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Design, synthesis and pharmacological evaluation of novel polycyclic heteroarene ethers as PDE10A inhibitors: Part II

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ABSTRACT

We report the design and synthesis of novel pyrrolo[3,2-*b*]quinoline containing heteroarene ethers as PDE10A inhibitors with good to excellent potency, selectivity and metabolic stability. Further optimization of this primary series resulted in the identification of 1-methyl-3-(4-{[3-(pyridine-4-yl)pyrazin-2-yl]oxy}phenyl)-1*H*-pyrrolo[3,2-*b*]pyridine **13a** with good hPDE10A potency (IC_{50}: 6.3 nM), excellent selectivity over other related PDEs and desirable physicochemical properties. The compound exhibited high peripheral and adequate brain levels upon oral dosing in rodents. The compound also showed excellent efficacy in multiple preclinical animal models related to psychiatric disorders, particularly schizophrenia.

Schizophrenia is a debilitating neuropsychiatric disorder consisting of positive or psychotic symptoms (bizarre delusions, hallucinations and paranoia), negative symptoms (lack of motivation and social withdrawal) and cognitive deficits (impaired executive functioning).[1] The currently available typical-(D2 receptor antagonists) and atypical antipsychotics (D2 and 5HT2a antagonists) are effective in treating only positive symptoms. These drugs are ineffective against negative symptoms and cognitive deficits of schizophrenia and are associated with undesired motor side effects, weight gain, diabetes and QT prolongation.[2] There is a high unmet need for new therapeutics that can address negative and cognitive symptoms along with good efficacy in treating positive symptoms of the disease with fewer side effects. Preclinical studies suggest that inhibition of PDE10A enzymatic activity can provide antipsychotic, pro-cognitive, negative symptom efficacy and an atypical anti-schizophrenic profile with improved safety.[3,4]

Several companies with prospective programs have reported large numbers of small molecule PDE10A inhibitors.[5] Pfizer's well-studied molecule MP-10 (PF-02545920) failed to achieve primary efficacy endpoints in schizophrenia trials and the molecule is now being re-evaluated for Huntington's disease.[6] Omeros has initiated phase 2 clinical trials of OMS824 for treating positive and negative symptoms associated with schizophrenia and Huntington's disease, and has received fast track designation from US FDA. Using an analogue-based design, we had reported novel pharmacophoric scaffolds having good PDE10A inhibitory activity.[7] Compound **1** (Fig. 1) from the above report inhibited PDE10A with an IC_{50} value of 123.2 nM.[7] The compound suffered from exhaustive metabolism with 0.2% and 0.1% remaining after 1.0 h incubation in the rat and human liver microsomes, respectively. This instability has mainly been attributed to the presence of

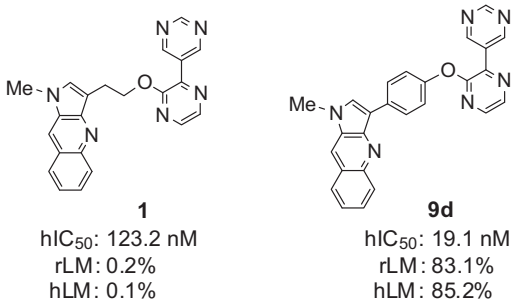

Figure 1. Comparison of PDE10A inhibitors **1** and **9d**.

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metabolically liable ethoxy ether linker as identified by our metabolite identification (Met-ID) studies.[7]

The problem of low metabolic stability was successfully resolved by replacing the ethoxy ether linker with phenoxy ether as in the case of compound **9d** (Fig. 1), that resulted in high microsomal stability (83.1% and 85.2%) and 6-fold improvement in potency to 19.1 nM. This lead compound was further optimized to improve potency, selectivity and physicochemical properties and the results are described in this Letter.

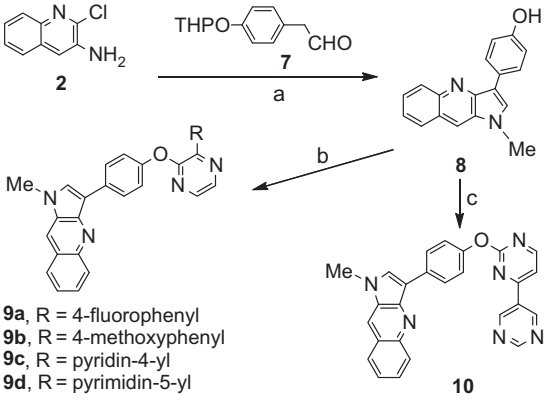
In our previous communication (Part 1), we had extensively studied SAR of tricyclic PDE10A inhibitors based on pyrrolo[3,2-*b*]quinolines and pyrido[2,3-*b*]indoles.[7] Based on the SAR data we focused on selected linker-modified derivatives of pyrrolo[3,2-*b*]quinolines as shown in Schemes 1 and 2. The approach employed for the synthesis of pyrrolo[3,2-*b*]quinoline linked compounds of the formula **5a**–**e** and **6** is outlined in Scheme 1. Condensation reaction of 2-chloroquinolin-3-amine **2**[8] with THP protected 2-(3-hydroxyphenyl)acetaldehyde **3**[9] gave 1*H*-pyrrolo[3,2-*b*]quinoline,[10] which on N-methylation followed by deprotection of THP group afforded the desired 3-substituted phenol derivative **4**. The coupling reaction of **4** with appropriately substituted 2-chloropyrimidine gave aryl ethers **5a**–**e** in 55–80% yield. Similarly, **4** was coupled with 5-(3-chloropyrazin-2-yl)pyrimidine to give **6** in 62% yield.

The inhibitory activity of compounds was measured using a scintillation proximity assay with [^{3}H]-cAMP as the substrate and by measuring hydrolysis of cAMP to AMP using recombinant human PDE10A enzyme and the results are shown in Table 1.[11] From amongst the 1,3-disubstituted pyrimidine derivatives **5a**–**e**, compound **5a** bearing a pyrazole ring at the 3-position showed good PDE10A inhibition with a potency of 20.9 nM. The fluorophenyl derivative **5b** and the methoxyphenyl derivative **5c** showed nearly 5-fold loss in potency. Compounds **5d** and **5e** with pyrimidine and morpholine substituent at 3-position showed a potency of 18.2 and 29.2 nM, respectively. However, compound **6** with a 1,2-substitution around the central pyrazine core resulted in poor potency.

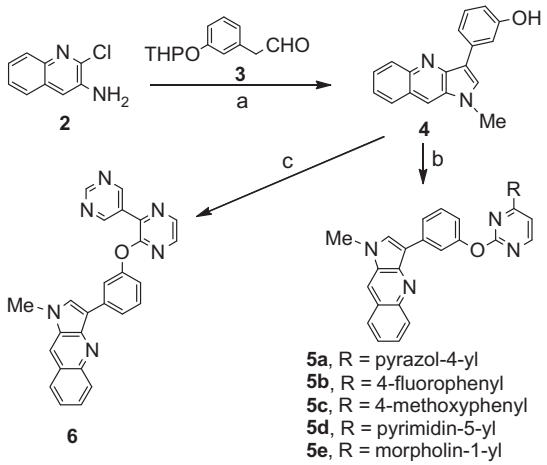
The synthesis of isomeric 4-substituted phenol derivative **8** and its use in the synthesis of compounds **9a**–**d** and **10** is shown in Scheme 2. As described above, condensation of **2** with THP protected 2-(4-hydroxyphenyl)acetaldehyde **7**[9] gave 1*H*-pyrrolo[3,2-*b*]quinoline, which on N-methylation and deprotection of the THP group afforded the desired 4-substituted phenol derivative **8**. The coupling reaction of **8** with appropriate 2-chloro-3-substituted pyrazine gave **9a**–**d** in 48–75% yield. Similarly, coupling reaction of **8** with 2-chloro-4,5′-bipyrimidine furnished **10** in moderate yield.

The 1,2-disubstituted pyrazine derivatives **9a** and **9b** with aryl substitution resulted in moderate potency of 177.2 and 153.1 nM, respectively. Introduction of a pyridine ring as in the case of **9c** and a pyrimidine ring as in the case of **9d** resulted in excellent potency of 8.5 and 19.1 nM, respectively. Compound **10** with a 1,3-substitution pattern around the central pyrimidine ring resulted in moderate PDE10A potency (entry 11).

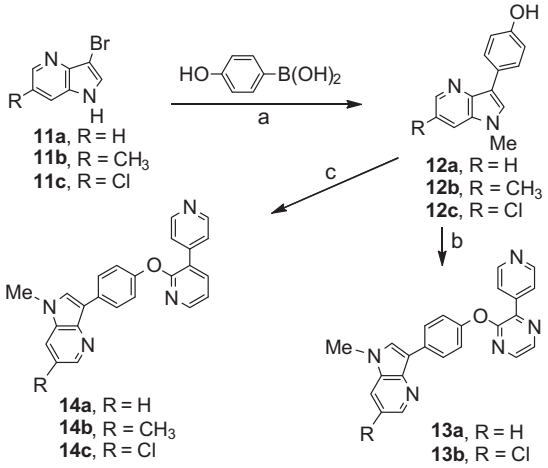
In order to understand the minimum structural requirement for good PDE10A inhibition, we considered the replacement of the tricyclic pyrrolo[3,2-*b*]quinoline moiety with the bicyclic pyrrolo[3,2-*b*]pyridine in selected derivatives. The approach employed for the synthesis of these compounds is depicted in Scheme 3. N-methylation of 3-bromopyrrolo[3,2-*b*]pyridine **11a**–**c** with methyl iodide followed by Suzuki coupling with 4-hydroxyphenylboronic acid gave the 4-hydroxyphenyl derivative **12a**–**c**. Phenol derivatives **12a** and **12c** were coupled with 2-chloro-3-(pyridin-4-yl)pyrazine to furnish the corresponding phenyl ethers **13a** and **13b** in



Scheme 2. Reagents and condition: (a) (i) (t-Bu)$_3$P.HBF$_4$, Pd$_2$(dba)$_3$, KOAc, DMA, 120 °C, N$_2$, 16 h, 37%, (ii) CH$_3$I, NaH, DMF, 0 °C to rt, 1 h, 82%, (iii) Concd HCl, MeOH, THF, 0 °C, 30 min, 62%; (b) 3-substituted-2-chloropyrazines, Cs$_2$CO$_3$, DMSO, 80 °C, 12 h, 48–75%; (c) 2-chloro-4,5′-bipyrimidine, Cs$_2$CO$_3$, DMSO, 80 °C; 10 h, 52%.



Scheme 1. Reagents and conditions: (a) (i) (t-Bu)$_3$P.HBF$_4$, Pd$_2$(dba)$_3$, KOAc, DMA, 120 °C, N$_2$, 16 h, 44%, (ii) CH$_3$I, NaH, DMF, 0 °C to rt, 1 h, 80%, (iii) Concd HCl, MeOH, THF, 0 °C, 30 min, 65%; (b) 3-substituted 2-chloropyrimidines, Cs$_2$CO$_3$, DMSO, 80 °C, 12–16 h, 55–80%; (c) 5-(3-chloropyrazin-2-yl)pyrimidine, Cs$_2$CO$_3$, DMSO, 80 °C, 16 h, 62%.



Scheme 3. Reagents and conditions: (a) (i) CH$_3$I, NaH, DMF, 0 °C to rt, 1 h, 66–85%, (ii) 4-hydroxyphenylboronic acid, Pd(PPh$_3$)$_4$, K$_2$CO$_3$, DMF, water, 80 °C, N$_2$, 12–16 h, 52–80%; (b) 2-chloro-3-(pyridin-4-yl)pyrazine, Cs$_2$CO$_3$, DMSO, 80 °C, 10 h, 58–70%, (c) 2-fluoro-3,4′-bipyridine, Cs$_2$CO$_3$, DMSO, 80 °C, 12 h, 55–65%.

58% and 70% yield, respectively. Similarly, phenols **12a–c** were coupled with 2-fluoro-3,4′-bipyridine to give the desired compounds **14a–c**.

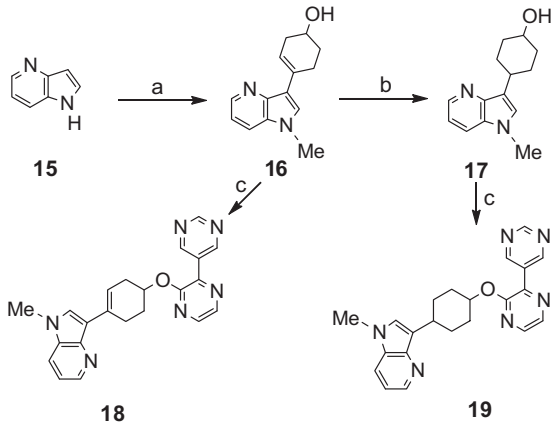
The compound **13a** bearing a bicyclic pyrrolo[3,2-*b*]pyridine core resulted in single digit potency of 6.3 nM. However, the corresponding chloro derivative **13b** showed 11-fold loss in potency. The compounds **14a–c** with the central pyridine core were more potent than the pyrazine derivatives **13a–b** as shown in Table 1.

Having accomplished good in-vitro potency with the bicyclic systems, we turned our attention towards the synthesis of the more flexible cyclohexene derivative **18** and cyclohexane derivative **19** as shown in Scheme 4. Condensation reaction of 1*H*-pyrrolo[3,2-*b*]pyridine **15** with 1,4-dioxaspiro[4,5]-decan-8-one in the presence of KOH followed by N-methylation, deprotection of 1,3-dioxolane moiety and finally carbonyl group reduction resulted in cyclohexenol **16**.[12] The alcohol **16** on reaction with 3-(pyrimidin-5-yl)pyrazin-2-ol under Mitsunobu reaction conditions afforded **18** in good yield. Similarly, the saturated alcohol **17**[13] obtained by double bond saturation of **16** on Mitsunobu reaction with 3-(pyrimidin-5-yl)pyrazin-2-ol gave **19**.

The non-planar cyclohexene derivative **18** showed substantial loss in potency (IC_{50}: 135.5 nM) compared to the aromatic derivatives (cf. Scheme 3), suggesting that flat molecules are ideal as PDE10A inhibitors.[14] The effect is more pronounced in the fully saturated derivative **19**, which showed an IC_{50} value of 552 nM (entry 18).

As a part of the lead optimization strategy, selected potent compounds listed in Table 1 were screened against a broader panel of PDEs and the results are shown in Table 2. The PDE selectivity assay of compounds **5a**, **5d–e**, **9c–d**, **13a–b** and **14a–c** was carried out using human recombinant PDEs 2–5, 7 and 11. The percentage inhibition of PDEs was measured at 1.0 and 10.0 μM concentrations of the compounds.[11] The compounds, in general, are highly selective over all other PDEs except in the case of **5e**, as it showed substantial inhibition of PDE11 at both 1.0 and 10.0 μM concentrations. The compounds **13a** and **13b** showed poor inhibition at both 1.0 and 10 μM concentrations for all related PDEs studied and are therefore most selective among the compounds studied.

Selected compounds were then subjected to in vitro metabolic stability studies using the male Wistar rat, male CD1 mouse, male Beagle dog, male cynomolgus monkey and pooled human liver microsomes and the results are shown in Table 3. The in vitro metabolic stability of compounds was determined by measuring the



Scheme 4. Reagents and conditions: (a) (i) 1,4-dioxaspiro[4.5]decan-8-one, KOH, MeOH, reflux, 16 h, 84%, (ii) CH_3I, NaH, DMF, 0 °C to rt, 1 h, 82%, (iii) 1 N HCl, THF, rt—reflux, 2 h, 91%, (iv) $NaBH_4$, MeOH, 0 °C, 30 min, 93%; (b) Pd-C, EtOH, H_2, rt, 2 h, 87%; (c) 3-(pyrimidin-5-yl)pyrazin-2-ol, DEAD, PPh_3, THF, 0 °C to rt, 10 h, 53–58%.

extent of disappearance of compounds in liver microsomal incubations at 37 °C for 60 min. The pyrimidine derivatives **5a** and **5d** showed moderate to poor stability, while **5e** showed poor stability across species suggesting that the morpholine ring is highly susceptible to oxidative metabolism.[15] The pyrazine derivatives **9c** and **9d** showed good stability across species. Compounds **13a–b** and **14a–c** based on the bicyclic core retained good metabolic stability across species. As expected, the metabolically more labile cyclohexene derivative **18** was less stable than the corresponding fully saturated analogue **19**.

Having achieved good potency, selectivity and in-vitro metabolic stability for several compounds (see Tables 1–3), we decided to study **13a** as a tool compound in in vivo efficacy models. From the overall profile of bicyclic compounds, **13a** and **14c** appear to be the best among all compounds studied. The calculated physicochemical properties of **13a** (Mol. Wt.: 379.4; *c*Log*P*: 3.2; tPSA: 61.9) were found to be superior to **14c** (Mol. Wt.: 412.8; *c*Log*P*: 4.7; tPSA: 49.5) and therefore **13a** was selected for further profiling. In a non-cell based PAMPA permeability assay, compound **13a** was found to be highly permeable (P_{app}: 2.97×10^{-6} cm/s).

The pharmacokinetic (PK) profile of **13a** was studied upon oral administration in male Swiss albino mice and male SD rats. Oral

Table 1
SAR of compounds **5a–e**, **6**, **9a–d**, **10**, **13a–b**, **14a–c**, **18–19**

Entry	Compd	% Inhib. (1.0 μM)[b]	hIC$_{50}$ (nM)[a]	rIC$_{50}$ (nM)[a]	mIC$_{50}$ (nM)[a]
1	**5a**	89.3	20.9 ± 2.9	122.4 ± 38.3	ND
2	**5b**	76.3	115.7 ± 7.5	ND	ND
3	**5c**	72.4	102.6 ± 3.9	ND	ND
4	**5d**	95.0	18.2 ± 1.7	90.3 ± 7.8	ND
5	**5e**	93.1	29.2 ± 2.2	166.9 ± 19.5	ND
6	**6**	76.3	266.7 ± 11.2	1450 ± 135.7	ND
7	**9a**	76.9	177.2 ± 21.3	ND	ND
8	**9b**	72.3	153.1 ± 5.8	132.2 ± 8.2	ND
9	**9c**	97.2	8.54 ± 1.2	29.4 ± 3.1	22.6 ± 0.4
10	**9d**	94.8	19.1 ± 1.2	31.1 ± 2.3	ND
11	**10**	85.3	128.1 ± 12.6	ND	ND
12	**13a**	98.0	6.3 ± 0.5	16.1 ± 2.1	11.7 ± 0.7
13	**13b**	79.7	71.0 ± 7.8	141.4 ± 21.7	ND
14	**14a**	98.0	1.3 ± 0.2	5.8 ± 0.9	4.1 ± 0.1
15	**14b**	98.3	0.3 ± 0.1	0.8 ± 0.1	1.2 ± 0.03
16	**14c**	95.4	2.6 ± 0.3	7.1 ± 0.8	6.7 ± 0.1
17	**18**	78.0	135.5 ± 14.1	552.2 ± 27.1	ND
18	**19**	68.9	552.1 ± 52.1	371.7 ± 2.5	ND

[a] IC_{50} values are mean ± SD of two independent experiments using 7 to 9-point concentration-response curve. ND refers to 'not determined'.
[b] Percentage inhibition values are for human PDE10A enzyme.

Table 2
PDE selectivity data for **5a**, **5d–e**, **9c**, **9d**, **13a–b**, **14a–c**[a]

Compd	Percentage inhibition at 1.0 and 10.0 μM concentration[a]					
	hPDE2	hPDE3	hPDE4	hPDE5	hPDE7	hPDE11
5a	16.1/40.8	4.5/27.5	7.9/34.7	8.2/19.0	16.7/27.2	27.3/38.5
5d	11.4/38.5	1.1/4.8	4.2/57.0	1.5/23.6	4.5/14.0	24.4/43.8
5e	15.7/76.2	0.3/21.5	5.6/1.0	16.0/33.3	5.8/19.5	44.6/76.3
9c	5.3/34.1	0.8/2.5	0.0/7.6	9.4/19.3	4.0/15.8	0.8/6.8
9d	8.9/14.2	0.3/9.4	1.3/19.5	9.4/17.3	6.0/20.2	3.3/21.8
13a	3.3/42.4	0.0/6.3	0.0/33.8	0.8/21.6	2.5/44.5	4.9/11.2
13b	11.3/16.1	0.7/9.8	4.1/25.4	0.1/19.3	5.9/53.1	3.1/5.7
14a	16.6/69.6	0.1/7.4	0.9/18.0	2.2/23.2	5.0/39.9	3.0/29.0
14b	24.9/43.0	0.9/6.4	0.0/10.8	9.6/16.7	3.7/28.3	0.1/8.3
14c	12.3/12.6	0.0/0.0	3.5/6.9	2.4/3.1	10.5/17.5	8.5/3.0

[a] Percentage inhibition (1.0/10 μM) values are mean of two independent experiments run in duplicate for both concentrations.

Table 3
Metabolic stability of **5a**, **5d–e**, **9c–d**, **13a–b**, **14a–c**, **18** and **19**[a]

Compd	Rat	Mouse	Dog	Monkey	Human
5a	17.3	60.4	52.0	38.1	75.4
5d	44.7	3.9	40.3	4.5	39.8
5e	0.4	0.6	1.3	0.6	8.2
9c	75.0	75.1	92.0	71.0	96.0
9d	83.1	76.1	77.0	68.3	85.2
13a	51.0	46.2	65.8	70.5	77.4
13b	68.0	70.5	55.3	40.7	77.0
14a	38.4	40.2	39.7	39.8	59.6
14b	46.2	48.1	32.3	13.7	62.5
14c	64.0	67.1	54.7	54.5	80.9
18	5.9	8.5	43.3	0.0	12.2
19	72.5	50.3	68.6	0.0	48.8

[a] Values are mean of three independent experiments.

administration of **13a** as methyl cellulose suspension in mice and rats at 10 mg/kg dose resulted in very good plasma concentrations and exposures as shown in Table 4. The systemic exposures of **13a** in SD rats were found to be around 13 fold higher than in Swiss albino mice. The significantly higher systemic clearance could be one of the major reasons for relatively poor oral PK in Swiss albino mice as compared to SD rats. The plasma clearance of **13a** after intravenous administration in Swiss albino mice was found to be significantly higher as compared to that in rats (68.4 mL/min/kg vs 1.6 mL/min/kg). Because of this higher systemic clearance of **13a** in mice, the relative oral bioavailability in mice was found to be only 8% to that in rats.

In a separate experiment, the concentrations of **13a** were measured in brain tissue upon oral administration in male SD rats. Further, the calculated total brain concentrations were converted to free brain concentrations using unbound fraction in brain determined in an in-vitro brain homogenate binding assay. The calculated free concentrations of **13a** in the brain at 1.0 h post-dose were at par with in vitro IC_{50} value and found to be in the range of 5–13 nM.

We next evaluated in-vivo efficacy of **13a** in four rodent models that are predictive of anti-psychotic activity in humans. To establish correlation between in-vitro potency, pharmacokinetics (PK) and pharmacodynamics (PD), compound **13a** was screened against rats and mice PDE10A enzyme. It showed an IC_{50} of 16.1 nM in rats and 11.7 nM in mice, which is close to the human potency of 6.3 nM.

Table 4
PK profile of **13a** in mice and rat at 10 mg/kg dose[a]

PK parameters	Swiss Albino mice[b]	Sprague Dawley rats[b]
C_{max} (ng/mL)	5490	27,642
T_{max} (h)	0.5	2.0
AUC_{0-t} (ng h/mL)	31,563	409,855
$T_{1/2}$ (h)	10.4	4.4

[a] Vehicle: 0.5% methyl cellulose suspension in water.
[b] Mean of 3 animals per time point.

First, the compound **13a** was evaluated in reversal of MK-801 (dizocilpine)-induced hyperactivity in SD rats and the results are shown in Figure 2.[16] The compound **13a** upon oral dosing at 1.0, 3.0 and 10.0 mg/kg in female rats produced significant dose-dependent efficacy on locomotion, stereotypy and ataxia parameters, demonstrating the ability of **13a** to alleviate glutamatergic dysfunction.[3] It showed an ED_{50} of 1.63 mg/kg on locomotor activity with a superior efficacy profile on all parameters when compared to the standard PDE10A inhibitor MP-10 (see Supplementary data).

The compound **13a** was then evaluated in the conditioned avoidance response (CAR) model in SD rats as shown in Figure 3.[3,17] The compound upon oral dosing at 1.0, 2.5 and 10.0 mg/kg produced significant dose-dependent efficacy in the CAR model of psychosis with an ED_{50} of 2.08 mg/kg on disruption of avoidance response. There was a good correlation between inhibition of

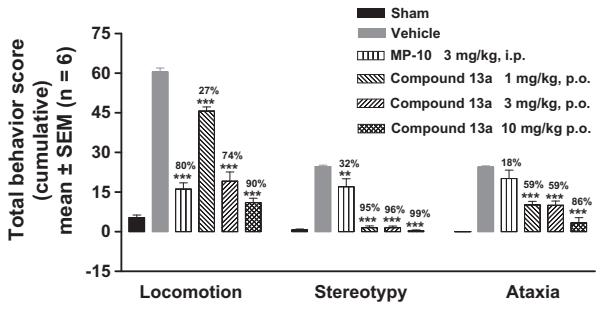


Figure 2. Effect of compound **13a** on MK-801- induced psychotic behavioral response in SD rats. $^{**}p$ value <0.01; $^{***}p$ value <0.001 for each dose.

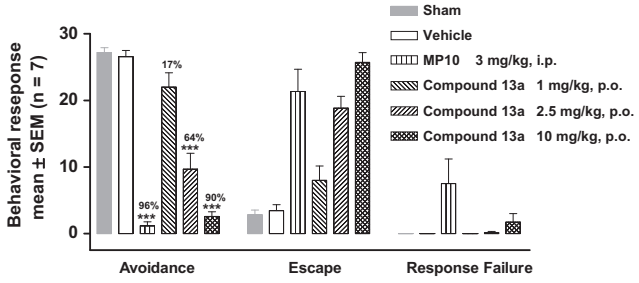


Figure 3. Effect of compound **13a** on conditioned avoidance response (CAR) in male SD rats, $^{***}p$ value <0.001 for each dose.

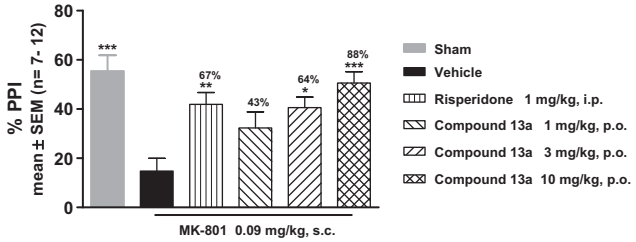


Figure 4. Effect of compound **13a** in reversing the MK-801-induced prepulse inhibition (PPI) deficit in male SD rats. *p value <0.05; **p value <0.01; ***p value <0.001.

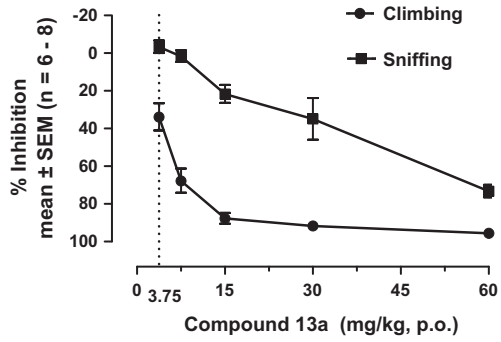


Figure 5. Effect of compound **13a** on apomorphine-induced climbing versus sniffing response in male Swiss-Albino mice.

avoidance and increase of escape responses with no response failure episodes even at the maximum efficacious dose of 10 mg/kg. The present results are in agreement with the ability of PDE10A inhibitors in disrupting the hyper-dopaminergic activity associated with the conditioning response (see Supplementary data).

The compound **13a** was also evaluated in MK-801-induced prepulse inhibition (PPI) deficit model in SD rats as shown in Figure 4.[3] Compound **13a** upon oral dosing at 1.0, 3.0 and 10 mg/kg produced a significant dose-dependent attenuation of MK-801 induced prepulse inhibition (PPI) deficit with an ED_{50} of 1.47 mg/kg when calculated on data collapsed across prepulse intensities (69, 74 and 79 dB) (see Supplementary data). The efficacy of compound **13a** was found to be superior to risperidone, the comparator molecule. With respect to startle response, **13a** showed equivalent response as that of risperidone with no trend of dose dependency and significance (data not shown). Our results further support the ability of PDE10A inhibitors improving the filtering and processing of sensory information in preclinical models of sensorimotor gating.

Finally, compound **13a** was tested in apomorphine-induced climbing (efficacy) versus sniffing (stereotypy) behavior in male Swiss Albino mice in a dose range of 3.75–60 mg/kg per oral to determine the effect of PDE10A inhibitors on striatal dopamine receptors.[18] The test provided a good ED_{50} ratio of 10.63 (sniffing/climbing), thus supporting an atypical anti-psychotic profile of the molecule as shown in Figure 5.

In summary, we have demonstrated that heteroarene ether derivatives of 1*H*-pyrrolo[3,2-*b*]quinoline and 1*H*-pyrrolo[3,2-*b*]pyridine displayed low nanomolar potency in in vitro radiometric PDE10A assay. Several compounds from the series showed very good selectivity over other related PDEs and good microsomal stability across species. The lead molecule **13a** showed excellent pharmacokinetics and ADME properties upon oral administration. The compound showed excellent efficacy in multiple antipsychotic models in rodents. The present study adds to a growing body of evidence suggesting the potential of PDE10A inhibitors for the management of various neuropsychiatric disorders in humans.

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Supplementary data

Supplementary data (synthetic procedures, selected analytical data, in vitro and in vivo experimental details and scanned spectra of selected compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.06.028.

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