

Fragment-Based Drug Discovery of Phosphodiesterase Inhibitors

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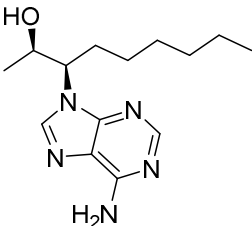
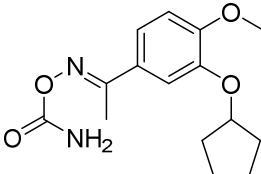
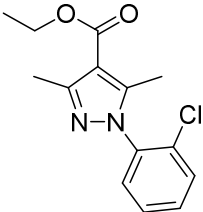
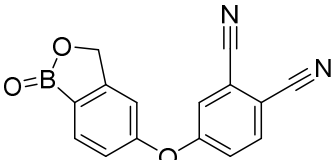
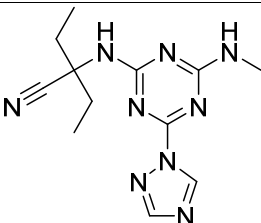
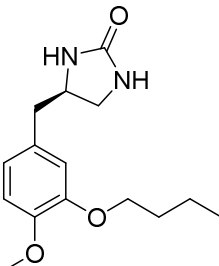
[‡] Centre for Molecular Informatics, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK

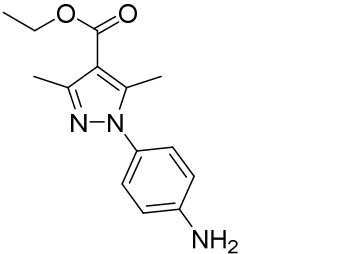
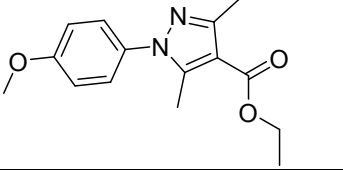
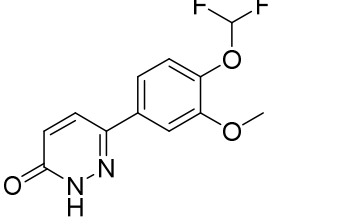
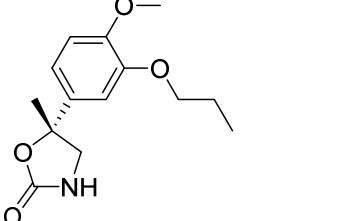
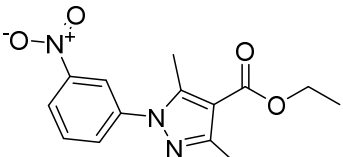
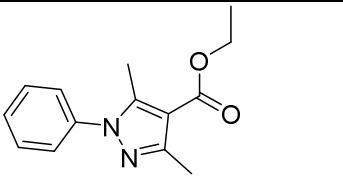
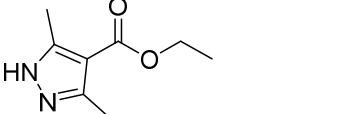
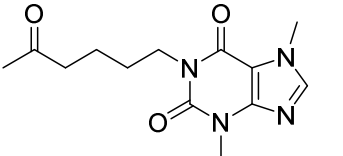
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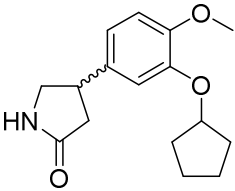
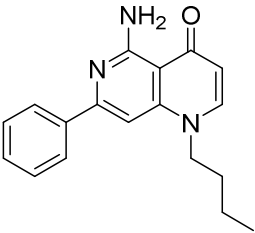
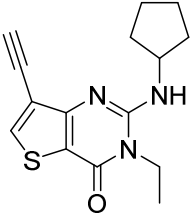
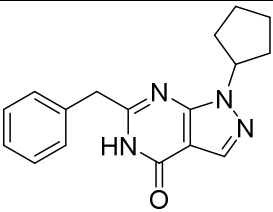
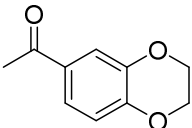
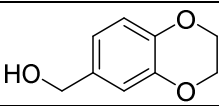
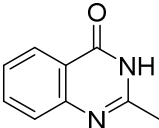
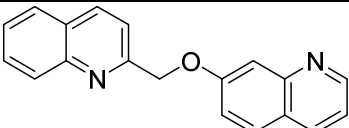
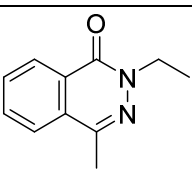
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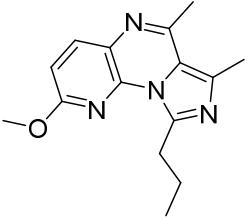
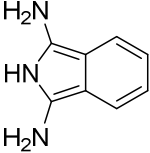
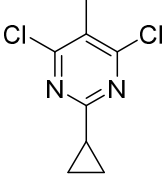
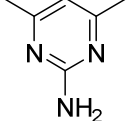
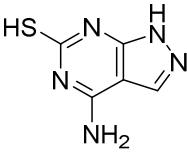
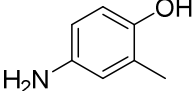
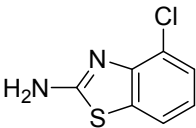
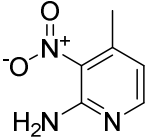
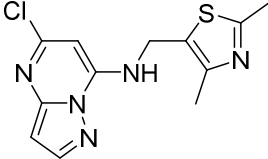
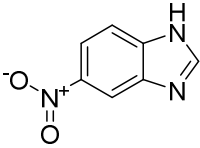
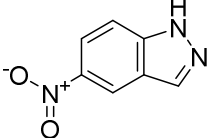
Co-crystallized fragment sized PDE inhibitors

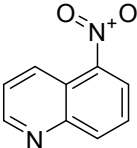
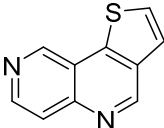
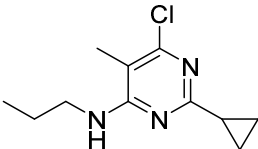
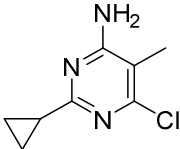
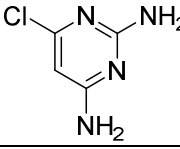
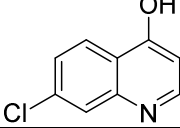
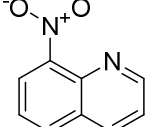
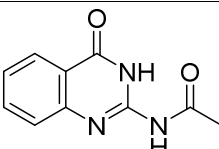
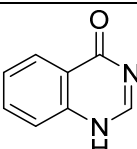
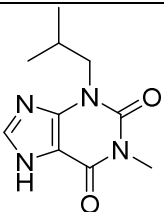
Table S1. Fragment-sized ligands co-crystallized in a PDE.

Structure	PDE	PDB IDs
	PDE2A	4cli
	PDE4B	1xlz
	PDE4B	1y2h
	PDE4B	3o0j
	PDE4B	4kp6
	PDE4A PDE4D	3i8v 3k4s

	PDE4D	1y2e
	PDE4D	1y2d
	PDE4D PDE4D	1xor 1mkd
	PDE4B	1xm6
	PDE4B PDE4D	1y2j 1y2k
	PDE4D	1y2c
	PDE4D	1y2b
	PDE4A	3tvx

	PDE4B PDE4B PDE4B PDE4B PDE4D PDE4D PDE4D PDE4D	4x0f 1xn0 1xmy 1ro6 1q9m 1tbb 3g4k 1oyn
	PDE5-4-Chimera	3hdz
	PDE7A	4pm0
	PDE9A	3jsi
	PDE10A	4lm3
	PDE10A	4lm2
	PDE10A	4llk
	PDE10A	4msc
	PDE10	4ajd

	PDE10A	3lxg
	PDE10A	4llj
	PDE10A	5c1w
	PDE10A	4llx
	PDE10A	4lkq
	PDE10A	4llp
	PDE10A	4msh
	PDE10A	4mrz
	PDE10A	5dh4
	PDE10A	4msa
	PDE10A	4lm0

	PDE10A	4lm1
	PDE10	4ajg
	PDE10A	5c29
	PDE10A	5c28
	PDE10A	4ms0
	PDE10A	4mrw
	PDE10A	4msn
	PDE10	4ajf
	PDE10A	4lm4
	PDE2A PDE3B PDE4D PDE5A PDE6-5-Chimera PDE7A PDE8A PDE9A PDE9A PDE9A PDE9A	3itu 1soj 1zkn 1rkp 3jwr 1zkl 3ecn 3dy8 3dys 2yy2 3dyq

	PDE9A	3n3z
	PDE9A	2hd1
	PDE9A	3dyn
	PDE9A	3qi4
	PDE9A	3dyl
	LmPDEB1	2r8q

ChEMBL Analysis

ChEMBL was mined for fragment sized inhibitors with an IC₅₀ or K_i value registered as “=” against one of the ChEMBL target IDs listed below.

Human PDEs

CHEMBL2095150:PDE1
CHEMBL3421:PDE1A
CHEMBL4425:PDE1B
CHEMBL4619:PDE1C
CHEMBL2652:PDE2A
CHEMBL2094125:PDE3
CHEMBL241:PDE3A
CHEMBL290:PDE3B
CHEMBL2093863:PDE4
CHEMBL254:PDE4A
CHEMBL275:PDE4B
CHEMBL291:PDE4C
CHEMBL288:PDE4D
CHEMBL1827:PDE5A
CHEMBL2097163:PDE6
CHEMBL3878:PDE6A
CHEMBL3977:PDE6C
CHEMBL3860:PDE6D
CHEMBL2111411:PDE7
CHEMBL3012:PDE7A
CHEMBL4716:PDE7B
CHEMBL2363067:PDE8
CHEMBL4408:PDE8B
CHEMBL4640:PDE8A
CHEMBL3535:PDE9A
CHEMBL4409:PDE10A

Parasite PDEs

CHEMBL2010636:TbrPDEB1
CHEMBL2169733:LmaPDEB1
CHEMBL1681621:TcrPDEC

Descriptor Calculation

Prior to descriptor calculations all compounds were prepared using Ligprep.¹

All descriptors were calculated using QikProp². QikProp considers only neutral molecules, therefore molecules that are inherently charged (i.e. quaternary amines) will not be included in the analysis.

1. **Schrödinger Release 2015-4:** LigPrep, Schrödinger, LLC, New York, NY, 2015.

2. **Schrödinger Release 2015-4:** QikProp, Schrödinger, LLC, New York, NY, 2015.

Properties of analysed fragments

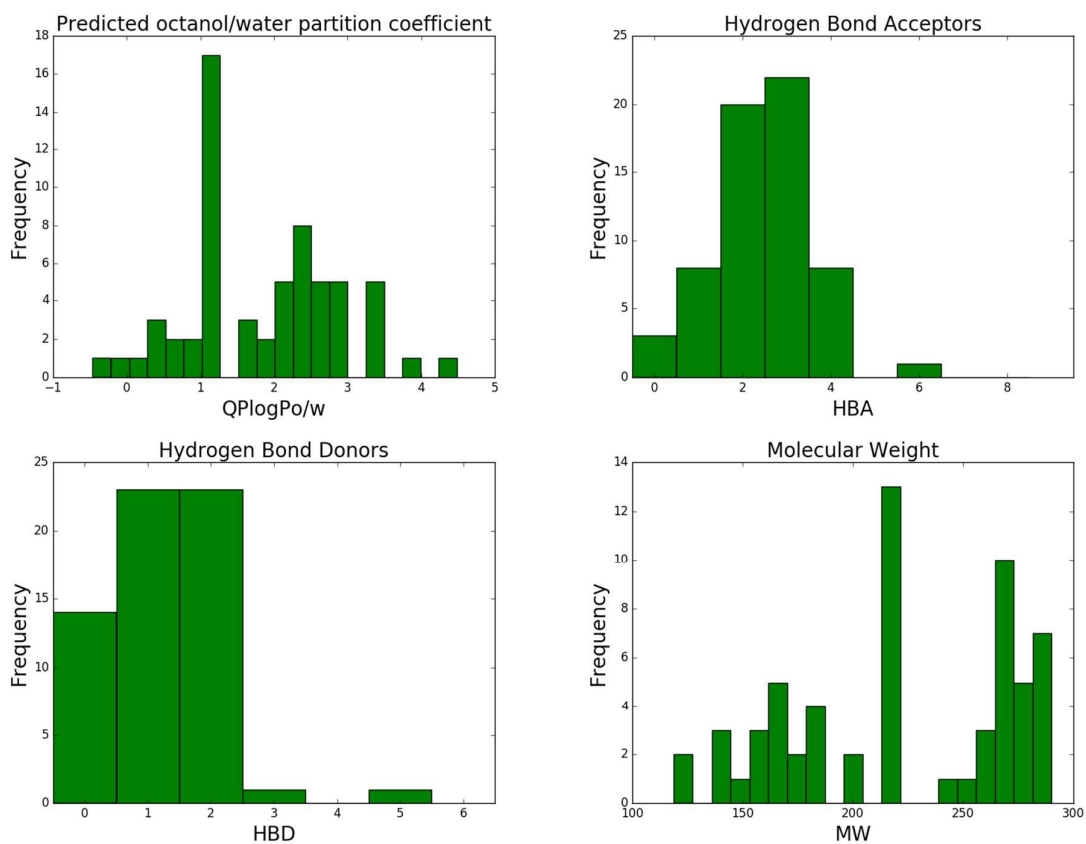
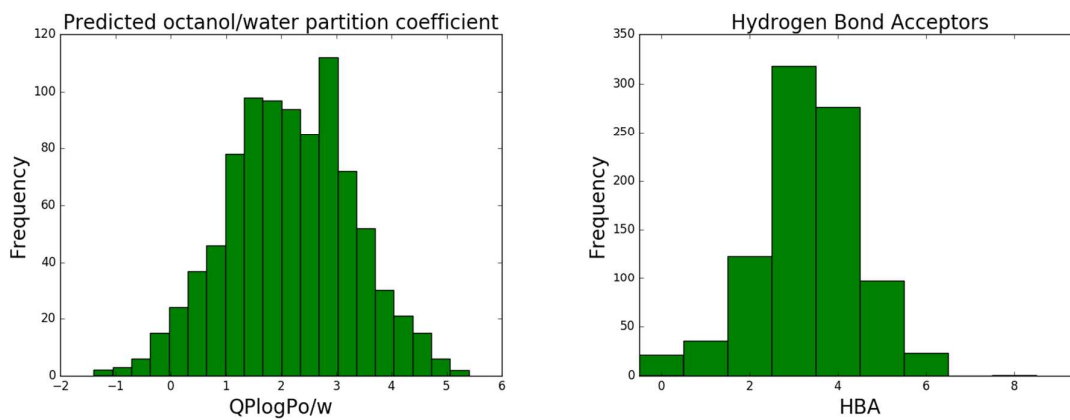


Figure S1. Calculated properties for fragment sized ligands in the PDB co-crystallized with a PDE.



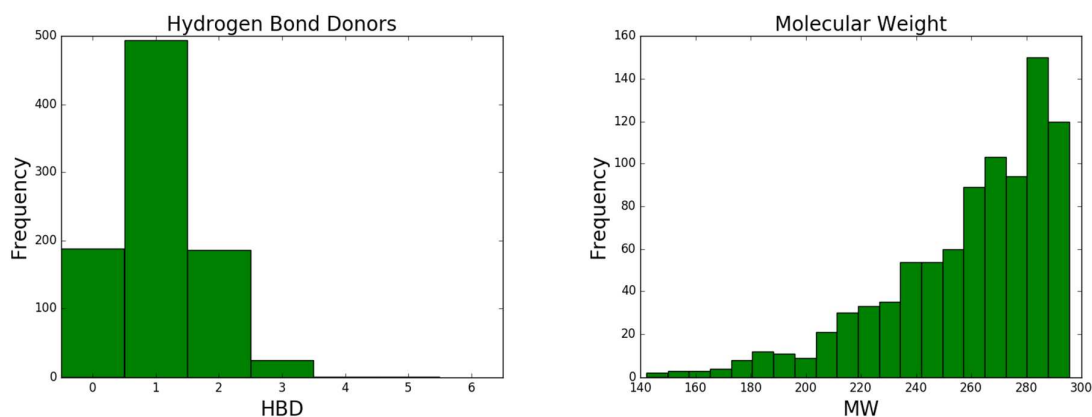


Figure S2. Calculated molecular properties for the PDE inhibitory fragments extracted from ChEMBL.

Number of crystal structures

Table S2. The number of crystal structures with a fragment sized inhibitor co-crystallized in the PDB, listed by PDE.

PDE	Number of structures
PDE2A	2
PDE3B	1
PDE4A	2
PDE4B	10
PDE4D	13
PDE5A	1
PDE7A	2
PDE8A	1
PDE9A	10
PDE10A	25
Chimeras	2
LmPDEB1	1

Number of ChEMBL fragments

Table S3. Number of activities reported in ChEMBL for fragment sized molecules against the respective PDE.

PDE	Number of fragment-IC50 pairs
PDE1	39
PDE1A	2
PDE1C	6
PDE2A	60
PDE3	287
PDE3A	30
PDE3B	3
PDE4	177
PDE4A	53
PDE4B	70
PDE4C	5
PDE4D	54
PDE5A	90
PDE7	1
PDE7A	98
PDE7B	5
PDE8B	26
PDE9A	6
PDE10A	50
TcrPDEC	5

Approved Drugs Interacting with a PDE

We mined DrugBank³ for all approved drugs with a PDE indicated as a target. This resulted in 39 drugs listed below.

3 Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, Chang Z, Woolsey J. *DrugBank: a comprehensive resource for in silico drug discovery and exploration*. Nucleic Acids Res. 2006 Jan 1;34(Database issue):D668-72

Milrinone
Enoximone
Ibudilast
Amrinone
Roflumilast
Anagrelide
Tadalafil
Crisaborole
Avanafil
Dyphylline
Tofisopam
Dipyridamole
Papaverine
Pentoxifylline
Iloprost
Drotaverine
Vardenafil
Apremilast
Enprofylline
Theobromine
Udenafil
Oxtriphylline
Theophylline
Levosimendan
Sildenafil
Cilostazol
Aminophylline
Triflusal
Bepidil
Caffeine
Nicardipine
Felodipine
Amifostine
Naloxone
Isoprenaline
Ribavirin

Amlodipine
Chlorpromazine
Desipramine