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(54) Title: MODULATORS OF UROTENSIN RECEPTOR AND METHODS OF USE THEREOF

(57) Abstract: Provided are compounds that are modulato rs of urotensin-II receptor activity, compositions containing the compounds a nd methods of use of the compounds and compositions. In certain embodiments, provide d are methods for treating or ameliorating diseases associated with modulati on of urotensin-II receptor activity.

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MODULATORS OF UROTENSIN RECEPTOR AND METHODS OF USE THEREOF

1. FIELD

[0001] Provided herein are compounds, compositions and methods for treating, preventing or ameliorating conditions associated with urotensin receptor activity. In certain embodiments, the compounds are urotensin-II receptor antagonists useful for treating urotensin-II mediated disorders.

2. BACKGROUND

[0002] Urotensin-II (U-II) is a cysteine-linked cyclic peptide, which exerts potent effects on the cardiovascular, renal, pancreatic, and central nervous systems. Originally, it was isolated from the urophysis (a caudal neurosecretory organ) of the goby fish (Gillichthys mirabilis) as a 12-mer, AGTAD-cyclo(CFWKYC)-V (D. Pearson *et al.*, *Proc. Natl. Acad. Sci.* USA 1980, 77, 5021-5024), but it has now been identified in all classes of vertebrates. The composition of U-II ranges from 11 amino acids in humans to 14 amino acids in mice, always with a conserved cysteine-linked macrocycle, CFWKYC. The UT receptor was identified (R. S. Ames *et al.*, *Nature* (London) 1999, 401, 282-286) as a G-protein-coupled receptor (GPCR) previously known as the GPR14 orphan receptor, (M. Tal *et al.*, *Biochem. Biophys. Res. Commun.* 1995, 209, 752-759; and A. Marchese *et al.*, *Genomics* 1995, 29, 335-344) which is expressed predominantly in cardiovascular tissues.

[0003] Goby U-II possesses powerful vasoconstrictor activity in fish, mammals, and humans (F. Bohm, J. Pernow, *Br. J. Pharmacol.* 2002, 135, 25-27). Relative to the role of U-II in chronic vascular disease, this peptide was reported to induce hypertrophy in cardiomyocytes (Y. Zou *et al.*, *FEBS Letters* 2001, 508, 57-60) and the proliferation of smooth muscle cells (T. Watanabe *et al.*, *Circulation* 2001, 104, 16-18), which suggests an involvement in heart failure and atherosclerosis. In addition, U-II has been shown to increase peripheral vascular tone, a characteristic of chronic heart failure (M. Lim *et al.* , *Circulation* 2004, 109, 1212-1214). Recent results have shown increased U-II receptor levels observed in the atherosclerotic lesions of the human aorta (N. Bousette *et al.*, *Atherosclerosis* 2004, 176, 117-123).

[0004] Recently, Kinoshita, M. and Kushida, H. in International Publication WO 2005/034873 disclosed the use of Urotensin-II antagonists for reducing nephrotoxicity and diarrhea caused by anti-neoplastic agents.

[0005]

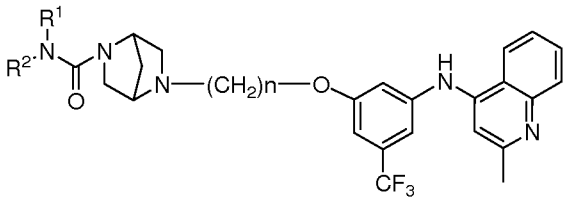
[0006] U-II has been described as a potential mediator in diabetes. For instance, U-II was shown to inhibit the release of insulin in the perfused rat pancreas in response to

increasing glucose levels (R. A. Silvestre *et al., Horm. Metab. Res.* 2001, 33, 379-381). Elevated U-II levels were seen in patients with diabetis mellitus (K. Totsune *et al.* , *Clin. Sci.* 2003, 104, 1-5) even without renal failure.

[0007] Because of the involvement of the urotensin receptor in a variety of diseases, there is a continuing need for compounds that modulate the binding or function of urotensin receptor.

3. SUMMARY

[0008] Provided herein are compounds that are modulators of a urotensin receptor, pharmaceutical compositions containing the compounds and methods of use thereof. In certain embodiments, the compounds for use in the compositions and methods provided herein are of Formula I:



or pharmaceutically acceptable derivatives thereof, wherein the variables are chosen such that the resulting compounds show activity as urotensin-II modulators.

[0009] Pharmaceutical compositions containing a compound of Formula I and a pharmaceutically acceptable carrier are provided herein. Also provided are methods for treating, preventing, or ameliorating one or more symptoms of urotensin-II receptor mediated diseases by administering the compounds and compositions provided herein.

[0010] In certain embodiments, provided herein are methods for modulating an activity of a urotensin-II receptor by contacting the receptor with a compound or composition provided herein. In one embodiment, provided herein are methods for antagonizing an action of a urotensin-II receptor by contacting the receptor with a compound or composition provided herein. In other embodiments, provided herein are methods for treatment, prevention, or amelioration of one or more symptoms of diseases or conditions associated with urotensin-II receptor activity, including, but not limited to cardiovascular disorders, such as hypertension and heart failure; atherosclerosis; renal failure; nephrotoxicity and diarrhea caused by anti-neoplastic agents; post-myocardial infarction; pulmonary hypertension/fibrosis; diabetes; diseases and disorders associated with CNS function, such as Parkinson's Disease, Alzheimer's Disease, convulsions, depression, migraine, psychosis, anxiety, neuromuscular deficit amylotrophic lateral sclerosis, muscular dystrophy, childhood spinal muscular atrophy, progressive spinal

muscular atrophy and progressive bulbar palsy; OPCA; ADHD; schizophrenia; sleep disorders such as insomnia; and autonomic dysfunctions such as Shy-Drager syndrome.

4. DETAILED DESCRIPTION

4.1 DEFINITIONS

[0011] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0012] As used herein "subject" is an animal, such as a mammal, including human, such as a patient.

[0013] The terms "urotensin-II receptor mediated disease, or "urotensin-II receptor mediated condition", as used herein, mean any disease or other deleterious condition or state in which urotensin-II receptor is known to play a role. Such diseases or conditions include, without limitation, cardiovascular disorders, such as hypertension and heart failure; atherosclerosis; renal failure; nephrotoxicity and diarrhea caused by anti-neoplastic agents; post-myocardial infarction; pulmonary hypertension/fibrosis; diabetes; diseases and disorders associated with CNS function, such as Parkinson's Disease, Alzheimer's Disease, convulsions, depression, migraine, psychosis, anxiety, neuromuscular deficit amylotrophic lateral sclerosis, muscular dystrophy, childhood spinal muscular atrophy, progressive spinal muscular atrophy and progressive bulbar palsy; OPCA; ADHD; schizophrenia; sleep disorders such as insomnia; and autonomic dysfunctions such as Shy-Drager syndrome.

[0014] As used herein, biological activity refers to the *in vivo* activities of a compound or physiological responses that result upon *in vivo* administration of a compound, composition or other mixture. Biological activity, thus, encompasses therapeutic effects and pharmacokinetic behaviour of such compounds, compositions and mixtures. Biological activities can be observed in *in vitro* systems designed to test for such activities.

[0015] As used herein, pharmaceutically acceptable derivatives of a compound include, but are not limited to, salts, esters, enol ethers, enol esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, solvates or hydrates thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs.

Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and inorganic salts, such as but not limited to, sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates, mesylates, and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula C=C(OR) where R is alkyl, alkenyl, alkynyl, aryl, aralkyl and cycloalkyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula C=C(OC(O)R) where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl and cycloalkyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

[0016] As used herein, treatment means any manner in which one or more of the symptoms of a disease or disorder are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating a cardiovascular disease.

[0017] As used herein, amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

[0018] As used herein, and unless otherwise indicated, the terms "manage," "managing" and "management" encompass preventing the recurrence of the specified disease or disorder in a patient who has already suffered from the disease or disorder, and/or lengthening the time that a patient who has suffered from the disease or disorder remains in remission. The terms encompass modulating the threshold, development and/or duration of

the disease or disorder, or changing the way that a patient responds to the disease or disorder.

[0019] As used herein, the IC_{50} refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response in an assay that measures such response.

[0020] It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. As such, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (S) form.

[0021] As used herein, substantially pure means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC) and mass spectrometry (MS), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter enzymatic and biological activities of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

[0022] As used herein, the nomenclature alkyl, alkoxy etc. is used as is generally understood by those of skill in this art.

[0023] As used herein, alkyl carbon chains, if not specified, contain from 1 to 20 carbons, or 1 to 16 carbons, and are straight or branched. Exemplary alkyl groups herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, sec-butyl, tert-butyl, isopentyl, neopentyl, tert-pentyl, isohexyl. As used herein, lower alkyl refers to carbon chains having from about 1 or about 2 carbons up to about 6 carbons.

[0024] As used herein, "cycloalkyl" refers to a saturated mono- or multicyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments of 3 to 6 carbon atoms.

[0025] As used herein, "halo", "halogen" or "halide" refers to F, Cl, Br or I.

[0026] As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include, but are not limited to, chloromethyl and trifluoromethyl.

[0027] As used herein, "aryl" refers to aromatic monocyclic or multicyclic groups containing from 6 to 19 carbon atoms. Aryl groups include, but are not limited to groups such as fluorenyl, substituted fluorenyl, phenyl, substituted phenyl, naphthyl and substituted naphthyl.

[0028] As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system, in certain embodiments, of about 5 to about 15 members where one or more, in one embodiment 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl, pyrrolyl, N-methylpyrrolyl, quinolinyl and isoquinolinyl.

[0029] As used herein, "heterocyclyl" refers to a monocyclic or multicyclic non-aromatic ring system, in one embodiment of 3 to 10 members, in another embodiment of 4 to 7 members, in a further embodiment of 5 to 6 members, where one or more, in certain embodiments, 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. In embodiments where the heteroatom(s) is(are) nitrogen, the nitrogen is optionally substituted with alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, acyl, guanidino, amidino or the nitrogen may be quaternized to form an ammonium group where the substituents are selected as above.

[0030] As used herein, "substituted aryl," "substituted heteroaryl" and "substituted heterocyclyl" refer to aryl, heteroaryl and heterocyclyl groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three or four substituents, where the substituents are as defined elsewhere herein.

[0031] As used herein, "hydroxycarbonyl" refers to -COOH.

[0032] As used herein, "alkoxycarbonyl" refers to -C(O)OR in which R is alkyl, including lower alkyl.

[0033] As used herein, "alkoxy" refers to RO- , in which R is alkyl, including lower alkyl.As used herein, "haloalkoxy" refers to RO- , in which R is haloalkyl, including halo lower alkyl.

[0034] As used herein, "amino" refers to $-NH_2$.

[0035] As used herein, "alkylamino" refers to -NHR in which R is alkyl, including lower alkyl. As used herein, "dialkylamino" refers to -NR'R in which R' and R are independently alkyl, including lower alkyl.

[0036]

[0037] As used herein, "aralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by an aryl.

[0038]

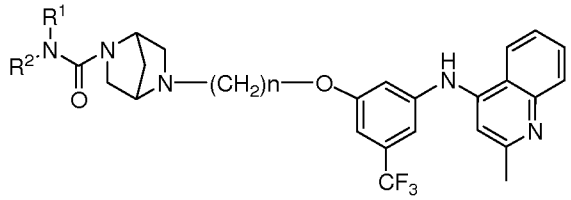
[0039] Where the number of any given substituent is not specified (e.g., "haloalkyl"), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens.

[0040] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) Biochem. 11:942-944).

4.2 COMPOUNDS

[0041] In certain embodiments, the compounds provided herein have enhanced tolerability as compared to similar compounds known in the art. Such enhanced tolerability is manifested through alteration of the pharmacokinetic profile of the compounds. The pharmacokinetic profile is based on a number of factors, including, but not limited to, bioavailability, *in vivo* half-life and *in vivo* efficacy. In certain embodiments, the compounds provided herein have improved properties including but not limited to *in vitro* or *in vivo* activity in modulation of a urotensin-II receptor activity, stability and receptor-selectivity as compared to similar compounds known in the art.

[0042] In certain embodiments, the compounds for use in the compositions and methods provided herein are of Formula I:



or a pharmaceutically acceptable derivative thereof, wherein R^1 and R^2 are selected as follows:

i) R^1 and R^2 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or heterocyclyl; or

ii) R^1 and R^2 together with the nitrogen atom on which they are substituted form a 3-7 membered heterocyclic or heteroaryl ring;

wherein R^1 and R^2 are each independently optionally substituted with one, two, three or four groups, independently from alkyl, halo, hydroxy, hydroxycarbonyl, nitro, amino, alkoxycarbonyl, alkylamino, haloalkyl, aminoalkyl, aryl, aralkyl, alkylaryl, haloaryl and alkoxy; and

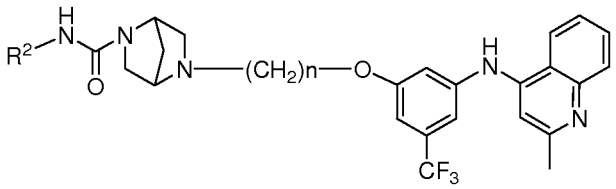
n is 1-4.

[0043] In certain embodiments, R^1 and R^2 are each independently hydrogen or alkyl. In certain embodiments, R^1 is hydrogen.

[0044] In certain embodiments, R^1 is hydrogen and R^2 is alkyl, cycloalkyl, heteroaryl, alkoxycarbonylalkyl, hydroxycarbonylalkyl, hydroxyalkyl, aralkyl or aryl. In certain embodiments, R^2 is alkyl, cycloalkyl, heteroaryl, alkoxycarbonylalkyl, hydroxycarbonylalkyl, hydroxyalkyl, aralkyl or aryl. In certain embodiments, R^2 is methyl, *tert*-butyl, 2-hydroxy-1,1-dimethylethyl, phenyl, cyclohexyl or benzyl. In certain embodiments, R^2 is substituted with one or two groups selected from , 2-hydroxy, hydroxycarbonyl and methoxycarbonyl.

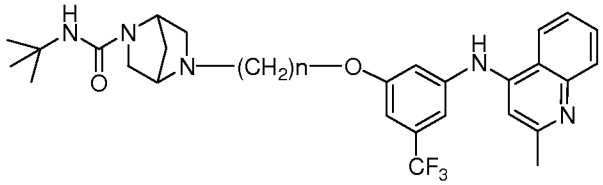
[0045] In certain embodiments, n is 1-4. In one embodiment, n is 2-4. In another embodiment, n is 2. In another embodiment, n is 3.

[0046] In certain embodiments, the compound is of formula:



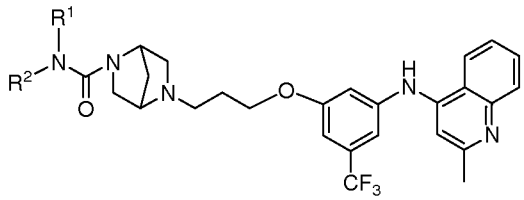
or a pharmaceutically acceptable derivative thereof.

[0047] In certain embodiments, the compound is of formula:



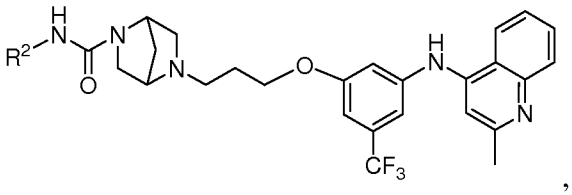
or a pharmaceutically acceptable derivative thereof.

[0048] In certain embodiments, the compound is of formula:



or a pharmaceutically acceptable derivative thereof.

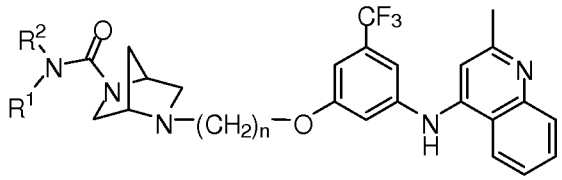
[0049] In certain embodiments, the compound is of formula:



,

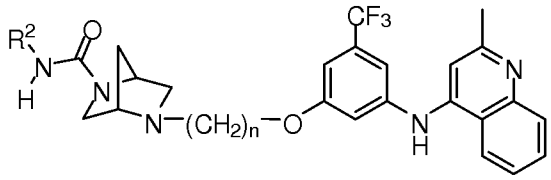
or a pharmaceutically acceptable derivative thereof.

[0050] In certain embodiments, the compound is of formula:



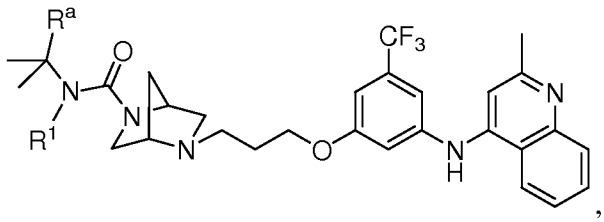
or a pharmaceutically acceptable derivative thereof.

[0051] In certain embodiments, the compound is of formula:



or a pharmaceutically acceptable derivative thereof.

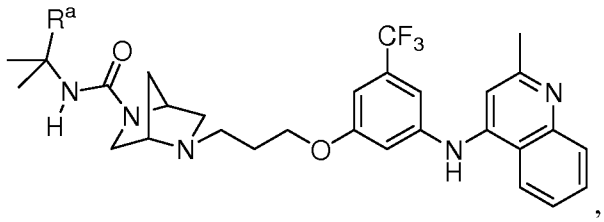
[0052] In certain embodiments, the compound is of formula:



,

or a pharmaceutically acceptable derivative thereof, wherein R^a is alkyl, hydroxycarbonyl, alkoxycarbonyl or hydroxyalkyl.

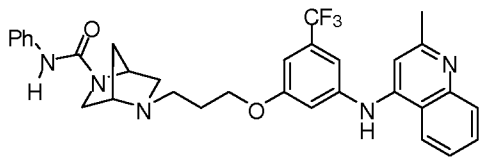
[0053] In certain embodiments, the compound is of formula:



,

or a pharmaceutically acceptable derivative thereof, wherein R^a is methyl, hydroxycarbonyl, methoxycarbonyl or hydroxymethyl.

[0054] In one embodiment, the compound provided herein is selected from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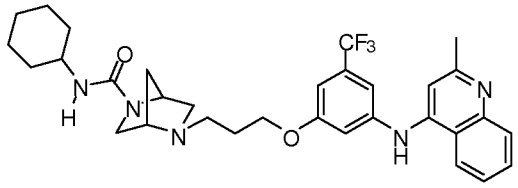
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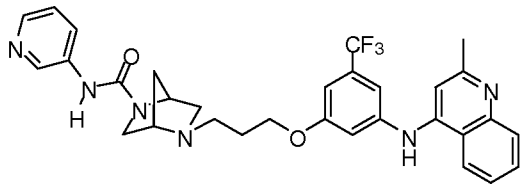
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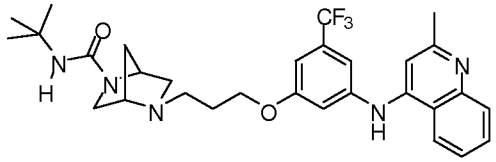
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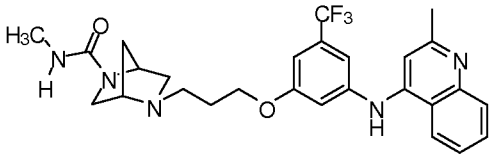
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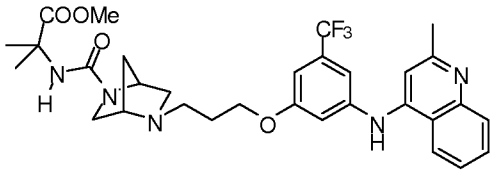
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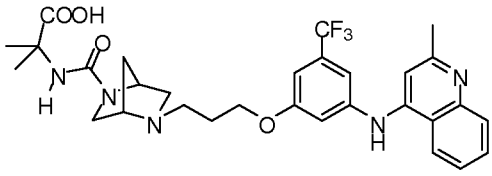
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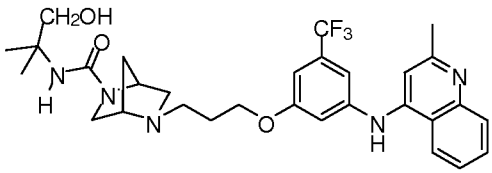
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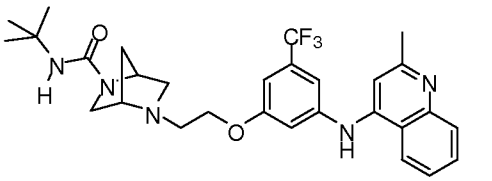
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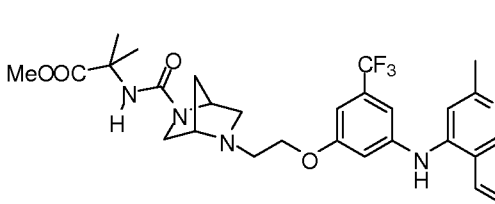
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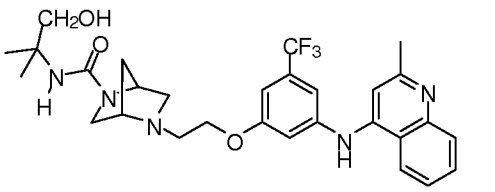
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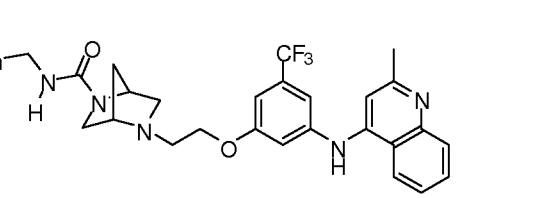
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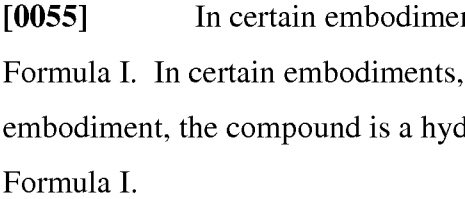
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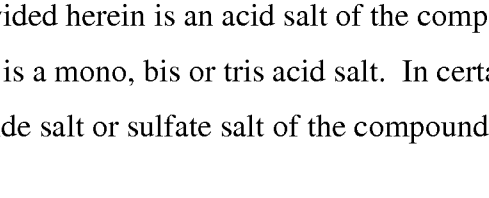

,

or a pharmaceutically acceptable derivative thereof.

[0055] In certain embodiments, provided herein is an acid salt of the compound of Formula I. In certain embodiments, the salt is a mono, bis or tris acid salt. In certain embodiment, the compound is a hydrochloride salt or sulfate salt of the compound of Formula I.

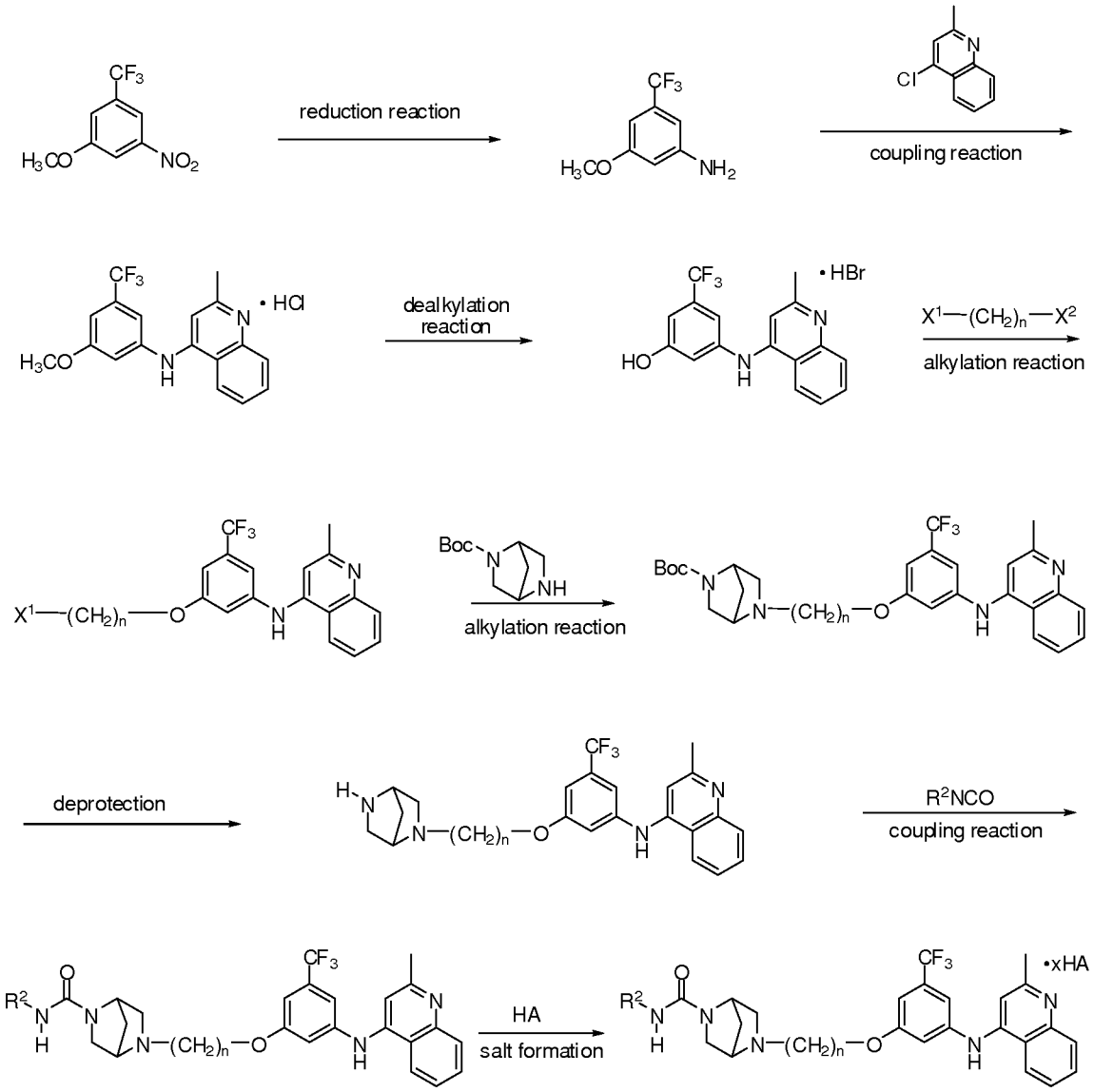
[0056] In certain embodiments, the compounds provided herein have improved properties over the compounds previously disclosed. Such properties include one or more of the following: activity in modulation of urotensin-II receptor activity, selectivity for

urotensin-II receptor, pharmacokinetic properties, toxicity, bioavailability and others.

4.2.1 PREPARATION OF THE COMPOUNDS

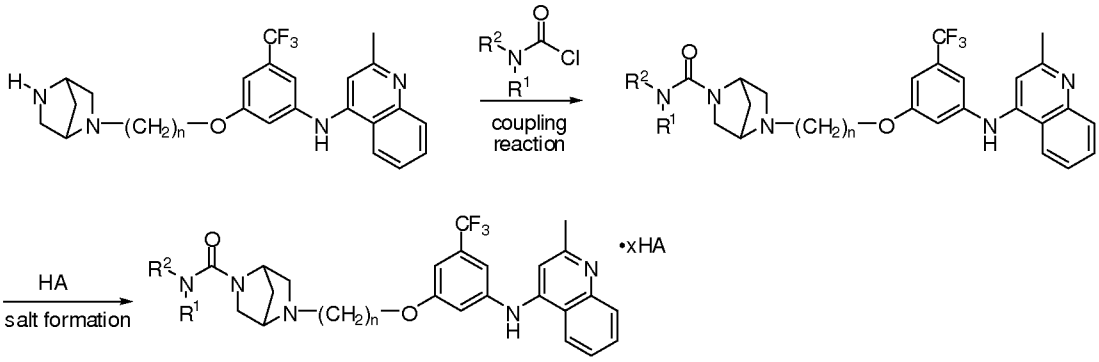
[0057] The compounds provided herein can be prepared by routine chemical reactions known to one of skill in the art. General schemes for preparation of exemplary compounds are illustrated below:

General Scheme 1



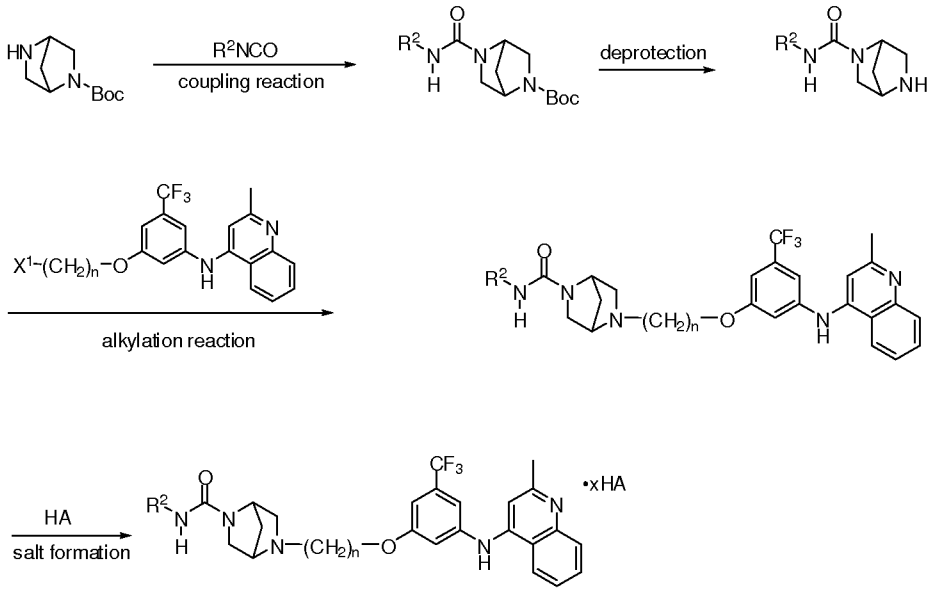
wherein R^2 and n are described herein, X^1 and X^2 are halogens, A is an organic or inorganic anion and x is 1 or 2.

General Scheme 2



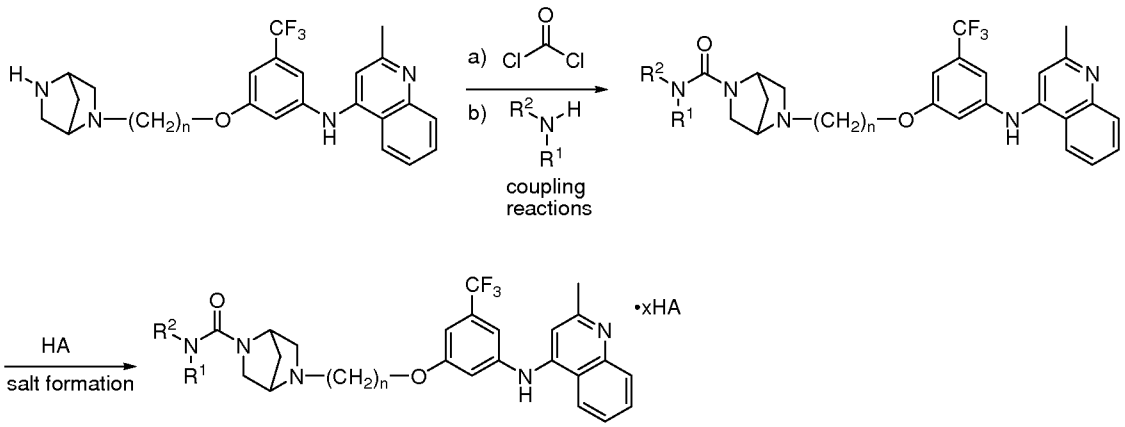
wherein R^1, R^2 and n are described herein, A is an organic or inorganic anion and x is 1 or 2.

General Sceme 3



wherein R^2 and n are described herein, X^1 is a halogen, A is an organic or inorganic anion and x is 1 or 2.

General Sceme 4



wherein R^1, R^2 and n are described herein, A is an organic or inorganic anion and x is 1 or 2.

4.3 FORMULATION OF PHARMACEUTICAL COMPOSITIONS

[0058] The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of compounds provided herein that are useful in the preventing, treating, or ameliorating a urotensin-II-modulated disease or one or more of the symptoms thereof. The pharmaceutical compositions comprise one or more compounds provided herein in a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

[0059] In one embodiment, provided herein are pharmaceutical compositions in modified release dosage forms, which comprise a compound of Formula I or a pharmaceutically acceptable derivative thereof, and one or more release controlling excipients as described herein. Suitable modified release dosage vehicles include, but are not limited to, hydrophilic or hydrophobic matrix devices, water-soluble separating layer coatings, enteric coatings, osmotic devices, multiparticulate devices, and combinations thereof. The pharmaceutical compositions may also comprise non-release controlling excipients.

[0060] Further provided herein are pharmaceutical compositions in enteric coated dosage forms, which comprise a compound of Formula I or a pharmaceutically acceptable derivative thereof, and one or more release controlling excipients for use in an enteric coated dosage form. The pharmaceutical compositions may also comprise non-release controlling excipients.

[0061] Additionally provided are pharmaceutical compositions in a dosage form that has an instant releasing component and at least one delayed releasing component, and is capable of giving a discontinuous release of the compound in the form of at least two consecutive pulses separated in time from 0.1 up to 24 hours. The pharmaceutical compositions comprise a compound of Formula I or a pharmaceutically acceptable derivative thereof, and one or more release controlling and non-release controlling excipients, such as those excipients suitable for a disruptable semi-permeable membrane and as swellable substances.

[0062] In certain embodiments, provided herein are pharmaceutical compositions in a dosage form for oral administration to a subject, which comprise a compound of Formula I or a pharmaceutically acceptable derivative thereof, and one or more pharmaceutically acceptable excipients or carriers, enclosed in an intermediate reactive layer comprising a gastric juice-resistant polymeric layered material partially neutralized with alkali and having cation exchange capacity and a gastric juice-resistant outer layer.

[0063] In one embodiment, the pharmaceutical compositions herein may be

provided in unit-dosage forms or multiple-dosage forms. Unit-dosage forms, as used herein, refer to physically discrete units suitable for administration to human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of unit-dosage forms include ampouls, syringes, and individually packaged tablets and capsules. Unit-dosage forms may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of multiple-dosage forms include vials, bottles of tablets or capsules, or bottles of pints or gallons.

[0064] The compound of Formula I provided herein may be administered alone, or in combination with one or more other compounds provided herein, one or more other active ingredients. The pharmaceutical compositions that comprise a compound provided herein may be formulated in various dosage forms for oral, parenteral, and topical administration. The pharmaceutical compositions may also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology*, Rathbone *et al.*, Eds., Drugs and the Pharmaceutical Science, Marcel Dekker, Inc.: New York, NY, 2002; Vol. 126).

[0065] The pharmaceutical compositions provided herein may be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

A. Oral Administration

[0066] The pharmaceutical compositions provided herein may be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, capsules, pills, troches, lozenges,

pastilles, cachets, pellets, medicated chewing gum, granules, bulk powders, effervescent or non-effervescent powders or granules, solutions, emulsions, suspensions, solutions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions may contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, and flavoring agents.

[0067] Binders or granulators impart cohesiveness to a tablet to ensure that the tablet remains intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (*e.g.*, STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, Panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

[0068] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets.

[0069] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as

sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[0070] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[0071] Suitable glidants include colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Coloring agents include any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Flavoring agents include natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Sweetening agents include sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suspending and dispersing agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrolidone. Preservatives include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Solvents include glycerin, sorbitol, ethyl alcohol, and syrup. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate.

[0072] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[0073] The pharmaceutical compositions provided herein may be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenylsalicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[0074] The tablet dosage forms may be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[0075] The pharmaceutical compositions provided herein may be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain

dissolution of the active ingredient.

[0076] The pharmaceutical compositions provided herein may be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquids or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde, *e.g.*, acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be measured conveniently for administration.

[0077] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono- or poly-alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations may further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[0078] The pharmaceutical compositions provided herein for oral administration may be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[0079] The pharmaceutical compositions provided herein may be provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[0080] Coloring and flavoring agents can be used in all of the above dosage forms.

[0081] The pharmaceutical compositions provided herein may be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[0082] The pharmaceutical compositions provided herein may be co-formulated with other active ingredients which do not impair the desired therapeutic action, or with substances that supplement the desired action, such as antacids, proton pump inhibitors, and H_2-receptor antagonists.

B. Parenteral Administration

[0083] The pharmaceutical compositions provided herein may be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, and subcutaneous administration.

[0084] The pharmaceutical compositions provided herein may be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy*, supra).

[0085] The pharmaceutical compositions intended for parenteral administration may include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[0086] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Water-miscible vehicles

include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, dimethylacetamide, and dimethylsulfoxide.

[0087] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzates, thimerosal, benzalkonium chloride, benzethonium chloride, methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents include those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including alpha-cyclodextrin, beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, sulfobutylether-beta-cyclodextrin, and sulfobutylether 7-beta-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[0088] The pharmaceutical compositions provided herein may be formulated for single or multiple dosage administration. The single dosage formulations are packaged in an ampule, a vial, or a syringe. The multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[0089] In one embodiment, the pharmaceutical compositions are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[0090] The pharmaceutical compositions provided herein may be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-,

controlled, targeted-, and programmed-release forms.

[0091] The pharmaceutical compositions may be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[0092] Suitable inner matrixes include polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[0093] Suitable outer polymeric membranes include polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

C. Topical Administration

[0094] The pharmaceutical compositions provided herein may be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, include (intra)dermal, conjuctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, uretheral, respiratory, and rectal administration.

[0095] The pharmaceutical compositions provided herein may be formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irrigations, sprays, suppositories, bandages, dermal patches. The topical formulation of the pharmaceutical compositions provided herein may also comprise liposomes, micelles, microspheres, nanosystems, and mixtures thereof.

[0096] Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations provided herein include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against

the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, penetration enhancers, cryopretectants, lyoprotectants, thickening agents, and inert gases.

[0097] The pharmaceutical compositions may also be administered topically by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free injection, such as POWDERJECT™ (Chiron Corp., Emeryville, CA), and BIOJECT™ (Bioject Medical Technologies Inc., Tualatin, OR).

[0098] The pharmaceutical compositions provided herein may be provided in the forms of ointments, creams, and gels. Suitable ointment vehicles include oleaginous or hydrocarbon bases, including such as lard, benzoinated lard, olive oil, cottonseed oil, and other oils, white petrolatum; emulsifiable or absorption bases, such as hydrophilic petrolatum, hydroxystearin sulfate, and anhydrous lanolin; water-removable bases, such as hydrophilic ointment; water-soluble ointment bases, including polyethylene glycols of varying molecular weight; emulsion bases, either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, including cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid (*see*, *Remington: The Science and Practice of Pharmacy*, supra). These vehicles are emollient but generally require addition of antioxidants and preservatives.

[0099] Suitable cream base can be oil-in-water or water-in-oil. Cream vehicles may be water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase is also called the "internal" phase, which is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation may be a nonionic, anionic, cationic, or amphoteric surfactant.

[00100] Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the liquid carrier. Suitable gelling agents include crosslinked acrylic acid polymers, such as carbomers, carboxypolyalkylenes, Carbopol®; hydrophilic polymers, such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulosic polymers, such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums, such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

[00101] The pharmaceutical compositions provided herein may be administered rectally, urethrally, vaginally, or perivaginally in the forms of suppositories, pessaries, bougies, poultices or cataplasm, pastes, powders, dressings, creams, plasters, contraceptives, ointments, solutions, emulsions, suspensions, tampons, gels, foams, sprays, or enemas. These dosage forms can be manufactured using conventional processes as described in *Remington: The Science and Practice of Pharmacy*, supra.

[00102] Rectal, urethral, and vaginal suppositories are solid bodies for insertion into body orifices, which are solid at ordinary temperatures but melt or soften at body temperature to release the active ingredient(s) inside the orifices. Pharmaceutically acceptable carriers utilized in rectal and vaginal suppositories include vehicles, such as stiffening agents, which produce a melting point in the proximity of body temperature, when formulated with the pharmaceutical compositions provided herein; and antioxidants as described herein, including bisulfite and sodium metabisulfite. Suitable vehicles include, but are not limited to, cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol), spermaceti, paraffin, white and yellow wax, and appropriate mixtures of mono-, di- and triglycerides of fatty acids, hydrogels, such as polyvinyl alcohol, hydroxyethyl methacrylate, polyacrylic acid; glycerinated gelatin. Combinations of the various vehicles may be used. Rectal and vaginal suppositories may be prepared by the compressed method or molding. The typical weight of a rectal and vaginal suppository is about 2 to 3 g.

[00103] The pharmaceutical compositions provided herein may be administered ophthalmically in the forms of solutions, suspensions, ointments, emulsions, gel-forming solutions, powders for solutions, gels, ocular inserts, and implants.

[00104] The pharmaceutical compositions provided herein may be administered intranasally or by inhalation to the respiratory tract. The pharmaceutical compositions may be provided in the form of an aerosol or solution for delivery using a pressurized container, pump, spray, atomizer, such as an atomizer using electrohydrodynamics to produce a fine mist, or nebulizer, alone or in combination with a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. The pharmaceutical compositions may also be provided as a dry powder for insufflation, alone or in combination with an inert carrier such as lactose or phospholipids; and nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, including chitosan or cyclodextrin.

[00105] Solutions or suspensions for use in a pressurized container, pump, spray, atomizer, or nebulizer may be formulated to contain ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active ingredient

provided herein, a propellant as solvent; and/or a surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[00106] The pharmaceutical compositions provided herein may be micronized to a size suitable for delivery by inhalation, such as 50 micrometers or less, or 10 micrometers or less. Particles of such sizes may be prepared using a comminuting method known to those skilled in the art, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

[00107] Capsules, blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the pharmaceutical compositions provided herein; a suitable powder base, such as lactose or starch; and a performance modifier, such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose. The pharmaceutical compositions provided herein for inhaled/intranasal administration may further comprise a suitable flavor, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium.

[00108] The pharmaceutical compositions provided herein for topical administration may be formulated to be immediate release or modified release, including delayed-, sustained-, pulsed-, controlled-, targeted, and programmed release.

D. Modified Release

[00109] The pharmaceutical compositions provided herein may be formulated as a modified release dosage form. As used herein, the term "modified release" refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate dosage form when administered by the same route. Modified release dosage forms include delayed-, extended-, prolonged-, sustained-, pulsatile- or pulsed-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphorism of the active ingredient(s).

[00110] Examples of modified release include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566;

5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500.

1. Matrix Controlled Release Devices

[00111] The pharmaceutical compositions provided herein in a modified release dosage form may be fabricated using a matrix controlled release device known to those skilled in the art (*see*, Takada et al in "Encyclopedia of Controlled Drug Delivery," Vol. 2, Mathiowitz ed., Wiley, 1999).

[00112] In one embodiment, the pharmaceutical compositions provided herein in a modified release dosage form is formulated using an erodible matrix device, which is water-swellable, erodible, or soluble polymers, including synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00113] Materials useful in forming an erodible matrix include, but are not limited to, chitin, chitosan, dextran, and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, and scleroglucan; starches, such as dextrin and maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; and cellulosics, such as ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethylhydroxy ethylcellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, NJ); poly(2-hydroxyethyl-methacrylate); polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly-D-(-)-3-hydroxybutyric acid; and other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl)methacrylate chloride.

[00114] In another embodiment, the pharmaceutical compositions are formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. Materials suitable for use as a non-erodible matrix device include, but are not limited to, insoluble plastics, such as polyethylene, polypropylene, polyisoprene,

polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, methyl acrylate-methyl methacrylate copolymers, ethylene-vinylacetate copolymers, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, polyvinyl chloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate,; and fatty compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

[00115] In a matrix controlled release system, the desired release kinetics can be controlled, for example, via the polymer type employed, the polymer viscosity, the particle sizes of the polymer and/or the active ingredient(s), the ratio of the active ingredient(s) versus the polymer, and other excipients in the compositions.

[00116] The pharmaceutical compositions provided herein in a modified release dosage form may be prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, melt-granulation followed by compression.

2. Osmotic Controlled Release Devices

[00117] The pharmaceutical compositions provided herein in a modified release dosage form may be fabricated using an osmotic controlled release device, including one-chamber system, two-chamber system, asymmetric membrane technology (AMT), and extruding core system (ECS). In general, such devices have at least two components: (a) the core which contains the active ingredient(s); and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

[00118] In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents water-swellable hydrophilic polymers, which are also referred to as "osmopolymers" and "hydrogels," include, but not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol

(PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00119] The other class of osmotic agents is osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-tolunesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00120] Osmotic agents of different dissolution rates may be employed to influence how rapidly the active ingredient(s) is initially delivered from the dosage form. For example, amorphous sugars, such as Mannogeme EZ (SPI Pharma, Lewes, DE) can be used to provide faster delivery during the first couple of hours to promptly produce the desired therapeutic effect, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In this case, the active ingredient(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted.

[00121] The core may also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

[00122] Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate,

cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxlated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00123] Semipermeable membrane may also be a hydrophobic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119. Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00124] The delivery port(s) on the semipermeable membrane may be formed post-coating by mechanical or laser drilling. Delivery port(s) may also be formed in situ by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation in the core. In addition, delivery ports may be formed during coating process, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

[00125] The total amount of the active ingredient(s) released and the release rate can substantially by modulated via the thickness and porosity of the semipermeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00126] The pharmaceutical compositions in an osmotic controlled-release dosage form may further comprise additional conventional excipients as described herein to promote performance or processing of the formulation.

[00127] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; Santus and Baker, *J. Controlled Release* **1995**, *35*, 1-21; Verma et al., *Drug Development and Industrial Pharmacy* **2000**, *26*, 695-708; Verma et al., *J. Controlled Release* **2002**, *79*, 7-27).

[00128] In certain embodiments, the pharmaceutical compositions provided herein are formulated as AMT controlled-release dosage form, which comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients. *See*, U.S. Pat. No. 5,612,059 and WO 2002/17918. The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including direct compression, dry granulation, wet granulation, and a dip-coating method.

[00129] In certain embodiment, the pharmaceutical compositions provided herein are formulated as ESC controlled-release dosage form, which comprises an osmotic membrane that coats a core comprising the active ingredient(s), hydroxylethyl cellulose, and other pharmaceutically acceptable excipients.

3. Multiparticulate Controlled Release Devices

[00130] The pharmaceutical compositions provided herein in a modified release dosage form may be fabricated as a multiparticulate controlled release device, which comprises a multiplicity of particles, granules, or pellets, ranging from about 10 μm to about 3 mm, about 50 μm to about 2.5 mm, or from about 100 μm to 1 mm in diameter. Such multiparticulates may be made by the processes know to those skilled in the art, including wet-and dry-granulation, extrusion/spheronization, roller-compaction, melt-congealing, and by spray-coating seed cores. *See,* for example, *Multiparticulate Oral Drug Delivery*; Marcel Dekker: 1994; and *Pharmaceutical Pelletization Technology*; Marcel Dekker: 1989.

[00131] Other excipients as described herein may be blended with the pharmaceutical compositions to aid in processing and forming the multiparticulates. The resulting particles may themselves constitute the multiparticulate device or may be coated by various film-forming materials, such as enteric polymers, water-swellable, and water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

4. Targeted Delivery

[00132] The pharmaceutical compositions provided herein may also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Examples include, but are not limited to, U.S. Pat. Nos. 6,316,652; 6,274,552; 6,271,359; 6,253,872; 6,139,865; 6,131,570; 6,120,751; 6,071,495; 6,060,082; 6,048,736; 6,039,975; 6,004,534; 5,985,307; 5,972,366; 5,900,252; 5,840,674; 5,759,542; and 5,709,874.

4.3.1 ARTICLES OF MANUFACTURE

[00133] The compounds or pharmaceutically acceptable derivatives can be packaged as articles of manufacture containing packaging material, a compound or pharmaceutically acceptable derivative thereof provided herein, which is used for treatment, prevention or amelioration of one or more symptoms associated with urotensin-II activity, and a label that indicates that the compound or pharmaceutically acceptable derivative thereof is used for treatment, prevention or amelioration of one or more symptoms of urotensin-II receptor mediated diseases.

[00134] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, e.g., U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated.

4.4 EVALUATION OF THE ACTIVITY OF THE COMPOUNDS

[00135] The urotensin-II antagonist activity of the compounds provided herein can be demonstrated by methods known to one of skill in the art. Exemplary methods are described in US Publication Nos. US 20050049286 and US 20050054850, which are incorporated herein by reference. An exemplary assays for determining urotensin-II antagonist activity of the compounds provided herein is provided below:

Inhibition of Human [^{125}I]-Urotensin-II Binding to Urotensin-II Receptor

[00136] Binding of human [^{125}I]-urotensin-II to human urotensin-II receptor (UTR) is done using cell membranes from either TE-671 rhabdomyosarcoma cells or CHO cells stably expressing recombinant UTR, in a homogeneous Scintillation Proximity Assay (SPA).

[00137] The UTR cells membranes are pre-coupled overnight at 4 °C to WGA-PVT beads (Amersham RPNQ0001) at a ratio of 5-25 μg membrane to 0.5 mg beads/assay. Assay is performed in 96-well microtiter Optiplates (Packard 6005290) by mixing coupled beads and 0.1 nM [^{125}I U-II (2200 Ci/mmol, NEN NEX379), in a total volume of 100 μl 20 mM HEPES, 5 mM $MgCl_2$, pH 7.4. Test compounds are diluted in DMSO and were put in the assay at a final concentration of 1% DMSO. Incubation is done for 3 hours at 37° C. followed by reading in a TopCount scintillation microplate reader. Nonspecific binding is

determined by adding 100 nM unlabeled human U-II (Phoenix Pharmaceuticals, 071-05) to the assay mixture. Analysis of the assay is performed using nonlinear least square fitting.

Inhibition of Human Urotensin-II-Induced Ca^{2+} Mobilization in UTR Cells

[00138] The function of urotensin-II is determined by measuring ligand-induced mobilization of intracellular Ca^{2+} in a FlexStation scanning fluorometer (Molecular Devices). UTR cells are plated overnight at 50,000 cells/well in 96-well black/clear plates (Costar brand, Fisher 07-200-588). Cells are labeled with fluo-4AM dye (Molecular Probes, F-14201) in Hank's balanced salt solution (HBSS), 20 mM HEPES, 25 mM probenecid, pH 7.4, and then washed with buffer. During the assay, cells are continuously monitored in the FlexStation and exposed to test compounds at a final concentration of 0.1% DMSO, followed by the addition of 1 nM human U-II. Fluorescence is read every 2 seconds for 2 minutes. The excitation and emission wavelengths used are 485 nm and 525 nm. Inhibition of the urotensin-II-induced signal is calculated using a nonlinear least square fitting program. Compounds of the present invention are active in these assays and have an IC_{50} of <10 μM.

4.5 METHODS OF TREATMENT AND PREVENTION

[00139] In certain embodiments, provided herein are methods for modulating an activity of urotensin-II receptor by contacting the receptor with a compound or composition provided herein. In one embodiment, provided herein are methods for antagonizing an action of urotensin-II receptor by contacting the receptor with a compound or composition provided herein.

[00140] In other embodiments, provided herein are methods for treatment, prevention, or amelioration of one or more diseases or conditions associated with urotensin-II receptor activity, including, but not limited to cardiovascular disorders, such as hypertension and heart failure; atherosclerosis; renal failure; nephrotoxicity and diarrhea caused by anti-neoplastic agents; post-myocardial infarction; pulmonary hypertension/fibrosis; diabetes; diseases and disorders associated with CNS function, such as Parkinson's Disease, Alzheimer's Disease, convulsions, depression, migraine, psychosis, anxiety, neuromuscular deficit amylotrophic lateral sclerosis, muscular dystrophy, childhood spinal muscular atrophy, progressive spinal muscular atrophy and progressive bulbar palsy; OPCA; ADHD; schizophrenia; sleep disorders such as insomnia; and autonomic dysfunctions such as Shy-Drager syndrome.

4.5.1 COMBINATION THERAPY WITH A SECOND ACTIVE AGENT

[00141] The compounds provided herein may be administered as the sole active ingredient or in combination with other active ingredients. Other active ingredients that may be used in combination with the compounds provided herein include but are not limited to, compounds known to treat diseases associated with urotensin-II receptor modulation or compounds known to modulate urotensin-II receptor activity. In certain embodiments, the compounds provided herein can be used in combination with one or more therapeutic agents selected from α and β-blockers, such as phentolamine, phenoxybenzamine, atenolol, propranolol, timolol, metoprolol, carteolol and carvedilol; with vasodilators, such as hydralazine, minoxidil, diazoxide, flosequinan, etc.; with calcium-antagonists such as diltiazem, nicardipine, nimodipine, verapamil, nifedipine; with angiotensin converting enzyme-inhibitors such as cilazapril, captopril, enalapril, lisinopril; with potassium channel activators, such as pinacidil, chromakalim; with angiotensin receptor antagonists, such as losartan, valsartan, candesartan, irbesartan, eprosartan, telmisartan, and tasosartan; with diuretics, such as hydrochlorothiazide, chlorothiazide, acetolamide, bumetanide, furosemide, metolazone, chlortalidone; with sympatholytics, such as methyldopa, clonidine, guanabenz, reserpine; with endothelin receptor antagonists, such as ambrisentan, atrasentan, bosentan, darusentan, enrasentan, sitaxsentan, and tezosentan; with anti-hyperlipidemic agents such as lovastatin, pravistatin, fluvastatin, atorvastatin, cerivastatin, simvastatin; phosphodiesterase 5 inhibitors, such as sildenafil, vardenafil and tadalafil; and other therapeutics which serve to treat high blood pressure, vascular disease or other disorders listed above.

[00142] Administration of the active ingredient combination may take place either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation.

[00143] It will be appreciated that every suitable combination of the compounds provided herein with one or more of the aforementioned compounds and optionally one or more further pharmacologically active substances is contemplated herein.

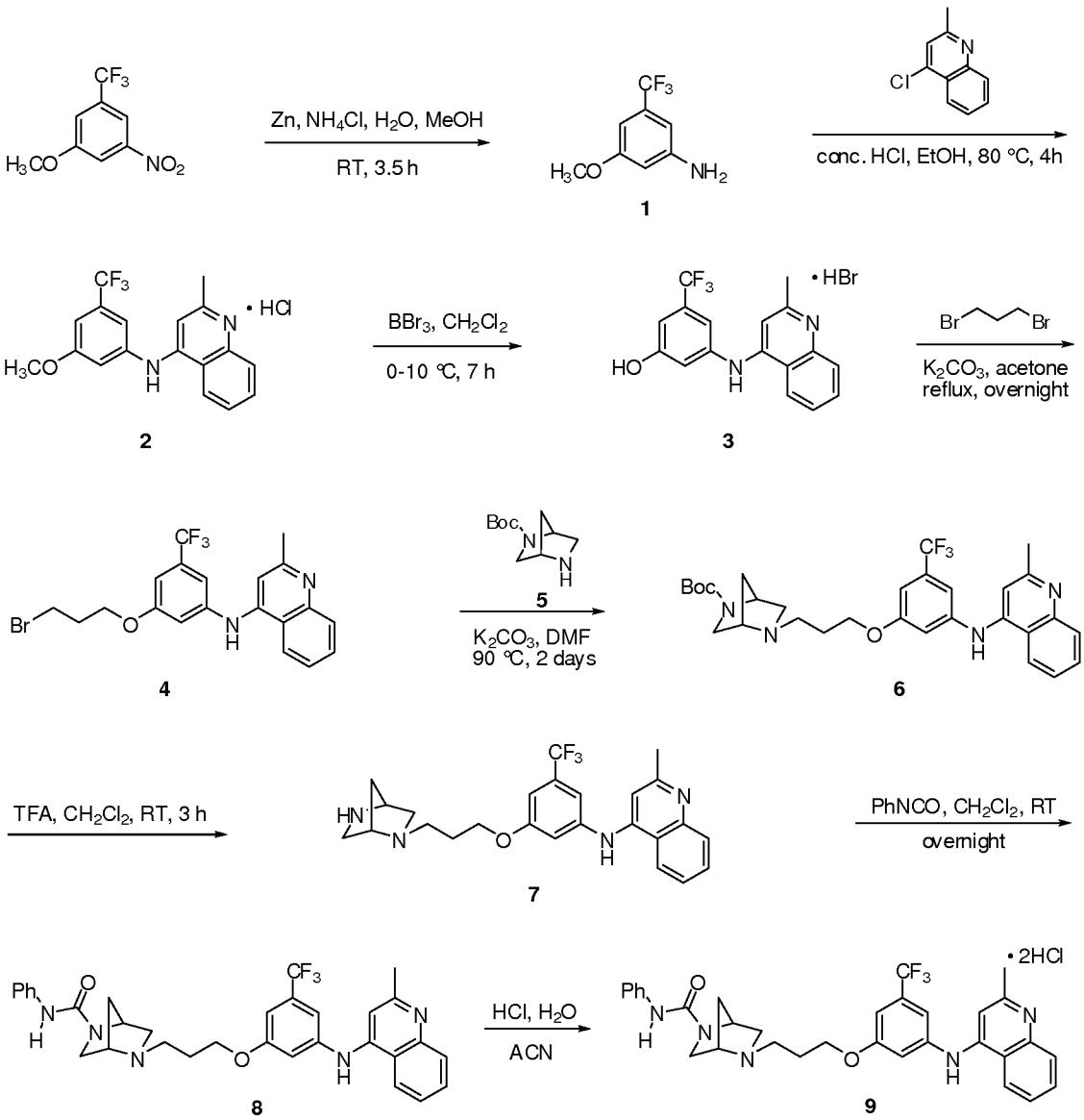
[00144] It is understood that the foregoing detailed description and accompanying examples are merely illustrative, and are not to be taken as limitations upon the scope of the subject matter. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates,

syntheses, formulations and/or methods of use provided herein, may be made without departing from the spirit and scope thereof. U.S. patents and publications referenced herein are incorporated by reference.

5. EXAMPLES

[00145] Certain embodiments of the claimed subject matter are illustrated by the following non-limiting examples.

Example 1: Preparation of 5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-N-phenyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (9)



I. 3-Methoxy-5-(trifluoromethyl)aniline (1)

To a solution of 3-methoxy-5-nitrobenzotrifluoride (83 g, 0.38 mol) in methanol (1660 mL), saturated aqueous ammonium chloride solution (830 mL) was added at such a rate to keep the internal reaction temperature below 25 °C. To the resulting mixture, zinc powder (160

g, 2.45 mol) was added in portions over 30 minutes at such a rate to keep the internal temperature below 35 °C. The resulting mixture was stirred for 3.5 hours at room temperature then filtered through a pad of Celite® washing twice with methanol (830 mL each). The filtrate was concentrated and the residue was taken up in ethanol (1160 mL) and stirred for 1 hour at room temperature. The resulting mixture was filtered, washing the solids with ethanol (500 mL) and the filtrate was concentrated under reduced pressure to give **1** (82.3 g). This material was used without purification.

II. N-[3-Methoxy-5-(trifluoromethyl)phenyl]-2-methylquinolin-4-amine hydrochloride (2)

To a solution of **1** (82.3 g, 0.38 mol theoretical for previous reaction) in ethanol (800 mL), 4-chloroquinaldine (63.2 g, 0.356 mol) and concentrated HCl (2.23 mL) were added. The resulting mixture was heated to 80 °C for 4 hours, cooled to room temperature and filtered. The solids were washed twice with diethyl ether (1000 mL each) then dried under vacuum to give **2** (125.3 g, 96% yield for two steps).

III. 3-[(2-Methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenol hydrobromide (3)

To a suspension of **2** (90.0 g, 0.244 mol) in dichloromethane (450 mL) cooled to 0 °C, boron tribromide (as a 1.0 M solution in dichloromethane; 270 mL, 270 mmol) was added dropwise over 25 minutes such that the internal temperature was maintained below 10 °C. The resulting mixture was stirred at 0 °C to 10 °C for 7 hours then methanol (360 mL) was added dropwise. The solvents were evaporated and the resulting material was taken up in a mixture of dichloromethane (1.8 L) and methanol (90 mL). The resulting mixture was stirred at room temperature for 18 h and then filtered. The collected solids were washed with dichloromethane (1.8 L) and dried to give **3** (87.7 g, 90% yield).

IV. N-[3-(3-Bromopropoxy)-5-(trifluoromethyl)phenyl]-2-methylquinolin-4-amine (4)

To a solution of **3** (4.5 g, 11.3 mmol) in acetone, 1,3-dibromopropane (18.1 g, 89.6 mmol) and K_2CO_3 (9.3 g, 67 mmol) were added. The resulting mixture was stirred at reflux overnight, cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography, eluting with ethyl acetate to give **4** (3.0 g, 60% yield).

V. *tert*-Butyl 5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl) phenoxy}propyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (6)

To a solution of *tert*-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**5,** 0.946 g, 4.77 mmol) in DMF (60 mL) at room temperature, **4** (2.095 g, 4.77 mmol) and K_2CO_3 (2.0 g, 14.5 mmol) were added. The resulting mixture was heated to 90 °C for two days then was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography, eluting with 9:1 ethyl acetate:methanol to give **6** (1.8 g, 67% yield) as a sticky yellow solid.

VI. N-{3-[3-(2,5-Diazabicyclo[2.2.1]hept-2-yl)propoxy]-5-(trifluoromethyl)phenyl}-2-methylquinolin-4-amine (7)

A solution of **6** (1.8 g, 3.2 mmol) in dichloromethane (10 mL) and trifluoroacetic acid (10 mL) was stirred at room temperature for 3 hours and then was concentrated under reduced pressure. The residue was taken up ethyl acetate and washed with 1N NaOH, water and brine. The organic layer was dried over $MgSO_4$ and filtered and the filtrate was concentrated under reduced pressure to give **7** (1.5 g, quantitative yield) as a yellow solid.

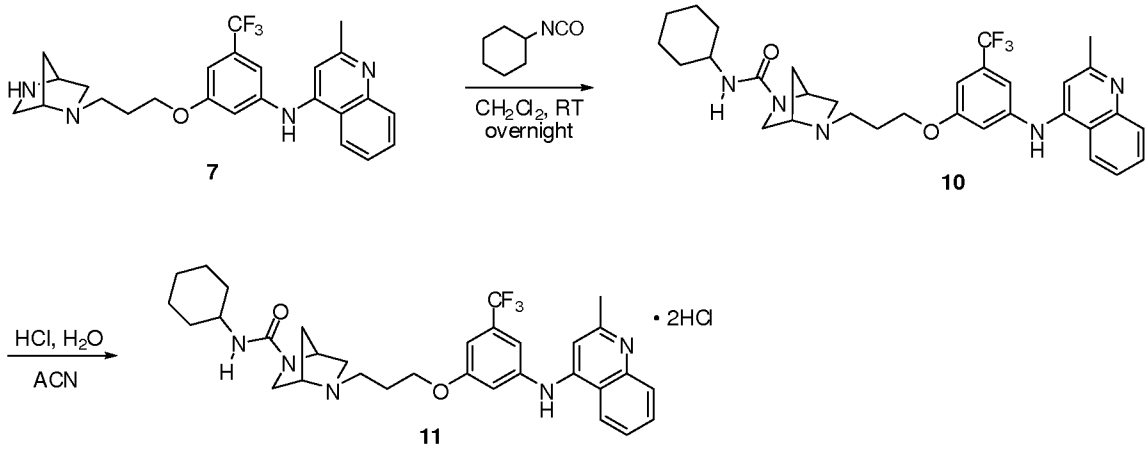
VII. 5-(3-{3-[(2-Methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-N-phenyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide (8)

To a solution of **7** (0.149 g, 0.33 mmol) in dichloromethane at room temperature, phenyl isocyanate (0.039 mL, 0.36 mmol) was added. The resulting mixture was stirred at room temperature overnight, then was diluted with dichloromethane and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 9:1 ethyl acetate:methanol to give **8** (0.038 g, 20% yield) as a solid.

VIII. 5-(3-{3-[(2-Methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-N-phenyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (9)

To a solution of **8** (0.038 g, 0.066 mmol) in acetonitrile at room temperature, 0.1 N HCl (1.46 mL, 0.146 mmol) was added. The resulting mixture was frozen using a dry ice/acetone batch and lyophilized to give **9** (0.035 g, 82% yield) as a yellow solid. Mass Spectra (m/z): Measured $(M+H)^+ = 576.31$; Calculated $(M+H)^+ = 576.26$.

Example 2: Preparation of N-cyclohexyl-5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (11)



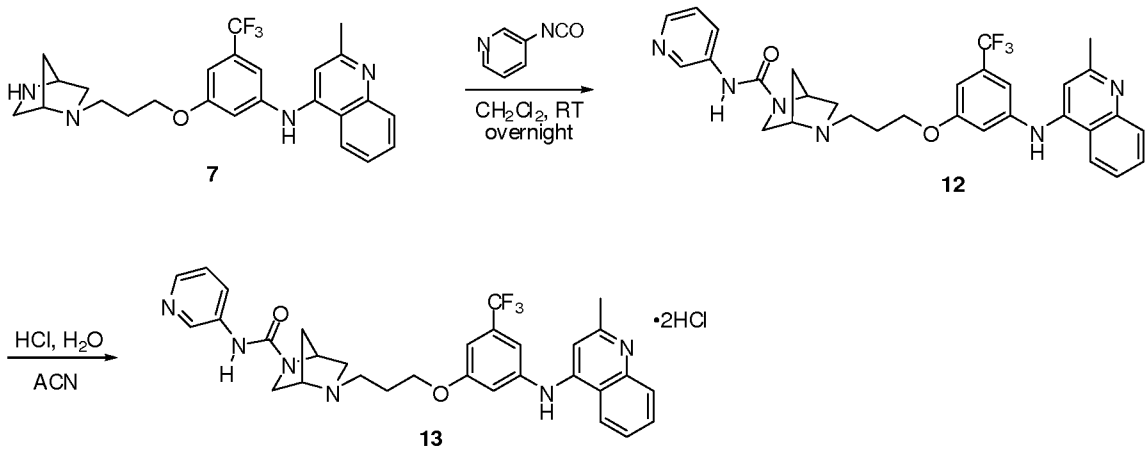
I. N-Cyclohexyl-5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl) phenoxy}propyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide (10)

To a solution of **7** (0.15 g, 0.33 mmol) in dichloromethane (10 mL) at room temperature, cyclohexyl isocyanate (0.046 mL, 0.36 mmol) was added. The resulting mixture was stirred at room temperature overnight, then was diluted with dichloromethane and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 9:1 ethyl acetate:methanol to give **10** (0.042 g, 22% yield) as a white solid.

II. N-Cyclohexyl-5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl) phenoxy}propyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (11)

To a solution of **10** (0.042 g, 0.072 mmol) in acetonitrile at room temperature, 0.1 N HCl (1.60 mL, 0.160 mmol) was added. The resulting mixture was frozen using a dry ice/acetone batch and lyophilized to give **11** (0.042 g, 89% yield) as a yellow solid. Mass Spectra (m/z): Measured $(M+H)^+$ = 582.40; Calculated $(M+H)^+$ = 582.31.

Example 3: Preparation of 5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-N-pyridin-3-yl-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (13)



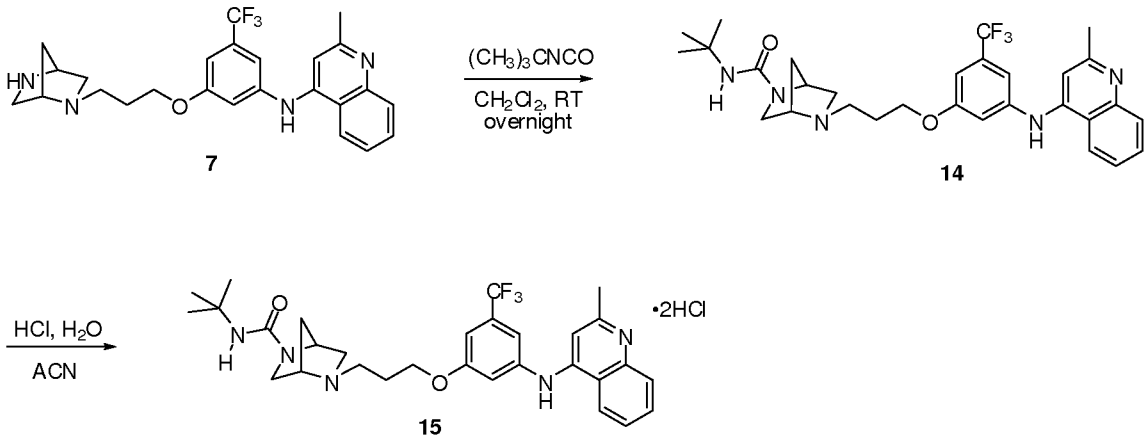
I. 5-(3-{3-[(2-Methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-N-pyridin-3-yl-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide (12)

To a solution of **7** (0.166 g, 0.364 mmol) in dichloromethane (10 mL) at room temperature, 3-pyridyl isocyanate (0.048 g, 0.40 mmol) was added. The resulting mixture was stirred at room temperature overnight, then was diluted with dichloromethane and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 9:1 ethyl acetate:methanol to give **12** (0.122 g, 57% yield) as a white solid.

II. 5-(3-{3-[(2-Methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-N-pyridin-3-yl-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (13)

To a solution of **12** (0.122 g, 0.212 mmol) in acetonitrile at room temperature, 0.1 N HCl (4.69 mL, 0.469 mmol) was added. The resulting mixture was frozen using a dry ice/acetone batch and lyophilized to give **13** (0.115 g, 83% yield) as a yellow solid. Mass Spectra (m/z): Measured $(M+H)^+$ = 577.33; Calculated $(M+H)^+$ = 577.25.

Example 4: Preparation of N-*tert*-butyl-5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (15)



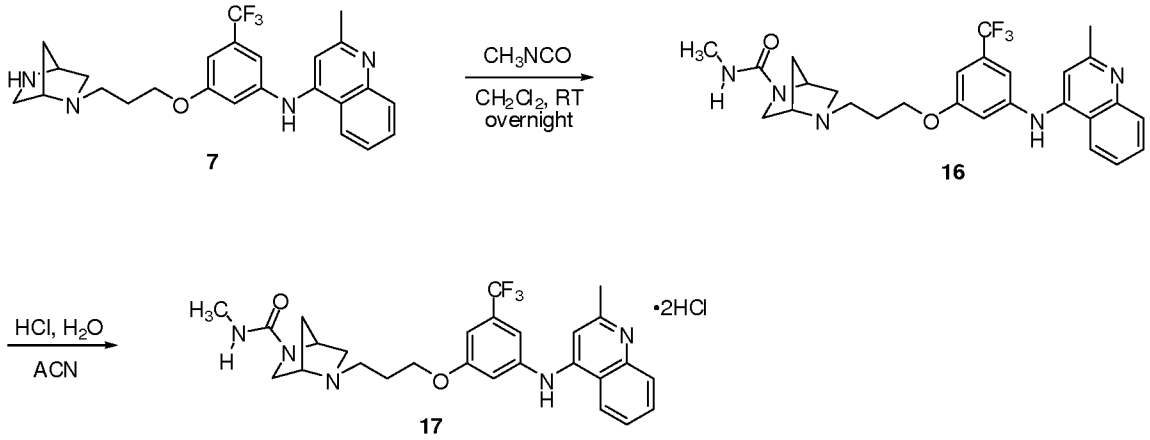
I. N-*tert*-Butyl-5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy} propyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide (14)

To a solution of **7** (0.231 g, 0.506 mmol) in dichloromethane (10 mL) at room temperature, *tert*-butyl isocyanate (0.063 mL, 0.55 mmol) was added. The resulting mixture was stirred at room temperature overnight, then was diluted with dichloromethane and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 9:1 ethyl acetate:methanol to give **14** (0.147 g, 52% yield) as a yellow solid.

II. N-*tert*-Butyl-5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy} propyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (15)

A solution of **14** (0.147 g, 0.265 mmol) in acetonitrile (5.82 mL), 0.1 N HCl (5.82 mL, 0.582 mmol) and water (5.82 mL) was frozen using a dry ice/acetone bath and lyophilized to give **15** (0.140 g, 84% yield) as a yellow solid. Mass Spectra (m/z): Measured $(M+H)^+$ = 556.27; Calculated $(M+H)^+$ = 556.29.

Example 5: Preparation of N-methyl-5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (17)



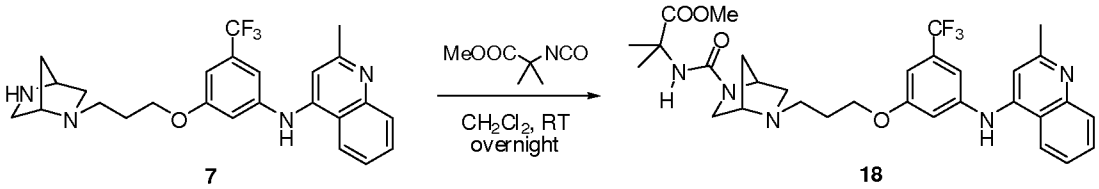
I. N-Methyl-5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy} propyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide (16)

To a solution of **7** (0.150 g, 0.33 mmol) in dichloromethane (10 mL) at room temperature, methyl isocyanate (0.0225 g, 0.39 mmol) was added. The resulting mixture was stirred at room temperature overnight, then was diluted with dichloromethane and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 9:1 ethyl acetate:methanol to give **16** (0.075 g, 44% yield) as a white solid.

II. N-Methyl-5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy} propyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (17)

A solution of **16** (0.075 g, 0.146 mmol) in acetonitrile (3.20 mL), 0.1 N HCl (3.20 mL, 0.32 mmol) and water (3.20 mL) was frozen using a dry ice/acetone bath and lyophilized to give **17** (0.085 g, 99% yield) as a yellow solid. Mass Spectra (m/z): Measured $(M+H)^+$ = 514.31; Calculated $(M+H)^+$ = 514.24.

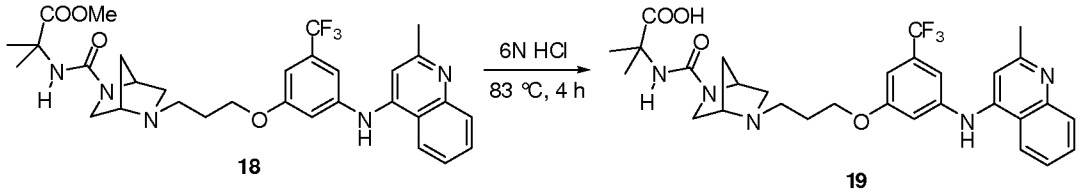
Example 6: Preparation of methyl 2-methyl-2-({[5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}amino)propanoate (18)



I. Methyl 2-methyl-2-({[5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl) phenoxy}propyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}amino)propanoate (18)

To a solution of **7** (0.80 g, 1.75 mmol) in dichloromethane (10 mL) at room temperature, methyl 2-isocyanato-2-methylpropanoate (0.26 g, 1.82 mmol) was added. The resulting mixture was stirred at room temperature overnight, then was diluted with dichloromethane and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 9:1 ethyl acetate:methanol to give **18** (0.250 g, 24% yield) as a yellow solid. Mass Spectra (m/z): Measured $(M+H)^+$ = 600.33; Calculated $(M+H)^+$ = 600.28.

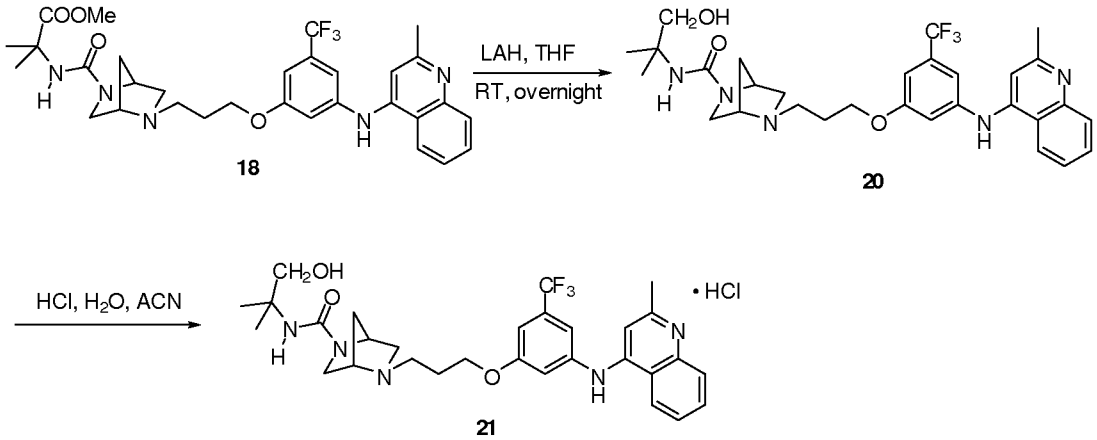
Example 7: Preparation of 2-methyl-2-({[5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}amino) propanoic acid (19)



I. 2-Methyl-2-({[5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy} propyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}amino)propanoic acid (19)

A solution of **18** (0.238 g, 0.397 mmol) in 6N HCl (3 mL, 18 mmol) was heated to 83 °C for 4 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was purified by reverse phase HPLC. Fractions containing **19** were diluted with ethyl acetate and washed with 2N aqueous NaOH, water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **19** (0.005 g, 2% yield) as a white solid. Mass Spectra (m/z): Measured $(M+H)^+$ = 586.35; Calculated $(M+H)^+$ = 586.26.

Example 8: Preparation of N-(2-hydroxy-1,1-dimethylethyl)-5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide hydrochloride (21)



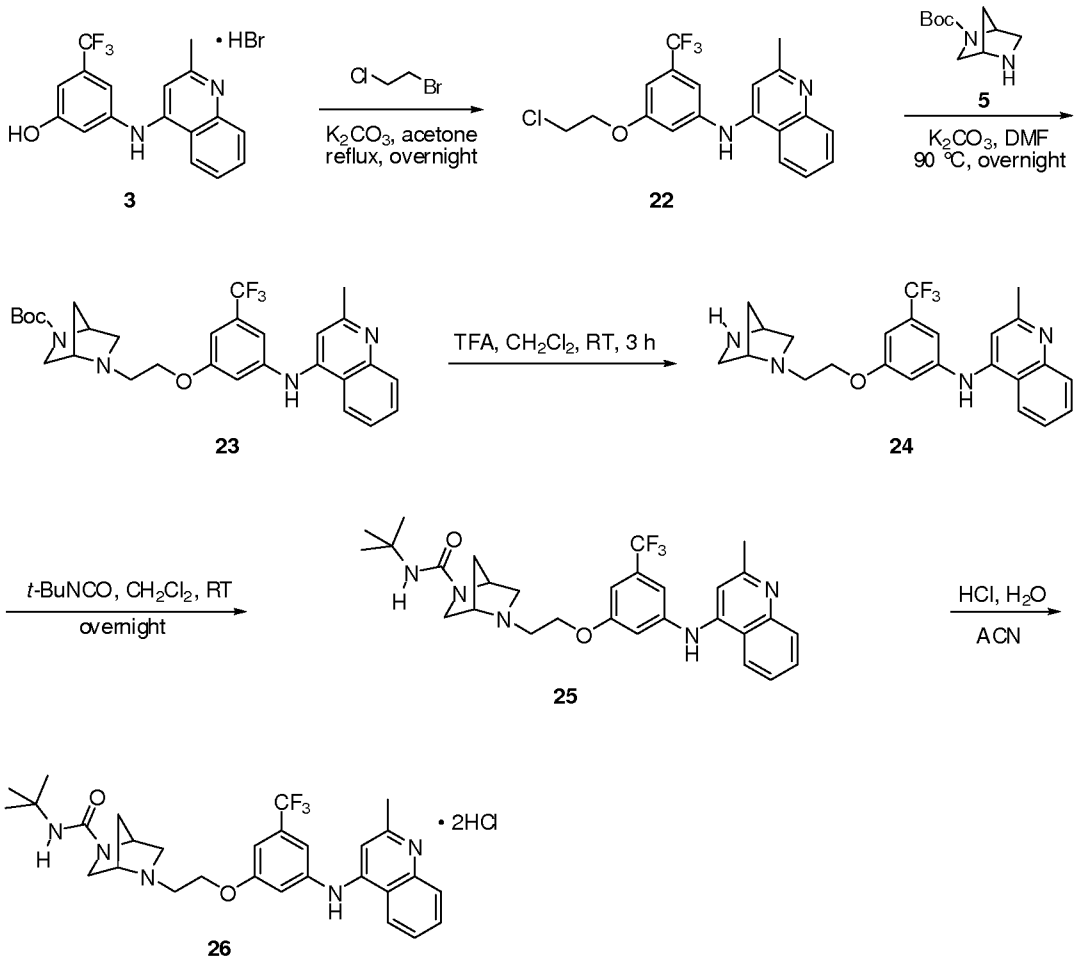
I. N-(2-Hydroxy-1,1-dimethylethyl)-5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide (20)

To a solution of **18** (0.100 g, 0.167 mmol) in THF at room temperature, LAH (1.0 M in THF, 0.50 mL, 0.50 mmol) was added. The resulting mixture was stirred at room temperature overnight, then was quenched by adding $Na_2SO_4 \bullet 10H_2O$ pellets. The mixture was diluted with ethyl acetate and water and the organic layer was washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **20** (0.0818 g, 86% yield) as a light yellow solid.

II. N-(2-Hydroxy-1,1-dimethylethyl)-5-(3-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}propyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide hydrochloride (21)

A solution of **20** (0.0818 g, 0.143 mmol) in acetonitrile (1.57 mL), 0.1 N HCl (1.57 mL, 0.157 mmol) and water (1.57 mL) was frozen using a dry ice/acetone bath and lyophilized to give **21** (0.070 g, 80% yield) as a fluffy white solid. Mass Spectra (m/z): Measured $(M+H)^+ = 572.31$; Calculated $(M+H)^+ = 572.28$.

Example 9: Preparation of N-*tert*-butyl-5-(2-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}ethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (26)



I. N-[3-(2-Chloroethoxy)-5-(trifluoromethyl)phenyl]-2-methylquinolin-4-amine (22)

To a solution of **3** (6.28 g, 15.7 mmol) in acetone (30 mL), 1-bromo-2-chloroethane (13.0 mL, 156 mmol) and K_2CO_3 (11.0 g, 79.6 mmol) were added. The resulting mixture was stirred at reflux overnight and then cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with ethyl acetate to give **22** (4.0 g, 67% yield) as a yellow solid.

II. *tert*-Butyl 5-(2-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}ethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (23)

To a solution of **22** (3.09 g, 8.11 mmol) in DMF (10 mL) at room temperature, **5** (1.60 g, 8.07 mmol) and K_2CO_3 (4.0 g, 29 mmol) were added. The resulting mixture was heated to 90 °C overnight then was cooled to room temperature. The resulting mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by

silica gel chromatography, eluting with 9:1 ethyl acetate:methanol to give **23** (1.6 g, 36% yield) as a yellow solid.

III. N-{3-[2-(2,5-Diazabicyclo[2.2.1]hept-2-yl)ethoxy]-5-(trifluoromethyl)phenyl}-2-methylquinolin-4-amine (24)

A solution of **23** (1.6 g, 2.9 mmol) in dichloromethane (10 mL) and trifluoroacetic acid (10 mL) was stirred at room temperature for 3 hours and then was concentrated under reduced pressure. The residue was taken up ethyl acetate and washed with 1N NaOH, water and brine. The organic layer was dried over $MgSO_4$ and filtered and the filtrate was concentrated under reduced pressure to give **24** (1.0 g, 79% yield) as a golden foamy solid.

IV. N-*tert*-Butyl-5-(2-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}ethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide (25)

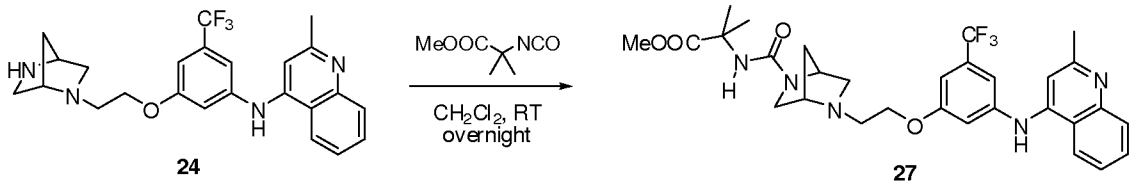
To a solution of **24** (0.104 g, 0.235 mmol) in dichloromethane (8 mL) at room temperature, *tert*-butylisocyanate (0.030 mL, 0.26 mmol) was added. The resulting mixture was stirred at room temperature overnight, then was diluted with dichloromethane and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 9:1 ethyl acetate:methanol to give **25** (0.0318 g, 25% yield) as a white solid

V. N-tert-Butyl-5-(2-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}ethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (26)

A clear solution of **25** (0.0318 g, 0.059 mmol) in acetonitrile, 0.1 N HCl (1.29 mL, 0.129 mmol) and water was frozen using a dry ice/acetone bath and lyophilized to give **26** (0.030 g, 83% yield) as a white solid. . Mass Spectra (m/z): Measured $(M+H)^+ = 542.33$; Calculated $(M+H)^+ = 542.27$.

Example 10: Preparation of methyl 2-methyl-2-({[5-(2-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}ethyl)-2,5-diazabicyclo[2.2.1]hept-2-

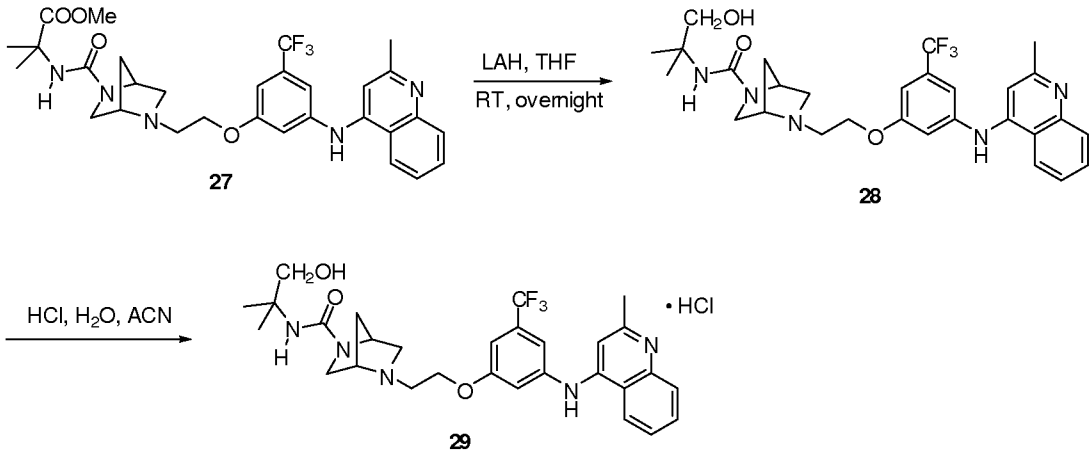
yl]carbonyl}amino)propanoate (27)



I. Methyl 2-methyl-2-({[5-(2-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl) phenoxy}ethyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}amino)propanoate (27)

To a solution of **24** (0.80 g, 1.8 mmol) in dichloromethane (10 mL) at room temperature, methyl 2-isocyanato-2-methylpropanoate (0.258 g, 1.80 mmol) was added. The resulting mixture was stirred at room temperature overnight, then was diluted with dichloromethane and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 9:1 ethyl acetate:methanol to give **27** (0.0631 g, 6% yield) as a yellow solid. . Mass Spectra (m/z): Measured $(M+H)^+$ = 586.32; Calculated $(M+H)^+$ = 586.26.

Example 11: Preparation of N-(2-hydroxy-1,1-dimethylethyl)-5-(2-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}ethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide hydrochloride (29)



I. N-(2-Hydroxy-1,1-dimethylethyl)-5-(2-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}ethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide (28)

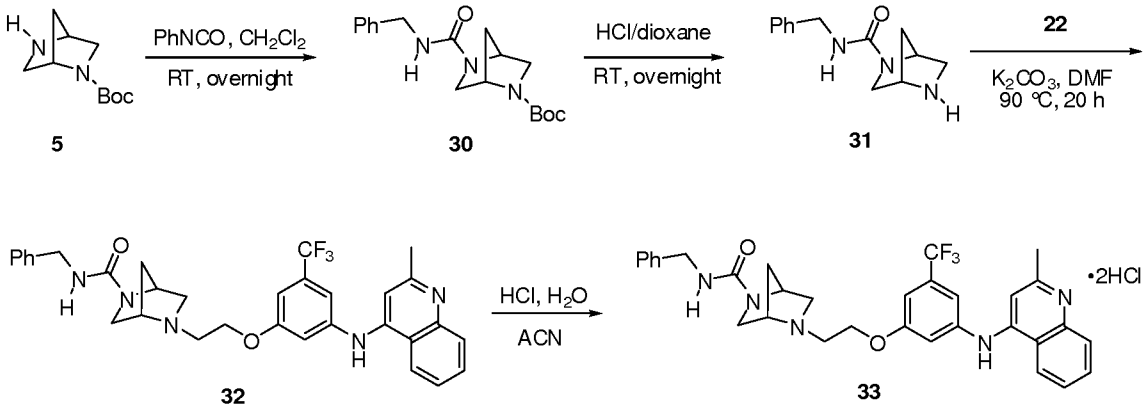
To a solution of **27** (0.0619 g, 106 mmol) in THF (2 mL) at room temperature, LAH (1.0 M in THF, 0.30 mL, 0.30 mmol) was added. The resulting mixture was stirred at room temperature overnight then was quenched by adding $Na_2SO_4 \cdot 10H_2O$ pellets. The mixture was filtered and the filtrate was diluted with ethyl acetate and water. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced

pressure. The residue was purified by reverse phase HPLC and fractions containing **28** were combined, diluted with ethyl acetate and the organic layer was washed with 2N aqueous NaOH, water and brine. The resulting organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **28** (0.008 g, 13% yield) as a foam.

II. N-(2-Hydroxy-1,1-dimethylethyl)-5-(2-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}ethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide hydrochloride (29)

A clear solution of **28** (0.008 g, 0.014 mmol) in acetonitrile, 0.1 N HCl (0.15 mL, 0.015 mmol) and water was frozen using a dry ice/acetone bath and lyophilized to give **29** (0.008 g, 93% yield) as a white solid. . Mass Spectra (m/z): Measured $(M+H)^+$ = 558.31; Calculated $(M+H)^+$ = 558.27.

Example 12: Preparation of N-benzyl-5-(2-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}ethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (33)



I. tert-Butyl 5-(benzylcarbamoyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (30)

To a solution of **5** (0.400 g, 2.02 mmol) in dichloromethane (5 mL) at room temperature, a solution of benzylisocyanate (322 mg, 2.42 mmol) in dichloromethane (1 mL) was added. The resulting mixture was stirred at room temperature overnight and was diluted with ethyl acetate and washed twice with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **30** (0.650 g, 97% yield) as a white solid.

II. N-Benzyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide (31)

A suspension of **30** (0.424 g, 1.28 mmol) in 4.0 M HCl in dioxane (10 mL, 40 mmol) was stirred at room temperature overnight. The resulting mixture was concentrated under reduced pressure to give **31** (0.355 g) as a white solid. This material was used without purification.

III. N-Benzyl-5-(2-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy} ethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide (32)

To a mixture of **31** (0.355 g, 1.28 mmol theoretical from previous step) and **20** (0.306 g, 0.80 mmol) in DMF (10 mL) at room temperature, K_2CO_3 (0.916 g, 6.6 mmol) was added. The resulting mixture was heated to 90 °C overnight. The resulting mixture was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 20:3 ethyl acetate:methanol to give **32** (0.060 g, 13% yield) as a yellow solid.

IV. N-Benzyl-5-(2-{3-[(2-methylquinolin-4-yl)amino]-5-(trifluoromethyl)phenoxy}ethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide dihydrochloride (33)

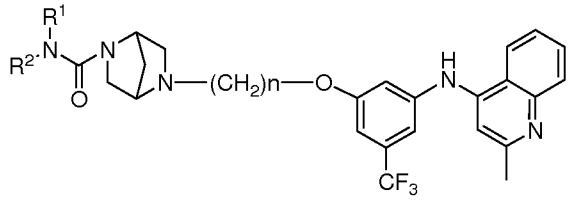
To a solution of **32** (0.060 g, 0.104 mmol) in acetonitrile at room temperature, 0.1 N HCl (2.09 mL, 0.209 mmol) was added. The resulting mixture was frozen using a dry ice/acetone batch and lyophilized to give **33** (0.0717 g, quantitative yield) as a yellow solid. Mass Spectra (m/z): Measured $(M+H)^+ = 576.24$; Calculated $(M+H)^+ = 576.26$.

[00146] The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the claimed subject matter and are encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A compound of formula I:



,

or a pharmaceutically acceptable derivative thereof, wherein R^1 and R^2 are selected as follows:

i) R^1 and R^2 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or heterocyclyl; or

ii) R^1 and R^2 together with the nitrogen atom on which they are substituted form a 3-7 membered heterocyclic or heteroaryl ring;

wherein R^1 and R^2 are each independently optionally substituted with one, two, three or four groups, independently selected from alkyl, halo, hydroxy, hydroxycarbonyl, nitro, cyano, amino, alkoxycarbonyl, alkylamino, dialkylamino, haloalkyl, haloalkoxy, aminoalkyl, aryl, aralkyl, alkylaryl, haloaryl and alkoxy; and

n is 2-4.

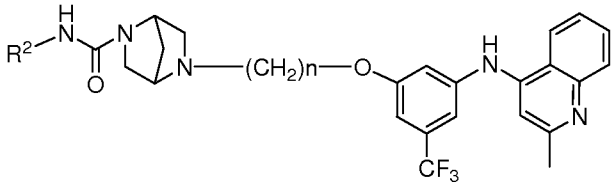
2. The compound of claim 1, wherein R^1 and R^2 are each independently hydrogen or alkyl.

3. The compound of claim 1 or 2, wherein R^1 is hydrogen.

4. The compound of any of claims 1-3, wherein R^2 is alkyl.

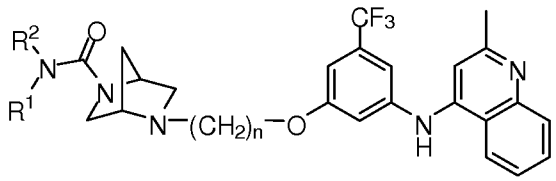
5. The compound of any of claims 1-3, wherein R^2 is methyl, *tert*-butyl, 2-hydroxy-1,1-dimethylethyl, phenyl, cyclohexyl or benzyl.

6. The compound of claim 1 having formula:



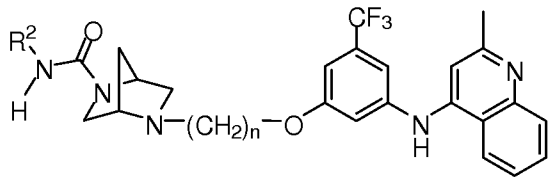
or a pharmaceutically acceptable derivative thereof.

7. The compound of claim 1 having formula:



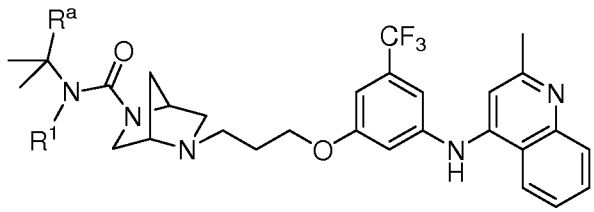
or a pharmaceutically acceptable derivative thereof.

8. The compound of claim 1 having formula:



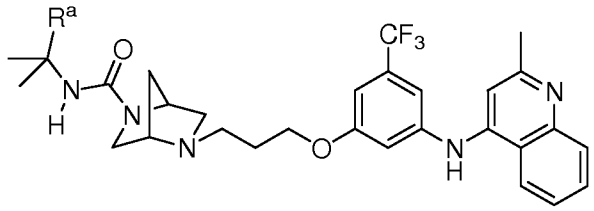
or a pharmaceutically acceptable derivative thereof.

9. The compound of claim 1 having formula:



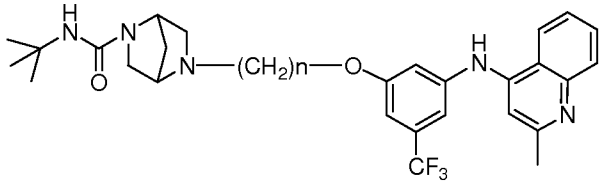
or a pharmaceutically acceptable derivative thereof, wherein R^a is alkyl, hydroxycarbonyl, alkoxycarbonyl or hydroxyalkyl.

10. The compound of claim 1 having formula:



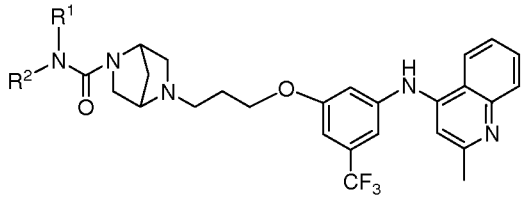
or a pharmaceutically acceptable derivative thereof, wherein R^a is methyl, hydroxycarbonyl, methoxycarbonyl or hydroxymethyl.

11. The compound of claim 1, wherein the compound is of formula:



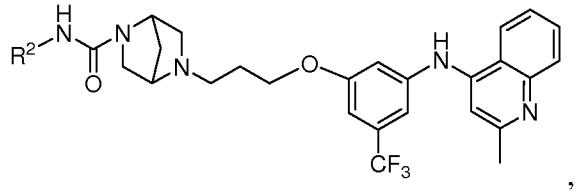
or a pharmaceutically acceptable derivative thereof.

12. The compound of claim 1, wherein the compound is of formula:



or a pharmaceutically acceptable derivative thereof.

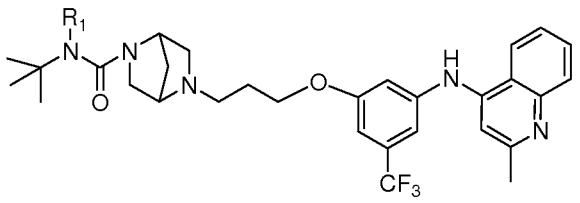
13. The compound of claim 1, wherein the compound is of formula:



,

or a pharmaceutically acceptable derivative thereof.

14. The compound of claim 1, wherein the compound is of formula:



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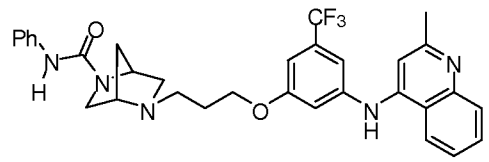
or a pharmaceutically acceptable derivative thereof.

15. A compound selected from: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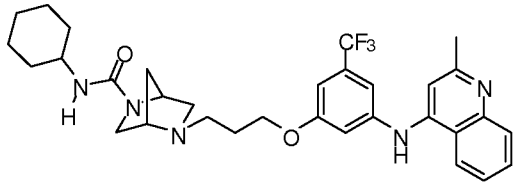
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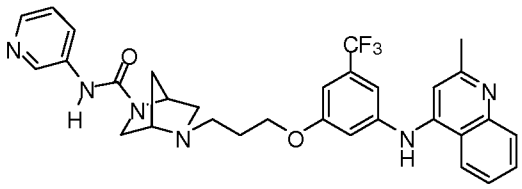
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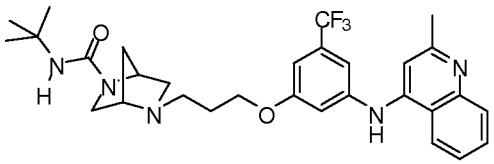
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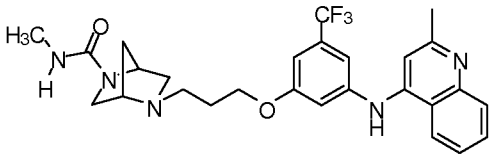
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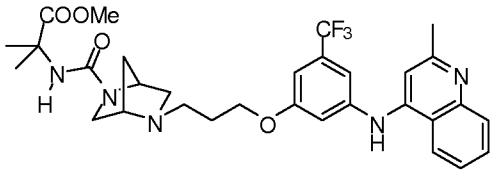
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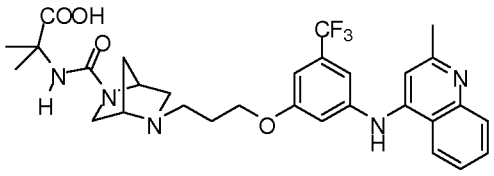
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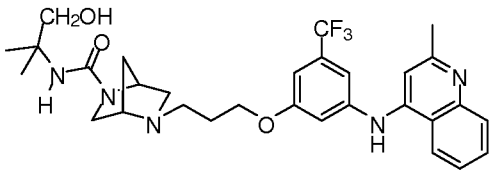
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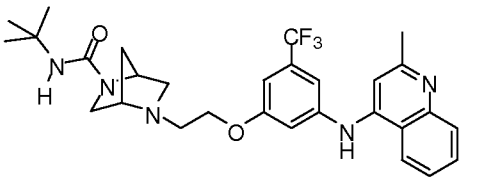
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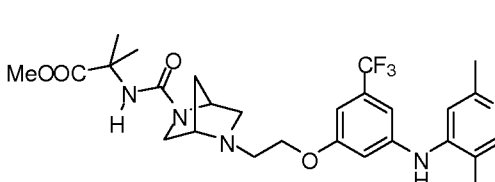
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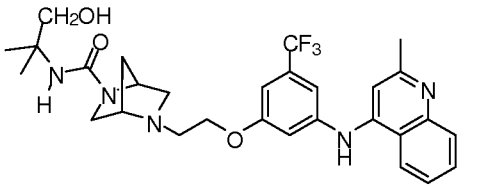
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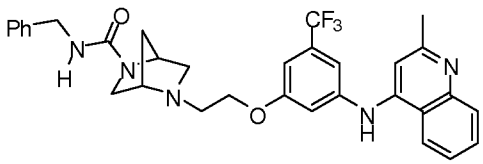

or a pharmaceutically acceptable derivative thereof.

16. A pharmaceutical composition comprising a compound of any of claims 1-15 or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

17. A method for modulating urotensin-II receptor activity comprising contacting the urotensin-II receptor with the compound of any of claims 1-15 or a pharmaceutically acceptable derivative thereof.

18. A method for treating, preventing or ameliorating a disease associated with urotensin-II receptor modulation comprising administering the compound of any of claims 1-15 or a pharmaceutically acceptable derivative thereof.

19. The method of claim 18, wherein the disease is a cardiovascular disorder, atherosclerosis, renal failure, nephrotoxicity and diarrhea caused by anti-neoplastic agents, post-myocardial infarction, pulmonary hypertension, diabetes or a CNS related disease.

20. The method of claim 18 further comprising administering one or more therapeutic agents selected from an α and β-blocker, vasodilator, calcium-antagonist, angiotensin converting enzyme-inhibitor, potassium channel activator, angiotensin receptor antagonist, diuretic, sympatholytic, endothelin receptor antagonist, anti-hyperlipidemic agent and phosphodiesterase 5 inhibitor.