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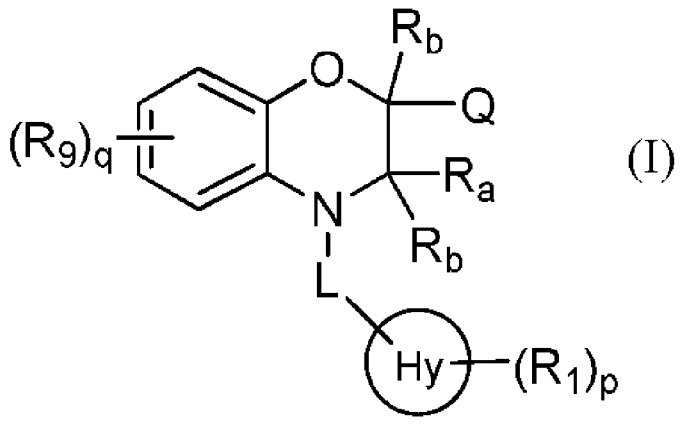
(54) Title: SUBSTITUTED 3,4-DIHYDRO-2H-BENZO[B] [1,4]OXAZINE COMPOUNDS AS CALCIUM SENSING RECEPTOR MODULATORS



(I)

(57) Abstract: The present invention provides calcium sensing receptor modulators (CaSR). In particular, the compounds described herein are useful for treating, managing, and/or lessening the severity of diseases, disorders, syndromes and/or conditions associated with the modulation of calcium sensing receptors (CaSR). The invention also provides herein the pharmaceutical compositions thereof, and methods for treating, managing, and/or lessening the severity of diseases, disorders, syndromes and/or conditions associated with the modulation of CaSR. The invention also relates to process for the preparation of the compounds of the invention. (Formula I) (I)

WO 2013/136288 A1

SUBSTITUTED 3,4-DIHYDRO-2*H*-BENZO[*b*][1,4]OXAZINE COMPOUNDS AS CALCIUM SENSING RECEPTOR MODULATORS

Related Applications

The present application claims the benefit of priority to Indian Provisional Patent Application No. 301/KOL/2012 filed on March 16, 2012. The entire provisional specifications are incorporated herein by reference.

Field of the Invention

The present invention relates to substituted 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine compounds, pharmaceutically acceptable salts thereof and pharmaceutical compositions for the treatment, management, and/or lessening the severity of diseases, disorders, syndromes or conditions associated with the modulation of calcium sensing receptors (CaSR). The invention also relates to methods of treating, managing and/or lessening the severity of diseases disorders, syndromes or conditions associated with the modulation of calcium sensing receptors (CaSR). The invention also relates to processes for the preparation of the compounds of the invention.

Background of the invention

Ca^{2+} is known to be an intracellular second messenger, with the molecular identification of an extracellular calcium sensing receptor (CaSR), it has further opened the possibility that Ca^{2+} might also function as a messenger outside the cells. Information about the local changes in extracellular concentration of Ca^{2+} is conveyed to the interior of many types of cells through this unique receptor.

Calcium-sensing receptor (CaSR) is a G-protein-coupled receptor (GPCR) that signals through the activation of phospholipase C, increasing levels of inositol 1,4,5-triphosphate and cytosolic calcium. The CaSR belongs to the subfamily C of the GPCR superfamily. Structurally, CaSR has an exceptionally large amino-terminal extracellular (ECD) domain (about 600 amino acids), a feature that is shared by all of the members of the family C GPCRs.

In mammals, the expression of CaSR is quite ubiquitous and its presence in the parathyroid gland plays an important role in the secretion of parathyroid hormone (PTH). The reduction in serum calcium leads to the secretion of PTH. Consequently, PTH secretion leads to conservation of serum Ca^{2+} by increasing kidney retention and intestinal absorption of Ca^{2+}. This happens indirectly through the PTH-induced synthesis of the active vitamin D metabolite, 25-dihydroxyvitamin D. In addition, the pulsatile action of PTH has anabolic effects on bone development and its sustained levels can lead to catabolic effects, in which the bones breakdown releasing Ca^{2+} as in the case of osteoporosis. All these systems converge in maintenance of baseline serum Ca^{2+} and it involves a tight regulation between serum PTH and extracellular calcium which is mediated by the remarkable receptor CaSR.

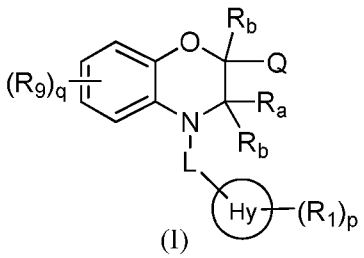
In conditions such as primary and secondary hyperparathyroidism, there is excessive secretion of parathyroid hormone due to hyperplasia of the glands. The most common cause of primary hyperparathyroidism (PHPT) is parathyroid adenoma resulting from clonal mutations (~97%) and associated hypercalcemia. In the case of secondary hyperparathyroidism (SHPT), it is most commonly seen in patients with chronic renal failure. The kidneys fail to convert enough vitamin D to its active form and also does not adequately excrete phosphorous. Excess phosphorous further depletes serum calcium forming calcium phosphate (kidney stones) leading to hypocalcemia.

Small molecules that are positive allosteric modulators called calcimimetics modulate and improve the receptors sensitivity to the already existing milieu of extracellular ionic calcium. This would eventually translate in lowering plasma PTH levels thereby improving conditions of hyperparathyroidism, calcium homeostasis and bone metabolism.

WO 2012/127388, WO 2012/120476, WO 2012/127385, WO 2012/069421, WO 2012/069419, WO 2012/069402, US 2011/0028452, WO 2010/150837, WO 2010/136037, WO 2010/042642, WO 2010/038895, WO 2009/065406, WO 2008/059854, WO 2006/123725, WO 2004/106280, WO 2004/069793, WO 2002/012181 and US 2003/0199497 applications disclose the compounds related to calcium sensing receptors (CaSR) for the treatment of various diseases mediated by CaSR. And also *J. Med. Chem.* (2006), 49, 5119-5128 discloses the compounds related to calcium sensing receptors (CaSR).

Summary of the Invention

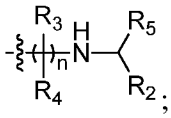
In accordance with one aspect, the invention provide compounds having the structure of Formula (I),



(I)

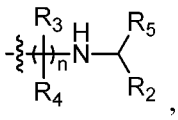
wherein,

Q is hydrogen or



;

R_a is selected from



,

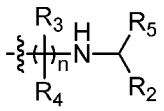
hydrogen, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted haloalkyl;

R_b, which may be same or different at each occurrence, is independently selected from hydrogen, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted haloalkyl;

or R_a and R_b together attached on the same carbon form C(O) or C(S);

provided that,

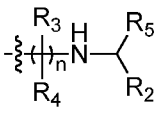
when Q is



then

R_a is selected from hydrogen, halogen, substituted or unsubstituted alkyl, cyano, substituted or unsubstituted cycloalkyl and substituted or unsubstituted haloalkyl; or

R_a and R_b together attached on the same carbon atom form C(O) or C(S);

when Q is hydrogen then R_a is  ;

L is selected from a bond, $-(CR_cR_d)_m$, -C(O)-, -C(S)-, $-C(O)NR_7$-, $-S(O)_2$-, $-S(O)_2-NR_7$, $-C(O)CH_2$-, $-CH_2C(O)$- and -C(O)O-;

R_c and R_d, which may be same or different at each occurrence, are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl;

ring 'Hy' is heteroaryl;

R_1, which may be same or different at each occurrence, is independently selected from halogen, nitro, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, -C(O)-Z, $-(CR_eR_f)_mC(O)$-Z, $-O(CR_eR_f)_m$-C(O)-Z, $-(CR_eR_f)_mO$-C(O)-Z, $-C(O)(CR_eR_f)_m$-C(O)-Z, $-C(O)NR_7$-C(O)-Z, $-C(O)NR_7(CR_eR_f)_m$-C(O)-Z, -cycloalkylene-C(O)-Z, -O-cycloalkylene-C(O)-Z, $-OR_6$, $-C(O)R_{10}$, $-NR_7R_8$, $-NR_7C(O)R_{10}$, $-S(O)_{0-2}R_6$, - $S(O)_2NR_7R_8$, and - $NR_7S(O)_2R_{10}$;

R_e and R_f, which may be same or different at each occurrence, are independently selected from hydrogen, halogen, hydroxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl and substituted or unsubstituted cycloalkyl; or R_e and R_f, together with the carbon atom to which they are attached, form a substituted or unsubstituted 3 to 7 membered saturated carbocyclic ring;

Z is $-OR_6$ or $-NR_7R_8$;

R_2 is selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocyclyl;

R_3 and R_4, which may be same or different at each occurrence, are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted

alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkoxy and substituted or unsubstituted cycloalkyl;

R_5 is substituted or unsubstituted alkyl or substituted or unsubstituted haloalkyl;

R_6, which may be same or different at each occurrence, is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl and substituted or unsubstituted alkynyl;

R_7 and R_8, which may be same or different at each occurrence, are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heterocyclylalkyl; or R_7 and R_8, together with the nitrogen atom to which they are attached, may form a substituted or unsubstituted, saturated or unsaturated 3 to 12 membered cyclic ring, wherein the unsaturated cyclic ring may have one or two double bonds;

R_9, which may be same or different at each occurrence, is independently selected from halogen, nitro, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, aryl, $-OR_6$, $-C(O)R_{10}$, $-C(O)OR_6$, $-(CH_2)_r-C(O)OR_6$, $-O(CH_2)_r-C(O)OR_6$, $-NR_7R_8$, $-C(O)NR_7R_8$, $-NR_7C(O)R_{10}$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_{10}$;

at each occurrence, R_{10} is substituted or unsubstituted alkyl or substituted or unsubstituted aryl;

'm' is an integer ranging from 1 to 3, both inclusive;

'n' is an integer ranging from 1 to 3, both inclusive;

'p' is an integer ranging from 0 to 4, both inclusive;

'q' is an integer ranging from 0 to 3, both inclusive; and

'r' is an integer ranging from 1 to 3, both inclusive;

or pharmaceutically acceptable salt thereof.

According to another embodiment, there are provided compounds of Formula (I) or pharmaceutically acceptable salt; wherein the pharmaceutically acceptable salt is hydrochloride salt.

According to another embodiment, there are provided compounds of Formula (I) structurally encompasses stereoisomers including enantiomers and diastereomers.

Below are the representative compounds, which are illustrative in nature only and are not intended to limit to the scope of the invention.

Methyl 6-(2-((((*R*)-1-(naphthalen-1-yl) ethyl) amino)methyl)-2*H*-benzo[*b*] [1,4]oxazin-4(3*H*)-yl) picolinate;

6-(2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl) picolinic acid hydrochloride;

Methyl 6-((*S*)-2-(2-(((*R*)-1-(naphthalen-1-yl)ethyl)amino)ethyl)-2*H*-benzo[*b*][1,4]oxazin-4(3H)-yl)picolinate;

6-((*S*)-2-(2-(((*R*)-1-(Naphthalen-1-yl)ethyl)amino)ethyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)picolinic acid;

(1*R*)-1-(Naphthalen-1-yl)-*N*-((4-(pyridin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)ethanamine hydrochloride;

(1*R*)-1-(3-Methoxyphenyl)-*N*-((4-(pyridin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)ethanamine hydrochloride;

5-((*S*)-2-(2-(((*R*)-1-(Naphthalen-1-yl)ethyl)amino)ethyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)picolinic acid hydrochloride and

6-((*S*)-2-(2-(((*R*)-1-(Naphthalen-1-yl)ethyl)amino)ethyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)nicotinic acid hydrochloride,

or pharmaceutically acceptable salts thereof.

In another aspect of the invention, there is provided a compound of Formula (I) useful in treating, preventing, managing and/or lessening the severity of diseases, disorders, syndromes or conditions associated with calcium sensing receptor (CaSR) modulators.

In another aspect, the invention provides a pharmaceutical composition comprising at least one compound of Formula (I) and at least one pharmaceutically acceptable excipient.

In another aspect, the invention provides a pharmaceutical composition of compound of formula (I) useful in treating, preventing, managing and/or lessening the severity of the diseases disorders, syndromes or conditions associated with calcium sensing receptor (CaSR) modulators in a subject, in need thereof by administering to the subject, one or more compounds described herein in a therapeutically effective amount to cause modulation of such receptor.

In another aspect, the invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable excipient.

Detailed description of the invention

Definitions and Abbreviations:

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below.

For purposes of interpreting the specification and claims, the following definitions will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa.

The terms "halogen" or "halo" means fluorine, chlorine, bromine, or iodine.

The term "alkyl" refers to an alkane derived hydrocarbon radical that includes solely carbon and hydrogen atoms in the backbone, contains no unsaturation, has from one to six carbon atoms, and is attached to the remainder of the molecule by a single bond, *e.g.*, methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, 1,1- dimethylethyl (t-butyl) and the like. Unless set forth or recited to the contrary, all alkyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkenyl" refers to a hydrocarbon radical containing from 2 to 10 carbon atoms and including at least one carbon-carbon double bond. Non-limiting examples of alkenyl groups include ethenyl, 1-propenyl, 2-propenyl (allyl), *iso*-propenyl, 2-methyl-l-propenyl, 1-butenyl, 2-butenyl and the like. Unless set forth or recited to the contrary, all alkenyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkynyl" refers to a hydrocarbon radical containing 2 to 10 carbon atoms and including at least one carbon- carbon triple bond. Non- limiting examples of alkynyl groups include ethynyl, propynyl, butynyl and the like. Unless set forth or recited to the contrary, all alkynyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkoxy" refers to an alkyl group attached via an oxygen linkage. Non-limiting examples of such groups are methoxy, ethoxy and propoxy and the like. Unless set forth or recited to the contrary, all alkoxy groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "haloalkyl" refers to an alkyl group as defined above that is substituted by one or more halogen atoms as defined above. Preferably, the haloalkyl may be monohaloalkyl, dihaloalkyl or polyhaloalkyl including perhaloalkyl. A monohaloalkyl can have one iodine, bromine, chlorine or fluorine atom. Dihaloalkyl and polyhaloalkyl groups can be substituted with two or more of the same halogen atoms or a combination of different halogen atoms. Preferably, a polyhaloalkyl is substituted with up to 12 halogen atoms. Non-limiting examples of a haloalkyl include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl and the like. A perhaloalkyl refers to an alkyl having all hydrogen atoms replaced with halogen atoms. Unless set forth or recited to the contrary, all haloalkyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "haloalkoxy" refers to a haloalkyl, defined herein, group attached via an oxygen linkage. Preferably, the haloalkoxy may be monohaloalkoxy, dihaloalkoxy or polyhaloalkoxy including perhaloalkoxy. Non-limiting examples of a haloalkoxy include fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, pentafluoroethoxy, heptafluoropropoxy, difluorochloromethoxy, dichlorofluoromethoxy, difluoroethoxy, difluoropropoxy, dichloroethoxy, dichloropropoxy, dichloroisopropoxy and the like. Unless set forth or recited to the contrary, all haloalkoxy group described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "cycloalkyl" refers to a non-aromatic mono or multicyclic ring system having 3 to 12 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. Examples of multicyclic cycloalkyl groups include, but are not limited to, perhydronaphththyl, adamantyl and norbornyl groups, bridged cyclic groups or spirobicyclic groups, *e.g.*, spiro(4,4)non-2-yl and the like. Unless set forth or recited to the contrary, all cycloalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "cycloalkylene" refers to a saturated divalent cyclic hydrocarbon radical that includes solely carbon and hydrogen atoms in the backbone. In particular, "C_3-C_7 cycloalkylene" means a saturated divalent cyclic hydrocarbon radical with 3 to 7 carbon atoms *e.g.* cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene and the like. Unless set forth or recited to the contrary, all cycloalkylene groups described or claimed herein may be substituted or unsubstituted.

The term "cycloalkenyl" refers to a non-aromatic mono or multicyclic ring system having 3 to 12 carbon atoms and including at least one carbon-carbon double bond, such as cyclopentenyl, cyclohexenyl, cycloheptenyl and the like. Unless set forth or recited to the contrary, all cycloalkenyl groups described or claimed herein may be substituted or unsubstituted.

The term "cycloalkylalkyl" refers to a cycloalkyl group as defined above, directly bonded to an alkyl group as defined above, *e.g.*, cyclopropylmethyl, cyclobutylmethyl,

cyclopentylmethyl, cyclohexylmethyl, cyclohexylethyl, etc. Unless set forth or recited to the contrary, all cycloalkylalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "aryl" refers to an aromatic radical having 6- to 14- carbon atoms, including monocyclic, bicyclic and tricyclic aromatic systems, such as phenyl, naphthyl, tetrahydronaphthyl, indanyl, and biphenyl and the like. Unless set forth or recited to the contrary, all aryl groups described or claimed herein may be substituted or unsubstituted.

The term "arylalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above, *e.g.*, $-CH_2C_6H_5$ and $-C_2H_4C_6H_5$. Unless set forth or recited to the contrary, all arylalkyl groups described or claimed herein may be substituted or unsubstituted.

A "carbocyclic ring" or "carbocycle" as used herein refers to a 3- to 10- membered saturated or unsaturated, monocyclic, fused bicyclic, spirocyclic or bridged polycyclic ring containing carbon atoms, which may optionally be substituted, for example, carbocyclic rings include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylene, cyclohexanone, aryl, naphthyl, adamentyl etc. Unless set forth or recited to the contrary, all carbocyclic groups or rings described or claimed herein may be aromatic or non aromatic.

A "3-12 membered cyclic ring" as used herein refers to a monocyclic, bicyclic, polycyclic heteroaryl or heterocyclic ring systems.

The term "heterocyclic ring" or "heterocyclyl ring" or "heterocyclyl", unless otherwise specified, refers to substituted or unsubstituted non-aromatic 3- to 15- membered ring which consists of carbon atoms and with one or more heteroatom(s) independently selected from N, O or S. The heterocyclic ring may be a mono-, bi- or tricyclic ring system, which may include fused, bridged or spiro ring systems and the nitrogen, carbon, oxygen or sulfur atoms in the heterocyclic ring may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized, the heterocyclic ring or heterocyclyl may optionally contain one or more olefinic bond(s), and one or two carbon

atoms(s) in the heterocyclic ring or heterocyclyl may be interrupted with -CF_2-, -C(O)-, -S(O)-, $S(O)_2$, -C(=N-alkyl)-, or –C(=N-cycloalkyl), etc. In addition heterocyclic ring may also be fused with aromatic ring. Non-limiting examples of heterocyclic rings include azetidinyl, benzopyranyl, chromanyl, decahydroisoquinolyl, indanyl, indolinyl, isoindolinyl, isochromanyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, oxazolinyl, oxazolidinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, octahydroindolyl, octahydroisoindolyl, perhydroazepinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, piperidinyl, phenothiazinyl, phenoxazinyl, quinuclidinyl, tetrahydroisquinolyl, tetrahydrofuryl, tetrahydropyranyl, thiazolinyl, thiazolidinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone indoline, benzodioxole, tetrahydroquinoline, tetrahydrobenzopyran and the like. The heterocyclic ring may be attached by any atom of the heterocyclic ring that results in the creation of a stable structure. Unless set forth or recited to the contrary, all heterocyclyl groups described or claimed herein may be substituted or unsubstituted; substituents may be on same or different ring atom.

The term "heteroaryl" unless otherwise specified, refers to a substituted or unsubstituted 5- to 14- membered aromatic heterocyclic ring with one or more heteroatom(s) independently selected from N, O or S. The heteroaryl may be a mono-, bi- or tricyclic ring system. The heteroaryl ring may be attached by any atom of the heteroaryl ring that results in the creation of a stable structure. Non-limiting examples of a heteroaryl ring include oxazolyl, isoxazolyl, imidazolyl, furyl, indolyl, isoindolyl, pyrrolyl, triazolyl, triazinyl, tetrazolyl, thienyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzothienyl, carbazolyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, naphthyridinyl, pteridinyl, purinyl, quinoxalinyl, quinolyl, isoquinolyl, thiadiazolyl, indolizinyl, acridinyl, phenazinyl, phthalazinyl and the like. Unless set forth or recited to the contrary, all heteroaryl groups described or claimed herein may be substituted or unsubstituted.

The term "heterocyclylalkyl" refers to a heterocyclic ring radical directly bonded to an alkyl group. The heterocyclylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Unless set

forth or recited to the contrary, all heterocyclylalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "heteroarylalkyl" refers to a heteroaryl ring radical directly bonded to an alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Unless set forth or recited to the contrary, all heteroarylalkyl groups described or claimed herein may be substituted or unsubstituted.

Unless otherwise specified, the term "substituted" as used herein refers to a group or moiety having one or more substituents attached to the structural skeleton of the group or moiety. Such substituents include, but are not limited to hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio (=S), alkyl, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heteroaryl, heterocyclic ring, heterocyclylalkyl, heteroarylalkyl, $-C(O)OR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-NR^xC(O)NR^yR^z$, $-N(R^x)S(O)R^y$, $-N(R^x)S(O)_2R^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-S(O)_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^y$, $-SR^x$, and $-S(O)_2R^x$; wherein each occurrence of R^x, R^y and R^z are independently selected from hydrogen, halogen, alkyl, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heteroaryl, heterocyclic ring, heterocyclylalkyl and heteroarylalkyl. The aforementioned “substituted” groups cannot be further substituted. For example, when the substituent on “substituted alkyl” is “aryl” or “alkenyl”, the aryl or alkenyl cannot be substituted aryl or substituted alkenyl, respectively.

The compounds of the present invention may have one or more chiral centers. The absolute stereochemistry at each chiral centre may be ‘R’ or ‘S’. The compounds of the invention include all diastereomers and enantiomers and mixtures thereof. Unless specifically mentioned otherwise, reference to one stereoisomer applies to any of the possible stereoisomers. Whenever the stereoisomeric composition is unspecified, it is to be understood that all possible stereoisomers are included.

The term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. The terms "racemate" or "racemic mixture" refer to a mixture of equal parts of enantiomers.

A "tautomer" refers to a compound that undergoes rapid proton shifts from one atom of the compound to another atom of the compound. Some of the compounds described herein may exist as tautomers with different points of attachment of hydrogen. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula (I).

The term "treating" or "treatment" of a state, disorder or condition includes: (a) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a subject that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition; (b) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof; c) lessening the severity of a disease disorder or condition or at least one of its clinical or subclinical symptoms or (d) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

The term “modulate” or “modulating” or “modulation” or “modulator” refers to an increase in the amount, quality, or effect of a particular activity or function of the receptor. By way of illustration and not limitation, it includes agonists, partial agonists, allosteric modulators of calcium sensing receptor (CaSR) of the present invention. Such modulation may be contingent on the occurrence of a specific event, such as activation of a signal transduction pathway.

The term "allosteric modulators of calcium-sensing receptor", refers to the ability of a compound that binds to calcium sensing receptors and induces a conformational change that reduces the threshold for calcium sensing receptor activation by the endogenous ligand Ca^{2+} depending on the concentration of the compound exposed to the calcium-sensing receptor.

The term “subject” includes mammals (especially humans) and other animals, such as domestic animals (e.g., household pets including cats and dogs) and non- domestic animals (such as wildlife).

A "therapeutically effective amount" means the amount of a compound that, when administered to a subject for treating a disease, disorder, syndrome or condition, is sufficient to cause the effect in the subject which is the purpose of the administration. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated.

Pharmaceutically Acceptable Salts:

The compounds of the invention may form salts with acid or base. The compounds of invention may be sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compound as a pharmaceutically acceptable salt may be appropriate. Non-limiting examples of pharmaceutically acceptable salts are inorganic, organic acid addition salts formed by addition of acids including hydrochloride salts. Non-limiting examples of pharmaceutically acceptable salts are inorganic, organic base addition salts formed by addition of bases. The compounds of the invention may also form salts with amino acids. Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion.

With respect to the overall compounds described by the Formula (I), the invention extends to these stereoisomeric forms and to mixtures thereof. To the extent prior art teaches

synthesis or separation of particular stereoisomers, the different stereoisomeric forms of the invention may be separated from one another by a method known in the art, or a given isomer may be obtained by stereospecific or asymmetric synthesis or chiral HPLC (high performance liquid chromatography. Tautomeric forms and mixtures of compounds described herein are also contemplated.

Screening of compounds of invention for calcium sensing receptor (CaSR) modulation activity can be achieved by using various in vitro and in vivo protocols mentioned herein below or methods known in the art.

Pharmaceutical Compositions

The invention relates to pharmaceutical compositions containing the compounds of the Formula (I) disclosed herein. In particular, pharmaceutical compositions containing a therapeutically effective amount of at least one compound of Formula (I) described herein and at least one pharmaceutically acceptable excipient (such as a carrier or diluent). Preferably, the contemplated pharmaceutical compositions include the compound(s) described herein in an amount sufficient to modulate calcium sensing receptor (CaSR) mediated diseases described herein when administered to a subject.

The subjects contemplated include, for example, a living cell and a mammal, including human mammal. The compound of the invention may be associated with a pharmaceutically acceptable excipient (such as a carrier or a diluent) or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. The pharmaceutically acceptable excipient includes pharmaceutical agent that does not itself induce the production of antibodies harmful to the individual receiving the composition, and which may be administered without undue toxicity.

Examples of suitable carriers or exciptients include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin,

amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, salicylic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, emulsifying agents, suspending agents, preserving agents, salts for influencing osmotic pressure, buffers, sweetening agents, flavoring agents, colorants, or any combination of the foregoing. The pharmaceutical composition of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the subject by employing procedures known in the art.

The pharmaceutical compositions described herein may be prepared by conventional techniques known in the art. For example, the active compound can be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of an ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container, for example, in a sachet.

The pharmaceutical compositions may be in conventional forms, for example, capsules, tablets, caplets, orally disintegrating tablets, aerosols, solutions, suspensions or products for topical application.

The route of administration may be any route which effectively transports the active compound of the invention to the appropriate or desired site of action. Suitable routes of administration include, but are not limited to, oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal, parenteral, rectal, depot, subcutaneous, intravenous, intraurethral,

intramuscular, intranasal, ophthalmic (such as with an ophthalmic solution) or topical (such as with a topical ointment).

Solid oral formulations include, but are not limited to, tablets, caplets, capsules (soft or hard gelatin), orally disintegrating tablets, dragees (containing the active ingredient in powder or pellet form), troches and lozenges. Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Liquid formulations include, but are not limited to, syrups, emulsions, suspensions, solutions, soft gelatin and sterile injectable liquids, such as aqueous or non-aqueous liquid suspensions or solutions. For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as pocketed tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, caplet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

For administration to subject patients, the total daily dose of the compounds of the invention depends, of course, on the mode of administration. For example, oral administration may require a higher total daily dose, than an intravenous (direct into blood). The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 10000 mg according to the potency of the active component or mode of administration.

Suitable doses of the compounds for use in treating the diseases and disorders described herein can be determined by those skilled in the relevant art. Therapeutic doses are generally identified through a dose ranging study in subject based on preliminary evidence

derived from the animal studies. Doses must be sufficient to result in a desired therapeutic benefit without causing unwanted side effects for the patient. For example, the daily dosage of the CaSR modulator can range from about 0.1 to about 30.0 mg/kg. Mode of administration, dosage forms, suitable pharmaceutical excipients, diluents or carriers can also be well used and adjusted by those skilled in the art. All changes and modifications are envisioned within the scope of the invention.

Methods of Treatment

In another aspect, the invention provides compounds and pharmaceutical compositions thereof that are useful in treating, managing and/or lessening the severity of diseases, disorders, syndromes or conditions modulated by calcium sensing receptor (CaSR). The invention further provides method of treating diseases, disorders, syndromes or conditions modulated by CaSR in a subject in need thereof by administering to the subject a therapeutically effective amount of a compound or a pharmaceutical composition of the invention.

In another aspect of the invention, the methods provided are also useful for diagnosis of conditions that can be treated by modulating CaSR for determining if a patient will be responsible to therapeutic agents.

In another aspect, the invention provides a method for the treatment of diseases, disorders or conditions through modulating CaSR. In this method, a subject in need of such treatment is administered a therapeutically effective amount of a compound of Formula (I) described herein.

The compound and pharmaceutical composition of the present invention is useful to a subject in need of the treatment having a disease, disorder, syndrome or condition characterized by one or more of the following: (a) abnormal calcium ion homeostasis, (b) an abnormal level of a messenger whose production or secretion is affected by the calcium sensing receptor (CaSR) activity or (c) an abnormal level of activity of a messenger whose

function is affected by the calcium sensing receptor activity. In one aspect, the patient has a disease, disorder, syndrome or condition characterized by an abnormal level of one or more calcium sensing receptor-regulated components and the compound is active on a CaSR of a cell including parathyroid cell, bone cells (pre-osteoclast, osteoclast, pre-osteoblast, osteoblast), juxtaglomerular kidney cell, kidney messengial cell, glomerular kidney cell, proximal tubule kidney cell, distal tubule kidney cell, cell of the thick ascending limb of Henle's loop and/or collecting duct, parafollicular cell in the thyroid (C-cell), intestinal cell, platelet, vascular smooth muscle cell, gastrointestinal tract cell, pituitary cell or hypothalamic cell. The messenger of the calcium sensing receptor is Calcium.

The compound of Formula (I), being modulators of CaSR, is potentially useful in treating, managing and/or lessening the severity, morbidity/mortality or complications of diseases, disorders, syndromes or conditions include but are not limited to primary hyperparathyroidism, secondary hyperparathyroidism, tertiary hyperparathyroidism, chronic renal failure (with or without dialysis), chronic kidney disease (with or without dialysis) parathyroid adenoma, parathyroid hyperplasia, parathyroid carcinoma, vascular & valvular calcification, abnormal calcium homeostasis such as hypercalcemia, abnormal phosphorous homeostasis such as hypophosphatemia, bone related diseases or complications arising due to hyperparathyroidism, chronic kidney disease or parathyroid carcinoma, bone loss post renal transplantation, osteitis fibrosa cystica, adynamic bone disease, renal bone diseases, cardiovascular complications arising due to hyperparathyroidism or chronic kidney disease, certain malignancies in which $(Ca^{2+})_e$ ions are abnormally high, cardiac, renal or intestinal dysfunctions, podocyte-related diseases, abnormal intestinal motility, diarrhea, augmenting gastrin or gastric acid secretion to directly or indirectly benefit in atrophic gastritis or to improve absorption of pharmacological compounds, drugs or supplements from gastro-intestinal tract by augmenting gastric acidity.

Primary hyperparathyroidism, is a disorder of one or more of the parathyroid glands, resulting from a hyper function of the parathyroid glands themselves (acquired sporadically or familial) resulting in PTH over secretion which could be due to single or double adenoma,

hyperplasia, multigland disease or rarely, carcinoma of the parathyroid glands. As a result, the blood calcium rises to a level that is higher than normal (called hypercalcemia). This elevated calcium level can cause many short-term and long-term complications.

Secondary hyperparathyroidism occurs when a decrease in circulating levels of Ca^{2+} level stimulates PTH secretion. One cause of secondary hyperparathyroidism is chronic renal insufficiency (also referred to as chronic kidney disease or CKD), such as that in renal polycystic disease or chronic pyelonephritis, or chronic renal failure, such as that in hemodialysis patients (also referred to as end stage renal disease or ESRD). Excess PTH may be produced in response to hypocalcemia resulting from low calcium intake, GI disorders, renal insufficiency, vitamin D deficiency, magnesium deficiency and renal hypercalciuria. Tertiary hyperparathyroidism may occur after a long period of secondary hyperparathyroidism and hypercalcemia.

In one aspect, the compound and composition of the present invention can be used in treating, managing and/or lessening the vascular or valvular calcification in a subject. In one aspect, administration of the compound of the invention retards or reverses the formation, growth or deposition of extracellular matrix hydroxyapatite crystal deposits. In another aspect of the invention, administration of the compound of the invention prevents the formation, growth or deposition of extracellular matrix hydroxyapatite crystal deposits. In one aspect, the compounds of the invention may also be used to prevent or treat atherosclerotic calcification and medial calcification and other conditions characterized by vascular calcification. In one aspect, vascular calcification may be associated with chronic renal insufficiency or end-stage renal disease or excess calcium or PTH itself. In another aspect, vascular calcification may be associated with pre- or post-dialysis or uremia. In a further aspect, vascular calcification may be associated with diabetes mellitus I or II. In yet another aspect, vascular calcification may be associated with a cardiovascular disorder.

Abnormal calcium homeostasis such as hyperparathyroidism related diseases can be characterized as described in standard medical textbooks, but not limited to Harrison's

Principles of Internal Medicine. The compound and composition of the present invention can be used, in particular, to participate in a reduction of the serum levels in the parathyroid hormone known as PTH: these products could thus be useful for the treatment of diseases such as hyperparathyroidism.

Abnormal phosphorous homeostasis such as hypophosphatemia can be characterized as described in standard medical textbooks, but not limited to Harrison's Principles of Internal Medicine. The compound and composition of the present invention can be used, in particular, to participate in a reduction of the serum levels in the parathyroid hormone known as PTH: these products could thus be useful for the treatment of diseases such as hypophosphatemia.

In one aspect, the podocyte diseases or disorders treated by methods of the present invention stem from the perturbations in one or more functions of podocytes. These functions of podocytes include: (i) a size barrier to protein; (ii) charge barrier to protein; (iii) maintenance of the capillary loop shape; (iv) counteracting the intraglomerular pressure; (v) synthesis and maintenance of the glomerular basement membrane (GMB); (vi) production and secretion of vascular endothelial growth factor (VEGF) required for the glomerular endothelial cell (GEN) integrity. Such disorders or diseases include but are not limited to loss of podocytes (podocytopenia), podocyte mutation, an increase in foot process width, or a decrease in slit diaphragm length. In one aspect, the podocyte-related disease or disorder can be effacement or a diminution of podocyte density. In one aspect, the diminution of podocyte density could be due to a decrease in a podocyte number, for example, due to apoptosis, detachment, lack of proliferation, DNA damage or hypertrophy.

In one aspect, the podocyte-related disease or disorder can be due to a podocyte injury. In one aspect, the podocyte injury can be due to mechanical stress such as high blood pressure, hypertension, or ischemia, lack of oxygen supply, a toxic substance, an endocrinologic disorder, an infection, a contrast agent, a mechanical trauma, a cytotoxic agent (cis-platinum, adriamycin, puromycin), calcineurin inhibitors, an inflammation (e.g.,

due to an infection, a trauma, anoxia, obstruction, or ischemia), radiation, an infection (e.g., bacterial, fungal, or viral), a dysfunction of the immune system (e.g., an autoimmune disease, a systemic disease, or IgA nephropathy), a genetic disorder, a medication (e.g., anti-bacterial agent, anti-viral agent, anti-fungal agent, immunosuppressive agent, anti-inflammatory agent, analgestic or anticancer agent), an organ failure, an organ transplantation, or uropathy. In one aspect, ischemia can be sickle-cell anemia, thrombosis, transplantation, obstruction, shock or blood loss. In one aspect, the genetic disorders may include congenital nephritic syndrome of the Finnish type, the fetal membranous nephropathy or mutations in podocyte-specific proteins.

In one aspect, the compounds of the invention can be used for treating abnormal intestinal motilities disorders such as diarrhea. The methods of the invention comprise administering to the subject a therapeutically effective amount of the compounds of Formula I. In a further aspect, diarrhea can be exudative diarrhea, i.e., resulting from direct damage to the small or large intestinal mucosa. This type of diarrhea can be caused by infectious or inflammatory disorders of the gut. In one aspect, exudative diarrhea can be associated with gastrointestinal or abdominal surgery, chemotherapy, radiation treatment, inflammation or toxic traumatic injury. In another aspect, diarrhea can be secretary, means that there is an increase in the active secretion, or there is an inhibition of absorption. There is little to no structural damage. The most common cause of this type of diarrhea is cholera. In another aspect, diarrhea can be due to acceleration of intestinal transit (rapid transit diarrhea). Such condition may occur because the rapid flow-through impairs the ability of the gut to absorb water.

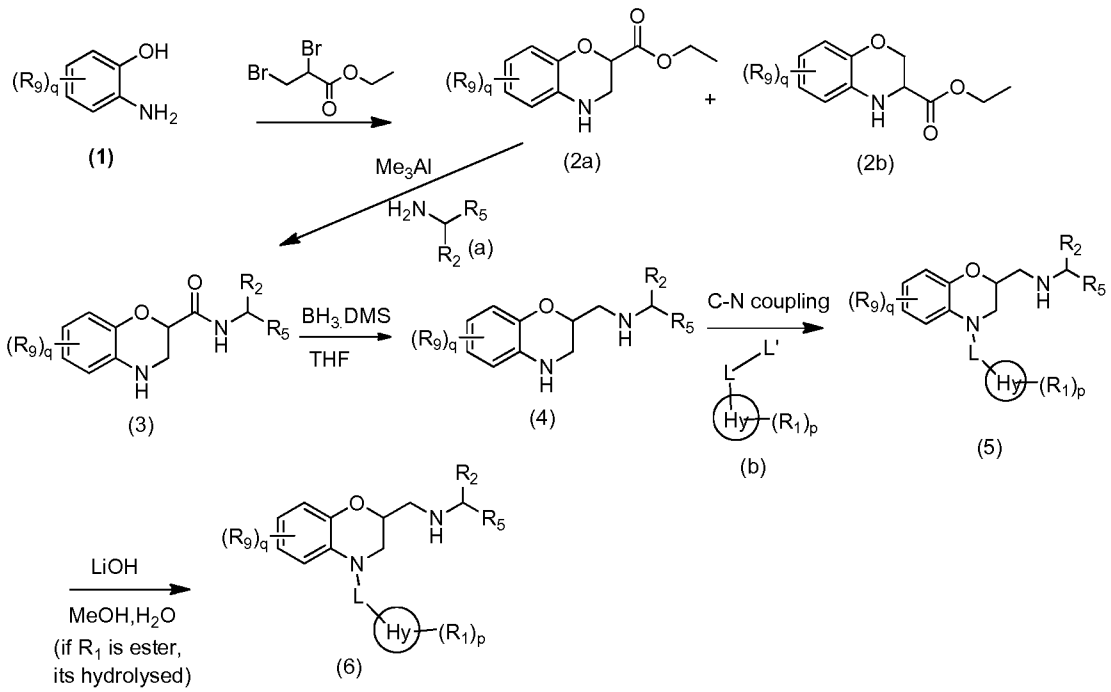
The compound and composition of the present invention can be used, in particular, to participate in an augmenting gastrin or gastric acid secretion to directly or indirectly benefit certain medical conditions such as but not limited to atrophic gastritis or to improve absorption of pharmacological compounds, drugs or supplements from gastro-intestinal tract by augmenting gastric acidity.

All of the patent, patent application and non-patent publications referred to in this specification are incorporated herein by reference in their entireties.

General Methods of Preparation

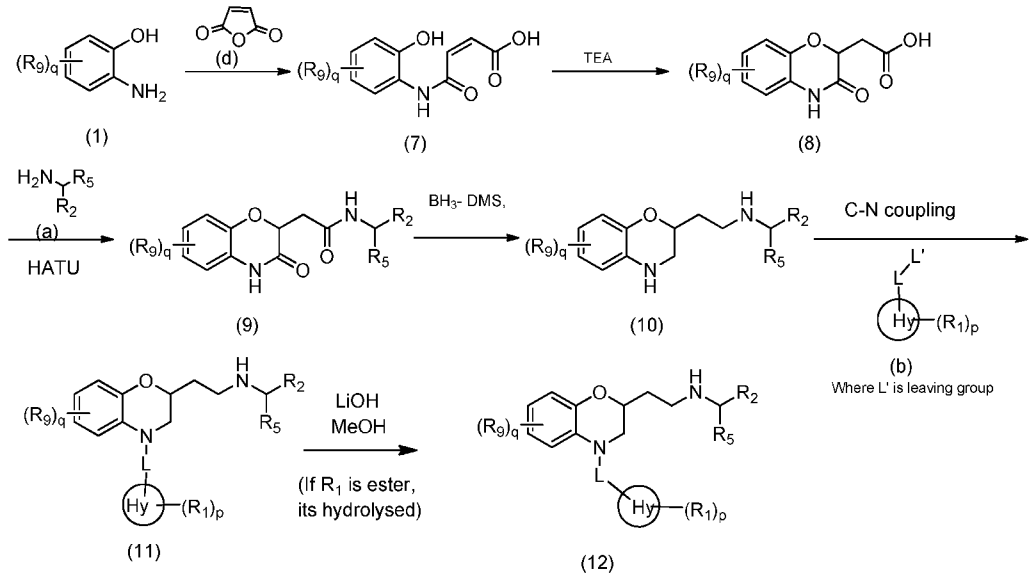
The compounds described herein may be prepared by techniques known in the art. In addition, the compounds described herein may be prepared by following the reaction sequence as depicted in Scheme-1 to Scheme-2. Further, in the following schemes, where specific bases, acids, reagents, solvents, coupling agents, etc., are mentioned, it is understood that other bases, acids, reagents, solvents, coupling agents etc., known in the art may also be used and are therefore included within the scope of the present invention. Variations in reaction conditions, for example, temperature and/or duration of the reaction, which may be used as known in the art, are also within the scope of the present invention. All the isomers of the compounds described in these schemes, unless otherwise specified, are also encompassed within the scope of this invention.

Scheme 1



The compound of formula (6), where R_1, R_2, R_5, R_9, L, ring Hy, p and 'q' are as defined herein above can be prepared by following the procedure as depicted in Scheme-1. The commercially available 2-aminophenol is reacted with ethyl 2,3-dibromo- propionate (*Journal of Heterocyclic Chemistry,* (2001), 38, 221–226) in the presence of base such as sodium carbonate, potassium carbonate or triethylamine to give the corresponding dihydro[1,4]-benzoxazines (2a) and (2b). The compound of formula (2a) is further reacted with amine of formula (a) in presence of trimethyl aluminium to give compound of formula (3). This compound of formula (3) undergoes reduction using suitable reducing agents for example borane-dimethyl sulfide (*Journal of Medicinal Chemistry,* **1998**, 46, 3142-3158) complex to give compound of formula (4). This compound of formula (4) undergoes carbon-nitrogen (C-N) coupling reaction with Formula (b) by following the methods known in the art for example Buchwald coupling reaction (when L is a bond) using suitable reagents known in the art. Further, if this compound of formula (5) is ester, it can be hydrolyzed to give corresponding acid compound of formula (6) using suitable base such as NaOH, LiOH, etc.

Scheme 2



The compound of formula (12), where R_1, R_2, R_5, R_9, L, Hy, p and 'q' are as defined herein above, can be prepared by following the procedure as depicted in Scheme-2. The Commercially available 2-aminophenol of formula (1) is reacted with maleic anhydride of formula (d) in suitable solvent for example toluene to give the corresponding 4-((2-hydroxyphenyl) amino)-4-oxobut-2-enoic acid (7). The compound of formula (7) undergoes cyclisation to give compound of formula (8) (*Aust. J. Chem.,* 1986, *39,* 503-510). The compound of formula (8) is reacted with formula (a) in presence of suitable coupling reagent and in suitable solvent to give compound of formula (9) which further undergoes reduction with borane-dimethyl sulfide complex *(Journal of Medicinal Chemistry,* (1998), 46, 3142-3158) to give compound of formula (10). The compound of formula (10) undergoes carbon-nitrogen (C-N) coupling reaction with formula (b) by following the methods known in the art for example Buchwald coupling reaction (when L is a bond) using suitable reagents known in the art. Further, if this compound of formula (11) is an ester, it can be hydrolyzed to give corresponding acid of formula (12) using suitable base such as NaOH, LiOH, etc.

Experimental

The invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. The examples set forth below demonstrate the synthetic procedures for the preparation of the representative compounds. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the invention. The aforementioned patents and patent applications are incorporated herein by reference.

Unless otherwise stated, work-up implies the following operations: distribution of the reaction mixture between the organic and aqueous phase, separation of layers, drying the organic layer over sodium sulfate, filtration and evaporation of the organic solvent. Purification, unless otherwise mentioned, implies purification by silica gel chromatographic techniques, generally using ethyl acetate/petroleum ether mixture of a suitable polarity as the mobile phase.

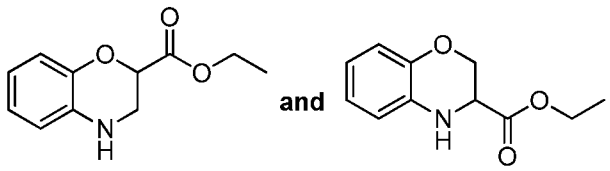
Intermediates

Intermediate-1a, 1b

Ethyl 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylate (1a)

and

Ethyl 3, 4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (1b)



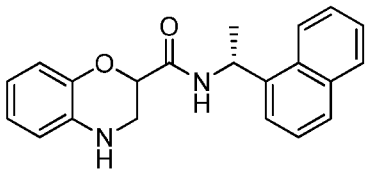
1a 1b

2-Aminophenol (68 g, 0.62mol) was added to a mixture of (430 g, 3.11mol) of potassium carbonate in DMF (1 L). The reaction mixture was stirred for 30 min at RT (room temperature) and then added ethyl 2, 3 dibromopropanoate (208 g, 0.80mol) in dropwise manner. The reaction mixture was heated to 45°C and further stirred for 15 h at the same

temperature. The progress of reaction was monitored by TLC. Reaction mixture was filtered and the filtrate was poured into water. The mixture was extracted with diethyl ether. The organic layer was dried over Na_2SO_4 and concentrated to get oily product (108 g). The resultant brown color oily product was purified by flash chromatography on a silica gel column eluted with mixture of 5% ethylacetate in hexane to give compound of 1a (25 g) as an oily mass and compound of 1b was eluted in 3% ethylacetate in hexane as an oil (15 g); (m/z 208.1).

Intermediate-2

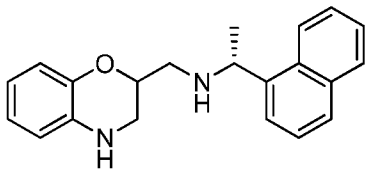
N-((*R*)-1-(Naphthalen-1-yl)ethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxamide



(*R*)-1-(Naphthalen-1-yl) ethanamine (1.65 g, 0.0096mol) was taken in dry toluene (10 mL) under nitrogen atmosphere. This solution was heated to 50ºC and added trimethyl aluminium (0.65 mL, 0.0072 mol, 2M solution in toluene). The reaction mixture was stirred for 15 min at the same temperature then slowly added a mixture of Intermediate-1a (1 g, 0.0048mol) in toluene (10 mL). The reaction mixture was heated to 110ºC and maintained for 5 h. The reaction progress was monitored by TLC. The reaction was quenched with dilute HCl and the product extracted with ethylacetate. Organic layer was washed with water followed by brine solution. The organic layers were combined, dried over sodium sulfate and concentrated to get the crude compound. Further this crude compound was purified by flash chromatography by using mixture of ethylacetate/hexane to get the title compound (1.45 g, 90.06%). m/z 333.2.

Intermediate-3

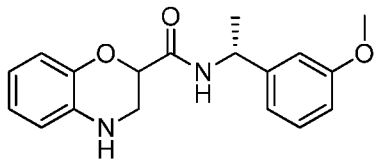
(1*R*)-*N*-((3,4-Dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)-1-(naphthalene-1yl) ethanamine



To a stirred solution of Intermediate-2 (6g, 18.05mmol) in dry THF (100mL) borane dimethyl sulphide complex (8.57ml, 90mmol,2M) was added at 0ºC then heated to 70ºC and further maintained for 12h. Tetrahydrofuran was distilled off under vacuum. The reaction mass was cooled to 0ºC then methanol (15mL) and dilute HCl (10mL) were added. Heated the reaction mass to 50ºC and further stirred for 40 minutes at the same temperature to break borane complex. Methanol was distilled off under vacuum. The reaction mixture was cooled to 0ºC and basified with 2M NaOH solution (pH=10]. The product was extracted into ethylacetate then the organic layer washed with water followed by brine solution. The organic layer dried over sodium sulphate and concentrated under vacuum to get the crude compound. Further this crude compound was purified by flash chromatography by using mixture of ethylacetate and hexane afforded the title compound as an oily mass (5.12 g, 89%). m/z 319.0.

Intermediate-4

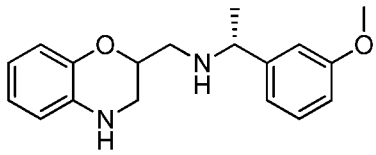
N-((*R*)-1-(3-Methoxyphenyl)ethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxamide



(*R*)-1-(3-Methoxyphenyl) ethanamine (1.46 g, 0.00966mol) was taken in dry toluene (10 mL) under nitrogen atmosphere. This solution was heated to 50ºC and then added trimethyl aluminium (0.65mL, 0.0072mol, 2M solution in toluene). The reaction mixture was stirred for 15 min at the same temperature then slowly added a mixture of ethyl 3,4-dihydro-2*H*-benzo[b][1, 4]oxazine-2-carboxylate (Intermediate-1a) (1 g, 0.0048 mol) in toluene (10 mL). The reaction mixture was heated to 110ºC and maintained for 5 hr. The progress of the reaction was monitored by TLC. The reaction was quenched with dilute HCl and the product extracted into ethyl acetate. Organic layer was washed with water followed by brine solution. The organic layers were combined, dried over sodium sulfate and concentrated to get amide. Purification was carried out by flash chromatography using a mixture of ethyl acetate /hexane afforded the title compound 1.40 g (92.71%). m/z 313.2.

Intermediate-5

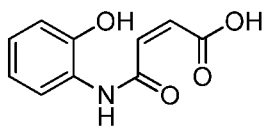
(1*R*)-*N*-((3,4-Dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)-1-(3-methoxyphenyl) ethanamine



To a mixture solution of Intermediate-4 (0.25 g , 0.80 mmol) in dry THF (10 mL) borane dimethyl sulphide complex (0.19 mL, 2.00 mmol) was added and heated to 60-70ºC and further maintained for 5 h. The progress of reaction was monitored by TLC. Tetrahydrofuran was distilled off under vacuum then methanol (5 mL) and dilute HCl (5 mL) was added at 0°C then heated to 65ºC and maintained for 40 minutes. Methanol was distilled off under vacuum. The reaction mixture was cooled to 0ºC and basified with 2M NaOH solution [pH=10]. The product was extracted into ethyl acetate and the organic layer washed with water followed by brine solution. The organic layers were combined, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by preparative HPLC (ACQUITY BEH C18, 50 X 2.1mm,1.7 µ) to afford title compound 0.18 g (75.41%). m/z 299.2

Intermediate-6

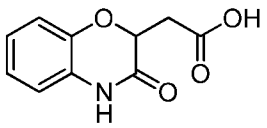
4-((2-Hydroxyphenyl) amino)-4-oxobut-2-enoic acid



To a solution of maleic anhydride (8.99g, 92mmol) in toluene (100 mL) o-aminophenol (10g, 92 mmol) was added at room temperature (RT) under stirring. Maintained the reaction mass for 3h and the resulting solid was filtered to afford the title compound (13 g, 62%); m/z 208.1.

Intermediate-7

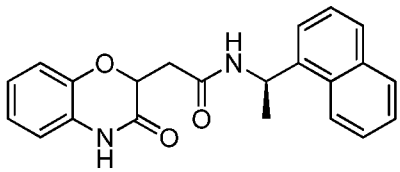
2-(3-Oxo-3, 4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)acetic acid



To a stirred solution of Intermediate-4 (10 g, 48.3mmol) in 1,4-dioxane (300 ml) triethylamine (20.18 ml, 145 mmol) was added in drop wise manner at RT. The reaction mixture was heated to reflux and further maintained for 12h. After completion of reaction, solvent was evaporated under vacuum. Reaction mass was acidified with 2N HCl (300ml) and extracted with ethylacetate (4x500ml). Organic layer was washed with water, brine, dried over sodium sulfate, concentrated under vacuum to afford the title compound (10 g, 93%); m/z 208.2.

Intermediate-8

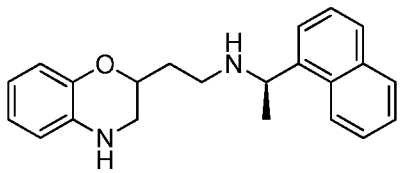
N-((*R*)-1-(Naphthalen-1-yl)ethyl)-2-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl) acetamide



To a ice cold solution of Intermediate-5 (9.5 g, 45.9 mmol) in DCM (150 ml), DIPEA (16ml, 92 mmol) and 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium (HATU) (20.9 g, 55mmol) were added sequentially. To the reaction mass (*R*)-1-(naphthalen-1-yl) ethanamine (9.41 g, 55 mmol) in DCM (50mL) was added slowly by dropping funnel. Reaction mass was then stirred at RT for 16 h. After completion of reaction the solid separated out was filtered and washed with ice cold DCM to get the title compound 12 g (85%); m/z 361.5.

Intermediate-9a, 9b

2-(3,4-Dihydro-2H-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl) ethanamine

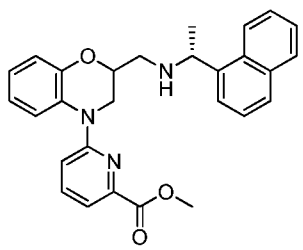


To a mixture of Intermediate-6 (9 g, 0.75mmol in dry THF(100 mL) borane dimethyl sulphide complex (39ml,78 mmol) was added at 0°C, then heated to 70°C and maintained for 12 h. Tetrahydrofuran was distilled off under vacuum. Methanol (10 mL) and dilute HCl (15 mL) were added at 0°C then heated to 50°C and further stirred for 40 min to break borane complex. Methanol was distilled off under vacuum. The reaction mixture was cooled to 0°C and basified with 2M NaOH solution [pH=10]. The product was extracted into ethylacetate then the organic layer washed with water followed by brine solution. The organic layer dried over sodium sulfate and concentrated under vacuum to get the racemic compound (7 g. 81%). Further, diastereomers were separated by chiral chromatography; CHIRAL PAK 1D, 250 x 4.6 MM 5u; mobile phase: A: hexane/IPA (90:10, %v/v, 0.1 % DEA) B: IPA (100%) A: B 80/20 % V/V; flow = 1.0 ml/min. m/z 333.1; 9a: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (d, *J*=7.6 Hz, 1H), 7.94-7.93 (dd, *J*=2.4 Hz, *J*=7.2 Hz, 1H), 7.8 (d, *J*=8.4 Hz, 1H), 7.68 (d, *J*=6.4 Hz, 1H), 7.53-7.48 (m, 3H), 6.61 (m, 1H), 6.57-6.51 (m, 2H), 6.41 (m, 1H), 5.68 (bs, 1H), 4.58 (m, 1H), 4.06 (m, 1H), 3.21 (d, 1H), 2.90 (m, 1H), 2.62 (s, 2H), 1.78 (m, 1H), 1.69 (m, 1H), 1.38 (d, *J*=6.8 Hz, 3H); m/z 333.1; 9b: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (m, 1H), 7.92 (m, 1H), 7.79(d, *J*=8.0 Hz, 1H),7.71 (d, *J*=6.4 Hz, 1H),7.53-7.47 (m, 3H), 6.62 (dt, *J*=1.6 Hz & *J*=7.8 Hz, 1H),6.53 (dt, *J*=1.2 Hz & *J*=8.2 Hz, 2H), 6.43 (dt, *J*=1.6 Hz & *J*=6.6 Hz, 1H), 5.70 (bs, 1H), 4.63 (m, 1H), 4.06 (m, 1H), 3.29 (d, *J*=12.0Hz, 1H), 2.92 (m, 1H), 2.59 (m, 2H), 1.76 (m, 1H), 1.69 (m, 1H), 1.39 (d, *J*=6.8 Hz, 3H).

EXAMPLES

Example-1

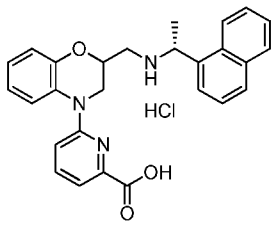
Methyl 6-(2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-2H-benzo[*b*][1,4]oxazin-4(3*H*)-yl) picolinate



To a mixture solution of Intermediate-3 (0.19g, 0.59mmol) and methyl 6-bromopicolinate (0.14g, 0.65 mmol), Cs_2CO_3 (0.19 g, 0.59 mmol) in toluene (3 mL) was degassed for 15 min by purging nitrogen. Then, bis (tri-tert-butylphosphine palladium (0) (0.030 g, 0.060 mmol) and tris dibenzylidene acetone dipalladium (0) (0.027 g, 0.030 mmol) were added. The reaction mixture was heated to 110ºC and further maintained for 20 h at the same temperature. The reaction mixture was cooled to RT and progress of reaction monitored by TLC. The mixture was diluted with ethylacetate, filtered through celite and concentrated under vacuum to get the crude product. The crude product was purified by flash chromatography using a mixture of 35% ethylacetate in hexane to get title compound. (0.21g, 80%) Mass (m/z) 454.2.

Example-2

6-(2-((((*R*)-1-(Naphthalen-1-yl) ethyl)amino)methyl)-2*H* -benzo [*b*][1,4]oxazin-4(3*H*) -yl)picolinic acid hydrochloride

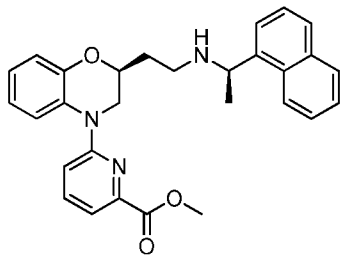


To a solution of racemic compound of Example-1 (0.04g, 0.088mmol) in MeOH (1 mL), THF (1mL), and water (1 mL) lithium hydroxide monohydrate (0.011 g, 0.441 mmol) was added. The reaction mixture was heated to 80°C and further maintained for 1h. The progress of reaction was monitored by TLC. Solvent was distilled off under vacuum then cooled to 0ºC and acidified with dilute HCl solution [pH=3 to 4]. Extracted the product into Ethyl acetate (5mL X 2), washed with water (2 mL X 2) followed by brine solution (5 mL), dried over sodium sulfate and concentrated under vacuum to get solid compound. This amino compound was dissolved in dry DCM, then slowly added 2M ethereal HCl solution and stirred for 10min. The solvent was evaporated and the resultant solid washed with diethyl ether followed by *n*-pentane to give hydrochloride salt of the desired compound (0.035g, 90%). m/z 439.92; ^{1}H NMR (400 MHz, DMSO): δ 10.2 (bs, 1H), 9.8 (bs, 1 H), 9.6 (bs, 1H), 9.4 (bs, 1H), 8.20 (m, 1H), 8.01-7.97 (m, 2H), 7.94-7.92 (m, 1H), 7.71 (m, 1H), 7.61-

7.55 (m, 3H), 7.53-7.50 (m, 1H), 7.37-7.33 (m, 2H), 7.24 (d, *J*=8.4, 1H), 7.01 (d, *J*=4.0, 1H), 6.98-6.88 (m, 1H), 5.45 (m, 1H), 4.65 (m, 1 H), 4.48 (m, 1H), 3.22 (m, 1H), 2.9 6 (m, 1H), 1.71(d, *J*=6.4 Hz, 3 H).

Example-3

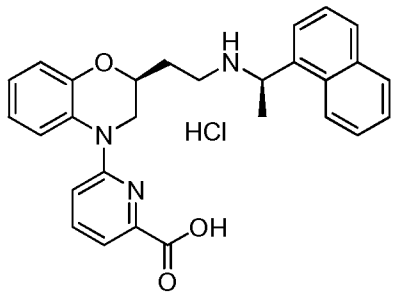
Methyl 6-((*S*)-2-(2-(((*R*)-1-(naphthalen-1-yl)ethyl)amino)ethyl)-2*H*-benzo[*b*][1,4]oxazin-4(3H)-yl)picolinate



To a mixture of Intermediate-9a (0.2g, 0.602mmol), methyl 6-bromopicolinate (0.152 g, 0.722 mmol), Cs_2CO_3 (0.29 g, 0.902 mmol) were added in toluene (3 mL) and degassed for 15 min by purging nitrogen. Then, bis (tri-tert-butylphosphine palladium (0) (0.015g, 0.030 mmol) and tris dibenzylidene acetone dipalladium (0) (0.028g, 0.030 mmol) were added. The reaction mixture was heated to 110°C and further maintained for 20 h at the same temperature. The reaction mixture was cooled to room temperature and progress of reaction monitored by TLC. The mixture was diluted with ethylacetate, filtered through celite and concentrated under vacuum to get the crude product. The crude product was purified by flash chromatography using a mixture of 60% ethylacetate in hexane to get title compound (0.15g, 53.1%) m/z 468.2.

Example-4

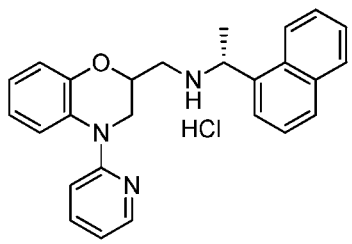
6-((*S*)-2-(2-(((*R*)-1-(Naphthalen-1-yl)ethyl)amino)ethyl)-2*H*-benzo[*b*][1,4]oxazin-4(3H)-yl)picolinic acid



To a solution of Example-3 (0.15g, 0.32 mmol) in MeOH (3 mL), and water (1mL) lithium hydroxide hydrate (0.38 g, 1.604 mmol) was added. The reaction mixture was heated to 80ºC and further maintained for 2 h. The progress of reaction was monitored by TLC. The reaction mixture was concentrated under vacuum then cooled to 0°C and acidified with dilute HCl solution [pH=3 to 4]. Extracted the product into Ethyl acetate (5mL X 2), washed with water (5 mL X 2) followed by brine solution (5 mL), dried over sodium sulfate and concentrated under vacuum to get solid. This amino compound was dissolved in dry DCM, then slowly added 2M ethereal HCl solution and stirred for 10min. The solvent was evaporated and the resultant solid washed with diethyl ether followed by *n*-pentane to give hydrochloride salt of the desired compound (0.1g, 63.6%). Mass (m/z) 454.1; ^{1}H NMR (400 MHz, DMSO): 10.2 (bs, 1H), 9.2 (bs, 1H), 8.19 (d, *J*=8.4Hz, 1H), 7.98 (t, *J*=8.4Hz, 2H), 7.80-7.76 (m, 2H), 7.62-7.57 (m, 3H), 7.54-7.52 (m, 1H), 7.41-7.36 (m,2H), 6.95-6.93 (m, 1H), 6.87-6.79 (m, 2H), 5.31-5.29 (m, 1H), 4.35-.28 (m, 2H), 3.61-3.59 (m, 1H), 3.25-3.23 (m, 1H), 3.14-3.08 (m, 1H), 1.98-1.95 (m, 2H), 1.64 (d, *J*= 6.8 Hz, 3H).

Example-5

(1*R*)-1-(Naphthalen-1-yl)-*N*-((4-(pyridin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)ethanamine hydrochloride

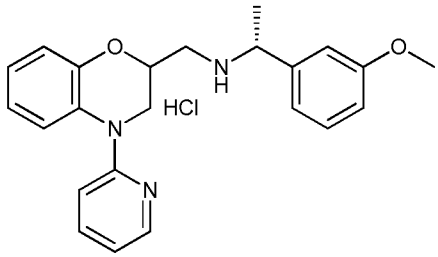


The title compound was prepared by following the similar procedure as described in Example-1 using Intermediate-2, 2-bromopyridine. Further the free base compound was

dissolved in dry DCM, then slowly added 2M ethereal HCl solution and stirred for 10min. The solvent was evaporated and the resultant solid washed with diethyl ether followed by *n*-pentane to give hydrochloride salt; m/z 396.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26-8.23 (m, 2H), 8.02-7.95 (m, 3H), 7.62-7.56 (m, 4H), 7.35-7.33 (m, 1H), 7.00-6.93 (m, 1H), 6.91-6.86 (m, 4H), 4.68 (m, 1H), 4.50-4.43 (m, 1H), 3.40-3.35 (m, 1H), 3.19-3.16 (m, 1H), 2.97 (d, *J*=8 Hz, 1H), 1.73 (d, *J*=6.4 Hz, 3H);

Example-6

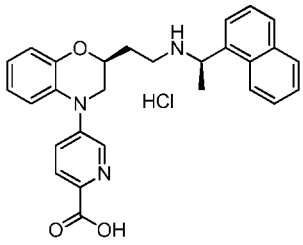
(1*R*)-1-(3-Methoxyphenyl)-*N*-((4-(pyridin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)ethanamine hydrochloride



The title compound was prepared by following the similar procedure as described in Example-1 using Intermediate-5, 2-bromopyridine. Further the free base compound was dissolved in dry DCM, then slowly added 2M ethereal HCl solution and stirred for 10min. The solvent was evaporated and the resultant solid washed with diethyl ether followed by *n*-pentane to give hydrochloride salt; m/z 376.3; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (m, 1H), 7.77-7.73 (m, 1H), 7.34-7.29 (m, 2H), 7.24-6.91 (m, 8H), 4.49 (m,1H), 4.38 (m, 1H), 3.76 (m, 3H), 3.57-3.48 (m, 1H), 3.35 (q, *J*=6.4 Hz, 1H), 3.19-2.99 (m,1H), 2.79-2.67 (m, 1H), 1.58 (d, *J*=6.4 Hz, 3H).

Example-7

5-((*S*)-2-(2-(((*R*)-1-(Naphthalen-1-yl)ethyl)amino)ethyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)picolinic acid hydrochloride



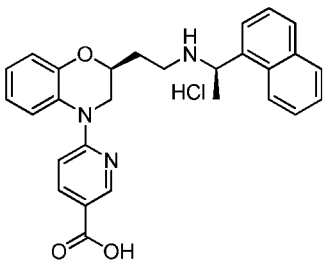
The title compound was prepared in two steps:

Step-1: Intermediate-9a was coupled with methyl 5-bromopicolinate by following the similar procedure as described in Example-1.

Step-2: Step-1 compound was under gone ester hydrolysis followed by HCl salt preparation by following the similar procedure as described in Example-2. Mass (m/z) 454.4; ^{1}H NMR (400 MHz, DMSO): 9.78 (bs, 1H), 9.74 (bs, 1H), 8.73 (m, 1H), 8.24 (d, *J*=8.0Hz, 1H), 8.05-8.0 (m, 3H), 7.97 (d, *J*=8Hz, 1H), 7.64-7.59 (m, 3H), 7.48 (d, *J*=8Hz, 1H), 7.25 (d, *J*=8.8Hz, 1H), 7.036 (t, *J*=6.8Hz, 1H), 6.91-6.87 (m, 2H), 5.30-5.28 (m, 1H), 4.33-4.25 (m, 2H), 3.61-3.59 (m, 1H), 3.24-3.22 (m, 1H), 3.13-3.10 (m, 1H), 1.94-1.90 (m, 2H), 1.62 (d, *J*= 6.4 Hz, 3H).

Example-8

6-((*S*)-2-(2-(((*R*)-1-(Naphthalen-1-yl)ethyl)amino)ethyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)nicotinic acid hydrochloride



The title compound was prepared in two steps:

Step-1: Intermediate-9a was coupled with methyl 6-bromopicolinate by following the similar procedure as described in Example-1.

Step-2: Step-1 compound was under gone ester hydrolysis followed by HCl salt preparation by following the similar procedure as described in Example-2. Mass (m/z) 454.4; ^{1}H NMR (400 MHz, DMSO): 9.96(bs, 1H), 9.26 (bs, 1H), 8.57 (m, 1H), 8.24 (d, *J*=8.0Hz, 1H), 8.027-

7.96 (m, 4H), 7.72-7.70 (m, 1H), 7.64-7.57 (m, 3H), 7.16 (d, *J*=7.6Hz, 1H), 6.91 (t, *J*=7.2 Hz, 1H), 6.84-6.80 (m, 2H), 5.33-5.30 (m, 1H), 4.29-4.27 (m, 2H), 3.61-3.59 (m, 1H), 3.21-3.19 (m, 1H), 3.15-3.13 (m, 1H), 2.08-2.048 (m, 2H), 1.68 (d, *J*= 6.4 Hz, 3H).

In-vitro Pharmacological activity

Certain illustrative compounds within the scope of the invention are screened for CaSR activity according to the procedure given below. The screening of the compounds may also be carried by other methods and procedures known to skilled in the art.

In-vitro assay method of Calcimimetics through modulation of Calcium Sensing Receptor (CaSR):

The ability of the compounds to modulate Calcium sensing receptor is determined by measuring an increase in intracellular calcium $[Ca^{2+}]_i$. Stably transfected HEK293 cells expressing hCaSR_pTriEx-3 hygro vector are developed. Cells are grown overnight on a 96-well plate to 80% confluency in Ham's F12 containing 20% FBS at 37ºC, 5% CO_2. Subsequently, cells are washed extensively with 20mM HEPES buffer containing 126mM $NaCl_2$, 1mM $MgCl_2$ and 4mM KCl to remove serum components that might interfere with the assay. Cells are loaded with calcium sensing Fluo4NW dye in HEPES base buffer containing 0.1% BSA and 1mg/ml glucose for 30 minutes to measure changes in intracellular calcium. The activities of the compounds are measured in FLIPR using 0.3mM $CaCl_2$ in 20mM HEPES base buffer. The effectiveness of the compound to modulate receptor activity is determined by calculating the EC_{50} responses for that compound in an 8-point assay and plotted using GraphPad Prism 5.

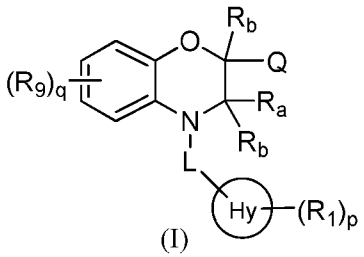
The compounds prepared were tested using the above assay procedure and have EC_{50} values less than 200 nano molar (nM). Thus, the above *in-vitro* assay method shows that the compounds of the invention were found to exhibit agonistic activity for CaSR, thereby showing utility for treating diseases, disorders associated with the modulation of CaSR.

All patents, patent applications and other publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

Although certain embodiments and examples have been described in detail above, those having ordinary skill in the art will clearly understand that many modifications are possible in the embodiments and examples without departing from the teachings thereof. All such modifications are intended to be encompassed within the below claims of the invention.

CLAIMS

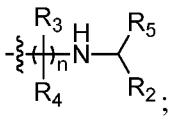
1. A compound of Formula (I):



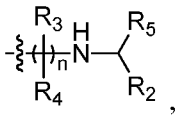
(I)

wherein,

Q is hydrogen or



R_a is selected from



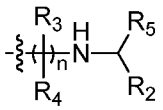
hydrogen, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted haloalkyl;

R_b, which may be same or different at each occurrence, is independently selected from hydrogen, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted haloalkyl;

or R_a and R_b together attached on the same carbon form C(O) or C(S);

provided that,

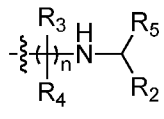
when Q is



then

R_a is selected from hydrogen, halogen, substituted or unsubstituted alkyl, cyano, substituted or unsubstituted cycloalkyl and substituted or unsubstituted haloalkyl; or

R_a and R_b together attached on the same carbon atom form C(O) or C(S);

when Q is hydrogen then R_a is  ;

L is selected from a bond, $-(CR_cR_d)_m$, -C(O)-, -C(S)-, $-C(O)NR_7$-, $-S(O)_2$-, $-S(O)_2-NR_7$, $-C(O)CH_2$-, $-CH_2C(O)$- and -C(O)O-;

R_c and R_d, which may be same or different at each occurrence, are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl;

ring 'Hy' is heteroaryl;

R_1, which may be same or different at each occurrence, is independently selected from halogen, nitro, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, -C(O)-Z, $-(CR_eR_f)_mC(O)$-Z, $-O(CR_eR_f)_m$-C(O)-Z, $-(CR_eR_f)_mO$-C(O)-Z, $-C(O)(CR_eR_f)_m$-C(O)-Z, $-C(O)NR_7$-C(O)-Z, $-C(O)NR_7(CR_eR_f)_m$-C(O)-Z, -cycloalkylene-C(O)-Z, -O-cycloalkylene-C(O)-Z, $-OR_6$, $-C(O)R_{10}$, $-NR_7R_8$, $-NR_7C(O)R_{10}$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_{10}$;

R_e and R_f, which may be same or different at each occurrence, are independently selected from hydrogen, halogen, hydroxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl and substituted or unsubstituted cycloalkyl; or R_e and R_f, together with the carbon atom to which they are attached, form a substituted or unsubstituted 3 to 7 membered saturated carbocyclic ring;

Z is $-OR_6$ or $-NR_7R_8$;

R_2 is selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocyclyl;

R_3 and R_4, which may be same or different at each occurrence, are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted

alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkoxy and substituted or unsubstituted cycloalkyl;

R_5 is substituted or unsubstituted alkyl or substituted or unsubstituted haloalkyl;

R_6, which may be same or different at each occurrence, is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl and substituted or unsubstituted alkynyl;

R_7 and R_8, which may be same or different at each occurrence, are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heterocyclylalkyl; or R_7 and R_8, together with the nitrogen atom to which they are attached, may form a substituted or unsubstituted, saturated or unsaturated 3 to 12 membered cyclic ring, wherein the unsaturated cyclic ring may have one or two double bonds;

R_9, which may be same or different at each occurrence, is independently selected from halogen, nitro, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, aryl, $-OR_6$, $-C(O)R_{10}$, $-C(O)OR_6$, $-(CH_2)_r-C(O)OR_6$, $-O(CH_2)_r-C(O)OR_6$, $-NR_7R_8$, $-C(O)NR_7R_8$, $-NR_7C(O)R_{10}$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_{10}$;

at each occurrence, R_{10} is substituted or unsubstituted alkyl or substituted or unsubstituted aryl;

'm' is an integer ranging from 1 to 3, both inclusive;

'n' is an integer ranging from 1 to 3, both inclusive;

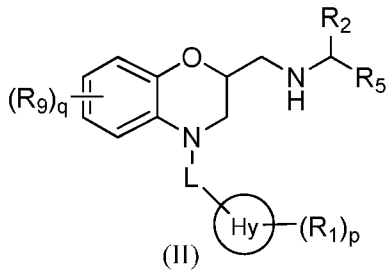
'p' is an integer ranging from 0 to 4, both inclusive;

'q' is an integer ranging from 0 to 3, both inclusive; and

'r' is an integer ranging from 1 to 3, both inclusive;

or pharmaceutically acceptable salt thereof.

2. The compound of claim 1 having the Formula (II):

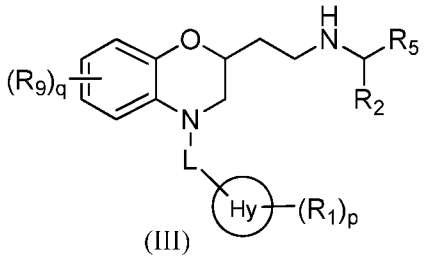


(II)

and pharmaceutically acceptable salt thereof;

wherein ring 'Hy', L, R_1, R_2, R_5, R_9, 'p' and 'q' are as defined in cliam-1.

3. The compound of claim 1 having the Formula (III):



(III)

or pharmaceutically acceptable salt thereof.

wherein ring 'Hy', L, R_1, R_2, R_5, R_9, 'p' and 'q' are as defined in cliam-1.

4. The compound of claim 1, which is selected from:

Methyl 6-(2-((((*R*)-1-(naphthalen-1-yl) ethyl) amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)picolinate;

6-(2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl) picolinic acid hydrochloride;

Methyl 6-((*S*)-2-(2-(((*R*)-1-(naphthalen-1-yl)ethyl)amino)ethyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)picolinate;

6-((*S*)-2-(2-(((*R*)-1-(Naphthalen-1-yl)ethyl)amino)ethyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)picolinic acid;

(1*R*)-1-(Naphthalen-1-yl)-*N*-((4-(pyridin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)ethanamine hydrochloride;

(1*R*)-1-(3-Methoxyphenyl)-*N*-((4-(pyridin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)ethanamine hydrochloride;

5-((*S*)-2-(2-(((*R*)-1-(Naphthalen-1-yl)ethyl)amino)ethyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)picolinic acid hydrochloride and

6-((*S*)-2-(2-(((*R*)-1-(Naphthalen-1-yl)ethyl)amino)ethyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)nicotinic acid hydrochloride,

or pharmaceutically acceptable salts thereof.

5. A pharmaceutical composition comprising one or more compounds of Formula (I) according to claim 1, and one or more pharmaceutically acceptable excipients.
6. A method of treating, managing and/or lessening the diseases or disorders, syndromes or conditions associated with the modulation of calcium sensing receptor (CaSR) in a subject in need thereof wherein the method comprises administering to the subject a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.
7. The method of claim 6, wherein the diseases, disorders, syndromes or conditions associated with the modulation of calcium sensing receptor (CaSR) are selected from hyperparathyroidism, chronic renal failure (with or without dialysis), chronic kidney disease (with or without dialysis) and their complications.
8. The method of claim 7, wherein hyperparathyroidism is primary hyperparathyroidism, secondary hyperparathyroidism or tertiary hyperparathyroidism.
9. The method of claim 6, wherein the diseases, disorders, syndromes or conditions associated with the modulation of CaSR receptors are selected from the group consisting of parathyroid adenoma, parathyroid hyperplasia, parathyroid carcinoma, vascular & valvular calcification, abnormal calcium homeostasis, hypercalcemia, abnormal phosphorous homeostasis, hypophosphatemia, bone related diseases or complications arising due to hyperparathyroidism, chronic kidney disease or parathyroid carcinoma, bone loss post renal transplantation, osteitis fibrosa cystica, adynamic bone disease, renal bone diseases, cardiovascular complications arising due to hyperparathyroidism or chronic kidney disease, certain malignancies in which

$(Ca^{2+})_e$ ions are abnormally high, cardiac, renal or intestinal dysfunctions, podocyte-related diseases, abnormal intestinal motility, diarrhea, augmenting gastrin or gastric acid secretion to directly or indirectly benefit in atrophic gastritis or to improve absorption of pharmacological compounds, drugs or supplements from gastro-intestinal tract by augmenting gastric acidity.

10. Use of a compound for the manufacture of a medicament for treating, managing and/or lessening the diseases or disorders, syndromes or conditions associated with the modulation of calcium sensing receptor (CaSR) in a subject in need thereof wherein the method comprises administering to the subject a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

11. The use of claim 10, wherein the diseases, disorders, syndromes or conditions associated with the modulation of calcium sensing receptor (CaSR) are selected from hyperparathyroidism, chronic renal failure (with or without dialysis), chronic kidney disease (with or without dialysis) and their complications.

12. The use of claim 11, wherein hyperparathyroidism is primary hyperparathyroidism, secondary hyperparathyroidism or tertiary hyperparathyroidism.

13. The use of claim 10, wherein the diseases, disorders, syndromes or conditions associated with the modulation of CaSR receptors are selected from the group consisting of parathyroid adenoma, parathyroid hyperplasia, parathyroid carcinoma, vascular & valvular calcification, abnormal calcium homeostasis, hypercalcemia, abnormal phosphorous homeostasis, hypophosphatemia, bone related diseases or complications arising due to hyperparathyroidism, chronic kidney disease or parathyroid carcinoma, bone loss post renal transplantation, osteitis fibrosa cystica, adynamic bone disease, renal bone diseases, cardiovascular complications arising due to hyperparathyroidism or chronic kidney disease, certain malignancies in which $(Ca^{2+})_e$ ions are abnormally high, cardiac, renal or intestinal dysfunctions, podocyte-related diseases, abnormal intestinal motility, diarrhea, augmenting gastrin or gastric acid secretion to directly or indirectly benefit in atrophic gastritis or to improve

absorption of pharmacological compounds, drugs or supplements from gastro-intestinal tract by augmenting gastric acidity.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/052018

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2012/127385 A1 (LUPIN LTD [IN]; SHUKLA MANOJKUMAR RAMPRASAD [IN]; ANKUSH SARDE GANGARA) 27 September 2012 (2012-09-27) page 65 - page 66; examples 1,2	1,2,4-13
A	WO 01/90069 A1 (CENTRE NAT RECH SCIENT [FR]; RUAT MARTIAL [FR]; DODD ROBERT [FR]; FAUR) 29 November 2001 (2001-11-29) cited in the application the whole document	1-13
A	WO 97/41090 A1 (NPS PHARMA INC [US]) 6 November 1997 (1997-11-06) the whole document	1-13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 May 2013	31/07/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bedel, Christian

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2013/052018

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