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Patent Highlight

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Potential Treatment of Cognitive Impairment in Schizophrenia by Phosphodiesterase 2 (PDE2) Inhibitors

Ahmed F. Abdel-Magid*

Therachem Research Medilab (India) Pvt. Ltd., Jaipur, India

Patent Application Title:	Pyrimidinone Amide Compounds as PDE2 Inhibitors		
Patent Application Number:	WO 2016/183741 A1	**Publication date:**	24 November 2016
Priority Application:		**Priority date:**	
Inventors:	Shen, D.-M.; Qian, X.; Harper, B.; Yang, M.; Wang, D.; Bo, Y.		
Applicant:	Merck Sharp & Dohme Corp.; 126 East Lincoln Avenue, Rahway, New Jersey 07065, USA		
Disease Area:	Schizophrenia, psychosis, Alzheimer disease, cognitive impairment, anxiety, depression, migraines, Huntington's disease, and Parkinson's disease	**Biological Target:**	Phosphodiesterase 2 (PDE2) enzyme

Summary:

The invention in this patent application relates to 6-pyrimidinone-4-carboxamide derivatives represented generally by formula (I), which act as inhibitors of the phosphodiesterase 2 (PDE2) enzyme. These compounds may be useful as therapeutic agents for the treatment of central nervous system and/or peripheral disorders associated with PDE2. They may also treat neurological and psychiatric disorders such as schizophrenia, psychosis, Alzheimer's, cognitive impairment, anxiety, depression, migraines, Huntington's disease, Parkinson's disease, Parkinson's disease dementia (PDD), and other diseases associated with striatal hypofunction or basal ganglia dysfunction.

Schizophrenia is a debilitating mental and behavioral disorder that affects the motor functions of the brain. It is associated with symptoms that are indicative of cognitive impairment and functional disabilities such as hallucinations and delusions and may cause anhedonia or social withdrawal. While there is no cure for schizophrenia, the symptoms may be managed and reduced primarily by the use of typical antipsychotic drugs, such as haloperidol, or atypical antipsychotics, such as clozapine or olanzapine. However, these drugs are unsatisfactory and can result in extremely high rate of noncompliance or discontinuation of medication. They may lack of efficacy and may cause intolerable and undesirable metabolic, extrapyramidal, prolactic, and cardiac adverse effects.

To determine the causes of pathogenesis of schizophrenia, researchers have focused their studies on the dysfunction in the role of glutamate/*N*-methyl-D-aspartate (NMDA) receptor and the dopaminergic receptors associated with the levels of cyclic adenosine monophosphate (cAMP). It is believed that cAMP regulates the activity of cAMP-dependent protein kinase (PKA), which in turn phosphorylates and regulates many types of proteins including ion channels, enzymes, and transcription factors. Cyclic guanosine monophosphate (cGMP) is thought to be similarly responsible for downstream regulation of kinases and ion channels.

The 3′,5′-cyclic nucleotide-specific phosphodiesterases (PDEs) superfamily includes 11 families of PDEs. The PDE enzymes catalyze the hydrolysis of cAMP and cGMP to regulate their intracellular concentrations. Thus, the regulation of PDEs may affect the levels of these cyclic nucleotides. The PDE families are subdivided according to their catalytic domain homology and substrate specificity into three groups:

1. cAMP-specific PDEs: include PDE4A-D, 7A, 7B, 8A, and 8B;
2. cGMP-specific PDEs: include PDE5A, 6A-C, and 9A;
3. Dual substrate PDEs: include PDE1A-C, 2A, 3A, 3B, 10A, and 11A.

The homology between the different PDE families ranges from 20% to 45%; therefore, it may be possible to develop selective inhibitors for each one of these families.

PDE2 is highly expressed in the brain, but it is also found in many other tissues. It plays important roles in many functions and utilities including but not limited to neuronal development, learning, and memory, prolactin and aldosterone secretion, bone cell differentiation, growth, and bone resorption, immunological response, vascular angiogenesis, inflammatory cell transit, cardiac contraction, platelet aggregation, female sexual arousal disorder, osteoarthritis pain, malignant melanoma, heart failure, pulmonary hypertension, depression and anxiety, and hypoxic pulmonary vasoconstriction.

Studies using multiple preclinical models of cognitive performance have shown that inhibition of PDE2 enhances cognitive functions such as recognition memory, social interactions, and working memory, which are all deficient in schizophrenia patients. It also improves cognitive deficits that develop as a result of aging or from Alzheimer's disease. PDE2 inhibition was also effective in preclinical models of anxiety and depression.

The role of PDE2 inhibition in cognitive disorders was further confirmed using BAY60-7550, which is a known potent and selective inhibitor of PDE2A. It suppresses the activity of PDE2 enzyme but showed no significant effects on other PDEs including PDE1, 3B, 4B, 5, 7B, 8A, 9A, 10A, and 11A. It was reported to have high clearance and limited brain penetration.

Increased activity of PDE2 was linked to increase in vascular permeability. PDE2 and PDE3 can control the concentration levels of cGMP in the endothelium to regulate endothelial permeability, which may be associated with migraine. Cerebral vasodilation is considered a major cause of migraine. Therefore, PDE2 inhibition may have utility as a treatment or prophylactic of migraine.

The modulation of PDE2 has become an increasingly important therapeutic target to develop treatments for multiple diseases and disorders associated with dysregulated PDE2 such as cognitive impairment associated with schizophrenia, depression, Alzheimer's disease, migraines, and many others. It is therefore desirable to identify novel selective inhibitors of PDE2, such as the compounds described in this patent application, which may be useful as therapeutics for a wide variety of neurological and psychiatric disorders that may benefit from increased levels of cAMP and/or cGMP within neurons.

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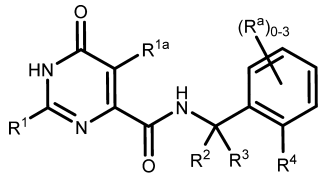
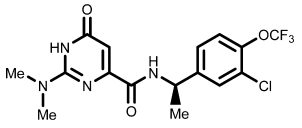
Important Compound Classes:



Formula (I)

Key Structures: The inventors described the synthesis and structures of 212 compounds of formula (I) including the following representative examples:



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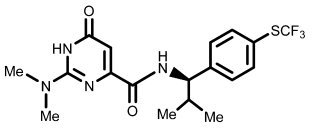

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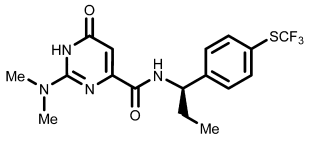

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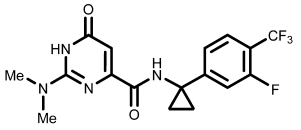

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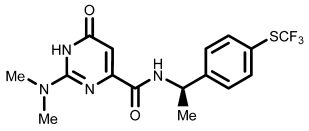

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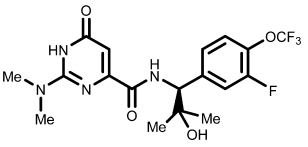

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Biological Assay: The activities of the compounds of formula (I) as PDE2 inhibitors were determined by their ability to inhibit the hydrolysis of the phosphate ester bond of a cyclic nucleotide.

Biological Data: The values of K_i (inhibitory constant) for the above examples are listed in the following table as conducted in two laboratories (Lab A or B):

Compound	Rhesus PDE2 Ki (nM) – Lab A	Rhesus PDE2 Ki (nM) – Lab B	Human PDE2 Ki (nM) – Lab A	Human PDE2 Ki (nM) – Lab A
3	0.82	1.5	ND	1.6
30	0.19	0.22	≤5.1	0.37
88	0.61	0.51	5.055	0.69
94	1.2	0.80	0.90	0.96
143	0.57	0.61	0.32	0.82
208	ND	ND	ND	0.12

Recent Review Articles:

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AUTHOR INFORMATION

Corresponding Author

*Address: 1383 Jasper Drive, Ambler, Pennsylvania 19002, United States. Tel: 215-913-7202. E-mail: afmagid@comcast.net.

Notes

The author declares no competing financial interest.

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