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Original article

Synthesis and in vitro evaluation of new analogues as inhibitors for phosphodiesterase 10A

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ABSTRACT

A series of analogues were synthesized by optimizing the structure of papaverine. The *in vitro* PDE10A binding affinity (IC_{50}) values for these new analogues were measured; for compounds that have IC_{50} value less than 60 nM for PDE10A, the binding affinities (IC_{50} value) for PDE3A and PDE3B were tested. Of these analogues, compounds **6a**, **6b**, **6n**, **8b**, **8c** and **11** displayed relatively higher PDE10A potency with IC_{50} value in the range of 28–60 nM. The most potent compound 1-(4-(2-(2-fluoroethoxy)ethoxy)-3-methoxybenzyl)-6,7-dimethoxyisoquinoline (**8c**) has the IC_{50} value of 28 ± 1.2 nM for PDE10A, 2200 ± 437 nM for PDE3A and 2520 ± 210 nM for PDE3B. Compared to papaverine, compound **8c** displayed similar PDE10A potency but improved selectivity to PDE10A versus PDE3A and PDE3B. To identify high potent PDE10A inhibitor, further optimization of the structures of these analogues is necessary.

1. Introduction

Abnormal striatal output is caused by the dysfunction of striatopallidal transmission, which is the major contributor to the pathophysiology of central nervous system (CNS) disorders including schizophrenia, Parkinson's disease, Huntington's disease, Tourette's syndrome, and drug abuse [1–4]. The cyclic nucleotide phosphodiesterase enzymes have 11 gene families that contain 21 phosphodiesterase genes. The cyclic nucleotide phosphodiesterase 10A (PDE10A) is one of the 11 gene families and is highly expressed in the primary input neurons of the basal ganglia circuit, which are striatal medium-sized spiny neurons (MSNs) [5]. The inhibition of PDE10A alternates the basal ganglia circuit output and increases striatopallidal MSN activation, which represents a new therapeutic approach for the treatment of some of CNS diseases [5–9].

PDEs regulate levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) by hydrolysis of the cyclic nucleotide into their respective nucleotide monophosphates. PDE10A is a unique dual specificity phosphodiesterase that can convert both cAMP to adenosine monophosphate (AMP) and cGMP to guanosine monophosphate (GMP) [10–12].

Across species, compared to other PDE families, the PDE10A protein has a high degree of homology and is uniquely localized in mammals. PDE10 enzyme is expressed only in the testis and the brain [10–12]. Within the brain, the expression of the PDE10A enzyme is the highest in striatum (caudate and putamen), nucleus accumbens, and the olfactory tubercle of MSNs [10,11,13,14]. Based on the fact that PDE10A expression parallels D_2 localization in the brain, inhibition of PDE10A may have similar functional effects as D_2 inhibition. The inhibition of PDE10A may mediate the clinical antipsychotic effects. However, there are distinct differences between PDE10A inhibition and classical antagonists of D_2 receptors. The D_2 receptor has signaling components besides cAMP [15] and the inhibition of PDE10A interferes with cAMP levels that may negatively modulate rather than directly antagonize dopamine signaling. The inhibition of PDE10A may avoid the limitations that are observed with strong D_2 antagonism to treat schizophrenia and other CNS diseases. Furthermore, PDE10A is also expressed in D_1 expressing striatal neurons [14]. The activation of the D_1 receptor leads to the stimulation of adenylate cyclases, which results in the increase of cAMP levels. Therefore, the inhibition of PDE10A is likely to have effects that simulate D_1 receptor agonism. Together, PDE10A inhibition will increase cAMP in cells and can be expected to increase cGMP levels. cGMP activates a number of target proteins in the cells like cAMP and it also interacts with the cAMP signaling pathways. Consequentially, inhibition of PDE10A to elevate cAMP

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Nomenclature

AMP	adenosine monophosphate
Anal	analysis
Calcd	calculated
cAMP	cyclic adenosine monophosphate
CDI	1,1′-carbonyldiimidazole
CIMS	chemical ionization mass spectrometry
CNS	central nervous system
cGMP	cyclic guanosine monophosphate
DCC	N,N′-dicyclohexylcarbodiimide
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
GMP	guanosine monophosphate
MSNs	medium-sized spiny neurons
ND	not determined
PA	papaverine
PCP	phenylcyclohexylpiperidine
PDE10A	phosphodiesterase 10A
PDE3A	phosphodiesterase 3A
PDE3B	phosphodiesterase 3B
PET	positron emission tomography
PLD	phospholipase D
THF	tetrahydrofuran
TLC	thin layer chromatography

and cGMP could be a novel therapeutic strategy for the treatment of associated neurological and psychiatric disorders and may avoid unwanted side effects such as extrapyramidal symptoms associated with conventional therapeutics.

Over the past 10 years, tremendous efforts have been made to develop PDE10A inhibitors for the treatment of schizophrenia and associated mental disorders [16–20]. The compounds in Fig. 1 have attracted more attention [18,19,21]. Although papaverine has only moderate potency (IC_{50} = 36 nM) and poor selectivity (9 fold) over other PDE isoforms, papaverine was the first compound used to explore the role of PDE10A in the CNS. It was reported that papaverine potentiated the cataleptic effect of the D_2 receptor antagonist haloperidol in rats, but did not cause catalepsy on its own. Papaverine as well as more potent and more selective PDE 10A inhibitors PQ-10, MP-10 and TP-10, were all able to reduce hyperactivity in rats induced by phenylcyclohexylpiperidine (PCP) and amphetamine [8]. Furthermore, PDE10A inhibition with papaverine reverses subchronic PCP-induced deficits in attention set-shifting in rats [22]. Papaverine has also shown efficacy in rat novel object recognition [23]. Together, these data suggest that PDE10A inhibition might alleviate cognitive deficits associated with schizophrenia and psychosis.

In this paper, we will report the synthesis and biological binding affinity measurement of the new analogues as PDE10A inhibitors based on the modification of the molecular structure of papaverine. Our investigation was inspired by (1) papaverine has PDE10A inhibition function with moderate potency for PDE10A and low selectivity; (2) the rapid *in vivo* metabolism of papaverine limits it serving as a PET ligand for imaging in PDE10A *in vivo* [24]; and (3) the demand of a suitable PET probe for imaging the PDE10A enzyme *in vivo*.

2. Results and discussion

2.1. Chemistry

Papaverine, 1-(3,4-dimethoxybenzyl-6,7-dimethoxy)isoquinoline, which possesses four methoxy groups in its molecular structure, is now known to be a potent inhibitor of phosphodiesterase 10A (PDE10A) and has been reported to increase cognitive performance in the rat model of schizophrenia. Radioactive [^{3}H]papaverine, [^{14}C]papaverine and [^{11}C]papaverine have successfully been made to conduct pharmacologic studies. To develop the F-18 labeled PDE10A PET tracer, we synthesized a series of analogues by replacing the methoxy group(s) with the fluoroethoxyl group or other groups.

The synthesis of the target analogues **6a**–**n**, **8a**–**c** and **11** was shown in Scheme 1–3. Substituted benzaldehydes **1a** and **1b** were condensed with nitromethane to generate 2-phenyl-1-nitroethene derivatives **2a** and **2b** [25], which reacted with sodium methoxide to give (1-methoxy-2-nitroethyl)benzene derivatives **3a** and **3b** [26]. It was found that the conversion of compounds **2a** and **2b** to **3a** and **3b** was complete in just 10 min when one equivalent of compound **2** was added into two equivalents of sodium methoxide solution in methanol. Reduction of the nitro group of **3a** and **3b** with $LiAlH_4$ in THF gave amines **4a** and **4b** [26]. Due to the higher hydrophilicity of **4a** and **4b**, the extraction of **4a** and **4b** with organic solvent from their aqueous solution was very difficult. To resolve this problem, the excess lithium aluminum hydride was decomposed by carefully adding a very small amount of water followed by filtering the reaction mixture through celite to remove the precipitate, which was washed with THF. The THF was directly evaporated under vacuum without washing with water. When this procedure was followed, the yields of **4a** and **4b** were improved from 40% to 90%. Amines **4a** and **4b** were coupled with the corresponding substituted benzyl carboxylic acid using 1,1′-carbonyldiimidazole as a coupling agent to give amide **5a**–**m** and **5o**. Commercially available 2-amino-1-(3,4-dimethylphenyl)ethanol reacted with 2-substituted acetyl chloride to afford intermediate compounds **5n** and **5p**. Cyclization reaction of **5a**–**p** with $POCl_3$ in acetonitrile afforded compounds **6a**–**p**. Compounds **6a**–**n** were converted into oxalic salts for *in vitro* affinity measurements. Based on our experiments, the yield of the cyclization reaction was very good when the reaction time was limited to 30 min, otherwise the

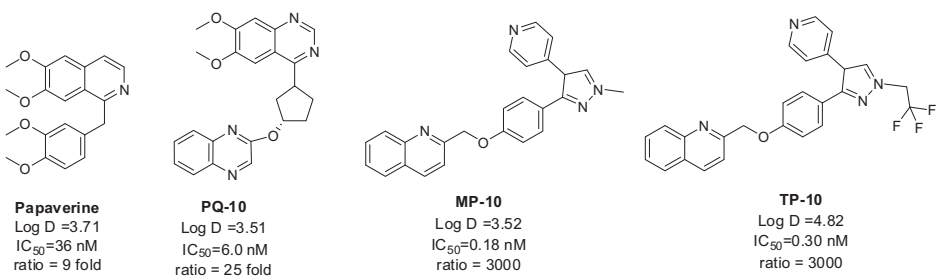
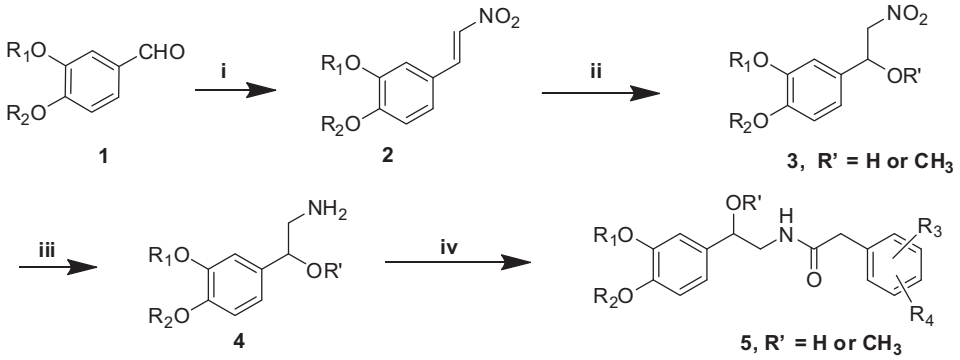
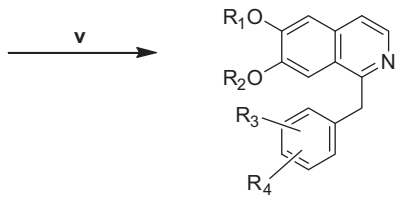


Fig. 1. Structures and in vitro assays of the lead compounds.



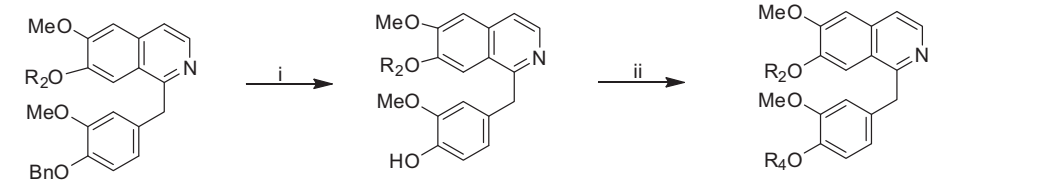
	R_1	R_2	R_3	R_4
6a	$-CH_2CH_2F$	Me	3-F	4-OMe
6b	$-CH_2CH_2F$	Me	3-Me	4-OMe
6c	$-CH_2CH_2F$	Me	H	4-SMe
6d	Me	$-CH_2CH_2F$	3-F	4-OMe
6e	Me	$-CH_2CH_2F$	3-Me	4-OMe
6f	Me	$-CH_2CH_2F$	H	4-SCH_3
6g	Me	$-CH_2CH_2F$	2-F	4-OMe
6h	Me	$-CH_2CH_2F$	2-OMe	5-Br
6i	Me	$-CH_2CH_2F$	3-Br	4-OMe
6j	Me	$-CH_2CH_2F$	3-F	H
6k	Me	$-CH_2CH_2F$	3-CH_2CH_2F	4-OMe
6l	Me	$-CH_2CH_2F$	3-OMe	5-OMe
6m	Me	$-CH_2CH_2F$	3-OMe	4-F
6n	Me	Me	3-$OCHCH_2F$	4-OMe
6o	Me	$-CH_2CH_2F$	3-OMe	4-OBn
6p	Me	Me	3-OMe	4-OBn



Reagents and conditions:

i) $MeNO_2$, NH_4OAc, HOAc; ii) MeONa/MeOH, THF; iii) $LiAlH_4$, THF;
iv) CDI, CH_2Cl_2, 2-(substituted phenyl)acetic acid or 2-(substituted phenyl)acetic chloride;
v) $POCl_3$, acetonitrile.

Scheme 1. Synthesis of compounds **6a**–**p**.



6o $R_2 = -CH_2CH_2F$
6p R_2 = Me

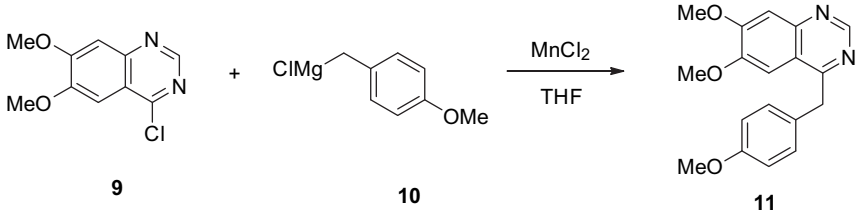
7a $R_2 = -CH_2CH_2F$
7b R_2 = Me

8a $R_2 = -CH_2CH_2F$, R_4=$-CH_2CH_2F$
8b R_2= Me, R_4= $-CH_2CH_2F$
8c R_2= Me, R_4=$-CH_2CH_2OCH_2CH_2F$

Reagents and conditions:

i) 1:1 HCl(aq), EtOH; ii) 2-bromo-1-fluoroethane or 1-chloro-2-(2-fluoroethoxy)ethane, K_2CO_3, DMF.

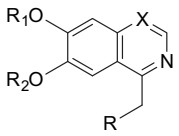
Scheme 2. Synthesis of compounds **8a**–**c**.

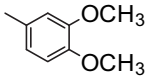
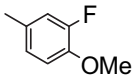
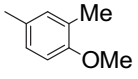
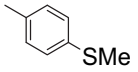
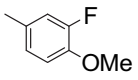
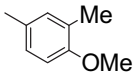
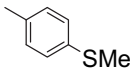
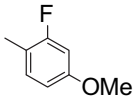
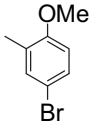
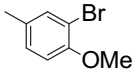
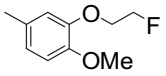
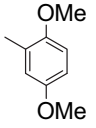
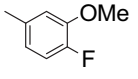
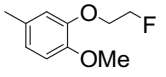


9 **10** **11**

Scheme 3. Synthesis of compound **11**.

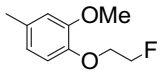
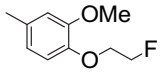
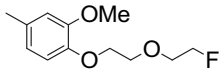
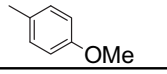
Table 1
Structure and affinities of new analogues[a].



	X	R_1	R_2	R	IC_{50} (nM)			Log P[b]
					PDE10A	PDE3A	PDE3B	
Papaverine	C	Me	Me		21 ± 1.2	917 ± 100	1030 ± 88	3.71
6a	C	$-CH_2CH_2F$	Me		49 ± 1.1	1290 ± 97	1250 ± 220	4.13
6b	C	$-CH_2CH_2F$	Me		58.5 ± 1.1	1190 ± 130	1670 ± 240	4.57
6c	C	$-CH_2CH_2F$	Me		112 ± 1.2	ND[c]	ND[c]	4.69
6d	C	Me	$-CH_2CH_2F$		198 ± 1.1	ND[c]	ND[c]	4.13
6e	C	Me	$-CH_2CH_2F$		244 ± 1.1	ND[c]	ND[c]	4.57
6f	C	Me	$-CH_2CH_2F$		237 ± 1.1	ND[c]	ND[c]	4.68
6g	C	Me	$-CH_2CH_2F$		500 ± 1.2	ND[c]	ND[c]	4.23
6h	C	Me	$-CH_2CH_2F$		872 ± 1.3	ND[c]	ND[c]	5.15
6i	C	Me	$-CH_2CH_2F$		248 ± 1.1	ND[c]	ND[c]	4.69
6j	C	Me	$-CH_2CH_2F$		469 ± 1.3	ND[c]	ND[c]	4.26
6k	C	Me	$-CH_2CH_2F$		200 ± 1.1	ND[c]	ND[c]	4.17
6l	C	Me	$-CH_2CH_2F$		262 ± 1.1	ND[c]	ND[c]	3.92
6m	C	Me	$-CH_2CH_2F$		303 ± 1.1	ND[c]	ND[c]	4.13
6n	C	Me	Me		55 ± 1.0	1940 ± 490	2510 ± 140	3.93

(*continued on next page*)

Table 1 (*continued*)

	X	R_1	R_2	R	IC_{50} (nM)			Log P[b]
					PDE10A	PDE3A	PDE3B	
8a	C	Me	$-CH_2CH_2F$		246 ± 1.1	ND[c]	ND[c]	4.17
8b	C	Me	Me		55 ± 1.2	1740 ± 390	2170 ± 260	3.93
8c	C	Me	Me		28 ± 1.2	2200 ± 440	2520 ± 210	3.54
11	C	Me	Me		48.8 ± 1.07	3980 ± 510	3100 ± 270	2.53

[a] IC_{50} is defined as the concentration of the inhibitor required to reduce the [^{3}H]cAMP hydrolysis activity of recombinant human PED10A by 50% with scintillation proximity assay.
[b] Calculated value at pH = 7.4 by ACD/I-Lab ver. 7.0 (Advanced Chemistry Development, Inc., Canada).
[c] Not determined.

yield was much lower. Hydrogenolysis to remove the benzyl group in **6o** and **6p** afforded phenol intermediates **7a** and **7b** which were reacted with 2-bromo-1-fluoroethane or 1-chloro-2-(2-fluoroethoxy)ethane via *O*-alkylation to afford compounds **8a**–**c**. Compounds **8a**–**c** were converted into oxalic salts for determining their binding affinities. To test whether replacing the isoquinoline ring with a quinazoline ring increases the binding affinity of PDE10A, compound **7** was synthesized according to Scheme 3. Starting with 4-chloro-6,7-dimethoxyquinazoline, **9** was treated with (4-methoxybenzyl) magnesium chloride, **10** in the presence of manganese (II) chloride in THF to afford compound **11** which was converted into its oxalate.

2.2. In vitro assessment of affinities

The binding affinities of PDE10A for the newly synthesized analogues were first determined by measuring IC_{50} values. It was reported that papaverine was not only a relatively potent inhibitor of PDE10A, but also exhibited moderate cross-reactivity versus PDE3A and PDE3B (Ki as 279, and 417 nM, respectively) [19]. The use of PDE3A/B inhibitor could lead to arrhythmia and increased mortality [27,28]. Therefore, compounds that had IC_{50} value less than 60 nM for PDE10A, were further determined by their binding affinities for PDE3A/B. The PDE activities were measured according to the procedure described in the experimental section. The binding affinities of the analogues were shown in Table 1.

To develop fluorine analogues, we took the following approach. First, we replaced the 6-methoxy in papaverine with a 6-fluoroethoxy group and replaced the 3-methoxy with a fluorine or methyl group. It was found that compounds **6a** and **6b** have a moderate affinity for PDE10A (IC_{50} value for **6a** was 49 nM and for **6b** was 58 nM). However, after replacing the 4-methoxy with a 4-methylthio group (**6c**), the IC_{50} value for PDE10A dropped to 112 nM. Second, when the 6-methoxy was retained and the 7-methoxy was replaced with a 7-fluroethoxy, compounds **6d**–**m** and **8a** were generated. Compared to **6a**–**c** and **8b**, the PDE10A binding affinities for **6d** vs. **6a**, **6e** vs. **6b**, **8a** vs. **8b** were reduced by 5 fold; for **6f** vs. **6c**, it was reduced by approximately 2 fold. The binding affinities were 49 ± 1.1, 58.5 ± 1.1, 112 ± 1.2 and 55 ± 1.2 nM for **6a**, **6b**, **6c** and **8b**, 198 ± 1.1, 244 ± 1.1, 237 ± 1.1 and 246 ± 1.1 nM for **6d**, **6e**, **6f** and **8a** respectively. Similar or even greater reduction in the PDE10A binding affinities was found for analogues **6g**–**m** and **8a**. Third, we retained both the 6 and 7-methoxy groups and replaced the 3-methoxy or 4-methoxy on the substituted benzyl group and found that both the **6n** and **8b** displayed modest affinities for PDE10A (IC_{50} value as 55 ± 1.0 nM for **6n** and 55 ± 1.2 nM for **8b**). Extending the 4-fluroethoxy group to a 4-(2-(2-fluoroethoxy))ethoxy group increased PDE10A affinity by 2-fold, from 55 ± 1.2 nM for **8b** to 28 ± 1.2 nM for **8c**). Fourth, we replaced 6,7-dimethoxyisoquinoline with 6,7-dimethoxy quinazoline, while removing the 3-methoxy group, which generated **11** that had a moderate PDE10A affinity of IC_{50} = 48.8 ± 1.07 nM.

3. Conclusions

In the current study, the papaverine structure was modified by incorporating fluorine containing substituted group(s) and replacing the isoquinoline ring with a quinazoline ring. The *in vitro* PDE10A binding affinity results of these compounds indicated that the compound **8c**, 1-(4-(2-(2-fluoroethoxy)ethoxy)-3-methoxybenzyl)-6,7-dimethoxyisoquinoline has a comparable binding affinity for PDE10A to that of papaverine. Compared to papaverine, compound **8c** has a much lower binding affinity for PDE3A (2200 nM for **8c** vs 279 nM for papaverine) and a lower binding affinity for PDE3B (2517 nM for **8c** vs 417 nM for papaverine) than that of papaverine [19]. Compound **8c** is a fluorine containing compound that can take advantage of the isotopic properties of F-18 (half-life is 110 min, widely commercial availability) compared to that of C-11 (half-live of 20 min; C-11 tracers have to be made in-house at a cyclotron facility). Fluorine-18 labeled probes are more suitable for conducting the imaging studies of PDE10A in living animals. The radioactive [^{18}**F**]**8c** will be radiosynthesized for *in vivo* evaluation to test its potential as a PET tracer for imaging the PDE10A *in vivo*.

4. Experimental

4.1. Chemistry

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 300 MHz NMR spectrometer. Chemical shifts were reported in δ values with respect to tetramethylsilane (TMS) as an internal reference standard. The following abbreviations are used for multiplicity of NMR signals: br s = broad singlet, s = singlet, d = doublet, dd = doublet of doublets,

dt = doublet of triplet, t = triplet, m = multiplet, q = quartet. Melting points were determined on an electrothermal melting point apparatus and were uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA, and were within ±0.4% of the calculated values. Mass spectrometry was provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954). All reactions were carried out under an inert atmosphere of nitrogen.

*4.1.1. Procedure A: synthesis of compounds **1a** and **1b***

*4.1.1.1. 4-(2-Fluoroethoxy)-3-methoxybenzaldehyde (**1a**).* Potassium carbonate (30.0 g, 0.22 mol) was added to a solution of 4-hydroxy-3-methoxybenzaldehyde (15.2 g, 0.1 mol) and 2-bromo-1-fluoroethane (25.4 g, 0.2 mol) in acetone (100 mL). The reaction mixture was refluxed overnight until the reaction was complete as determined by thin layer chromatography (TLC). After the solvent was removed, 200 mL of water was added to the flask, and the mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate. Filtered and concentrated, the crude product was purified by silica gel column chromatography with EtOAc/MeOH (95/5, v/v) as mobile phase to give **1a** (15.3 g, 77%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 3 H), 4.37 (dt, J = 27.3, 4.2 Hz, 2 H), 4.83 (dt, J = 47.4, 4.2 Hz, 2 H), 7.01 (d, J = 8.1 Hz, 1 H), 7.44–7.47 (m, 2 H), 9.87 (s, 1 H).

*4.1.1.2. 3-(2-Fluoroethoxy)-4-methoxybenzaldehyde (**1b**).* Starting with 3-hydroxy-4-methoxybenzaldehyde, Procedure A was followed to afford compound **1b** (5.9 g, 80%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 3 H), 4.34 (dt, J = 27.3, 4.2 Hz, 2 H), 4.83 (dt, J = 47.4, 4.2 Hz, 2 H), 7.01 (d, J = 8.4 Hz, 1 H), 7.43 (d, J = 2.1 Hz, 1 H), 7.51 (dd, J = 8.4, 2.1 Hz, 1 H), 9.86 (s, 1 H).

*4.1.2. Procedure B: synthesis of compounds **2a** and **2b***

*4.1.2.1. (E)-1-(2-Fluoroethoxy)-2-methoxy-4-(2-nitrovinyl)benzene (**2a**).* A stirred mixture of **1a** (12.5 g, 63.1 mmol), nitromethane (12.0 mL, 221.7 mmol) and anhydrous ammonium acetate (12.0 g, 155.8 mmol) in glacial acetic acid (28 mL) was refluxed for 30 min. After cooling to room temperature, the reaction mixture was poured into water (200 mL). The solid was collected by filtration to give **2a** (13.0 g, 85%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3 H), 4.34 (dt, J = 27.3, 4.2 Hz, 2 H), 4.82 (dt, J = 47.4, 4.2 Hz, 2 H), 6.94 (d, J = 8.1 Hz, 1 H), 7.03 (d, J = 2.1 Hz, 1 H), 7.15 (dd, J = 8.1, 2.1 Hz, 1 H), 7.53 (d, J = 13.8 Hz, 1 H), 7.96 (d, J = 13.8 Hz, 1 H).

*4.1.2.2. (E)-2-(2-Fluoroethoxy)-1-methoxy-4-(2-nitrovinyl)benzene (**2b**).* Starting with compound **1b**, procedure B was followed to afford compound **2b** (7.8 g, 78%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 3 H), 4.34 (dt, J = 27.3, 4.2 Hz, 2 H), 4.83 (dt, J = 47.4, 4.2 Hz, 2 H), 7.01–7.13 (m, 2 H), 7.51 (d, J = 8.4Hz, 1 H), 7.56 (d, J = 13.5Hz, 1 H), 7.90 (d, J = 13.5Hz, 1 H).

*4.1.3. Procedure C: synthesis of compounds **3a** and **3b***

*4.1.3.1. 1-(2-Fluoroethoxy)-2-methoxy-4-(1-methoxy-2-nitroethyl) benzene (**3a**).* A solution of **2a** (3.3 g, 13.7 mmol) in dry THF (50 mL) was added in one portion to a stirred solution of sodium methoxide (25% in MeOH, 9 mL) at room temperature. The resulting mixture was stirred for 5 min and poured into water. The crude product was collected by filtration to give **3a** (2.6 g, 70%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27 (s, 3H), 3.89 (s, 3H), 4.29 (dt, J = 27.3, 3.9 Hz, 2 H), 4.38 (dd, J = 12.6, 3.6 Hz, 1 H), 4.61 (dd, J = 12.3, 9.9 Hz, 1 H), 4.70–4.92 (m, 3 H), 6,88–6.95 (m, 3 H).

*4.1.3.2. 2-(2-Fluoroethoxy)-1-methoxy-4-(1-methoxy-2-nitroethyl) benzene (**3b**).* Starting with **2b**, procedure C was followed to afford compound **3b** (7.3 g, 78%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 3 H), 3.88 (s, 3 H), 4.24–4.40 (m, 3 H), 4.60 (dd, J = 10.8, 9.9 Hz, 1 H), 4.71–4.91 (m, 3 H), 6.90–6.97 (m, 3 H).

*4.1.4. Procedure D: synthesis of compounds **4a** and **4b***

*4.1.4.1. 2-(4-(2-Fluoroethoxy)-3-methoxyphenyl)-2-methoxyethanamine (**4a**).* A solution of **3a** (2.6 g, 9.5 mmol) in THF (45 mL) was added to lithium aluminum hydride (1.1 g, 29.1 mmol) in dry THF (15 mL) dropwise. The reaction mixture was refluxed for 6–8 h. The excess lithium aluminum hydride was decomposed by carefully adding a small amount of water. The suspension was filtered through (celite) and washed with THF. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography with CH_2Cl_2/MeOH/Et_3N (95/5/1, v/v/v) as mobile phase to give **4a** (1.53 g, 66%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81(dd, J = 13.6, 4.8 Hz, 1 H), 2.92 (dd, J = 13.2, 7.5 Hz, 1 H), 3.27 (s, 3 H), 4.08 (dd, J = 7.5, 4.2 Hz, 1 H), 3.88 (s, 3H), 4.28 (dt, J = 27.3, 4.5 Hz, 2 H), 4.78 (dt, J = 47.4, 4.5 Hz, 2 H), 6,83–6.91 (m, 3 H).

*4.1.4.2. 2-(3-(2-Fluoroethoxy)-4-methoxyphenyl)-2-methoxyethanamine (**4b**).* Starting with **3b**, procedure D was followed to afford compound **4b** (1.90 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81(dd, J = 13.2, 4.2 Hz, 1 H), 2.90 (dd, J = 13.2, 7.5 Hz, 1 H), 3.25 (s, 3 H), 3.88 (s, 3 H), 4.06 (dd, J = 7.5, 4.2 Hz, 1 H), 4.28 (dt, J = 27.9, 3.9 Hz, 2 H), 4.78 (dt, J = 47.7, 3.9 Hz, 2 H), 6.87 (s, 3 H).

*4.1.5. Procedure E: synthesis of compounds **5a–o***

*4.1.5.1. 2-(3-Fluoro-4-methoxyphenyl)-N-(2-(3-(2-fluoroethoxy)-4-methoxyphenyl)-2-methoxyethyl)acetamide (**5a**).* In a typical conversion, 1,1′-Carbonyldiimidazole (CDI, 0.32 g, 2 mmol) was added to a solution of 2-(4-fluoro-3-methoxyphenyl)acetic acid (0.37 g, 2 mmol) in 20 mL of dichloromethane, and the mixture was stirred at room temperature for 2 h, at which point, 2-(4-(2-fluoroethoxy)-3-methoxyphenyl)-2-methoxyethanamine **4a** (0.48 g, 2.0 mmol) was added and the mixture was stirred overnight. The reaction mixture was washed with saturated sodium carbonate solution, dried over anhydrous sodium sulfate. After concentrating, the residue **5a** was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17–3.26 (m, 4 H), 3.47 (s, 2 H), 3.59 (m, 1 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 4.13 (dd, J = 8.4, 4.5 Hz, 1 H), 4.26 (dt, J = 27.9, 4.2 Hz, 2 H), 4.77 (dt, J = 47.4, 4.2 Hz, 2 H), 5.74 (br, 1 H), 6.78–6.99 (m, 6 H).

*4.1.5.2. N-(2-(3-(2-Fluoroethoxy)-4-methoxyphenyl)-2-methoxyethyl)-2-(4-methoxy-3-methylphenyl)acetamide (**5b**).* Procedure E was followed to prepare compound **5b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3 H), 3.1–3.22 (m, 4 H), 3.47 (s, 2 H), 3.58 (m, 1 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 4.12 (dd, J = 8.4, 4.5 Hz, 1 H), 4.24 (dt, J = 27.3, 4.5 Hz, 2 H), 4.77 (dd, J = 47.4, 4.5 Hz, 2 H), 5.77 (br, 1 H), 6.70–7.01 (m, 6 H).

*4.1.5.3. N-(2-(3-(2-Fluoroethoxy)-4-methoxyphenyl)-2-methoxyethyl)-2-(4-(methylthio)phenyl)acetamide (**5c**).* Procedure E was followed to prepare compound **5c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49 (s, 3 H), 3.15–3.23 (m, 4 H), 3.51 (s, 2 H), 3.59 (m, 1 H), 3.87 (s, 3 H), 4.11 (m, 1 H), 4.24 (dt, J = 27.6, 4.5 Hz, 2 H), 4.77 (dt, J = 47.1, 4.5 Hz, 2 H), 5.74 (br, 1 H), 6.73–6.85 (m,3 H), 7.13–7.25 (m, 4 H).

*4.1.5.4. 2-(3-Fluoro-4-methoxyphenyl)-N-(2-(4-(2-fluoroethoxy)-3-methoxyphenyl)-2-methoxyethyl)acetamide (**5d**).* Procedure E was followed to prepare compound **5d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.20–3.28 (m, 4 H), 3.49 (s, 2 H), 3.62 (m, 1 H), 3.85 (s, 3 H), 3.89 (s, 3 H), 4.13 (m, 1 H), 4.27 (dt, J = 27.3, 4.2 Hz, 2 H), 4.79 (dt, J = 47.4, 4.2 Hz, 2 H), 5.77 (br, 1 H), 6.72–6.94 (m, 6 H).

*4.1.5.5. N-(2-(4-(2-Fluoroethoxy)-3-methoxyphenyl)-2-methoxyethyl)-2-(4-methoxy-3-methylphenyl)acetamide (**5e**).* Procedure E was followed to prepare compound **5e**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3 H), 3.15–3.23 (m, 4 H), 3.48 (s, 2 H), 3.59 (m, 1 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 4.13 (m, 1 H), 4.26 (dt, J = 27.3, 4.2 Hz, 2 H), 4.78 (dt, J = 47.4, 4.2 Hz, 2 H), 5.78 (br, 1 H), 6.71–6.86 (m, 4 H), 6.98–7.01 (m, 2 H).

*4.1.5.6. N-(2-(4-(2-Fluoroethoxy)-3-methoxyphenyl)-2-methoxyethyl)-2-(4-(methylthio)phenyl)acetamide (**5f**).* Procedure E was followed to afford compound **5f**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 3 H), 3.21–3.27 (m, 4 H), 3.55 (s, 2 H), 3.63 (m, 1 H), 3.87 (s, 3 H), 4.13 (m, 1 H), 4.30 (dt, J = 27.3, 4.2 Hz, 2 H), 4.71 (dt, J = 47.4, 4.2 Hz, 2 H), 5.77 (br, 1 H), 6.73–6.86 (m, 3 H), 6.89–7.26 (m, 4 H).

*4.1.5.7. 2-(2-Fluoro-4-methoxyphenyl)-N-(2-(4-(2-fluoroethoxy)-3-methoxyphenyl)-2-methoxyethyl)acetamide (**5g**).* Procedure E was followed to prepare compound **5g**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14–3.26 (m, 4 H), 3.51 (s, 2 H), 3.62 (m, 1 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 4.15 (m, 1 H), 4.26 (dt, J = 27.6, 4.2 Hz, 2 H), 4.78 (dt, J = 47.1, 4.2 Hz, 2 H), 5.85 (br, 1 H), 6.62–6.87 (m, 5 H), 7.15 (m, 1 H).

*4.1.5.8. 2-(5-Bromo-2-methoxyphenyl)-N-(2-(4-(2-fluoroethoxy)-3-methoxyphenyl)-2-methoxyethyl)acetamide (**5h**).* Procedure E was followed to prepare compound **5h**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04–3.13 (m, 4 H), 3.43 (s, 2 H), 3.55 (m, 1 H), 3.74 (s, 3 H), 3.76 (s, 3 H), 4.03 (m, 1 H), 4.24 (dt, J = 27.9, 4.2 Hz, 2 H), 4.70 (dt, J = 47.4, 4.2 Hz, 2 H), 6.06 (br, 1 H), 6.63–6.79 (m, 4 H), 7.19 (s, 1 H), 7.30 (m, 1 H).

*4.1.5.9. 2-(3-Bromo-4-methoxyphenyl)-N-(2-(4-(2-fluoroethoxy)-3-methoxyphenyl)-2-methoxyethyl)acetamide (**5i**).* Procedure E was followed to prepare compound **5i**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16–3.27 (m, 4 H), 3.47 (s, 2 H), 3.61 (m, 1 H), 3.85 (s, 3 H), 3.89 (s, 3 H), 4.15 (m, 1 H), 4.27 (dd, J = 27.3, 4.2 Hz, 2 H), 4.78 (dd, J = 47.1, 4.2 Hz, 2 H), 5.75 (br, 1 H), 6.70–6.88 (m, 4 H), 7.15 (m, 1 H), 7.43 (s, 1 H).

*4.1.5.10. N-(2-(4-(2-Fluoroethoxy)-3-methoxyphenyl)-2-methoxyethyl)-2-(3-fluorophenyl)acetamide (**5j**).* Procedure E was followed to prepare compound **5j**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14–3.26 (m, 4 H), 3.56 (s, 2 H), 3.64 (m, 1 H), 3.85 (s, 3 H), 4.15 (m, 1 H), 4.27 (dt, J = 27.6, 4.5 Hz, 2 H), 4.70 (dt, J = 47.1, 4.5 Hz, 2 H), 5.80 (br, 1 H), 6.73–6.80 (m, 3 H), 6.96–7.04 (m, 3 H), 7.27–7.35 (m, 1 H).

*4.1.5.11. N-(2-(4-(2-Fluoroethoxy)-3-methoxyphenyl)-2-methoxyethyl)-2-(3-(2-fluoroethoxy)-4-methoxyphenyl)acetamide (**5k**).* Procedure E was followed to prepare compound **5k**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17–3.25 (m, 4 H), 3.49 (s, 2 H), 3.58 (m, 1 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 4.13 (m, 1 H), 4.19–4.33 (m, 4 H), 4.86–4.88 (m, 4 H), 5.76 (br, 1 H), 6.70–6.87 (m, 6 H).

*4.1.5.12. 2-(3,5-Dimethoxyphenyl)-N-(2-(4-(2-fluoroethoxy)-3-methoxyphenyl)-2-methoxyethyl)acetamide (**5l**).* Procedure E was followed to prepare compound **5l**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18–3.24 (m, 4 H), 3.50 (s, 2 H), 3.60 (m, 1 H), 3.78 (s, 6 H), 3.85 (s, 3 H), 4.12 (m, 1 H), 4.26 (dt, J = 27.3, 4.5 Hz, 2 H), 4.78 (dt, J = 47.4, 4.5 Hz, 2 H), 5.84 (br, 1 H), 6.38 (m, 3 H), 6.70–6.86 (m, 3 H).

*4.1.5.13. 2-(4-Fluoro-3-methoxyphenyl)-N-(2-(4-(2-fluoroethoxy)-3-methoxyphenyl)-2-methoxyethyl)acetamide (**5m**).* Procedure E was followed to prepare compound **5m**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18–3.25 (m, 4 H), 3.51 (s, 2 H), 3.61 (m, 1 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 4.12 (m, 1 H), 4.27 (dt, J = 27.3, 4.5 Hz, 2 H), 4.78 (dt, J = 47.4, 4.5 Hz, 2 H), 5.79 (br, 1H), 6.69–6.87 (m, 4 H), 7.00–7.11 (m, 2 H).

*4.1.5.14. N-(2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl)-2-(3-(2-fluoroethoxy)-4-methoxyphenyl)acetamide (**5n**).* Procedure E was followed to afford compound **5n**. The ^{1}H NMR (300 MHz, $CDCl_3$) is δ 3.33 (m, 1 H), 3.51 (s, 2 H), 3.59 (m, 1 H), 3.89 (m, 9 H), 4.24 (dt, J = 28.8, 4.5 Hz, 2 H), 4.74 (dd, J = 8.1, 3.6Hz, 1 H), 4.78 (dt, J = 47.4, 4.5 Hz, 2 H), 5.81 (br, 1 H), 6.78–6.86 (m, 6 H).

*4.1.5.15. 2-(4-(Benzyloxy)-3-methoxyphenyl)-N-(2-(4-(2-fluoroethoxy)-3-methoxyphenyl)-2-ethoxyethyl)acetamide (**5o**).* Procedure E was followed to prepare compound **5o**. The ^{1}H NMR (300 MHz, $CDCl_3$) is δ 3.14–3.20 (m, 3 H), 3.49 (s, 2 H), 3.60 (m, 1 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 4.15 (m, 1 H), 4.22 (dt, J = 27.3, 4.5 Hz, 2 H), 4.82 (dt, J = 47.4, 4.5 Hz, 2 H), 5.16 (s, 2 H), 5.79 (br, 1 H), 6.67–6.87 (m, 4 H), 7.20–7.50 (m, 7 H).

*4.1.6. Procedure F: synthesis of compound **5p***

*4.1.6.1. 2-(4-(Benzyloxy)-3-methoxyphenyl)-N-(2-(3,4-dimethoxyphenyl)-2-hydroxyethyl)acetamide (**5p**).* Saturated sodium carbonate solution (5 mL) was added to a mixture of 2-amino-1-(3,4-dimethoxyphenyl)ethanol hydrochloride (0.41 g, 1.75 mmol) in ether (10 mL) and the mixture was stirred for 5 min. To the mixture, 2-(4-(benzyloxy)-3-methoxyphenyl)acetyl chloride (0.57 g, 1.96 mmol) in ether was added dropwise. The mixture was stirred for 2 h. The solid was collected by filtration to give **5p** (0.70 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (br, 1 H), 3.28–3.38 (m, 1 H), 3.52 (s, 2 H), 3.53–3.62 (m, 1 H), 3.86 (s, 9 H), 4.75 (m, 1 H), 5.15 (s, 2 H), 5.80 (br, 1 H), 6.66–6.87 (m, 6 H), 7.25–7.46 (m, 5 H).

*4.1.7. Procedure G: synthesis of compounds **6a–p***

*4.1.7.1. 1-(3-Fluoro-4-methoxybenzyl)-6-(2-fluoroethoxy)-7-methoxyisoquinoline oxalate (**6a**).* A mixture of **5a** and $POCl_3$ (0.5 mL**)** in acetonitrile (20 mL) was stirred under reflux for 30 min. After being cooled to room temperature and quenched with 25 mL of saturated sodium bicarbonate, the mixture was extracted with methylene chloride (10 mL × 3) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) as mobile phase to give the isoquinoline **6a** (0.41 g, 66%) as a white solid. To a solution of the **6a** in ethyl acetate/methanol (5 mL) was added 1 equivalent of oxalic acid in MeOH (5 mL), and the resulting mixture was stirred for 1 h at room temperature to give a crude oxalate salt. The white solid was filtered, washed thoroughly with ethyl acetate and methanol, separately. The free base was converted into oxalate salt for *in vitro* affinity measurements and elemental analysis. Mp (oxalate salt): 179.7–180.9 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.83 (s, 3 H), 3.89 (s, 3 H), 4.39 (dt, J = 27.0, 4.2 Hz, 2 H), 4.51 (s, 2 H), 4.87 (dt, J = 47.7, 4.2 Hz, 2 H), 6.81–7.00 (m, 3 H), 7.08 (s, 1 H), 7.28 (s, 1 H), 7.42 (d, J = 5.7 Hz, 1 H), 8.35 (d, J = 5.7 Hz, 1 H). ^{13}C NMR (75 MHz, free base, $CDCl_3$) δ 40.4, 55.1 (d, J = 33 Hz), 66.9 (d, J = 20.5 Hz), 76.2, 80.4 (d, J = 168.6 Hz), 103.5, 105.9, 112.6, 115.3 (d, J = 18.2 Hz), 117.8, 122.2, 123.0 (d, J = 3.4 Hz), 131.7 (d, J = 5.6 Hz), 132.2, 140.1, 145.1 (d, J = 11.4 Hz), 149.2, 150.5, 151.4 (d, J = 244.8 Hz), 156.3. Anal. Calcd for $C_{20}H_{19}F_2NO_3 \cdot H_2C_2O_4$: C, 58.80; H, 4.71; N, 3.12. Found: C, 58.75; H, 4.64; N, 3.09.

*4.1.7.2. 6-(2-Fluoroethoxy)-7-methoxy-1-(4-methoxy-3-methylbenzyl)-isoquinoline oxalate (**6b**).* Starting with **5b**, procedure G was followed to prepare compound **6b** as a white solid. Mp (oxalate salt): 172.9–175.0 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 2.14 (s, 3 H), 3.76 (s, 3 H), 3.89 (s, 3 H), 4.38 (dt, J = 27.0, 4.2 Hz, 2 H), 4.50 (s, 2 H), 4.86 (dt, J = 47.4, 4.2 Hz, 2 H), 6.71 (d, J = 8.7 Hz, 1 H), 7.04–7.07 (m, 3 H), 7.38 (s, 1 H), 7.39 (d, J = 5.7 Hz, 1 H), 8.36 (d, J = 6.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.1, 41.0, 55.8 (d, J = 47.8 Hz), 68.2 (d, J = 20.5 Hz), 77.4, 80.4 (d, J = 168.6 Hz), 105.3, 107.0, 110.4, 119.4, 126.9, 127.0, 130.3, 130.6, 131.1, 134.0, 135.3, 139.1, 150.8, 154.0, 157.8.

Anal. Calcd for ($C_{21}H_{22}FNO_3 \cdot H_2C_2O_4$: C, 62.02; H, 5.43; N, 3.14. Found: C, 6175; H, 5.52; N, 3.12.

*4.1.7.3. 6-(2-Fluoroethoxy)-7-methoxy-1-(4-(methylthio)benzyl)isoquinoline oxalate (**6c**).* Starting with **5c**, procedure G was followed to prepare compound **6c** (0.23 g, 72%) as a white solid. Mp (oxalate salt): 138.5–140.0 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 2.42 (s, 3 H), 3.88 (s, 3 H), 4.38 (dt, J = 27.0, 4.2 Hz, 2 H), 4.55 (s, 2 H), 4.86 (dt, J = 47.4, 4.2 Hz, 2 H), 7.06 (s, 1 H), 7.14–7.21 (m, 4 H), 7.38 (s, 1H), 7.41 (d, J = 6.0 Hz, 1 H), 8.36 (d, J = 6.0 Hz, 1 H). Anal. Calcd for $C_{20}H_{20}FNO_2S \cdot H_2C_2O_4 \cdot 0.5H_2O$: C, 57.88; H, 5.08; N, 3.07. Found: C, 57.89; H, 5.03; N, 2.93.

*4.1.7.4. 1-(4-Fluoro-3-methoxybenzyl)-7-(2-fluoroethoxy)-6-methoxyisoquinoline oxalate (**6d**).* Starting with **5d**, procedure G was followed to prepare **6d** (0.21 g, 66%) as a white solid. Mp (oxalate salt): 207.7–208.7 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.83 (s, 3 H), 4.00 (s, 3 H), 4.27 (dt, J = 27.3, 3.9 Hz, 2 H), 4.50 (s, 2 H), 4.81 (dt, J = 47.1, 3.9 Hz, 2 H), 6.82–7.00 (m, 3 H), 7.07 (s, 1 H), 7.31 (s, 1 H), 7.44 (d, J = 5.7 Hz, 1 H), 8.37 (d, J = 5.7 Hz, 1 H). Anal. Calcd for $C_{20}H_{19}F_2NO_3 \cdot H_2C_2O_4$: C, 58.80; H, 4.71; N, 3.12. Found: C, 58.78; H, 4.73; N, 3.23.

*4.1.7.5. 7-(2-Fluoroethoxy)-6-methoxy-1-(4-methoxy-3-methylbenzyl)-isoquinoline oxalate (**6e**).* Starting with **5e**, procedure G was followed to prepare compound **6e** (0.13 g, 61%) as a white solid. Mp (oxalate salt): 179.4–180.2 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 2.14 (s, 3 H), 3.76 (s, 3 H), 3.99 (s, 3 H), 4.26 (dt, J = 27.3, 4.5 Hz, 2 H), 4.48 (s, 2 H), 4.80 (dt, J = 47.4, 4.5 Hz, 2 H), 6.70 (d, J = 7.8 Hz, 1 H), 7.00–7.10 (m, 3 H), 7.39 (s, 1 H), 7.41 (d, J = 5.7 Hz, 1 H), 8.37 (d, J = 5.7 Hz, 1 H). Anal. Calcd for $C_{21}H_{22}FNO_3 \cdot H_2C_2O_4$: C, 62.02; H, 5.43; N, 3.14. Found: C, 62.09; H, 5.51; N, 3.26.

*4.1.7.6. 7-(2-Fluoroethoxy)-6-methoxy-1-(4-(methylthio)benzyl)isoquinoline oxalate (**6f**).* Starting with **5f**, procedure G was followed to prepare compound **6f** (0.15 g, 70%) as a white solid. Mp (oxalate salt): 199.5–200.5 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 2.43 (s, 3 H), 3.99 (s, 3 H), 4.26 (dt, J = 27.0, 4.2 Hz, 2 H), 4.53 (s, 2 H), 4.80 (dt, J = 47.4, 4.2 Hz, 2 H), 7.07 (s, 1 H), 7.16 (m, 4 H), 7.32 (s, 1 H), 7.43 (d, J = 5.7 Hz, 1 H), 8.37 (d, J = 5.7 Hz, 1 H). Anal. Calcd for $C_{20}H_{20}FNO_2S \cdot H_2C_2O_4$: C, 59.05; H, 4.96; N, 3.13. Found: C, 59.06; H, 4.93; N, 3.10.

*4.1.7.7. 1-(2-Fluoro-4-methoxybenzyl)-7-(2-fluoroethoxy)-6-methoxyisoquinoline oxalate (**6g**).* Starting with **5g**, procedure G was followed to prepare compound **6g** (0.13 g, 67%) as a pale solid. Mp (oxalate salt): 203.5–204.2 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.74 (s, 3 H), 3.99 (s, 3 H), 4.35 (dt, J = 27.3, 4.2 Hz, 2 H), 4.49 (s, 2 H), 4.85 (dt, J = 47.4, 4.2 Hz, 2 H), 6.55 (dd, J = 8.7, 1.8 Hz, 1 H), 6.64 (dd, J = 12.0, 2.7 Hz, 1 H), 7.00–7.13 (m, 2 H), 7.40–7.43 (m, 2 H), 8.36 (d, J = 5.7 Hz, 1 H). Anal. Calcd for $C_{20}H_{19}F_2NO_3 \cdot H_2C_2O_4$: C, 58.80; H, 4.71; N, 3.12. Found: C, 58.90; H, 4.75; N, 3.11.

*4.1.7.8. 1-(5-Bromo-2-methoxybenzyl)-7-(2-fluoroethoxy)-6-methoxyisoquinoline oxalate (**6h**).* Starting with **5h**, procedure G was followed to prepare compound **6h** (0.14 g, 49%) as a white solid. Mp (oxalate salt): 195.7–197.3 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.90 (s, 3 H), 4.00 (s, 3 H), 4.27 (dt, J = 27.1, 4.5 Hz, 2 H), 4.52 (s, 2 H), 4.81 (dt, J = 47.4, 4.5 Hz, 2 H), 6.78 (d, J = 9.0 Hz, 1 H), 7.07 (s, 1 H), 7.16–7.43 (m, 4 H), 8.37 (d, J = 5.7 Hz, 1 H). Anal. Calcd for $C_{20}H_{19}BrFNO_3 \cdot H_2C_2O_4$: C, 51.78; H, 4.15; N, 2.74. Found: C, 51.90; H, 4.21; N, 2.80.

*4.1.7.9. 1-(3-Bromo-4-methoxybenzyl)-7-(2-fluoroethoxy)-6-methoxyisoquinoline oxalate (**6i**).* Starting with **5i**, procedure G was followed to prepare compound **6i** (0.16 g, 47%) as a white solid. Mp (oxalate salt): 208.4–209.2 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.83 (s, 3 H), 4.00 (s, 3 H), 4.29 (dt, J = 27.3, 4.5 Hz, 2 H), 4.49 (s, 2 H), 4.83 (dt, J = 47.4, 4.5 Hz, 2 H), 6.78 (d, J = 8.1 Hz, 1 H), 7.07 (s, 1H), 7.13 (dd, J = 8.1, 1.8 Hz, 1 H), 7.32 (s, 1 H), 7.43 (d, J = 5.7 Hz, 1 H), 7.49 (d, J = 1.8 Hz, 1 H), 8.37 (d, J = 5.7 Hz, 1 H). Anal. Calcd for $C_{20}H_{19}BrFNO_3 \cdot H_2C_2O_4$: C, 51.78; H, 4.15; N, 2.74. Found: C, 51.92; H, 4.21; N, 2.80.

*4.1.7.10. 1-(3-Fluorobenzyl)-7-(2-fluoroethoxy)-6-methoxyisoquinoline oxalate (**6j**).* Starting with **5j**, procedure G was followed to prepare compound **6j** (0.12 g, 35%) as a white solid. Mp (oxalate salt): 182.4–183.4 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.92 (s, 3 H), 4.18 (dt, J = 27.3, 4.2 Hz, 2 H), 4.49 (s, 2 H), 4.73 (dt, J = 47.4, 4.2 Hz, 2 H), 6.76–6.87 (m, 2 H), 6.95–7.00 (m, 2 H), 7.10–7.21 (m, 2 H), 7.37 (d, J = 5.7 Hz, 1 H), 8.36 (d, J = 5.7 Hz, 1 H). Anal. Calcd for $C_{19}H_{17}F_2NO_2 \cdot H_2C_2O_4$: C, 60.14; H, 4.57; N, 3.34. Found: C, 59.98; H, 4.65; N, 3.42.

*4.1.7.11. 7-(2-Fluoroethoxy)-1-(3-(2-fluoroethoxy)-4-methoxybenzyl)-6-methoxyisoquinoline oxalate (**6k**).* Starting with **5k**, procedure G was followed to prepare compound **6k** (0.14 g, 58%) as a white solid. Mp (oxalate salt): 171.2–172.0 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.74 (s, 3 H), 3.99 (s, 3 H), 4.16–4.35 (m, 4 H), 4.49 (s, 2 H), 4.70–4.80 (m, 4 H), 6.55–7.13 (m, 4 H), 7.40–7.43 (m, 2 H), 8.36 (d, J = 5.7 Hz, 1 H). Anal. Calcd for $C_{22}H_{23}F_2NO_4 \cdot H_2C_2O_4$: C, 58.42; H, 5.11; N, 2.84. Found: C, 58.58; H, 5.22; N, 2.94.

*4.1.7.12. 1-(3,5-Dimethoxybenzyl)-7-(2-fluoroethoxy)-6-methoxyisoquinoline oxalate (**6l**).* Starting with **5l**, procedure G was followed to prepare compound **6l** (75 mg, 22%) as a white solid. Mp (oxalate salt): 176.2–176.7 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.70 (s, 6 H), 3.97 (s, 3 H), 4.26 (dt, J = 27.3, 4.5 Hz, 2 H), 4.50 (s, 2 H), 4.78(dt, J = 47.4, 4.5 Hz, 2 H), 6.28 (*t*, J = 2.4 Hz, 1 H), 6.41 (m, 2 H), 7.04 (s, 1 H), 7.36 (s, 1 H), 7.41 (d, J = 5.7 Hz, 1 H), 8.36 (d, J = 5.7 Hz, 1 H). Anal. Calcd for $C_{21}H_{22}FNO_4 \cdot H_2C_2O_4$: C, 59.87; H, 5.24; N, 3.04. Found: C, 59.91; H, 5.22; N, 3.07.

*4.1.7.13. 1-(4-Fluoro-3-methoxybenzyl)-7-(2-fluoroethoxy)-6-methoxyisoquinoline oxalate (**6m**).* Starting with **5m**, procedure G was followed to prepare compound **6m** (65 mg, 36%) as a white solid. Mp (oxalate salt): 154.8–155.6 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.76 (s, 3 H), 3.99 (s, 3 H), 4.26 (dt, J = 27.3, 4.5 Hz, 2 H), 4.48 (s, 2 H), 4.80 (dt, J = 47.4, 4.5 Hz, 2 H), 6.70 (d, J = 7.8 Hz, 1 H), 7.00–7.10 (m, 3 H), 7.39 (s, 1 H), 7.41 (d, J = 5.7 H z, 1 H), 8.37 (d, J = 5.7 Hz, 1 H). Anal. Calcd for $C_{20}H_{19}F_2NO_3 \cdot H_2C_2O_4$: C, 58.80; H, 4.71; N, 3.12. Found: C, 58.82; H, 4.81; N, 3.21.

*4.1.7.14. 1-(3-(2-Fluoroethoxy)-4-methoxybenzyl)-6,7-dimethoxyisoquinoline (**6n**).* Starting with **5n**, procedure G was followed to prepare compound **6n** (125 mg, 50%) as a pale solid. Mp (oxalate salt): 149.7–150.6 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.81 (s, 3 H), 3.90 (s, 3 H), 4.01 (s, 3 H), 4.16 (dt, J = 27.9, 4.5 Hz, 2 H), 4.52 (s, 2 H), 4.70 (dt, J = 47.1, 4.5 Hz, 2 H), 6.78–6.89 (m, 3 H), 7.05 (s, 1 H), 7.32 (s, 1 H), 7.43 (d, J = 5.7, 1 H), 8.36 (d, J = 5.7 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.2, 56.3, 56.6, 56.9, 69.3 (d, J = 21.6 Hz), 80.9 (d, J = 169.6 Hz), 105.0, 106.0, 112.6, 115.5, 121.6, 122.1, 122.9, 128.5, 131.5, 136.9, 152.7, 154.7, 157.0, 160.7, 163.3. Anal. Calcd for $C_{21}H_{22}FNO_4 \cdot H_2C_2O_4$: C, 59.87; H, 5.24; N, 3.04. Found: C, 59.78; H, 5.26; N, 3.04.

*4.1.7.15. 1-(4-(Benzyloxy)-3-methoxybenzyl)-7-(2-fluoroethoxy)-6-methoxyisoquinoline (**6o**).* Starting with **5o**, procedure G was followed to prepare compound **6o** (0.16 g, 40%) as a white solid. ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.77 (s, 3 H), 3.99 (s, 3 H), 4.25

(dt, J = 27.3, 4.5 Hz, 2 H), 4.50 (s, 2 H), 4.85 (dt, J = 47.4, 4.5 Hz, 2 H), 5.09 (s, 2 H), 6.70–6.80 (d, J = 7.8 Hz, 4 H), 7.06 (s, 1 H), 7.29–7.44 (m, 6 H), 8.37 (d, J = 5.7 Hz, 1 H).

*4.1.7.16. 1-(4-(Benzyloxy)-3-methoxybenzyl)-7-(2-methoxy)-6-methoxyisoquinoline (**6p**).* Starting with **5p,** procedure G was followed to prepare compound **6p** (0.23 g, 29%) as a white solid. ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.77 (s, 3 H), 3.86 (s, 3 H), 4.00 (s, 3 H), 4.44 (d, J = 5.7 Hz, 2 H), 4.52 (s, 2 H), 5.09 (s, 2 H), 6.75 (s, 1 H), 6.76 (s, 1 H), 6.83 (s, 1 H), 7.05 (s, 1 H), 7.30–7.44 (m, 8 H), 8.70 (d, J = 7.5 Hz, 1 H).

*4.1.8. Procedure H: synthesis of compounds **7a** and **7b***

*4.1.8.1. 4-((7-(2-Fluoroethoxy)-6-methoxyisoquinolin-1-yl)methyl)-2-methoxyphenol (**7a**).* A mixture of **6o** (0.45 g, 1.0 mmol), hydrochloric acid (4.0 M, 3 mL), and ethanol (5 mL) was refluxed for 2 h. After diluting the reaction mixture with ethyl acetate (20 mL), saturated $NaHCO_3$ solution was added and then extracted with ethyl acetate (30 mL × 3). The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified on a silica gel column with CH_2Cl_2/MeOH (20/1, v/v/) as mobile phase to give **7a** (180 mg, 50%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) is δ 3.75 (s, 3 H), 3.99 (s, 3 H), 4.26 (dt, J = 27.3, 4.5 Hz, 2 H), 4.50 (s, 1 H), 4.81 (dt, J = 47.4, 4.5 Hz, 2 H), 5.58 (br, 1 H), 6.7–6.82 (m, 3 H), 7.06 (s, 1 H), 7.39 (s, 1 H), 7.43 (d, J = 5.7 Hz, 1 H), 8.37 (d, J = 5.7 Hz, 1 H).

*4.1.8.2. 4-((6,7-Dimethoxyisoquinolin-1-yl)methyl)-2-methoxyphenol (**7b**).* Starting with **6p**, following the above procedure H to afford **7b** (0.12 g, 49%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3 H), 3.90 (s, 3 H), 4.00 (s, 3 H), 4.52 (s, 2 H), 5.65 (br, 1 H), 6.76 (s, 1 H), 6.82 (s, 2 H), 7.05 (s, 1 H), 7.35 (s, 1 H), 7.42 (d, J = 5.7 Hz, 1 H), 8.36 (d, J = 5.7 Hz, 1 H).

*4.1.9. Synthesis of compounds **8a** and **8b***

*4.1.9.1. 7-(2-Fluoroethoxy)-1-(4-(2-fluoroethoxy)-3-methoxybenzyl)-6-methoxyisoquinoline oxalate (**8a**).* Starting with **7a**, procedure A was followed to prepare **8a** (0.15 g, 42%) as a pale solid. The oxalate salt of **8a** was prepared from **8a** according to the procedure described for the oxalate salt of **6a**. Mp (oxalate salt): 167.2–168.0 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) is δ 3.76 (s, 3 H), 3.99 (s, 3 H), 4.20 (dt, J = 27.3, 4.5 Hz, 2 H), 4.26 (dt, J = 27.3, 4.2 Hz, 2 H), 4.52 (s, 2H), 4.73 (dt, J = 47.4, 4.2 Hz, 2 H), 4.80 (dt, J = 47.7, 4.5 Hz, 2 H), 6.75–6.83 (m, 3 H), 7.07 (s, 1H), 7.38 (s, 1 H), 7.43 (d, J = 5.4 Hz, 1 H), 8.38 (d, J = 5.4 Hz, 1 H). Anal. Calcd for $C_{22}H_{23}F_2NO_4 \cdot H_2C_2O_4$: C, 58.42; H, 5.11; N, 2.84. Found: C, 58.45; H, 5.14; N, 2.75.

*4.1.9.2. 1-(4-(2-Fluoroethoxy)-3-methoxybenzyl)-6,7-dimethoxyisoquinoline oxalate (**8b**).* Starting with **7b**, procedure A was followed to prepare **8b** (0.17 g, 55%) as a white sold. The oxalate salt of **8b** was prepared from **8b** according to the procedure described for the oxalate salt of **6a**. Mp (oxalate salt): 157.3–158.2 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3 H), 3.90 (s, 3 H), 4.01 (s, 3 H), 4.21 (dt, J = 27.6, 3.9 Hz, 2 H), 4.54 (s, 2 H), 4.74 (dt, J = 47.7, 3.9 Hz, 2 H), 6.80–6.86 (m, 3 H), 7.05 (s, 1 H), 7.33 (s, 1 H), 7.43 (d, J = 5.4 Hz, 1 H), 8.37 (d, J = 5.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.4, 56.4, 56.6, 56.9, 69.0 (d, J = 21.6 Hz), 82.2 (d, J = 169.6 Hz), 105.0, 106.0, 113.2, 115.3, 120.9, 122.6, 122.9, 130.0, 131.6, 136.9, 147.6, 150.8, 154.6, 157.0, 163.3. Anal. Calcd for $C_{21}H_{22}FNO_4 \cdot H_2C_2O_4$: C, 59.87; H, 5.24; N, 3.04. Found: C, 59.70; H, 5.21; N, 2.96.

*4.1.10. Procedure I: synthesis of compound **8c***

*4.1.10.1. 1-(4-(2-(2-Fluoroethoxy)ethoxy)-3-methoxybenzyl)-6,7-dimethoxyisoquinoline oxalate (**8c**).* A mixture of **7b** (0.2 g, 0.62 mmol), 1-chloro-2-(2-fluoroethoxy)ethane (0.2 g, 1.59 mmol), and K_2CO_3 (0.25 g, 1.81 mmol) in DMF (10 mL) was stirred at room temperature overnight. The mixture was poured into water (50 mL) and extracted with ethyl acetate (10 mL × 3). The organic layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel column chromatography with CH_2Cl_2/MeOH (20/1, v/v/) as mobile phase to give **8c** (0.14 g, 54%) as a white solid. The oxalate salt of **8c** was prepared from **8c** according to the procedure described for the oxalate salt of **6a**. Mp (oxalate salt): 152.2–153.0 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.74 (s, 3 H), 3.83–3.90 (m, 7 H), 4.00 (s, 3 H), 4.14 (*t*, J = 5.4 Hz, 2 H), 4.53 (s, 2 H), 4.55 (dt, J = 47.7, 4.2 Hz, 2 H), 6.80–6.84 (m, 3 H), 7.05 (s, 1 H), 7.33 (s, 1 H), 7.43 (d, J = 5.7 Hz, 1 H), 8.37 (d, J = 5.7 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.5, 56.4, 56.6, 56.9, 69.1, 70.0, 70.5 (d, J = 21.8 Hz), 83.3 (d, J = 168.4 Hz), 105.1, 106.0, 113.0, 114.7, 120.9, 121.6, 123.0, 139.4, 131.6, 136.9, 148.0, 152.6, 154.7, 157.0, 163.3. Anal. Calcd for $C_{23}H_{26}FNO_5 \cdot H_2C_2O_4$: C, 59.40; H, 5.58; N, 2.77. Found: C, 59.26; H, 5.60; N, 2.78.

*4.1.11. Procedure J: synthesis of compound **11***

*4.1.11.1. 6,7-Dimethoxy-4-(4-methoxybenzyl)quinazoline oxalate (**11**).* To a solution of 4-chloro-6,7-dimethoxyquinazoline, **9** (0.25 g, 1.1 mmol) and manganese (II) chloride (12.6 mg, 0.1 mmol) in THF (20 mL) was added 4-methoxybenzyl magnesium chloride, **10** (3.3 mmol). After the reaction mixture was stirred at room temperature for 6 h, water (30 mL) was added, and the mixture was extracted with ethyl acetate (20 mL × 3). The organic layer was dried over anhydrous sodium sulfate. After concentrating, the residue was purified by silica gel column with CH_2Cl_2/MeOH (20/1, v/v/) as mobile phase to give **11** (0.21 g, 58%) as a white solid. The oxalate salt of **11** was prepared from **11** according to the procedure described for the oxalate salt of **6a**. Mp (oxalate salt): 127.6–128.4 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 3.76 (s, 3 H), 3.93 (s, 3 H), 4.03 (s, 3 H), 4.48 (s, 2 H), 6.81–6.85 (m, 2 H), 7.19–7.30 (m, 4 H), 9.09 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.9, 55.3, 56.1, 56.4, 102.6, 107.3, 114.2, 119.5, 129.8, 130.1, 148.5, 150.2, 153.7, 155.6, 158.5, 166.3. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.53; H, 5.81; N, 8.99.

4.2. In vitro assessment of affinities

To determine the potency of the new synthesized analogues, first, compounds were screened *in vitro* for their affinities toward PDE10A to determine IC_{50} values. Compounds having a high affinity for PDE10A (IC_{50} values < 60 nM), were further assessed for their selectivity for PDE10A versus other PDE isoforms, PDE3A and PDE3B. All compounds were independently assayed at least two times.

4.2.1. PDE10A enzyme assay protocol

The screening method followed published procedures [10–12,19,29]. PDE activity was measured using the Phosphodiesterase [^{3}H]cAMP Scintillation Proximity Assay (SPA) (Cat. #TRKQ7090, Perkin Elmer, Waltham, MA) with minor modifications to the manufacturer's protocol. Briefly, the effect of PDE inhibitors was determined by assaying a fixed amount of enzyme in the presence of varying compound concentrations and a low [^{3}H] cAMP substrate concentration; the substrate concentration used in the assay is 1/3 of the K_m concentration, allowing for comparisons of IC_{50} values across a panel of different PDE enzymes. Reactions are initiated with enzyme, incubated to give ~30% substrate turnover, and terminated with yttrium silicate SPA beads. Plates are sealed, allowed to settle, and counted on a Trilux Micro-Beta Counter (PerkinElmer, Waltham, MA). Radioactivity units can be converted to percent activity of an uninhibited control (100%), plotted against inhibitor concentration and inhibitor IC_{50} values were calculated.

4.2.2. Measure the in vitro affinities for PDE 3A and PDE 3B to determine selectivity of PDE10A vs PDE3A and PDE3B for analogues with high PDE10A affinity

Compounds with high affinity for PDE10A ($IC_{50} < 60$ nM) were further assessed for their PDE10A selectivity over other PDE3A and PDE3B. The screening method is the same as the protocol for PDE10A except the assays used other PDE isoforms and their concentrations are adjusted based on the K_i value for the different PDE isoforms.

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