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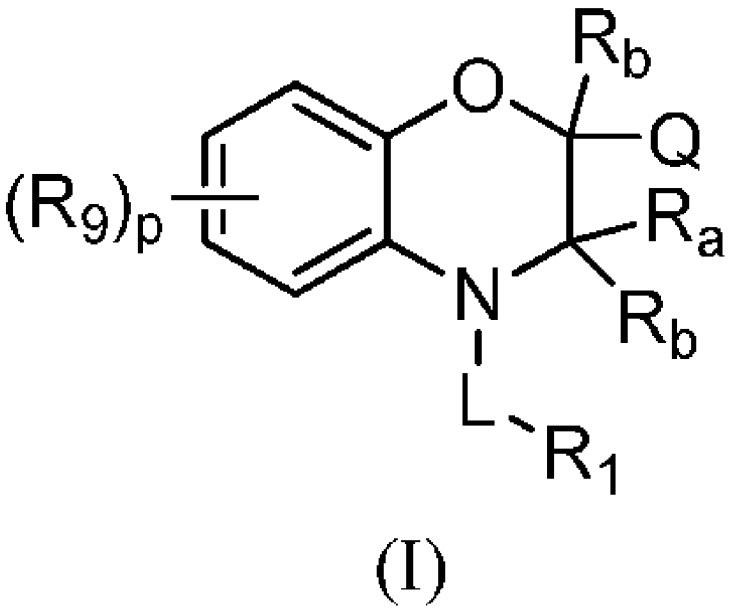
*[Continued on next page]*

(54) Title: BENZO [B] [1, 4] OXAZIN DERIVATIVES AS CALCIUM SENSING RECEPTOR MODULATORS




(I)

(57) Abstract: Compounds of Formula (I) along with processes for their preparation that are useful for treating, managing and/or lessening the diseases, disorders, syndromes or conditions associated with the modulation of calcium sensing (Ca SR) receptors. Methods of treating, managing and/or lessening the diseases, disorders, syndromes or conditions associated with the modulation of calcium sensing (Ca SR) receptors of Formula (I).

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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# BENZO[B][1,4]OXAZIN DERIVATIVES AS CALCIUM SENSING RECEPTOR MODULATORS

## Related Applications

This application claims the benefit of Indian patent application no. 0367/KOL/2011 filed on March 18, 2011 which is hereby incorporated by reference in their entirety.

## Field of the Invention

The present invention relates to substituted heterocyclic 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 aminoacids), 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.

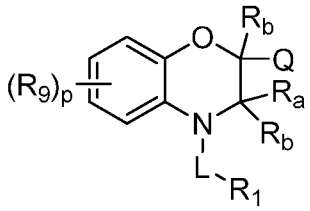
In conditions such as primary and secondary hyperparathyroidism, there is excessive secretion of parathyroid hormone due to hyperplasia of the glands. The most common cause of primary hyperparathyroidism (PHPT) is parathyroid adenoma resulting from clonal mutations (~97%) and associated hypercalcemia. 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.

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

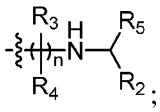
In accordance with another aspect, the invention provides compounds having the structure of Formula (I),



(I)

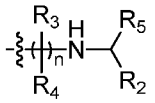
wherein,

Q is hydrogen or



;

$R_a$ is selected from



,

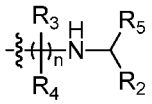
hydrogen, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted haloalkyl;

$R_b$ is 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

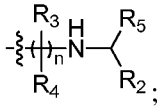


then

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

or

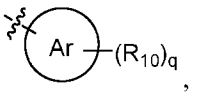
$R_a$ and $R_b$ together attached on the same carbon atom form C(O) or C(S);

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;

$R_1$ is selected from



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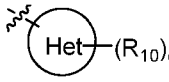


, substituted or unsubstituted alkyl, $-(CR_cR_d)_{1-3}-C(O)OR_6$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted cycloalkenyl;

ring Ar is phenyl or naphthyl;

ring Het is heteroaryl;

$R_{10}$, 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, substituted or unsubstituted hydroxyalkyl, $-OR_6$, $-C(O)R_6$, $-NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$;

provided that,

$R_{10}$ is not alkyl substituted with $-C(O)OR^x$ or $-OC(O)OR^x$ or $-C(O)NR^yR^z$ or $-OC(O)NR^yR^z$; wherein $R^x$ is selected from hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heteroaryl, heterocyclic ring, heterocyclylalkyl and heteroarylalkyl; and $R^y$ and $R^z$ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl;

$R_2$ 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, form a substituted or unsubstituted 3 to 12 membered cyclic ring, where the cyclic ring may be heteroaryl or heterocyclyl;

$R_9$, 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, substituted or unsubstituted aryl, $-OR_6$, $-C(O)R_6$, $-C(O)OR_6$, $-(CH_2)_r-C(O)OR_6$, $-O(CH_2)_r-C(O)OR_6$, $-NR_7R_8$, $-C(O)NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$;

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

'm' 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 4, both inclusive; and

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

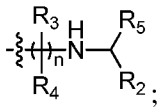
or pharmaceutically acceptable salt thereof.

In accordance with another aspect, the invention provides compounds having the structure of Formula (I),

wherein L, Q, $R_a$, $R_b$, $R_1$ and $R_9$ are as defined herein above,

with the proviso that:

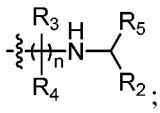
when $R_9$ is halogen, alkyl, alkoxy; 'p' is 0 or 1;

Q is  ;

$R_3$ and $R_4$ are hydrogen; 'n' is 1; $R_2$ is aryl; $R_5$ is alkyl; L is a bond, then $R_1$ is not alkyl or aryl; wherein aryl is substituted with halogen, nitro, alkyl or alkoxy;

or

when $R_9$ is halogen, alkyl, alkoxy or 'p' is 0 or 1;

Q is  ;

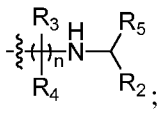
$R_3$ and $R_4$ are hydrogen; 'n' is 1; $R_2$ is aryl; $R_5$ is alkyl; L is $-S(O)_2$ then $R_1$ is not alkyl, aryl, arylalkyl; wherein aryl is substituted with halogen, nitro, alkyl or alkoxy.

In accordance with another aspect, the invention provides compounds having the structure of Formula (I),

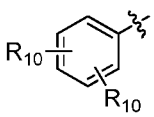
wherein L, Q, $R_a$, $R_b$, $R_1$ and $R_9$ are as defined herein above,

with the proviso that:

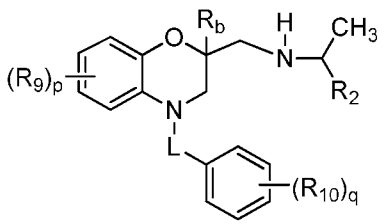
when $R_9$ is halogen, hydroxyl, alkyl, alkoxy, amino, nitro, trihaloalkyl; 'p' is 0 or 1;

Q is  ;

$R_3$ and $R_4$ are H; 'n' is 1; $R_2$ is phenyl; and $R_5$ is alkyl; and

L is a bond, then $R_1$ is not  wherein each of $R_{10}$ is selected from hydrogen, halogen, nitro, amino or trihaloalkyl.

According to one embodiment, there are provided compounds of the formula (II):



(II)

or its pharmaceutically acceptable salt thereof;

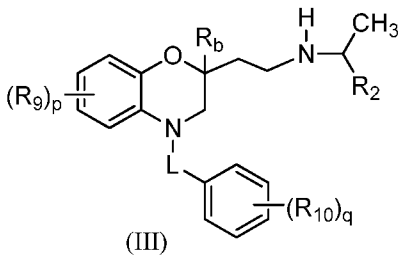
wherein,

$R_2$ is substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl;

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

$R_b$, $R_c$, $R_d$, $R_7$, $R_9$, $R_{10}$, 'm', 'p' and 'q' are as defined in Formula (I).

According to another embodiment, there are provided compounds of the formula (III):



(III)

or its pharmaceutically acceptable salt thereof;

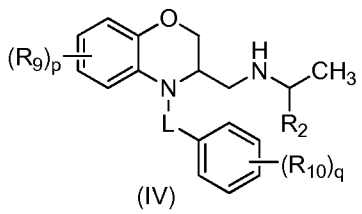
wherein,

$R_2$ is substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl;

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

$R_b$, $R_c$, $R_d$, $R_7$, $R_9$, $R_{10}$, 'm', 'p' and 'q' are as defined in Formula (I).

According to another embodiment, there provided compounds of the formula (IV):



(IV)

or its pharmaceutically acceptable salt thereof;

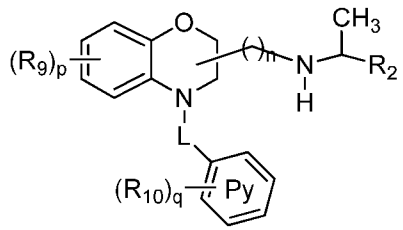
wherein,

$R_2$ is substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl;

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

$R_c$, $R_d$, $R_7$, $R_9$, $R_{10}$, 'm', 'p' and 'q' are as defined in Formula (I).

According to another embodiment, there are provided compounds of the formula (V):



(V)

or pharmaceutically acceptable salt thereof,

wherein,

ring 'Py' is pyridyl;

$R_2$ is substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl;

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

$R_c$, $R_d$, $R_7$, $R_9$, $R_{10}$, 'm', 'n' 'p' and 'q' are as defined in Formula (I).

It should be understood that the Formula (I), Formula (II), Formula (III), Formula (IV) and Formula (V) structurally encompasses all tautomers, stereoisomers, enantiomers and diastereomers, including isotopes wherever applicable and pharmaceutically acceptable salts that may be contemplated from the chemical structure of the genera described herein.

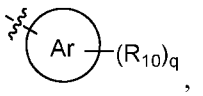
The details of one or more embodiments of the invention set forth in the below are illustrative in nature only and not intended to limit to the scope of the invention. Other features, objects and advantages of the inventions will be apparent from the description and claims.

According to another sub embodiment, there are provided compounds of formula (I) in which 'n' is 1.

According to another sub embodiment, there are provided compounds of formula (I) in which 'n' is 2.

According to another sub embodiment, there are provided compounds of formulae (II), and/or (III) in which $R_b$ is hydrogen or alkyl.

According to one sub embodiment, there are provided compounds of formulae (I) in which $R_1$ is selected from



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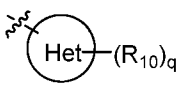


, substituted or unsubstituted alkyl, $-(CR_cR_d)_{1-3}$-C(O)$OR_6$, substituted or unsubstituted haloalkyl and substituted or unsubstituted cycloalkyl;

ring Ar is phenyl or naphthyl;

ring Het is heteroaryl;

$R_c$ and $R_d$ are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl;

$R_{10}$ is independently selected from halogen, nitro, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted hydroxyalkyl, -$OR_6$, -$NR_7R_8$, -$NR_7C(O)R_6$, -$S(O)_{0-2}R_6$, -$S(O)_2NR_7R_8$, and -$NR_7S(O)_2R_6$;

wherein, $R_7$ and $R_8$ are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, and substituted or unsubstituted aryl;

$R_6$ is hydrogen, or substituted or unsubstituted alkyl; and

'q' is 0 to 3;

or its pharmaceutically acceptable salt thereof.

According to another sub embodiment, there are provided compounds of formulae (II), (III), (IV) and/or (V) in which $R_2$ is substituted or unsubstituted aryl, wherein aryl is phenyl or naphthyl and the aryl is substituted with one or more substituents independently selected from halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy and substituted or unsubstituted haloalkoxy.

According to another sub embodiment, there are provided compounds of formula (I) in which 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-; wherein $R_c$ and $R_d$ are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl; $R_7$ is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, and substituted or unsubstituted aryl, and 'm' is 1 or 2.

According to another sub embodiment, there are provided compounds of formulae (II), (III), (IV) and/or (V) in which L is a bond $-(CR_cR_d)_m$-, -C(O)-, -C(O)NH-, $-C(O)CH_2$, or $-CH_2C(O)$-, wherein $R_c$ and $R_d$ are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl; and 'm' is 1 or 2.

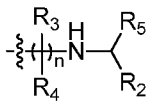
According to one sub embodiment, there are provided compounds of formulae (II), (III), (IV) and/or (V) in which $R_9$ is selected from halogen, nitro, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, $-OR_6$, $-C(O)R_6$, $-C(O)OR_6$, $-(CH_2)_r-C(O)OR_6$, $-O(CH_2)_r-C(O)OR_6$, $-NR_7R_8$, $-C(O)NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$; wherein $R_6$ is hydrogen, or substituted or unsubstituted alkyl; $R_7$ and $R_8$ are independently selected from hydrogen, substituted or unsubstituted

alkyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted aryl; and 'r' is 1 to 3; and 'p' is 0 to 3.

According to one sub embodiment, there are provided compounds of formulae (II), (III), (IV) and/or (V) in which $R_{10}$ is independently selected from halogen, nitro, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted hydroxyalkyl, $-OR_6$, $-C(O)R_6$, $-NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$; wherein $R_6$ is hydrogen, or substituted or unsubstituted alkyl; $R_7$ and $R_8$ are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, and substituted or unsubstituted aryl; and 'q' is 0 to 3.

According to one sub embodiment, there are provided compounds of formula (I) in which $R_1$ is aryl or heteroaryl, wherein aryl is phenyl or naphthyl; and heteroaryl is 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, or 6-pyridyl.

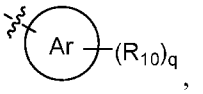
According to another sub embodiment, there are provided compounds of formula (I) in which Q is

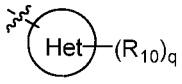


; $R_a$ is hydrogen; $R_b$ is hydrogen or substituted or unsubstituted alkyl;

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

$R_1$ is selected from



, 

, substituted or unsubstituted alkyl, $-(CR_cR_d)_{1-3}$-$C(O)OR_6$, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted cycloalkenyl;

ring Ar is phenyl or naphthyl;

ring Het is heteroaryl;

$R_{10}$, 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 hydroxyalkyl, $-OR_6$, $-NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$;

$R_c$ and $R_d$ are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl;

$R_2$ is substituted or unsubstituted aryl, wherein the substituent(s) may be one or more, same or different and are independently selected from halogen, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy and substituted or unsubstituted haloalkoxy;

$R_3$ and $R_4$ hydrogen;

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

$R_6$ is hydrogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl;

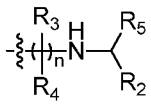
$R_7$ and $R_8$ are hydrogen or substituted or unsubstituted alkyl;

$R_9$, 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 cycloalkyl, substituted or unsubstituted aryl, $-OR_6$, $-C(O)OR_6$, $-(CH_2)_r-C(O)OR_6$, $-O(CH_2)_r-C(O)OR_6$, $-NR_7R_8$, $-C(O)NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$;

'm' is 1 or 2; 'n' is 1 or 2; 'p' is 0 to 3; 'q' is 0 to 3; and 'r is 1 to 3;

or pharmaceutically acceptable salt thereof.

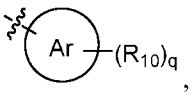
According to another sub embodiment, there are provided compounds of formula (I) in which $R_a$ is

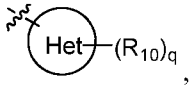


; Q is hydrogen; $R_b$ is hydrogen or substituted or unsubstituted alkyl;

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

$R_1$ is selected from





, substituted or unsubstituted alkyl, -$(CR_cR_d)_{1-3}$-$C(O)OR_6$, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted cycloalkenyl;

ring Ar is phenyl or naphthyl;

ring Het is heteroaryl;

$R_{10}$, 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 hydroxyalkyl, $-OR_6$, $-NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$;

$R_c$ and $R_d$ are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl;

$R_2$ is substituted or unsubstituted aryl, wherein the substituent(s) may be one or more same or different and are independently selected from halogen, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy and substituted or unsubstituted haloalkoxy;

$R_3$ and $R_4$ hydrogen;

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

$R_6$ is hydrogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl;

$R_7$ and $R_8$ are hydrogen or substituted or unsubstituted alkyl;

$R_9$, 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 cycloalkyl, substituted or unsubstituted aryl, $-OR_6$, $-C(O)OR_6$, $-(CH_2)_r-C(O)OR_6$, $-O(CH_2)_r-C(O)OR_6$, $-NR_7R_8$, $-C(O)NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$;

'm' is 1 or 2; 'n' is 1 or 2; 'p' is 0 to 3; 'q' is 0 to 3; and 'r is 1 to 3;

or pharmaceutically acceptable salt thereof.

According to another sub embodiment, there are provided compounds of formula (I) in which the compounds are used as either the free base or a pharmaceutically

acceptable salt; where the pharmaceutically acceptable salt is monohydrochloride or dihydrochloride salt.

According to another sub embodiment, the provided compounds of formula (I) structurally encompasses stereoisomers including enantiomers and diastereomers.

The below compound is specifically excluded from the present invention:
1-(5-Methoxy-3-(((1-phenylethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl) ethanone.

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

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

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

(2-((((*R*)-1-(3-Methoxyphenyl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl) (phenyl) methanone;

(2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl) (phenyl)methanone;

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

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

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

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

(3-Fluorophenyl)(2-((((*R*)-1-(3-methoxyphenyl)ethyl) amino)methyl)-2*H*-benzo [*b*][1,4]oxazin-4(3H)-yl) methanone hydrochloride;

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

(2-((((*R*)-1-(3-Methoxy phenyl)ethyl)amino)methy)-2*H*-benzo[*b*][1,4] oxazin-4(3*H*)-yl)(m-tolyl) methanone;

(2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4 (3*H*)yl)(m-tolyl)methanone;

(2-((((*R*)-1(3-Methoxy phenyl)ethyl)amino) methyl)-2*H*-benzo[*b*][1,4] oxazin-4(3*H*)yl)(3(trifluoro methyl)phenyl)methanone hydrochloride;

(2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)(3-(trifluoro methyl) phenyl) methanone;

(3-Fluoro-5-(trifluoro methyl)phenyl) (2-((((*R*)-1-(3methoxyphenyl)ethyl) amino)methyl)-2*H*-benzo [*b*][1,4]oxazin-4(3*H*)-yl) methanone;

(3-Fluoro-5-(trifluoro- methyl)phenyl)(2-((((*R*)-1-(naphthalen-1-yl)ethyl) amino)methyl)-2*H*-benzo [*b*][1,4]oxazin-4(3*H*)-yl) methanone;

1-(2-((((*R*)-1-(3-Methoxy phenyl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)-2-phenyl;

1-(2-((((*R*)-1-(Naphthalen-1-yl)ethyl) amino)methyl)-2*H*-benzo[*b*][1,4] oxazin-4 (3*H*)-yl)-2-phenyl ethanone;

2-((((*R*)-1-(3-Methoxy phenyl)ethyl)amino) methyl)-*N*-(3(trifluoro methyl)phenyl)-2*H*-benzo[*b*][1,4]oxazine-4 (3*H*)-carboxamide hydrochloride;

2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino) methyl)-*N*-(3-(trifluoro methyl)phenyl)-2*H*-benzo[*b*][1,4]oxazine-4 (3*H*)-carboxamide hydrochloride;

*N*-(4-Fluorophenyl)-2-((((*R*)-1-(3methoxy phenyl)ethyl)amino) methyl)-2*H*-benzo[*b*] [1,4]oxazine-4(3*H*)-carboxamide hydrochloride;

N-(4-Fluorophenyl)-2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4] oxazine-4(3*H*)-carboxamide;

(1*R*)-*N*-((4(3-Methoxy phenyl)-3,4-dihydro-2*H*-benzo[*b*] [1,4] oxazin-2-yl) methyl) 1(naphthalen-1-yl) ethanamine;

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

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

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

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

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

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

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

2-Methyl-5-(2-((((*R*)-1-(naphthalen-1-yl) ethyl)amino)methyl)-2*H*-benzo[*b*][1,4] oxazin-4(3*H*)-yl) phenol hydrochloride;

(1*R*)-1-(3-Methoxy phenyl)-*N*-((4-(p-tolyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-2-yl)methyl) ethanamine;

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

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

(1*R*)-1-(3-Methoxy phenyl)-*N*-((4-(m-tolyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-2-yl)methyl) ethanamine;

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

(1*R*)-*N*-((6-Bromo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)-1-(naphthalen -1-yl)ethanamine hydrochloride;

(1*R*)-*N*-((7-Bromo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)-1-(naphthalen -1-yl)ethanamine hydrochloride;

(1*R*)-*N*-((4-Methyl-6-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-2-yl)methyl)-1 (naphthalen-1-yl) ethanamine hydrochloride;

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

4-Methyl-2-((((*R*)-1-(naphthalen-1yl) ethyl amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine-7carbonitrile hydrochloride;

Ethyl 3-(4-methyl-2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)propanoate;

3-(4-Methyl-2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-7-yl)propanoic acid hydrochloride;

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

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

4-Methyl-2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine-7-carboxylic acid hydrochloride;

4-Methyl-2-((((*R*)-1-(naphthalen-1-yl) ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine -6-carboxylic acid hydrochloride;

Isopropyl 4-methyl-2-((((*R*)-1-(naphthalen-1yl)ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo [*b*][1,4]oxazine-6-carboxylate hydrochloride;

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

(1*R*)-1-(Naphthalen-1-yl)-*N*-(2-(4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*] [1,4]oxazin-2-yl)ethyl)ethanamine;

(1*S*)-1-(Naphthalen-1-yl)-*N*-(2-(4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*] [1,4] oxazin-2-yl)ethyl)ethanamine hydrochloride;

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

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

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

1-(2-((((*R*)-1-(3-Methoxyphenyl) ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl) ethanone hydrochloride;

2-(4-(4-Methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(4-(4-Fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(4-(3-Fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine hydrochloride;

2-(4-(3-Fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(8-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(8-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine hydrochloride;

2-(8-Fluoro-4-(3-fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(8-Fluoro-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(8-Fluoro-4-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(3-fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(3-fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(5-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(5-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(5-Fluoro-4-(3-fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(5-Fluoro-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(5-Fluoro-4-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;
2-(5-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine; and
2-(5-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;
or pharmaceutically acceptable salts thereof or stereoisomers thereof.

In another aspect of the invention, there is provided a compound of formula (I) useful in treating, managing 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, managing 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 stereoisomer, salt, or in vivo hydrolysable ester thereof together with a pharmaceutically acceptable excipient.

Also provided herein are processes for preparing compounds described herein.

## Detailed description of the invention

### Definitions and Abbreviations:

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

For purposes of interpreting the specification, 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.

Unless otherwise stated, in the present application "oxo" means C(=O) group. Such an oxo group may be a part of either a cycle or a chain in the compounds of the present invention.

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. Non-limiting examples of such groups are monohaloalkoxy, dihaloalkoxy or polyhaloalkoxy including perhaloalkoxy. 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 "hydroxyalkyl" refers to an alkyl group, as defined above that is substituted by one or more hydroxy groups. Preferably, the hydroxyalkyl is monohydroxyalkyl or dihydroxyalkyl. Non-limiting examples of a hydroxyalkyl include 2- hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, and the like. Unless set forth or recited to the contrary, all hydroxyalkyl 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, perhydronaphthyl, 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 "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.

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 to the main structure at any heteroatom or carbon atom 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 to the main structure at any heteroatom or carbon atom 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 center 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.

The compound of the invention may form salts. Non-limiting examples of pharmaceutically acceptable salts include salts derived from inorganic bases, salts of organic bases, salts of chiral bases, salts of natural amino acids and salts of non-natural amino acids.

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 excipients 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, 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 formulation.

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 an embodiment, the invention provides compounds and pharmaceutical compositions thereof that are useful in treating, managing 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 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 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.

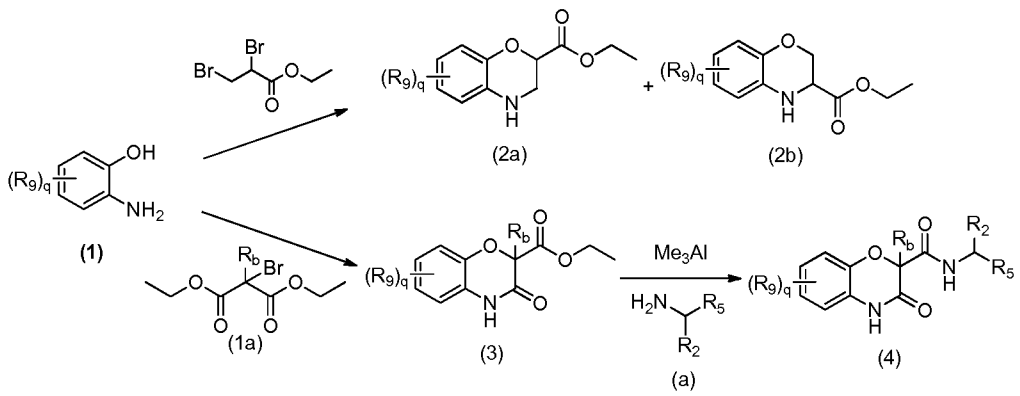
The compound and composition of the present invention can be used, in particular, to participate in an augmenting gastrin or gastric acid secretion to directly or indirectly benefit certain medical conditions such as but not limited to atrophic gastritis or to improve absorption of pharmacological compounds, 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-7. 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 in described in these schemes, unless otherwise specified, are also encompassed within the scope of this invention.

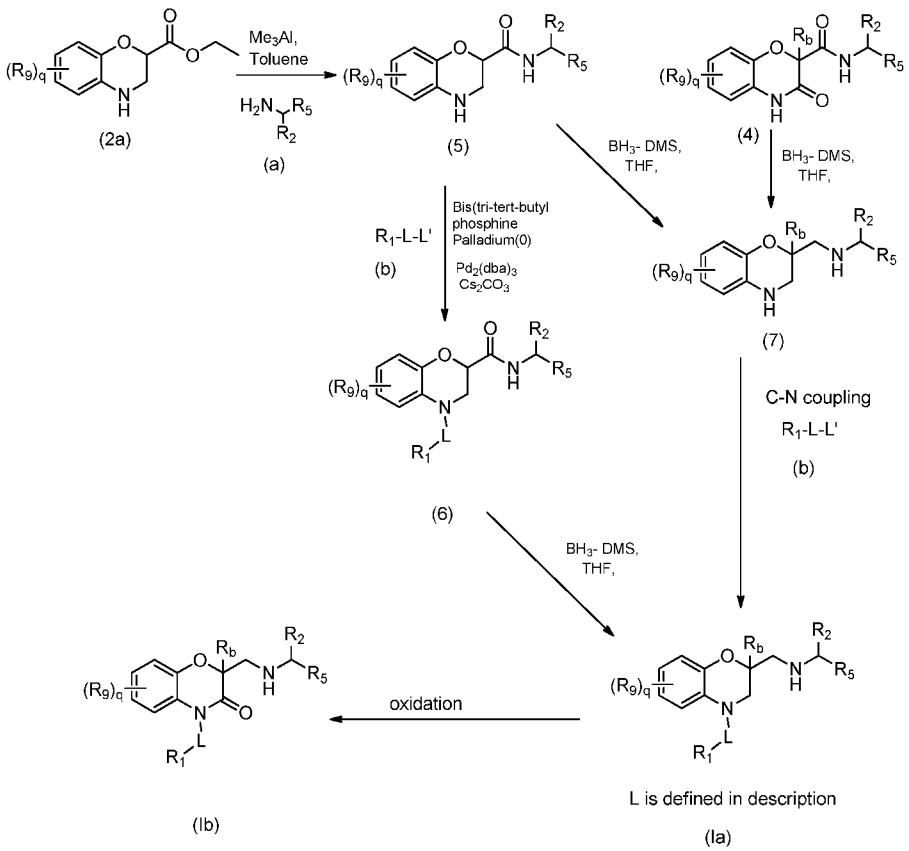
**Scheme-1**




The compound of formula (4), where $R_b$, $R_2$, $R_5$, $R_9$ and 'p' 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). Alternatively, the commercially available 2-aminophenol is reacted with diethyl 2-bromo-2-methyl malonate in the presence of base such as sodium carbonate, potassium carbonate or triethylamine to give compound of formula (3). The compound of formula (3) is further reacted with amine of formula (a) in presence of trimethyl aluminium to give compound of formula (4).

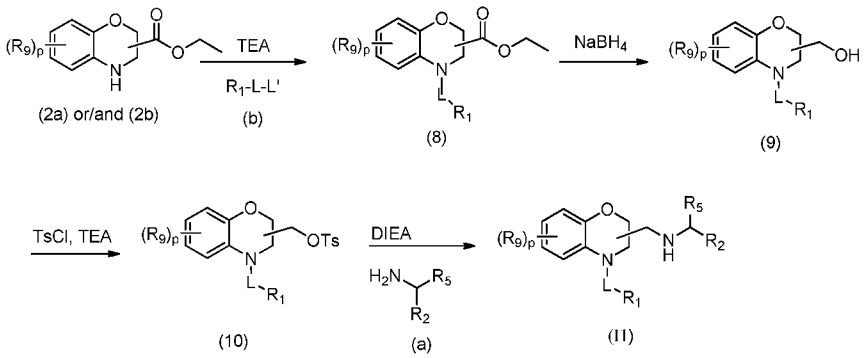
**Scheme-2**




The compound of formula (Ia), where ring L, $R_b$, $R_1$, $R_2$, $R_5$, $R_9$, and 'p' are as defined herein above, can be prepared by following the procedure as depicted in Scheme-2. The compound of formula (2a) is reacted with amine of formula (a) in presence of trimethyl aluminium to obtain compound of formula (5). This compound of formula (5) 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, or the coupling reaction (when L is not a bond) is carried out by using suitable base for example triethylamine (TEA), DIPEA or $K_2CO_3$ etc., and in suitable solvent for example dichloromethane (DCM), THF etc., to give compound of formula (6). This compound of formula (6) undergoes reduction by reducing agents such as $LiAlH_4$, borane-dimethyl sulfide etc., *(Journal of Medicinal*

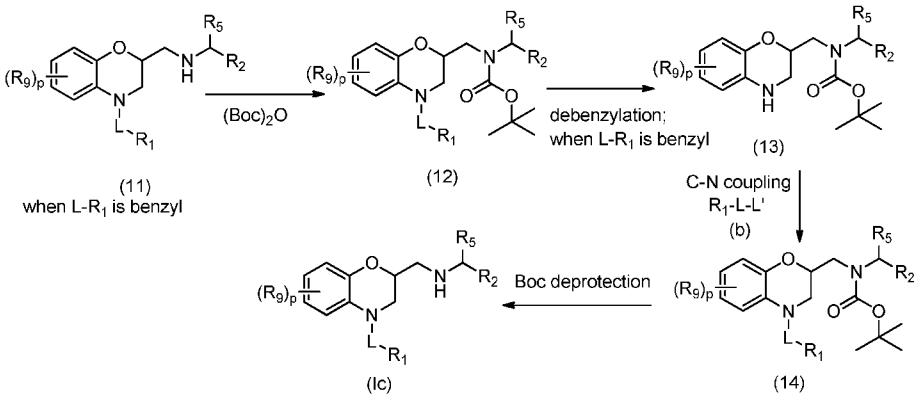
*Chemistry,* **1998**, 46, 3142-3158) complex to give compound of formula (Ia). This compound of formula (Ia) undergoes oxidation with suitable oxidizing agent for example $KMnO_4$ in suitable solvent like acetonitrile, DCM etc., to give compound of formula (Ib). Alternatively, the compound of formula (Ia) is prepared from formula (4) or formula (5) by carrying out reduction reaction using suitable reducing agents such as borane-dimethyl sulfide complex, $LiAlH_4$ etc., and in suitable solvent(s). This compound of formula (7) 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, or the coupling reaction (when L is not a bond) is carried out by using suitable base for example TEA, DIPEA or $K_2CO_3$ etc., and in suitable solvent for example DCM, THF etc., to give compound of formula (Ia).

**Scheme-3**



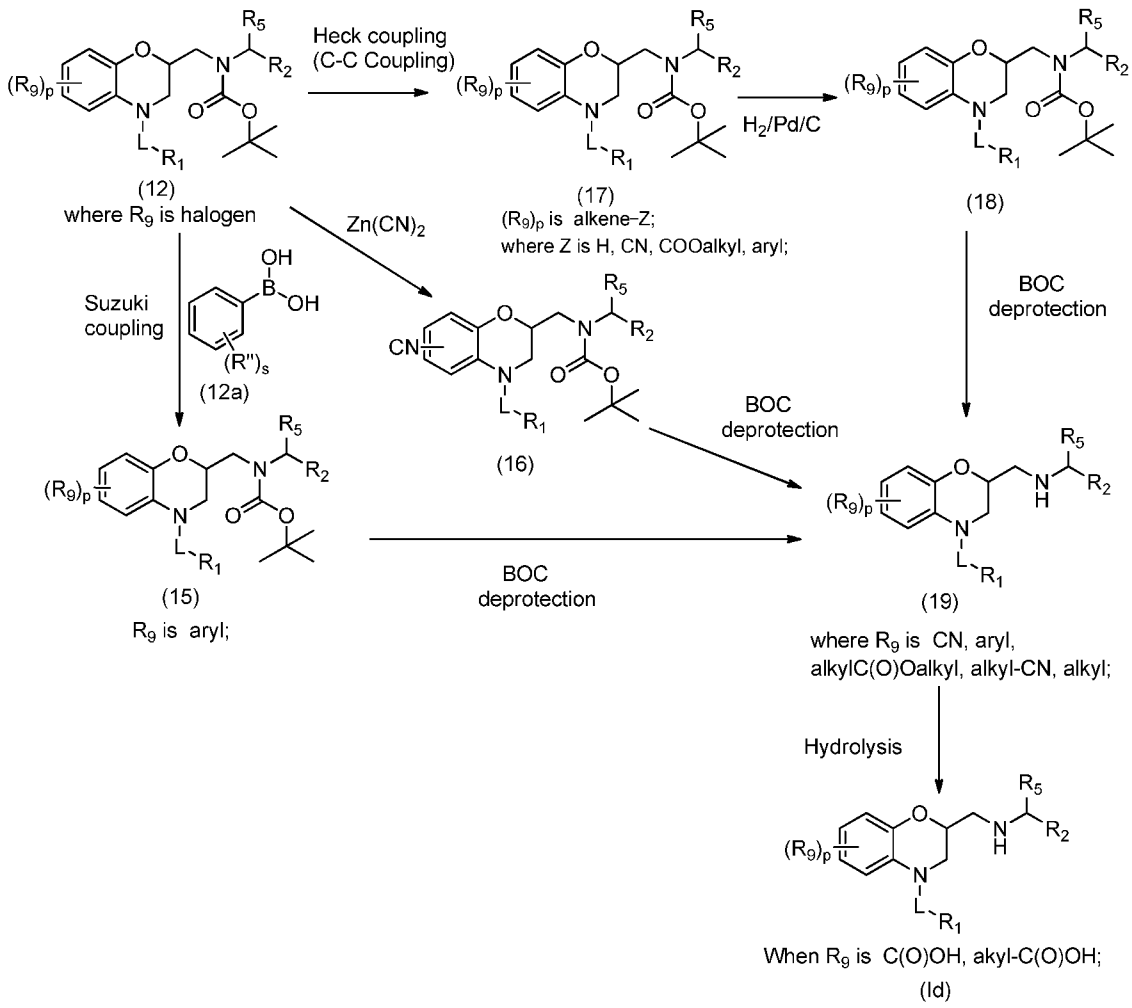

The compound of formula (11), where L, $R_1$, $R_2$, $R_5$, $R_9$ and 'p' are defined herein above, can be prepared by following the procedure as depicted in Scheme-3. The compound of formula (2a) or/and formula (2b) is reacted with formula (b) in presence of base such as triethylamine to give compound of formula (8) (*Journal of Heterocyclic Chemistry*, **1985**, 22, 177 to 181). Reduction of the ester group in compound of formula (8) by using sodium borohydride in suitable solvent to afford alcohol of formula (9), which further protected with *p*-toluene sulfonyl chloride in presence of triethylamine to give corresponding *O*-tosylated compound of formula (10). This compound of formula (10) undergoes coupling reaction with amine of formula (a) in basic conditions such as Hunig's base to give compound of formula (11).

**Scheme-4a**




The compound of formula (Ic), where L, $R_1$, $R_2$, $R_5$, $R_9$ and 'p' are defined herein above, can be prepared by following the procedure as depicted in Scheme-4a. The compound of formula (11) is reacted with di-*tert*-butyl dicarbonate (Boc anhydride) in presence of base such as triethylamine, *N,N-d*iisopropylethylamine (DIPEA) etc., to give compound of formula (12). Hydrogenation of benzyl group in compound of formula (12) (when L-$R_1$ is benzyl) by using Pd/C in suitable solvent to afford compound of formula (13). This compound of formula (13) 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, or the coupling reaction (when L is not a bond) is carried out by using suitable base for example TEA, DIPEA or $K_2CO_3$ etc. and in suitable solvent for example DCM (dichloromethane), THF etc., to give compound of formula (14). Which further undergoes Boc deprotection to give compound of formula (Ic).

**Scheme-4b**

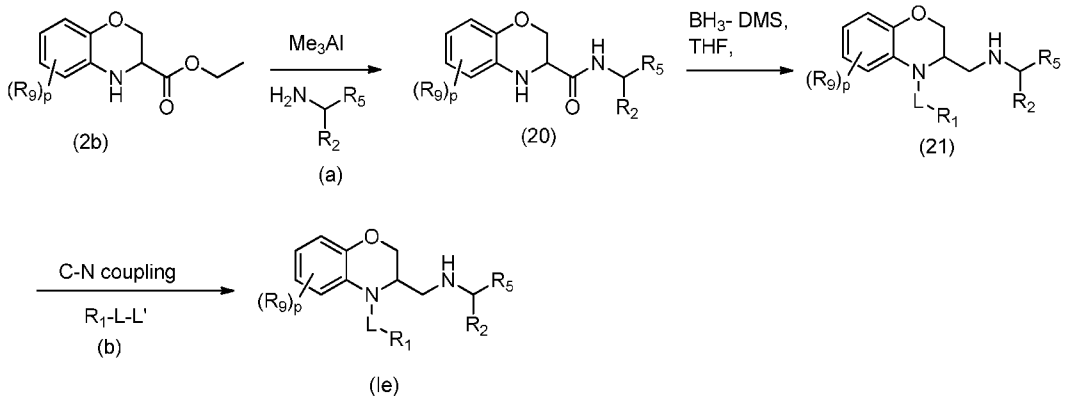



This compound of formula (12) where X' is halogen, undergoes carbon-carbon (C-C) coupling reaction with formula (12a) (where R" is substituent as described herein in the detailed description and 's' is 0 to 3) by following the methods known in the art for example Suzuki coupling reaction using suitable reagents known in the art to give compound of formula (15). Simultaneously, formula (12) undergoes cyanation *(Tetrahedron Letters 40(1999), 8193-8195)* using $Zn(CN)_2$ in presence of suitable solvent such as DMF(Dimethylformamide), toluene etc., to give compound of formula (16). Also compound of formula (12) undergoes carbon-carbon (C-C) coupling reaction by following the methods known in the art for example Heck coupling reaction using suitable reagents known in the art to give compound of formula (17), which further

reduction of double bond in compound of formula (17) by using Pd/C in suitable solvent to afford formula (18).

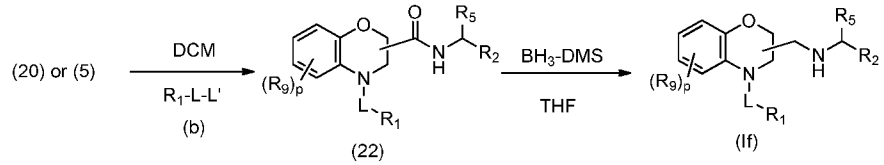
After that compound of formula (15), formula (16) and formula (18) undergoes Boc deprotection using HCl to give compound of formula (19). Further, if these compound of formula (19) (when $R_9$ is CN or alkylC(O)O-alkyl) undergoes hydrolysis to give corresponding acid of formula (Id) using suitable base such as NaOH, LiOH etc.,

**Scheme-5**



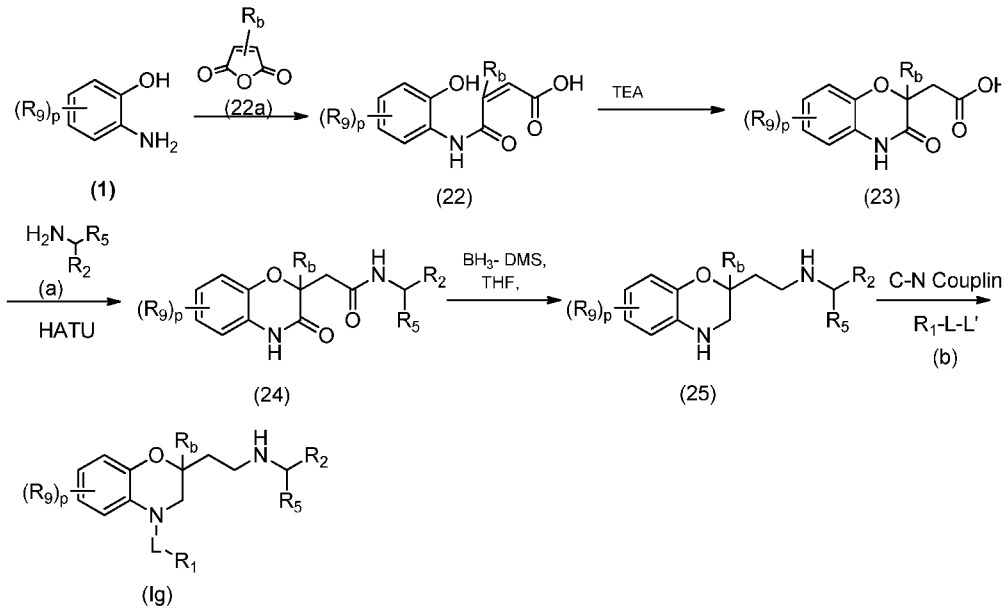

The compound of formula (2b) is reacted with amine of formula (a) in presence of trimethyl aluminium in suitable solvent such as toluene, THF etc., to obtain compound of formula (20). This compound of formula (20) undergoes reduction using suitable reducing agents for example borane-dimethyl sulfide *(Journal of Medicinal Chemistry,* **1998**, 46, 3142-3158) complex to give compound of formula (21). This compound of formula (21) 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, or the coupling reaction (when L is not a bond) is carried out by using suitable base for example TEA, DIPEA or $K_2CO_3$ etc., and in suitable solvent for example DCM, THF (tetrahydrofuran) etc., to give compound of formula (Ie) where L, $R_1$, $R_2$, $R_5$, $R_9$ and 'p' are defined herein above.

**Scheme-6**




The compound of formula (5) or formula (20) 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, or the coupling reaction (when L is not a bond) is carried out by using suitable base for example TEA, DIPEA or $K_2CO_3$ etc. and in suitable solvent for example DCM, THF etc., to give compound of formula (22). This further undergoes reduction with borane-dimethyl sulfide complex (*Journal of Medicinal Chemistry*, **1998**, 46, 3142-3158) to give compound of formula (If) where L, $R_1$, $R_2$, $R_5$, $R_9$ and 'p' are as defined herein above.

**Scheme-7**




The commercially available 2-aminophenol is reacted with maleic anhydride of formula (22a) in suitable solvent for example toluene to give the corresponding (*Z*)-4-((2-hydroxyphenyl) amino)-4-oxobut-2-enoic acid (22). The compound of formula (22)

undergoes cyclization to give compound of formula (23) (*Aust. J. Chem.,* 1986, *39,* 503-510). The compound of formula (23) is reacted with formula (a) in presence of suitable coupling reagent and in suitable solvent to give compound of formula (24) which further undergoes reduction with borane-dimethyl sulfide complex *(Journal of Medicinal Chemistry,* (1998), 46, 3142-3158) to give compound of formula (25). The compound of formula (25) 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, or the coupling reaction (when L is not a bond) carried out by using suitable base for example TEA, DIPEA or $K_2CO_3$ etc., and in suitable solvent for example DCM, THF etc. to afford compound of formula (Ig) L, $R_b$, $R_1$, $R_2$, $R_5$, $R_9$, and 'p' are defined herein above.

## 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.

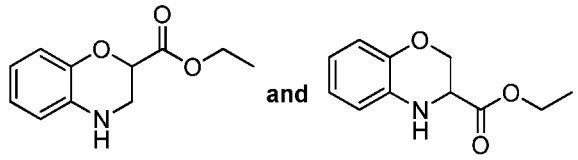
## Intermediates

### Intermediate-1a, 1b

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

and

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



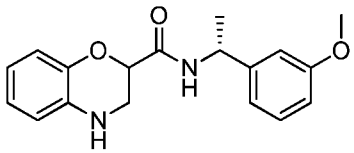

1a 1b

2-Aminophenol (68 g, 0.62mol) was added to a mixture of (430 g, 3.11 mol) of potassium carbonate in DMF (1 liter). The reaction mixture was stirred for 30 min at RT (room

temperature) and then added ethyl-2, 3-dibromopropanoate (208 g, 0.80 mol) 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% ethyl acetate in hexane to give compound of 1a (25 g) as an oily mass (M+H) (m/z 208.1) and compound of 1b was eluted in 3% ethyl acetate in hexane (15 g) as an oil (m/z 208.1).

Intermediate-2

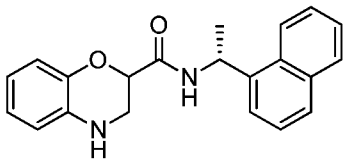
*N*-((*R*)-1-(3-Methoxyphenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxamide



(*R*)-1-(3-Methoxyphenyl)ethanamine (1.46 g, 0.00966 mol) was taken in dry toluene (10 mL) under nitrogen atmosphere. This solution was heated to 50°C and then added trimethyl aluminium (0.65 mL, 0.0072 mol, 2 M 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, 0.0048 mol) in toluene (10 mL). The reaction mixture was heated to 110°C and further maintained for 5 h. The progress of the reaction was monitored by TLC. The reaction mixture 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 crude compound. Purification was carried out by flash chromatography using a mixture of 15%ethyl acetate in hexane afforded the title compound 1.40 g (92.71%). m/z 313.2.

Intermediate-3

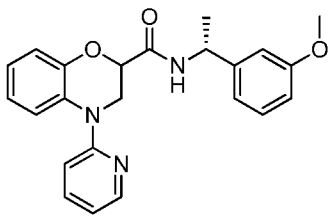
*N*-((*R*)-1-(Naphthalen-1-yl)ethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxamide



(*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 50°C and added trimethyl aluminium (0.65 mL, 0.0072 mol, 2 M 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, 0.0048 mol ) in toluene(10 mL). The reaction mixture was heated to 110°C and further maintained for 5 h. The reaction progress was monitored by TLC. The reaction mixture was quenched with dilute HCl and the product extracted with 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 15% ethyl acetate in hexane afforded the title compound 1.45 g (90.06%). m/z 333.2

Intermediate-4a, 4b

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

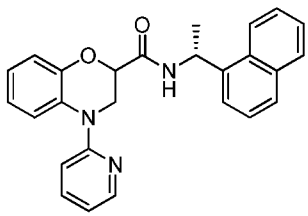


The mixture of Intermediate-2 (0.3 g, 0.96mmol), 1-bromopyridine (0.11mL, 1.153mmol) and $Cs_2CO_3$ (0.47g, 1.44mmol) in toluene (7mL) was degassed for 15 minutes by purging nitrogen. Then bis(tri-tert-butylphosphine palladium(0) (0.049 g, 0.0961mmol) and tris dibenzylidene acetone dipalladium(0) (0.044 g, 0.048 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 ethyl acetate, filtered through celite, and

concentrated under vacuum to give crude racemic compound. Further, diastereomers were separated by flash chromatography using a mixture of 15% ethyl acetate in hexane. (0.28 g, 74.85%). m/z 390.2.

Intermediate-5a, 5b

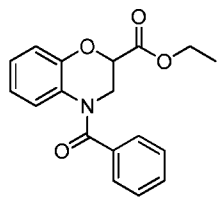
*N*-((*R*)-1-(Naphthalen-1-yl)ethyl)-4-(pyridin-2-yl)-3,4dihydro2*H*-benzo[*b*][1,4] oxazine-2-carboxamide



The mixture of Intermediate-3 (0.3g, 0.90mmol) and 1-bromopyridine (0.11 mL, 1.08 mmol), $Cs_2CO_3$ (0.44 g, 1.35mmol) in toluene (7 mL) was degassed for 15 min by purging nitrogen. Then bis(tri-tert-butylphosphine palladium (0) (0.046 g, 0.09 mmol) and tris dibenzylidene acetone dipalladium (0) (0.041 g, 0.045 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 ethyl acetate, filtered through celite and concentrated under vacuum to give crude racemic compound. Further, diastereomers were separated by flash chromatography using a mixture of 15% ethyl acetate in hexane (0.13g, 0.16 g, 81.43%); m/z 410.2.

Intermediate-6

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

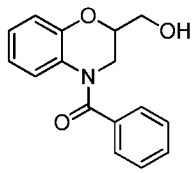


Intermediate-1a (1 g, 4.83 mmol) was dissolved in DCM (20 mL) and cooled to 0°C. To this solution triethylamine (1.2 mL, 8.6 mmol) was added and stirred for 15 min then benzoyl chloride (0.67 mL, 5.79 mmol) was added slowly. The reaction mixture was allowed to room temperature and stirred overnight. The progress of reaction was monitored by TLC. The mixture was diluted with DCM. Organic layer was washed with

water followed by brine solution. The organic layer was dried over sodium sulfate and concentrated which was further purified by flash chromatography using a mixture of ethyl acetate in hexane as eluent to give title compound as an oily mass 1.2 g (80%). m/z 312.1

Intermediate-7

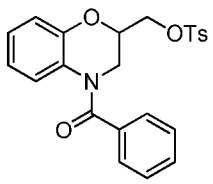
(2-(Hydroxymethyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)(phenyl)methanone




Intermediate-6 (1.2 g, 3.835 mmol) was dissolved in methanol (30 mL) and cooled to 0°C. To this solution sodium borohydride (1.16 g, 30.8 mmol) was added in 3 successive portions. The reaction mixture was allowed to room temperature and stirred overnight. The progress of reaction was monitored by TLC. MeOH was distilled off under vacuum. Cooled this mixture at 0 to 5°C and acidified with dilute HCl till to get pH acidic. 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 to get crude product. Purification was carried out by flash chromatography using a mixture of ethyl acetate/hexane afforded the title compound 0.61 g (59 %). m/z 270.01.

Intermediate-8

(4-Benzoyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl-4-methylbenzene sulfonate

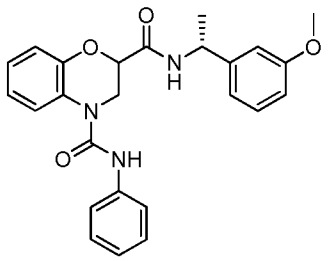



Intermediate-7 (0.6 g, 2.23 mmol) was dissolved in dry DCM (15 mL) and cooled to 0°C. To this solution triethylamine (0.46 mL, 3.34 mmol) was added and stirred for 15 min then added *p*-toluene sulfonyl chloride (0.508 g, 2.67 mmol). The reaction mixture was allowed to room temperature and stirred for 12 h. The progress of reaction was monitored by TLC. The product was extracted into DCM and the organic layer washed with water followed by brine solution. The organic layers were combined, dried over sodium sulfate

and concentrated under vacuum. Purification was carried out by flash chromatography using a mixture of ethyl acetate /hexane afforded the title compound as yellow solid (0.85g, 91 %). m/z 424.2.

Intermediate-9

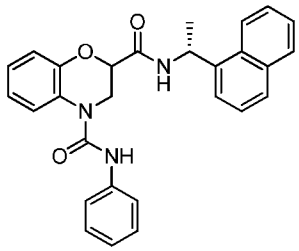
*N*-2-((*R*)-1-(3-Methoxyphenyl)ethyl)-*N*-4-phenyl-2*H*-benzo[*b*][1,4]oxazine-2,4(3*H*) dicarboxamide



To a stirred solution of Intermidiate-2 (300 mg, 0.73 mmol) in DCM (6 mL), phenyl isocynate (0.091 g, 0.77mmol) in dry DCM (2 mL) was added in drop wise manner at 0°C. The reaction mixture was allowed to room temperature and maintained overnight. The progress of reaction was monitored by TLC. The reaction mixture was diluted with DCM and washed with water followed by brine solution. The organic layers were combined, dried over sodium sulfate and concentrated under vacuum. Purification was carried out by flash chromatography using a mixture of ethyl acetate /hexane afforded the title compound. (0.3 g, 96.77%). m/z 432.2

Intermediate-10

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

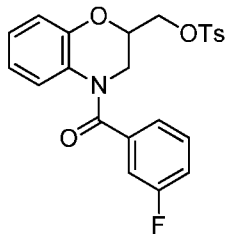


To a stirred solution of Intermidiate-3 (0.3 g, 0.90 mmol) in dry DCM (6 mL), phenyl isocynate (0.12 mg, 0.99 mmol) in DCM (2 mL) was added in dropwise manner at 0°C. The reaction mixture was allowed to RT and maintained overnight. The progress of

reaction was monitored by TLC. The reaction mixture was diluted with DCM and washed with water followed by brine solution. The organic layers were combined, dried over sodium sulfate and concentrated under vacuum. Purification was carried out by flash chromatography using a mixture of ethyl acetate /hexane afforded the title compound (0.32 g, 78.81%); m/z 452.2.

Intermediate-11

(4-(3-Fluorobenzoyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl4-methyl benzene sulfonate




The title compound was prepared in three steps:

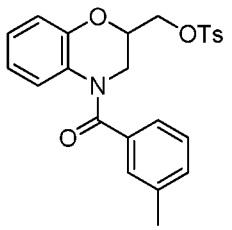
Step-1: Coupling reaction of Intermediate-1a with 3-fluorobenzoyl chloride by following the similar procedure as described in Intermediate-6;

Step-2: Reduction of step-1 intermediate using sodium borohydride by following the similar procedure as described in intermediate-7;

Step-3: Tosylation of step-2 intermediate using *p*-toluene sulfonyl chloride by following the similar procedure as described in Intermediate-8; m/z 442.2.

Intermediate-12

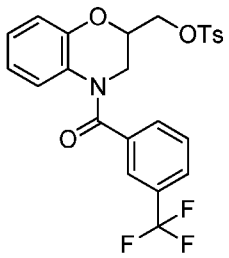
(4-(3-Methylbenzoyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl-4-methylbenzene sulfonate




The title compound was prepared by following the similar procedure as described in Step-1, Step-2 and Step-3 of Intermediate-11 sequentially, by using Intermediate-1a and 3-methylbenzoyl chloride; m/z 438.1.

Intermediate-13

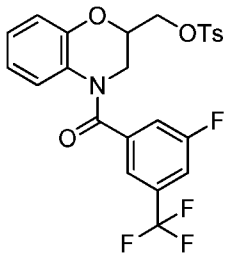
(4-(3-(Trifluoromethyl) benzoyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-2-yl)methyl4-methyl benzenesulfonate



The title compound was prepared by following the similar procedure as described in Step-1, Step-2 and Step-3 of Intermediate-11 sequentially, by using Intermediate-1a and 3-(trifluoromethyl)benzoyl chloride; m/z 492.1

Intermediate-14

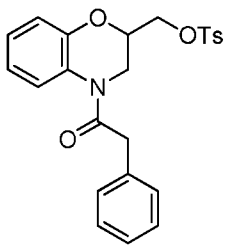
(4-(3-Fluoro-5-(trifluoro methyl) benzoyl)-3,4dihydro-2*H* benzo[*b*][1,4] oxazin-2-yl) methyl-4-methyl benzene sulfonate



The title compound was prepared by following the similar procedure as described in Step-1, Step-2 and Step-3 of Intermediate-11 sequentially, by using Intermediate-1a and 3-fluoro-5-(trifluoromethyl)benzoyl chloride; m/z 510.2

Intermediate-15

(4-(2-Phenylacetyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl-4-methylbenzene sulfonate



The title compound was prepared in three steps:

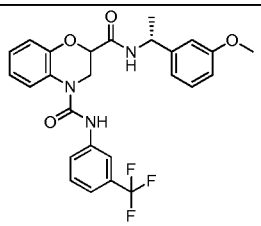
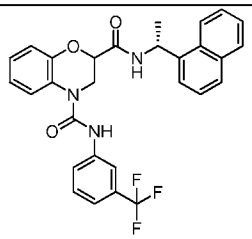
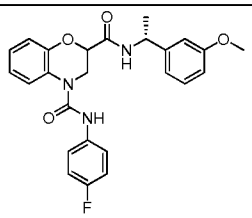
Step-1: Coupling reaction of intermediate-1a with 2-phenylacetyl chloride by following similar procedure as described in Intermediate-6;

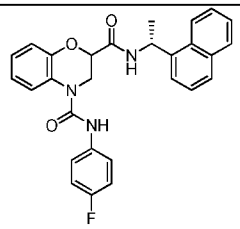
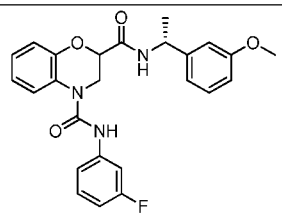
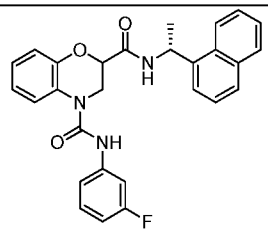
Step-2: Reduction of step-1 intermediate using sodium borohydride by following the similar procedure as described in Intermediate-7;

Step-3: Tosylation of step-2 intermediate using *p*-toluene sulfonyl chloride by following the similar procedure as described in Intermediate-8. m/z 438.1

The below intermediates 16 to 21 given in Table-1, were prepared by following the similar procedure as described in Intermediate-9 or Intermediate-10 by using Intermediate-2 or Intermediate-3 and appropriately substituted isocyanates.

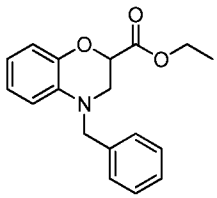
Table-1:

| **Intermediate** | **Structure** | **Chemical Name** | **Starting material** | **Mass (m/z)** |
|---|---|---|---|---|
| 16 |  | *N*2-((*R*)-1-(3-Methoxyphenyl) ethyl)-*N*-4-(3-(trifluoromethyl) phenyl)-2*H*-benzo[*b*][1,4] oxazine -2,4(3*H*)-dicarboxamide | Intermediate-2 | 500.2 |
| 17 |  | *N*2-((*R*)-1-(Naphthalen-1-yl) ethyl)-*N*4-(3-(trifluoromethyl) phenyl)-2*H*-benzo[*b*][1,4] oxazine-2,4(3*H*)-dicarboxamide | Intermediate-3 | 520.2 |
| 18 |  | *N*4-(4-Fluorophenyl)-*N*2-((R)-1-(3-methoxyphenyl)ethyl)-2*H*-benzo[*b*][1,4] oxazine-2,4(3*H*)-dicarboxamide | Intermediate-2 | 450.2 |

| | | | | |
|---|---|---|---|---|
| 19 |  | *N*4-(4-Fluorophenyl)-*N*2-((*R*)-1-(naphthalen-1-yl)ethyl)-2*H* benzo[*b*][1,4]oxazine-2,4(3*H*) dicarboxamide | Intermedia te-3 | 470.2 |
| 20 |  | *N*4-(3-Fluorophenyl)-*N*2-((*R*)-1-(3-methoxyphenyl)ethyl)-2*H*-benzo[*b*][1,4]oxazine-2,4(3*H*) dicarboxamide | Intermedia te-2 | 450.2 |
| 21 |  | *N*4-(3-Fluorophenyl)-*N*2-((*R*)-1-(naphthalen-1-yl)ethyl)-2*H*-benzo[*b*][1,4]oxazine-2,4(3*H*)-dicarboxamide | Intermedia te-3 | 470.2 |

Intermediate-22

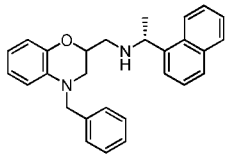
Ethyl 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylate



Intermediate-1a (3 g, 14.4 mmol) was dissolved in DMF (20 mL) and cooled to 0°C. To this solution $K_2CO_3$ (3g, 21.7mmol) was added and stirred for 15 min then benzyl chloride (2 mL, 17.3 mmol) was added slowly. The reaction mixture was allowed to room temperature and further stirred for 20h. The progress of reaction was monitored by TLC. The mixture was diluted with ethyl acetate. Organic layer was washed with water followed by brine solution. The organic layer was dried over sodium sulfate and concentrated to get crude compound. which was further purified by flash chromatography using a mixture of ethyl acetate/hexane as eluent to give title compound as an oily mass (4.2 g, 98%). m/z 298.1.

Intermediate-23

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



The title compound was prepared in 3 steps:

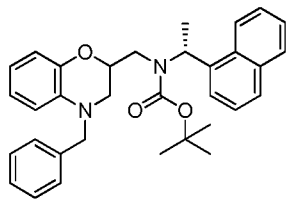
Step-1: Reduction of Intermediate-22 using sodium borohydride by following the similar procedure as described in Intermediate-7;

Step-2: Tosylation of step-1 intermediate using *p*-toluene sulfonyl chloride by following the similar procedure as described in intermediate-8;

Step-3: To the solution of Step-2 intermediate (0.4 g, 0.977 mmol) in DCM (1 mL) DIPEA (2 mL, 34 mmol) and *R*-1-(naphthalen-1-yl)ethanamine (0.25 g, 1.47 mmol) was added and stirred for 22 h at 100°C. The progress of reaction was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and the organic layer washed with water followed by brine solution. The organic layer was dried over sodium sulfate and concentrated under vacuum to get crude product. m/z 409.22.

Intermediate-24

*tert*-Butyl ((4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)((*R*)-1-(naphthalen-1-yl)ethyl)carbamate

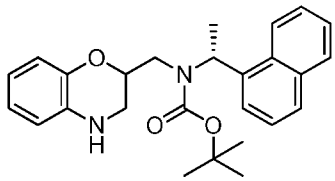


Intermediate-23 (0.7 g, 18 mmol) was dissolved in DCM (20 mL) and cooled to 0°C. To this solution triethylamine (0.38 mL, 27mmol) was added and stirred for 15 min then di-*tert*-butyl dicarbonate (0.47g, 21.6 mmol) was added slowly followed by catalytic amount of DMAP. The reaction mixture was allowed to RT and stirred overnight. The progress of reaction was monitored by TLC. The mixture was diluted with ethyl acetate. Organic layer was washed with water followed by brine solution. The organic layer was dried over

sodium sulfate and concentrated which was further purified by flash chromatography using a mixture of ethyl acetate/hexane as eluent to give title compound as an oily mass (0.66 g, 75.18%). m/z-509.27.

Intermediate-25

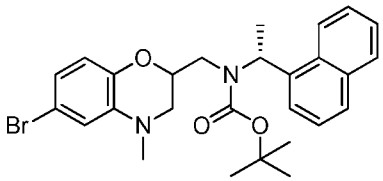
*tert*-Butyl ((3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)((*R*)-1-(naphthalen-1-yl)ethyl) carbamate



To a mixture of Intermediate-24 (0.65 g, 1.55 mmol) in ethyl acetate (5 mL) and AcOH (5 mL) 5% palladium on carbon (65mg) was carefully added and the mixture was stirred overnight under pressure of hydrogen balloon. The progress of reaction was monitored by TLC. Reaction mixture was filtered through celite and the filtrate concentrated to get the crude product (0.62g, 98 % yield) this was directly used for next reaction; m/z-419.23.

Intermediate-26

*tert*-Butyl ((6-bromo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)((*R*)-1-(naphthalen-1-yl)ethyl)carbamate



The title compound was prepared in six steps:

Step-1: Cyclisation reaction of 2-amino-4-bromophenol with 2,3 dibromo propionate by following similar procedure as described in Intermediate-1a;

Step-2: Coupling reaction of step-1 with methyl iodide by following similar procedure as described in Intermediate-22;

Step-3: Reduction of step-2 intermediate using sodium borohydride by following the similar procedure as described in Intermediate-7;

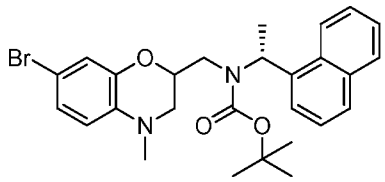
Step-4: Tosylation of step-3 intermediate using *p*-toluene sulfonyl chloride by following the similar procedure as described in Intermediate-8;

Step-5: Conversion of step-4 to corresponding amine by following the similar procedure as described in Step-3 of Intermediate-23 by taking (*R*)-1-(naphthalen -1-yl) ethanamine;

Step-6: Boc protection of step-4 by using di-*tert*-butyl dicarbonate by following the similar procedure as described in Intermediate-24; m/z 512.1.

Intermediate-27

*tert*-Butyl ((7-bromo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)((*R*)-1-(naphthalen-1-yl)ethyl)carbamate




The title compound was prepared in six steps:

Step-1: Cyclisation reaction of 2-amino-5-bromophenol with 2,3 dibromo propionate by following similar procedure as described in Intermediate-1a;

Step-2: Coupling reaction of step-1 with methyl iodide by following similar procedure as described in Intermediate-22;

Step-3: Reduction of step-2 intermediate using sodium borohydride by following the similar procedure as described in Intermediate-7;

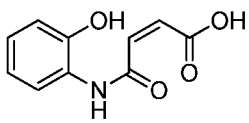
Step-4: Tosylation of step-3 intermediate using *p*-toluene sulfonyl chloride by following the similar procedure as described in Intermediate-8;

Step-5: Conversion of step-4 to corresponding amine by following the similar procedure as described in Step-3 of Intermediate-23 by taking (*R*)-1-(naphthalen -1-yl) ethanamine;

Step-6: Boc protection of step-4 by using di-*tert*-butyl dicarbonate by following the similar procedure as described in Intermediate-24. m/z 512.1.

Intermediate-28

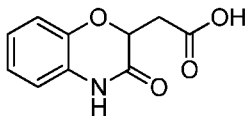
4-((2-Hydroxyphenyl) amino)-4-oxobut-2-enoic acid




To a solution of maleic anhydride (8.99 g, 92mmol) in toluene (100 mL) o-aminophenol (10g, 92 mmol) was added at RT under stirring. Maintained the reaction mass for 3h at RT and the resulting solid was filtered get the title compound (13 g, 62%) m/z 208.05.

Intermediate-29

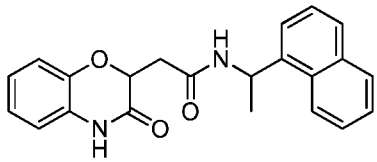
2-(3-Oxo-3,4-dihydro-2*H*-benzo[*b*][1, 4]oxazin-2-yl)acetic acid



To a stirred solution of Intermediate-28 (10 g, 48.3mmol) in 1,4-dioxane (300 ml) triethyl amine (20.18 ml, 145 mmol) was added dropwise at RT. Reaction mixture was heated to reflux and further maintained for 12 h. After completion of reaction, solvent was evaporated under vacuum. Reaction mass was acidified with 2N HCl (300ml) and extracted with ethyl acetate (4x500ml). Organic layer was washed with water, brine, dried over sodium sulfate, concentrated in vacuum to get the title compound (10 g, 93%). m/z 208.05.

Intermediate-30

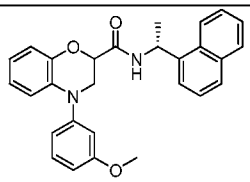
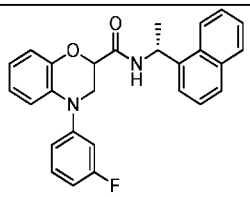
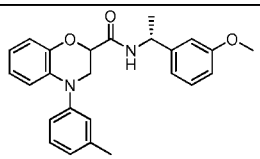
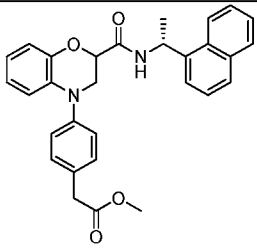
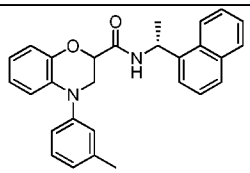
*N*-((*R*)-1-(Naphthalen-1-yl)ethyl)-2-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl) acetamide

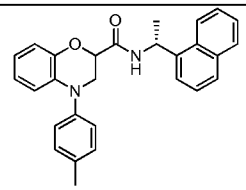
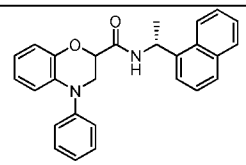
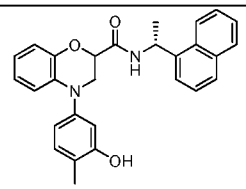
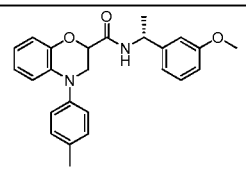
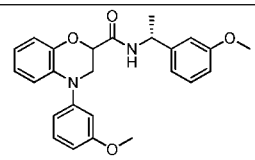


To a ice cooled solution of Intermediate-29 (9.5 g, 45.9 mmol) in DCM (150 ml), DIPEA (16ml, 92 mmol) and 2-(1H-7-Azabenzotriazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU) (20.9 g, 55mmol) was added sequentially. To the reaction mass solution of (*R*)-1-(naphthalen -1-yl) 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 was filtered. Solid compound was washed with ice cold DCM to afford the title compound (12 g, 85%). m/z 361.15.

The below Intermediates 31 to 44 given Table-2 were prepared by following the similar procedure as described in Intermediate-4 or Intermediate-5 by using appropriate Intermediate 2 or Intermediate-3 and appropriately substituted halo benzene or halo alkyl.

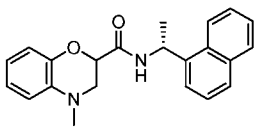
Table-2:

| Intermediate | Structure | Chemical Name | Starting Material | Mass m/z |
|---|---|---|---|---|
| 31 |  | 4-(3-Methoxyphenyl)-*N*-((*R*)-1-(naphthalen-1-yl) ethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2 carboxamide | Intermediate-3 | 439.5 |
| 32 |  | 4-(3-Fluorophenyl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine- 2-carboxamide | Intermediate-3 | 427.5 |
| 33 |  | *N*-((*R*)-1-(3-Methoxy phenyl)ethyl)-4-(m-tolyl) -3,4-dihydro-2*H*-benzo [*b*][1,4]oxazine-2-carboxamide | Intermediate-2 | 403.5 |
| 34 |  | Methyl2-(4-(2-(((*R*)-1-(naphthalen-1-yl)ethyl) carbamoyl)-2*H*-benzo[*b*][1,4] oxazin-4(3*H*)-yl) phenyl)acetate | Intermediate-3 | 481.5 |
| 35 |  | *N*-((*R*)-1-(Naphthalen-1-yl)ethyl)-4-(m-tolyl)-3,4-dihydro-2*H*-benzo[*b*] [1,4]oxazine-2-carboxamide | Intermediate-3 | 423.5 |

| | | | | |
|---|---|---|---|---|
| 36 |  | *N*-((*R*)-1-(Naphthalen-1-yl)ethyl)-4-(p-tolyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxamide | Intermediate-3 | 423.5 |
| 37 |  | *N*-((*R*)-1-(Naphthalen-1-yl)ethyl)-4-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxamide | Intermediate-3 | 409.5 |
| 38 |  | 4-(3-Hydroxy-4-methylphenyl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxamide | Intermediate-3 | 439.5 |
| 39 |  | *N*-((*R*)-1-(3-Methoxy phenyl)ethyl)-4-(p-tolyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxamide | Intermediate-2 | 403.5 |
| 40 |  | 4-(3-Methoxyphenyl)-*N*-((*R*)-1-(3-methoxy phenyl)ethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxamide | Intermediate-2 | 419.1 |

Intermediate-41

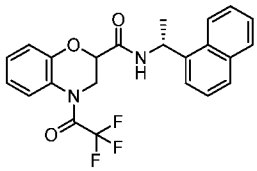
4-Methyl-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxamide



The title compound was prepared by following the similar procedure as described in Intermediate-6 by using Intermediate-3 and methyl iodide; Mass (m/z) 347.2.

Intermediate-42

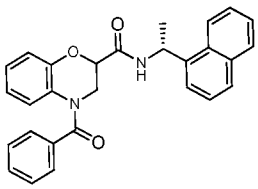
*N*-((*R*)-1-(Naphthalen-1-yl)ethyl)-4-(2,2,2-trifluoroacetyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine-2-carboxamide



The title compound was prepared by following the similar procedure as described in Intermediate-6 by using Intermediate-3 and trifluoro acetic anhydride; Mass (m/z) 429.1.

Intermediate-43

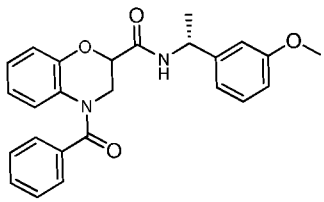
4-Benzoyl-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)-3,4-dihydro-2*H*-benzo[b] [1,4]oxazine-2-carboxamide



The title compound was prepared by following the similar procedure as described in Intermediate-6 by using Intermediate-3 and benzoyl chloride; Mass (m/z) 437.5.

Intermediate-44

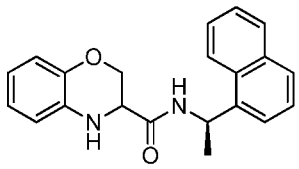
4-Benzoyl-*N*-((*R*)-1-(3-methoxyphenyl)ethyl)-3,4-dihydro-2*H*-benzo [*b*][1,4]oxazine-2-carboxamide



The title compound was prepared by following the similar procedure as described in Intermediate-6 by using Intermediate-2 and benzoyl chloride; Mass (m/z) 417.5.

Intermediate-45a, 45b

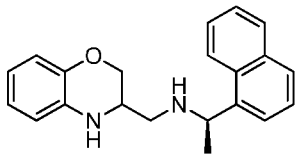
*N*-((*R*)-1-(naphthalen-1-yl)ethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxamide



(*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 50°C 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 Intermediate-1b (1 g, 0.0048mol) in toluene (10 mL). The reaction mixture was heated to 110°C and further maintained for 5 h .The reaction progress was monitored by TLC. The reaction was quenched with dilute HCl and the product extracted with 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 crude compound. Further diastereomers were separated by flash chromatography using a mixture of 40% ethyl acetate in hexane (0.065, and 0.08g, 90.06%). m/z 333.2.

Intermediate-46a, 46b

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

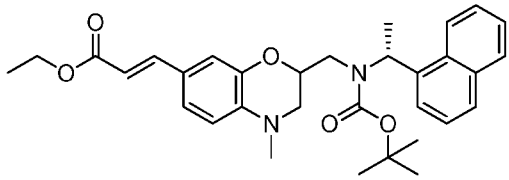


To a mixture solution of Intermediate-45a (0.25 g, 0.75mmol) in dry THF(10 mL) borane dimethyl sulphide complex (0.18 mL,1.88 mmol) was added then heated to 60 to 70°C and further maintained for 5 h. The progress of reaction was monitored by TLC. Tetrahydrofuran was distilled off under vacuum then methanol (5mL) and dilute HCl (5 mL) was added at 0°C then heated to 65°C and further stirred for 40 minutes 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 ethyl acetate then the organic layer washed with water followed by brine solution. The organic layer dried over sodium sulfate and concentrated under vacuum. m/z 319.17

Similarly, Intermediate-46b was prepared by taking Intermediate-45b using this procedure.

Intermediate-47

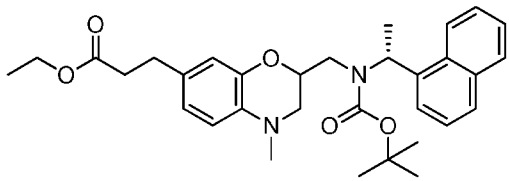
(*E*)-Ethyl 3-(2-(((*tert*-butoxycarbonyl)((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)acrylate



Intermediate-27 (0.2g, 0.39mmol) was dissolved in DMF (5mL), then ethyl acrylate (0.13mL, 1.2mmol), palladium acetate (II) (0.009g, 0.04mmol), $Cs_2CO_3$ (0.19 g, 0.59mmol) and o-tri tolyl phosphine (0.023 g, 0.007 mmol) were added under nitrogen atmosphere. The reaction mixture was heated to 120°C in sealed tube and further maintained for 5 h. The progress of reaction was monitored by TLC. The separated out solid was filtered through Celite. The filtrate was extracted with ethyl acetate (10mLX2) and washed with water (10 mL) and brine solution (10mL). The organic layer was dried over sodium sulfate and filtered. Filtrate was concentrated under reduced pressure to get crude product. The crude compound was purified with silica gel flash column chromatography (15% ethyl acetate: Hexane) to get title compound (0.18g, 87%). m/z 531.28.

Intermediate-48

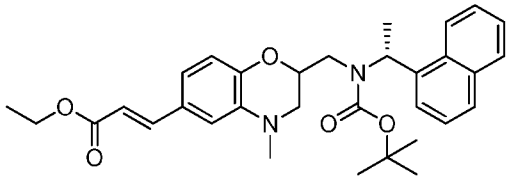
Ethyl3-(2-(((*tert*-butoxycarbonyl)((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)propanoate



To a mixture of Intermediate-47 (0.18 g, 0.39 mmol) in MeOH (5 mL), 5% palladium on carbon (40mg) was carefully added and the mixture was stirred overnight under a pressure of hydrogen balloon. The progress of reaction was monitored by TLC. Reaction mixture was filtered through celite and the filtrate concentrated to get the crude product (0.17g, 94 %), this was directly used in next reaction. m/z 533.28.

Intermediate-49

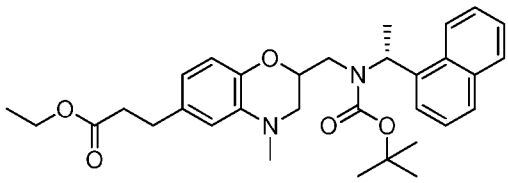
(*E*)-Ethyl 3-(2-(((*tert*-butoxycarbonyl)((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)acrylate



The title compound was prepared following the similar procedure as described in intermediate-47 by taking Intermediate-26 and ethyl acrylate. m/z 531.28

Intermediate-50

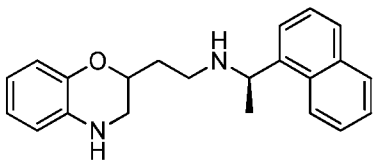
Ethyl 3-(2-(((*tert*-butoxycarbonyl)((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)propanoate



The title compound was prepared following similar reduction procedure as described in Intermediate-48 by taking Intermediate-49. m/z 533.28

Intermediate-51a, 51b

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



To a mixture of Intermediate-30 (9g,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 further maintained for 12 h. Tetrahydrofuran was distilled off under vacuum. Methanol (10 mL) and dilute HCl (15 mL) was 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 ethyl acetate then the organic layer washed with water followed by

brine solution. The organic layer dried over sodium sulfate and concentrated under vacuum to afford the title compound 7 g (81%)

Diastereomers were separated by chiral chromatography.

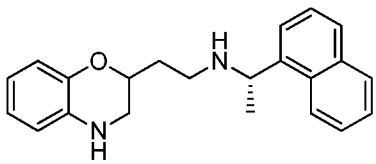
CHIRAL PAK 1D, 250 x 4.6 MM 5u; mobile phase: A: hexane/IPA (90:10, %v/v, 0.1 % DEA) B:IPA (100%) A:B 80/20%v/v, flow = 1.0 ml/min. m/z 333.1.

a: ($t_R$ = 5.47) (retention time); $^1$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);

b: ($t_R$ = 6.34); $^1$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 and *J*=7.8 Hz, 1H), 6.53 (dt, *J*=1.2 Hz and *J*=8.2 Hz, 2H), 6.43 (dt, *J*=1.6 Hz and *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);

Intermediate-52

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



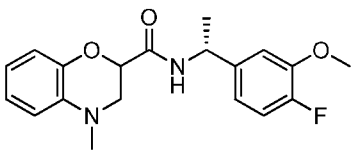
The title compound was prepared in two steps:

Step-1: Condensation of Intermediate-29- with (S)-1-(naphthalen -1-yl) ethanamine by following similar procedure as described in intermediate-30;

Step-2: Reduction of step-1 with borane dimethyl complex by following similar procedure as described in Intermediate-51. m/z 333.1.

Intermediate-53

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



The title compound was prepared in two steps:

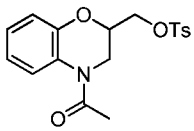
Step-1: Condensation of Intermediate-1a with (*R*)-1-(4-Fluoro-3-methoxy phenyl) ethanamine by following the similar procedure as described in Intermediate-2.

Step-2: N-alkylation

Step-1 intermediate (0.4 g, 1.21 mmol) was dissolved in DMF (5 mL) and cooled to 0°C. To this solution $K_2CO_3$ (0.25g, 1.82mmol) was added and further stirred for 15 min then methyl iodide (0.23 mL, 3.63 mmol) was added slowly. The reaction mixture was allowed to room temperature and stirred for 20h. The progress of reaction was monitored by TLC. The mixture was diluted with ethyl acetate. Organic layer was washed with water followed by brine solution. The organic layer was dried over sodium sulfate and concentrated which was further purified by flash chromatography using a mixture of ethyl acetate/hexane as eluent to give title compound as an oily mass (0.35g, 84%) m/z 345.1.

Intermediate-54

(4-Acetyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl 4-methylbenzenesulfonate



The title compound was prepared in three steps:

Step-1: Coupling reaction of Intermediate-1a with acetic anhydride by following the similar procedure as described in Intermediate-6;

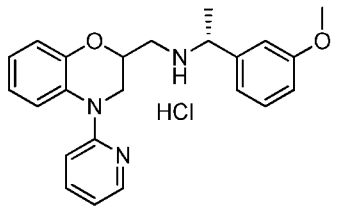
Step-2: Reduction of step-1 intermediate using sodium borohydride by following the similar procedure as described in Intermediate-7;

Step-3: Tosylation of step-2 intermediate using *p*-toluene sulfonyl chloride by following the similar procedure as described in Intermediate-8; m/z 362.1.

Examples

Example-1

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

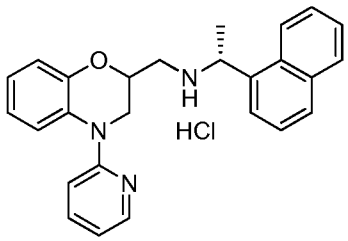



To a solution of racemic compound of Intermediate-4 (0.1 g, 0.26mmol) in dry tetrahydrofuran (10 mL) borane dimethyl sulphide complex (0.061 mL, 0.64 mmol) was added. The reaction mixture was heated to 50°C and maintained for 2 h. The progress of reaction was monitored by TLC (thin layer chromatography). Tetrahydrofuran was distilled off under vacuum then added MeOH/HCl (5 mL) at 0°C. The reaction mixture was heated to 50°C and stirred for 10 minutes. Methanol was distilled off under vacuum and cooled to 0°C then acidified with dilute HCl solution [pH=3 to 4]. Extract the product with ethyl acetate (10mLX2), washed with water (5mLX2) followed by brine solution (5mL), dried over sodium sulfate and concentrated under vacuum to get solid. The crude product was purified by flash chromatography using a mixture of 15% ethyl acetate/hexane. Ethereal HCl (2mL) was added and stirred for 10 min. The solvent was evaporated and solid washed by diethyl ether (2mL) followed by *n*-pentane (2mL), dried to get crude product the title compound as solid (0.065g, 67.4%). m/z 376.3.

$^1$H NMR (400 MHz, DMSO-$d_6$): m/z 376.3 :δ8.26 (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-2

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

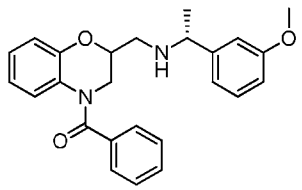



To a solution of racemic compound of Intermediate-5 (0.27 g 0.68mmol) in dry THF (10 mL), borane dimethyl sulphide complex (0.16 mL, 1.71mmol) was added and heated to 50°C and further maintained for 2 h. The progress of reaction was monitored by TLC. Tetrahydrofuran was distilled off under vacuum then added MeOH/HCl (5 mL) at 0°C then heated 50°C and stirred for 10 minutes. Methanol was distilled off under vacuum and cooled to 0°C then acidified with dilute HCl solution [pH=3 to 4]. Extract the product with ethyl acetate (10mLX2), washed with water (5mLX2) followed by brine solution (5mL), dried over sodium sulfate and concentrated under vacuum to get solid. The crude product was purified by flash chromatography using a mixture of 15% ethyl acetate/hexane. Amino compound was dissolved in dry DCM, then slowly added with 2 M ethereal HCl solution and stirred for 10 min. The solvent was evaporated and the resultant solid washed with diethyl ether followed by *n*-pentane to give hydrochloride salt of the desired compound. (0.19 g, 74.62%).

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-3

(2-((((*R*)-1-(3-Methoxyphenyl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl) (phenyl) methanone



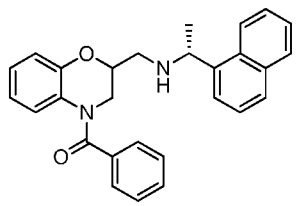

To stirred solution of Intermediate-8 (0.4 g, 0.0945 mmol) in DCM (1 mL), DIPEA (2 mL, 34 mmol) and (*R*)-1-(3-methoxyphenyl) ethanamine (0.016 g, 0.103 mmol) were added, then heated to 100°C and further stirred for 22 h at the same temperature. The

progress of reaction was monitored by TLC. The reaction mixture was cooled to room temperature and diluted with ethyl acetate and the organic layer washed with water followed by brine solution. The organic layer was dried over sodium sulfate and concentrated under vacuum to get the crude product. This crude product was further purified by flash chromatography using a mixture of 10% ethyl acetate in hexane (0.4 g, 52.63%).

m/z 403.2; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.43-7.30 (m, 5H), 7.23-7.17 (m,1H), 6.98.6.95 (m,1H), 6.92-6.90 (m,1H), 6.85 (m,2H), 6.77 (t, *J*=8.8 Hz, 2H), 6.6 (m,1H), 4.48 (m,1H), 4.11(m,1H), 3.86 (m,1H), 3.75 (m,6H), 3.69-3.64 (m, 1H), 2.80-2.80 (m,2H), 1.43 (d, *J* = 6.4 Hz,3H).

Example-4

(2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl) (phenyl)methanone

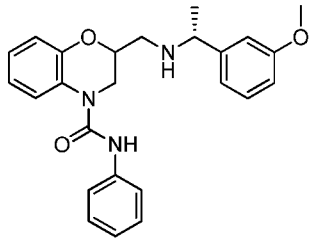


To the solution of Intermediate-8 (0.4 g, 0.0945 mmol) in DCM (1 mL) DIPEA (2 mL, 34 mmol) and *R*-1-(naphthalen-1-yl)ethanamine (0.018 g, 0.103 mmol) was added then heated to 100°C and further stirred for 22 h at the same temperature. The progress of reaction was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and the organic layer washed with water followed by brine solution. The organic layer was dried over sodium sulfate and concentrated under vacuum to get the crude product. This crude product was further purified by flash chromatography using a mixture of 10% ethyl acetate in hexane as solid (0.097g).

m/z 424.2; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.18-8.12 (m, 1H), 7.87-7.85 (d, *J*=7.2, 1H), 7.76-7.71 (m, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.52-7.47 (m, 2H), 7.45-7.37 (m, 3H), 7.34-7.28 (m, 3H), 6.98 (m, 2H), 6.95 (m, 1H), 6.63 (m, 1H), 4.79-4.71 (m, 1H), 4.49 (s, 1H), 3.77 (m, 1H), 3.66-3.60 (m, 1H), 2.86 (m, 2H), 1.54 (s, 3H).

Example-5

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

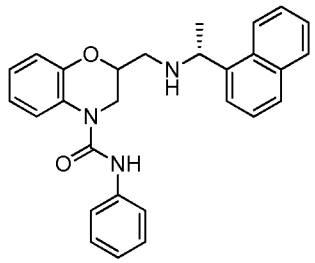


To a mixture solution of Intermediate-9 (0.2 g,0.46mmol) in dry THF (10 mL) borane dimethyl sulphide complex (0.044 mL,1.15mmol) was added and heated to 50 to 70°C and further maintained for 2h. The progress of reaction was monitored by TLC. Tetrahydrofuran was distilled off under vacuum then methanol (5 mL) and MeOH/HCl (5 mL) was added at 0°C then heated to 65°C and maintained for 40 minutes. Methanol was distilled off under vacuum, then the reaction mixture was cooled to 0°C and basified with saturated $Na_2CO_3$ solution [pH=9]. The product was extracted into ethyl acetate and the organic layer was washed with water followed by brine solution. The organic layer was dried over sodium sulfate and concentrated under vacuum to give crude compound. This crude product was further purified by flash chromatography using a mixture of 15% ethyl acetate in hexane (0.05 g, 26.31%).

m/z 418.3,$^1$H NMR (400 MHz, $CDCl_3$): δ 7.31-7.28 (m, 3H), 7.24 (m, 2H), 7.17-7.09 (m, 2H), 7.05-7.04 (m, 4H), 6.90-6.81 (m, 2H), 4.96 (m, 1H), 4.39 (m, 1H), 3.80 (m, 3H), 3.50-3.36 (m, 2H), 2.97-2.81 (m, 2H), 1.83 (m, 3H).

Example-6

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

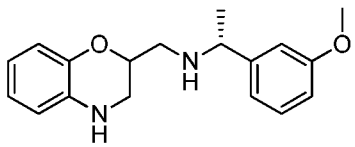


To a mixture solution of Intermediate-10 (0.31g, 0.69 mmol) in dry THF (10 mL), borane dimethyl sulphide complex (0.16 mL, 1.72 mmol) was added and heated to 50 to 70°C and further maintained for 2 h. The progress of reaction was monitored by TLC. Tetrahydrofuran was distilled off under vacuum then methanol (5 mL) and MeOH/HCl (5 mL) was added at 0°C then heated to 65°C and maintained for 40 minutes. Methanol was distilled off under vacuum, reaction mixture was cooled to 0°C and basified with saturated $Na_2CO_3$ solution [pH=9]. The product was extracted into ethyl acetate and the organic layer was washed with water followed by brine solution. The organic layer dried over sodium sulfate and concentrated under vacuum to give crude compound. This crude product was further purified by flash chromatography using a mixture of 10% ethyl acetate in hexane 0.1g of get the title compound.

m/z 438.2; $^1$H NMR (400 MHz, DMSO-$d_6$): δ8.21 (d, *J*=8.8 Hz, 1H), 8.0 (t, *J*=7.6 Hz, 2H), 7.87 (m, 1H), 7.63-7.57 (m, 3H), 7.39-7.24 (m, 4H), 7.01-6.88 (m, 3H), 5.41 (m, 1H), 4.58 (m, 1H), 4.17 (d, *J*=12 Hz, 1H), 3.41 (m, 3H), 3.08 (m, 1H), 1.71 (s, 3H).

Example-7

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

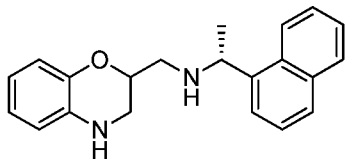


To a mixture solution of Intermediate-2 (0.25 g , 0.80 mmol) in dry THF (10 mL) borane dimethyl sulphide complex (0.19 mL, 2.00 mmol) was added and heated to 60-70°C and further maintained for 5 h. The progress of reaction was monitored by TLC. Tetrahydrofuran was distilled off under vacuum then methanol (5 mL) and dilute HCl (5 mL) was added at 0°C then heated to 65°C and maintained for 40 minutes. 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 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. This crude product was further purified by flash chromatography using a mixture of 20% ethyl acetate in hexane (0.18 g, 75.41%).

m/z 299.2;$^1$H NMR (400 MHz, $CDCl_3$): δ 6.93-6.88 (m, 3H), 6.80-6.73 (m, 3H), 6.65 (m, 1H), 6.58-6.56 (m, 1H), 4.26 (m, 1H), 3.86-3.80 (m, 3H), 3.35-3.29 (m, 1H), 3.24-3.19 (m, 1H), 3.16-3.11 (m, 1H), 2.83-2.73 (m, 1H), 2.67-2.61 (m, 2H), 1.42 (d, *J* = 6.8 Hz, 3H).

Example-8

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

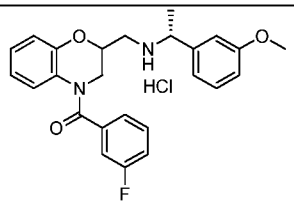
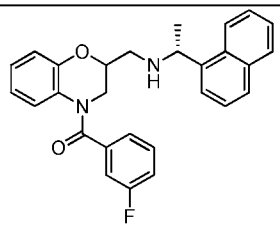


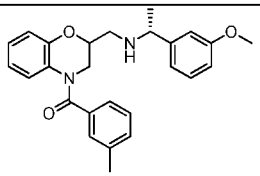
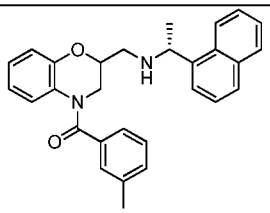
To a mixture solution of Intermediate-3 (0.25 g, 0.75mmol) in dry THF(10 mL) borane dimethyl sulphide complex (0.18 mL,1.88 mmol) was added then heated to 60 to 70°C and further maintained for 5 h. The progress of reaction was monitored by TLC. Tetrahydrofuran was distilled off under vacuum then methanol (5 mL) and dilute HCl (5 mL) was added at 0°C then heated to 65°C and further stirred for 40 minutes 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 ethyl acetate then the organic layer washed with water followed by brine solution. The organic layer dried over sodium sulfate and concentrated under vacuum. This crude product was further purified by flash chromatography using a mixture of 20% ethyl acetate in hexane (0.19 g, 79.61%).

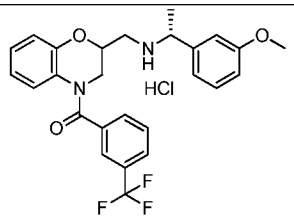
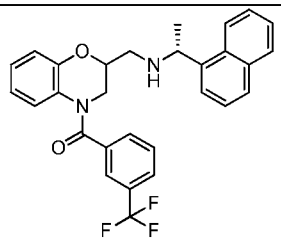
m/z 319.2; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.20-8.12 (m, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.76 (m, 1H), 7.64 (d, *J*=7.2, 1H), 7.53-7.43 (m, 3H), 6.82-6.73 (m, 3H), 6.64 (m, 1H), 4.81-4.74 (m, 1H), 4.32-4.30 (m, 1H), 3.38-3.28 (m, 1H), 3.20-3.19 (m, 1H), 2.79-2.76 (m, 1H), 2.61 (s, 1H), 1.57 (s, 3H).

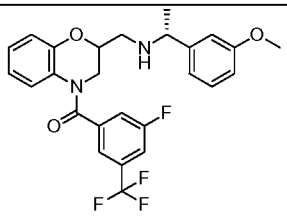
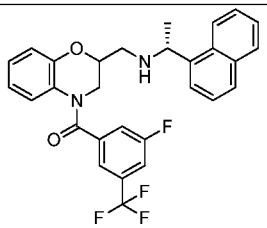
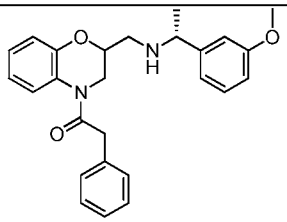
The below Examples 9 to 18 given in Table-3 were prepared by following the similar procedure as described in Example-3a, 3b or Example-4a, 4b by using corresponding *O*-tosylated intermediate and (*R*)-1-(3-methoxyphenyl)ethanamine or *R*-1-(naphthalen-1-yl)ethanamine.

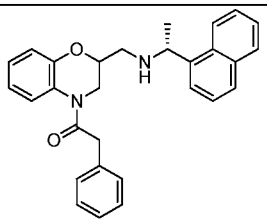
Table-3:

| Example No. | Structure | Intermediate | Mass (m/z) and $^1$HNMR |
|---|---|---|---|
| 9 |  (3-Fluorophenyl)(2-((((*R*)-1-(3-methoxyphenyl)ethyl) amino)methyl)-2*H*-benzo [*b*][1,4]oxazin-4(3H)-yl) methanone hydrochloride | Intermediate-11 | m/z 421.2; $^1$H NMR (400 MHz, $CDCl_3$): δ 11.32 (bs,1H), 9.33 (bs,1H), 7.60 (m, 4H), 6.93-6.90 (m, 4H), 6.74 (m, 1H), 6.57 (m, 3H), 5.29 (m, 1H), 4.37 (m,1H), 3.81 (m, 3H), 3.67 (m, 1H), 3.52-3.44 (m, 1H), 3.11-2.95 (m, 2H), 2.07 (m, 3H); |
| 10a, 10b |  (3-Fluorophenyl)(2-((((*R*)-1-(naphthalen-1-yl)ethyl) amino)methyl)-2*H*-benzo [*b*][1,4]oxazin-4(3*H*)-yl) methanone | Intermediate-11 | 10a: m/z 441.2; $^1$H NMR (400MHz, $CDCl_3$): δ 8.10-8.04 (m,1H), 7.92-7.82 (m, 2H), 7.57-7.55 (m,3H), 7.25-7.07 (m, 2H), 7.69-6.85 (m, 4H), 6.60 (m, 2H), 5.36 (m, 1H), 5.10 (m, 1H), 4.19 (d, *J*=10.42 Hz, 1H), 3.51-3.44 (m, 2H), 3.06-2.95 (m, 2H), 1.96 (s, 3H);<br><br>10b: $^1$H NMR (400MHz, $CDCl_3$): δ 8.07-8.00(m, 2H), 7.9-7.83 (m, 2H), 7.56-7.51 (m, 3H), 7.17 (m, 1H),7.04-6.89 (m, 3H), 6.89 (m, 1H), 6.73 (m, 1H) ,6.6 (m, 2H), 5.21 (m, 1H), 5.02 (m, 1H), 3.95 (d, *J*=9. 6Hz, 1H), 3.57 (m, 1H), 3.49(m, 1H), 3.14(d,*J*=10.8, 1H), 2.03(s, 3H), 1.19 (s, 3H); |

| | | | |
|---|---|---|---|
| 11a, 11b |  (2-((((*R*)-1-(3-Methoxy phenyl)ethyl)amino)methyl )-2*H*-benzo[*b*][1,4] oxazin-4(3*H*)-yl)(m-tolyl) methanone | Intermediate-12 | 11a: m/z 417.2; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, 1H), 7.23-7.17 (m, 3H), 7.14 (m, 1H), 6.99-6.95 (m, 1H), 6.92-6.90 (m, 1H), 6.87-6.85 (m, 3H), 6.78-6.75 (m, 1H), 6.6 (m, 1H), 4.38 (m, 1H), 4.16 (m, 1H), 3.78 (m, 3H), 3.76-3.64 (m, 2H), 2.82-2.69 (m, 2H), 2.34 (d, *J*=6.0 Hz, 3H), 1.35 (m, 3H);<br>11b: $^1$H NMR (400 MHz, $CDCl_3$): δ 11.38 (bs, 1H), 9.36 (bs, 1H), 7.21 (m, 4H), 7.07 (m, 3H), 6.94-6.88 (m, 3H), 6.63-6.57 (m, 3H), 5.18 (m, 1H), 4.33 (m, 1H), 3.80 (m, 3H), 3.63 (m, 1H), 3.50-3.44 (m, 1H), 3.00-2.94 (m, 2H), 2.29 (m, 3H), 2.05 (m, 3H); |
| 12a, 12b |  (2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4 (3*H*)yl)(m-tolyl)methanone | Intermediate-12 | 12a: m/z 437.2; $^1$H NMR (400 MHz, $CDCl_3$: δ 8.08 (d, *J* = 8Hz, 2H), 7.92-7.82 (m, 1H), 7.59-7.52 (m, 3H), 7.16-7.14 (m, 2H), 7.04-7.10 (m, 1H), 6.92-6.80 (m, 4H), 6.60 (m, 1H), 5.41 (m, 1H), 5.29 (m, 1H), 4.10 (m, 1H), 3.51-3.46 (m, 2H), 3.05-2.95 (m, 1H), 2.24 (s,3H), 1.99 (s, 3H);<br>12b: $^1$H NMR (400 MHz, $CDCl_3$): δ 11.75 (bs, 1H), 9.56 (bs, 1H), 8.18 (m,1H), 7.96-7.85 (m, 3H), 7.58-7.52 (m,3H), 7.13-7.09 (m, 2H), 6.99-6.87 (m,2H), 6.72-6.56 (m, 3H), 5.32 (m,1H), 5.13 (m, 2H), 3.86-3.83 (m, 1H), 3.52-3.47(m, 1H), 3.15 (m, 1H), 2.96 (m, |

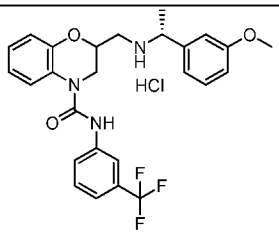
| | | | |
|---|---|---|---|
| | | | 1H), 2.24 (s, 3H), 2.16 (s, 3H); |
| 13a,<br>13b |  <br>(2-((((*R*)-1(3-Methoxy phenyl)ethyl)amino) methyl)-2*H*-benzo[*b*][1,4] oxazin-4(3*H*)yl)(3(trifluoro methyl)phenyl)methanone hydrochloride | Intermediate-13 | 13a: m/z 471.2; $^1$H NMR (400 MHz, $CDCl_3$): 10.40 (bs, 1H), 7.71 (s, 1H), 7.66 (d, *J*=8 Hz, 1H), 7.34-7.28 (m, 3H), 7.11 (m, 2H), 7.02-7.00 (m, 1H), 6.91 (d, *J*=8.4 Hz, 1H), 6.63 (m, 2H), 4.29 (m, 1H), 4.63 (m, 1H), 4.29 (m, 1H), 3.79 (m, 3H), 3.61-3.58 (m, 1H), 3.14 (m, 1H), 2.93 (m, 1H), 1.97 (m, 3H);<br>13b: $^1$HNMR (400 MHz, $CDCl_3$): δ 10.40 (bs, 1H), 7.71 (s, 1H), 7.66 (d, *J*=8Hz, 1H), 7.34-7.28 (m, 3H), 7.11 (m, 2H), 7.02-7.00 (m, 1H), 6.91 (d, *J*=8.4 Hz, 1H), 6.63 (m, 2H), 4.29 (m, 1H), 4.63 (m, 1H), 4.29 (m, 1H), 3.79 (m, 3H), 3.61-3.58 (m, 1H), 3.14 (m, 1H), 2.93 (m, 1H), 1.97 (m, 3H); |
| 14a,<br>14b |  <br>(2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)(3-(trifluoro methyl) phenyl) methanone | Intermediate-13 | 14a: m/z 491.2; $^1$H NMR (400MHz, MeOD): δ 8.21-8.12 (m, 3H), 7.97-7.89 (m, 3H), 7.67-7.64 (m, 6H), 7.02-6.94 (m, 2H), 6.60 (m, 1H), 5.64 (m, 1H), 4.35 (m, 1H), 3.53-3.47 (m, 2H), 3.08 (m, 2H), 2.18-2.07 (m, 3H),<br>14b: $^1$H NMR (400 MHz, MeOD): δ 7.89 (m, 3H), 7.59-7.55 (m, 5H), 6.99-6.97 (m, 4H), 6.59 (m, 3H), 5.49 (m, 1H), 3.9 (m, 1H), 3.57-3.44 (m, 2H), 3.10 (m, 2H), 2.33 (m, 3H), |

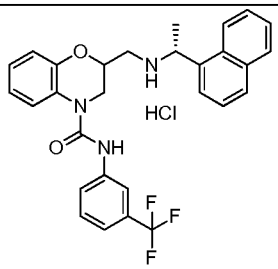
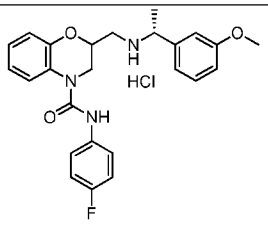
| | | | |
|---|---|---|---|
| 15 |  (3-Fluoro-5-(trifluoro methyl)phenyl) (2-((((*R*)-1-(3methoxyphenyl)ethyl) amino)methyl)-2*H*-benzo [*b*][1,4]oxazin-4(3*H*)-yl) methanone | Intermediate-14 | m/z 489.2; $^1$H NMR (400 MHz, MeOD): δ 7.67-7.63 (m, 2H), 7.52 (m, 1H), 7.48-7.39 (m, 1H),7.17-7.02 (m, 5H), 6.81 (m, 2H), 4.74 (m, 1H), 4.64 (m, 1H), 4.50 (m, 1H), 3.84 (m, 3H),3.60-3.49 (m, 2H), 3.21 (m, 1H), 1.74 (m, 3H); |
| 16 |  (3-Fluoro-5-(trifluoro-methyl)phenyl)(2-((((*R*)-1-(naphthalen-1-yl)ethyl) amino)methyl)-2*H*-benzo [*b*][1,4]oxazin-4(3*H*)-yl) methanone | Intermediate-14 | m/z 509.2; $^1$H NMR (400 MHz, MeOD): δ 8.27-8.25 (m, 1H), 8.03-7.99 (m, 2H), 7.83-7.58 (m, 7H), 7.14-7.06 (m, 3H), 6.53 (m, 1H), 5.57-5.53 (m, 1H), 4.75 (m, 1H), 3.58-40 (m, 3H), 3.1 (m, 1H), 1.89 (m, 3H); |
| 17 |  1-(2-((((*R*)-1-(3-Methoxy phenyl)ethyl)amino)methyl )-2*H*-benzo[*b*][1,4]oxazin- | Intermediate-15 | m/z 417.2; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.77 (m, 1H), 7.36-7.10 (m, 9H), 7.00-6.77 (m, 3H), 4.64-4.59 (m, 1H), 4.43-4.32 (m, 2H), 4.04-3.89 (m, 1H), 3.77 (m, 3H), 3.50-3.44(m, 1H), 3.27-3.16 (m, 1H), 3.00-2.99 (m, 1H), 2.80-2.77 (m, 1H), 1.64 (m, 3H); |

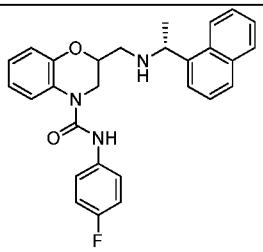
| | | | |
|---|---|---|---|
| | 4(3*H*)-yl)-2-phenyl ethanone | | |
| 18 |  1-(2-((((*R*)-1-(Naphthalen-1-yl)ethyl) amino)methyl)-2*H*-benzo[*b*][1,4] oxazin-4 (3*H*)-yl)-2-phenyl ethanone | Intermediate-15 | m/z 437.2; $^1$H NMR (400 MHz, DMSO-D6): δ 8.23 (d, *J*=4.8 Hz, 1H), 8.02-7.89 (m, 3H), 7.67-7.58 (m, 4H), 7.28-7.10 (m, 6H), 6.67-6.90 (m, 2H), 5.39-5.37 (m, 1H), 4.17 (m, 1H), 4.39 (m, 1H), 4.37-4.33 (m, 2H), 3.49 (m, 3H), 3.19 (s, 3H), 1.74 (s, 3H); |

The below Examples 19 to 22 given in Table-4 were prepared by following the similar procedure as described in Example-5 or Example-6 by using corresponding amide intermediates.

Table-4:

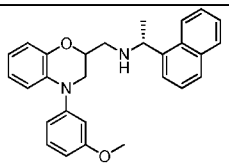
| **Example No.** | **Structure** | **Starting Material** | **Mass (m/z) and NMR** |
|---|---|---|---|
| 19 |  2-((((*R*)-1-(3-Methoxy phenyl)ethyl)amino) methyl)-*N*-(3(trifluoro methyl)phenyl)-2*H*-benzo[*b*][1,4]oxazine-4 | Intermediate-16 | m/z 486.2; $^1$H NMR (400 MHz, $CDCl_3$): δ 10.10 (bs, 1H), 9.6 (bs, 1H), 9.35 (bs, 1H), 7.90 (m, 1H), 7.75 (m, 1H), 7.54-7.47 (m, 2H), 7.35-7.31 (m, 2H), 7.22 (m, 1H), 7.13-7.11 (m, 1H), 7.04-6.91 (m, 4H), 4.61 (m, 1H), 4.44 (m, 1H), 4.31 (m, 1H), 3.76 (m, 3H), 3.44-3.40 (m, 2H), 3.11-3.06 (m, 1H), 1.63 (m, 3H); |

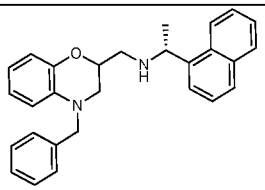
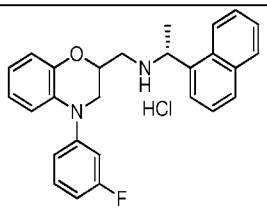
| | | | |
|---|---|---|---|
| | (3*H*)-carboxamide hydrochloride | | |
| 20 |  2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino) methyl)-*N*-(3-(trifluoro methyl)phenyl)-2*H*-benzo[*b*][1,4]oxazine-4 (3*H*)-carboxamide hydrochloride | Intermediate-17 | m/z 506.2; $^1$HNMR (400 MHz, DMSO-D6): δ 10.3 (bs, 1H), 9.98 (bs, 1H), 9.64 (bs, 1H), 9.47 (bs, 1H), 8.23 (t, *J*=9.2 Hz, 1H), 8.02-7.97 (m, 3H), 7.91 (s, 1H), 7.75 (d, *J*=8Hz, 1H), 7.65-7.57 (m, 3H), 7.53-7.48 (m, 2H), 7.35 (d, *J*=7.6Hz, 1H),7.03-6.89 (m, 3H), 5.44 (m, 1H), 4.69 (m, 1H), 6.46-3.40 (m, 2H), 3.28 (m, 1H), 3.08 (m, 1H), 1.74 (d, *J* = 6 Hz, 3H); |
| 21 |  *N*-(4-Fluorophenyl)-2-((((*R*)-1-(3methoxy phenyl)ethyl)amino) methyl)-2*H*-benzo[*b*] [1,4]oxazine-4(3*H*)-carboxamide hydrochloride | Intermediate-18 | m/z 436.2; $^1$HNMR (400 MHz, $CDCl_3$): δ 10.10 (bs, 1H) ,9.6 (bs, 1H), 9.4 (bs, 1H), 9.23 (bs, 1H), 7.49 (m, 3H), 7.35-7.34 (m, 1H), 7.22 (s, 1H), 7.14-7.10 (m, 3H), 7.00-6.90 (m, 4H), 4.58 (m, 1H), 4.45 (m, 1H), 4.28-4.22 (m, 1H), 3.76 (m, 3H), 3.09-3.05 (m, 1H), 2.82 (m, 1H), 1.63 (m, 3H); |

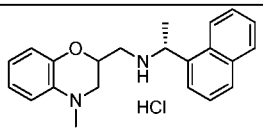
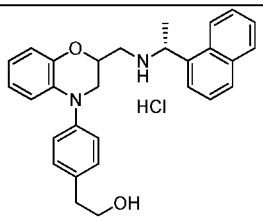
| | | | |
|---|---|---|---|
| 22 |  <br>N-(4-Fluorophenyl)-2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4] oxazine-4(3*H*)-carboxamide | Intermediate-19 | m/z 456.2; $^1$HNMR (400 MHz, $CDCl_3$): δ 8.16 (m, 1H), 7.87-7.84 (m, 1H), 7.74 (d, *J*=8.4 Hz, 1H), 7.65-7.63 (d, *J*=7.2Hz, 1H), 7.51-7.42 (m, 3H), 7.32-7.28 (m, 2H), 7.14-7.10 (m, 2H), 7.02-6.94 (m, 4H), 4.65 (m, 1H), 4.35-4.24 (m, 1H), 3.61-3.49 (m, 2H), 2.91-2.87 (m, 1H), 2.80-2.76 (m, 1H), 1.49 (m, 3H); |

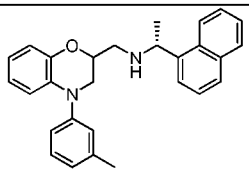
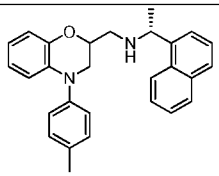
The below Examples 23 to 36 given in Table-5 were prepared by following the similar amide reduction procedure by using borane dimethyl sulphide complex as described in Example-1 or Example-2 by taking appropriate intermediate. Further, diastereomers were separated by flash chromatography using ethylacetate/hexane.

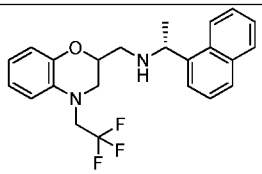
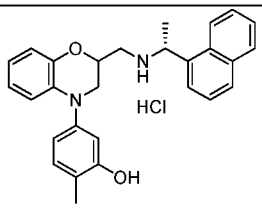
Table-5:

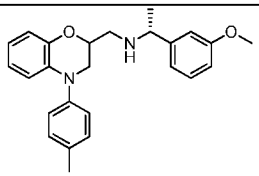
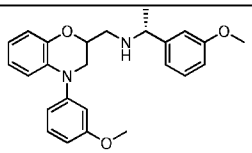
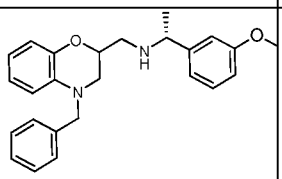
| **Example No.** | **Structure** | **Intermediate** | **Mass (m/z) and $^1$HNMR** |
|---|---|---|---|
| 23a, 23b |  <br>(1*R*)-*N*-((4(3-Methoxy phenyl)-3,4-dihydro-2*H*-benzo[*b*] [1,4] oxazin-2-yl) methyl) 1(naphthalen-1-yl) ethanamine | 31 | 23a: m/z 425.1; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, 1H), 7.85 (m, 1H), 7.74 (d, *J*=8.0 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.49-7.44 (m, 3H), 7.21 (d, J=8.4 Hz, 1H), 6.99 (d, *J*=7.6 Hz, 1H), 6.91-6.89 (m, 1H), 6.77-6.71 (m, 4H), 6.61 (m, 1H), 4.67-4.62 (m, 1H), 3.78 (s, 3H), 3.67-3.66 (m, 1H), 3.49-3.44 (m, 1H), 2.89-2.85 (m, 1H), 2.75-2.71 (m, 1H), 1.52 (s, 3H);<br>23b: $^1$H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J*=7.6, 1H), 7.86 (m, 1H), 7.75 (d, *J*=8.0 Hz, |

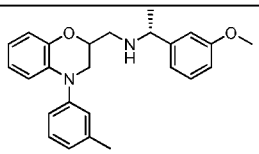
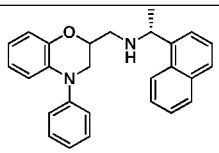
| | | | |
|---|---|---|---|
| | | | 1H), 7.63 (d, *J* = 6.8 Hz, 1H), 7.50-7.46 (m, 3H), 7.21 (t, *J*=8.4 Hz, 1H), 6.99-6.96 (m, 1H), 6.92-6.90 (m, 1H), 6.79-6.71 (m, 4H), 6.62 (m, 1H), 4.66-4.62 (m, 1H), 4.32-4.28 (m, 1H), 3.76 (s, 3H), 3.68-3.65 (m, 2H), 2.85 (d, *J*=5.6, 2H), 1.52 (s, 3H); |
| 24 |  <br>(1*R*)-*N*-((4-Benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)-1-(naphthalen-1-yl) ethanamine | 43 | m/z 409.2; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.88 (m, 1H), 7.86 (m, 1H), 7.68 (m, 1H), 7.59 (m, 1H), 7.59-7.44 (m, 4H), 7.22-7.19 (m, 3H), 6.86-6.75 (m, 2H), 6.67-6.63 (m, 2H), 4.78-4.74 (m, 1H), 4.42-4.32 (m, 3H), 3.25-3.11 (m, 2H), 2.92-2.85 (m, 2H), 1.55 (s, 3H); |
| 25a, 25b |  <br>(1*R*)-*N*-((4-(3-Fluorophenyl)-3,4-dihydro-2*H*-benzo [*b*][1,4]oxazin-2-yl) methyl)-1-(naphthalen-1-yl) ethanamine hydrochloride | 32 | m/z 413.2; 25a: $^1$H NMR(400 MHz,$CDCl_3$): δ 10.54 (bs, 2H), 8.16 (m, 1H), 7.97-7.85 (m, 3H), 7.56 (m, 3H), 7.11 (d, *J*=6.8, 1H), 6.87 (m, 1H), 6.80 (d, *J*=6.8, 1H), 6.70-6.62 (m, 3H), 6.65 (d, *J*=10 Hz, 1H), 5.52 (m, 1H), 5.08 (m, 1H), 3.50-3.45 (m, 1H), 3.23 (m, 1H), 3.07-2.98 (m, 1H), 2.09 (s, 3H), 1.57 (s, 3H);<br>25b: $^1$H NMR (400 MHz, $CDCl_3$): δ 11.55 (bs, 1H), 9.13 (bs, 1H), 8.11 (m, 1H), 7.91 (d, *J*=7.6 Hz, 2H), 7.83 (d, *J*=7.6 Hz, 1H), 7.55 (d, *J*=6.4, 2H), 7.51 (d, *J*=16 Hz, 1H), 7.18 (m, 1H), 6.99-6.96 (m, 1H), 6.76-6.68 (m, 4H), 6.59 (t, *J*=8 Hz, 1H), 6.47 (d, *J*=10 Hz, 2H), 5.29 (m, 1H), 5.00 (m, 1H), 3.50-3.40 (m, 1H), 3.27 (m, 1H), 3.09 (m, 1H), 2.88 (m, 1H), 2.12 (s, 3H); |

| | | | |
|---|---|---|---|
| 26 |  <br>(1*R*)-*N*-((4-Methyl-3,4-dihydro-2 benzo[*b*][1,4]oxazin-2-yl)methyl)-1-(naphthalen-1-yl) ethanamine hydrochloride | 41 | m/z 332.19; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.31 (bs, 1H), 9.95 (bs, 1H), 9.6 (bs, 1H), 9.35 (bs, 1H), 8.21 (m, 1H), 8.01-7.91 (m, 3H), 7.65-7.57 (m, 3H), 6.80-6.77 (m, 1H), 6.72-6.61 (m, 3H), 5.45 (m, 1H), 4.67 (m, 1H), 3.29-3.25 (m, 1H), 3.21-3.16 (m, 1H), 3.06-2.99 (m, 2H), 2.77 (s, 3H), 1.72 (s, 3H); |
| 27 |  <br>2-(4-(2-((((*R*)-1-(Naphthalen-1-yl) ethyl)amino)methyl)-2*H*-benzo[*b*][1,4] oxazin-4(3*H*)-yl) phenyl)ethanol hydrochloride | 34 | m/z 439.2; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.25 (bs, 1H), 9.95 (bs, 1H), 9.6 (bs, 1H), 9.35 (bs, 1H), 8.23 (m, 1H), 8.02-7.92 (m, 3H), 7.63-7.56 (m, 3H), 7.21-7.14 (m, 2H), 7.06-6.97 (m, 2H), 6.92-6.90 (m, 1H), 6.76-6.71 (m, 1H), 5.45-5.36 (m, 1H), 4.63 (m, 1H), 3.81 (d, *J*=11 Hz, 1H), 3.59-3.55 (m, 3H), 3.21 (m, 1H), 3.02 (m, 1H), 2.70-2.65 (m, 2H), 1.72 (s, 3H); |

| | | | |
|---|---|---|---|
| 28a, 28b |  (1*R*)-1-(Naphthalen-1-yl)-*N*-((4-(m-tolyl)-3,4-dihydro-2*H*benzo[*b*][1,4]oxazin-2-yl) methyl)ethanamine | 35 | m/z 409.2; 28a: $^1$H NMR (400 MHz, $CDCl_3$): δ 8.23 (m, 1H), 7.89-7.87 (m, 1H), 7.77 (d, *J*=8 Hz, 1H), 7.69 (d, *J* = 6.8 Hz, 1H), 7.54-7.44 (m, 3H), 7.22 (t, *J*=8 Hz, 2H), 7.02-6.98 (m, 2H), 6.94-6.89 (m, 2H), 6.77-6.73 (m, 2H), 4.69-4.67 (m, 1H), 4.37 (m, 1H), 3.70 (dd, *J*=2.4 Hz, *J*=12.4 Hz, 1H), 3.51-3.46 (m, 1H), 2.93-2.88 (m, 1H), 2.78-2.74 (m, 1H), 2.33 (s, 3H), 1.28 (s, 3H);<br>28b: $^1$H NMR (400 MHz, $CDCl_3$): δ 8.23 (m, 1H), 7.86-7.84 (m, 1H), 7.73 (d, *J*=8 Hz, 1H), 7.62 (d, *J* = 6.8 Hz, 1H), 7.48-7.41 (m, 3H), 7.18 (t, *J*=7.6 Hz, 1H), 6.96-6.94 (m, 2H), 6.90-6.87 (m, 3H), 6.75-6.71 (m, 2H), 4.64-4.62 (m, 1H), 4.29 (m, 1H), 3.61-3.58 (m, 2H), 2.84 (d, *J*=6.4 Hz, 2H), 2.29 (s, 3H), 1.47 (d, *J*=6.4 Hz, 3H); |
| 29a, 29b |  (1*R*)-1-(Naphthalen-1-yl)-*N*-((4-(p-tolyl)-3,4-dihydro-2*H*-benzo[*b*] [1,4]oxazin-2-yl)methyl) ethanamine | 36 | m/z 409.2; 29a: $^1$H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 9.2 Hz, 1H), 7.82 (d, *J*=3.2 Hz, 1H), 7.8 (d, *J* = 2.4 Hz, 1H), 7.7 (d, *J* = 8 Hz, 1H), 7.51-7.4 (m, 3H), 7.1 (d, *J*=8 Hz, 2H), 7.07 (d, J=8.4 Hz, 2H), 6.88-6.90 (m, 1H), 6.82-6.80 (m, 1H), 6.74-6.70 (m, 2H), 4.64-4.62 (m, 1H), 4.34-4.29 (m, 1H), 3.61-3.58 (m, 2H), 2.87-2.84 (m, 2H), 2.32 (s, 3H), 1.50 (s, 3H);<br>29b: $^1$H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 7.6 Hz, 1H), 7.87 (m, 1H) 7.74 (d, *J*=8.4 Hz, 1H), 7.67 (d, *J* = 6.8 Hz, 1H), 7.49-7.43 (m, 3H), 7.14 (d, *J*=8 Hz, 2H), 7.07 (d, *J*=8.4 Hz, 2H), 6.90-6.88 (m, 1H), 6.83-6.81 (m, 1H), 6.73-6.71 (m, 2H), 4.66-4.64 (m, 1H), 4.35-4.32 |

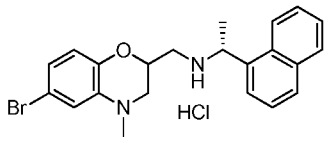
| | | | |
|---|---|---|---|
| | | | (m, 1H), 3.64-3.60 (m, 1H), 3.48-3.43 (m, 1H), 2.91-2.86 (m, 1H), 2.76-2.71 (m, 1H), 2.32 (s, 3H), 1.51 (s, 3H); |
| 30 |  (1*R*)-1-(Naphthalen-1-yl)-*N*-((4-(2,2,2-trifluoroethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl) methyl) ethanamine | 42 | m/z 401.32; $^1$H NMR (400 MHz,$CDCl_3$): δ 8.2 (m,1H),7.87-7.85(m,1H),7.57(d,*J*=8.4Hz,1H), 6.69-6.61 (m, 1H), 7.52-7.42 (m, 3H), 6.84-6.79 (m, 2H), 6.72-6.66 (m, 2H), 4.72 (m, 1H), 4.22 (m, 1H), 3.77-3.65 (m, 2H), 3.37-3.26 (m, 2H), 2.88-2.7 (m, 2H), 1.53 (d, *J*=6.4 Hz, 3H); |
| 31a, 31b |  2-Methyl-5-(2-((((*R*)-1-(naphthalen-1-yl) ethyl)amino)methyl)-2*H*-benzo[*b*][1,4] oxazin-4(3*H*)-yl) phenol hydrochloride | 38 | m/z 425.2; 31a: $^1$H NMR(400 MHz,DMSO-$d_6$):δ 9.9 (bs,1H),9.4(bs,1H),8.26(d, *J*=8.4 Hz, 1H), 8.03-7.97(m, 3H), 7.65-7.60 (m, 3H), 7.03 (d, *J*=8.4 Hz,1H), 6.85-6.82 (m, 1H), 6.76-6.71 (m, 3H), 6.62 (d, *J*=2 Hz, 1H), 6.49-6.47 (m, 1H), 5.47-5.42 (m, 1H), 4.62 (m, 1H), 3.77-3.73 (m, 1H), 3.40-3.35 (m, 1H), 3.24 (m, 2H), 2.08 (s, 3H), 1.72 (d, *J*=6.8 Hz, 3H);<br>31b: $^1$H NMR 400MHz, DMSO-$d_6$): δ10.01(bs, 1H), 9.32 (bs, 1H), 8.22 (d, *J*=8.4 Hz, 1H), 8.03-7.97 (m, 2H), 7.91 (d, *J*=7.2 Hz, 1H), 7.65-7.58 (m, 3H), 6.99 (d, *J*=8 Hz, 1H), 6.91-6.89 (m, 1H), 6.75-6.72 (m, 3H), 6.60 (d, *J*=2 Hz, 1H), 6.43 (m, 1H), 5.43 (m, 1H), 4.58-4.54 (m, 1H), 3.76-3.72 (m, 1H), 3.06-3.04 (m, 1H), 2.06 (s, 3H), 1.71 (d, *J*=6.4 Hz, 3H); |

| | | | |
|---|---|---|---|
| 32 |  (1*R*)-1-(3-Methoxy phenyl)-*N*-((4-(p-tolyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-2-yl)methyl) ethanamine | 39 | m/z 389.2; $^1$H NMR (400 MHz, $CDCl_3$): 7.21 (t, *J* = 8.8 Hz, 1H), 7.14 (d, *J*=8 Hz, 2H), 7.08-7.05 (m, 2H), 6.89-6.86 (m, 3H), 6.83-6.80 (m, 1H), 6.78-6.74 (m, 1H), 6.72-6.68 (m, 2H), 4.27-4.26 (m, 1H), 3.79 (s, 3H), 3.77-3.74 (m, 1H), 3.63-3.40 (m, 2H), 2.82-2.58 (m, 2H), 2.32 (s, 3H); |
| 33a, 33b |  (1*R*)-1-(3-Methoxy phenyl)-*N*-((4-(3-methoxyphenyl)-3,4-dihydro-2*H*-benzo [*b*][1,4]oxazin-2-yl) methyl)ethanamine | 40 | m/z 405.2; 33a: $^1$H NMR (400 MHz, $CDCl_3$): δ 7.24-7.19 (m, 2H), 6.98 (dd, *J*=2 Hz, *J*=7.6 Hz, 1H), 6.91-6.87 (m, 3H), 6.78-6.71 (m, 5H), 6.62 (dd, *J*=2.4Hz, *J*=8.4Hz, 1H), 4.26-4.24 (m, 1H),3.82-3.74(m, 6H), 3.69-3.63 (m, 2H), 3.46-3.41 (m, 1H), 2.82-2.77 (m, 1H), 2.62-2.58 (m, 1H), 1.25 (d, *J*=10 Hz, 3H);<br>33b: $^1$H NMR(400MHz,$CDCl_3$): δ7.23-7.19(m, 2H), 6.98 (dd, *J*=2 Hz, *J*=7.6 Hz, 1H), 6.90-6.85 (m, 3H), 6.78-6.75 (m, 3H), 6.73-6.71 (m, 2H), 6.62 (dd, *J*=2 Hz, *J*=10 Hz, 1H), 4.26-4.24 (m, 1H), 3.79 (m, 6H), 3.66-3.62(m, 2H), 3.57-3.52 (m, 1H), 2.74-2.72 (m, 2H), 1.34 (d, *J*=6.4 Hz, 3H); |
| 34 |  (1*R*)-*N*-((4-Benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)-1-(3- | 44 | m/z 389.2; $^1$H NMR (400 MHz, $CDCl_3$): 7.29-7.19 (m, 7H), 6.93-6.77 (m, 4H), 6.65-6.60 (m, 2H), 4.51 (m, 2H), 4.42 (m, 1H) 3.94-3.79 (m, 1H), 3.79 (m, 3H), 3.23-3.07 (m, 2H), 2.87-2.62 (m, 2H), 1.46 (m, 3H); |

| | | | |
|---|---|---|---|
| | methoxyphenyl)ethanamine | | |
| 35a, 35b |  (1*R*)-1-(3-Methoxyphenyl)-*N*-((4-(m-tolyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)ethanamine | 33 | m/z 389.2; 35a: $^1$H NMR (400 MHz, $CDCl_3$): 7.23-7.18 (m, 2H), 6.99-6.96 (m, 2H), 6.91-6.87 (m, 5H), 6.78-6.71 (m, 3H), 4.23 (m, 1H), 3.79 (m, 3H), 3.76-3.74 (m, 1H), 3.67-3.64 (m, 1H), 3.46-3.41 (m, 1H), 2.82-2.74 (m, 1H), 2.62-2.58 (m, 1H), 2.32(s, 3H), 1.36-1.36 (m, 3H);<br>35b: $^1$H NMR (400 MHz, $CDCl_3$): 7.23-7.18 (m, 2H), 6.99-6.96 (m, 2H), 6.91-6.86 (m, 5H), 6.78-6.71 (m, 3H), 4.23 (m, 1H), 3.79 (m, 3H), 3.74 (m, 1H), 3.64-3.53 (m, 2H), 2.74 (m, 2H), 2.32 (s, 3H), 1.36-1.32 (d, *J*=6.8Hz, 3H); |
| 36a, 36b |  (1*R*)-1-(Naphthalen-1-yl)-*N*-((4-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)ethanamine | 37 | m/z 395.2; 36a: $^1$H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* =7.6 Hz, 1H), 7.82 (d, *J*=6.8Hz, 1H), 7.89 (d, *J*=2.4Hz, 1H), 7.87 (d, *J*=8Hz, 1H), 7.51-7.4 (m, 3H), 7.1 (d, *J*=8 Hz, 2H), 7.07 (d, J=8.4 Hz, 2H), 6.88-6.90 (m, 1H), 6.82-6.80 (m, 2H), 6.74-6.70 (m, 2H), 4.64-4.62 (m, 1H), 4.34-4.29 (m, 1H), 3.72-3.68 (m, 1H), 3.52-3.47 (m, 1H), 2.93-2.89 (m, 1H), 2.78 -2.74 (m, 1H), 1.52 (s, 3H);<br>36b: $^1$H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 7.6 Hz, 1H), 7.88 (m, 1H) 7.73 (d, *J*=8.4 Hz, 1H), 7.64 (d, *J* = 6.8 Hz, 1H), 7.52-7.47 (m, 3H), 7.14 (d, *J*=8 Hz, 2H), 7.07 (d, *J*=8.4 Hz, 2H), 6.90-6.88 (m, 1H), 6.83-6.81 (m, 2H), 6.73-6.71 (m, 2H), 4.66-4.64 (m, 1H), 4.35-4.32 (m, 1H), 3.68-3.57 (m, 2H), 3.48-3.43 (m, 1H), 2.84-2.82 (m, 2H), 1.51 (s, 3H); |

Example-37

(1*R*)-*N*-((6-Bromo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)-1-(naphthalen -1-yl)ethanamine hydrochloride

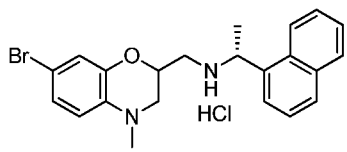



Intermediate-26 (0.1 g, 0.20 mmol) was dissolved in DCM (5 mL) and MeOH/HCl (10 mL, 3N). The reaction mixture was stirred at 35°C overnight. The progress of reaction was monitored by TLC.The reaction was evaporated under reduced pressure then added saturated $Na_2CO_3$ solution (5 mL). The mixture was extracted with ethyl acetate (10mLX2) and washed with water (5mLX2) followed by brine solution (5 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. This was further purified by flash chromatography (15% ethyl acetate-Hexane) to give the free base. Ethereal HCl (2 mL) was added and stirred for 10 min. The solvent was evaporated and solid washed by diethyl ether (2 mL) followed by *n*-pentane (2 ml), dried to get to get title (0.07g, 85%).

m/z 411.33; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.2 (bs, 1H), 9.9 (bs, 1H), 9.45 (bs, 1H), 9.3 (bs, 1H), 8.24 (m, 1H), 8.02-7.90 (m, 3H), 7.66-7.57 (m, 3H), 6.82-6.64 (m, 4H), 5.42 (m, 1H), 4.64 (m, 1H), 3.44 (m,2H), 3.29(m,1H),3.19(m,1H), 2.79 (s, 3H),1.71 (d, *J*=6.4 Hz, 3H).

Example-38

(1*R*)-*N*-((7-Bromo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)-1-(naphthalen -1-yl)ethanamine hydrochloride



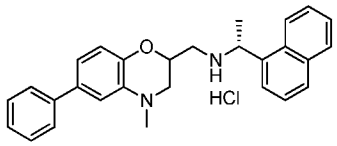

The title compound was prepared by following the above procedure Example-37 by taking Intermediate-27; m/z 413.16.

$^1$H NMR(400 MHz,DMSO-$d_6$): δ 10.65 (bs,1H),10.10(bs,1H), 9.85 (bs, 1H), 9.35 (bs,1H),8.24 (m,1H),8.02-7.95 (m, 3H),7.65-7.55(m,3H),6.96-6.90 (m, 1H), 6.76 (d, *J*=2

Hz ,1H), 6.64 (d, *J*=8.8 Hz,1H), 5.46 (m, 1H),4.75(m,1H), 3.40-3.26 (m, 2H), 3.16-3.03 (m, 2H), 2.76(s,3H),1.73(d, *J*=6.4 Hz, 3H).

Example-39

(1*R*)-*N*-((4-Methyl-6-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-2-yl)methyl)-1 (naphthalen-1-yl) ethanamine hydrochloride

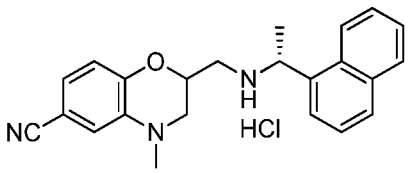



Intermediate-26 (0.1g, 0.20 mmol) was dissolved in toluene (5mL), phenyl boronic acid (0.29 g, 0.24 mmol, Pd $(Ph_3P)_4$ (0.012 g, 0.01 mmol) and $Na_2CO_3$ (0.032 g, 4.51 mmol) was added under nitrogen atmosphere. The reaction mixture was heated to 120°C and further maintained for 5 h. The progress of reaction was monitored by TLC. The separated out solid was filtered through Celite. The filtrate was extracted with ethyl acetate (25 mLX2) and washed with water (15 mL) and brine solution (15 mL). The organic layer was dried over sodium sulfate and filtered. Filtrate was concentrated under reduced pressure to get crude product. The crude compound was purified with silica gel flash column chromatography (15% ethyl acetate: Hexane) to give free base. Ethereal HCl (2mL) was added and stirred for 10 min. The solvent was evaporated and solid washed by diethyl ether (2 mL) followed by *n*-pentane (2 ml), dried to get title compound (0.07g, 85%).

m/z 409.29; $^1$H NMR (400 MHz, DMSO-$d_6$): 10.01 (bs, 1H), 9.7 (bs, 1H), 9.5 (bs, 1H), 9.35 (bs, 1H), 8.25 (m, 1H), 8.04-7.89 (m, 3H), 7.67-7.58 (m, 4H), 7.41 (t, *J*=7.6 Hz, 2H), 7.31-7.27 (m, 1H), 6.95-6.91 (m, 2H), 6.88-6.81 (m, 2H), 5.44 (m, 1H), 4.69 (m, 1H), 3.10-3.05 (m, 4H), 2.87 (s, 3H), 1.72 (d, *J*=6.8 Hz, 3H).

Example-40

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

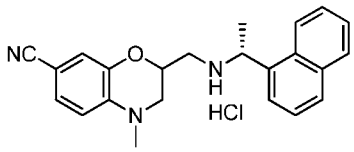


Intermediate-26 (0.15g, 0.29 mmol) was dissolved in DMF (5mL), water (0.1 mL), zinc cyanide (0.021 g, 0.18 mmol), tris dibenzylidene acetone dipalladium (0) (0.014 g, 0.015 mmol) and 1,1'-Bis(diphenylphosphino) ferrocene(0.02g,0.036mmol)was added under nitrogen atmosphere. The reaction mixture was heated to 120°C and further maintained for 5 h. The progress of reaction was monitored by TLC. The separated out solid was filtered through Celite. The filtrate was extracted with ethyl acetate (25 mLX2) and washed with water (15 mL) and brine solution (15 mL). The organic layer was dried over sodium sulfate and filtered. Filtrate was concentrated under reduced pressure to get crude product. The crude compound was purified with silica gel flash column chromatography (15% ethyl acetate: Hexane) to give free base. Ethereal HCl (2mL) was added and stirred for 10 min. The solvent was evaporated and solid washed by diethyl ether (2 mL) followed by *n*-pentane (2 ml), dried to get title compound (0.07g, 64.9%).

m/z 358.1; $^1$H NMR (400 MHz, DMSO-d6): 10.5 (bs, 1H), 9.9 (bs, 1H), 9.6 (bs, 1H), 9.35 (bs, 1H), 8.23 (m, 1H), 8.01-7.93 (m, 3H), 7.65-7.56 (m, 3H), 7.11 (m, 2H), 6.91-6.84 (m, 1H), 5.45 (m, 1H), 4.77 (m, 1H), 3.28-3.10 (m, 3H), 3.01-3.0 (m, 1H), 2.82 (s, 3H), 1.72 (d, *J*=6.4 Hz, 3H).

Example-41

4-Methyl-2-((((*R*)-1-(naphthalen-1yl) ethyl amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine-7carbonitrile hydrochloride

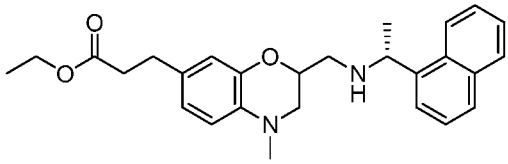



The title compound was prepared by following the above procedure Example-40 by taking Intermediate-27.

m/z 358.01; $^1$H NMR (400 MHz, DMSO-$d_6$):10.65(bs,1H),10.10 (bs,1H), 9.85 (bs, 1H), 9.35 (bs, 1H), 8.25-8.01 (m, 1H), 8.0-7.96 (m, 3H), 7.64-7.58(m, 3H), 7.26-7.22(m, 1H), 7.08 (d, *J*=2 Hz, 1H), 6.95 (d, *J*=2 Hz, 1H), 6.77 (dd, *J*=8.8 Hz,1H), 5.46-5.37(m, 1H), 4.69 (d, *J*=2.4 Hz, 1H), 3.48-3.47(m,1H), 3.28-3.24 (m, 1H), 3.23-3.18 (m, 1H), 2.89 (m, 3H) 1.73 (m, 3H).

Example-42

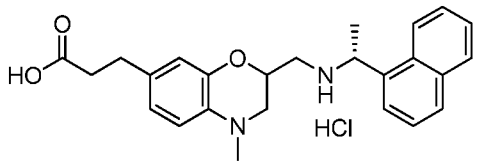
Ethyl 3-(4-methyl-2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)propanoate



Intermediate-48 (0.15 g, 0.35 mmol) was dissolved in DCM (5mL) and MeOH/HCl (10 mL, 3N). The reaction mixture was stirred at 35°C overnight. The progress of reaction was monitored by TLC. The reaction was evaporated under reduced pressure then added saturated $Na_2CO_3$ solution (5mL). The mixture was extracted with ethyl acetate (10mLX2) and washed with water (5mLX2) followed by brine solution (5mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to get title compound (0.1g,82%) m/z-433.5.

Example-43

3-(4-Methyl-2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-7-yl)propanoic acid hydrochloride

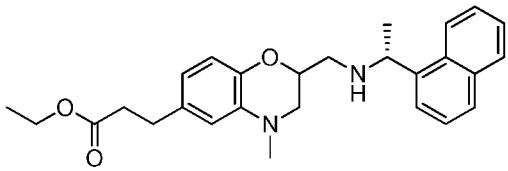


To a solution of Example-42 (0.09g, 0.21mmol) in MeOH (5mL), THF (5.00mL) and water (0.5mL) lithium hydroxide hydrate (0.044g, 1.04 mmol) was added. The reaction mixture was heated to 80°C and further maintained for 2 hr. The progress of reaction was monitored by TLC. The reaction mixture was concentrated under vacuum then cooled to 0°C and acidified with dilute HCl solution [pH=3 to 4]. Extract the product with ethyl acetate (10mLX2), washed with water (5mL X2) followed by brine solution (5 mL), dried over sodium sulfate and concentrated under vacuum to get solid. Ethereal HCl (2 mL) was added and stirred for 10 min. The solvent was evaporated and solid washed by diethyl ether (2 mL) followed by *n*-pentane (2 ml), dried to get crude product (75 mg, 82 % yield).

m/z 405.1;$^1$HNMR(400MHz,DMSO-$d_6$):δ10.5 (bs, 1H), 10.01 (bs, 1H), 9.7 (bs, 1H), 9.35 (bs, 1H), 8.24 (t, *J*=8.4 Hz, 1H), 8.01-7.96 (m, 3H), 7.66-7.56 (m, 3H), 6.67-6.62 (m, 2H), 6.61-6.59 (m, 1H), 5.45 (m, 1H), 4.69 (m, 1H), 3.99-3.35 (m, 1H), 3.33-3.15 (m, 2H), 3.02-2.94 (m, 1H), 2.69 (m, 3H), 2.66-2.63 (m, 2H), 2.47-2.40 (m, 2H), 1.73 (d, *J*=6.4 Hz, 3H).

Example-44

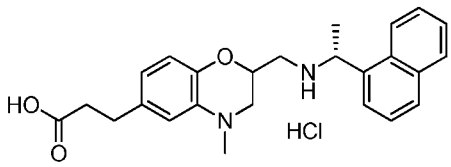
Ethyl 3-(4-methyl-2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo[*b*] [1,4]oxazin-6-yl)propanoate



The title compound was prepared following similar procedure as described in Example-42 by taking Intermediate-50.

Example-45

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

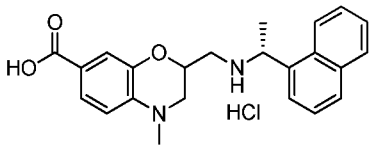


The title compound was prepared following similar procedure as described in Example-43 by taking Example-44.

m/z 405.1; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.6 (bs, 1H), 9.9 (bs, 1H), 9.7(bs, 1H), 9.35 (bs, 1H), 8.25 (t, *J*=8.4 Hz, 1H), 8.03-7.95 (m, 3H), 7.65-7.55 (m, 3H), 6.68-6.56 (m, 2H), 6.49-6.44 (m, 1H), 5.45 (m, 1H), 4.69 (m, 1H),3.37 (m, 2H), 3.27-3.23 (m, 1H), 3.1 (m, 1H), 3.02 (m, 2H), 2.76 (m, 3H), 2.70-2.66 (m, 2H),2.46-2.44 (m, 2H), 1.72 (d, *J*=6.4 Hz, 3H).

Example-46

4-Methyl-2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine-7-carboxylic acid hydrochloride

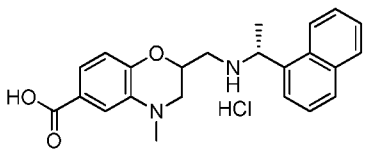


To solution of Example-41 (0.09g, 0.25mmol) in MeOH (5mL) and water (2mL) sodium hydroxide (0.050 g, 1.26 mmol) was added. The reaction mixture was heated to 90°C for 18 hr. The progress of reaction was monitored by TLC. Methanol was distilled off under vacuum then cooled to 0°C and acidified with dilute HCl solution [pH=3 to 4]. Extract the product with ethyl acetate (10mLX2), washed with water (5mLX2) followed by brine solution (5 mL), dried over sodium sulfate and concentrated under vacuum to get solid. Ethereal HCl (2 mL) was added and stirred for 10 min. The solvent was evaporated and solid washed by diethyl ether (2 mL) followed by *n*-pentane (2 ml), dried to get crude product of the title compound (0.075 g, 72.1%).

m/z 377.1; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 12.1 (bs, 1H), 10.01 (bs, 1H), 9.7 (bs, 1H), 9.35 (bs, 1H) 9.12 (bs, 1H), 8.24 (m, 1H), 8.01-7.96 (m, 3H), 7.66-7.56 (m, 3H), 7.47-7.42 (m, 1H), 7.31-7.20 (m, 1H), 6.72 (m, 1H), 5.45 (m, 1H), 4.63 (m, 1H), 3.38-3.17 (m, 1H), 2.89 (s, 3H), 1.73 (d, *J*=6.4 Hz, 3H).

Example-47

4-Methyl-2-((((*R*)-1-(naphthalen-1-yl) ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine -6-carboxylic acid hydrochloride

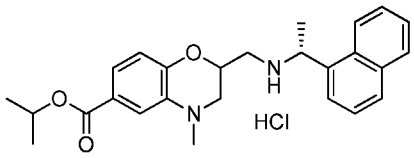


The title compound was prepared following similar procedure as described in Example-46 by taking Example-40.

m/z 377.4; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 12.1 (bs, 1H), 10.01 (bs, 1H), 9.7 (bs, 1H), 9.35 (bs, 1H),9.12(bs, 1H), 8.24 (t, *J* = 9.2 Hz, 1H), 8.01-7.96 (m, 2H), 7.84-7.77 (m, 2H), 7.29-7.25 (m, 1H), 6.86-6.79 (m, 1H), 5.43 (m, 1H), 4.7 (m, 1H), 4.65 (m, 1H), 3.30-3.27 (m, 3H), 3.06-3.04 (m, 2H), 1.69 (s, 3H).

Example-48

Isopropyl 4-methyl-2-((((*R*)-1-(naphthalen-1yl)ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo [*b*][1,4]oxazine-6-carboxylate hydrochloride

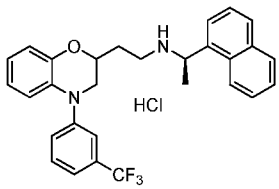



To solution of Example-47 (50mg, 0.22mmol) in 2-propanol (5mL) and catalytic amount of conc.$H_2SO_4$ was added. The reaction mixture was heated to 90°C for 18 hr. The progress of reaction was monitored by TLC. Organic solvent was distilled off under vacuum then cooled to 0°C and basified with 10% $Na_2CO_3$.Extract the product with ethyl acetate (10mLX2), washed with water (5mLX2)followed by brine solution (5mL), dried over sodium sulfate and concentrated under vacuum to get solid. This crude product was purified by flash chromatography using a mixture of 10% ethylacetate in hexane. Ethereal HCl (2mL) was added and stirred for 10 min. The solvent was evaporated and solid washed by diethyl ether (2 mL) followed by *n*-pentane (2 ml), dried to get the title compound as solid (45mg, 82%).

m/z 419.1; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.5 (bs, 1H), 10.01 (bs, 1H), 9.7 (bs, 1H), 9.35 (bs, 1H), 9.12 (bs, 1H), 8.24 (m, 1H), 8.01-7.96 (m, 2H),7.84-7.77(m, 1H), 7.66-7.55 (m, 3H), 7.29-7.25 (m, 1H), 7.20-7.17 (m, 1H), 6.89-6.80 (m, 1H), 5.39 (m, 1H), 5.07 (m,1H), 4.65 (m, 1H), 3.39-3.33 (m, 1H), 3.24-3.23 (m, 2H), 2.79 (s, 3H), 1.69 (s, 3H), 1.67 (d, *J*=6.4 Hz, 6H).

Example-49a

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




The mixture of Intermediate-51a (150mg, 0.45mmol), 1-iodo-3(trifluoromethyl)benzene (0.18g,0.68 mmol) and $Cs_2CO_3$ (0.22 g, 0.68 mmol) in toluene (7mL) was degassed for 15 min by purging nitrogen followed by addition of bis (tri-tert-butylphosphine palladium(0) (11.53mg, 0.023 mmol) and tris dibenzylidene acetone dipalladium (0)(20.66mg,0.023 mmol). The reaction mixture was heated to 110°C and further maintained for 20 hr at the same temperature. The reaction mixture was cooled to room

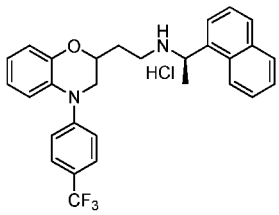
temperature and progress of reaction monitored by TLC. The mixture was diluted with ethyl acetate, filtered through celite and concentrated under vacuum to give crude compound. This crude compound was further purified by flash chromatography using a mixture of 20% ethylacetate in hexane (0.17g, 79%).

Ethereal HCl (2 mL) was added and stirred for 10 min. The solvent was evaporated and solid washed by diethyl ether (2 mL) followed by *n*-pentane (2 ml), dried to get HCl salt of title compound.

m/z 477.2; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.64 (bs, 1H), 9.10 (bs, 1H), 8.24 (d, *J*=8.4 Hz, 1H), 8.03 (t, *J*=8.8 Hz, 2H), 7.89 (d, *J*=7.2 Hz, 1H), 7.63-7.48 (m, 6H), 7.37(d, *J*=7.6 Hz, 1H), 6.93 (d, *J*=7.2 Hz, 1H), 6.80-6.77 (m, 3H), 5.34 (m,1H), 4.28 (m, 1H),3.85 (m,1H), 3.47-3.10 (m, 3H), 2.03 (m, 2H), 1.67 (d, *J*=6.8 Hz, 3H).

Example-50a

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

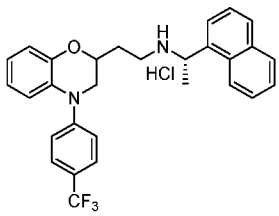



The title compound was prepared following similar procedure as described in above Example- 49 by taking Intermediate-51a and 1-iodo-4(trifluoromethyl)benzene.

m/z 477.2; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.74 (bs, 1H), 9.15 (bs, 1H), 8.24 (d, *J*=8.4 Hz, 1H), 8.03-7.90 (m, 3H), 7.66-7.58 (m, 5H), 7.35 (d, *J*=8. 8Hz, 2H), 7.08 (m, 1H), 6.88-6.81 (m, 3H), 5.34 (m, 1H), 4.28 (m, 1H), 3.89 (m, 1H), 3.47-3.08 (m, 3H), 2.02(m, 2H), 1.67 (d, *J*=6.8 Hz, 3H).

Example-51

(1*S*)-1-(Naphthalen-1-yl)-*N*-(2-(4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-2-yl)ethyl)ethanamine hydrochloride

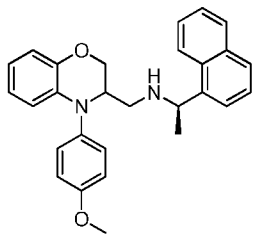


The title compound was prepared following similar procedure as described in Example-49 by taking Intermediate-52 and 1-iodo-4(trifluoromethyl)benzene.

m/z=477.2; $^1$H NMR (400 MHz, DMSO-d6): δ10.9 (bs, 1H), 9.10 (bs, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.03-8.0 (m, 3H),7.92 (d, *J* = 6.8 Hz,1H), 7.65-7.57 (m, 5H), 7.35-7.33, (m,2H) , 6.87-6.77 (m, 3H), 5.33-5.31 (m, 1H), 4.28-4.26 (m, 1H), 3.90-3.87 (m,1H), 3.46-3.44 (m, 1H), 3.24-3.22 (m, 1H) 3.0-2.98 (m, 1H), 2.04-1.99 (m, 2H), 1.64-1.63 (d, *J*= 6.8 Hz, 3H).

Example-52a, 52b

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



To a mixture of Intermediate-46a (0.2g,0.63mmol) and 1-Bromo-4-methoxybenzene (0.14g, 0.75mmol), $Cs_2CO_3$ (0.31 g, 0.94mmol) in toluene (7 mL) was degassed for 15 min by purging nitrogen followed by addition of bis (tri-tert-butylphosphine palladium (0) (0.016 g, 0.031 mmol) and tris dibenzylidene acetone dipalladium (0) (0.029 g, 0.031 mmol). The reaction mixture was heated to110°Cand 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 ethyl acetate, filtered through celite and concentrated under vacuum. The crude product purified by flash chromatography using a mixture of ethyl acetate/hexane to get title compound (0.18g, 67.5%).

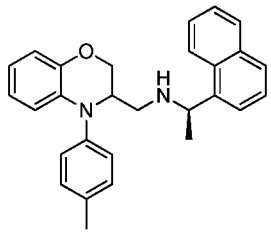
a:m/z 425; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.2 (d ,*J* =7.2 Hz, 1H), 7.86-7.84 (m, 1H) ,7.82-7.80 (m, 3H), 7.54-7.48 (m, 3H) 6.80-6.76 (m, 4H), 6.75-6.73 (m, 2H), 4.21-4.18 (m, 1H),4.02-4.0 (m, 1H), 3.8 (s, 3H), 3.70-3.66 (m, 2H), 2.67-2.65 (m, 1H), 2.52-2.5 (m, 1H), 1.26 (d, *J* = 7.2 Hz, 3H).

Similarly, Example-52b was prepared by taking Intermediate-46b.

b: m/z 425.0; $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.2 (d, *J*=7.2 Hz, 1H), 7.84-7.82 (m, 2H), 7.8-7.76 (m, 3H), 7.5-7.45 (m, 3H) 6.78-6.72 (m, 4H), 6.72-6.70 (m, 2H), 4.2-4.18 (m, 1H), 4.06-4.02 (m, 1H), 3.82 (s, 3H), 3.69 -3.67 (m, 2H), 2.68-2.65 (m, 1H), 2.53-2.5(m, 1H), 1.26 (d, *J* = 7.2 Hz, 3H).

Example-53a, 53b

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



The title Examples 53a was prepared by following the similar procedure as described in Example-52a, 52b by taking Intermediate-46a with 1-bromo-4-methylbenzene.

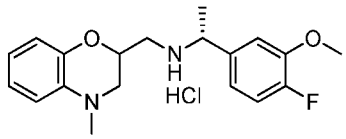
a: m/z 409.5; $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.86-7.82 (m, 2H), 7.75-7.73 (m, 1H), 7.53-7.5(m,2H), 7.42-7.40 (m, 1H), 7.09-6.98 (m, 4H), 6.88-6.85 (m, 3H), 6.77-6.75 (m, 2H), 5.09-5.10 (m, 1H), 4.28-4.26 (m, 2H), 4.01-3.98 (m, 1H), 3.49-3.47 (m, 1H), 2.85-2.79 (m, 1H), 2.28 (s, 3H), 1.89 (d, *J*=7.2 Hz ,3H).

Similarly, Example-53b was prepared by taking Intermediate-46b.

b: m/z 409.5; $^1$H-NMR (400 MHz ,$CDCl_3$): δ 7.84-7.80 (m, 2H), 7.73-7.71 (m, 1H), 7.51-7.49 (m, 2H), 7.4-7.38 (m, 1H), 7.05-6.98 (m, 4H), 6.85-6.83 (m, 3H), 6.75-6.73 (m, 2H), 5.1-4.9 (m, 1H) ,4.26-4.24 (m, 2H) ,4.0-3.99 (m, 1H), 3.42-3.40 (m, 1H), 2.82-2.79 (m, 1H), 2.26 (s, 3H), 1.85 (d, *J* = 7.2 Hz, 3H).

Example-54

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



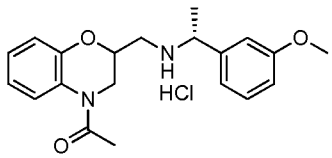
To a mixture of Intermediate-53 (0.3g, 0.87mmol) in dry tetrahydrofuran (10 mL) borane dimethyl sulphide complex (0.87 mL, 1.74mmol,2M ) was added. The reaction mixture was heated to 50°C and maintained for 2 h. The progress of reaction was monitored by

TLC. Tetrahydrofuran was distilled off under vacuum then added MeOH/HCl (5 mL) at 0°C. The reaction mixture was heated to 50°C and stirred for 10 minutes. Methanol was distilled off under vacuum and cooled to 0°C then acidified with dilute HCl solution [pH=3 to 4]. Extract the product with ethyl acetate (10mLX2), washed with water (5mLX2) followed by brine solution (5mL), dried over sodium sulfate and concentrated under vacuum to get solid. The crude product was purified by flash chromatography using a mixture of 15% ethyl acetate/hexane. Ethereal HCl (2mL) was added and stirred for 10 min. The solvent was evaporated and solid washed by diethyl ether (2mL) followed by *n*-pentane (2mL), dried to get the title compound as solid (0.15g, 52.1%).

m/z 331.1; 1H NMR (400 MHz, DMSO-d6): δ 10.15 (bs, 1H), 9.81 (bs, 1H), 9.6 (bs, 1H), 9.35 (bs, 1H), 7.57-7.53 (m, 1H), 7.28-7.23 (m, 1H), 7.12-7.10 (m, 1H), 6.83-6.69 (m, 3H), 6.65-6.59 (m, 1H), 4.62-4.60 (m, 1H), 4.44 (m, 1H), 3.86 (m, 3H), 3.38 (d, J=7.2 Hz, 1H), 3.28-3.24 (m, 1H), 3.16-3.13 (m, 1H), 3.06-3.00 (m, 1H), 2.78 (m, 3H), 1.64 (d, J=6.8 Hz, 3H).

Example-55

1-(2-((((*R*)-1-(3-Methoxyphenyl) ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl) ethanone hydrochloride

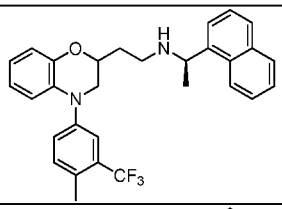
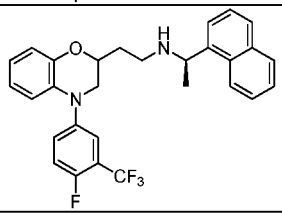
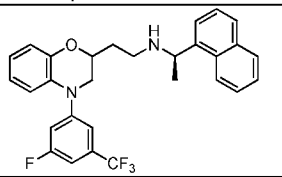
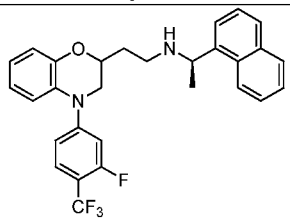
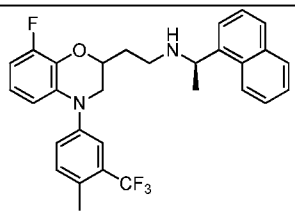
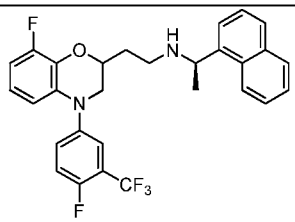


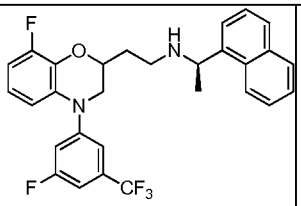
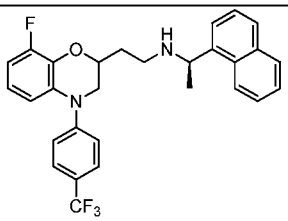
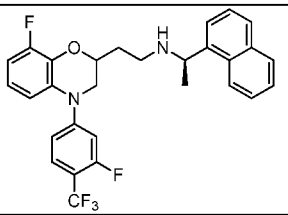
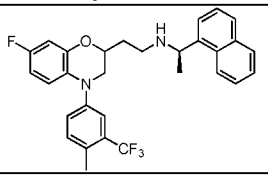
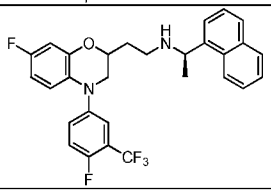
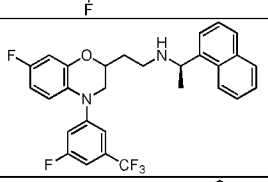
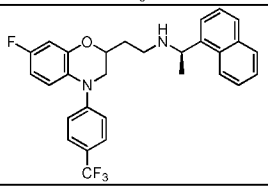
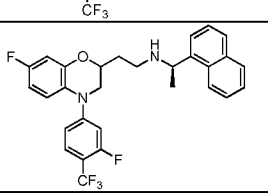

The title compound was prepared by following the similar procedure as described in Example-3a, 3b by taking Intermediate-54 and (*R*)-1-(3-methoxyphenyl) ethanamine.

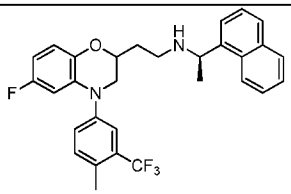
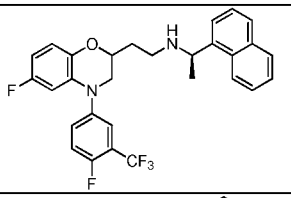
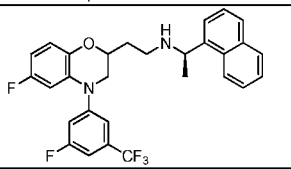
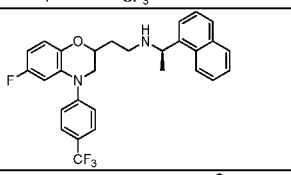
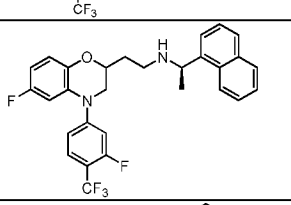
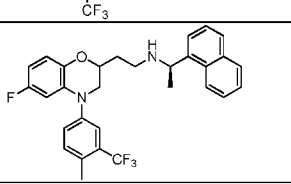
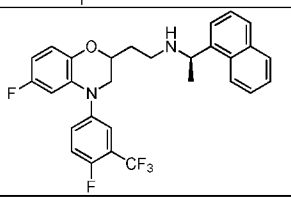
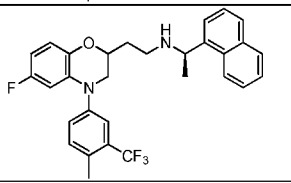
m/z 341.2; 1H NMR (400 MHz, DMSO-d6): δ10.80 (bs, 1H), 10.53 (bs, 1H), 10.09 (bs, 1H), 9.72 (bs, 1H), 7.33 (m, 1H), 7.22 (m, 1H), 7.15 (m, 1H), 7.05 (m, 3H), 6.90-6.84 (m, 2H), 4.55 (m, 1H), 4.29 (m, 1H), 3.85 (m, 3H), 3.49-3.38 (m, 1H), 3.00 (m, 1H), 2.79 (m, 1H), 2.16 (m, 3H), 1.87 (m, 3H).

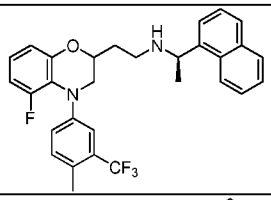
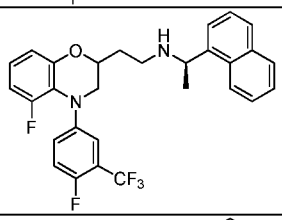
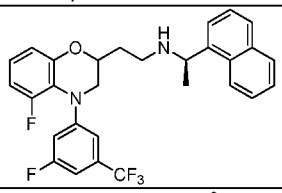
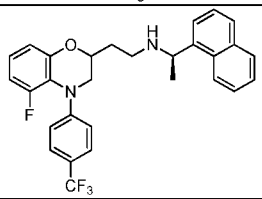
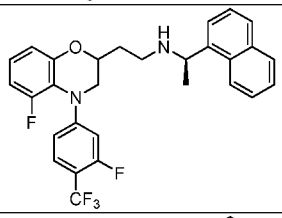
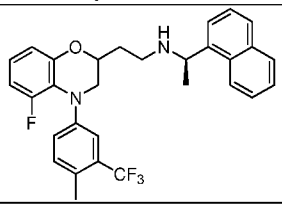
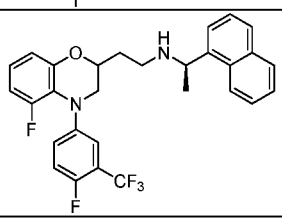
The following Examples 56 to 84 given Table-6 are prepared by following the similar procedures as described in Example-49 by taking appropriately substituted intermediate and appropriately substituted halobenzene.

**Table-6:**

| Example | Structure | Chemical name |
|---|---|---|
| 56 |  | 2-(4-(4-Methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 57 |  | 2-(4-(4-Fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 58 |  | 2-(4-(3-Fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine hydrochloride |
| 59 |  | 2-(4-(3-Fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 60 |  | 2-(8-Fluoro-4-(4-methyl-3-(trifluoromethyl) phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 61 |  | 2-(8-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine hydrochloride |

| | | |
|---|---|---|
| 62 |  | 2-(8-Fluoro-4-(3-fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 63 |  | 2-(8-Fluoro-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 64 |  | 2-(8-Fluoro-4-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 65 |  | 2-(7-Fluoro-4-(4-methyl-3-(trifluoromethyl) phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 66 |  | 2-(7-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 67 |  | 2-(7-Fluoro-4-(3-fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 68 |  | 2-(7-Fluoro-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 69 |  | 2-(7-Fluoro-4-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |

| | | |
|---|---|---|
| 70 |  | 2-(6-Fluoro-4-(4-methyl-3-(trifluoromethyl) phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 71 |  | 2-(6-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 72 |  | 2-(6-Fluoro-4-(3-fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 73 |  | 2-(6-Fluoro-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 74 |  | 2-(6-Fluoro-4-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 75 |  | 2-(6-Fluoro-4-(4-methyl-3-(trifluoromethyl) phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 76 |  | 2-(6-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 77 |  | 2-(6-Fluoro-4-(4-methyl-3-(trifluoromethyl) phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |

| | | |
|---|---|---|
| 78 |  | 2-(5-Fluoro-4-(4-methyl-3-(trifluoromethyl) phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 79 |  | 2-(5-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 80 |  | 2-(5-Fluoro-4-(3-fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 81 |  | 2-(5-Fluoro-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 82 |  | 2-(5-Fluoro-4-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 83 |  | 2-(5-Fluoro-4-(4-methyl-3-(trifluoromethyl) phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |
| 84 |  | 2-(5-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine |

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 Calcimemtics 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 37°C, 5% $CO_2$. Subsequently, cells are washed extensively with 20mM HEPES buffer containing 126mM NaCl, 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 the results obtained are given below. The $EC_{50}$ (nM) values of few representative compounds are set forth in Table-7.

Activity data has been given in Table-7 for representative compounds.

Table-7:

| Example number | $EC_{50}$ Range |
|---|---|
| 2, 21, 22, 26, 38 | Less than 20nM |
| 4, 6, 10b, 14b, 25a, 28a, 29b, 30, 40 | between 20-50 nM |
| 12a, 14a, 18, 23a, 23b, 24, 25b, 27, 28b, 29a, 31a, 31b, 36a, 36b, 37, 39, 41 | between 50-200 nM |

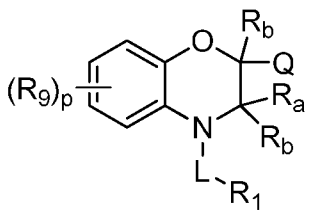
Through the use of above described assay method, compounds were found to exhibit agonistic activity thus to be particularly well suited for the treatment of the diseases or disorders as described herein above.

All patents, patent applications and 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

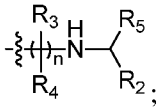
1. A compound of Formula (I):



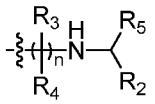
(I)

wherein,

Q is hydrogen or

 ;

$R_a$ is selected from

 ,

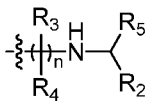
hydrogen, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted haloalkyl;

$R_b$ is 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

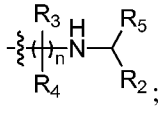


then

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

or

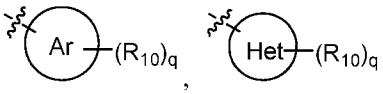
$R_a$ and $R_b$ together attached on the same carbon atom form C(O) or C(S);

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;

$R_1$ is selected from

 , substituted or unsubstituted alkyl, $-(CR_cR_d)_{1-3}-C(O)OR_6$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted cycloalkenyl;

ring Ar is phenyl or naphthyl;

ring Het is heteroaryl;

$R_{10}$, 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, substituted or unsubstituted hydroxyalkyl, $-OR_6$, $-C(O)R_6$, $-NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$;

provided that,

$R_{10}$ is not alkyl substituted with $-C(O)OR^x$ or $-OC(O)OR^x$ or $-C(O)NR^yR^z$ or $-OC(O)NR^yR^z$; where $R^x$ is selected from hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heteroaryl, heterocyclic ring, heterocyclylalkyl and heteroarylalkyl; and $R^y$ and $R^z$ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclyalkyl;

$R_2$ 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, form a substituted or unsubstituted 3 to 12 membered cyclic ring, where the cyclic ring may be heteroaryl or heterocyclyl;

$R_9$, 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, substituted or unsubstituted aryl, $-OR_6$, $-C(O)R_6$, $-C(O)OR_6$, $-(CH_2)_r-C(O)OR_6$, $-O(CH_2)_r-C(O)OR_6$, $-NR_7R_8$, $-C(O)NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$;

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

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

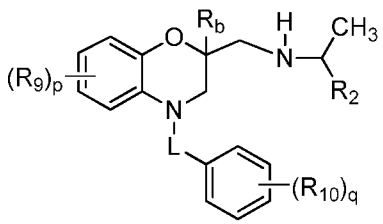
'p' is an integer ranging from 0 to 4, both inclusive;

'q' is an integer ranging from 0 to 4, 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)

wherein,

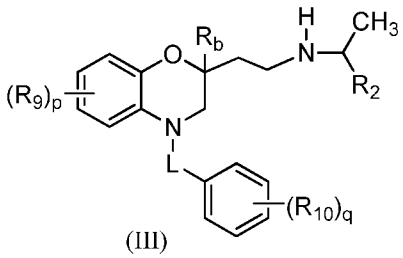
$R_2$ is substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl;

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

$R_b$, $R_c$, $R_d$, $R_7$, $R_9$, $R_{10}$, 'm', 'p' and 'q' are as defined in claim 1;

or pharmaceutically acceptable salt thereof.

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



(III)

wherein,

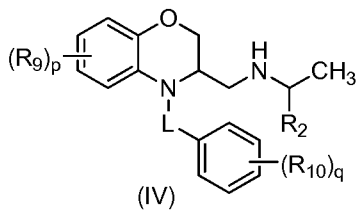
$R_2$ is substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl;

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

$R_b$, $R_c$, $R_d$, $R_7$, $R_9$, $R_{10}$, 'm', 'p' and 'q' are as defined in claim 1;

or pharmaceutically acceptable salt thereof.

4. The compound of claim 1, having the Formula (IV):



(IV)

wherein,

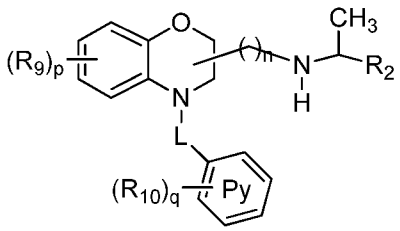
$R_2$ is substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl;

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

$R_c$, $R_d$, $R_7$, $R_9$, $R_{10}$, 'm', 'p' and 'q' are as defined in claim 1;

or pharmaceutically acceptable salt thereof.

5. The compound of claim 1, having the Formula (V):



(V)

wherein,

ring 'Py' is pyridyl;

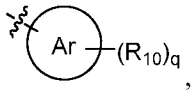
$R_2$ is substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl;

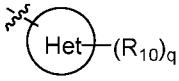
L is selected from a bond, $-(CR_cR_d)_m$, -C(O)-, $-C(O)NR_7$-, $-C(O)CH_2$-, and -$CH_2C(O)$-;

$R_c$, $R_d$, $R_7$, $R_9$, $R_{10}$, 'm', 'n' 'p' and 'q' are as defined in claim 1;

or pharmaceutically acceptable salt thereof.

6. The compound of claim 1, wherein $R_1$ is selected from





, substituted or unsubstituted alkyl, -($CR_cR_d$)$_{1-3}$-$C(O)OR_6$, substituted or unsubstituted haloalkyl and substituted or unsubstituted cycloalkyl;

ring Ar is phenyl or naphthyl;

ring Het is heteroaryl;

$R_c$ and $R_d$ are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl;

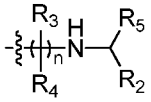
$R_{10}$ is independently selected from halogen, nitro, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted hydroxyalkyl, $-OR_6$, $-NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$;

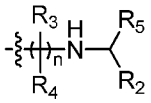
wherein $R_6$ is hydrogen, or substituted or unsubstituted alkyl;

$R_7$ and $R_8$ are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, and substituted or unsubstituted aryl;

and 'q' is 0 to 3;

or pharmaceutically acceptable salt thereof.

7. The compound of claim 1, wherein Q is  ; $R_3$ and $R_4$ are hydrogen; 'n' is 1 or 2; $R_2$ is aryl; $R_5$ is alkyl; $R_a$ is hydrogen; and $R_b$ is hydrogen or alkyl.

8. The compound of claim 1, wherein $R_a$ is  ; $R_3$ and $R_4$ are hydrogen; 'n' is 1 or 2; $R_2$ is aryl; $R_5$ is alkyl; Q is hydrogen; and $R_b$ is hydrogen or alkyl.

9. The compound of claim 1, wherein 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-; wherein $R_c$ and $R_d$ are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl; $R_7$ is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, and substituted or unsubstituted aryl and 'm' is 1 or 2.

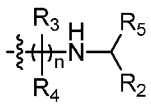
10. The compound of claim 1, wherein $R_2$ is substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl and the substituents are one or more, same or different and are independently selected from halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy and substituted or unsubstituted haloalkoxy.

11. The compound of claim 1, wherein $R_1$ is heteroaryl, wherein heteroaryl is 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, or 6-pyridyl.

12. The compound of claim 1, wherein $R_9$ 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 cycloalkyl, substituted or unsubstituted aryl, $-OR_6$, $-C(O)R_6$, $-C(O)OR_6$, $-(CH_2)_r-C(O)OR_6$, $-O(CH_2)_r-C(O)OR_6$, $-NR_7R_8$, $-C(O)NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$; wherein $R_6$ is hydrogen, or substituted or unsubstituted alkyl; $R_7$ and $R_8$ are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, and substituted or unsubstituted aryl; 'r' is 1 to 3; and 'p' is 0 to 3.

13. The compound of claim 1, wherein $R_{10}$ 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 hydroxyalkyl, $-OR_6$, $-C(O)R_6$, $-NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$; wherein $R_6$ is hydrogen, or substituted or unsubstituted alkyl; $R_7$ and $R_8$ are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, and substituted or unsubstituted aryl; and 'q' is 0 to 3.

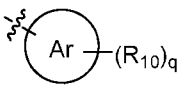
14. The compound of claim1 wherein Q is

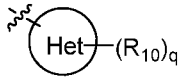


; $R_a$ is hydrogen; $R_b$ is hydrogen or substituted or unsubstituted alkyl;

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

$R_1$ is selected from



,


, substituted or unsubstituted alkyl, $-(CR_cR_d)_{1-3}$-$C(O)OR_6$, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted cycloalkenyl;

ring Ar is phenyl or naphthyl;

ring Het is heteroaryl;

$R_{10}$, 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 hydroxyalkyl, $-OR_6$, $-NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$;

$R_c$ and $R_d$ are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl;

$R_2$ is substituted or unsubstituted aryl, wherein the substituent(s) may be one or more same or different and independently selected from halogen, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy and substituted or unsubstituted haloalkoxy;

$R_3$ and $R_4$ are hydrogen;

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

$R_6$ is hydrogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl;

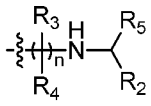
$R_7$ and $R_8$ are independently hydrogen or substituted or unsubstituted alkyl;

$R_9$, 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 cycloalkyl, substituted or unsubstituted aryl, $-OR_6$, $-C(O)OR_6$, $-(CH_2)_r$-$C(O)OR_6$, $-O(CH_2)_r$-$C(O)OR_6$, $-NR_7R_8$, $-C(O)NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$;

'm' is 1 or 2; 'n' is 1 or 2; 'p' is 0 to 3; 'q' is 0 to 3; and 'r is 1 to 3;

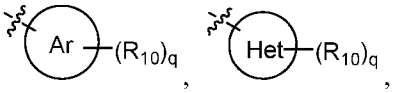
or pharmaceutically acceptable salt thereof.

15. The compound of claim 1, wherein $R_a$ is


; Q is hydrogen; $R_b$ is hydrogen or substituted or unsubstituted alkyl;

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

$R_1$ is selected from


, substituted or unsubstituted alkyl, $-(CR_cR_d)_{1-3}-C(O)OR_6$, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted cycloalkenyl;

ring Ar is phenyl or naphthyl;

ring Het is heteroaryl;

$R_{10}$, 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 hydroxyalkyl, $-OR_6$, $-NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$;

$R_c$ and $R_d$ are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl;

$R_2$ is substituted or unsubstituted aryl, wherein the substituent(s) may be one or more same or different and independently selected from halogen, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy and substituted or unsubstituted haloalkoxy;

$R_3$ and $R_4$ are hydrogen;

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

$R_6$ is hydrogen, substituted or unsubstituted alkyl and substituted or unsubstituted haloalkyl;

$R_7$ and $R_8$ are independently hydrogen or substituted or unsubstituted alkyl;

$R_9$, 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 cycloalkyl, substituted or unsubstituted aryl, $-OR_6$,

$-C(O)OR_6$, $-(CH_2)_r-C(O)OR_6$, $-O(CH_2)_r-C(O)OR_6$, $-NR_7R_8$, $-C(O)NR_7R_8$, $-NR_7C(O)R_6$, $-S(O)_{0-2}R_6$, $-S(O)_2NR_7R_8$, and $-NR_7S(O)_2R_6$;

'm' is 1 or 2; 'n' is 1 or 2; 'p' is 0 to 3; 'q' is 0 to 3; and 'r is 1 to 3;

or pharmaceutically acceptable salt thereof.

16. The compound of claim 1, wherein the pharmaceutically acceptable salt is hydrochloride salt.

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

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

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

(2-((((*R*)-1-(3-Methoxyphenyl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl) (phenyl) methanone;

(2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl) (phenyl)methanone;

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

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

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

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

(3-Fluorophenyl)(2-((((*R*)-1-(3-methoxyphenyl)ethyl) amino)methyl)-2*H*-benzo [*b*][1,4]oxazin-4(3H)-yl) methanone hydrochloride;

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

(2-((((*R*)-1-(3-Methoxy phenyl)ethyl)amino)methy)-2*H*-benzo[*b*][1,4] oxazin-4(3*H*)-yl)(m-tolyl) methanone;

(2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4 (3*H*)yl)(m-tolyl)methanone;

(2-((((*R*)-1(3-Methoxy phenyl)ethyl)amino) methyl)-2*H*-benzo[*b*][1,4] oxazin-4(3*H*)yl)(3(trifluoro methyl)phenyl)methanone hydrochloride;

(2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)(3-(trifluoro methyl) phenyl) methanone;

(3-Fluoro-5-(trifluoro methyl)phenyl) (2-((((*R*)-1-(3methoxyphenyl)ethyl) amino)methyl)-2*H*-benzo [*b*][1,4]oxazin-4(3*H*)-yl) methanone;

(3-Fluoro-5-(trifluoro- methyl)phenyl)(2-((((*R*)-1-(naphthalen-1-yl)ethyl) amino)methyl)-2*H*-benzo [*b*][1,4]oxazin-4(3*H*)-yl) methanone;

1-(2-((((*R*)-1-(3-Methoxy phenyl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)-2-phenyl;

1-(2-((((*R*)-1-(Naphthalen-1-yl)ethyl) amino)methyl)-2*H*-benzo[*b*][1,4] oxazin-4 (3*H*)-yl)-2-phenyl ethanone;

2-((((*R*)-1-(3-Methoxy phenyl)ethyl)amino) methyl)-*N*-(3(trifluoro methyl)phenyl)-2*H*-benzo[*b*][1,4]oxazine-4 (3*H*)-carboxamide hydrochloride;

2-((((*R*)-1-(Naphthalen-1-yl)ethyl)amino) methyl)-*N*-(3-(trifluoro methyl)phenyl)-2*H*-benzo[*b*][1,4]oxazine-4 (3*H*)-carboxamide hydrochloride;

*N*-(4-Fluorophenyl)-2-((((*R*)-1-(3methoxy phenyl)ethyl)amino) methyl)-2*H*-benzo[*b*] [1,4]oxazine-4(3*H*)-carboxamide hydrochloride;

N-(4-Fluorophenyl)-2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-2*H*-benzo[*b*][1,4] oxazine-4(3*H*)-carboxamide;

(1*R*)-*N*-((4(3-Methoxy phenyl)-3,4-dihydro-2*H*-benzo[*b*] [1,4] oxazin-2-yl) methyl) 1(naphthalen-1-yl) ethanamine;

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

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

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

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

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

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

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

2-Methyl-5-(2-((((*R*)-1-(naphthalen-1-yl) ethyl)amino)methyl)-2*H*-benzo[*b*][1,4] oxazin-4(3*H*)-yl) phenol hydrochloride;

(1*R*)-1-(3-Methoxy phenyl)-*N*-((4-(p-tolyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-2-yl)methyl) ethanamine;

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

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

(1*R*)-1-(3-Methoxy phenyl)-*N*-((4-(m-tolyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-2-yl)methyl) ethanamine;

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

(1*R*)-*N*-((6-Bromo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)-1-(naphthalen -1-yl)ethanamine hydrochloride;

(1*R*)-*N*-((7-Bromo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl)-1-(naphthalen -1-yl)ethanamine hydrochloride;

(1*R*)-*N*-((4-Methyl-6-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-2-yl)methyl)-1 (naphthalen-1-yl) ethanamine hydrochloride;

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

4-Methyl-2-((((*R*)-1-(naphthalen-1yl) ethyl amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine-7carbonitrile hydrochloride;

Ethyl 3-(4-methyl-2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)propanoate;

3-(4-Methyl-2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-7-yl)propanoic acid hydrochloride;

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

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

4-Methyl-2-((((*R*)-1-(naphthalen-1-yl)ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine-7-carboxylic acid hydrochloride;

4-Methyl-2-((((*R*)-1-(naphthalen-1-yl) ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine -6-carboxylic acid hydrochloride;

Isopropyl 4-methyl-2-((((*R*)-1-(naphthalen-1yl)ethyl)amino)methyl)-3,4-dihydro-2*H*-benzo [*b*][1,4]oxazine-6-carboxylate hydrochloride;

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

(1*R*)-1-(Naphthalen-1-yl)-*N*-(2-(4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*] [1,4]oxazin-2-yl)ethyl)ethanamine;

(1*S*)-1-(Naphthalen-1-yl)-*N*-(2-(4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*] [1,4] oxazin-2-yl)ethyl)ethanamine hydrochloride;

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

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

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

1-(2-((((*R*)-1-(3-Methoxyphenyl) ethyl)amino)methyl)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl) ethanone hydrochloride;

2-(4-(4-Methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(4-(4-Fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(4-(3-Fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine hydrochloride;

2-(4-(3-Fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(8-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(8-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine hydrochloride;

2-(8-Fluoro-4-(3-fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(8-Fluoro-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(8-Fluoro-4-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(3-fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(7-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(3-fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(6-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(5-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(5-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(5-Fluoro-4-(3-fluoro-5-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(5-Fluoro-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(5-Fluoro-4-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

2-(5-Fluoro-4-(4-methyl-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine; and

2-(5-Fluoro-4-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)ethanamine;

or pharmaceutically acceptable salts thereof or stereoisomers thereof.

18. A pharmaceutical composition comprising one or more compounds of Formula (I) according to claim 1, and one or more pharmaceutically acceptable excipients.

19. A method of treating, managing and/or lessening 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.

20. The method of claim 19, 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.

21. The method of claim 20, wherein hyperparathyroidism is primary hyperparathyroidism, secondary hyperparathyroidism or tertiary hyperparathyroidism.

22. The method of claim 19, 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/IB2012/051263

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/04 C07D265/36 A61K31/538
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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | EP 1 882 684 A1 (ASTELLAS PHARMA INC [JP]) 30 January 2008 (2008-01-30) cited in the application claims 1, 15 | 1-22 |
| A | US 2010/029687 A1 (HACHIYA SHUNICHIRO [JP] ET AL) 4 February 2010 (2010-02-04) cited in the application claims 1, 14 | 1-22 |
| 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 claims 1, 14 | 1-22 |

☐ 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

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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 |
|---|---|
| 23 May 2012 | 31/05/2012 |

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

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Information on patent family members

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