, 3H), 4.37 (d, J=5.90Hz, 1H), 4.42(q, J=7.03Hz, 1H), 5.20-5.25 (m, 2H), 6.67 (s, 1 H), 7.10-7.12 (m, 2H), 7.13-7.20 (m, 1 H), 7.55 (s, 1 H).

Example 11

Intermediate 12

2-*tert*-Butoxycarbonylamino-3-phenyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0072] The title compound was prepared from (S)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol (216mg, 1.0mmol), Boc-L-Phenylalanine(795mg, 3.0mmol), EDCI(671mg, 3.5mmol) and DMAP(427mg, 3.5mmol) according to the procedure described in **Example 3. Intermediate 12** was purified by a column chromatography using 35-100% ethyl acetate in hexane.

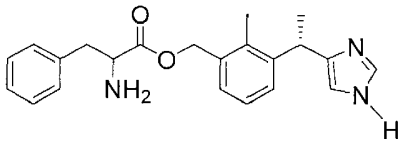
[0073] ^{1}H-NMR (CD_3OD; δ ppm): 1.36 (s, 9H), 1.55 (d, J=7.03Hz, 3H), 2.28 (s, 3H), 2.85-2.95 (m, 1H), 3.05-3.11 (m, 1H), 4.38(m, 1H), 4.40(q, J=7.03Hz, 1H), 5.17(s, 2H), 6.69 (s, 1H), 7.08-7.24 (m, 8H), 7.55 (s, 1H).

Example 12

Compound 10

2-Amino-3-phenyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0074]



[0075] The title compound was prepared from **Intermediate 12** (240mg, 0.52mmol) with 8ml of 4N HCl/Dioxane according to the procedure described in **Example 5.**

[0076] ^{1}H-NMR (CD_3OD; δ ppm): 1.54 (d, J=7.03Hz, 3H), 2.26 (s, 3H), 2.90-3.00 (m, 2H), 3.73 (t, J=6.40Hz, 1H), 4.40(q, J=7.03Hz, 1H), 5.13-5.18(m, 2H), 6.68 (s, 1H), 7.08-7.12 (m, 5H), 7.13-7.22 (m, 3H), 7.55 (s, 1 H).

[0077] The following assay was used to demonstrate the potency and selectivity of the compounds according to the invention.

Example 13

FLIPR Ca^{+2} Influx Assay

[0078] HEK 293 cells stably expressing the bovine α_{1A} receptor, human alpha 2A receptor and the chimeric G protein G_{qi5}, are plated in poly-D-lysine coated 384-well plates at 20,000 - 40,000 cells per well and grown overnight in DMEM supplemented with

10% fetal bovine serum. For FLIPR (fluorometric image plate reader) evaluation, cells are washed twice with HBSS/HEPES Buffer (1X Hanks Buffered Salt Solution, 20 mM HEPES, pH 7.4) prior to the addition of Fluo-4-AM (4 uM Fluo-4-AM, 0.04% pluronic acid in HBSS/HEPES Buffer), a calcium-sensitive dye. Cells are loaded with dye for 40 minutes at 37°C, then washed 4 times with HBSS/HEPES Buffer. For both the agonist and antagonist assay, the test compounds are tested between 0.64 nM - 10,000 nM.

[0079] For an agonist assay, the reaction is initiated by the addition of the appropriate dilutions of compounds and the transient calcium signal captured. The peak height of the calcium curve is determined and utilized for calculation of EC_{50} and efficacy using ActivityBase. Norepinephrine is the standard full agonist used for evaluating alpha-1 and alpha-2 receptor activity.

[0080] For an antagonist assay, the addition of the drug does not elicit a transient calcium signal. However, the antagonist blocks the transient calcium signal of the standard agonist norepinephrine in a dose-dependent manner. The residual norepinephrine peak height is compared to the non-antagonized norepinephrine peak height for the determination of % antagonism.

Table 3

In Vitro Pharmacology of (S)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol and its prodrugs at adrenergic receptor subtypes			
Entry	**Compound Number**	**FLIPR Assay**	
		a1A	**a2A**
1	**Brimonidine**	600-2400 (0.3)	5 (0.95)
2	**(S)-(3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol**	340-2400 (0.7)	25 (0.9)
3	**Compound 1**	n/a	n/a
4	**Compound 2**	n/a	n/a
EC50 (eff) nM. n/a: Not active			

REFERENCES CITED IN THE DESCRIPTION

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PATENTKRAV

1. Forbindelse udvalgt fra følgende forbindelser eller farmaceutisk acceptabelt salt deraf:
iso-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2,2-dimethyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
eddikesyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
benzoesyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
3-phenyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2-amino-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyI-benzylester;
2-(2-amino-3-methyl-butyrylamino)-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4yl)-ethyl]-2-methyl-benzylester;
2-(2-amino-acetylamino)-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2methyl-benzylester og
2-amino-3-phenyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester.

2. Forbindelse udvalgt fra følgende forbindelser eller farmaceutisk acceptabelt salt deraf:
iso-smørsyre 3-[(*S*)-1-(1-iso-butyryl-1H-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2,2-dimethyl-propionsyre 3-{(*S*)-1-[1-(2,2-dimethyl-propiony)-1*H*-imidazol-4-yl]ethyl}-2-methyl-benzylester;
eddikesyre 3-[(*S*)-1-(1-acetyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
benzoesyre 3-[(*S*)-1-(1-benzoyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
3-methyl-smørsyre 2-methyl-3-{(*S*)-1-[1-(3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-benzylester;
phenyl-propionsyre 2-methyl-3-{(*S*)-1-[1-(3-phenyl-propiony)-1*H*-imidazol-4-yl]ethyl}-benzylester;

2-*tert*-butoxycarbonylamino-3-methyl-smørsyre 3-{(*S*)-1-[1-(2-*tert*-butoxy
carbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzylester;
2-*tert*-butoxycarbonylamino-3-methyl-smørsyre 3-((*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2-(2-*tert*-butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-smørsyre
{(*S*)-1-[1-(2-*tert*-butoxycarbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2methyl-benzylester;
2-(2-*tert*-butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-smørsyre 3[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2-(2-*tert*-butoxycarbonylamino-acetylamino)-3-methyl-smørsyre 3-[(*S*)-1-(1*H*imidazol-4-yl)-ethyl]-2-methyl-benzylester og
2-*tert*-butoxycarbonylamino-3-phenyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester.

3. Farmaceutisk sammensætning omfattende en forbindelse eller farmaceutisk acceptabelt salt deraf som defineret i krav 1.

4. Forbindelse eller farmaceutisk acceptabelt salt deraf som defineret i krav 1 til anvendelse i en fremgangsmåde til behandling eller forebyggelse af en tilstand eller en sygdom, der lindres af alpha 2A-, 2B-, 2C-aktivering, hvilken tilstand eller sygdom er udvalgt fra glaukom, forhøjet intraokulært tryk, iskæmisk neuropati, optisk neuropati, smerte, en retinal degenerativ tilstand, såsom diabetisk retinopati, apopleksi, en kognitiv svækkelse, en neuropsykiatrisk tilstand, lægemiddelafhængighed og -misbrug, abstinenssymptomer, obsessiv-kompulsiv tilstand, fedme, insulinresistens, en stress-relateret tilstand, diarre, diurese, nasal kongestion, spasticitet, ADHD, psykoser, angst, depression, autoimmun sygdom, Crohns sygdom, gastritis, en neurodegenerativ sygdom, såsom Alzheimers sygdom, Parkinsons sygdom og ALS, akne, aldersrelateret makuladedegeneration, våd makuladedegeneration, tør makuladedegeneration, geografisk atrofi, diabetisk makulaødem, en tumor, et sår, inflammation og retinal

veneokklusion, synstab, såsom grundet glaukom, retinitis pigmentosa eller neuritis sekundær til multipel sklerose, rosacea (udvidelse af blodkar lige under huden), solforbrænding, kronisk solskade, diskret erytem, psoriasis, menopause-forbunden hedeture, hedeture som følge af orchiektomi-atopisk dermatitis, fotoældning, seborrhoisk dermatitis, allergisk dermatitis, huderytem (rødmen), telangiektasi (udvidelser af tidligere eksisterende små *blodkar) i ansigtet, rhinophyma (hypertrofi af næsen med* follikeludvidelse), rød bulbøs næse, akne-lignende hududbrud, brændende eller svidende fornemmelse i ansigtet, irriterede og blodskudte og løbende øjne, kutan hyperaktivitet med udvidelse af blodkar i huden, Lyells syndrom, Stevens-Johnson-syndrom, erythema multiforme minor og erythema multiforme major.

5. Farmaceutisk sammensætning ifølge krav 3 til anvendelse i en fremgangsmåde til behandling eller forebyggelse af en tilstand eller sygdom, der er udvalgt fra de tilstande eller sygdomme, der er defineret i krav 4.

6. Sammensætning eller salt deraf til anvendelse ifølge krav 4 eller farmaceutisk sammensætning til anvendelse ifølge krav 5, hvor smerten er udvalgt fra visceral smerte, hornhindesmerte, hovedpinesmerte, migrænesmerte, cancersmerte, rygsmerte, smerte ved irritabel tarmsyndrom, muskelsmerte og smerte forbundet med diabetisk neuropati.