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Discovery of tetrahydropyridopyrimidine phosphodiesterase 10A inhibitors for the treatment of schizophrenia

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ABSTRACT

We describe the discovery of potent and orally bioavailable tetrahydropyridopyrimidine inhibitors of phosphodiesterase 10A by systematic optimization of a novel HTS lead. Lead compound **THPP-1** exhibits nanomolar potencies, excellent pharmacokinetic properties, and a clean off-target profile. It displays *in vivo* target engagement as measured by increased rat striatal cGMP levels upon oral dosing. It shows dose-dependent efficacy in a key pharmacodynamic assay predictive of antipsychotic activity, the psychostimulant-induced rat hyperlocomotion assay. Further, **THPP-1** displays significantly fewer preclinical adverse events in assays measuring prolactin secretion, catalepsy, and weight gain, in contrast to the typical and atypical antipsychotics haloperidol and olanzapine.

Schizophrenia is a chronic and debilitating mental disorder affecting close to 1% of the world population. With disease onset typically occurring in the early-to-mid 20s and with no known cure, patients require life-long treatment or institutionalization, compounding the disease burden on the individual, their families, and society.[1] Schizophrenia is marked by three key symptom domains. The well-known positive symptoms include the hallucinations and delusions that typify the disease. The less understood negative symptoms include anhedonia and withdrawal from society. Cognitive impairment also accompanies the disease, and is often predictive of the functional outcome. A large number of marketed therapeutics exists for the treatment of schizophrenia in the form of the typical antipsychotics (haloperidol, fluphenazine) and atypical antipsychotics (clozapine, olanzapine). However, not only do the vast majority of these drugs treat only the positive symptoms of the disease, but they suffer from a high rate of discontinuation due to a lack of both efficacy and tolerability.[1b–h] The wide array of adverse events that accompany treatment with typical and atypical antipsychotics include significant weight gain, the onset of diabetes, tardive dyskinesia, dystonia, akatheisa, increased prolactin release, and cardiac events. To this end, improved treatment for schizophrenia continues to represent an unmet medical need.

The phosphodiesterases (PDEs) are a superfamily of 11 enzymes encoded by 21 genes.[2] The PDEs catalyze the hydrolytic degradation of cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP), thereby playing a critical role in regulating the circulating levels of these important and ubiquitous second messengers. Over the past decades, efforts toward elucidating the physiological roles of these enzymes have resulted in the identification of numerous PDE inhibitors, both selective and non-selective, that have subsequently led to the identification of potential therapeutic opportunities.

PDE10A, first identified in 1999,[3] is a dual phosphodiesterase that hydrolyzes both cGMP (K_m = 3 μM) and cAMP (K_m = 0.05 μM). It is expressed nearly exclusively in the medium spiny neurons of the mammalian striatum.[4] The striatum is involved in both motor

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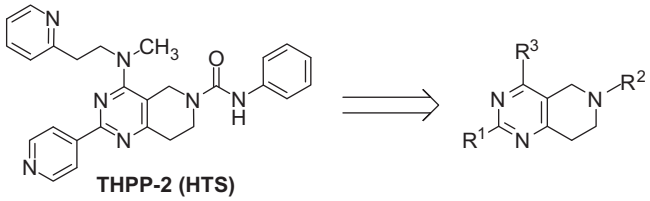
and cognitive function through the integration of signalling from the midbrain dopaminergic pathway and cortical glutamatergic pathway, and abnormal striatal output is implicated in the pathophysiology of schizophrenia.[5] It has therefore been hypothesized that PDE10A inhibition in the striatum will result in increased second messenger signaling and striatal output, restoring the behavioral inhibition that is impaired in schizophrenic patients.[3e] Preclinical studies further support the antipsychotic potential of PDE10 inhibition.[6] Recent publications report that PDE10A inhibitors are efficacious in a number of assays predictive of antipsychotic activity, including the psychostimulant-induced rat hyperlocomotion assay (LMA), as well as the conditioned avoidance response assay (CAR) and pre-pulse inhibition assay (PPI).[7] Further, PDE10A inhibitors have been shown to improve performance in models of cognition, including executive function and episodic memory.[8] Additionally, they display fewer preclinical adverse events (AEs) relative to marketed typical and atypical antipsychotics. Together, these data suggest that PDE10A inhibitors have the potential to affect not only positive symptoms, but cognitive dysfunction as well.

Following a successful high throughput screening campaign, our laboratory was drawn to compounds in the tetrahydropyridopyrimidne class (THPP), as exemplified by **THPP-2** (Table 1, entry 1).[9] Early synthetic efforts to access compounds in this class followed a 5-step sequence described in a previous publication from our laboratory.[10] While suboptimal, the overall synthesis was high-yielding and modular, facilitating rapid generation of SAR in the series.

Beginning with **THPP-2**, we carried out systematic optimization of the R^1 and R^2 positions of the core, with the initial goal of improving compound potency while maintaining overall physical properties. As highlighted in Table 1, no improvement in potency was realized with this effort, as flat SAR existed for all-carbon aromatic, heteroaromatic, amine, and aliphatic substituents (Table 1, entries 2–7). At R^2, urea, carbamate, amido, and sulfonyl functionalities were tolerated, but provided no improvements in compound potency (Table 1, entries 8–15). Moreover, compounds bearing amino substitution at the R^3 position were typically substrates of both rat and human P-glycoprotein (P-gp) with BA/AB ratios of >3.5. To this end, we turned our attention to the R^3 position, and were gratified to discover that replacement of the R^3 amino group with alkoxy substitution not only ameliorated P-gp susceptibility, but also, for the first time, provided marked improvements in compound potency (Table 1 entries 16–20), particularly with the installation of an isopropoxy group. Unfortunately, the change to this functionality came at the expense of overall compound solubility.[11] In order to address this issue, we looked to introduce basic nitrogen functionality in the periphery of the molecule. Installation of a tertiary amine at R^3 in the form of an *N*-methyl piperidine (Table 1, Entry 21), provided potent compounds with improved overall physical properties. However, this structural change resulted in high plasma clearance (Cl = >100 mL/min/kg) and P-gp susceptibility (BA/AB ratio = 22.1) in rats. Ultimately, our strategy proved fruitful as transposition of this basic nitrogen from a tertiary amine at R^3 to an aromatic amine at R^2 led to the identification of **THPP-3** (Table 1, entry 22), an important benchmark molecule that facilitated assay validation for the program.

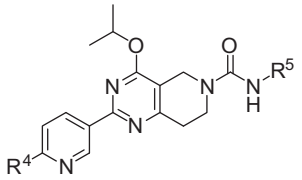
While holding constant the R^3 alkoxy group, we carried out a second round of optimization of the R^1 heterocycle of the THPP core. We discovered that functionalization ortho to the pyridyl nitrogen had a dramatic effect on compound potency (Table 2, R^4), with halogenation providing a consistent potency improvement ranging from 2- to 10-fold. However, compounds bearing halo-substituted pyridines suffered from lower aqueous solubilities than compounds bearing unsubsituted pyridines (<10 μM vs. >75 μM at pH 7), possibly due to a loss in compound basicity.

Table 1
Initial optimization and SAR of the THPP framework



Entry	R^1	R^2	R^3	PDE10 K_i (nM)
1 **(THPP-2)**	4-Pyridyl	$C(O)NHC_6H_5$	$N(CH_3)CH_2CH_2$(2-pyr)	94
2	3-Pyridyl	$C(O)NHC_6H_5$	$N(CH_3)CH_2CH_2$(2-pyr)	121
3	2-Pyridyl	$C(O)NHC_6H_5$	$N(CH_3)CH_2CH_2$(2-pyr)	864
4	C_6H_5	$C(O)NHC_6H_5$	$N(CH_3)CH_2CH_2$(2-pyr)	500
5	3-Br-C_6H_4	$C(O)NHC_6H_5$	$N(CH_3)CH_2CH_2$(2-pyr)	991
6	CH_3	$C(O)NHC_6H_5$	$N(CH_3)CH_2CH_2$(2-pyr)	4340
7	$N(CH_3)_2$	$C(O)NHC_6H_5$	$N(CH_3)CH_2CH_2$(2-pyr)	512
8	4-Pyridyl	C(O)NH(4-pyr)	$N(CH_3)CH_2CH_2$(2-pyr)	117
9	4-Pyridyl	C(O)NH(4-$OCH_3C_6H_4$)	$N(CH_3)CH_2CH_2$(2-pyr)	122
10	4-Pyridyl	C(O)NH(3-FC_6H_4)	$N(CH_3)CH_2CH_2$(2-pyr)	156
11	4-Pyridyl	C(O)O*t*-Bu	$N(CH_3)CH_2CH_2$(2-pyr)	186
12	4-Pyridyl	C(O)NH*t*-Bu	$N(CH_3)CH_2CH_2$(2-pyr)	223
13	4-Pyridyl	C(O)(4-ClC_6H_4)	$N(CH_3)CH_2CH_2$(2-pyr)	522
14	4-Pyridyl	C(O)*i*-Bu	$N(CH_3)CH_2CH_2$(2-pyr)	868
15	4-Pyridyl	SO_2CH_3	$N(CH_3)CH_2CH_2$(2-pyr)	843
16	4-Pyridyl	$C(O)NHC_6H_5$	OCH_3	422
17	4-Pyridyl	$C(O)NHC_6H_5$	$OCH_2CH_2OCH_3$	135
18	4-Pyridyl	$C(O)NHC_6H_5$	O*i*-Pr	98
19	3-Pyridyl	$C(O)NHC_6H_5$	OCH_3	93
20	3-Pyridyl	$C(O)NHC_6H_5$	O*i*-Pr	17
21	3-Pyridyl	C(O)NH(3-EtC_6H_4)	O-(4-*N*-Methylpiperidine)	14
22 **(THPP-3)**	3-Pyridyl	C(O)NH(4-CH_3-3-pyr)	O*i*-Pr	7.9

Table 2
Optimization of pyridine substitution

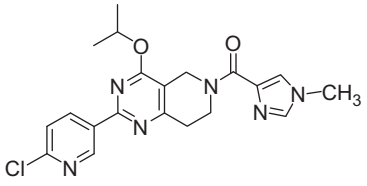


Entry	R^4	R^5	PDE10 K_i (nM)
1 (**THPP-3**)	H	4-CH_3-3-pyr	7.9
2	CH_3	4-CH_3-3-pyr	8.0
3	F	4-CH_3-3-pyr	3.0
4	Cl	4-CH_3-3-pyr	0.6
5	OH	4-CH_3-3-pyr	63
6	CF_3	4-CH_3-3-pyr	247
7	Cl	*N*-CH_3-4-Pyrazole	1.0

Re-investigation of the R^2 portion of the core served to ameliorate some of concerns around the aqueous solubilities of our compounds. To this end, an improvement was realized by changing the urea linker to an amide, thereby eliminating a hydrogen bond donor, and installing a more basic heterocycle at R^2; **THPP-4** contains an imidazole amide (Fig. 1). While compound potency was slightly compromised relative to the corresponding pyridyl urea analog (Table 2, entry 4), **THPP-4** had higher solubility, bore excellent PK, and provided in vivo efficacy in the LMA assay upon oral administration.

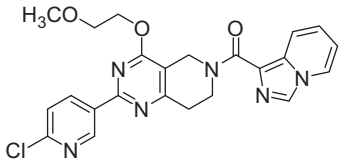
The LMA assay is a well-established model for antipsychotic activity that measures the ability of compounds to attenuate the psychomotor activating response produced by psychostimulants, such as MK-801; all currently marketed antipsychotics are efficacious in this assay.[7] **THPP-4** displayed dose-dependent efficacy in the rat LMA assay, with full attenuation achieved following an oral dose of 4.5 mg/kg PO ($[\textbf{THPP-4}]_{t=2h,plasma}$ = 3.0 μM).[12] Additionally, unlike previous amido compounds bearing a chloropyridine, the higher pKa of the imidazole allowed **THPP-4** to be isolated as a stable hydrochloride salt providing excellent dose proportionality in in vivo studies.

With an advanced promising series identified in the THPPs, we sought to improve their overall synthesis by employing **THPP-4** as a model system. While the initial synthetic route was robust and versatile, typically providing products in overall yields ranging from 5–25%, we were attracted to the possibility of employing a more convergent synthesis that harnessed the nucleophilic character of an intermediate pyrimidinone oxygen. The optimization of this chemistry is detailed in an earlier publication,[10] and provided a general three-component coupling (3CC) methodology amenable to the synthesis of **THPP-4**. With this advance, the synthesis of



THPP-4
PDE 10 K_i = 4.5 nM
pH 7 solubility = 69 μM
Rat PK: Cl= 2.4 mL/min/kg
Dog PK: Cl= 0.94 mL/min/kg
LMA: (+) at 4.5 mpk PO

Figure 1. Structure and profile of **THPP-4**.



THPP-1
PDE 10K_i = 1.0 nM
B-A/A-B (h,r): 0.6, 0.8 (Papp= 32x10^{-6} cm/s)
pH 7 solubility = 20 μM
cGMP: (+)at 10 mpk PO
LMA: (+) at 3 mpk PO

Figure 2. Structure and profile of **THPP-1**.

THPP-4 was shortened from six steps and 6% overall yield to two steps and 45% overall yield requiring no silica gel purification.

While no replacement for the potency-enhancing chloropyridine was identified, significant structural variation was tolerated at both R^2 and R^3, and we continued to interrogate these regions of the THPP core in a more synthetically streamlined manner. Our efforts culminated in the identification of **THPP-1** (Fig. 2), which bears a moderately basic imidazopyridine amide at R^2 and a methoxyethyl ether linkage at R^3. These functionalities provided moderate solubility and improved potency over **THPP-4** while maintaining a similar overall profile. **THPP-1** is a 1-nM inhibitor of PDE10A. It is not a P-gp substrate and has high passive permeability. It is not a significant reversible or time-dependent inhibitor of CYP enzymes and does not activate the pregnane-X receptor at drug concentrations tested, indicating a low potential to be a perpetrator of DDIs via CYP inhibition or induction. Additionally, **THPP-1** has a good PDE selectivity profile, with >1000-fold selectivity over most PDEs except for PDE5A, PDE6A, and PDE11A (Table 3).

The synthesis of **THPP-1** (Scheme 1) harnessed a slightly modified version of the previously described 3CC reaction. 1-*Tert*-butyl 3-ethyl 4-oxopiperidine-1,3-dicarboxylate undergoes facile 3CC with 6-chloropyridine-3-carboximidamide hydrochloride and 2-bromoethyl methyl ether. Boc removal with HCl followed by amide coupling provides **THPP-1** in 3 steps and 36% overall yield. [13]

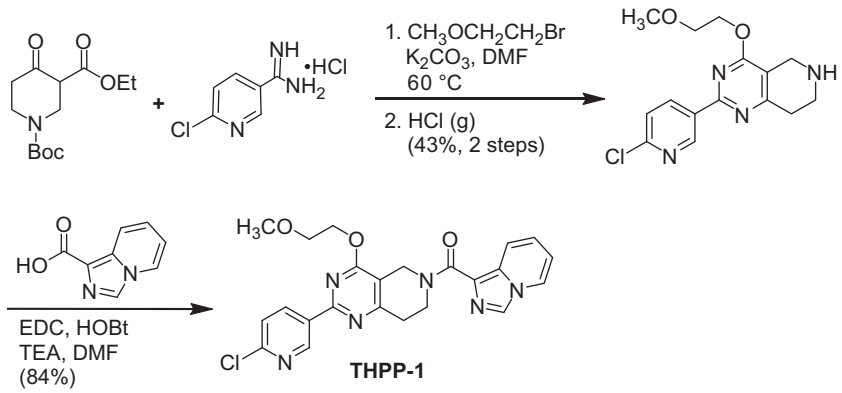
THPP-1 bears an excellent PK profile across preclinical species (Table 4), with moderate clearances (3.8–7.7 mL/min/kg) and half-lives (1.4–7.7 h), and good oral bioavailability (31–79%).

THPP-1 also has a favorable preclinical safety profile. **THPP-1** was negative in a 5-strain Ames assay up to 5000 μg per plate, produced no significant hits in an 117-assay PanLabs off-target panel, and had no observable QT_c prolongation in an in vivo cardiovascular dog model with an anticipated margin of up to a 50-fold.[14]

The in vivo profile of **THPP-1** revealed robust dose-dependent activity in our primary efficacy and target engagement assays.

Table 3
Selectivity of **THPP-1** for PDE10A compared to other human PDE families

PDE	PDE10A K_i (nM)	Selectivity
PDE1A	>50000	>1000×
PDE2A	1200	>1000×
PDE3A	3300	>1000×
PDE4A	5900	>1000×
PDE5A	116	116×
PDE6A	44	44×
PDE7A	11200	>1000×
PDE8A	>50000	>1000×
PDE9A	>50000	>1000×
PDE11A	298	300×



Scheme 1. Synthesis of **THPP-1**.

Table 4
Preclinical PK profile of **THPP-1**

Species	Cl (mL/min/kg)	$t_{1/2}$ (h)	F (%)
Rat	6.0	1.4	47
Dog	3.8	7.2	79
Monkey	7.7	1.4	31

THPP-1 displayed full attenuation of hyperlocomotion at 3 mg/kg PO ([**THPP-1**]$_{t=2h,plasma}$ = 730 nM) in the rat LMA assay (Fig. 3a) as well as increased striatal cGMP at doses >10 mg/kg PO (>150% relative to vehicle, Figure 3b), an in vivo marker for target engagement. **THPP-1** displayed similar dose-dependent efficacy in the CAR assay (data not shown), another well-established preclinical model for antipsychotic activity.[12] Additionally, it displayed an increase in cognitive function when dosed up to 1 mg/kg PO, as measured in a NOR assay, with effects comparable to those of donepezil.[12]

THPP-1 showed negligible activity in our AE assays. It did not significantly influence circulating prolactin levels nor induce catalepsy following oral dosing up to 50 mg/kg PO (Fig. 3c and d), compared to a clinically relevant dose of haloperidol (1.5 mg/kg). Notably, chronic dosing (7 days) of **THPP-1** to rats significantly decreased body weight gain, total body fat, and lean body mass compared to the positive control olanzapine (Fig. 4a–c). This AE profile is significantly distinguished from those of both typical and atypical antipsychotics, suggesting the potential for improved patient compliance.

The PDE10A active site possesses a number of regions critical for inhibitor binding and potency.[15] Among these are a H-bond interaction with Q726 and a pi-stacking interaction (hydrophobic clamp) with F729. In addition, studies with selective PDE10A inhibitors such as MP-10 (PF-02545920) suggest that the formation of a

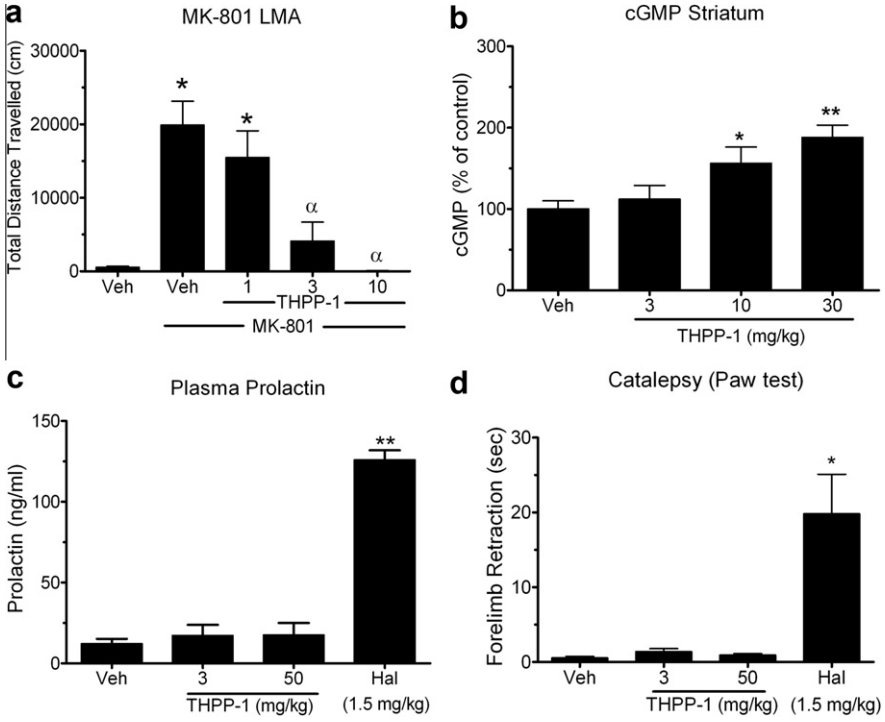


Figure 3. (a) Effect of **THPP-1** administration on the attenuation of MK-801-induced rat hyperlocomotion. Asterisks indicate significantly greater activity compared to vehicle (Veh) only ($^{*}p$ <0.05, $^{**}p$ <0.01). Alpha indicates significantly less activity compared to animals receiving MK-801. (b) Effect of **THPP-1** administration on cGMP concentration in the rat striatum 2 h after administration compared to Veh injected control. (c) Circulating prolactin levels in rat upon oral administration of **THPP-1** (control = haloperidol; 1.5 mg/kg). (d) Assessment of rat catalepsy by fore-limb retraction (paw test) upon oral administration of **THPP-1** (control = haloperidol; 1.5 mg/kg).

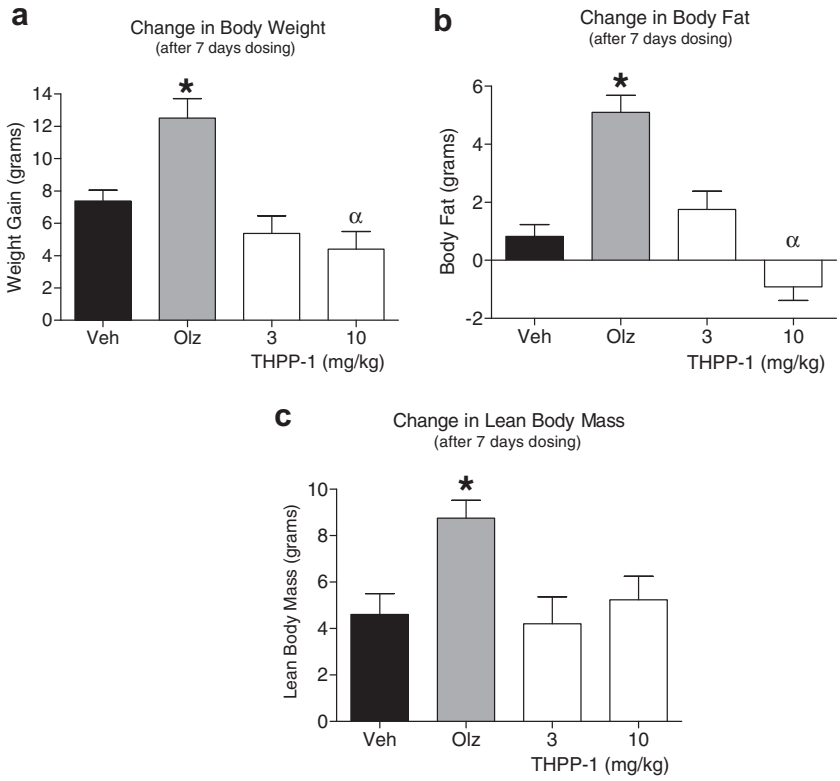


Figure 4. (a) Influence of THPP-1 and olanzapine (Olz; 4 mg/kg) on weight gain, (b) body fat, and (c) lean body mass following 7 days of dosing. Asterisks indicate significantly greater than vehicle (Veh) and alpha indicates significantly less than Veh, $n = 12$/group.

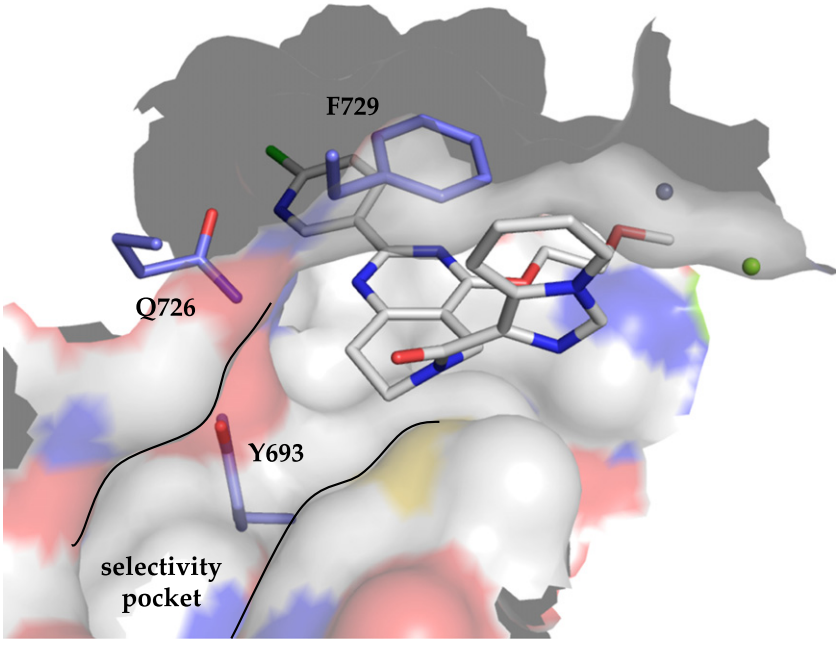


Figure 5. Computational model of **THPP-1** docked in the PDE10A active site.

H-bond with non-conserved Y693 in the so-called 'selectivity pocket' of the active site is crucial for selectivity across the PDE families.[6b] Indeed, MP-10 displays exquisite PDE10A selectivity of >5000-fold over all other PDEs.

A computationally docked model of **THPP-1** bound in the active site of PDE10A is shown in Figure 5, and the two conserved interactions described above are highlighted.[16] This model agrees very well with the corresponding X-ray crystal stucture (data not shown). The suboptimal PDE5A, PDE6A, and PDE11A selectivities of **THPP-1** (Table 3) are explained by a lack of interaction with Y693 in the PDE10A 'selectivity pocket.'

In summary, we have described the discovery of a novel tetrahydropyridopyrimidine PDE10A inhibitor for the treatment of the positive symptoms of schizophrenia. **THPP-1** was identified

through systematic optimization of a proprietary HTS lead, aided by the development of novel facilitating methodology that assembles the full structural framework in a single 3CC transformation. **THPP-1** is potent, selective, and possesses a highly favorable PK profile across preclinical species. It is efficacious in two models of antipsychotic activity (LMA, CAR) and possesses a promising AE profile, significantly distinguishing it and other PDE10A inhibitors from currently marketed antipsychotics. **THPP-1** is positioned for further advancement as a leading compound and additional progress will be detailed in due course.

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13. Experimental procedure for the synthesis of **THPP-1**: *2-(6-chloropyridin-3-yl)-4-(2-methoxyethoxy)-5,6,7,8-tetrahydropyrido[4,3-]pyrimidine.* A mixture of 1-*tert*-butyl 3-ethyl 4-oxopiperidine-1,3-dicarboxylate (5.1 g, 18.80 mmol), 6-chloropyridine-3-carboximidamide hydrochloride (5.95 g, 26.3 mmol) and K_2CO_3 (5.72 g, 41.4 mmol) was diluted with dimethylformamide (75 mL) and treated with 2-bromoethyl methyl ether (4.42 mL, 47.0 mmol) with stirring. The mixture was heated to 65 °C. After 2 h, the mixture was treated with additional 2-bromoethyl methyl ether (4.42 ml, 47.0 mmol) and K_2CO_3 (5.72 g, 41.4 mmol) and heated for an additional 4 h. The mixture was diluted with EtOAc (150 mL), and washed with water (150 mL) and brine (150 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was dissolved in EtOAc (100 mL) and treated with HCl gas until the solvent was saturated. The mixture stirred at room temperature for 30 min, treated again with HCl gas, and then stirred for an additional 30 min. The mixture was concentrated to dryness and the amine HCl salt was dissolved in water (50 mL). The solution was washed with ethyl acetate (2 × 200 mL) and then basified with aqueous 4 N NaOH. The aqueous phase was extracted with 4:1 $CHCl_3$:isopropanol (2 × 200 mL). The combined organic phases were concentrated in vacuo, and the residue dissolved in CH_2Cl_2 (300 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified by gradient elution on silica gel (0–100% [9% methanol in CH_2Cl_2] in CH_2Cl_3) to provide the title compound as a white solid (2.6 g, 43%, 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.35 (1H, d, J = 2.34 Hz), 8.61 (1H, dd, J = 8.30, 2.41 Hz), 7.40 (1H, d, J = 8.32 Hz), 4.66 (2 H, t, J = 4.71 Hz), 3.96 (3H, s), 3.80 (2H, t, J = 4.71 Hz), 3.45 (2H, d, J = 0.74 Hz), 3.22 (2H, t, J = 5.85 Hz), 2.88 (2H, t, J = 5.86 Hz); LRMS [M+H]: 321.3 found, 321.7 required. *[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***). A solution of 2-(6-chloropyridin-3-yl)-4-(2-methoxyethoxy)-5,6,7,8-tetrahydropyrido-[4,3-*d*]pyrimidine (2.0 g, 6.23 mmol), imidazo[1,5-*a*]pyridine-1-carboxylic acid (1.1 g, 6.86 mmol), EDC (1.32 g, 6.86 mmol), and HOBt (0.9 g, 5.92 mmol) in dimethylformamide (31 mL) was treated with triethylamine (2.61 mL, 18.7 mmol) at room temperature. The mixture was heated to 60 °C for 40 min. The mixture was diluted with EtOAc (100 mL) and washed with sat. aq. $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting material was purified by gradient elution on silica gel (0–45% [10% methanol in CH_2Cl_2] in CH_2Cl_2) to provide **THPP-1** as a light yellow solid (2.66 g, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36 (1H, s), 8.62 (1H, d, J = 8.41 Hz), 8.28 (1H, d, J = 9.27 Hz), 8.09 (1H, s), 8.03 (1H, d, J = 6.99 Hz), 7.40 (1H, d, J = 8.35 Hz), 7.04 (1H, t, J = 7.85 Hz), 6.77 (1H, t, J = 6.75 Hz), 5.8–4.0 (4H, bm), 4.69 (2H, t, J = 4.68 Hz), 3.83 (2H, t, J = 4.62 Hz), 3.47 (3H, s), 3.14 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.88, 163.93, 158.71, 152.95, 149.83, 138.05, 134.73, 132.23, 126.14, 124.89, 123.85, 123.23, 122.47, 120.71, 114.30, 113.21, 70.51, 65.92, 59.25, 44.4–41.8 (1C, br s), 41.8–39.0 (1C, br s), 33.2–31.2 (1C, br s). HRMS [M+H]: 465.1426 found, 465.1436 required.
14. **THPP-1** was administered intravenously during 3 sequential 30-minute periods at 13, 29, and 42 mg/kg in DMSO (10 mL/30 min) to evaluate the effects of the test article on cardiovascular function in 3 anesthetized, vagotomized dogs. Heart rate (HR), mean blood pressure (MBP) and electrocardiographic parameters (PR, QRS and QT_cB intervals; QT_cB-heart rate correction using Bazett's method) were monitored and blood samples were collected for plasma drug concentration analysis. The cardiovascular effects of the vehicle alone (30 mL/90 min) were evaluated in a separate set of 3 dogs, for time-matched comparison with the respective doses of **THPP-1**.
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16. Using the 3UI7 (Yang, S.-H., et al., *Bioorg. Med. Chem. Lett.* **2012**, *22*, 235.) PDB structure, the **THPP-1** structure was docked into the active site using Glide SP (Schrodinger, LLC, Glide, version 9.1, Schrödinger, Inc., New York, NY, 2009) with default options. The grid was computed and a hydrogen bond to the invariant Gln726 was defined. Poses were examined and the depicted structure in Figure 5 was within the top 5 poses retrieved.