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(72) **Inventeurs/Inventors**:
JONES, DAVID, US;
GOWDA, RAJU BORE, US;
XIE, RONGYUAN, US

(73) **Propriétaire/Owner**:
VTV THERAPEUTICS LLC, US

(74) **Agent**: SMART & BIGGAR

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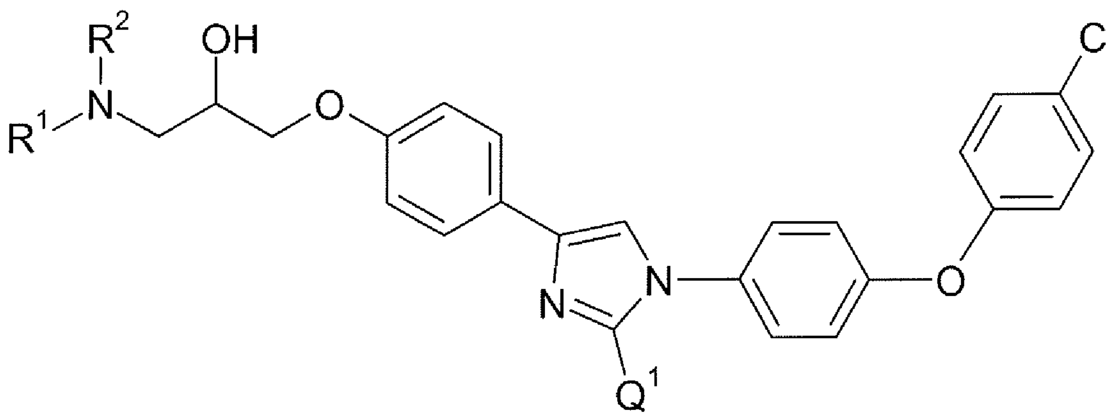
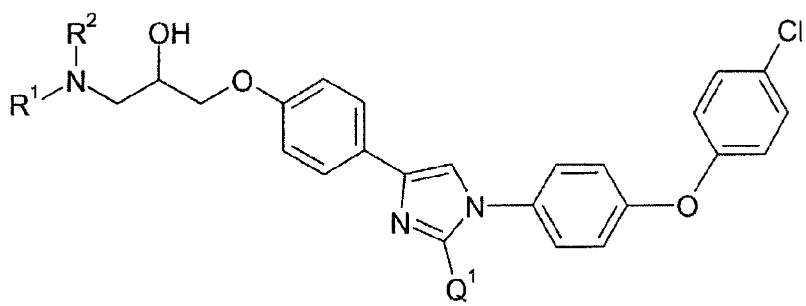


(I)

(57) **Abrégé/Abstract**:
The present invention provides imidazole derivatives of Formula (I): (see formula I) and pharmaceutically acceptable salts thereof, wherein R^1, R^2 and Q^1 are as defined herein. The present invention further relates to methods for the preparation of compounds of Formula (I) and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such compounds.

ABSTRACT

The present invention provides imidazole derivatives of Formula (I):



Formula (I)

and pharmaceutically acceptable salts thereof, wherein R^1, R^2 and Q' are as defined herein. The present invention further relates to methods for the preparation of compounds of Formula (I) and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such compounds.

SUBSTITUTED IMIDAZOLE DERIVATIVES

FIELD OF THE INVENTION

This invention relates to compounds which are inhibitors of the interaction between the receptor for advanced glycation endproducts (RAGE) and its physiological ligands such as advanced glycated end products (AGEs), S100/calgranulin/EN-RAGE, β-amyloid, and amphoterin.

BACKGROUND OF THE INVENTION

The Receptor for Advanced Glycated Endproducts (RAGE) is a member of the immunoglobulin super family of cell surface molecules. The extracellular (N-terminal) domain of RAGE includes three immunoglobulin-type regions, one V (variable) type domain followed by two C-type (constant) domains (Neeper et al., J. Biol. Chem. 267:14998-15004 (1992)). A single transmembrane spanning domain and a short, highly charged cytosolic tail follow the extracellular domain. The N-terminal, extracellular domain can be isolated by proteolysis of RAGE to generate soluble RAGE (sRAGE) comprised of the V and C domains.

RAGE is expressed in most tissues, and in particular, is found in cortical neurons during embryogenesis (Hori et al. (1995)). Increased levels of RAGE are also found in aging tissues (Schleicher et al., J. Clin. Invest. 99 (3): 457-468 (1997)), and the diabetic retina, vasculature and kidney (Schmidt et al., Nature Med. 1:1002-1004 (1995)). Activation of RAGE in different tissues and organs leads to a number of pathophysiological consequences. RAGE has been implicated in a variety of conditions including: acute and chronic inflammation (Hofmann et al., Cell 97:889-901 (1999)), the development of diabetic late complications such as increased vascular permeability (Wautier et al., J. Clin. Invest. 97:238-243 (1996)), nephropathy (Teillet et al., J. Am. Soc. Nephrol. 11:1488-1497 (2000)), atherosclerosis (Vlassara et. al., The Finnish Medical Society DUODECIM, Ann. Med. 28:419-426 (1996)), and retinopathy (Hammes et al., Diabetologia 42:603-607 (1999)). RAGE has also been implicated in Alzheimer's disease (Yan et al., Nature 382: 685-691 (1996)), erectile dysfunction, and in tumor invasion and metastasis (Taguchi et al., Nature 405: 354-357 (2000)).

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Advanced glycation endproducts (AGEs) have been implicated in a variety of disorders including complications associated with diabetes and normal aging. Incubation of proteins or lipids with aldose sugars results in nonenzymatic glycation and oxidation of amino groups on proteins to form Amadori adducts. Over time, the adducts undergo additional rearrangements, dehydrations, and cross-linking with other proteins to form complexes known as AGEs. Factors which promote formation of AGEs include delayed protein turnover (e.g. as in amyloidoses), accumulation of macromolecules having high lysine content, and high blood glucose levels (e.g. as in diabetes) (Hori et al., J. Biol. Chem. 270: 25752-761, (1995)).

AGEs display specific and saturable binding to cell surface receptors on endothelial cells of the microvasculature, monocytes and macrophages, smooth muscle cells, mesengial cells, and neurons.

In addition to AGEs, other compounds can bind to, and inhibit the interaction of physiological ligands with RAGE. In normal development, RAGE interacts with amphoterin, a polypeptide which mediates neurite outgrowth in cultured embryonic neurons (Hori et al., (1995)). RAGE has also been shown to interact with EN-RAGE, a protein having substantial similarity to calgranulin (Hofmann et al. (1999)). RAGE has also been shown to interact with β-amyloid (Yan et al., Nature 389:689-695 (1997); Yan et al., Nature 382:685-691 (1996); Yan et al., Proc. Natl. Acad. Sci., 94:5296-5301 (1997)).

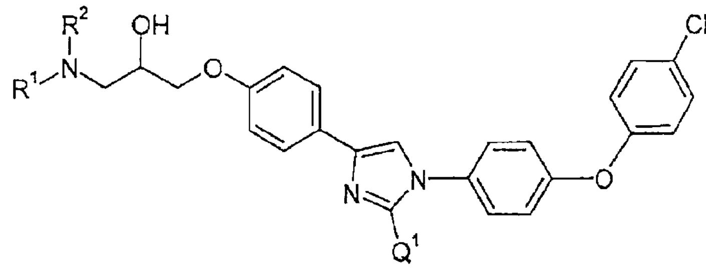
Binding of ligands such as AGEs, S100/calgranulin/EN-RAGE, β-amyloid, CML (Nε-Carboxymethyl lysine), and amphoterin to RAGE has been shown to modify expression of a variety of genes. For example, in many cell types interaction between RAGE and its ligands generates oxidative stress, which thereby results in activation of the free radical sensitive transcription factor NF-κB, and the activation of NF-κB regulated genes, such as the cytokines IL-1β, TNF-α, and the like.

In addition, several other regulatory pathways, such as those involving p21ras, MAP kinases, ERK1 and ERK2, have been shown to be activated by binding of AGEs and other ligands to RAGE. In fact, transcription of RAGE itself is regulated at least in part by NF-κB. Thus, an ascending, and often detrimental, spiral is fueled by a positive feedback loop initiated by ligand binding. Inhibiting binding of physiological ligands to RAGE provides for the down-regulation of the pathophysiological changes brought about by excessive concentrations of AGEs and other ligands for RAGE as described above.

Thus, there is a need for the development of compounds that inhibit the binding of physiological ligands to RAGE.

SUMMARY OF THE INVENTION

The present invention relates to compounds of Formula (I):



Formula (I)

or pharmaceutically acceptable salts thereof, wherein

R^1 and R^2 are independently selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, and $-CH_2CH_2CH_3$; and

Q^1 is selected from the group consisting of $-CH_2OCH_2CH_3$ and $-CH_2CH_2CH_2CH_3$.

This invention also provides for methods of preparation of compounds of Formula (I) or pharmaceutically acceptable salts thereof, pharmaceutical compositions comprising compounds of Formula (I) or pharmaceutically acceptable salts thereof.

Compounds of Formula (I) or pharmaceutically acceptable salts thereof are useful as inhibitors of the interaction of the receptor for advanced glycation endproducts (RAGE) with ligands such as advanced glycated end products (AGEs), S100/calgranulin/EN-RAGE, β-amyloid, and amphoterin.

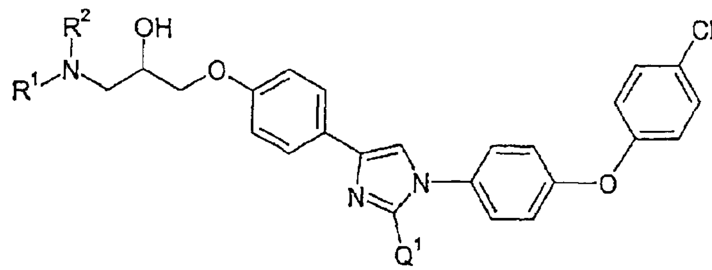
The scope of the present invention includes combinations of the various aspects, embodiments, and preferences as herein described.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions are meant to clarify, but not limit, the terms defined. If a particular term used herein is not specifically defined, such term should not be considered indefinite. Rather, such terms are used within their plain and ordinary meanings.

As used herein, the various functional groups represented will be understood to have a point of attachment at the functional group having the hyphen. In other words, in the case of $-CH_2CH_2CH_3$, it will be understood that the point of attachment is the CH_2 group at the far left.

In a first embodiment, the present invention includes a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 and R^2 are independently selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, and $-CH_2CH_2CH_3$; and

Q^1 is selected from the group consisting of $-CH_2OCH_2CH_3$ and $-CH_2CH_2CH_2CH_3$.

In a second embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof wherein R^1 is $-CH_3$.

In a third embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof wherein R^1 is $-CH_2CH_3$.

In a fourth embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of the previous embodiments wherein R^2 is $-CH_3$.

In a fifth embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of the first to third embodiments wherein R^2 is–CH_2CH_3.

In a sixth embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of the previous embodiments wherein Q^1 is –$CH_2OCH_2CH_3$.

In a seventh embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of the first to fifth embodiments wherein Q^1 is –$CH_2CH_2CH_2CH_3$.

In an eighth embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of the first to seventh embodiments wherein the compound is a free amine.

In a ninth embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of the first to seventh embodiments wherein the compound is a pharmaceutically acceptable salt.

In a tenth embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of the first to seventh embodiments wherein the compound is a hydrochloride salt.

In an eleventh embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of the first to tenth embodiments wherein the group –$CH_2CH(OH)CH_2NR^1R^2$ is in the S configuration.

In a twelfth embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of the first to tenth embodiments wherein the group –CH_2-$CH(OH)$-CH_2-NR^1R^2 is in the R configuration.

Specific embodiments of the compound of Formula (I) or a pharmaceutically acceptable salt thereof include:

(R)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol;

(R)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol;

(S)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol;

(S)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol;

(R)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol;

(S)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol;

(R)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol; and

(S)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol;

or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention includes a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Pharmaceutically acceptable salts of the compounds of the present invention are also included within the scope of the invention. The term "pharmaceutically acceptable salt(s)" as used herein refers to non-toxic salts of a compound of Formula (I) which are generally prepared by reacting the free base (i.e. free amine) of the compound of Formula (I) with a suitable organic or inorganic acid such as, but not limited to, hydrochloride, hydrobromide, phosphate, sulfate, trifluoroacetate, trichloroacetate, acetate, oxalate, maleate, pyruvate, malonate, succinate, citrate, tartrate, fumarate, mandelate, benzoate, cinnamate, methiodide, methbromide, methchloride, methanesulfonate, ethanesulfonate, picrate and the like, and include acids related to the pharmaceutically-acceptable salts listed in the Journal of Pharmaceutical Science, 66, 2 (1977) p. 1-19. Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of the invention and these form a further aspect of the invention.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of a hydrogen atom by a deuterium or tritium, or the replacement of a carbon atom by a ^{13}C- or ^{14}C-enriched carbon are within the scope of the invention.

The compound of Formula (I) contains one chiral center. The scope of the present invention includes mixtures of stereoisomers as well as purified enantiomers or enantiomerically/diastereomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by the formulae of the present invention, as well as any wholly or partially equilibrated mixtures thereof. The present invention also includes any tautomers of the compounds represented by the formulas above.

Examples of compounds of Formula (I) or a pharmaceutically acceptable salt thereof having potentially useful biological activity are herein described. The ability of compounds of Formula (I) or pharmaceutically acceptable salts thereof to inhibit the interaction of RAGE with its physiological ligands was established with representative compounds of Formula (I) or a pharmaceutically acceptable salt thereof using the assay(s) described in the Examples section below.

The invention further provides pharmaceutical compositions comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The term "pharmaceutical composition" is used herein to denote a composition that may be administered to a mammalian host, e.g., orally, topically, parenterally, by inhalation spray, or rectally, in unit dosage formulations containing conventional non-toxic carriers, diluents, adjuvants, vehicles and the like. The term "parenteral" as used herein, includes subcutaneous injections, intravenous, intramuscular, intracisternal injection, or by infusion techniques.

The pharmaceutical compositions containing a compound of the invention 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 known method, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically-acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example 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. They may also be coated by the techniques described in U.S. Patent Nos. 4,356,108; 4,166,452; and 4,265,874, to form osmotic therapeutic tablets for controlled release.

Formulations for oral use may also be presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions may contain the active compounds in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide such as lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as a liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active compound in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring, and coloring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example a liquid paraffin, or a mixture thereof. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known methods using suitable dispersing or wetting agents and suspending agents described above. 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. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conveniently employed as solvent or suspending medium. For this purpose, any bland fixed oil may be employed using synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compositions may also be in the form of suppositories for rectal administration of the compounds of the invention. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will thus melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols, for example.

For topical use, creams, ointments, jellies, solutions or suspensions, lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols etc., containing the compounds of the invention are contemplated. These topical formulations may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 0.1% up to about 99% of the formulation. More usually they will form up to about 80% of the formulation. For the purpose of this application, topical applications shall include mouth washes and gargles.

The compounds of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes may be formed from a variety of phospholipids.

The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Compounds that antagonize the interaction of RAGE with its physiological ligands are potentially useful in treating diseases or conditions that may be responsive to the inhibiting of the RAGE receptor.

I. RAGE and the Complications of Diabetes

It has been shown that nonezymatic glycoxidation of macromolecules ultimately resulting in the formation of advanced glycation endproducts (AGEs) is enhanced at sites of inflammation, in renal failure, in the presence of hyperglycemia and other conditions associated with systemic or local oxidant stress (Dyer, D., et al., J. Clin. Invest., 91:2463-2469 (1993); Reddy, S., et al., Biochem., 34:10872-10878 (1995); Dyer, D., et al., J. Biol. Chem., 266:11654-11660 (1991); Degenhardt, T., et al., Cell Mol. Biol., 44:1139-1145 (1998)). Accumulation of AGEs in the vasculature can occur focally, as in the joint amyloid composed of AGE-ß2-microglobulin found in patients with dialysis-related amyloidosis (Miyata, T., et al., J. Clin. Invest., 92:1243-1252 (1993); Miyata, T., et al., J. Clin. Invest., 98:1088-1094 (1996)), or generally, as exemplified by the vasculature and tissues of patients with diabetes (Schmidt, A-M., et al., Nature Med., 1:1002-1004 (1995)). The progressive accumulation of AGEs over time in patients with diabetes suggests that endogenous clearance mechanisms are not able to function effectively at sites of AGE deposition. Such accumulated AGEs have the capacity to alter cellular properties by a number of mechanisms. Although RAGE is expressed at low levels in normal tissues and vasculature, in an environment where the receptor's ligands accumulate, it has been shown that RAGE becomes upregulated (Li, J. et al., J. Biol. Chem., 272:16498-16506 (1997); Li, J., et al., J. Biol. Chem., 273:30870-30878 (1998); Tanaka, N., et al., J. Biol. Chem,. 275:25781-25790(2000)). RAGE expression is increased in endothelium, smooth muscle cells and infiltrating mononuclear phagocytes in diabetic vasculature. Also, studies in cell culture have demonstrated that AGE-RAGE interaction caused changes in cellular properties important in vascular homeostasis.

II. RAGE and Cellular Dysfunction in the Amyloidoses

RAGE appears to be a cell surface receptor which binds ß-sheet fibrillary material regardless of the compositions of the subunits (amyloid-ß peptide, Aß, amylin, serum amyloid A, prion-derived peptide) (Yan, S. -D., et al., Nature, 382:685-691 (1996); Yan, S-D., et al., Nat. Med., 6:643-651 (2000)). Deposition of amyloid has been shown to result in enhanced expression of RAGE. For example, in the brains of patients with Alzheimer's disease (AD), RAGE expression increases in neurons and glia (Yan, S. -D., et al., Nature 382:685-691 (1996)). The consequences of Aß interaction with RAGE appear to be quite different on neurons versus microglia. Whereas microglia become activated as a consequence of Aß-RAGE interaction, as reflected by increased motility and expression of cytokines, early RAGE-mediated neuronal activation is superceded by cytotoxicity at later times. Further evidence of a role for RAGE in cellular interactions of Aß concerns inhibition of Aß-induced cerebral vasoconstriction and transfer of the peptide across the blood-brain barrier to brain parenchyma when the receptor was blocked (Kumar, S., et al., Neurosci. Program, p141 (2000)). Inhibition of RAGE-amyloid interaction has been shown to decrease expression of cellular RAGE and cell stress markers (as well as NF-kB activation), and diminish amyloid deposition (Yan, S-D., et al., Nat. Med., 6:643-651 (2000)) suggesting a role for RAGE-amyloid interaction in both perturbation of cellular properties in an environment enriched for amyloid (even at early stages) as well as in amyloid accumulation.

In other studies using a mouse model of Alzheimer's Disease, it has been shown that RAGE antagonists can reverse the formation of plaques and the loss of cognition. In U.S. Patent Publication No. US 2005/0026811, small molecule RAGE antagonists were used to inhibit the progression of Aβ deposition and reduced the volume of preexisting plaques in Alzheimer's Disease mice (US 2005/0026811 at paragraphs 581-586). Furthermore, treatment with such small molecule RAGE antagonists improved cognition in these Alzheimer's Disease mouse models (US 2005/0026811 at paragraphs 587-590). Thus, in a mouse model of Alzheimer's Disease, those mice who had developed Aβ plaques and cognitive loss and were treated with small molecule RAGE antagonists exhibited a reduction in plaque volume and an improvement in cognitive performance as compared to those Alzheimer's Disease mice who were not treated with the small molecule RAGE antagonists, showing that the RAGE antagonist compounds may delay or slow loss of cognitive performance, or may improve cognitive performance of a subject suffering from dementia of Alzheimer's type.

Also, it had been shown in both cellular assays and in animal studies that RAGE mediates the transcytosis of circulating Aβ across the blood-brain barrier (BBB). Such increased transcytosis of Aβ results in neuronal oxidant stress and sustained reductions in cerebral blood flow. The effects of RAGE can be inhibited by a RAGE modulator (e.g., anti-RAGE antibody or sRAGE) (see e.g., Mackic et al., J. Clin. Invest., 102:734-743 (1998); see also Kumar et al., Neurosci., Program, p 141 (2000)). These finding were confirmed by additional studies (see e.g., U.S. Patent No. 6,825,164 at col. 17, line 48 to col. 18, line 43; Deane et al., Nature Medicine, 9:907-913 (2003)). Reduced cerebral perfusion can promote ischemic lesions which can act synergistically with Aβ to exacerbate dementia. Also, insufficient cerebral blood flow may alter Aβ trafficking across the blood brain barrier thereby reducing Aβ clearance and promoting accumulation of Aβ in brain (see Girouard and Iadecola, J. Appl. Physiol., 100, 328-335 (2006) at page 332). Thus, the increase in cerebral blood flow promoted by RAGE antagonists may reduce the symptoms or delay onset of development of Alzheimer's Disease, or both. For example, RAGE antagonists may delay or slow loss of cognitive performance, or may improve cognitive performance of a subject suffering from dementia of Alzheimer's type, or both.

III. RAGE and Propagation of the Immune/Inflammatory Response

S100/calgranulins have been shown to comprise a family of closely related calcium-binding polypeptides characterized by two EF-hand regions linked by a connecting peptide (Schafer, B. et al., TIBS, 21:134-140 (1996); Zimmer, D., et al., Brain Res. Bull., 37:417-429 (1995); Rammes, A., et al., J. Biol. Chem., 272:9496-9502 (1997); Lugering, N., et al., Eur. J. Clin. Invest., 25:659-664 (1995)). Although they lack signal peptides, it has long been known that S100/calgranulins gain access to the extracellular space, especially at sites of chronic immune/inflammatory responses, as in cystic fibrosis and rheumatoid arthritis. RAGE is a receptor for many members of the S100/calgranulin family, mediating their proinflammatory effects on cells such as lymphocytes and mononuclear phagocytes. Also, studies on delayed-type hypersensitivity response, colitis in IL-10 null mice, collagen-induced arthritis, and experimental autoimmune encephalitis models suggest that RAGE-ligand interaction (presumably with S100/calgranulins) has a proximal role in the inflammatory cascade as implicated in the inflammatory diseases such as but not limited to rheumatoid arthritis and multiple sclerosis.

RAGE is also implicated in inflammatory diseases of the skin such as but not limited to atopic dermatitis, eczema, and psoriasis. Psoriasis in particular is characterized by inflamed itchy lesions. Psoriasis may be accompanied by arthropathic symptoms that are similar to those in seen in rheumatoid arthritis. There is considerable evidence that psoriasis is a polygenic autoimmune disorder. Psoriatic lesions are rich in cytokines, in particular IL-1 and IL-8, both potent proinflammatory mediators. IL-8 in particular is a chemotactic factor for neutrophils; neutrophils are also known to synthesize and secrete S100 proteins, one of the ligands for RAGE which is implicated in propagation of the immune and inflammatory response. Psoriasin, (S100A7) a new member of the S100 gene family, is a secreted protein isolated from psoriatic skin. Semprini et al. (Hum. Genet. 2002 Oct, 111(4-5), 310-3) have shown a linkage of psoriasis genetic susceptibility to distinct overexpression of S100 proteins in skin.

IV. RAGE and Amphoterin

Amphoterin is a high mobility group I nonhistone chromosomal DNA binding protein (Rauvala, H., et al., J. Biol. Chem., 262:16625-16635 (1987); Parkikinen, J., et al., J. Biol. Chem. 268:19726-19738 (1993)) which has been shown to interact with RAGE. It has been shown that amphoterin promotes neurite outgrowth, as well as serving as a surface for assembly of protease complexes in the fibrinolytic system (also known to contribute to cell mobility). In addition, a local tumor growth inhibitory effect of blocking RAGE has been observed in a primary tumor model (C6 glioma), the Lewis lung metastasis model (Taguchi, A., et al., Nature 405:354-360 (2000)), and spontaneously arising papillomas in mice expressing the v-Ha-ras transgene (Leder, A., et al., Proc. Natl. Acad. Sci., 87:9178-9182 (1990)).

V. RAGE and Respiratory Diseases

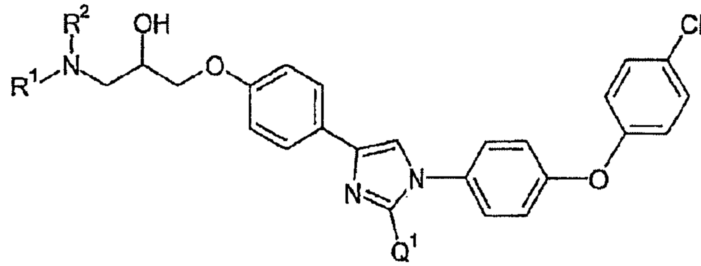
Airway inflammation is important in the pathogenesis of asthma. Such inflammation may give rise to significant exacerbations and increases in asthma severity, as well as to be a major factor in a decline in asthmatic status. In severe exacerbations of asthma there is an intense, mechanistically heterogeneous inflammatory response involving neutrophil and eosinophil accumulation and activation. Neutrophils are a significant source of S100 proteins, key ligands for RAGE implicated in the propagation of the immune response and inflammation.

Further, the propagation step in the immune response in the lung driven by S100 – RAGE interaction would be expected to lead to the activation and/or recruitment of inflammatory cells, such as neutrophils, which in chronic obstructive pulmonary diseases such as emphysema, are significant sources of damaging proteases.

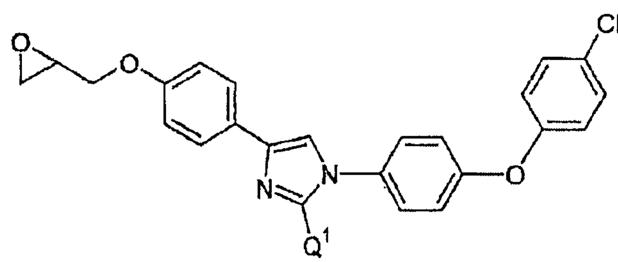
The compounds of this invention may be made by a variety of methods well known to those of ordinary skill in the art including the methods are set out below in the Examples.

In another aspect, the present invention also provides a method for the synthesis of compounds useful as intermediates in the preparation of compounds of the present invention along with methods for their preparation.

In an embodiment, the present invention provides a method for synthesizing a compound of Formula (I) or a pharmaceutically acceptable salt thereof



comprising: mixing a compound of Formula (X)



Formula (X)

and an amine having the formula R^1R^2NH,

wherein

R^1 and R^2 are independently selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, and $-CH_2CH_2CH_3$; and

Q^1 is selected from the group consisting of $-CH_2OCH_2CH_3$ and $-CH_2CH_2CH_2CH_3$, and optionally converting the obtained compound of Formula (I) to a pharmaceutically acceptable salt thereof.

In an embodiment of the method of synthesis, R^1 and R^2 are the same.

In another embodiment of the method of synthesis, R^1 and R^2 are $-CH_3$.

In another embodiment of the method of synthesis, R^1 and R^2 are $-CH_2CH_3$.

In another embodiment of the method of synthesis, Q^1 is $-CH_2OCH_2CH_3$.

In another embodiment of the method of synthesis, Q^1 is $-CH_2CH_2CH_2CH_3$.

In another embodiment of the method of synthesis, the compound of Formula (X) is in the S configuration.

In another embodiment of the method of synthesis, the compound of Formula (X) is in the R configuration.

In another embodiment of the method of synthesis, mixture of the compound of Formula (X) and R^1R^2NH is heated above room temperature. In a further embodiment, the mixture may be heated with microwave radiation.

In another embodiment of the method of synthesis, the compound of Formula (X) and R^1R^2NH are mixed in a solvent. The solvent may be selected from an aprotic solvent. A suitable aprotic solvent includes THF.

EXAMPLES

LC-MS data were obtained using gradient elution on a parallel MUX™ system, running four Waters 1525 binary HPLC pumps, equipped with a Mux-UV 2488 multichannel UV-Vis detector (recording at 215 and 254 nM) and a Leap Technologies HTS PAL Auto sampler using a Sepax GP-C18 4.6x50 mm column. A three minute gradient may be run from 25% of solution B (97.5% acetonitrile, 2.5% water, 0.05% TFA) and 75% of solution A (97.5% water, 2.5% acetonitrile, 0.05% TFA) to 100% of solution B. The system is interfaced with a Waters Micromass ZQ mass spectrometer using electrospray ionization. All MS data was obtained in the positive mode unless otherwise noted.

^{1}H NMR data was obtained on a Varian 400 MHz spectrometer.

Abbreviations used in the Examples are as follows:

d = day

DCM = dichloromethane

DMF = N, N-dimethylformamide

DMSO = dimethylsulfoxide

ELISA = enzyme - linked immunosorbent assay

ether = diethyl ether

EtOAc = ethyl acetate

g = gram

h = hour

Hz = hertz

L = liter

LC = liquid chromatography

M = molar

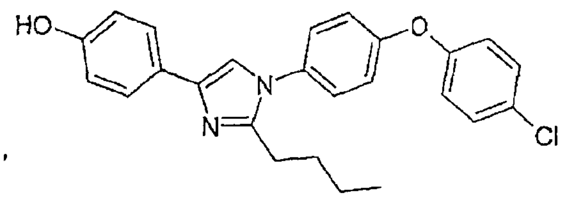
m/z = mass to charge ratio

MeOH = methanol

mg = milligram
min = minute
mL = milliliter
mM = millimolar
mmol = millimole
mol = mole
MS = mass spectrometry
N = normal
NMR = nuclear magnetic resonance spectroscopy
ppm = parts per million
rt or RT= room temperature
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TLC = thin layer chromatography

Intermediate A1

4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenol



Pyridinium bromide perbromide (33.6g, 0.105 mole) was added to a solution of 4-acetylphenyl acetate (17.8 g, 0.1 mole) in dioxane (100 mL). The heterogeneous mixture was stirred for 5 hours. During the course of the reaction the intensity of the red color decreased and a white solid was formed. The reaction mixture was diluted with ether (200 mL) and washed with water (3X100 mL), brine (75 mL), dried ($MgSO_4$) and removed *in vacuo* to give the desired product as an oil, which solidified upon standing at room temperature (26.0 g). This product was used in the next transformation without further purification.

A solution of acetic acid 4-(2-bromo-acetyl)-phenyl ester (8.6 g, 33.6 mmol) in DCM (20mL) was added to a mixture of 4-(4-chlorophenoxy)aniline (6.4 g, 29.2 mmol) and $NaHCO_3$ (4.2 g, 50 mmol) in methanol (100 mL). The formation of a yellow precipitate occurred after 1h, but the reaction still did not go completion as indicated by both TLC and HPLC. The reaction mixture was further stirred overnight. The solvents were removed *in vacuo* and the residue was added to ice-water (200 g). The flask was then rinsed with more water (100 mL). After 1 hour, the yellow solid was collected by filtration and washed with water (200 mL). The filtrate (water) in the filtering flask was removed and vacuum kept going on for an hour to remove most of the water. To dry further, the solid was washed with isovaleryl ester, and the amide of the unreacted aniline.

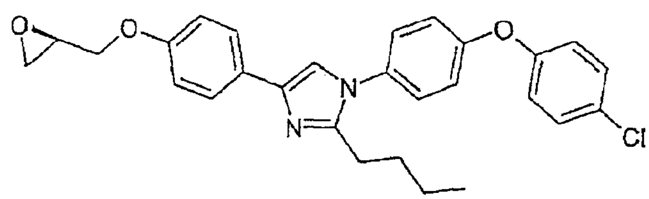
A solution of acetic acid 4-{2-[4-(4-chloro-phenoxy)-phenylamino]-acetyl}-phenyl ester (79.17 g, 200 mmol, 1.0 eq.) in dichloromethane (800 mL) and triethylamine (56 mL, 400 mmol, 2.0 eq.) was cooled to -0° C and treated with valeryl chloride (35.6 mL, 300 mmol, 1.5 eq.). The reaction mixture was stirred and warmed to room temperature over 24 h. This reaction mixture was then further treated with additional triethylamine (28 mL, 200 mmol, 1.0 eq.) and valeryl chloride (11.9 mL, 100 mmol, 0.5 eq.). Analysis of the reaction by TLC and LC/MS showed that some starting material remained, but the desired keto-amide was the major product. The reaction was evaporated *in vacuo*, recharged with ethyl acetate and filtered. The solvent was evaporated *in vacuo*, and the residue was then purified by flash column chromatography over silica gel (EtOAc/hexanes ~ 25%). The resultant oil was dissolved in ethyl acetate, washed with 1N HCl, dried and evaporated *in vacuo*. This material was then used as is in the next transformation.

A mixture of acetic acid 4-(2-{[4-(4-chloro-phenoxy)-phenyl]-pentanoyl-amino}-acetyl)-phenyl ester (from above, based on 200 mmol) with ammonium acetate (308 g, 4000 mmol, 20.0 eq) in acetic acid (300 mL) was stirred at 100-110°C overnight. After completion of the reaction (indicated by HPLC), the mixture was cooled below 60°C and poured over ice. After stirring, the solid was filtered, washed with diethyl ether (twice), ethyl acetate (twice), ether (once) and air dried, yielding ~ 55.0 g (65.6%) of 4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenol as a finely divided off-white solid.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.65 (d, 2H), 7.37 (d, 2H), 7.30 (d, 2H), 7.13 (s, 1H), 7.09 (d, 2H), 7.03 (d, 2H), 6.84 (d, 2H), 2.70-2.66 (m, 2H), 1.69-1.61 (m, 2H), 1.33-1.28 (m, 2H), 0.86 (t, 3H).

Intermediate A2

2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-((R)-1-oxiranylmethoxy)-phenyl]-1H-imidazole



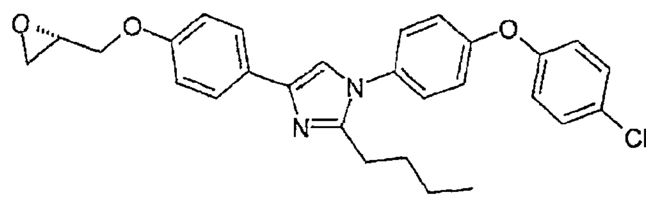
A mixture of 4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenol (0.42 g, 1.0 mmol, 1.0 eq.) and Cs_2CO_3 (1.0 g, 3.0 mmol, 3.0 eq.) in DMF (3 mL) was stirred and preheated to 80° C. The reaction mixture was then treated with a solution of (2R)-(-)-

glycidyl tosylate (0.27 g, 1.2 mmol, 1.2 eq.) in 1 mL of DMF dropwise, and further stirred at 80° C for ~ 30-60 min following completion of the addition. Analysis of the reaction by TLC and LC/MS showed that the starting phenol had been consumed and the desired alkylated-phenol was the major product. The reaction was then cooled and diluted with EtOAc and washed with brine. The organic phase was dried with Na_2SO_4 and evaporated *in vacuo*. The crude alkylated-phenol was then purified by flash column chromatography over silica gel (EtOAc/hexanes ~ 1:3).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.72 (d, 2H), 7.36 (d, 2H), 7.30 (d, 2H), 7.15 (s, 1H), 7.09 (d, 2H), 7.03 (d, 2H), 6.94 (d, 2H), 4.26-4.22 (m, 1H), 4.02-3.98 (m, 1H), 3.40-3.36 (m, 1H), 2.92-2.90 (m, 1H), 2.79-2.77 (m, 1H), 2.69-2.65 (m, 2H), 1.71-1.63 (m, 2H), 1.37-1.27 (m, 2H), 0.86 (t, 3H).

Intermediate A3

2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-((S)-1-oxiranylmethoxy)-phenyl]-1H-imidazole

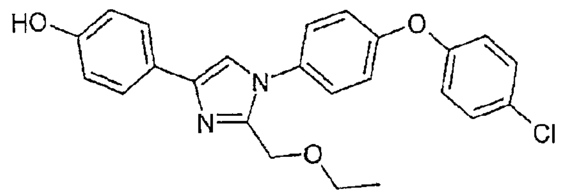


A mixture of 4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenol (0.42 g, 1.0 mmol, 1.0 eq.) and Cs_2CO_3 (1.0 g, 3.0 mmol, 3.0 eq.) in DMF (3 mL) was stirred and preheated to 80° C. The reaction mixture was then treated with a solution of (2S)-(+)-glycidyl tosylate (0.27 g, 1.2 mmol, 1.2 eq.) in 1 mL of DMF dropwise, and further stirred at 80° C for ~ 30-60 min following completion of the addition. Analysis of the reaction by TLC and LC/MS showed that the starting phenol had been consumed and the desired alkylated-phenol was the major product. The reaction was then cooled and diluted with EtOAc and washed with brine. The organic phase was dried with Na_2SO_4 and evaporated *in vacuo*. The crude alkylated-phenol was then purified by flash column chromatography over silica gel (EtOAc/hexanes ~ 1:3).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.72 (d, 2H), 7.36 (d, 2H), 7.30 (d, 2H), 7.15 (s, 1H), 7.09 (d, 2H), 7.03 (d, 2H), 6.94 (d, 2H), 4.26-4.23 (m, 1H), 4.01-3.98 (m, 1H), 3.40-3.36 (m, 1H), 2.93-2.91 (m, 1H), 2.79-2.77 (m, 1H), 2.69-2.65 (m, 2H), 1.71-1.63 (m, 2H), 1.37-1.25 (m, 2H), 0.86 (t, 3H).

Intermediate B1

4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenol



Pyridinium bromide perbromide (33.6g, 0.105 mole) was added to a solution of 4-acetylphenyl acetate (17.8 g, 0.1 mole) in dioxane (100 mL). The heterogeneous mixture was stirred for 5 hours. During the course of the reaction the intensity of the red color decreased and a white solid was formed. The reaction mixture was diluted with ether (200 mL) and washed with water (3X100 mL), brine (75 mL), dried ($MgSO_4$) and removed *in vacuo* to give the desired product as an oil, which solidified upon standing at room temperature (26.0 g). This product was used in the next transformation without further purification.

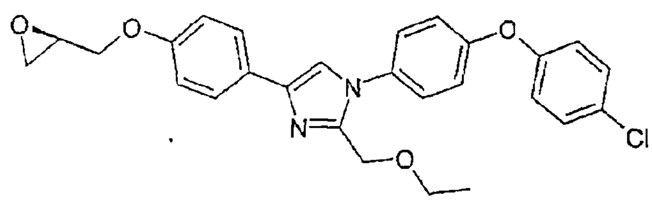
A solution of acetic acid 4-(2-bromo-acetyl)-phenyl ester (8.6 g, 33.6 mmol) in DCM (20mL) was added to a mixture of 4-(4-chlorophenoxy)aniline (6.4 g, 29.2 mmol) and $NaHCO_3$ (4.2 g, 50 mmol) in methanol (100 mL). The formation of a yellow precipitate occurred after 1h, but the reaction still did not go completion as indicated by both TLC and HPLC. The reaction mixture was further stirred overnight. The solvents were removed *in vacuo* and the residue was added to ice-water (200 g). The flask was then rinsed with more water (100 mL). After 1 hour, the yellow solid was collected by filtration and washed with water (200 mL). The filtrate (water) in the filtering flask was removed and vacuum kept going on for an hour to remove most of the water. To dry further, the solid was washed with isovaleryl ester, and the amide of the unreacted aniline.

A solution of acetic acid 4-{2-[4-(4-chloro-phenoxy)-phenylamino]-acetyl}-phenyl ester (0.33 mmol, 1.0 eq.) in THF (3 mL) was cooled to -78° C, treated with ethoxyacetyl chloride (0.33 mmol, 1.0 eq.) and stirred for ~ 5 min. This cold reaction mixture was then treated with pyridine (0.33 mmol, 1.0 eq.) dropwise and allowed to stir for ~ 1h. Analysis of the reaction by TLC and LC/MS showed that the starting material has been consumed and the desired keto-amide was the major product. The reaction was then diluted with Et_2O and washed with H_2O, the organic phase was dried with Na_2SO_4 and evaporated *in vacuo*, and the crude keto-aniline was used in the subsequent step without further purification.

A mixture of N-(4-chlorophenoxyphenyl)-N-(4-acetoxybenzoylmethyl) -n-pentanamide (0.1011 mol, 1.0 eq) and ammonium acetate (175 g, 2.27 mol, 22.4 eq) in acetic acid (150 mL) was heated at 100-110°C. After completion of the reaction as indicated by HPLC or TLC, the mixture was cooled below 60°C and is added to chilled water. The solid was filtered, washed with water and ethyl acetate and air dried to produce the desired 4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenol.

Intermediate B2

1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-4-[4-((R)-1-oxiranylmethoxy)-phenyl]-1H-imidazole

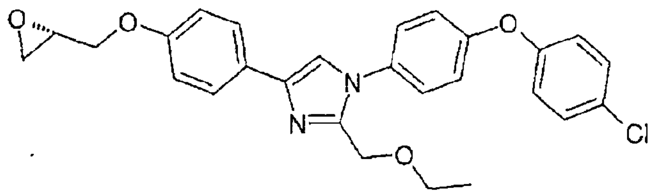


A mixture of 4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenol (0.21 g, 0.5 mmol, 1.0 eq.) and Cs_2CO_3 (0.49 g, 1.5 mmol, 3.0 eq.) in DMF (2 mL) was stirred and preheated to 80° C. The reaction mixture was then treated with a solution of (2R)-(-)-glycidyl tosylate (0.17 g, 0.75 mmol, 1.5 eq.) in 1 mL of DMF dropwise, and further stirred at 80° C for ~ 30 min following completion of the addition. Analysis of the reaction by TLC and LC/MS showed that the starting phenol had been consumed and the desired alkylated-phenol was the major product. The reaction was then cooled and diluted with EtOAc and washed with brine. The organic phase was dried with Na_2SO_4 and evaporated *in vacuo*. The crude alkylated-phenol was then purified by flash column chromatography over silica gel (EtOAc/hexanes ~ 1:3).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.74 (d, 2H), 7.49 (d, 2H), 7.36 (d, 2H), 7.28 (s, 1H), 7.09 (d, 2H), 7.03 (d, 2H), 6.95 (d, 2H), 4.48 (s, 2H), 4.27-4.23 (m, 1H), 4.03-3.99 (m, 1H), 3.62-3.57 (m, 2H), 3.40-3.37 (m, 1H), 2.94-2.92 (m, 1H), 2.80-2.78 (m, 1H), 1.21 (t, 3H).

Intermediate B3

1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-4-[4-((S)-1-oxiranylmethoxy)-phenyl]-1H-imidazole

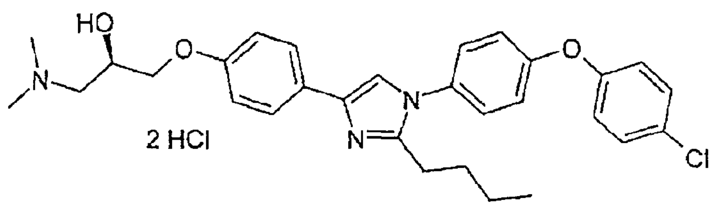


A mixture of 4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenol (0.21 g, 0.5 mmol, 1.0 eq.) and Cs_2CO_3 (0.49 g, 1.5 mmol, 3.0 eq.) in DMF (2 mL) was stirred and preheated to 80° C. The reaction mixture was then treated with a solution of (2S)-(+)-glycidyl tosylate (0.17 g, 0.75 mmol, 1.5 eq.) in 1 mL of DMF dropwise, and further stirred at 80° C for ~ 30 min following completion of the addition. Analysis of the reaction by TLC and LC/MS showed that the starting phenol had been consumed and the desired alkylated-phenol was the major product. The reaction was then cooled and diluted with EtOAc and washed with brine. The organic phase was dried with Na_2SO_4 and evaporated *in vacuo*. The crude alkylated-phenol was then purified by flash column chromatography over silica gel (EtOAc/hexanes ~ 1:3).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.74 (d, 2H), 7.49 (d, 2H), 7.36 (d, 2H), 7.28 (s, 1H), 7.09 (d, 2H), 7.03 (d, 2H), 6.95 (d, 2H), 4.48 (s, 2H), 4.27-4.24 (m, 1H), 4.03-3.99 (m, 1H), 3.62-3.57 (m, 2H), 3.40-3.37 (m, 1H), 2.94-2.92 (m, 1H), 2.80-2.78 (m, 1H), 1.20 (t, 3H).

Example 1

(R)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol dihydrochloride



A solution of 2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-((R)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (100 mg, 2.1 mmol, from intermediate A2) in 3 mL of dimethylamine in THF (2M) was stirred at 76°C for 1h in a microwave reactor. Upon completion (determined by LC/MS), the reaction was evaporated *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 96% EtOAc/(2M

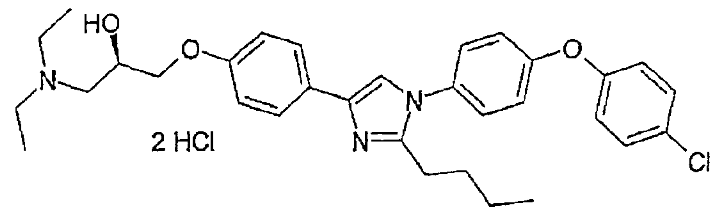
NH_3/MeOH) as an eluent to afford (R)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo*.

^{1}H-NMR (400 MHz; CD_3OD): δ 7.90 (s, 1H), 7.73 (d, 2H), 7.62 (d, 2H), 7.44 (d, 2H), 7.23 (d, 2H), 7.16-7.10 (m, 4H), 4.39 (m, 1H), 4.09 (d, 2H), 3.37 (d, 2H), 2.98-2.96 (m, 8H), 1.69 -1.66 (m, 2H), 1.37-1.31 (m, 2H), 0.88 (t, 3H).

Example 2

(R)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol dihydrochloride



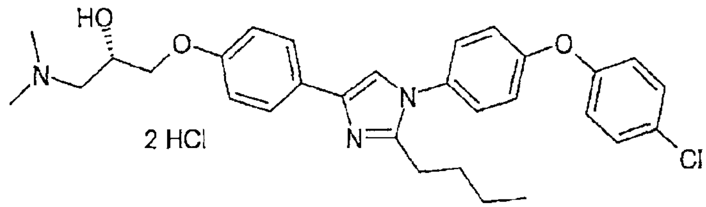
A solution of 2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-((R)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (100 mg, 2.1 mmol, from intermediate A2) in 1 mL of diethylamine and 2 mL of THF was stirred at 76°C for 1h in a microwave reactor. Upon completion (determined by LC/MS), the reaction was evaporated *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 96% EtOAc/(2M NH_3/MeOH) as an eluent to afford (R)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo*.

^{1}H-NMR (400 MHz; CD_3OD): δ 7.90 (s, 1H), 7.74 (d, 2H), 7.62 (d, 2H), 7.45 (d, 2H), 7.24 (d, 2H), 7.17-7.10 (m, 4H), 4.42-4.38 (m, 1H), 4.11 (d, 2H), 3.45-3.27 (m, 6H), 2.97 (t, 2H), 1.72 -1.64 (m, 2H), 1.39-1.30 (m, 8H), 0.89 (t, 3H).

Example 3

(S)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol dihydrochloride



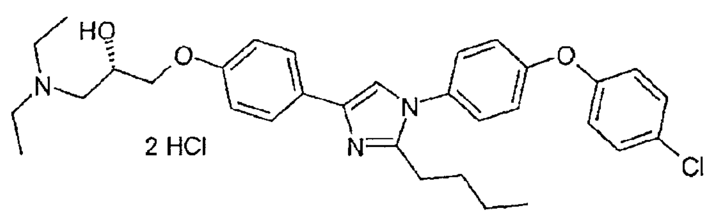
A solution of 2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-((S)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (from intermediate A3) in 3 mL of dimethylamine in THF (2M) was stirred at 76°C for 1h in a microwave reactor. Upon completion (determined by LC/MS), the reaction was evaporated *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 96% EtOAc/(2M NH_3/MeOH) as an eluent to afford (S)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo*.

^{1}H-NMR (400 MHz; CD_3OD): δ 7.90 (s, 1H), 7.73 (d, 2H), 7.61 (d, 2H), 7.44 (d, 2H), 7.23 (d, 2H), 7.16-7.10 (m, 4H), 4.38 (m, 1H), 4.09 (d, 2H), 3.37 (d, 2H), 2.98-2.96 (m, 8H), 1.71 -1.63 (m, 2H), 1.37-1.30 (m, 2H), 0.88 (t, 3H).

Example 4

(S)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol dihydrochloride



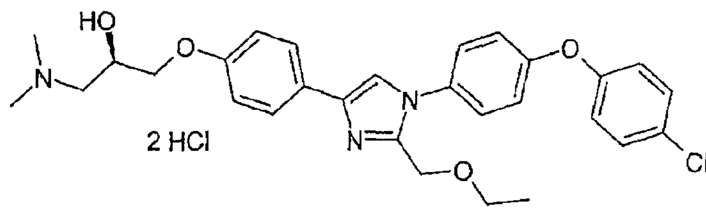
A solution of 2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-((S)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (from intermediate A3) in 1 mL of diethylamine and 2 mL of THF was stirred at 76°C for 1h in a microwave reactor. Upon completion (determined by LC/MS), the reaction was evaporated *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 96% EtOAc/(2M NH_3/MeOH) as an eluent to afford (S)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo.*

^{1}H-NMR (400 MHz; CD_3OD): δ 7.90 (s, 1H), 7.73 (d, 2H), 7.61 (d, 2H), 7.45 (d, 2H), 7.24 (d, 2H), 7.16-7.10 (m, 4H), 4.42-4.37 (m, 1H), 4.10 (d, 2H), 3.42-3.26 (m, 6H), 2.96 (t, 2H), 1.71 -1.63 (m, 2H), 1.38-1.31 (m, 8H), 0.88 (t, 3H).

Example 5

(R)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol dihydrochloride



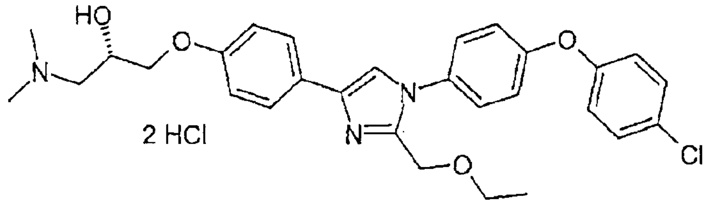
A solution of 1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-4-[4-((R)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (~ 100 mg, ~ 0.20 mmol, from intermediate B2) in 3 mL of dimethylamine in THF (2M) was stirred at 60°C overnight in a teflon-capped vial. Upon completion (determined by LC/MS), the reaction was dried *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 4% ammonia/MeOH (2.0M) in EtOAc as an eluent to afford (R)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo.*

^{1}H-NMR (400 MHz; CD_3OD): δ 8.05 (s, 1H), 7.75 (d, 2H), 7.65 (d, 2H), 7.44 (d, 2H), 7.23 (d, 2H), 7.16-7.10 (m, 4H), 4.69 (s, 2H), 4.42-4.36 (m, 1H), 4.11 (d, 2H), 3.60 (q, 2H), 3.37 (d, 2H), 2.99 (s, 3H), 2.96 (s, 3H) 1.20 (t, 3H).

Example 6

(S)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol dihydrochloride



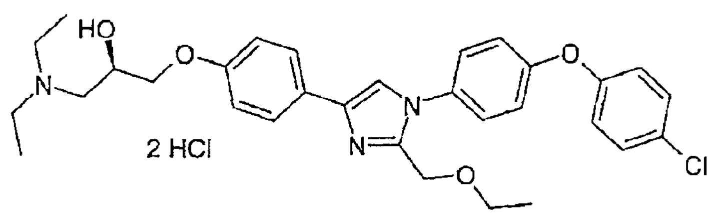
A solution of 1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-4-[4-((S)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (~ 100 mg, ~ 0.20 mmol, from intermediate B3) in 3 mL of dimethylamine in THF (2M) was stirred at 60°C overnight in a teflon-capped vial. Upon completion (determined by LC/MS), the reaction was dried *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 4% ammonia/MeOH (2.0M) in EtOAc as an eluent to afford (S)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo*.

^{1}H-NMR (400 MHz; CD_3OD): δ 8.05 (s, 1H), 7.76 (d, 2H), 7.65 (d, 2H), 7.44 (d, 2H), 7.23 (d, 2H), 7.16-7.10 (m, 4H), 4.69 (s, 2H), 4.42-4.36 (m, 1H), 4.10 (d, 2H), 3.60 (q, 2H), 3.37 (d, 2H), 2.99 (s, 3H), 2.96 (s, 3H) 1.20 (t, 3H).

Example 7

(R)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol dihydrochloride



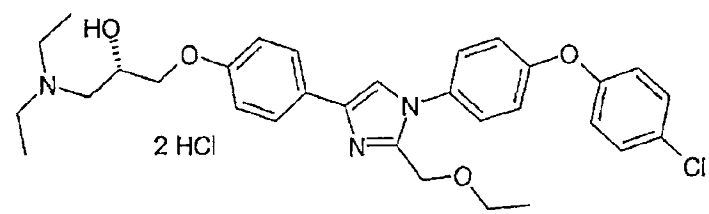
A solution of 1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-4-[4-((R)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (~ 100 mg, ~ 0.20 mmol, from intermediate B2) in 1 mL of diethylamine and 2 mL of THF was stirred at 60°C overnight in a teflon-capped vial. Upon completion (determined by LC/MS), the reaction was dried *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 4% ammonia/MeOH (2.0M) in EtOAc as an eluent to afford (R)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo.*

^{1}H-NMR (400 MHz; CD_3OD): δ 8.06 (s, 1H), 7.76 (d, 2H), 7.66 (d, 2H), 7.43 (d, 2H), 7.22 (d, 2H), 7.16 (d, 2H), 7.10 (d, 2H), 4.69 (s, 2H), 4.42-4.36 (m, 1H), 4.11 (d, 2H), 3.62-3.56 (q, 2H), 3.41-3.24 (m 6H), 1.36 (t, 6H), 1.19 (t, 3H).

Example 8

(S)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol dihydrochloride



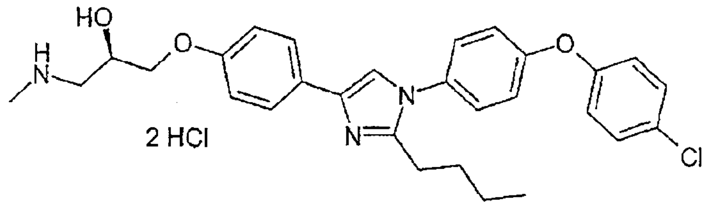
A solution of 1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-4-[4-((S)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (~ 100 mg, ~ 0.20 mmol, from intermediate B3) in 1 mL of diethylamine and 2 mL of THF was stirred at 60°C overnight in a teflon-capped vial. Upon completion (determined by LC/MS), the reaction was dried *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 4% ammonia/MeOH (2.0M) in EtOAc as an eluent to afford (S)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo.*

^{1}H-NMR (400 MHz; CD_3OD): δ 8.06 (s, 1H), 7.75 (d, 2H), 7.65 (d, 2H), 7.43 (d, 2H), 7.22 (d, 2H), 7.16 (d, 2H), 7.10 (d, 2H), 4.69 (s, 2H), 4.42-4.36 (m, 1H), 4.11 (d, 2H), 3.62-3.56 (q, 2H), 3.41-3.24 (m, 6H), 1.36 (t, 6H), 1.19 (t, 3H).

Example 9

(R)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-methylamino-propan-2-ol dihydrochloride



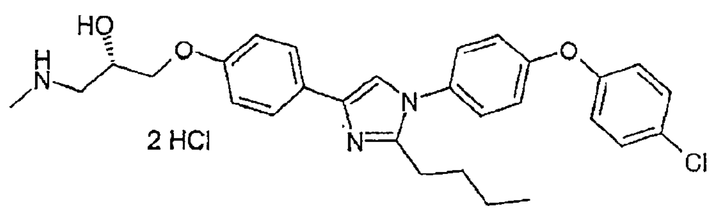
A solution of 2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-((R)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (50 mg, 0.11 mmol, from intermediate A2) in 4 mL of methylamine in MeOH (2M) was stirred at 60°C overnight in a teflon-capped vial. Upon completion (determined by LC/MS), the reaction was dried *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 4% ammonia/MeOH (2.0M) in EtOAc as an eluent to afford (R)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-methylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo*.

^{1}H-NMR (400 MHz; CD_3OD): δ 7.90 (s, 1H), 7.73 (d, 2H), 7.61 (d, 2H), 7.43 (d, 2H), 7.23 (d, 2H), 7.15-7.10 (m, 4H), 4.34-4.24 (m, 1H), 4.14-4.06 (m, 2H), 3.30-3.16 (m, 2H), 2.96 (t, 2H), 2.76 (s, 3H), 1.70-1.63 (m, 2H), 1.40-1.28 (m, 2H), 0.87 (t, 3H).

Example 10

(S)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-methylamino-propan-2-ol dihydrochloride



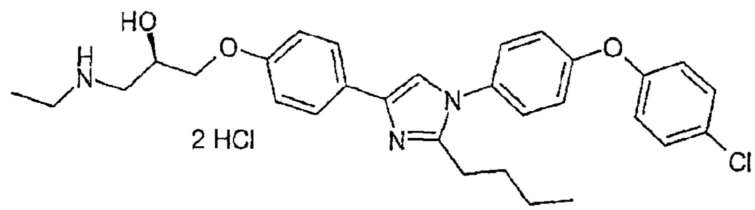
A solution of 2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-((S)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (50 mg, 0.11 mmol, from intermediate A3) in 4 mL of methylamine in MeOH (2M) was stirred at 60°C overnight in a teflon-capped vial. Upon completion (determined by LC/MS), the reaction was dried *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 4% ammonia/MeOH (2.0M) in EtOAc as an eluent to afford (S)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-methylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo*.

^{1}H-NMR (400 MHz; CD_3OD): δ 7.90 (s, 1H), 7.73 (d, 2H), 7.61 (d, 2H), 7.43 (d, 2H), 7.23 (d, 2H), 7.15-7.10 (m, 4H), 4.34-4.24 (m, 1H), 4.12-4.06 (m, 2H), 3.30-3.16 (m, 2H), 2.96 (t, 2H), 2.76 (s, 3H), 1.70-1.63 (m, 2H), 1.40-1.28 (m, 2H), 0.87 (t, 3H).

Example 11

(R)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-ethylamino-propan-2-ol dihydrochloride



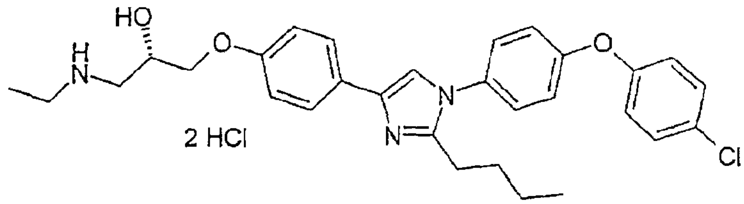
A solution of 2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-((R)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (50 mg, 0.11 mmol, from intermediate A2) in 4 mL of ethylamine in MeOH (2M) was stirred at 60°C overnight in a teflon-capped vial. Upon completion (determined by LC/MS), the reaction was dried *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 4% ammonia/MeOH (2.0M) in EtOAc as an eluent to afford (R)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-ethylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo*.

^{1}H-NMR (400 MHz; CD_3OD): δ 7.90 (s, 1H), 7.73 (d, 2H), 7.61 (d, 2H), 7.44 (d, 2H), 7.23 (d, 2H), 7.15-7.10 (m, 4H), 4.34-4.24 (m, 1H), 4.14-4.06 (m, 2H), 3.34-3.28 (m, 1H), 3.19-3.11 (m, 3H), 2.96 (t, 2H), 1.71-1.63 (m, 2H), 1.38-1.30 (m, 5H), 0.88 (t, 3H).

Example 12

(S)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-ethylamino-propan-2-ol dihydrochloride



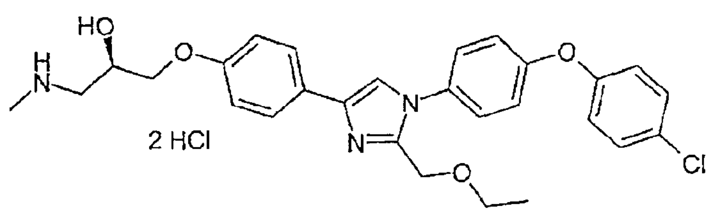
A solution of 2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-((S)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (50 mg, 0.11 mmol, from intermediate A3) in 4 mL of ethylamine in MeOH (2M) was stirred at 60°C overnight in a teflon-capped vial. Upon completion (determined by LC/MS), the reaction was dried *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 4% ammonia/MeOH (2.0M) in EtOAc as an eluent to afford (S)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-ethylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo*.

^{1}H-NMR (400 MHz; CD_3OD): δ 7.90 (s, 1H), 7.73 (d, 2H), 7.61 (d, 2H), 7.44 (d, 2H), 7.23 (d, 2H), 7.16-7.10 (m, 4H), 4.34-4.24 (m, 1H), 4.14-4.06 (m, 2H), 3.34-3.28 (m, 1H), 3.18-3.11 (m, 3H), 2.96 (t, 2H), 1.71-1.63 (m, 2H), 1.38-1.29 (m, 5H), 0.88 (t, 3H).

Example 13

(R)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-methylamino-propan-2-ol dihydrochloride



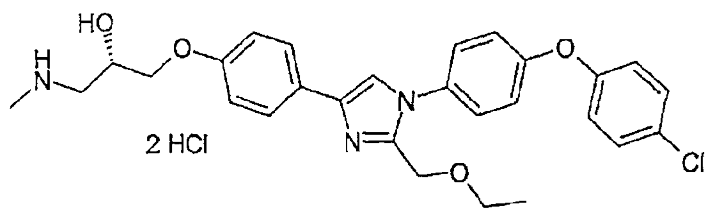
A solution of 1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-4-[4-((R)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (50 mg, 0.11 mmol, from intermediate B2) in 4 mL of methylamine in MeOH (2M) was stirred at 60°C overnight in a teflon-capped vial. Upon completion (determined by LC/MS), the reaction was dried *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 4% ammonia/MeOH (2.0M) in EtOAc as an eluent to afford (R)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-methylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo*.

^{1}H-NMR (400 MHz; CD_3OD): δ 8.06 (s, 1H), 7.75 (d, 2H), 7.65 (d, 2H), 7.43 (d, 2H), 7.23 (d, 2H), 7.16-7.10 (m, 4H), 4.69 (s, 2H), 4.31-4.26 (m, 1H), 4.13-4.07 (m, 2H), 3.60 (q, 2H), 3.32-3.28 (m, 1H), 3.21-3.15 (m, 1H), 2.76 (s, 3H), 1.19 (t, 3H).

Example 14

(S)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-methylamino-propan-2-ol dihydrochloride



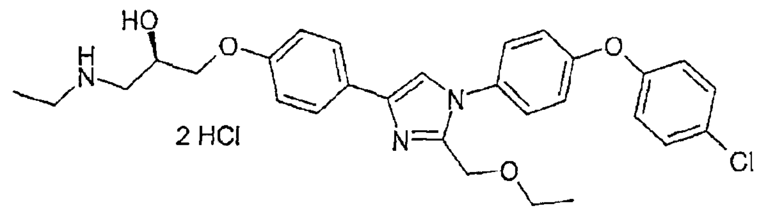
A solution of 1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-4-[4-((S)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (50 mg, 0.11 mmol, from intermediate B3) in 4 mL of methylamine in MeOH (2M) was stirred at 60°C overnight in a teflon-capped vial. Upon completion (determined by LC/MS), the reaction was dried *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 4% ammonia/MeOH (2.0M) in EtOAc as an eluent to afford (S)-1-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-methylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo*.

^{1}H-NMR (400 MHz; CD_3OD): δ 8.06 (s, 1H), 7.75 (d, 2H), 7.65 (d, 2H), 7.44 (d, 2H), 7.23 (d, 2H), 7.16-7.10 (m, 4H), 4.69 (s, 2H), 4.31-4.26 (m, 1H), 4.13-4.07 (m, 2H), 3.60 (q, 2H), 3.32-3.28 (m, 1H), 3.21-3.15 (m, 1H), 2.76 (s, 3H), 1.20 (t, 3H).

Example 15

(R)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-ethylamino-propan-2-ol dihydrochloride



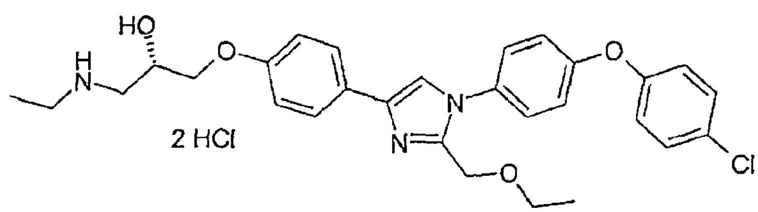
A solution of 1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-4-[4-((R)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (50 mg, 0.11 mmol, from intermediate B2) in 4 mL of ethylamine in MeOH (2M) was stirred at 60°C overnight in a teflon-capped vial. Upon completion (determined by LC/MS), the reaction was dried *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 4% ammonia/MeOH (2.0M) in EtOAc as an eluent to afford (R)-1-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-ethylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo.*

^{1}H-NMR (400 MHz; CD_3OD): δ 8.02 (s, 1H), 7.75 (d, 2H), 7.64 (d, 2H), 7.44 (d, 2H), 7.23 (d, 2H), 7.16-7.10 (m, 4H), 4.67 (s, 2H), 4.29-4.25 (m, 1H), 4.13-4.06 (m, 2H), 3.60 (q, 2H), 3.32-3.28 (m 1H), 3.19-3.11 (m, 3H), 1.35 (t, 3H), 1.20 (t, 3H).

Example 16

(S)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-ethylamino-propan-2-ol dihydrochloride



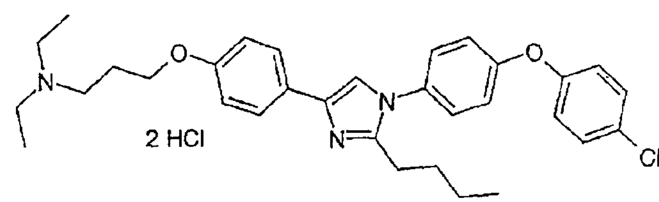
A solution of 1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-4-[4-((S)-1-oxiranylmethoxy)-phenyl]-1H-imidazole (50 mg, 0.11 mmol, from intermediate B3) in 4 mL of ethylamine in MeOH (2M) was stirred at 60°C overnight in a teflon-capped vial. Upon completion (determined by LC/MS), the reaction was dried *in vacuo* and purified by silica gel flash column chromatography using a gradient of EtOAc to 4% ammonia/MeOH (2.0M) in EtOAc as an eluent to afford (S)-1-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-ethylamino-propan-2-ol.

The resultant free base was converted to the corresponding dihydrochloride salt by dissolution in 1 mL of DCM and 3 mL of HCl/dioxane (4.0 M) and removal of solvent *in vacuo*.

^{1}H-NMR (400 MHz; CD_3OD): δ 8.04 (s, 1H), 7.75 (d, 2H), 7.65 (d, 2H), 7.44 (d, 2H), 7.23 (d, 2H), 7.16-7.10 (m, 4H), 4.68 (s, 2H), 4.29-4.25 (m, 1H), 4.13-4.06 (m, 2H), 3.60 (q, 2H), 3.32-3.28 (m 1H), 3.19-3.11 (m, 3H), 1.35 (t, 3H), 1.20 (t, 3H).

Example Z

[3-(4-{2-butyl-1-[4-(4-chlorophenoxy)-phenyl]-1H-imidazole-4-yl}-phenoxy)-propyl]-diethyl-amine dihydrochloride



Example Z may be prepared according to the method described in PCT publication number WO 2003/075921 for Example 406.

Biological Assay

The following assay method may be used to identify compounds of Formula (I) or pharmaceutically acceptable salts thereof which are useful as inhibitors of binding of physiological RAGE ligands, such as S100b and β-amyloid, to RAGE.

S100b, β-amyloid, or CML (500 ng/100μL/well) in 100 mM sodium bicarbonate/sodium carbonate buffer (pH 9.8) is loaded onto the wells of a NUNC Maxisorp flat bottom 96 -well microtitre plate. The plate is incubated at 4°C overnight. The wells are aspirated and treated with 50 mM imidazole buffer saline (pH 7.2) (with 5mM $CaCl_2/MgCl_2$) containing 1% bovine serum albumin (BSA) (300 μL/well) for 1 h at RT. The wells are aspirated.

Test compounds are dissolved in nanopure water (concentration: 10-100 µM). DMSO may be used as co-solvent. 25 µL of test compound solution in 4% DMSO is added, along with 75 µL sRAGE (6 nM FAC) to each well and samples are incubated for 1 h at 37°C. The wells are washed several times with 155 mM NaCl pH 7.2 buffer saline and are soaked for several seconds between each wash.

Non-radioactive detection is performed by adding:

10 µL Biotinylated goat F(ab')2 Anti-mouse IgG. (8.0 x 10–4 mg/mL, FAC), 5 µL Alk-phos-Streptavidin (3 x 10-3 mg/mL FAC), 0.42 µL per 5 mL Monoclonal antibody for sRAGE (FAC 6.0 x 10-3 mg/mL) to 5 mL 50mM imidazole buffer saline (pH 7.2) containing 0.2% bovine serum albumin and 5mM $CaCl_2$. The mixture is incubated for 30 minutes at RT.

100 µL of complex is added to each well and incubation is allowed to proceed at rt for 1 h. Wells are washed several times with wash buffer and soaked several seconds between each wash. 100 µL 1mg/mL (pNPP) in 1 M diethanolamine (pH adjusted to 9.8 with HCl) is added. Color is allowed to develop in the dark for 30 min to 1 h at rt. The reaction is quenched with 10 µL of stop solution (0.5-1.0 N NaOH in 50% ethanol) and the absorbance is measured spectrophotometrically with a microplate reader at 405 nm.

The Examples 1-16 (hydrochloride salt form) were tested according to the assay method described above, employing S100b or β-amyloid as the RAGE ligand, and were found to possess IC50 shown below. IC50 (µM) of in the ELISA assay represents the concentration of compound at which 50% signal has been inhibited.

Example	IC50 (β-amyloid) (µM)	IC50 (S100b) (µM)
1	0.85	0.66
2	0.76	0.55
3	0.80	0.84
4	0.65	0.54
5	1.02	0.71
6	0.78	0.77
7	1.17	1.05
8	1.26	0.80
9	1.59	1.13
10	1.32	1.14
11	1.02	0.81
12	1.19	0.98
13	2.16	4.61
14	2.37	4.56
15	2.47	3.14
16	1.55	3.13

Pharmacokinetics

Pharmacokinetic screening in rats was performed on various compounds to measure brain and plasma concentrations at 6 hour time point.

The parameters for the pharmacokinetic protocol were as follows.

Amount of compound: 5 mg/kg

Species: Rat; Strain: Sprague Dawley; Sex : Male

Average body weight at dose: weight ranged from 271 to 423 grams

Average age at dose: age ranged from 9 to 14 weeks

Diet Status: Overnight fasting

Number of Animals (n) for each time point: 2

Dosing: Oral (PO)

Formulation: 2% Tween 80 in distilled water

Each formulation was administered once by oral gavage. The dose volume was 5 mL/kg for all animals. The actual volume administered to each animal was calculated and adjusted based on the most recent body weight.

Blood samples (approximately 300 μL whole blood) at (1, 2, and 4 h) was collected from each animal via tail vein except for terminal blood samples. Terminal blood (6 h) samples were collected via cardiac puncture. All samples were collected into tubes containing lithium heparin (Multivette 600 LH-Gel, Sarstedt, Newton, NC, USA). Following collection, the tubes were placed in refrigerator (maximum 30 minutes) or until centrifugation under refrigeration (at 2 to 8°C) at 1500g for approximately 15 minutes. Each harvested plasma sample was then transferred into 1.2 mL polypropylene tubes, on the 96-Well Plate according to the 96-Well Plate plasma sample map and kept in freezer. Plasma samples were then analyzed for test substances.

Brain samples were collected immediately after the animals were euthanized at designated time points. Brain samples were rinsed with saline, blotted dry, and weighed. Brain samples were placed into individual containers and kept in freezer (-20°C). Brain samples were then analyzed for test articles.

After analysis, all the plasma results are reported as ng/mL and brain sample results are reported as ng/g. In the table below, "ND" stands for not determined and "NA" stands for not applicable.

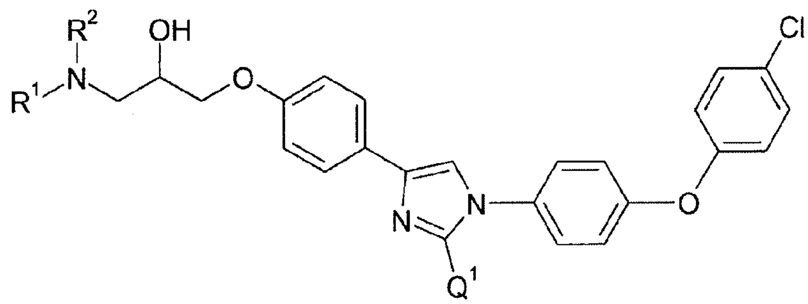
Ex.	Brain (ng/g)	Plasma (ng/mL)	B/P Ratio	R^1	R^2	Q^1	Config
Z	697	92	7.7	$-CH_3CH_2$	$-CH_3CH_2$	butyl	NA
1	626	18	34.1	$-CH_3$	$-CH_3$	butyl	R
2	718	24	30.6	$-CH_3CH_2$	$-CH_3CH_2$	butyl	R
3	1120	48	23.3	$-CH_3$	$-CH_3$	butyl	S
4	610	74	8.8	$-CH_3CH_2$	$-CH_3CH_2$	butyl	S
5	3325	200	16.7	$-CH_3$	$-CH_3$	ethoxymethyl	R
6	3905	155	25.3	$-CH_3$	$-CH_3$	ethoxymethyl	S
7	1385	153	9.1	$-CH_3CH_2$	$-CH_3$	ethoxymethyl	R
8	2705	137	19.6	$-CH_3CH_2$	$-CH_3$	ethoxymethyl	S
9	537	76	7.2	H	$-CH_3$	butyl	R
10	212	74	2.9	H	$-CH_3$	butyl	S
11	343	72	4.8	H	$-CH_3CH_2$	butyl	R
12	540	124	4.5	H	$-CH_3CH_2$	butyl	S
13	ND	ND	ND	H	$-CH_3$	ethoxymethyl	R
14	ND	ND	ND	H	$-CH_3$	ethoxymethyl	S
15	ND	ND	ND	H	$-CH_3CH_2$	ethoxymethyl	R
16	ND	ND	ND	H	$-CH_3CH_2$	ethoxymethyl	S

The specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with practice of the present invention.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention.

CLAIMS:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 and R^2 are independently selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, and $-CH_2CH_2CH_3$; and

Q^1 is selected from the group consisting of $-CH_2OCH_2CH_3$ and $-CH_2CH_2CH_2CH_3$.

2. The compound of Formula (I) of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^1 is $-CH_3$.

3. The compound of Formula (I) of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^1 is $-CH_2CH_3$.

4. The compound of Formula (I) of any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein R^2 is $-CH_3$.

5. The compound of Formula (I) of any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein R^2 is $-CH_2CH_3$.

6. The compound of Formula (I) of any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, wherein Q^1 is $-CH_2OCH_2CH_3$.

7. The compound of Formula (I) of any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, wherein Q^1 is $-CH_2CH_2CH_2CH_3$.

8. The compound of any one of claims 1 to 7, wherein the compound is a free amine.

9. The compound of any one of claims 1 to 7, wherein the compound is a pharmaceutically acceptable salt.

10. The compound of claim 9, wherein the compound is a hydrochloride salt.

11. The compound of claim 1, wherein the compound is selected from the group consisting of

(R)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol;

(R)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol;

(S)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol;

(S)-1-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol;

(R)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol; and

(S)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-diethylamino-propan-2-ol;

or a pharmaceutically acceptable salt thereof.

12. A compound, wherein the compound is (R)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol or a pharmaceutically acceptable salt thereof.

13. The compound of claim 12, wherein the compound is (R)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol.

14. A compound, wherein the compound is (S)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol or a pharmaceutically acceptable salt thereof.

15. The compound of claim 14, wherein the compound is (S)-1-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-ethoxymethyl-1H-imidazol-4-yl}-phenoxy)-3-dimethylamino-propan-2-ol.

16. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. A pharmaceutical composition comprising a compound of claim 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

18. A pharmaceutical composition comprising a compound of claim 3, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

19. A pharmaceutical composition comprising a compound of claim 4, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

20. A pharmaceutical composition comprising a compound of claim 5, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

21. A pharmaceutical composition comprising a compound of claim 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

22. A pharmaceutical composition comprising a compound of claim 7, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

23. A pharmaceutical composition comprising a compound of claim 8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

24. A pharmaceutical composition comprising a compound of claim 9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

25. A pharmaceutical composition comprising a compound of claim 10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

26. A pharmaceutical composition comprising a compound of claim 11, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

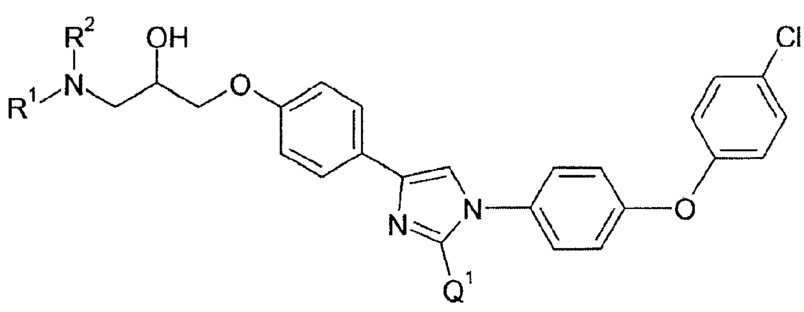
27. A pharmaceutical composition comprising a compound of claim 12, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

28. A pharmaceutical composition comprising a compound of claim 13 and a pharmaceutically acceptable carrier.

29. A pharmaceutical composition comprising a compound of claim 14, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

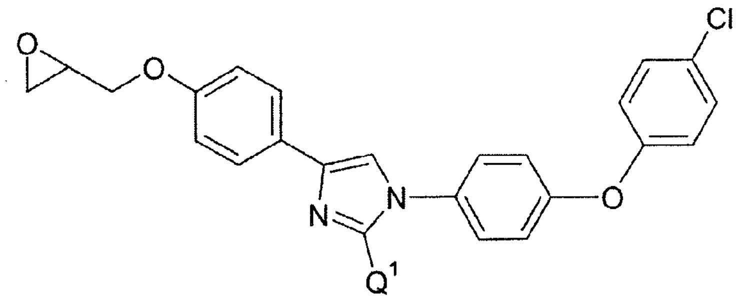
30. A pharmaceutical composition comprising a compound of claim 15 and a pharmaceutically acceptable carrier.

31. A method for synthesizing a compound of Formula (I) or a pharmaceutically acceptable salt thereof



Formula (I)

comprising: mixing a compound of Formula (X)



Formula (X)

and an amine having the formula R^1R^2NH, wherein

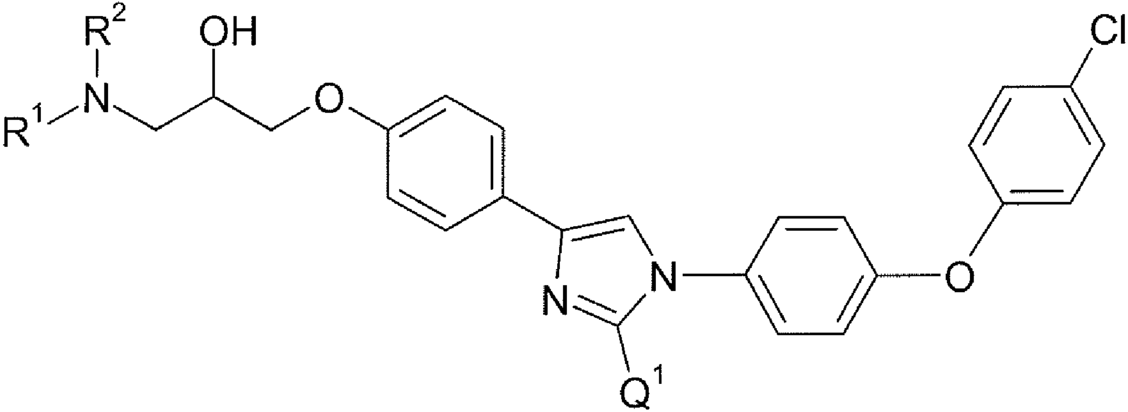
R^1 and R^2 are independently selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, and $-CH_2CH_2CH_3$; and

Q^1 is selected from the group consisting of $-CH_2OCH_2CH_3$ and $-CH_2CH_2CH_2CH_3$;

and optionally converting the obtained compound of Formula (I) to a pharmaceutically acceptable salt thereof.

32. Use of the compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, for inhibiting the binding of S100b or β-amyloid to the receptor for advanced glycation endproducts (RAGE).

33. Use of the pharmaceutical composition of any one of claims 16 to 30 for inhibiting the binding of S100b or β-amyloid to the receptor for advanced glycation endproducts (RAGE).



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