

Supporting Information

Discovery of selective phosphodiesterase 1 inhibitors with memory enhancing properties.

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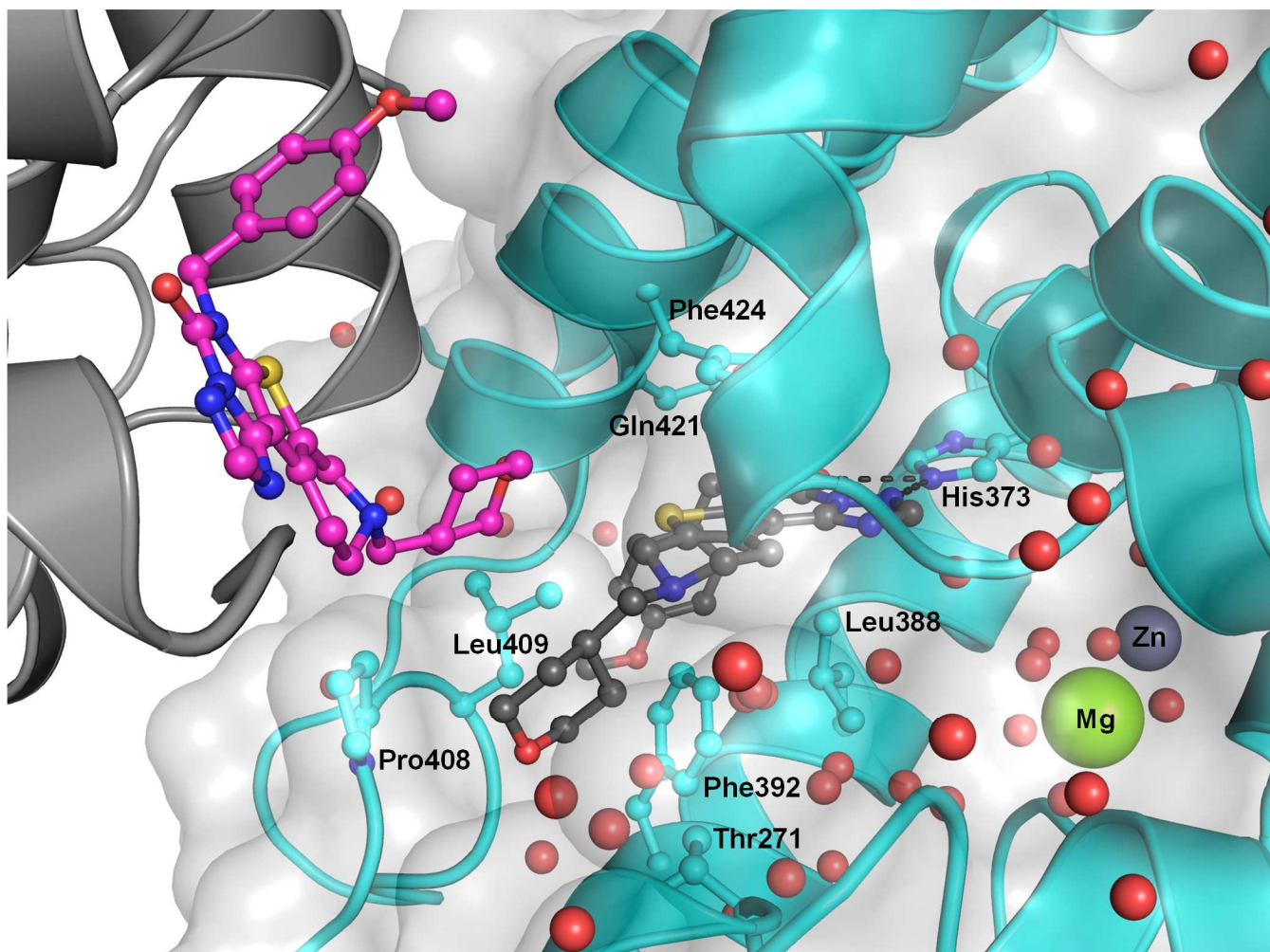


FIGURE S1. Crystal packing in the crystal structure of **16j** bound to the catalytic domain of PDE1B. A second **16j** molecule (magenta) is bound between two crystal symmetry related protein molecules (teal and gray cartoon). The position of the tetrahydropyranylmethyl group of **16j** bound in the active site could potentially be influenced by the presence of the second **16j** molecule. Key residues are labeled, including the hydrophobic clamp (Phe424 and Leu388).

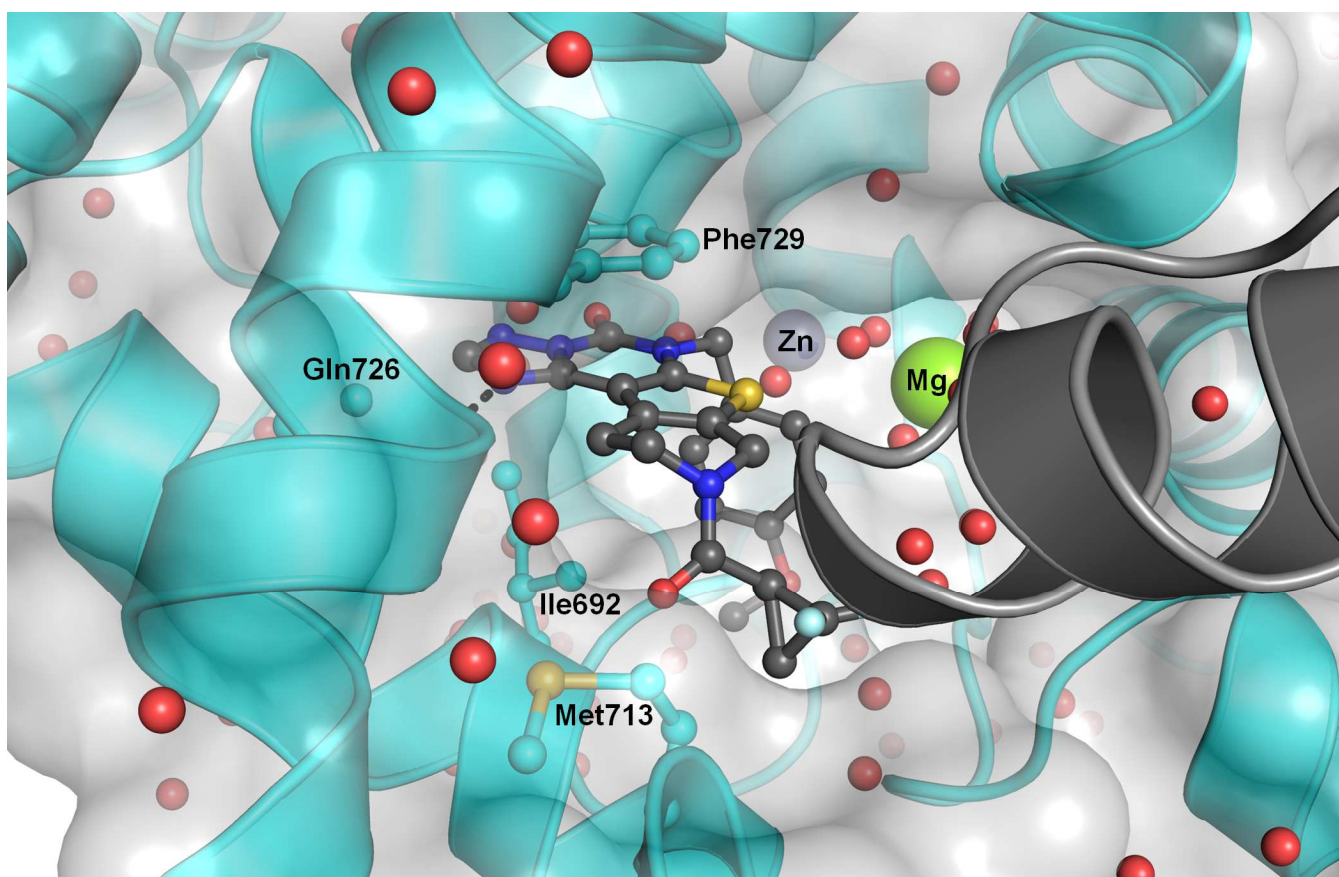


FIGURE S2. Crystal packing in the crystal structure of **16d** bound to the catalytic domain of PDE10A. The position of the carboxamide arm of **16d** in chain B is influenced by the presence of the crystal symmetry related protein molecule (gray cartoon). Key residues are labeled, including the hydrophobic clamp (Phe729 and Ile692).

Table S1. X-ray data processing and structure refinement statistics

	PDE1B-3 (5UP0)	PDE10A-16d (5UWF)	PDE1B-16j (5UOY)
Processing			
Resolution range (Å)*	61.79 - 2.04 (2.09 - 2.04)	37.40 - 1.87 (1.91 - 1.87)	61.88 - 1.82 (1.87 - 1.82)
Space group	<i>P</i> 4 ₃ 2 ₁ 2	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 4 ₃ 2 ₁ 2
Unit cell			
a, b, c (Å)	87.38, 87.38, 135.09	49.72, 81.24, 158.61	87.51, 87.51, 134.71
α, β, γ (°)	90, 90, 90	90, 90, 90	90, 90, 90
Unique reflections*	34119 (2482)	54103 (3463)	47503 (3451)
Multiplicity*	10.3 (10.5)	7.4 (7.4)	10.4 (9.7)
Completeness (%)*	100.0 (100.0)	100.0 (100.0)	99.8 (99.9)
I/σ (I)*	14.2 (1.6)	11.9 (2.4)	14.1 (1.3)
CC1/2*	0.999 (0.653)	0.998 (0.840)	0.999 (0.489)
R-pim*	0.033 (0.723)	0.055 (0.430)	0.032 (0.896)
Refinement			
Resolution range (Å)*	61.79 - 2.04 (2.11 - 2.04)	37.40 - 1.87 (1.94 - 1.87)	61.88 - 1.82 (1.89 - 1.82)
Number of reflections*	34053 (3333)	54029 (5325)	47452 (4642)
R-work / R-free	0.197 / 0.226	0.188 / 0.248	0.189 / 0.221
Number of atoms			
protein	2597	5233	2597
ligands	27	70	68
water	105	438	140
R.m.s. deviation			
Bond length (Å)	0.008	0.006	0.008
Bond angles (°)	1.061	0.840	1.014
Ramachandran plot (%)			
Preferred	97.48	99.00	97.48
Allowed	2.52	1.10	2.21
Outliers	0	0	0.32
Average B-factor			
Protein	49.0	32.9	40.7
Ligands	57.4	29.3	44.0
Solvent	45.5	33.6	42.0
* Values in parentheses correspond to the highest resolution shell.			

Table S2. Off-target selectivity profile for **16k**

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.	IC ₅₀ *	K _i	n _H	R
Compound DNS-0056, PT #: 1157131										
107710	ATPase, Na ⁺ /K ⁺ , Heart, Pig	308012	pig	2	10 µM	6				
112100	Camitine Palmitoyltransferase-1 (CPT-1)	308204	rat	2	10 µM	11				
104010	Cholinesterase, Acetyl, ACES	307828	hum	2	10 µM	29				
143000	Nitric Oxide Synthase, Endothelial (eNOS)	308014	bov	2	10 µM	8				
142000	Nitric Oxide Synthase, Neuronal (nNOS)	308013	rat	2	10 µM	-3				
107300	Peptidase, Angiotensin Converting Enzyme	308011	rabbit	2	10 µM	9				
165050	Peptidase, Tissue Plasminogen Activator (tPA)	308205	hum	2	10 µM	4				
176760	Protein Serine/Threonine Kinase, MAPK13 (p38δ)	308243	hum	2	10 µM	40				
200510	Adenosine A ₁	307846	hum	2	10 µM	19				
200610	Adenosine A _{2A}	307795	hum	2	10 µM	-2				
200720	Adenosine A ₃	307796	hum	2	10 µM	3				
203100	Adrenergic α _{1A}	307850	rat	2	10 µM	19				
203200	Adrenergic α _{1B}	307905	rat	2	10 µM	9				
203400	Adrenergic α _{1D}	307855	hum	2	10 µM	-2				
203620	Adrenergic α _{2A}	307906	hum	2	10 µM	7				
204010	Adrenergic β ₁	307856	hum	2	10 µM	0				
204110	Adrenergic β ₂	307900	hum	2	10 µM	7				
285010	Androgen (Testosterone) AR	307886	rat	2	10 µM	8				
212510	Bradykinin B ₁	307922	hum	2	10 µM	6				
212620	Bradykinin B ₂	307923	hum	2	10 µM	4				
214510	Calcium Channel L-Type, Benzothiazepine	307908	rat	2	10 µM	12				
214600	Calcium Channel L-Type, Dihydropyridine	307802	rat	2	10 µM	24				
216000	Calcium Channel N-Type	307892	rat	2	10 µM	2				
217030	Cannabinoid CB ₁	307803	hum	2	10 µM	10				
219500	Dopamine D ₁	307909	hum	2	10 µM	2				
219700	Dopamine D _{2S}	307867	hum	2	10 µM	6				
219800	Dopamine D ₃	308018	hum	2	10 µM	29				
219900	Dopamine D _{4.2}	308019	hum	2	10 µM	2				
224010	Endothelin ET _A	307893	hum	2	10 µM	-5				
224110	Endothelin ET _B	307894	hum	2	10 µM	-3				
225510	Epidermal Growth Factor (EGF)	307924	hum	2	10 µM	12				
226010	Estrogen ERα	307925	hum	2	10 µM	-2				
226600	GABA _A , Flunitrazepam, Central	307869	rat	2	10 µM	-5				

Note: Items meeting criteria for significance (≥50% stimulation or inhibition) are highlighted.

* Batch: Represents compounds tested concurrently in the same assay(s).

R=See Remarks (if any) at end of this section.

bov=Bovine; ham=Hamster; hum=Human

Table S2 (continued). Off-target selectivity profile for **16k**

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.	IC ₅₀ *	K _i	n _H	R
226500	GABA _A , Muscimol, Central	307868	rat	2	10 µM	0				
228610	GABA _{B1A}	307926	hum	2	10 µM	13				
232030	Glucocorticoid	307805	hum	2	10 µM	16				
232700	Glutamate, Kainate	307804	rat	2	10 µM	18				
232810	Glutamate, NMDA, Agonism	307896	rat	2	10 µM	3				
232910	Glutamate, NMDA, Glycine	307927	rat	2	10 µM	16				
233000	Glutamate, NMDA, Phencyclidine	307870	rat	2	10 µM	7				
239610	Histamine H ₁	307871	hum	2	10 µM	-5				
239710	Histamine H ₂	307928	hum	2	10 µM	16				
239820	Histamine H ₃	307929	hum	2	10 µM	3				
241000	Imidazoline I ₂ , Central	307888	rat	2	10 µM	20				
243520	Interleukin IL-1	307806	mouse	2	10 µM	-1				
250460	Leukotriene, Cysteinyl CysLT ₁	307930	hum	2	10 µM	-3				
251600	Melatonin MT ₁	307932	hum	2	10 µM	4				
252610	Muscarinic M ₁	307978	hum	2	10 µM	5				
252710	Muscarinic M ₂	307872	hum	2	10 µM	4				
252810	Muscarinic M ₃	307873	hum	2	10 µM	-1				
257010	Neuropeptide Y Y ₁	308035	hum	2	10 µM	-11				
257110	Neuropeptide Y Y ₂	307933	hum	2	10 µM	-13				
258590	Nicotinic Acetylcholine	307874	hum	2	10 µM	18				
258700	Nicotinic Acetylcholine α, Bungarotoxin	307875	hum	2	10 µM	12				
260130	Opiate δ ₁ (OP1, DOP)	307808	hum	2	10 µM	-1				
260210	Opiate κ(OP2, KOP)	307809	hum	2	10 µM	19				
260410	Opiate μ(OP3, MOP)	307810	hum	2	10 µM	9				
264500	Phorbol Ester	307876	mouse	2	10 µM	5				
265010	Platelet Activating Factor (PAF)	307877	hum	2	10 µM	16				
265600	Potassium Channel [K _{ATP}]	307878	ham	2	10 µM	12				
265900	Potassium Channel hERG	308075	hum	2	10 µM	77				
268420	Prostanoid EP ₄	307880	hum	2	10 µM	4				
268700	Purinergic P _{2X}	308020	rabbit	2	10 µM	2				
268810	Purinergic P _{2Y}	307811	rat	2	10 µM	-14				
270000	Rolipram	307881	rat	2	10 µM	18				
271110	Serotonin (5-Hydroxytryptamine) 5-HT _{1A}	307899	hum	2	10 µM	-4				
271700	Serotonin (5-Hydroxytryptamine) 5-HT _{2A}	307813	hum	2	10 µM	-1				
271910	Serotonin (5-Hydroxytryptamine) 5-HT ₃	307934	hum	2	10 µM	17				

Note: Items meeting criteria for significance (≥50% stimulation or inhibition) are highlighted.

* Batch: Represents compounds tested concurrently in the same assay(s).

R=See Remarks (if any) at end of this section.

bov=Bovine; ham=Hamster; hum=Human

Table S2 (continued). Off-target selectivity profile for **16k**

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.	IC ₅₀ *	K _i	n _H	R
278110	Sigma σ_1	307884	hum	2	10 μ M	9				
255520	Tachykinin NK ₁	307897	hum	2	10 μ M	6				
285900	Thyroid Hormone	307937	rat	2	10 μ M	2				
220320	Transporter, Dopamine (DAT)	307799	hum	2	10 μ M	1				
226400	Transporter, GABA	307807	rat	2	10 μ M	-7				
204410	Transporter, Norepinephrine (NET)	307798	hum	2	10 μ M	19				
274030	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	307800	hum	2	10 μ M	2				

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