TITLE OF THE INVENTION

CGRP RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

CGRP (Calcitonin Gene-Related Peptide) is a naturally occurring 37-amino acid peptide that is generated by tissue-specific alternate processing of calcitonin messenger RNA and is widely distributed in the central and peripheral nervous system. CGRP is localized predominantly in sensory afferent and central neurons and mediates several biological actions, including vasodilation. CGRP is expressed in alpha- and beta-forms that vary by one and three amino acids in the rat and human, respectively. CGRP-alpha and CGRP-beta display similar biological properties. When released from the cell, CGRP initiates its biological responses by binding to specific cell surface receptors that are predominantly coupled to the activation of adenylyl cyclase. CGRP receptors have been identified and pharmacologically evaluated in several tissues and cells, including those of brain, cardiovascular, endothelial, and smooth muscle origin.

CGRP-mediated vasodilation of rat middle meningeal artery was shown to sensitize neurons of the trigeminal nucleus caudalis (Williamson et al., The CGRP Family: Calcitonin Gene-Related Peptide (CGRP), Amylin, and Adrenomedullin, Landes Bioscience, 2000, 245-247). Similarly, distention of dural blood vessels during migraine headache may sensitize trigeminal neurons. Some of the associated symptoms of migraine, including extra-cranial pain and facial allodynia, may be the result of sensitized trigeminal neurons (Burstein et al., Ann. Neurol. 2000, 47, 614-624). A CGRP antagonist may be beneficial in attenuating, preventing or reversing the effects of neuronal sensitization.

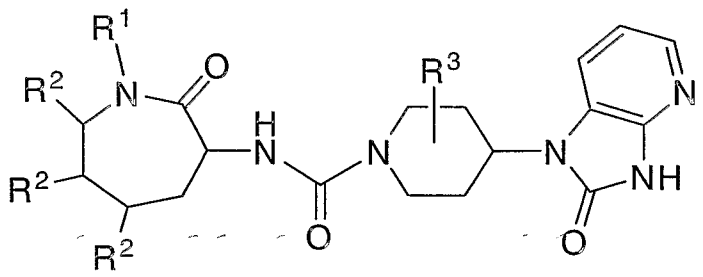
The ability of the compounds of the present invention to act as CGRP antagonists makes them useful pharmacological agents for disorders that involve CGRP in humans and animals, but particularly in humans. Such disorders include migraine and cluster headache (Doods, Curr Opin Inves Drugs, 2001, 2 (9), 1261-1268; Edvinsson et al., Cephalalgia, 1994, 14, 320-327); chronic tension type headache (Ashina et al., Neurology, 2000, 14, 1335-1340); pain (Yu et al., Eur. J. Pharm., 1998, 347, 275-282); chronic pain (Hulsebosch et al., Pain, 2000, 86, 163-175); neurogenic inflammation and inflammatory pain (Holzer, Neurosci., 1988, 24, 739-768; Delay-Goyet et al., Acta Physiol. Scanda. 1992, 146, 537-538; Salmon et al., Nature Neurosci., 2001, 4(4), 357-358); eye pain (May et al. Cephalalgia, 2002, 22, 195-196), tooth pain (Awawdeh et al., Int. Endocrin. J., 2002, 35, 30-36), non-insulin dependent diabetes mellitus (Molina et al., Diabetes, 1990, 39, 260-265); vascular disorders; inflammation (Zhang et al., Pain, 2001, 89, 265), arthritis, asthma (Foster et al., Ann. NY Acad. Sci., 1992, 657, 397-404; Schini et al., Am. J. Physiol., 1994, 267, H2483-H2490; Zheng et al., J. Virol., 1993, 67, 5786-5791); shock, sepsis (Beer et al., Crit. Care Med., 2002, 30 (8), 1794-1798); opiate withdrawal

syndrome (Salmon et al., Nature Neurosci., 2001, 4(4), 357-358) morphine tolerance (Menard et al., J. Neurosci., 1996, 16 (7), 2342-2351); hot flashes in men and women (Chen et al., Lancet, 1993, 342, 49; Spetz et al., J. Urology, 2001, 166, 1720-1723); allergic dermatitis (Wallengren, Contact Dermatitis, 2000, 43 (3), 137-143); encephalitis, brain trauma, ischaemia, stroke, epilepsy, and neurodegenerative diseases (Rohrenbeck et al., Neurobiol. of Disease 1999, 6, 15-34); skin diseases (Geppetti and Holzer, Eds., Neurogenic Inflammation, 1996, CRC Press, Boca Raton, FL), neurogenic cutaneous redness, skin rosaceousness and erythema. Of particular importance is the acute or prophylactic treatment of headache, including migraine and cluster headache.

The present invention relates to compounds that are useful as ligands for CGRP receptors, in particular antagonists for CGRP receptors, processes for their preparation, their use in therapy, pharmaceutical compositions comprising them and methods of therapy using them.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula I:

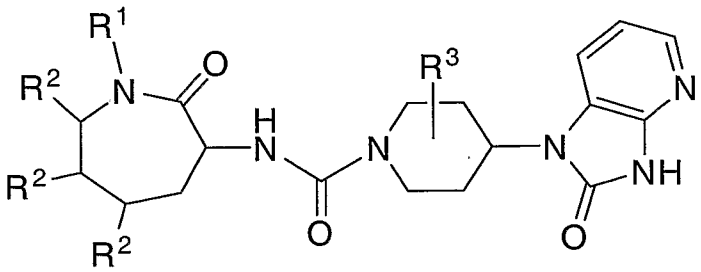


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(where variables R^1, R^2 and R^3 are as defined herein) useful as antagonists of CGRP receptors and useful in the treatment or prevention of diseases in which the CGRP is involved, such as headache, migraine and cluster headache. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which CGRP is involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to CGRP antagonists which include compounds of Formula I:



I

wherein:

R^1 is selected from:

H, C_1-C_6 alkyl, C_{3-6} cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents independently selected from:

C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, heteroaryl, heterocycle, $(F)_pC_{1-3}$ alkyl, halogen, OR^4, $O(CH_2)_sOR^4$, CO_2R^4, CN, $NR^{10}R^{11}$, $O(CO)R^4$,

where said phenyl, said heteroaryl and said heterocycle are each independently unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,

where said heteroaryl is selected from: imidazole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, and thiazole;

where said heterocycle is selected from: azetidine, dioxane, dioxolane, morpholine, oxetane, piperazine, piperidine, pyrrolidine, tetrahydrofuran, and tetrahydropyran;

aryl, or heteroaryl selected from: phenyl, imidazole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, and thiazole,

where said aryl and said heteroaryl are each independently unsubstituted or substituted with one or more substituents independently selected from: C_{1-6} alkyl, C_{3-6} cycloalkyl, $(F)_pC_{1-3}$ alkyl, halogen, OR^4, CO_2R^4, $(CO)NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$, $N(R^{10})SO_2R^{11}$, $S(O)_mR^4$, CN, $NR^{10}R^{11}$ and $O(CO)R^4$;

R^2 is selected from:

H, C_0-C_6 alkyl, C_{3-6} cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents independently selected from:

C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, heteroaryl, heterocycle, $(F)_pC_{1-3}$ alkyl, halogen, OR^4, $O(CH_2)_sOR^4$, CO_2R^4, CN, $NR^{10}R^{11}$ and $O(CO)R^4$,

where said phenyl, said heteroaryl, and said heterocycle are each independently unsubstituted or substituted with 1-5 substituents independently selected from R^4,

where said heteroaryl is selected from: benzimidazole, benzothiophene, furan, imidazole, indole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiazole, thiophene, and triazole;

where said heterocycle is selected from: azetidine, imidazolidine, imidazoline, isoxazoline, isoxazolidine, morpholine, oxazoline, oxazolidine, oxetane, pyrazolidine, pyrazoline, pyrroline, tetrahydrofuran, tetrahydropyran, thiazoline, and thiazolidine;

aryl or heteroaryl, selected from: phenyl, benzimidazole, benzothiophene, furan, imidazole, indole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiazole, thiophene, and triazole;

where said aryl and said heteroaryl are each independently unsubstituted or substituted with one or more substituents independently selected from: C_{1-6} alkyl, C_{3-6} cycloalkyl, $(F)_pC_{1-3}$ alkyl, halogen, OR^4, CO_2R^4, $(CO)NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$, $N(R^{10})$ SO_2R^{11}, $S(O)_mR^4$, CN, $NR^{10}R^{11}$ and $O(CO)R^4$;

R^{10} and R^{11} are independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_1-C_6 alkoxy, where R^{10} and R^{11} may be joined together to form a ring selected from: azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4;

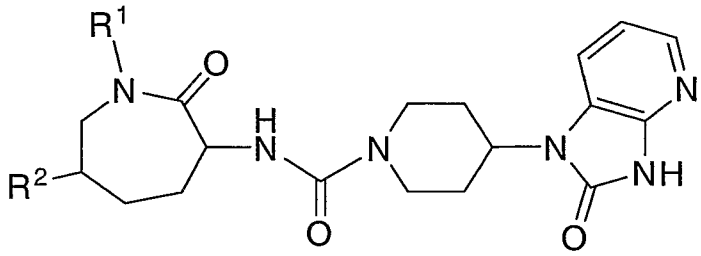
R^4 is independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and phenyl, unsubstituted or substituted with hydroxy or C_1-C_6 alkoxy;

R^3 is independently selected from H, substituted or unsubstituted C_1-C_3 alkyl, CN and CO_2R^4;

p is 0 to 2q+1, for a substituent with q carbons;
m is 0, 1 or 2;
s is 1, 2 or 3;

and pharmaceutically acceptable salts and individual diastereomers thereof.

In one embodiment, the invention is directed to compounds of the Formula:



wherein:

R^1 is selected from:

C_1-C_6 alkyl unsubstituted or substituted with one or more substituents independently selected from:C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, heteroaryl, heterocycle, $(F)_pC_{1-3}$ alkyl, halogen, OR^4, $O(CH_2)_sOR^4$, CO_2R^4, CN, $NR^{10}R^{11}$, and $O(CO)R^4$,

R^2 is selected from:

aryl, unsubstituted or substituted with one or more substituents independently selected from: C_{1-6} alkyl, C_{3-6} cycloalkyl, $(F)_pC_{1-3}$ alkyl, halogen, OR^4, CO_2R^4, $(CO)NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$, $N(R^{10})$ SO_2R^{11}, $S(O)_mR^4$, CN, $NR^{10}R^{11}$ and $O(CO)R^4$;

R^{10} and R^{11} are independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_1-C_6 alkoxy, where R^{10} and R^{11} may be joined together to form a ring selected from: azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4;

R^4 is independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and phenyl, unsubstituted or substituted with hydroxy or C_1-C_6 alkoxy;

p is	0 to 2q+1, for a substituent with q carbons;
m is	0, 1 or 2;
s is	1, 2 or 3;

and pharmaceutically acceptable salts and individual diastereomers thereof.

It is to be understood that where one or more of the above recited structures or substructures recite multiple substituents having the same designation each such variable may be the same or different from each similarly designated variable. For example, R^2 is recited four times in Formula I, and each R^2 in Formula I may independently be any of the substructures defined under R^2. The invention is not limited to structures and substructures wherein each R^2 must be the same for a given structure. The same is true with respect to any variable appearing multiple time in a structure or substructure.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diasteromeric derivatives may then be converted to

the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

As will be appreciated by those of skill in the art, not all of the R^{10} and R^{11} substituents are capable of forming a ring structure. Moreover, even those substituents capable of ring formation may or may not form a ring structure.

Also as appreciated by those of skill in the art, halo or halogen as used herein are intended to include chloro, fluoro, bromo and iodo.

As used herein, "alkyl" is intended to mean linear, branched and cyclic structures having no double or triple bonds. Thus C_{1-6}alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C_{1-6}alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl and hexyl. "Cycloalkyl" is an alkyl, part or all of which which forms a ring of three or more atoms. C_0 or C_0alkyl is defined to identify the presence of a direct covalent bond.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon-to-carbon double bond. C_{2-6}alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

The term "alkynyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon triple bond. Thus C_{2-6}alkynyl is defined to identify the group as having 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C_{2-6}alkynyl specifically includes 2-hexynyl and 2-pentynyl.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, napthyl, tetrahydronapthyl, indanyl, or biphenyl.

The term "heterocycle" or "heterocyclic", as used herein except where noted, represents a stable 5- to 7-membered monocyclic- or stable 8- to 11-membered bicyclic heterocyclic ring system which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene

ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include, but are not limited to, azetidine, chroman, dihydrofuran, dihydropyran, dioxane, dioxolane, hexahydroazepine, imidazolidine, imidazolidinone, imidazoline, imidazolinone, indoline, isochroman, isoindoline, isothiazoline, isothiazolidine, isoxazoline, isoxazolidine, morpholine, morpholinone, oxazoline, oxazolidine, oxazolidinone, oxetane, 2-oxohexahydroazepin, 2-oxopiperazine, 2-oxopiperidine, 2-oxopyrrolidine, piperazine, piperidine, pyran, pyrazolidine, pyrazoline, pyrrolidine, pyrroline, quinuclidine, tetrahydrofuran, tetrahydropyran, thiamorpholine, thiazoline, thiazolidine, thiomorpholine and N-oxides thereof.

The term "heteroaryl", as used herein except where noted, represents a stable 5- to 7-membered monocyclic- or stable 9- to 10-membered fused bicyclic heterocyclic ring system which contains an aromatic ring, any ring of which may be saturated, such as piperidinyl, partially saturated, or unsaturated, such as pyridinyl, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heteroaryl groups include, but are not limited to, benzimidazole, benzisothiazole, benzisoxazole, benzofuran, benzothiazole, benzothiophene, benzotriazole, benzoxazole, carboline, cinnoline, furan, furazan, imidazole, indazole, indole, indolizine, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and N-oxides thereof.

The term "alkoxy," as in C_1-C_6 alkoxy, is intended to refer to include alkoxy groups of from 1 to 6 carbon atoms of a straight, branched and cyclic configuration. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as

amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The number of certain variables present in certain instances is defined in terms of the number of carbons present. For example, variable "p" is occasionally defined as follows: "p is 0 to 2q+1, for a substituent with q carbons". Where the substituent is "$(F)_pC_{1-3}$ alkyl" this means that when there is one carbon, there are 2(1) + 1 = 3 fluorines. When there are two carbons, there are 2(2) + 1 = 5 fluorines, and when thre are three carbons there are 2(3) = 1 = 7 fluorines.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. In one aspect of the invention the salts are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein. Specific compounds within the present invention include a compound which selected from the group consisting of the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

The subject compounds are useful in a method of antagonism of CGRP receptors in a patient such as a mammal in need of such antagonism comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as antagonists of CGRP receptors. In addition to primates, especially humans, a variety of other mammals can be treated according to the method of the present invention.

Another embodiment of the present invention is directed to a method for the treatment, control, amelioration, or reduction of risk of a disease or disorder in which the CGRP receptor is involved in a patient that comprises administering to the patient a therapeutically effective amount of a compound that is an antagonist of CGRP receptors.

The present invention is further directed to a method for the manufacture of a medicament for antagonism of CGRP receptors activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The subject treated in the present methods is generally a mammal, for example a human being, male or female, in whom antagonism of CGRP receptor activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. As used herein, the term "treatment" refers both to the treatment and to the prevention or prophylactic therapy of the mentioned conditions, particularly in a patient who is predisposed to such disease or disorder.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The utility of the compounds in accordance with the present invention as antagonists of CGRP receptor activity may be demonstrated by methodology known in the art. Inhibition of the binding of ^{125}I-CGRP to receptors and functional antagonism of CGRP receptors were determined as follows:

BINDING ASSAY: The binding of ^{125}I-CGRP to receptors in SK-N-MC cell membranes was carried out essentially as described (Edvinsson *et al.* (2001) *Eur. J. Pharmacol.* **415**, 39-44). Briefly, membranes (25 □g) were incubated in 1 ml of binding buffer [10 mM HEPES, pH 7.4, 5 mM $MgCl_2$ and 0.2% bovine serum albumin (BSA)] containing 10 pM ^{125}I-CGRP and inhibitor. After incubation at room temperature for 3 h, the assay was terminated by filtration through GFB glass fibre filter plates (Millipore) that had been blocked with 0.5% polyethyleneimine for 3 h. The filters were

washed three times with ice-cold assay buffer, then the plates were air dried. Scintillation fluid (50 □l) was added and the radioactivity was counted on a Topcount (Packard Instrument). Data analysis was carried out by using Prism and the K_i was determined by using the Cheng–Prusoff equation (Cheng & Prusoff (1973) *Biochem. Pharmacol.* **22**, 3099-3108).

FUNCTIONAL ASSAY: SK-N-MC cells were grown in minimal essential medium (MEM) supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 0.1 mM non-essential amino acids, 1 mM sodium pyruvate, 100 units/ml penicillin and 100 □g/ml streptomycin at 37 °C, 95% humidity, and 5% CO_2. For cAMP assays, cells were plated at 5×10^5 cells/well in 96-well poly-D-lysine-coated plates (Becton-Dickinson) and cultured for ~ 18 h before assay. Cells were washed with phosphate-buffered saline (PBS, Sigma) then pre-incubated with 300 □M isobutylmethylxanthine in serum-free MEM for 30 min at 37 °C. □-CGRP-(8-37) was added and the cells were incubated for 10 min before the addition of CGRP. The incubation was continued for another 15 min, then the cells were washed with PBS and processed for cAMP determination according to the manufacturer's recommended protocol. Maximal stimulation over basal was defined by using 100 nM CGRP. Dose–response curves were generated by using Prism. Dose-ratios (DR) were calculated and used to construct full Schild plots (Arunlakshana & Schild (1959) *Br. J. Pharmacol.* **14**, 48-58).

In particular, the compounds of the following examples had activity as antagonists of the CGRP receptor in the aforementioned assays, generally with a K_i or IC_{50} value of less than about 50 □M. Such a result is indicative of the intrinsic activity of the compounds in use as antagonists of CGRP receptors.

The ability of the compounds of the present invention to act as CGRP antagonists makes them useful pharmacological agents for disorders that involve CGRP in humans and animals, but particularly in humans.

The compounds of the present invention have utility in treating, preventing, ameliorating, controlling or reducing the risk of one or more of the following conditions or diseases: headache; migraine; cluster headache; chronic tension type headache; pain; chronic pain; neurogenic inflammation and inflammatory pain; neuropathic pain; eye pain; tooth pain; diabetes; non-insulin dependent diabetes mellitus; vascular disorders; inflammation; arthritis; asthma; shock; sepsis; opiate withdrawal syndrome; morphine tolerance; hot flashes in men and women; allergic dermatitis; encephalitis; brain trauma; epilepsy; neurodegenerative diseases; skin diseases; neurogenic cutaneous redness, skin rosaceousness and erythema; and other conditions that may be treated or prevented by antagonism of CGRP receptors. Of particular importance is the acute or prophylactic treatment of headache, including migraine and cluster headache.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the aforementioned diseases, disorders and conditions in combination with other agents.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of the invention or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with inventive compounds. When an inventive compound is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the inventive compound may be used. However, the combination therapy may also include therapies in which the inventive sompounds and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to an inventive compound or compounds.

For example, the present compounds may be used in conjunction with an anti-inflammatory or analgesic agent or an anti-migraine agent, such as an ergotamine or 5-HT_1 agonists, especially a 5-$HT_{1B/1D}$ agonist, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, donitriptan, and rizatriptan; a cyclooxygenase inhibitor, such as a selective cyclooxygenase-2 inhibitor, for example rofecoxib, etoricoxib, celecoxib, valdecoxib or paracoxib; a non-steroidal anti-inflammatory agent or a cytokine-suppressing anti-inflammatory agent, for example with a compound such as aspirin, ibuprofen, ketoprofen, fenoprofen, naproxen, indomethacin, sulindac, meloxicam, piroxicam, tenoxicam, lornoxicam, ketorolac, etodolac, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, diclofenac, oxaprozin, apazone, nimesulide, nabumetone, tenidap, etanercept, tolmetin, phenylbutazone, oxyphenbutazone, diflunisal, salsalate, olsalazine or sulfasalazine and the like; or a steroidal analgesic. Similarly, the instant compounds may be administered with a pain reliever such as acetaminophen, phenacetin, codeine, fentanyl, sufentanil, methadone, acetyl methadol, buprenorphine or morphine.

Additionally, the present compounds may be used in conjunction with an interleukin inhibitor, such as an interleukin-1 inhibitor; an NK-1 receptor antagonist, for example aprepitant; an

NMDA antagonist; an NR2B antagonist; a bradykinin-1 receptor antagonist; an adenosine A1 receptor agonist; a sodium channel blocker, for example lamotrigine; an opiate agonist such as levomethadyl acetate or methadyl acetate; a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase; an alpha receptor antagonist, for example indoramin; an alpha receptor agonist; a vanilloid receptor antagonist; an mGluR5 agonist, antagonist or potentiator; a GABA A receptor modulator, for example acamprosate calcium; nicotinic antagonists or agonists including nicotine; muscarinic agonists or antagonists; a selective serotonin reuptake inhibitor, for example fluoxetine, paroxetine, sertraline, duloxetine, escitalopram, or citalopram; a tricyclic antidepressant, for example amitriptyline, doxepin, protriptyline, desipramine, trimipramine, or imipramine; a leukotriene antagonist, for example montelukast or zafirlukast; an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide.

Also, the present compounds may be used in conjunction with ergot alkaloids, for example ergotamine, ergonovine, ergonovine, methylergonovine, metergoline, ergoloid mesylates, dihydroergotamine, dihydroergocornine, dihydroergocristine, dihydroergocryptine, dihydro-I-ergocryptine, dihydro-ϑ-ergocryptine, ergotoxine, ergocornine, ergocristine, ergocryptine, I-ergocryptine, ϑ-ergocryptine, ergosine, ergostane, bromocriptine, or methysergide.

Additionally, the present compounds may be used in conjunction with a beta-adrenergic antagonist such as timolol, propanolol, atenolol, or nadolol, and the like; a MAO inhibitor, for example phenelzine; a calcium channel blocker, for example flunarizine, nimodipine, lomerizine, verapamil, nifedipine, prochlorperazine or gabapentin; neuroleptics such as olanzapine and quetiapine; an anticonvulsant such as topiramate, zonisamide, tonabersat, carabersat or divalproex sodium; an angiotensin II antagonist, for example losartan and candesartan cilexetil; an angiotensin converting enzyme inhibitor such as lisinopril; or botulinum toxin type A.

The present compounds may be used in conjunction with a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextromethorphan; a diuretic; a prokinetic agent such as metoclopramide or domperidone, and a sedating or non-sedating antihistamine.

In one embodiment the present compounds are used in conjunction with an anti-migraine agent, such as: an ergotamine; a 5-HT_1 agonist, especially a 5-$HT_{1B/1D}$ agonist, in particular, sumatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, donitriptan and rizatriptan; and a cyclooxygenase inhibitor, such as a selective cyclooxygenase-2 inhibitor, in particular, rofecoxib, etoricoxib, celecoxib, meloxicam, valdecoxib or paracoxib.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds. Likewise, compounds of the present invention may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is possible. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the compound of the present invention to the other active ingredient(s) may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, or from about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s), and via the same or different routes of administration.

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the

pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release. Oral tablets may also be formulated for immediate release, such as fast melt tablets or wafers, rapid dissolve tablets or fast dissolve films.

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

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for

example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

In the treatment, prevention, control, amelioration, or reduction of risk of conditions which require antagonism of CGRP receptor activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are may be provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0. 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, or may be administered once or twice per day.

When treating, preventing, controlling, ameliorating, or reducing the risk of headache, migraine, cluster headache, or other diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body

weight, given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, or from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein.

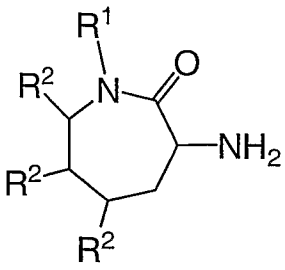
The compounds of the present invention can be prepared readily according to the following Schemes and specific examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art but are not mentioned in greater detail. The general procedures for making the compounds claimed in this invention can be readily understood and appreciated by one skilled in the art from viewing the following Schemes.

The synthesis of caprolactam azabenzimidazolone intermediates may be conducted as described in Schemes 1-6.

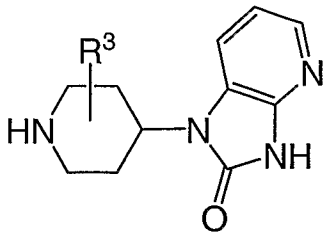
The preparation of final compounds proceeds through intermediates such as those of Formula **I** and Formula **II**, and the synthesis of each intermediate is described herein.

REACTION SCHEMES

The preparation of final compounds proceeds through intermediates such as those of Formula III and Formula IV, and the synthesis of each intermediate is described herein.



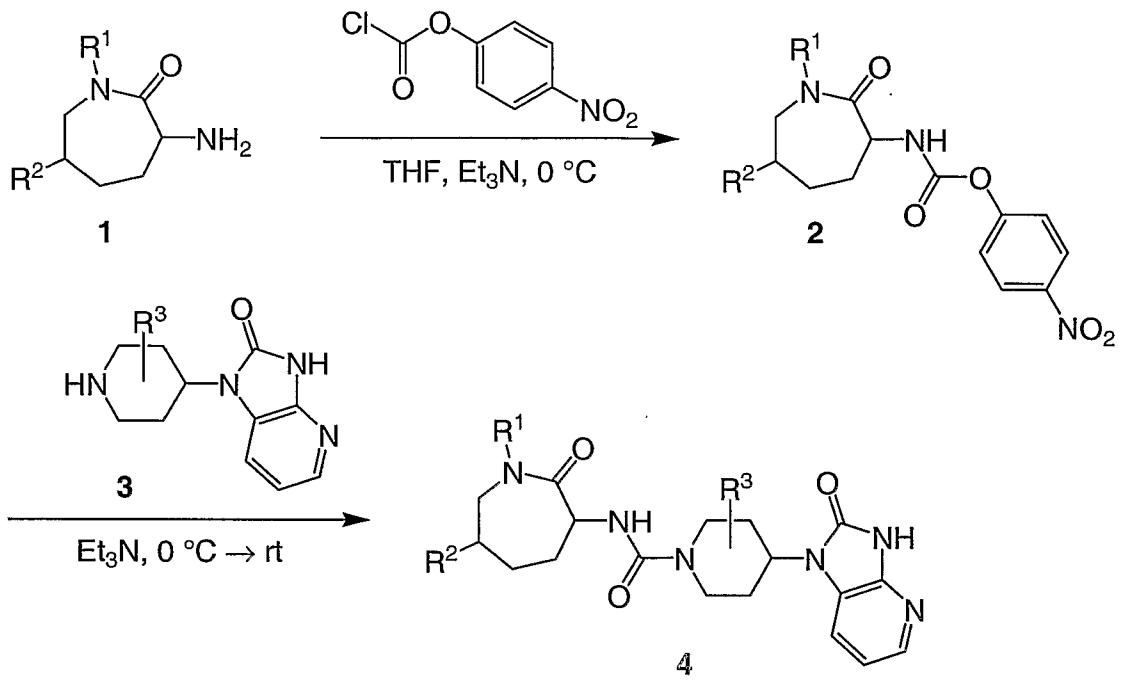
III



IV

In general, intermediates of the Formulae III and IV can be coupled through a urea linkage as shown in Scheme 1. Amine intermediate **1** can be converted to a reactive carbamate, for example p-nitrophenylcarbamate **2**, which is subsequently reacted with an amine like that of intermediate **3** to produce urea **4**. Other activated intermediates known to those skilled in the art can be used to prepare compounds like **4**. For example, amine **1** can be directly acylated with the appropriate carbamoyl chloride.

SCHEME 1

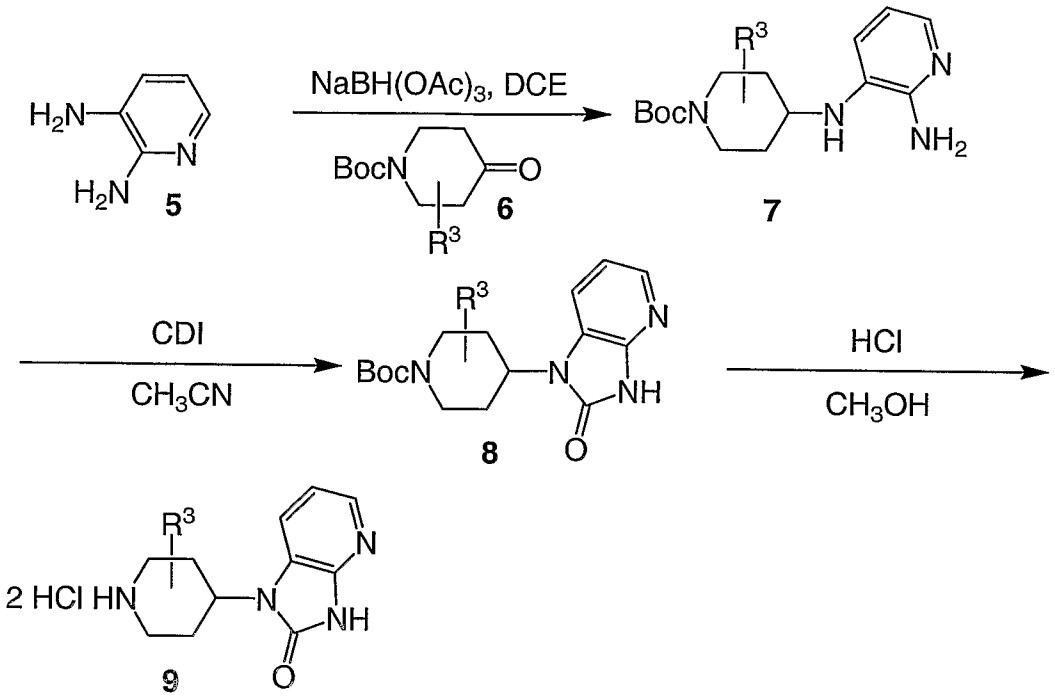


1 2 3 4

The synthesis of compounds represented by Intermediate II can be accomplished by procedures similar to those described in Henning et al., J. Med. Chem., 1987, 30, 814-819; Carpino et al., WO 96/35713; Brown et al., J. Chem. Soc. 1957, 682-686; Barlin et al., Aust. J. Chem. 1982, 35 (11), 2299-2306; and references cited therein.

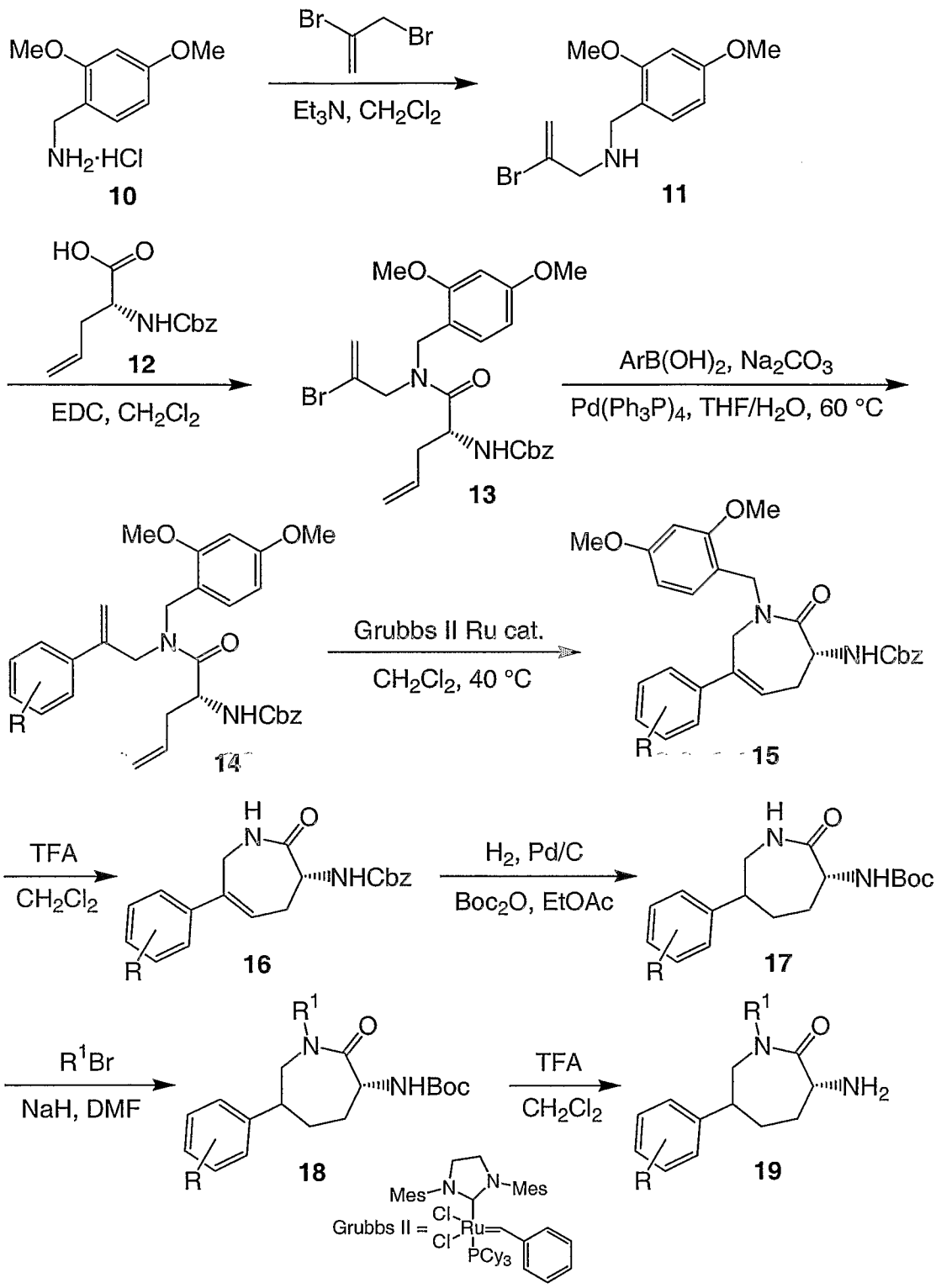
Additionally, the synthesis of compounds represented by Intermediate II can be accomplished according to Scheme 2. For example, a diamino heterocycle, such as 2,3-diaminopyridine **5**, can be reductively alkylated with ketones such as **6** to give the monalkylated product **7**. Ring closure with carbonyldiimidazole furnishes imidazolone **8**. Final deprotection under standard conditions gives the final product **9**.

SCHEME 2



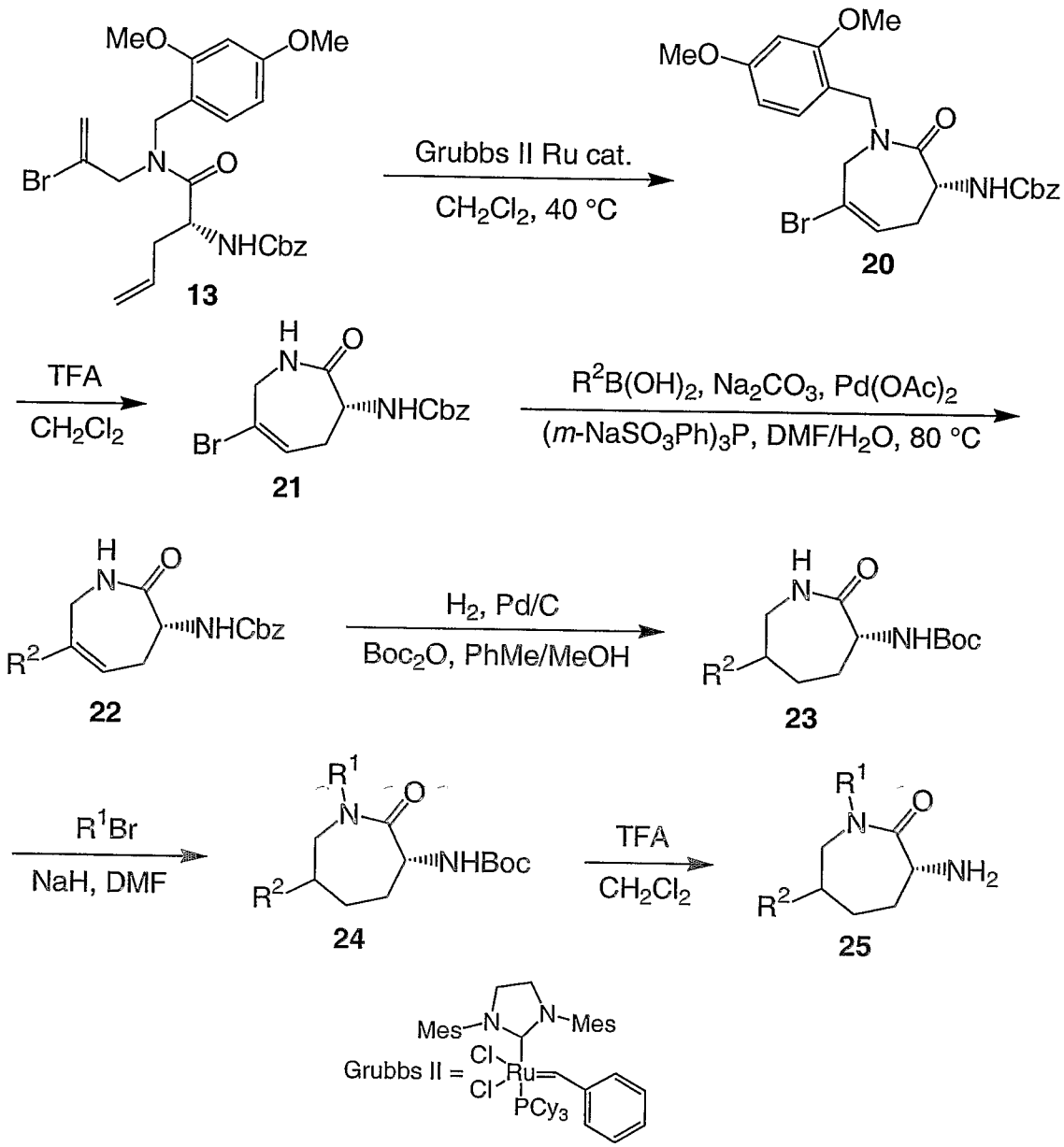
Caprolactams can be assembled following an olefin metathesis strategy as outlined in Scheme 3. 2,4-Dimethoxybenzylamine hydrochloride is alkylated with 2,3-dibromopropene under mild basic conditions to give amine **11**. (2*R*)-2-{[(benzyloxy)carbonyl]amino}pent-4-enoic acid **12**, prepared in one step from commercially available D-allyl glycine according to known procedures (J. Chem. Soc., 1962, 3963-3968), can be coupled to amine **11** under a variety of conditions to give amide **13**. A variety of transition metal catalyzed cross couplings can be performed on the vinyl bromide, for example palladium-mediated arylations with phenylboronic acid and sodium carbonate, yielding styrene derivative **14**. Ring-closing metathesis occurs in the presence of the Grubbs second generation ruthenium catalyst in dichloromethane with mild heating to afford lactam **15**. Removal of the dimethoxybenzyl group and hydrogenation with *in situ* protection of the primary amine gives the corresponding saturated lactam **17**. After selective alkylation of the amide nitrogen with various electrophiles such as alkyl bromides, deprotection under acidic conditions yields compounds of the general formula **19**.

SCHEME 3


MeO
OMe
NH2·HCl
10
Br
Br
Et3N, CH2Cl2
NH
11
HO
O
NHCbz
12
EDC, CH2Cl2
N
13
ArB(OH)2, Na2CO3
Pd(Ph3P)4, THF/H2O, 60 °C
R
14
Grubbs II Ru cat.
CH2Cl2, 40 °C
15
TFA
CH2Cl2
16
H2, Pd/C
Boc2O, EtOAc
NHBoc
17
R1Br
NaH, DMF
18
NH2
19
Grubbs II =
Mes
Cl
Ru
PCy3

Variation at the 6-position of the caprolactams can be introduced by employing a similar strategy (Scheme 4). Ring-closing metathesis can be performed directly on vinyl bromide **13** using the Grubbs second generation ruthenium catalyst to give cyclic vinyl bromide **20**. Removal of the dimethoxybenzyl group and palladium-mediated cross coupling, in this case with a boronic acid, furnishes compounds of the general formula **22**. The transformation of **21** to **22** is not limited to boronic acid derivatives. After standard hydrogenation, the amide nitrogen can be selectively alkylated with various electrophiles, for example alkyl bromides, using sodium hydride as base. Deprotection yields lactams of the general formula **25**.

SCHEME 4

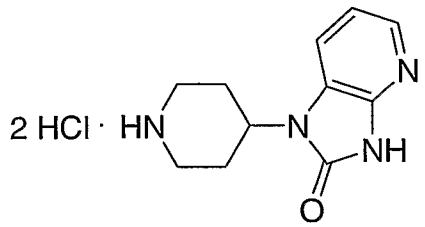


In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

EXAMPLES

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

INTERMEDIATE 1



2-Oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride

Step A. 2-Amino-3-[(1-t-butoxycarbonylpiperidin-4-yl)amino)pyridine

Sodium triacetoxyborohydride (14.5 g, 68.7 mmol) was added to a solution of 2,3-diaminopyridine (5.00 g, 45.8 mmol) and N-(t-butoxycarbonyl)-4-piperidone (9.58 g, 48.1 mmol) in dichloroethane (75 mL) at room temperature. After 5 h, additional sodium triacetoxyborohydride was added (1.8 g) and again after another 2.5 h. The reaction was stirred overnight, and quenched with 5% aqueous sodium hydroxide. This was extracted with methylene chloride, and washed with 5% aqueous sodium hydroxide, water and saturated sodium chloride solution. After drying over sodium sulfate, the solution was filtered and evaporated to give the crude product. This was purified by chromatorgraphy (silica gel, 3 to 5% methanol in methylene chloride gradient elution), which gave the title compound (4.44 g). MS 293 (M+1) ^{1}H NMR (500 MHz, CD_3OD) □ 7.32 (dd, J=1, 5 Hz, 1H), 6.85 (dd, J=1, 8 Hz, 1H), 6.59 (dd, J=5, 8 Hz, 1H), 4.04 (d, J=13 Hz, 2H), 3.46 (m, 1H), 2.98 (br s, 2H), 2.01 (dd, J=2, 12 Hz, 2H), 1.46 (s, 9H), 1.37 (qd, J=4, 12 Hz, 2H).

Step B. 2-Oxo-1-(1-t-butoxycarbonylpiperidin-4-yl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine

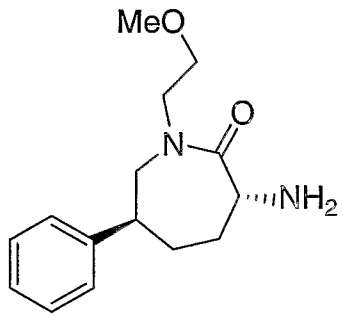
Carbonyldiimidazole (0.70 g, 4.33 mmol) was added to a solution of 2-amino-3-[(1-t-butoxycarbonylpiperidin-4-yl)amino]pyridine (1.15 g, 3.93 mmol) in acetonitrile (150 mL) at room temperature. After several hours, an additional amount of carbonyldiimidazole was added (0.81 g), and the reaction stirred overnight. The acetonitrile was evaporated in vacuo, the residue partitioned between water and chloroform, and the organic phase washed with saturated brine and dried over magnesium

sulfate. The crude product was purified by chromatorgraphy (silica gel, 1.2 to 2.5% methanol in methylene chloride gradient elution), which gave the title compound (1.09 g). ^{1}H NMR (500 MHz, $CDCl_3$) □ 9.39 (br s, 1H), 8.04 (dd, J=1, 5 Hz, 1H), 7.33 (dd, J=1, 8 Hz, 1H), 6.99 (dd, J=5, 8 Hz, 1H), 4.50 (m, 1H), 4.32 (br s, 2H), 2.86 (br s, 2H), 2.20 (m, 2H), 1.86 (d, J=12 Hz, 2H), 1.50 (s, 9H).

Step C. 2-Oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride

2-Oxo-1-(1-t-butoxycarbonylpiperidin-4-yl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine (1.03 g, 3.23 mmol) was dissolved in methanol (25 mL) and a solution of 2N hydrochloric acid in ether (8 mL) was added at room temperature. After 2 h, the volatiles were removed in vacuo, to give the title compound (0.92 g). MS 219 (M + 1). ^{1}H NMR (500 MHz, CD_3OD) □ 8.01 (dd, J=1, 6 Hz, 1H), 7.83 (d, J=8 Hz, 1H), 7.28 (dd, J=6, 8 Hz, 1H), 4.60 (m, 1H), 3.59 (d, J=12 Hz, 2H), 3.21 (t, J=12 Hz, 2H), 2.70 (dq, J=4, 13 Hz, 2H), 2.12 (d, J=13 Hz, 2H).

INTERMEDIATE 2



(3*R*,6*S*)-3-Amino-1-(2-methoxyethyl)-6-phenylazepan-2-one

Step A: 2-Bromo-*N*-(2,4-dimethoxybenzyl)prop-2-en-1-amine

Triethylamine (16.0 mL, 114 mmol) was added to a solution of 2,4-dimethoxybenzylamine hydrochloride (11.1 g, 54.5 mmol) and 2,3-dibromopropene (10.9 g, 54.5 mmol) in dichloromethane (200 mL). After 18 h, water was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography [100% dichloromethane → 95% dichloromethane/ 5% (10% ammonium hydroxide/ methanol)] gave the title compound (7.85 g).

Step B: Benzyl (1*R*)-1-{[(2-bromoprop-2-enyl)(2,4-dimethoxybenzyl) amino]carbonyl}but-3-enylcarbamate

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (55 mg, 0.285 mmol) was added to a solution of 2-bromo-*N*-(2,4-dimethoxybenzyl)prop-2-en-1-amine (73 mg, 0.256 mmol) and (2*R*)-2-{[(benzyloxy)carbonyl]amino}pent-4-enoic acid (71 mg, 0.285 mmol) in dichloromethane (5 mL). After 18 h the mixture was concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 30% ethyl acetate/ hexanes) gave the title compound (77 mg). MS 517 (M+1).

Step C: Benzyl (1*R*)-1-{[(2,4-dimethoxybenzyl)(2-phenylprop-2-enyl)amino]carbonyl}but-3-enylcarbamate

Tetrakis(triphenylphosphine)palladium(0) (1.11 g, 0.962 mmol) was added to a solution of benzyl (1*R*)-1-{[(2-bromoprop-2-enyl)(2,4-dimethoxybenzyl) amino]carbonyl}but-3-enylcarbamate (2.49 g, 4.81 mmol), phenylboronic acid (0.65 g, 5.29 mmol) and sodium carbonate (2M in water; 4.81 mL, 9.63 mmol) in tetrahydrofuran (54 mL) and water (20 mL), and the mixture heated to 60 □C. After 1 h, the mixture was allowed to cool to ambient temperature and extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 30% ethyl acetate/ hexanes) gave the title compound (2.02 g). MS 515 (M+1).

Step D: Benzyl (3*R*)-1-(2,4-dimethoxybenzyl)-2-oxo-6-phenyl-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate

[1,3-bis-(2,4,6-trimethylphenyl-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium] (Grubbs second generation catalyst) (0.68 g, 0.79 mmol) was added to a solution of benzyl (1*R*)-1-{[(2,4-dimethoxybenzyl)(2-phenylprop-2-enyl)amino]carbonyl}but-3-enylcarbamate (2.02 g, 3.93 mmol) in dichloromethane (395 mL) and heated to 40 □C. After 40 h, the mixture was allowed to cool to ambient temperature and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 30% ethyl acetate/ hexanes) gave the title compound (1.00 g). MS 487 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$) □7.39-7.31 (m, 5H), 7.26-7.19 (m, 3H), 7.17 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 7.1 Hz, 2H), 6.41 (dd, J = 8.3, 2.0 Hz, 1H), 6.33 (s, 1H), 6.22 (d, J = 6.4 Hz, 1H), 5.77-5.76 (m, 1H), 5.16-5.09 (m, 3H), 4.82 (d, J = 14.7 Hz, 1H), 4.65 (dd, J = 17.6, 2.7 Hz, 1H), 4.54 (d, J = 14.4 Hz, 1H), 3.93 (d, J = 17.6 Hz, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 2.91-2.86 (m, 1H), 2.42-2.36 (m, 1H).

Step E: Benzyl (3*R*)-2-oxo-6-phenyl-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate

A solution of L-methionine (2.56 g, 17.2 mmol) in trifluoroacetic acid (15 mL) was added to a solution of benzyl (3*R*)-1-(2,4-dimethoxybenzyl)-2-oxo-6-phenyl-2,3,4,7-tetrahydro-1H-

azepin-3-ylcarbamate (0.84 g, 1.72 mmol) in dichloromethane (20 mL). After 18 h, the mixture was concentrated and water was added. The mixture was extracted with ethyl acetate, washed with water (2x), saturated aqueous sodium bicarbonate (2x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 50% ethyl acetate/ hexanes) gave the title compound (0.44 g). MS 337 (M+1).

Step F: *tert*-Butyl (3*R*,6*S*)-2-oxo-6-phenylazepan-3-ylcarbamate

10% palladium on carbon (75 mg) was added to a solution of benzyl (3*R*)-2-oxo-6-phenyl-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate (596 mg, 1.77 mmol) and di-*tert*-butyl dicarbonate (773 mg, 3.54 mmol) in ethyl acetate (30 mL). The reaction vessel is evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After 2 h, the mixture was filtered and concentrated. Purification by silica gel chromatography (30% ethyl acetate/ hexanes → 50% ethyl acetate/ hexanes) gave the title compound (289 mg).

Step G: *tert*-Butyl (3*R*,6*S*)-1-(2-methoxyethyl)-2-oxo-6-phenylazepan-3-ylcarbamate

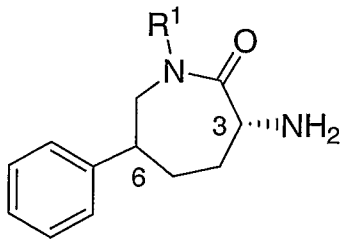
Sodium hydride (60% dispersion in mineral oil; 6.2 mg, 0.158 mmol) was added to a solution of *tert*-butyl (3*R*,6*R*)-2-oxo-6-phenylazepan-3-ylcarbamate (40 mg, 0.131 mmol) and 2-bromoethyl methyl ether (0.013 mL, 0.138 mmol) in *N*,*N*-dimethylformamide (2 mL) at 0 □C. After addition, the mixture was allowed to warm to ambient temperature. After 4 h, the reaction was quenched with water and the mixture was extracted with ethyl acetate. The organic layer was washed with water (3x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 30% ethyl acetate/ hexanes) gave the title compound (41 mg). MS 363 (M+1).

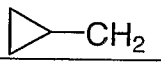
Step H: (3*R*,6*S*)-3-Amino-1-(2-methoxyethyl)-6-phenylazepan-2-one

Trifluoroacetic acid (2.5 mL) was added to a solution of *tert*-butyl (3*R*,6*S*)-1-(2-methoxyethyl)-2-oxo-6-phenylazepan-3-ylcarbamate (41 mg, 0.113 mmol) in dichloromethane (5 mL). After 1 h, the solution was concentrated. Saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. MS 263 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$) □ 7.32 (t, J = 7.3 Hz, 2H), 7.25-7.22 (m, 1H), 7.18 (d, J = 8.3 Hz, 2H), 3.83-3.76 (m, 3H), 3.56-3.49 (m, 3H), 3.35 (s, 3H), 3.34-3.30 (m, 1H), 2.77-2.72 (m, 1H), 2.13-2.10 (m, 1H), 2.03-1.94 (m, 2H), 1.74-1.68 (m, 1H).

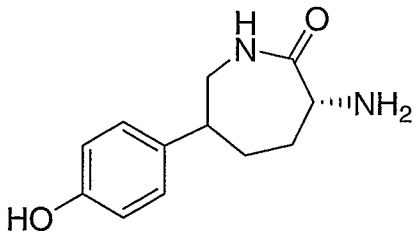
Essentially following the procedures outlined for the preparation of Intermediate 2, the Intermediates in Table I-1 were prepared.

TABLE I-1



Intermediate	C-3	C-6	R^1	MS (M+1)
3	R	S	H	205
4	R	R	H	205
5	R	S	CH_3	219
6	R	S	CH_2CH_3	233
7	R	S	CH_2CF_3	287
8	R	S	$CH_2CO_2CH_3$	277
9	R	S	$(CH_2)_2OCH_2CH_3$	277
10	R	S	CH_2CN	244
11	R	S		259

INTERMEDIATE 12



(3*R*)-3-Amino-6-(4-hydroxyphenyl)azepan-2-one

Step A: Benzyl (3*R*)-6-bromo-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate

[1,3-bis-(2,4,6-trimethylphenyl-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium] (Grubbs second generation catalyst) (1.78 g, 2.05 mmol) was added to a solution of benzyl (1*R*)-1-{[(2-bromoprop-2-enyl)(2,4-dimethoxybenzyl) amino]carbonyl}but-3-enylcarbamate (5.29 g, 10.2 mmol) in dichloromethane (1000 mL) and heated to 40 □C. After 18 h, the mixture was allowed to cool to ambient temperature and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 30% ethyl acetate/ hexanes) gave the title compound (0.79 g). MS 489 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$) □ 7.36-7.35 (m, 4H), 7.33-7.30 (m, 1H), 7.17-7.15 (m, 1H), 6.46-6.43 (m, 2H), 6.13 (d, J = 6.1 Hz, 1H), 6.04-6.03 (m, 1H), 5.13-5.07 (m, 2H), 4.93-4.88 (m, 1H), 4.75 (d, J = 14.4 Hz, 1H), 4.64-4.60 (m, 1H), 4.47 (d, J = 14.4 Hz, 1H), 3.86 (d, J = 18.3 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.68-2.63 (m, 1H), 2.24-2.05 (m,1H).

Step B: Benzyl (3*R*)-6-bromo-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate

A solution of L-methionine (274 mg, 1.84 mmol) in trifluoroacetic acid (5 mL) was added to a solution of benzyl (3*R*)-6-bromo-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate (90 mg, 0.184 mmol) in dichloromethane (5 mL). After 18 h, the mixture was concentrated. Purification by reverse phase HPLC (C-18, 95% water/ acetonitrile → 5% water/ acetonitrile with 0.1% trifluoroacetic acid) gave the title compound (17 mg). MS 339 (M+1).

Step C: Benzyl (3*R*)-6-(4-hydroxyphenyl)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate

Palladium acetate (1 mg, 0.003 mmol) was added to a solution of benzyl (3*R*)-6-bromo-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate (18 mg, 0.053 mmol), 4-hydroxyphenylboronic acid (9 mg, 0.064 mmol), sodium carbonate (2M in water; 0.066 mL, 0.133 mmol) and trisodium 3-[bis(3-sulfonatophenyl)phosphino] benzenesulfonate (5 mg, 0.088 mmol) in *N*,*N*-dimethylformamide (0.45 mL) and water (0.15 mL) and heated to 80 □C. After 1.5 h, the mixture was allowed to cool to ambient

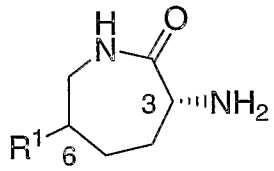
temperature and filtered. Purification by reverse phase HPLC (C-18, 95% water/ acetonitrile → 5% water/ acetonitrile with 0.1% trifluoroacetic acid) gave the title compound (15 mg). MS 353 (M+1).

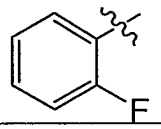
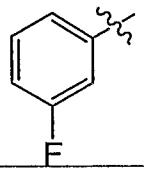
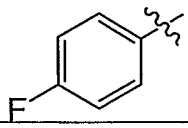
Step D: (3*R*)-3-Amino-6-(4-hydroxyphenyl)azepan-2-one

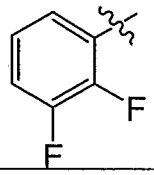
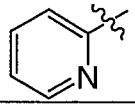
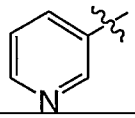
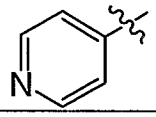
10% palladium on carbon (10 mg) was added to a solution of benzyl (3*R*)-6-(4-hydroxyphenyl)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate (15 mg, 0.043 mmol) in toluene (5 mL) and methanol (1 mL). The reation vessel is evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After 18 h, the mixture was filtered and concentrated. MS 221 (M+1).

Essentially following the procedures outlined for the preparation of Intermediate 12, the Intermediates in Table I-2 were prepared.

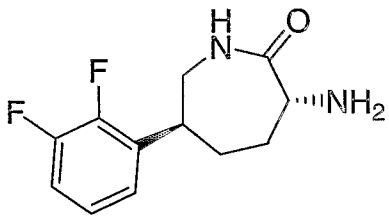
TABLE I-2



Intermediate	C-3	C-6	R^1	MS (M+1)
13	R	R,S		223.2
14	R	R,S		223.2
15	R	R,S		223.2

15a	R	R,S		241.2
16	R	R,S		206.3
17	R	R,S		206.3
18	R	R,S		206.2

INTERMEDIATE 22



(3R,6S)-3-Amino-6-(2,3-difluorophenyl)azepan-2-one

Step A: 2-Bromo-*N*-(2,4-dimethoxybenzyl)prop-2-en-1-amine

Triethylamine (16.0 mL, 114 mmol) was added to a solution of 2,4-dimethoxybenzylamine hydrochloride (11.1 g, 54.5 mmol) and 2,3-dibromopropene (10.9 g, 54.5 mmol) in dichloromethane (200 mL). After 18 h, water was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography [100% dichloromethane → 95% dichloromethane/ 5% (10% ammonium hydroxide/ methanol)] gave the title compound (7.85 g).

Step B: Benzyl (1*R*)-1-{[(2-bromoprop-2-enyl)(2,4-dimethoxybenzyl) amino]carbonyl}but-3-enylcarbamate

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (55 mg, 0.285 mmol) was added to a solution of 2-bromo-*N*-(2,4-dimethoxybenzyl)prop-2-en-1-amine (73 mg, 0.256 mmol)

and (2*R*)-2-{[(benzyloxy)carbonyl]amino}pent-4-enoic acid (71 mg, 0.285 mmol) in dichloromethane (5 mL). After 18 h the mixture was concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 30% ethyl acetate/ hexanes) gave the title compound (77 mg). MS 517 (M+1).

Step C: Benzyl (1R)-1-{[[2-(2,3-difluorophenyl)prop-2-enyl](2,4-dimethoxybenzyl)amino]carbonyl}but-3-enylcarbamate

Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium dichloromethane adduct (0.726 g, 0.889 mmol) was added to a solution of benzyl (1*R*)-1-{[(2-bromoprop-2-enyl)(2,4-dimethoxybenzyl) amino]carbonyl}but-3-enylcarbamate (9.2 g, 17.8 mmol), 2,3-difluorophenylboronic acid (2.95 g, 18.7 mmol) and sodium carbonate (2M in water; 19.6 mL, 39.1 mmol) in *N,N*-dimethylformamide (60 mL) and the mixture was heated to 75 □C. After 2 h, the mixture was allowed to cool to ambient temperature and extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 55% ethyl acetate/ hexanes) gave the title compound (6.8 g). MS 551.2 (M+1).

Step D: Benzyl (3*R*)-6-(2,3-difluorophenyl)-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate

[1,3-bis-(2,4,6-trimethylphenyl-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium] (Grubbs second generation catalyst) (2.62 g, 3.09 mmol) was added to a solution of benzyl (1R)-1-{[[2-(2,3-difluorophenyl)prop-2-enyl](2,4-dimethoxybenzyl)amino]carbonyl}but-3-enylcarbamate (6.8 g, 12.35 mmol) in dichloromethane (1800 mL) and the solution was heated to 40 □C. After 48 h, additional catalyst was added (0.52 g, 0.61 mmol) and the reaction continued to heat at 40 □C for an additional 48 h. The mixture was allowed to cool to ambient temperature and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 55% ethyl acetate/ hexanes) gave the title compound (3.71 g). MS 523.1 (M+1).

Step E: Benzyl (3*R*)-6-(2,3-difluorophenyl)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate

Trifluoroacetic acid (60 mL) was added to a solution of benzyl (3*R*)-6-(2,3-difluorophenyl)-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate (3.70 g, 7.08 mmol) in dichloromethane (40 mL). After 18 h, the mixture was concentrated at 25 □C, methanol (150 mL) was added, and the precipitate filtered. The filtrate was concentrated, diluted with dichloromethane (100 mL), washed with water (2x), saturated aqueous sodium bicarbonate (2x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel

chromatography (5% ethyl acetate/ hexanes → 65% ethyl acetate/ hexanes) gave the title compound (1.75 g). MS 373.1 (M+1).

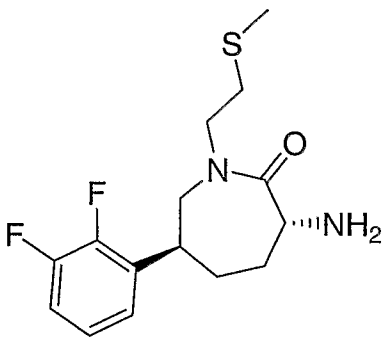
Step F: *tert*-Butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxoazepan-3-ylcarbamate

10% palladium on carbon (700 mg) was added to a solution of benzyl (3*R*)-6-(2,3-difluorophenyl)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate (2.6 g, 6.98 mmol) and di-*tert*-butyl dicarbonate (5.03 g, 23.0 mmol) in toluene (200 mL). The reaction vessel was evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After 24 h, the mixture was filtered and concentrated. Purification by preparative reverse phase chromatography (DeltaPak C18, 15 □, 47 mm x 300 mm, 70 mL/min : 80% H_2O/NH_4OAc : 20% CH_3CN to 100% CH_3CN over 60 min) afforded the pure trans title compound (1.2 g). MS 341.2 (M+1). ^1H NMR (500 MHz, $CDCl_3$) □ 7.07-7.04 (m, 2H), 6.91-6.89 (m,1H), 6.04 (br s, 1H), 5.93 (d, J = 5.6 Hz, 1H), 4.46 (dd, J = 10.5, 4.6 Hz, 1H), 3.65-3.59 (m, 1H), 3.21 (dd, J = 15.1, 7.3 Hz, 1H), 3.05-3.00 (m, 1H), 2.25-2.20 (m, 1 H), 2.17-2.10 (m, 2H), 1.79-1.71 (m, 1H), 1.46 (s, 9H).

Step G: (3R,6S)-3-Amino-6-(2,3-difluorophenyl)azepan-2-one

Trifluoroacetic acid (4 mL) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxoazepan-3-ylcarbamate (82 mg, 0.241 mmol) in dichloromethane (4 mL). After 1 h, the solution was concentrated. Saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. MS 241.0 (M+1)

INTERMEDIATE 23



(3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-[2-(methylthio)ethyl]azepan-2-one

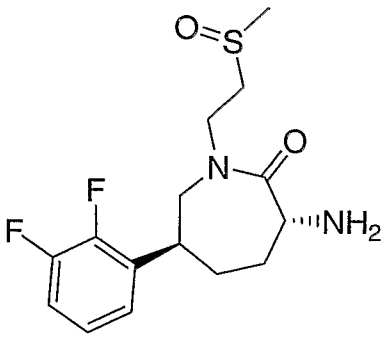
Step A: *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-1-[2-(methylthio)ethyl]-2-oxoazepan-3-ylcarbamate

Sodium hydride (60% dispersion in mineral oil; 40 mg, 0.600 mmol) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxoazepan-3-ylcarbamate (170 mg, 0.500 mmol) in *N*,*N*-dimethylformamide (4 mL) at 0 □C . After 5 min the mixture was cooled to -30 °C and 1-iodo-2-(methylthio)ethane [prepared according to known procedures: J. Org. Chem., 1987, 52, 2299-2301 (158 mg, 0.782 mmol)] was added. Additional sodium hydride (33 mg, 0.50 mmol) was added and after 4 h excess sodium hydride (33 mg, 0.50 mmol) and 1-iodo-2-(methylthio)ethane (75.6 mg, 0.374 mmol) were added. After 3 h, the final portions of sodium hydride (33 mg, 0.50 mmol) and 1-iodo-2-(methylthio)ethane (75.6 mg, 0.374 mmol) were added and the mixture stirred at -20 °C overnight. The reaction was quenched with water and the mixture was extracted with ethyl acetate. The organic layer was washed with water (3x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (0% ethyl acetate/ hexanes → 50% ethyl acetate/ hexanes) gave the title compound (77 mg). MS 415 (M+1).

Step B: (3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-[2-(methylthio)ethyl]azepan-2-one

Trifluoroacetic acid (2 mL) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-1-[2-(methylthio)ethyl]-2-oxoazepan-3-ylcarbamate (77 mg, 0.186 mmol) in dichloromethane (10 mL). After 30 min, the solution was concentrated and azeotroped with toluene (2x). Saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. MS 315.2 (M+1).

INTERMEDIATE 24



(3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-[2-(methylsulfinyl)ethyl]azepan-2-one

Step A: *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-1-[2-(methylsulfinyl)ethyl]-2-oxoazepan-3-ylcarbamate

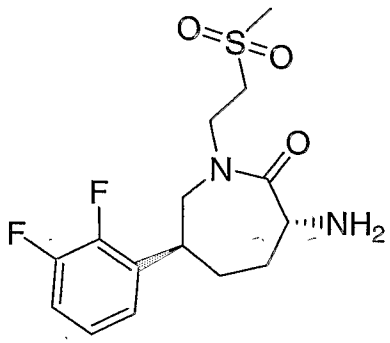
Sodium periodate (11.3 mg, 0.053 mmol) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-1-[2-(methylthio)ethyl]-2-oxoazepan-3-ylcarbamate (22 mg, 0.053 mmol) in

methanol (2 mL) and water (2mL) . After 30 min excess sodium periodate (22 mg, 0.11 mmol) was added. After 18 h, saturated aqueous sodium carbonate was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium carbonate (3x), saturated brine, dried over magnesium sulfate, filtered and concentrated to give the title compound. MS 431 (M+1).

Step B: (3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-[2-(methylsulfinyl)ethyl]azepan-2-one

Trifluoroacetic acid (1 mL) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-1-[2-(methylsulfinyl)ethyl]-2-oxoazepan-3-ylcarbamate (23 mg, 0.053 mmol) in dichloromethane (2 mL). After 3 h, the solution was concentrated. Saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated to give the title compound. MS 331 (M+1).

INTERMEDIATE 25



(3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-[2-(methylsulfonyl)ethyl]azepan-2-one

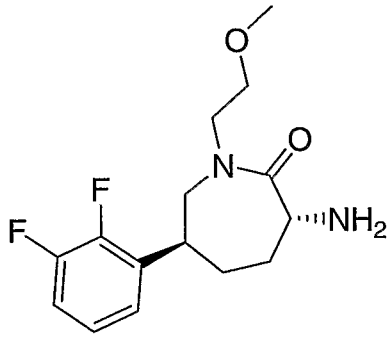
Step A: *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-1-[2-(methylsulfonyl)ethyl]-2-oxoazepan-3-ylcarbamate

Oxone (16.1 mg, 0.11 mmol) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-1-[2-(methylthio)ethyl]-2-oxoazepan-3-ylcarbamate (22 mg, 0.053 mmol) in methanol (2 mL) and water (2mL) . After 6 h excess oxone (32 mg, 0.22 mmol) was added. After 18 h, the reaction was quenched with aqueous sodium sulfite solution and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium carbonate (3x), saturated brine, dried over magnesium sulfate, filtered and concentrated to give the title compound. MS 447 (M+1).

Step B: (3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-[2-(methylsulfonyl)ethyl]azepan-2-one

Trifluoroacetic acid (1 mL) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-1-[2-(methylsulfonyl)ethyl]-2-oxoazepan-3-ylcarbamate (23.7 mg, 0.053 mmol) in dichloromethane (2 mL). After 4 h, the solution was concentrated. Saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated to give the title compound. MS 347 (M+1).

INTERMEDIATE 26



(3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-(2-methoxyethyl)azepan-2-one

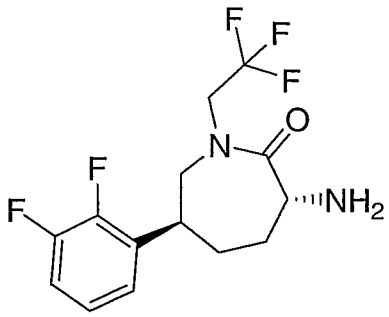
Step A: *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-1-(2-methoxyethyl)-2-oxoazepan-3-ylcarbamate

Sodium hydride (60% dispersion in mineral oil; 17.6 mg, 0.264 mmol) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxoazepan-3-ylcarbamate (75 mg, 0.220 mmol) in *N*,*N*-dimethyl formamide (2 mL) at 0 □C . After 5 min, 2-bromoethyl methyl ether (0.025 mL, 0.264 mmol) was added and the mixture was allowed to warm to ambient temperature. After 3 h, the reaction was quenched with water and the mixture was extracted with ethyl acetate. The organic layer was washed with water (2x), saturated brine, dried over magnesium sulfate, filtered and concentrated to give the title compound. MS 421 (M+Na).

Step B: (3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-(2-methoxyethyl)azepan-2-one

Trifluoroacetic acid (2.5 mL) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-1-(2-methoxyethyl)-2-oxoazepan-3-ylcarbamate (99 mg, 0.248 mmol) in dichloromethane (5 mL). After 1 h, the solution was concentrated and azeotroped with toluene (2x). Saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. MS 299.2 (M+1).

INTERMEDIATE 27



(3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one

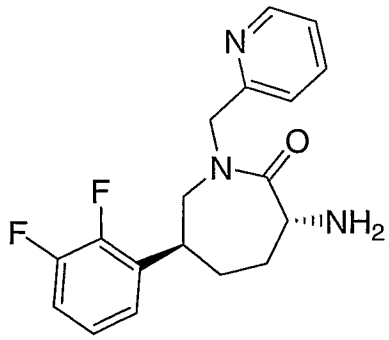
Step A: *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-ylcarbamate

Sodium hydride (60% dispersion in mineral oil; 70.7 mg, 1.06 mmol) was added to a solution of *tert*-butyl (3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxoazepan-3-ylcarbamate (301 mg, 0.884 mmol) in *N*,*N*-dimethylformamide (7 mL) at -35 □C. After 15 min, 2,2,2-trifluoroethyl trichloromethanesulfonate (0.314 mL, 1.91 mmol) was added and the reaction was stirred at -35 °C. After 30 min, an additional amount of sodium hydride (27 mg, 0.40 mmol) and 2,2,2-trifluoroethyl trichloromethanesulfonate (0.140 mL, 0.85 mmol) were added. After 2 h, the reaction was quenched with water and the mixture was extracted with ethyl acetate. The organic layer was washed with water (3x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (0% ethyl acetate/ hexanes → 30% ethyl acetate/ hexanes) gave the title compound (306 mg). MS 423 (M+1).

Step B: (3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one

Trifluoroacetic acid (2.5 mL) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-ylcarbamate (135 mg, 0.320 mmol) in dichloromethane (5 mL). After 30 min, the solution was concentrated and azeotroped with toluene (2x). Saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. MS 323.1 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$) □ 7.11-7.03 (m, 2H), 6.93-6.89 (m, 1H), 4.21-4.13 (m, 1H), 4.10-3.98 (m, 2H), 3.85 (d, *J* = 11.0 Hz, 1H), 3.35 (d, *J* = 15.4 Hz, 1H), 3.04-2.99 (m, 1H), 2.13-2.09 (m, 2H), 2.08-2.02 (m, 1H), 1.78-1.70 (m, 3H).

INTERMEDIATE 28



(3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-(pyridin-2-ylmethyl)azepan-2-one

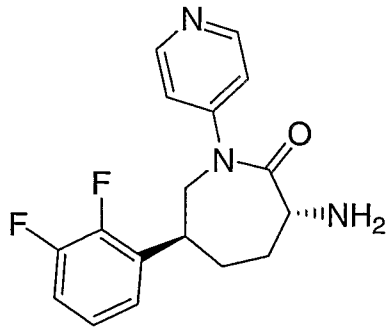
Step A: *tert*-Butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-(pyridin-2-ylmethyl)azepan-3-ylcarbamate

Sodium hydride (60% dispersion in mineral oil; 30 mg, 1.175 mmol) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxoazepan-3-ylcarbamate (160 mg, 0.470 mmol) in *N*,*N*-dimethylformamide (6 mL) at 0 □C . After 30 min, 2-bromomethyl pyridine (0.125 mg, 0.494 mmol) was added. After 1 h, the reaction was quenched with water and the mixture was extracted with ethyl acetate. The organic layer was washed with water (2x), saturated brine, dried over magnesium sulfate, filtered and concentrated to give the title compound (202 mg). MS 432.2 (M+1).

Step B: (3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-(pyridin-2-ylmethyl)azepan-2-on

Trifluoroacetic acid (3 mL) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-(pyridin-2-ylmethyl)azepan-3-ylcarbamate (202 mg, 0.468 mmol) in dichloromethane (4 mL). After 18 h, the solution was concentrated. Saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. MS 332.2 (M+1).

INTERMEDIATE 29



(3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-pyridin-4-ylazepan-2-one

Step A: *tert*-Butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-pyridin-4-ylazepan-3-ylcarbamate

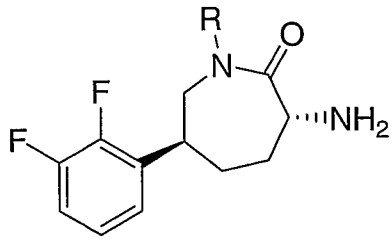
4-Bromopyridine (286 mg, 1.47 mmol) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxoazepan-3-ylcarbamate (200 mg, 0.588 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (20 mg, 0.035 mmol), tris(dibenzylideneacetone)dipalladium(0) (22 mg, 0.024 mmol), and cesium carbonate (268 mg, 0.823 mmol) in dioxane (6 mL) and the mixture was heated at 150 □C in a Personal Chemistry Smith Creator microwave reactor. After 30 min, an additional amount of 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (20 mg, 0.035 mmol) and tris(dibenzylideneacetone)dipalladium(0) (22 mg, 0.024 mmol) were added. After 30 min, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with water (2x), saturated brine, dried over magnesium sulfate, filtered and concentrated to give the title compound (55 mg). MS 418.2 (M+1).

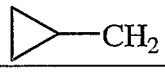
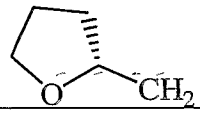
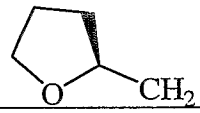
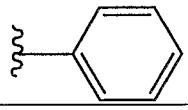
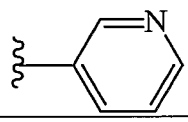
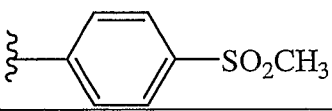
Step B: (3R,6S)-3-Amino-6-(2,3-difluorophenyl)-1-pyridin-4-ylazepan-2-one

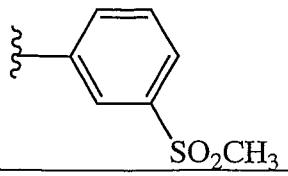
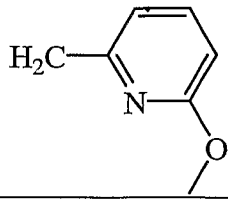
Trifluoroacetic acid (2 mL) was added to a solution of *tert*-butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-pyridin-4-ylazepan-3-ylcarbamate (55 mg, 0.132 mmol) in dichloromethane (2 mL). After 1 h, the solution was concentrated. Saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. MS 318.2 (M+1).

Essentially following the procedures outlined for the preparation of Intermediates 23-28, the Intermediates in Table I-3 were prepared.

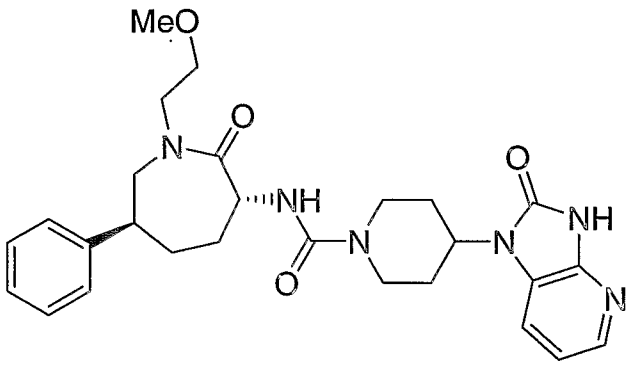
TABLE I-3



Intermediate	R	MS (M+1)
30	CH_3	255.2
31	CH_2CH_3	269.2
32		295.2
33	CH_2CH_2F	287
34	CH_2CHF_2	305.1
35		325.2
36		325.2
37	$CH_2CO_2CH_3$	313.1
38		317.2
39		318.1
40		395.1

41		395.1
42		362.2

EXAMPLE 1

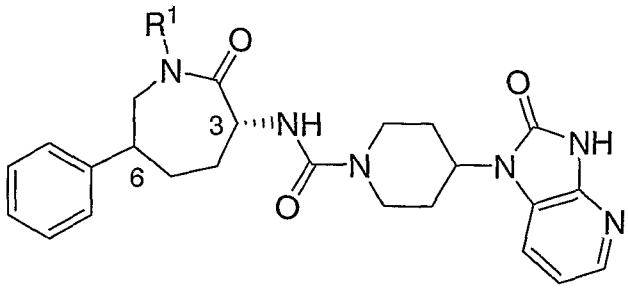


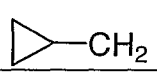
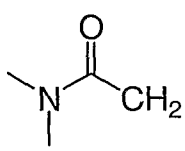
N-[(3*R*,6*S*)-1-(2-Methoxyethyl)-2-oxo-6-phenylazepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide

Triethylamine (0.015 mL, 0.107 mmol) was added to a solution of (3*R*,6*S*)-3-amino-1-(2-methoxyethyl)-6-phenylazepan-2-one (28 mg, 0.107 mmol) and 4-nitrophenyl chloroformate (22 mg, 0.107 mmol) in tetrahydrofuran (2 mL) at 0 □C. After 30 min, 2-oxo-1-piperidinium-4-yl-2,3-dihydro-1H-imidazo[4,5-b]pyridin-4-ium dichloride (37 mg, 0.128 mmol), diisopropylethylamine (0.074 mL, 0.427 mmol) and dichloromethane (2.5 mL) were added and the mixture allowed to warm to ambient temperature. After 18 h, saturated aqueous sodium carbonate was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium carbonate (3x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (100% dichloromethane → 93% dichloromethane/ methanol) gave the title compound (45 mg). MS 507.2737 (M+1).

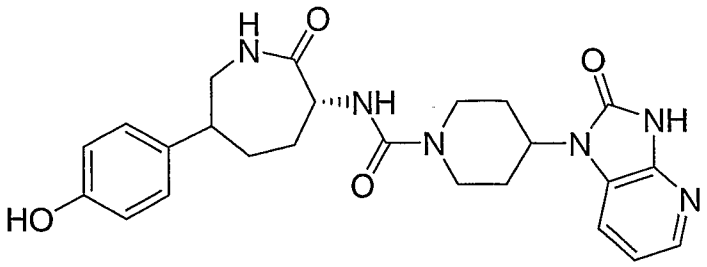
Essentially following the procedures outlined for the preparation of Example 1, the Examples in Table E-1 were prepared.

TABLE E-1



Examples	C-3	C-6	R^1	MS (M+1)
2	R	S	H	449
3	R	R	H	449
4	R	S	CH_3	463
5	R	S	CH_2CH_3	477
6	R	S	CH_2CF_3	531.2326
7	R	S	$CH_2CO_2CH_3$	521.2481
8	R	S	CH_2CO_2H	507.2353
9	R	S	$(CH_2)_2OCH_2CH_3$	521.2910
10	R	S	CH_2CN	488.2378
11	R	S	$(CH_2)_2OH$	493.2555
12	R	S		503
13	R	S		534.2791

EXAMPLE 14

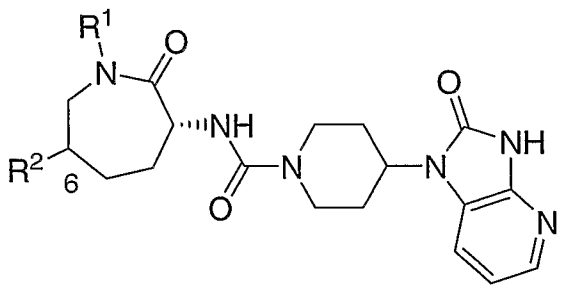


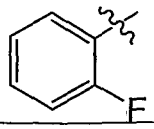
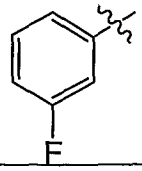
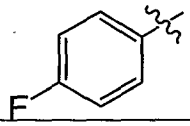
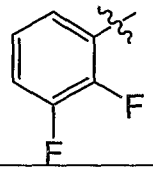
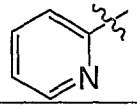
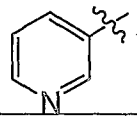
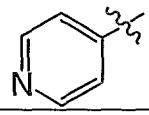
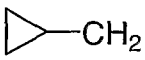
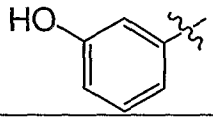
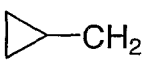
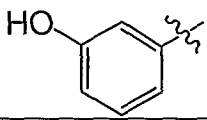
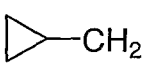
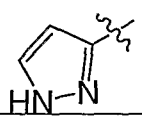
N-[(3*R*)-6-(4-Hydroxyphenyl)-2-oxoazepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide

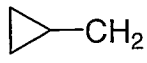
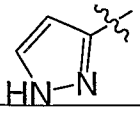
Triethylamine (0.009 mL, 0.091 mmol) was added to a solution of (3*R*)-3-amino-6-(4-hydroxyphenyl)azepan-2-one (10 mg, 0.045 mmol) and 4-nitrophenyl chloroformate (18 mg, 0.091 mmol) in *N*,*N*-dimethylformamide (0.2 mL) and tetrahydrofuran (0.2 mL) at 0 □C. After 1 h, 2-oxo-1-piperidinium-4-yl-2,3-dihydro-1H-imidazo[4,5-b]pyridin-4-ium dichloride (26 mg, 0.091 mmol) and diisopropylethylamine (0.032 mL, 0.182 mmol) were added and the mixture was allowed to warm to ambient temperature. After 18 h, the mixture was purified by reverse phase HPLC (C-18, 95% water/ acetonitrile → 5% water/ acetonitrile with 0.1% trifluoroacetic acid) to give the title compound (7 mg). MS 465.2243 (M+1).

Essentially following the procedures outlined for the preparation of Example 14, the Examples in Table E-2 were prepared.

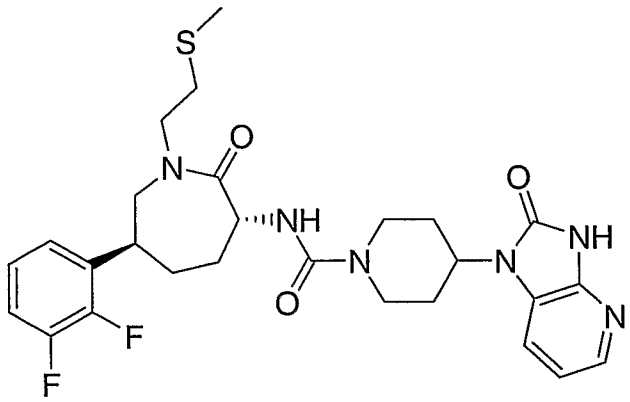
TABLE E-2



Examples	C-6	R^1	R^2	MS (M+1)
15	R,S	H		467.2189
16	R,S	H		467.2201
17	R,S	H		467.2203
17a	R,S	H		485.2076
18	R,S	H		450
19	R,S	H		450.2241
20	R,S	H		450.2262
21	R,S			519
22	S			519
23	S			493

24	R			493

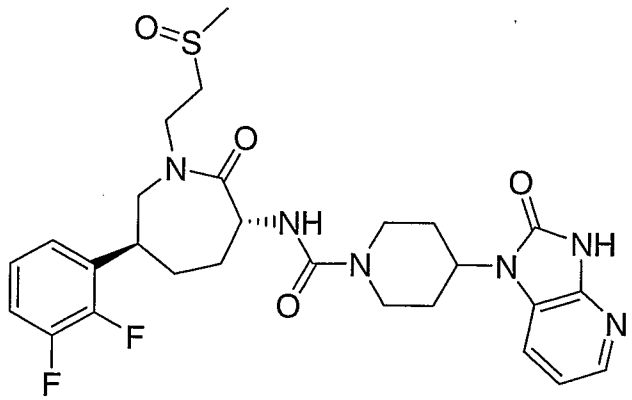
EXAMPLE 34



N-{(3R,6S)-6-(2,3-difluorophenyl)-1-[2-(methylthio)ethyl]-2-oxoazepan-3-yl}-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide

Triethylamine (0.020 mL, 0.143 mmol) was added to a solution of (3R,6S)-3-amino-6-(2,3-difluorophenyl)-1-[2-(methylthio)ethyl]azepan-2-one (45 mg, 0.143 mmol) and 4-nitrophenyl chloroformate (29 mg, 0.143 mmol) in tetrahydrofuran (3 mL) at 0 □C. After 15 min, 2-oxo-1-piperidinium-4-yl-2,3-dihydro-1H-imidazo[4,5-b]pyridin-4-ium dichloride (46 mg, 0.157 mmol), triethylamine (0.080 mL, 0.572 mmol) and dichloromethane (5 mL) were added and the mixture was heated to 50 □C. After 30 min, the mixture was allowed to cool to ambient temperature and concentrated. Purification by silica gel chromatography [100% dichloromethane → 95% dichloromethane/ methanol (10% ammonium hydroxide/ methanol)] gave the title compound (60 mg). The title compound was converted to the HCl salt with 2M HCl in ether. MS 559.2 (M+1). ^{1}H NMR (500 MHz, CD_3OD) □ 8.11 (dd, *J* = 7.8 Hz, 1.0 Hz, 1H), 7.99 (dd, *J* = 6.1 Hz, 1.0 Hz, 1H), 7.38-7.35 (m, 1H), 7.18-7.14 (m, 3H), 4.76 (d, *J* = 10.7 Hz, 1H), 4.61-4.54 (m, 1H), 4.31-4.26 (m, 2H), 4.15-4.09 (m, 1H), 3.85-3.80 (m, 1H), 3.67-3.58 (m, 1H), 3.37 (d, *J* = 15.4 Hz, 1H), 3.20-3.16 (m, 1H), 3.08-2.96 (m, 2H), 2.75-2.70 (m, 2H), 2.49-2.41 (m, 1H), 2.34-2.26 (m, 1H), 2.21-2.16 (m, 1H), 2.14 (s, 3H), 2.11-2.07 (m, 2H), 1.90-1.85 (m, 3H).

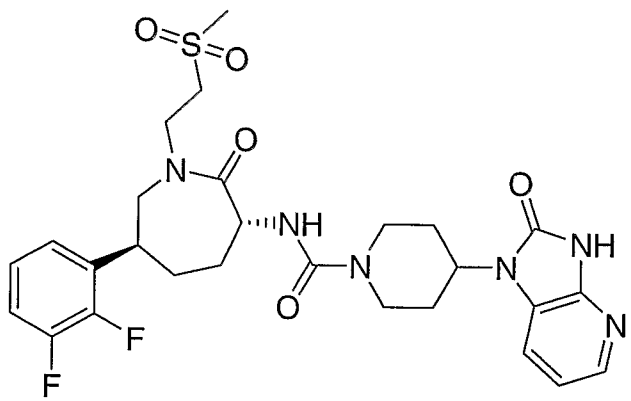
EXAMPLE 35



N-{(3R,6S)-6-(2,3-difluorophenyl)-1-[2-(methylsulfinyl)ethyl]-2-oxoazepan-3-yl}-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide

Triethylamine (0.010 mL, 0.027 mmol) was added to a solution of (3R,6S)-3-amino-6-(2,3-difluorophenyl)-1-[2-(methylsulfinyl)ethyl]azepan-2-one (8.9 mg, 0.027 mmol) and 4-nitrophenyl chloroformate (5.4 mg, 0.027 mmol) in tetrahydrofuran (0.700 mL) at 0 □C. After 45 min, 2-oxo-1-piperidinium-4-yl-2,3-dihydro-1H-imidazo[4,5-b]pyridin-4-ium dichloride (7.9 mg, 0.027 mmol) and triethylamine (0.040 mL, 0.108 mmol) were added and the mixture allowed to warm to ambient temperature. After 16 h, the mixture was concentrated. Purification by reverse phase HPLC (C-18, 95% water/acetonitrile → 5% water/acetonitrile with 0.1% trifluoroacetic acid) gave the title compound. MS 575 (M+1).

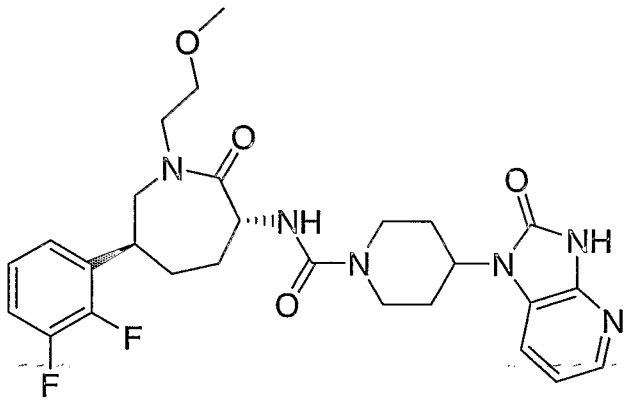
EXAMPLE 36



N-{(3R,6S)-6-(2,3-difluorophenyl)-1-[2-(methylsulfonyl)ethyl]-2-oxoazepan-3-yl}-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide

Triethylamine (0.010 mL, 0.023 mmol) was added to a solution of (3R,6S)-3-amino-6-(2,3-difluorophenyl)-1-[2-(methylsulfonyl)ethyl]azepan-2-one (8 mg, 0.023 mmol) and 4-nitrophenyl chloroformate (4.6 mg, 0.023 mmol) in tetrahydrofuran (0.700 mL) at 0 □C. After 15 min, 2-oxo-1-piperidinium-4-yl-2,3-dihydro-1H-imidazo[4,5-b]pyridin-4-ium dichloride (6.7 mg, 0.023 mmol) and triethylamine (0.040 mL, 0.092 mmol) were added and the mixture allowed to warm to ambient temperature. After 16 h, the mixture was concentrated. Purification by reverse phase HPLC (C-18, 95% water/acetonitrile → 5% water/acetonitrile with 0.1% trifluoroacetic acid) gave the title compound. MS 591 (M+1).

EXAMPLE 37

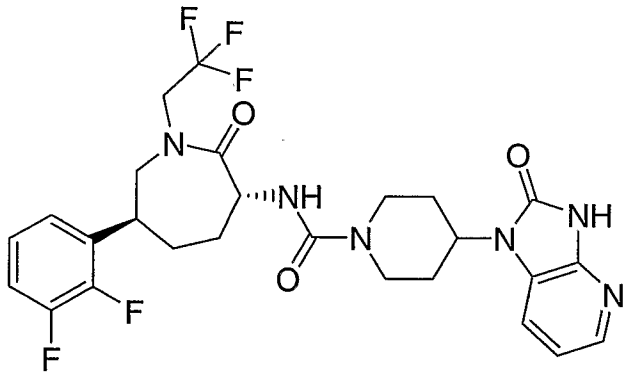


N-[(3R,6S)-6-(2,3-difluorophenyl)-1-(2-methoxyethyl)-2-oxoazepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide

Triethylamine (0.030 mL, 0.218 mmol) was added to a solution of (3R,6S)-3-amino-6-(2,3-difluorophenyl)-1-(2-methoxyethyl)azepan-2-one (65 mg, 0.218 mmol) and 4-nitrophenyl chloroformate (44 mg, 0.218 mmol) in tetrahydrofuran (3 mL) at 0 □C. After 30 min, 2-oxo-1-piperidinium-4-yl-2,3-dihydro-1H-imidazo[4,5-b]pyridin-4-ium dichloride (70 mg, 0.240 mmol), triethylamine (0.120 mL, 0.872 mmol), and dichloromethane (5 mL) were added and the mixture allowed to warm to ambient temperature. After 4.5 h, the mixture was concentrated. Purification by silica gel chromatography [100% dichloromethane → 95% dichloromethane/ methanol (10% ammonium hydroxide/ methanol)] gave the title compound (88 mg). The title compound was converted to the HCl salt with 2M HCl in ether. MS 543.3 (M+1). ^{1}H NMR (500 MHz, CD_3OD) □ 8.09 (dd, J = 7.8 Hz, 1.0 Hz, 1H), 7.99 (dd, J = 6.1 Hz, 1.0 Hz, 1H), 7.36(m, 1H), 7.17-7.10 (m, 3H), 4.78 (d, J = 11.0 Hz, 1H),

4.61-4.54 (m, 1H), 4.31-4.24 (m, 2H), 4.18-4.13 (m, 1H), 3.94-3.89 (m, 1H), 3.57-3.53 (m, 2H), 3.48-3.43 (m, 1H), 3.39 (d, J = 15.1 Hz, 1H), 3.34 (s, 3H), 3.19-3.15 (m, 1H), 3.07-2.96 (m, 2H), 2.49-2.41 (m, 1H), 2.35-2.26 (m, 1H), 2.19-2.06 (m, 3H), 1.90-1.76 (m, 3H).

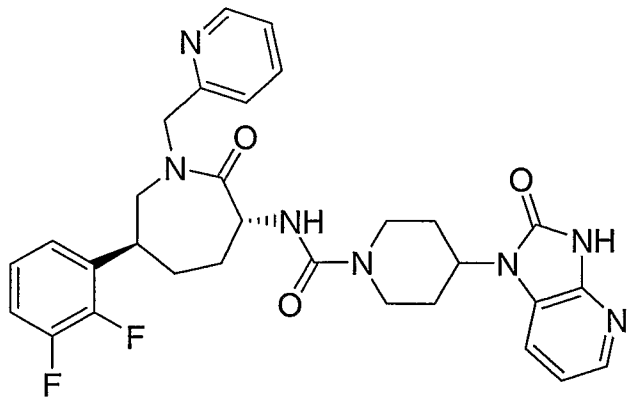
EXAMPLE 38



N-[(3R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide

Triethylamine (0.038 mL, 0.276 mmol) was added to a solution of (3R,6S)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one (89 mg, 0.276 mmol) and 4-nitrophenyl chloroformate (56 mg, 0.276 mmol) in tetrahydrofuran (3 mL) at 0 □C. After 30 min, 2-oxo-1-piperidinium-4-yl-2,3-dihydro-1H-imidazo[4,5-b]pyridin-4-ium dichloride (88 mg, 0.304 mmol), triethylamine (0.152 mL, 1.104 mmol), and dichloromethane (5 mL) were added and the mixture allowed to warm to ambient temperature. After 48 h, the mixture was concentrated. Purification by silica gel chromatography [100% dichloromethane → 95% dichloromethane/ methanol (10% ammonium hydroxide/ methanol)] gave the title compound (98 mg). The title compound was converted to the HCl salt with 2M HCl in ether. MS 567.2 (M+1). ^{1}H NMR (500 MHz, CD_3OD) □ 8.11 (dd, J = 7.8 Hz, 1.0 Hz, 1H), 8.00 (dd, J = 5.9 Hz, 1.0 Hz, 1H), 7.34- 7.31 (m, 1H), 7.19-7.13 (m, 3H), 4.86-4.83 (m,1H), 4.62-4.57 (m, 1H), 4.49-4.41 (m, 1H), 4.33-4.25 (m, 3H), 4.12-4.04 (m, 1H), 3.51-3.46 (m, 1H), 3.18-3.14 (m, 1H), 3.09-2.96 (m, 2H), 2.51-2.44 (m, 1H), 2.33-2.25 (m, 1H), 2.22-2.10 (m, 3H), 1.90-1.81 (m, 3H).

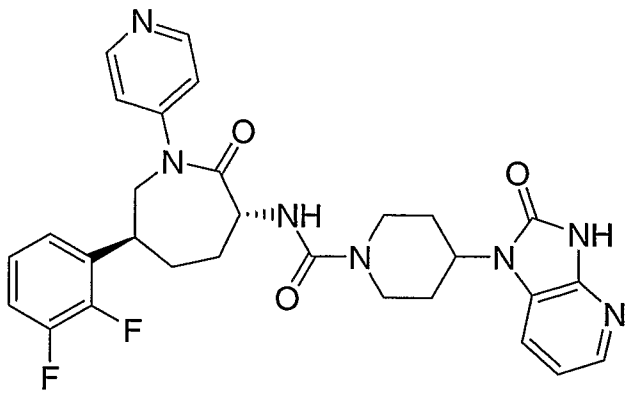
EXAMPLE 39



N-[(3R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-(pyridin-2-ylmethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide

Triethylamine (0.065 mL, 0.468 mmol) was added to a solution of (3R,6S)-3-amino-6-(2,3-difluorophenyl)-1-(pyridin-2-ylmethyl)azepan-2-one (180 mg, 0.417 mmol) and 4-nitrophenyl chloroformate (94 mg, 0.468 mmol) in tetrahydrofuran (3 mL) at 0 □C. After 1 h, 2-oxo-1-piperidinium-4-yl-2,3-dihydro-1H-imidazo[4,5-b]pyridin-4-ium dichloride (136 mg, 0.468 mmol) and triethylamine (0.195 mL, 1.404 mmol) were added and the mixture allowed to warm to ambient temperature. After 18 h, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with water (2x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography [100% dichloromethane → 95% dichloromethane/ methanol (10% ammonium hydroxide/ methanol)] gave the title compound (240 mg). The title compound was converted to the HCl salt with 2M HCl in ether. MS 576.3 (M+1). ^{1}H NMR (500 MHz, CD_3OD) □ 8.78 (d, *J* = 5.9 Hz, 1H), 8.62-8.59 (m, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 8.03-7.98 (m, 3H), 7.32 (dd, *J* = 8.1 Hz, 6.1, 1H), 7.18-7.15 (m, 3H), 5.43 (d, *J* = 16.9 Hz, 1H), 4.75 (d, *J* = 17.1 Hz, 1H), 4.56-4.51 (m, 1H), 4.36-4.28 (m, 3H), 3.51 (d, *J* = 15.1 Hz, 1H), 3.48 (s, 1H), 3.22-3.17 (m, 1H), 3.05-2.98 (m, 2H), 2.44-2.40 (m, 1H), 2.34-2.23 (m, 2H), 2.18-2.14 (m, 2H), 1.97-1.92 (m, 1H), 1.89-1.88 (m, 2H).

EXAMPLE 40

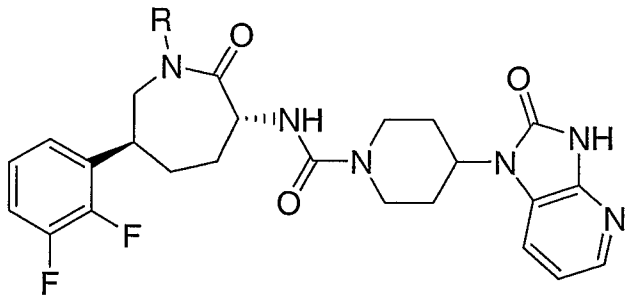


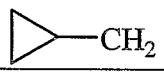
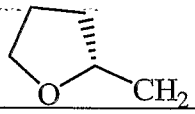
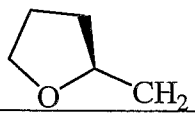
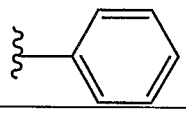
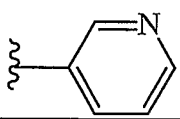
N-[(3R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-pyridin-4-ylazepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide

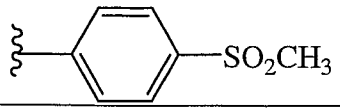
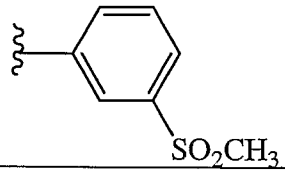
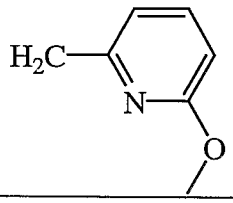
Triethylamine (0.018 mL, 0.132 mmol) was added to a solution of (3R,6S)-3-amino-6-(2,3-difluorophenyl)-1-pyridin-4-ylazepan-2-one (42 mg, 0.132 mmol) and 4-nitrophenyl chloroformate (27 mg, 0.132 mmol) in tetrahydrofuran (2 mL) at 0 □C. After 1 h, 2-oxo-1-piperidinium-4-yl-2,3-dihydro-1H-imidazo[4,5-b]pyridin-4-ium dichloride (38 mg, 0.132 mmol) and triethylamine (0.054 mL, 0.396 mmol) were added and the mixture allowed to warm to ambient temperature. After 18 h, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with water (2x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography [100% dichloromethane → 95% dichloromethane/ methanol (10% ammonium hydroxide/ methanol)] gave the title compound (53 mg). The title compound was converted to the HCl salt with 2M HCl in ether. MS 562.2 (M+1). ^{1}H NMR (500 MHz, CD_3OD) □ 8.76 (d, J = 7.6 Hz, 2H), 8.11 (d, J = 7.3 Hz, 2H), 8.00 (d, J = 6.4 Hz, 2H), 7.30 (t, J = 7.0 Hz, 1H), 7.27-7.21 (m, 3H), 5.11 (d, J = 11.5 Hz, 1H), 4.72-4.65 (m, 1H), 4.60-4.55 (m, 1H), 4.35-4.33 (m, 2H), 4.14 (d, J = 16.1 Hz, 1H), 3.42-3.39 (m, 1H), 3.09-3.02 (m, 2H), 2.47-2.44 (m, 1H), 2.37-2.30 (m, 2H), 2.24-2.18 (m, 2H), 2.06-2.03 (m, 1H), 1.91 (br. s, 2H).

Essentially following the procedures outlined for the preparation of Examples 34-40, the Examples in Table E-4 were prepared.

TABLE E-4



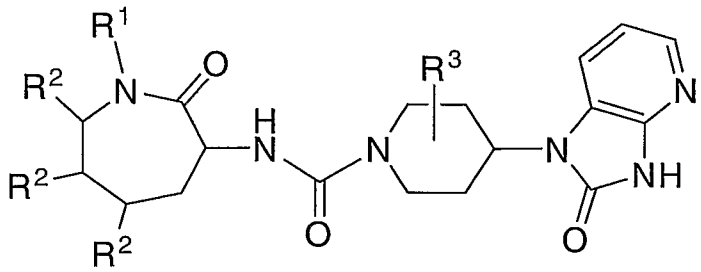
Example	R	MS (M+1)
41	CH_3	499.2
42	CH_2CH_3	513.2
43		539.3
44	CH_2CH_2F	531.1
45	CH_2CHF_2	549.1
46		569.3
47		569.3
48	$CH_2CO_2CH_3$	557.2
49		561.2
50		562.2

51		639.2
52		639.2
53		606.3

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above.

WHAT IS CLAIMED IS:

1. A compound of the Formula I:



I

wherein:

R^1 is selected from:

H, C_1-C_6 alkyl, C_{3-6} cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents independently selected from:

C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, heteroaryl, heterocycle, $(F)_pC_{1-3}$ alkyl, halogen, OR^4, $O(CH_2)_sOR^4$, CO_2R^4, CN, $NR^{10}R^{11}$, $O(CO)R^4$,

where said phenyl, said heteroaryl and said heterocycle are each independently unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,

where said heteroaryl is selected from: imidazole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, and thiazole;

where said heterocycle is selected from: azetidine, dioxane, dioxolane, morpholine, oxetane, piperazine, piperidine, pyrrolidine, tetrahydrofuran, and tetrahydropyran;

aryl, or heteroaryl selected from: phenyl, imidazole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, and thiazole,

where said aryl and said heteroaryl are each independently unsubstituted or substituted with one or more substituents independently selected from: C_{1-6} alkyl, C_{3-6} cycloalkyl, $(F)_pC_{1-3}$ alkyl, halogen, OR^4, CO_2R^4, $(CO)NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$, $N(R^{10})SO_2R^{11}$, $S(O)_mR^4$, CN, $NR^{10}R^{11}$ and $O(CO)R^4$;

R^2 is selected from:

H, C_0-C_6 alkyl, C_{3-6} cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents independently selected from:

C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, heteroaryl, heterocycle, $(F)_pC_{1-3}$ alkyl, halogen, OR^4, $O(CH_2)_sOR^4$, CO_2R^4, CN, $NR^{10}R^{11}$ and $O(CO)R^4$,

where said phenyl, said heteroaryl, and said heterocycle are each independently unsubstituted or substituted with 1-5 substituents independently selected from R^4,

where said heteroaryl is selected from: benzimidazole, benzothiophene, furan, imidazole, indole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiazole, thiophene, and triazole;

where said heterocycle is selected from: azetidine, imidazolidine, imidazoline, isoxazoline, isoxazolidine, morpholine, oxazoline, oxazolidine, oxetane, pyrazolidine, pyrazoline, pyrroline, tetrahydrofuran, tetrahydropyran, thiazoline, and thiazolidine;

aryl or heteroaryl, selected from: phenyl, benzimidazole, benzothiophene, furan, imidazole, indole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiazole, thiophene, and triazole;

where said aryl and said heteroaryl are each independently unsubstituted or substituted with one or more substituents independently selected from: C_{1-6} alkyl, C_{3-6} cycloalkyl,

$(F)_pC_{1-3}$ alkyl, halogen, OR^4, CO_2R^4, $(CO)NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$, $N(R^{10})$ SO_2R^{11}, $S(O)_mR^4$, CN, $NR^{10}R^{11}$ and $O(CO)R^4$;

R^{10} and R^{11} are independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_1-C_6 alkoxy, where R^{10} and R^{11} may be joined together to form a ring selected from: azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4;

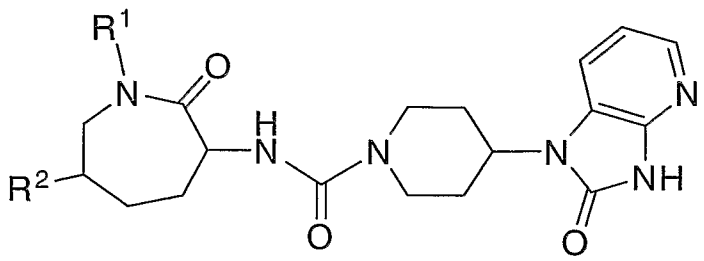
R^4 is independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and phenyl, unsubstituted or substituted with hydroxy or C_1-C_6 alkoxy;

R^3 is independently selected from H, substituted or unsubstituted C_1-C_3 alkyl, CN and CO_2R^4;

p is 0 to 2q+1, for a substituent with q carbons;
m is 0, 1 or 2;
s is 1, 2 or 3;

and pharmaceutically acceptable salts and individual diastereomers thereof.

2. A compound of the Formula:



wherein:

R^1 is selected from:

C_1-C_6 alkyl unsubstituted or substituted with one or more substituents independently selected from:C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, heteroaryl, heterocycle, $(F)_pC_{1-3}$ alkyl, halogen, OR^4, $O(CH_2)_sOR^4$, CO_2R^4, CN, $NR^{10}R^{11}$, and $O(CO)R^4$,

R^2 is selected from:

aryl, unsubstituted or substituted with one or more substituents independently selected from: C_{1-6} alkyl, C_{3-6} cycloalkyl, $(F)_pC_{1-3}$ alkyl, halogen, OR^4, CO_2R^4, $(CO)NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$, $N(R^{10})$ SO_2R^{11}, $S(O)_mR^4$, CN, $NR^{10}R^{11}$ and $O(CO)R^4$;

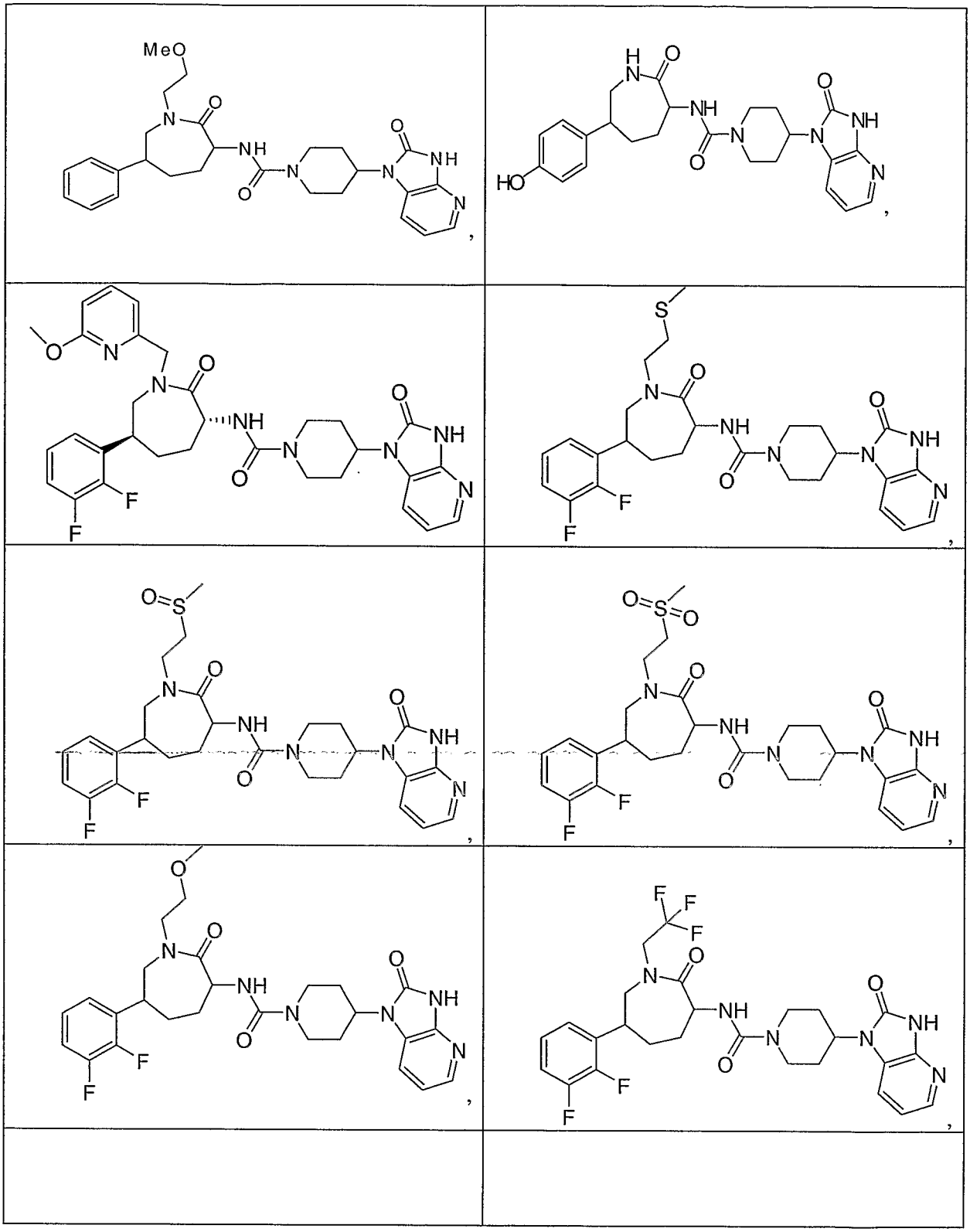
R^{10} and R^{11} are independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_1-C_6 alkoxy, where R^{10} and R^{11} may be joined together to form a ring selected from: azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4;

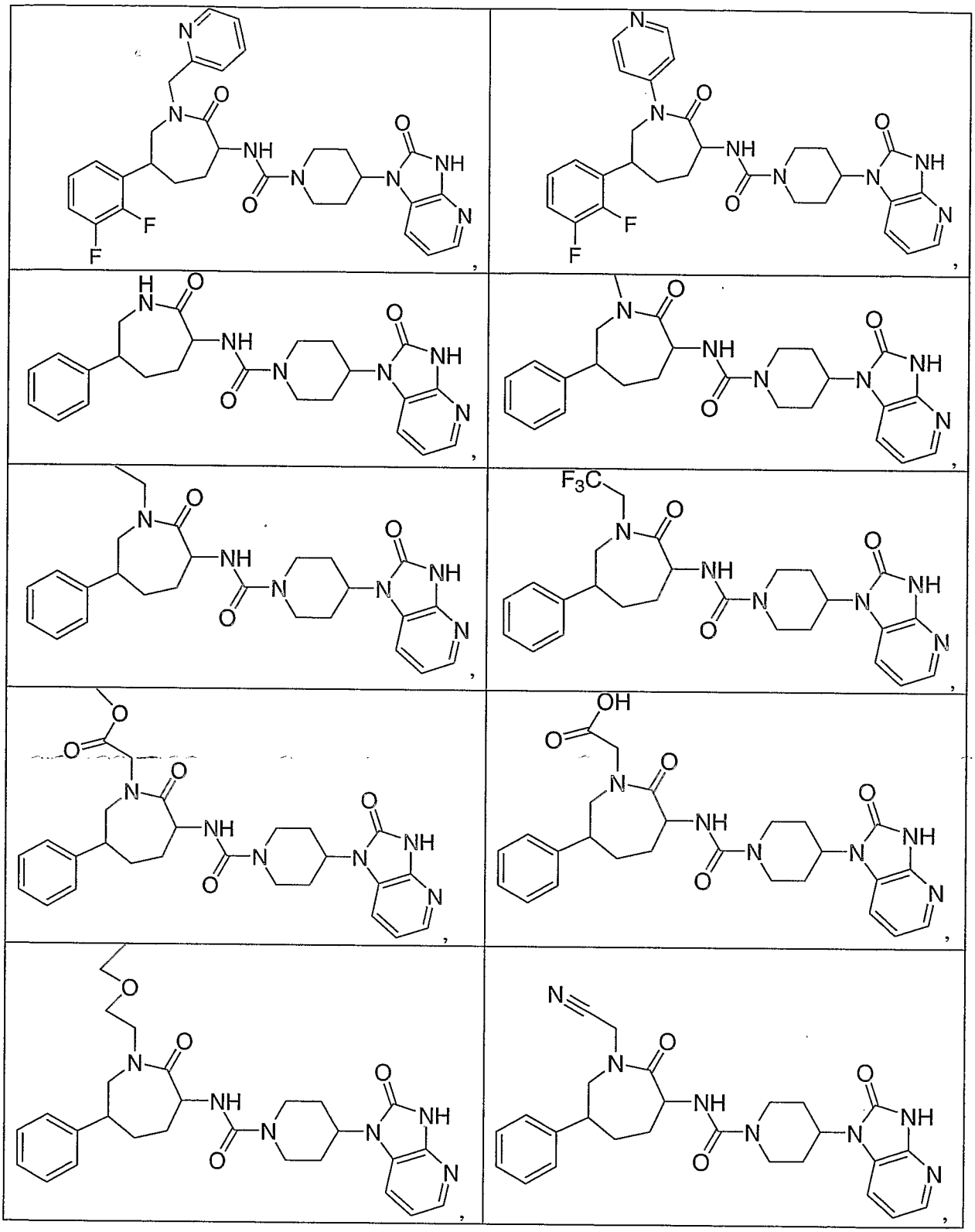
R^4 is independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and phenyl, unsubstituted or substituted with hydroxy or C_1-C_6 alkoxy;

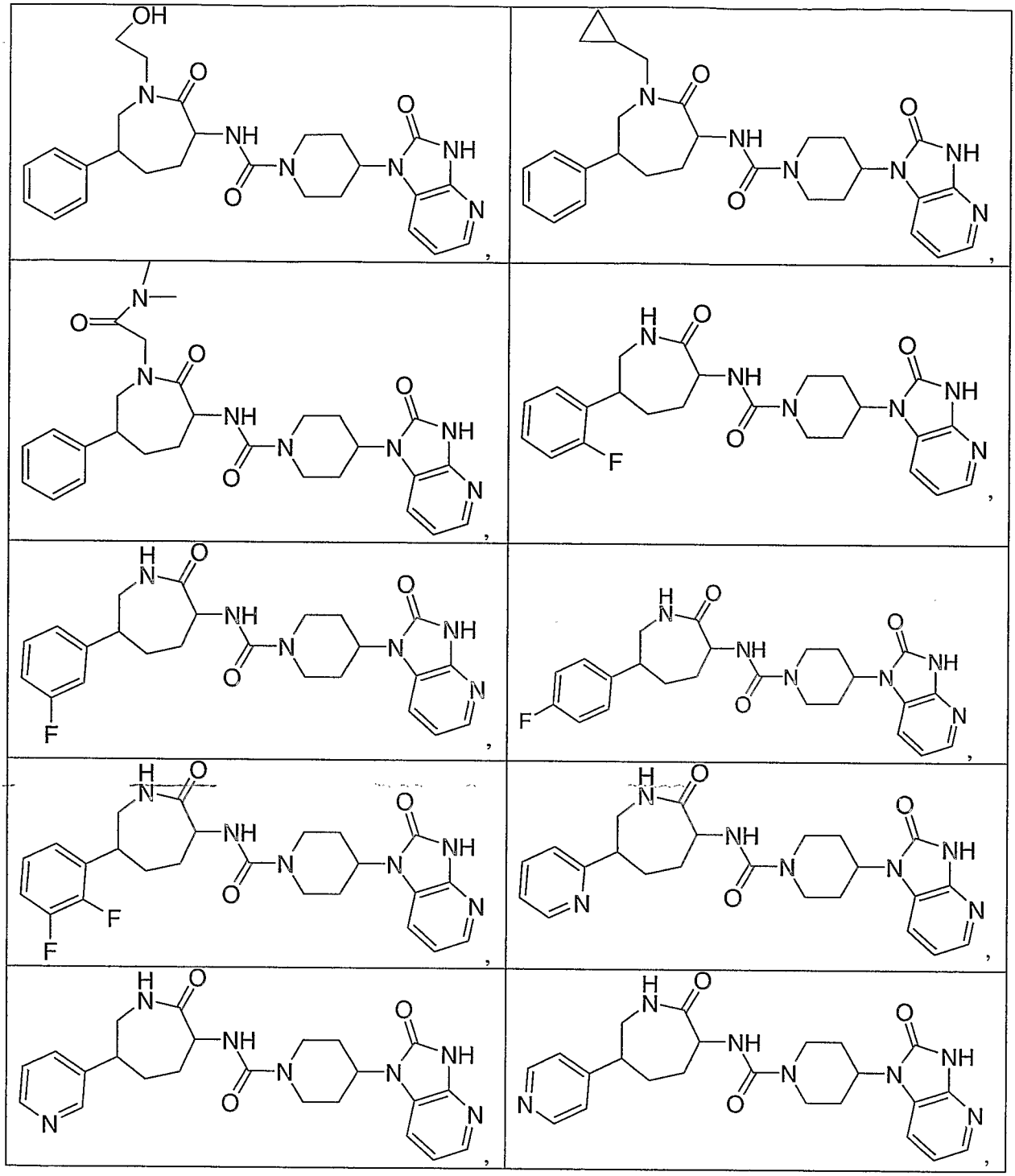
p is 0 to 2q+1, for a substituent with q carbons;
m is 0, 1 or 2;
s is 1, 2 or 3;

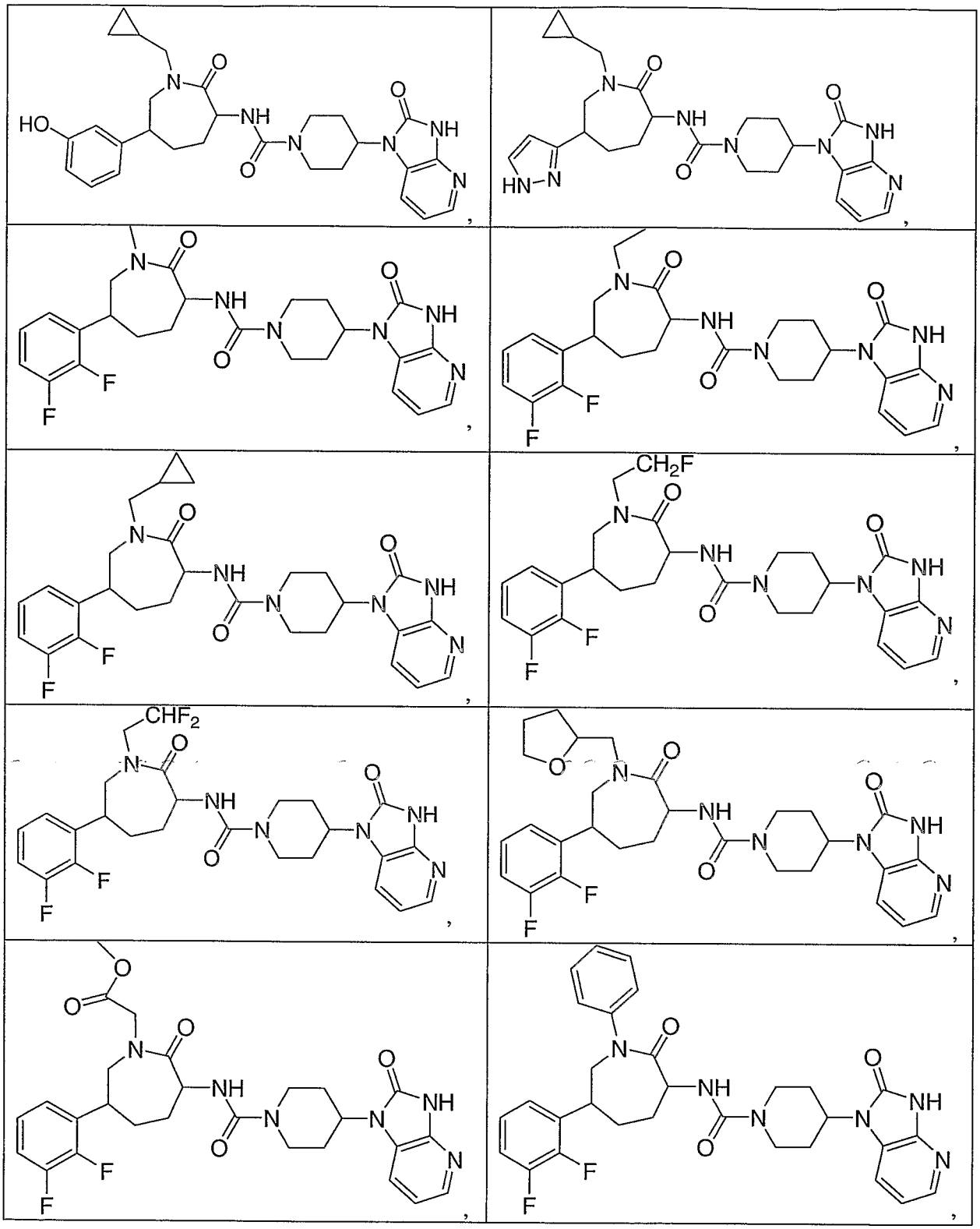
and pharmaceutically acceptable salts and individual diastereomers thereof.

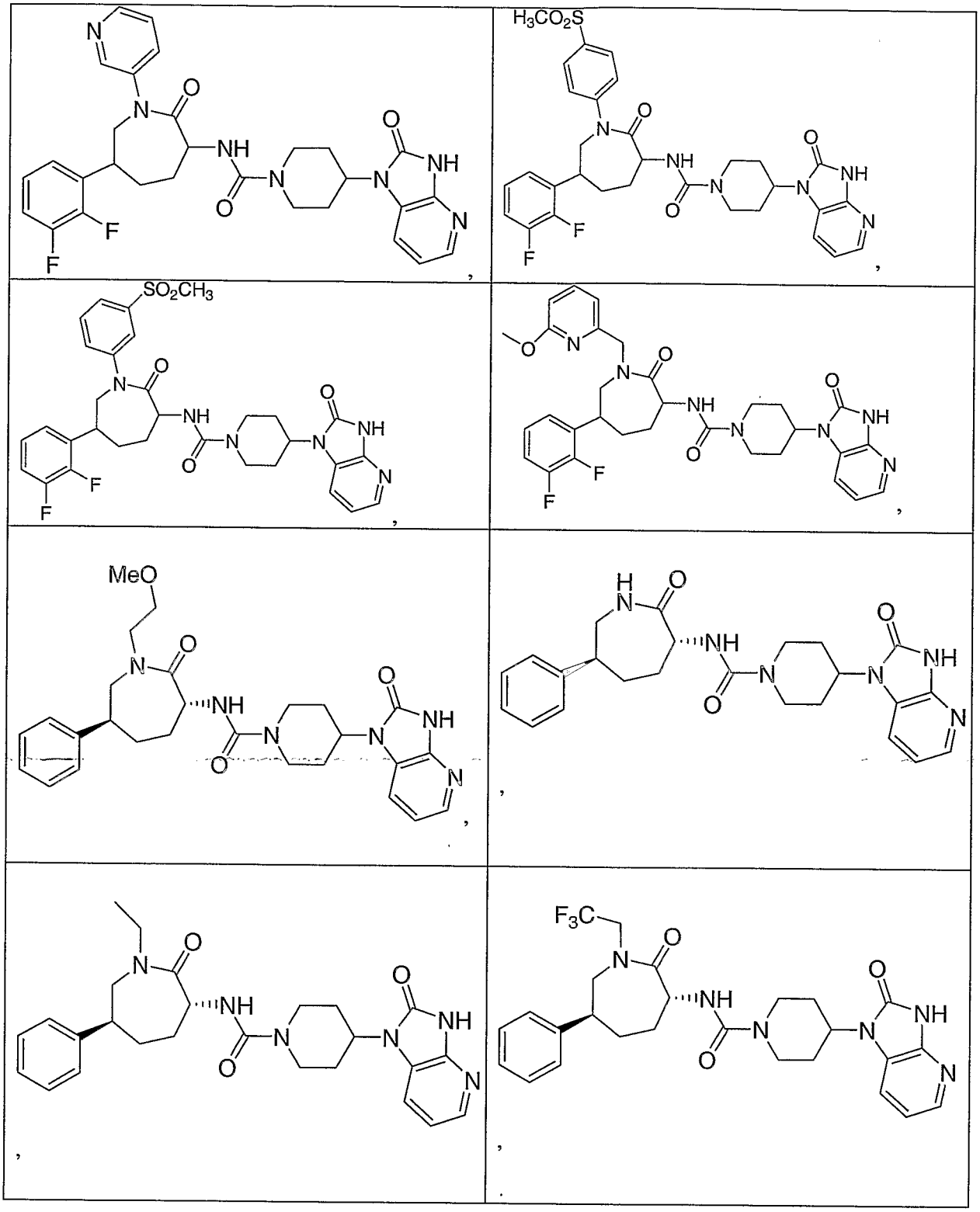
3. A compound selected from:

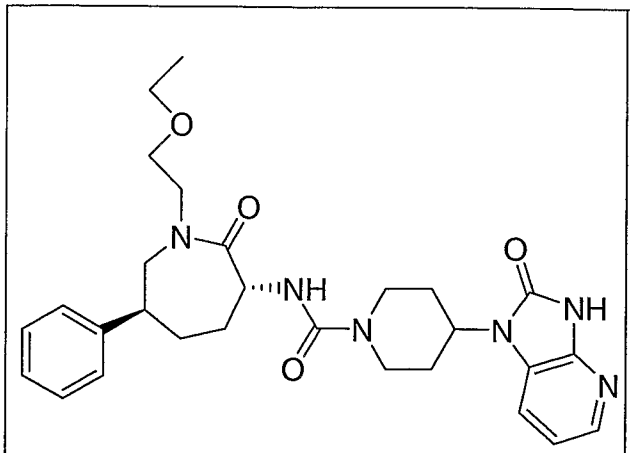


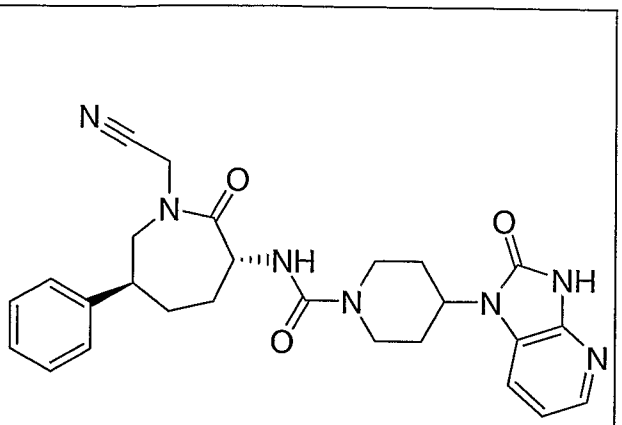


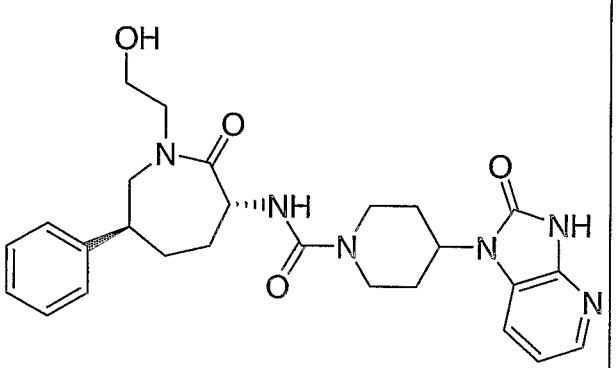


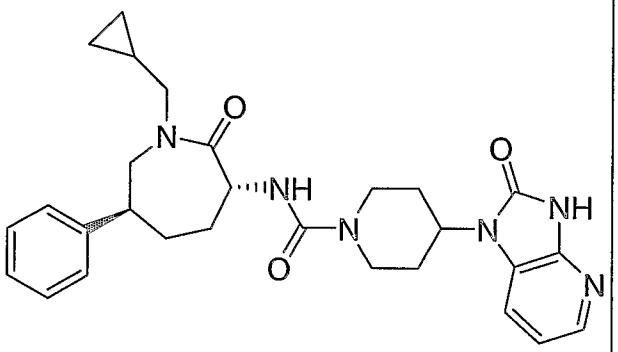


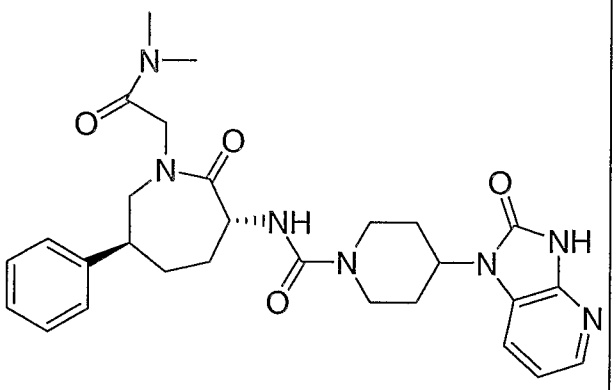


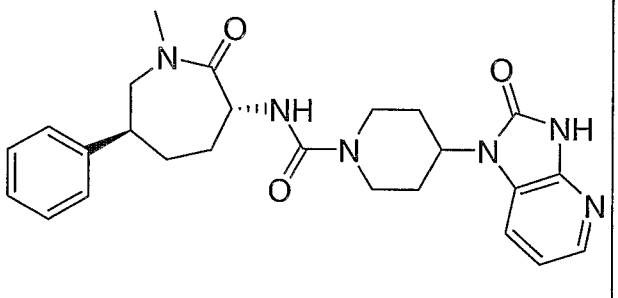

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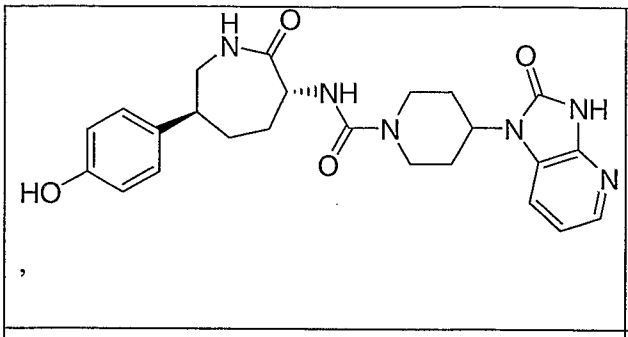

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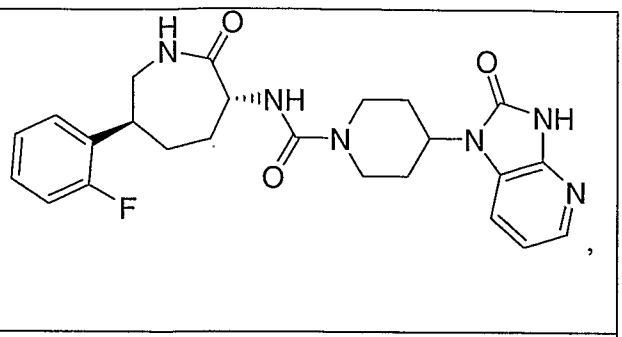

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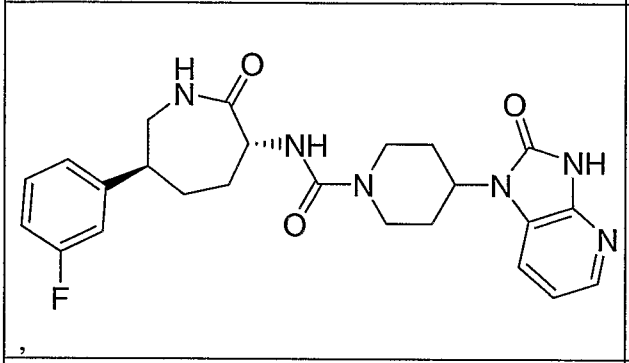

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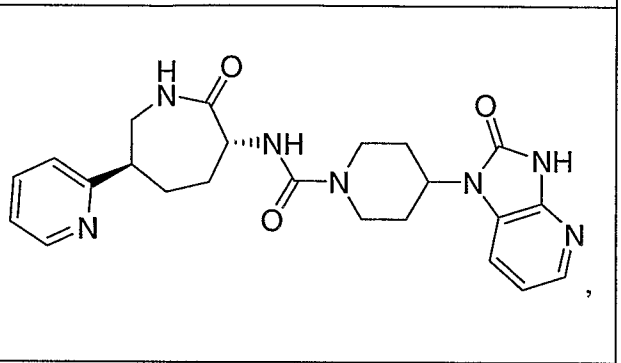

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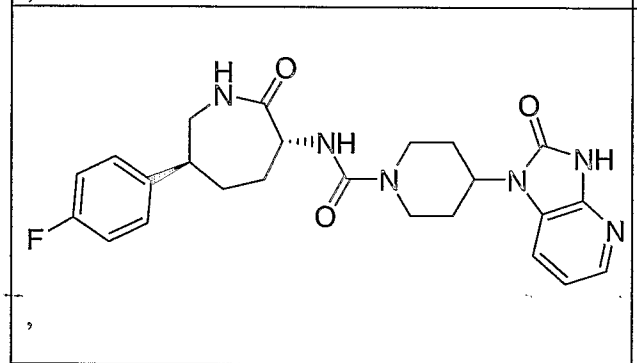

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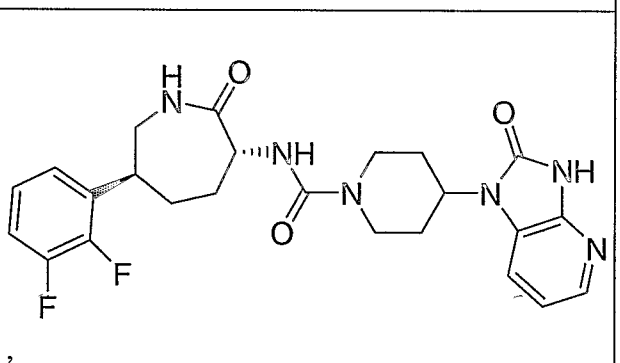

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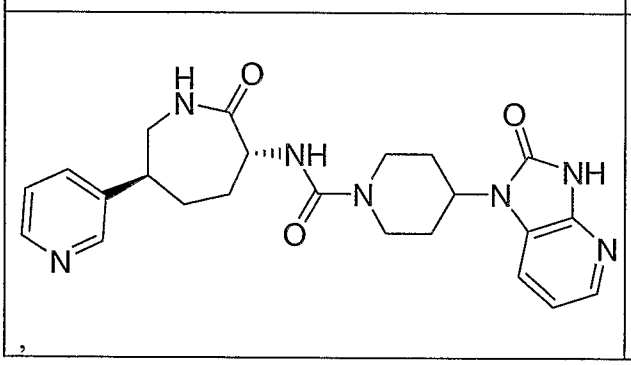

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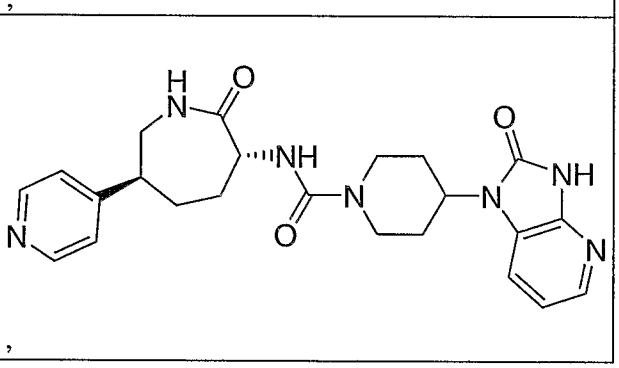

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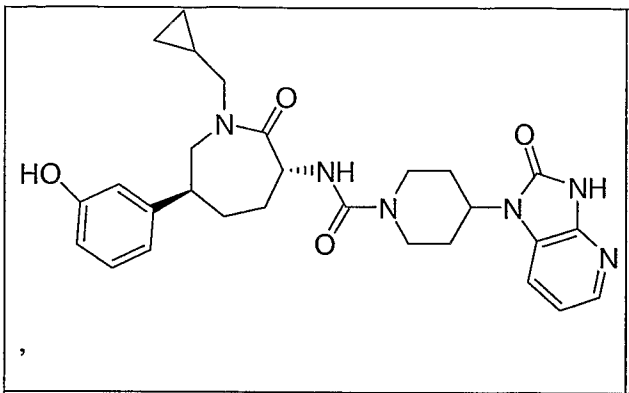

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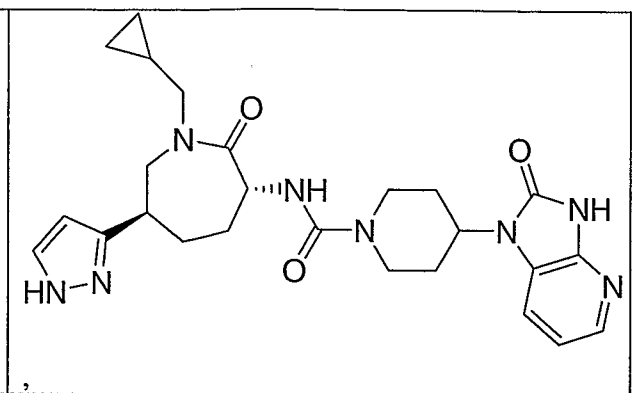

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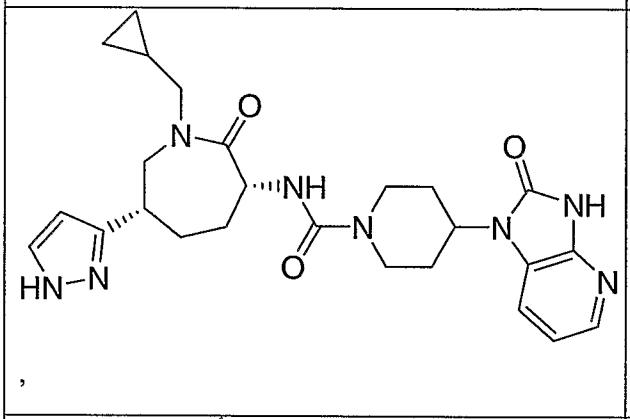

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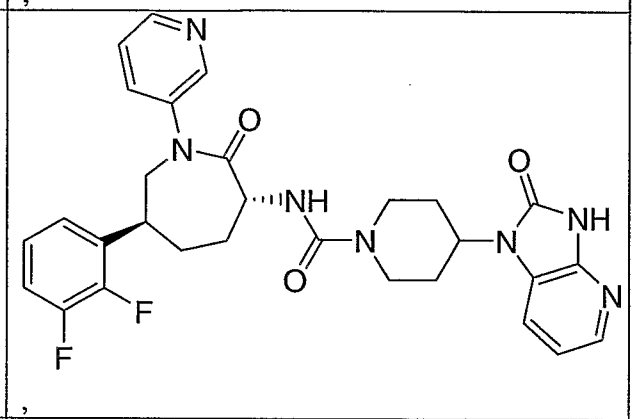

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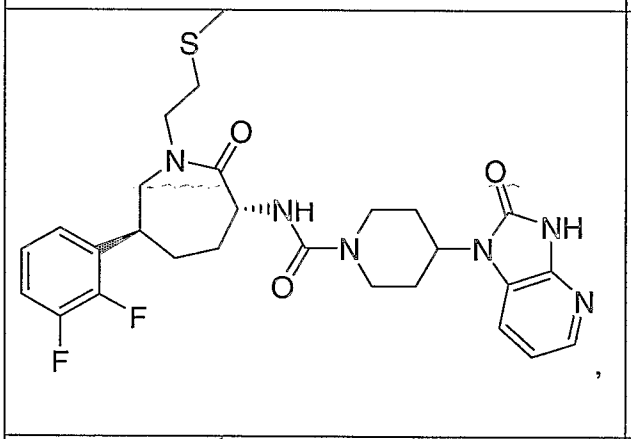

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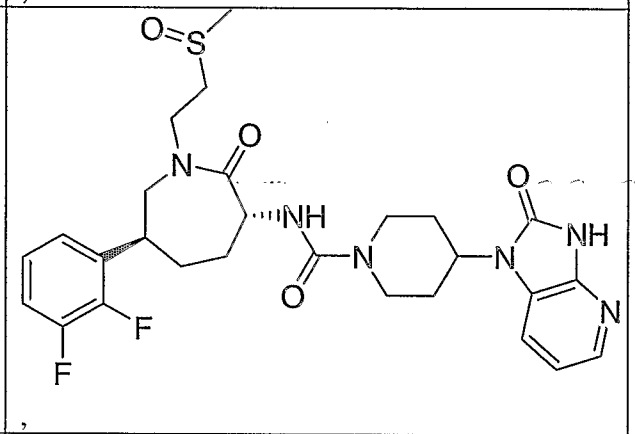

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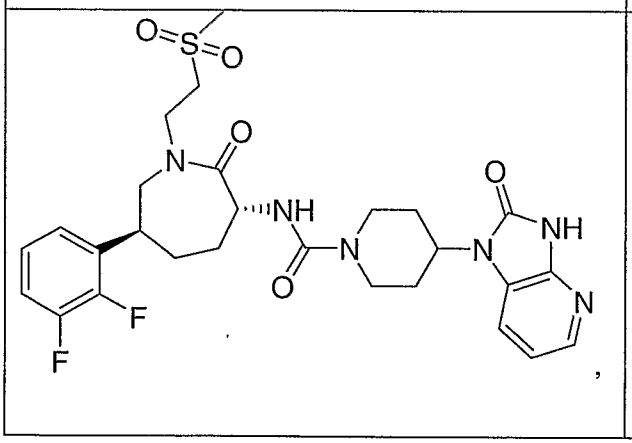

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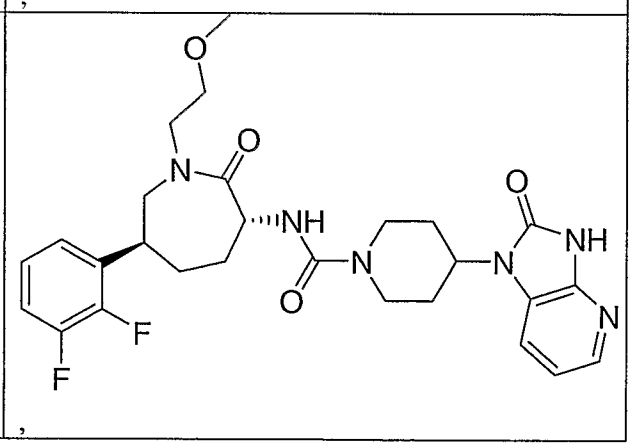

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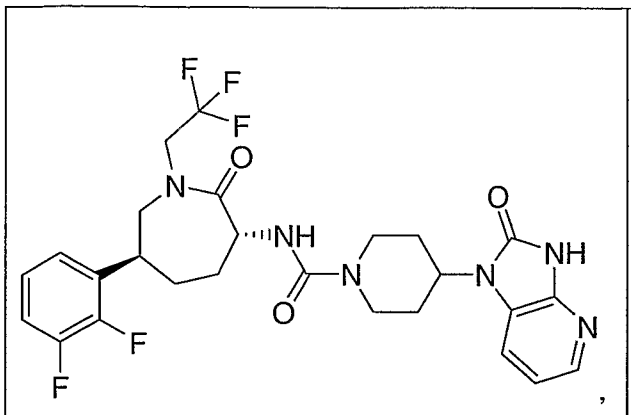

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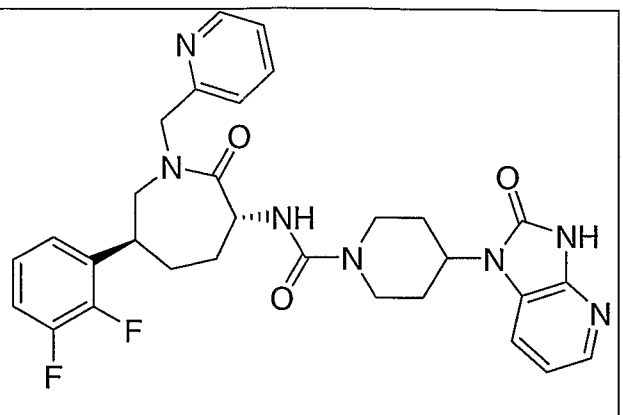

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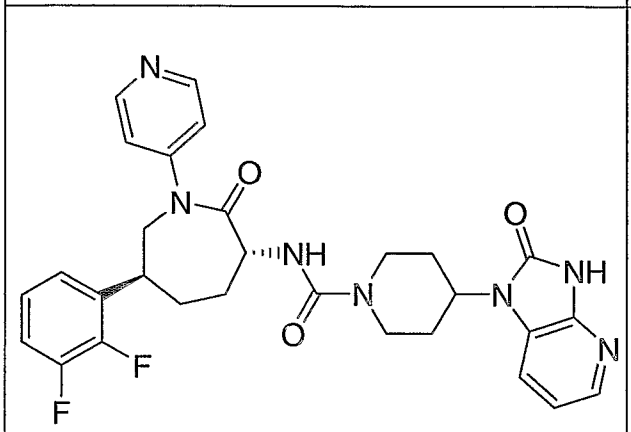

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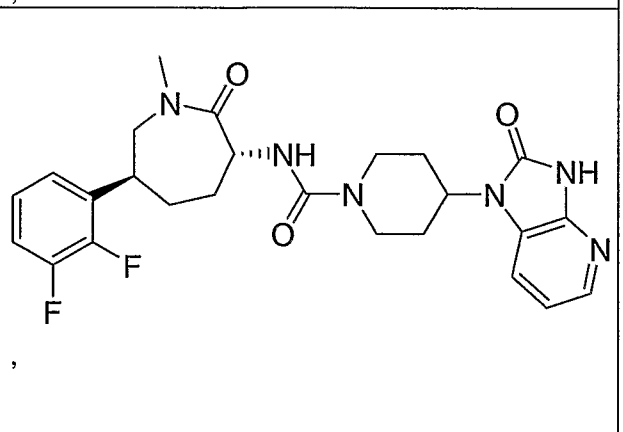
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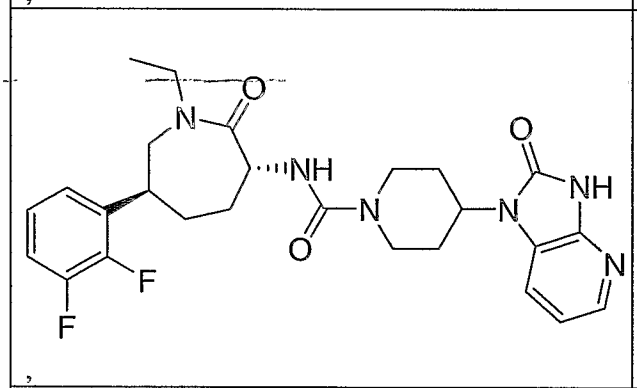
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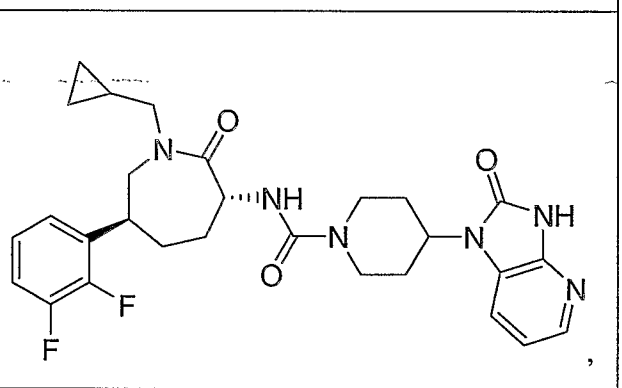
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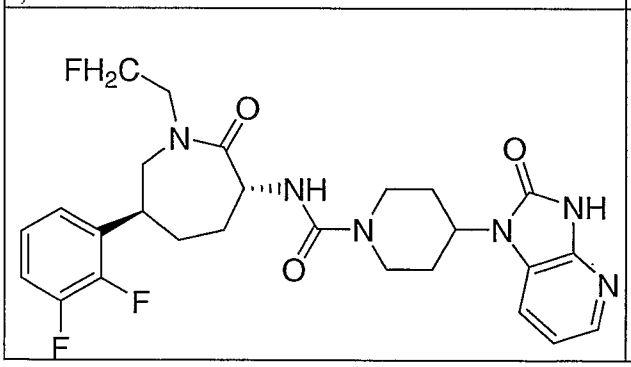
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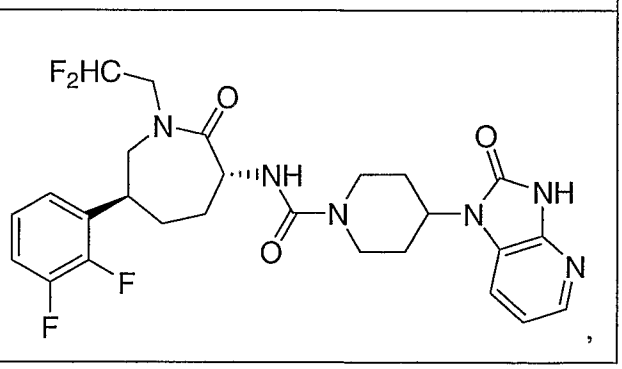


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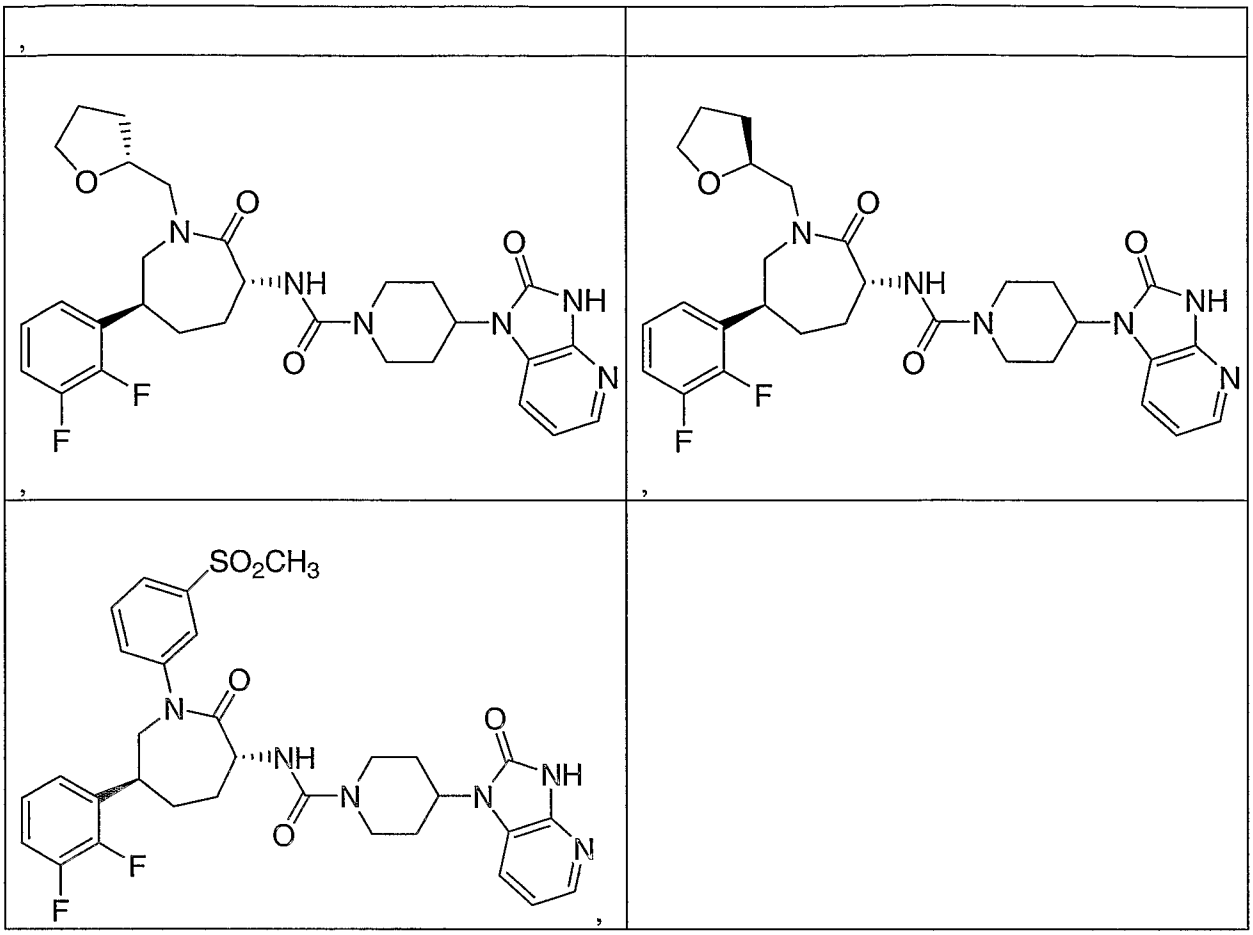


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and pharmaceutically acceptable salts and individual diastereomers thereof.

4. A pharmaceutical composition which comprises an inert carrier and the compound of Claim 1.

5. The use of the compound of Claim 1 for the preparation of a medicament useful in the treatment of headache, migraine or cluster headache.