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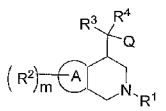
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(54) Title: NOVEL MONOAMINE RE-UPTAKE INHIBITOR



(I)

(57) Abstract: The present invention relates to novel compounds of Formula (I), their pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers including R and S isomers, polymorphs, prodrugs, metabolites, salts or solvates thereof. The invention also relates to the processes for the synthesis of novel compounds of Formula I, their pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers, polymorphs, prodrugs, metabolites, salts or solvates thereof. The present invention further provides pharmaceutical compositions comprising compounds of Formula I and methods of treating or preventing one or more disorders of the central and/or peripheral nervous system that are responsive to inhibition of biogenic amines, in particular one or more, or any combination of serotonin, norepinephrine and dopamine.

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NOVEL MONOAMINE RE-UPTAKE INHIBITORS

Field of the invention

The present invention relates to novel compounds of Formula (I), their pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers including *R* and *S* isomers, polymorphs, prodrugs, metabolites, salts or solvates thereof. The invention also relates to the processes for the synthesis of novel compounds of Formula I, their pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers, polymorphs, prodrugs, metabolites, salts or solvates thereof. The present invention further provides pharmaceutical compositions comprising compounds of Formula I and methods of treating or preventing one or more disorders of the central and/or peripheral nervous system that are responsive to inhibition of biogenic amines, in particular one or more, or any combination of serotonin, norepinephrine and dopamine.

Background of the invention

The present invention is directed to compounds useful for treating or preventing one or more disorders of the central and/or peripheral nervous system that are responsive to inhibition of biogenic amines, in particular one or more, or any combination of serotonin (also called 5-hydroxytryptaimne or 5-HT), norepinephrine (also called noradrenaline) and dopamine. There is a large body of scientific evidence pointing to the physiological role of these monoamines as neurotransmitters. Consequently, compounds which are capable of inhibiting the uptake of these monoamines find utility in the treatment of disorders of the central nervous system (CNS) including peripheral disorders. These disorders include depression, eating disorders, schizophrenia, inflammatory bowel disorders, pain, addiction disorders, urinary incontinence, dementia, Alzheimer's memory loss, Parkinsonism, stroke, anxiety, attention-deficit disorder, social phobia, obsessive compulsive disorder, substance abuse and withdrawal, cognitive disorders, fibromyalgia and sleep disorders.

The increase in the number of individuals with some or other form of CNS or peripheral disorders has resulted in tremendous efforts towards the development of drugs for CNS. Several classes of drugs with a range of binding selectivities have been discovered and used in the treatment of various CNS disorders. The activity of earlier drugs was due to their binding to a broad range of neurotransmitters which led to many undesirable side effects. The increased understanding of the role of monoamine neurotransmitters in various CNS disorders resulted in the rational design of potent drugs

which have very selective binding properties, thus minimizing the side effects. The treatment of the various CNS disorders has been revolutionized by the introduction of drugs whose primary pharmacological effect consists of inhibiting the reuptake of biogenic monoamine neurotransmitters serotonin, norepinephrine or dopamine (Magnus W. Walter, "Monoamine Reuptake Inhibitors: Highlights of Recent Research Developments" *Drug Development Research*, **2005**, *65*, 97-118).

Biogenic monoamine neurotransmitters play a key role in various CNS or peripheral activities, and optimum levels of their availability in brain circuit is vital for maintaining good emotional or mental health, and physical well being. These neurotransmitters are produced in the cell body of the neuron by various complex chemical routes. Neurotransmitters travel from the terminal of a neuron (presynaptic) across a small gap (i.e., the synaptic cleft) and bind to receptor proteins on the surface of a second neuron resulting in intracellular changes that initiate and activate a response in the postsynaptic neuron. Inactivation occurs primarily by reuptake of the neurotransmitter back into the presynaptic neuron. Thus, the basis for the treatment of CNS disorders including neuropsychiatric disorders is to enhance the levels of neurotransmitters (Slattery, D.A et al, "The evolution of antidepressant mechanisms", *Fundamental and Clinical pharmacology*, **2004**, *18*, 1-21 and Scholas. P. et al, "New insights into the mechanism of antidepressant therapy", *Pharmacology and therapeutics*, **2004**, *102*, 47-60).

The design for CNS and/or neuropsychiatric drugs has been moving towards the use of dual serotonin and norepinephrine reuptake inhibitors (SNRI) for first line treatment of various indications (Stahl, S.M et al, "SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants" *CNS Spectr.* **2005**, *10* (9), 732-747). This is evidenced by the recent development of SNRIs such as Venlafaxine (Effexor®), duloxetine (Cymbalta®), milnacipran and imipramine (Toffranil®). This contrasts with the earlier use of selective serotonin reuptake inhibitors (SSRI) which were accociated with many side effects including sexual dysfunction, gastrointestinal irritation and headaches (Moller HJ, "Selective serotonin and noradrenaline reuptake inhibitors: a step forward in the treatment of depression?" *MMW Fortscher Med.* **2005**, *147* (3), 43-45). Drugs claimed to be SSRIs are for example fluoxitine (Prozac®), sertraline (zoloft®) and paroxetine (Paxil®)). PCT applications WO 2006064332, WO2006064336 and WO 2006064351 disclose heterocyclic amide derivatives as serotonin and/or norepinephrine reuptake inhibitors.

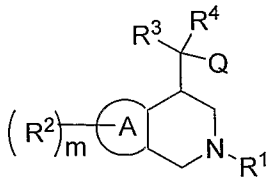
Another class of antidepressants - the triple reuptake inhibitors (also called as broad spectrum inhibitors) are characterized by their ability to inhibit the reuptake of serotonin, norepinephrine as well as dopamine (Skolnick P et al, "Triple reuptake inhibitors (broad spectrum antidepressants)", *CNS Neurol Disord Drug Targets* **2007**, *6*(2), 141-149). Based on the pivotal role proposed for dopamine in depression, it has been hypothesized that a broad spectrum antidepressant will produce a more rapid onset and/or higher efficacy than agents inhibiting the reuptake of serotonin and/or norepinephrine. There is clinical evidence that increasing dopaminergic transmission in individuals receiving SSRIs/SNRIs will produce an enhanced therapeutic response. Triple reuptake inhibitors are expected to have fewer side effects, in particular, a lack of drug-associated weight gain and sexual dysfunction, common with many of the currently available medications. A few triple reuptake inhibitors have been disclosed in the patent application numbers US04131611, WO2006023659, WO2006096810, WO2007016155, WO2006102029, WO2006064031, WO2006007843, WO2007011820, US20070093526, WO2008057575, WO2008153937, WO2009027293, WO2009027294 and WO2009027295, wherein a variety of chemical scaffolds have been shown to be useful for treating CNS disorders.

Tetrahydroisoquinolines having selectivity as 5-HT_7 antagonists are disclosed in PCT applications WO 2006018308 and WO 2006018309. PCT applications WO 2004050628, WO 2004050629 and WO 2004050630 disclose 4-phenyl substituted tetrahydroisoquinoline derivatives as norepinephrine reuptake inhibitors. PCT applications WO 09743262, WO 09806699, WO 09849145, WO 09850363, WO 09850364, WO 09851671 and WO 00024717 disclose tetrahydroisoquinolines as modulators of dopamine D3 receptors. US patent application US 20080318952 discloses diaryl-substituted tetrahydroisoquinolines as histamine H3 receptor and serotonin transporter modulators. Tetrahydroisoquinoline derived triple reuptake inhibitors are disclosed in PCT applications WO 2006020049, WO 200132625, WO 200132624, US patent application US 20040248933 and Eupopean patent application EP 00400319.

Despite the existence of a few triple reuptake inhibitors, still there is no molecule in the market. To understand the exact ratio of reuptake inhibition of different monoamines, it would be advantageous to provide further "broad spectrum" reuptake inhibitors which can become potential drugs for CNS disorders including peripheral disorders, thus accelerating the onset of treatment. These may advantageously possess characteristics such as enhanced selectivity toward these monoamine neurotransmitters, enhanced pharmacokinetic properties and/or enhanced potency.

Summary of the invention

The present invention relates to the novel compounds of the Formula **I**,



Formula I

their pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers including *R* and *S* isomers, polymorphs, prodrugs, metabolites, salts or solvates thereof, wherein,

ring A is either aryl or heteroaryl;

R^1 is selected from C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl;

R^2 and/or each R^2 (when R^2 is more than one) is independently selected from hydrogen, halogen, CN, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, C_{1-12} haloalkyl, C_{1-12} haloalkoxy, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_n$-cycloalkyl, $-(CH_2)_n$-heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, $-O(CH_2)_n-NR^aR^b$, $-O(CH_2)_n$-cycloalkyl, $-O(CH_2)_n$-cycloalkoxy, $-OR^a$, $-SR^a$, $-NO_2$, $-NR^aR^b$, $-N(R^a)(CO)R^b$, $-N(R^a)(CO)OR^b$, $-N(R^a)(CO)NR^aR^b$, $-(CO)R^a$, $-C(=N-OR^b)R^a$, $-(CO)NR^aR^b$, $-O(CO)R^a$, $-O(CO)OR^a$, $-O(CO)NR^aR^b$, $-COOR^a$, $-S(O)_dR^a$ or $-S(O)_dNR^aR^b$;

Q is selected from halogen, R^a, $-OR^a$, $-O(CO)R^a$, $-O(CO)OR^a$ $-COOR^a$, $-C(=N-OR^b)R^a$, $-SR^a$ or $-NR^aR^b$;

R^3 and R^4 are either same or different and independently selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkoxy, C_{1-12} haloalkoxy, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-cycloalkenyl, $(CH_2)_n$-cycloalkynyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl, each of which may be optionally substituted at any available position by one or more substituents independently selected from R^c or $R^{c'}$,

or

R^3 and R^4 are joined together along with the carbon atom to which they are attached to form a 3 to 10 membered cycloalkyl, cycloalkenyl, cycloalkynyl or heterocyclic ring which

may contain from one to three heteroatoms independently selected from O, S and N, the ring formed may optionally be substituted with one or more substituents independently selected from R^c or $R^{c'}$; the ring thus formed may further be fused with 3 to 7 membered unsaturated or saturated aromatic or non-aromatic ring, which may contain from one to three heteroatoms independently selected from O, S or N, the fused ring may optionally be substituted with one or more substituents R^c or $R^{c'}$;

R^a and R^b can independently be selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, aryloxy, heteroaryloxy, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl, $(CH_2)_n$-heteroaryl or -$COOR^a$; each of which may be optionally substituted at any available position by one or more R^c or $R^{c'}$; or

R^a and R^b may be joined together along with the nitrogen atom to which they are attached to form a heterocyclic or heteroaryl ring which may additionally contain from one to three heteroatoms independently selected from O, S or N, the ring formed may optionally be substituted with one or more substituents selected from R^c or $R^{c'}$; the ring thus formed may further be fused with 3 to 7 membered unsaturated or saturated ring, which may contain from one to three heteroatoms independently selected from O, S or N, the fused ring may optionally be substituted with one or more substituents R^c or $R^{c'}$;

R^c or $R^{c'}$ can independently be selected from halogen, oxo, hydroxyl, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-8} cycloalkyl, C_{1-12} haloalkyl, C_{1-12} haloalkoxy, C_{2-12} haloalkenyl, aryl, heterocyclyl, heteroaryl, $(CH_2)_n$-aryl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-heteroaryl, $(CH_2)_n$-cycloalkyl, -CH_2OR^5, CN, –OR^5, -NO_2, -NR^5R^6, $(CH_2)_n$-NR^5R^6, $N(R^5)(CO)R^6$, $N(R^5)(CO)OR^6$, $N(R^6)(CO)NR^5R^6$, -$C(=L)R^5$ (wherein L is O or S), -$(CO)NR^5R^6$, -$(CO)(CH_2)_nNR^5R^6$, -$O(CO)R^5$, -$C(=N\text{-}OR^5)R^6$, -$O(CO)NR^5R^6$, -$COOR^5$, -SR^5, $S(O)_dR^5$, $S(O)_dNR^5R^6$, SO_3H or $NHSO_2R^5$;

R^5 and R^6 can independently be selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl, each of which may be optionally substituted with halogen, hydroxyl or C_{1-6} alkoxy; or $R^5$and R^6 may be joined together to form a heterocyclic or heteroaryl ring which may contain from one to three heteroatoms independently selected from O, S or N, which may optionally be substituted with one or more substituents independently selected from R^c or $R^{c'}$;

n is 1,2,3,4 or 5;

m is 1,2,3 or 4;

d is 1 or 2.

Another aspect of the invention provides the processes for the preparation of the novel compounds of Formula I, their pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers including *R* and *S* isomers, polymorphs, prodrugs, metabolites, salts or solvates thereof.

A further aspect of the present invention provides pharmaceutical compositions, containing compounds of Formula I, their pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers including *R* and *S* isomers, polymorphs, prodrugs, metabolites, salts or solvates thereof in combination with one or more pharmaceutically acceptable carrier(s), adjuvants and vehicles.

Another aspect of the invention relates to methods of using the compounds of Formula I of the present invention or compositions comprising the compounds of Formula I for the prophylaxis, amelioration and/or treatment of one or more condition(s)/disease(s)/ disorder(s) of the central and/or peripheral nervous system that are responsive to inhibition of biogenic amines, in particular one or more, or any combination of serotonin, norepinephrine and dopamine, which comprises administering to a subject in need thereof the compounds of Formula I or compositions comprising a pharmaceutically effective amount of the compounds of Formula I.

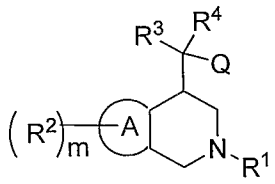
A further aspect of the present invention is the use of a compound of Formula I for the manufacture of a medicament for the prophylaxis, amelioration and/or treatment of one or more condition(s)/disease(s)/ disorder(s) of the central and/or peripheral nervous system that are responsive to inhibition of biogenic amines, in particular one or more, or any combination of serotonin, norepinephrine and dopamine, in a subject in need thereof preferably a mammal including a human.

The present invention also encompasses prodrugs and active metabolites of the compounds of the Formula (I).

Other aspects of the invention will be set forth in the description which follows, and in part will be apparent from the description, or may be learnt by the practice of the invention.

Detailed description of the invention

The present invention relates to the novel compounds of the Formula **I**,



Formula I

their pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers including *R* and *S* isomers, polymorphs, prodrugs, metabolites, salts or solvates thereof, wherein,

ring A is either aryl or heteroaryl;

R^1 is selected from C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl;

R^2 and/or each R^2 (when R^2 is more than one) is independently selected from hydrogen, halogen, CN, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, C_{1-12} haloalkyl, C_{1-12} haloalkoxy, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_n$-cycloalkyl, $-(CH_2)_n$-heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, $-O(CH_2)_n-NR^aR^b$, $-O(CH_2)_n$-cycloalkyl, $-O(CH_2)_n$-cycloalkoxy, $-OR^a$, $-SR^a$, $-NO_2$, $-NR^aR^b$, $-N(R^a)(CO)R^b$, $-N(R^a)(CO)OR^b$, $-N(R^a)(CO)NR^aR^b$, $-(CO)R^a$, $-C(=N-OR^b)R^a$, $-(CO)NR^aR^b$, $-O(CO)R^a$, $-O(CO)OR^a$, $-O(CO)NR^aR^b$, $-COOR^a$, $-S(O)_dR^a$ or $-S(O)_dNR^aR^b$;

Q is selected from halogen, R^a, $-OR^a$, $-O(CO)R^a$, $-O(CO)OR^a$ $-COOR^a$, $-C(=N-OR^b)R^a$, $-SR^a$ or $-NR^aR^b$;

R^3 and R^4 are either same or different and independently selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkoxy, C_{1-12} haloalkoxy, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-cycloalkenyl, $(CH_2)_n$-cycloalkynyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl, each of which may be optionally substituted at any available position by one or more substituents independently selected from R^c or $R^{c'}$

or

R^3 and R^4 are joined together along with the carbon atom to which they are attached to form a 3 to 10 membered cycloalkyl, cycloalkenyl, cycloalkynyl or heterocyclic ring which may contain from one to three heteroatoms independently selected from O, S and N, the ring formed may optionally be substituted with one or more substituents independently selected from R^c or $R^{c'}$; the ring thus formed may further be fused with 3 to 7 membered

unsaturated or saturated aromatic or non-aromatic ring, which may contain from one to three heteroatoms independently selected from O, S or N, the fused ring may optionally be substituted with one or more substituents R^c or $R^{c'}$;

R^a and R^b can independently be selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, aryloxy, heteroaryloxy, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl, $(CH_2)_n$-heteroaryl or -$COOR^a$; each of which may be optionally substituted at any available position by one or more R^c or $R^{c'}$; or

R^a and R^b may be joined together along with the nitrogen atom to which they are attached to form a heterocyclic or heteroaryl ring which may additionally contain from one to three heteroatoms independently selected from O, S or N, the ring formed may optionally be substituted with one or more substituents selected from R^c or $R^{c'}$; the ring thus formed may further be fused with 3 to 7 membered unsaturated or saturated ring, which may contain from one to three heteroatoms independently selected from O, S or N, the fused ring may optionally be substituted with one or more substituents R^c or $R^{c'}$;

R^c or $R^{c'}$ can independently be selected from halogen, oxo, hydroxyl, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-8} cycloalkyl, C_{1-12} haloalkyl, C_{1-12} haloalkoxy, C_{2-12} haloalkenyl, aryl, heterocyclyl, heteroaryl, $(CH_2)_n$-aryl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-heteroaryl, $(CH_2)_n$-cycloalkyl, -CH_2OR^5, CN, $-OR^5$, -NO_2, -NR^5R^6, $(CH_2)_n$-NR^5R^6, $N(R^5)(CO)R^6$, $N(R^5)(CO)OR^6$, $N(R^6)(CO)NR^5R^6$, -$C(=L)R^5$ (wherein L is O or S), -$(CO)NR^5R^6$, -$(CO)(CH_2)_nNR^5R^6$, -$O(CO)R^5$, -$C(=N\text{-}OR^5)R^6$, -$O(CO)NR^5R^6$, -$COOR^5$, -SR^5, $S(O)_dR^5$, $S(O)_dNR^5R^6$, SO_3H or $NHSO_2R^5$;

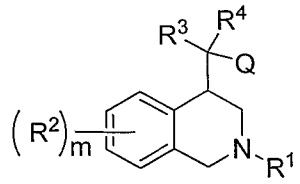
R^5 and R^6 can independently be selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl, each of which may be optionally substituted with halogen, hydroxyl or C_{1-6} alkoxy; or $R^5$and R^6 may be joined together to form a heterocyclic or heteroaryl ring which may contain from one to three heteroatoms independently selected from O, S or N, which may optionally be substituted with one or more substituents independently selected from R^c or $R^{c'}$;

n is 1,2,3,4 or 5;

m is 1,2,3 or 4;

d is 1 or 2.

One embodiment of the present invention provides compounds of Formula Ia, wherein



Formula Ia

R^1, R^2, R^3, R^4, Q and m are as defined herein; their pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers including *R* and *S* isomers, polymorphs, prodrugs, metabolites, salts or solvates thereof.

In an embodiment of the compounds of the present invention of Formula I, Q is selected from $-OR^a$, $-O(CO)R^a$, $-O(CO)OR^a$ or $-COOR^a$, wherein R^a is as defined herein.

In another embodiment of the compounds of the present invention of Formula I, R^1 is selected from C_{1-12} alkyl, C_{3-20} cycloalkyl, $-(CH_2)_n$-cycloalkyl or $(CH_2)_n$-aryl.

In still another embodiment of the compounds of the present invention of Formula I, each R^2 is independently selected from hydrogen, halogen, CN, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, $-OR^a$, $-O(CH_2)_n-NR^aR^b$, $-O(CH_2)_n$-cycloalkyl, $-O(CH_2)_n$-cycloalkoxy, $-NR^aR^b$, $N(R^a)(CO)R^b$, $N(R^a)(CO)OR^b$, $N(R^a)(CO)NR^aR^b$, $-(CO)R^a$, $-(CO)NR^aR^b$, $-O(CO)R^a$, $-O(CO)NR^aR^b$ or $-COOR^a$, wherein R^a & R^b are as defined herein.

In another embodiment of the compounds of the present invention of Formula I, it is preferred that R^3 and R^4 can be either same or different and independently represent hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, heterocyclyl, aryl or heteroaryl, each of which may be optionally substituted at any available position by one or more substituents independently selected from R^c or $R^{c'}$, wherein R^c or $R^{c'}$ are as defined herein.

In another embodiment of the compounds of the present invention of Formula I, it is preferred that R^3 and R^4 may be joined together along with the carbon atom to which they are attached to form a 3 to 10 membered cycloalkyl, cycloalkenyl, cycloalkynyl or heterocyclic ring which may contain from one to three heteroatoms independently selected from O, S or N, the ring formed may optionally be substituted with one or more substituents independently selected from R^c or $R^{c'}$.

Relative to the above description of the compounds of the present invention, the following definitions apply:

The term "alkyl" as used herein alone or as part of another group refers to a straight or branched hydrocarbon consisting of carbon and hydrogen atoms, having from 1 to 12 carbon atoms. Examples of alkyl include, but are not limited to, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *t*-butyl, *n*-pentyl, and the like.

The term "alkenyl" as used herein alone or as part of another group refers to an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched chain having from 2 to 12 carbon atoms. Examples of alkenyl include, but are not limited to, for example, ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, and the like.

The term "alkynyl" as used herein alone or as part of another group refers to a straight or branched hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched chain having from 2 to 12 carbon atoms. . Examples of alkynyl include, but are not limited to, for example, ethynyl, propynyl, and butynyl.

The term "alkoxy" refers to an above defined alkyl group attached via an oxygen linkage to the rest of the molecule. Non-limiting examples of such groups include $-OCH_3$, $-OC_2H_5$ and the like.

The term "alkylcarbonyl" refers to an above defined alkyl group attached via a carbonyl linkage to the rest of the molecule. Non-limiting examples of such groups include $-C(O)CH_3$, $-C(O)C_2H_5$, and the like.

The term "alkoxycarbonyl" refers to an above defined alkoxy group attached via a carbonyl linkage to the rest of the molecule. Non-limiting examples of such groups include $-C(O)$-O CH_3, $-C(O)$-OC_2H_5, and the like.

The term "haloalkyl" refers to an above-defined "alkyl" group, which is substituted with the "halogen" group, as defined herein, at any one or more of the 1 to 12 carbon atoms of the alkyl group. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoromethyl, trifluoromethyl, trichloromethyl, difluoroethyl, trifluoroethyl, dichloroethyl, 1-methyl-3-chloropropyl and the like.

The term "haloalkoxy" refers to an above defined "haloalkyl" group, appended to the parent molecular moiety through an oxygen atom.

The term "haloalkenyl" refers to atleast one halogen as defined herein, appended to the parent molecular moiety through an above defined alkenyl group. Representative examples of haloalkenyl include, but are not limited to, chloroethylenyl, 2-fluroethylenyl, triflurobutenyl, 1-methyl-3-chloroprop-2-enyl, dichloropropenyl and the like.

The term "haloalkynyl" refers to atleast one halogen as defined herein, appended to the parent molecular moiety through an above defined alkynyl group. Representative examples of haloalkynyl include, but are not limited to, chloroethylynyl, 2-fluroethylyne, triflurobutynyl and dichloropropynyl.

The term "cycloalkyl" refers to cyclic alkyl groups constituting of 3 to 20 carbon atoms having monocyclic ring or condensed ring systems, for example, fused or spiro systems which may optionally contain one or more olefinic bonds, unless otherwise constrained by the definition. Such cycloalkyl groups include, by way of example, monocyclic ring structures, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, and the like, or condensed ring structures, for example, adamantyl, camphenyl and bicyclo[2.2.1] heptyl, or cyclic alkyl groups to which is fused an aryl group, for example, indanyl and the like or spiro ring system, for example, spiro[5.5]undecanyl and the like.

The term "aryl" herein refers to a carbocyclic aromatic group, for example phenyl or naphthyl ring and the like optionally substituted with one or more substituents selected from but not limited to, for example, halogen, hydroxyl, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, CF_3, $-COR^d$ (wherein R^d can be hydrogen, alkyl, aryl, alkoxy, amine), cyano, nitro, heterocyclyl or heteroaryl. The aryl group may optionally be fused with cycloalkyl group, wherein the said cycloalkyl group may optionally contain heteroatoms selected from O, N, S or oxo.

The term "heteroaryl" unless and otherwise specified refers to an aromatic ring structure containing 5 to 8 carbon atoms, fully or partially unsaturated, or a polycyclic aromatic group, with one or more heteroatom(s) independently selected from N, O and S and optionally substituted with 1 to 4 substituent(s) selected from but not limited to halogen, hydroxyl, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxyl, aryl, alkoxy, aralkyl, cyano, nitro, heterocyclyl, or heteroaryl. Examples of heteroaryl groups include but are not limited to oxazolyl, imidazolyl, pyrrolyl, 1,2,3,-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl, oxadiazolyl, benzoimidazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, benzodiazepinyl and the like.

The term "heterocyclyl" unless otherwise specified refers to a non-aromatic monocyclic or polycyclic cycloalkyl group, fully or partially unsaturated, with one or more heteroatom(s) independently selected from N, O and S, and are optionally benzofused or fused heteroaryl of 5-6 ring members and/or are optionally substituted wherein the substituents are selected from but not limited to halogen, oxo, hydroxyl, alkyl, alkenyl,

alkynyl, cycloalkyl, acyl, carboxyl, aryl, alkoxy, aralkyl, cyano, nitro, heterocyclyl, or heteroaryl. Examples of heterocyclyl groups include but are not limited to oxazolidinyl, tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, dihydroisooxazolyl, dihydrobenzofuryl, azabicyclohexyl, dihydroindonyl, piperidinyl, benzodiazepinyl or piperazinyl.

Halogen refers to Br, Cl, F or I.

"Hydroxy" or "hydroxyl" refers to the group –OH.

The term "Protecting Group" or "PG" refers to a group which is in a modified form to preclude undesired side reactions at the protected site. The term protecting group, unless otherwise specified, may be used with groups, for example, hydroxyl, amino, carboxyl and examples of such groups are found in T.W. Greene. et al. "*Protecting Groups in Organic Synthesis*," 3rd Ed, Wiley, New York, which is incorporated herein by reference. The species of the carboxylic protecting groups, amino protecting groups or hydroxyl protecting groups employed are not critical, as long as the derivatised moieties/moiety is/are stable to conditions of subsequent reactions and can be removed without disrupting the remainder of the molecule. Examples of suitable hydroxyl and amino protecting groups include but are not limited to trimethylsilyl, triethylsilyl, *o*-nitrobenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, *t*-butyldiphenylsilyl, *t*-butyldimethylsilyl, acetyl, trifluoroacetyl, benzyloxycarbonyl (CBz), *t*-butoxycarbonyl (Boc), 9-fluorenylnethylenoxycarbonyl (Fmoc), 2,2,2-trichloroethyloxycarbonyl, allyloxycarbonyl and the like. Examples of suitable carboxyl protecting groups are benzhydryl, *o*-nitrobenzyl, *p*-nitrobenzyl, 2-naphthylmethyl, allyl, 2-chloroallyl, benzyl, 2,2,2- trichloroethyl, trimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, 2-(trimethylsilyl)ethyl, phenacyl, *p*-methoxybenzyl, acetonyl, *p*-methoxyphenyl, 4-pyridylmethyl, *t*-butyl and the like.

The term "therapeutically effective amount" as used herein means the amount of a compound that, when administered to a mammal for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity, weight, physical condition and responsiveness of the mammal to be treated, among other factors.

A "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids.

Asymmetric centres may exist in the compounds of the present invention. The compounds of Formula I may have one or more stereogenic centres and so can exhibit

optical isomerism. All such isomers including enantiomers, diastereomers, and epimers are included within the scope of this invention. Furthermore, the invention includes such compounds as single isomers (*R* and /or *S)* and as mixtures, including racemates. If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation may be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. Starting materials of particular stereochemistry may either be commercially available or may be made by the methods described herein and resolved by techniques well known in the art. The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modifications.

Certain compounds according to Formula I, can also exist as tautomers, which have different points of attachment of hydrogen accompanied by one or more double bond shifts. These tautomers, either separately or as mixtures, are also considered to be within the scope of the invention.

The present invention also encompasses geometrical isomers of compounds of Formula I and the mixtures thereof.

Particularly useful examples of the present invention include but are not limited to the following compounds, including their pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers including *R* and *S* isomers, polymorphs, prodrugs, metabolites, salts or solvates thereof.

Compound No. 1: 1-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

Compound No. 2: 1-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentanol

Compound No. 3: 1-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cycloheptanol

Compound No. 4: 2-(7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol

Compound No. 5: 2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-adamantan-2-ol

Compound No. 6: 1-(7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-cyclohexanol

Compound No. 7: 1-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-cyclohexanol

Compound No. 8: 2-(7-Methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol

Compound No. 9: 2-(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol

Compound No. 10: 2-(6-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol

Compound No. 11: 2-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)propan-2-ol

Compound No. 12: 3-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)pentan-3-ol

Compound No. 13: Tetrahydro-4-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)-2H-pyran-4-ol

Compound No. 14: 4-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)-4-hydroxycyclohexanone

Compound No. 15: 1-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)-1-phenylethanol

Compound No. 16: 4-(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-hydroxycyclohexanone oxime

Compound No. 17: 4-(Prop-2-en-1-yloxy)-1-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl) cyclohexanol

Compound No. 18: 4-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)piperidin-4-ol

Compound No. 19: (1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)(pyrrolidin-2-yl)methanol

Compound No. 20: 1-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)cyclohexane-1,4-diol

Compound No. 21: 1-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)-4-methoxycyclohexanol

Compound No. 22: (1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)(thiophen-2-yl)methanol

Compound No. 23: (3,4-Dichlorophenyl)(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)methanol

Compound No. 24: 1-(2-(Cyclopropylmethyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-4-yl)cyclohexanol

Compound No. 25: 3-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)pentan-3-ol

Compound No. 26: Tetrahydro-4-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)-2*H*-pyran-4-ol

Compound No. 27: 1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)-1-phenylethanol

Compound No. 28: 1-(2-(Cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

Compound No. 29: 2-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)propan-2-ol

Compound No. 30: (3,4-dichlorophenyl)(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)methanol

Compound No. 31: 4-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)-4-hydroxycyclohexanone

Compound No. 32: 4-(Allyloxy)-1-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)cyclohexanol

Compound No. 33: 1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)cyclohexane-1,4-diol

Compound No. 34: 4-Hydroxy-4-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanoneoxime

Compound No. 35: 1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)-2-methyl-5-(prop-1-en-2-yl)cyclohexanol

Compound No. 36: (1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)(thiophen-2-yl)methanol

Compound No. 37: Cyclohexyl(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)methanol

Compound No. 38: 1,2,3,4-Tetrahydro-1-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)naphthalen-1-ol

Compound No. 39: 1-(7-Fluoro-1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)cyclohexanol

Compound No. 40: tert-butyl 4-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)-4-hydroxypiperidine-1-carboxylate

Compound No. 41: 1-(2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

Compound No. 42: 4-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)piperidin-4-ol

Compound No. 43: 1,2,3,4-Tetrahydro-1-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)-6-methoxynaphthalen-1-ol

Compound No. 44: 1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)-2,2-dimethylpropan-1-ol

Compound No. 45: Tetrahydro-4-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)-2*H*-thiopyran-4-ol

Compound No. 46: 1-(6,7-Dichloro-2-ethyl-1,2,3,4-tetrahydroisoquino yl)cyclohexanol

Compound No. 47: (1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)(phenyl)methanol

Compound No. 48: 1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)-1-(thiophen-2-yl)ethanol

Compound No. 49: 1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)cyclohexylacetate

Compound No. 50: 1-(1,2,3,4-Tetrahydro-2-phenethylisoquinolin-4-yl)cyclohexanol

Compound No. 51: 1-(2-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

Compound No. 52: 4-tert-Butyl-1-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)cyclohexanol

Compound No. 53: 1-Biphenyl-4-yl-1-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)ethanol

Compound No. 54: 1-(2-Ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

Compound No. 55: 1-(1,2,3,4-Tetrahydro-2-isopropylisoquinolin-4-yl)cyclohexanol

Compound No. 56: 1-(2-Butyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

Compound No. 57: 1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)-2-methyl-5-(prop-1-en-2-yl)cyclohexanol

Compound No. 58: Dicyclohexyl(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)methanol

Compound No. 59: 1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)cyclohex-2-enol

Compound No. 60: 1-(1,2,3,4-Tetrahydro-2-methylbenzo[h]isoquinolin-4-yl)cyclohexanol

Compound No. 61: 1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)cyclohexylmorpholine-4-carboxylate

Compound No. 62: 1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)cyclohexylcyclopropane carboxylate

Compound No. 63: Dicyclohexyl(1,2,3,4-tetrahydro-2-isopropylisoquinolin-4-yl)methanol

Compound No. 64: 1-(1,2,3,4-Tetrahydro-2-(2-morpholinoethyl)isoquinolin-4-yl)cyclohexanol

Compound No. 65: (2-Butyl-1,2,3,4-tetrahydroisoquinolin-4-yl)dicyclohexylmethanol

Compound No. 66: 1-(1,2,3,4-Tetrahydro-2,7-dimethylisoquinolin-4-yl)cyclohexanol

Compound No. 67: 1-[2-(4-Methylbenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl]cyclohexanol

Compound No. 68: 1-[2-(4-Methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl]cyclohexanol

Compound No. 69: 1-(2-(4-Isopropoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

Compound No. 70: Tetrahydro-4-(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)-2*H*-pyran-4-ol

Compound No. 71: tert-butyl 4-(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)-4-hydroxypiperidine-1-carboxylate

Compound No. 72: 4-(1,2,3,4-Tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)piperidin-4-ol

Compound No. 73: 4-(1,2,3,4-Tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)-4-hydroxycyclohexanone

Compound No. 74: 3-(1,2,3,4-Tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)pentan-3-ol

Compound No. 75: 1,2,3,4-Tetrahydro-1-(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)naphthalen-1-ol

Compound No. 76: 1,2,3,4-Tetrahydro-4-(1-hydroxycyclohexyl)-2-methylisoquinolin-7-ol

Compound No. 77: 1-(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)-2-methyl-5-(prop-1-en-2-yl)- cyclohexanol

Compound No. 78: 4-*tert*-Butyl-1-(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)cyclohexanol

Compound No. 79: 1-(1,2,3,4-Tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)-1-phenylethanol

Compound No. 80: (3,4-Dichlorophenyl)(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)methanol

Compound No. 81: Cyclohexyl(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)methanol

Compound No. 82: 1-(7-Butoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 83: 1-(7-Ethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 84: 1-(7-Cyclopentyloxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 85: 1-(7-Cyclopentylmethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 86: 1-(2-Methyl-7-phenethyloxy-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 87: Dicyclohexyl-(7-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-methanol

Compound No. 88: 1-[2-Methyl-7-(2-morpholin-4-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Compound No. 89: 1-(7-Hexyloxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No.90: 1-(7-Butoxy-2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 91: 1-[2-Methyl-7-(3-methyl-butoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Compound No. 92: 1-(7-Isopropoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 93: 1-[2-Methyl-7-(3-morpholin-4-yl-propoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Compound No. 94: 1-[2-Methyl-7-(2-piperidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Compound No. 95: 1-[2-Methyl-7-(2-thiomorpholin-4-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]- cyclohexanol

Compound No. 96: 1-[2-Methyl-7-(2-pyrrolidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Compound No. 97: 1-[7-(2-Dimethylamino-ethoxy)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Compound No. 98: 1-{2-Methyl-7-[2-(4-methyl-piperazin-1-yl)-ethoxy]-1,2,3,4-tetrahydro-isoquinolin-4-yl}-cyclohexanol

Compound No. 99: 1-[7-(2-Hydroxy-ethoxy)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Compound No. 100: 1-[7-(2-Methoxy-ethoxy)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Compound No. 101: 1-[2-Methyl-7-(2,2,2-trifluoro-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Compound No. 102: 1-(7-Benzyloxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 103: 1-(2-Methyl-7-prop-2-ynyloxy-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 104: 1-(2-Methyl-7-phenoxy-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 105: 1-[2-Methyl-7-(thiophen-2-ylmethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Compound No. 106: 2-[4-(1-Hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy]-1-morpholin- 4-yl-ethanone

Compound No. 107: 1-[2-Methyl-7-(2-thiophen-2-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Compound No. 108: 4-(1-Methoxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinoline

Compound No. 109: Carbonic acid ethyl ester 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester

Compound No. 110: 1-{7-[2-(4,4-Difluoro-piperidin-1-yl)-ethoxy]-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl}- cyclohexanol

Compound No. 111: 1-{2-[4-(1-Hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy]-ethyl}- piperidin-4-one

Compound No. 112: Carbonic acid ethyl ester 1-(7-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)- cyclohexyl ester

Compound No. 113: 1-[7-(2-Diallylamino-ethoxy)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Compound No. 114: Benzoic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester

Compound No. 115: Carbonic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester phenyl ester

Compound No. 116: Carbonic acid 4-(1-ethoxycarbonyloxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7- yl ester ethyl ester

Compound No. 117: 2,4-Dimethoxy-benzoic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin- 7-yl ester

Compound No. 118: Carbonic acid 4-(1-isobutoxycarbonyloxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin- 7-yl ester isobutyl ester

Compound No. 119: 2-Chloro-benzoic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester

Compound No. 120: Pentanoic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester

Compound No. 121: Nicotinic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester

Compound No. 122: Carbonic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester isobutyl ester

Compound No. 123: Benzoic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester

Compound No. 124: 1-Biphenyl-4-yl-1-(7-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-ethanol

Compound No. 125: 1-(6,7,8-Trimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 126: 1-(7-Butyl-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 127: 1-[2-(2,2,2-Trifluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Compound No. 128: 1-(7-Diethylamino-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 129: 1-(2-Methyl-7-phenyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Compound No. 130: 2-cyclopropyl-4-(1-hydroxycyclohexyl)-1,2,3,4-tetrahydroisoquinoline

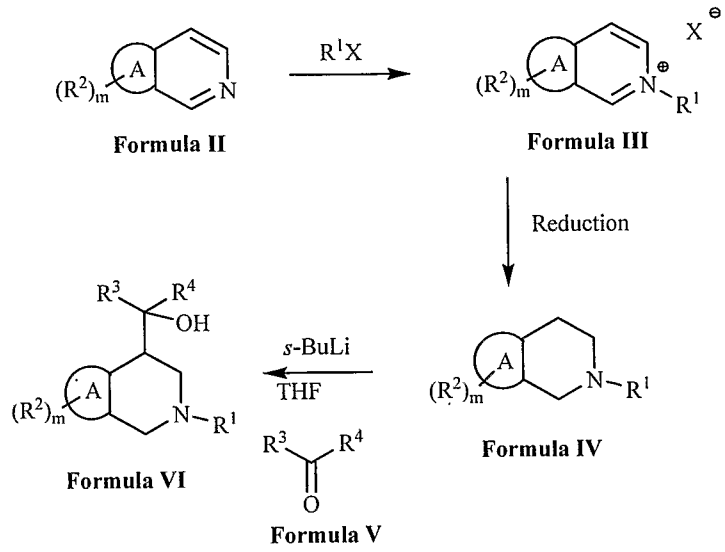
Compound No. 131: 4-(1-fluorocyclohexyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline

Compound No. 132: 1-(2-methyl-1,2,3,4-tetrahydrobenzo[h]isoquinolin-4-yl)-1-phenylethanol

Compound No. 133: cyclohexyl(2-methyl-1,2,3,4-tetrahydrobenzo[h]isoquinolin-4-yl)methanol

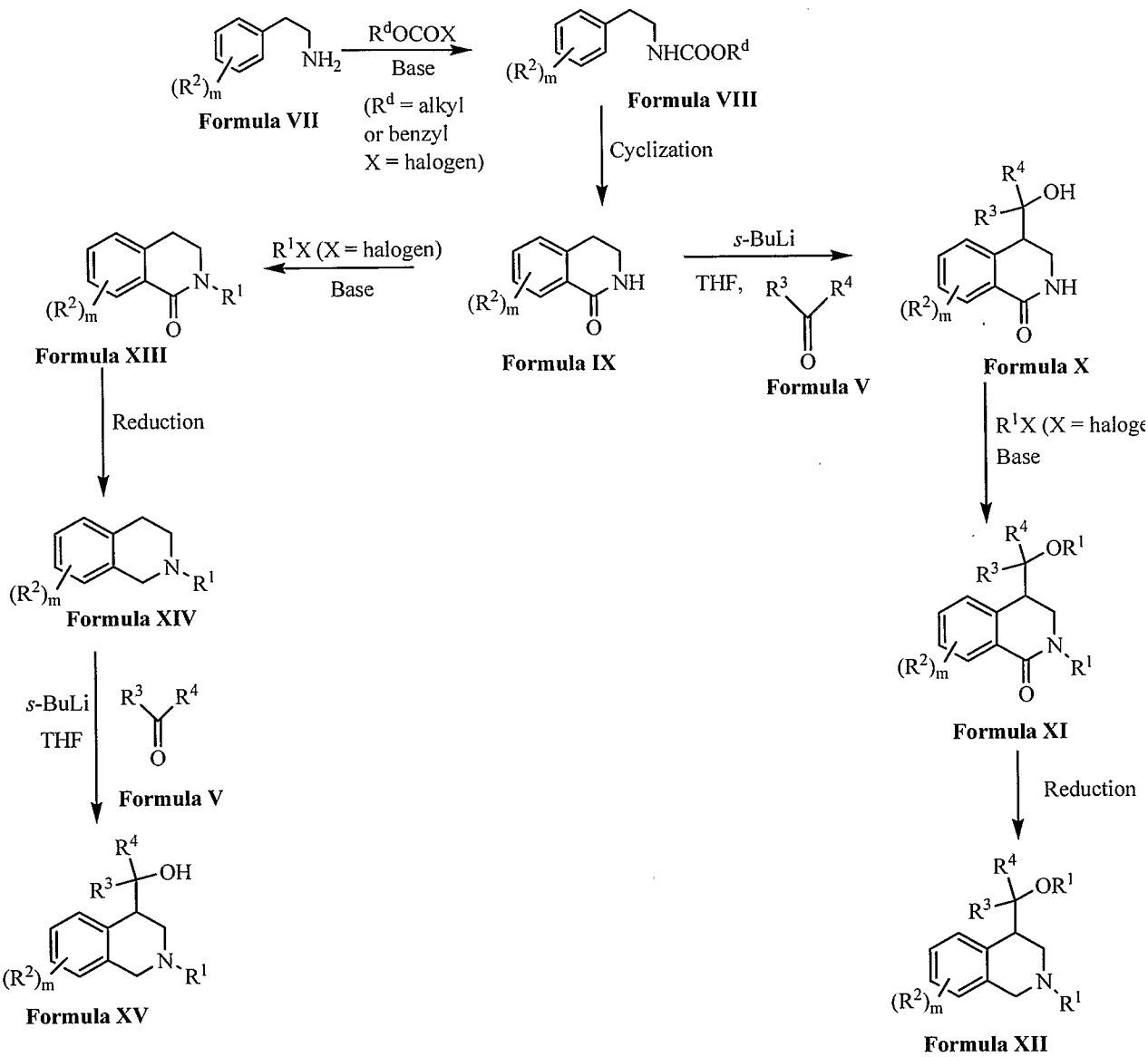
The compounds of the present invention are prepared in accordance with the Schemes discussed herein after. All of the starting materials are either commercially available or can be prepared by procedures that would be well known to one of ordinary skill in organic chemistry. Some common routes for the preparation of such compounds are illustrated in Scheme I, II and III.

Scheme I



Compounds of Formula VI can be synthesized from compounds of Formula II as described in scheme I. Compounds of Formula II can be converted into compounds of Formula III by reacting with R^1X (where R^1 is as defined herein and X is halogen) in a suitable alcoholic solvent such as methanol, ethanol and the like or mixtures thereof. The compounds of Formula II can be easily synthesized following the procedure as described in *J. Chem. Soc. Perkin Trans I*, **1987**, 689. The compounds of Formula III can then be reduced to compounds of Formula IV in the presence of a suitable reducing agent including, but not limited to, for example, sodium borohydride, lithium borohydride, diisobutylaluminium hydride or lithium aluminium hydride. The reduction can also be carried out by catalytic hydrogenation using suitable catalyst including, but not limited to, for example, PtO_2, Pd/C, raney nickel and the like in the presence of a suitable solvent including, for example, ethanol, methanol, ether, THF, dioxane, toluene, water or the mixtures thereof. The compounds of Formula IV are converted into compounds of Formula VI by first generating anion at the β-position and then quenching with appropriate electrophile $R^3C(O)R^4$ of formula V (where R^3 and R^4 are as defined herein).

Scheme II



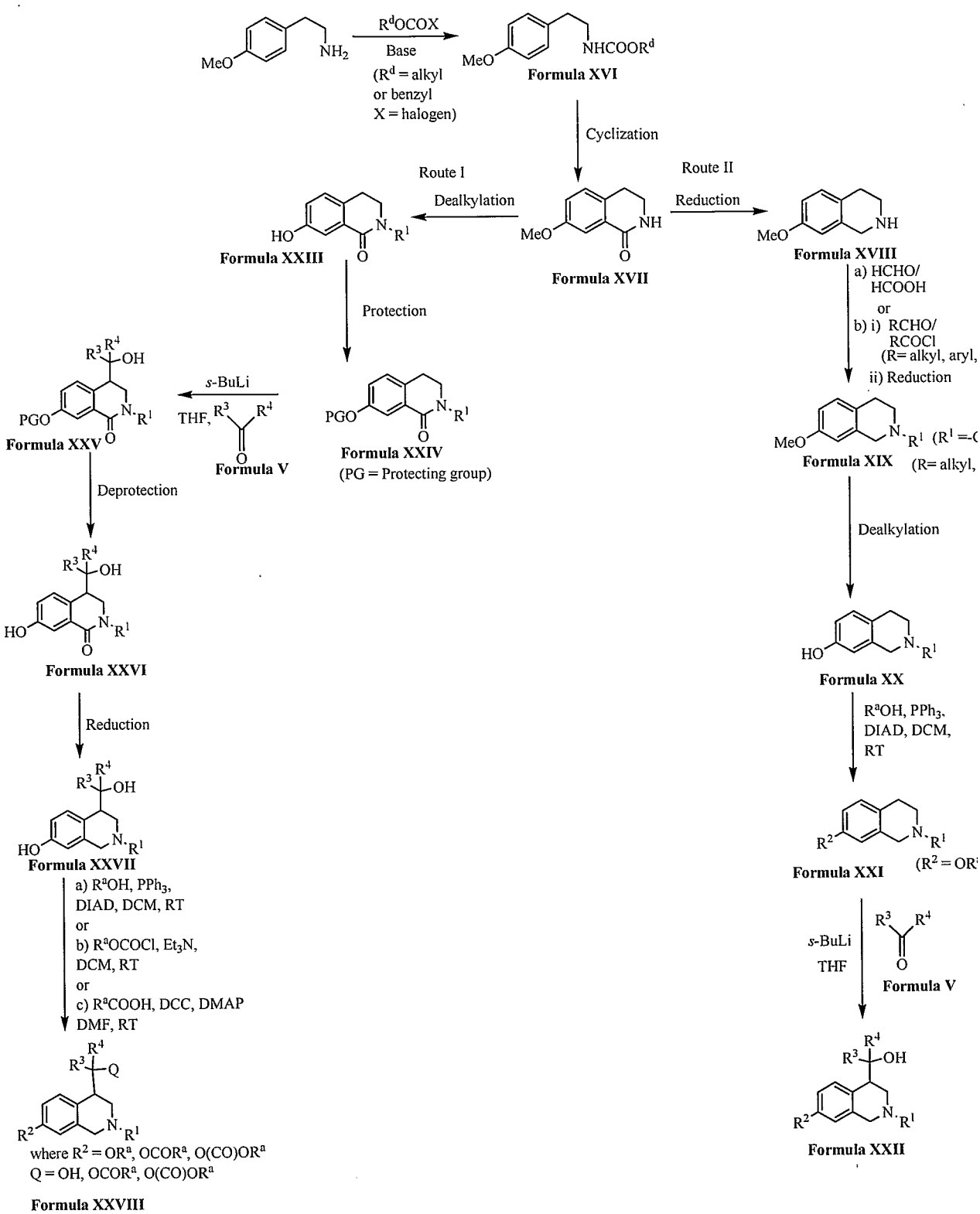
Compounds of Formula XV and Formula XII can be synthesized starting from compounds of Formula VII as described in scheme II. Compounds of Formula VII can be converted into compounds of Formula VIII by reacting with R^dOCOX (where R^d can be C_{1-12} alkyl or C_{1-12} benzyl and X is halogen) in the presence of a base including, for example, but not limited to triethylamine, DIPEA, potassium carbonate and the like in a suitable solvent such as acetonitrile, tetrahydrofuran, methylene dichloride, dichloroethane and the like or mixtures thereof. Compounds of Formula IX can be obtained by reacting compounds of Formula VIII with dehydrating agents including, for example, but not limited to, polyphosphoric acid, sulphuric acid and the like or mixtures thereof. Compounds of formula IX can be converted to compounds of formula X via metallation

reaction as described in scheme I. Compounds of formula XI can be obtained by reacting compounds of formula X with suitable base including, but not limited to, for example, sodium hydride, butyl lithium in a suitable solvent including, but not limited to, for example, DMF, THF, DMSO and the like or mixtures thereof followed by addition of R^1X (where R^1 is as defined earlier and X is the halogen). In an alternate route, compounds of formula XIII can be obtained by alkylation reaction of compounds of formula IX as described herein. Compounds of Formula XIV can be obtained by reduction of compounds of Formula XIII as discussed above. Compounds of formula XV can be obtained by metallation of compounds of Formula XIV as described in scheme I.

Compounds of Formula XXII and Formula XXVIII can be obtained starting from 2-(4-Methoxyphenyl)ethyl amine as described in scheme III. 2-(4-Methoxyphenyl)ethyl amine can be converted into compounds of formula XVI and then to compounds of Formula XVII as described in scheme II. Compounds of Formula XVII can be reduced to compounds of Formula XVIII as described above in scheme II. Compounds of Formula XVIII can be converted to compounds of Formula XIX depending upon the nature of the required R^1 group. In case the required R^1 group is $-CH_3$, the compounds of Formula XVIII can be treated with formaldehyde in formic acid. In case of any other R^1 group, the compounds of Formula XVIII can be treated accordingly with either RCHO or RCOCl (where R is alkyl, aryl or heteroaryl), followed by standard reduction conditions as known to a person skilled in the art to obtain compounds of Formula XIX. Compounds of Formula XIX can then be dealkylated to compounds of Formula XX in the presence of a suitable acid including, but not limited to, for example, aqueous HCl, aqueous HBr or aqueous HI or aqueous BBr_3 or the like. Compounds of Formula XXI can be obtained by coupling compounds of Formula XX with R^aOH (where R^a is as described herein) in presence of DIAD or DEAD and triphenylphosphine in a suitable solvent such as dichloromethane, tetrahydrofuran, acetonitrile and the like or mixtures thereof under Mitsunobu reaction conditions. Compounds of Formula XXII can be obtained from metallation of compounds of Formula XXI as described in scheme I. In an alternate route the compounds of the formula XVII can be dealkylated to compounds of Formula XXIII in the presence of a suitable acid including, but not limited to, for example, aqueous HCl, aqueous HBr or aqueous HI or BBr_3 or the like. The protection of compounds of Formula XXIII with phenol protecting groups including but not limited to, for example TBDMSCl, TMSCl, TBDPSCl in presence of a suitable base including but not limited to, for example imidazole, 2,6-lutidine, DIPEA in a suitable solvent such as dimethylformamide,

tetrahydrofuran, DMSO and the like or mixtures thereof give the compounds of Formula XXIV. The compounds of Formula XXIV can be converted into compounds of Formula XXV by anion generation followed by quenching with electrophile of Formula V as described in scheme I. The protecting group present in the compounds of Formula XXV can be removed to give compounds of Formula XXVI following the techniques well known in the art and familiar to the skilled organic chemist, including but not limited to, for example TBAF or HF/pyridine in a suitable solvent such as dimethylformamide, tetrahydrofuran and the like or mixtures thereof. The compounds of Formula XXVII can be obtained by reduction of compounds of Formula XXVI as described above in scheme II. Compounds of Formula XXVII can be converted to compounds of Formula XXVIII depending upon the nature of the R^2, as well as the nature of the Q. If R^2 is OR^a (where R^a is as described herein) and Q is OH then it can be obtained by coupling compounds of Formula XXVI with R^aOH (where R^a is as described herein) in presence of DIAD or DEAD and triphenylphosphine in a suitable solvent such as dichloromethane, tetrahydrofuran, acetonitrile and the like or mixtures thereof under Mitsunobu reaction conditions. If R^2 is $OCOR^a$ (where R^a is as described herein) and the Q is either OH or $OCOR^a$ (where R^a as described herein) then it can be obtained by coupling compounds of Formula XXVI using appropriate equivalents of R^aCOOH (where R^a is as described herein) including but not limited to, for example in the presence of DCC and DMAP in a suitable solvent such as dimethylformamide, tetrahydrofuran, acetonitrile and the like or mixtures thereof. If R^2 is $O(CO)OR^a$ (where R^a is as described herein) and Q is either OH or $O(CO)OR^a$ (where R^a is as described herein) then it can be obtained by coupling compounds of Formula XXVI with different equivalents of R^aOCOCl (where R^a is as described herein) in the presence of a suitable base including but not limited to, for example triethylamine, 2,6-lutidine, DIPEA in a suitable solvent such as dichloromethane, tetrahydrofuran, acetonitrile and the like or mixtures thereof.

Scheme III



It is understood that, as used herein, references to the compounds of structural Formula I are meant to also include the pharmaceutically acceptable salts, and also salts

that are not pharmaceutically acceptable when they are used as precursors to the free compounds or their pharmaceutically acceptable salts or in other synthetic manipulations. The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. The salts may be prepared during the final isolation and purification of the compounds or separately by making basic or acidic addition salts. Representative salts of basic compounds of the present invention can be prepared by reacting free base form of the compound with a suitable acid, including, but not limited to acetate, trifluoroacetate, adipate, citrate, aspartate, benzoate, benzenesulphonate, bisulfate, besylate, butyrate, camphorsulphonate, difluconae, hemisulfate, heptanoate, formate, fumarate, lactate, maleate, methanesulfonate, naphthylsulfonate, nicotinate, oxalate, picrate, pivalate, succinate, tartrate, tirchloracetat, glutamate, *p*-toluenesulphonate, hydrochloric, hydrobromic, sulphuric, phosphoric and the like. Representative salts of acidic compounds of the present invention can be prepared by reacting free acid form of the compound with a suitable base, including, but not limited to ammonium, calcium, magnesium, potassium, sodium salts, salts of primary, secondary and tertiary amines, substituted amines including naturally occurring ones e.g., arginine, betaine, caffeine, choline, glucamine, glucosamine, histidine, lysine, morpholine, piperazine, piperidine, purine, triethylamine and the like. Compounds of the present invention that contain a carboxylic acid (-COOH) or alcohol group, their pharmaceutically acceptable esters of carboxylic acids such as methyl, ethyl and the like, or acyl derivatives of alcohols such as acetate and the like, can be employed. Compounds of the present invention that comprise basic nitrogen atom may be quaternized with alkyl halides, alkyl sulfates and the like. Such salts permit the preparation of both water soluble and oil soluble compounds of the present invention. It should be recognized that the free base or free acid forms will typically differ from their respective salt forms somewhat in physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free forms for the purpose of the invention.

The "pharmaceutically acceptable solvates" refer to solvates with water (i.e., hydrates) or pharmaceutically acceptable solvents, for example, ethanol and the like.

The invention also encompasses "prodrugs" of the compounds of the present invention which upon *in-vivo* administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general such prodrugs

will be functional derivatives of a compound of the invention which are readily convertible *in vivo* into the compound of the invention. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Targeted prodrug design to optimize drug delivery", *AAPS PharmaSci* **2000**, *2*(1), E6.

The invention also encompasses active "metabolites" of the compound of the present invention. When a metabolite of a drug produces a therapeutic effect it is considered an active metabolite.

Various "polymorphs" of a compound of general Formula I forming part of this invention may be prepared by crystallization of a compound of Formula I under different conditions. For example, by using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations, heating or melting the compound followed by gradual or fast cooling may also obtain polymorphs. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The present invention also provides pharmaceutical compositions, comprising compounds of general Formula I or their pharmaceutically acceptable analogs, tautomeric forms, stereoisomers, polymorphs, prodrugs, metabolites, salts or solvates thereof together with one or more pharmaceutically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compound into preparations, which can be used pharmaceutically. The pharmaceutical compositions may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions, emulsions, pills, granules, suppositories, pellets, depot formulations and the like, may contain flavourants, sweeteners etc in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 0.1 to 99.9 % by weight of active compound, the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents. The pharmaceutical compositions of the present invention can be manufactured by the processes well known in the art, for example, by means of conventional mixing, dissolving, dry granulation, wet granulation, dragee-making, levigating, emulsifying, encapsulating, entrapping, lyophilizing processes or spray drying. The compounds or the pharmaceutical compositions comprising such compounds of the present invention may be administered in the form of any pharmaceutical formulation. The pharmaceutical formulation will depend upon the nature of the active compound and its route of administration. Any route of

administration may be used, for example oral, buccal, pulmonary, topical, parenteral (including subcutaneous, intramuscular and intravenous), transdermal, ocular (ophthalmic), by inhalation, intranasal, transmucosal, implant or rectal administration. Preferably the compounds of the present invention are administered orally, parenterally or topically.

In an embodiment, the amount of the novel compounds having the Formula I according to the present invention to be incorporated into the pharmaceutical compositions of the present invention can vary over a wide range depending on known factors such as, for example, the disorder to be treated, the severity of the disorder, the patient's body weight, the dosage form, the chosen route of administration and the number of administration per day. Typically, the amount of the compound of Formula I in the pharmaceutical compositions of the present invention will range from approximately 0.01 mg to about 5000 mg. In an embodiment, the daily dose of composition comprising the novel compounds having the Formula I is in the range of about 0.01 mg/kg to about 100 mg/kg based on the body weight of the subject in need thereof which may be administered as a single or multiple doses.

In an embodiment, the novel compounds having the Formula I according to the present invention are particularly useful for the treatment of disease(s) or disorder(s) which are particularly acute in nature and which require a short term but mild to moderate treatment, or even some chronic conditions which favorably respond to or are alleviated by the novel compounds having the Formula I or compositions comprising them. The compositions comprising the novel compounds having the Formula-I are useful prophylactically or therapeutically depending upon the pathological condition intended to be prevented or treated respectively.

A further embodiment of the present invention is the use of a compound of Formula I for the manufacture of a medicament for the prophylaxis, amelioration and/or treatment of one or more condition(s)/disease(s)/ disorder(s) of the central and/or peripheral nervous system that are responsive to inhibition of biogenic amines, in particular one or more, or any combination of serotonin, norepinephrine and dopamine, in a subject in need thereof preferably a mammal including a human; for example by simultaneously inhibiting or blocking the reuptake of serotonin and/or norepinephrine and/or dopamine.

The compounds of the present invention are useful for the prophylaxis, amelioration and/or treatment of one or more condition(s)/disease(s)/ disorder(s) of the central and/or peripheral nervous system that are responsive to inhibition of biogenic amines, in particular one or more, or any combination of serotonin, norepinephrine and dopamine, in a subject in

need thereof preferably a mammal including a human. For example, such disorders include, but not limited to, depression, eating disorders, schizophrenia, inflammatory bowel disorders, pain, addiction disorders, urinary incontinence, dementia, Alzheimer's memory loss, Parkinsonism, stroke, anxiety, attention-deficit disorder, social phobia, obsessive compulsive disorder, substance abuse and withdrawal, cognitive disorders, fibromyalgia, sleep disorders, obesity, dyslipidemia, mania, bipolar disorder or hypomania.

Another embodiment of the present invention provides methods for the prophylaxis, amelioration and/or treatment of one or more one or more condition(s)/disease(s)/ disorder(s) of the central and/or peripheral nervous system that are responsive to inhibition of biogenic amines, in particular one or more, or any combination of serotonin, norepinephrine and dopamine, in a subject in need thereof preferably a mammal including a human, that comprises administering a therapeutically effective amount of compound of Formula I.

In still another embodiment of the present invention is provided use of the dosage form compositions comprising the novel compounds of Formula I for the treatment of one or more condition(s)/disease(s)/ disorder(s) of the central and/or peripheral nervous system that are responsive to inhibition of biogenic amines, in particular one or more, or any combination of serotonin, norepinephrine and dopamine, in a subject in need thereof a pharmaceutically effective amount of the composition.

In another embodiment the compounds or their pharmaceutically acceptable salts according to the present invention can be used in combination with at least one other therapeutic agent. The therapeutic agent may be, but is not restricted to anti-depressants, anti-anxiolytic agents, anti-psychotic drugs, anti-obesity drugs, anti-attention deficit hyperactivity disorder agents, anti-additive disorder agents, anti-alcohol agents, anti-nicotine agents, anti-opiate agents, anti-cocaine agents, anti-Parkinson's-disease agent, anti-schizophernia agent, anti-epilepsy agents, appetite suppressants, anti-inflammatory agents, anti-diabetic agents, anti-hypertensive agents, anti-lysergic acid diethylamide ("anti-LCD") agent and anti-phencyclidine ("anti-PCP") agent.

EXAMPLES

The invention is explained in detail in the following examples which are given solely for the purpose of illustration only and therefore should not be construed to limit the scope of the invention. All of the starting materials are either commercially available or can be prepared by procedures that would be well known to one of ordinary skill in organic chemistry.

Solvents were dried prior to use wherever necessary by standard methods (Perrin, D.D.; Armarego, W.L.F. Purification of Laboratory Chemicals, Pergamon Press: Oxford, 1988). Mass spectra (MS) were obtained by electron spray ionization (ESI) eV using Applied biosystem 4000 Q TRAP. ^{1}H NMR were recorded on Bruker 400 MHz Avance II NMR spectrometer. Chemical shifts are reported as δ values in parts per million (ppm), relative to TMS as internal standard. All coupling constants (*J*) values are given in Hz.

Abbreviations

The following abbreviations are employed in the examples and elsewhere herein:

^{1}H NMR	Proton nuclear magnetic resonance
BBr_3	Boron tribromide
br s	Broad singlet
C	centigrade
$CDCl_3$	deuterated chloroform
$CHCl_3$	chloroform
DCC	Dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublet
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIPEA	diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDC	*N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiiimide hydrochloride
ESIMS	electron spray ionization mass Spectroscopy
Et_3N	Triethylamine
EtOAc	ethylacetate
EtOH	ethanol
g	gram(s)
h	hour(s)
HBr	Hydrobromic acid
HCl	Hydrochloric acid
HF	Hydrogen fluoride

HI	Hydroiodic acid
HOBT	1-hydroxybenzotriazole
Hz	Hertz
J	coupling constant
m	multiplet
MeOH	methanol
mg	milligram
MHz	Megahertz
min	minutes
mL	milliliter
mmol	millimoles
mp	melting point
Na	Sodium metal
NMM	*N*-Methyl morpholine
NMR	Nuclear magnetic resonance
Pd/C	Palladium on carbon
Pet. ether	Petroleum ether
PG	Protecting Group
ppm	parts per million
PtO_2	Platinum(IV) oxide
q	quartet
RT	room temperature
s	singlet
s-BuLi	*sec*-Butyl lithium
t	triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
td	Triplet of doublet
THF	tetrahydrofuran
TMSCl	Trimethylsilyl chloride

EXAMPLES

Examples set forth below demonstrate the general synthetic procedures for the preparation of representative compounds. The examples are provided to illustrate particular aspect of the disclosure and should not be constrained to limit the scope of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare the compounds of the present invention.

General procedure for metalation/substitution of compounds of Formula IV

A solution of tertiary amine IV (1.0 mmol) in tetrahydrofuran (0.3 mL) under nitrogen atmosphere was cooled to -78 °C and *s*-BuLi (2.2 equiv) was added dropwise. The solution was stirred at same temperature for one h. The resulting solution was treated with appropriate electrophile $R^3C(O)R^4$ (2.2 equiv). After 30 min, temperature of reaction mixture was allowed to rise to room temperature. The reaction mixture was quenched with 10% HCl and contents were poured into ether (30 mL) and extracted with 10% HCl (3x10 mL). The acidic layer was washed with ether (2x10 mL), basified with sodium carbonate (500 mg) and extracted with DCM (3x15 mL). Combined organic layer was washed with brine and dried over anhydrous sodium sulphate. The solvent was evaporated *in vacuo* to afford the crude product which was purified by column chromatography.

Example I: 1-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-cyclohexanol

Step 1: Synthesis of 2-methyl-isoquinolinium iodide

Methyl iodide (1.21 mL, 19.38 mmol) was added to a solution of isoquinoline (0.5 g, 3.8 mmol) in methanol (10 mL) at 0 °C with constant stirring to obtain the title compound as yellow solid which was purified by washing with diethyl ether (3x10 mL) to yield 1-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-cyclohexanol (0.95 g, 90 %) as white solid.

ESIMS (m/z): 145.3 (M+1)

Step 2: Synthesis of 2-methyl-1,2,3,4-tetrahydroisoquinoline

Sodium borohydride (0.42 g, 11.07 mmol) was added in portions to a solution of 2-methyl-isoquinolinium iodide (1.0 g, 3.69 mmol) in methanol (18.45 mL, 5 mL / mmol) at 0 °C with constant stirring. The reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (3x20 mL)

and a 1:19 mixture of MeOH and $CHCl_3$ (2 x 20 mL). Organic layers were combined, dried over anhydrous sodium sulphate and concentrated to obtain the compound as brown oil, which was purified by column chromatography

(silica gel, 7:93 EtOAc : Pet Ether) to yield the title compound (0.4 g, 80.0%) as brown oil.

ESIMS (m/z): 148.0 (M+1)

Step 3: Synthesis of 1-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-cyclohexanol

The reaction of 2-methyl-1,2,3,4-tetrahydroisoquinoline (0.5 g, 3.4 mmol) with cyclohexanone (0.78 mL, 7.48 mmol) as an electrophile according to general procedure of metalation/substitution furnished yellow liquid, which was purified by column chromatography (silica gel, 1:19 EtOAc : Pet ether) to yield the title compound (0.31 g, 37 %) as a white solid.

ESIMS (m/z): 246.2 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27-1.92 (m, 10H), 2.4 (s, 3H), 2.45 (dd, J = 2.9, 11.7 Hz, 1H), 2.62 (s, 1H), 3.28 (d, J = 15.3 Hz, 1H), 3.40 (d, J = 11.7 Hz, 1H), 4.02 (d, J = 15.2 Hz, 1H), 6.65 (br s, 1H), 7.03 (d, J = 8.5 Hz, 1H), 7.15 (m, 3H)

Example II: 1-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-4yl)-cyclopentanol

The metalation of 2-methyl-1,2,3,4-tetrahydroisoquinoline (0.5 g, 3.4 mmol) using cyclopentanone (7.6 mmol, 0.64 g, 0.67 mL) as an electrophile by general metalation process gave crude material, which was purified by column chromatography (silica gel, 1:19 EtOAc : Pet ether) to yield the title compound (0.625 g, 77 %) as white solid.

ESIMS (m/z): 232.1 (M+1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53-1.45 (m, 1H), 1.65-1.58 (m, 4H), 1.70-1.85 (m, 1H), 1.82-1.75 (m, 2H), 2.34 (s, 3H), 2.50 (dd, J = 3.0, 11.4 Hz, 1H), 2.59 (s, 1H), 3.22 (d, J = 14.4 Hz, 2H), 3.92 (d, J = 15.3 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 7.09 (m, 3H).

Example III: 1-(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-cyclohexanol

The metalation of 6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (2.5 mmol, 0.5 mL; prepared according to the procedure described in *Organic Reactions*, **1975**, 6, 151-189) and subsequent reaction with cyclohexanone (0.6 mL, 5.45 mmol) by general procedure of metalation gave an oil, which was purified by column chromatography (silica gel, 1:3 EtOAc : Pet Ether) to yield the title compound (0.463 g, 60 %) as a white solid.

ESIMS (m/z): 306.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (m, 1H), 1.54 (m, 7H), 1.73 (m, 1H), 1.93 (d, 1H), 2.40 (s, 3H), 2.43 (dd, J = 2.96, 11.7 Hz, 1H), 2.54 (s, 1H), 3.22 (d, J = 14.8 Hz, 1H), 3.38 (d, J = 11.6 Hz, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 3.94 (d, J = 14.8 Hz, 1H), 6.53 (s, 1H), 6.62 (s, 1H).

Example IV: 1-(7-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-cyclohexanol

Step1: Synthesis of methyl 4-methoxyphenethylcarbamate

To a stirred solution of 4-methoxyphenethylamine (10 g, 66.23 mmol) in tetrahydrofuran (40 mL) was added triethylamine (55.3 mL, 397.4 mmol). The reaction mixture was cooled to 0 °C and solution of methyl chloroformate (20.46 mL, 265 mmol) in THF (25 mL) was added dropwise and stirring was continued for 24 h at room temperature. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (5x25 mL). The combined organic layer was washed with 10% hydrochloric acid, water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude compound, which was purified by column chromatography (silica gel, 1:4 EtOAc : Pet Ether) to yield the title compound (9.1 g, 65.7 %) as white solid.

ESIMS (m/z): 231.8 (M+Na), 209.9 (M+1)

Step 2: Synthesis of 7-methoxy-3,4-dihydroisoquinolin-1(*2H*)-one

Methyl 4-methoxyphenethylcarbamate (500 mg, 2.39 mmol) was added to hot polyphosphoric acid (2.8 g) and the reaction mixture was stirred at 145° C for 10 min. The hot reaction mixture was added to crushed ice (5 g) and was extracted with DCM (5x25 mL). The organic layer was dried and concentrated under reduced pressure to yield crude material (223 mg, 52.6 %) which was used as such in next step.

ESIMS (m/z): 177.7 (M+1)

Step 3: Synthesis of 7-methoxy-1,2,3,4-Tetrahydro-isoquinoline

To a slurry of lithium aluminium hydride (2.42 g, 63.56 mmol) in dry tetrahydrofuran at 0 °C was added 3,4-dihydro-7-methoxyisoquinolin-1(*2H*)-one (4.5 g, 25.4 mmol) dissolved in tetrahydrofuran and the solution refluxed for 2 h with stirring. Reaction mixture was quenched at 0 °C with water (2.5 mL), 10% sodium hydroxide solution (2.5 mL) and water (7.5 mL). The stirring was continued at room temperature for 30 min. It was filtered through a celite bed which was thoroughly washed with $CHCl_3$ (~100 mL). The $CHCl_3$ was concentrated under reduced pressure to give crude material (2.9 g, 70 %) which was used as such for next step.

ESIMS (m/z): 186.0 (M+Na), 164.1 (M+1)

Step 4: Synthesis of 7-methoxy-1,2,3,4-tetrahydro-2-methylisoquinoline

To a stirred solution of 1,2,3,4-tetrahydro-7-methoxyisoquinoline (2.9 g, 17.79 mmol) in formic acid (3.42 mL, 88.95 mmol) was added 37% formaldehyde aqueous solution (3.2 mL, 39.14 mmol) and reaction mixture was stirred at 90 °C for 16 h. Reaction mixture was neutralized with sodium carbonate (1.5 g) and extracted with EtOAc (3x25 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 1:99 MeOH : $CHCl_3$) to yield the title compound (2 g, 63.5 %) as brown liquid.

ESIMS (m/z): 178.3(M+1)

Step 5: Synthesis of 1-(7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-cyclohexanol

The reaction of 7-methoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (0.3 mL, 1.95 mmol) with cyclohexanone (0.44 mL, 4.29 mmol) according to general procedure resulted into a crude material, which was purified by column chromatography (silica gel, 7:93 EtOAc : Pet ether) to give a mixture of two products, which on further separation by column chromatography (silica gel, 1:49 $CHCl_3$: MeOH) gave the title compound (0.22 g, 40 %) and second compound corresponding to substitution at C_1-position (157 mg, 30 %) as an oil.

ESIMS (m/z): 273.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.27-1.92 (m, 10H), 2.40 (s, 3H), 2.44 (dd, J = 2.9, 11.7 Hz, 1H), 2.57 (s, 1H), 3.26 (d, J = 15.3 Hz, 1H), 3.39 (d, J = 11.8 Hz, 1H), 3.77 (s, 3H), 3.98 (d, J = 15.3 Hz, 1H), 6.57 (d, J = 2.6 Hz, 1H), 6.71 (dd, J = 2.7, 8.5 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H)

Example V: 2-(7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol

The general metalation process of 7-methoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (0.3 mL 1.95 mmol) which was prepared as described in Example IV (step 4), using D-camphor (4.3 mmol, 0.654 g) as electrophile resulted into crude product which was purified by column chromatography (silica gel, 1:19 EtOAc : Pet ether) to give a product (0.228 g, 38 %) corresponding to substitution at C_1-positon of 2-methyl-1,2,3,4-tetrahydroisoquinoline. Further elution (1:3 EtOAc : Pet ether) gave the title compound (0.246 g, 45 %) as white solid.

ESIMS (m/z): 330.5 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (s, 3H), 0.90-0.85 (m, 1H), 1.01 (s, 3H), 1.11 (s, 3H), 1.57-1.50 (m, 3H), 1.66 (t, J = 4.5 Hz, 1H), 1.85-1.70 (m, 1H), 1.98 (d, J = 13.4 Hz, 1H), 2.37 (s, 3H), 2.40 (dd, J = 2.9, 11.5 Hz, 1H), 2.82(s, 1H), 3.25 (d, J = 15.3 Hz, 1H), 3.38 (d, J = 11.5 Hz, 1H), 3.76 (s, 3H), 4.02 (d, J = 15.3 Hz, 1H), 6.57 (d, J = 2.6 Hz, 1H). 6.70 (dd, J = 2.7, 8.5 Hz, 2H), 7.19 (d, J = 8.5 Hz, 1H).

Example VI: 1-[2-Methyl-7-(2-morpholin-4-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Step 1: Synthesis of 2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-ol

Aqueous HBr (64 mL) was added to 7-methoxy-1,2,3,4-tetrahydro-2-methoxyisoquinoline (8 g, 45.2 mmol) which was prepared as described in Example IV (step 4), and reaction mixture was heated at 80 °C overnight. The reaction mixture was neutralized with sodium carbonate (2 g) and extracted with DCM (5x25 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to yield the title compound (6.8 g, 92.3%) as white solid.

ESIMS (m/z): 200.2 (M+Na), 178.2 (M+1)

Step 2: Synthesis of 2-methyl-7-(2-morpholin-4-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinoline

To a stirred solution of 2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-ol (1.5 g, 9.17 mmol) and triphenylphosphine (2.64 g, 10.08 mmol) in DCM (20 mL) was added 4-(2-hydroxy ethyl)morpholine (1.22 mL, 10.1 mmol) followed by the addition of diisopropylazodicarboxylate (1.77 mL, 10.08 mmol) diluted with DCM (10 mL) and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated to give crude material which was purified through column chromatography (silica gel, 2:98 MeOH : $CHCl_3$) to yield the title compound (720 mg, 28.4 %) as viscous liquid.

ESIMS (m/z): 299.0 (M+Na), 276.8 (M+1)

Step 3: Synthesis of 1-[2-methyl-7-(2-morpholin-4-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

To a stirred solution of 2-methyl-7-(2-morpholin-4-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinoline (720 mg, 2.609 mmol) in dry toluene (2 mL) was added *s*-BuLi (3.59 ml, 5.74 mmol) at -78 °C and stirring was continued for 1 h. Cyclohexanone (0.6 ml, 5.74 mmol) was added and reaction mixture was stirred at -78 °C for 1 h and at room temperature for overnight. Reaction mixture was quenched with 10% hydrochloric acid (2 mL) and poured into ether. HCl layer was washed with ether (2x25 mL), neutralized with sodium carbonate (1 g) and extracted with DCM (3x25 mL). The combined organic layer was then dried over

sodium sulfate and concentrated under reduced pressure to give crude material which was purified through column chromatography (silica gel, 2:98 MeOH : $CHCl_3$) to yield the title compound (150 mg,15.4 %) as viscous liquid.

ESIMS (m/z): 397.2 (M+Na), 375.4 (M+1)

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.65-1.20 (m, 6H), 1.80-1.65 (m, 2H), 2.0-1.90 (m, 2H), 2.40 (s, 3H), 2.43 (dd, *J* = 2.9, 11.7 Hz, 1H), 2.65-2.50 (m, 5H), 2.78 (t, *J* = 5.7 Hz, 2H), 3.25 (d, *J* = 15.2 Hz, 1H), 3.39 (d, *J* = 11.6 Hz, 1H), 3.73 (t, *J* = 4.6 Hz, 4H), 3.97 (d, *J* = 15.3 Hz, 1H), 4.07 (t, *J* = 5.7 Hz, 2H), 6.58 (d, *J* = 2.5 Hz, 1H), 6.71 (dd, *J* = 2.6, 8.5 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H).

Example VII: Synthesis of 1-[2-Methyl-7-(2-pyrrolidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Step 1: Synthesis of 7-(2-chloro-ethoxy)-2-methyl-3,4-dihydro-*2H*-isoquinolin-1-one

To a stirred solution of 7-hydroxy-2-methyl-3,4-dihydro-*2H*-isoquinolin-1-one (10 g, 56.5 mmol) in dimethylformamide (50 mL) was added potassium carbonate (23.39 g, 169.5 mmol) and DCM (22.4 mL, 282.5 mmol) and stirring was continued for 18 h at 100 °C. The reaction mixture was quenched with water (2 mL) and extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (50 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield the title compound (11.25 g, 83 %) as off white solid.

ESIMS (m/z): 263.1 (M+Na), 241.2 (M+1)

Step 2: Synthesis of 2-methyl-7-(2-pyrrolidin-1-yl-ethoxy)-3,4-dihydro-*2H*-isoquinolin-1-one

To a stirred solution of 7-(2-chloro-ethoxy)-2-methyl-3,4-dihydro-*2H*-isoquinolin-1-one (1.7 g, 7.08 mmol) in dimethylformamide (8 mL) was added potassium carbonate (2.93 g, 21.24 mmol) and pyrrolidine (0.7 mL, 8.50 mmol) and stirring was continued for 2 h at 100° C. The reaction mixture was quenched with water (1 mL) and extracted with EtOAc (3x25 mL). The combined organic layers was washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield the title compound (1.87 g, 96%) as viscous liquid.

ESIMS (m/z): 276.1 (M+1)

Step 3: Synthesis of 2-methyl-7-(2-pyrrolidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinoline

To a slurry of lithium aluminium hydride (643 mg, 16.2 mmol) in dry tetrahydrofuran (4 mL) was added 2-methyl-7-(2-pyrrolidin-1-yl-ethoxy)-3,4-dihydro-*2H*-isoquinolin-1-one

(1.86 g, 6.76 mmol) and stirring was continued for 2 h at room temperature. The reaction mixture was quenched with water (0.7 mL) and 10% sodium hydroxide (0.7 mL) at 0° C and diluted with chloroform (50 mL), filtered through celite bed and filtrate concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 6:94, MeOH : $CHCl_3$) to yield title compound (643 mg, 53.8%) as viscous liquid.

ESIMS (m/z): 262.0 (M+1)

Step 4: Synthesis of 1-[2-methyl-7-(2-pyrrolidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

To a stirred solution of 2-methyl-7-(2-pyrrolidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinoline (550 mg, 2.11 mmol) in toluene (2 mL) was added *s*-BuLi (3.31 mL, 4.64 mmol) at -78 °C and stirring was continued for 2 h, cyclohexanone (0.48 mL, 4.64 mmol) was added and stirred for 1 h at -78 °C and then at room temperature for 18 h. The reaction mixture was quenched with 10% hydrochloric acid (5 mL) and washed with diethyl ether (3x15 mL), acid layer was neutralized with sodium carbonate (1 g) and extracted with DCM (3x25 mL). Combined DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 5:95, MeOH : $CHCl_3$) to yield the title compound (35 mg, 5%) as viscous liquid.

ESIMS (m/z): 359.9 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70-1.15 (m, 10H), 1.90-1.75 (m, 4H), 2.40 (s, 3H), 2.44 (dd, J = 3.0, 11.7 Hz, 1H), 2.56 (s, 1H), 2.60-2.50 (m, 4H), 2.88 (t, J = 6.0 Hz, 2H), 3.24 (d, J = 15.3 Hz, 1H), 3.39 (d, J = 11.5 Hz, 1H), 3.96 (d, J = 15.3 Hz, 1H), 4.07 (t, J = 6.0 Hz, 2H), 6.59 (d, J = 2.5 Hz, 1H), 6.72 (dd, J = 2.5, 8.5 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H)

Example VIII: Synthesis of 4-(1-methoxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinoline

Step1: Synthesis of 3,4-dihydro-*2H*-isoquinolin-1-one

To Phenethylcarbamic acid methyl ester (3 g, 16.76 mmol) was added polyphosphoric acid (16.8 g) and stirred at 145 °C for 20 min. The reaction mixture was quenched with water and extracted with DCM (3x50 mL). The combined organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 60:40, EtOAc : Pet ether), to yield the title compound (925mg, 37.5%).

ESIMS (m/z): 147.3 (M+1)

Step 2: Synthesis of 4-(1-hydroxy-cyclohexyl)-3,4-dihydro-*2H*-isoquinolin-1-one

To a stirred solution of 3,4-dihydro-*2H*-isoquinolin-1-one (1.80 g, 12.24 mmol) in tetrahydrofuran (25 mL) was added *s*-BuLi (24.5 mL, 36.73 mmol) at -78 ° C and stirring was continued for 2 h. Cyclohexanone (3.79 mL, 36.73 mmol) was added and stirring was continued for 2 h at -78 °C. Reaction mixture was then quenched with saturated ammonium chloride solution (20 mL) and extracted with EtOAc (4x25 mL). Combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 3.5:97.5, MeOH : $CHCl_3$) to yield the title compound (950 mg, 31.7%) as viscous liquid.

ESIMS (m/z): 268.5 (M+Na), 246.0 (M+1)

Step 3: Synthesis of 4-(1-methoxy-cyclohexyl)-2-methyl-3,4-dihydro-2*H*-isoquinolin-1-one

To a slurry of sodium hydride (40 mg, 1.63 mmol) in dimethylformamide (0.5 mL) was added 4-(1-hydroxy-cyclohexyl)-3,4-dihydro-*2H*-isoquinolin-1-one (200 mg, 0.82 mmol) in dimethylformamide (0.5 mL) and methyl iodide (0.08 mL, 1.23 mmol). The reaction mixture was stirred for 1 h at 80 °C. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3x10 mL). The combined organic layer was washed with water (2x20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 2:98, MeOH : $CHCl_3$) to yield the title compound as viscous liquid.

ESIMS (m/z): 296.3 (M+Na), 274.1 (M+1)

Step 4: Synthesis of 4-(1-methoxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline

To a slurry of lithium aluminium hydride (14 mg, 0.37 mmol) in dry tetrahydrofuran (1 mL) was added 4-(1-methoxy-cyclohexyl)-2-methyl-3,4-dihydro-*2H*-isoquinolin-1-one (50 mg, 0.18 mmol) in dry tetrahydrofuran and stirring was continued for 40 min at room temperature. The reaction mixture was quenched with water (0.1 mL) and 10% sodium hydroxide (0.1 mL) at 0° C and diluted with $CHCl_3$ (10 mL). The solution was passed through celite bed and concentrated under reduced pressure to give crude material which was purified by column chromatography (basic aluminium oxide, 5:95 EtOAc : Pet ether) to yield the title compound (32 mg, 69%) as off-white solid.

ESIMS (m/z): 260.3 (M+1)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.60-0.90 (m, 9H), 2.02 (d, J = 11.0 Hz, 1H), 2.38 (s, 3H), 2.57 (dd, J = 5.9, 11.7 Hz, 1H), 2.68 (dd, J = 5.5, 11.7 Hz, 1H), 3.22 (t, J = 5.8 Hz, 1H),

3.29 (s, 3H), 3.37 (d, J = 14.2 Hz, 1H), 3.60 (d, J = 14.8 Hz, 1H), 7.01-6.99 (m, 1H), 7.12 (t, J = 4.5 Hz, 2H), 7.42-7.39 (m, 1H)

Example IX: Synthesis of 1-(7-butoxy-2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Step 1: Synthesis of 2-isopropyl-7-methoxy-3,4-dihydro-*2H*-isoquinolin-1-one

To a slurry of sodium hydride (671 mg, 27.97 mmol) in tetrahydrofuran (5 mL) was added 7-methoxy-3,4-dihydro-*2H*-isoquinolin-1-one, obtained in example IV (step 2), in tetrahydrofuran (5 ml) and isopropyl iodide (1.40 ml, 13.98 mmol). The reaction mixture was stirred for 1 h at 80 °C. The reaction mixture was quenched with water (15 mL) and extracted with EtOAc (3x30 mL). The combined organic layer was washed with water (2x30 mL) and brine (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 2:98 MeOH : $CHCl_3$) to yield the title compound (1.62 g, 79 %) as viscous liquid.

ESIMS (m/z): 219.3 (M+1)

Step 2: Synthesis of 2-isopropyl-7-methoxy-1,2,3,4-tetrahydro-isoquinoline

To a slurry of lithium aluminium hydride (842 mg, 22.15 mmol) in dry tetrahydrofuran (10 mL) was added 2-isopropyl-7-methoxy-3,4-dihydro-*2H*-isoquinolin-1-one and stirring was continued for 40 min at room temperature. The reaction mixture was quenched with water (0.9 mL) and 10% sodium hydroxide (0.9 mL) at 0 °C and diluted with $CHCl_3$ (150 mL). The mixture was passed through celite bed and concentrated under reduced pressure to give crude material which was purified by column chromatography (basic aluminium oxide, 5:95 EtOAc : Pet ether) to yield the title compound (1.4 g, 91 %) as off white solid.

ESIMS (m/z): 205.6 (M+1)

Step 3: Synthesis of 2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-ol

To a stirred solution of 2-isopropyl-7-methoxy-1,2,3,4-tetrahydro-isoquinoline (1.37 g, 6.67 mmol) was added aqueous HBr (5.4 mL) and reaction mixture was refluxed at 100 °C overnight. The reaction mixture was neutralized with saturated solution of sodium bicarbonate (20 mL) and then extracted with DCM (5x25 mL). Combined DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude product (1.09 g, 85 %) which was used as such for next step.

ESIMS (m/z): 191.4 (M+1)

Step 4: Synthesis of 7-butoxy-2-isopropyl-1,2,3,4-tetrahydro-isoquinoline

To a stirred solution of 2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-ol (1.09 g, 5.68 mmol), triphenylphosphine (1.64 g, 6.24 mmol) in DCM (15 mL) was added *n*-butanol (0.57 mL, 6.24 mmol) followed by the addition of diethylazodicarboxylate (1.1 mL, 6.24 mmol) diluted with DCM (5 mL) and reaction mixture was stirred for 24 h. The reaction mixture was concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 1:99 MeOH : $CHCl_3$) to yield the title compound (1.01 g, 72 %) as viscous liquid.

ESIMS (m/z): 247.2 (M+1)

Step 5: Synthesis of 1-(7-butoxy-2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

To a stirred solution of 7-butoxy-2-isopropyl-1,2,3,4-tetrahydro-isoquinoline (1.01 g, 4.09 mmol) in tetrahydrofuran (15 mL) was added *s*-BuLi (5.60 mL, 8.99 mmol) at -78 °C and stirring was continued for 2 h. Cyclohexanone (0.93 mL, 8.99 mmol) was added and stirring was continued for 1 h at -78 °C and then at room temperature for 12 h. The reaction mixture was quenched with 10% HCl solution (5 mL) and poured into ether (20 mL). The ether layer was extracted with 10% HCl (2x10 mL). The combined acid layer was neutralized with sodium carbonate (1.5 g) and extracted with DCM (4x25 mL). Combined DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 1:99, MeOH : $CHCl_3$) and repurified by column chromatography (basic aluminium oxide, 4:96 EtOAc : Pet ether) to yield the title compound (150 mg, 10 %) as viscous liquid.

ESIMS (m/z): 345.9 (M+1),

^{1}H NMR (400 MHz, $CDCl_3$): 0.96 (t, J = 7.4 Hz, 3H), 1.14 (dd, J = 1.9, 6.6 Hz, 6H), 1.50-1.40 (m, 10H), 1.70-1.68 (m, 3H), 1.95-1.90 (m, 1H), 2.50 (dd, J = 2.8, 11.7 Hz,1H), 2.56 (s, 1H), 2.95-2.85 (m, 1H), 3.48 (d, J = 11.6 Hz, 1H), 3.58 (d, J = 15.2 Hz ,1H), 3.92 (t, J = 5.5 Hz, 3H), 6.59 (d, J = 2.6 Hz, 1H), 6.69 (dd, J = 2.6, 8.4 Hz, 1H,), 6.99 (br s, 1H), 7.01 (d, J = 8.5 Hz, 1H)

Example X: Synthesis of 1-(6,7,8-trimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Step 1: Synthesis of *N*-methyl-2-(3,4,5-trimethoxy-phenyl)-acetamide

To a stirred solution of 3,4,5-trimethoxyphenylacetic acid (9 g, 39.82 mmol), methylamine hydrochloride (8.07 g, 119.46 mmol), EDC (9.89 g, 51.77 mmol) and HOBT (6.99 g, 51.77 mmol) in dry DCM (50 mL) was added DIPEA (26.96 mL, 159.28 mmol) and reaction

mixture was stirred overnight at room temperature. Reaction mixture was diluted with DCM (100 mL). The organic layer was washed with saturated solution of sodium bicarbonate (50 mL), 10% HCl (50 mL) and water (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 6:94 MeOH : $CHCl_3$) to yield the title compound (8.98 gm, 94.35 %) as white solid.

ESIMS (m/z): 239.8 (M+1)

Step 2: Synthesis of methyl-[2-(3,4,5-trimethoxy-phenyl)-ethyl]-amine

To a stirred solution of *N*-methyl-2-(3,4,5-trimethoxyphenyl)acetamide (6 g, 25.10 mmol) in dry THF (50 mL) was added borontrifluoride diethyletherate (5.2 mL) dropwise and stirred for 15 min at 80 °C followed by addition of boranedimethylsulphide complex (75.30 mL, 75.30 mmol). The reaction mixture was stirred overnight at 80 °C. Reaction mixture was cooled to 0 °C and quenched with MeOH (20 mL) and 10 % HCl (30 mL) dropwise and the MeOH was evaporated under reduced pressure. HCl layer was washed with ether (2x20 mL), neutralized with sodium bicarbonate (3.0 g) and extracted with DCM (5x30 mL), DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield the title compound (4.7 g, 83.23 %) as viscous liquid.

ESIMS (m/z): 225.3 (M+1)

Step 3: Synthesis of methyl-[2-(3,4,5-trimethoxy-phenyl)-ethyl]-carbamicacidmethylether

To a stirred solution of methyl-[2-(3,4,5-trimethoxy-phenyl)-ethyl]amine (4.7 g, 20.89 mmol) in dry DCM (15 mL) was added triethylamine (20.34 ml, 146.23 mmol), methylchloroformate (8.07 mL, 04.45 mmol) in dry dichloromethane (15 mL) and reaction mixture was stirred for 1 h. The reaction mixture was diluted with DCM (20 mL). The organic layer was washed with 10% HCl (30 mL) and water (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 60:40, EtOAC : Pet ether) to yield the title compound (5.0 g, 84.58 %) as viscous liquid.

ESIMS (m/z): 306.3 (M+Na), 284.2 (M+1)

Step 4: Synthesis of 6,7,8-trimethoxy-2-methyl-3,4-dihydro-2*H*-isoquinoline-1-one

To methyl-[2-(3,4,5-trimethoxy-phenyl)-ethyl]-carbamicacidmethylether (100 mg, 0.71 mmol) was added polyphosphoric acid (1.2 g) and the reaction mixture was stirred for 35 min at 120 °C. Reaction mixture was quenched with ice cold water and extracted with DCM (5x10 mL). Organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column

chromatography (silica gel, 2:98, MeOH : $CHCl_3$) to yield the title compound (10 mg, 11.26 %) as offwhite solid.

ESIMS (m/z): 252.5 (M+1)

Step 5: Synthesis of 6,7,8-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

To a slurry of lithium aluminium hydride (189.05 mg, 4.98 mmol) in dry tetrahydrofuran (2 mL) was added 6,7,8-trimethoxy-2-methyl-3,4-dihydro-2*H*-isoquinoline-1-one (500 mg, 1.93 mmol) in dry tetrahydrofuran (3 mL) and stirring was continued for 45 min at room temperature. The reaction mixture was quenched with water (0.2 mL) and 10% sodium hydroxide (0.2 mL) at 0 °C and diluted with $CHCl_3$ (30 mL), filtered through celite bed and the filtrate was concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 2.3:97.7, MeOH : $CHCl_3$) to yield the title compound (315 mg, 66.83 %) as viscous liquid.

ESIMS (m/z): 236.5 (M+1)

Step 6: Synthesis of 1-(6,7,8-trimethoxy-2-methyl-1,2,3,4-tetrahydro-isoqunoline-4-yl)-cyclohexanol

To a stirred solution of 6,7,8-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (300 mg, 1.27 mmol) in dry tetrahydrofuran (5 mL) was added *s*-BuLi (2.52 mL, 3.78 mmol) at -78 °C and stirring was continued for 1 h. Cyclohexanone (0.39 mL, 3.78 mmol) was added and stirring was continued for 2 h at -78 ° C. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (3x20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 1.8:98.2, MeOH : $CHCl_3$) to yield the title compound (130 mg, 30.7 %) as white solid.

ESIMS (m/z): 358.9 (M+Na), 337.4 (M+2).

^{1}H NMR (400 MHz, $CDCl_3$) : 1.94-1.26 (m, 10H), 2.40 (dd, J = 2.9, 11.9 Hz, 1H), 2.43 (s, 3H), 2.53 (s, 1H), 3.07 (d, J = 15.6 Hz, 1H), 3.36 (d, J = 11.7 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 4.00 (d, J = 15.7 Hz, 1H), 6.43 (s, 1H), 6.78 (br s, 1H).

Example XI: Synthesis of 1-(2-methyl-7-phenoxy-1,2,3,4-tetrahydro isoquinolin-4-yl)-cyclohexanol

Step1: Synthesis of 7-methoxy-2-methyl-3,4-dihydro-*2H*-isoquinolin-1-one

To a slurry of sodium hydride (5.42 g, 113.0 mmol) in dimethylformamide (45 mL) was added 3,4-dihydro-7-methoxyisoquinolin-1(*2H*)-one (8 g, 45.2 mmol) as prepared in Example IV (step 2), in dimethylformamide (15 ml), and methyl iodide (5.65 ml, 90.39 mmol). The

reaction mixture was stirred for 1 h at 80 °C. The reaction mixture was quenched with water (15 mL) and extracted with EtOAc (3x50 mL). The combined organic layer was washed with water (2x40 mL) and brine (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give title compound (8.0 g, 92.6%) as viscous liquid.

ESIMS (m/z): 191.3 (M+1)

Step 2: Synthesis of 7-hydroxy-2-methyl-3,4-dihydro-2H-isoquinolin-1-one

To a stirred solution of 7-methoxy-2-methyl-3,4-dihydro-2H-isoquinolin-1-one (8.0 g, 41.88 mmol) was added aqueous HBr (29.91 mL) and reaction mixture was refluxed at 100 °C overnight. The reaction mixture was quenched with water (25 mL) and then extracted with DCM (5x50 mL), DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield the title compound (4.90 g, 66.10 %) as white solid.

ESIMS (m/z): 178.3 (M+1)

Step 3: Synthesis of 7-(*tert*-butyl-dimethyl-silanyloxy)-2-methyl-3,4-dihydro-*2H*-isoquinolin-1-one

To a stirred solution of 7-hydroxy-2-methyl-3,4-dihydro-*2H*-isoquinolin-1-one (8.0 g, 45.20 mmol) in dimethylformamide (50 mL) was added imidazole (9.22 g, 135.59 mmol) and *tert*-butyldimethylsilyl chloride (13.55 g, 90.40 mmol) and reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with water (25 mL) and extracted with EtOAc (3x50 mL). The combined organic layer was washed with water (100 mL) and brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield the title compound (12.0 g, 91.23 %) as viscous liquid.

ESIMS (m/z): 291.6 (M+1)

Step 4: Synthesis of 7-(tert-butyl-dimethyl-silanyloxy)-2-methyl-1,2,3,4-tetrahydro-isoquinoline

To a slurry of lithium aluminium hydride (4.70 g, 123.71 mmol) in dry tetrahydrofuran (80 mL) was added 7-(tert-butyl-dimethyl-silanyloxy)-2-methyl-3,4-dihydro-*2H*-isoquinolin-1-one (12.0 g, 41.24 mmol) and stirring was continued for 1 h at room temperature. The reaction mixture was quenched with water (4 mL) and 10% sodium hydroxide (4 mL) at 0 °C and diluted with chloroform (250 mL), filtered through celite bed and the filtrate was concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 2.5:97.5 MeOH : $CHCl_3$) to yield title compound (6.10 g, 53.40%) as viscous liquid.

ESIMS (m/z): 277.4 (M+1)

Step 5: Synthesis of 1-[7-(*tert*-butyl-dimethyl-silanyloxy)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

To a stirred solution of 7-(*tert*-butyl-dimethyl-silanyloxy)-2-methyl-1,2,3,4-tetrahydro-isoquinoline (8.8 g, 31.77 mmol) in toluene (65 mL) was added *s*-BuLi (63.53 mL, 101.66 mmol) at -78 °C and stirring was continued for 2 h. Cyclohexanone (7.21 mL, 69.89 mmol) was added and stirred for 1 h at -78 °C and at room temperature for 18 h. The reaction mixture was quenched with saturated ammonium chloride solution (65 mL) and extracted with EtOAc (3x50 mL). The combined organic layer was washed with water (50 mL) and brine (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure which was purified by column chromatography (silica gel, 0.5:99.5 MeOH : $CHCl_3$) to yield the title compound (2.1 g, 17.62 %) as viscous liquid.

ESIMS (m/z): 375.6 (M+1)

Step 6: Synthesis of 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-ol

To a stirred solution of 1-[7-(*tert*-butyl-dimethyl-silanyloxy)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol (2.1 g, 5.60 mmol) in tetrahydrofuran (15 mL) was added tetrabutylammonium fluoride (3.55 g, 11.20 mmol) and stirred at room temperature for 18 h. The reaction mixture was quenched with water (5 mL) and extracted with DCM (4x25 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 3.5:97.5 MeOH : $CHCl_3$) to yield the title compound (680 mg, 46.52 %) as white solid.

ESIMS (m/z): 261.5 (M+1)

Step 7: Synthesis of 1-(2-methyl-7-phenoxy-1,2,3,4-tetrahydro isoquinolin-4-yl)-cyclohexanol

A round bottom flask was charged with 4-(1-hydroxycyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-ol (100 mg, 0.383 mmol), copper (II) acetate (69.5 mg, 0.383 mmol), phenyl boronic acid (140.1mg, 1.149 mmol) and powdered 4-A° molecular sieves. The reaction mixture was dissolved in DCM (10 mL) and triethylamine (0.25 mL, 1.195 mmol) was added. The reaction mixture was stirred at room temperature for 48 h and then filtered. Filtrate was washed with 10% sodium hydroxide (10 mL) and with water (10 mL), dried over sodium sulphate and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography (silica gel, 0.8:99.2 MeOH : $CHCl_3$) and further purified by column chromatography (basic aluminium oxide, 10:90, EtOAc : Pet ether) to yield the title compound (25 mg, 19.37 %) as viscous liquid.

ESIMS (m/z): 338.2 (M+1),

^{1}H NMR (400 MHz, $CDCl_3$) : 1.96-0.88 (m, 10H), 2.46 (s, 3H), 2.45 (dd, J = 2.9, 11.8 Hz, 1H), 2.60 (s, 1H), 3.23 (d, J = 15.4 Hz, 1H), 3.41 (d, J = 11.8 Hz, 1H), 3.95 (d, J = 15.5 Hz, 1H), 6.68 (d, J = 2.5 Hz, 1H), 6.80 (dd, J = 2.5, 8.4 Hz, 1H), 7.03-7.00 (m, 2H), 7.11-7.07 (m, 2H), 7.35-7.30 (m, 2H).

Example XII: Synthesis of Carbonic acid ethyl ester 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7- yl ester

To a stirred solution of 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-ol (100 mg, 0.38 mmol) as prepared in Example XI (step 7), in DCM (2 mL) was added triethylamine (0.16 mL, 1.14 mmol) and ethylchloroformate (0.04 mL, 0.42 mmol) and stirring was continued for 90 min at room temperature. The reaction mixture was quenched with water (10 mL) and extracted with DCM (4x10 mL). The combined organic layer was washed with water (10 ml) and brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 55:45 EtOAc : Pet ether) to yield the title compound (35 mg, 27.6 %) as viscous liquid.

ESIMS (m/z): 357.3 (M+Na), 334.2 (M+1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, J = 7.1 Hz, 3H), 2.00-1.25 (m, 10H), 2.41 (s, 3H), 2.45 (dd, J = 3.0, 11.7 Hz, 1H), 2.62 (s, 1H), 3.30 (d, J = 15.5 Hz, 1H), 3.40 (d, J = 11.7 Hz, 1H), 4.00 (d, J = 15.2 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 6.87 (d, J = 2.4 Hz, 1H), 6.96 (dd, J = 2.5, 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H).

Example XIII: Synthesis of Nicotinic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester

To a stirred solution of 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-ol (250 mg, 0.96 mmol) as prepared in Example XI (step 7), in dimethylformamide (2 mL) was added *N,N*-dicyclohexylcarbodiimide (297 mg, 1.44 mmol), 4-dimethylaminopyridine (11 mg, 0.096 mmol) and nicotinic acid (177 mg, 1.44 mmol) and stirring was continued for 16 h at room temperature. Reaction mixture was filtered and filtrate was diluted with water (10 mL) and extracted with EtOAc (3x10 mL). The combined organic layer was washed with water (2x10 mL) and brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 60:40 EtOAc : Pet ether) to yield the title compound (275 mg, 78 %) as white solid

ESIMS (m/z): 367.7 (M+1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.0-1.3 (m, 10H), 2.43 (s, 3H), 2.48 (dd, J = 2.9, 11.8 Hz, 1H), 2.66 (s, 1H), 3.33 (d, J = 15.6 Hz, 1H), 3.42 (d, J = 11.5 Hz, 1H), 4.63 (d, J = 15.7 Hz, 1H), 6.54 (br s, 1H), 6.93 (d, J = 2.4 Hz, 1H), 7.13 (dd, J = 2.5, 8.5 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 4.9, 7.3 Hz, 1H), 8.43 (td, J = 2.0, 8.0 Hz, 1H), 8.85 (dd, J = 1.7, 4.8 Hz, 1H), 9.38 (d, J = 1.5 Hz, 1H).

Example XIV: Synthesis of 1-(2-Methyl-7-phenyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Step 1: Synthesis of 2-biphenyl-4-yl-*N*-methyl-acetamide

To a stirred solution of biphenyl-4-yl-acetic acid (2.2 g, 10.36 mmol) in dry DCM (50 mL) was added NMM (4.5 mL), EDC (2 g, 11.40 mmol), HOBT (1.5 g, 11.39 mmol) and methylamine hydrochloride (700 mg, 10.36 mmol) and reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with water (40 mL) and extracted with DCM (4x40 mL). The combined organic layer was washed with water (20 ml) and brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 20:80 EtOAc : Pet ether) to yield the title compound (2.1 g, 91 %) as white solid.

ESIMS (m/z): 226.7 (M+1)

Step 2: Synthesis of (2-biphenyl-4-yl-ethyl)-methyl-amine

To a stirred solution of 2-biphenyl-4-yl-*N*-methyl-acetamide (2.1 g, 9.77 mmol) in dry tetrahydrofuran (70 mL) was added borontrifluoride diethyletherate (1.94 mL, 0.2mL/mmol) dropwise and stirred for 15 min at 80 °C followed by addition of boranedimethylsulphide complex (39.09 mL, 39.09 mmol) and reaction mixture was stirred further for 3 h at 80 °C. Reaction mixture was cooled to 0 °C and quenched with 10 % HCl (30 mL) and HCl layer was washed with ether (2x20 mL). HCl layer was neutralized with sodium bicarbonate (4.0 g) and extracted with EtOAc (5x30 mL). Combined EtOAc layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield the title compound (1.0 g, 50 %) as viscous liquid.

ESIMS (m/z): 212.3 (M+1)

Step 3: Synthesis of (2-biphenyl-4-yl-ethyl)-methyl-carbamic acid methyl ester

To a stirred solution of (2-biphenyl-4-yl-ethyl)-methyl-amine (1.56 g, 7.39 mmol) in

tetrahydrofuran (40 mL) was added triethylamine (1.54 mL, 11.08 mmol) and methyl chloroformate (2.8 mL, 36.96 mmol) and stirring was continued for 90 min at room temperature. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (3x30 mL). The combined organic layer was washed with water (30 mL) and dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 10:90 EtOAc : Pet ether) to yield the title compound (1.56 g, 78 %).

ESIMS (m/z): 270.8 (M+1)

Step 4: Synthesis of 2-methyl-7-phenyl-3,4-dihydro-*2H*-isoquinolin-1-one

To (2-biphenyl-4-yl-ethyl)-methyl-carbamic acid methyl ester (1.56g, 5.82 mmol) was added polyphosphoric acid (35 g, 6 g / mmol) and the reaction mixture was stirred for 2 h at 120 °C. Reaction mixture was quenched with ice cold water and extracted with EtOAc (3x100 mL). Organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 20:80 EtOAc : Pet ether) to yield the title compound (637 mg, 46.4 %).

ESIMS (m/z): 260.8 (M+Na), 238.4 (M+1)

Step 5: Synthesis of 2-methyl-7-phenyl-1,2,3,4-tetrahydro-isoquinoline

To a slurry of lithium aluminium hydride (306 mg, 8.04 mmol) in dry tetrahydrofuran (2 mL) was added 2-methyl-7-phenyl-3,4-dihydro-2*H*-isoquinolin-1-one (637 mg, 2.68 mmol) in dry tetrahydrofuran (3 mL) and stirring was continued for 2 h at room temperature. The reaction mixture was quenched with water (0.3 mL) and 10 % sodium hydroxide (0.3 mL) at 0 °C and diluted with $CHCl_3$, passed through celite bed and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 1:99 MeOH : $CHCl_3$) to yield the title compound (432 mg, 72 %).

ESIMS (m/z): 224.3 (M+1)

Step 6: Synthesis of 1-(2-methyl-7-phenyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

To a stirred solution of 2-methyl-7-phenyl-1,2,3,4-tetrahydro-isoquinoline (300 mg, 1.34 mmol) in dry tetrahydrofuran (8 mL) was added *s*-BuLi (3.1 mL, 4.03 mmol) at -78 °C and stirring was continued for 1 h. Cyclohexanone (0.30 mL, 2.95 mmol) was added and stirring was continued for 2 h at -78 ° C. The reaction mixture was quenched with 10 % HCl (15 mL) and poured into ether. The ether layer was extracted with 10% HCL (2x15 mL). The combined acid layer was washed with ether (2x20 mL) and then neutralized with

sodium carbonate (3.0 g) and then extracted with DCM (4x30 mL). The combined DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, 1:4 EtOAc : Pet ether) to yield the title compound (70 mg, 16.0 %).

ESIMS (m/z): 322.4 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90-0.83 (m, 1H), 1.35–1.24 (m, 2H), 1.63-1.46 (m, 5H), 1.78-1.71 (m, 1H), 1.88-2.11 (m, 1H), 2.24 (s, 3H), 2.50 (dd, *J* = 2.9, 11.7 Hz, 1H,), 2.68 (s, 1H), 3.35 (d, *J* =15.3 Hz, 1H), 3.44 (d, *J* = 11.7 Hz ,1H), 4.10 (d, *J* = 15.26 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.37-7.30 (m, 3H), 7.42 (td, *J* = 1.5 , 6.7 Hz, 2H), 7.56-7.53 (m, 2H).

Example XV: Binding assay

1. <u>Norepinephrine Binding assay</u>

The Membrane protein of 0.4ml size vial, with protein concentration of 2.8mg/ml was bought from Perkin Elmer, stored in -80°C until required.

[^{3}H]-Nisoxetine Binding assay:

Each well of 96 well microtitre plate was set up to contain the following:

20µl	Test compound (1-1000nM), assay buffer (total binding) or 10µM Desipramine (Non specific binding)
50µl	Assay buffer (50mM Tris-HCl pH 7.4 containing 120mM NaCl and 5mM KCl)
20µl	10nM [N-methyl-^{3}H]-Nisoxetine hydrochloride (60-90 Ci/mmol, from ARC)
10µl	Membrane (3µg/100µl)

The microtitre plates were incubated at 4°C for 60 mins; reaction was stopped by filtration in GF/C filter plate (presoaked in 0.5% Polyethylenimine) and then added 50µl of microscint 40. Radioactivity was measured on Scintillation counter (Perkin Elmer).

2. <u>Serotonin Binding assay</u>

The Membrane protein of 0.4 mL size vial, with protein concentration of 4.8mg/ml was bought from Perkin Elmer, stored in -80 °C until required.

[^{3}H]-Citalopram Binding assay:

Each well of 96 well microtitre plate was set up to contain the following:

20µl Test compound (1-1000 nM), assay buffer (total binding) or 100 µM Paroxetine (Non specific binding)

50µl Assay buffer (50 mM Tris-HCl pH 7.4 containing 120 mM NaCl and 5 mM KCl)

20µl 10 nM [^{3}H]-Citalopram (70-90 Ci/mmol, from American Radiolabeled Chemicals, Inc.)

10µl Membrane (5 µg/ 100µl)

The microtitre plates were incubated at 27 °C for 30 min; reaction was stopped by filtration in GF/C filter plate (presoaked in 0.5% Polyethylenimine) and then added 50 µL of microscint 40. Radioactivity was measured on Scintillation counter (Perkin Elmer).

3. <u>Dopamine Binding assay</u>

The Membrane protein of 1ml size vial, with protein concentration of 3.92 mg/ mL was bought from Perkin Elmer, stored in -80 °C until required.

[^{3}H]- WIN35,428 Binding assay:

Each well of 96 well microtitre plate was set up to contain the following:

20µl Test compound (1-1000 nM), assay buffer (total binding) or 100 µM Nomifensine (Non specific binding)

50µl Assay buffer (50 mM Tris-HCl pH 7.4 containing 120 mM NaCl and 5 mM KCl)

20µl 10 nM [^{3}H] - WIN35, 428 (60-90Ci/mmol, from ARC)

10µl Membrane (10 µg/100 µl, dilution made in incubation buffer)

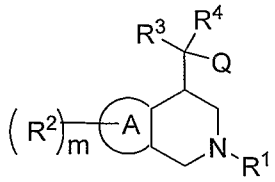
The microtitre plates were incubated at 4 °C for 120 min; reaction was stopped by filtration in GF/C filter plate (presoaked in 0.5% Polyethylenimine) and then added 50 µL of microscint 40. Radioactivity was measured on Scintillation counter (Perkin Elmer).

In-vitro Data:

	SERT	NET	DAT
	% Citalopram displacement	%Nisoxetine displacement	% WIN 35428 displacement
Compound No.	10nM	10nM	10nM
06	53.7	17.49	40.94
07	33.35	34.22	34.57
09	35.98	38.03	37.3
27	51	29.01	33.1
48	45.6	26.89	35.98
53	41.8	16.22	39.66
55	49.4	36.48	48.4
77	53	22.66	55.2
79	52	27.24	51.7
83	41.2	15.87	47.5
84	53	23.93	40.84
85	54.8	24	25.1
91	21.21	19.66	24.56
93	46.48	37.69	27.65
100	39.06	33.12	19.5
105	33.19	32.7	22.4
108	34.87	40.86	30.5
109	35.81	40.82	32.88
129	45.36	28.69	31.2
Venlafaxine	63.03	52.06	26.48

CLAIMS

1. A compound of the Formula **I**,



Formula I

its pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers including *R* and *S* isomers, polymorphs, prodrugs, metabolites, salts or solvates thereof, wherein,

ring A is either aryl or heteroaryl;

R^1 is selected from C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl;

R^2 and/or each R^2 (when R^2 is more than one) is independently selected from hydrogen, halogen, CN, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, C_{1-12} haloalkyl, C_{1-12} haloalkoxy, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_n$-cycloalkyl, $-(CH_2)_n$-heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, $-O(CH_2)_n-NR^aR^b$, $-O(CH_2)_n$-cycloalkyl, $-O(CH_2)_n$-cycloalkoxy, $-OR^a$, $-SR^a$, $-NO_2$, $-NR^aR^b$, $-N(R^a)(CO)R^b$, $-N(R^a)(CO)OR^b$, $-N(R^a)(CO)NR^aR^b$, $-(CO)R^a$, $-C(=N-OR^b)R^a$, $-(CO)NR^aR^b$, $-O(CO)R^a$, $-O(CO)OR^a$, $-O(CO)NR^aR^b$, $-COOR^a$, $-S(O)_dR^a$ or $-S(O)_dNR^aR^b$;

Q is selected from halogen, R^a, $-OR^a$, $-O(CO)R^a$, $-O(CO)OR^a$ $-COOR^a$, $-C(=N-OR^b)R^a$, $-SR^a$ or $-NR^aR^b$;

R^3 and R^4 are either same or different and independently selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkoxy, C_{1-12} haloalkoxy, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-cycloalkenyl, $(CH_2)_n$-cycloalkynyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl, each of which may be optionally substituted at any available position by one or more substituents independently selected from R^c or $R^{c'}$

or

R^3 and R^4 are joined together along with the carbon atom to which they are attached to form a 3 to 10 membered cycloalkyl, cycloalkenyl, cycloalkynyl or heterocyclic ring which

may contain from one to three heteroatoms independently selected from O, S and N, the ring formed may optionally be substituted with one or more substituents independently selected from R^c or $R^{c'}$; the ring thus formed may further be fused with 3 to 7 membered unsaturated or saturated aromatic or non-aromatic ring, which may contain from one to three heteroatoms independently selected from O, S or N, the fused ring may optionally be substituted with one or more substituents R^c or $R^{c'}$;

R^a and R^b can independently be selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, aryloxy, heteroaryloxy, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl, $(CH_2)_n$-heteroaryl or $-COOR^a$; each of which may be optionally substituted at any available position by one or more R^c or $R^{c'}$; or

R^a and R^b may be joined together along with the nitrogen atom to which they are attached to form a heterocyclic or heteroaryl ring which may additionally contain from one to three heteroatoms independently selected from O, S or N, the ring formed may optionally be substituted with one or more substituents selected from R^c or $R^{c'}$; the ring thus formed may further be fused with 3 to 7 membered unsaturated or saturated ring, which may contain from one to three heteroatoms independently selected from O, S or N, the fused ring may optionally be substituted with one or more substituents R^c or $R^{c'}$;

R^c or $R^{c'}$ can independently be selected from halogen, oxo, hydroxyl, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-8} cycloalkyl, C_{1-12} haloalkyl, C_{1-12} haloalkoxy, C_{2-12} haloalkenyl, aryl, heterocyclyl, heteroaryl, $(CH_2)_n$-aryl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-heteroaryl, $(CH_2)_n$-cycloalkyl, $-CH_2OR^5$, CN, $-OR^5$, $-NO_2$, $-NR^5R^6$, $(CH_2)_n-NR^5R^6$, $N(R^5)(CO)R^6$, $N(R^5)(CO)OR^6$, $N(R^6)(CO)NR^5R^6$, $-C(=L)R^5$ (wherein L is O or S), $-(CO)NR^5R^6$, $-(CO)(CH_2)_nNR^5R^6$, $-O(CO)R^5$, $-C(=N-OR^5)R^6$, $-O(CO)NR^5R^6$, $-COOR^5$, $-SR^5$, $S(O)_dR^5$, $S(O)_dNR^5R^6$, SO_3H or $NHSO_2R^5$;

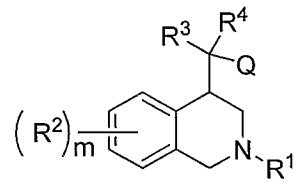
R^5 and R^6 can independently be selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl, each of which may be optionally substituted with halogen, hydroxyl or C_{1-6} alkoxy; or $R^5$and R^6 may be joined together to form a heterocyclic or heteroaryl ring which may contain from one to three heteroatoms independently selected from O, S or N, which may optionally be substituted with one or more substituents independently selected from R^c or $R^{c'}$;

n is 1,2,3,4 or 5;

m is 1,2,3 or 4;

d is 1 or 2.

2. The compound according to claim 1 having the Formula Ia, wherein



Formula Ia

R^1, R^2, R^3, R^4, Q and m are as defined in claim 1; its pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers, polymorphs, prodrugs, metabolites, salts or solvates thereof.

3. The compound according to claim 1, wherein Q is selected from $-OR^a$, $-O(CO)R^a$ or $-COOR^a$.

4. The compound according to claim 1, wherein R^1 is selected from C_{1-12} alkyl, C_{3-20} cycloalkyl, $-(CH_2)_n$-cycloalkyl or $(CH_2)_n$-aryl.

5. The compound according to claim 1, wherein R^2 and/or each R^2 (when R^2 is more than one), is is independently selected from hydrogen, halogen, CN, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, $-OR^a$, $-O(CH_2)_n-NR^aR^b$, $-O(CH_2)_n$-cycloalkyl, $-O(CH_2)_n$-cycloalkoxy, $-NR^aR^b$, $N(R^a)(CO)R^b$, $N(R^a)(CO)OR^b$, $N(R^a)(CO)NR^aR^b$, $-(CO)R^a$, $-(CO)NR^aR^b$, $-O(CO)R^a$, $-O(CO)NR^aR^b$ or $-COOR^a$.

6. The compound according to claim 1, wherein R^3 and R^4 can be either same or different and independently represent hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, heterocyclyl, aryl or heteroaryl, each of which may be optionally substituted at any available position by one or more substituents independently selected from R^c or $R^{c'}$.

7. The compound according to claim 1, wherein R^3 and R^4 may be joined together along with the carbon atom to which they are attached to form a 3 to 10 membered cycloalkyl, cycloalkenyl, cycloalkynyl or heterocyclic ring which may contain from one to three heteroatoms independently selected from O, S or N, the ring formed may optionally be substituted with one or more substituents independently selected from R^c or $R^{c'}$.

8. A compound which is selected from:

1-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

1-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentanol
1-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cycloheptanol
2-(7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol
2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-adamantan-2-ol
1-(7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-cyclohexanol
1-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-cyclohexanol
2-(7-Methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol
2-(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol
2-(6-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol
2-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)propan-2-ol
3-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)pentan-3-ol
Tetrahydro-4-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)-2H-pyran-4-ol
4-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)-4-hydroxycyclohexanone
1-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)-1-phenylethanol
4-(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-hydroxycyclohexanone oxime
4-(Prop-2-en-1-yloxy)-1-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl) cyclohexanol
4-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)piperidin-4-ol
(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)(pyrrolidin-2-yl)methanol
1-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)cyclohexane-1,4-diol
1-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)-4-methoxycyclohexanol
(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)(thiophen-2-yl)methanol
(3,4-Dichlorophenyl)(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolin-4-yl)methanol
1-(2-(Cyclopropylmethyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-4-yl)cyclohexanol
3-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)pentan-3-ol
Tetrahydro-4-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)-2H-pyran-4-ol
1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)-1-phenylethanol
1-(2-(Cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

2-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)propan-2-ol

(3,4-dichlorophenyl)(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)methanol

4-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)-4-hydroxycyclohexanone

4-(Allyloxy)-1-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)cyclohexanol

1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)cyclohexane-1,4-diol

4-Hydroxy-4-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanoneoxime

1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)-2-methyl-5-(prop-1-en-2-yl)cyclohexanol

(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)(thiophen-2-yl)methanol

Cyclohexyl(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)methanol

1,2,3,4-Tetrahydro-1-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)naphthalen-1-ol

1-(7-Fluoro-1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)cyclohexanol

tert-butyl 4-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)-4-hydroxypiperidine-1-carboxylate

1-(2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

4-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)piperidin-4-ol

1,2,3,4-Tetrahydro-1-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)-6-methoxynaphthalen-1-ol

1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)-2,2-dimethylpropan-1-ol

Tetrahydro-4-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)-2H-thiopyran-4-ol

1-(6,7-Dichloro-2-ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)(phenyl)methanol

1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)-1-(thiophen-2-yl)ethanol

1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)cyclohexylacetate

1-(1,2,3,4-Tetrahydro-2-phenethylisoquinolin-4-yl)cyclohexanol

1-(2-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

4-tert-Butyl-1-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)cyclohexanol

1-Biphenyl-4-yl-1-(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)ethanol

1-(2-Ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

1-(1,2,3,4-Tetrahydro-2-isopropylisoquinolin-4-yl)cyclohexanol

1-(2-Butyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)-2-methyl-5-(prop-1-en-2-yl)cyclohexanol

Dicyclohexyl(1,2,3,4-tetrahydro-2-methylisoquinolin-4-yl)methanol

1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)cyclohex-2-enol

1-(1,2,3,4-Tetrahydro-2-methylbenzo[h]isoquinolin-4-yl)cyclohexanol

1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)cyclohexylmorpholine-4-carboxylate

1-(1,2,3,4-Tetrahydro-2-methylisoquinolin-4-yl)cyclohexylcyclopropanecarboxylate

Dicyclohexyl(1,2,3,4-tetrahydro-2-isopropylisoquinolin-4-yl)methanol

1-(1,2,3,4-Tetrahydro-2-(2-morpholinoethyl)isoquinolin-4-yl)cyclohexanol

(2-Butyl-1,2,3,4-tetrahydroisoquinolin-4-yl)dicyclohexylmethanol

1-(1,2,3,4-Tetrahydro-2,7-dimethylisoquinolin-4-yl)cyclohexanol

1-[2-(4-Methylbenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl]cyclohexanol

1-[2-(4-Methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl]cyclohexanol

1-(2-(4-Isopropoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexanol

Tetrahydro-4-(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)-2*H*-pyran-4-ol

tert-butyl 4-(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)-4-hydroxypiperidine-1-carboxylate

4-(1,2,3,4-Tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)piperidin-4-ol

4-(1,2,3,4-Tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)-4-hydroxycyclohexanone

3-(1,2,3,4-Tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)pentan-3-ol

1,2,3,4-Tetrahydro-1-(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)naphthalen-1-ol

1,2,3,4-Tetrahydro-4-(1-hydroxycyclohexyl)-2-methylisoquinolin-7-ol

1-(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)-2-methyl-5-(prop-1-en-2-yl)-cyclohexanol

4-*tert*-Butyl-1-(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)cyclohexanol

1-(1,2,3,4-Tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)-1-phenylethanol

(3,4-Dichlorophenyl)(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)methanol

Cyclohexyl(1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinolin-4-yl)methanol

1-(7-Butoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

1-(7-Ethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

1-(7-Cyclopentyloxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

1-(7-Cyclopentylmethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

1-(2-Methyl-7-phenethyloxy-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

Dicyclohexyl-(7-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-methanol

1-[2-Methyl-7-(2-morpholin-4-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

1-(7-Hexyloxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

1-(7-Butoxy-2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol

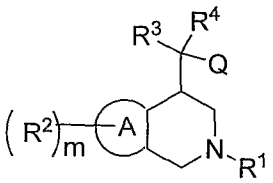
1-[2-Methyl-7-(3-methyl-butoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol
1-(7-Isopropoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol
1-[2-Methyl-7-(3-morpholin-4-yl-propoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol
1-[2-Methyl-7-(2-piperidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol
1-[2-Methyl-7-(2-thiomorpholin-4-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol
1-[2-Methyl-7-(2-pyrrolidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol
1-[7-(2-Dimethylamino-ethoxy)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol
1-{2-Methyl-7-[2-(4-methyl-piperazin-1-yl)-ethoxy]-1,2,3,4-tetrahydro-isoquinolin-4-yl}-cyclohexanol
1-[7-(2-Hydroxy-ethoxy)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol
1-[7-(2-Methoxy-ethoxy)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol
1-[2-Methyl-7-(2,2,2-trifluoro-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol
1-(7-Benzyloxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol
1-(2-Methyl-7-prop-2-ynyloxy-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol
1-(2-Methyl-7-phenoxy-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol
1-[2-Methyl-7-(thiophen-2-ylmethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol
2-[4-(1-Hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy]-1-morpholin- 4-yl-ethanone
1-[2-Methyl-7-(2-thiophen-2-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol
4-(1-Methoxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinoline
Carbonic acid ethyl ester 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester
1-{7-[2-(4,4-Difluoro-piperidin-1-yl)-ethoxy]-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl}- cyclohexanol
1-{2-[4-(1-Hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy]-ethyl}-piperidin-4-one
Carbonic acid ethyl ester 1-(7-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexyl ester

1-[7-(2-Diallylamino-ethoxy)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol

Benzoic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester
Carbonic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester phenyl ester
Carbonic acid 4-(1-ethoxycarbonyloxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7- yl ester ethyl ester
2,4-Dimethoxy-benzoic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin- 7-yl ester
Carbonic acid 4-(1-isobutoxycarbonyloxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin- 7-yl ester isobutyl ester
2-Chloro-benzoic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester
Pentanoic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester
Nicotinic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester
Carbonic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester isobutyl ester
Benzoic acid 4-(1-hydroxy-cyclohexyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl ester
1-Biphenyl-4-yl-1-(7-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-ethanol
1-(6,7,8-Trimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol
1-(7-Butyl-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol
1-[2-(2,2,2-Trifluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-4-yl]-cyclohexanol
1-(7-Diethylamino-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol
1-(2-Methyl-7-phenyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol
2-cyclopropyl-4-(1-hydroxycyclohexyl)-1,2,3,4-tetrahydroisoquinoline
4-(1-fluorocyclohexyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline
1-(2-methyl-1,2,3,4-tetrahydrobenzo[h]isoquinolin-4-yl)-1-phenylethanol
cyclohexyl(2-methyl-1,2,3,4-tetrahydrobenzo[h]isoquinolin-4-yl)methanol

9. A pharmaceutical composition, comprising a compound according to claim 1, its pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers, polymorphs, prodrugs, metabolites, salts or solvates thereof, optionally in combination with one or more pharmaceutically acceptable carrier(s), adjuvants and vehicles.

10. A method for the prophylaxis, amelioration and/or treatment of one or more condition(s)/disease(s)/ disorder(s) of the central and/or peripheral nervous system that are responsive to inhibition of one or more biogenic amine neurotransmitter(s) selected from serotonin, norepinephrine and dopamine, in a subject in need thereof, which comprises administering a therapeutically effective amount of compound of Formula I



Formula I

its pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers including *R* and *S* isomers, polymorphs, prodrugs, metabolites, salts or solvates thereof, wherein,

ring A is either aryl or heteroaryl;

R^1 is selected from C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl;

R^2 and/or each R^2 when R^2 is more than 1, is independently selected from hydrogen, halogen, CN, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, C_{1-12} haloalkyl, C_{1-12} haloalkoxy, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_n$-cycloalkyl, $-(CH_2)_n$-heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, $-O(CH_2)_n$-NR^aR^b, $-O(CH_2)_n$-cycloalkyl, $-O(CH_2)_n$-cycloalkoxy, $-OR^a$, $-SR^a$, $-NO_2$, $-NR^aR^b$, $-N(R^a)(CO)R^b$, $-N(R^a)(CO)OR^b$, $-N(R^a)(CO)NR^aR^b$, $-(CO)R^a$, $-C(=N-OR^b)R^a$, $-(CO)NR^aR^b$, $-O(CO)R^a$, $-O(CO)OR^a$, $-O(CO)NR^aR^b$, $-COOR^a$, $-S(O)_dR^a$ or $-S(O)_dNR^aR^b$;

Q is selected from halogen, R^a, $-OR^a$, $-O(CO)R^a$, $-COOR^a$, $-C(=N-OR^b)R^a$, $-SR^a$ or $-NR^aR^b$;

R^3 and R^4 are either same or different and independently selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkoxy, C_{1-12} haloalkoxy, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-cycloalkenyl, $(CH_2)_n$-

cycloalkynyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl, each of which may be optionally substituted at any available position by one or more substituents independently selected from R^c or $R^{c'}$;

or

R^3 and R^4 are joined together along with the carbon atom to which they are attached to form a 3 to 10 membered cycloalkyl, cycloalkenyl, cycloalkynyl or heterocyclic ring which may contain from one to three heteroatoms independently selected from O, S and N, the ring formed may optionally be substituted with one or more substituents independently selected from R^c or $R^{c'}$; the ring thus formed may further be fused with 3 to 7 membered unsaturated or saturated aromatic or non-aromatic ring, which may contain from one to three heteroatoms independently selected from O, S or N, the fused ring may optionally be substituted with one or more substituents R^c or $R^{c'}$;

R^a and R^b can independently be selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, aryloxy, heteroaryloxy, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl, $(CH_2)_n$-heteroaryl or -$COOR^a$; each of which may be optionally substituted at any available position by one or more R^c or $R^{c'}$; or

R^a and R^b may be joined together along with the nitrogen atom to which they are attached to form a heterocyclic or heteroaryl ring which may additionally contain from one to three heteroatoms independently selected from O, S or N, the ring formed may optionally be substituted with one or more substituents selected from R^c or $R^{c'}$; the ring thus formed may further be fused with 3 to 7 membered unsaturated or saturated ring, which may contain from one to three heteroatoms independently selected from O, S or N, the fused ring may optionally be substituted with one or more substituents R^c or $R^{c'}$;

R^c or $R^{c'}$ can independently be selected from halogen, oxo, hydroxyl, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-8} cycloalkyl, C_{1-12} haloalkyl, C_{1-12} haloalkoxy, C_{2-12} haloalkenyl, aryl, heterocyclyl, heteroaryl, $(CH_2)_n$-aryl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-heteroaryl, $(CH_2)_n$-cycloalkyl, $-CH_2OR^5$, CN, $-OR^5$, $-NO_2$, $-NR^5R^6$, $(CH_2)_n$-NR^5R^6, $N(R^5)(CO)R^6$, $N(R^5)(CO)OR^6$, $N(R^6)(CO)NR^5R^6$, $-C(=L)R^5$ (wherein L is O or S), $-(CO)NR^5R^6$, $-(CO)(CH_2)_nNR^5R^6$, $-O(CO)R^5$, $-C(=N-OR^5)R^6$, $-O(CO)NR^5R^6$, $-COOR^5$, $-SR^5$, $S(O)_dR^5$, $S(O)_dNR^5R^6$, SO_3H or $NHSO_2R^5$;

R^5 and R^6 can independently be selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl, each of which may be optionally substituted with halogen, hydroxyl or C_{1-6} alkoxy; or $R^5$and R^6 may be joined together to form a heterocyclic or heteroaryl ring which may contain from one to three heteroatoms independently selected from O, S or N, which may optionally be substituted with one or more substituents independently selected from R^c or $R^{c'}$;

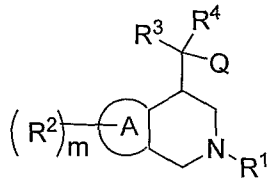
n is 1,2,3,4 or 5;

m is 1,2,3 or 4;

d is 1 or 2.

11. A method according to claim 10 , wherein the diseases, disorders and conditions are selected from depression, eating disorders, schizophrenia, inflammatory bowel disorders, pain, addiction disorders, urinary incontinence, dementia, Alzheimer's memory loss, Parkinsonism, stroke, anxiety, attention-deficit disorder, social phobia, obsessive compulsive disorder, substance abuse and withdrawal, cognitive disorders, fibromyalgia, sleep disorders, obesity, dyslipidemia, mania, bipolar disorder or hypomania, which comprises administering a therapeutically effective amount of compound according to claim 1, or its pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers, polymorphs, prodrugs, metabolites, salts or solvates thereof.

12. Use of a compound of Formula I



Formula I

its pharmaceutically acceptable derivatives, tautomeric forms, stereoisomers including *R* and *S* isomers, polymorphs, prodrugs, metabolites, salts or solvates thereof, wherein,

ring A is either aryl or heteroaryl;

R^1 is selected from C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl;

R^2 and/or each R^2 when R^2 is more than 1, is independently selected from hydrogen, halogen, CN, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, C_{1-12} haloalkyl, C_{1-12} haloalkoxy, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_n$-cycloalkyl, $-(CH_2)_n$-heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, $-O(CH_2)_n-NR^aR^b$, $-O(CH_2)_n$-cycloalkyl, $-O(CH_2)_n$-cycloalkoxy, $-OR^a$, $-SR^a$, $-NO_2$, $-NR^aR^b$, $-N(R^a)(CO)R^b$, $-N(R^a)(CO)OR^b$, $-N(R^a)(CO)NR^aR^b$, $-(CO)R^a$, $-C(=N-OR^b)R^a$, $-(CO)NR^aR^b$, $-O(CO)R^a$, $-O(CO)OR^a$, $-O(CO)NR^aR^b$, $-COOR^a$, $-S(O)_dR^a$ or $-S(O)_dNR^aR^b$;

Q is selected from halogen, R^a, $-OR^a$, $-O(CO)R^a$, $-COOR^a$, $-C(=N-OR^b)R^a$, $-SR^a$ or $-NR^aR^b$;

R^3 and R^4 are either same or different and independently selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkoxy, C_{1-12} haloalkoxy, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-cycloalkenyl, $(CH_2)_n$-cycloalkynyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl, each of which may be optionally substituted at any available position by one or more substituents independently selected from R^c or $R^{c'}$;

or

R^3 and R^4 are joined together along with the carbon atom to which they are attached to form a 3 to 10 membered cycloalkyl, cycloalkenyl, cycloalkynyl or heterocyclic ring which may contain from one to three heteroatoms independently selected from O, S and N, the ring formed may optionally be substituted with one or more substituents independently selected from R^c or $R^{c'}$; the ring thus formed may further be fused with 3 to 7 membered unsaturated or saturated aromatic or non-aromatic ring, which may contain from one to three heteroatoms independently selected from O, S or N, the fused ring may optionally be substituted with one or more substituents R^c or $R^{c'}$;

R^a and R^b can independently be selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, aryloxy, heteroaryloxy, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{2-12} haloalkynyl, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl, $(CH_2)_n$-heteroaryl or $-COOR^a$; each of which may be optionally substituted at any available position by one or more R^c or $R^{c'}$; or

R^a and R^b may be joined together along with the nitrogen atom to which they are attached to form a heterocyclic or heteroaryl ring which may additionally contain from

one to three heteroatoms independently selected from O, S or N, the ring formed may optionally be substituted with one or more substituents selected from R^c or $R^{c'}$; the ring thus formed may further be fused with 3 to 7 membered unsaturated or saturated ring, which may contain from one to three heteroatoms independently selected from O, S or N, the fused ring may optionally be substituted with one or more substituents R^c or $R^{c'}$;

R^c or $R^{c'}$ can independently be selected from halogen, oxo, hydroxyl, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} alkoxy, C_{1-12} alkylcarbonyl, C_{1-12} alkoxycarbonyl, C_{3-8} cycloalkyl, C_{1-12} haloalkyl, C_{1-12} haloalkoxy, C_{2-12} haloalkenyl, aryl, heterocyclyl, heteroaryl, $(CH_2)_n$-aryl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-heteroaryl, $(CH_2)_n$-cycloalkyl, $-CH_2OR^5$, CN, $-OR^5$, $-NO_2$, $-NR^5R^6$, $(CH_2)_n-NR^5R^6$, $N(R^5)(CO)R^6$, $N(R^5)(CO)OR^6$, $N(R^6)(CO)NR^5R^6$, $-C(=L)R^5$ (wherein L is O or S), $-(CO)NR^5R^6$, $-(CO)(CH_2)_nNR^5R^6$, $-O(CO)R^5$, $-C(=N-OR^5)R^6$, $-O(CO)NR^5R^6$, $-COOR^5$, $-SR^5$, $S(O)_dR^5$, $S(O)_dNR^5R^6$, SO_3H or $NHSO_2R^5$;

R^5 and R^6 can independently be selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{1-12} haloalkyl, C_{2-12} haloalkenyl, C_{3-20} cycloalkyl, heterocyclyl, aryl, heteroaryl, $(CH_2)_n$-cycloalkyl, $(CH_2)_n$-heterocyclyl, $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl, each of which may be optionally substituted with halogen, hydroxyl or C_{1-6} alkoxy; or $R^5$and R^6 may be joined together to form a heterocyclic or heteroaryl ring which may contain from one to three heteroatoms independently selected from O, S or N, which may optionally be substituted with one or more substituents independently selected from R^c or $R^{c'}$;

n is 1,2,3,4 or 5;

m is 1,2,3 or 4;

d is 1 or 2;

for the manufacture of a medicament for the for the prophylaxis, amelioration and/or treatment of one or more condition(s)/disease(s)/ disorder(s) of the central and/or peripheral nervous system that are responsive to inhibition of one or more biogenic amine neurotransmitter(s) selected from serotonin, norepinephrine and dopamine, in a subject in need thereof.

13. Use according to claim 12, wherein the compound is in combination with at least one other therapeutic agent selected from anti-depressants, anti-anxiolytic agents, anti-psychotic drugs, anti-obesity drugs, anti-attention deficit hyperactivity disorder agents, anti-additive disorder agents, anti-alcohol agents, anti-nicotine agents, anti-opiate agents, anti-cocaine agents, anti-Parkinson's-disease agent, anti-schizophernia agent,

anti-epilepsy agents, appetite suppressants, anti-inflammatory agents, anti-diabetic agents, anti-hypertensive agents, anti-lysergic acid diethylamide ("anti-LCD") agent or anti-phencyclidine ("anti-PCP") agent.

14. Use according to claim 12 and 13, wherein the medicament is administered via oral, buccal, pulmonary, topical, subcutaneous, intramuscular, intravenous, transdermal, ocular (ophthalmic), by inhalation, intranasal, transmucosal, implant or rectal route.

15. The compounds of Formula I, processes, methods and compositions as described and illustrated herein.