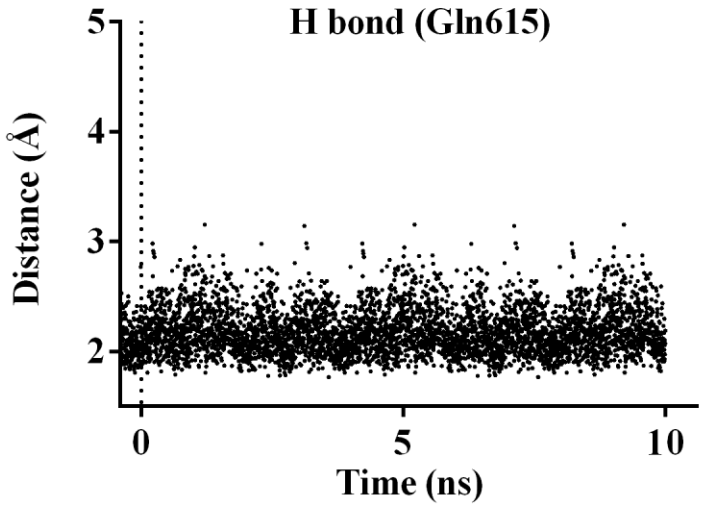
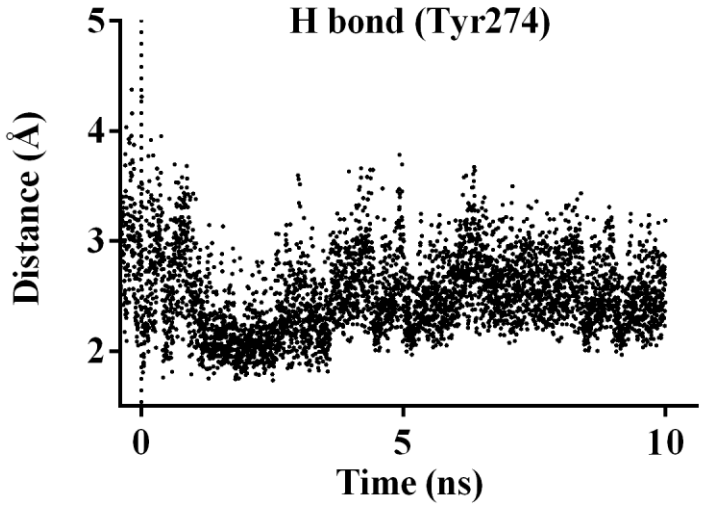
Electronic Supplementary Material (ESI) for RSC Advances.

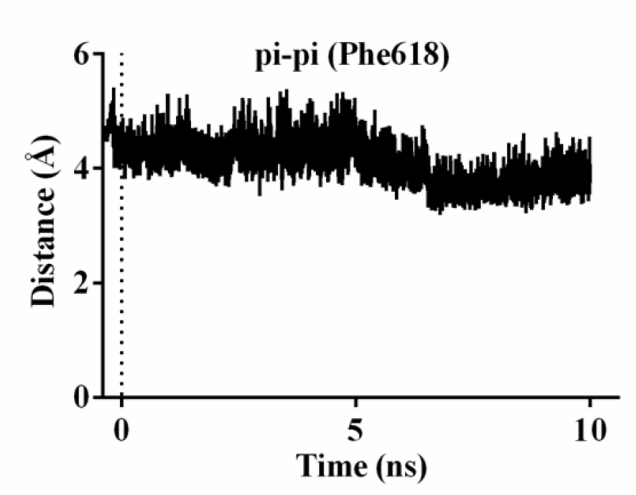
SUPPLEMENTARY FIGURES



Supplementary Fig. 1. H-bond distance pattern with Gln615 during 10ns run of MD simulation.



Supplementary Fig. 2. H-bond distance pattern with Tyr274 during 10ns of MD simulation.



Supplementary Fig.3. Pi-pi interaction distance pattern with Phe618 during 10ns of MD simulation.

SUPPLEMENTARY TABLES

Supplementary Table 1 List of all hypotheses produced. Hypothesis AADRR.1108 was considered for 3D-QSAR development and virtual screening.

ID	Survival	Survival - inactive	Site	Vector	Volume	# Matches	Energy	Activity	Inactive
AADRR.1268	42.7	41.3	0.4	0.8	0.4	40	1.7	8.7	1.4
AADRR.1114	36.4	34.4	0.8	1.0	0.7	38	1.0	7	2.0
AADRR.1108	36.4	34.6	0.8	0.9	0.7	38	1.0	7.4	1.8
AADRR.1512	36.4	34.7	0.7	0.9	0.7	38	0.0	7	1.7
AADRR.1509	36.3	34.6	0.7	0.9	0.7	38	1.5	7.5	1.7
AADRR.1111	36.0	34.2	0.6	0.8	0.5	38	4.2	9.1	1.8
AADRR.1524	33.4	31.2	0.8	1.0	0.7	37	0.1	7	2.2
AADRR.1511	33.4	31.3	0.8	1.0	0.7	37	0.3	7.1	2.1
AADRR.1523	33.3	31.3	0.8	1.0	0.6	37	1.7	8.5	2.0
AADRR.1514	33.3	31.2	0.8	1.0	0.6	37	1.7	8.5	2.1
AADRR.770	33.3	31.9	0.8	1.0	0.6	37	0.3	5.5	1.4
AADRR.1118	33.3	31.4	0.7	0.9	0.7	37	0.0	6.3	1.9
ADDRR.50	27.9	25.9	0.7	0.9	0.7	35	2.4	8.8	2.0
ADDRR.33	27.8	25.9	0.7	0.9	0.7	35	0.1	7	1.9
ADDRR.32	27.8	25.9	0.7	0.9	0.7	35	0.1	7	1.9
ADDRR.29	27.7	25.7	0.6	0.9	0.6	35	1.7	8.5	1.9
ADDRR.24	27.7	25.9	0.6	0.9	0.6	35	0.2	7	1.8
ADDRR.38	27.7	25.7	0.7	0.9	0.5	35	1.9	8.5	2.0
ADDRR.35	27.5	25.7	0.6	0.9	0.5	35	4.1	11.1	1.8
ADDRR.34	27.5	25.7	0.6	0.9	0.5	35	4.1	11.1	1.8
ADDRR.83	27.1	25.7	0.3	0.8	0.4	35	1.4	8.7	1.4

Survival: Weighted combination of the vector, site, volume, and survival scores, and a term for the number of matches.

Survival –inactives: Survival score for actives with a multiple of the survival score for inactives subtracted.

Site: Site score, measures how closely the site points are superimposed in an alignment to the pharmacophore of the structures that contribute to this hypothesis, based on the RMS deviation of the site points of a ligand from those of the reference ligand.

Vector: Vector alignment score. This score measures how well the vectors for acceptors, donors, and aromatic rings are aligned in the structures that contribute to this hypothesis, when the structures themselves are aligned to the pharmacophore.

Volume: Measures how much the volumes of the contributing structures overlap when aligned on the pharmacophore. The volume score is the average of the individual volume scores. The individual volume score is the overlap of the volume of an aligned ligand with that of the reference ligand, divided by the total volume occupied by the two ligands.

Matches: Number of actives that match the hypothesis.

Energy: Relative energy of the reference ligand in kcal/mol. This is the energy of the reference conformation relative to the lowest-energy conformation.

Activity: Activity of the reference ligand.

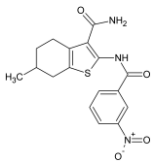
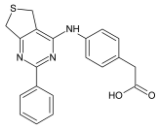
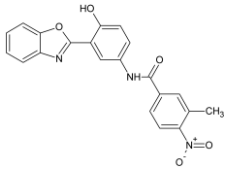
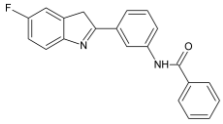
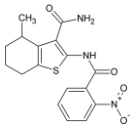
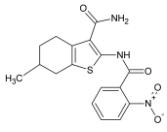
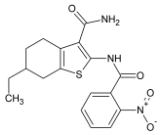
Inactive: Survival score of inactives. The scoring function is the same as for actives.

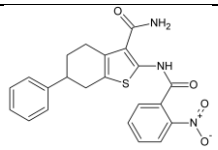
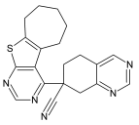
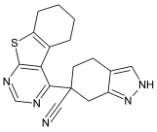
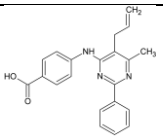
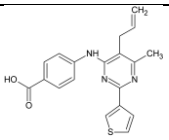
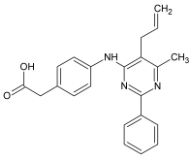
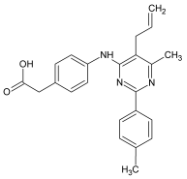
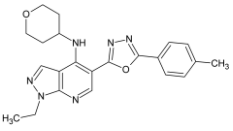
Supplementary Table 2 List of all quinoline analogues with their QSAR set and pharma set classification. Reported and predicted activity (PLS 4) is given in pIC50 values along with the fitness value of the ligands in the considered pharmacophore hypothesis.

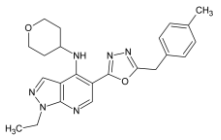
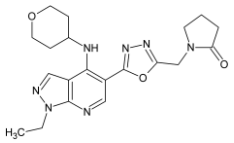
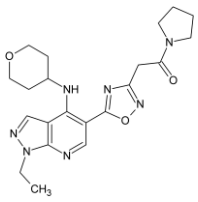
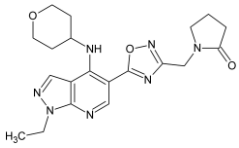
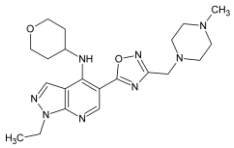
Ligand_names	QSAR Set	Activity	Predicted Activity 1	Predicted Activity 2	Predicted Activity 3	Predicted Activity 4	Pharm Set	Fitness
W_1	training	8.4	7.4	7.6	7.7	8.3	active	2.8
W_2	training	11.1	9.3	10.2	11.1	11.5	active	2.8
W_3	test	8.8	9.0	9.0	8.9	8.9	active	3.0
W_4	training	8.5	8.6	8.4	8.3	8.7	active	2.8
W_5	training	6.7	6.2	5.5	7.6	7.1	active	0.9
W_6	test	6.8	6.5	6.0	7.7	7.3	active	1.0
W_7	test	7.5	8.0	7.7	7.6	7.7	active	2.6
W_8	training	7.6	8.2	8.0	7.8	7.9	active	2.6
W_9	training	9.1	8.2	8.2	8.5	9.0	active	2.7
W_10	test	8.7	8.6	8.5	8.5	8.9	active	2.8
W_11	training	8	8.9	8.9	8.4	8.3	active	3.0
W_12	training	8.5	6.6	8.0	8.0	8.4	active	1.9
W_13	training	8.2	8.8	8.8	8.4	8.2	active	3.0
W_14	training	7.4	8.4	8.0	7.2	7.6	active	2.8
W_15	training	7.4	8.8	8.8	8.3	8.0	active	3.0
W_16	training	8.6	8.2	8.3	8.9	8.9	active	2.9
W_17	training	7.9	8.5	8.2	7.6	7.9	active	2.8
W_18	test	9.9	9.1	9.3	9.4	9.7	active	2.9
W_19	test	9.2	9.0	9.3	9.2	9.3	active	2.9
W_20	training	11	9.2	9.9	10.6	11.1	active	2.8
W_21	training	8.8	9.1	9.3	9.3	9.2	active	2.8
W_22	test	10	9.0	9.3	9.4	9.7	active	2.9
W_23	training	10.7	9.2	9.6	10.0	10.5	active	2.9
L_1	training	7	6.7	8.1	7.6	7.3	active	2.0
L_2	training	8.4	7.6	7.8	7.9	8.3	active	2.8
L_3	training	8.8	7.9	9.0	9.4	8.9	active	3.0
L_4	training	5.5	7.6	6.4	6.1	5.7	active	2.6
L_5		4.7					inactive	
L_6	test	6.3	7.1	6.5	7.1	7.0	active	1.8
L_7	training	6.6	5.8	6.0	6.1	6.8	active	1.7

L_8	training	4.9	5.7	5.4	5.0	5.5		1.7
L_9	training	5.5	7.5	6.0	5.9	5.6	active	2.5
L_10	training	4.7	6.0	6.0	4.7	4.8	inactive	1.7
L_11	training	4.8	5.5	4.5	4.1	4.9	inactive	1.5
L_12	training	5.1	6.6	4.9	4.9	4.8		1.5
L_13	training	4.5	5.6	4.7	4.0	4.5	inactive	1.6
L_14	training	4.5	5.6	5.0	4.7	4.3	inactive	1.5
L_15	training	7.8	6.5	7.5	7.7	7.9	active	1.8
L_16	training	7.7	7.0	6.1	7.8	7.9	active	1.7
L_17	training	8.6	7.8	7.0	7.7	7.9	active	2.6
L_18	training	7	8.2	7.5	6.8	6.9	active	2.9
L_19	training	7.1	6.6	8.0	7.6	7.2	active	1.9
L_20	training	5.3	8.1	7.2	6.3	5.9		2.8
L_21	training	7.5	6.5	7.9	8.1	7.8	active	1.8
L_22	training	8.2	6.5	7.7	7.7	8.0	active	1.9
L_23	training	6	6.7	5.2	6.4	5.9	active	1.4
L_24	training	9.5	6.9	8.7	8.8	8.8	active	1.9
L_25	training	8.3	6.8	8.5	8.3	8.3	active	1.9
L_26	training	9.4	8.4	8.8	8.92	9.18	active	2

Supplementary Table 3. External r^2 prediction of activity of dataset of reported PDE4B inhibitors for validation of developed QSAR model.

S.No.	Molecule	Experimental pIc_{50}	Predicted pIc_{50}
1.		6.8	6.9
2.		7.5	7.2
3.		6.4	6.0
4.		8.6	8.8
5.		5.3	4.9
6.		7.3	7.2
7.		8.0	8.2

8.		6.4	6.1
9.		5.3	5.0
10.		5.7	5.4
11.		6.7	6.5
12.		7.1	7.2
13.		5.7	5.4
14.		6.0	6.1
15.		8.9	9.0

16.		8.0	8.1
17.		8.4	8.2
18.		9.1	9.0
19.		9.4	9.6
20.		7.8	7.9

Supplementary Table 4 Predicted absorption, distribution, metabolism and Excretion (ADME) properties of all PDE4B selective molecules

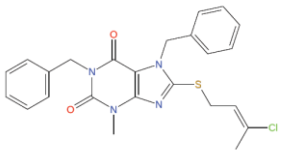
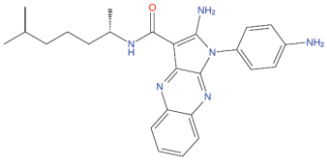
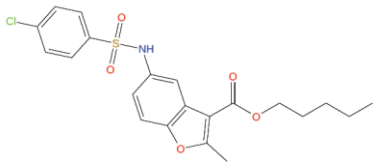
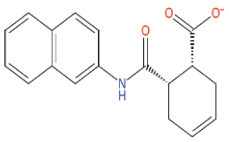
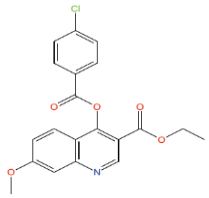
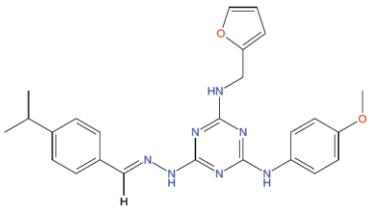
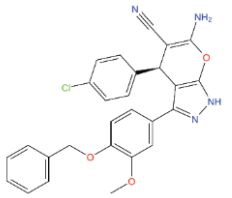
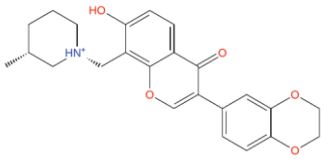
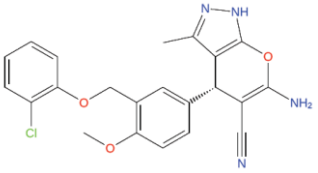
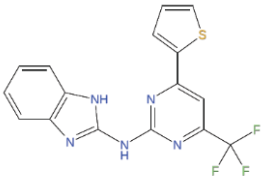
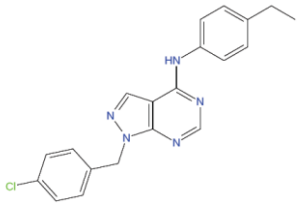
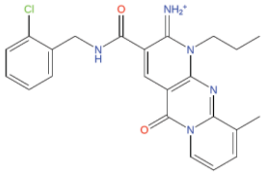
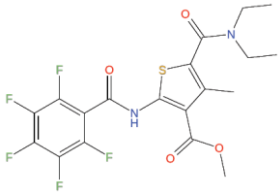
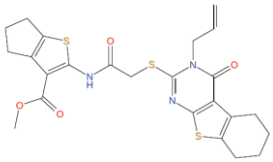
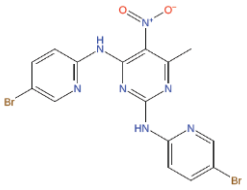
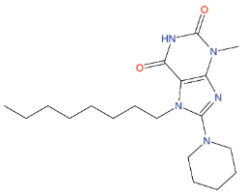
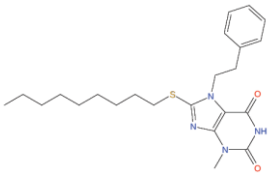
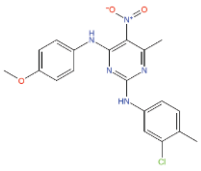
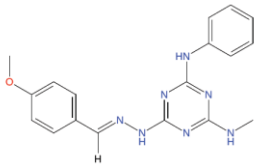
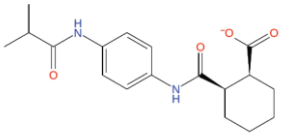
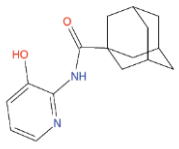
Molecule	#rtvFG	CNS	mol_MW	SASA	FOSA	FISA	donorHB	accptHB	QPlogPo/w	QPPCaco	QPlogBB	#metab	QPlogKhsa	% HumanOralAbsorption	RuleOfFive	Rule of three
AO-022/43453692	0	-1	435.9	735.2	249.3	110.3	1	7	4.4	891.7	-0.8	2	0.5	100	0	1
AQ-390/42425549	0	-2	435.9	767.8	319.7	115.0	1	7	4.5	804.4	-1.1	2	0.5	100	0	1
AG-205/36564043	0	-1	295.3	532.9	90.2	99.9	2	4.5	3.4	283.3	-0.5	4	0.0	91.0	0	0
AP-964/40915318	0	-2	422.9	692.2	193.6	177.6	3	5	4.0	204.8	-1.5	5	0.6	91.4	0	1
AO-022/43390834	0	-2	430.6	773.5	311.7	136.5	3.5	5	4.9	502.6	-1.4	1	0.9	100	0	1
AK-968/12386394	0	0	464.4	705.3	327.3	118.4	0	6.5	4.4	745.9	-0.6	2	0.3	100	0	1
AG-690/10252051	0	-1	481.1	669.2	78.0	140.1	2	6	3.7	464.5	-0.9	4	0.3	96.1	0	1
AF-399/15335138	0	-1	515.7	845.5	542.2	102.7	0	7.5	5.4	1052.9	-0.7	8	0.7	86.8	2	2
AG-690/36873050	0	-2	457.5	776.7	316.4	105.9	3	7.8	4.4	981.1	-1.2	4	0.4	100	0	0
AO-476/43407280	2	0	385.8	640.3	211.3	97.6	0	6.3	3.5	1175.0	-0.5	2	0.0	100	0	0
AF-399/42316263	0	1	407.5	673.0	371.5	84.4	1	6.8	3.3	390.9	-0.1	3	0.5	92.9	0	0
AT-057/43469096	0	1	361.3	604.1	0.7	76.1	2	4	4.3	1880.0	0.1	1	0.5	100	0	1
AF-399/41980308	0	0	363.8	667.4	166.6	72.3	1	3.5	5.3	2044.4	-0.3	3	0.9	100	1	1
AG-690/36276042	0	0	467.0	802.8	245.3	60.7	0	5	6.7	2631.3	-0.3	4	1.2	100	1	1
AJ-292/42152568	0	-2	484.9	737.6	90.6	173.3	3	5	4.9	225.1	-1.4	4	0.95	100.0	0	1
AG-690/36276051	0	-1	361.5	670.0	556.5	97.9	1	5.5	3.9	1169.4	-0.8	0	0.4	100	0	0
AG-690/11972161	0	-2	428.6	780.2	469.4	95.8	1	5	5.7	1224.0	-1.2	1	1.0	100	1	1
AK-968/37005156	0	-1	399.8	692.8	250.9	105.0	2	4.8	4.5	1000.5	-0.8	4	0.6	100	0	1
AG-205/33161053	0	-2	349.4	683.7	198.4	100.9	3	7.3	3.0	1093.7	-1.0	2	-0.05	100.0	0	0
AG-690/15437723	0	-2	396.5	692.9	229.7	134.4	1	8	3.2	526.2	-1.1	1	0.1	94.5	0	0
AP-124/43383688	0	-1	313.4	639.9	386.1	103.3	1	5.5	3.4	1037.8	-0.8	5	0.4	100	0	0

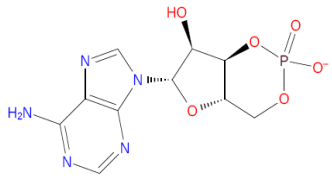
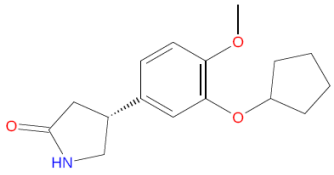
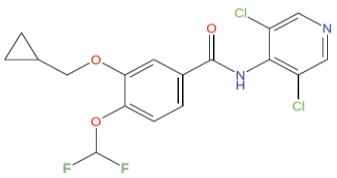
Parameters

#rtvFG	Number of reactive functional groups. The presence of these groups can lead to false positives in HTS assays and to decomposition, reactivity, or toxicity problems in vivo (0-2)
CNS	Predicted central nervous system activity -2 (inactive) to 2(active)
mol_MW	Molecular weight of the molecule
SASA	Total solvent accessible surface area (SASA) in square angstroms using a probe with a 1.4 Å radius (300.0 – 1000.0)

FOSA	Hydrophobic component of the SASA (saturated carbon and attached hydrogen)
FISA	Hydrophilic component of the SASA (SASA on N, O, and H on heteroatoms).
donorHB	Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution
accptHB	Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution
QPlogPo/w	Predicted octanol/water partition coefficient.
QPPCaco	Predicted apparent Caco-2 cell permeability in nm/sec (<25 poor >500 great)
QPlogBB	Predicted brain/blood partition coefficient (range or recommended value for 95% of known drugs -3 – 1.2);
#metab	Number of likely metabolic reactions (1 – 8)
QPlogKhsa	Prediction of binding to human serum albumin. (-1.5 – 1,5)
% Human Oral Absorption	Predicted human oral absorption on 0 to 100% scale (25% - 80%). The prediction is based on a quantitative multiple linear regression model. This property usually correlates well with HumanOralAbsorption, as both measure the same property.
Rule Of Five	Indicates the number of violation of Lipinski's rule of five. Compounds that satisfy these rules are considered drug-like (maximum is 4)
Rule of Three	Number of violations of Jorgensen's rule of three. The three rules are: QPlogS > -5.7, QP PCaco > 22 nm/s, # Primary Metabolites < 7. Compounds with fewer (and preferably no)violations of these rules are more likely to be orally available (maximum is 3)

Supplementary Table 5 Chemical structure of all PDE4B selective molecules and their Specs IDs

AG-690/36276042 	AO-022/43390834 	AQ-390/42425549 
AG-205/36564043 	AO-476/43407280 	AG-690/36873050 
AJ-292/42152568 	AF-399/42316263 	AP-964/40915318 
AT-057/43469096 	AF-399/41980308 	AO-022/43453692 
AK-968/12386394 	AF-399/15335138 	AG-690/10252051 
AG-690/36276051 	AG-690/11972161 	AK-968/37005156 
AG-205/33161053 	AG-690/15437723 	AP-124/43383688 

cAMP 	 Rolipram	 Roflumilast