SUPPORTING INFORMATION

Discovery and Optimization of a Series of Pyrimidine-based Phosphodiesterase 10A (PDE10A) Inhibitors Through Fragment Screening, Structure-Based Design, and Parallel Synthesis

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Contents:

General analytical experimental information

^{1}H NMR spectra were recorded using Varian VXR spectrometers. Chemical shifts are reported in δ (ppm) using tetramethylsilane (δ 0 ppm) as an internal standard. High resolution mass spectral data were obtained using either a Waters Synapt G1 Mass Spectrometer under positive electrospray (ES) ionization mode (**5**) or a Bruker Daltonics FTICR/MS in electrospray (ES) ionization mode (**9s**, **15h**). HPLC spectra were obtained using Agilent 1100 HPLC systems.

Statement of purity

All key compounds (**5**, **9s**, **15h**) possess a purity of at least 95%. All compounds produced from parallel (library) synthesis possess a purity of at least 90%.

HPLC purity determination for key compounds 5, 9s, and 15h

Method A: Analytical reversed phase high performance liquid chromatography – mass spectrometry (LC-MS) was performed on an Agilent 1100 HPLC system equipped with an autosampler, a high pressure binary pump, a single quadrupole (SQD) mass spectrometer, and a photodiode array detector. Purity of the final compounds was quantified using UV detection (λ = 214 nm). A C18 chromatographic method was employed for purity determination, as described below.

Column: YMC J'sphere C18 (4 μM, 3.0 mm x 50 mm). Mobile phase A: 0.05% TFA in water. Mobile phase B: acetonitrile with 0.05% TFA. Flow rate: 1.1 mL/min. Elution profile: gradient elution from 5% to 100% B over 3.6 minutes followed by isocratic elution at 100% B for 0.45 minutes.

Method B: Analytical reversed phase high performance liquid chromatography – mass spectrometry (LC-MS) was performed on a Waters Acquity UPLC system equipped with an autosampler, binary solvent manager (BSM), single quadrupole (SQD) mass spectrometer, and a tunable UV/Vis detector (TUv). Purity of the final compounds was quantified using UV detection (λ = 254 nm). A C18 chromatographic method was employed for purity determination, as described below.

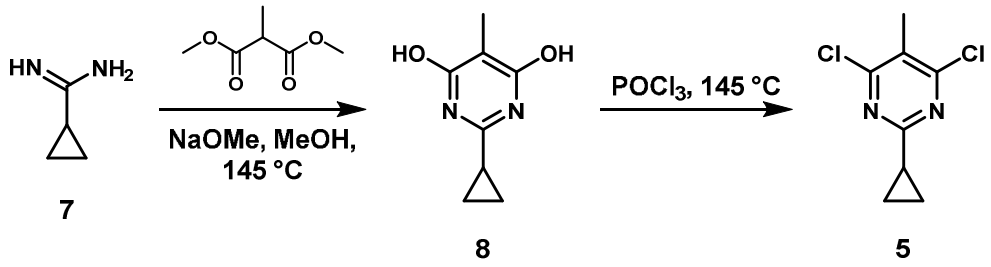
Column: Waters Acquity UPLC BEH C18 (1.7 μM, 1.0 mm x 50 mm). Mobile phase A: 0.05% TFA in water. Mobile phase B: acetonitrile with 0.05% TFA. Flow rate: 0.3 mL/min. Elution profile: gradient elution from 5% to 95% B over 1.6 minutes followed by isocratic elution at 95% B for 0.4 minutes.

Compound	HPLC method	Retention time (min)	Area under peak (%)
5	A	3.58	99.0

9s	A	2.19	95.0
15h	B	0.91	96.1

Synthesis and characterization of key compounds (5, 9s, 15h)

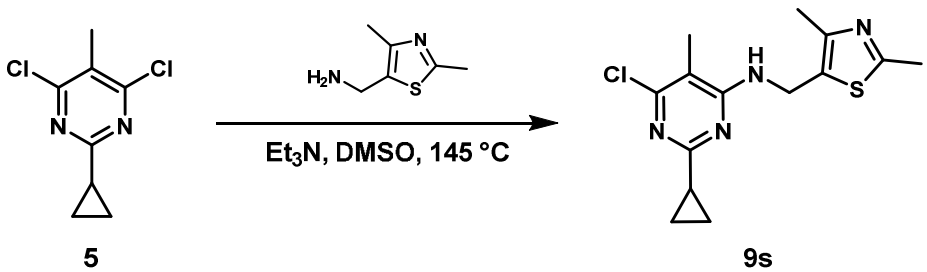
4,6-dichloro-2-cyclopropyl-5-methylpyrimidine (5)



2-cyclopropyl-5-methylpyrimidine-4,6-diol (8). Cyclopropanecarboxamidine hydrochloride (2.00 g, 16.6 mmol) and dimethyl 2-methylpropanedioate (3.64 g, 24.9 mmol) were placed in a 20 mL vial and diluted with 10 mL of methanol. A solution of sodium methoxide (8.96 g, 49.8 mmol) in methanol (10 mL) was slowly added. The mixture was irradiated in a microwave reactor at 145 °C for 30 min. After cooling to ambient temperature, the resulting slurry was concentrated *in vacuo*, then dissolved in water. The aqueous solution was made acidic with concentrated HCl, causing a precipitate to form. Filtration yielded 2.0 g (76%) of **8** as a white solid. MS (ES): m/z 167.0 $[M+H]^+$.

4,6-dichloro-2-cyclopropyl-5-methylpyrimidine (5). Dihydroxypyrimidine **8** (1.80 g, 10.8 mmol) was combined with phosphoryl chloride (10 mL, 108 mmol) in a 20 mL vial. The mixture was irradiated in a microwave reactor at 145 °C for 30 min. After cooling to ambient temperature, the mixture was poured onto ice, causing a precipitate to form. Filtration yielded 1.78 g (81%) of **5** as an off-white solid. ^{1}H NMR (DMSO-d_6, 499 MHz): δ_H 0.99-0.96 (2H, m), 1.13-1.09 (2H, m), 2.14 (1H, tt, J = 8.1, 4.6 Hz), 2.34 (3H, s). HRMS (ES): m/z 203.0139 $[M+H]^+$.

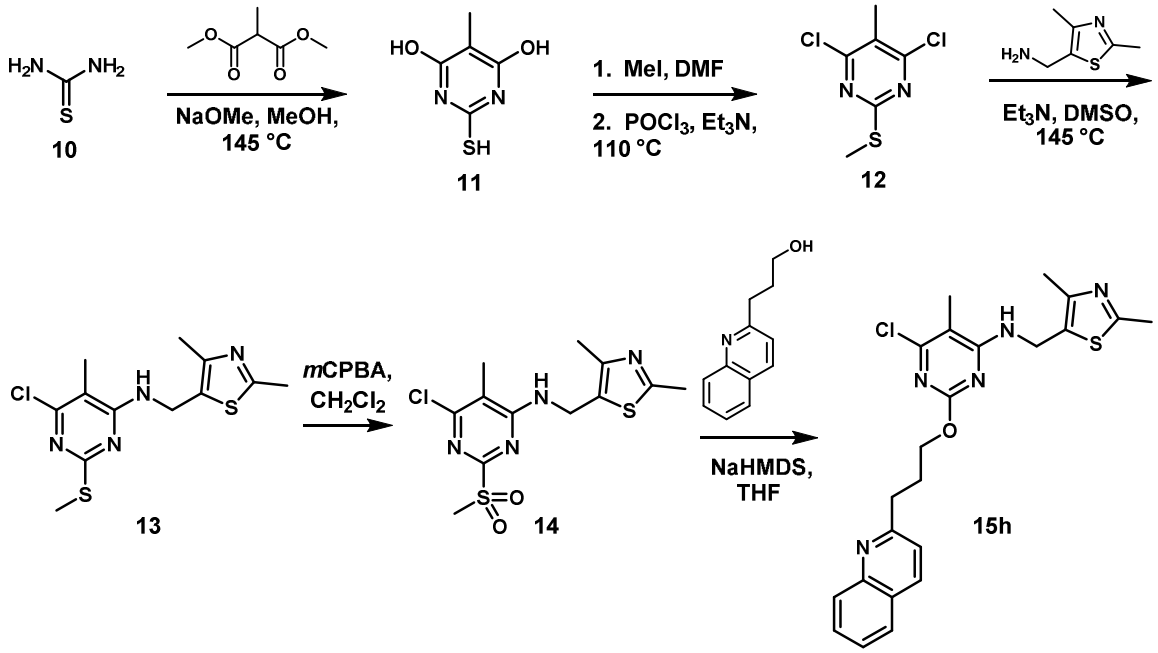
6-chloro-2-cyclopropyl-*N*-((2,4-dimethylthiazol-5-yl)methyl)-5-methylpyrimidin-4-amine (9s)



6-chloro-2-cyclopropyl-*N*-((2,4-dimethylthiazol-5-yl)methyl)-5-methylpyrimidin-4-amine (9s). 4,6-dichloro-2-cyclopropyl-5-methyl-pyrimidine (**5**) (500 mg, 2.46 mmol) was combined with (2,4-dimethylthiazol-5-yl)methanamine (350 mg, 2.46 mmol) and triethylamine (249 mg, 2.46 mmol) in a 20 mL vial. DMSO (5 mL) was added, and the mixture was irradiated in a microwave reactor at 100 °C for 20 min. After cooling to

ambient temperature, the mixture was added to water and a solid precipitated from the mixture. The crude material obtained by filtration was then purified on silica gel, giving 594 mg (78%) of **9s** as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 4.85 (1H, s), 4.72 (2H, s), 2.62 (3H, s), 2.40 (3H, s), 2.07 (3H, s), 1.29-1.22 (1H, m), 1.13-1.06 (2H, m), 1.00-0.91 (2H, m). HRMS (ES): m/z 309.0936 $[M+H]^+$.

6-chloro-*N*-((2,4-dimethylthiazol-5-yl)methyl)-5-methyl-2-(3-(quinolin-2-yl)propoxy)pyrimidin-4-amine (15h)



2-mercapto-5-methylpyrimidine-4,6-diol (11). Thiourea (300 mg, 3.94 mmol) and dimethyl 2-methylpropanedioate (576 mg, 3.94 mmol) were placed in a 5 mL vial and diluted with 3 mL of methanol. A solution of sodium methoxide (710 mg, 3.94 mmol) in methanol (0.75 mL) was slowly added. The mixture was irradiated in a microwave reactor at 150 °C for 30 min. After cooling to ambient temperature, the resulting slurry was concentrated *in vacuo*. 340 mg (54%) of **11** were isolated as a white solid by filtration. MS (ES): m/z 159.0 $[M+H]^+$.

4,6-dichloro-5-methyl-2-(methylthio)pyrimidine (12). 2-mercapto-5-methylpyrimidine-4,6-diol **11** (340 mg, 2.15 mmol) and DMF (10 mL) were placed in a 50 mL flask. Iodomethane (366 mg, 2.58 mmol) was added, and the reaction was stirred overnight. The mixture was then diluted with water (50 mL). 247 mg (67%) of the intermediate methylthioether were isolated as a white solid by filtration. MS (ES): m/z 173.2 $[M+H]^+$.

The thioether (247 mg, 1.43 mmol) was combined with phosphoryl chloride (2.6 mL, 28.7 mmol) and diisopropylethylamine (185 mg, 1.43 mmol) in a 20 mL vial. The mixture was irradiated in a microwave reactor at 145 °C for 30 min. After cooling to

ambient temperature, excess phosphoryl chloride was removed in vacuo. The resulting mixture was then poured onto ice and extracted with dichloromethane (3 x 10 mL). The crude material was purified by elution through a silica plug, yielding 280 mg (93%) of **12** as a white, crystalline solid. MS (ES): m/z 210.1 $[M+H]^+$.

6-chloro-N-((2,4-dimethylthiazol-5-yl)methyl)-5-methyl-2-(methylthio)pyrimidin-4-amine (13). 4,6-dichloro-5-methyl-2-methylsulfanyl-pyrimidine **12** (973 mg, 4.65 mmol) was combined with (2,4-dimethylthiazol-5-yl)methanamine (728 mg, 5.12 mmol) and triethylamine (1.2 g, 9.31 mmol) in a 20 mL vial. DMSO (5 mL) was added, and the mixture was irradiated in a microwave reactor at 100 °C for 20 min. After cooling to ambient temperature, the mixture was added to water, causing a precipitate to form. Filtration yielded 1.01 g (70%) of product **13** as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ_H 7.89 (1H, s), 4.57 (2H, d, J = 5.79 Hz), 2.48 (3H, s), 2.41 (3H, s), 2.31 (3H, s), 2.00 (3H, s). HRMS (ES): m/z 315.0500 $[M+H]^+$.

6-chloro-N-((2,4-dimethylthiazol-5-yl)methyl)-5-methyl-2-(methylsulfonyl)pyrimidin-4-amine (14). 6-chloro-*N*-[(2,4-dimethylthiazol-5-yl)methyl]-5-methyl-2-methylsulfanyl-pyrimidin-4-amine **13** (1.36 g, 4.32 mmol) was placed in a 250 mL flask and diluted with dichloromethane (100 mL). To the resultant slurry was added mCPBA (1.49 g, 8.64 mmol), and the solution was stirred for 1 hr. 1 N aqueous NaOH (100 mL) was then added, and the organic layer was separated and concentrated *in vacuo* to give 1.3 g (87%) of **14** as a white foam. MS (ES): m/z 347.8 $[M+H]^+$.

6-chloro-*N*-((2,4-dimethylthiazol-5-yl)methyl)-5-methyl-2-(3-(quinolin-2-yl)propoxy)pyrimidin-4-amine (15h). To a solution of **14** (51 mg, 0.15 mmol) and 3-(quinolin-2-yl)propan-1-ol (25 mg, 0.13 mmol) in 3 mL of THF was added LiHMDS (200 μL of a 1 M solution in THF, 0.20 mmol). After stirring for 2 h, the reaction was quenched by the addition of a saturated solution of NH_4Cl. The mixture was partitioned between a saturated solution of $NaHCO_3$ and EtOAc, the layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes gradient) to provide 17 mg (28%) of **15h** as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.1 – 8.0 (2H, m), 7.75 (1H, m), 7.65 (1H, m), 7.5 (1H, m), 7.35 (1H, m), 4.9 (1H, m), 4.7 (2H, d), 4.4 (2H, t), 3.15 (2H, t), 2.6 (3H, s), 2.35 (5H, m), 2.0 (3H, s). HRMS (ES): m/z 454.1455 $[M+H]^+$.

Crystallographic methods and acknowledgments

Human PDE10A protein was concentrated to 10 mg/mL in buffer containing 20 mM Tris-HCl pH 7.5, 50 mM NaCl, 1 mM 2-mercaptoethanol, and 1 mM EDTA. Apo crystals of human PDE10A were formed by the hanging drop vapor diffusion method at room temperature with a reservoir solution containing 100 mM HEPES pH 7.0, 20% PEG3350, 200 mM $MgCl_2$, and 10 mM 2-mercaptoethanol. Inhibitors were introduced to crystals by soaking in a harvest buffer containing 100 mM HEPES pH 7.0, 30% PEG3350, 200 mM $MgCl_2$, and 10 mM 2-mercaptoethanol.

Due to crystal packing constraints, it was found that some inhibitors could not soak directly into the crystals. A method was developed, referred to as the "double soaking method", where an intermediate-sized compound with a moderate affinity was introduced for an hour. This compound could then be displaced by a larger compound when soaked for a longer period of time. The soaking time for the compound of interest varied and was empirically determined for each compound. After soaking, a solution containing 80% of the harvest buffer and 20% PEG400 was used to cryo-protect the crystal for data collection.

Use of the IMCA-CAT beamline 17-ID (or 17-BM) at the Advanced Photon Source was supported by the companies of the Industrial Macromolecular Crystallography Association through a contract with Hauptman-Woodward Medical Research Institute. Data were collected at Southeast Regional Collaborative Access Team (SER-CAT) 22-ID (or 22-BM) beamline at the Advanced Photon Source, Argonne National Laboratory. Supporting institutions may be found at www.ser-cat.org/members.html.

Use of the Advanced Photon Source was supported by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences, under Contract No. DE-AC02-06CH11357. The Advanced Light Source is supported by the Director, Office of Science, Office of Basic Energy Sciences, of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231.

In vitro PDE assays

PDE10A2 was amplified from human fetal brain cDNA (Clontech) using the forward primer, 5'-GCC ACC ATG GAA GAT GGA CCT TCT AAT-3' containing a Kozak consensus sequence and the reverse primer, 5'-TCA ATC TTC AGA TGC AGC TGC-3'. PCR primers were designed using human PDE10A2 as template (Genbank ID: 4894716). The final amino acid sequence was identical to Genbank Protein Accession ID: BAA84467.1. AD293 cells were transiently transfected with human PDE10A2/pcDNA3.3-TOPO using Lipofectamine 2000 according to manufacturer specifications (Invitrogen). Cells were harvested 48 h post-transfection and lysed by sonication in a buffer containing 20 mM HEPES, 1 mM EDTA and protease inhibitor cocktail (Roche). Lysate was collected by centrifugation at 75,000 × g for 20 min and the resulting supernatant was used for evaluation of PDE10A2 activity.

Phosphodiesterase (PDE) activity was determined using an IMAP® FP kit (Molecular Devices, Sunnyvale, CA) as previously described.[1] Human PDE10A2 and rhesus monkey PDE2A3 enzymes were prepared from cytosolic fractions of transiently transfected AD293 cells as describe above. All other PDEs (PDE1A, PDE3A, PDE4A1A, PDE5A1, PDE6C, PDE7A, PDE8A1, PDE9A2, and PDE11A4) were GST Tagged human enzymes expressed in insect cells and were obtained from BPS Bioscience (San Diego, CA). PDE activity assays were performed in duplicate at room temperature. The apparent inhibition constants (K_i) for test compounds against all 11 PDEs were determined as described by Mosser et al.[2] using the following apparent K_M values for each enzyme and substrate combination: human PDE1A (cGMP, 70 nM), rhesus PDE2A3 (cAMP, 10,000 nM), human PDE3A (cAMP, 50 nM), human PDE4A1A (cAMP, 1500 nM), human PDE5A1 (cGMP, 400 nM), human PDE6C (cGMP, 700 nM), human PDE7A (cAMP, 150 nM), human PDE8A1 (cAMP, 50 nM), human PDE9A2 (cGMP, 100 nM), human PDE10A2 (cAMP, 50 nM), human PDE11A4 (cAMP, 1000 nM).

Measurement of MK-801-induced psychomotor activity for 15h

Male Wistar Hannover rats (n = 40) were used to examine the influence of **15h** on MK-801-induced locomotor activity. Animals were received and housed for 7 days with food and water available *ad libitum*. Following acclimation, animals were given vehicle (10% Tween 80/90% water) or **15h** (1, 3, or 5 mg/kg, ip; 1 mL/kg dosing volume) followed 120 min later by vehicle (saline) or MK-801 (0.23 mg/kg, sc). Animals were placed in locomotor activity monitors (43.2 cm × 43.2 cm, Med Associates, St. Albans, VT) 90 min following the first injection and left in the activity monitors 90 min after being given MK-801. Total distance traveled was used to assess the influence of administration of

[1] Huang, W., Zhang, Y., Sportsman, J. R. A fluorescence polarization assay for cyclic nucleotide phosphodiesterases. *J. Biomol. Screen*. **2002**, *7*, 215–222.

[2] Mosser, S. D.; Gaul, S. L.; Bednar, B.; Koblan, K. S.; Bednar R. A. Automation of *in vitro* dose-inhibition assays utilizing the Tecan Genesis and an integrated software package to support the drug discovery process. *JALA* **2003**, *8* (4), 54–63.

15h on activity during habituation and following MK-801 treatment. Locomotor activity was analyzed with one-way ANOVA (group as a between subjects factor) and group differences were further examined using post-hoc comparisons (Fisher's LSD).

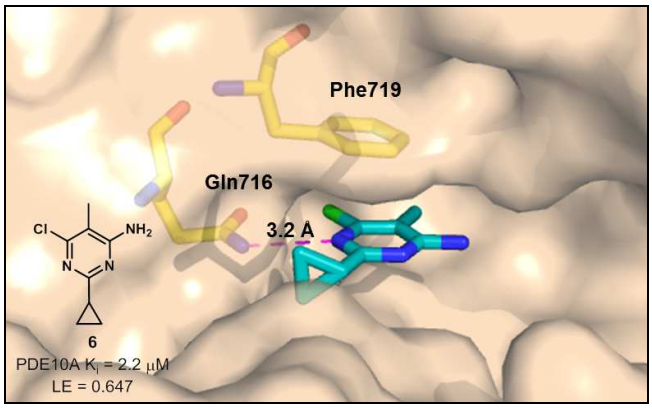


Figure S1. Co-crystal structure of optimized pyrimidine fragment **6** and PDE10A.

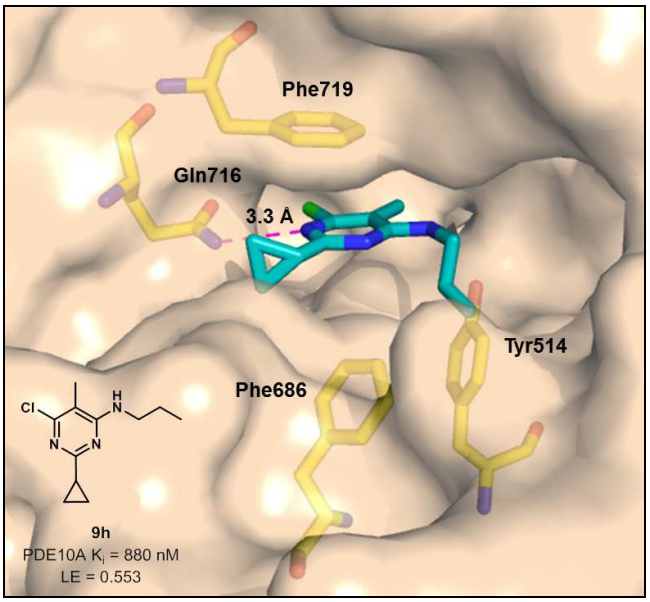


Figure S2. Co-crystal structure of pyrimidine **9h** and PDE10A.

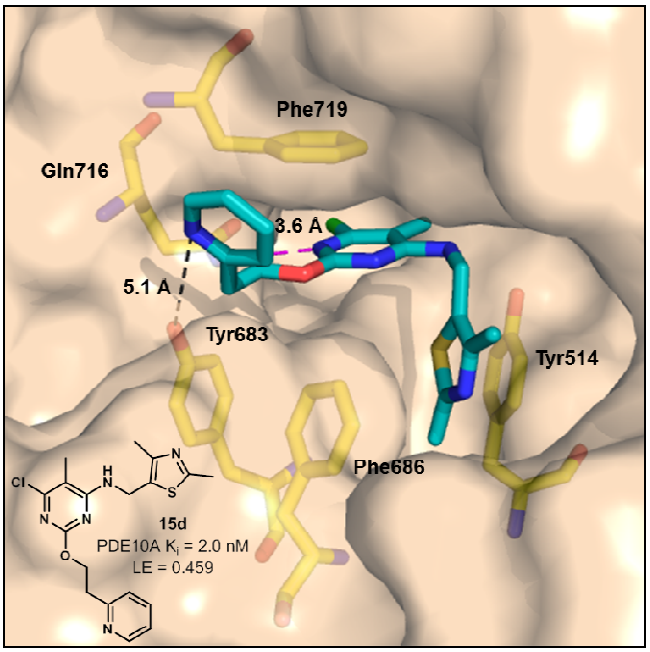


Figure S3. Co-crystal structure of pyrimidine **15d** and PDE10A.

Analog **15d** (PDE10A K_i of 2.0 nM) represented an incremental improvement in potency by comparison to **9s** (PDE10A K_i of 4.8 nM), but didn't provide benefits for PDE selectivity (see Table S3). This was adequately explained by the PDE10A-**15d** x-ray co-crystal structure, in which the terminal pyridine group was found to bind in a conformation neither exploiting the hydrophobic selectivity pocket nor engaging Tyr683. The distance between the *N* atom of the pyridyl group and the *O* atom of the Tyr683 sidechain is 5.1 Å.

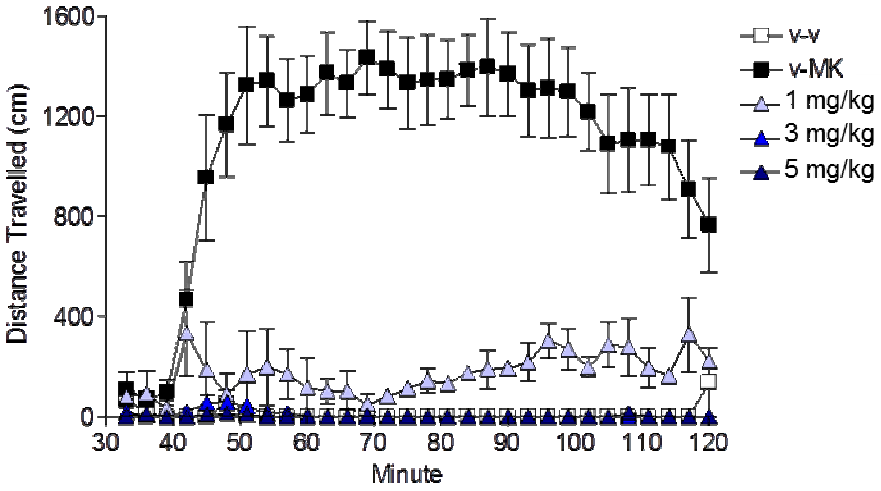
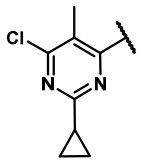


Figure S4. Time-course effect of administration of **15h** in the MK-801 psychomotor activity assay.

Table S1. Survey of low molecular weight amino substitutions at the pyrimidine 6-position.



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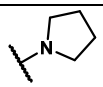
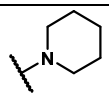
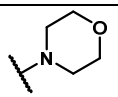
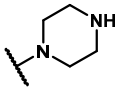
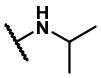
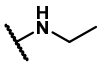
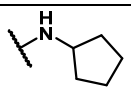
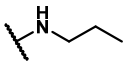
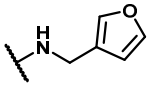
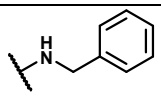
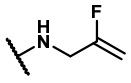
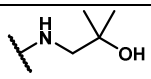
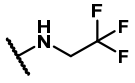
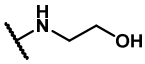
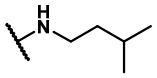
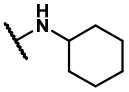
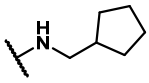
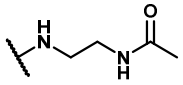
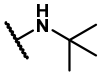
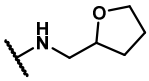
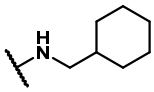
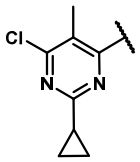
Entry	6-substituent	PDE10A K_i (nM)[a]	LE[b]
9a		5300±870	0.45
9b		2100±570	0.46
9c		4600±540	0.43
9d		13000±1500	0.39
9e		3600±570	0.50
9f		1200±26	0.58
9g		2800±190	0.45
9h		880±130	0.55
9i		680±210	0.47
9j		1400±130	0.42
9k		180±41	0.58
S-9ee		950±240	0.48
S-9ff		2000±140	0.46
S-9gg		3100±480	0.50

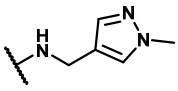
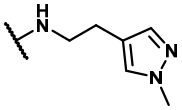
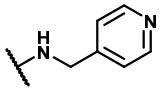
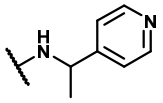
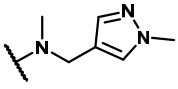
S-9hh		3200±930	0.44
S-9ii		3300±850	0.42
S-9jj		4600[c]	0.41
S-9kk		5200±420	0.40
S-9ll		8300±520	0.44
S-9mm (racemic)		22000±1300	0.36
S-9nn		26000[c]	0.33

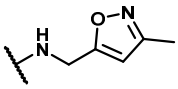
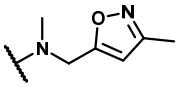
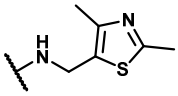
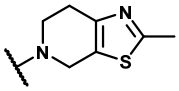
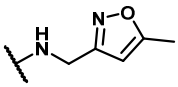
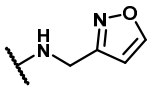
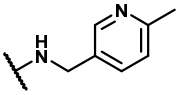
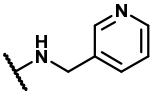
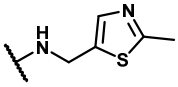
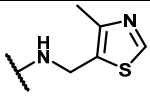
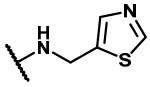
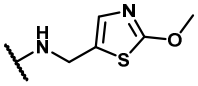
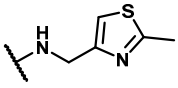
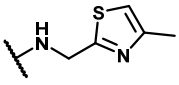
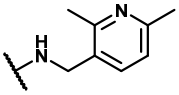
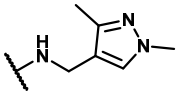
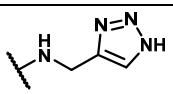
[a]Each K_i value reported is an average of at least two measurements with a 10-point dose response curve. [b]LE = ligand efficiency. [c]Only one K_i measurement was recorded, so no standard devation is reported.

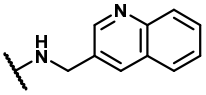
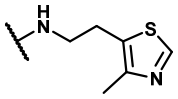
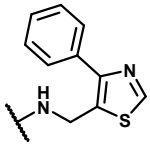
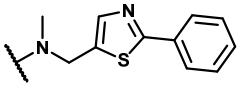
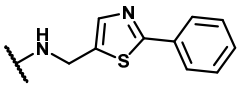
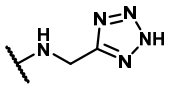
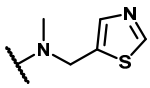
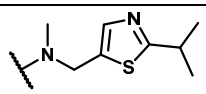
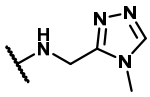
Table S2. Focused survey of amino substitutions at the pyrimidine 6-position.



9

Entry	6-substituent	PDE10A K_i (nM)[a]	LE[b]
9l		37±13	0.54
9m		1500±270	0.40
9n		200±110	0.48
9o (racemic)		890±52	0.42
9p		220±40	0.46

9q		38±14	0.53
9r		540±36	0.43
9s		4.8±1.7	0.57
9t		1300±25	0.38
9u		51±9.5	0.53
9v		810±170	0.46
9w		130±3	0.47
9x		1000±180	0.43
9y		26±0.04	0.55
9z		1600±110	0.42
9aa		1000±540	0.45
9bb		10±1.6	0.55
9cc		18±7.0	0.56
9dd		6800±490	0.37
S-9oo		16±4.1	0.51
S-9pp		65±34	0.49
S-9qq		170±30	0.52

S-9rr		330±90	0.39
S-9ss		400±90	0.44
S-9tt		460±78	0.36
S-9uu		460±41	0.35
S-9vv		930±190	0.34
S-9ww		1200±360	0.43
S-9xx		3000±420	0.40
S-9yy		4300±900	0.35
S-9zz		13000±120	0.35

[a]Each K_i value reported is an average of at least two measurements with a 10-point dose response curve. [b]LE = ligand efficiency.

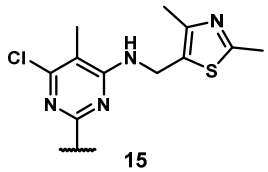
Table S3. PDE selectivity ratios[a] vs. PDE10A.

Entry	PDE1	PDE2	PDE3	PDE4	PDE5	PDE7	PDE8	PDE9	PDE11
5	6.7	11	5.8	11	10	8.6	5.8	6.3	11
9h	66	110	52	6.7	24	85	57	62	45
9s	2900	2500	3500	890	220	16000	10000	11000	87
15d	16000	240	5100	600	16	9100	13000	27000	660
15h	800000	20000	450000	49000	5900	3600000	2000000	6700000	640000

[a]selectivity ratio = PDEx K_i / PDE10A K_i

Measurements of PDE selectivity as a ratio of PDEx K_i/PDE10A K_i were influenced by the selected concentration range of the PDE selectivity assay, and any ratios reported for less potent compounds are accordingly more conservative.

Table S4. Survey of alkoxide substitutions at the pyrimidine 2-position (expanded version of Table 3).



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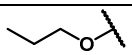
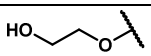
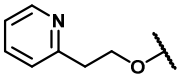
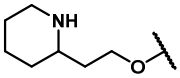
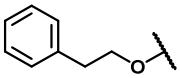
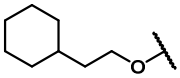
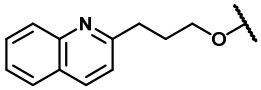
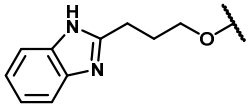
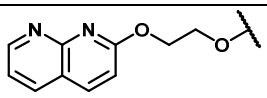
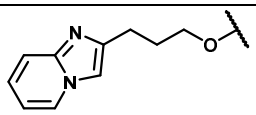
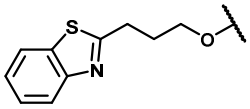
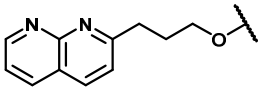
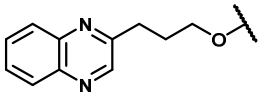
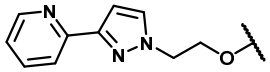
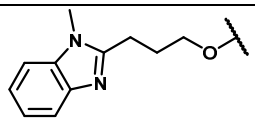
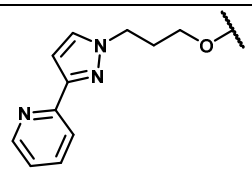
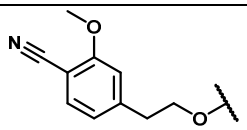
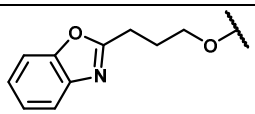
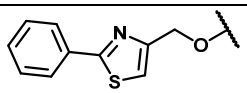
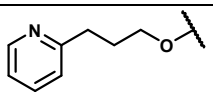
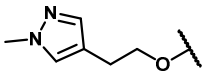
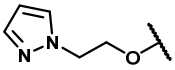
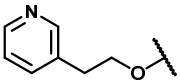
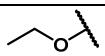
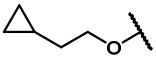
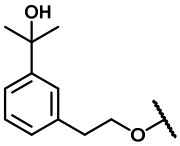
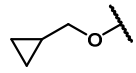
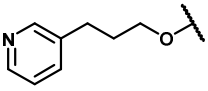
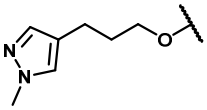
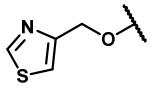
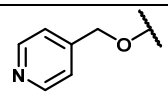
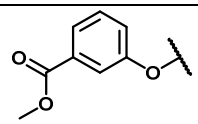
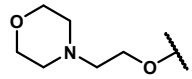
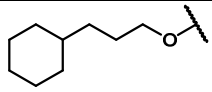
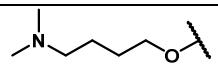
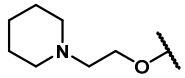
Entry	2-substituent	PDE10A K_i (nM)[a]	LE[b]
15a		5.1±1.3	0.541
15b		8.5±6.8	0.578
15c		12±2.8	0.516
15d		2.0±0.14	0.459
15e		590±160	0.328
15f		9.0±3.0	0.423
15g		400±110	0.336
15h		0.0082±0.0026	0.490
15i		0.020±0.0062	0.488
15j		0.040±0.012	0.459
15k		0.047±0.0029	0.472
15l		0.055±0.0028	0.469
15m		0.11±0.010	0.440
15n		0.37±0.014	0.417
S-15o		0.042±0.0028	0.459

S-15p		0.048±0.0044	0.456
S-15q		0.19±0.0094	0.416
S-15r		0.28±0.068	0.436
S-15s		0.35±0.053	0.432
S-15t		0.67±0.063	0.419
S-15u		1.0±0.028	0.456
S-15v		2.9±0.24	0.451
S-15w		2.9±.12	0.468
S-15x		5.4±1.3	0.435
S-15y		6.2±1.7	0.562
S-15z		6.3±0.65	0.489
S-15aa		6.9±0.49	0.373
S-15bb		7.8±0.81	0.505
S-15cc		21±12	0.387
S-15dd		23±2.0	0.387
S-15ee		27±3.7	0.432

S-15ff		41±19	0.402
S-15gg		90±9.5	0.345
S-15hh		170[c]	0.357
S-15ii		300±83	0.330
S-15jj		520±4.7	0.345
S-15kk		1500±170	0.307

[a]Each K_i value reported is an average of at least two measurements with a 10-point dose response curve. [b]LE = ligand efficiency. [c]Only one K_i measurement was recorded, so no standard devation is reported.