

PDE10 Inhibitors as Potential Treatment for Schizophrenia

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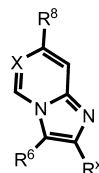
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Title:	Inhibitors of PDE10		
Patent Application Number:	WO 2013/003298 A2	Publication Date:	January 3, 2013
Priority Application:	US 61/502,481	Priority Date:	June 29, 2011
Inventors:	Schmitz, W. D.; Debenedetto, M. V.; Kimura, S. R.		
Assignee Company:	Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, United States		
Disease Area:	Schizophrenia and other psychiatric and neurological diseases	Biological Target:	Phosphodiesterase 10 (PDE10)

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.

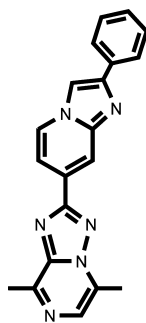
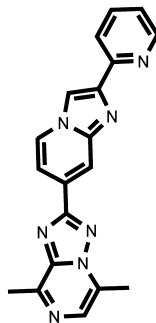
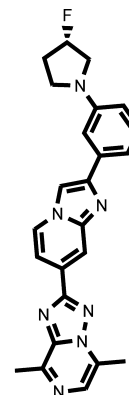
The inhibitors of PDE10 such as the molecules of Formula (I) may potentially treat psychiatric and neurological diseases. Some of the diseases mentioned in the application include schizophrenia; delusional disorder; substance-induced psychotic disorder; anxiety disorders; movement disorders such as Parkinson's 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:

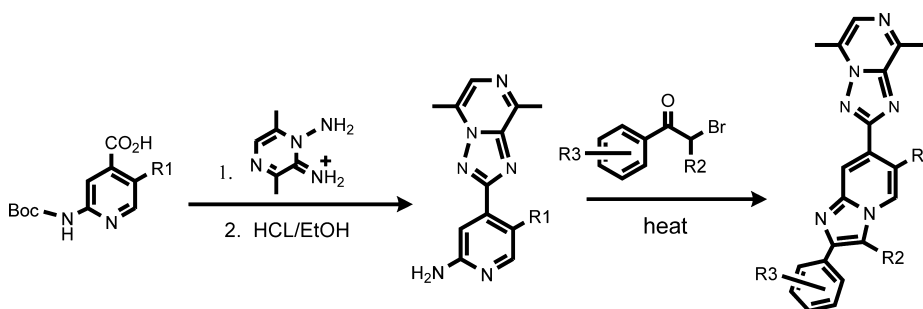
The patent application describes the preparation of 30 compounds of Formula (I); the three compounds, **1**, **14**, and **28**, are representative examples:

**1****14****28****Received:** January 14, 2013**Published:** January 25, 2013

Biological Assay: LE-PDE10A inhibition assay
Biological Data: The IC₅₀ data for the three compounds shown above as key structures:

Compound	PDE10 IC ₅₀ (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

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 Kehler, J.; Nielsen, J. *Curr. Pharm. Des.* **2011**, *17* (2), 137–150.

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Notes

The authors declare no competing financial interest.