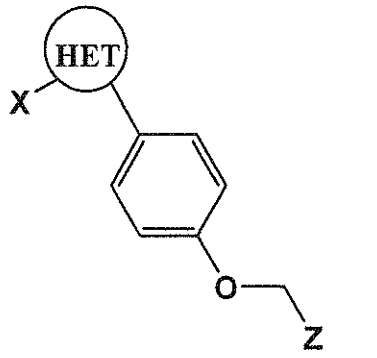
neurological, neurodegenerative and psychiatric disorders including but not limited to those comprising cognitive deficits or schizophrenic symptoms.

In one aspect, there is provided a compound of Formula (I)



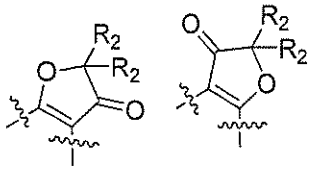
,

(I)

or a pharmaceutically acceptable salt thereof,

wherein:

HET is a heterocyclic ring having formula A29 or A31



A29 A31 ,

wherein the left most radical is connected to the X group in Formula (I);

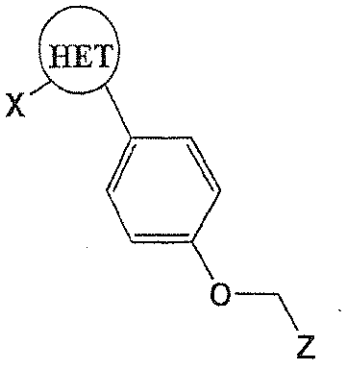
X is optionally substituted aryl or optionally substituted heteroaryl, wherein the substituents are selected from the group consisting of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyloxy, C_1-C_4 alkoxy, CF_3, carboxy, alkoxyalkyl, C_1-C_4 cycloalkylalkoxy, amino, alkylamino, dialkylamino, amido, alkylamido, dialkylamido, thioalkyl, halogen, cyano, alkylsulfonyl and nitro;

Z is imidazo[1,2-*a*]pyridin-2-yl, imidazo[1,2-*b*]pyridazin-2-yl or imidazo[1,2-*b*]pyridazin-6-yl, each of which can be optionally substituted, wherein the substituents are selected from the group consisting of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyloxy, C_1-C_4 alkoxy, CF_3, carboxy, alkoxyalkyl, C_1-C_4 cycloalkylalkoxy, amino, alkylamino,

dialkylamino, amido, alkylamido, dialkylamido, thioalkyl, halogen, cyano, alkylsulfonyl and nitro; and

each R_2 is independently optionally fluoro-substituted C_1-C_4 alkyl, or two R_2 groups taken together with the carbon to which they are attached form a 3-membered cycloalkyl ring.

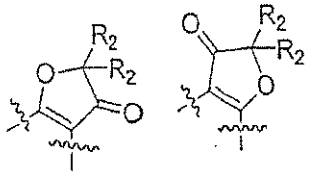
Described herein are compounds of Formula (I) that are inhibitors of at least one phosphodiesterase 10:



(I)

Wherein:

HET is a heterocyclic ring selected from Formulas A29, A31 and A39 below



A29 A31

and the left most radical is connected to the X group;

X is selected from optionally substituted aryl and optionally substituted heteroaryl;

Z is optionally substituted heteroaryl;

Each R_2 is independently selected from C_1-C_4 alkyl, or two R_2 groups taken together with the carbon to which they are attached form a 3 membered cycloalkyl ring;

In one embodiment, R_2 is C_1-C_4 alkyl.

In another embodiment, R_2 is methyl.

In another embodiment, two R_2 groups taken together form a 3 membered cycloalkyl ring.

In another aspect, there is provided a compound selected from any one of Examples 1-185 and 187-732 or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided 4-(4-(imidazo[1,2-b]pyridazin-2-ylmethoxy)phenyl)-2,2-dimethyl-5-(pyridin-4-yl)furan-3(2H)-one or a pharmaceutically acceptable salt thereof.

Compounds of the disclosure may contain asymmetric centers and exist as different enantiomers or diastereomers or a combination of these therein. All enantiomeric, diastereomeric forms of Formula (I) are embodied herein.

In another aspect, there is provided a pharmaceutical composition comprising: (i) the compound as defined above or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier or excipient.

Compounds in the disclosure may be in the form of pharmaceutically acceptable salts. The phrase "pharmaceutically acceptable" refers to salts prepared from pharmaceutically acceptable non-toxic bases and acids, including inorganic and organic bases and inorganic and organic acids. Salts derived from inorganic bases include lithium, sodium, potassium, magnesium, calcium and zinc. Salts derived from organic bases include ammonia, primary, secondary and tertiary amines, and amino acids. Salts derived from inorganic acids include sulfuric, hydrochloric, phosphoric, hydrobromic. Salts derived from organic acids include C_{1-6} alkyl carboxylic acids, di-carboxylic acids and tricarboxylic acids such as acetic acid, proprionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, adipic acid and citric acid, and alkylsulfonic acids such as methanesulphonic, and aryl sulfonic acids such as *para*-tolouene sulfonic acid and benzene sulfonic acid.

Compounds in the disclosure may be in the form of a solvate. This occurs when a compound of Formula (I) has an energetically favorable interaction with a solvent, crystallizes in a manner that it incorporates solvent molecules into the crystal lattice or a complex is formed with solvent molecules in the solid or liquid state. Examples of solvents forming solvates are water (hydrates), MeOH, EtOH, iPrOH, and acetone.

Compounds in the disclosure may exist in different crystal forms known as polymorphs. Polymorphism is the ability of a substance to exist in two or more crystalline phases that have different arrangements and/or conformations of the molecule in the crystal lattice.

Compounds in the disclosure may exist as isotopically labeled compounds of Formula (I) where one or more atoms are replaced by atoms having the same atomic number but a different atomic mass from the atomic mass which is predominantly seen in nature. Examples of isotopes include, but are not limited to hydrogen isotopes (deuterium, tritium), carbon isotopes (^{11}C, ^{13}C, ^{14}C) and nitrogen isotopes (^{13}N, ^{15}N). For example, substitution with heavier isotopes such as deuterium (^{2}H) may offer certain therapeutic advantages resulting from greater metabolic stability which could be preferable and lead to longer *in vivo* half-life or dose reduction in a mammal or human.

Prodrugs of compounds embodied by Formula (I) are also within the scope of this disclosure. Particular derivatives of compounds of Formula (I) which may have little to negligible pharmacological activity themselves, can, when administered to a mammal or human, be converted into compounds of Formula (I) having the desired biological activity.

In another aspect, there is provided the use of the pharmaceutical composition as defined above in the manufacture of a medicament for treating a CNS disorder in a human in need thereof.

In another aspect, there is provided the use of the pharmaceutical composition as defined above in the manufacture of a medicament for treating eating disorders, obesity, compulsive gambling, sexual disorders, narcolepsy, sleep disorders, diabetes, metabolic syndrome or smoking cessation in a human in need thereof.

Compounds in the disclosure and their pharmaceutically acceptable salts, prodrugs, as well as metabolites of the compounds, may also be used to treat certain eating disorders, obesity, compulsive gambling, sexual disorders, narcolepsy, sleep disorders, diabetes, metabolic syndrome, neurodegenerative disorders and CNS disorders/conditions as well as in smoking cessation treatment.

In another aspect, there is provided the use of the pharmaceutical composition as defined above in the manufacture of a medicament for treating obesity, schizophrenia, schizo-affective conditions, Huntington's disease, bipolar disorders, dystonic conditions and tardive dyskinesia in a human in need thereof.

In another aspect, there is provided the use of the pharmaceutical composition as defined above in the manufacture of a medicament for treating bipolar disorders in a human in need thereof.

In one embodiment the treatment of CNS disorders and conditions by the compounds of the disclosure can include Huntington's disease, schizophrenia and schizo-affective conditions, delusional disorders, drug-induced psychoses, panic and obsessive compulsive disorders, post-traumatic stress disorders, age-related cognitive decline, attention deficit/hyperactivity disorder, bipolar disorders, personality disorders of the paranoid type, personality disorders of the schizoid type, psychosis induced by alcohol,

amphetamines, phencyclidine, opioids hallucinogens or other drug-induced psychosis, dyskinesia or choreiform conditions including dyskinesia induced by dopamine agonists, dopaminergic therapies, psychosis associated with Parkinson's disease, psychotic symptoms associated with other neurodegenerative disorders including Alzheimer's disease, dystonic conditions such as idiopathic dystonia, drug-induced dystonia, torsion dystonia, and tardive dyskinesia, mood disorders including major depressive episodes, post-stroke depression, minor depressive disorder, premenstrual dysphoric disorder, dementia including but not limited to multi-infarct dementia, AIDS-related dementia, and neurodegenerative dementia,

In another embodiment, compounds of the disclosure may be used for the treatment of eating disorders, obesity, compulsive gambling, sexual disorders, narcolepsy, sleep disorders as well as in smoking cessation treatment.

In a further embodiment, compounds of the disclosure may be used for the treatment of obesity, schizophrenia, schizo-affective conditions, Huntington's disease, dystonic conditions and tardive dyskinesia.

In another embodiment, compounds of the disclosure may be used for the treatment of schizophrenia, schizo-affective conditions, Huntington's disease and obesity.

In another aspect, there is provided the use of the pharmaceutical composition as defined above in the manufacture of a medicament for treating schizophrenia and schizo-affective conditions in a human in need thereof.

In a further embodiment, compounds of the disclosure may be used for the treatment of schizophrenia and schizo-affective conditions.

In another aspect, there is provided the use of the pharmaceutical composition as defined above in the manufacture of a medicament for treating Huntington's disease in a human in need thereof.

In an additional embodiment, compounds of the disclosure may be used for the treatment of Huntington's disease.

In another aspect, there is provided the use of the pharmaceutical composition as defined above in the manufacture of a medicament for treating obesity and metabolic syndrome in a human in need thereof.

In another embodiment, compounds of the disclosure may be used for the treatment of obesity and metabolic syndrome.