

**PIPERIDINE SUBSTITUTED COMPOUNDS AS MUSCARINIC M4 RECEPTOR  
POSITIVE ALLOSTERIC MODULATORS (M4 PAMs)**

**FIELD OF INVENTION**

5           The present invention relates to piperidine substituted compounds of formula (I), or their isotopic forms, stereoisomers, or pharmaceutically acceptable salts thereof as muscarinic M4 receptor positive allosteric modulators (M4 PAMs). The present invention also describes methods of making such compounds, pharmaceutical compositions comprising such compounds, and their use in the treatment of psychiatric and/or neurological disorders.

10       **BACKGROUND OF THE INVENTION**

          Currently, the available pharmacological treatments for psychiatric and/or neurological disorders such as schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, depression have shown modest improvement with dose-limiting side effects leading to non-compliance and a partial response.

15           Targeting muscarinic acetylcholine receptors (mAChRs) is a promising approach for treating psychiatric and/or neurological disorders, as it provides new and improved pharmacological options. mAChRs, a G protein-coupled receptors (GPCRs), are widely expressed throughout the body. Five subtypes termed M1 through M5 that respond to the endogenous neurotransmitter acetylcholine (ACh) have been identified till date. They play  
20   key role in regulating the activity of many important functions of the central and peripheral nervous system. The M1, M3, and M5 receptor subtypes usually couple to the G proteins Gq/G11, whereas the M2 and M4 receptor subtypes primarily couple to Gi/Go proteins (*Wess et al., 1996, Crit Rev Neurobiol.;10(1):69-99; Langmead et al, 2008, Pharmacol Ther.;117(2):232-243*).

25           The M4 mAChR subtype is of major therapeutic interest due to its expression in regions of the brain that are rich in dopamine and dopamine receptors, where it regulates dopaminergic neurons implicated in cognition, schizophrenia, psychosis, and addiction (*Kentaro et al., 2018, Chem. Pharm. Bull. 66(1), 37-44; Daniel et al., 2019, Drug Discov Today;24(12):2307-2314*).

30           Xanomeline, a M1/M4-preferring mAChR agonist, has shown to significantly reduce the behavioral symptoms in patients with Alzheimer's disease (*Bodick et al., 1997, Arch Neurol.;54(4):465-73*) although gastrointestinal side effects led to a high drop-out rate in clinical trials. In a separate study, Xanomeline was shown to be efficacious against positive

and negative symptoms of schizophrenia (Shekhar et al., 2008, *Am J Psychiatry*;165(8):1033-9). Xanomeline has shown antipsychotic-like activity in various preclinical behavioral models (Mirza et al., 2003, *CNS Drug Rev.*;9(2):159-86). Subsequent studies indicated that the antipsychotic-like effects of Xanomeline were absent in M4-KO mice (Woolley et al., 2009 *Eur J Pharmacol*;603(1-3):147-9). There is a high degree of conservation between muscarinic receptor subtypes at their orthosteric acetylcholine ligand binding sites which makes it difficult to identify a muscarinic subtype selective agonist. To circumvent this issue of selectivity and safety with the agonists, an alternative approach consists of developing selective muscarinic M4 receptor PAMs that act at the less conserved allosteric binding sites.

In this connection, a number of muscarinic M4 receptor PAMs have been described in the literature indicating cognitive enhancement and antipsychotic-like activity. For example, VU0467154 demonstrated antipsychotic-like activity, in rodent assays predictive of antipsychotic effects (Gould et al., 2018, *Neuropharmacology*;128:492-502). In addition, muscarinic M4 receptor PAMs have demonstrated procognitive benefits in rodent models of learning and memory (Bubser et al., 2014 *ACS Chem Neurosci.*;5(10):920-42).

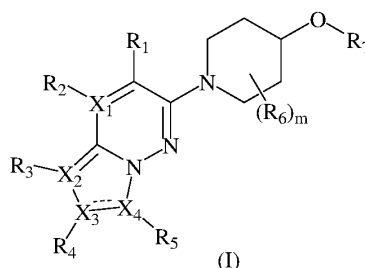
Patent publications WO2018/118736, WO2018/002760, WO2018/234953, WO2021/099527, WO2023/064584, and US20180028501 disclose compounds that are muscarinic M4 receptor PAMs. While several muscarinic M4 receptor PAMs have been disclosed in the literature till date, no muscarinic M4 receptor PAM compound is launched in the market for the treatment of M4-mediated disease or disorders such as schizophrenia, Alzheimer's disease, psychosis, Parkinson's disease, pain, addiction and Huntington's disease. Therefore, there remains an unmet need for developing novel and more effective muscarinic M4 receptor PAMs for treatment of disorders that are affected by the muscarinic M4 receptors.

Literature suggests that compounds that acts on Muscarinic M2 receptor mediates cholinergic side effects such as bradycardia and hypotension (Grauer et al., 2020 *Brain Research*; 1737:146814; Sundaram et al., 1989 *Brain research*, 477(1-2), 358–362; Mirza et al., 2003 *CNS drug reviews*, 9(2), 159–186). Additionally there exists a similarity in allosteric binding pocket for M4 as well as M2 muscarinic acetylcholine receptors which pose key challenges in development of a M4 PAM with subtype selective against M2. Our compounds exhibit minimal activity towards muscarinic M2 receptor (Wood et al., 2016 *ACS medicinal chemistry letters*, 8(2), 233–238; Butler et al., 2024 *Journal of medicinal chemistry*, 67(13), 10831–10847; Croy et al., 2014 *Molecular pharmacology*, 86(1), 106–115).

The present invention discloses novel compounds that are muscarinic M4 receptor PAMs with desirable profile. The compounds of this invention have potent affinity at muscarinic M4, selectivity over muscarinic subtype receptors like M1, M2, M3 and M5, acceptable pharmacokinetic properties, good brain penetration, receptor occupancy and efficacy in animal models.

## SUMMARY OF THE INVENTION

In first aspect, the present invention relates to a compound of formula (I),



or an isotopic form, or a stereoisomer, or a pharmaceutically acceptable salt thereof, wherein,

**---** can be each independently a single bond or a double bond;

X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, and X<sub>4</sub>, are independently selected from N or C; provided that when X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, or X<sub>4</sub> is N then R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, or R<sub>5</sub> is absent;

R<sub>1</sub> is selected from halogen, cyano, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, or -OC<sub>1</sub>-C<sub>4</sub>haloalkyl;

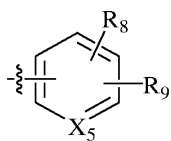
R<sub>2</sub> when present is selected from hydrogen, deuterium, halogen, cyano, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;

R<sub>3</sub> when present is selected from hydrogen, deuterium, halogen, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;

R<sub>4</sub> when present is selected from hydrogen, deuterium, halogen, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;

R<sub>5</sub> when present is selected from hydrogen, deuterium, halogen, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;

R<sub>6</sub> when present is selected from hydrogen, deuterium, halogen, cyano, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;



R<sub>7</sub> is

“” represents point of attachment;

X<sub>5</sub> is N or C;

R<sub>8</sub> and R<sub>9</sub> are independently selected from hydrogen, halogen, cyano, -OH, -NH<sub>2</sub>, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkoxyalkyl, -NHC<sub>1</sub>-C<sub>4</sub>alkyl; or alternatively R<sub>8</sub> and R<sub>9</sub> together with the carbon atoms to which they are attached, form a 5-8 membered heterocyclic ring, wherein heterocyclic ring is optionally substituted with one to five substituents independently selected from the group consisting of hydrogen, oxo, deuterium, halogen, cyano, -OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, and -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl; and m is 0, 1 or 2.

In another aspect, the present invention relates to a process for the preparation of the compound of formula (I), or an isotopic form, or a stereoisomer, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to the compound of formula (I), or an isotopic form, or a stereoisomer, or a pharmaceutically acceptable salt thereof for use as muscarinic M<sub>4</sub> receptor positive allosteric modulator.

In another aspect, the present invention relates to a method of treating muscarinic M<sub>4</sub> receptor mediated diseases or disorders comprising administering to a patient in need thereof a therapeutically effective amount of the compound of formula (I), or an isotopic form, or a stereoisomer, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a pharmaceutical composition comprising the compound of formula (I), or an isotopic form, or a stereoisomer, or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable excipients.

## DETAILED DESCRIPTION OF THE INVENTION

Disclosed herein are muscarinic M<sub>4</sub> receptor PAMs, methods of making such compounds, pharmaceutical compositions comprising such compounds, and method of treating muscarinic M<sub>4</sub> receptor mediated diseases or disorders such as psychiatric and/or neurological disorders.

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

The term, “-C<sub>1</sub>-C<sub>4</sub>alkyl” as used herein refers to branched or linear chain aliphatic hydrocarbon containing from one to four carbon atoms. Examples of -C<sub>1</sub>-C<sub>4</sub>alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl.

5       The term, “-C<sub>1</sub>-C<sub>4</sub>haloalkyl” as used herein refers to -C<sub>1</sub>-C<sub>4</sub>alkyl as defined above wherein one or more hydrogen of the same or different carbon atoms is substituted with halogen atom. Examples of the -C<sub>1</sub>-C<sub>4</sub>haloalkyl include, but are not limited to, fluoromethyl, 2-fluoroethyl, difluoromethyl and trifluoromethyl.

10       The term, “-C<sub>3</sub>-C<sub>7</sub>cycloalkyl” as used herein refers to a saturated monocyclic hydrocarbon ring containing from three to seven carbon atoms. Examples of -C<sub>3</sub>-C<sub>7</sub>cycloalkyl group include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

15       The term, “-C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl” as used herein refers to -C<sub>1</sub>-C<sub>4</sub>alkyl as defined above wherein one or more hydrogen of the same or different carbon atoms is substituted with -OC<sub>1</sub>-C<sub>4</sub>alkyl group. Examples of -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl group include, but are not limited to, methoxymethyl, ethoxymethyl, propoxymethyl and butoxymethyl.

20       The term, “-OC<sub>1</sub>-C<sub>4</sub>alkyl” as used herein refers to -C<sub>1</sub>-C<sub>4</sub>alkyl as defined above, attached to the parent molecular moiety through an oxygen atom. Examples of the -OC<sub>1</sub>-C<sub>4</sub>alkyl include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy and butyloxy.

25       The term, “-NHC<sub>1</sub>-C<sub>4</sub>alkyl” as used herein refers to -C<sub>1</sub>-C<sub>4</sub>alkyl as defined above, attached to the parent molecular moiety through a nitrogen atom. Examples of the -NHC<sub>1</sub>-C<sub>4</sub>alkyl include, but are not limited to, methylamine, ethylamine, propylamine, and butylamine.

30       The term “-OC<sub>1</sub>-C<sub>4</sub>haloalkyl” as used herein refers to -C<sub>1</sub>-C<sub>4</sub>haloalkyl as defined above that is bonded to the oxygen atom. Examples of the -OC<sub>1</sub>-C<sub>4</sub>haloalkyl include, but are not limited to, -OCH<sub>2</sub>F, -OCHF<sub>2</sub>, and -OCF<sub>3</sub>.

      The term, “halogen” as used herein refers to fluorine, chlorine, bromine or iodine. Preferably, halogen is fluorine, chlorine or bromine.

35       The phrase “5-8 membered heterocyclic ring” as used herein refers to a saturated or unsaturated ring that contains 5 to 8 carbon atoms, in which at least one carbon atom is substituted with a heteroatom independently selected from oxygen, nitrogen, or sulphur. Non-limiting examples of 5-8 membered heterocyclic ring include 1H-pyrazolyl, 1-methyl-1H-pyrazolyl, 1H-pyrrolyl, 1-methyl-1H-pyrrolyl, oxazolyl, isoxazolyl, 2-methyl oxazolyl,

thiazolyl, 1H-imidazolyl, 1,4-dioxanyl, 1,3-dioxanyl, morpholinyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, and piperziny.

The phrase, "isotopic form" as used herein refers to the compound of formula (I), wherein one or more atoms of the compound of formula (I) are substituted by their respective isotopes. Examples of isotopes that may be incorporated into the compounds disclosed herein include, but are not limited to, isotopes of hydrogen such as  $^2\text{H}$  (deuterium or D) and  $^3\text{H}$  (tritium or T), carbon such as  $^{11}\text{C}$ ,  $^{13}\text{C}$  and  $^{14}\text{C}$ , nitrogen such as  $^{13}\text{N}$  and  $^{15}\text{N}$ , oxygen such as  $^{15}\text{O}$ ,  $^{17}\text{O}$  and  $^{18}\text{O}$ , chlorine such as  $^{36}\text{Cl}$ , fluorine such as  $^{18}\text{F}$ , iodine such as  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{125}\text{I}$  and  $^{131}\text{I}$  and sulphur such as  $^{35}\text{S}$ . Substitution with heavier isotopes, for example, replacing one or more key carbon-hydrogen bonds with carbon-deuterium bond may show certain therapeutic advantages, resulting from longer metabolism cycles (e.g., increases in-vivo half life or reduced dosage requirements), improved safety or greater effectiveness and hence may be preferred in certain circumstances.

Representative examples of isotopic forms of the compounds of formula (I) can include, without limitation, deuterated compounds of formula (I). The term "deuterated" as used herein, by itself or used to modify a compound or group, refers to replacement of one or more hydrogen atom(s), which is attached to carbon(s), with a deuterium atom. For example, the compounds of formula (I) can include in the definitions of one or more of its various variables, wherever applicable, deuterium, deuterated-alkyl, deuterated-alkoxy, deuterated-cycloalkyl, deuterated-heterocyclyl, deuterated-aryl, deuterated-heteroaryl and the like. The term "deuterated-alkyl" refers to an  $-\text{C}_{1-4}\text{alkyl}$  group as defined above, wherein at least one hydrogen atom bound to carbon is replaced by a deuterium. That is, in a deuterated alkyl group, at least one carbon atom is bound to a deuterium. In a deuterated alkyl group, it is possible for a carbon atom to be bound to more than one deuterium; it is also possible that more than one carbon atom in the alkyl group is bound to a deuterium. Analogously, the term "deuterated" and the terms deuterated-heterocyclyl, deuterated-heteroaryl, deuterated-cycloalkyl, deuterated-aryl, deuterated-alkoxy each refer to the corresponding chemical moiety wherein at least one carbon is bound to a deuterium.

The term, "stereoisomer" as used herein refers to isomers of the compound of formula (I) that differ in the arrangement of their atoms in space. Compounds disclosed herein may exist as a single stereoisomer, racemates and/or mixtures of enantiomers and/or diastereomers. All such pure stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention.

The phrase, "pharmaceutically acceptable salt" as used herein refers to a salt of the active compound i.e. the compound of formula (I), and is prepared by reaction with the appropriate acid or base, depending on the particular substituents found on the compounds described herein.

5           The phrase, "therapeutically effective amount" as used herein refers to an amount of a compound of the present invention that (i) treats the particular disease, condition or disorder, (ii) eliminates one or more symptoms of the particular disease, condition or disorder, and/or (iii) delays the onset of one or more symptoms of the particular disease, condition or disorder described herein.

10           The phrase "M4 receptor positive allosteric modulators (PAMs)" as used herein refers to a ligand which interacts with an allosteric site of a receptor to augment the response produced by the endogenous ligand at the orthosteric binding site. The compounds of the invention are allosteric modulators of the M4 muscarinic acetylcholine receptor, including as positive allosteric modulators of the M4 muscarinic acetylcholine receptor and silent  
15 allosteric modulators of the M4 muscarinic acetylcholine receptor.

The phrase, "psychiatric disorders" as used herein refers to diseases or disorders such as anxiety, personality disorders, depression, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, substance use disorders and other psychotic disorders.

20           The phrase, "neurological diseases or disorders" as used herein refers to diseases or disorders such as Alzheimer's disease, Rett syndrome, Huntington's disease, vascular dementia, Parkinson's disease, and amyotrophic lateral sclerosis (ALS).

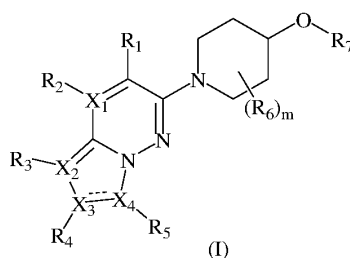
The phrase, "cognitive disorders" as used herein refers to diseases or disorders such as amnesia, dementia, amnesic disorder, dementia due to Alzheimer's diseases, dementia due to  
25 human immunodeficiency virus (HIV) disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, Lewy body dementia, vascular dementia, frontotemporal dementia (FTD), senile dementia, dementia associated with Down syndrome, dementia associated with Tourette's syndrome, dementia associated with post-menopause, dementia in Creutzfeldt-Jakob disease, substance-induced persisting dementia, dementia in Pick's disease,  
30 dementia in Huntington's disease, traumatic brain injury, prion disease, and HIV-associated neurocognitive disorders, and mild cognitive impairment.

The term, "patient" as used herein refers to an animal. Preferably the term "patient" refers to a mammal. The term mammal includes mice, rats, dogs, rabbits, pigs, monkeys, horses, guinea pigs and humans. More preferably the patient is human.

## Embodiments

The present invention encompasses all the compounds described by the compound of formula (I) without any limitation, however, preferred aspects and elements of the invention are discussed herein below in the following embodiments.

- 5 In one embodiment, the present invention relates to the compound of formula (I),



or an isotopic form, or a stereoisomer, or a pharmaceutically acceptable salt thereof,

wherein,

**---** can be each independently a single bond or a double bond;

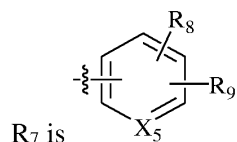
- 10  $X_1, X_2, X_3$ , and  $X_4$  are independently selected from N or C; provided that when  $X_1, X_2, X_3$ , or  $X_4$  is N then  $R_2, R_3, R_4$ , or  $R_5$  is absent;

$R_1$  is selected from halogen, cyano,  $-C_1-C_4$ alkyl,  $-C_1-C_4$ haloalkyl,  $-C_3-C_7$ cycloalkyl,  $-C_1-C_4$ alkoxyalkyl,  $-OC_1-C_4$ alkyl, or  $-OC_1-C_4$ haloalkyl;

- $R_2$  when present is selected from hydrogen, deuterium, halogen, cyano,  $-OH$ ,  $-CH_2OH$ ,  $-C_1-C_4$ alkyl,  $-C_1-C_4$ haloalkyl,  $-C_3-C_7$ cycloalkyl,  $-OC_1-C_4$ alkyl,  $-OC_1-C_4$ haloalkyl, or  $-C_1-C_4$ alkoxyalkyl;
- 15  $R_3$  when present is selected from hydrogen, deuterium, halogen,  $-OH$ ,  $-CH_2OH$ ,  $-C_1-C_4$ alkyl,  $-C_1-C_4$ haloalkyl,  $-C_3-C_7$ cycloalkyl,  $-OC_1-C_4$ alkyl,  $-OC_1-C_4$ haloalkyl, or  $-C_1-C_4$ alkoxyalkyl;

- $R_4$  when present is selected from hydrogen, deuterium, halogen,  $-OH$ ,  $-CH_2OH$ ,  $-C_1-C_4$ alkyl,  $-C_1-C_4$ haloalkyl,  $-C_3-C_7$ cycloalkyl,  $-OC_1-C_4$ alkyl,  $-OC_1-C_4$ haloalkyl, or  $-C_1-C_4$ alkoxyalkyl;
- 20  $R_5$  when present is selected from hydrogen, deuterium, halogen,  $-OH$ ,  $-CH_2OH$ ,  $-C_1-C_4$ alkyl,  $-C_1-C_4$ haloalkyl,  $-C_3-C_7$ cycloalkyl,  $-OC_1-C_4$ alkyl,  $-OC_1-C_4$ haloalkyl, or  $-C_1-C_4$ alkoxyalkyl;

- $R_6$  when present is selected from hydrogen, deuterium, halogen, cyano,  $-OH$ ,  $-CH_2OH$ ,  $-C_1-C_4$ alkyl,  $-C_1-C_4$ haloalkyl,  $-C_3-C_7$ cycloalkyl,  $-OC_1-C_4$ alkyl,  $-OC_1-C_4$ haloalkyl, or  $-C_1-C_4$ alkoxyalkyl;
- 25  $R_7$  is



“” represents point of attachment;

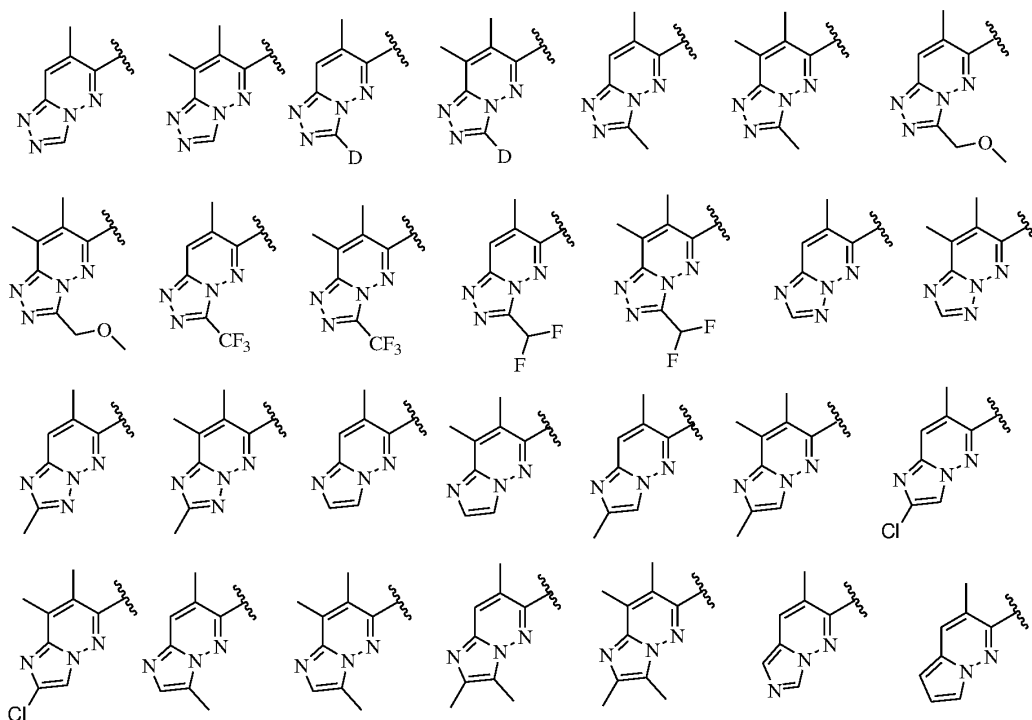
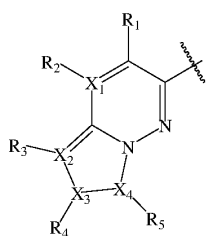
$X_5$  is N or C;

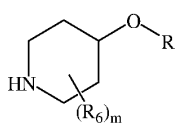
R<sub>8</sub> and R<sub>9</sub> are independently hydrogen, halogen, cyano, -OH, -NH<sub>2</sub>, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkoxyalkyl, -

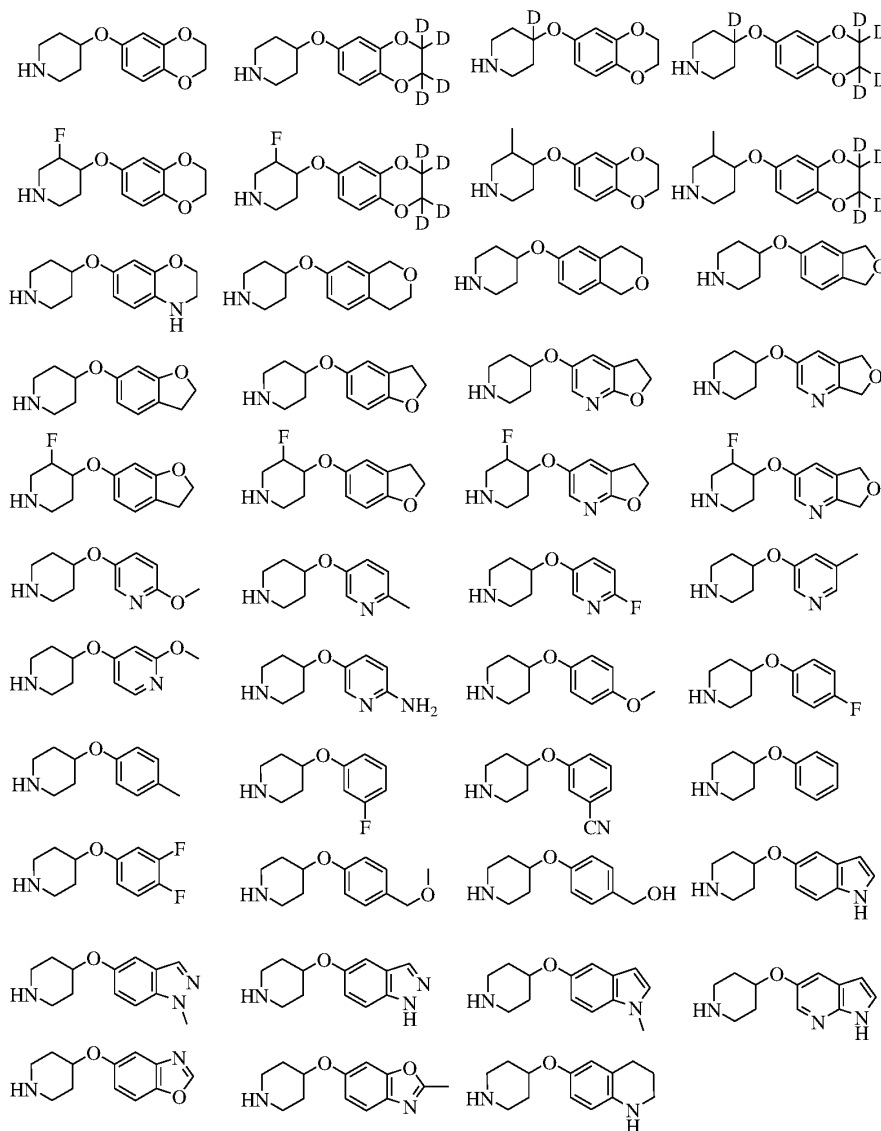
5 NHC<sub>1</sub>-C<sub>4</sub>alkyl; or alternatively R<sub>8</sub> and R<sub>9</sub> together with the carbon atoms to which they are attached, form a 5-8 membered heterocyclic ring, wherein heterocyclic ring is optionally substituted with one to five substituents independently selected from the group consisting of hydrogen, oxo, deuterium, halogen, cyano, -OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, and -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl; and

10  $m$  is 0, 1 or 2.

In another embodiment, the ring

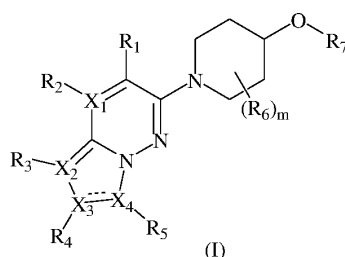


In another embodiment, the ring  is selected from,



In another embodiment, the present invention relates to method of treating or preventing diseases or disorders mediated by muscarinic M4 receptors, comprising

5 administering to a patient in need thereof a compound of formula (I),



or an isotopic form, or a stereoisomer, or a pharmaceutically acceptable salt thereof,  
wherein,

--- can be each independently a single bond or a double bond;

- 5 X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, and X<sub>4</sub> are independently selected from N or C; provided that when X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, or X<sub>4</sub> is N then R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, or R<sub>5</sub> is absent;

R<sub>1</sub> is selected from halogen, cyano, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, or -OC<sub>1</sub>-C<sub>4</sub>haloalkyl;

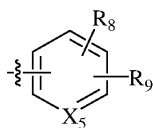
- 10 R<sub>2</sub> when present is selected from hydrogen, deuterium, halogen, cyano, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;

R<sub>3</sub> when present is selected from hydrogen, deuterium, halogen, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;

- 15 R<sub>4</sub> when present is selected from hydrogen, deuterium, halogen, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;

R<sub>5</sub> when present is selected from hydrogen, deuterium, halogen, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;

- 20 R<sub>6</sub> when present is selected from hydrogen, deuterium, halogen, cyano, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;



R<sub>7</sub> is

“~” represents point of attachment;

X<sub>5</sub> is N or C;

- 25 R<sub>8</sub> and R<sub>9</sub> are independently hydrogen, halogen, cyano, -OH, -NH<sub>2</sub>, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkoxyalkyl -NHC<sub>1</sub>-C<sub>4</sub>alkyl; or alternatively R<sub>8</sub> and R<sub>9</sub> together with the carbon atoms to which they are attached, form a 5-8 membered heterocyclic ring, wherein heterocyclic ring is optionally substituted

with one to five substituents independently selected from the group consisting of hydrogen, oxo, deuterium, halogen, cyano, -OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, and -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl; and

m is 0, 1 or 2.

- 5 In another embodiment, the present invention relates to the compound of formula (I) or an isotopic form, a stereoisomer, or a pharmaceutically acceptable salt thereof is selected from:

6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;

- 10 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine;

6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;

- 15 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;

- 20 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;

3-[1-(7,8-Dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile;

6-[4-(2,5-Difluoro-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;

- 25 6-[4-(6-Fluoro-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;

- 30 6-[4-(6-Fluoro-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;

7-Methyl-6-[4-(6-methyl-pyridin-3-yloxy)-piperidin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;

3-[1-(7-Methyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile;

- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 5 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-
- 10 [1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 15 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 3-[1-(3,7,8-Trimethyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile;
- 6-[4-(2-Methoxy-pyridin-4-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 20 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[3-Fluoro-4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 25 b]pyridazine;
- 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 30 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine;

- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 5 3-[1-(3,7-Dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile;  
6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-3,7-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 10 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;  
6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 6-[4-(2-Methoxy-pyridin-4-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 15 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 20 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 25 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 30 3-Difluoromethyl-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 3-Difluoromethyl-6-[4-(1,3-dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;

- 3-Difluoromethyl-6-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 3-Difluoromethyl-6-[4-(2,3-dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 5 3-Difluoromethyl-6-[4-(2,3-dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 3-Difluoromethyl-6-[4-(4-methoxy-phenoxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 10 3-[1-(3-Methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-  
yloxy]-benzonitrile;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-3-methoxymethyl-7,8-  
dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 15 3-Methoxymethyl-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 20 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 25 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-3-methoxymethyl-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 3-Methoxymethyl-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-3-methoxymethyl-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 30 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-3-methoxymethyl-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-3-methoxymethyl-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;

- 3-Difluoromethyl-6-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 3-Difluoromethyl-6-[4-(2,3-dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 5 3-Difluoromethyl-6-[4-(1,3-dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 3-Difluoromethyl-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 3-Difluoromethyl-6-[4-(4-methoxy-phenoxy)-piperidin-1-yl]-7,8-dimethyl-  
10 [1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-  
[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-  
15 b]pyridazine;
- 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 20 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-  
25 b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 30 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-  
[1,2,4]triazolo[1,5-b]pyridazine;

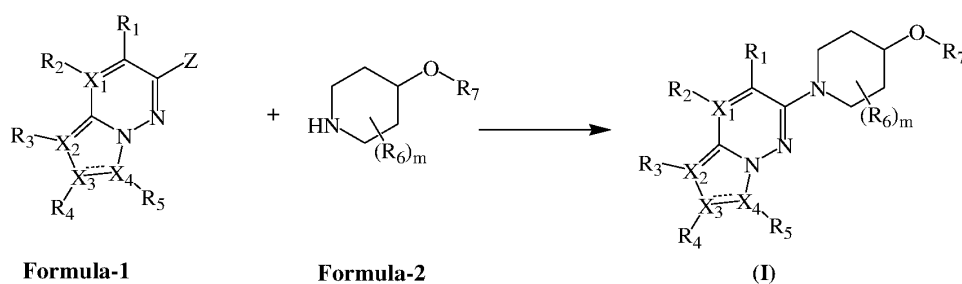
- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 5 6-[4-(2-Methoxy-pyridin-4-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 10 3-[1-(2,7,8-Trimethyl-[1,2,4]triazolo[1,5-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile;
- 6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 15 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 20 6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 25 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,7-dimethyl-imidazo[1,2-b]pyridazine;
- 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-imidazo[1,2-b]pyridazine;
- 30 6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-2,7,8-trimethyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2-fluoromethyl-7,8-dimethyl-imidazo[1,2-b]pyridazine;

- 2-Fluoromethyl-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine;
- 2-Fluoromethyl-6-[4-(2-methoxy-pyridin-4-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine;
- 5 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2-fluoromethyl-7-methyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,3,7-trimethyl-imidazo[1,2-b]pyridazine;
- 2-Chloro-6-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-
- 10 imidazo[1,2-b]pyridazine;
- 2-Chloro-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine;
- 15 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine;
- 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine;
- 20 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine;
- 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine; or
- 25 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine.

### Experimental procedure

- The below scheme depicts a general process for the preparation of the compound of formula
- 30 (I), wherein X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, and m are as defined herein above. Further, Z is selected from halogen, mesylate, triflate, tosylate and others.

### Scheme:



#### Method-I: Preparation of the compound of formula (I)

A compound of formula-1, compound of formula-2, cesium fluoride and triethylamine are added in a solvent selected from DMF or DMSO and heated to 100 - 120 °C for 8 to 24 h.

- 5 The obtained reaction mixture was extracted with suitable organic solvent, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to get a residual mass that was purified by column chromatography to obtain the compound of formula (I).

#### Method-II: Preparation of the compound of formula (I)

A compound of formula-1 is reacted with a compound of formula-2 in a suitable solvent selected from toluene or 1,4-dioxane under palladium catalysed cross coupling reactions using suitable palladium metal catalyst like Pd<sub>2</sub>(dba)<sub>3</sub>, a phosphine ligand like xantphos or BINAP and a base like NaO<sup>t</sup>Bu, KO<sup>t</sup>Bu or Cs<sub>2</sub>CO<sub>3</sub> at reflux temperature for 10 to 24 h. The obtained reaction mixture was extracted with suitable organic solvent, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to get a residual mass that was purified

- 15 by column chromatography to obtain the compound of formula (I).

#### Preparation of pharmaceutically acceptable salts of the compound of formula (I)

The compound of formula (I) can optionally be converted into its pharmaceutically acceptable salt by reaction with the appropriate acid or base. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art. The salts are formed with inorganic acids e.g., hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid, or organic acids e.g., oxalic, succinic, maleic, acetic, citric, malic, tartaric, benzoic, p-toluic, p-toluenesulfonic, benzenesulfonic, methanesulfonic or naphthalene sulfonic acid.

#### Preparation of stereoisomer's of the compound of formula (I)

The stereoisomer's of the compounds of formula (I) may be prepared by one or more conventional ways presented below:

- a. One or more of the reagents may be used in their optically active form.

- b. Optically pure catalyst or chiral ligands along with metal catalyst may be employed in the reduction process. The metal catalyst may be rhodium, ruthenium, indium and the like. The chiral ligands may preferably be chiral phosphines.
- 5 c. The mixture of stereoisomers may be resolved by conventional methods such as forming diastereomeric salts with chiral acids, chiral amines, chiral amino alcohols or chiral amino acids. The resulting mixture of diastereomers may then be separated by methods such as fractional crystallization, chromatography and the like, which is followed by an additional step of isolating the optically active product from the resolved material salt.
- 10 d. The mixture of stereoisomers may be resolved by conventional methods such as microbial resolution, resolving the diastereomeric salts formed with chiral acids or chiral bases. Chiral acids that can be employed may be tartaric acid, mandelic acid, lactic acid, camphorsulfonic acid, amino acids and the like. Chiral bases that can be employed may be cinchona alkaloids, brucine or a basic amino acid such as lysine,
- 15 arginine and the like.

In another embodiment, the suitable pharmaceutically acceptable salt includes acetate, hydrochloride, hydrobromide, oxalate, fumarate, tartrate, maleate, benzoate, mesylate and succinate.

20 In another embodiment of the present invention, the compound of formula (I) or an isotopic form, a stereoisomer or a pharmaceutically acceptable salt thereof, for use as muscarinic M4 receptor positive allosteric modulators (PAMs).

In another embodiment of the present invention, the compound of formula (I) or an isotopic form, a stereoisomer or a pharmaceutically acceptable salt thereof, for use in the manufacture of medicament for treating or preventing diseases or disorders mediated by

25 muscarinic M4 receptors.

In another embodiment, the present invention relates to a method of treating or preventing diseases or disorders mediated by muscarinic M4 receptors in a patient, comprising administering to the patient in need thereof a therapeutically effective amount of the compound of formula (I) or an isotopic form, a stereoisomer or a pharmaceutically

30 acceptable salt thereof.

In another embodiment, the present invention relates to a method of treating or preventing diseases or disorders mediated by muscarinic M4 receptors are selected from

psychiatric disorders, neurological disorders, pain disorders, sleep disorders, or cognitive disorders.

In another embodiment, the present invention relates to a compound of formula (I), or an isotopic form, or a stereoisomer or a pharmaceutically acceptable salt thereof, for use in the treatment of diseases or disorders selected from psychiatric disorders, neurological disorders, pain disorders, sleep disorders, or cognitive disorders.

In another embodiment, the present invention relates to a use of the compound of formula (I), or an isotopic form, or a stereoisomer or a pharmaceutically acceptable salt thereof, for the treatment of diseases or disorders selected from psychiatric disorders, neurological disorders, pain disorders, sleep disorders, or cognitive disorders.

In another embodiment, the present invention relates to a use of the compound of formula (I), or an isotopic form, or a stereoisomer or a pharmaceutically acceptable salt thereof, in the manufacture of medicament for treatment of diseases or disorders selected from psychiatric disorders, neurological disorders, pain disorders, sleep disorders, or cognitive disorders.

In some embodiments, the psychiatric disorders are selected from the group consisting of anxiety, personality disorders, depression, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, substance use disorders and other psychotic disorders.

In some embodiments, other psychotic disorders include psychosis associated with Alzheimer's disease, psychosis associated with Parkinson's disease, psychotic depression, psychosis associated with stroke, psychosis associated with epilepsy, psychosis associated with multiple sclerosis, psychosis associated with traumatic brain injury, substance-induced persisting delirium, or any other diseases with psychotic features.

In some embodiments, the neurological diseases or disorders are selected from the group consisting of Alzheimer's disease, Rett syndrome, Huntington's disease, vascular dementia, Parkinson's disease, and amyotrophic lateral sclerosis (ALS).

In some embodiments, the cognitive disorders are selected from the group consisting of amnesia, dementia, amnesic disorder, dementia due to Alzheimer's diseases, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, Lewy body dementia, vascular dementia, frontotemporal dementia (FTD), senile dementia, dementia associated with Down syndrome, dementia associated with Tourette's syndrome, dementia associated with post-menopause, dementia in Creutzfeldt-Jakob disease, substance-induced persisting dementia, dementia in Pick's disease, dementia in Huntington's disease,

traumatic brain injury, prion disease, HIV-associated neurocognitive disorders, mild cognitive impairment or any other diseases with cognitive symptoms.

In some embodiments, the present invention relates to a method of treating or preventing diseases or disorders mediated by muscarinic M4 receptors are selected from schizophrenia.

In some embodiments, the treatment of schizophrenia includes treatment of cognitive impairment in schizophrenia, positive symptoms of schizophrenia and/or negative symptoms of schizophrenia.

In some embodiments, cognitive impairment in schizophrenia include but are not limited to attention and vigilance, concentration, executive functions, processing speed, verbal learning, working memory, problem solving and/or social cognition.

In some embodiments, positive symptoms of schizophrenia include but are not limited to hallucinations, delusions, conceptual disorganization, excitement, grandiosity, suspiciousness/persecution and hostility.

In some embodiments, negative symptoms of schizophrenia include but are not limited to blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking.

In another embodiment, the present invention comprises pharmaceutical compositions. Such pharmaceutical compositions comprise the compound of formula (I), or an isotopic form or a stereoisomer or a pharmaceutically acceptable salt thereof, of the invention presented with a pharmaceutically acceptable carrier. The carrier can be a solid, a liquid, or both, and may be formulated with the compound as a unit-dose composition, for example, pills, tablets, coated tablets, capsules, powder, granules, pellets, patches, implants, films, liquids, semi-solids, gels, aerosols, emulsions, elixirs and the like.

The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and compositions, for example, may be administered orally, rectally, parenterally, or topically.

The dose of the active compounds can vary depending on factors such as age and weight of patient, nature and severity of the disease to be treated and other factors. Therefore, any reference regarding therapeutically effective amounts of the compounds of general formula (I), stereoisomers and pharmaceutically acceptable salts thereof refer to the aforementioned factors.

The following abbreviations are used herein

|    |                                     |   |                                                               |
|----|-------------------------------------|---|---------------------------------------------------------------|
|    | AMP                                 | : | Adenosine monophosphate                                       |
|    | BINAP                               | : | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl                   |
|    | CDCl <sub>3</sub>                   | : | Deuterated chloroform                                         |
| 5  | Cs <sub>2</sub> CO <sub>3</sub>     | : | Cesium carbonate                                              |
|    | DCM                                 | : | Dichloromethane                                               |
|    | DIAD                                | : | Diisopropyl azodicarboxylate                                  |
|    | DMA.DMA                             | : | <i>N, N</i> -Dimethylacetamide dimethyl acetal                |
|    | DMF.DMA                             | : | <i>N, N</i> -Dimethylformamide dimethyl acetal                |
| 10 | DMAP                                | : | 4-(Dimethylamino)pyridine                                     |
|    | DMF                                 | : | <i>N, N</i> -Dimethyl formamide                               |
|    | DMSO                                | : | Dimethylsulfoxide                                             |
|    | EC <sub>50</sub>                    | : | Half maximal effective concentration                          |
|    | EtOAc                               | : | Ethyl Acetate                                                 |
| 15 | g                                   | : | Gram                                                          |
|    | h                                   | : | Hour(s)                                                       |
|    | hM4 PAM                             | : | human muscarinic M4 Positive Allosteric Modulator             |
|    | IPA                                 | : | Isopropyl alcohol                                             |
|    | KO <sup>t</sup> Bu                  | : | Potassium <i>tert</i> -butoxide                               |
| 20 | MeOH                                | : | Methanol                                                      |
|    | mL                                  | : | Millilitre                                                    |
|    | mmol                                | : | Millimole                                                     |
|    | Na <sub>2</sub> SO <sub>4</sub>     | : | Sodium sulphate                                               |
|    | NaO <sup>t</sup> Bu                 | : | Sodium <i>tert</i> -butoxide                                  |
| 25 | ppm                                 | : | Parts per million                                             |
|    | Pd(dppf)Cl <sub>2</sub>             | : | 1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) dichloride |
|    | Pd <sub>2</sub> (dba <sub>3</sub> ) | : | Tris(dibenzylideneacetone)dipalladium                         |
|    | Ph <sub>3</sub> P                   | : | Triphenylphosphine                                            |
|    | RT                                  | : | Room Temperature                                              |
| 30 | THF                                 | : | Tetrahydrofuran                                               |
|    | Xantphos                            | : | 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene               |

**EXAMPLES**

The compounds of the present invention were prepared according to the following experimental procedures, using appropriate materials and conditions. The following examples are provided by way of illustration only but not to limit the scope of the present invention.

**5 Preparation of Intermediates:****Intermediate-1: 6-Chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine**

To a stirred solution of 3,6-dichloro-4,5-dimethyl-pyridazine (2 g, 11.29 mmol) in 1-butanol (20 mL), formic hydrazide (2 g, 33.90 mmol) was added at RT and the reaction mixture was refluxed for 16 h. The volatiles were removed under reduced pressure and the resulting solid obtained was purified by silica gel column chromatography using 1 - 2 % MeOH in DCM to obtain the title compound. Yield: 1.2 g (60 %); <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm: 2.43 (s, 3H), 2.74 (s, 3H), 8.96 (s, 1H); Mass (m/z): 183.0, 185.1 (M+H)<sup>+</sup>.

**Intermediate-2: 6-Chloro-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine**

To a stirred solution of 3,6-dichloro-4-methyl-pyridazine (2.0 g, 12.26 mmol) in 1-butanol (30 mL), formic hydrazide (1.8 g, 30.67 mmol) was added at RT and the reaction mixture was refluxed for 16 h. The volatiles were removed under reduced pressure and the resulting mixture of methyl regioisomers (1:1) was purified by column chromatography. The title compound was obtained using 60 – 80 % EtOAc in n-hexane. Yield: 0.3 g (18 %); <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm: 2.50 (s, 3H), 7.95 (s, 1H), 8.99 (s, 1H); Mass (m/z): 168.6, 170.4 (M+H)<sup>+</sup>.

**Intermediate-3: 6-Chloro-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine**

Intermediate-3 was obtained by following the procedure given for intermediate-1 by using 3,6-dichloro-4,5-dimethyl-pyridazine and acetohydrazide as starting materials with some non-critical variations. <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm: 2.41 (s, 3H), 2.71 (s, 3H), 2.77 (s, 3H); Mass (m/z): 196.9, 198.8 (M+H)<sup>+</sup>.

**Intermediate-4: 6-Chloro-7,8-dimethyl-3-trifluoromethyl[1,2,4]triazolo[4,3b]pyridazine****Step-1: (6-Chloro-4,5-dimethyl-pyridazin-3-yl)-hydrazine**

Hydrazine hydrate (0.42 mL, 8.4 mmol) was added to stirred solution of 3,6-dichloro-4,5-dimethyl-pyridazine (0.1 g, 5.6 mmol) in 1,4-dioxane (10 mL) and the reaction mixture was refluxed for 7 h during which solids precipitated. These solids were filtered and dried in vacuo to obtain the title compound. Yield: 0.78 g (80 %); Mass (m/z): 172.8, 174.8 (M+H)<sup>+</sup>

**Step-2: 6-Chloro-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine**

A stirred suspension of (6-chloro-4,5-dimethyl-pyridazin-3-yl)-hydrazine (0.3 g, 1.7 mmol) in trifluoroacetic acid (0.71 mL, 8.7 mmol) were heated in a sealed tube at 120 °C for 2 h. Water (20 mL) was added to the reaction mixture and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine solution (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to get title compound. Yield: 0.19 g (44 %); <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm: 2.48 (s, 3H), 2.79 (s, 3H); Mass (m/z): 250.7, 252.7 (M+H)<sup>+</sup>.

**Intermediate-5: 6-Chloro-3-difluoromethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine**

Intermediate-5 was obtained by following the procedure given for intermediate-4 by using (6-chloro-4,5-dimethyl-pyridazin-3-yl)-hydrazine (step-1 of Intermediate-4) and difluoro-acetic acid as starting materials with some non-critical variations. <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm: 2.47 (s, 3H), 2.77 (s, 3H), 7.07 – 7.33 (m, 1H); Mass (m/z): 233.8, 235.7 (M+H)<sup>+</sup>.

**Intermediate-6: 6-Chloro-3,7-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine**

Intermediate-6 was obtained by following the procedure given for intermediate-2 by using 3,6-dichloro-4-methyl-pyridazine and acetohydrazide as starting materials with some non-critical variations. <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm: 2.47 (s, 3H), 2.79 (s, 3H), 7.87 (s, 1H); Mass (m/z): 182.9, 184.8 (M+H)<sup>+</sup>.

**Intermediate-7: 6-Chloro-7-methyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine**

**Step-1: (6-Chloro-5-methyl-pyridazin-3-yl)-hydrazine**

Hydrazine hydrate (6.6 mL, 13.5 mmol) was added to stirred solution of 3,6-dichloro-4-methyl-pyridazine (20 g, 12.3 mmol) in 1,4-dioxane (100 mL) and the reaction mixture was refluxed for 7 h during which solids precipitated. These solids were filtered and dried in vacuo to obtain the title compound. Yield: 18.0 g (91 %); Mass (m/z): 158.8, 160.8 (M+H)<sup>+</sup>.

**Step-2: 6-Chloro-7-methyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine**

A stirred suspension of (6-chloro-5-methyl-pyridazin-3-yl)-hydrazine (4.0 g, 2.5 mmol) in trifluoroacetic acid (10.3 mL, 12.6 mmol) were heated in a sealed tube at 120 °C for 4 h. Water (20 mL) was added to the reaction mixture and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine solution (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to get mixture of methyl regioisomers (1:1).

The title compound was obtained using 40 % EtOAc in n-hexane. Yield: 1.8 g (30.5 %);  $^1\text{H}$  – NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 2.56 (s, 3H), 8.04 (s, 1H); Mass (m/z): 236.8, 238.9 (M+H) $^+$

**Intermediate-8: 6-Chloro-3-difluoromethyl-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine**

Intermediate-8 was obtained by following the procedure given for intermediate-7 by using (6-chloro-5-methyl-pyridazin-3-yl)-hydrazine (step-1 of intermediate-7) and difluoroacetic acid as starting materials with some non-critical variations.  $^1\text{H}$  – NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 2.54 (s, 3H), 7.21 – 7.34 (m, 1H), 8.01 (s, 1H); Mass (m/z): 218.6, 220.7 (M+H) $^+$ .

**Intermediate-9: 6-Chloro-3-methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine**

Intermediate-9 was obtained by following the procedure given for intermediate-4 by using (6-chloro-4,5-dimethyl-pyridazin-3-yl)-hydrazine (step-1 of Intermediate-4) and 2-methoxyacetyl chloride as starting materials with some non-critical variations.  $^1\text{H}$  – NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 2.57 (s, 3H), 2.98 (s, 3H), 3.50 (s, 3H), 5.04 (s, 2H); Mass (m/z): 226.8, 228.7 (M+H) $^+$ .

**Intermediate-10: 6-Chloro-3-methoxymethyl-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine**

Intermediate-10 was obtained by following the procedure given for intermediate-7 by using (6-chloro-5-methyl-pyridazin-3-yl)-hydrazine (step-1 of intermediate-7) and 2-methoxyacetyl chloride as starting materials with some non-critical variations.  $^1\text{H}$  – NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 2.50 (s, 3H), 3.48 (s, 3H), 4.99 (s, 2H), 7.94 (s, 1H); Mass (m/z): 213.1, 216.0 (M+H) $^+$ .

**Intermediate-11: 6-Chloro-7,8-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine**

To a stirred solution of 6-chloro-4,5-dimethyl-pyridazin-3-ylamine (0.5 g, 31.84 mmol) in 2-propanol (15 mL), DMF-DMA (0.46 g, 4.14 mmol) was added and the mixture was heated at 90 °C for 3 h. Then the reaction mixture was cooled to 55 - 60 °C, and then hydroxylamine hydrochloride (0.27 g, 4.14 mmol) was added and stirred further for 2 h at 55 - 60 °C. The volatiles were removed under reduced pressure, and polyphosphoric acid (5 g) was added at RT. The reaction mixture was further heated at 110 °C for 3 h. Then the reaction mixture was cooled to RT and aqueous ammonia was added slowly to the reaction mixture during which solids were precipitated. These solids were filtered and dried under reduced pressure to obtain the title compound. Yield: 0.5 g (32 %);  $^1\text{H}$  – NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 2.49 (s, 3H), 2.71 (s, 3H), 8.38 (s, 1H); Mass (m/z): 182.9, 184.7 (M+H) $^+$ .

**Intermediate-12: 6-Chloro-7-methyl-[1,2,4]triazolo[1,5-b]pyridazine**

Intermediate-12 was obtained by following the procedure given for intermediate-11 by using 6-chloro-5-methyl-pyridazin-3-ylamine and DMF-DMA as starting materials with some non-critical variations.  $^1\text{H}$  – NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 2.47 (s, 3H), 7.52 (s, 1H), 7.87 (s, 1H); Mass (m/z): 168.9, 170.8 (M+H) $^+$ .

5 **Intermediate-13: 6-Chloro-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine**

Intermediate-13 was obtained by following the procedure given for intermediate-11 by using 6-chloro-4,5-dimethyl-pyridazin-3-ylamine and DMA-DMA as starting materials with some non-critical variations.  $^1\text{H}$  – NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 2.46 (s, 3H), 2.62 (s, 3H), 2.66 (s, 3H); Mass (m/z): 196.9, 198.8 (M+H) $^+$ .

10 **Intermediate-14: 6-Chloro-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine**

Intermediate-14 was obtained by following the procedure given for intermediate-11 by using 6-chloro-5-methyl-pyridazin-3-ylamine and DMA-DMA as starting materials with some non-critical variations.  $^1\text{H}$  – NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 2.52 (s, 3H), 2.63 (s, 3H), 7.82 (s, 1H); Mass (m/z): 182.9, 184.8 (M+H) $^+$ .

15 **Intermediate-15: 6-Chloro-2,7-dimethyl-imidazo[1,2-b]pyridazine**

To a stirred solution of 6-chloro-5-methyl-pyridazin-3-ylamine (0.42 g, 2.60 mmol) in 1-butanol (10 mL), chloroacetone (2 g, 10.65 mmol) was added at RT and the reaction mixture was refluxed for 8 h. The volatiles were removed under reduced pressure, and the resulting solid obtained was purified by silica gel column chromatography using 1 - 2 %  
20 MeOH in DCM to obtain the title compound. Yield: 0.15 g (38 %);  $^1\text{H}$  – NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 2.43 (s, 3H), 2.47 (s, 3H), 7.64 (m, 2H); Mass (m/z): 181.7, 182.8 (M+H) $^+$ .

**Intermediate-16: 6-Chloro-2,7,8-trimethyl-imidazo[1,2-b]pyridazine**

Intermediate-16 was obtained by following the procedure given for intermediate-15 by using 6-chloro-4,5-dimethyl-pyridazin-3-ylamine and chloroacetone as starting materials  
25 with some non-critical variations.  $^1\text{H}$  – NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 2.38 (s, 3H), 2.47 (s, 3H), 2.63 (s, 3H), 7.59 (s, 1H); Mass (m/z): 196.0, 197.8 (M+H) $^+$ .

**Intermediate-17: 6-Chloro-2-fluoromethyl-7,8-dimethyl-imidazo[1,2-b]pyridazine**

To a stirred solution of 6-chloro-4,5-dimethyl-pyridazin-3-ylamine (0.5 g, 3.1 mmol) in ethanol (20 mL), 1,3-difluoroacetone (0.5 mL, 6.3 mmol) was added at RT and the reaction  
30 mixture was refluxed for 16 h. The volatiles were removed under reduced pressure, and the resulting solid obtained was purified by silica gel column chromatography using 30 – 40 % EtOAc in n-hexane to obtain the title compound. Yield: 0.25 g (36.8 %);  $^1\text{H}$  – NMR (DMSO-

$d_6$ , 400 MHz)  $\delta$  ppm: 2.36 (s, 3H), 2.59 (s, 3H), 5.43 (s, 1H), 5.55 (s, 1H), 8.36 (s, 1H); Mass (m/z): 213.8, 215.8 (M+H)<sup>+</sup>

**Intermediate-18: 6-Chloro-2-fluoromethyl-7-methyl-imidazo[1,2-b]pyridazine**

Intermediate-18 was obtained by following the procedure given for intermediate-17 by using 6-chloro-5-methyl-pyridazin-3-ylamine and 1,3-difluoroacetone as starting materials with some non-critical variations <sup>1</sup>H – NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  ppm: 2.38 (s, 3H), 5.43 (s, 1H), 5.55 (s, 1H), 7.96 (s, 1H), 8.36 (s, 1H); Mass (m/z): 199.8, 201.7 (M+H)<sup>+</sup>

**Intermediate-19: 6-Chloro-2,3,7-trimethyl-imidazo[1,2-b]pyridazine**

To a stirred solution of 6-chloro-5-methyl-pyridazin-3-ylamine (0.3 g, 2.08 mmol) in ethanol (10 mL), 3-bromo-2-butanone (0.6 g, 2.49 mmol) was added at RT and the reaction mixture was refluxed for 16 h. The volatiles were removed under reduced pressure, and the resulting solid obtained was purified by silica gel column chromatography using 1 - 2 % MeOH in DCM to obtain the title compound. Yield: 0.2 g (75 %); <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  ppm: 2.42 (s, 3H), 2.43 (s, 3H), 2.47 (s, 3H), 7.63 (m, 1H); Mass (m/z): 196.0, 197.8 (M+H)<sup>+</sup>.

**Intermediate-20: 2,6-Dichloro-7,8-dimethyl-imidazo[1,2-b]pyridazine**

Chloro acetic acid (0.43 g, 63.0 mmol), triethylamine (0.6 mL, 4.90 mmol) were added sequentially to a stirred solution of 6-chloro-4,5-dimethyl-pyridazin-3-ylamine (0.77 g, 4.90 mmol) in ethanol : water (1:1 mL) at RT. The reaction mixture was heated at 110 °C for 10 - 12 h and then cooled to RT. Water (50 mL) was added to the reaction mixture and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine solution (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to get crude compound which was purified by silica gel column chromatography using 2 - 4 % MeOH in DCM to obtain the title compound. Yield: 0.34 g (38 %) Mass (m/z): 217.2, 219.5 (M+H)<sup>+</sup>.

**Intermediate-21: 6-Chloro-7-methyl-imidazo[1,2-b]pyridazine**

To a stirred solution of 6-chloro-5-methyl-pyridazin-3-ylamine (0.42 g, 2.60 mmol) in 1-butanol (10 mL), chloroacetaldehyde (2 g, 10.65 mmol) was added at RT and the reaction mixture was refluxed for 16 h. The volatiles were removed under reduced pressure, and the resulting solid obtained was purified by silica gel column chromatography using 1 - 2 % MeOH in DCM to obtain the title compound. Yield: 0.4 (88 %); <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 400

MHz)  $\delta$  ppm: 2.45 (s, 3H), 7.71 (s, 1H), 7.77 (s, 1H), 7.87. (s, 1H); Mass (m/z): 167.6, 170.0 (M+H)<sup>+</sup>.

**Intermediate-22: 6-Chloro-7,8-dimethyl-imidazo[1,2-b]pyridazine**

Intermediate-22 was obtained by following the procedure given for intermediate-21  
5 by using 6-chloro-4,5-dimethyl-pyridazin-3-ylamine and chloroacetaldehyde as starting materials with some non-critical variations. <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  ppm: 2.44 (s, 3H), 2.67 (s, 3H), 8.17 (s, 1H), 8.52 (s, 1H); Mass (m/z): 181.8, 184.2 (M+H)<sup>+</sup>.

**Intermediate-23: 4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidine hydrochloride**

**Step-1: 4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester**  
10 **ester**

To a stirred solution of 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (15.86 g, 78.94 mmol) in anhydrous THF (120 mL), 2,3-dihydro-benzo[1,4]dioxin-6-ol (12 g, 78.94 mmol) and Ph<sub>3</sub>P (25 g, 94.73 mmol) were added sequentially at RT. After cooling the mixture to 0 - 5 °C, DIAD (32 g, 157.8 mmol) was added and the reaction mixture was  
15 brought to RT, and stirred further for 16 h at RT. The volatiles were removed under reduced pressure, and the resulting mass was purified by silica gel column chromatography using 10 - 12 % EtOAc in n-hexane to obtain the title compound. Yield: 12.6 g (48 %); <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  ppm: 1.42 – 1.46 (s, 9H), 1.69 – 1.72 (m, 2H), 1.85 – 1.87 (m, 2H), 3.25 – 3.31 (m, 2H), 3.66 – 3.72 (m, 2H), 4.20 – 4.23 (m, 4H), 4.24 – 4.31 (m, 1H), 6.41 – 6.46  
20 (m, 2H), 6.74 – 6.77 (d, *J* = 8.8 Hz, 1H); Mass (m/z): 336.2 (M+H)<sup>+</sup>.

**Step-2: 4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidine hydrochloride**

IPA.HCl (30 mL, 10 vol., 12 % w/v solution) was added to a stirred solution of 4-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (12.6 g, 37.61 mmol) in MeOH (10 mL) and the reaction mixture was maintained at RT for 4 h. The  
25 volatiles were removed under reduced pressure to obtain the title compound. Yield: 9.2 g (90 %); <sup>1</sup>H – NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  ppm: 1.74 – 1.77 (m, 2H), 2.01 – 2.06 (m, 2H), 3.01 – 3.02 (m, 2H), 3.17 (m, 2H), 4.16 – 4.20 (m, 4H), 4.46 – 4.49 (m, 1H), 6.45 – 6.46 (m, 1H), 6.54 – 6.55 (d, *J* = 2.8 Hz, 1H), 6.75 – 6.77 (d, *J* = 8.8 Hz, 1H), 8.87 (bs, 2H); Mass (m/z): 236.0 (M+H)<sup>+</sup>.

30 The below intermediates 24 to 35 were prepared by following the experimental procedure given in step-1 and step-2 of intermediate-23 with some non-critical variations using suitable starting material as given in the table below.

| Intermediate | IUPAC name                                                     | Starting material              | Characterization Data                                                                                                                                                                                                                                                                                                          |
|--------------|----------------------------------------------------------------|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24           | 4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidine hydrochloride | 1,3-Dihydro-isobenzofuran-5-ol | $^1\text{H}$ – NMR (DMSO- $d_6$ , 400 MHz) $\delta$ ppm: 1.82 – 1.85 (m, 2H), 2.06 – 2.11 (m, 2H), 3.04 – 3.05 (m, 2H), 3.20 (m, 2H), 4.60 – 4.63 (m, 1H), 4.92 – 4.94 (d, 4H), 6.89 – 6.91 (d, $J$ = 8.0 Hz, 1H), 6.96 (s, 1H), 7.20 – 7.22 (d, $J$ = 8.4 Hz, 1H), 9.02 (bs, 2H); Mass (m/z): 220.0 (M+H) $^+$ .              |
| 25           | 4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidine hydrochloride    | 2,3-Dihydro-benzofuran-5-ol    | $^1\text{H}$ – NMR (DMSO- $d_6$ , 400 MHz) $\delta$ ppm: 1.76 – 1.79 (m, 2H), 1.99 – 2.01 (m, 2H), 3.04 (m, 2H), 3.13 – 3.20 (t, 2H), 3.20 – 3.24 (m, 2H), 4.43 (m, 1H), 4.45 – 4.49 (t, 2H), 6.64 – 6.66 (d, $J$ = 8.8 Hz, 1H), 6.70 – 6.72 (d, $J$ = 8.8 Hz, 1H) 6.92 (s, 1H), 8.56 (bs, 2H); Mass (m/z): 220.0 (M+H) $^+$ . |
| 26           | 4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidine hydrochloride    | 2,3-Dihydro-benzofuran-6-ol    | $^1\text{H}$ – NMR (DMSO- $d_6$ , 400 MHz) $\delta$ ppm: 2.13 – 2.16 (m, 2H), 2.22 – 2.28 (m, 2H), 3.11 – 3.16 (t, 2H), 3.28 (m, 2H), 3.34 (m, 2H), 4.56 – 4.60 (m, 3H), 6.36 – 6.38 (m, 2H), 7.06 – 7.08 (d, $J$ = 8.0 Hz, 1H), 9.62 (bs, 2H); Mass (m/z): 219.8 (M+H) $^+$ .                                                 |

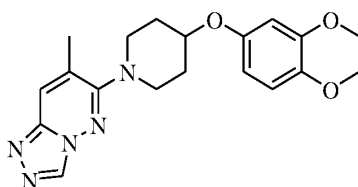
|    |                                                                   |                            |                                                                                                                                                                                                                                                                                                                                                                                                              |
|----|-------------------------------------------------------------------|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 27 | 4-(4-Methoxy-<br>phenoxy)-<br>piperidine<br>hydrochloride         | 4-Methoxy-<br>phenol       | <sup>1</sup> H – NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ<br>ppm: 1.75 – 1.78 (m, 2H), 2.01 –<br>2.07 (m, 2H), 3.11 (m, 2H), 3.19 –<br>3.20 (m, 2H), 3.69 (s, 3H), 4.47 –<br>4.50 (m, 1H), 6.85 – 6.87 (d, <i>J</i> = 8.8<br>Hz, 2H), 6.92 – 6.95 (d, <i>J</i> = 8.0 Hz,<br>2H), 8.76 (bs, 2H); Mass (m/z):<br>208.1 (M+H) <sup>+</sup> .                                                               |
| 28 | 2-Methoxy-5-<br>(piperidin-4-<br>yloxy)-pyridine<br>hydrochloride | 6-Methoxy-<br>pyridin-3-ol | <sup>1</sup> H – NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ<br>ppm: 1.79 – 1.82 (m, 2H), 2.05 –<br>2.10 (m, 2H), 3.02 – 3.03 (m, 2H),<br>3.20 – 3.31 (m, 2H), 3.79 (s, 3H),<br>4.52 – 4.56 (m, 1H), 6.78 – 6.80 (d,<br><i>J</i> = 8.8 Hz, 1H), 7.46 – 7.49 (dd, <i>J</i> =<br>8.8, 2.8 Hz, 1H), 7.92 – 7.93 (d, <i>J</i> =<br>2.8 Hz, 1H) 8.98 – 9.05 (bs, 2H);<br>Mass (m/z): 209.1 (M+H) <sup>+</sup> . |
| 29 | 2-Methyl-5-<br>(piperidin-4-<br>yloxy)-pyridine;<br>hydrochloride | 6-Methyl-pyridin-<br>3-ol  | <sup>1</sup> H – NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ<br>ppm: 1.83 – 1.90 (m, 2H), 2.12 –<br>2.18 (m, 2H), 2.66 (s, 3H), 3.03 –<br>3.06 (m, 2H), 3.22 – 3.25 (m, 2H),<br>4.89 – 4.93 (m, 1H), 7.80 – 7.82 (d,<br><i>J</i> = 8.8 Hz, 1H), 8.13 – 8.16 (m,<br>1H), 8.60 – 8.61 (d, <i>J</i> = 2.8 Hz, 1H),<br>9.27 (bs, 2H); Mass (m/z): 193.1<br>(M+H) <sup>+</sup> .                                |
| 30 | 3-(Piperidin-4-<br>yloxy)-<br>benzonitrile;<br>hydrochloride      | 3-Hydroxy-<br>benzonitrile | <sup>1</sup> H – NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ<br>ppm: 1.78 – 1.86 (m, 2H), 2.08 –<br>2.13 (m, 2H), 3.04 – 3.07 (m, 2H),<br>3.23 – 3.32 (m, 2H), 4.71 – 4.76 (m,                                                                                                                                                                                                                             |

|    |                                                        |                       |                                                                                                                                                                                                                                                                                                          |
|----|--------------------------------------------------------|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                                        |                       | 1H), 7.23 – 7.36 (m, 1H), 7.41 – 7.43 (m, 1H), 7.48 – 7.54 (m, 2H), 8.80 (bs, 2H); Mass (m/z): 203.5 (M+H) <sup>+</sup> .                                                                                                                                                                                |
| 31 | 2-Fluoro-5-(piperidin-4-yloxy)-pyridine; hydrochloride | 6-Fluoro-pyridin-3-ol | <sup>1</sup> H – NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ ppm: 1.80 – 1.89 (m, 2H), 2.08 – 2.13 (m, 2H), 3.00 – 3.07 (m, 2H), 3.21 – 3.23 (m, 2H), 4.64 – 4.70 (m, 1H), 7.13 – 7.16 (m, 1H), 7.66 – 7.71 (m, 1H), 7.97 – 7.98 (m, 1H), 8.99 – 9.02 (bs, 2H); Mass (m/z): 197.2 (M+H) <sup>+</sup> . |
| 32 | 4-(2,5-Difluorophenoxy)-piperidine; hydrochloride      | 2,5-Difluorophenol    | <sup>1</sup> H – NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ ppm: 1.81 – 1.88 (m, 2H), 2.09 – 2.13 (m, 2H), 3.02 – 3.07 (m, 2H), 3.18 – 3.33 (m, 2H), 4.66 – 4.70 (m, 1H), 6.78 – 6.84 (m, 1H), 7.24 – 7.31 (m, 2H), 8.81 (bs, 2H); Mass (m/z): 214.0 (M+H) <sup>+</sup> .                             |
| 33 | 4-(4-Fluorophenoxy)-piperidine; hydrochloride          | 4-Fluorophenol        | <sup>1</sup> H – NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ ppm: 1.77 – 1.85 (m, 2H), 2.05 – 2.10 (m, 2H), 3.03 – 3.05 (m, 2H), 3.20 (m, 2H), 4.56 – 4.59 (m, 1H), 6.94 – 7.04 (m, 1H), 7.11 – 7.15 (m, 2H), 8.87 – 8.91 (bs, 2H); Mass (m/z): 196.0 (M+H) <sup>+</sup>                               |

|    |                                                                  |                        |                                                                                                                                                                                                                                                                                                                                                 |
|----|------------------------------------------------------------------|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 34 | 4-(3-Fluoro-phenoxy)-piperidine; hydrochloride                   | 3-Fluoro-phenol        | <sup>1</sup> H – NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ ppm: 1.78 – 1.87 (m, 2H), 2.07 – 2.12 (m, 2H), 3.05 – 3.06 (m, 2H), 3.21 (m, 2H), 4.64 – 4.69 (m, 1H), 6.75 – 6.80 (m, 1H), 6.83 – 6.85 (m, 1H), 7.29 – 7.35 (m, 1H), 8.90 (bs, 2H); Mass (m/z): 196.3                                                                           |
| 35 | 5-(3-Fluoro-piperidin-4-yloxy)-2-methoxy-pyridine; hydrochloride | 6-Methoxy-pyridin-3-ol | <sup>1</sup> H – NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ ppm: 1.86 – 1.90 (m, 2H), 2.12 – 2.17 (m, 2H), 3.06 (bs, 2H), 3.83 (s, 3H), 4.66 (bs, 1H), 4.94 – 5.02 (m, 1H), 6.79 – 6.82 (d, <i>J</i> = 8.8 Hz, 1H), 7.52 – 7.55 (m, 1H), 7.98 – 7.99 (d, <i>J</i> = 2.8 Hz, 1H) 8.96 – 9.11 (bs, 2H); Mass (m/z): 227.1 (M+H) <sup>+</sup> . |

### Method-I

#### Example-1: 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine

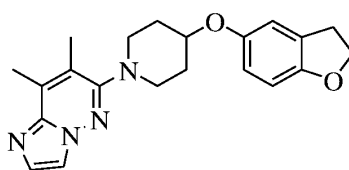


- 5 Cesium fluoride (1.4 g, 9.43 mmol), triethylamine (1.8 mL, 12.58 mmol) were added sequentially to a stirred solution of 4-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-piperidine hydrochloride (0.85 g, 3.14 mmol, intermediate-23) and 6-chloro-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine (0.53 g, 3.14 mmol, intermediate-2) in DMSO (15 mL) at RT. The reaction mixture was heated at 110 °C for 10 - 12 h and then cooled to RT. Water
- 10 (50 mL) was added to the reaction mixture and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine solution (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to get crude compound which was purified by silica gel

column chromatography using 2 - 4 % MeOH in DCM to obtain the title compound. Yield: 0.54 g (50 %);  $^1\text{H}$  - NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 1.92 – 1.99 (m, 2H), 2.08 – 2.13 (m, 2H), 2.40 (s, 3H), 3.08 – 3.13 (m, 2H), 3.43 – 3.49 (m, 2H), 4.21 – 4.25 (m, 4H), 4.37 – 4.41 (m, 1H), 6.45 – 6.48 (m, 1H), 6.50 – 6.51 (d,  $J$  = 2.4 Hz, 1H), 6.77 – 6.79 (d,  $J$  = 8.4 Hz, 1H), 7.74 (s, 1H), 8.83 (s, 1H); Mass ( $m/z$ ): 368.0 ( $\text{M}+\text{H}$ ) $^+$ .

## Method-II

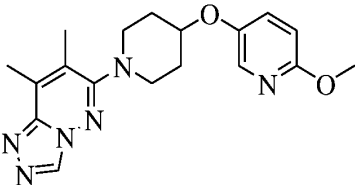
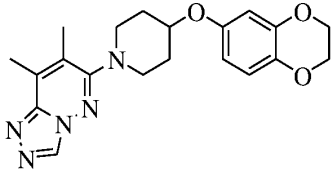
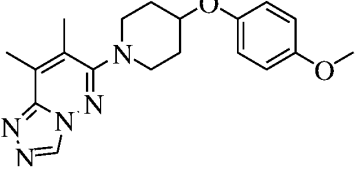
### Example-2: 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine

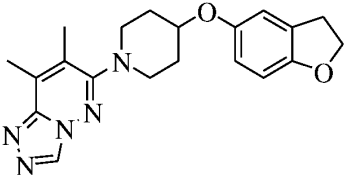
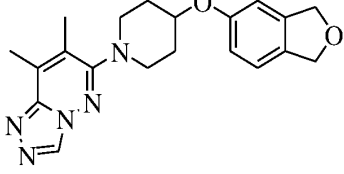


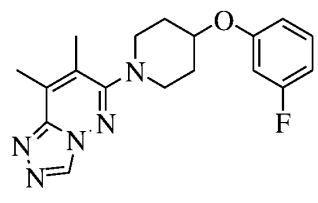
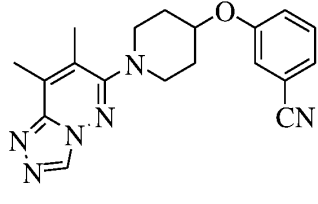
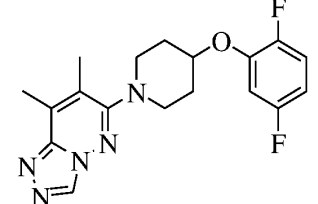
Pd<sub>2</sub>dba<sub>3</sub> (0.02g, 0.02 mmol), BINAP (0.013 g, 0.02 mmol) followed by NaOtBu (0.84 g, 0.8 mmol) were added sequentially to a stirred solution of 4-(2,3-dihydro-benzofuran-6-yloxy)-piperidine hydrochloride (0.05 g, 0.2 mmol, intermediate-25) and 6-chloro-7,8-dimethyl-imidazo[1,2-b]pyridazine (0.04 g, 0.2 mmol, intermediate-22) in toluene (20 mL) at RT. The reaction mixture was then refluxed under N<sub>2</sub> atmosphere for 16 h. The reaction mixture was cooled to RT and poured on to water (30 mL) and product was extracted using EtOAc (100 mL x 3). The organic extracts were combined, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to obtain a residual mass that was purified by column chromatography using 2 - 4 % MeOH in DCM to obtain title compound. Yield: 0.05 g (62.5 %);  $^1\text{H}$  - NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 1.92 – 1.98 (m, 2H), 2.08 – 2.13 (m, 2H), 2.28 (s, 3H), 2.28 (s, 3H), 2.95 – 3.02 (m, 2H), 3.17 – 3.21 (t,  $J$  = 8.8Hz, 2H), 3.35 – 3.41 (m, 2H), 4.31 – 4.33 (m, 1H), 4.53 – 4.57 (t,  $J$  = 8.4 Hz, 2H), 6.82 – 6.71 (m, 2H), 6.85 – 6.85 (d,  $J$  = 1.2 Hz, 1H), 7.53 – 7.54 (d,  $J$  = 1.2 Hz, 1H), 7.69 – 7.69 (d,  $J$  = 1.2 Hz, 1H); Mass ( $m/z$ ): 365.2 ( $\text{M}+\text{H}$ ) $^+$ .

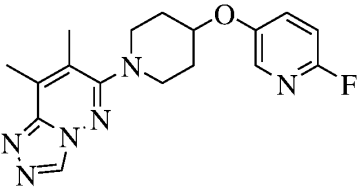
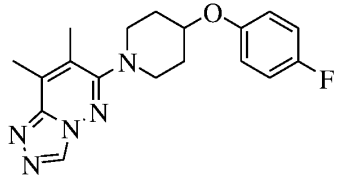
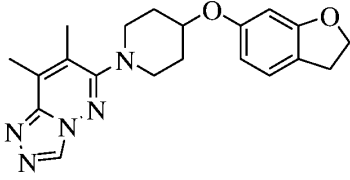
The below Examples-3 to Example-126 were prepared by following the experimental procedure of preparation as provided in the Example-1 or Example-2 using suitable intermediates (synthesised above) with some non critical variations.

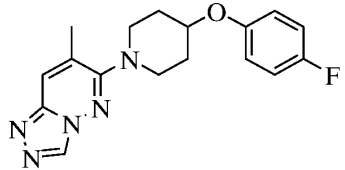
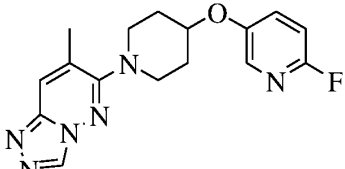
| Example | Method of | Chemical structure and IUPAC | Characterization Data |
|---------|-----------|------------------------------|-----------------------|
|---------|-----------|------------------------------|-----------------------|

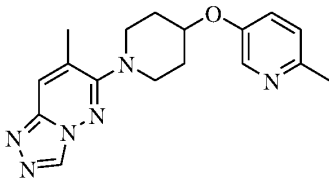
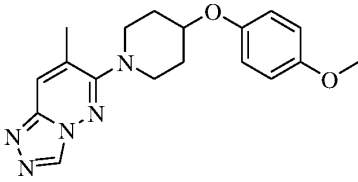
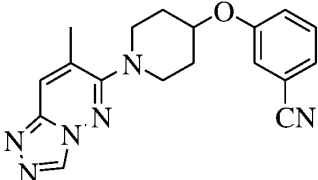
| No. | synthesis | Name                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                               |
|-----|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3   | I         |  <p>6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>              | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 2.11 – 2.13 (m, 2H), 2.15 – 2.16 (m, 2H), 2.22 (s, 3H), 2.62 (s, 3H), 3.02 – 3.07 (m, 2H), 3.40 – 3.44 (m, 2H), 3.90 (s, 3H) 4.38 – 4.40 (m, 1H), 6.70 – 6.72 (d, <i>J</i> = 8.8 Hz, 1H), 7.26 (s, 1H), 7.87 – 7.88 (d, <i>J</i> = 2.4 Hz, 1H), 8.83 (s, 1H); Mass (m/z): 355.0 (M+H) <sup>+</sup> .                |
| 4   | I         |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93 – 1.98 (m, 2H), 2.08 – 2.13 (m, 2H), 2.29 (s, 3H), 2.62 (s, 3H), 3.01 – 3.07 (m, 2H), 3.38 – 3.42 (m, 2H), 4.21 – 4.25 (m, 4H), 4.36 – 4.39 (m, 1H), 6.45 – 6.48 (m, 1H), 6.50 – 6.51 (d, <i>J</i> = 2.4 Hz, 1H), 6.77 – 6.79 (d, <i>J</i> = 8.4 Hz, 1H), 8.82 (s, 1H); Mass (m/z): 382.1 (M+H) <sup>+</sup> . |
| 5   | I         |  <p>6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>                    | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.92 – 1.97 (m, 2H), 1.98 – 2.14 (m, 2H), 2.30 (s, 3H), 2.62 (s, 3H), 3.02 – 3.07 (m, 2H), 3.39 – 3.44 (m, 2H), 3.78 (s,                                                                                                                                                                                            |

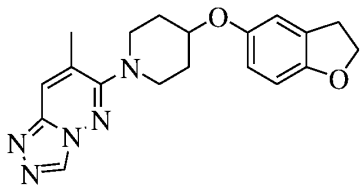
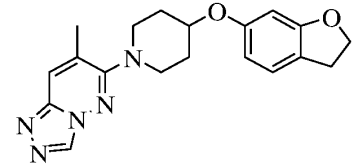
|   |   |                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                |
|---|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|   |   | [1,2,4]triazolo[4,3-b]pyridazine                                                                                                                                                                  | 3H), 4.38 – 4.41 (m, 1H), 6.83 – 6.85 (d, $J = 9.2$ Hz, 2H), 6.89 – 6.91 (d, $J = 8.8$ Hz, 2H), 8.83 (m, 1H); Mass (m/z): 354.0 (M+H) <sup>+</sup> .                                                                                                                                                                                                           |
| 6 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>      | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.92– 1.99 (m, 2H), 2.07 – 2.17(m, 2H), 2.30 (s, 3H), 2.62 (s, 3H), 3.01 – 3.07 (m, 2H), 3.11 – 3.21 (t, $J = 8.4$ Hz 2H), 3.39 – 3.45 (m, 2H), 4.32 – 4.37 (m, 1H), 4.53 – 4.59 (t, $J = 8.8$ Hz 2H), 6.68 – 6.73 (m, 2H), 6.85 (s, 1H), 8.83 (s,1H); Mass (m/z): 365.9 (M+H) <sup>+</sup> . |
| 7 | I |  <p>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.97 – 1.99 (m, 2H), 2.11 – 2.17 (m, 2H), 2.30 (s, 3H), 2.62 (s, 3H), 3.05 – 3.11 (m, 2H), 3.39 – 3.45 (m, 2H), 4.50 – 4.54 (m, 1H), 5.06 – 5.07 (m, 4H), 6.83 – 6.88 (m, 2H), 7.13 – 7.16 (d, $J = 8.4$ Hz, 1H), 8.83 (s, 1H); Mass (m/z): 366.3 (M+H) <sup>+</sup> .                        |

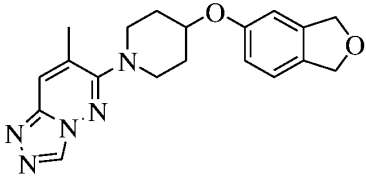
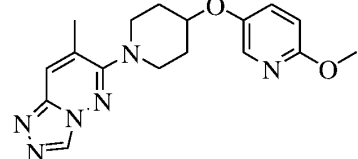
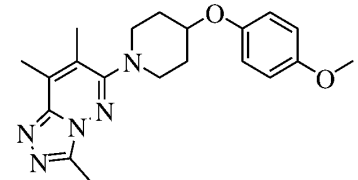
|    |   |                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                     |
|----|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 8  | I |  <p>6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>       | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.95 – 1.99 (m, 2H), 2.00 – 2.04 (m, 2H), 2.30 (s, 3H), 2.62 (s, 3H), 3.06 – 3.12 (m, 2H), 3.38 – 3.44 (m, 2H), 4.50 – 4.55 (m, 1H), 6.64 – 6.65 (m, 1H), 6.67 – 6.67 (d, J = 1.2 Hz, 1H), 6.69 – 6.74 (m, 1H), 7.21 – 7.23 (s, 1H), 8.83 (s, 1H); Mass (m/z): 342.1 (M+H) <sup>+</sup> . |
| 9  | I |  <p>3-[1-(7,8-Dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile</p>   | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 2.01 – 2.03 (m, 2H), 2.14 – 2.19 (m, 2H), 2.31 (s, 3H), 2.63 (s, 3H), 3.08 – 3.13 (m, 2H), 3.39 – 3.44 (m, 2H), 4.56 – 4.58 (m, 1H), 7.17 – 7.23 (m, 2H), 7.26 – 7.41 (m, 2H), 8.84 (s, 1H); Mass (m/z): 349.1 (M+H) <sup>+</sup> .                                                       |
| 10 | I |  <p>6-[4-(2,5-Difluoro-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.99 – 2.07 (m, 2H), 2.13 – 2.18 (m, 2H), 2.30 (s, 3H), 2.62 (s, 3H), 3.05 – 3.11 (m, 2H), 3.42 – 3.47 (m, 2H), 4.49 – 4.52 (m, 1H), 6.62 – 6.66 (m, 1H), 6.74 – 6.79 (m, 1H), 7.01 – 7.07 (m, 1H),                                                                                       |

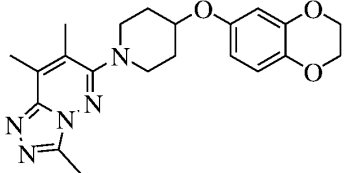
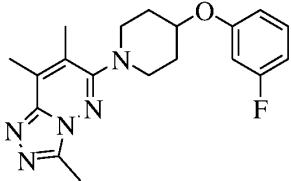
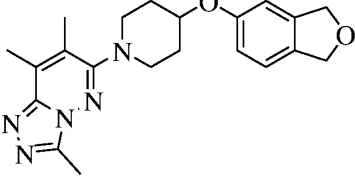
|    |   |                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                         |
|----|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   |                                                                                                                                                                                                | 8.83 (s, 1H); Mass (m/z):360.1 (M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                                                     |
| 11 | I |  <p>6-[4-(6-Fluoro-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>         | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.97– 2.02 (m, 2H), 2.12 – 2.13 (m, 2H), 2.41 (s, 3H), 2.72 (s, 3H), 3.13 – 3.19 (m, 2H), 3.45 – 3.51(m, 2H), 4.50 – 4.54 (m, 1H), 6.87 – 6.90 (d, <i>J</i> = 8.8 Hz, 1H), 7.36 – 7.40 (m, 1H), 7.88 – 7.89 (d, <i>J</i> = 2.8 Hz, 1H), 8.85 (s, 1H); Mass (m/z): 343.37 (M+H) <sup>+</sup> . |
| 12 | I |  <p>6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>               | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.94 – 2.01 (m, 2H), 2.09 – 2.15 (m, 2H), 2.41 (s, 3H), 2.66 (s, 3H), 3.10 – 3.16 (m, 2H), 3.44 – 3.50 (m, 2H), 4.44 – 4.48 (m, 1H), 6.88 – 6.91 (m, 2H), 6.96 – 7.01 (m, 2H), 8.84 (m, 1H); Mass (m/z): 342.4 (M+H) <sup>+</sup> .                                                           |
| 13 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.95 – 1.99 (m, 2H), 2.10 – 2.15 (m, 2H), 2.29 (s, 3H), 2.61 – 2.62 (s, 3H), 3.02 – 3.08 (m, 2H), 3.12 – 3.17 (t, <i>J</i> = 8.4 Hz, 2H), 3.38 – 3.42 (m,                                                                                                                                     |

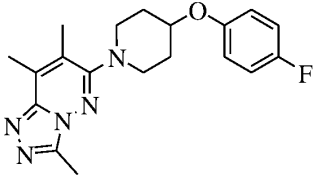
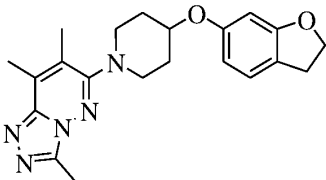
|    |   |                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                     |
|----|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   |                                                                                                                                                                                      | 2H), 4.45 – 4.47(m, 1H), 4.56 – 4.60 (t, $J = 8.4$ Hz, 2H), 6.43– 6.46 (m, 2H), 7.06 – 7.08 (d, $J = 8.4$ Hz, 1H), 8.83 (s, 1H); Mass (m/z): 366.2 (M+H) <sup>+</sup> .                                                                                                                                                                                             |
| 14 | I |  <p>6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p>           | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.94 – 2.01 (m, 2H), 2.09 – 2.15 (m, 2H), 2.41 (s, 3H), 3.10 – 3.16 (m, 2H), 3.44 – 3.50 (m, 2H), 4.44 – 4.48 (m, 1H), 6.88 – 6.91 (m, 2H), 6.96 – 7.01 (m, 2H), 8.09 (m, 1H), 8.84 (m, 1H); Mass (m/z): 328.4 (M+H) <sup>+</sup> .                                                                |
| 15 | I |  <p>6-[4-(6-Fluoro-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.97– 2.02 (m, 2H), 2.12 – 2.13 (m, 2H), 2.41 (s, 3H), 3.13 – 3.19 (m, 2H), 3.45 – 3.51(m, 2H), 4.50 – 4.54 (m, 1H), 6.87 – 6.90 (dd, $J = 8.8$ Hz, 3.6 Hz, 1H), 7.36 – 7.40 (m, 1H), 7.77 (s, 1H), 7.88 – 7.89 (dd, $J = 2.8$ Hz, 2 Hz, 1H), 8.85 (s, 1H); Mass (m/z): 329.1 (M+H) <sup>+</sup> . |

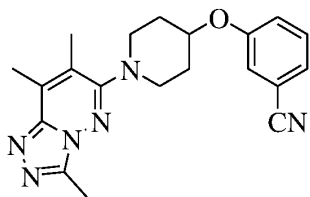
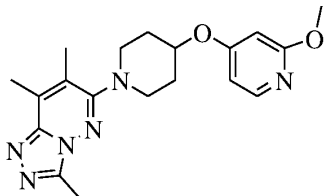
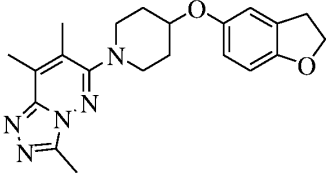
|    |   |                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                        |
|----|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 16 | I |  <p>7-Methyl-6-[4-(6-methyl-pyridin-3-yloxy)-piperidin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.60 – 1.99 (m, 2H), 2.11 – 2.18 (m, 2H), 2.41 (s, 3H), 2.50 (s, 3H), 3.12 – 3.18 (m, 2H), 3.45 – 3.51 (m, 2H), 4.51 – 4.57 (m, 1H), 7.08 – 7.10 (d, <i>J</i> = 8.4 Hz, 1H), 7.15 – 7.18 (m, 1H), 7.76 (s, 1H), 8.23 – 8.23 (d, <i>J</i> = 2.8 Hz, 1H), 8.76 (m, 1H); Mass (m/z): 324.9 (M+H) <sup>+</sup> . |
| 17 | I |  <p>6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p>      | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93 – 1.99 (m, 2H), 2.08 – 2.13 (m, 2H), 2.40 (s, 3H), 3.08 – 3.14 (m, 2H), 3.45 – 3.50 (m, 2H), 3.78 (s, 3H), 4.40 – 4.43 (m, 1H), 6.83 – 6.86 (m, 2H), 6.89 – 6.91 (m, 2H), 7.74 (m, 1H), 8.83 (s, 1H); Mass (m/z): 340.4 (M+H) <sup>+</sup> .                                                            |
| 18 | I |  <p>3-[1-(7-Methyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile</p>    | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.96 – 2.02 (m, 2H), 2.13 – 2.19 (m, 2H), 2.41 (s, 3H), 3.14 – 3.20 (m, 2H), 3.44 – 3.50 (m, 2H), 4.57 – 4.60 (m, 1H), 7.17 – 7.19 (m, 2H), 7.27 (s, 1H), 7.38 – 7.42 (m,                                                                                                                                    |

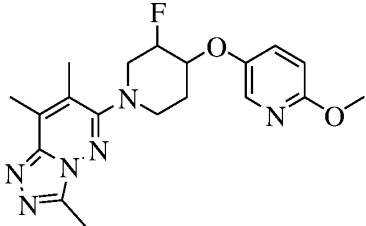
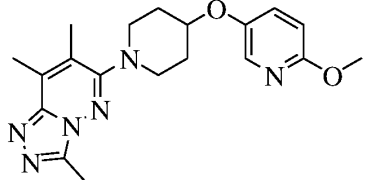
|    |   |                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | benzonitrile                                                                                                                                                                               | <sup>1</sup> H), 7.77 (s, 1H), 8.84 (s, 1H); Mass (m/z): 335.1(M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                                                                                 |
| 19 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p>   | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93 – 1.94(m, 2H), 1.97 – 2.00 (m, 2H), 2.40 (s, 3H), 3.07 – 3.13 (m, 2H), 3.17 – 3.27 (t, <i>J</i> = 8.4 Hz, 2H), 3.45 – 3.50 (m, 2H), 4.35 – 4.38 (m, 1H), 4.53 – 4.57 (t, <i>J</i> = 8.4 Hz, 2H), 6.68 – 6.70 (d, <i>J</i> = 8.8 Hz, 1H), 6.85 (s, 2H), 7.74 (s, 1H), 8.82 – 8.83 (d, <i>J</i> = 4.8 Hz, 1H); Mass (m/z): 352.1 (M+H) <sup>+</sup> . |
| 20 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.99 (m, 2H), 2.09 – 2.14 (m, 2H), 2.40 (s, 3H), 3.09 – 3.17 (m, 4H), 3.44 – 3.48 (m, 2H), 4.47 – 4.48 (m, 1H), 4.56 – 4.61 (t, <i>J</i> = 8.4 Hz, 2H), 6.43 – 6.45 (m, 2H), 7.06 – 7.08 (d, <i>J</i> = 8 Hz, 1H), 7.74 (s, 1H), 8.83 (s, 1H); Mass (m/z): 352.2 (M+H) <sup>+</sup> .                                                                    |

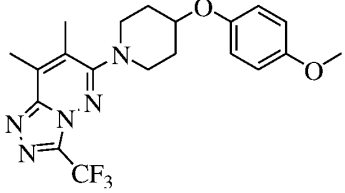
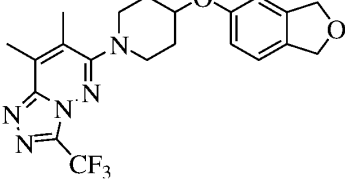
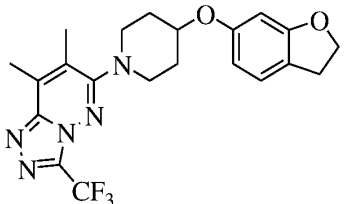
|    |    |                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                 |
|----|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 21 | II |  <p>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.98 – 2.02 (m, 2H), 2.11 – 2.16 (m, 2H), 2.41 (s, 3H), 3.11 – 3.17 (m, 2H), 3.45 – 3.50 (m, 2H), 4.53 – 4.55 (m, 1H), 5.06– 5.07 (m, 4H), 6.83 – 6.71 (m, 2H), 7.14 – 7.16 (d, <i>J</i> = 8.4 Hz, 1H), 7.75 (s, 1H), 8.83 (s, 1H); Mass (m/z): 352.2 (M+H) <sup>+</sup> .                            |
| 22 | I  |  <p>6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p>        | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.94 – 2.01 (m, 2H), 2.10 – 2.15 (m, 2H), 2.41 (s, 3H), 3.09 – 3.15 (m, 2H), 3.45 – 3.50 (m, 2H), 3.90 (s, 3H), 4.39 – 4.42 (m, 1H), 6.70 – 6.72 (d, <i>J</i> = 8.8 Hz, 1H), 7.28 (s, 1H), 7.75 (s, 1H), 7.87 – 7.88 (d, <i>J</i> = 2.8 Hz, 1H), 8.83 (s, 1H); Mass (m/z): 341.0 (M+H) <sup>+</sup> . |
| 23 | I  |  <p>6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>        | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.94 – 1.97 (m, 2H), 1.98 – 2.00 (m, 2H), 2.28 (s, 3H), 2.59 (s, 3H), 2.69 (s, 3H), 3.04 – 3.09 (m, 2H), 3.41 – 3.45 (m, 2H), 3.78 (s, 3H), 4.39 – 4.41 (m, 1H), 6.83 – 6.86 (d, <i>J</i> = 9.2 Hz, 2H), 6.89 – 6.92                                                                                  |

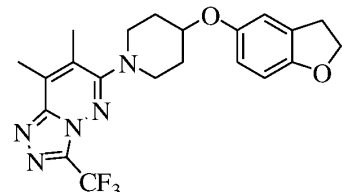
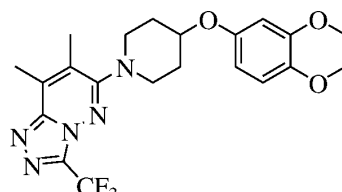
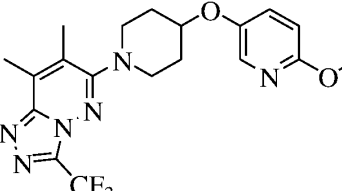
|    |   |                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                        |
|----|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   |                                                                                                                                                                                                       | (d, $J = 9.2$ Hz, 2H); Mass (m/z): 367.9 (M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                          |
| 24 | I |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H –NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.92 – 2.00 (m, 2H), 2.08 – 2.17 (m, 2H), 2.28 (s, 3H), 2.59 (s, 3H), 2.69 (s, 3H), 3.03 – 3.09 (m, 2H), 3.39 – 3.45 (m, 2H), 4.21 – 4.26 (m, 4H), 4.36 – 4.26 (m, 1H), 6.46 – 6.48 (m, 2H), 6.77 – 6.79 (d, $J = 8.8$ Hz, 1H); Mass (m/z): 396.3 (M+H) <sup>+</sup> . |
| 25 | I |  <p>6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>                   | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 2.02 – 2.03 (m, 2H), 2.13 – 2.18 (m, 2H), 2.29 (s, 3H), 2.59 (s, 3H), 2.70 (s, 3H), 3.08 – 3.14 (m, 2H), 3.40 – 3.45 (m, 2H), 4.52 – 4.54 (m, 1H), 6.65 – 6.69 (m, 2H), 6.72 – 6.74 (d, $J = 7.6$ Hz, 1H), 7.21 (s, 1H); Mass (m/z): 356.4 (M+H) <sup>+</sup> .       |
| 26 | I |  <p>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>  | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 2.01 – 2.03 (m, 2H), 2.13 – 2.14 (m, 2H), 2.26 (s, 3H), 2.59 (s, 3H), 2.68 (s, 3H), 3.07 – 3.13 (m, 2H), 3.41 – 3.46 (m, 2H), 6.81 (d, $J = 8.8$ Hz, 1H); Mass (m/z): 396.3 (M+H) <sup>+</sup> .                                                                      |

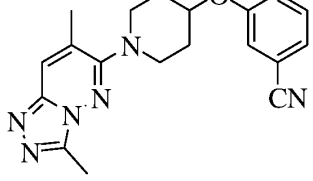
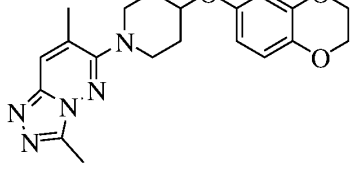
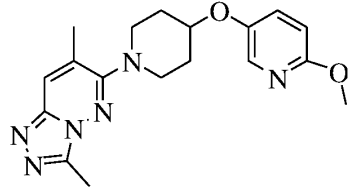
|    |   |                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                  |
|----|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | trimethyl-[1,2,4]triazolo[4,3-b]pyridazine                                                                                                                                                        | (m, 2H), 4.51 – 4.53 (m, 1H), 5.06 – 5.07 (m, 4H), 6.83 – 6.88 (m, 2H), 7.14 – 7.16 (d, $J = 8.4$ Hz, 1H); Mass (m/z): 380.3 (M+H) <sup>+</sup> .                                                                                                                                                                                                                |
| 27 | I |  <p>6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>                 | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.94 – 1.99 (m, 2H), 2.00 – 2.04 (m, 2H), 2.30 (s, 3H), 2.62 (s, 3H), 2.86 (s, 3H), 3.06 – 3.12 (m, 2H), 3.38 – 3.44 (m, 2H), 4.50 – 4.55 (m, 1H), 6.89 – 6.99 (m, 2H), 7.01 – 7.16 (m, 2H); Mass (m/z): 356.1(M+H) <sup>+</sup> .                                                              |
| 28 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.95 – 1.99 (m, 2H), 2.00 – 2.10 (m, 2H), 2.20 (s, 3H), 2.59 (s, 3H), 2.69 (s, 3H), 3.07 – 3.09 (m, 2H), 3.12 – 3.15 (t, $J = 8.4$ Hz 2H), 3.40 – 3.42 (m, 2H), 4.46 – 4.47 (m, 1H), 4.56 – 4.60 (t, $J = 8.8$ Hz, 2H), 6.44 – 6.46 (m, 2H), 7.08(s, 1H); Mass (m/z): 380.4(M+H) <sup>+</sup> . |

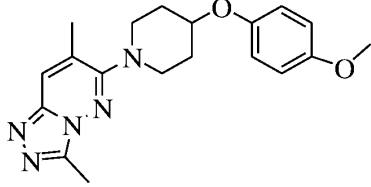
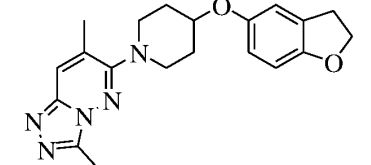
|    |   |                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                      |
|----|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 29 | I |  <p>3-[1-(3,7,8-Trimethyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile</p>              | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 2.02 (m, 2H), 2.14 – 2.16 (m, 2H), 2.29 (s, 3H), 2.60 – 2.61 (s, 3H), 2.70 (s, 3H), 3.11 – 3.15 (m, 2H), 3.40 – 3.49 (m, 2H), 4.57 (m, 1H), 7.10 – 7.21 (m, 2H), 7.26 (m, 1H), 7.52 (m, 1H); Mass (m/z): 363.4(M+H) <sup>+</sup> .                                                                         |
| 30 | I |  <p>6-[4-(2-Methoxy-pyridin-4-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>       | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 2.02 – 2.03 (m, 2H), 2.14 – 2.19 (m, 2H), 2.29 (s, 3H), 2.60 (s, 3H), 2.70 (s, 3H), 3.09 – 3.14 (m, 2H), 3.39 – 3.43 (m, 2H), 3.93 (s, 3H), 4.58 – 4.60 (m, 1H), 6.23 – 6.23 (d, <i>J</i> = 1.2 Hz, 1H), 6.49 – 6.51 (m, 1H), 7.98 – 8.00 (d, <i>J</i> = 6 Hz, 1H); Mass (m/z): 369.5 (M+H) <sup>+</sup> . |
| 31 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93– 1.97 (m, 2H), 1.98 – 2.00 (m, 2H), 2.28 (s, 3H), 2.59 (s, 3H), 2.69 (s, 3H), 3.03 – 3.08 (m, 2H), 3.17 – 3.21 (t, <i>J</i> = 8.4 Hz, 2H), 3.41 – 3.45 (m, 2H), 4.35 – 4.36 (m, 1H), 4.53 – 4.57 (t, <i>J</i> = 8.8 Hz,                                                                               |

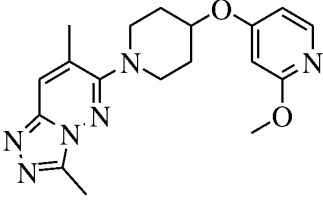
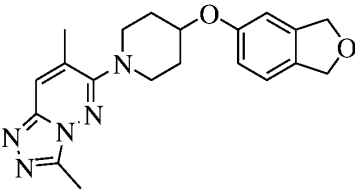
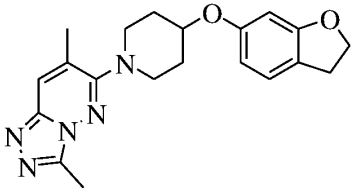
|    |   |                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                        |
|----|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   |                                                                                                                                                                                                     | 2H), 6.68 – 6.70 (m, 2H), 6.85 (s, 1H); Mass (m/z); 380.2(M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                                          |
| 32 | I |  <p>6-[3-Fluoro-4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.96 – 1.99 (m, 2H), 2.17 – 2.20 (m, 2H), 2.58 (s, 3H), 2.61 (s, 3H), 2.69 (s, 3H), 3.04 – 3.12 (m, 2H), 3.90 (s, 3H), 3.98 – 4.01 (s, 1H), 4.36 – 4.42 (m, 1H), 6.71 – 6.73 (d, <i>J</i> = 8.8 Hz, 1H), 7.26 – 7.28 (m, 1H), 7.92 – 7.93 (d, <i>J</i> = 2.4 Hz, 1H); Mass (m/z): 387.8 (M+H) <sup>+</sup> . |
| 33 | I |  <p>6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>        | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.99 (m, 2H), 2.11 – 2.16 (m, 2H), 2.28 (s, 3H), 2.59 (s, 3H), 2.70 (s, 3H), 3.04 – 3.09 (m, 2H), 3.41 – 3.48 (m, 2H), 3.90 (s, 3H), 4.38 – 4.40 (m, 1H), 6.70 – 6.72 (d, <i>J</i> = 8.8 Hz, 1H), 7.31 – 7.31 (m, 1H), 7.87 – 7.88 (d, <i>J</i> = 2.8 Hz, 1H); Mass(m/z): 368.9 (M+H) <sup>+</sup> .         |

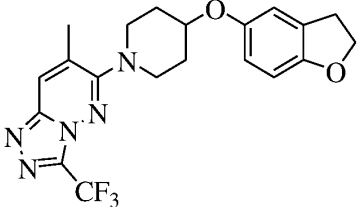
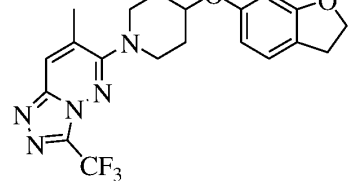
|    |   |                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                         |
|----|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 34 | I |  <p>6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>                  | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93 – 2.01 (m, 2H), 2.08 – 2.16 (m, 2H), 2.33 (s, 3H), 2.65 (s, 3H), 3.11 – 3.17 (m, 2H), 3.46 – 3.51 (m, 2H), 3.78 (s, 3H), 4.40 – 4.44 (m, 1H), 6.86 – 6.89 (m, 4H); Mass (m/z): 421.8 (M+H) <sup>+</sup> .                                                |
| 35 | I |  <p>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.96 – 2.04 (m, 2H), 2.13 – 2.18 (m, 2H), 2.34 (s, 3H), 2.66 (s, 3H), 3.14 – 3.20 (m, 2H), 3.46 – 3.52 (m, 2H), 4.51 – 4.56 (m, 1H), 5.06 – 5.07 (m, 4H), 6.83 – 6.88 (m, 2H), 7.14 – 7.16 (d, <i>J</i> = 8.0 Hz, 1H); Mass (m/z): 434.0 (M+H) <sup>+</sup> . |
| 36 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>   | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.94 – 2.02 (m, 2H), 2.10 – 2.17 (m, 2H), 2.33 (s, 3H), 2.65 (s, 3H), 3.12 – 3.18 (m, 4H), 3.46 – 3.51 (m, 2H), 4.46 – 4.50 (m, 1H), 4.56 – 4.60 (t, <i>J</i> = 8.8 Hz, 2H), 6.43 – 6.45 (m, 2H), 7.06 – 7.08 (m, 1H); Mass (m/z): 434.2                      |

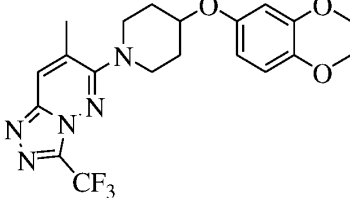
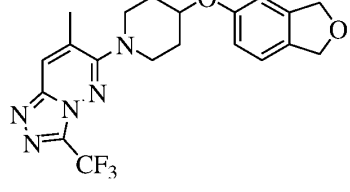
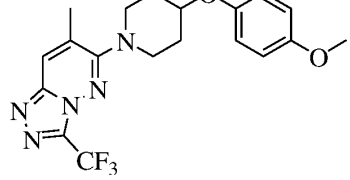
|    |   |                                                                                                                                                                                                                       | (M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                                                    |
|----|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 37 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>        | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.92 – 2.00 (m, 2H), 2.08 – 2.15 (m, 2H), 2.33 (s, 3H), 2.65 (s, 3H), 3.10 – 3.21 (m, 4H), 3.46 – 3.52 (m, 2H), 4.34 – 4.40 (m, 1H), 4.53 – 4.57 (t, <i>J</i> = 8.4 Hz, 2H), 6.68 – 6.78 (m, 2H), 6.84 – 6.85 (m, 1H); Mass (m/z): 434.7 (M+H) <sup>+</sup> . |
| 38 | I |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.97 – 1.99 (m, 2H), 2.09 – 2.14 (m, 2H), 2.33 (s, 3H), 2.65 (s, 3H), 3.11 – 3.16 (m, 2H), 3.45 – 3.50 (m, 2H), 4.21 – 4.25 (m, 4H), 4.39 – 4.40 (m, 1H), 6.46 – 6.50 (m, 2H), 6.77 – 6.79 (d, <i>J</i> = 8.8 Hz, 1H); Mass (m/z): 450.3(M+H) <sup>+</sup> .  |
| 39 | I |  <p>6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>           | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.94 – 2.02 (m, 2H), 2.11 – 2.17 (m, 2H), 2.34 (s, 3H), 2.66 (s, 3H), 3.12 – 3.18 (m, 2H), 3.46 – 3.52 (m, 2H), 3.70 (s, 3H), 4.36 – 4.44 (m, 1H),                                                                                                            |

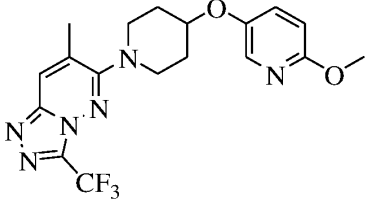
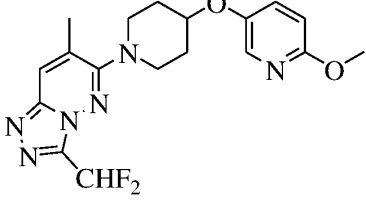
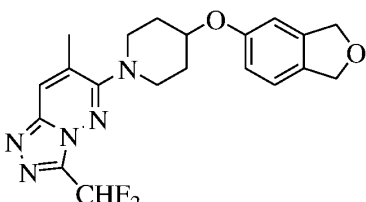
|    |   |                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                  |
|----|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | [1,2,4]triazolo[4,3-b]pyridazine                                                                                                                                                                    | 6.70– 6.72 (m, 1H), 7.26 (m, 1H), 7.87 – 7.87 (d, $J = 2.8$ Hz, 1H); Mass (m/z): 423.2 (M+H) <sup>+</sup> .                                                                                                                                                                                                                      |
| 40 | I |  <p>3-[1-(3,7-Dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile</p>                   | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.99 – 2.05 (m, 2H), 2.13 – 2.17 (m, 2H), 2.61 (s, 3H), 2.71 (s, 3H), 3.17 – 3.22 (m, 2H), 3.45 – 3.51 (m, 2H), 4.58 – 4.60 (m, 1H), 7.19 – 7.26 (m, 2H), 7.38 – 7.40 (m, 1H), 7.52 – 7.54 (m, 1H), 7.70 – 7.72 (m, 1H); Mass (m/z): 348.7 (M+H) <sup>+</sup> .        |
| 41 | I |  <p>6-[4-(2,3-Dihydrobenzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.92 – 1.99 (m, 2H), 2.09 – 2.10 (m, 2H), 2.39 (s, 3H), 2.71 (s, 3H), 3.10 – 3.13 (m, 2H), 3.47 – 3.49 (m, 2H), 4.22 – 4.24 (m, 4H), 4.37 – 4.41 (m, 1H), 6.48 – 6.51 (m, 2H), 6.77 – 6.80 (d, $J = 8.8$ Hz, 1H), 7.71 (s, 1H); Mass (m/z): 382.0 (M+H) <sup>+</sup> . |
| 42 | I |                                                                                                                  | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.95 – 2.02 (m, 2H), 2.11 – 2.16 (m, 2H), 2.39 (s, 3H), 2.70 (s,                                                                                                                                                                                                       |

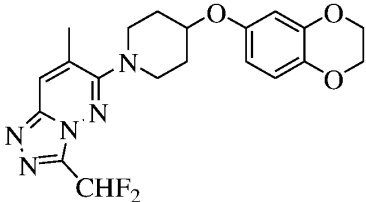
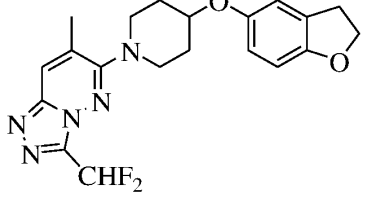
|    |   |                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                     |
|----|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine                                                                                             | <sup>1</sup> H), 3.10 – 3.16 (m, 2H), 3.46 – 3.51 (m, 2H), 3.90 (s, 3H), 4.39 – 4.43 (m, 1H), 6.70 – 6.72 (d, <i>J</i> = 8.8 Hz, 1H), 7.27 – 7.28 (d, <i>J</i> = 3.2 Hz, 1H), 7.69 (s, 1H), 7.89 – 7.88 (d, <i>J</i> = 2.4 Hz, 1H); Mass (m/z): 354.9(M+H) <sup>+</sup> .                                                                                           |
| 43 | I | <br>6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine               | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93 – 1.99 (m, 2H), 2.00 – 2.12 (m, 2H), 2.39 (s, 3H), 2.70 (s, 3H), 3.10 – 3.16 (m, 2H), 3.46 – 3.52 (m, 2H), 3.78 (s, 3H), 4.40 – 4.44 (m, 1H), 6.84 – 6.87 (m, 2H), 6.89 – 6.92 (m, 2H), 7.69 (m, 1H); Mass (m/z): 354.2 (M+H) <sup>+</sup> .                                                         |
| 44 | I | <br>6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.94– 2.01 (m, 2H), 2.08 – 2.14 (m, 2H), 2.39 (s, 3H), 2.70 (s, 3H), 3.09 – 3.13 (m, 2H), 3.17 – 3.21 (t, <i>J</i> = 8.4 Hz 2H), 3.45 – 3.51 (m, 2H), 4.35 – 4.39 (m, 1H), 4.53 – 4.59 (t, <i>J</i> = 8.8 Hz, 2H), 6.68 – 6.71 (m, 2H), 6.85 (s, 1H), 7.68 (s, 1H); Mass (m/z): 365.9(M+H) <sup>+</sup> . |

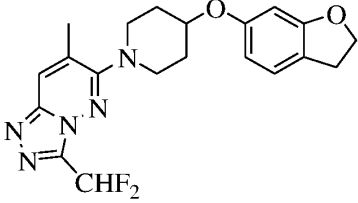
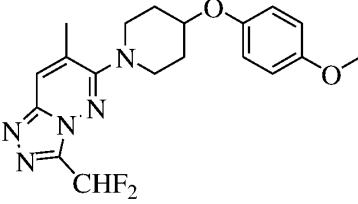
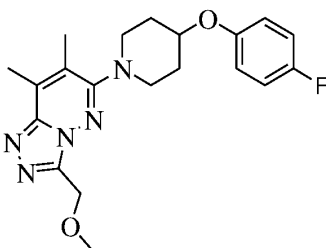
|    |   |                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                      |
|----|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 45 | I |  <p>6-[4-(2-Methoxy-pyridin-4-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>           | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.99 – 2.05 (m, 2H), 2.14 – 2.19 (m, 2H), 2.39 (s, 3H), 2.71 (s, 3H), 3.15 – 3.21 (m, 2H), 3.44 – 3.49 (m, 2H), 3.93 (s, 3H), 4.60 – 4.62 (m, 1H), 6.23 – 6.23 (d, <i>J</i> = 1.2 Hz, 1H), 6.49 – 6.51 (m, 1H), 7.70 (s, 1H), 7.99 – 8.00 (d, <i>J</i> = 6 Hz, 1H); Mass (m/z): 355.0 (M+H) <sup>+</sup> . |
| 46 | I |  <p>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 2.02 – 2.02 (m, 2H), 2.12 – 2.17 (m, 2H), 2.39 (s, 3H), 2.70 (s, 3H), 3.13 – 3.18 (m, 2H), 3.46 – 3.51 (m, 2H), 4.53 – 4.55 (m, 1H), 5.07 – 5.08 (m, 4H), 6.83 (s, 1H), 6.86 – 6.88 (d, <i>J</i> = 8 Hz, 1H), 7.14 – 7.16 (d, <i>J</i> = 8 Hz, 1H), 7.69 (s, 1H); Mass (m/z): 366.7 (M+H) <sup>+</sup> .   |
| 47 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>    | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.95 – 1.99 (m, 2H), 2.00 – 2.10 (m, 2H), 2.20 (s, 3H), 2.69 (s, 3H), 3.07 – 3.09 (m, 2H), 3.12 – 3.15 (t, <i>J</i> = 8.4 Hz, 2H), 3.40 – 3.42 (m, 2H),                                                                                                                                                    |

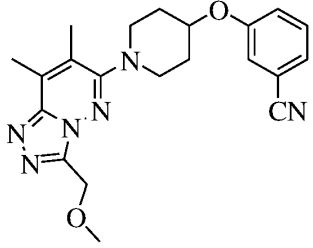
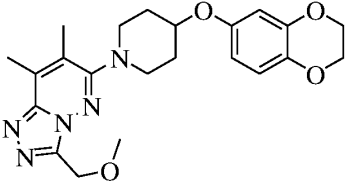
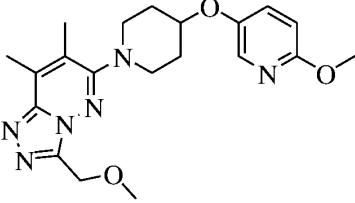
|    |   |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                          |
|----|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | b]pyridazine                                                                                                                                                                                                 | 4.46 – 4.47 (m, 1H), 4.56 – 4.60 (t, $J = 8.8$ Hz, 2H), 6.44 – 6.46 (m, 2H), 7.08 (s, 1H), 7.45 (s, 1H); Mass (m/z): 366.21 (M+H) <sup>+</sup> .                                                                                                                                                                                                                                         |
| 48 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>   | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.93 – 2.01 (m, 2H), 2.08 – 2.15 (m, 2H), 2.45 – 2.46 (s, 3H), 3.17 – 3.19 (t, $J = 5.2$ Hz, 2H), 3.20 – 3.24 (m, 2H), 3.52 – 3.58 (m, 2H), 4.36 – 4.42 (s, 1H), 4.53 – 4.58 (t, $J = 8.4$ Hz, 2H), 6.70 – 6.71 (m, 2H), 6.85 (d, $J = 0.8$ Hz, 1H), 7.81 (d, $J = 0.8$ Hz, 1H); Mass (m/z): 420.4 (M+H) <sup>+</sup> . |
| 49 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.95 – 2.02 (m, 2H), 2.09 – 2.16 (m, 2H), 2.45 (s, 3H), 3.13 – 3.17 (t, $J = 8.4$ Hz, 2H), 3.20 – 3.26 (m, 2H), 3.51 – 3.57 (m, 2H), 4.48 – 4.53 (m, 1H), 4.56 – 4.61 (t, $J = 8.4$ Hz, 2H), 6.45 (d, $J = 0.8$ Hz, 2H), 7.06 (d, $J = 0.8$ Hz, 1H), 7.81 (d, $J = 1.2$ Hz, 1H); Mass (m/z): 420.1 (M+H) <sup>+</sup> . |

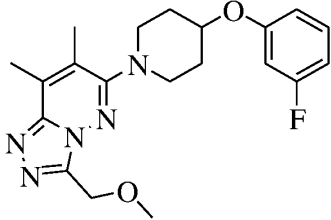
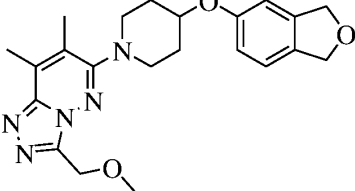
|    |   |                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                             |
|----|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 50 | I |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ ppm: 1.72 – 1.81 (m, 2H), 2.00 – 2.05 (m, 2H), 2.50 (s, 3H), 3.00 – 3.06 (m, 2H), 3.17 – 3.23 (m, 2H), 4.15 – 4.21 (m, 4H), 4.45 – 4.49 (m, 1H), 6.45 – 6.48 (m, 1H), 6.54 – 6.55 (d, <i>J</i> = 2.80 Hz, 1H), 6.75 – 6.77 (d, <i>J</i> = 8.80 Hz, 1H), 8.68 (s, 1H); Mass (m/z): 435.8 (M+H) <sup>+</sup> . |
| 51 | I |  <p>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>  | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.99 – 2.02 (m, 2H), 2.04 – 2.17 (m, 2H), 2.46 (s, 3H), 3.22 – 3.28 (m, 2H), 3.52 – 3.59 (m, 2H), 4.54 – 4.59 (m, 1H), 5.07 – 5.09 (m, 4H), 6.83 – 6.88 (m, 2H), 7.14 – 7.16 (d, <i>J</i> = 8.0 Hz, 1H), 7.79 (s, 1H); Mass (m/z): 420.0 (M+H) <sup>+</sup> .                                                     |
| 52 | I |  <p>6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>                  | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.94 – 2.01 (m, 2H), 2.09 – 2.15 (m, 2H), 2.46 (s, 3H), 3.19 – 3.25 (m, 2H), 3.52 – 3.58 (m, 2H), 3.78 (s, 3H), 4.41 – 4.47 (m, 1H), 6.83 – 6.91 (m, 4H), 7.81 (s, 1H); Mass                                                                                                                                      |

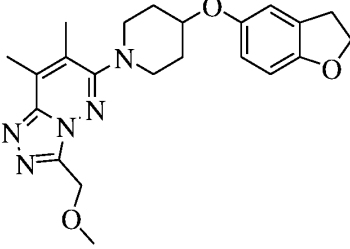
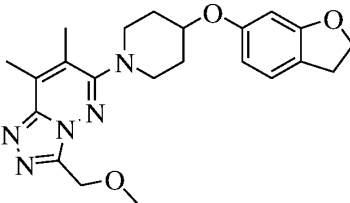
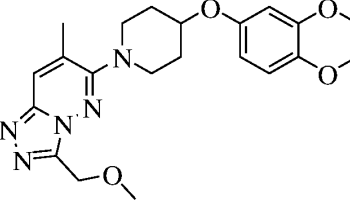
|    |   |                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                          |
|----|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | [1,2,4]triazolo[4,3-b]pyridazine                                                                                                                                                                               | (m/z): 407.9 (M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                                                                        |
| 53 | I |  <p>6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>          | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.97 – 2.03 (m, 2H), 2.11 – 2.16 (m, 2H), 2.46 (s, 3H), 3.20 – 3.26 (m, 2H), 3.53 – 3.59 (m, 2H), 3.90 (s, 3H), 4.42 – 4.45 (m, 1H), 6.70 – 6.73 (d, <i>J</i> = 8.8 Hz, 1H), 7.25 – 7.28 (m, 1H), 7.82 (s, 1H), 7.87 – 7.88 (d, <i>J</i> = 2.8 Hz, 1H); Mass (m/z): 409.0 (M+H) <sup>+</sup> . |
| 54 | I |  <p>3-Difluoromethyl-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p>         | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.96 – 2.02 (m, 2H), 2.11 – 2.16 (m, 2H), 2.44 (s, 3H), 3.18 – 3.24 (m, 2H), 3.52 – 3.57 (m, 2H), 3.90 (s, 3H), 4.42 – 4.43 (m, 1H), 6.70 – 6.72 (d, <i>J</i> = 8.8 Hz, 1H), 7.15 – 7.26 (m, 2H), 7.80 (s, 1H), 7.87 – 7.87 (d, <i>J</i> = 2.8 Hz, 1H); Mass (m/z): 391.3 (M+H) <sup>+</sup> . |
| 55 | I |  <p>3-Difluoromethyl-6-[4-(1,3-dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.98 – 2.05 (m, 2H), 2.12 – 2.18 (m, 2H), 2.45 (s, 3H), 3.20 – 3.26 (m, 2H), 3.51 – 3.57 (m, 2H), 4.53 – 4.58 (m, 1H), 5.07 – 5.08 (m, 4H),                                                                                                                                                    |

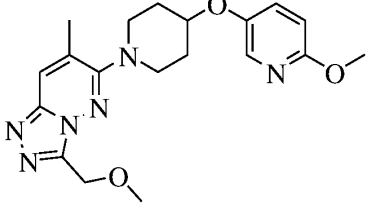
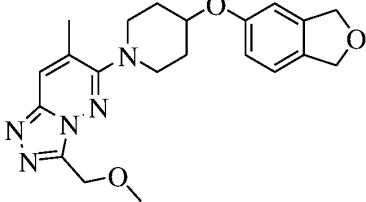
|    |   |                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                  |
|----|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | [1,2,4]triazolo[4,3-b]pyridazine                                                                                                                                                                                | 6.83 – 6.88 (m, 2H), 7.14 – 7.28 (m, 2H), 7.80 (s, 1H);<br>Mass (m/z): 402.1 (M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                                                |
| 56 | I |  <p>3-Difluoromethyl-6-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.94 – 2.00 (m, 2H), 2.08 – 2.14 (m, 2H), 2.43 (s, 3H), 3.17 – 3.23 (m, 2H), 3.48 – 3.56 (m, 2H), 4.21 – 4.26 (m, 4H), 4.39 – 4.42 (m, 1H), 6.45 – 6.50 (m, 2H), 6.77 – 6.80 (d, <i>J</i> = 8.8 Hz, 1H), 7.02 – 7.28 (m, 1H), 7.78 (s, 1H); Mass (m/z): 418.0 (M+H) <sup>+</sup> .                                                     |
| 57 | I |  <p>3-Difluoromethyl-6-[4-(2,3-dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p>     | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93 – 2.01 (m, 2H), 2.08 – 2.15 (m, 2H), 2.46 (s, 3H), 3.17 – 3.19 (t, <i>J</i> = 5.2 Hz, 2H), 3.20 – 3.24 (m, 2H), 3.52 – 3.58 (m, 2H), 4.36 – 4.42 (s, 1H), 4.53 – 4.58 (t, <i>J</i> = 8.4 Hz, 2H), 6.70 – 6.71 (m, 2H), 6.85 (d, <i>J</i> = 0.8 Hz, 1H), 7.15 – 7.28 (s, 1H), 7.81 (s, 1H); Mass (m/z): 402.1 (M+H) <sup>+</sup> . |

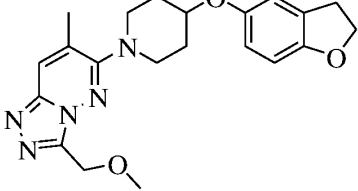
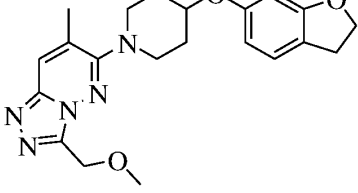
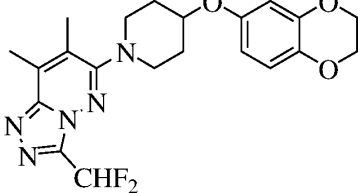
|    |   |                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                         |
|----|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 58 | I |  <p>3-Difluoromethyl-6-[4-(2,3-dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.96 – 2.02 (m, 2H), 2.10 – 2.15 (m, 2H), 2.44 (s, 3H), 3.13 – 3.17 (t, <i>J</i> = 8.8 Hz, 2H), 3.18 – 3.24 (m, 2H), 3.50 – 3.56 (m, 2H), 4.49 – 4.50 (m, 1H), 4.56 – 4.61 (t, <i>J</i> = 8.8 Hz, 2H), 6.43 – 6.45 (m, 2H), 7.08 – 7.08 (d, <i>J</i> = 1.2 Hz, 1H), 7.15 – 7.28 (m, 1H), 7.79 (s, 1H); Mass (m/z): 402.1 (M+H) <sup>+</sup> . |
| 59 | I |  <p>3-Difluoromethyl-6-[4-(4-methoxy-phenoxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p>            | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.96 – 2.02 (m, 2H), 2.11 – 2.16 (m, 2H), 2.44 (s, 3H), 3.18 – 3.24 (m, 2H), 3.52 – 3.57 (m, 2H), 3.90 (s, 3H), 4.42 – 4.43 (m, 1H), 6.70 – 6.72 (m, 2H), 7.15 – 7.26 (m, 2H), 7.19 – 7.31 (m, 1H), 7.80 (s, 1H); Mass (m/z): 390.3 (M+H) <sup>+</sup> .                                                                                      |
| 60 | I |  <p>6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-7-methyl-3-(methoxymethyl)-[1,2,4]triazolo[4,3-b]pyridazine</p>            | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.98 – 1.99 (m, 2H), 2.10 – 2.15 (m, 2H), 2.30 (s, 3H), 2.59 – 2.61 (s, 3H), 3.09 – 3.13 (m, 2H), 3.43 (m, 2H), 3.46 – 3.50 (m, 3H), 4.44 – 4.45 (m, 2H), 7.08 – 7.10 (d, <i>J</i> = 1.2 Hz, 1H), 7.15 – 7.28 (m, 1H), 7.79 (s, 1H); Mass (m/z): 402.1 (M+H) <sup>+</sup> .                                                                   |

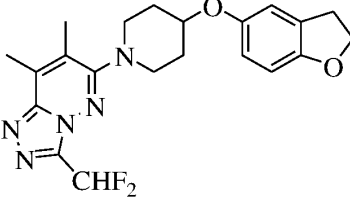
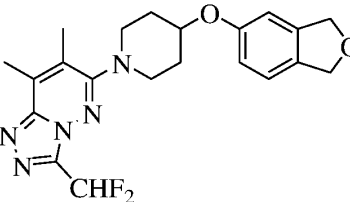
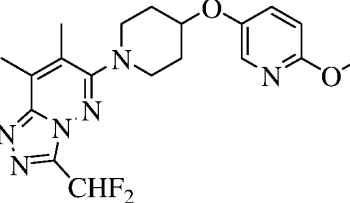
|    |   |                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                       |
|----|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine                                                                                                                                       | <sup>1</sup> H), 4.91 – 4.94 (s, 2H), 6.89 – 6.91 (m, 2H), 6.97 – 6.99 (m, 2H); Mass (m/z): 386.0 (M+H) <sup>+</sup> .                                                                                                                                                                                                                |
| 61 | I |  <p>3-[1-(3-Methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile</p>                   | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 2.01 (m, 2H), 2.14 – 2.18 (m, 2H), 2.32 (s, 3H), 2.61 – 2.63 (s, 3H), 3.13 – 3.18 (m, 2H), 3.43 (m, 2H), 3.46 (s, 3H) 4.56–4.58 (m, 1H), 4.94 (s, 2H), 7.16 – 7.19 (m, 2H), 7.37 – 7.39 (m, 2H); Mass (m/z): 392.8 (M+H) <sup>+</sup> .                                     |
| 62 | I |  <p>6-[4-(2,3-Dihydrobenzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.94 – 1.98 (m, 2H), 2.09 – 2.14 (m, 2H), 2.29 (s, 3H), 2.61 (s, 3H), 3.07 – 3.11 (m, 2H), 3.42 – 3.49 (m, 5H), 4.21 – 4.25 (m, 4H), 4.37 – 4.39 (m, 1H), 4.94 (s, 2H), 6.45 – 6.50 (m, 2H), 6.77 – 6.79 (d, <i>J</i> = 8.8 Hz, 1H); Mass (m/z): 426.4 (M+H) <sup>+</sup> . |
| 63 | I |  <p>3-Methoxymethyl-6-[4-(6-methoxypyridin-2-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>            | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.99 (m, 2H), 2.12 – 2.13 (m, 2H), 2.30 (s, 3H), 2.62 (s, 3H), 3.08 – 3.12 (m, 2H), 3.46 (m, 5H),                                                                                                                                                                           |

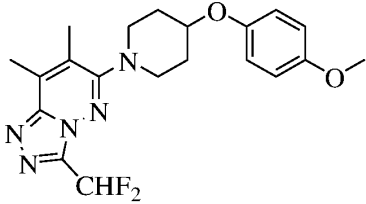
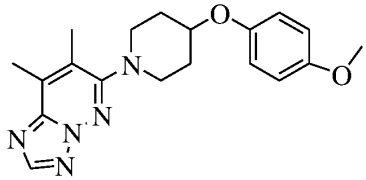
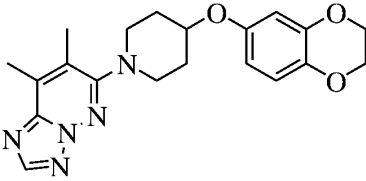
|    |   |                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                             |
|----|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine                                                                                                                            | 3.90 (s, 3H), 4.39 – (m, 1H), 4.94 (s, 2H), 6.70 – 6.72 (d, $J = 8.8$ Hz, 1H), 7.26 (s, 1H), 7.87 – 7.87 (d, $J = 2$ Hz, 1H); Mass (m/z): 399.1(M+H) <sup>+</sup> .                                                                                                                                                                         |
| 64 | I |  <p>6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>                    | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 2.03 – 2.01 (m, 2H), 2.13 – 2.15 (m, 2H), 2.30 (s, 3H), 2.62 (s, 3H), 3.11 – 3.17 (m, 2H), 3.43 – 3.44 (m, 2H), 3.46 (s, 3H), 4.52 – 4.53 (m, 1H), 4.94 (s, 2H), 6.64 – 6.65 (d, $J = 2$ Hz, 2H), 6.67 – 6.73 (m, 1H), 7.21 – 7.25 (m, 1H); Mass (m/z): 385.8(M+H) <sup>+</sup> . |
| 65 | I |  <p>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.97 – 2.03 (m, 2H), 2.12 – 2.17 (m, 2H), 2.30 (s, 3H), 2.62 (s, 3H), 3.10 – 3.15 (m, 2H), 3.44 – 3.49 (m, 5H), 4.50 – 4.54 (m, 1H), 4.94 (s, 2H), 5.06 – 5.07 (m, 4H), 6.83 – 6.87 (m, 2H), 7.13 – 7.15 (d, $J = 8.0$ Hz, 1H); Mass (m/z): 410.4 (M+H) <sup>+</sup> .            |

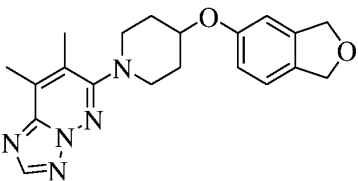
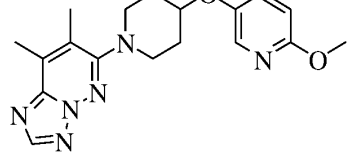
|    |   |                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                    |
|----|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 66 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>     | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.92 – 2.00 (m, 2H), 2.09 – 2.14 (m, 2H), 2.30 (s, 3H), 2.61 (s, 3H), 3.06 – 3.12 (m, 2H), 3.17 – 3.21 (t, <i>J</i> = 8.60 Hz, 2H), 3.43 (s, 3H), 3.46 – 3.49 (m, 2H), 4.34 – 4.38 (m, 1H), 4.55 – 4.58 (m, 2H), 4.94 (s, 2H), 6.68 – 6.73 (m, 2H), 6.99 (s, 1H); Mass (m/z): 410.0 (M+H) <sup>+</sup> . |
| 67 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>    | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.97 – 2.03 (m, 2H), 2.12 – 2.17 (m, 2H), 2.30 (s, 3H), 2.46 (s, 3H), 3.11 – 3.31 (m, 4H), 3.44 – 3.49 (m, 5H), 4.50 – 4.54 (m, 3H), 4.94 (s, 2H), 6.83 – 6.87 (m, 2H), 7.13 – 7.15 (d, <i>J</i> = 8.0 Hz, 1H); Mass (m/z): 410.2 (M+H) <sup>+</sup> .                                                   |
| 68 | I |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-3-methoxymethyl-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.94 – 1.99 (m, 2H), 2.08 – 2.13 (m, 2H), 2.40 (s, 3H), 3.13 – 3.19 (m, 2H), 3.47 (s, 3H), 3.50 – 3.52 (m, 2H), 4.21 – 4.26 (m, 4H), 4.39 – 4.40 (m, 1H), 4.94 (s, 2H), 6.45 – 6.48 (m, 1H), 6.50 – 6.50 (d,                                                                                             |

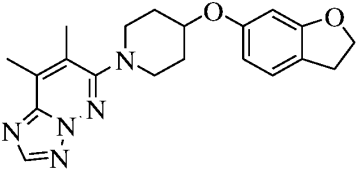
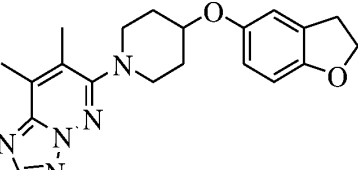
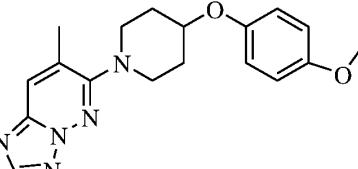
|    |   |                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                   |
|----|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | b]pyridazine                                                                                                                                                                                                  | $J = 2.4$ Hz, 1H), 6.77 – 6.80 (d, $J = 8.8$ Hz, 1H), 7.73 – 7.73 (d, $J = 1.6$ Hz, 1H); Mass (m/z): 412.1 (M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                   |
| 69 | I |  <p>3-Methoxymethyl-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p>           | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.99 – 2.00 (m, 2H), 2.11 – 2.12 (m, 2H), 2.41 (s, 3H), 3.17 – 3.19 (m, 2H), 3.47 (s, 3H), 3.48 – 3.52 (m, 2H), 3.90 (s, 3H), 4.41 – (m, 1H), 4.94 (s, 2H), 6.70 – 6.72 (d, $J = 9.2$ Hz, 1H), 7.25 – 7.28 (m, 1H), 7.74 – 7.75 (d, $J = 1.2$ Hz, 1H), 7.87 – 7.87 (d, $J = 2.8$ Hz, 1H); Mass (m/z): 384.9 (M+H) <sup>+</sup> . |
| 70 | I |  <p>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-3-methoxymethyl-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.98 – 2.03 (m, 2H), 2.12 – 2.17 (m, 2H), 2.41 (s, 3H), 3.16 – 3.22 (m, 2H), 3.47 (s, 3H), 3.48 – 3.54 (m, 2H), 4.53 – 4.55 (m, 1H), 4.94 (s, 2H), 5.07 – 5.08 (m, 4H) 6.83 – 6.87 (m, 2H), 7.14 – 7.16 (d, $J = 8.4$ Hz, 1H), 7.74 (s, 1H); Mass (m/z): 396.1 (M+H) <sup>+</sup> .                                              |

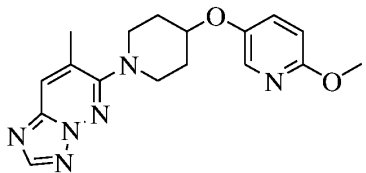
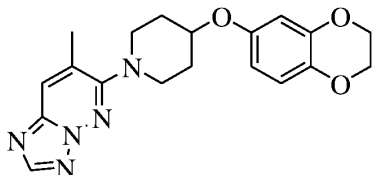
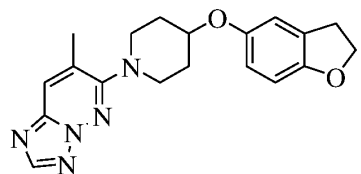
|    |   |                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                 |
|----|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 71 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-3-methoxymethyl-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p>              | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.97 – 1.98 (m, 2H), 2.08 – 2.11 (m, 2H), 2.41 (s, 3H), 3.13 – 3.21 (m, 4H), 3.48 (s, 3H), 3.50 – 3.52 (m, 2H), 4.37 – 4.38 (m, 1H), 4.53 – 4.58 (m, 2H), 4.94 (s, 2H), 6.70 – 6.71 (m, 2H), 6.85 – 6.85 (m, 1H), 7.73 (s, 1H) Mass (m/z): 396.2 (M+H) <sup>+</sup> . |
| 72 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-3-methoxymethyl-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine</p>             | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.97 – 2.03 (m, 2H), 2.12 – 2.17 (m, 2H), 2.30 (s, 3H), 3.11 – 3.31 (m, 4H), 3.44 – 3.49 (m, 5H), 4.50 – 4.54 (m, 3H), 4.94 (s, 2H), 6.83 – 6.87 (m, 2H), 7.13 – 7.15 (d, <i>J</i> = 8.0 Hz, 1H), 8.12 (s, 1H); Mass (m/z): 396.2 (M+H) <sup>+</sup> .                |
| 73 | I |  <p>3-Difluoromethyl-6-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.97 (m, 2H), 2.09 – 2.17 (m, 2H), 2.32 (s, 3H), 2.61 (s, 3H), 3.11 – 3.15 (m, 2H), 3.45 – 3.41 (m, 2H), 4.21 – 4.25 (m, 4H), 4.38 – 4.40 (m, 1H), 6.45 – 6.50 (m, 2H), 6.77 – 6.79 (m, 1H), 7.02 – 7.15 (d,                                                          |

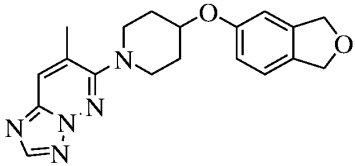
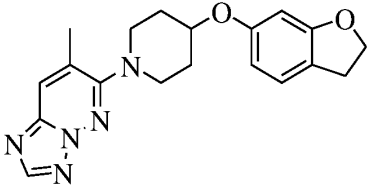
|    |   |                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                          |
|----|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | b]pyridazine                                                                                                                                                                                                       | <sup>1</sup> H); Mass (m/z): 432.0 (M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                                                                                                  |
| 74 | I |  <p>3-Difluoromethyl-6-[4-(2,3-dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>      | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93 – 2.00 (m, 2H), 2.09 – 2.14 (m, 2H), 2.32 (s, 3H), 2.64 (s, 3H), 3.09 – 3.15 (m, 2H), 3.17 – 3.21 (t, <i>J</i> = 8.4 Hz, 2H), 3.45 – 3.51 (m, 2H), 4.34 – 4.39 (m, 1H), 4.53 – 4.59 (t, <i>J</i> = 8.4 Hz, 2H), 6.68 – 6.71 (m, 2H), 6.85 – 6.85 (d, <i>J</i> = 2.8 Hz, 1H), 7.02 – 7.15 (m, 1H); Mass (m/z): 416.45 (M+H) <sup>+</sup> . |
| 75 | I |  <p>3-Difluoromethyl-6-[4-(1,3-dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.98 – 2.04 (m, 2H), 2.13 – 2.18 (m, 2H), 2.33 (s, 3H), 2.64 (s, 3H), 3.13 – 3.19 (m, 2H), 3.46 – 3.51 (m, 2H), 4.53 – 4.55 (m, 1H), 5.06 – 5.07 (m, 4H), 6.83 – 6.87 (m, 2H), 7.02 – 7.15 (m, 2H); Mass (m/z): 416.01 (M+H) <sup>+</sup> .                                                                                                    |
| 76 | I |  <p>3-Difluoromethyl-6-[4-(6-methoxy-pyridin-2-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p>         | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.96 – 2.02 (m, 2H), 2.11 – 2.16 (m, 2H), 2.44 (s, 3H), 2.65 (s, 3H), 3.18 – 3.24 (m, 2H),                                                                                                                                                                                                                                                     |

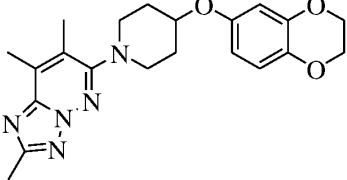
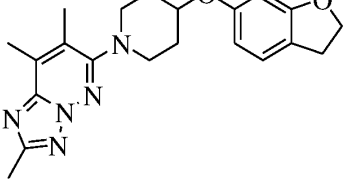
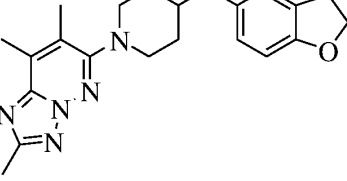
|    |   |                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                           |
|----|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine                                                                                                           | 3.52 – 3.57 (m, 2H), 3.90 (s, 3H), 4.42 – 4.43 (m, 1H), 6.70 – 6.72 (d, $J = 8.8$ Hz, 1H), 7.15 – 7.26 (m, 2H), 7.18 – 7.32 (m, 1H); Mass (m/z): 405.3 (M+H) <sup>+</sup> .                                                                                                                                               |
| 77 | I |  <p>3-Difluoromethyl-6-[4-(4-methoxy-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.96 – 2.02 (m, 2H), 2.11 – 2.16 (m, 2H), 2.44 (s, 3H), 2.51 (s, 3H), 3.18 – 3.24 (m, 2H), 3.52 – 3.57 (m, 2H), 3.90 (s, 3H), 4.42 – 4.43 (m, 1H), 6.70 – 6.72 (m, 2H), 7.15 – 7.26 (m, 2H), 7.19 – 7.31 (m, 1H); Mass (m/z): 404.3 (M+H) <sup>+</sup> . |
| 78 | I |  <p>6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p>                | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.92 – 2.00 (m, 2H), 2.10 – 2.35 (m, 2H), 2.35 (s, 3H), 2.60 (s, 3H), 3.06 – 3.12 (m, 2H), 3.45 – 3.51 (m, 2H), 3.78 (s, 3H), 4.36 – 4.41 (m, 1H), 6.83 – 6.92 (m, 4H), 8.27 (s, 1H); Mass (m/z): 353.8 (M+H) <sup>+</sup> .                             |
| 79 | I |                                                                                                               | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.91 – 1.99 (m, 2H), 2.11 – 2.18 (m,                                                                                                                                                                                                                     |

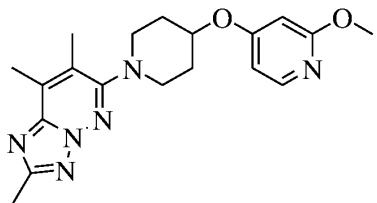
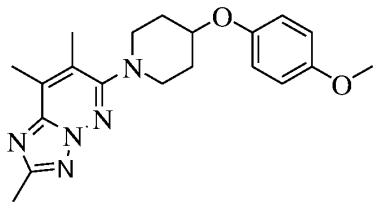
|    |   |                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                              |
|----|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine                                                                                   | 2H), 2.35 (s, 3H), 2.61 (s, 3H), 3.05 – 3.12 (m, 2H), 3.44 – 3.50 (m, 2H), 4.21 – 4.26 (m, 4H), 4.33 – 4.39 (m, 1H), 6.45 – 6.51 (m, 2H), 6.77 – 6.79 (d, $J = 8.8$ Hz, 1H), 8.24 (s, 1H); Mass (m/z): 382.4 (M+H) <sup>+</sup> .                                                                                                                            |
| 80 | I | <br>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.95 – 2.04 (m, 2H), 2.13 – 2.19 (m, 2H), 2.36 (s, 3H), 2.60 (s, 3H), 3.09 – 3.15 (m, 2H), 3.45 – 3.51 (m, 2H), 4.48 – 4.54 (m, 1H), 5.06 – 5.08 (m, 4H), 6.83 – 6.88 (m, 2H), 7.13 – 7.15 (d, $J = 8.4$ Hz, 1H), 8.25 (s, 1H); Mass (m/z): 365.9 (M+H) <sup>+</sup> .                      |
| 81 | I | <br>6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine       | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.94 – 1.97 (m, 2H), 1.99 – 2.01 (m, 2H), 2.35 (s, 3H), 2.60 (s, 3H), 3.07 – 3.12 (m, 2H), 3.13 – 3.48 (m, 2H), 3.90 (s, 3H), 4.36 – 4.40 (m, 1H), 6.70 – 6.72 (d, $J = 8.8$ Hz, 1H), 7.28 (s, 1H), 7.87 – 7.88 (d, $J = 2.8$ Hz, 1H), 7.65 (s, 1H); Mass (m/z): 355.0 (M+H) <sup>+</sup> . |

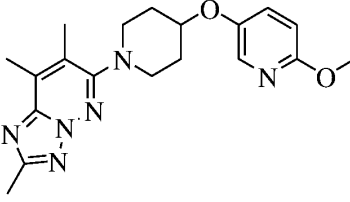
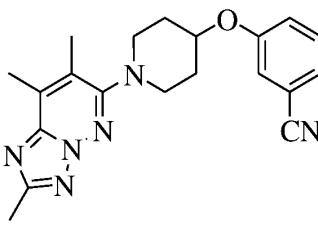
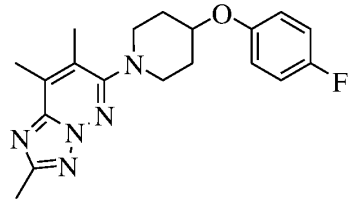
|    |   |                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                        |
|----|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 82 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p>  | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93 – 2.01 (m, 2H), 2.12 – 2.17 (m, 2H), 2.35 (s, 3H), 2.60 (s, 3H), 3.07 – 3.14 (m, 4H), 3.44 – 3.50 (m, 2H), 4.42 – 4.48 (m, 1H), 4.56 – 4.60 (t, <i>J</i> = 8.6 Hz, 2H), 6.43 – 6.46 (m, 2H), 7.06 – 7.08 (m, 1H), 8.24 (s, 1H); Mass (m/z): 366.2 (M+H) <sup>+</sup> .                                  |
| 83 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.92 – 2.00 (m, 2H), 2.10 – 2.15 (m, 2H), 2.35 (s, 3H), 2.60 (s, 3H), 3.05 – 3.11 (m, 2H), 3.17 – 3.21 (t, <i>J</i> = 8.6 Hz, 2H), 3.45 – 3.50 (m, 2H), 4.31 – 4.36 (m, 1H), 4.53 – 4.57 (t, <i>J</i> = 8.6 Hz, 2H), 6.68 – 6.73 (m, 2H), 6.85 (s, 1H), 8.25 (s, 1H); Mass (m/z): 366.2 (M+H) <sup>+</sup> . |
| 84 | I |  <p>6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-b]pyridazine</p>                 | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93 – 2.00 (m, 2H), 2.10 – 2.16 (m, 2H), 2.46 (s, 3H), 3.12 – 3.18 (m, 2H), 3.50 – 3.56 (m, 2H), 3.78 (s, 3H), 4.38 – 4.43 (m, 1H), 6.83 – 6.92 (m, 4H), 7.77 – 7.77 (d, <i>J</i> =                                                                                                                         |

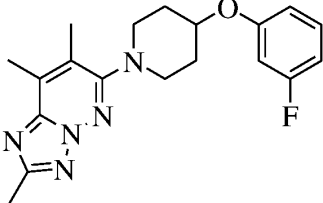
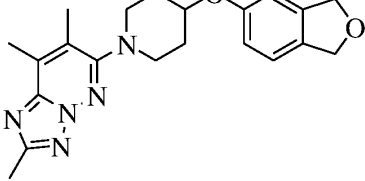
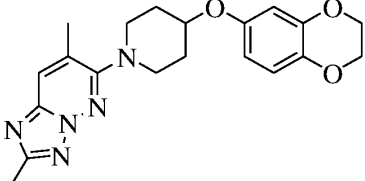
|    |   |                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                 |
|----|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   |                                                                                                                                                                                                  | 1.2 Hz, 1H), 8.27 (s, 1H);<br>Mass (m/z): 340.5 (M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                                            |
| 85 | I |  <p>6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-b]pyridazine</p>              | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.96 – 2.02 (m, 2H), 2.13 – 2.17 (m, 2H), 2.46 (s, 3H), 3.12 – 3.18 (m, 2H), 3.50 – 3.55 (m, 2H), 3.90 (s, 3H), 4.39 – 4.40 (m, 1H), 6.70 – 6.72 (d, <i>J</i> = 8.8 Hz, 1H), 7.26 (s, 1H), 7.78 (s, 1H), 7.87 – 7.88 (d, <i>J</i> = 2.8 Hz, 1H), 8.28 (s, 1H); Mass (m/z): 340.9 (M+H) <sup>+</sup> . |
| 86 | I |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.94 – 1.97 (m, 2H), 2.10 – 2.15 (m, 2H), 2.45 (s, 3H), 3.11 – 3.17 (m, 2H), 3.50 – 3.54 (m, 2H), 4.21 – 4.25 (m, 4H), 4.37 – 4.39 (m, 1H), 6.45 – 6.51 (m, 2H), 6.77 – 6.79 (d, <i>J</i> = 8.8 Hz, 1H), 7.77 (s, 1H), 8.27 (s, 1H); Mass (m/z): 368.2 (M+H) <sup>+</sup> .                           |
| 87 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-b]pyridazine</p>       | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.92– 2.00 (m, 2H), 2.10 – 2.16 (m, 2H), 2.54 (s, 3H), 3.11 – 3.13 (m, 2H), 3.30 – 3.32 (t, <i>J</i> = 8 Hz,                                                                                                                                                                                          |

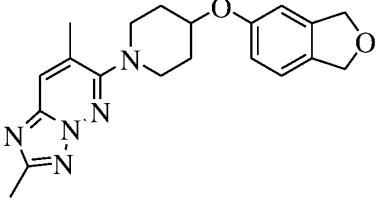
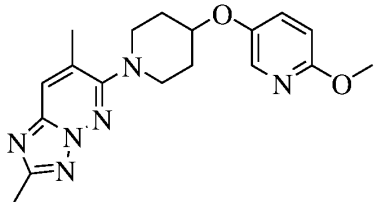
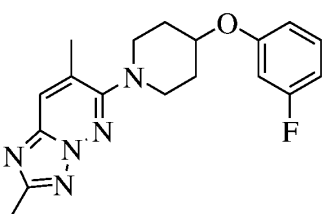
|    |   |                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                              |
|----|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | [1,2,4]triazolo[1,5-b]pyridazine                                                                                                                                                            | 2H), 3.50 – 3.56 (m, 2H), 4.34 – 4.37 (m, 1H), 4.53 – 4.37 (t, $J = 8$ Hz, 2H), 6.68 – 6.73 (m, 2H), 6.85 – 6.85 (d, $J = 1.2$ Hz, 1H), 7.77 (s, 1H), 8.27 (s, 1H); Mass (m/z): 352.2(M+H) <sup>+</sup> .                                                                                                                                                    |
| 88 | I |  <p>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.99– 2.04 (m, 2H), 2.13 – 2.19 (m, 2H), 2.46 (s, 3H), 3.15 – 3.21 (m, 2H), 3.50 – 3.5 (m, 2H), 4.32 (m, 1H), 5.06 – 5.08 (m, 4H), 6.68 – 6.73 (m, 2H), 7.13 – 7.16 (d, $J = 8.4$ Hz, 1H), 7.78 (s, 1H), 8.28 (s, 1H); Mass (m/z): 351.(M+H) <sup>+</sup> .                                 |
| 89 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-b]pyridazine</p>  | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.93 – 2.01 (m, 2H), 2.11 – 2.18 (m, 2H), 2.45 (s, 3H), 3.12 – 3.22 (m, 4H), 3.49 – 3.55 (m, 2H), 4.44 – 4.49 (m, 1H), 4.56 – 4.60 (t, $J = 8.6$ Hz, 2H), 6.43 – 6.46 (m, 2H), 7.06 – 7.08 (m, 1H), 7.77 – 7.77 (d, $J = 0.8$ Hz, 1H), 8.27 (s, 1H); Mass (m/z): 351.8 (M+H) <sup>+</sup> . |

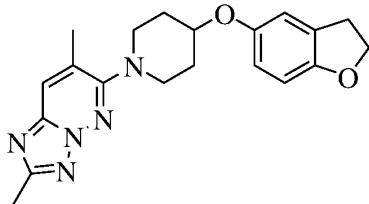
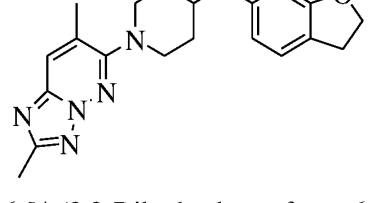
|    |   |                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                 |
|----|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 90 | I |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 2.11 – 2.12 (m, 2H), 2.14 – 2.15 (m, 2H), 2.32 (s, 3H), 2.55 – 2.58 (d, 6H), 3.02 – 3.07 (m, 2H), 3.40 – 3.49 (m, 2H), 4.21 – 4.25 (m, 4H), 4.32 – 4.36 (m, 1H), 6.45 – 6.50 (m, 2H), 6.77 – 6.79 (d, <i>J</i> = 8.8 Hz, 1H); Mass (m/z): 395.9 (M+H) <sup>+</sup> .                                                                  |
| 91 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p>     | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.78 – 1.80 (m, 2H), 2.06 – 2.16 (m, 2H), 2.29 (s, 3H), 2.43 (s, 3H), 2.50 (s, 3H), 3.11 – 3.13 (m, 2H), 3.30 – 3.32 (t, <i>J</i> = 8.0 Hz, 2H), 3.50 – 3.56 (m, 2H), 4.34 – 4.37 (m, 1H), 4.49 – 4.53 (t, <i>J</i> = 8.0 Hz, 2H), 6.44 – 6.46 (m, 2H), 7.08 – 7.10 (d, <i>J</i> = 7.6 Hz, 1H); Mass (m/z): 380.2(M+H) <sup>+</sup> . |
| 92 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p>     | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.92 – 2.00 (m, 2H), 2.10 – 2.17 (m, 2H), 2.42 (s, 3H), 2.57 (s, 3H), 2.66 (s, 3H), 3.09 – 3.16 (m, 4H), 3.46 – 3.52 (m, 2H), 4.39 – 4.58 (m,                                                                                                                                                                                         |

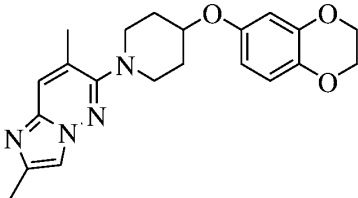
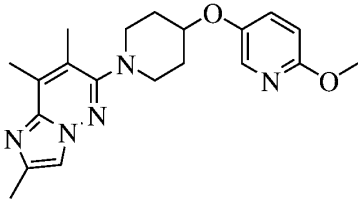
|    |   |                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                   |
|----|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |   | trimethyl-[1,2,4]triazolo[1,5-b]pyridazine                                                                                                                                                 | <sup>1</sup> H), 4.60 – 4.65 (m, 2H), 6.43 – 6.45 (m, 2H), 7.06 – 7.08 (m, 1H); Mass (m/z): 379.9 (M+H) <sup>+</sup> .                                                                                                                                                                                                                                                            |
| 93 | I |  <p>6-[4-(2-Methoxy-pyridin-4-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.95- 2.02 (m, 2H), 2.14 – 2.19 (m, 2H), 2.33 (s, 3H), 2.56 – 2.59 (s, 6H), 3.07 – 3.13(m, 2H), 3.41 – 3.45 (m, 2H), 3.92 (s, 3H) 4.55 – 4.57 (m, 1H), 6.22 – 6.22 (d, <i>J</i> = 1.6 Hz 1H), 6.48 – 6.50 (dd, <i>J</i> = 6 Hz, 2 Hz, 1H), 7.98 – 7.99 (d, <i>J</i> = 4 Hz, 1H); Mass (m/z): 368.1 (M+H) <sup>+</sup> . |
| 94 | I |  <p>6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p>       | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93 – 1.98 (m, 2H), 2.11 – 2.15 (m, 2H), 2.33 (s, 3H), 2.56 (s, 3H), 2.58 (s, 3H), 3.02 – 3.08 (m, 2H), 3.42 – 3.46 (m, 2H), 3.78 (s, 3H), 4.36 – 4.38 (m, 1H), 6.83 – 6.85 (d, <i>J</i> = 9.2 Hz, 2H), 6.89 – 6.91 (d, <i>J</i> = 9.2 Hz, 2H); Mass (m/z): 368.0 (M+H) <sup>+</sup> .                                 |

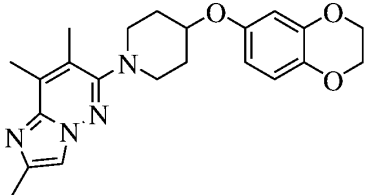
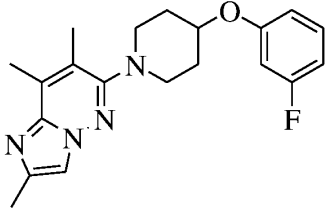
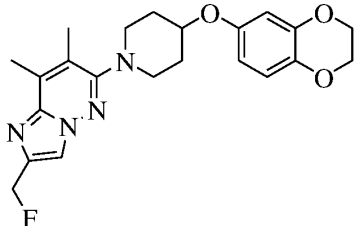
|    |   |                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                        |
|----|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 95 | I |  <p>6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.92 – 1.99 (m, 2H), 2.10 – 2.12 (m, 2H), 2.41 (s, 3H), 2.54 (s, 3H), 2.57 (s, 3H), 3.12 – 3.16 (m, 2H), 3.47 – 3.49 (m, 2H), 3.87 (s, 3H), 4.53 – 4.60 (m, 1H), 6.77 – 6.79 (d, <i>J</i> = 8.8 Hz, 1H), 7.43 – 7.46 (m, 1H), 7.86 – 7.87 (d, <i>J</i> = 2.8 Hz, 1H); Mass (m/z): 368.9 (M+H) <sup>+</sup> . |
| 96 | I |  <p>3-[1-(2,7,8-Trimethyl-[1,2,4]triazolo[1,5-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile</p>      | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.96 – 2.03 (m, 2H), 2.14 – 2.16 (m, 2H), 2.33 (s, 3H), 2.57 (s, 3H), 2.59 (s, 3H), 3.08 – 3.14 (m, 2H), 3.43 – 3.47 (m, 2H), 4.53 – 4.56 (m, 1H), 7.16 – 7.22 (m, 2H), 7.37 – 7.41 (m, 2H); Mass (m/z): 363.43(M+H) <sup>+</sup> .                                                                          |
| 97 | I |  <p>6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p>        | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.97 – 2.03 (m, 2H), 2.17 – 2.19 (m, 2H), 2.33 (s, 3H), 2.56 (s, 3H), 2.58 (s, 3H), 3.07 – 3.12 (m, 2H), 3.44 – 3.46 (m, 2H), 4.42 – 4.51 (m, 1H), 6.90 – 6.91 (m, 2H), 6.96 – 6.98 (m, 2H); Mass                                                                                                            |

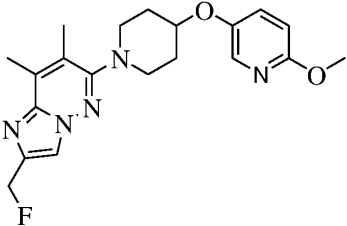
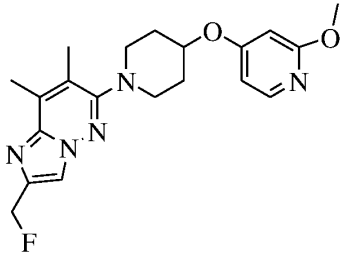
|     |   |                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                       |
|-----|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |   |                                                                                                                                                                                                      | (m/z): 356.1(M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                                                      |
| 98  | I |  <p>6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p>                    | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.95 – 2.02 (m, 2H), 2.13 – 2.18 (m, 2H), 2.33 (s, 3H), 2.56 (s, 3H), 2.59 (s, 3H), 3.06 – 3.12 (m, 2H), 3.42 – 3.46 (m, 2H), 4.48 – 4.51 (m, 1H), 6.64 – 6.67 (m, 2H), 7.20 – 7.26 (m, 2H); Mass (m/z): 355.9(M+H) <sup>+</sup> .                                          |
| 99  | I |  <p>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p>  | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.95 – 2.02 (m, 2H), 2.12 – 2.18 (m, 2H), 2.33 (s, 3H), 2.56 (s, 3H), 2.58 (s, 3H), 3.05 – 3.06 (m, 2H), 3.43 – 3.47 (m, 2H), 4.47 – 4.51 (m, 1H), 5.06 – 5.08 (m, 4H), 6.83 – 6.87 (m, 2H), 7.13 – 7.15 (d, <i>J</i> = 8.0 Hz, 1H); Mass (m/z): 379.8 (M+H) <sup>+</sup> . |
| 100 | I |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.56 – 1.98 (m, 2H), 2.10 – 2.14 (m, 2H), 2.42 (s, 3H), 2.57 (s, 3H), 3.07 – 3.13 (m, 2H), 3.46 – 3.50 (m, 2H), 4.21 – 4.25 (m, 4H), 4.34 – 4.38 (m, 1H), 6.45 – 6.50 (m,                                                                                                   |

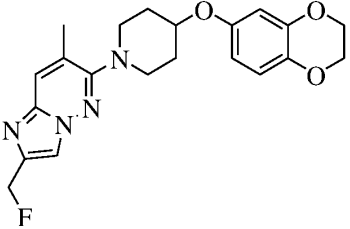
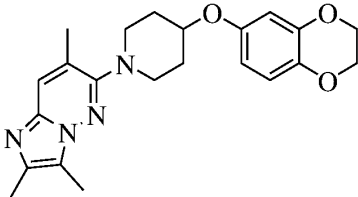
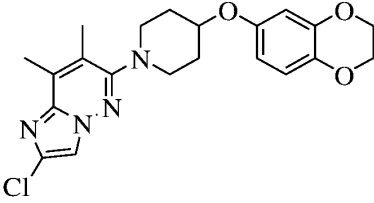
|     |   |                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                              |
|-----|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |   |                                                                                                                                                                                                 | 2H), 6.77 – 6.79 (d, $J = 8.8$ Hz, 1H), 7.67 (s, 1H); Mass (m/z): 382.0 (M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                 |
| 101 | I |  <p>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.95 – 2.00 (m, 2H), 2.12 – 2.18 (m, 2H), 2.44 (s, 3H), 2.58 (s, 3H), 3.11 – 3.17 (m, 2H), 3.47 – 3.53 (m, 2H), 4.49 – 4.53 (m, 1H), 5.07 – 5.08 (m, 4H), 6.83 – 6.88 (m, 2H), 7.13 – 7.15 (d, $J = 8.4$ Hz, 1H), 7.65 (s, 1H); Mass (m/z): 365.9 (M+H) <sup>+</sup> .                      |
| 102 | I |  <p>6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p>       | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 2.12 – 2.13 (m, 2H), 2.16 – 2.17 (m, 2H), 2.43 (s, 3H), 2.58 (s, 3H), 3.08 – 3.14 (m, 2H), 3.47 – 3.53 (m, 2H), 3.90 (s, 3H), 4.36 – 4.39 (m, 1H), 6.69 – 6.72 (d, $J = 8.8$ Hz, 1H), 7.27 (s, 1H), 7.65 (s, 1H), 7.86 – 7.87 (d, $J = 2.8$ Hz, 1H); Mass (m/z): 354.9 (M+H) <sup>+</sup> . |
| 103 | I |                                                                                                              | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.95 – 2.02 (m, 2H), 2.13 – 2.18 (m, 2H), 2.43 (s, 3H), 2.58 (s,                                                                                                                                                                                                                            |

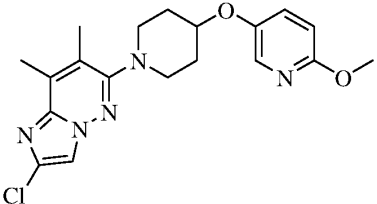
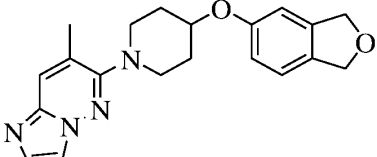
|     |   |                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                  |
|-----|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |   | 6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine                                                                                                          | 3H), 3.12 – 3.18 (m, 2H), 3.46 – 3.52 (m, 2H), 4.50 – 4.53 (m, 1H), 6.64 – 6.67 (m, 3H), 7.20 – 7.22 (m, 1H), 7.65 (s, 1H); Mass (m/z): 341.9 (M+H)+.                                                                                                                                                                                                            |
| 104 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p>   | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.92 – 2.00 (m, 2H), 2.10 – 2.17 (m, 2H), 2.42 (s, 3H), 2.57 (s, 3H), 3.09 – 3.16 (m, 4H), 3.46 – 3.52 (m, 2H), 4.39 – 4.58 (m, 1H), 4.60 – 4.65 (t, <i>J</i> = 8.80 Hz, 2H), 6.43 – 6.45 (m, 2H), 7.06 – 7.08 (m, 1H), 7.64 – 7.64 (d, <i>J</i> = 1.2 Hz, 1H); Mass (m/z): 365.6 (M+H) <sup>+</sup> . |
| 105 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.92 – 2.00 (m, 2H), 2.11 – 2.17 (m, 2H), 2.42 (s, 3H), 2.57 (s, 3H), 3.09 – 3.16 (m, 4H), 3.46 – 3.51 (m, 2H), 4.43 – 4.47 (m, 1H), 4.56 – 4.60 (t, <i>J</i> = 8.60 Hz, 2H), 6.43 – 6.45 (m, 2H), 7.06 – 7.08 (d, <i>J</i> = 8.40 Hz, 1H), 7.64 (s, 1H); Mass (m/z): 366.6 (M+H) <sup>+</sup> .       |

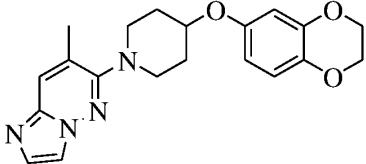
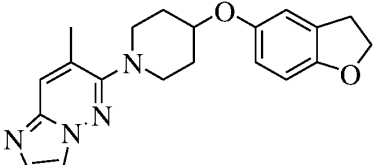
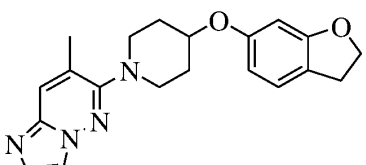
|     |   |                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                           |
|-----|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 106 | I |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,7-dimethyl-imidazo[1,2-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.74 – 1.81 (m, 2H), 2.04 – 2.12 (m, 2H), 2.44 (s, 3H), 2.67 (s, 3H), 3.10 – 3.15 (m, 2H), 3.43 – 3.44 (m, 2H), 4.16 – 4.21 (m, 4H), 4.48 – 4.50 (m, 1H), 6.64 – 6.65 (m, 2H), 6.75 – 6.77 (d, <i>J</i> = 8.8 Hz, 1H), 8.09 (s, 1H), 8.15 (s, 1H), 8.17; Mass (m/z): 381.0 (M+H) <sup>+</sup> . |
| 107 | I |  <p>6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-imidazo[1,2-b]pyridazine</p>       | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.92 – 1.99 (m, 2H), 2.10 – 2.12 (m, 2H), 2.26 (s, 3H), 2.45 (s, 3H), 2.53 (s, 3H), 2.95 – 3.00 (m, 2H), 3.34 – 3.38 (m, 2H), 3.90 (s, 3H), 4.33 – 4.36 (m, 1H), 6.69 – 6.71 (d, <i>J</i> = 9.2 Hz, 1H), 7.27 (s, 1H), 7.46 (s, 1H), 7.87 (s, 1H); Mass (m/z): 368.3 (M+H) <sup>+</sup> .       |

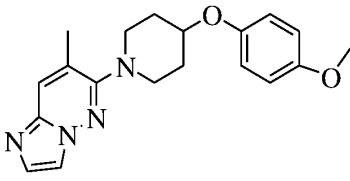
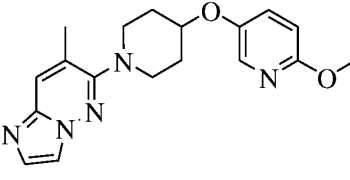
|     |   |                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                            |
|-----|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 108 | I |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-imidazo[1,2-b]pyridazine</p>  | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.90 – 1.95 (m, 2H), 2.09 – 2.11 (m, 2H), 2.25 (s, 3H), 2.42 – 2.44 (s, 3H), 2.50 (m, 3H), 2.94 – 2.99 (m, 2H), 3.33 – 3.36 (m, 2H), 4.21 – 4.25 (m, 4H), 4.32 – 4.25 (m, 1H), 6.45 – 6.65 (m, 2H), 6.76 – 6.79 (d, <i>J</i> = 8.8 Hz, 1H), 7.46 (s, 1H); Mass (m/z): 394.9 (M+H) <sup>+</sup> . |
| 109 | I |  <p>6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-2,7,8-trimethyl-imidazo[1,2-b]pyridazine</p>                     | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.91 – 1.96 (m, 2H), 2.09 – 2.11 (m, 2H), 2.25 (s, 3H), 2.42 – 2.44 (s, 3H), 2.53 (m, 3H), 2.94 – 2.99 (m, 2H), 3.33 – 3.36 (m, 2H), 4.48 – 4.48 (m, 1H), 6.64 – 6.66 (m, 2H), 6.71 – 6.73 (m, 2H), 7.46 (s, 1H); Mass (m/z): 354.9 (M+H) <sup>+</sup> .                                         |
| 110 | I |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2-fluoromethyl-imidazo[1,2-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.95 – 1.99 (m, 2H), 2.11 – 2.13 (m, 2H), 2.27 (s, 3H), 2.55 (s, 3H), 2.99 – 3.05 (m, 2H), 3.36 – 3.39 (m, 2H), 4.22 – 4.25 (m, 4H), 4.34 – 4.39 (m, 1H), 5.45 (s, 1H), 5.57                                                                                                                     |

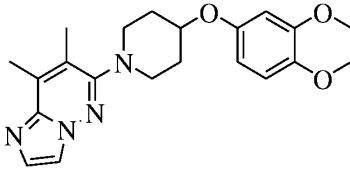
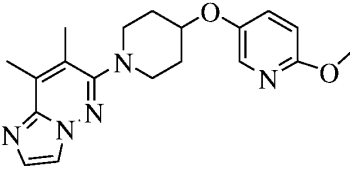
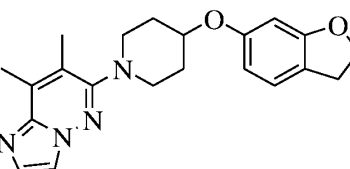
|     |   |                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |   | 7,8-dimethyl-imidazo[1,2-b]pyridazine                                                                                                                                                           | (s, 1H), 6.45 – 6.51 (m, 2H), 6.77 – 6.79 (d, $J = 8.8$ Hz, 1H), 7.77 (s, 1H); Mass (m/z): 413.4 (M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                                        |
| 111 | I |  <p>2-Fluoromethyl-6-[4-(6-methoxypyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine</p>   | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.95 – 1.99 (m, 2H), 2.12 – 2.13 (m, 2H), 2.28 (s, 3H), 2.56 (s, 3H), 2.98 – 3.03 (m, 2H), 3.37 – 3.41 (m, 2H), 3.90 (s, 3H), 4.36 – 4.37 (m, 1H), 5.41 (s, 1H), 5.57 (s, 1H), 6.69 – 6.72 (d, $J = 9.2$ Hz, 1H), 7.77 – 7.78 (d, $J = 2.8$ Hz, 1H), 7.88 (s, 1H), 8.06 (s, 1H); Mass (m/z): 386.4 (M+H) <sup>+</sup> .                            |
| 112 | I |  <p>2-Fluoromethyl-6-[4-(2-methoxypyridin-4-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.98 – 2.02 (m, 2H), 2.13 – 2.18 (m, 2H), 2.56 (s, 3H), 2.28 (s, 3H), 3.02 – 3.07 (m, 2H), 3.35 – 3.38 (m, 2H), 3.92 (s, 3H), 4.55 – 4.57 (s, 1H), 5.45 (s, 1H), 5.58 (s, 1H), 6.23 – 6.23 (d, $J = 1.2$ Hz, 1H), 6.48 – 6.50 (m, 1H), 7.78 – 7.88 (d, $J = 3.2$ Hz, 1H), 7.98 – 7.99 (d, $J = 6$ Hz, 1H); Mass (m/z): 386.44 (M+H) <sup>+</sup> . |

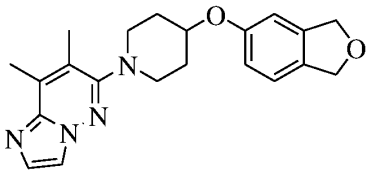
|     |   |                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                        |
|-----|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 113 | I |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2-fluoromethyl-7-methyl-imidazo[1,2-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93 – 1.95 (m, 2H), 2.09 – 2.12 (m, 2H), 2.36 (s, 3H), 3.02 – 3.07 (s, 2H), 3.40 – 3.44 (m, 2H), 4.22 – 4.25 (m, 4H), 4.35 – 4.37 (m, 1H), 5.43 (s, 1H), 5.55 (s, 1H), 6.45 – 6.51 (m, 2H), 6.77 – 6.79 (m, 1H), 7.56 (s, 1H), 7.78 – 7.79 (d, <i>J</i> = 2.8 Hz, 1H); Mass (m/z): 399.0 (M+H) <sup>+</sup> .               |
| 114 | I |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,3,7-trimethyl-imidazo[1,2-b]pyridazine</p>       | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.78 – 1.80 (m, 2H), 2.05 – 2.08 (m, 2H), 2.43 (s, 3H), 2.44 (s, 3H), 2.47 (s, 3H), 3.16 – 3.20 (m, 2H), 3.49 – 3.50 (m, 2H), 4.16 – 4.21 (m, 4H), 4.51 – 4.52 (m, 1H), 6.47 – 6.50 (m, 2H), 6.75 – 6.77 (d, <i>J</i> = 8.8 Hz, 1H), 8.09 (s, 1H); Mass (m/z): 395.3 (M+H) <sup>+</sup> .                                    |
| 115 | I |  <p>2-Chloro-6-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine</p>     | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93 – 1.96 (m, 2H), 2.09 – 2.13 (m, 2H), 2.26 (s, 3H), 2.51 (s, 3H), 2.96 – 3.00 (m, 2H), 3.34 – 3.36 (m, 2H), 4.21 – 4.24 (m, 4H), 4.34 – 4.35 (s, 1H), 5.43 (s, 1H), 5.55 (s, 1H), 6.45 – 6.51 (m, 2H), 6.77 – 6.79 (m, 1H), 7.56 (s, 1H), 7.78 – 7.79 (d, <i>J</i> = 2.8 Hz, 1H); Mass (m/z): 415.0 (M+H) <sup>+</sup> . |

|     |   |                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |   | piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine                                                                                                                                    | <sup>1</sup> H), 6.43 – 6.51 (m, 2H), 6.77 – 6.79 (m, <i>J</i> = 8.0 Hz, 1H), 7.59 (s, 1H); Mass (m/z): 415.1, 417.0 (M+H) <sup>+</sup> .                                                                                                                                                                                                                                                                             |
| 116 | I |  <p>2-Chloro-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.94 – 1.96 (m, 2H), 2.14 – 2.17 (m, 2H), 2.24 – 2.27 (s, 3H), 2.51 – 2.54 (s, 3H), 2.97 – 3.02 (m, 2H), 3.37 (m, 2H), 3.90 (s, 3H), 4.36 (m, 1H), 6.69 – 6.72 (d, <i>J</i> = 9.2 Hz, 1H), 7.11 (s, 1H), 7.51 – 7.59 (s, 1H), 7.87 (s, 1H); Mass (m/z): 387.9, 390.0 (M+H) <sup>+</sup> .                                                                   |
| 117 | I |  <p>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine</p>    | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.77 – 1.84 (m, 2H), 2.07 – 2.11 (m, 2H), 2.32 (s, 3H), 3.00 – 3.07 (m, 2H), 3.29 – 4.09 (m, 2H), 4.57 – 4.60 (m, 1H), 4.93 – 4.95 (m, 4H), 6.89 – 6.92 (m, 1H), 6.97 – 6.98 (d, <i>J</i> = 1.6 Hz, 1H), 7.19 – 7.21 (d, <i>J</i> = 8.4 Hz, 1H), 7.52 – 7.52 (d, <i>J</i> = 1.2 Hz, 1H), 7.80 (s, 1H), 7.97 (s, 1H); Mass (m/z): 351.3 (M+H) <sup>+</sup> . |

|     |   |                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 118 | I |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.90 – 1.98 (m, 2H), 2.07 – 2.14 (m, 2H), 3.01 – 3.07 (m, 2H), 3.39 – 3.45 (m, 2H), 4.20 – 4.26 (m, 4H), 4.34 – 4.38 (m, 1H), 6.45 – 6.48 (m, 4H), 6.50 – 6.51 (d, <i>J</i> = 2.8 Hz, 1H), 6.77 – 6.79 (d, <i>J</i> = 8.4 Hz, 1H), 7.56 (s, 1H), 7.62 (s, 1H), 7.71 (s, 1H); Mass (m/z): 367.4 (M+H) <sup>+</sup> .                                  |
| 119 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine</p>     | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.90 – 1.98 (m, 2H), 2.07 – 2.14 (m, 2H), 2.37 (s, 3H), 3.01 – 3.07 (m, 2H), 3.17 – 3.21 (t, <i>J</i> = 8.8 Hz, 2H), 3.40 – 3.46 (m, 2H), 4.32 – 4.35 (m, 1H), 4.53 – 4.57 (t, <i>J</i> = 8.4 Hz, 2H), 6.70 – 6.71 (m, 2H), 6.85 – 6.85 (d, <i>J</i> = 1.2 Hz, 1H), 7.52 (s, 1H), 7.64 (s, 1H), 7.71 (s, 1H); Mass (m/z): 350.8 (M+H) <sup>+</sup> . |
| 120 | I |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine</p>     | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.90 – 2.00 (m, 2H), 2.10 – 2.15 (m, 2H), 2.36 (s, 3H), 3.02 – 3.08 (m, 2H), 3.39 – 3.49 (m, 2H), 4.43 – 4.46 (m,                                                                                                                                                                                                                                    |

|     |    |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                               |
|-----|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |    | imidazo[1,2-b]pyridazine                                                                                                                                                      | 1H), 4.56 – 4.60 (m, 4H), 6.44 – 6.46 (m, 2H), 6.98 – 6.99 (m, 1H), 7.06 – 7.08 (m, 1H), 7.52 – 7.55 (m, 1H), 7.71 – 7.73 (m, 1H) ; Mass (m/z): 351.3 (M+H) <sup>+</sup> .                                                                                                                                                                                                    |
| 121 | I  |  <p>6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine</p>           | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.90 – 1.99 (m, 2H), 2.03 – 2.07 (m, 2H), 2.29 (s, 3H), 3.00 – 3.04 (m, 2H), 3.34 – 3.38 (m, 2H), 3.71 (s, 3H), 4.07 – 4.10 (m, 1H), 6.76 – 6.79 (m, 2H), 6.82 – 6.85 (m, 2H), 7.45 – 7.48 (m, 2H), 7.54 (s, 1H); Mass (m/z): 339.3 (M+H) <sup>+</sup> .                                                            |
| 122 | II |  <p>6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.92 – 1.99 (m, 2H), 2.10 – 2.15 (m, 2H), 2.36 (s, 3H), 3.02 – 3.08 (m, 2H), 3.41 – 3.49 (m, 2H), 3.90 (s, 3H), 4.37 – 4.40 (m, 1H), 6.70 – 6.72 (d, <i>J</i> = 8.8 Hz, 1H), 7.26 (s, 1H), 7.56 (s, 1H), 7.61 (s, 1H), 7.71 (s, 1H), 7.87 – 7.88 (d, <i>J</i> = 2.8 Hz, 1H); Mass (m/z): 339.8 (M+H) <sup>+</sup> . |

|     |    |                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                               |
|-----|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 123 | II |  <p>6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine</p> | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.93 – 1.95 (m, 2H), 2.10 – 2.13 (m, 2H), 2.27 (s, 3H), 2.56 (s, 3H), 2.97 – 3.01 (m, 2H), 3.35 – 3.39 (m, 2H), 4.21 – 4.25 (m, 4H), 4.36 – 4.26 (m, 1H), 6.46 – 6.51 (m, 2H), 6.77 – 6.79 (d, <i>J</i> = 8.8 Hz, 1H), 7.54 (s, 1H), 7.69 (s, 1H); Mass (m/z): 381.3 (M+H) <sup>+</sup> .                           |
| 124 | II |  <p>6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine</p>          | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.92 – 1.99 (m, 2H), 2.00 – 2.16 (m, 2H), 2.28 (s, 3H), 2.56 (s, 3H), 2.97 – 3.03 (m, 2H), 3.36 – 3.49 (m, 2H), 3.90 (s, 3H), 4.34 – 4.39 (m, 1H), 6.69 – 6.72 (d, <i>J</i> = 8.8 Hz, 1H), 7.26 (s, 1H), 7.54 (s, 1H), 7.70 (s, 1H), 7.87 – 7.88 (d, <i>J</i> = 2.8 Hz, 1H); Mass (m/z): 354.2 (M+H) <sup>+</sup> . |
| 125 | II |  <p>6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine</p>     | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) δ ppm: 1.95 – 1.99 (m, 2H), 2.10 – 2.15 (m, 2H), 2.29 (s, 3H), 2.61 – 2.62 (s, 3H), 3.02 – 3.08 (m, 2H), 3.12 – 3.17 (t, <i>J</i> = 8.4 Hz, 2H), 3.38 – 3.42 (m,                                                                                                                                                           |

|     |    |                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |    | b]pyridazine                                                                                                                                                                        | 2H), 4.45 – 4.47 (m, 1H), 4.56 – 4.60 (t, $J = 8.4$ Hz, 2H), 6.43– 6.46 (m, 2H), 7.06 – 7.08 (d, $J = 8.4$ Hz, 1H), 8.72 (s, 1H), 8.89 (s, 1H); Mass (m/z): 365.2 (M+H) <sup>+</sup> .                                                                                                                                                                                                                              |
| 126 | II | <br>6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine | <sup>1</sup> H – NMR (CDCl <sub>3</sub> , 400 MHz) $\delta$ ppm: 1.92 – 1.98 (m, 2H), 2.08 – 2.13 (m, 2H), 2.28 (s, 3H), 2.28 (s, 3H), 2.95 – 3.02 (m, 2H), 3.17 – 3.21 (m, 2H), 3.35 – 3.41 (m, 2H), 4.31– 4.33 (m, 1H), 4.53 – 4.57 (m, 2H), 6.82 – 6.71 (m, 2H), 6.85 – 6.85 (d, $J = 1.2$ Hz, 1H), 7.53 – 7.54 (d, $J = 1.2$ Hz, 1H), 7.69 – 7.69 (d, $J = 1.2$ Hz, 1H); Mass (m/z): 365.2 (M+H) <sup>+</sup> . |

**Example-127: Determination of allosteric potency EC<sub>50</sub> values for muscarinic M4 receptor**

The compounds were tested for their ability to activate the muscarinic M4 receptor. Experimental procedures and results are provided below.

- 5 **A. CRE-Luc reporter assay** - A CHO-K1 cell line (Chinese hamster ovary (CHO) K1 (ATCC CCL-61) was purchased from ATCC), engineered to stably express recombinant human muscarinic M4 receptor and pCRE-Luc reporter system was used for cell-based assay. The assay offers a non-radioactive based approach to determine binding of a compound to GPCRs. In this specific assay, the level of intracellular cyclic AMP which is modulated by

activation or inhibition of the receptor is measured. The recombinant cells harbor luciferase reporter gene under the control of cyclic AMP response element.

The above cells were grown in 96 well clear bottom white plates in Hams F12 medium containing 10% fetal bovine serum (FBS, was purchased from ThermoFisher Scientific). Prior to the addition of compounds or standard agonist, cells were serum starved overnight. Increasing concentrations of test compounds were added along with EC<sub>20</sub> of acetylcholine and forskolin (1  $\mu$ M) in Opti-MEM medium to the cells.

The incubation was continued at 37°C in CO<sub>2</sub> incubator for 4 h. After removal of medium, cells were lysed using lysis buffer, detection reagent was added and luciferase activity was measured in a Luminometer. The reference agonist (10  $\mu$ M) in the presence of forskolin (1  $\mu$ M) stimulated luciferase activity was assigned a value of 100 % while basal luciferase activity i.e. only forskolin (1  $\mu$ M) in the absence of a reference agonist was assigned a value of 0 %. Rest of the luminescent values obtained for compounds at various doses were calculated with reference to stimulated after correcting for basal luciferase activities. Compound activity (%) vs compound concentration was plotted and dose response curves were analyzed using a 4-parameter logistic fit model of GraphPad Prism software. EC<sub>50</sub> values of the compounds were defined as the concentration required in stimulating the luciferase activity by 50 % in presence of EC<sub>20</sub> of acetylcholine and the results are provided in table 1A as EC<sub>50</sub>.

**Table 1A:** Allosteric potency EC<sub>50</sub> values for muscarinic M4 receptor

| Example No. | Human muscarinic M4 receptor PAM EC50 (nM) | Example No. | Human muscarinic M4 receptor PAM EC50 (nM) |
|-------------|--------------------------------------------|-------------|--------------------------------------------|
|             | CRE-Luc reporter assay                     |             | CRE-Luc reporter assay                     |
| <b>1</b>    | 24                                         | <b>42</b>   | 205                                        |
| <b>3</b>    | 102                                        | <b>44</b>   | 16                                         |
| <b>4</b>    | 11.3                                       | <b>46</b>   | 67                                         |
| <b>5</b>    | 100                                        | <b>62</b>   | 32                                         |
| <b>6</b>    | 10                                         | <b>65</b>   | 63                                         |
| <b>7</b>    | 19.3                                       | <b>73</b>   | 17                                         |
| <b>9</b>    | 64                                         | <b>79</b>   | 10                                         |
| <b>11</b>   | 469                                        | <b>80</b>   | 24                                         |
| <b>15</b>   | 475                                        | <b>86</b>   | 48.3                                       |
| <b>16</b>   | 238                                        | <b>87</b>   | 44                                         |
| <b>17</b>   | 154.3                                      | <b>88</b>   | 48                                         |

|    |      |     |     |
|----|------|-----|-----|
| 18 | 136  | 91  | 12  |
| 19 | 48   | 95  | 65  |
| 20 | 30   | 99  | 17  |
| 21 | 49   | 100 | 43  |
| 22 | 355  | 101 | 112 |
| 23 | 85   | 106 | 85  |
| 24 | 12.7 | 108 | 32  |
| 26 | 21   | 117 | 124 |
| 28 | 49   | 118 | 66  |
| 31 | 16   | 119 | 98  |
| 33 | 56   | 123 | 53  |
| 41 | 165  |     |     |

**B. Glosensor cAMP assay** - A HEK293 cell line (human embryonic kidney cells (HEK-293) (ATCC CRL-1573) was purchased from ATCC), engineered to transiently express recombinant human muscarinic M4 receptor and pGloSensor-22F cAMP was used for Glosensor cAMP assay. The assay offers a non-radioactive based approach to determine binding of a compound to GPCRs, uses genetically encoded biosensor variants with cAMP binding domains fused to mutant forms of Photinus pyralis luciferase. Upon binding to cAMP, conformational changes occur that promote large increases in light output. Following pre-equilibration with substrate, cells transiently or stably expressing a biosensor variant can be used to assay GPCR function using a live-cell, nonlytic assay format, enabling facile kinetic measurements of cAMP accumulation or turnover in living cells.

The above cells were grown in 96 well clear bottom white plates in Dulbecco's Modified Eagle Medium containing Glutamax and 10 % fetal bovine serum (FBS, was purchased from ThermoFisher Scientific) at 37 °C in CO<sub>2</sub> incubator for overnight. Prior to the addition of compounds or standard agonist, cells were pre-equilibrated with substrate in CO<sub>2</sub> independent medium containing 10% FBS for 2 h at RT. Increasing concentrations of test compounds were added along with EC<sub>20</sub> of acetylcholine and isoprenaline (0.1 μM) in CO<sub>2</sub> independent medium containing 10 % FBS to the cells.

The incubation was continued at room temperature for 12 minutes. After incubation, luciferase activity was measured in a Luminometer. The reference agonist (10 μM) in the presence of isoprenaline stimulated luciferase activity was assigned a value of 100 % while basal luciferase activity i.e., only isoprenaline in the absence of a reference agonist was assigned a value of 0 %. Rest of the luminescent values obtained for compounds at various doses were calculated with reference to stimulated after correcting for basal luciferase

activities. Compound activity (%) vs compound concentration was plotted and dose response curves were analyzed using a 4-parameter logistic fit model of GraphPad Prism software. EC<sub>50</sub> values of the compounds were defined as the concentration required in stimulating the luciferase activity by 50 % in presence of EC<sub>20</sub> of acetylcholine and the results are provided in table 1B as EC<sub>50</sub>.

**Table 1B:** Allosteric potency EC<sub>50</sub> values for muscarinic M4 receptor

| Example No. | Human muscarinic M4 receptor PAM EC <sub>50</sub> (nM) |
|-------------|--------------------------------------------------------|
|             | Glosensor cAMP assay                                   |
| 1           | 58                                                     |
| 4           | 3.4                                                    |
| 7           | 4                                                      |
| 17          | 22                                                     |
| 19          | 17                                                     |
| 20          | 20                                                     |
| 21          | 95                                                     |
| 22          | 92                                                     |
| 23          | 31                                                     |
| 26          | 57                                                     |
| 42          | 36                                                     |
| 86          | 28                                                     |
| 88          | 19                                                     |
| 99          | 4                                                      |

**C. Muscarinic M2 CRE-Luc reporter assay** - A CHO-K1 cell line (Chinese hamster ovary (CHO) K1 (ATCC CCL-61) was purchased from ATCC), engineered to stably express recombinant human muscarinic M2 receptor and pCRE-Luc reporter system was used for cell-based assay. The assay offers a non-radioactive based approach to determine binding of a compound to GPCRs. In this specific assay, the level of intracellular cyclic AMP which is modulated by activation or inhibition of the receptor is measured. The recombinant cells harbor luciferase reporter gene under the control of cyclic AMP response element.

The above cells were grown in 96 well clear bottom white plates in Hams F12 medium containing 10% fetal bovine serum (FBS, was purchased from ThermoFisher Scientific). Prior to the addition of compounds or standard agonist, cells were serum starved overnight. Increasing concentrations of test compounds were added along with EC<sub>20</sub> of acetylcholine and forskolin (1  $\mu$ M) in Opti-MEM medium to the cells.

The incubation was continued at 37°C in CO<sub>2</sub> incubator for 4 h. After removal of medium, cells were lysed using lysis buffer, detection reagent was added and luciferase activity was measured in a Luminometer. The reference agonist (10 µM) in the presence of forskolin (1 µM) stimulated luciferase activity was assigned a value of 100 % while basal luciferase activity i.e. only forskolin (1 µM) in the absence of a reference agonist was assigned a value of 0 %. Rest of the luminescent values obtained for compounds at various doses were calculated with reference to stimulated after correcting for basal luciferase activities. Compound activity (%) vs compound concentration was plotted and dose response curves were analyzed using a 4-parameter logistic fit model of GraphPad Prism software.

EC<sub>50</sub> values of the compounds were defined as the concentration required in stimulating the luciferase activity by 50 % in presence of EC<sub>20</sub> of acetylcholine and the results are provided in table 1C as EC<sub>50</sub>.

**Table 1C:** Allosteric potency EC<sub>50</sub> values for muscarinic M2 receptor

| Example No. | Human muscarinic M2 receptor PAM EC50 (nM) |
|-------------|--------------------------------------------|
|             | CRE-Luc reporter assay                     |
| <b>1</b>    | 3001                                       |
| <b>7</b>    | >10000                                     |
| <b>17</b>   | >10000                                     |
| <b>18</b>   | >10000                                     |
| <b>21</b>   | 3366                                       |
| <b>23</b>   | >10000                                     |
| <b>26</b>   | 2282                                       |
| <b>86</b>   | >10000                                     |

**Example-128: Rodent pharmacokinetic study**

Male Wistar rats (250 ± 50 grams) were used as experimental animals. Animals were housed individually in polypropylene cages. Two days prior to study, male Wistar rats were anesthetized with isoflurane for surgical placement of jugular vein catheter. Rats were administered with test compound at a dose of 5 mg/kg and 2 mL/kg as dose volume. Rats received food and water *ad libitum* during acclimatization, surgical recovery and study.

Formulation for intraperitoneal administration was prepared using 5 % v/v DMSO + 5 % v/v Solutol HS15 + 90 % v/v Water for injection as vehicle. The dose formulations were prepared freshly on the day of dosing.

Post dosing, 200  $\mu$ L of blood sample was collected at each time point through the jugular vein and replenished with an equivalent volume of normal saline. The collected blood sample was transferred into a labeled eppendorf tube containing 10  $\mu$ L of sodium heparin (1000 IU/mL) as an anticoagulant. Blood samples were collected at 0.08, 0.25, 0.5, 1, 2, 3, 5, 7 and 24 h post-dose. Blood was centrifuged at 4,000 revolutions per minute (rpm) for 10 min. Plasma was separated and stored frozen at -80 °C until analysis. The concentrations of the test compounds were quantified in plasma by qualified LC-MS/MS method using a suitable extraction technique. Study samples were analyzed using calibration samples in the batch and quality control samples spread across the batch.

10

Pharmacokinetic parameters  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-t}$ ,  $t_{1/2}$  were calculated using a standard non-compartmental model by using Phoenix WinNonlin 8.1 version Software package. The pharmacokinetic profile of the test compounds is given in the table-2 below:

15 **Table 2:** Pharmacokinetic profile of the compounds of the present invention

| Example No. | $C_{max}$<br>(ng/mL) | $T_{max}$<br>(h) | $AUC_{0-t}$<br>(ng.h/mL) | $t_{1/2}$<br>(h) |
|-------------|----------------------|------------------|--------------------------|------------------|
| <b>1</b>    | 10713 $\pm$ 2106     | 0.25             | 41475 $\pm$ 41126        | 1.94 $\pm$ 1.44  |
| <b>7</b>    | 10515 $\pm$ 4685     | 0.56 $\pm$ 0.31  | 93175 $\pm$ 51019        | 3.45 $\pm$ 0.86  |
| <b>19</b>   | 3688 $\pm$ 870       | 0.31 $\pm$ 0.13  | 4475 $\pm$ 487           | 0.84 $\pm$ 0.43  |

#### Example-129: Antagonism of amphetamine induced hyperlocomotion

Male Wistar rats of 230-250 g weight were used. The body weights of the rats were recorded. Rats were randomized according to their body weights. Animals were brought to the laboratory 1 h prior to acclimatizing to the laboratory conditions. The open field is a black colored arena of 51 x 51 x 51 cm enclosed by black plastic walls of same dimensions. Rats were habituated to the open field arena for a period of 30 minutes. Animals were administered respective treatments (vehicle or test compounds) based on the brain exposures. After the habituation period, animals were challenged with amphetamine (0.5 mg/kg, *s.c.*) or vehicle. Then the animals were placed in open field arenas and distance traveled by rats was tracked for 120 minutes using Videomot software. Data was analyzed using GraphPad prism. The results of the test compounds are given in the table 3 below:

25

**Table-3:** Antipsychotic like activity of the compounds of the present invention

| Example No. | Percent Rerversal    |                       | Inference |
|-------------|----------------------|-----------------------|-----------|
|             | 3 mg/kg, <i>i.p.</i> | 10 mg/kg, <i>i.p.</i> |           |
| <b>1</b>    | 26                   | 67                    | Active    |
| <b>7</b>    | 59                   | 73                    | Active    |
| <b>19</b>   | 41                   | 61                    | Active    |

**Example-130: Receptor Occupancy Study in Rats**

Male Wistar rats (250 ± 50 grams) were used as experimental animals. Animals were housed individually in polypropylene cages and acclimatized to the experimental condition for 4 days. On the day of the experiment, rats were administered with vehicle (10 mL/Kg) or test compound (3, 10 or 30 mg/Kg) intraperitoneally. At T<sub>max</sub> of the test compound, all rats were intravenously administered with MK-6884, 3 µg/Kg (tracer), through lateral tail vein. After 5 minutes of tracer administration, rats were killed by cervical dislocation, brain was separated from the skull, splashed with ice cold water, and two brain regions (striatum and cerebellum) were isolated and transferred into respective pre-labeled/weighed microcentrifuge tubes and stored on dry ice or -80 °C until processed for tracer extraction and analysis using LC-MS/MS based method. Study samples were analyzed for tracer concentrations with calibration samples in the batch and quality control samples spread across the batch. Receptor occupancy in striatum was calculated using ratio method.

**Table 4:** Receptor occupancy of test compounds of the present invention

| Example No. | Receptor Occupancy (%) |                       |
|-------------|------------------------|-----------------------|
|             | 10 mg/kg, <i>i.p.</i>  | 30 mg/kg, <i>i.p.</i> |
| <b>1</b>    | 37.7 ± 5.8             | 52.5 ± 3.9            |
| <b>7</b>    | 47.0 ± 3.8             | 62.5 ± 3.6            |
| <b>19</b>   | 34.0 ± 4.5             | 63.7 ± 4.1            |

**Example-131: Contextual Fear Conditioning Memory**

Rodent fear conditioning chambers (L x W x H, rat: 26 x 30 x 33 cm, Coulbourn instruments, USA) placed in sound attenuating cabinets were used. Stainless steel grid floors (L x W, rat: 26 x 30 cm), connected to shock scramblers were used to deliver the shock. A ventilation fan provided a background noise of 60 dB. A light bulb (fixed on the right wall, and 27 cm above the floor of the chamber) provided ambient illumination. Experiment was recorded using

video camera, mounted on the cabinet ceiling and images were analyzed with freeze frame 3 software (V3.2.1). The fear conditioning chambers has transparent acrylic panels.

On day 0, rats were randomized based on the body weight, housed two rats per each cage.

On day 1, rats were brought to the laboratory at least 1 hr prior to experimentation. Rats were  
 5 acclimatized to fear conditioning chamber for 2 min. After acclimatization the rats were received unavoidable foot shock (unconditioned stimulus (US): electric shock of 0.7 mA for 3 seconds). Following a 79 sec interval between each administration, shock was repeated to deliver a total of eight US. One minute after the last US, the animal were transferred to the home cage. The chambers were cleaned with 70% ethanol between tests. Test treatments  
 10 were administered prior conditioning phase based on the Tmax. Amphetamine 2 mg/kg, s.c. was administer 25 min prior to conditioning phase.

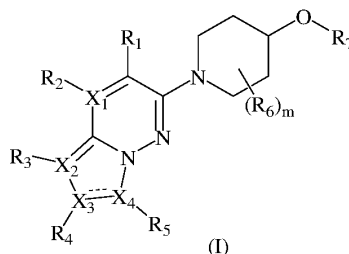
On day 2, rats were brought to the laboratory at least 1 hr prior to experimentation. The freezing behavior of animal was recorded for 733 sec (starting from the time the animal is placed in the fear conditioning chamber). After the 733 sec behavioral recording, the animals  
 15 were transferred to the home cage. The duration of freezing was recorded as (no movement for about of 3 seconds or more was scored a freezing behavior). The freezing threshold was set at 10 in the motion index for analysis. The chambers were cleaned with 70% ethanol between tests.

20 **Table-5:** Procognitive activity of the compounds of the present invention

| Example No. | Observation                                    |                                                | Inference |
|-------------|------------------------------------------------|------------------------------------------------|-----------|
|             | 30 mg/kg, <i>i.p.</i>                          | 60 mg/kg, <i>i.p.</i>                          |           |
| <b>1</b>    | Statistically significant reversal of deficits | Statistically significant reversal of deficits | Active    |
| <b>7</b>    | Statistically significant reversal of deficits | Statistically significant reversal of deficits | Active    |

**We claim:**

1. A compound of formula (I)



- 5 or an isotopic form, or a stereoisomer, or a pharmaceutically acceptable salt thereof, wherein,

**---** can be each independently a single or a double bond;

X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, and X<sub>4</sub> are independently selected from N or C; provided that when X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, or X<sub>4</sub> is N then R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, or R<sub>5</sub> is absent;

- 10 R<sub>1</sub> is selected from halogen, cyano, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, or -OC<sub>1</sub>-C<sub>4</sub>haloalkyl;

R<sub>2</sub> when present is selected from hydrogen, deuterium, halogen, cyano, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;

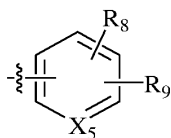
- 15 R<sub>3</sub> when present is selected from hydrogen, deuterium, halogen, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;

R<sub>4</sub> when present is selected from hydrogen, deuterium, halogen, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;

R<sub>5</sub> when present is selected from hydrogen, deuterium, halogen, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl,

- 20 -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;

R<sub>6</sub> when present is selected from hydrogen, deuterium, halogen, cyano, -OH, -CH<sub>2</sub>OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl;



R<sub>7</sub> is

- 25 “” represents point of attachment;

R<sub>8</sub> and R<sub>9</sub> are independently hydrogen, halogen, cyano, -OH, -NH<sub>2</sub>, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkoxyalkyl, -

NHC<sub>1</sub>-C<sub>4</sub>alkyl; or alternatively R<sub>8</sub> and R<sub>9</sub> together with the carbon atoms to which they are attached, form a 5-8 membered heterocyclic ring, wherein heterocyclic ring is optionally substituted with one to five substituents independently selected from the group consisting of hydrogen, oxo, deuterium, halogen, cyano, -OH, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>1</sub>-C<sub>4</sub>haloalkyl, -C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -OC<sub>1</sub>-C<sub>4</sub>alkyl, -OC<sub>1</sub>-C<sub>4</sub>haloalkyl, or -C<sub>1</sub>-C<sub>4</sub>alkoxyalkyl; and  
 5 m is 0, 1 or 2.

2. The compound of formula (I) or an isotopic form, or a stereoisomer, or a pharmaceutically acceptable salt thereof according to preceding embodiments, wherein the compound is  
 10 selected from:

- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine;
- 15 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 20 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 25 3-[1-(7,8-Dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile;
- 6-[4-(2,5-Difluoro-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(6-Fluoro-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 30 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(6-Fluoro-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 7-Methyl-6-[4-(6-methyl-pyridin-3-yloxy)-piperidin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine;

- 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;  
3-[1-(7-Methyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile;  
6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;  
5 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;  
6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;  
6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-b]pyridazine;  
10 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;  
6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;  
6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;  
6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;  
15 b]pyridazine;  
6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;  
6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;  
3-[1-(3,7,8-Trimethyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile;  
20 6-[4-(2-Methoxy-pyridin-4-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;  
6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;  
6-[3-Fluoro-4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;  
25 [1,2,4]triazolo[4,3-b]pyridazine;  
6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-3,7,8-trimethyl-[1,2,4]triazolo[4,3-b]pyridazine;  
6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine;  
30 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine;  
6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine;

- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 5 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 3-[1-(3,7-Dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-3,7-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 10 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 15 6-[4-(2-Methoxy-pyridin-4-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-3,7-dimethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 20 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 25 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 30 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-3-trifluoromethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 3-Difluoromethyl-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;

- 3-Difluoromethyl-6-[4-(1,3-dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 3-Difluoromethyl-6-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 5 3-Difluoromethyl-6-[4-(2,3-dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 3-Difluoromethyl-6-[4-(2,3-dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 3-Difluoromethyl-6-[4-(4-methoxy-phenoxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[4,3-  
10 b]pyridazine;
- 6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-  
b]pyridazine;
- 3-[1-(3-Methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-piperidin-4-  
yloxy]-benzonitrile;
- 15 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-3-methoxymethyl-7,8-  
dimethyl-[1,2,4]triazolo[4,3-b]pyridazine;
- 3-Methoxymethyl-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-  
20 b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 25 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-3-methoxymethyl-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-3-methoxymethyl-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 3-Methoxymethyl-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 30 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-3-methoxymethyl-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-3-methoxymethyl-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;

- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-3-methoxymethyl-7-methyl-  
[1,2,4]triazolo[4,3-b]pyridazine;  
3-Difluoromethyl-6-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;  
5 3-Difluoromethyl-6-[4-(2,3-dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;  
3-Difluoromethyl-6-[4-(1,3-dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;  
3-Difluoromethyl-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-  
10 [1,2,4]triazolo[4,3-b]pyridazine;  
3-Difluoromethyl-6-[4-(4-methoxy-phenoxy)-piperidin-1-yl]-7,8-dimethyl-  
[1,2,4]triazolo[4,3-b]pyridazine;  
6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine;  
6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-  
15 [1,2,4]triazolo[1,5-b]pyridazine;  
6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;  
6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;  
20 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;  
6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;  
6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-b]pyridazine;  
25 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-b]pyridazine;  
6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-  
b]pyridazine;  
6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-  
b]pyridazine;  
30 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-  
b]pyridazine;  
6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-[1,2,4]triazolo[1,5-  
b]pyridazine;

- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-  
[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 5 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 6-[4-(2-Methoxy-pyridin-4-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 10 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 3-[1-(2,7,8-Trimethyl-[1,2,4]triazolo[1,5-b]pyridazin-6-yl)-piperidin-4-yloxy]-benzonitrile;
- 6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 15 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,7-dimethyl-  
[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 20 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 25 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-2,7-dimethyl-[1,2,4]triazolo[1,5-  
b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,7-dimethyl-imidazo[1,2-  
b]pyridazine;
- 30 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,7,8-trimethyl-imidazo[1,2-  
b]pyridazine;
- 6-[4-(3-Fluoro-phenoxy)-piperidin-1-yl]-2,7,8-trimethyl-imidazo[1,2-b]pyridazine;

- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2-fluoromethyl-7,8-dimethyl-imidazo[1,2-b]pyridazine;
- 2-Fluoromethyl-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine;
- 5 2-Fluoromethyl-6-[4-(2-methoxy-pyridin-4-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2-fluoromethyl-7-methyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-2,3,7-trimethyl-imidazo[1,2-b]pyridazine;
- 10 b]pyridazine;
- 2-Chloro-6-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine;
- 2-Chloro-6-[4-(6-methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine;
- 15 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-5-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine;
- 20 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine;
- 6-[4-(4-Methoxy-phenoxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine;
- 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7-methyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine;
- 25 6-[4-(6-Methoxy-pyridin-3-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine;
- 6-[4-(2,3-Dihydro-benzofuran-6-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine; or
- 6-[4-(1,3-Dihydro-isobenzofuran-5-yloxy)-piperidin-1-yl]-7,8-dimethyl-imidazo[1,2-b]pyridazine.

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3. The compound of formula (I), or an isotopic form, a stereoisomer, or a pharmaceutically acceptable salt thereof as claimed in claim 1 or claim 2, for use as a muscarinic M4 receptor positive allosteric modulator (M4 PAM).

4. A pharmaceutical composition comprising the compound of formula (I), or an isotopic form, or a stereoisomer, or a pharmaceutically acceptable salt thereof as claimed in claim 1 or claim 2 and pharmaceutically acceptable excipients.
5. The pharmaceutical composition as claimed in claim 4, for use in the treatment of disease or disorder mediated by muscarinic M4 receptors, wherein said disease or disorder is selected from psychiatric disorders, neurological disorders, pain disorders, sleep disorders, or cognitive disorders.
6. A compound of formula (I) or an isotopic form, a stereoisomer, or a pharmaceutically acceptable salt thereof as claimed in claim 1 or claim 2, for use in the treatment of diseases or disorders mediated by muscarinic M4 receptors, wherein said disease or disorder is selected from psychiatric disorders, neurological disorders, pain disorders, sleep disorders, or cognitive disorders.
7. The compound for use as claimed in claim 6, wherein the psychiatric disorders are selected from the group consisting of, anxiety, personality disorders, depression, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), psychosis, schizophrenia, substance use disorders and other psychotic disorders.
8. The compound for use as claimed in claim 6, wherein the neurological diseases or disorders are selected from the group consisting of Alzheimer's disease, Rett syndrome, Huntington's disease, vascular dementia, Parkinson's disease, and amyotrophic lateral sclerosis (ALS).
9. The compound for use as claimed in claim 6, wherein the cognitive disorders are selected from the group consisting of amnesia, dementia, amnestic disorder, dementia due to Alzheimer's disease, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, Lewy body dementia, vascular dementia, frontotemporal dementia, senile dementia, dementia associated with Down syndrome, dementia associated with Tourette's syndrome, dementia associated with post-menopause, dementia in Creutzfeldt-Jakob disease, substance-induced persisting dementia, dementia in Pick's disease, dementia in Huntington's disease, traumatic brain injury, prion disease, HIV-associated

neurocognitive disorders, mild cognitive impairment and any other diseases with cognitive symptoms.

10. The compound for use as claimed in claim 7, wherein the schizophrenia is selected from  
5 cognitive impairment in schizophrenia, positive symptoms of schizophrenia and/or negative symptoms of schizophrenia.

11. The compound for use as claimed in claim 7, wherein the psychotic disorders are selected  
10 from psychosis associated with Alzheimer's disease, psychosis associated with Parkinson's disease, psychotic depression, psychosis associated with stroke, psychosis associated with epilepsy, psychosis associated with multiple sclerosis, psychosis associated with traumatic brain injury, substance-induced persisting delirium, or any other diseases with psychotic features.

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