



## SUPPLEMENTARY MATERIALS

# S1. Chemical structure and biological potency of the hybrids 2-29 as F508del CFTR correctors.



8	-CH <sub>2</sub>		5.64
9	-CH <sub>2</sub>	S N N	5.80
10	-CH <sub>2</sub>	F	6.05
11	-CH <sub>2</sub>	S N CI	5.54
12	-CH <sub>2</sub>	S N Br	5.31
13	-CH <sub>2</sub>	S N CI	5.09
14	-CH <sub>2</sub>	S N N	5.92
15	-CH2	S N F	5.68
16	-CH <sub>2</sub>	S N OH	5.74

17	-CH <sub>2</sub>	у Nон	5.64
18	-CH <sub>2</sub>	, NОн	5.92
19	-CH2	s N OH	5.41
20	-CH <sub>2</sub>	<sup>S</sup> N → OH	5.30
21	-CH2	s N O OH	5.53
22	-CH <sub>2</sub>	S N H H O	5.30
23	-CF <sub>2</sub>	S N Br	5.42
24	-CF <sub>2</sub>		5.27
25	-CF <sub>2</sub>	\$ NОн	5.89



**S2.** Chemical structure and biological potency of the tetrahydropyridopyrimidines **30-56** as F508del CFTR correctors.



Cp.	R	$\mathbf{R}_1$	<b>R</b> 2	pEC50
30	Y C	}_NOH	N	5.55
31			K N	5.85
32	Y	J−N N−NH₂	K N	5.55
33	Y		N	5.51
34	Y		N	5.82





S3. Chemical structure and biological potency of cyanoquinolines 57-80 as F508del CFTR correctors.





58	HN N O O	4.96
59		5.52
60		4.00
61		5.57
62		5.14
63		4.00
64		5.38
65		5.82
66		5.17
67		5.57
68		5.43
69		4.00





**S5.** Binding affinity values obtained by molecular docking studies of **VX-809**, **ALK-809**, **SUL-809**.

hNBD1/(CFTR)-	Binding Affinity Energy		Score	
Corrector Complex	ΔG (K	J/mol)		
(LeadIT)				
hNBD1/(CFTR)-	-23.0	-25.0	-21.5663	-35.6469
VX-809				
hNBD1/(CFTR)-	-21.0	-22.0	-21.9843	-31.4063
ALK-809				
hNBD1/(CFTR)-	-24.0	-22.0	-24.5672	-35.2638
SUL-809				

<mark>S6.</mark> Binding affinity values obtained by molecular docking studies of hybrid correctors.

hNBD1/(CFTR)-	Binding Affi	nity Energy	Sco	ore
Corrector Complex	ΔG (kJ	/mol)		
(LeadIT)				
hNBD1/(CFTR)-	-19.0	-21.0	-24.8888	-28.4416
2				
hNBD1/(CFTR)-	-18.0	-16.0	-24.3256	-23.3950
3				
hNBD1/(CFTR)-	-18.0	-20.0	-23.4393	-23.2050
4				
hNBD1/(CFTR)-	-19.0	-21.0	-24.4022	-23.3299
5				

hNBD1/(CFTR)- <b>6</b>	-14.0	-12.0	-21.1282	-23.0777
hNBD1/(CFTR)-	-10.0	-13.0	-21.3208	-23.0264
7 hNBD1/(CFTR)-	-15.0	-17.0	-19.6742	-23.5280
8				
hNBD1/( <i>CFTR</i> )- <b>9</b>	-16.0	-18.0	-19.2015	-22.9820
hNBD1/( <i>CFTR</i> )- <b>10</b>	-14.0	-12.0	-21.3407	-22.7400
hNBD1/( <i>CFTR</i> )- 11	-14.0	-16.0	-22.1238	-22.0175
hNBD1/( <i>CFTR</i> )- 12	-15.0	-17.0	-20.4414	-21.9677
hNBD1/( <i>CFTR</i> )-	-14.0	-12.0	-21.5660	-22.6050
hNBD1/( <i>CFTR</i> )- 14	-17.0	-19.0	-21.9788	-22.3278
hNBD1/( <i>CFTR</i> )- <b>15</b>	-16.0	-14.0	-21.4102	-22.9320
hNBD1/( <i>CFTR</i> )- <b>16</b>	-17.0	-19.0	-20.5806	-24.5206
hNBD1/( <i>CFTR</i> )- 17	-14.0	-16.0	-19.8188	-25.1833
hNBD1/( <i>CFTR</i> )- <b>18</b>	-15.0	-13.0	-20.4794	-25.7335
hNBD1/( <i>CFTR</i> )- <b>19</b>	-12.0	-10.0	-20.1269	-25.5958
hNBD1/( <i>CFTR</i> )- <b>20</b>	-13.0	-15.0	-20.3380	-34.2077
hNBD1/( <i>CFTR</i> )- <b>21</b>	-16.0	-18.0	-19.6181	-33.4221
hNBD1/( <i>CFTR</i> )- <b>22</b>	-14.0	-16.0	-18.7362	-30.3549
hNBD1/( <i>CFTR</i> )- <b>23</b>	-14.0	-12.0	-17.4095	-22.7536
hNBD1/( <i>CFTR</i> )- <b>24</b>	-16.0	-18.0	-16.1613	-23.1016
hNBD1/( <i>CFTR</i> )- <b>25</b>	-10.0	-12.0	-22.8956	-25.9998

hNBD1/(CFTR)-	-17.0	-19.0	-20.3272	-25.7090
26				
hNBD1/(CFTR)-	-16.0	-17.0	-20.0106	-22.7284
27				
hNBD1/(CFTR)-	-17.0	-18.0	-21.8150	-20.3860
28				
hNBD1/(CFTR)-	-16.0	-15.0	-23.5860	-22.0357
29				

<mark>S7.</mark> Binding affinity values obtained by molecular docking studies of tetrahydropyridopyrimidines.

**58.** Binding affinity values obtained by molecular docking studies of cyanoquinolines.

hNBD1/(CFTR)-	Binding Affinity Energy Score		ore	
Corrector Complex	ΔG (kJ/r	ΔG (kJ/mol)		
HNBUT/(CFTR)-	Binding Affini	ity Energy	Sco	pre
Convertor/(Complex	-20.0ΔG (kJ/r	nol) -18.0	-25.6464	-27.9264
(LeadIT) <sup>30</sup>				
hNBD1/(CFTR)=	=28:0	= <b><u>2</u>6</b> :0	=23.2908	=37:3798
87				
hNBD1/(CFTR)=	=19.0	=13.0	-24.2288	=37:6388
38				
hNBD1/(CFTR)=	=14:0	=16:0	=27.3952	=27:3953
33				
hNBD1/(CFTR)=	=20:0	=15:0	=20:2773	-38:9895
66				
hNBD1/(CFTR)=	=19.0	=17:0	=20.8574	=28:0 <del>3</del> 38
65				
hNBD1/(CFTR)=	=10.0	=13:0	=18.8848	-29:4933
96				
hNBD1/(CFTR)=	=19:0	= <b>2</b> ∂:0	=20.3899	=2 <i>5</i> :0 <del>3</del> 38
63				
hNBD1/(CFTR)=	=20:0	= <b>1\$</b> :0	=20.7850	=29:34 <b>⊕</b> 9
64				
hNBD1/(CFTR)=	=19.0	=18.0	=19.3995	-29:2688
69				
hNBD1/(CFTR)=	=20:0	=15.0	=29:5569	-28:3039
40				

hNBD1/( <i>CFTR</i> )- <b>47</b>	-19.0	-19.0	- <b>22.<del>9</del>73</b> 7	-35.9483
hNBD1/( <i>CFTR</i> )-	-18.0	-14.0	-12.9443	-29.0303
hNBD1/( <i>CFTR</i> )- <b>49</b>	-18.0	-20.0	-20.2490	-29.0330
hNBD1/( <i>CFTR</i> )- <b>79</b>	-19.0	-20.0	-29.2289	-20.9982
hNBD1/( <i>CFTR</i> )- <b>45</b>	-16.0	-18.0	-29.3883	-30.5299
hNBD1/( <i>CFTR</i> )- <b>78</b>	-28.0	-20.0	-20.9873	-28.8329
hNBD1/( <i>CFTR</i> )- <b>43</b>	-20.0	-28.0	-25.8890	-29.3976
hNBD1/( <i>CFTR</i> )- <b>78</b>	-18.0	-14.0	-28.8308	-23.1832
hNBD1/( <i>CFTR</i> )- <b>49</b>	-14.0	-14.0	-15.6700	-24.4880
hNBD1/( <i>CFTR</i> )- <b>50</b>	-10.0	-12.0	-19.1205	-28.0889
hNBD1/( <i>CFTR</i> )- <b>51</b>	-18.0	-18.0	-26.8108	-25.9090
hNBD1/( <i>CFTR</i> )- <b>58</b>	-197.00	-15.0	-22.9000	-23.8393
hNBD1/( <i>CFTR</i> )- <b>59</b>	-12.0	-10.0	-22.3338	-28.0010
hNBD1/( <i>CFTR</i> )- <b>89</b>	-18.0	-19600	-20.8005	-28.6989
hNBD1/( <i>CFTR</i> )- 55	-9.0	-11.0	-10.1093	-33.5767
hNBD1/( <i>CFTR</i> )- 56	-11.0	-13.0	-10.5794	-29.5519

**S9.** Distribution of the score value obtained by the molecular docking at the NBD1 domain, concerning the VX-809 analogues (magenta dots), tetrahydropyridopyrimidines (red dots) and cyanoquinolines (cyan dots) with respect to their experimental potency values (Exp.pEC<sub>50</sub>).



**S10.** Distribution of the score value obtained by the molecular docking at the modelled F508del-CFTR, concerning the VX-809 analogues (magenta dots), tetrahydropyridopyrimidines (red dots) and cyanoquinolines (cyan dots) with respect to their experimental potency values (Exp.pEC<sub>50</sub>).



**S11.** Ligplot of the most relevant key contacts detected by LeadIT software concerning the docking mode of ALK-809 and SUL-809 at the modelled F508del-CFTR.



**S12.** Docking mode of **3** (*C* atom; dark cyan) (A) and **4** (*C* atom; pink) (B) at the *h*NBD1 domain of the F508del CFTR mutant.



**S13.** Pattern of the most important interactions observed for **2**, **3**, **10** chosen as potent reference derivatives based on the substituent at the position five of the thiazole as putative NBD1-targeting correctors.

Corrector	Н	I-bonds	π-π sta	cking
	Amino acid	Ligand portion	Amino acid	Ligand
	residues		residues	portion
2	N659	Carboxamide	Y577	Benzoyl
		moiety		moiety
	K464	Benzodioxole		
	T465	moiety		

3	K464 T465	Benzodioxole moiety	¥577	p-Br-phenyl ring	
	Y577	Hydroxyl group			
4	K464 T465	Benzodioxole moiety	Y577	m-Cl-phenyl ring	
	E656	Oxygen atom of the			
		carbonyl group			
10	T465	Benzodioxole	Y577	p-F-phenyl	
	K464	moiety		ring	
	N659	Carboxamide group			
		•	-		of the most

S14. Ligplot

relevant key contacts detected by LeadIT software concerning the docking mode of 3 compared to

VX-809 at the modelled F508del-CFTR.



**S15.** Ligplot of the most relevant key contacts detected by LeadIT software concerning the docking mode of **6 c**ompared to ALK-809 at the modelled F508del-CFTR.



**S16.** Selected docking mode of **6** (*C* atom; green) and **7** (*C* atom; orange) within the modelled CFTR. The most important residues are labelled.



S17. Ligplot of the most relevant key contacts detected by LeadIT software concerning the docking

mode of **21** compared to VX-809 at the modelled F508del-CFTR.



S18. Selected docking mode of 6 (C atom; green) and 18 (C atom; cyan) within the modelled CFTR

mutant. The most important residues are labelled.



**S19.** Pattern of the most important interactions observed for **31**, **45**, **51** at the NBD1 domain, which have been chosen as potent reference tetrahydropyridopyrimidine correctors based on the most effective substitutions.

Corrector	H-	bonds	π-π stacking			
	Amino acid residues	Ligand portion	Amino acid residues	Ligand portion		
43	G461	Methoxy group	F575	Benzyl moiety		
	K464					
	S573	Piperazine ring				
	N659	Hydroxyl group				
46	G461	Methoxy group	F575	Benzyl moiety		

	K464			
	S573	Piperazine ring		
	T604	Hydroxyl group		
45	T604	methoxy group	F575	Benzyl moiety
	S605			
	N659	Imidazolyl group		
50	T465	Pyridine nitrogen atom	F575	4-F-benzyl moiety
	Q493	Nitrogen atom on linker		
51	T465	Pyridine nitrogen atom	F575	Benzyl moiety
	Q493	Nitrogen atom on linker		

S20. Docking mode of 43 (C atom; green) within the F508del CFTR hNBD1 domain. The most

important residues are labelled.



**S21.** Pattern of the most important interactions observed for **57**, **59**, **65**, **67** and **73** at the NBD1 domain. These compounds have been chosen as potent reference cyanoquinoline correctors based on the most effective substitutions.

Corrector		H-bonds	π-π sta	cking
	Amino acid residues	Ligand portion	Amino acid residues	Ligand portion
57	S573	Carboxamide linker	Y577	Quinoline core
	N659			
	T465	Methoxy group		
	G461			
	K464			
59	N659	Methoxy group	Y577	Quinoline core
	G461			
	K464			
65	G461	Dimethoxy substituted phenyl ring	Y577	Quinoline core

	K464 T465			
	S573	Carboxamide group		
	N659			
67	T465	Methoxy group	Y577	Quinoline core
	S573	Amide group		
	N659			
73	K464	Quinoline nitrogen atom	F575	Nicotinamide ring
	G461			
	T604	Carboxamide group		

S22. Selected docking mode of 65 (C atom; blue) and 73 (C atom; dark green) within the modelled

CFTR. The most important residues are labelled.



# S23. Experimental (Exp.pEC50) and predicted (Pred.pEC50) values of the training set compounds

according to the refined QSAR model A.

Cp.	Exp. pEC <sub>50</sub>	E_nb	ASA-	vsa_pol	CASA+	CASA-	E_ang	Pred. pEC <sub>50</sub>	Residual
3	6.52	40.201546	311.06015	43.506508	1127.1584	786.98218	121.59032	6.24	0.2800
4	6.26	40.071484	295.21408	43.506508	1153.6713	754.27197	122.66916	6.39	-0.1316
5	6.05	39.974373	292.46686	43.506508	1154.363	746.96039	121.56782	6.43	-0.3811
6	5.54	37.910526	281.6275	29.939585	792.55768	580.71594	121.07256	5.47	0.0664
7	5.72	38.121964	305.53513	29.939585	768.17029	622.6806	121.0268	5.20	0.5169
8	5.64	37.865238	282.59271	29.939585	791.71173	582.98877	121.37415	5.47	0.1736
9	5.80	37.621845	236.54544	29.939585	842.57831	492.01453	121.02081	5.92	-0.1225
10	6.05	36.758995	252.77013	29.939585	846.78784	542.69745	122.49203	6.01	0.0352
11	5.54	37.211922	277.50491	29.939585	728.87549	562.22498	120.49342	5.35	0.1880
12	5.31	37.436359	298.69312	29.939585	708.33789	597.98364	120.47495	5.10	0.2088
13	5.09	37.212086	280.57724	29.939585	743.19354	569.01068	120.71957	5.37	-0.2798
15	5.68	35.795937	244.57336	29.939585	795.67621	516.53894	122.20341	5.98	-0.2962
16	5.74	37.433041	230.66957	43.506508	890.95435	525.00391	121.43837	5.75	-0.0125
17	5.64	37.343327	234.04518	43.506508	893.51337	533.62299	121.48071	5.76	-0.1192
18	5.92	38.131062	238.4789	43.506508	966.19189	552.31714	121.81725	5.90	0.0249
23	5.42	35.323212	381.84894	29.939585	698.24213	844.64984	120.17078	5.32	0.0989
24	5.27	35.113384	358.79428	29.939585	723.77502	802.6228	120.48874	5.57	-0.3021

25	5.89	34.822216	308.6485	43.506508	804.03973	757.4234	120.57159	5.84	0.0467
26	5.77	34.670029	308.59375	43.506508	799.9693	756.05463	120.56307	5.84	-0.0710
27	5.40	34.575485	355.2095	29.939585	662.57629	782.17133	119.65387	5.42	-0.0218
30	5.55	82.923752	171.84309	30.614649	1648.9868	370.83737	20.736029	5.68	-0.1298
31	5.85	82.42186	184.62444	48.35714	1847.3866	444.39102	22.800692	5.61	0.2405
32	5.55	106.46642	171.46677	48.35714	2676.562	455.58719	27.980944	5.44	0.1107
37	4.00	144.48102	122.29909	22.730305	3444.0505	287.52515	32.371471	4.37	-0.3663
38	4.00	153.96991	127.36039	17.047728	3526.8616	297.38651	36.52422	3.73	0.2738
39	4.00	147.62102	126.22911	22.730305	3584.5537	293.60892	32.575783	4.36	-0.3587
40	4.00	154.23276	123.18449	17.047728	3532.3589	284.55618	35.389881	3.73	0.2680
41	4.00	158.429	119.46897	19.551485	4025.5757	309.06622	38.373356	4.62	-0.6234
42	4.00	153.73146	153.67113	17.047728	3514.4336	374.03552	36.782146	3.71	0.2902
43	6.40	110.90891	133.17619	33.118404	3017.5261	351.71832	33.262741	6.52	-0.1196
44	5.46	87.505989	170.54222	50.860893	2184.323	448.35553	26.178873	6.06	-0.5979
45	6.70	84.29599	134.07512	30.916637	2102.2649	341.48932	57.236408	6.49	0.2082
46	5.64	111.44763	156.84193	50.860893	3098.0825	451.54794	31.014784	6.08	-0.4432
47	6.52	93.705719	173.39532	33.118404	2326.9932	451.52142	33.383991	6.42	0.0951
49	6.15	86.606331	225.05911	36.297226	1873.995	530.46436	21.122585	5.62	0.5286
50	6.70	74.338272	152.44916	41.979801	1729.2054	368.77454	21.081335	6.62	0.0827
54	6.05	148.64999	98.055092	17.047728	3884.696	228.27225	34.709503	5.37	0.6825
55	4.00	132.28711	164.27565	30.614649	2949.2405	432.04498	31.816795	4.15	-0.1528
56	4.00	123.07984	190.38725	49.064251	2928.6514	488.53369	46.862576	3.77	0.2313
57	5.66	55.075397	237.48724	50.860893	923.78021	500.8606	22.470055	5.35	0.3140
58	4.96	58.179813	234.20871	50.860893	911.40234	502.84613	22.384676	5.06	-0.1031
59	5.52	56.934811	234.43777	50.860893	922.17236	493.72595	22.341722	5.16	0.3606
60	4.00	54.783257	230.61339	54.039715	789.38843	457.07571	20.474987	4.76	-0.7638
61	5.57	51.930538	229.52635	54.039715	774.53314	448.72403	19.566298	5.01	0.5581
62	5.14	50.999371	214.56854	54.039715	781.28369	413.47357	20.403036	5.17	-0.0281
63	4.00	51.904221	252.33662	48.35714	709.98688	475.40222	19.385567	4.85	-0.8527
65	5.82	63.475273	226.01973	53.364651	1141.8444	538.83099	24.826355	5.33	0.4917
66	5.17	57.026089	191.64943	59.72229	882.32562	403.23041	19.090767	4.93	0.2428
67	5.57	60.584358	218.01747	56.543472	1009.9583	490.53931	24.855558	4.98	0.5911
68	5.43	62.59671	226.41823	53.364651	1151.2058	546.57361	23.791538	5.51	-0.0800
70	5.34	58.139511	219.83636	50.860893	882.26208	469.1308	15.243285	5.19	0.1472
71	5.37	57.90588	214.09308	50.860893	880.84534	456.23233	15.861175	5.23	0.1426
73	5.52	54.521137	204.4958	54.039715	790.16455	404.9017	12.876506	5.11	0.4106
74	4.88	52.395954	204.63695	54.039715	747.9267	399.45132	13.675772	5.17	-0.2899
75	4.00	71.220154	226.46532	39.495743	989.84216	478.97415	20.628365	4.45	-0.4482
76	4.00	71.40937	230.99619	39.495743	977.70166	479.77908	22.155819	4.28	-0.2833
77	4.00	71.750427	227.05901	39.495743	986.42834	470.92038	22.093498	4.29	-0.2889
78	4.00	70.656143	224.05431	42.674564	843.64532	437.12994	19.305321	3.78	0.2229
79	4.00	66.774406	216.00131	42.674564	835.51776	415.37051	20.192486	4.16	-0.1615

### S24. Experimental (Exp.pEC50) and predicted (Pred.pEC50) values of the test set compounds according

								Pred.	
Cp.	Exp. pEC50	E_nb	ASA-	vsa_pol	CASA+	CASA-	E_ang	pEC50	Residual
1	5.59	48.448597	381.67267	57.073425	725.31787	1243.8712	108.23756	5.93	-0.3400
2	7.06	53.35915	305.88519	43.506508	1120.5023	774.80719	121.30415	6.65	0.4051
14	5.92	37.931583	304.58237	29.939585	707.73633	608.5556	120.34983	5.41	0.5145
19	5.41	38.162426	238.59331	43.506508	953.86444	551.62775	121.88371	5.85	-0.4416
20	5.30	39.625359	255.47565	57.073425	1019.7084	648.90814	19.199339	5.63	-0.3321
21	5.53	40.260384	255.33957	57.073425	1096.9369	657.75476	19.016466	5.83	-0.3000
22	5.30	40.724495	233.93356	49.189083	1171.973	592.08582	18.133121	5.65	-0.3458
28	5.10	36.033928	246.28993	24.25701	585.13702	430.02222	106.14865	4.32	0.7800
29	5.66	48.590977	206.37631	29.939585	706.36316	397.68716	107.79346	5.34	0.3218
33	5.51	146.15053	133.94344	22.730305	3419.7056	318.91934	30.880795	5.14	0.3719
34	5.82	153.23914	136.87323	17.047728	3544.1233	323.7052	35.1539	5.87	-0.0456
35	4.00	82.230225	180.92363	48.35714	1837.0845	429.87457	25.189426	4.33	-0.3304
36	4.00	106.19363	165.49545	48.35714	2657.3655	434.75656	29.022572	4.38	-0.3754
<b>48</b>	4.00	89.662857	233.99181	30.614649	1898.8805	553.62463	30.238689	4.97	-0.9700
51	6.70	98.400475	154.97318	22.730305	2273.0305	328.85309	26.189623	5.97	0.7289
52	6.70	138.94405	110.62077	17.047728	3588.1072	261.39685	55.438435	6.18	0.5214
53	6.52	158.92085	142.09158	17.047728	3969.3804	352.67133	36.833698	6.42	0.0959
64	5.38	63.195755	223.05199	53.364651	1137.3612	529.30237	24.910639	5.64	-0.2592
69	4.00	61.174698	178.73625	50.860893	932.14954	388.21515	14.915898	4.27	-0.2692
72	4.00	54.135616	218.24225	54.039715	736.79474	438.01221	13.264742	3.96	0.0440

#### to the refined QSAR model A.

**S25.** PCA score plot computed on the data matrix of molecular descriptors and model response. The training set and the test set compounds selected by the Kennard Stone algorithm are represented in black and in red, respectively.

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S26. Experimental (Exp.pEC50) and predicted (Pred.pEC50) values of the training set compounds

according to the refined QSAR model B.

Ср	Exp.							Pred.	Residu
•	pEC <sub>50</sub>	E_nb	ASA-	vsa_pol	CASA+	CASA-	E_ang	pEC <sub>50</sub>	al
1	5.59	48.44859	381.6726	57.07342	725.3178	1243.871	108.2375	5.61	-0.0209
		7	7	5	7	2	6		
2	7.06	53.35915	305.8851	43.50650	1120.502	774.8071	121.3041	5.25	1.8127
			9	8	3	9	5		
3	6.52	40.20154	311.0601	43.50650	1127.158	786.9821	121.5903	6.35	0.1692
		6	5	8	4	8	2		
5	6.05	39.97437	292.4668	43.50650	1154.363	746.9603	121.5678	6.51	-0.4591
		3	6	8		9	2		
9	5.80	37.62184	236.5454	29.93958	842.5783	492.0145	121.0208	5.81	-0.0101
		5	4	5	1	3	1		
10	6.05	36.75899	252.7701	29.93958	846.7878	542.6974	122.4920	6.15	-0.0956
		5	3	5	4	5	3		
11	5.54	37.21192	277.5049	29.93958	728.8754	562.2249	120.4934	5.60	-0.0568
		2	1	5	9	8	2		
12	5.31	37.43635	298.6931	29.93958	708.3378	597.9836	120.4749	5.40	-0.0854
		9	2	5	9	4	5		
13	5.09	37.21208	280.5772	29.93958	743.1935	569.0106	120.7195	5.61	-0.5246
		6	4	5	4	8	7		

14	5.92	37.93158	304.5823	29.93958	707.7363	608.5556	120.3498	5.32	0.6010
		3	7	5	3		3		
15	5.68	35.79593	244.5733	29.93958	795.6762	516.5389	122.2034	6.11	-0.4272
		7	6	5	1	4	1		
18	5.92	38.13106	238.4789	43.50650	966.1918	552.3171	121.8172	6.08	-0.1582
		2		8	9	4	5		
19	5.41	38.16242	238.5933	43.50650	953.8644	551.6277	121.8837	6.04	-0.6319
		6	1	8	4	5	1		
20	5.30	39.6254	255.4757	57.0734	1.019.708	648.9081	19.1993	5.35	-0.0491
					4				
21	5.53	40.2604	255.3396	57.0734	1.096.936	657.7548	19.0165	5.56	-0.0300
					9				
22	5.30	40.7245	233.9336	49.1891	1.171.973	592.0858	18.1331	4.97	0.3346
					0				
23	5.42	35.32321	381.8489	29.93958	698.2421	844.6498	120.1707	5.54	-0.1183
		2	4	5	3	4	8		
26	5.77	34.67002	308.5937	43.50650	799.9693	756.0546	120.5630	5.97	-0.2045
		9	5	8		3	7		
27	5.40	34.57548	355.2095	29.93958	662.5762	782.1713	119.6538	5.61	-0.2125
		5		5	9	3	7		
28	5.10	36.03392	246.2899	24.25701	585.1370	430.0222	106.1486	5.55	-0.4541
		8	3		2	2	5		
29	5.66	8 48.59097	3 206.3763	29.93958	2 706.3631	2 397.6871	5 107.7934	4.98	0.6847
29	5.66	8 48.59097 7	3 206.3763 1	29.93958 5	2 706.3631 6	2 397.6871 6	5 107.7934 6	4.98	0.6847
29 30	5.66	8 48.59097 7 82.92375	3 206.3763 1 171.8430	29.93958 5 30.61464	2 706.3631 6 1648.986	2 397.6871 6 370.8373	5 107.7934 6 20.73602	4.98	0.6847
29 30	5.66	8 48.59097 7 82.92375 2	3 206.3763 1 171.8430 9	29.93958 5 30.61464 9	2 706.3631 6 1648.986 8	2 397.6871 6 370.8373 7	5 107.7934 6 20.73602 9	4.98 5.58	0.6847
29 30 31	5.66 5.55 5.85	8 48.59097 7 82.92375 2 82.42186	3 206.3763 1 171.8430 9 184.6244	29.93958 5 30.61464 9 48.35714	2 706.3631 6 1648.986 8 1847.386	2 397.6871 6 370.8373 7 444.3910	5 107.7934 6 20.73602 9 22.80069	4.98 5.58 5.58	0.6847 -0.0263 0.2712
29 30 31	5.66 5.55 5.85	8 48.59097 7 82.92375 2 82.42186	3 206.3763 1 171.8430 9 184.6244 4	29.93958 5 30.61464 9 48.35714	2 706.3631 6 1648.986 8 1847.386 6	2 397.6871 6 370.8373 7 444.3910 2	5 107.7934 6 20.73602 9 22.80069 2	4.98 5.58 5.58	0.6847 -0.0263 0.2712
29 30 31 32	5.66 5.55 5.85 5.55	8 48.59097 7 82.92375 2 82.42186 106.4664	3 206.3763 1 171.8430 9 184.6244 4 171.4667	29.93958 5 30.61464 9 48.35714 48.35714	2 706.3631 6 1648.986 8 1847.386 6 2676.562	2 397.6871 6 370.8373 7 444.3910 2 455.5871	5 107.7934 6 20.73602 9 22.80069 2 2 27.98094	4.98 5.58 5.58 5.61	0.6847 -0.0263 0.2712 -0.0648
29 30 31 32	5.66 5.55 5.85 5.55	8 48.59097 7 82.92375 2 82.42186 106.4664 2	3 206.3763 1 171.8430 9 184.6244 4 171.4667 7	29.93958 5 30.61464 9 48.35714 48.35714	2 706.3631 6 1648.986 8 1847.386 6 2676.562	2 397.6871 6 370.8373 7 444.3910 2 455.5871 9	5 107.7934 6 20.73602 9 22.80069 2 2 27.98094 4	4.98 5.58 5.58 5.61	0.6847 -0.0263 0.2712 -0.0648
29 30 31 32 34	5.66 5.55 5.85 5.55 5.82	8 48.59097 7 82.92375 2 82.42186 106.4664 2 153.2391	3 206.3763 1 171.8430 9 184.6244 4 171.4667 7 136.8732	29.93958 5 30.61464 9 48.35714 48.35714 17.04772	2 706.3631 6 1648.986 8 1847.386 6 2676.562 3544.123	2 397.6871 6 370.8373 7 444.3910 2 455.5871 9 323.7052	5 107.7934 6 20.73602 9 22.80069 2 2 27.98094 4 35.1539	4.98 5.58 5.58 5.61 4.54	0.6847 -0.0263 0.2712 -0.0648 1.2820
29 30 31 32 34	5.66   5.55   5.85   5.55   5.82	8 48.59097 7 82.92375 2 82.42186 106.4664 2 153.2391 4	3 206.3763 1 171.8430 9 184.6244 4 171.4667 7 136.8732 3	29.93958 5 30.61464 9 48.35714 48.35714 17.04772 8	2 706.3631 6 1648.986 8 1847.386 6 2676.562 3544.123 3	2 397.6871 6 370.8373 7 444.3910 2 455.5871 9 323.7052	5 107.7934 6 20.73602 9 22.80069 2 27.98094 4 35.1539	4.98 5.58 5.58 5.61 4.54	0.6847 -0.0263 0.2712 -0.0648 1.2820
29 30 31 32 34 38	5.66   5.55   5.85   5.55   5.82   4.00	8 48.59097 7 82.92375 2 82.42186 106.4664 2 153.2391 4 153.9699	3 206.3763 1 171.8430 9 184.6244 4 171.4667 7 136.8732 3 127.3603	29.93958 5 30.61464 9 48.35714 48.35714 17.04772 8 17.04772	2 706.3631 6 1648.986 8 1847.386 6 2676.562 3544.123 3 3526.861	2 397.6871 6 370.8373 7 444.3910 2 455.5871 9 323.7052 297.3865	5 107.7934 6 20.73602 9 22.80069 2 27.98094 4 35.1539 36.52422	4.98 5.58 5.58 5.61 4.54 4.43	0.6847 -0.0263 0.2712 -0.0648 1.2820 -0.4326
29 30 31 32 34 38	5.66   5.55   5.85   5.55   5.82   4.00	8 48.59097 7 82.92375 2 82.42186 106.4664 2 153.2391 4 153.9699 1	3 206.3763 1 171.8430 9 184.6244 4 171.4667 7 136.8732 3 127.3603 9	29.93958 5 30.61464 9 48.35714 48.35714 17.04772 8 17.04772 8	2 706.3631 6 1648.986 8 1847.386 6 2676.562 3544.123 3 3526.861 6	2 397.6871 6 370.8373 7 444.3910 2 455.5871 9 323.7052 297.3865 1	5 107.7934 6 20.73602 9 22.80069 2 27.98094 4 35.1539 36.52422	4.98 5.58 5.58 5.61 4.54 4.43	0.6847 -0.0263 0.2712 -0.0648 1.2820 -0.4326
29 30 31 32 34 38 39	5.66   5.55   5.85   5.55   5.82   4.00   4.00	8 48.59097 7 82.92375 2 82.42186 106.4664 2 153.2391 4 153.9699 1 147.6210	3 206.3763 1 171.8430 9 184.6244 4 171.4667 7 136.8732 3 127.3603 9 126.2291	29.93958 5 30.61464 9 48.35714 48.35714 17.04772 8 17.04772 8 22.73030	2 706.3631 6 1648.986 8 1847.386 6 2676.562 3544.123 3 3526.861 6 3584.553	2 397.6871 6 370.8373 7 444.3910 2 455.5871 9 323.7052 297.3865 1 293.6089	5 107.7934 6 20.73602 9 22.80069 2 27.98094 4 35.1539 36.52422 32.57578	4.98 5.58 5.58 5.61 4.54 4.43 4.94	0.6847   -0.0263   0.2712   -0.0648   1.2820   -0.4326   -0.9381
29 30 31 32 34 38 39	5.66   5.55   5.85   5.55   5.82   4.00   4.00	8 48.59097 7 82.92375 2 82.42186 106.4664 2 153.2391 4 153.9699 1 147.6210 2	3 206.3763 1 171.8430 9 184.6244 4 171.4667 7 136.8732 3 127.3603 9 126.2291 1	29.93958 5 30.61464 9 48.35714 48.35714 17.04772 8 17.04772 8 22.73030 5	2 706.3631 6 1648.986 8 1847.386 6 2676.562 3544.123 3 3526.861 6 3584.553 7	2 397.6871 6 370.8373 7 444.3910 2 455.5871 9 323.7052 297.3865 1 293.6089 2	5 107.7934 6 20.73602 9 22.80069 2 27.98094 4 35.1539 36.52422 32.57578 3	4.98 5.58 5.58 5.61 4.54 4.43 4.94	0.6847 -0.0263 0.2712 -0.0648 1.2820 -0.4326 -0.9381
29 30 31 32 34 38 39 41	5.66   5.55   5.85   5.55   5.82   4.00   4.00   4.00	8 48.59097 7 82.92375 2 82.42186 106.4664 2 153.2391 4 153.9699 1 147.6210 2 158.429	3 206.3763 1 171.8430 9 184.6244 4 171.4667 7 136.8732 3 127.3603 9 126.2291 1 119.4689	29.93958 5 30.61464 9 48.35714 48.35714 17.04772 8 17.04772 8 22.73030 5 19.55148	2 706.3631 6 1648.986 8 1847.386 6 2676.562 3544.123 3 3526.861 6 3584.553 7 4025.575	2 397.6871 6 370.8373 7 444.3910 2 455.5871 9 323.7052 297.3865 1 293.6089 2 309.0662	5 107.7934 6 20.73602 9 22.80069 2 27.98094 4 35.1539 36.52422 32.57578 3 38.37335	4.98   5.58   5.58   5.61   4.54   4.43   4.94   5.25	0.6847   -0.0263   0.2712   -0.0648   1.2820   -0.4326   -0.9381   -1.2455
29 30 31 32 34 38 39 41	5.66   5.55   5.85   5.55   5.82   4.00   4.00   4.00	8 48.59097 7 82.92375 2 82.42186 106.4664 2 153.2391 4 153.9699 1 147.6210 2 158.429	3 206.3763 1 171.8430 9 184.6244 4 171.4667 7 136.8732 3 127.3603 9 126.2291 1 119.4689 7	29.93958 5 30.61464 9 48.35714 48.35714 17.04772 8 17.04772 8 22.73030 5 19.55148 5	2 706.3631 6 1648.986 8 1847.386 6 2676.562 3544.123 3 3526.861 6 3584.553 7 4025.575 7	2 397.6871 6 370.8373 7 444.3910 2 455.5871 9 323.7052 297.3865 1 293.6089 2 309.0662 2	5 107.7934 6 20.73602 9 22.80069 2 2 27.98094 4 35.1539 36.52422 32.57578 3 38.37335 6	4.98   5.58   5.58   5.61   4.54   4.43   4.94   5.25	0.6847   -0.0263   0.2712   -0.0648   1.2820   -0.4326   -0.9381   -1.2455
29 30 31 32 34 38 39 41 42	5.66   5.55   5.85   5.55   5.82   4.00   4.00   4.00   4.00   4.00	8     48.59097     7     82.92375     2     82.42186     106.4664     2     153.2391     4     153.9699     1     147.6210     2     158.429     153.7314	3 206.3763 1 171.8430 9 184.6244 4 171.4667 7 136.8732 3 127.3603 9 126.2291 1 119.4689 7 153.6711	29.93958 5 30.61464 9 48.35714 48.35714 17.04772 8 17.04772 8 22.73030 5 19.55148 5 17.04772	2 706.3631 6 1648.986 8 1847.386 6 2676.562 3544.123 3 3526.861 6 3584.553 7 4025.575 7	2 397.6871 6 370.8373 7 444.3910 2 455.5871 9 323.7052 297.3865 1 293.6089 2 309.0662 2 374.0355	5 107.7934 6 20.73602 9 22.80069 2 27.98094 4 35.1539 36.52422 32.57578 3 38.37335 6 36.78214	4.98   5.58   5.58   5.61   4.54   4.43   4.94   5.25   4.41	0.6847   -0.0263   0.2712   -0.0648   1.2820   -0.4326   -0.9381   -1.2455   -0.4097
29 30 31 32 34 38 39 41 42	5.66   5.55   5.85   5.55   5.82   4.00   4.00   4.00   4.00	8 48.59097 7 82.92375 2 82.42186 106.4664 2 153.2391 4 153.9699 1 147.6210 2 158.429 153.7314 6	3 206.3763 1 171.8430 9 184.6244 4 171.4667 7 136.8732 3 127.3603 9 126.2291 1 119.4689 7 153.6711 3	29.93958 5 30.61464 9 48.35714 48.35714 17.04772 8 17.04772 8 22.73030 5 19.55148 5 17.04772 8	2 706.3631 6 1648.986 8 1847.386 6 2676.562 3544.123 3 3526.861 6 3584.553 7 4025.575 7 3514.433 6	2 397.6871 6 370.8373 7 444.3910 2 455.5871 9 323.7052 297.3865 1 293.6089 2 309.0662 2 374.0355 2	5 107.7934 6 20.73602 9 22.80069 2 27.98094 4 35.1539 36.52422 32.57578 3 38.37335 6 38.37335 6	4.98   5.58   5.58   5.61   4.54   4.43   4.94   5.25   4.41	0.6847   -0.0263   0.2712   -0.0648   1.2820   -0.4326   -0.9381   -1.2455   -0.4097
29 30 31 32 34 38 39 41 42 43	5.66   5.55   5.85   5.55   5.82   4.00   4.00   4.00   4.00   4.00   4.00   4.00   4.00   4.00   4.00   4.00   4.00	8 48.59097 7 82.92375 2 82.42186 106.4664 2 153.2391 4 153.9699 1 147.6210 2 158.429 153.7314 6 110.9089	3 206.3763 1 171.8430 9 184.6244 4 171.4667 7 136.8732 3 127.3603 9 126.2291 1 119.4689 7 153.6711 3 133.1761	29.93958 5 30.61464 9 48.35714 48.35714 48.35714 17.04772 8 17.04772 8 22.73030 5 19.55148 5 17.04772 8 33.11840	2 706.3631 6 1648.986 8 1847.386 6 2676.562 3544.123 3 3526.861 6 3584.553 7 4025.575 7 3514.433 6 3017.526	2 397.6871 6 370.8373 7 444.3910 2 455.5871 9 323.7052 2 97.3865 1 293.6089 2 309.0662 2 309.0662 2 374.0355 2 351.7183	5 107.7934 6 20.73602 9 22.80069 2 27.98094 4 35.1539 36.52422 36.52422 32.57578 3 38.37335 6 38.37335 6 36.78214 6 33.26274	4.98   5.58   5.58   5.61   4.54   4.43   4.94   5.25   4.41   6.55	0.6847   -0.0263   0.2712   -0.0648   1.2820   -0.4326   -0.9381   -1.2455   -0.4097   -0.1504

44	5.46	87.50598	170.5422	50.86089	2184.323	448.3555	26.17887	6.01	-0.5489
		9	2	3		3	3		
45	6.70	84.29599	134.0751	30.91663	2102.264	341.4893	57.23640	6.46	0.2391
			2	7	9	2	8		
46	5.64	111.4476	156.8419	50.86089	3098.082	451.5479	31.01478	6.22	-0.5776
		3	3	3	5	4	4		
47	6.52	93.70571	173.3953	33.11840	2326.993	451.5214	33.38399	6.33	0.1853
		9	2	4	2	2	1		
48	4.00	89.66285	233.9918	30.61464	1898.880	553.6246	30.23868	5.44	-1.4435
		7	1	9	5	3	9		
49	6.15	86.60633	225.0591	36.29722	1873.995	530.4643	21.12258	5.57	0.5850
		1	1	6		6	5		
50	6.70	74.33827	152.4491	41.97980	1729.205	368.7745	21.08133	6.34	0.3561
		2	6	1	4	4	5		
51	6.70	98.40047	154.9731	22.73030	2273.030	328.8530	26.18962	5.94	0.7553
		5	8	5	5	9	3		
52	6.70	138.9440	110.6207	17.04772	3588.107	261.3968	55.43843	5.69	1.0133
		5	7	8	2	5	5		
53	6.52	158.9208	142.0915	17.04772	3969.380	352.6713	36.83369	5.07	1.4543
		5	8	8	4	3	8		
54	6.05	148.6499	98.05509	17.04772	3884.696	228.2722	34.70950	5.80	0.2471
		9	2	8		5	3		
55	4.00	132.2871	164.2756	30.61464	2949.240	432.0449	31.81679	4.64	-0.6378
		1	5	9	5	8	5		
56	4.00	123.0798	190.3872	49.06425	2928.651	488.5336	46.86257	4.42	-0.4237
		4	5	1	4	9	6		
57	5.66	55.07539	237.4872	50.86089	923.7802	500.8606	22.47005	5.21	0.4507
		7	4	3	1		5		
59	5.52	56.93481	234.4377	50.86089	922.1723	493.7259	22.34172	5.06	0.4595
		1	7	3	6	5	2		
61	5.57	51.93053	229.5263	54.03971	774.5331	448.7240	19.56629	4.92	0.6509
		8	5	5	4	3	8		
62	5.14	50.99937	214.5685	54.03971	781.2836	413.4735	20.40303	5.05	0.0896
		1	4	5	9	7	6		
64	5.38	63.19575	223.0519	53.36465	1137.361	529.3023	24.91063	5.24	0.1396
		5	9	1	2	7	9		
65	5.82	63.47527	226.0197	53.36465	1141.844	538.8309	24.82635	5.23	0.5890
		3	3	1	4	9	5		
66	5.17	57.02608	191.6494	59.72229	882.3256	403.2304	19.09076	4.87	0.3011
		9	3		2	1	7		
67	5.57	60.58435	218.0174	56.54347	1009.958	490.5393	24.85555	4.94	0.6261
1		8	7	2	3	1	8		

68	5.43	62.59671	226.4182	53.36465	1151.205	546.5736	23.79153	5.37	0.0599
			3	1	8	1	8		
69	4.00	61.17469	178.7362	50.86089	932.1495	388.2151	14.91589	5.11	-1.1142
		8	5	3	4	5	8		
71	5.37	57.90588	214.0930	50.86089	880.8453	456.2323	15.86117	5.08	0.2940
			8	3	4	3	5		
72	4.00	54.13561	218.2422	54.03971	736.7947	438.0122	13.26474	4.83	-0.8345
		6	5	5	4	1	2		
73	5.52	54.52113	204.4958	54.03971	790.1645	404.9017	12.87650	4.97	0.5528
		7		5	5		6		
74	4.88	52.39595	204.6369	54.03971	747.9267	399.4513	13.67577	5.01	-0.1328
		4	5	5		2	2		
75	4.00	71.22015	226.4653	39.49574	989.8421	478.9741	20.62836	4.48	-0.4822
		4	2	3	6	5	5		
76	4.00	71.40937	230.9961	39.49574	977.7016	479.7790	22.15581	4.36	-0.3586
			9	3	6	8	9		
79	4.00	66.77440	216.0013	42.67456	835.5177	415.3705	20.19248	4.24	-0.2422
		6	1	4	6	1	6		

# **S27.** Experimental (Exp.pEC50) and predicted (Pred.pEC50) values of the test set compounds according

# to the refined QSAR model B.

								Pred.	
Cp.	Exp. pEC <sub>50</sub>	E_nb	ASA-	vsa_pol	CASA+	CASA-	E_ang	pEC50	Residual
4	6.26	40.071484	295.21408	43.506508	1153.6713	754.27197	122.66916	6.48	-0.2219
6	5.54	37.910526	281.6275	29.939585	792.55768	580.71594	121.07256	5.70	-0.1649
7	5.72	38.121964	305.53513	29.939585	768.17029	622.6806	121.0268	5.49	0.2333
8	5.64	37.865238	282.59271	29.939585	791.71173	582.98877	121.37415	5.70	-0.0602
16	5.74	37.433041	230.66957	43.506508	890.95435	525.00391	121.43837	5.95	-0.2126
17	5.64	37.343327	234.04518	43.506508	893.51337	533.62299	121.48071	5.96	-0.3180
24	5.27	35.113384	358.79428	29.939585	723.77502	802.6228	120.48874	5.74	-0.4730
25	5.89	34.822216	308.6485	43.506508	804.03973	757.4234	120.57159	5.98	-0.0867
33	5.51	146.15053	133.94344	22.730305	3419.7056	318.91934	30.880795	4.72	0.7905
35	4.00	82.230225	180.92363	48.35714	1837.0845	429.87457	25.189426	4.53	-0.5273
36	4.00	106.19363	165.49545	48.35714	2657.3655	434.75656	29.022572	5.17	-1.1682
37	4.00	144.48102	122.29909	22.730305	3444.0505	287.52515	32.371471	4.92	-0.9154
40	4.00	154.23276	123.18449	17.047728	3532.3589	284.55618	35.389881	4.43	-0.4347
58	4.96	58.179813	234.20871	50.860893	911.40234	502.84613	22.384676	4.98	-0.0186
60	4.00	54.783257	230.61339	54.039715	789.38843	457.07571	20.474987	4.73	-0.7267
63	4.00	51.904221	252.33662	48.35714	709.98688	475.40222	19.385567	4.78	-0.7768

70	5.34	58.139511	219.83636	50.860893	882.26208	469.1308	15.243285	5.05	0.2946
77	4.00	71.750427	227.05901	39.495743	986.42834	470.92038	22.093498	4.36	-0.3648
78	4.00	70.656143	224.05431	42.674564	843.64532	437.12994	19.305321	3.93	0.0680
80	4.00	65.905418	207.23102	42.674564	843.74304	392.70279	19.777443	4.36	-0.3568

S28. Distribution of the experimental (Exp.pEC50) potency values of the test set compounds with respect to the E\_nb and CASA<sup>+</sup> (Å<sup>2</sup>) descriptors. All the test set correctors are reported as magenta crosses.



**S29.** Distribution of the experimental (Exp.pEC<sub>50</sub>) potency values of the hybrids included in the training set with respect to the E\_ang (Kcal/mol). ASA- (Å<sup>2</sup>) and CASA- (Å<sup>2</sup>). descriptors. Hybrid derivatives are reported as cyan spheres.



**S30.** Distribution of the experimental (Exp.pEC<sub>50</sub>) potency values of the tetrahydropyridopyrimidines included in the training set with respect to the ASA- (Å<sup>2</sup>) and CASA- (Å<sup>2</sup>) and vsa\_pol descriptors. Tetrahydropyridopyrimidine derivatives are reported as orange spheres.

