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The novel phosphodiesterase 10A inhibitor THPP-1 has antipsychotic-like effects in rat and improves cognition in rat and rhesus monkey

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Abstract

Phosphodiesterase 10A (PDE10A) is a novel target for the treatment of schizophrenia that may address multiple symptomatic domains associated with this disorder. PDE10A is highly expressed in the brain and functions to metabolically inactivate the important second messengers cAMP and cGMP. Here we describe effects of a potent and orally bioavailable PDE10A inhibitor [2-(6-chloropyridin-3-yl)-4-(2-methoxyethoxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl](imidazo[1,5-a]pyridin-1-yl)methanone (THPP-1) on striatal signaling pathways, in behavioral tests that predict antipsychotic potential, and assays that measure episodic-like memory in rat and executive function in rhesus

monkey. THPP-1 exhibits nanomolar potency on the PDE10A enzyme, demonstrates excellent pharmacokinetic properties in multiple preclinical animal species, and is selective for PDE10A over other PDE families of enzymes. THPP-1 significantly increased phosphorylation of proteins in the striatum involved in synaptic plasticity, including the α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor (AMPA) GluR1 subunit, extracellular receptor kinase (ERK), and cAMP-response element binding protein (CREB). THPP-1 produced dose-dependent effects in preclinical assays predictive of antipsychotic activity including attenuation of MK-801-induced psychomotor activation and condition avoidance responding in rats. At similar plasma exposures, THPP-1 significantly increased object recognition memory in rat and attenuated a ketamine-induced deficit in the object retrieval detour task in rhesus monkey. These findings suggest that PDE10A inhibitors have the potential to impact multiple symptomatic domains of schizophrenia including positive symptoms and cognitive impairment.

This article is part of a Special Issue entitled "Cognitive Enhancers".

Highlights

• THPP-1 is a potent PDE10A inhibitor with excellent pharmacokinetic properties. • THPP-1 is fully efficacious in assays predictive of antipsychotic activity. • THPP-1 significantly increased object recognition memory in rat. • THPP-1 was efficacious in the object retrieval detour task in rhesus monkey.



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Keywords

Phosphodiesterase 10A; Striatum; Schizophrenia; Cognition

Abbreviations

PDE10A, phosphodiesterase 10A; AMPA, α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; ERK, extracellular receptor kinase; CREB, cAMP-response element binding protein; CNS, central nervous system; cAMP/cGMP, adenosine/guanosine 3',5'-cyclic monophosphate; CAR, conditioned avoidance responding; NOR, novel object recognition; THPP-1, [2-(6-chloropyridin-3-yl)-4-(2-methoxyethoxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl](imidazo[1,5-a]pyridin-1-yl)methanone]; ORD, object retrieval detour

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