

# PDE10 Inhibitors as Potential Treatment for Schizophrenia

## Ahmed F. Abdel-Magid\*

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

Title: Inhibitors of PDE10

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Inventors: Schmitz, W. D.; Debenedetto, M. V.; Kimura, S. R.

Assignee Company: Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, United States

Disease Area: Schizophrenia and other psychiatric and Biological Target: Phosphodiesterase 10 (PDE10)

neurological diseases

Summary: This patent application discloses compounds represented generally by Formula (I) that inhibit the enzyme phosphodiesterase

10 (PDE10) and can potentially treat schizophrenia and other psychiatric and neurological diseases.

Phosphodiesterases (PDEs) are intracellular enzymes that hydrolyze either cyclic adenosine monophosphate (cAMP) to adenosine monophosphate (AMP) or cyclic guanosine monophosphate (cGMP) to guanosine monophosphate (GMP) or both. The PDE10 enzyme hydrolyzes both cAMP and cGMP. It is expressed primarily in the brain, mostly in the medium spiny neurons (MSN) of the striatum. Inhibition of PDE10 is likely to increase the levels of cAMP and/or cGMP that serve as secondary messengers in several cellular pathways, thereby enhancing levels of signaling, which can impact key neural functions in this part of the brain.

The inhibitors of PDE10 such as the molecules of Formula (I) may potentially treat psychiatric and neurological diseases. Some of the diseases mentioned in the application include schizophrenia; delusional disorder; substance-induced psychotic disorder; anxiety disorders; movement disorders such as Parkinson's disease, Huntington's disease, or restless leg syndrome; cognition deficiency disorders, such as Alzheimer's disease or multi-infarct dementia; and many others.

Important Compound Classes:

Formula (I)

Key Structures:

The patent application describes the preparation of 30 compounds of Formula (I); the three compounds, 1, 14, and 28, are representative examples:

Received: January 14, 2013 Published: January 25, 2013 Biological Assay: LE-PDE10A inhibition assay

Biological Data: The IC<sub>50</sub> data for the three compounds shown above as key structures:

Compound	PDE10 IC <sub>50</sub> (nM)
1	0.10
14	0.16
28	0.16

Synthesis: General synthesis of compounds of Formula (I):

Claims: Claims 1-5: Composition of matter, variations of Formula (I)

Claim 6: A list of 32 compounds claimed by chemical name

Claim 7: Pharmaceutical composition

Claim 8-9: Method of treating schizophrenia and other disorders

Recent Review Articles: Chappie, T. A.; Helal, C. J.; Hou, X. J. Med. Chem. 2012, 55 (17), 7299-7331.

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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 authors declare no competing financial interest.