

therefore important regulators of a wide variety of physiological processes. PDEs are expressed differentially throughout the organism and cyclic nucleotide signaling is highly compartmentalized within individual cells. Thus, different PDE isozymes can serve distinct physiological functions. Compounds that can selectively inhibit distinct PDE families or isozymes may offer additional therapeutic benefits, fewer side effects, or both.

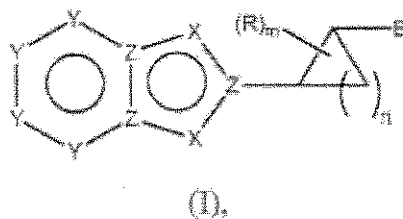
[0010] PDE-10 was first reported in 1999 (Soderling *et al.*, *Proc. Natl. Acad. Sci.*, 1999, 96, 7071-76; Loughney *et al.*, *Gene*, 1999, 234, 109-17; Fujishige *et al.*, *J. Biol. Chem.*, 1999, 274, 18438-45). Homology screening revealed mouse PDE-10A as the first member of the PDE-10 family of enzymes. The human PDE-10 sequence is highly homologous to both the rat and mouse PDE-10 enzymes. The PDE-10 family of enzymes has a lower degree of sequence homology as compared to previously identified PDE families. PDE-10 can hydrolyze both cAMP ($K_m = 0.26 \text{ } \mu\text{M}$) and cGMP ($K_m = 7.2 \text{ } \mu\text{M}$), and has a five-fold greater V_{max} for cGMP than for cAMP.

[0011] PDE-10A is primarily expressed in the brain, also found in testes. PDE-10A mRNA and protein are abundant in brain tissues, and are mainly detected at high levels in the medium spiny neurons (MSN) of the striatum, a distribution conserved across mammalian species. The striatal MSNs provide input to the basal ganglia circuit, affecting action selection and execution, and suppressing undesired responses to sensory stimuli. PDE-10A has become an emerging target for the development of new anti-psychotics. Inhibitors of PDE-10A have been shown to increase cAMP and cGMP levels in striatal tissue and have demonstrated efficacy against not only positive but also negative and cognitive symptoms in animal models of schizophrenia. PDE-10A is also useful in treating metabolic disorders, such as diabetes, obesity, and metabolic syndrome.

[0012] Citation of any references in this Section of the application is not to be construed as an admission that such reference is prior art to the present application.

III. SUMMARY

[0012a] In a first aspect of the present disclosure, there is provided a compound of formula (I):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

n is 1, 2, or 3;

m is 0, 1, 2, 3, 4, 5, 6, 7, or 8; provided that (i) when n is 1, m is 0, 1, 2, 3, or 4; (ii) when

n is 2, m is 0, 1, 2, 3, 4, 5, or 6; and (iii) when n is 3, m is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

each R is independently halo or (C₁-C₄)alkyl;

each X is independently N, CR¹, O, or NR²;

each Z is independently N or C;

each Y is independently Nor CR³;

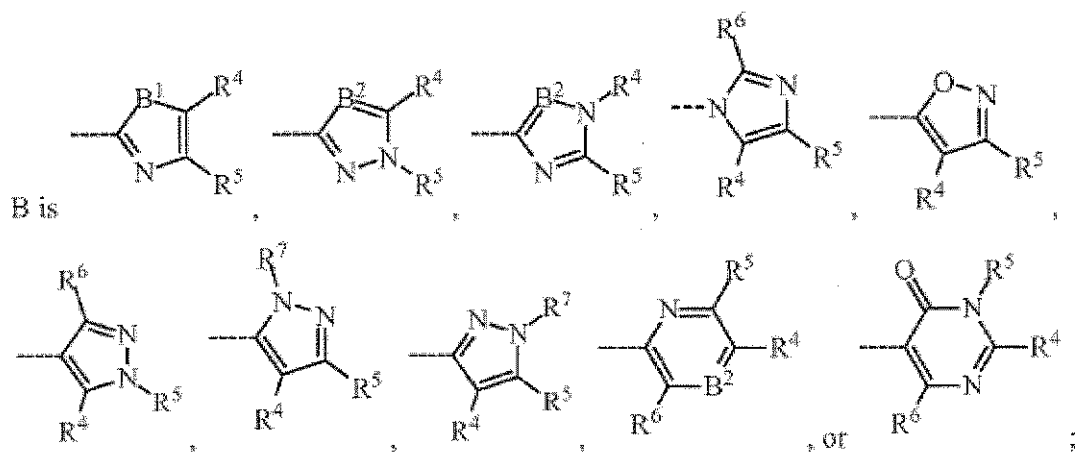


provided that _____ contains 1, 2, 3, 4, or 5 nitrogen ring atoms;

R¹ is hydrogen, halo, cyano, alkyl, alkenyl, alkoxyl, aminoalkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, amino, amido, carbonyl, thiol, sulfinyl, or sulfonyl;

R² is hydrogen, alkyl, alkenyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, carbonyl, or sulfonyl;

each R³ is independently (i) hydrogen, halo, cyano, alkyl, alkenyl, alkoxyl, aminoalkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, amino, amido, carbonyl, thiol, sulfinyl, or sulfonyl; or (ii) two adjacent occurrences of R³ together with the carbon atoms to which they are attached form an aryl, heteroaryl, cycloalkyl, or heterocyclyl ring;



(i) R⁴ and R⁵ together with the atoms to which they are attached form a monocyclic or multicyclic aryl, heteroaryl, cycloalkyl, or heterocyclyl ring; or (ii) R⁴ and R⁵ are each independently hydrogen, cyano, halo, alkyl, alkenyl, alkoxyl, aminoalkyl, heteroalkyl, cycloalkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, heterocyclyl, hydroxyl, amino, imino, amido, carbonyl, thiol, sulfinyl, or sulfonyl;

B¹ is O, S, or NR⁸;

B² is CR⁹ or N;

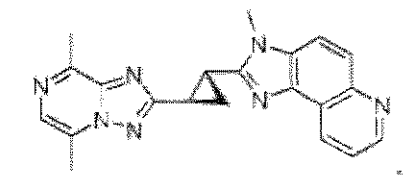
R⁶ is hydrogen, halo, cyano, alkyl, alkenyl, alkoxyl, aminoalkyl, heteroalkyl, cycloalkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, heterocyclyl, amino, amido, carbonyl, thiol, sulfinyl, or sulfonyl;

R^7 is hydrogen, alkyl, alkenyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, carbonyl, or sulfonyl;

R^8 is hydrogen, alkyl, alkenyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, carbonyl, or sulfonyl; and

R^9 is hydrogen, halo, cyano, alkyl, alkenyl, alkoxy, aminoalkyl, heteroalkyl, cycloalkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, heterocyclyl, amino, amido, carbonyl, thiol, sulfinyl, or sulfonyl;

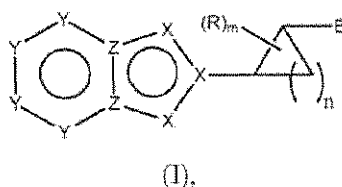
provided that a compound of formula (I) is not:



[0012b] In a second aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound of the first aspect or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable excipient, diluent, or carrier.

[0012c] In a third aspect of the present disclosure, there is provided a use of a compound of the first aspect, or a pharmaceutically acceptable salt or stereoisomer thereof, for the manufacture of a medicament for the treatment, prevention or management of a CNS or metabolic disorder, wherein a therapeutically or prophylactically effective amount of said medicament is to be administered to a subject.

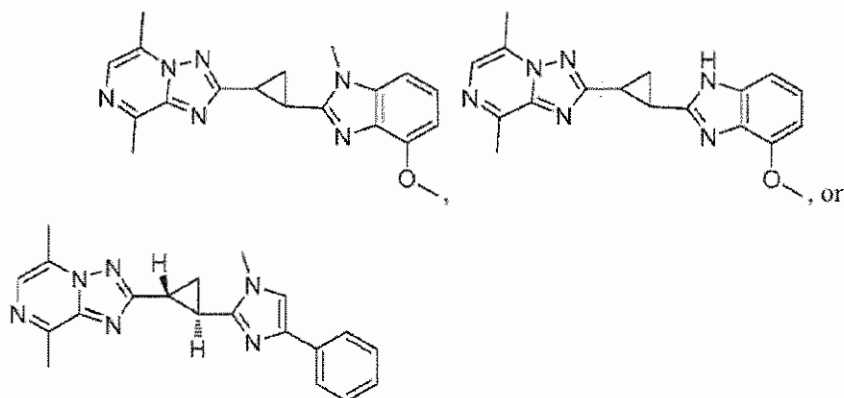
[0013] Provided herein are compounds of formula (I), or pharmaceutically acceptable salts or stereoisomers thereof:



wherein X, Y, Z, R, B, m, and n are defined herein elsewhere. The compounds are useful for treating various diseases or disorders, such as CNS disorders and metabolic disorders.

[0014] Also provided herein are compositions and dosage forms comprising, a compound

31. The compound of claim 32, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

32. A pharmaceutical composition comprising a compound of any one of claims 1 to 31 or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable excipient, diluent, or carrier.

33. The pharmaceutical composition of claim 32, which further comprises one or more additional active agents.

34. Use of a compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt or stereoisomer thereof, for the manufacture of a medicament for the treatment, prevention or management of ~~A method of treating, preventing, or managing a CNS or metabolic disorder, wherein comprising administering to a subject a therapeutically or prophylactically effective amount of said medicament is to be administered to a subject~~ a compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt or stereoisomer thereof.

35. ~~The method use~~ of claim 34, wherein the disorder is a neurological disorder, schizophrenia, schizophrenia-related disorder, schizophrenia spectrum disorder, acute schizophrenia, chronic schizophrenia, NOS schizophrenia, schizoaffective disorder, schizophreniform disorder, paraphrenia, paranoid personality disorder, schizoid personality disorder, schizotypal personality disorder, delusional disorder, psychosis, disease having a psychosis component, psychotic disorder, brief psychotic disorder, Alzheimer's psychosis, Parkinson's psychosis, shared psychotic disorder, substance-induced psychotic disorder, psychotic disorder due to a general medical condition, psychoaffective disorder, aggression, delirium, excitative psychosis, Tourette's syndrome, manic disorder, organic psychosis, NOS psychosis, convulsion, seizure, agitation, posttraumatic stress disorder, behavior disorder, neurodegenerative disease, Huntington's disease, Alzheimer's disease, Parkinson's disease, dyskinesia, dementia,

mood disorder, bipolar disorder, anxiety, depression, major depressive disorder, unipolar depression, treatment resistant depression, dysthymia, affective disorder, seasonal affective disorder, obsessive-compulsive disorder, attention deficit disorder, attention deficit hyperactivity disorder, vertigo, pain, neuropathic pain, sensitization accompanying neuropathic pain, inflammatory pain, fibromyalgia, migraine, cognitive impairment, cognitive impairment associated with schizophrenia, cognitive deficit in Alzheimer's disease, cognitive deficit in Parkinson's disease, movement disorder, restless leg syndrome, multiple sclerosis, sleep disorder, substance abuse or dependency, addiction, eating disorder, autism, obesity, undesirable weight retention or weight gain, metabolic syndrome, diabetes, non-insulin dependent diabetes, impaired glucose tolerance, or hyperglycemia.

36. The ~~method-use~~ of claim 34, wherein the disorder is schizophrenia, cognitive impairment associated with schizophrenia, cognitive impairment, psychosis, depression, or Huntington's disease.

37. The ~~method-use~~ of any one of claims 34 to 36, ~~wherein further comprising administering to the subject a second active agent is to be further administered to said subject.~~