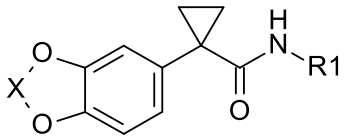
International Journal of
Molecular Sciences

MDPI

SUPPLEMENTARY MATERIALS

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



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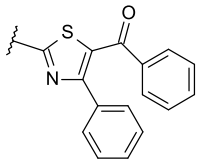
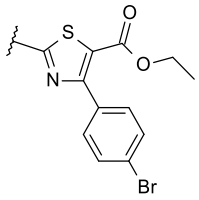
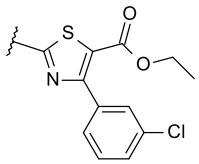
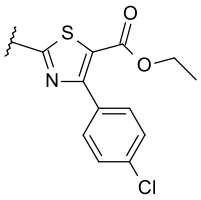
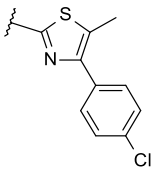
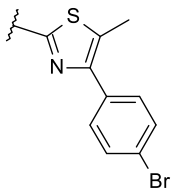
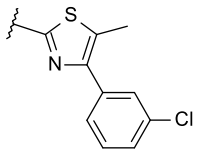
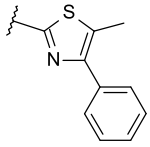
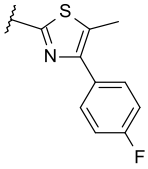
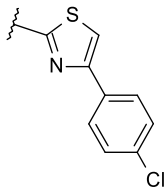
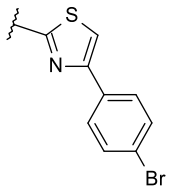
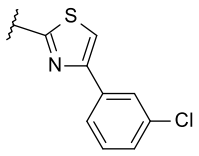
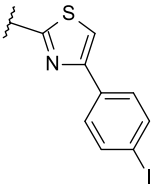
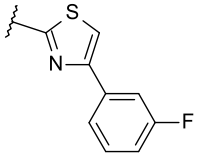
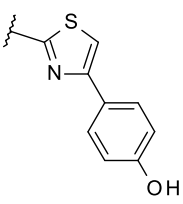
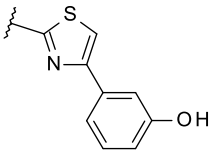
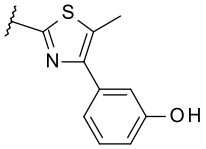
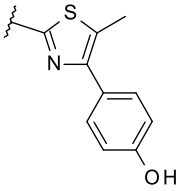
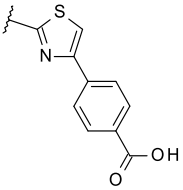
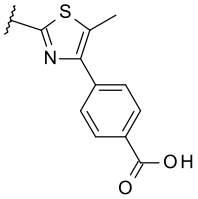
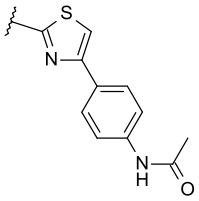
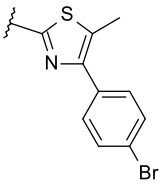
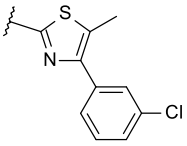
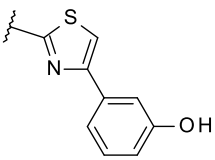
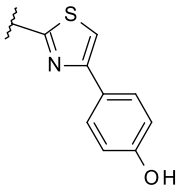
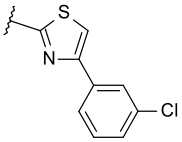
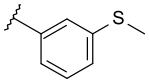
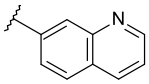
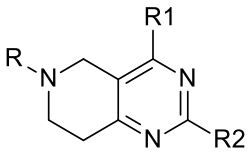
2	-CH_2		7.06
3	-CH_2		6.52
4	-CH_2		6.26
5	-CH_2		6.05
6	-CH_2		5.54
7	-CH_2		5.72

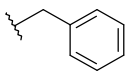
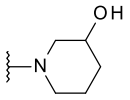
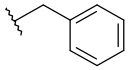
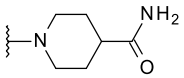
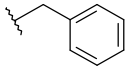
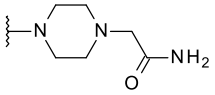
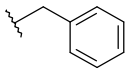
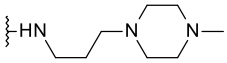
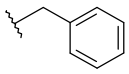
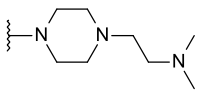
8	-CH_2		5.64
9	-CH_2		5.80
10	-CH_2		6.05
11	-CH_2		5.54
12	-CH_2		5.31
13	-CH_2		5.09
14	-CH_2		5.92
15	-CH_2		5.68
16	-CH_2		5.74

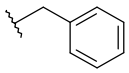
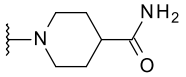
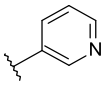
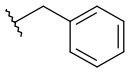
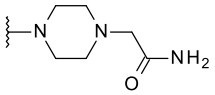
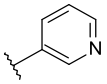
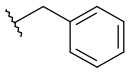
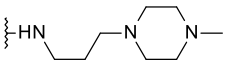
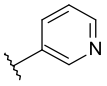
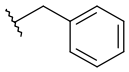
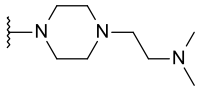
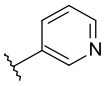
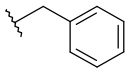
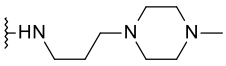
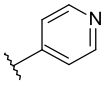
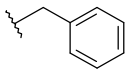
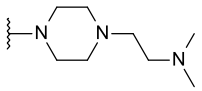
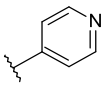
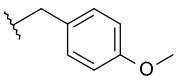
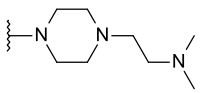
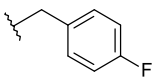
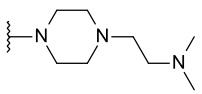
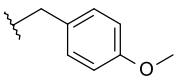
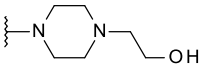
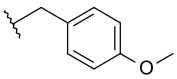
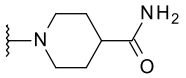
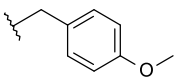
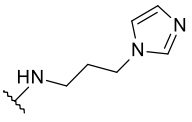
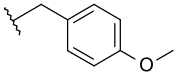
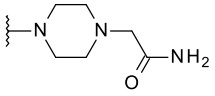
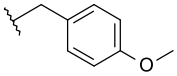
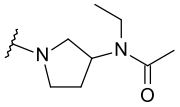
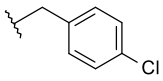
17	-CH_2		5.64
18	-CH_2		5.92
19	-CH_2		5.41
20	-CH_2		5.30
21	-CH_2		5.53
22	-CH_2		5.30
23	-CF_2		5.42
24	-CF_2		5.27
25	-CF_2		5.89

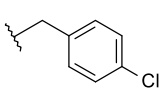
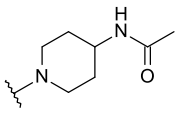
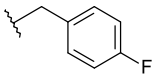
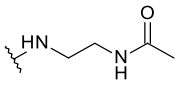
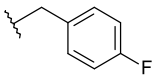
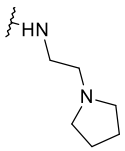
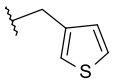
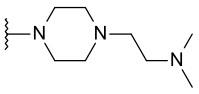
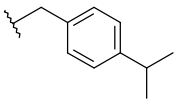
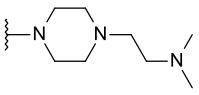
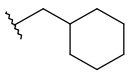
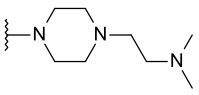
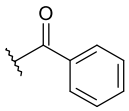
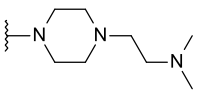
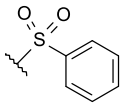
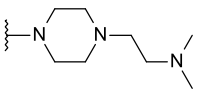
26	-CF_2		5.77
27	-CF_2		5.40
28	-CH_2		5.10
29	-CH_2		5.66

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

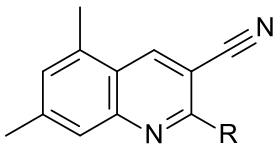


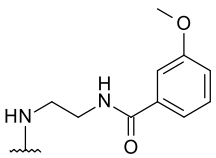
Cp.	R	R_1	R_2	pEC_{50}
30				5.55
31				5.85
32				5.55
33				5.51
34				5.82

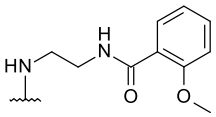
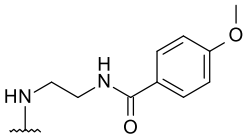
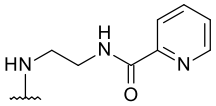
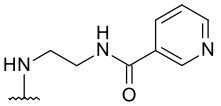
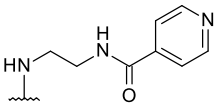
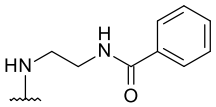
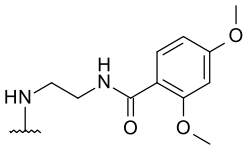
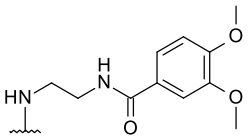
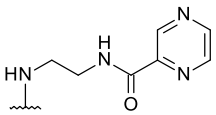
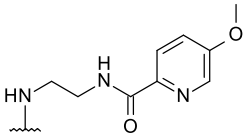
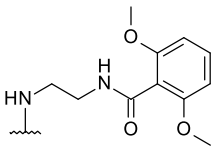
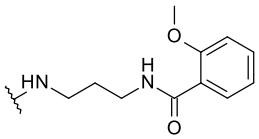
35				4.00
36				4.00
37				4.00
38				4.00
39				4.00
40				4.00
41				4.00
42				4.00
43				6.40
44				5.46
45				6.70
46				5.64
47				6.52
48				4.00

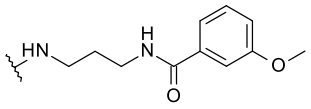
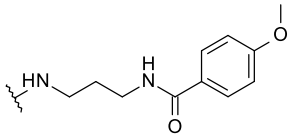
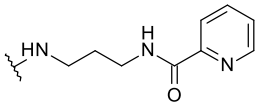
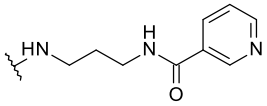
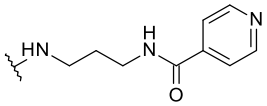
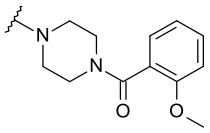
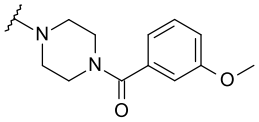
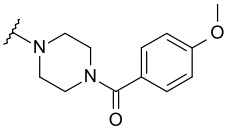
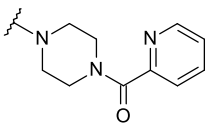
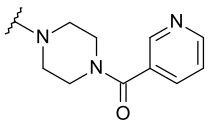
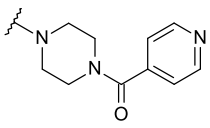
49				6.15
50				6.70
51				6.70
52				6.70
53				6.52
54				6.05
55				4.00
56				4.00

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

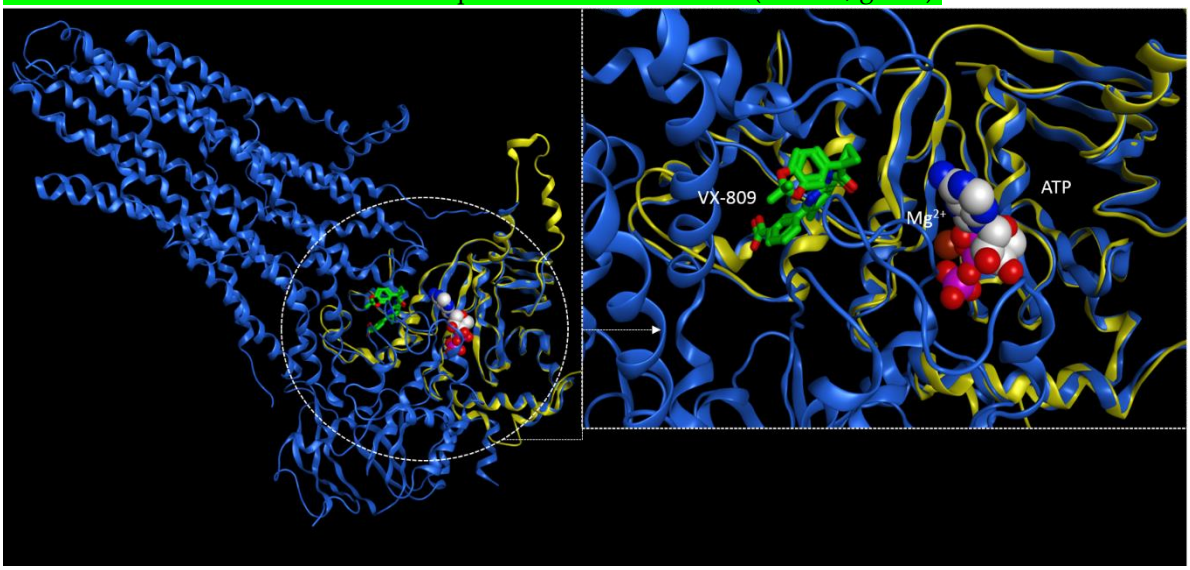


Cp.	R	pEC_{50}
57		5.66

58		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

70		5.34
71		5.37
72		4.00
73		5.52
74		4.88
75		4.00
76		4.00
77		4.00
78		4.00
79		4.00
80		4.00

S4. (*left*) Superimposition of the modelled F508del-CFTR (*blu*) onto the 4WZ6 pdb code (*yellow*) is shown. (*right*)A detail of the comparison is depicted. Mg^{2+} and ATP are reported in spacefill mode while the docked VX-809 at the whole protein is shown in stick (*C* atom; green).



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

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

S6. Binding affinity values obtained by molecular docking studies of hybrid correctors.

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

hNBD1/(*CFTR*)-**6**	-14.0	*-12.0*	-21.1282	*-23.0777*
hNBD1/(*CFTR*)-**7**	-10.0	*-13.0*	-21.3208	*-23.0264*
hNBD1/(*CFTR*)-**8**	-15.0	*-17.0*	-19.6742	*-23.5280*
hNBD1/(*CFTR*)-**9**	-16.0	*-18.0*	-19.2015	*-22.9820*
hNBD1/(*CFTR*)-**10**	-14.0	*-12.0*	-21.3407	*-22.7400*
hNBD1/(*CFTR*)-**11**	-14.0	*-16.0*	-22.1238	*-22.0175*
hNBD1/(*CFTR*)-**12**	-15.0	*-17.0*	-20.4414	*-21.9677*
hNBD1/(*CFTR*)-**13**	-14.0	*-12.0*	-21.5660	*-22.6050*
hNBD1/(*CFTR*)-**14**	-17.0	*-19.0*	-21.9788	*-22.3278*
hNBD1/(*CFTR*)-**15**	-16.0	*-14.0*	-21.4102	*-22.9320*
hNBD1/(*CFTR*)-**16**	-17.0	*-19.0*	-20.5806	*-24.5206*
hNBD1/(*CFTR*)-**17**	-14.0	*-16.0*	-19.8188	*-25.1833*
hNBD1/(*CFTR*)-**18**	-15.0	*-13.0*	-20.4794	*-25.7335*
hNBD1/(*CFTR*)-**19**	-12.0	*-10.0*	-20.1269	*-25.5958*
hNBD1/(*CFTR*)-**20**	-13.0	*-15.0*	-20.3380	*-34.2077*
hNBD1/(*CFTR*)-**21**	-16.0	*-18.0*	-19.6181	*-33.4221*
hNBD1/(*CFTR*)-**22**	-14.0	*-16.0*	-18.7362	*-30.3549*
hNBD1/(*CFTR*)-**23**	-14.0	*-12.0*	-17.4095	*-22.7536*
hNBD1/(*CFTR*)-**24**	-16.0	*-18.0*	-16.1613	*-23.1016*
hNBD1/(*CFTR*)-**25**	-10.0	*-12.0*	-22.8956	*-25.9998*

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

S7. Binding affinity values obtained by molecular docking studies of tetrahydropyridopyrimidines.

S8. Binding affinity values obtained by molecular docking studies of cyanoquinolines.

hNBD1/(*CFTR*)-Corrector Complex (LeadIT)	**Binding Affinity Energy ΔG (kJ/mol)**		**Score**	
hNBD1/(*CFTR*)-**30**	-20.0	*-18.0*	-25.6464	*-27.9264*
hNBD1/(*CFTR*)-**31**	-20.0	*-22.0*	-23.1906	*-31.3780*
hNBD1/(*CFTR*)-**32**	-11.0	*-13.0*	-14.2103	*-27.0360*
hNBD1/(*CFTR*)-**33**	-14.0	*-16.0*	-17.9342	*-24.8135*
hNBD1/(*CFTR*)-**34**	-20.0	*-18.0*	-20.2775	*-31.9695*
hNBD1/(*CFTR*)-**35**	-19.0	*-17.0*	-20.9774	*-27.0538*
hNBD1/(*CFTR*)-**36**	-16.0	*-18.0*	-18.8641	*-25.6758*
hNBD1/(*CFTR*)-**37**	-19.0	*-20.0*	-20.8618	*-26.0331*
hNBD1/(*CFTR*)-**38**	-20.0	*-18.0*	-20.1370	*-25.3469*
hNBD1/(*CFTR*)-**39**	-19.0	*-16.0*	-19.8917	*-25.2137*
hNBD1/(*CFTR*)-**40**	-20.0	*-18.0*	-21.4913	*-28.9089*

hNBD1/(*CFTR*)-**47**	-19.0	*-19.0*	-11.9737	*-35.2083*
hNBD1/(*CFTR*)-**48**	-16.0	*-14.0*	-12.9443	*-29.0503*
hNBD1/(*CFTR*)-**49**	-18.0	*-16.0*	-20.2496	*-24.0340*
hNBD1/(*CFTR*)-**50**	-18.0	*-20.0*	-19.2769	*-30.9983*
hNBD1/(*CFTR*)-**51**	-16.0	*-18.0*	-19.3884	*-30.5294*
hNBD1/(*CFTR*)-**52**	-18.0	*-16.0*	-20.9675	*-36.8329*
hNBD1/(*CFTR*)-**53**	-20.0	*-18.0*	-18.8290	*-29.3976*
hNBD1/(*CFTR*)-**54**	-16.0	*-14.0*	-18.8705	*-25.1832*
hNBD1/(*CFTR*)-**79**	-14.0	*-16.0*	-15.4790	*-24.1680*
hNBD1/(*CFTR*)-**50**	-17.0	*-12.0*	-14.1205	*-28.0889*
hNBD1/(*CFTR*)-**57**	-18.0	*-16.0*	-16.6125	*-25.9090*
hNBD1/(*CFTR*)-**58**	-17.0	*-15.0*	-22.9060	*-23.8393*
hNBD1/(*CFTR*)-**59**	-19.0	*-17.0*	-22.3538	*-28.0070*
hNBD1/(*CFTR*)-**80**	-18.0	*-16.0*	-20.6065	*-28.6991*
hNBD1/(*CFTR*)-**55**	-9.0	-11.0	-10.1093	*-33.5767*
hNBD1/(*CFTR*)-**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_{50}).

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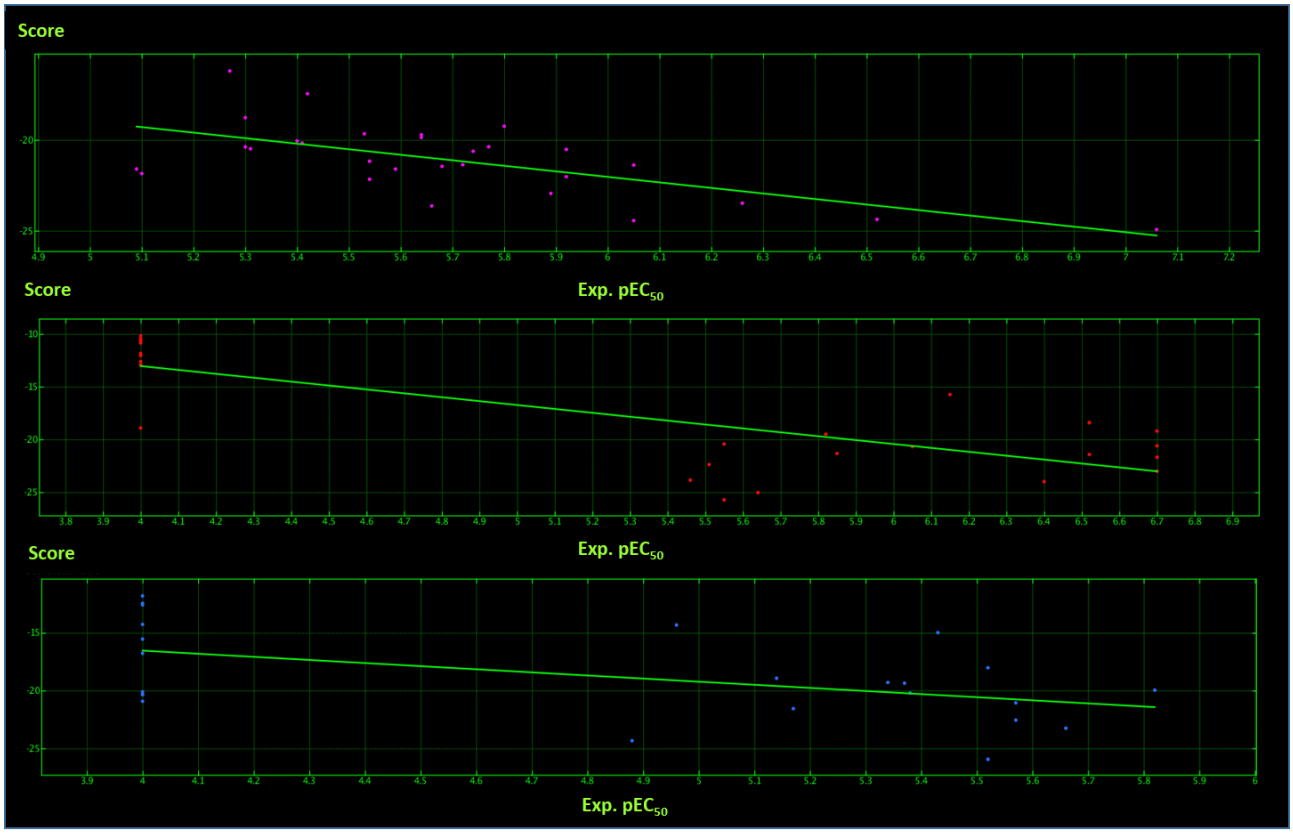
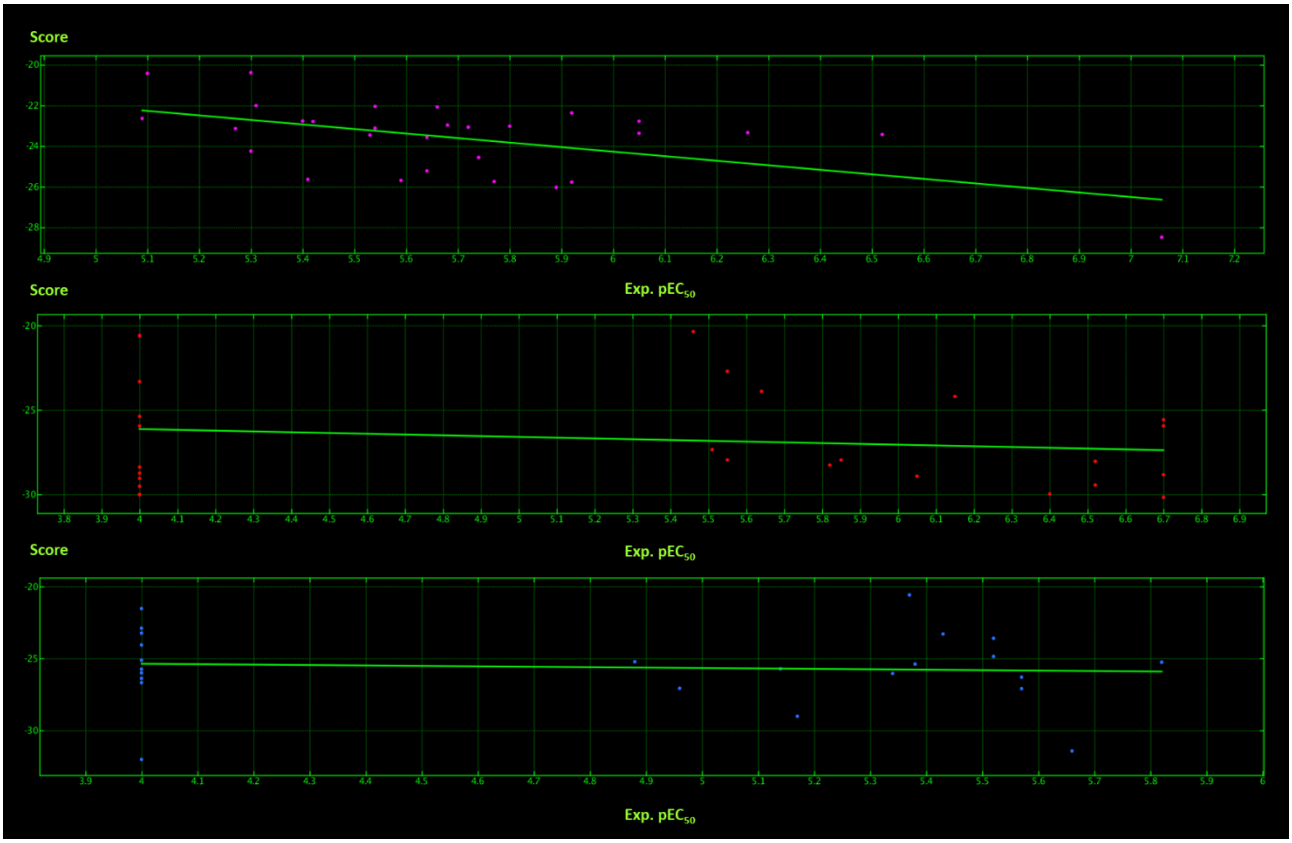
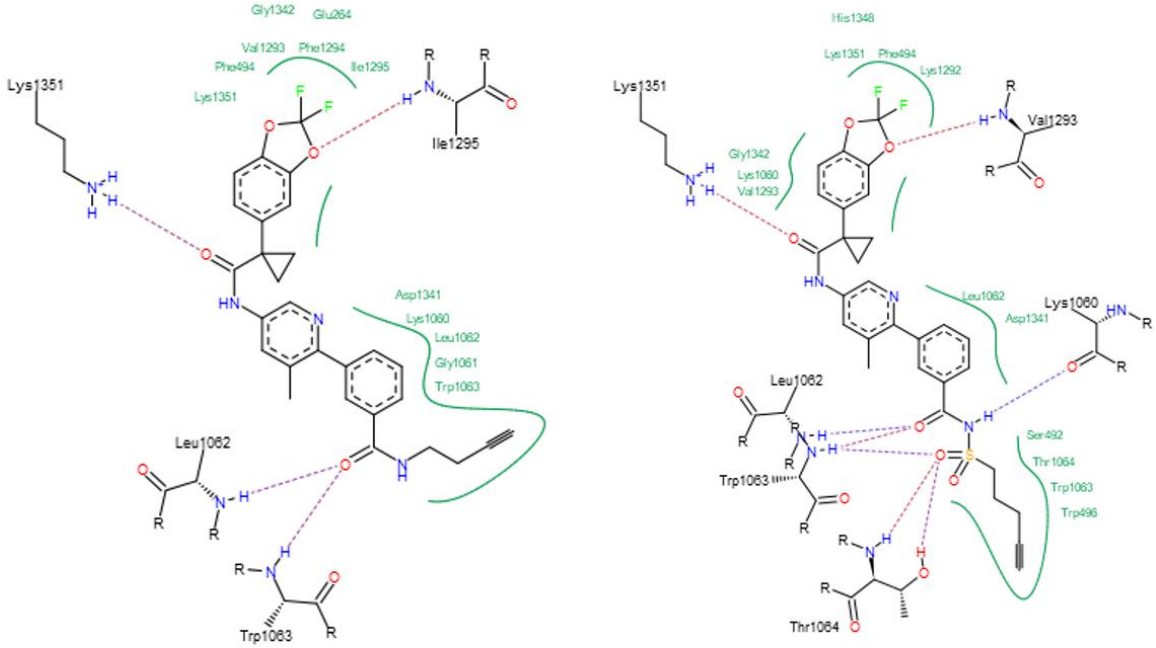


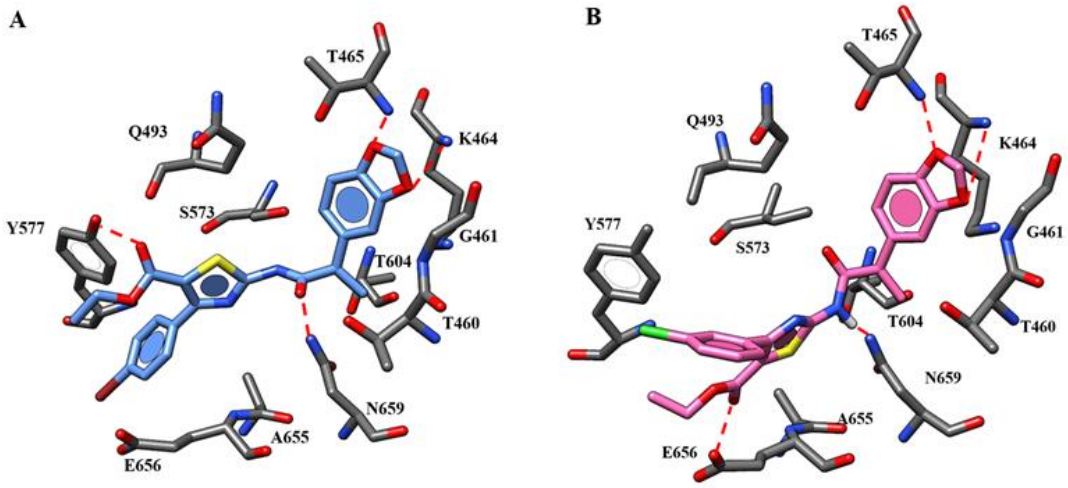
S10. Distribution of the score value obtained by the molecular docking at the modelled F508del-CFTR, concerning the VX-809 analogues (magenta dots), tetrahydropyridopyrimidines (red dots) and cyanoquinolines (cyan dots) with respect to their experimental potency values (Exp.pEC$_{50}$).



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.

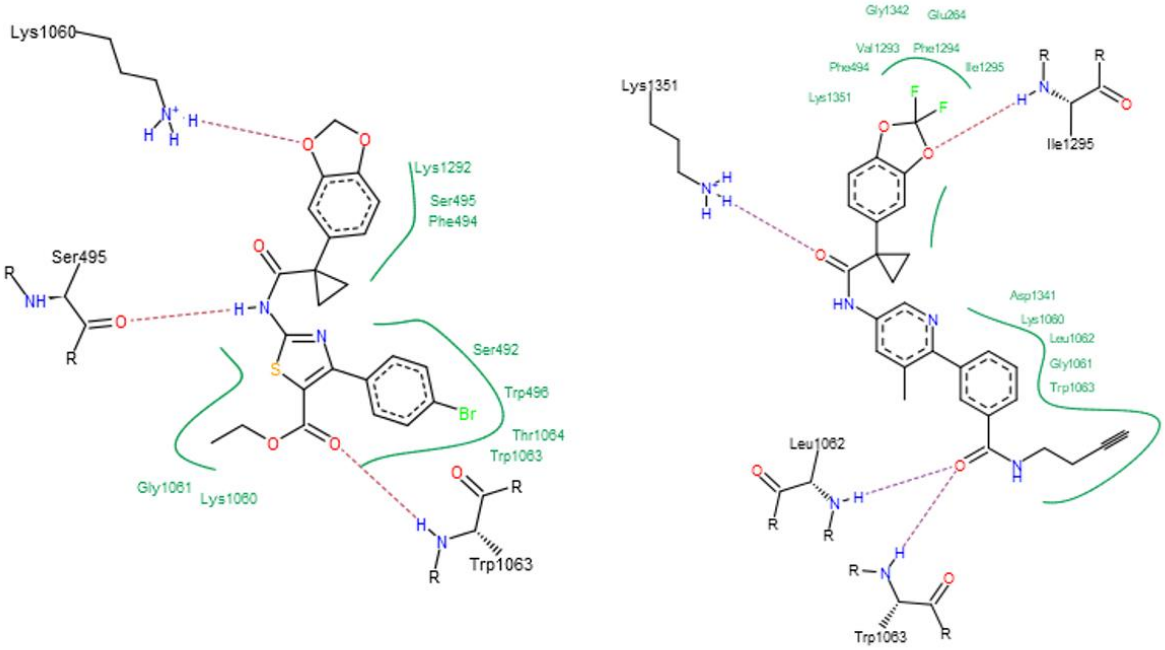


S13. Pattern of the most important interactions observed for **2**, **3**, **10** chosen as potent reference derivatives based on the substituent at the position five of the thiazole as putative NBD1-targeting correctors.

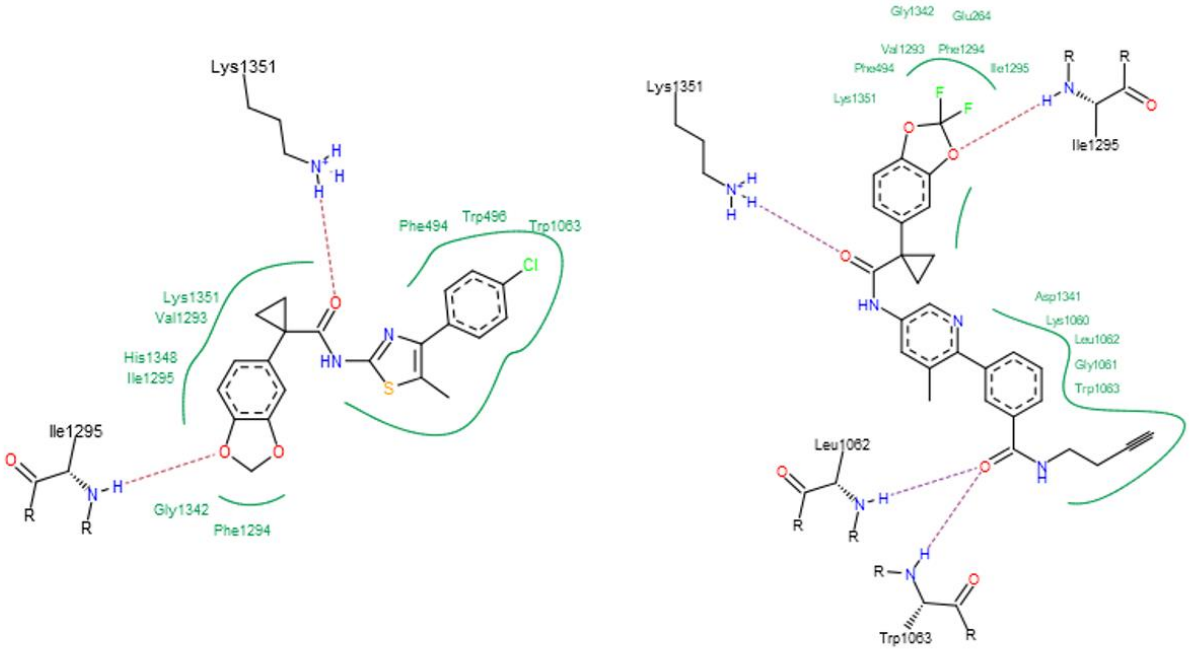
Corrector	H-bonds		π-π stacking	
	Amino acid residues	Ligand portion	Amino acid residues	Ligand portion
2	N659	Carboxamide moiety	Y577	Benzoyl moiety
	K464 T465	Benzodioxole moiety		

3	K464 T465	Benzodioxole moiety	Y577	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 K464	Benzodioxole moiety	Y577	p-F-phenyl ring
	N659	Carboxamide group		

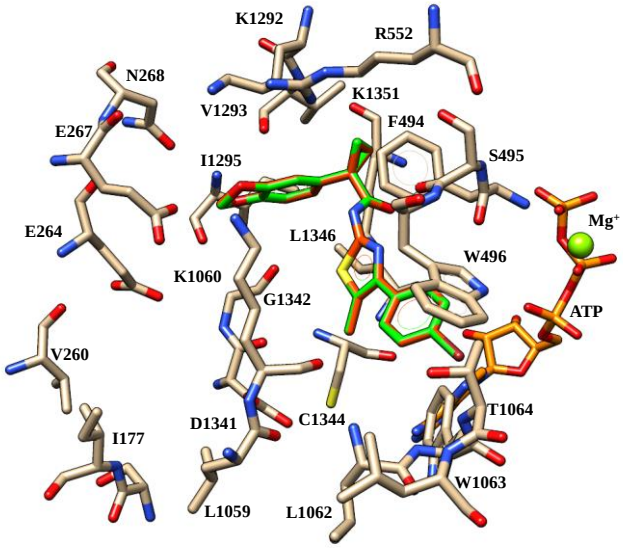
S14. Ligplot of the most relevant key contacts detected by LeadIT software concerning the docking mode of **3** compared to VX-809 at the modelled F508del-CFTR.



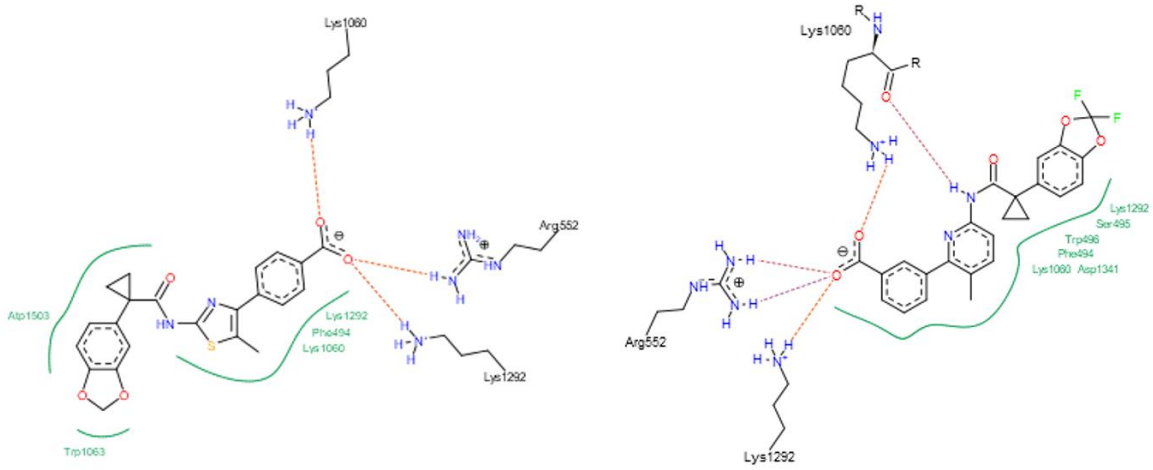
S15. Ligplot of the most relevant key contacts detected by LeadIT software concerning the docking mode of **6** compared to ALK-809 at the modelled F508del-CFTR.



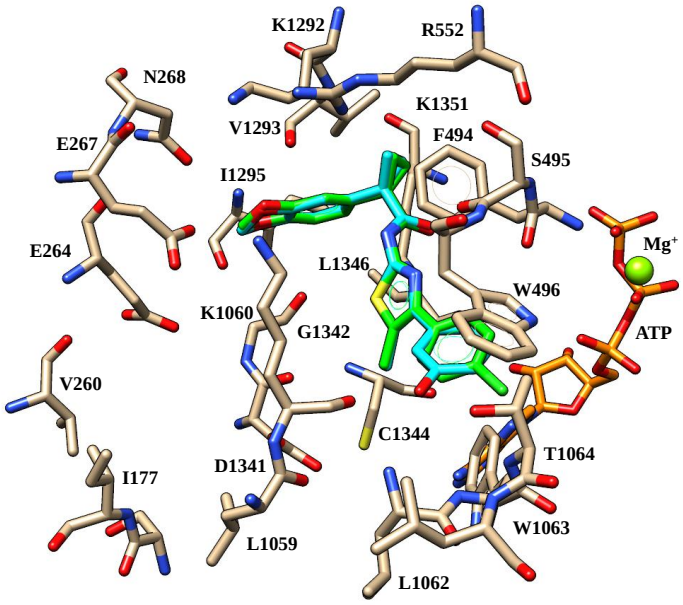
S16. Selected docking mode of **6** (*C* atom; green) and **7** (*C* atom; orange) within the modelled CFTR. The most important residues are labelled.



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.

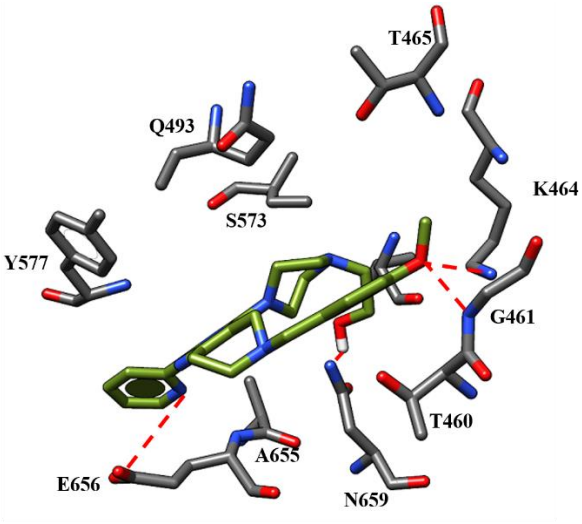


S19. Pattern of the most important interactions observed for **31**, **45**, **51** at the NBD1 domain, which have been chosen as potent reference tetrahydropyridopyrimidine correctors based on the most effective substitutions.

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

	K464			
	S573	Piperazine ring		
	T604	Hydroxyl group		
45	T604 S605	methoxy group	F575	Benzyl moiety
	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 *h*NBD1 domain. The most important residues are labelled.

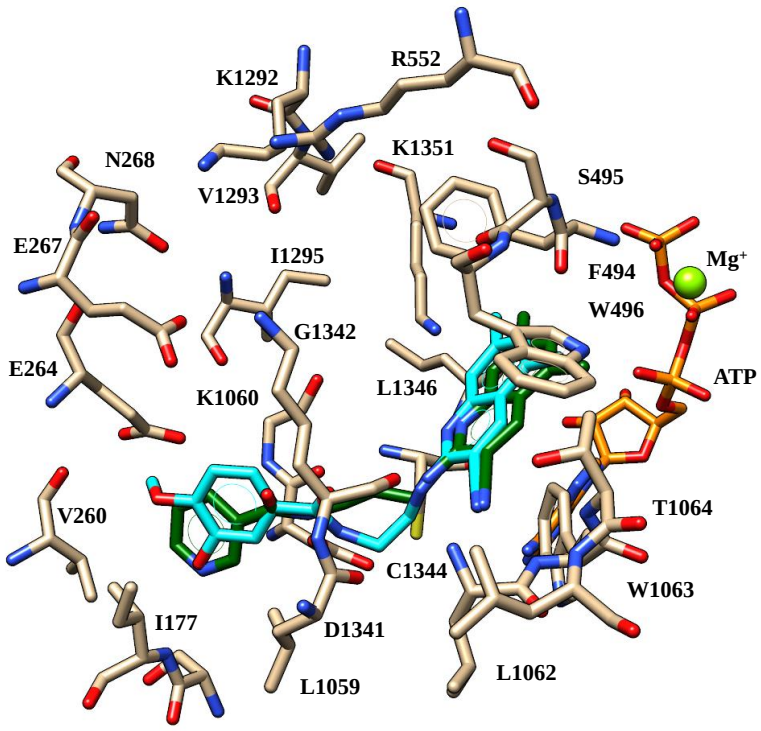


S21. Pattern of the most important interactions observed for **57**, **59**, **65, 67** and **73** at the NBD1 domain. These compounds have been chosen as potent reference cyanoquinoline correctors based on the most effective substitutions.

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

	K464 T465			
	S573 N659	Carboxamide group		
67	T465	Methoxy group	Y577	Quinoline core
	S573 N659	Amide group		
73	K464 G461	Quinoline nitrogen atom	F575	Nicotinamide ring
	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.pEC$_{50}$) and predicted (Pred.pEC$_{50}$) values of the training set compounds according to the refined QSAR model A.

Cp.	Exp. pEC$_{50}$	E_nb	ASA-	vsa_pol	CASA+	CASA-	E_ang	Pred. pEC$_{50}$	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

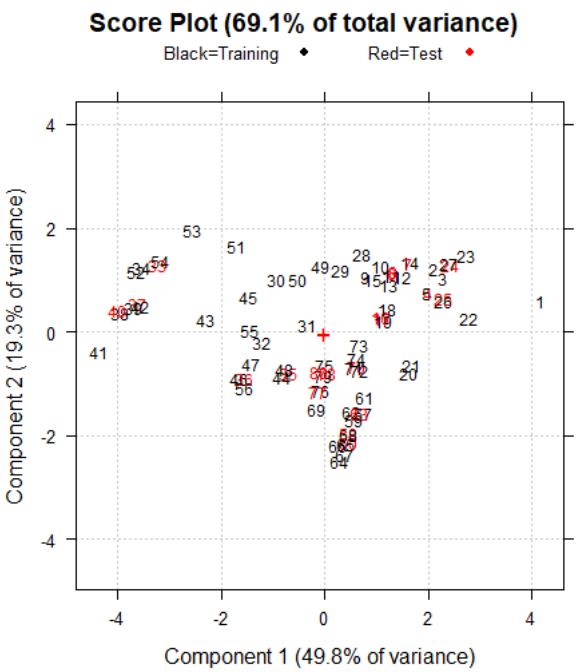
25	5.89	34.822216	308.6485	43.506508	804.03973	757.4234	120.57159	5.84	0.0467
26	5.77	34.670029	308.59375	43.506508	799.9693	756.05463	120.56307	5.84	-0.0710
27	5.40	34.575485	355.2095	29.939585	662.57629	782.17133	119.65387	5.42	-0.0218
30	5.55	82.923752	171.84309	30.614649	1648.9868	370.83737	20.736029	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

80	4.00	65.905418	207.23102	42.674564	843.74304	392.70279	19.777443	4.30	-0.3036

S24. Experimental (Exp.pEC$_{50}$) and predicted (Pred.pEC$_{50}$) values of the test set compounds according to the refined QSAR model A.

Cp.	**Exp. pEC$_{50}$**	**E_nb**	**ASA-**	**vsa_pol**	**CASA+**	**CASA-**	**E_ang**	**Pred. pEC$_{50}$**	**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
48	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

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.



S26. Experimental (Exp.pEC$_{50}$) and predicted (Pred.pEC$_{50}$) values of the training set compounds according to the refined QSAR model B.

Cp.	Exp. pEC$_{50}$	E_nb	ASA-	vsa_pol	CASA+	CASA-	E_ang	Pred. pEC$_{50}$	Residual
1	5.59	48.448597	381.67267	57.073425	725.31787	1243.8712	108.23756	5.61	-0.0209
2	7.06	53.35915	305.88519	43.506508	1120.5023	774.80719	121.30415	5.25	1.8127
3	6.52	40.201546	311.06015	43.506508	1127.1584	786.98218	121.59032	6.35	0.1692
5	6.05	39.974373	292.46686	43.506508	1154.363	746.96039	121.56782	6.51	-0.4591
9	5.80	37.621845	236.54544	29.939585	842.57831	492.01453	121.02081	5.81	-0.0101
10	6.05	36.758995	252.77013	29.939585	846.78784	542.69745	122.49203	6.15	-0.0956
11	5.54	37.211922	277.50491	29.939585	728.87549	562.22498	120.49342	5.60	-0.0568
12	5.31	37.436359	298.69312	29.939585	708.33789	597.98364	120.47495	5.40	-0.0854
13	5.09	37.212086	280.57724	29.939585	743.19354	569.01068	120.71957	5.61	-0.5246

14	5.92	37.931583	304.58237	29.939585	707.73633	608.5556	120.34983	5.32	0.6010
15	5.68	35.795937	244.57336	29.939585	795.67621	516.53894	122.20341	6.11	-0.4272
18	5.92	38.131062	238.4789	43.506508	966.19189	552.31714	121.81725	6.08	-0.1582
19	5.41	38.162426	238.59331	43.506508	953.86444	551.62775	121.88371	6.04	-0.6319
20	5.30	39.6254	255.4757	57.0734	1.019.7084	648.9081	19.1993	5.35	-0.0491
21	5.53	40.2604	255.3396	57.0734	1.096.9369	657.7548	19.0165	5.56	-0.0300
22	5.30	40.7245	233.9336	49.1891	1.171.9730	592.0858	18.1331	4.97	0.3346
23	5.42	35.323212	381.84894	29.939585	698.24213	844.64984	120.17078	5.54	-0.1183
26	5.77	34.670029	308.59375	43.506508	799.9693	756.05463	120.56307	5.97	-0.2045
27	5.40	34.575485	355.2095	29.939585	662.57629	782.17133	119.65387	5.61	-0.2125
28	5.10	36.033928	246.28993	24.25701	585.13702	430.02222	106.14865	5.55	-0.4541
29	5.66	48.590977	206.37631	29.939585	706.36316	397.68716	107.79346	4.98	0.6847
30	5.55	82.923752	171.84309	30.614649	1648.9868	370.83737	20.736029	5.58	-0.0263
31	5.85	82.42186	184.62444	48.35714	1847.3866	444.39102	22.800692	5.58	0.2712
32	5.55	106.46642	171.46677	48.35714	2676.562	455.58719	27.980944	5.61	-0.0648
34	5.82	153.23914	136.87323	17.047728	3544.1233	323.7052	35.1539	4.54	1.2820
38	4.00	153.96991	127.36039	17.047728	3526.8616	297.38651	36.52422	4.43	-0.4326
39	4.00	147.62102	126.22911	22.730305	3584.5537	293.60892	32.575783	4.94	-0.9381
41	4.00	158.429	119.46897	19.551485	4025.5757	309.06622	38.373356	5.25	-1.2455
42	4.00	153.73146	153.67113	17.047728	3514.4336	374.03552	36.782146	4.41	-0.4097
43	6.40	110.90891	133.17619	33.118404	3017.5261	351.71832	33.262741	6.55	-0.1504

44	5.46	87.505989	170.54222	50.860893	2184.323	448.35553	26.178873	6.01	-0.5489
45	6.70	84.29599	134.07512	30.916637	2102.2649	341.48932	57.236408	6.46	0.2391
46	5.64	111.44763	156.84193	50.860893	3098.0825	451.54794	31.014784	6.22	-0.5776
47	6.52	93.705719	173.39532	33.118404	2326.9932	451.52142	33.383991	6.33	0.1853
48	4.00	89.662857	233.99181	30.614649	1898.8805	553.62463	30.238689	5.44	-1.4435
49	6.15	86.606331	225.05911	36.297226	1873.995	530.46436	21.122585	5.57	0.5850
50	6.70	74.338272	152.44916	41.979801	1729.2054	368.77454	21.081335	6.34	0.3561
51	6.70	98.400475	154.97318	22.730305	2273.0305	328.85309	26.189623	5.94	0.7553
52	6.70	138.94405	110.62077	17.047728	3588.1072	261.39685	55.438435	5.69	1.0133
53	6.52	158.92085	142.09158	17.047728	3969.3804	352.67133	36.833698	5.07	1.4543
54	6.05	148.64999	98.055092	17.047728	3884.696	228.27225	34.709503	5.80	0.2471
55	4.00	132.28711	164.27565	30.614649	2949.2405	432.04498	31.816795	4.64	-0.6378
56	4.00	123.07984	190.38725	49.064251	2928.6514	488.53369	46.862576	4.42	-0.4237
57	5.66	55.075397	237.48724	50.860893	923.78021	500.8606	22.470055	5.21	0.4507
59	5.52	56.934811	234.43777	50.860893	922.17236	493.72595	22.341722	5.06	0.4595
61	5.57	51.930538	229.52635	54.039715	774.53314	448.72403	19.566298	4.92	0.6509
62	5.14	50.999371	214.56854	54.039715	781.28369	413.47357	20.403036	5.05	0.0896
64	5.38	63.195755	223.05199	53.364651	1137.3612	529.30237	24.910639	5.24	0.1396
65	5.82	63.475273	226.01973	53.364651	1141.8444	538.83099	24.826355	5.23	0.5890
66	5.17	57.026089	191.64943	59.72229	882.32562	403.23041	19.090767	4.87	0.3011
67	5.57	60.584358	218.01747	56.543472	1009.9583	490.53931	24.855558	4.94	0.6261

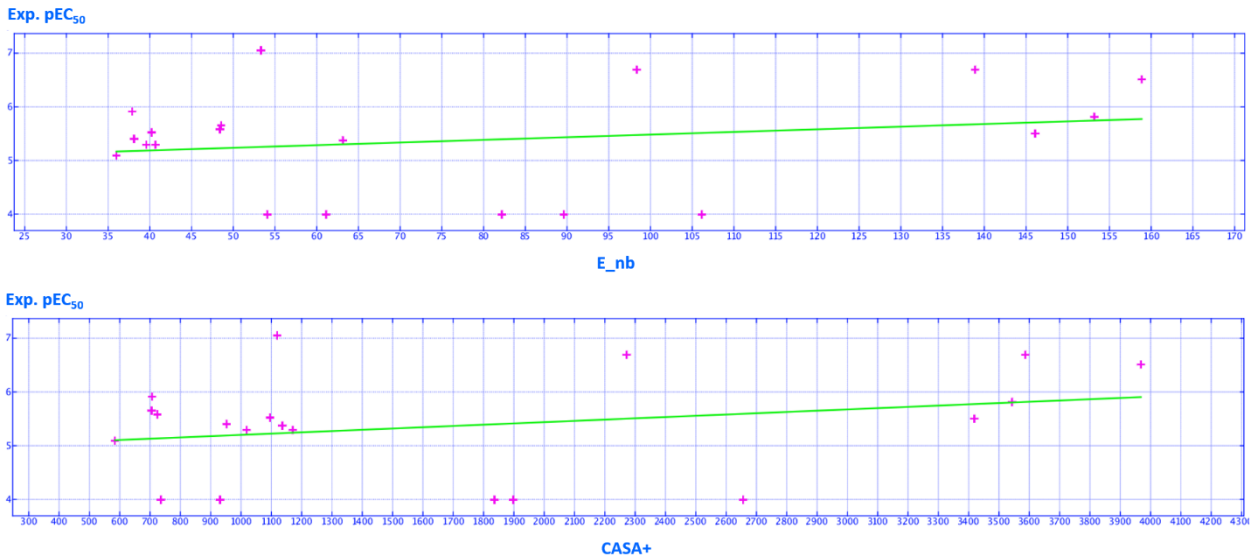
68	5.43	62.59671	226.41823	53.364651	1151.2058	546.57361	23.791538	5.37	0.0599
69	4.00	61.174698	178.73625	50.860893	932.14954	388.21515	14.915898	5.11	-1.1142
71	5.37	57.90588	214.09308	50.860893	880.84534	456.23233	15.861175	5.08	0.2940
72	4.00	54.135616	218.24225	54.039715	736.79474	438.01221	13.264742	4.83	-0.8345
73	5.52	54.521137	204.4958	54.039715	790.16455	404.9017	12.876506	4.97	0.5528
74	4.88	52.395954	204.63695	54.039715	747.9267	399.45132	13.675772	5.01	-0.1328
75	4.00	71.220154	226.46532	39.495743	989.84216	478.97415	20.628365	4.48	-0.4822
76	4.00	71.40937	230.99619	39.495743	977.70166	479.77908	22.155819	4.36	-0.3586
79	4.00	66.774406	216.00131	42.674564	835.51776	415.37051	20.192486	4.24	-0.2422

S27. Experimental (Exp.pEC_{50}) and predicted (Pred.pEC_{50}) values of the test set compounds according to the refined QSAR model B.

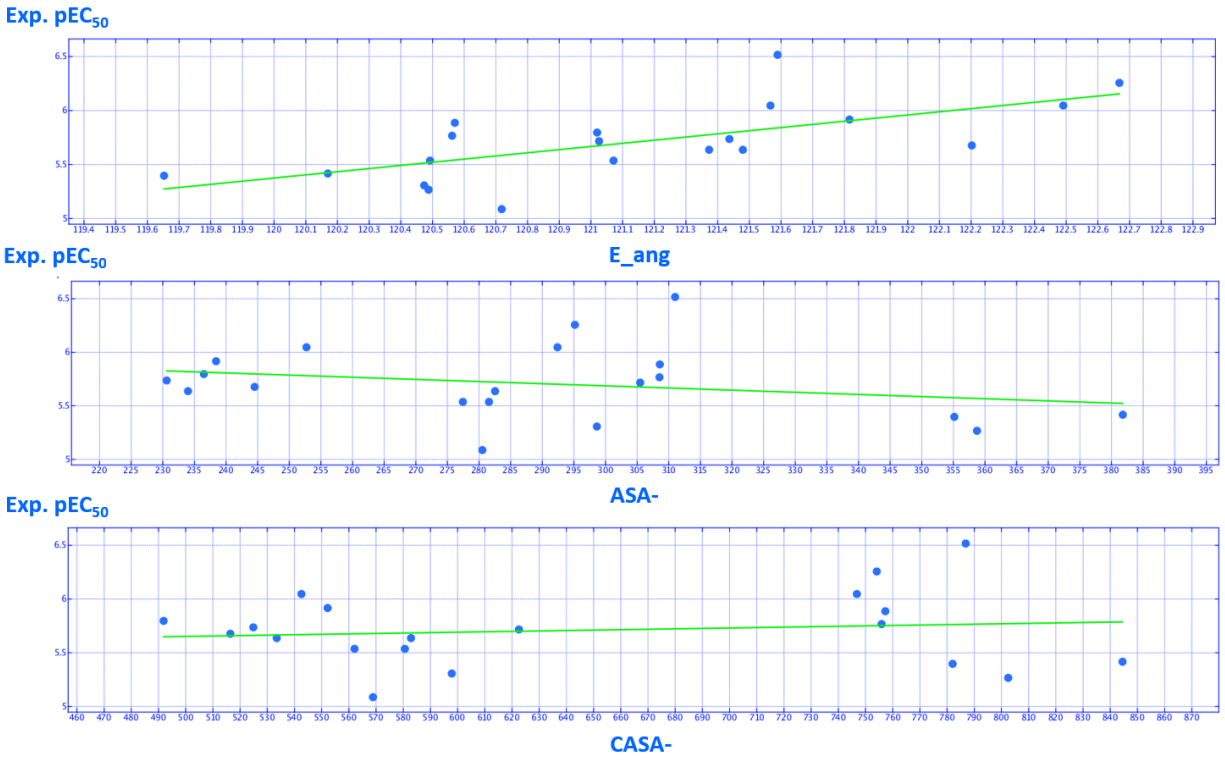
Cp.	**Exp. pEC_{50}**	**E_nb**	**ASA-**	**vsa_pol**	**CASA+**	**CASA-**	**E_ang**	**Pred. pEC_{50}**	**Residual**
4	6.26	40.071484	295.21408	43.506508	1153.6713	754.27197	122.66916	6.48	-0.2219
6	5.54	37.910526	281.6275	29.939585	792.55768	580.71594	121.07256	5.70	-0.1649
7	5.72	38.121964	305.53513	29.939585	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.pEC$_{50}$) potency values of the test set compounds with respect to the E_nb and CASA^{+} (Å^2) descriptors. All the test set correctors are reported as magenta crosses.



S29. Distribution of the experimental (Exp.pEC$_{50}$) potency values of the hybrids included in the training set with respect to the E_ang (Kcal/mol). ASA- (Å^2) and CASA- (Å^2). descriptors. Hybrid derivatives are reported as cyan spheres.



S30. Distribution of the experimental (Exp.pEC50) potency values of the tetrahydropyridopyrimidines included in the training set with respect to the ASA- (Å²) and CASA- (Å²) and vsa_pol descriptors. Tetrahydropyridopyrimidine derivatives are reported as orange spheres.