How Good is Jarzynski's Equality for Computer-Aided Drug Design?

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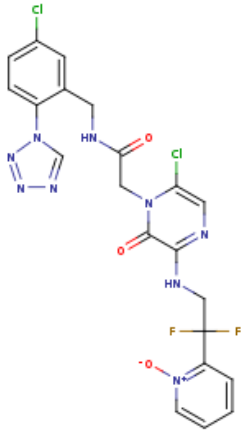
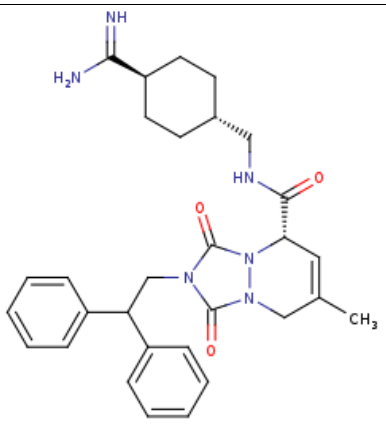
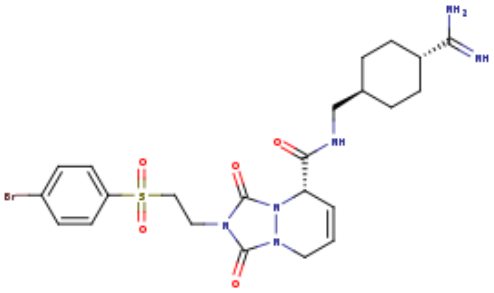
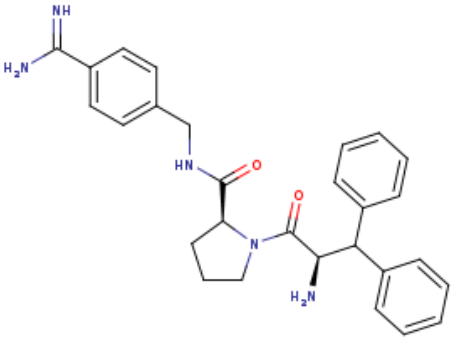
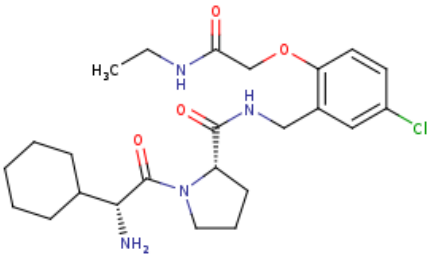
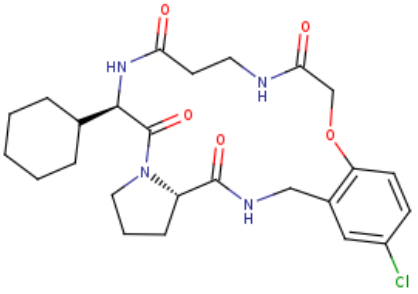
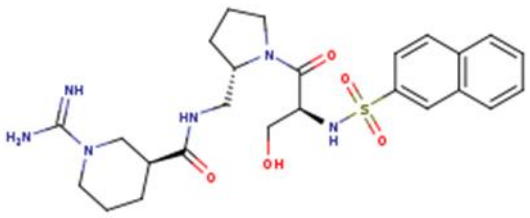
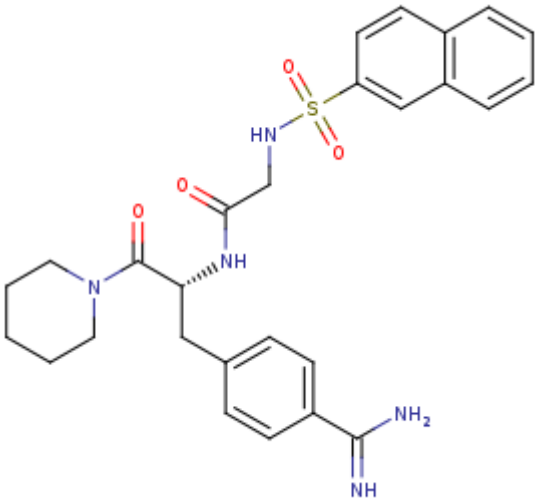
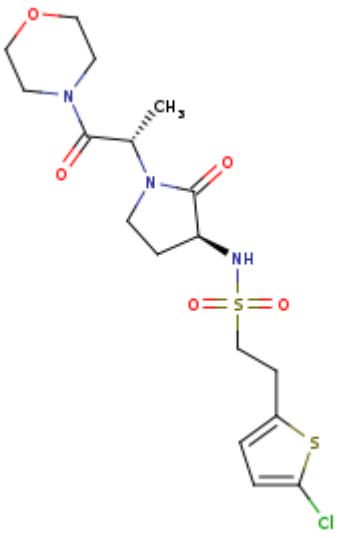
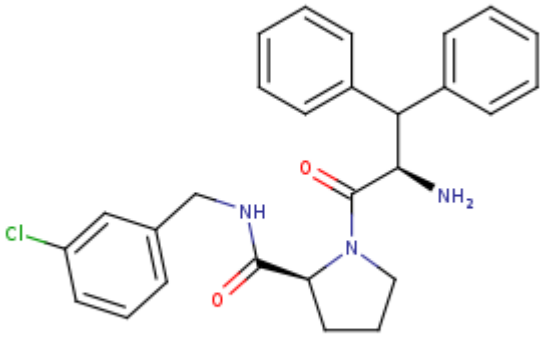
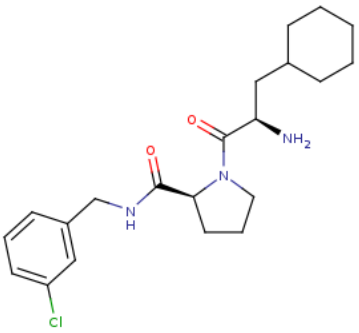
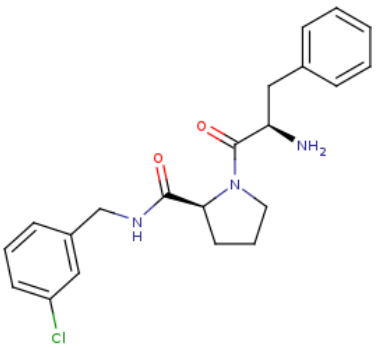
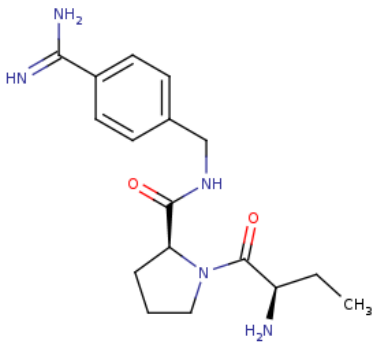
Supporting informartion

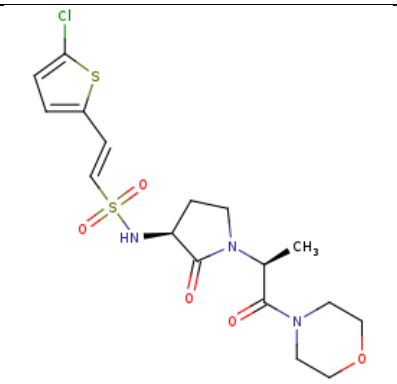
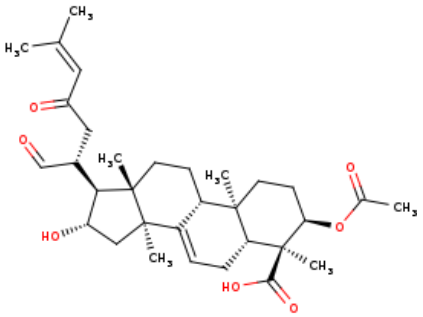
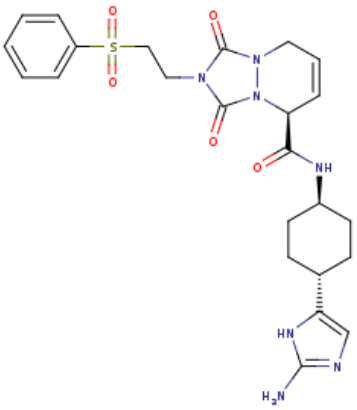
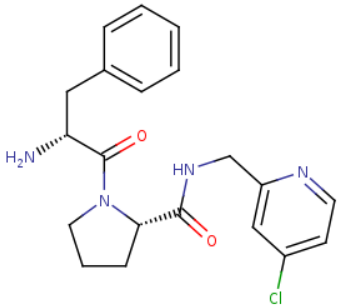
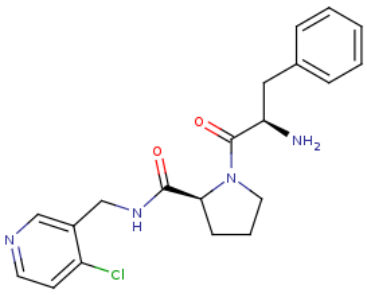
Table S1 - Inhibition constant, molecular weight, chemical formula and 2D structure of the 23 studied ligands of thrombin. Their ID is given in the third column, while the second column refers to PDB ID of their complex with thrombin protein.

No.	PDB ID	Ligand ID	Inhibition constant Ki (nM)	Molecular weight (g/mol)	Chemical formular	2D structure
1	1SL3	170	0.0014 [1]	552.32	$C_{21}H_{17}Cl_2F_2N_9O_3$	
2	1C4V	IH2	0.016 [2]	528.64	$C_{30}H_{36}N_6O_3$	

3	1C4U	IH1	0.043 [2]	581.48	$C_{23}H_{29}BrN_6O_5S$	
4	2ZO3	33U	0.1 [3]	469.58	$C_{28}H_{31}N_5O_2$	
5	1TA6	177	0.74 [4]	479.01	$C_{24}H_{35}Cl\ N_4O_4$	
6	1NT1	T76	1.3 [5]	505.01	$C_{25}H_{33}C_lN_4O_5$	

7	1BMN	BM9	3.6 [6]	530.64	$C_{25}H_{34}N_6O_5S$	
8	1ETS	MID	6 [7]	521.63	$C_{27}H_{31}N_5O_4S$	
9	2JH6	894	17 [8]	449.97	$C_{17}H_{24}ClN_3O_5S_2$	

10	3DHK	23U	47 [3]	461.98	$C_{27}H_{28}ClN_3O_2$	
11	3DUX	64U	100 [3]	391.94	$C_{21}H_{30}ClN_3O_2$	
12	2ZC9	22U	180 [3]	385.89	$C_{21}H_{24}ClN_3O_2$	
13	2ZGX	29U	180 [3]	331.41	$C_{17}H_{25}N_5O_2$	

14	2JH5	895	367 [8]	447.96	$C_{17}H_{22}ClN_3O_5S_2$	
15	1AWH	GR3	830 [9]	542.70	$C_{32}H_{46}O_7$	
16	1D6W	00R	1100 [2]	527.60	$C_{24}H_{29}N_7O_5S$	
17	3SHC	B01	1900 [10]	386.88	$C_{20}H_{23}ClN_4O_2$	
18	3SHA	P97	2600 [10]	386.88	$C_{20}H_{23}ClN_4O_2$	

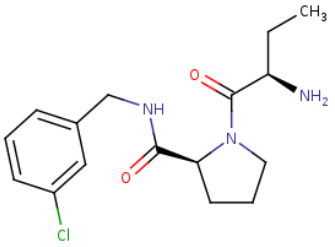
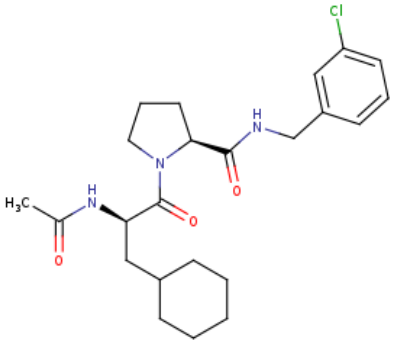
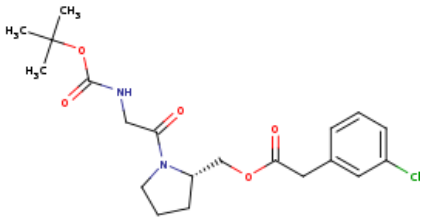
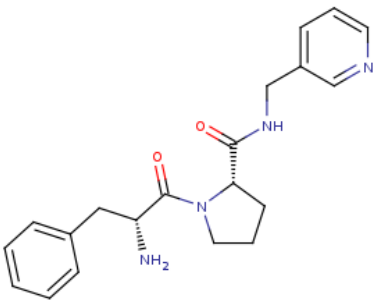
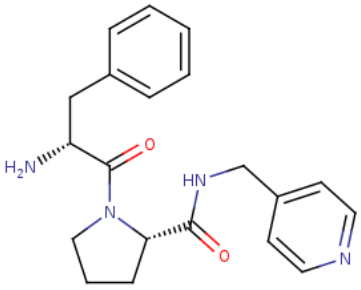
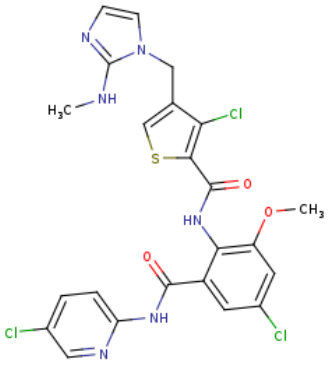
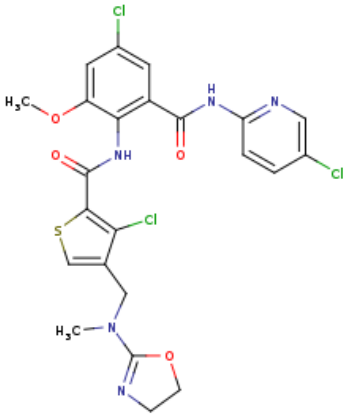
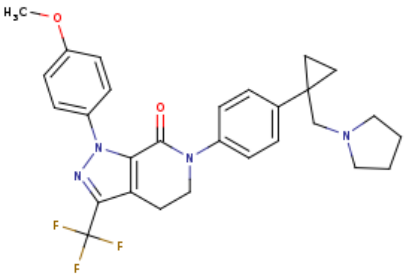
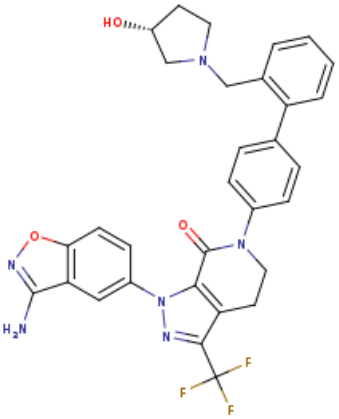
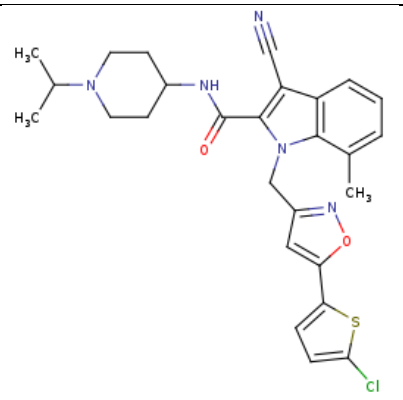
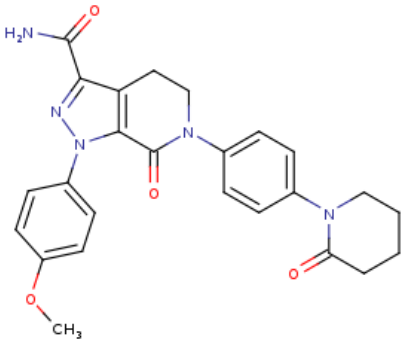
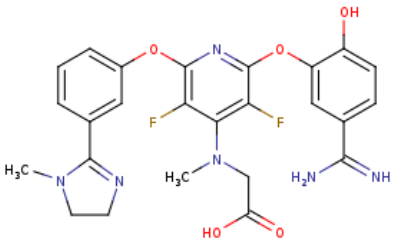
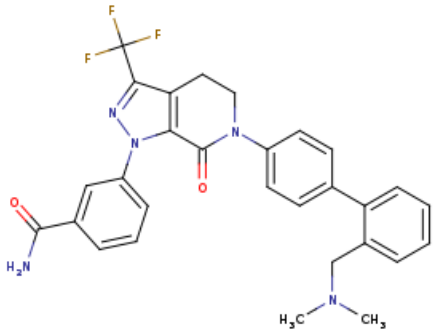
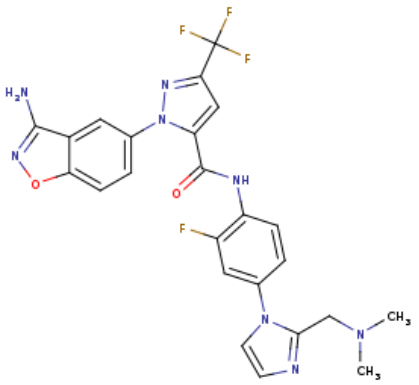
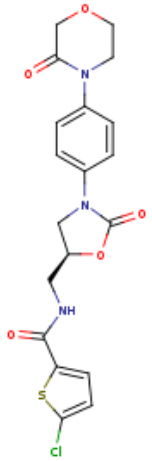
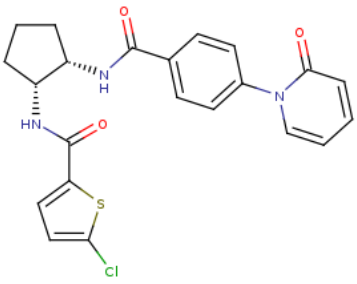
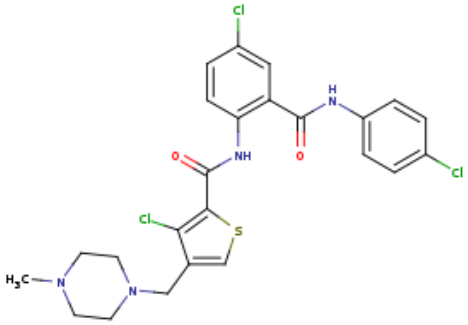
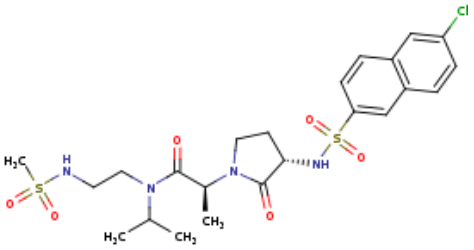
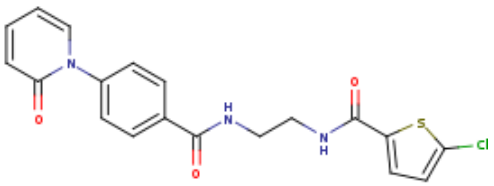
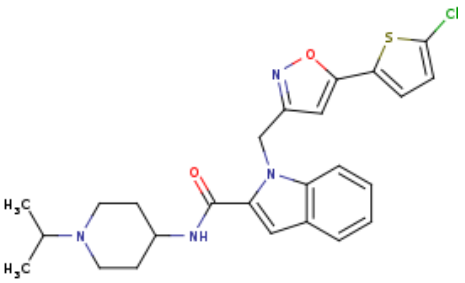
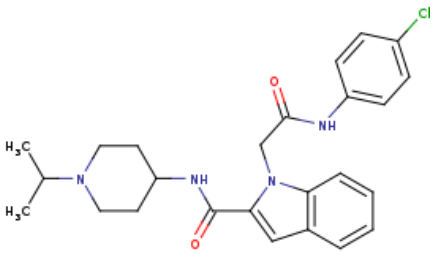
19	2ZFP	19U	6800 [3]	323.82	$C_{16}H_{22}ClN_3O_2$	
20	3F68	91U	8700 [3]	433.97	$C_{23}H_{32}ClN_3O_3$	
21	3EGK	M18	22000 [11]	410.89	$C_{20}H_{27}ClN_2O_5$	
22	3P17	99P	33400 [10]	352.43	$C_{20}H_{24}N_4O_2$	
23	3SV2	P05	64000 [10]	352.43	$C_{20}H_{24}N_4O_2$	

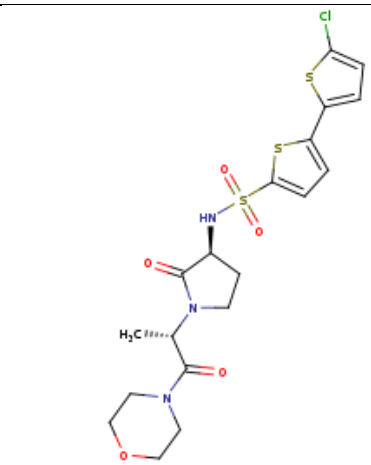
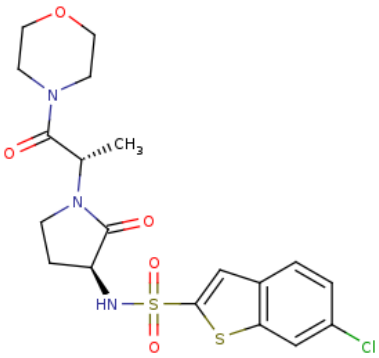
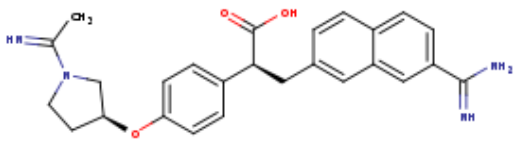
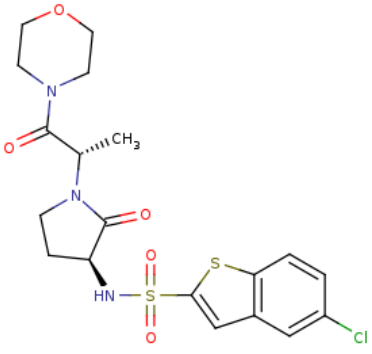
Table S2 - Inhibition constant, molecular weight, chemical formula and 2D structure of the 23 studied ligands of factor Xa. Their ID is given in the third column, while the second column refers to PDB ID of their complex with factor Xa protein.

No.	PDB ID	Ligand ID	Inhibition constant Ki (nm)	Molecular weight (g/mol)	Chemical formula	2D structure
1	2P3T	993	0.005 [12]	565.68	$C_{23}H_{19}C_{l3}N_6O_3S$	
2	1MQ6	XLD	0.007 [13]	568.86	$C_{23}H_{20}C_{l3}N_5O_4S$	
3	3CS7	LG0	0.021 [14]	510.55	$C_{28}H_{29}F_3N_4O_2$	
4	2FZZ	5QC	0.03 [15]	588.58	$C_{31}H_{27}F_3N_6$ O3	

5	2BQ6	IIB	0.07 [16]	522.06	$C_{27}H_{28}C_lN_5O_2S$	
6	2P16	GG2	0.08 [17]	459.50	$C_{25}H_{25}N_5O_4$	
7	1FJS	Z34	0.11 [18]	526.49	$C_{25}H_{24}F_2N_6O_5$	
8	2G00	4QC	0.18 [19]	533.54	$C_{29}H_{26}F_3N_5O_2$	

9	1Z6E	IK8	0.19 [20]	528.46	$C_{24}H_{20}F_4N_8O_2$	
10	2W26	RIV	0.4 [21]	435.88	$C_{19}H_{18}ClN_3O_5S$	
11	2P95	ME5	0.43 [22]	441.93	$C_{22}H_{20}ClN_3O_3S$	
12	1MQ5	XLC	1 [13]	537.89	$C_{24}H_{23}Cl_3N_4O_2S$	

13	2J4I	GSJ	1 [23]	559.10	$C_{23}H_{31}ClN_4O_6S_2$	
14	2P93	ME1	1.5 [22]	401.87	$C_{19}H_{16}ClN_3O_3S$	
15	2BOH	IIA	3 [16]	483.02	$C_{25}H_{27}ClN_4O_2S$	
16	2BQW	IIE	3 [16]	452.98	$C_{25}H_{29}ClN_4O_2$	

17	2J95	GSX	4 [24]	504.04	$C_{19}H_{22}C_lN_3O_5S_3$	
18	2J34	GS6	15 [25]	471.98	$C_{19}H_{22}C_lN_3O_5S_2$	
19	1FAX	DX9	41 [26]	444.53	$C_{26}H_{28}N_4O_3$	
20	2J38	GS5	47 [25]	471.98	$C_{19}H_{22}C_lN_3O_5S_2$	

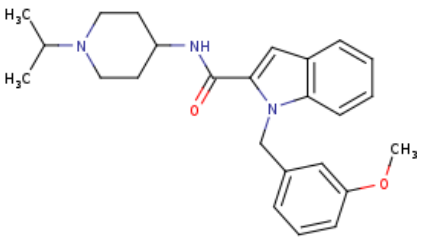
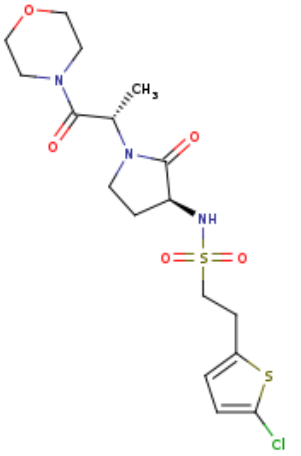
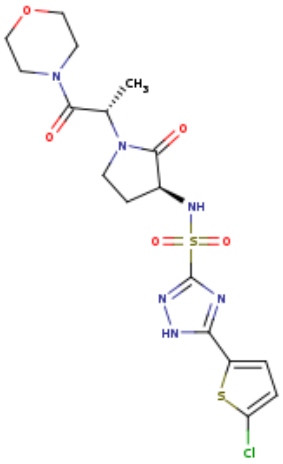
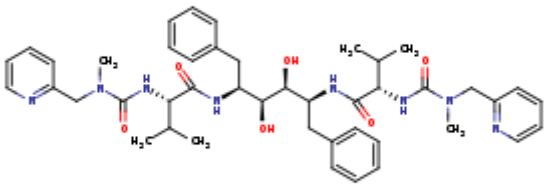
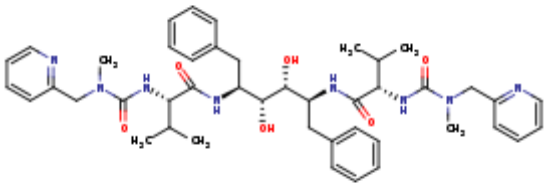
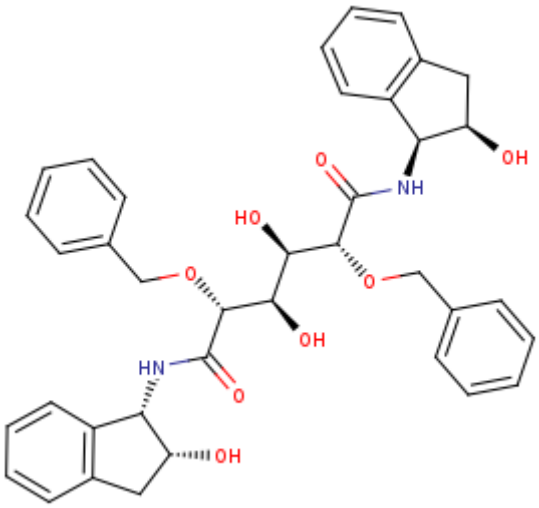
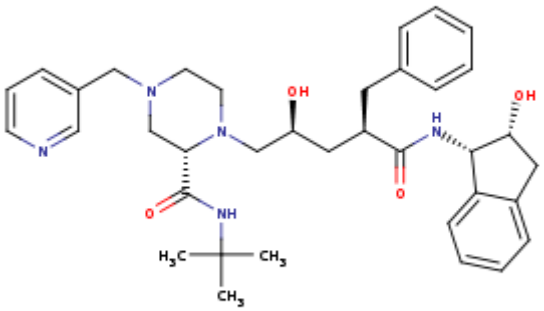
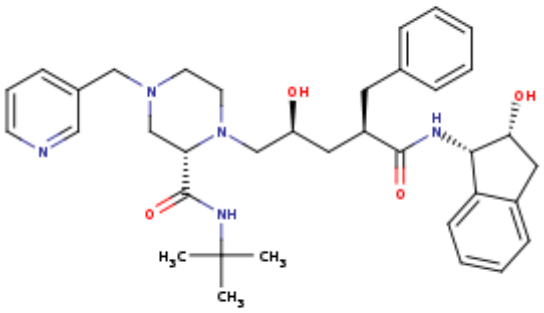
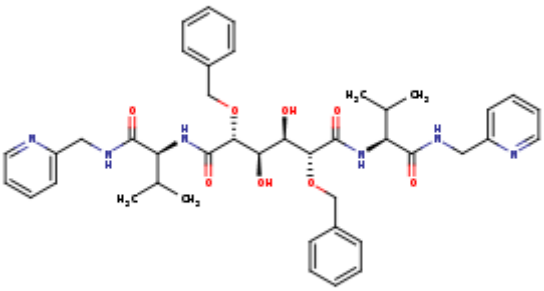
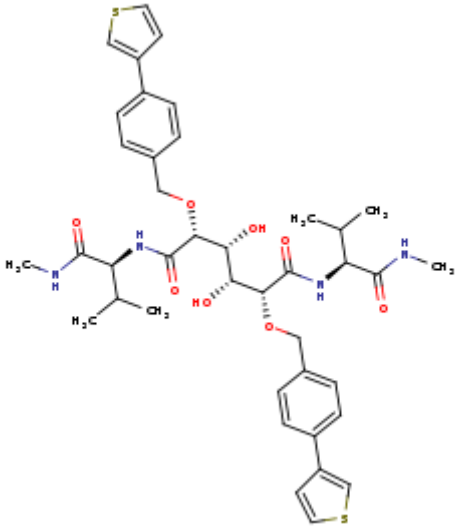
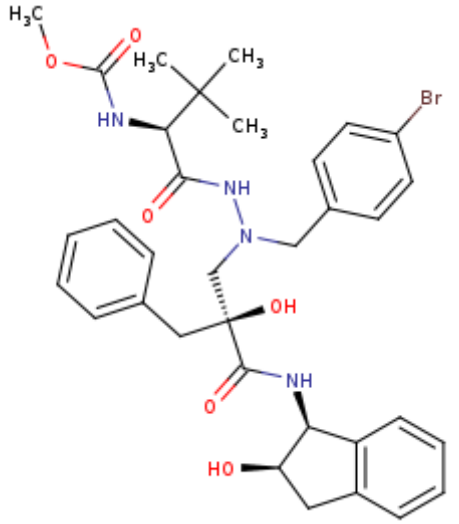
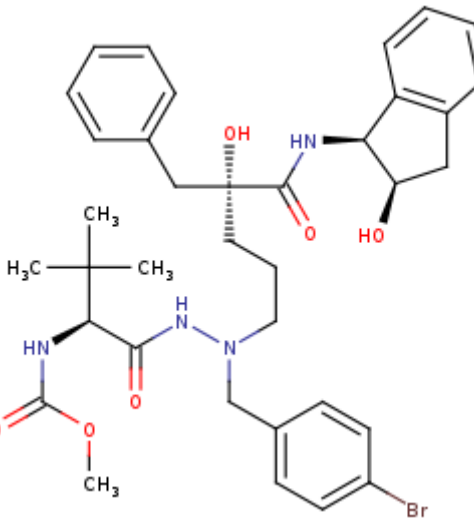
21	2BQ7	IID	89 [16]	405.53	$C_{25}H_{31}N_3O_2$	
22	2UWP	894	154 [27]	449.97	$C_{17}H_{24}ClN_3O_5S_2$	
23	2J94	G15	534 [24]	488.97	$C_{17}H_{21}ClN_6O_5S_2$	

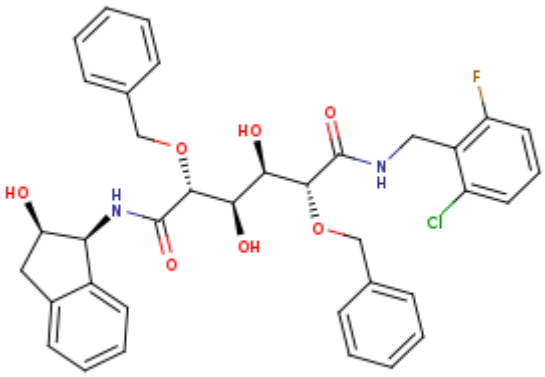
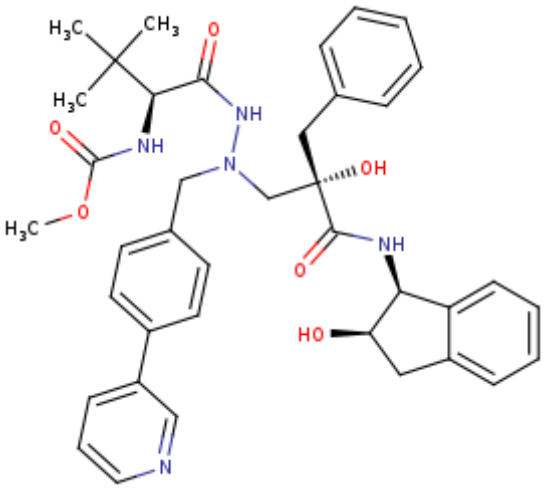
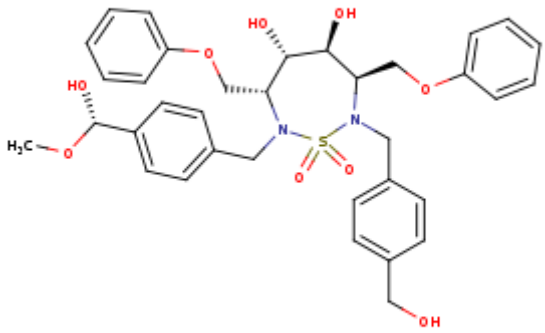
Table S3 - Inhibition constant, molecular weight, chemical formula and 2D structure of 23 studied ligands of HIV-1. Their ID is given in the third column, while the second column refers to PDB ID of their complex with the HIV-1 protein.

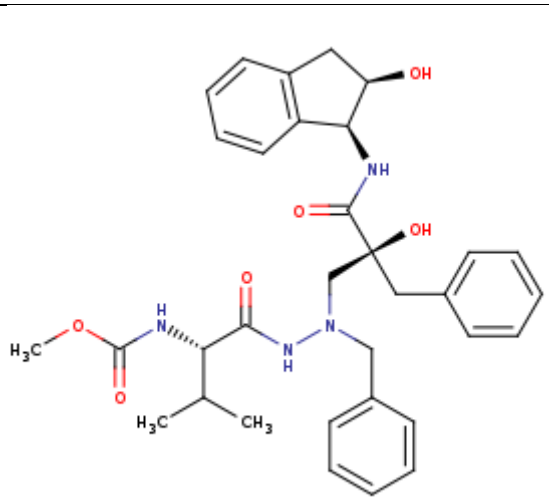
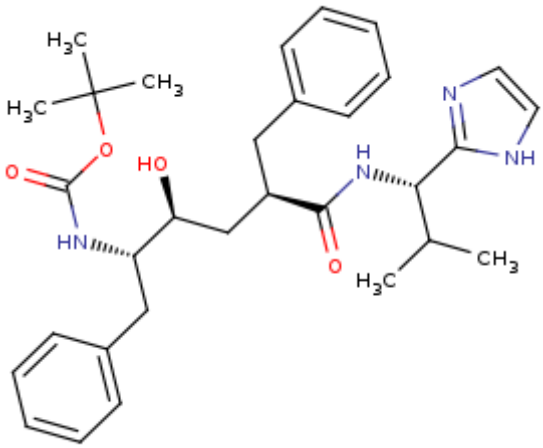
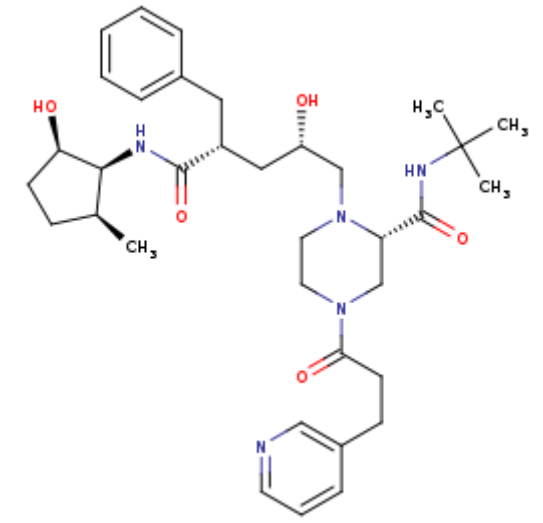
No.	PDB ID	Ligand ID	Inhibition constant Ki (nM)	Molecular weight (g/mol)	Chemical formular	2D structure

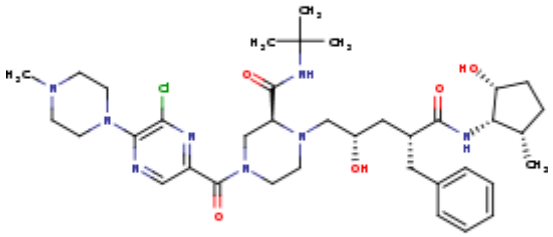
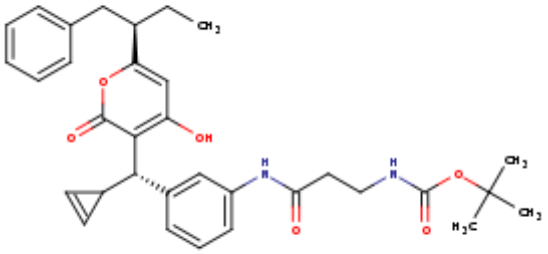
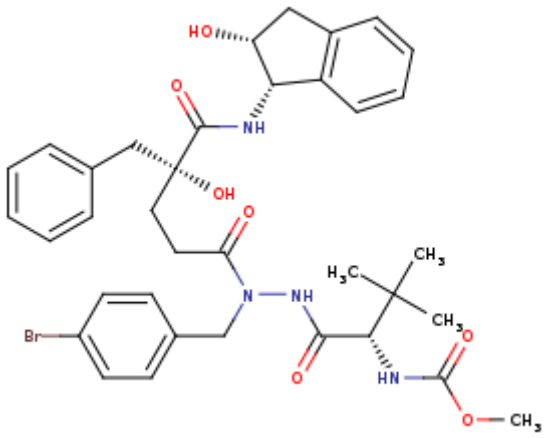
1	1HVK	A79	0.011 [28]	794.98	$C_{44}H_{58}N_8O_6$	
2	1HVL	A76	0.112 [28]	794.98	$C_{44}H_{58}N_8O_6$	
3	1EBY	BEB	0.2 [29]	652.73	$C_{38}H_{40}N_2O_8$	

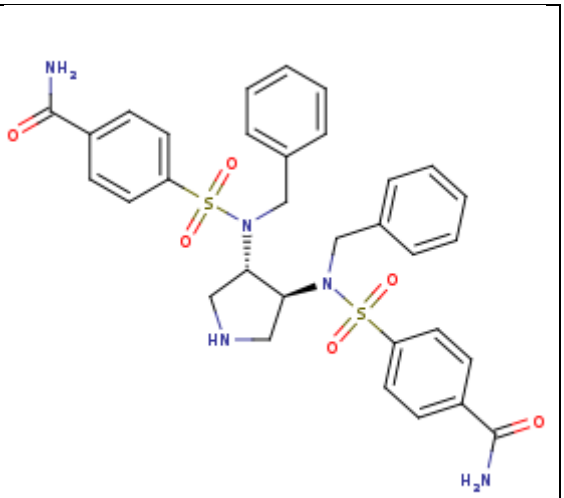
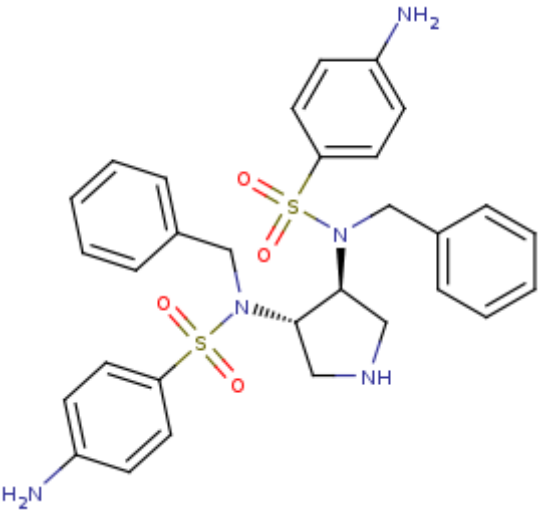
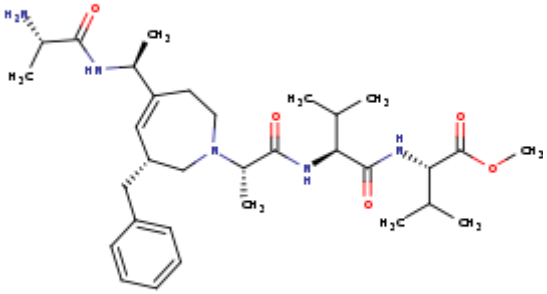
4	1C6Y	MK1	0.31 [30]	613.79	$C_{36}H_{47}N_5O_4$	
5	2BPX	MK1	0.4 [31]	613.79	$C_{36}H_{47}N_5O_4$	
6	1EC3	MS3	0.92 [29]	768.90	$C_{42}H_{52}N_6O_8$	

7	1EC1	BEE	1.2 [29]	778.98	C_{40} H_{50} N_4 O_8 S_2	
8	2CEJ	1AH	2.4 [32]	681.62	C_{34} H_{41} Br N_4 O_6	
9	2UXZ	HI1	3.3 [33]	709.67	C_{36} H_{45} Br N_4 O_6	

10	1D4J	MSC	4.4 [29]	663.13	C_{36} H_{36} Cl F N_2 O_7	
11	2CEN	4AH	5 [32]	679.80	C_{39} H_{45} N_5 O_6	
12	1G35	AHF	7.3 [34]	664.76	C_{35} H_{40} N_2 O_9 S	

13	2BQV	A1A	9 [35]	588.69	$C_{33}\ H_{40}\ N_4\ O_6$	
14	1SBG	IM1	18 [36]	534.69	$C_{31}\ H_{42}\ N_4\ O_4$	
15	2BPV	1IN	21.2 [31]	621.81	$C_{35}\ H_{51}\ N_5\ O_5$	

16	2BPY	3IN	39.8 [31]	727.34	C_{37} H_{55} Cl N_8 O_5	
17	2UPJ	U02	41 [37]	558.66	C_{33} H_{38} N_2 O_6	
18	2UY0	HV1	120 [33]	723.65	C_{36} H_{43} Br N_4 O_7	

19	2PWR	G4G	260 [38]	647.76	$C_{32}H_{33}N_5O_6S_2$	
20	2PWC	G3G	270 [38]	591.74	$C_{30}H_{33}N_5O_4S_2$	
21	1HBV	GAN	430 [39]	585.78	$C_{32}H_{51}N_5O_5$	

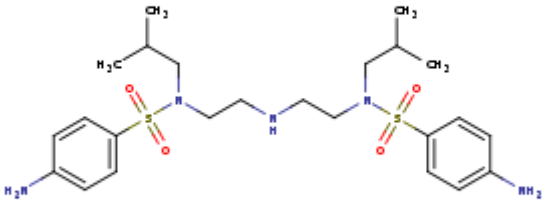
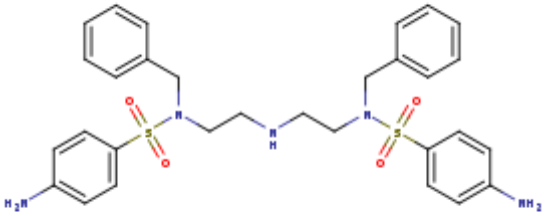
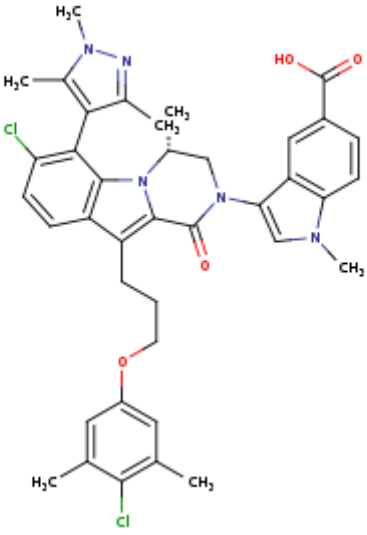
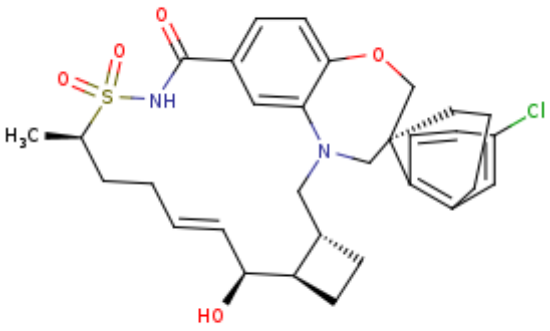
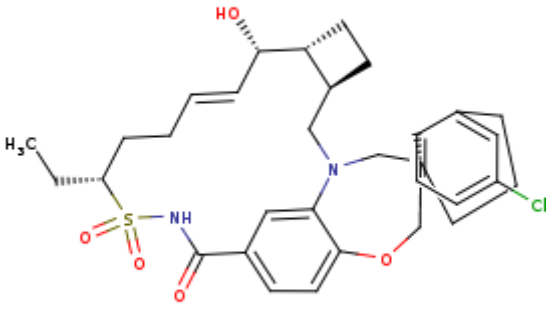
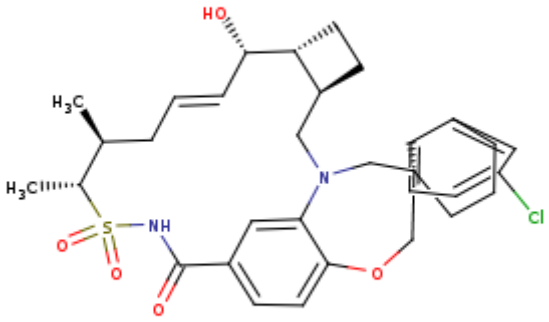
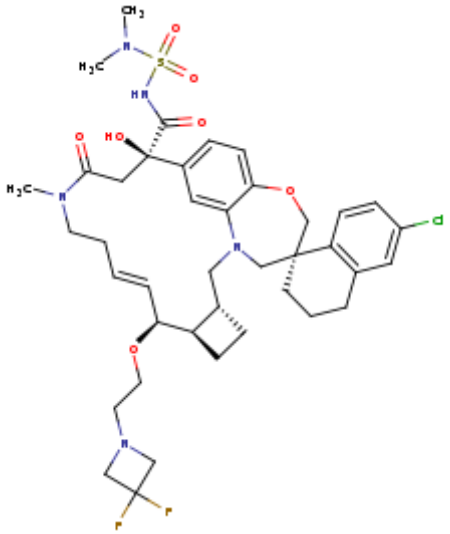
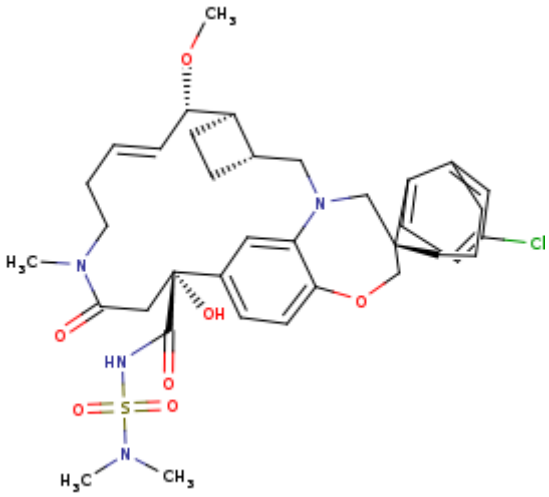
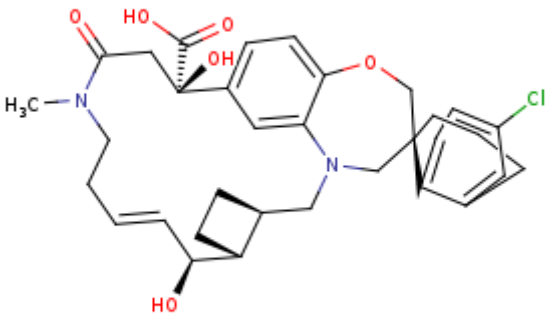
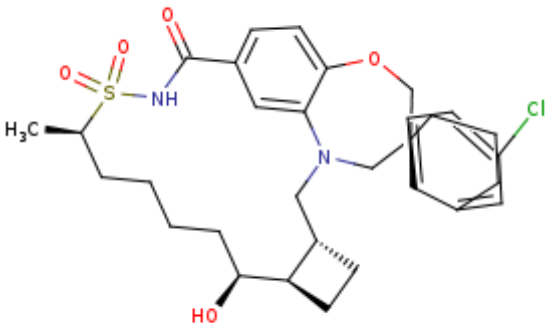
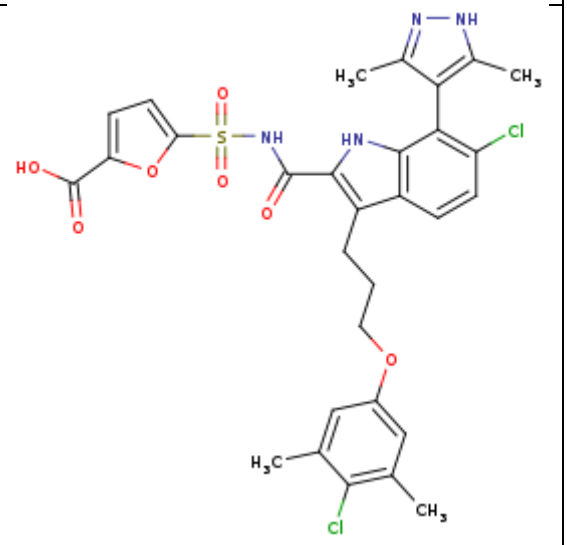
22	3BGB	LJG	900 [40]	525.73	$C_{24}H_{39}N_5O_4S_2$	
23	3BGC	LJH	9600 [40]	593.76	$C_{30}H_{35}N_5O_4S_2$	

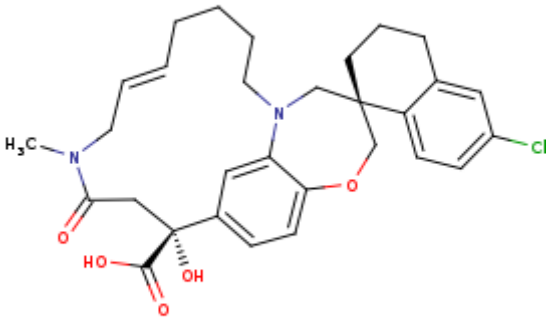
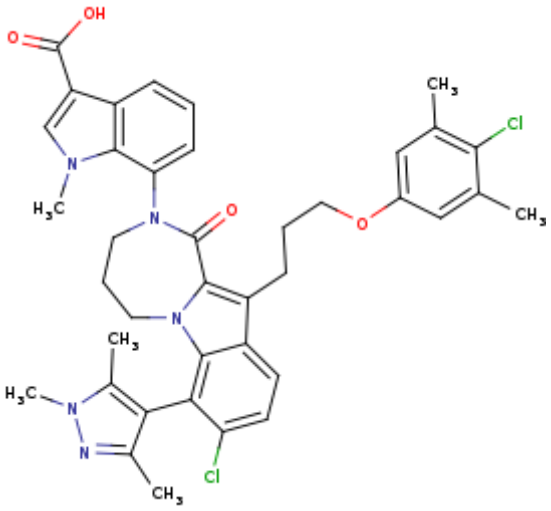
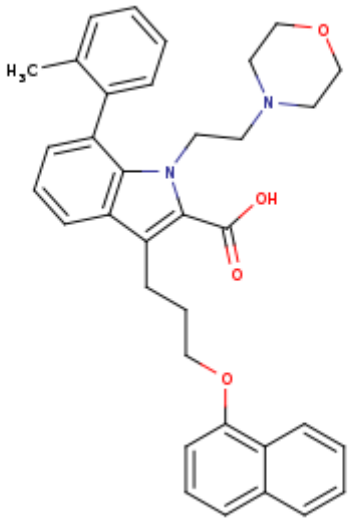
Table S4 - Inhibition constant, molecular weight, chemical formula and 2D structure of 23 studied ligands of MCL-1. Their ID is given in the third column, while the second column refers to PDB ID of their complex with the mcl-1 protein.

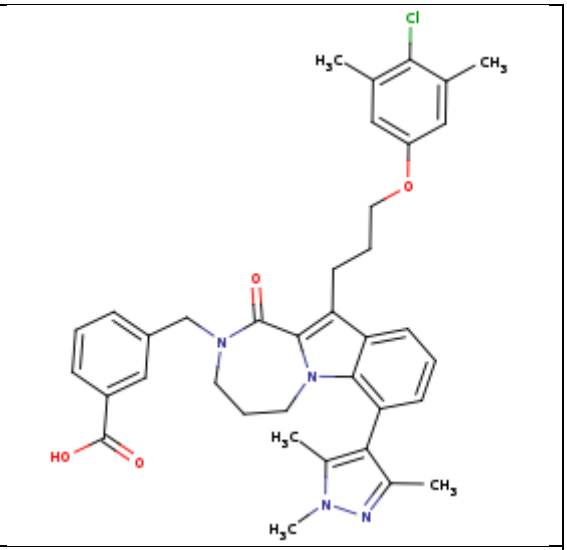
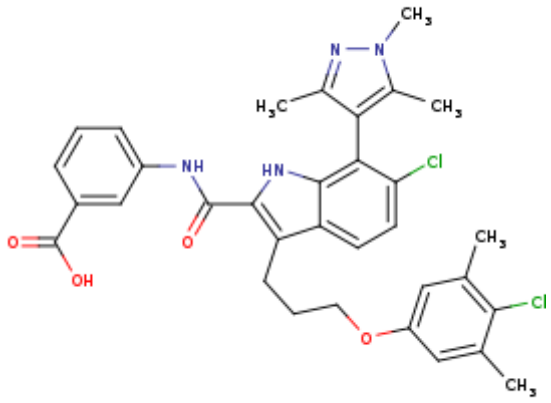
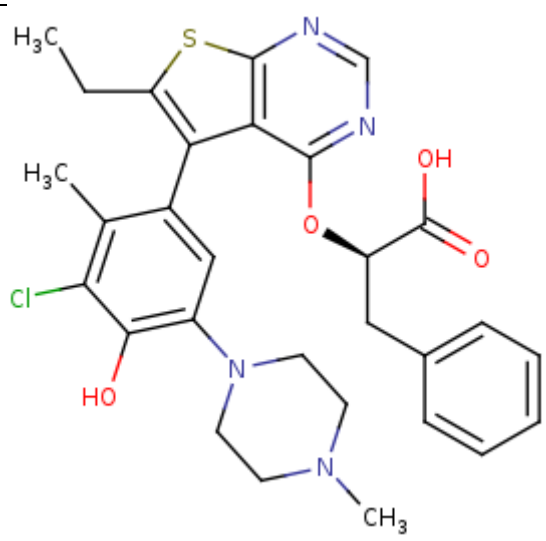
No.	PDB ID	Ligand ID	Inhibition constant Ki (nM)	Molecular weight (g/mol)	Chemical formular	2D structure

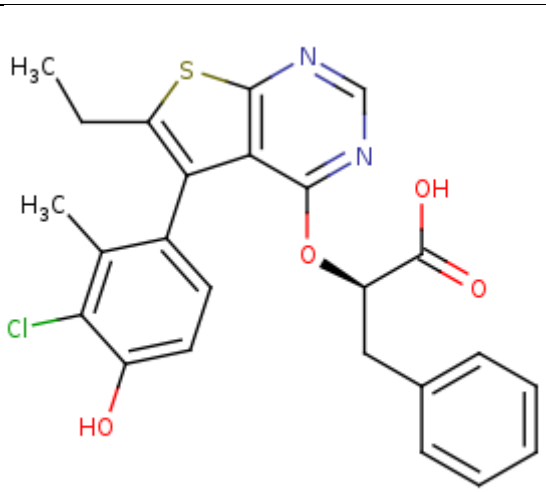
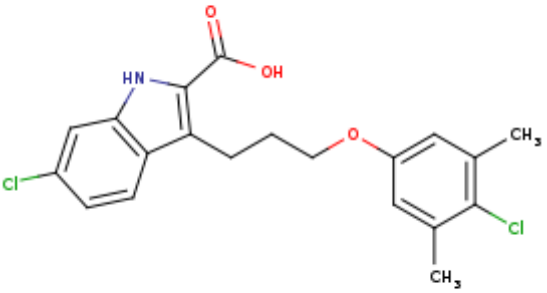
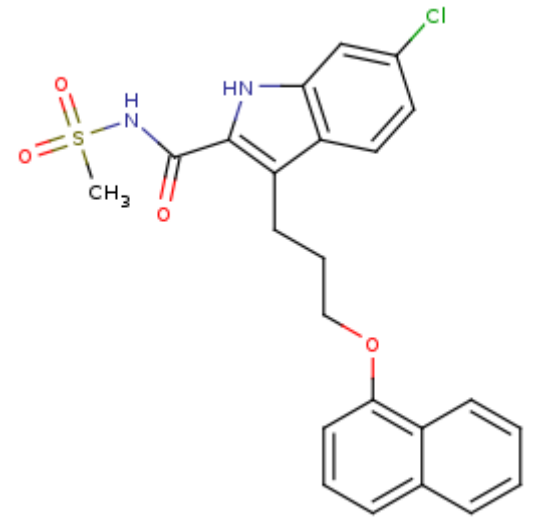
1	6NE5	KJP	0.03 [41]	712.66	C_{39} H_{39} Cl_2 N_5 O_4	
2	6OQC	N0S	0.04 [42]	585.15	C_{31} H_{37} Cl N_2 O_5 S	
3	6OQB	N0J	0.05 [42]	599.18	C_{32} H_{39} Cl N_2 O_5 S	

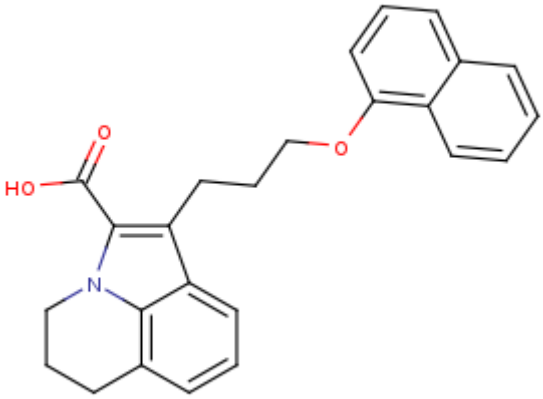
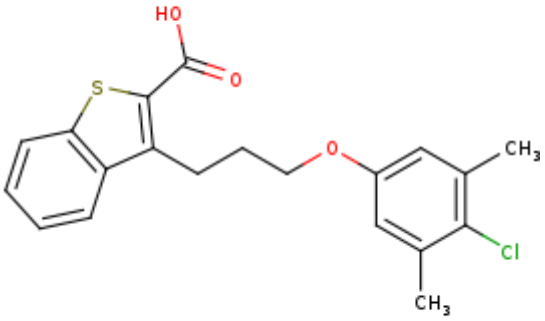
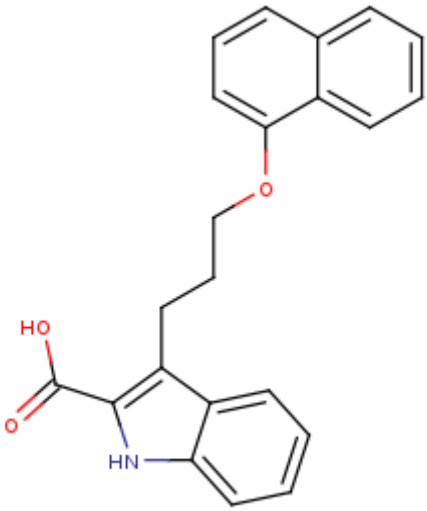
4	6UDV	Q51	0.051 [43]	599.18	C_{32} H_{39} Cl N_2 O_5 S	
5	6UD2	Q4D	0.062 [43]	820.38	C_{40} H_{52} Cl F_2 N_5 O_7 S	
6	6UDI	Q4S	0.1 [43]	715.30	C_{36} H_{47} Cl N_4 O_7 S	

7	6UDT	Q4V	0.1 [43]	595.13	C_{33} H_{39} Cl N_2 O_6	
8	6OQD	N0M	0.14 [42]	587.17	C_{31} H_{39} Cl N_2 O_5 S	
9	5FDR	5X3	0.4 [44]	659.54	C_{30} H_{28} Cl_2 N_4 O_7 S	

10	6UDU	Q4Y	0.5 [43]	539.06	C_{30} H_{35} Cl N_2 O_5	
11	6BW8	ECM	0.65 [45]	712.66	C_{39} H_{39} Cl_2 N_5 O_4	
12	6B4U	CN7	9 [46]	548.67	C_{35} H_{36} N_2 O_4	

13	6BW2	ECY	21 [45]	639.18	C_{37} H_{39} Cl N_4 O_4	
14	5IEZ	6AL	23 [47]	619.54	C_{33} H_{32} Cl_2 N_4 O_4	
15	6QYP	JL5	46 [48]	567.10	C_{29} H_{31} Cl N_4 O_4 S	

16	6QZ8	JL8	51 [48]	468.95	C_{24} H_{21} Cl N_2 O_4 S	
17	4HW2	19H	55 [49]	392.28	C_{20} H_{19} Cl_2 N O_3	
18	5FC4	5WL	231 [44]	456.94	C_{23} H_{21} Cl N_2 O_4 S	

19	4ZBI	4M6	310 [50]	385.45	C_{25} H_{23} N O_3	
20	4HW3	19G	320 [49]	374.88	C_{20} H_{19} Cl O_3 S	
21	6B4L	CJY	340 [46]	345.39	C_{22} H_{19} N O_3	

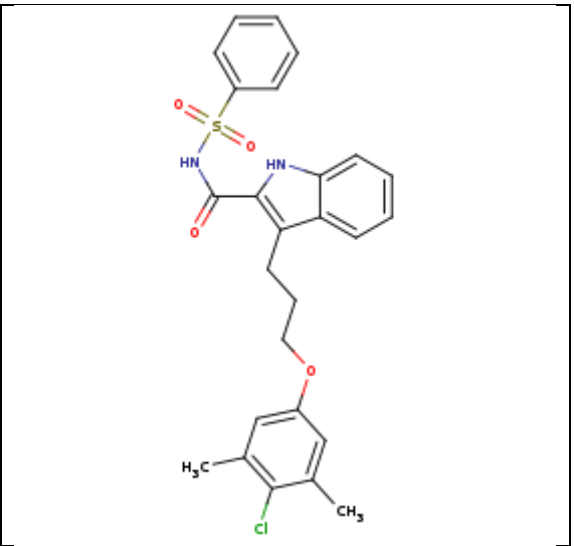
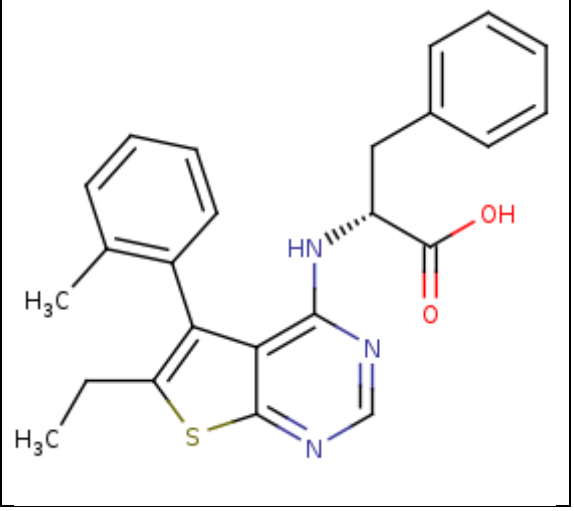
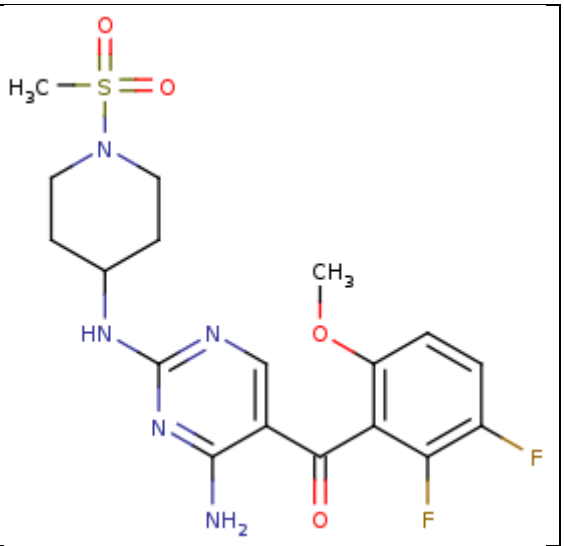
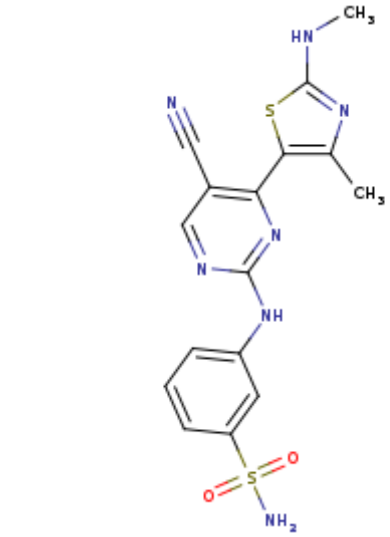
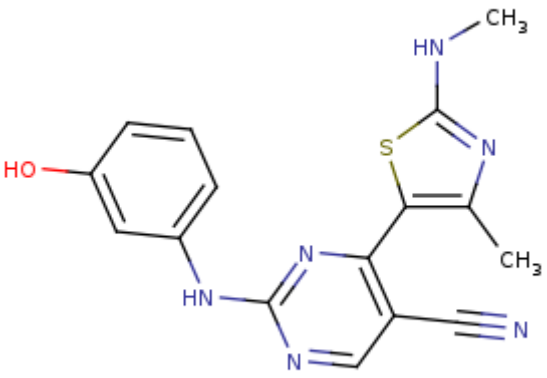
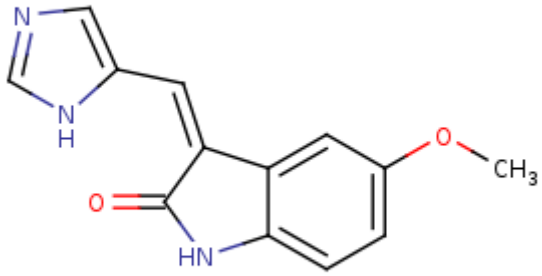
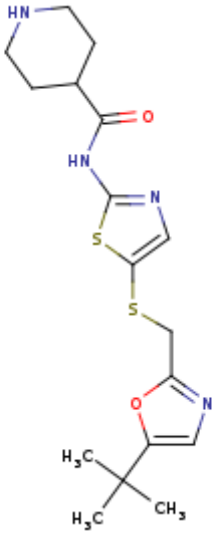
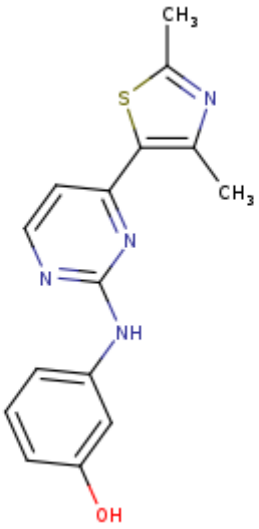
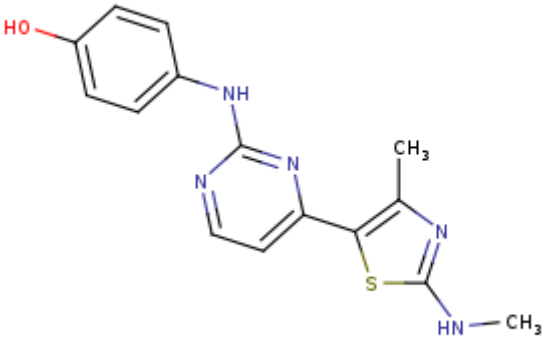
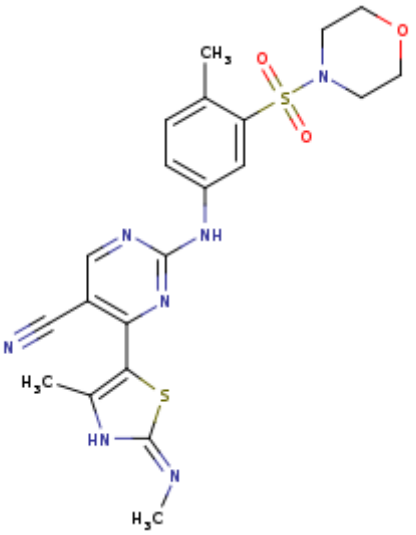
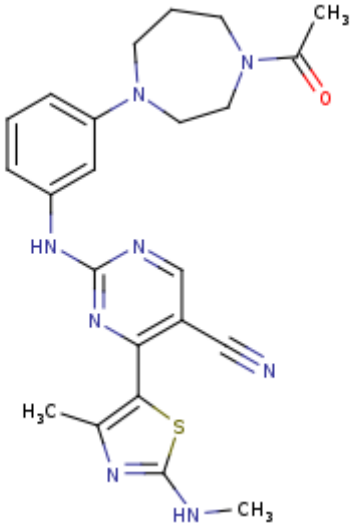
22	5FDO	5X2	361 [44]	497.01	C_{26} H_{25} Cl N_2 O_4 S	
23	6QZB	JLK	2400 [48]	417.52	C_{24} H_{23} N_3 O_2 S	

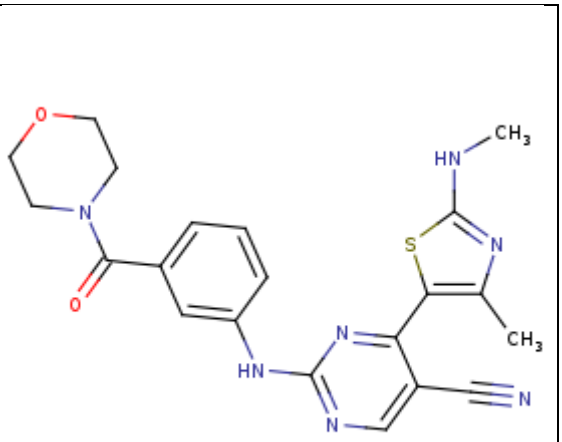
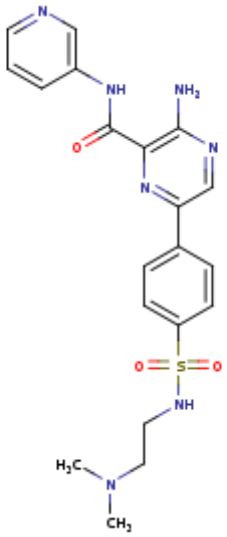
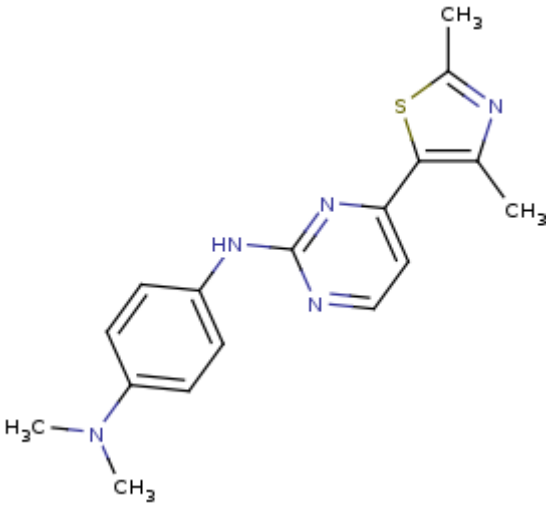
Table S5 - Inhibition constant, molecular weight, chemical formula and 2D structure of 23 studied ligands of CDK-2. Their ID is given in the third column, while the second column refers to PDB ID of their complex with the cdk-2 protein.

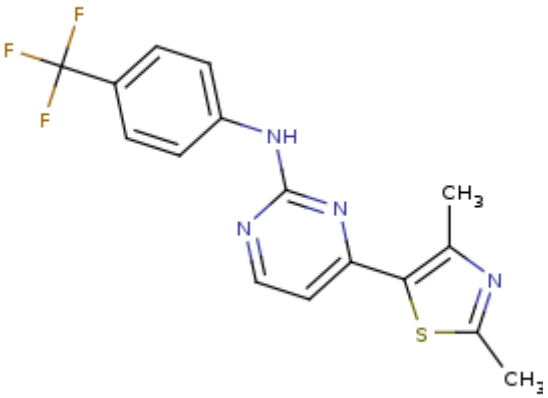
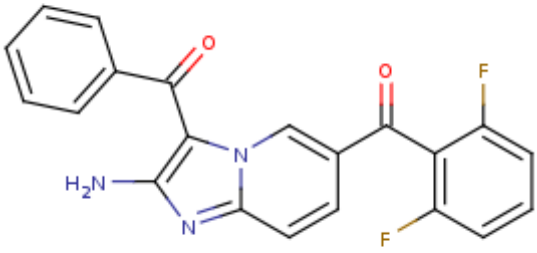
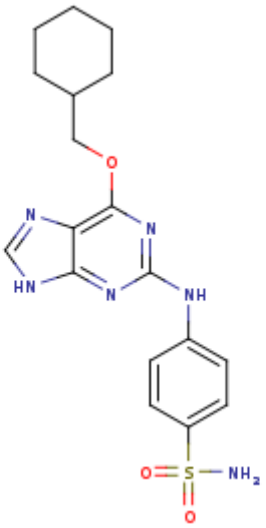
No.	PDB ID	Ligand ID	Inhibition constant Ki (nM)	Molecular weight (g/mol)	Chemical formular	2D structure

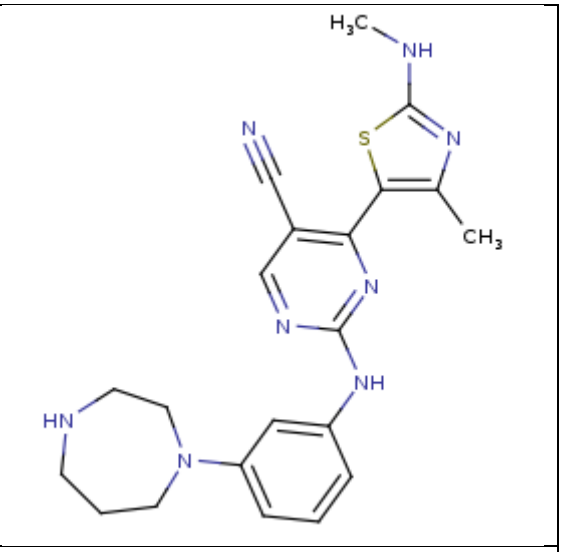
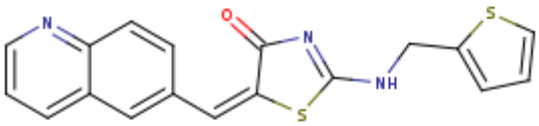
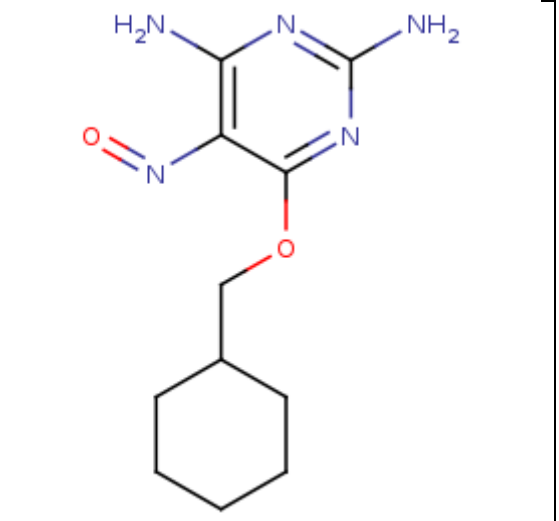
1	2FVD	LIA	3 [51]	441.45	C_{18} H_{21} F_2 N_5 O_4 S	
2	4BCK	T3E	4 [52]	401.47	C_{16} H_{15} N_7 O_2 S_2	
3	4BCN	T9N	12 [52]	338.39	C_{16} H_{14} N_6 O S	

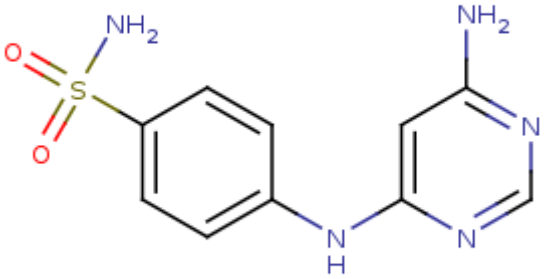
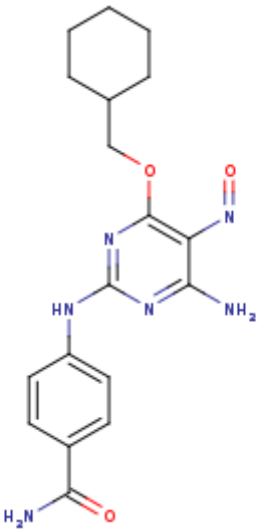
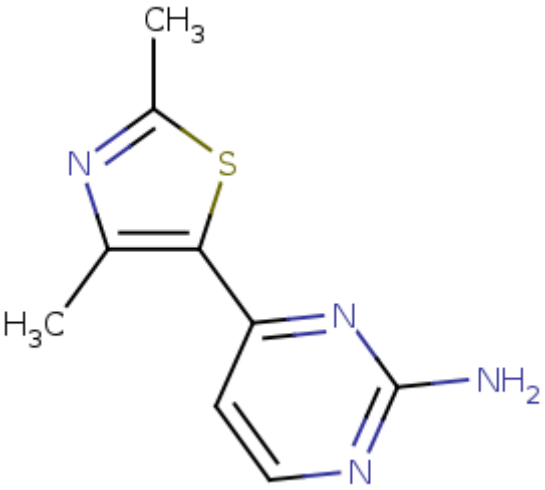
4	1PF8	SU9	31 [53]	241.25	C_{13} H_{11} N_3 O_2	
5	5D1J	56H	38 [54]	380.53	C_{17} H_{24} N_4 O_2 S_2	
6	1PXM	CK5	60 [55]	298.36	C_{15} H_{14} N_4 O S	

7	1PXN	CK6	70 [55]	313.38	C_{15} H_{15} N_5 O S	
8	4BCM	T7Z	123 [52]	485.58	C_{21} H_{23} N_7 O_3 S_2	
9	4BCO	T6Q	131 [52]	462.57	C_{23} H_{26} N_8 O S	

10	4BCQ	TJF	147 [52]	435.50	C_{21} H_{21} N_7 O_2 S	
11	4ACM	7YG	210 [56]	441.51	C_{20} H_{23} N_7 O_3 S	
12	1PXP	CK8	220 [55]	325.43	C_{17} H_{19} N_5 S	

13	1PXL	CK4	290 [57]	350.36	$C_{16}H_{13}F_3N_4S$	
14	1PYE	PM1	386 [58]	377.34	$C_{21}H_{13}F_2N_3O_2$	
15	4EOR	4SP	500 [59]	402.47	$C_{18}H_{22}N_6O_3S$	

16	4BCP	T3C	568 [60]	420.53	C_{21} H_{24} N_8 S	
17	4EOS	1RO	890 [59]	351.44	C_{18} H_{13} N_3 O S_2	
18	1E1X	NW1	1300 [61]	251.28	C_{11} H_{17} N_5 O_2	

19	1JSV	U55	2000 [62]	265.29	C_{10} H_{11} N_5 O_2 S	
20	1OGU	ST8	2400 [63]	370.41	C_{18} H_{22} N_6 O_3	
21	1PXJ	CK2	6500 [57]	206.27	C_9 H_{10} N_4 S	

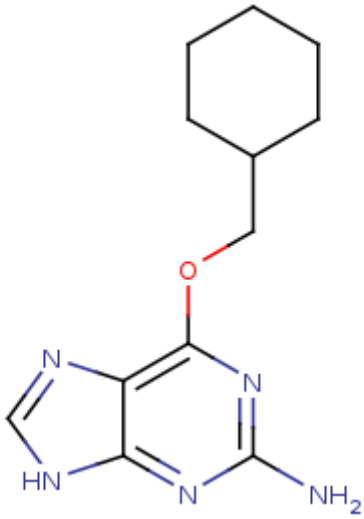
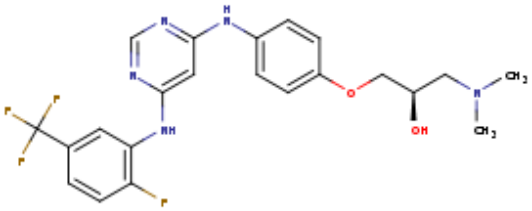
22	1E1V	CMG	12000 [61]	247.30	C_{12} H_{17} N_5 O	
23	1V1K	3FP	35000 [64]	465.44	C_{22} H_{23} F_4 N_5 O_2	

Table S6 - Scale factor β for thrombin complexes.

No.	Ligand PDB ID	Complex PDB ID	β
1	170	1SL3	0.50
2	IH2	1C4V	0.43
3	IH1	1C4U	0.43
4	33U	2ZO3	0.43
5	177	1TA6	0.43
6	T76	1NT1	0.43
7	BM9	1BMN	0.37
8	MID	1ETS	0.43
9	894	2JH6	0.43
10	23U	3DHK	0.43
11	64U	3DUX	0.43
12	22U	2ZC9	0.43
13	29U	2ZGX	0.43
14	895	2JH5	0.43
15	GR3	1AWH	0.33
16	00R	1D6W	0.43
17	B01	3SHC	0.43

18	P97	3SHA	0.43
19	19U	2ZFP	0.43
20	91U	3F68	0.43
21	M18	3EGK	0.43
22	99P	3P17	0.43
23	P05	3SV2	0.43

Table S7 - Scale factor β for factor Xa complexes

No.	Ligand PDB ID	PDB ID	β
1	993	2P3T	0.43
2	XLD	1MQ6	0.43
3	LG0	3CS7	0.43
4	5QC	2FZZ	0.37
5	IIB	2BQ6	0.43
6	GG2	2P16	0.43
7	Z34	1FJS	0.33
8	4QC	2G00	0.43
9	IK8	1Z6E	0.43
10	RIV	2P95	0.43
11	ME5	2W26	0.43
12	XLC	1MQ5	0.43
13	GSJ	2J4I	0.43
14	ME1	2P93	0.43
15	IIA	2BOH	0.43
16	IIE	2BQW	0.43
17	GSX	2J95	0.43
18	GS6	2J34	0.43
19	DX9	1FAX	0.37
20	GS5	2J38	0.43
21	IID	2BQ7	0.43
22	894	2UWP	0.43
23	G15	2J94	0.43

Table S8 - Scale factor β for beta-lactamase complexes

No.	Ligand PDB ID	PDB ID	β
1	HTC	1XGJ	0.33
2	23C	2R9W	0.33
3	NST	1XGI	0.37
4	WH6	2R9X	0.33
5	18U	4JXS	0.33
6	1MW	4JXW	0.33
7	STC	1L2S	0.37
8	1MU	4JXV	0.33
9	DK2	2PU2	0.33
10	4A1	4KZ4	0.37
11	NZ9	4KZA	0.37
12	ZB6	4KZ6	0.37
13	G14	3GRJ	0.37
14	1U1	4KZ3	0.43
15	1U6	4KZ8	0.37
16	GF1	3GSG	0.37

17	GF4	3GR2	0.33
18	3GV	3GVB	0.37
19	1U5	4KZ7	0.37
20	F12	2HDU	0.37
21	GV9	3GV9	0.37
22	1U3	4KZ5	0.37
23	4A3	2HDR	0.33

Table S9 - Scale factor β for HIV-1 complexes

No.	Ligand PDB ID	PDB ID	β
1	A79	1HVK	0.33
2	A76	1HVL	0.33
3	BEB	1EBY	0.33
4	MK1	1C6Y	0.33
5	MK1	2BPX	0.33
6	MS3	1EC3	0.33
7	BEE	1EC1	0.33
8	1AH	2CEJ	0.33
9	HI1	2UXZ	0.33
10	MSC	1D4J	0.33
11	4AH	2CEN	0.33
12	AHF	1G35	0.33
13	A1A	2BQV	0.33
14	IM1	1SBG	0.37
15	1IN	2BPV	0.33
16	3IN	2BPY	0.33
17	U02	2UPJ	0.37
18	HV1	2UY0	0.33
19	G4G	2PWR	0.43
20	G3G	2PWC	0.43
21	GAN	1HBV	0.43
22	LJG	3BGB	0.43
23	LJH	3BGC	0.43

Table S10 - Scale factor β for mcl-1 complexes

No.	Ligand PDB ID	PDB ID	β
1	KJP	6NE5	0.37
2	N0S	6OQC	0.37
3	N0J	6OQB	0.37
4	Q51	6UDV	0.37
5	Q4D	6UD2	0.37
6	Q4S	6UDI	0.37
7	Q4V	6UDT	0.33
8	N0M	6OQD	0.37
9	5X3	5FDR	0.37

10	Q4Y	6UDU	0.33
11	ECM	6BW8	0.37
12	CN7	6B4U	0.37
13	ECY	6BW2	0.37
14	6AL	5IEZ	0.37
15	JL5	6QYP	0.33
16	JL8	6QZ8	0.33
17	19H	4HW2	0.37
18	5WL	5FC4	0.43
19	4M6	4ZBI	0.37
20	19G	4HW3	0.37
21	CJY	6B4L	0.37
22	5X2	5FDO	0.43
23	JLK	6QZB	0.37

Table S11 - Scale factor β for CDK-2 complexes

No.	Ligand PDB ID	PDB ID	β
1	LIA	2FVD	0.43
2	T3E	4BCK	0.43
3	T9N	4BCN	0.37
4	SU9	1PF8	0.43
5	56H	5D1J	0.43
6	CK5	1PXM	0.37
7	CK6	1PXN	0.37
8	T7Z	4BCM	0.43
9	T6Q	4BCO	0.43
10	TJF	4BCQ	0.43
11	7YG	4ACM	0.43
12	CK8	1PXP	0.43
13	CK4	1PXL	0.43
14	PM1	1PYE	0.43
15	4SP	4EOR	0.43
16	T3C	4BCP	0.43
17	1RO	4EOS	0.43
18	NW1	1E1X	0.43
19	U55	1JSV	0.43
20	ST8	1OGU	0.43
21	CK2	1PXJ	0.43
22	CMG	1E1V	0.43
23	3FP	1V1K	0.37

Table S12. SMD results obtained for 23 factor Xa complexes. ΔG_{neq}^{Jar}, $\Delta G_{unbind}^{\ddagger}$, and $\Delta G_{bind}^{\ddagger}$ were obtained using the Jarzynski's equality.

No.	Ligand	Complex	ΔG_{exp}	F_{max}	W_{pull}	ΔG_{neq}^{Jar}	t_{max}	$\Delta G_{unbind}^{\ddagger}$	$\Delta G_{bind}^{\ddagger}$

	PDB ID	PDB ID	(kcal/mol)	(pN)	(kcal/mol)	(kcal/mol)	(ps)	(kcal/mol)	(kcal/mol)
1	993	2P3T	-15.5	1057 ± 38	115 ± 9	-95.0 ± 1.9	231 ± 12	73.6 ± 8.1	188.7 ± 14.0
2	XLD	1MQ6	-15.3	1199 ± 101	140 ± 17	-90.5 ± 1.9	250 ± 20	101.4 ± 18.2	240.7 ± 34.4
3	LG0	3CS7	-14.6	1108 ± 86	115 ± 11	-96.0 ± 1.9	232 ± 18	86.6 ± 14.5	200.7 ± 24.4
4	5QC	2FZZ	-14.4	1038 ± 106	117 ± 14	-83.4 ± 1.9	223 ± 17	71.9 ± 18.4	188.4 ± 31.0
5	IIB	2BQ6	-13.9	928 ± 93	97 ± 12	-76.3 ± 1.9	191 ± 20	62.0 ± 12.0	158.3 ± 22.5
6	GG2	2P16	-13.8	1150 ± 132	126 ± 19	-84.0 ± 1.9	237 ± 27	95.5 ± 20.7	221.0 ± 38.6
7	Z34	1FJS	-13.7	1132 ± 89	124 ± 14	-87.8 ± 1.9	240 ± 18	86.4 ± 16.6	210.3 ± 28.1
8	4QC	2G00	-13.4	1056 ± 118	119 ± 18	-92.1 ± 1.8	217 ± 27	79.0 ± 17.6	197.6 ± 35.4
9	IK8	1Z6E	-13.3	990 ± 117	107 ± 14	-88.8 ± 1.7	213 ± 24	67.3 ± 19.0	174.1 ± 31.0
10	RIV	2W26	-12.9	1079 ± 80	124 ± 16	-80.2 ± 1.9	230 ± 22	78.9 ± 13.2	202.7 ± 24.5
11	ME5	2P95	-12.8	864 ± 31	82 ± 5	-72.0 ± 1.9	188 ± 7	51.3 ± 5.5	132.5 ± 6.8
12	XLC	1MQ5	-12.4	911 ± 80	97 ± 9	-76.9 ± 1.9	197 ± 19	55.7 ± 12.2	152.2 ± 18.7
13	GSJ	2J4I	-12.4	1028 ± 133	120 ± 16	-86.1 ± 1.9	227 ± 26	68.5 ± 21.6	187.8 ± 37.3
14	ME1	2P93	-12.1	844 ± 74	80 ± 6	-70.6 ± 1.7	176 ± 16	50.9 ± 9.1	130.5 ± 13.8
15	IIA	2BOH	-11.7	911 ± 50	91 ± 5	-77.9 ± 1.9	187 ± 10	59.7 ± 7.4	150.2 ± 10.8
16	IIE	2BQW	-11.7	1067 ± 112	111 ± 17	-82.3 ± 1.9	217 ± 22	82.4 ± 18.3	192.8 ± 35.6
17	GSX	2J95	-11.5	816 ± 56	82 ± 6	-72.7 ± 1.7	172 ± 14	47.2 ± 7.0	129.1 ± 12.0
18	GS6	2J34	-10.7	782 ± 68	80 ± 6	-67.5 ± 1.9	166 ± 11	42.7 ± 10.2	122.0 ± 14.9
19	DX9	1FAX	-10.1	868 ± 77	98 ± 9	-78.3 ± 1.9	193 ± 18	48.5 ± 14.9	145.9 ± 18.3
20	GS5	2J38	-10.0	767 ± 66	73 ± 7	-62.1 ± 1.8	168 ± 12	39.2 ± 9.6	112.0 ± 15.5
21	IID	2BQ7	-9.7	960 ± 125	92 ± 16	-66.2 ± 1.9	194 ± 28	67.7 ± 18.1	159.2 ± 34.0
22	894	2UWP	-9.4	822 ± 74	88 ± 9	-70.3 ± 1.8	182 ± 20	43.4 ± 13.4	130.7 ± 16.6
23	G15	2J94	-8.6	695 ± 51	71 ± 5	-62.8 ± 1.9	174 ± 12	27.3 ± 7.5	98.2 ± 10.7

Table S13. SMD results obtained for 23 HIV-1 complexes. ΔG_{neq}^{Jar}, $\Delta G_{unbind}^{\ddagger}$, and $\Delta G_{bind}^{\ddagger}$ were obtained using the Jarzynski's equality.

No.	Ligand PDB ID	Complex PDB ID	ΔG_{exp} (kcal/mol)	F_{max} (pN)	W_{pull} (kcal/mol)	$\Delta G_{\mathrm{neq}}^{Jar}$ (kcal/mol)	t_{max} (ps)	$\Delta G_{unbind}^{\ddagger}$ (kcal/mol)	$\Delta G_{bind}^{\ddagger}$ (kcal/mol)
1	A79	1HVK	-15.04	1984 ± 229	359 ± 58	-280.2 ± 1.9	423 ± 44	272.7 ± 69.7	631.6 ± 127.3
2	A76	1HVL	-13.66	2065 ± 255	392 ± 71	-260.6 ± 1.9	446 ± 50	293.0 ± 80.6	684.9 ± 151.6
3	BEB	1EBY	-13.31	1782 ± 221	321 ± 52	-236.7 ± 1.9	397 ± 46	214.2 ± 62.0	534.6 ± 113.8
4	MK1	1C6Y	-13.05	1620 ± 248	281 ± 51	-183.4 ± 2.0	366 ± 45	174.4 ± 63.1	455.0 ± 114.0
5	MK1	2BPX	-12.9	1989 ± 240	386 ± 74	-250.3 ± 2.0	441 ± 58	259.4 ± 71.1	645.3 ± 144.8
6	MS3	1EC3	-12.4	2244 ± 325	444 ± 102	-247.2 ± 2.0	470 ± 67	360.8 ± 106.0	804.1 ± 208.2
7	BEE	1EC1	-12.24	1695 ± 217	302 ± 51	-206.1 ± 1.9	389 ± 49	183.9 ± 57.6	485.2 ± 108.8
8	1AH	2CEJ	-11.83	2011 ± 288	361 ± 78	-208.2 ± 2.0	432 ± 61	280.1 ± 83.2	640.6 ± 161.7
9	HI1	2UXZ	-11.64	1939 ± 174	337 ± 44	-243.0 ± 2.0	415 ± 35	258.0 ± 50.8	595.0 ± 95.3

10	MSC	1D4J	-11.47	2082 ± 237	382 ± 66	-250.2 ± 2.0	442 ± 49	301.7 ± 66.8	683.6 ± 132.4
11	4AH	2CEN	-11.39	1838 ± 252	323 ± 63	-195.1 ± 2.0	401 ± 56	230.9 ± 61.7	554.0 ± 124.5
12	AHF	1G35	-11.17	2090 ± 245	382 ± 72	-214.1 ± 2.0	451 ± 48	300.9 ± 74.2	682.0 ± 146.0
13	A1A	2BQV	-11.04	2037 ± 233	362 ± 61	-239.2 ± 2.0	433 ± 48	289.2 ± 69.0	650.8 ± 130.2
14	IM1	1SBG	-10.63	1485 ± 198	242 ± 34	-168.7 ± 2.0	325 ± 42	152.0 ± 41.2	393.6 ± 75.1
15	1IN	2BPV	-10.53	1713 ± 274	285 ± 64	-188.3 ± 2.0	373 ± 55	203.2 ± 67.8	487.9 ± 132.0
16	3IN	2BPY	-10.16	1532 ± 203	253 ± 37	-163.9 ± 2.0	337 ± 44	160.8 ± 42.2	413.4 ± 79.4
17	U02	2UPJ	-10.14	1394 ± 221	212 ± 44	-127.2 ± 2.0	322 ± 52	126.0 ± 41.3	337.8 ± 85.4
18	HV1	2UY0	-9.5	1942 ± 232	344 ± 54	-231.2 ± 1.9	418 ± 46	260.4 ± 66.1	603.7 ± 120.4
19	G4G	2PWR	-9.04	1613 ± 262	253 ± 54	-146.2 ± 2.0	348 ± 54	182.0 ± 60.1	434.5 ± 113.8
20	G3G	2PWC	-9.02	1425 ± 188	213 ± 38	-134.3 ± 2.0	310 ± 44	143.6 ± 41.4	356.1 ± 79.6
21	GAN	1HBV	-8.74	1712 ± 328	291 ± 77	-125.7 ± 2.0	372 ± 71	209.4 ± 77.6	500.0 ± 154.3
22	LJG	3BGB	-8.3	1354 ± 200	206 ± 32	-146.3 ± 2.0	290 ± 45	130.2 ± 38.6	335.6 ± 70.3
23	LJH	3BGC	-6.89	1300 ± 211	207 ± 35	-130.0 ± 1.9	294 ± 43	113.5 ± 37.5	319.8 ± 72.8

Table S14. SMD results obtained for 23 MCL-1 complexes. ΔG_{neq}^{Jar}, $\Delta G_{unbind}^{\ddagger}$, and $\Delta G_{bind}^{\ddagger}$ were obtained using the Jarzynski's equality.

No.	Ligand PDB ID	Complex PDB ID	ΔG_{exp} (kcal/mol)	F_{max} (pN)	W_{pull} (kcal/mol)	$\Delta G_{\mathrm{neq}}^{Jar}$ (kcal/mol)	t_{max} (ps)	$\Delta G_{unbind}^{\ddagger}$ (kcal/mol)	$\Delta G_{bind}^{\ddagger}$ (kcal/mol)
1	KJP	6NE5	-14.44	1088 ± 111	120 ± 18	-81.7 ± 1.9	246 ± 24	77.7 ± 16.6	197.2 ± 34.3
2	N0S	6OQC	-14.27	1239 ± 147	135 ± 26	-84.8 ± 2.0	257 ± 32	111.5 ± 25.4	246.6 ± 51.6
3	N0J	6OQB	-14.14	1135 ± 100	119 ± 15	-77.8 ± 2.0	241 ± 21	90.6 ± 17.6	209.4 ± 32.5
4	Q51	6UDV	-14.13	1126 ± 106	118 ± 16	-76.0 ± 1.9	243 ± 22	88.0 ± 16.8	205.7 ± 32.5
5	Q4D	6UD2	-14.01	1397 ± 155	180 ± 33	-79.9 ± 2.0	304 ± 35	130.5 ± 27.5	309.7 ± 60.4
6	Q4S	6UDI	-13.73	1408 ± 134	171 ± 28	-88.0 ± 2.0	299 ± 29	138.8 ± 26.3	309.3 ± 53.8
7	Q4V	6UDT	-13.73	1093 ± 214	116 ± 33	-61.8 ± 2.0	234 ± 45	86.7 ± 32.5	202.9 ± 65.3
8	N0M	6OQD	-13.53	999 ± 117	104 ± 16	-68.4 ± 2.0	214 ± 26	69.8 ± 17.4	173.4 ± 33.6
9	5X3	5FDR	-12.9	756 ± 90	73 ± 8	-57.4 ± 1.8	165 ± 19	40.3 ± 9.6	112.6 ± 17.6
10	Q4Y	6UDU	-12.77	1452 ± 152	174 ± 31	-95.1 ± 2.0	302 ± 31	151.5 ± 31.3	325.3 ± 62.8
11	ECM	6BW8	-12.61	1108 ± 109	121 ± 20	-91.2 ± 1.8	237 ± 24	85.3 ± 16.3	205.7 ± 35.9
12	CN7	6B4U	-11.04	728 ± 97	67 ± 8	-52.1 ± 1.9	158 ± 21	38.8 ± 11.0	105.7 ± 18.8
13	ECY	6BW2	-10.54	761 ± 142	77 ± 13	-46.6 ± 1.8	164 ± 30	42.1 ± 14.5	118.8 ± 27.5
14	6AL	5IEZ	-10.48	731 ± 73	74 ± 7	-58.4 ± 2.0	163 ± 16	37.6 ± 8.0	110.8 ± 15.2
15	JL5	6QYP	-10.07	712 ± 77	62 ± 8	-40.3 ± 2.0	152 ± 16	36.8 ± 7.9	98.1 ± 16.5
16	JL8	6QZ8	-10.01	760 ± 87	62 ± 8	-45.3 ± 1.9	158 ± 20	43.3 ± 9.5	105.4 ± 18.1
17	19H	4HW2	-9.96	833 ± 94	78 ± 12	-46.5 ± 2.0	181 ± 21	49.3 ± 10.5	127.5 ± 22.2
18	5WL	5FC4	-9.11	537 ± 58	50 ± 7	-34.0 ± 2.0	125 ± 19	21.3 ± 4.8	71.0 ± 12.1
19	4M6	4ZBI	-8.93	800 ± 107	75 ± 10	-55.1 ± 1.9	173 ± 22	46.5 ± 11.5	121.1 ± 21.2
20	19G	4HW3	-8.91	815 ± 124	76 ± 13	-49.2 ± 1.9	178 ± 28	47.5 ± 13.9	123.3 ± 27.2
21	CJY	6B4L	-8.88	773 ± 93	67 ± 11	-43.8 ± 2.0	165 ± 24	43.2 ± 9.0	110.0 ± 20.2
22	5X2	5FDO	-8.84	798 ± 110	76 ± 10	-57.2 ± 1.9	171 ± 25	45.3 ± 12.4	120.6 ± 22.0
23	JLK	6QZB	-7.71	613 ± 82	48 ± 7	-26.9 ± 2.0	131 ± 18	27.8 ± 7.5	75.0 ± 14.6

Table S15. SMD results obtained for 23 CDK-2 complexes. ΔG_{neq}^{Jar}, $\Delta G_{unbind}^{\ddagger}$, and $\Delta G_{bind}^{\ddagger}$ were obtained using the Jarzynski's equality.

No.	Ligand PDB ID	Complex PDB ID	ΔG_{exp} (kcal/mol)	F_{max} (pN)	W_{pull} (kcal/mol)	$\Delta G_{\mathrm{neq}}^{Jar}$ (kcal/mol)	t_{max} (ps)	$\Delta G_{unbind}^{\ddagger}$ (kcal/mol)	$\Delta G_{bind}^{\ddagger}$ (kcal/mol)
1	LIA	2FVD	-11.7	1602 ± 230	230 ± 43	-153.0 ± 1.9	334 ± 44	194.0 ± 48.4	423.9 ± 107.7
2	T3E	4BCK	-11.53	1346 ± 207	200 ± 30	-159.8 ± 1.9	296 ± 42	149.9 ± 34.0	312.7 ± 70.2
3	T9N	4BCN	-10.87	1492 ± 124	226 ± 18	-154.6 ± 1.9	330 ± 31	151.7 ± 27.6	376.8 ± 39.0
4	SU9	1PF8	-10.31	1285 ± 114	156 ± 28	-118.7 ± 1.9	281 ± 26	113.2 ± 21.8	264.6 ± 42.1
5	56H	5D1J	-10.18	1611 ± 131	219 ± 27	-158.7 ± 1.9	344 ± 27	173.5 ± 22.7	403.3 ± 53.5
6	CK5	1PXM	-9.91	999 ± 191	139 ± 51	-103.9 ± 1.8	220 ± 41	88.2 ± 22.1	226.9 ± 52.4
7	CK6	1PXN	-9.82	1630 ± 236	219 ± 57	-125.8 ± 2.0	344 ± 48	185.5 ± 52.9	409.8 ± 99.6
8	T7Z	4BCM	-9.48	1212 ± 94	191 ± 25	-145.5 ± 1.8	300 ± 47	91.2 ± 18.1	279.1 ± 36.9
9	T6Q	4BCO	-9.45	1394 ± 143	186 ± 26	-138.2 ± 1.9	303 ± 27	128.4 ± 25.8	324.8 ± 59.1
10	TJF	4BCQ	-9.38	1214 ± 152	153 ± 29	-90.0 ± 1.9	267 ± 31	101.7 ± 27.6	254.1 ± 53.5
11	7YG	4ACM	-9.17	1176 ± 192	178 ± 28	-120.5 ± 1.9	275 ± 47	92.7 ± 25.5	269.9 ± 49.2
12	CK8	1PXP	-9.14	1062 ± 237	140 ± 27	-97.0 ± 1.9	233 ± 48	96.5 ± 35.2	235.6 ± 60.3
13	CK4	1PXL	-8.97	1210 ± 164	144 ± 24	-102.1 ± 1.9	260 ± 32	105.4 ± 29.7	246.5 ± 46.0
14	PM1	1PYE	-8.8	990 ± 111	130 ± 21	-80.7 ± 1.9	220 ± 32	69.6 ± 15.4	198.6 ± 30.8
15	4SP	4EOR	-8.65	1372 ± 124	177 ± 24	-111.3 ± 1.9	305 ± 26	123.7 ± 24.5	300.3 ± 47.2
16	T3C	4BCP	-8.57	1458 ± 267	192 ± 34	-122.5 ± 1.9	311 ± 54	134.5 ± 40.0	360.8 ± 101.4
17	1RO	4EOS	-8.3	1239 ± 236	168 ± 44	-95.7 ± 1.9	285 ± 44	110.9 ± 43.1	276.6 ± 92.4
18	NW1	1E1X	-8.08	1084 ± 177	128 ± 28	-73.9 ± 1.9	244 ± 43	82.1 ± 23.9	201.2 ± 50.4
19	U55	1JSV	-7.82	1061 ± 234	131 ± 33	-90.2 ± 1.9	231 ± 41	96.0 ± 42.7	206.5 ± 73.6
20	ST8	1OGU	-7.71	1106 ± 171	123 ± 27	-78.6 ± 1.9	241 ± 34	87.7 ± 27.6	210.0 ± 53.9
21	CK2	1PXJ	-7.12	1207 ± 161	152 ± 41	-99.8 ± 1.9	260 ± 34	117.7 ± 40.3	261.2 ± 70.4
22	CMG	1E1V	-6.75	926 ± 191	128 ± 24	-75.8 ± 1.9	235 ± 52	84.1 ± 28.8	208.1 ± 45.8
23	3FP	1V1K	-6.12	946 ± 136	122 ± 19	-74.8 ± 1.9	227 ± 30	56.8 ± 17.0	174.9 ± 35.0

Table S16 - Average polar and non-polar interaction energy in the bound and free state for 23 factor Xa complexes. Absolute binding free energy ΔG_{LIE} was obtained for α=1 (optimal value for a set of 23 compounds).

No.	Factor Xa PDB ID	ΔG_{exp}	$\langle V^{\mathrm{elec}} \rangle_{\mathrm{bound}}$	$\langle V^{\mathrm{elec}} \rangle_{\mathrm{free}}$	$\langle V^{\mathrm{vdw}} \rangle_{\mathrm{bound}}$	$\langle V^{\mathrm{vdw}} \rangle_{\mathrm{free}}$	ΔG_{LIE} $\alpha = 1$
1	2P3T	-15.5	-43.1 ± 4.7	-37.1 ± 3	-118.9 ± 5.8	-37.1 ± 3.1	-84.4 ± 12.3
2	1MQ6	-15.3	-41.7 ± 3.1	-31.3 ± 2.6	-135.4 ± 5.1	-35 ± 2.9	-104.8 ± 10.4
3	3CS7	-14.6	-20.9 ± 2.1	-16.4 ± 1.6	-121.8 ± 5.5	-41.4 ± 2.5	-82.3 ± 9.6
4	2FZZ	-14.4	-38.6 ± 3.8	-29.6 ± 2.6	-121.2 ± 6.8	-40.7 ± 3.4	-83.8 ± 12.6
5	2BQ6	-13.9	-25 ± 2.9	-20.1 ± 2.3	-119.6 ± 3.9	-38.6 ± 2.6	-83.1 ± 8.7
6	2P16	-13.8	-30.8 ± 4.1	-27.9 ± 3	-111 ± 5.3	-34.8 ± 3.2	-77.4 ± 11.5
7	1FJS	-13.7	-50.4 ± 5.5	-49.1 ± 3.4	-104.5 ± 4.5	-27.7 ± 4.2	-77.2 ± 11.6
8	2G00	-13.4	-29.3 ± 2.8	-26.6 ± 2.6	-114.2 ± 5.4	-38.4 ± 3.1	-76.9 ± 10.9
9	1Z6E	-13.3	-41.7 ± 5	-30.7 ± 2.9	-113.4 ± 4.4	-36 ± 3.1	-82.1 ± 10.9
10	2W26	-12.9	-31.5 ± 3.1	-24.4 ± 2.5	-106.6 ± 3.4	-33.2 ± 2.5	-76.4 ± 8.3
11	2P95	-12.8	-28.5 ± 2.5	-25.6 ± 2.3	-101.8 ± 3.3	-32.8 ± 2.7	-70.3 ± 7.9
12	1MQ5	-12.4	-33.8 ± 3.5	-22.9 ± 2.2	-117.4 ± 6.4	-36 ± 2.8	-86 ± 11.6
13	2J4I	-12.4	-53.4 ± 4.6	-37.3 ± 2.5	-122.2 ± 5.3	-31 ± 2.9	-98.2 ± 11.2
14	2P93	-12.1	-26.8 ± 2.7	-23 ± 2.2	-97.8 ± 3.9	-29.6 ± 2.9	-69.9 ± 8.9
15	2BOH	-11.7	-17.8 ± 2.8	-17.5 ± 1.9	-116.2 ± 3.8	-39.1 ± 2.6	-77.3 ± 8.4
16	2BQW	-11.7	-28.5 ± 2.4	-23.4 ± 2.3	-116.9 ± 4.5	-31.2 ± 2.9	-87.9 ± 9.5

17	2J95	-11.5	-39.6 ± 3.8	-26.8 ± 2.4	-114.6 ± 3.2	-29.4 ± 3	-90.7 ± 8.8
18	2J34	-10.7	-32.4 ± 3.1	-28 ± 2.5	-106.8 ± 3.9	-31.7 ± 2.9	-76.9 ± 9.2
19	1FAX	-10.1	-56.7 ± 5.4	-42.2 ± 3.1	-100.3 ± 6.4	-28.9 ± 3.5	-76.8 ± 13
20	2J38	-10.0	-29.1 ± 5.6	-25.7 ± 2.6	-97.8 ± 5.2	-29.6 ± 3.1	-69.6 ± 11.9
21	2BQ7	-9.7	-19 ± 3.1	-18.8 ± 2.1	-105 ± 3.4	-30.8 ± 2.5	-74.3 ± 8.1
22	2UWP	-9.4	-38.1 ± 3.6	-26.9 ± 3	-101.6 ± 3.9	-28.2 ± 2.7	-78.2 ± 9.4
23	2J94	-8.6	-42.8 ± 3.3	-37.9 ± 2.8	-105.2 ± 4.3	-31.1 ± 3.3	-76.2 ± 10.2

Table S17 - Average polar and non-polar interaction energy in the bound and free state for 23 Thrombin complexes. Absolute binding free energy $\Delta G_{\mathrm{LIE}}$was obtained for α=0.16 (optimal value for a set of 23 compounds).

No.	Thrombin PDB ID	ΔG_{exp}	$\langle V^{\mathrm{elec}} \rangle_{\mathrm{bound}}$	$\langle V^{\mathrm{elec}} \rangle_{\mathrm{free}}$	$\langle V^{\mathrm{vdw}} \rangle_{\mathrm{bound}}$	$\langle V^{\mathrm{vdw}} \rangle_{\mathrm{free}}$	ΔG_{LIE} $\alpha = 0.16$
1	1SL3	-16.3	-48.4 ± 3.5	-33.1 ± 3.1	-114.3 ± 5.9	-34.9 ± 3.1	-20.3 ± 4.8
2	1C4V	-14.8	-47.5 ± 3.8	-38 ± 2.9	-114 ± 6	-35.5 ± 3.7	-16.7 ± 4.4
3	1C4U	-14.2	-52.7 ± 4.7	-35.1 ± 3.1	-62.4 ± 4.5	-17.3 ± 3.2	-14.8 ± 4.6
4	2ZO3	-13.7	-47.4 ± 4.5	-40.4 ± 3.3	-96.9 ± 5.9	-32.1 ± 3.5	-13.3 ± 4.9
5	1TA6	-12.5	-31.4 ± 3.7	-30.3 ± 2.7	-110.1 ± 5.5	-34.6 ± 2.9	-12.6 ± 4.1
6	1NT1	-12.2	-39.4 ± 3.9	-30.9 ± 2.6	-110.6 ± 5.5	-33.8 ± 3	-15.9 ± 4.1
7	1BMN	-11.6	-43.4 ± 5.7	-47.7 ± 3.3	-110.4 ± 6.9	-28.8 ± 3.6	-11.5 ± 5
8	1ETS	-11.3	-50.1 ± 6.1	-41.2 ± 3.8	-103.5 ± 7.8	-31.9 ± 3.5	-15.3 ± 6.1
9	2JH6	-10.7	-31.2 ± 4	-29.3 ± 3.6	-101.9 ± 4.7	-29.4 ± 3.3	-12.4 ± 4.5
10	3DHK	-10.0	-28.9 ± 4.1	-27.6 ± 2.4	-99.4 ± 4.8	-33.8 ± 2.7	-11 ± 4
11	3DUX	-9.6	-18.5 ± 3.3	-21.1 ± 2.4	-98.5 ± 5.4	-30.1 ± 2.6	-9.8 ± 3.7
12	2ZC9	-9.2	-24.8 ± 3.9	-24.5 ± 2.5	-85.5 ± 5.5	-27.7 ± 2.5	-9.3 ± 4.1
13	2ZGX	-9.2	-30.2 ± 3.9	-35.8 ± 3	-85.2 ± 5	-22.1 ± 2.8	-7.7 ± 4.2
14	2JH5	-9.0	-31.9 ± 3.3	-27.9 ± 2.9	-101.7 ± 5	-30.2 ± 2.9	-13.2 ± 3.9
15	1AWH	-8.3	-42.4 ± 4.1	-36.4 ± 2.9	-98.7 ± 6.3	-31.2 ± 3.6	-12.8 ± 3.9
16	1D6W	-8.2	-53.2 ± 5.4	-46.9 ± 3.2	-104 ± 7.1	-30.7 ± 3.4	-14.4 ± 5.4
17	3SHC	-7.8	-25.8 ± 3.3	-30 ± 2.8	-87.7 ± 4.6	-27 ± 3	-7.9 ± 3.8
18	3SHA	-7.7	-26.7 ± 3.3	-28.2 ± 2.9	-87.8 ± 5.3	-27 ± 2.8	-9.1 ± 4
19	2ZFP	-7.1	-24.8 ± 3.8	-21.8 ± 2.3	-74.8 ± 5.9	-22.8 ± 2.6	-9.6 ± 4
20	3F68	-6.9	-21 ± 4.4	-19 ± 2.2	-100 ± 5.5	-32.4 ± 2.3	-11.7 ± 4.1
21	3EGK	-6.4	-21.4 ± 2.4	-20.8 ± 2.4	-90.5 ± 5.4	-32.4 ± 2.7	-9.5 ± 3.4
22	3P17	-6.1	-24.3 ± 4	-31.9 ± 2.6	-79.7 ± 5	-25.5 ± 3.1	-5.4 ± 4.2
23	3SV2	-5.8	-27.1 ± 4.3	-30.7 ± 2.6	-78.2 ± 5.1	-25.5 ± 3.2	-6.9 ± 4.3

Table S18 - Average polar and non-polar interaction energy in the bound and free state for 23 HIV-1 complexes. Absolute binding free energy $\Delta G_{\mathrm{LIE}}$was obtained for α=0.16 (optimal value for a set of 23 compounds).

No.	HIV-1 PDB ID	ΔG_{exp}	$\langle V^{\text{elec}} \rangle_{\text{bound}}$	$\langle V^{\text{elec}} \rangle_{\text{free}}$	$\langle V^{\text{vdw}} \rangle_{\text{bound}}$	$\langle V^{\text{vdw}} \rangle_{\text{free}}$	ΔG_{LIE} $\alpha = 0.43$
1	1HVK	-15.04	-72.8 ± 6.4	-85.8 ± 4.0	-103.5 ± 10.9	-48.6 ± 4.7	-19.3 ± 10.2
2	1HVL	-13.66	-73.8 ± 6.2	-82.5 ± 4.4	-101.8 ± 10.8	-49.3 ± 4.7	-19.7 ± 10.1
3	1EBY	-13.31	-63.7 ± 6.4	-81.3 ± 2.5	-88.4 ± 11.8	-39.9 ± 3.4	-15.0 ± 9.5
4	1C6Y	-13.05	-55.4 ± 5.2	-73.8 ± 4.3	-84.1 ± 8.5	-40.9 ± 5.1	-12.5 ± 9.0
5	2BPX	-12.9	-70.2 ± 6.9	-68.3 ± 3.9	-78.3 ± 7.7	-41.3 ± 4.0	-16.5 ± 8.6
6	1EC3	-12.4	-87.9 ± 8.0	-83.4 ± 4.4	-110.5 ± 11.6	-50.3 ± 3.9	-27.4 ± 10.7
7	1EC1	-12.24	-65.8 ± 6.1	-86.4 ± 3.6	-94.1 ± 9.6	-49.4 ± 4.4	-12.4 ± 9.2
8	2CEJ	-11.83	-57.5 ± 8.3	-71.8 ± 3.6	-71.7 ± 8.1	-40.1 ± 3.1	-8.9 ± 8.7
9	2UXZ	-11.64	-57.6 ± 4.3	-77.7 ± 3.2	-81.6 ± 7.7	-40.7 ± 5.1	-11.0 ± 8.0
10	1D4J	-11.47	-65.4 ± 5.0	-76.3 ± 3.5	-76.9 ± 9.1	-42.3 ± 3.7	-11.3 ± 8.3
11	2CEN	-11.39	-57.3 ± 6.7	-77.5 ± 3.4	-89.0 ± 9.2	-41.7 ± 4.0	-13.7 ± 9.0
12	1G35	-11.17	-68.7 ± 5.6	-71.4 ± 3.4	-73.1 ± 7.6	-40.8 ± 3.7	-13.0 ± 7.8
13	2BQV	-11.04	-55.8 ± 5.8	-69.5 ± 3.2	-75.6 ± 7.3	-36.7 ± 3.1	-12.2 ± 7.5
14	1SBG	-10.63	-42.9 ± 6.6	-64.3 ± 3.2	-73.9 ± 8.6	-32.7 ± 3.2	-9.8 ± 8.7
15	2BPV	-10.53	-58.7 ± 4.9	-74.7 ± 3.2	-83.1 ± 9.7	-42.9 ± 4.0	-12.0 ± 8.6
16	2BPY	-10.16	-71.8 ± 5.4	-82.9 ± 3.8	-89.2 ± 9.6	-48.7 ± 4.2	-13.7 ± 9.0
17	2UPJ	-10.14	-60.7 ± 7.0	-61.9 ± 3.8	-64.0 ± 6.1	-41.5 ± 3.5	-9.2 ± 8.1
18	2UY0	-9.5	-45.7 ± 7.0	-80.8 ± 3.5	-82.4 ± 7.9	-41.5 ± 3.9	-6.0 ± 8.5
19	2PWR	-9.04	-61.9 ± 6.4	-66.5 ± 3.8	-89.9 ± 8.2	-35.9 ± 3.8	-21.2 ± 9.6
20	2PWC	-9.02	-53.0 ± 5.9	-61.1 ± 2.9	-79.2 ± 8.4	-29.4 ± 3.8	-17.9 ± 9.0
21	1HBV	-8.74	-70.6 ± 8.4	-64.0 ± 4.5	-74.6 ± 8.6	-38.8 ± 4.0	-18.2 ± 11.0
22	3BGB	-8.3	-48.7 ± 5.1	-63.1 ± 2.9	-76.7 ± 6.5	-34.2 ± 4.0	-12.1 ± 8.0
23	3BGC	-6.89	-47.4 ± 7.4	-69.0 ± 3.4	-86.2 ± 8.3	-35.0 ± 5.2	-12.7 ± 10.4

Table S19 - Average polar and non-polar interaction energy in the bound and free state for 23 MCL-1 complexes. Absolute binding free energy $\Delta G_{\text{LIE}}$was obtained for α=0.16 (optimal value for a set of 23 compounds) and α=0.11 (optimal value for a combined set of 69 compounds).

No.	MCL-1 PDB ID	ΔG_{exp}	$\langle V^{\text{elec}} \rangle_{\text{bound}}$	$\langle V^{\text{elec}} \rangle_{\text{free}}$	$\langle V^{\text{vdw}} \rangle_{\text{bound}}$	$\langle V^{\text{vdw}} \rangle_{\text{free}}$	ΔG_{LIE} $\alpha = 1$
1	6NE5	-14.44	-130.1 ± 3.0	-140.8 ± 7.6	-60.5 ± 2.0	-35.2 ± 4.0	-21.3 ± 10.0
2	6OQC	-14.27	-45.4 ± 2.6	-56.5 ± 5.8	-69.4 ± 1.4	-39.2 ± 3.5	-26.1 ± 8.0
3	6OQB	-14.14	-45.9 ± 2.8	-57.0 ± 5.8	-69.4 ± 1.6	-40.6 ± 3.3	-24.7 ± 8.0
4	6UDV	-14.13	-53.9 ± 3.2	-61.8 ± 6.2	-69.4 ± 2.0	-40.8 ± 3.8	-25.7 ± 9.2
5	6UD2	-14.01	-57.2 ± 7.7	-71.8 ± 9.8	-89.5 ± 1.6	-57.1 ± 3.9	-27.1 ± 12.0
6	6UDI	-13.73	-49.4 ± 4.7	-62.4 ± 7.8	-75.3 ± 1.8	-47.5 ± 3.7	-22.9 ± 10.1
7	6UDT	-13.73	-46.3 ± 5.8	-51.3 ± 7.4	-64.6 ± 2.7	-39.8 ± 3.6	-23.1 ± 10.6
8	6OQD	-13.53	-45.4 ± 2.6	-57.8 ± 5.9	-67.2 ± 1.5	-39.9 ± 3.5	-22.7 ± 8.1

9	5FDR	-12.9	-86.0 ± 2.6	-96.4 ± 7.4	-54.4 ± 1.9	-35.6 ± 4.5	-15.0 ± 10.0
10	6UDU	-12.77	-48.0 ± 10.0	-49.5 ± 5.8	-62.1 ± 1.9	-35.8 ± 3.4	-25.8 ± 10.5
11	6BW8	-12.61	-53.6 ± 1.9	-62.4 ± 6.1	-68.9 ± 1.6	-42.7 ± 3.8	-22.9 ± 8.3
12	6B4U	-11.04	-32.4 ± 6.4	-51.2 ± 5.6	-59.3 ± 2.7	-36.8 ± 3.6	-15.5 ± 10.7
13	6BW2	-10.54	-49.6 ± 3.9	-65.9 ± 6.0	-63.7 ± 3.3	-40.2 ± 3.4	-17.4 ± 10.4
14	5IEZ	-10.48	-73.3 ± 2.7	-75.7 ± 8.0	-53.6 ± 1.6	-34.8 ± 4.1	-17.9 ± 9.7
15	6QYP	-10.07	-52.1 ± 3.6	-52.6 ± 5.3	-50.8 ± 2.0	-36.3 ± 3.3	-14.3 ± 8.2
16	6QZ8	-10.01	-48.3 ± 3.6	-54.0 ± 5.8	-44.8 ± 1.4	-26.4 ± 3.2	-16.5 ± 7.8
17	4HW2	-9.96	-41.2 ± 1.7	-45.0 ± 4.7	-42.6 ± 1.7	-24.4 ± 2.8	-16.8 ± 6.9
18	5FC4	-9.11	-53.0 ± 2.5	-58.6 ± 5.5	-43.7 ± 2.2	-29.9 ± 3.0	-11.4 ± 8.7
19	4ZBI	-8.93	-30.2 ± 2.2	-37.2 ± 4.9	-46.8 ± 1.2	-27.0 ± 2.7	-17.2 ± 6.6
20	4HW3	-8.91	-24.1 ± 2.7	-31.6 ± 4.7	-45.9 ± 2.0	-26.1 ± 2.8	-17.0 ± 7.6
21	6B4L	-8.88	-34.0 ± 3.0	-48.9 ± 5.7	-42.0 ± 1.4	-23.0 ± 2.9	-13.4 ± 7.6
22	5FDO	-8.84	-50.7 ± 2.6	-58.4 ± 5.1	-53.5 ± 1.2	-34.0 ± 3.4	-16.2 ± 7.9
23	6QZB	-7.71	-31.2 ± 4.2	-35.8 ± 7.8	-44.0 ± 1.3	-28.5 ± 3.1	-13.8 ± 8.8

Table S20 - Average polar and non-polar interaction energy in the bound and free state for 23 CDK-2 complexes. Absolute binding free energy ΔG_{LIE} was obtained for α=0.16 (optimal value for a set of 23 compounds) and α=0.11 (optimal value for a combined set of 69 compounds).

No.	CDK-2 PDB ID	ΔG_{exp}	$\langle V^{\mathrm{elec}} \rangle_{\mathrm{bound}}$	$\langle V^{\mathrm{elec}} \rangle_{\mathrm{free}}$	$\langle V^{\mathrm{vdw}} \rangle_{\mathrm{bound}}$	$\langle V^{\mathrm{vdw}} \rangle_{\mathrm{free}}$	ΔG_{LIE} $\alpha = 1$
1	2FVD	-11.7	-39.3 ± 5.4	-61.1 ± 7.6	-55.3 ± 3.2	-29.7 ± 4.4	-16.1 ± 13.2
2	4BCK	-11.53	-56.7 ± 6.8	-63.2 ± 8.8	-43.2 ± 4.1	-27.2 ± 4.5	-13.3 ± 15.3
3	4BCN	-10.87	-40.2 ± 5.1	-43.9 ± 6.2	-41.7 ± 3.5	-37.0 ± 3.8	-3.3 ± 11.6
4	1PF8	-10.31	-20.9 ± 3.4	-37.3 ± 6.3	-35.0 ± 2.4	-19.7 ± 3.6	-8.2 ± 10.2
5	5D1J	-10.18	-36.3 ± 4.8	-41.5 ± 6.4	-48.0 ± 3.5	-33.1 ± 3.9	-12.7 ± 12.2
6	1PXM	-9.91	-32.6 ± 5.3	-36.3 ± 5.7	-37.6 ± 3.6	-23.3 ± 3.5	-12.9 ± 11.2
7	1PXN	-9.82	-37.4 ± 5.1	-41.3 ± 6.6	-39.9 ± 3.5	-23.9 ± 3.5	-14.6 ± 11.4
8	4BCM	-9.48	-32.3 ± 6.0	-54.4 ± 7.0	-58.0 ± 3.7	-37.9 ± 4.0	-10.5 ± 13.3
9	4BCO	-9.45	-40.6 ± 5.9	-57.4 ± 7.0	-61.0 ± 3.8	-36.7 ± 4.0	-17.1 ± 13.4
10	4BCQ	-9.38	-47.2 ± 6.7	-53.5 ± 7.0	-45.0 ± 3.8	-32.4 ± 4.1	-9.9 ± 13.8
11	4ACM	-9.17	-61.4 ± 8.9	-72.5 ± 8.4	-54.2 ± 4.5	-33.5 ± 4.6	-16.0 ± 16.6
12	1PXP	-9.14	-19.7 ± 4.4	-34.6 ± 5.5	-47.4 ± 3.3	-27.6 ± 3.1	-13.4 ± 10.6
13	1PXL	-8.97	-25.4 ± 3.8	-24.3 ± 4.6	-43.8 ± 3.1	-33.0 ± 3.0	-11.2 ± 9.8
14	1PYE	-8.8	-31.9 ± 5.3	-44.5 ± 6.5	-39.2 ± 3.3	-26.4 ± 4.1	-7.3 ± 12.5
15	4EOR	-8.65	-53.6 ± 8.3	-57.5 ± 8.0	-48.8 ± 4.1	-28.5 ± 4.1	-18.6 ± 15.2
16	4BCP	-8.57	-66.6 ± 7.3	-67.5 ± 7.7	-48.4 ± 4.1	-32.3 ± 5.2	-15.7 ± 15.8
17	4EOS	-8.3	-24.9 ± 5.2	-30.8 ± 5.8	-43.5 ± 3.7	-30.2 ± 3.5	-10.8 ± 12.0
18	1E1X	-8.08	-24.8 ± 5.6	-32.8 ± 7.4	-34.6 ± 3.0	-23.8 ± 3.7	-7.4 ± 12.3
19	1JSV	-7.82	-57.5 ± 7.4	-55.1 ± 9.2	-30.0 ± 4.0	-16.6 ± 4.4	-14.5 ± 15.6

20	1OGU	-7.71	-35.2 ± 5.7	-42.3 ± 6.9	-49.2 ± 3.6	-29.3 ± 3.6	-16.8 ± 12.6
21	1PXJ	-7.12	-24.5 ± 3.6	-25.6 ± 5.2	-30.6 ± 2.4	-16.5 ± 2.8	-13.6 ± 9.0
22	1E1V	-6.75	-27.0 ± 3.7	-39.6 ± 6.1	-33.0 ± 3.2	-23.1 ± 3.3	-4.5 ± 10.7
23	1V1K	-6.12	-44.0 ± 6.0	-46.4 ± 6.7	-50.6 ± 3.9	-35.6 ± 4.4	-14.1 ± 12.9

Table S21 - Minimum value of RMSED and αmin for all studied data sets. Correlation coefficient R at αmin is given in the last column.

Dataset	min RMSED (kcal/mol)	α_{min}	*R* at α_{min}
Beta-lactamase	2.9	0.16	0.53
Factor Xa	3.7	0.12	0.17
Thrombin	3.1	0.13	0.80
HIV-1	4.2	0.35	0.23
MCL-1	1.4	0.61	0.78
CDK-2	46.4	0	0
All six sets	7.5	0.19	0.28
Combined set of thrombin, factor Xa, beta-lactamase, and MCL-1	6.3	0.15	0.35
Combined set of HIV-1 and CDK-2	5.9	0.40	0.47
Combined set of thrombin, factor Xa, beta-lactamase	4.4	0.13	0.85

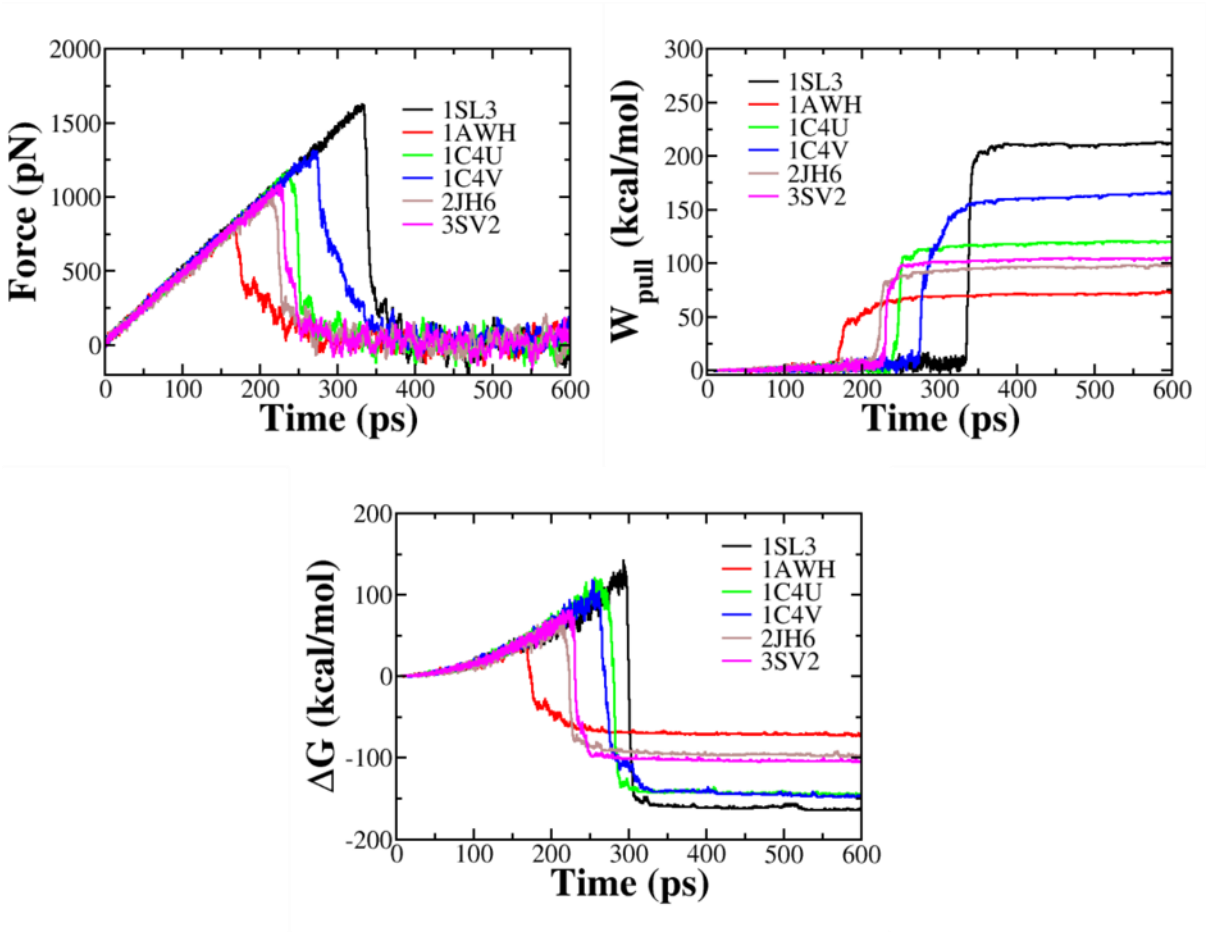


Figure S1 - Time dependence of the force, pulling work, and Jarzynski's binding free energy for six reference ligands of thrombin. Results were obtained in one SMD run.

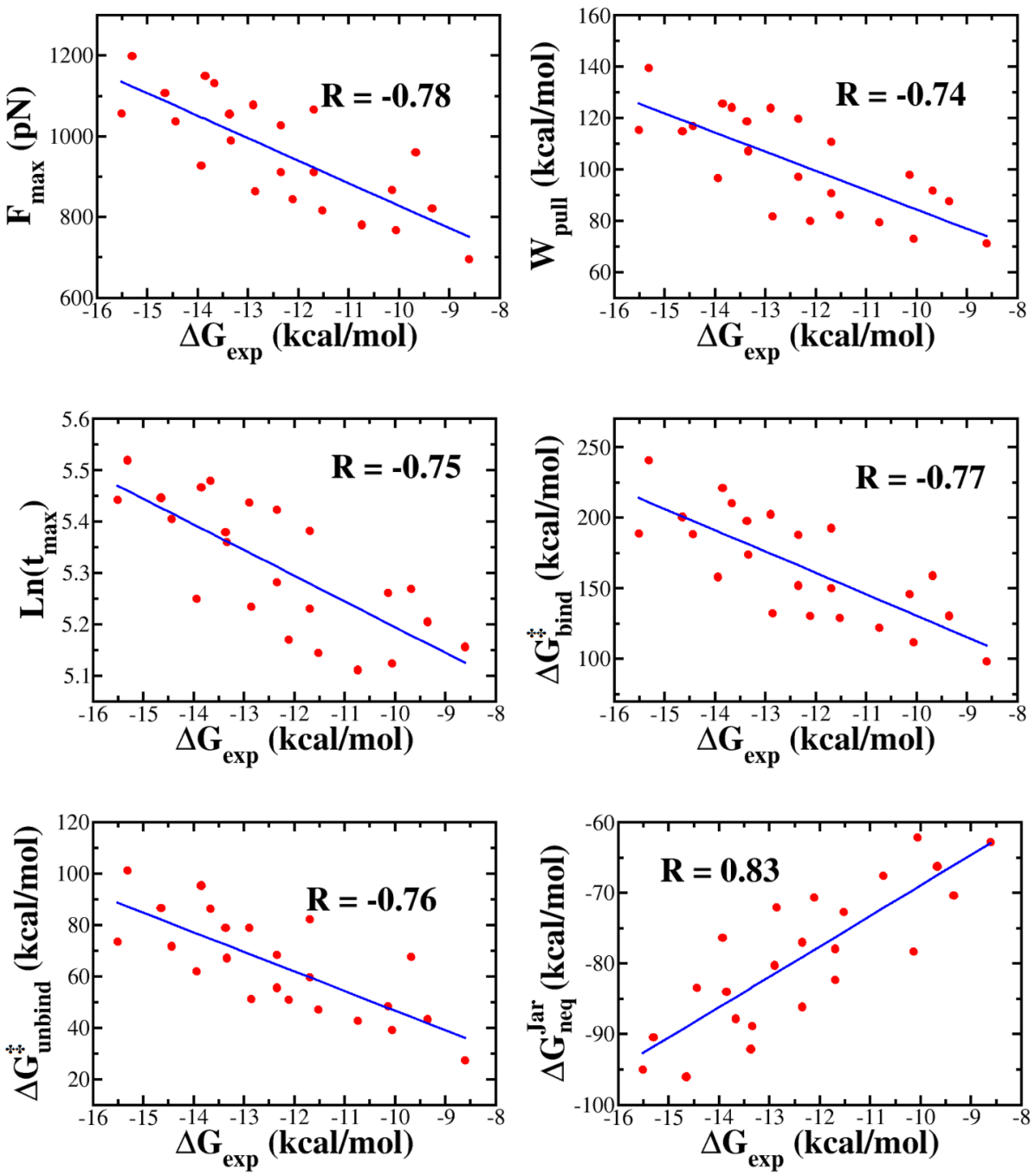


Figure S2 - Correlation between the experimental binding free energy ΔG_{exp} and the rupture force F_{max}, pulling work W_{pull}, rupture time t_{max}, binding $\Delta G^{\ddagger}_{bind}$ and unbinding $\Delta G^{\ddagger}_{unbind}$ barriers and Jarzynski's binding free energy ΔG^{Jar}_{neq}, obtained in the SMD simulation for the factor Xa complexes. Correlation coefficient R is also shown.

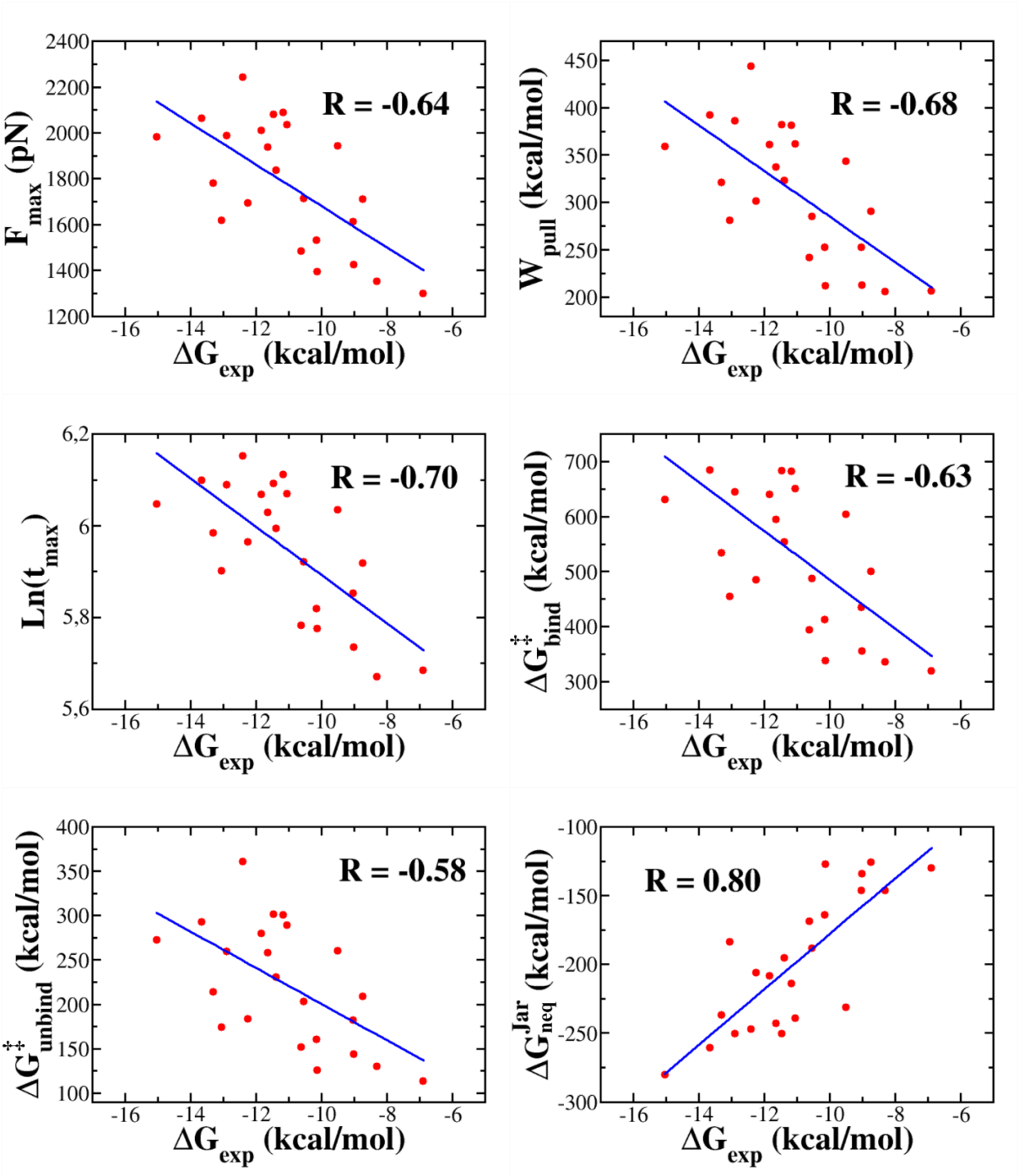


Figure S3 - Correlation between the experimental binding free energy ΔG_{exp} and the rupture force F_{max}, pulling work W_{pull}, rupture time t_{max}, binding $\Delta G^{\ddagger}_{bind}$ and unbinding $\Delta G^{\ddagger}_{unbind}$ barriers and Jarzynski's binding free energy ΔG^{Jar}_{neq}, obtained in the SMD simulation for the HIV-1 complexes. Correlation coefficient R is also shown.

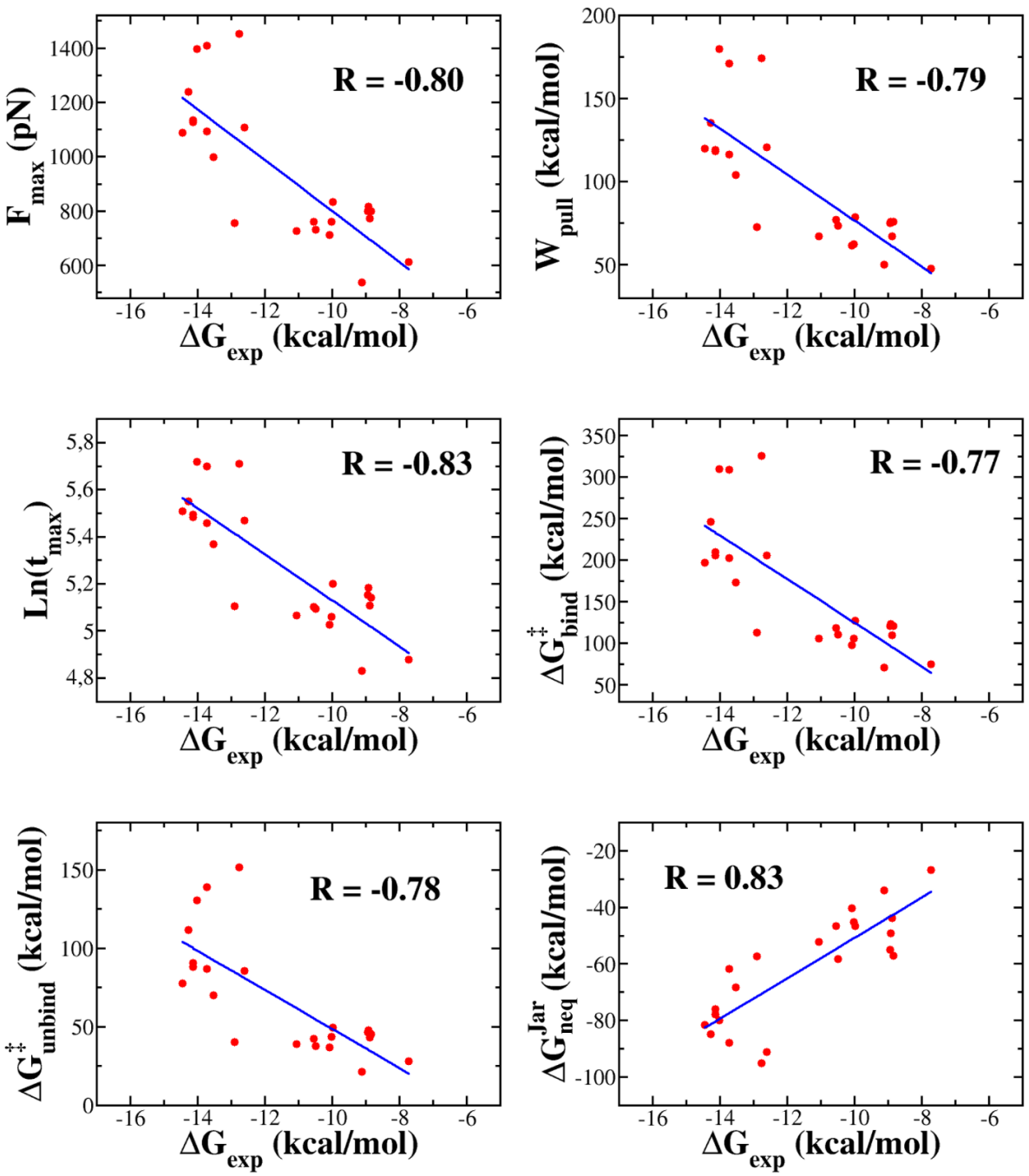


Figure S4 - Correlation between the experimental binding free energy ΔG_{exp} and the rupture force F_{max}, pulling work W_{pull}, rupture time t_{max}, binding $\Delta G^{\ddagger}_{bind}$ and unbinding $\Delta G^{\ddagger}_{unbind}$ barriers and Jarzynski's binding free energy ΔG^{Jar}_{neq}, obtained in the SMD simulation for the MCL-1 complexes. Correlation coefficient R is also shown.

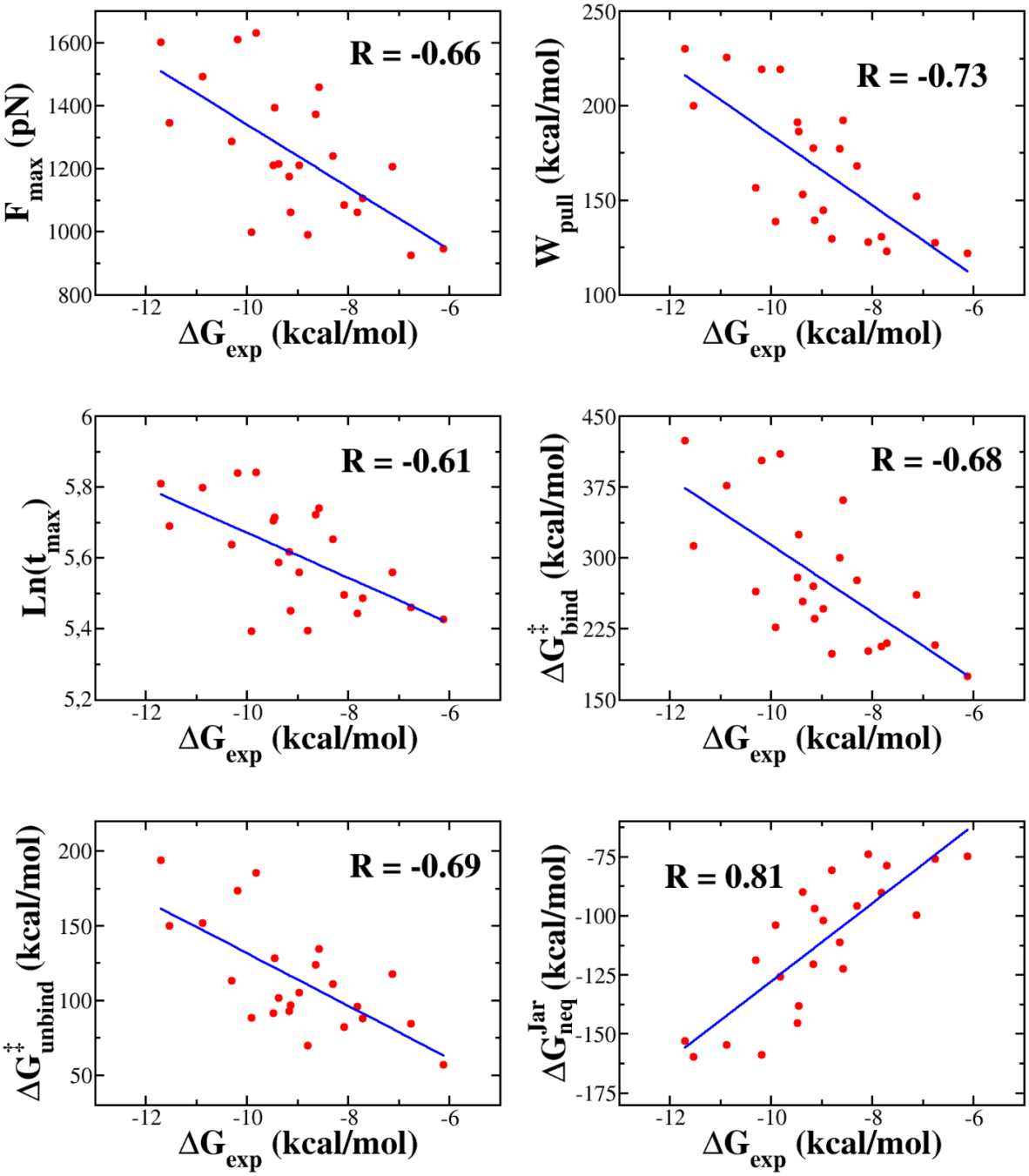


Figure S5 - Correlation between the experimental binding free energy ΔG_{exp} and the rupture force F_{max}, pulling work W_{pull}, rupture time t_{max}, binding $\Delta G^{\ddagger}_{bind}$ and unbinding $\Delta G^{\ddagger}_{unbind}$ barriers and Jarzynski's binding free energy ΔG^{Jar}_{neq}, obtained in the SMD simulation for the CDK-2 complexes. Correlation coefficient R is also shown.

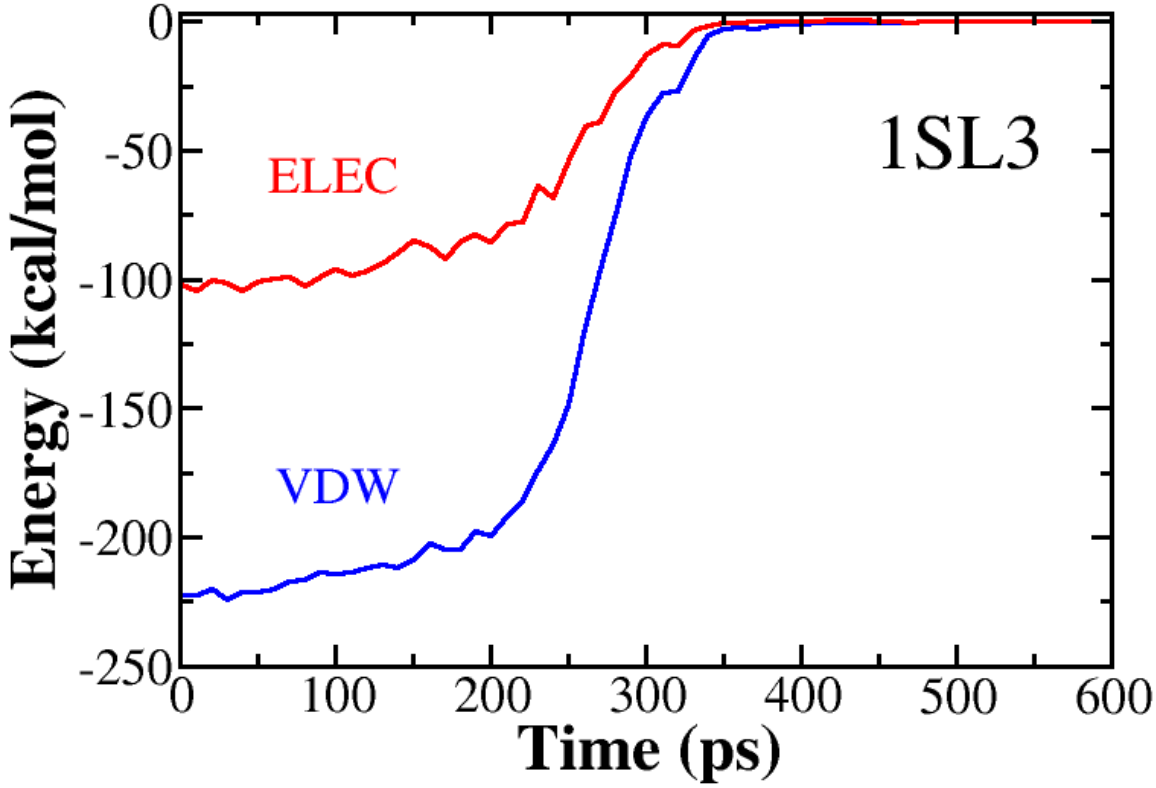


Figure S6 - The time dependence of polar and non-polar interaction energy between the ligand and protein in the absence of water for the 1SL3 complex from the thrombin set. The data were obtained by averaging over 20 trajectories.

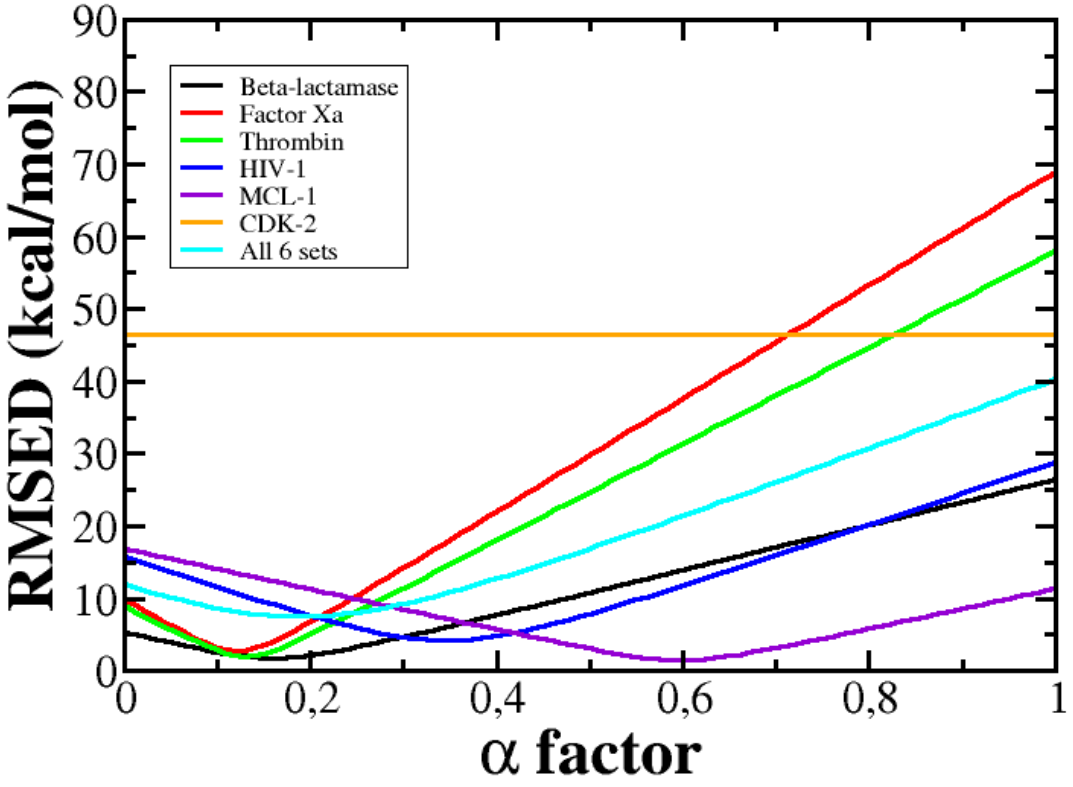


Figure S7 - Dependence of RMSED on α for six data sets and the combination of all 6 sets.

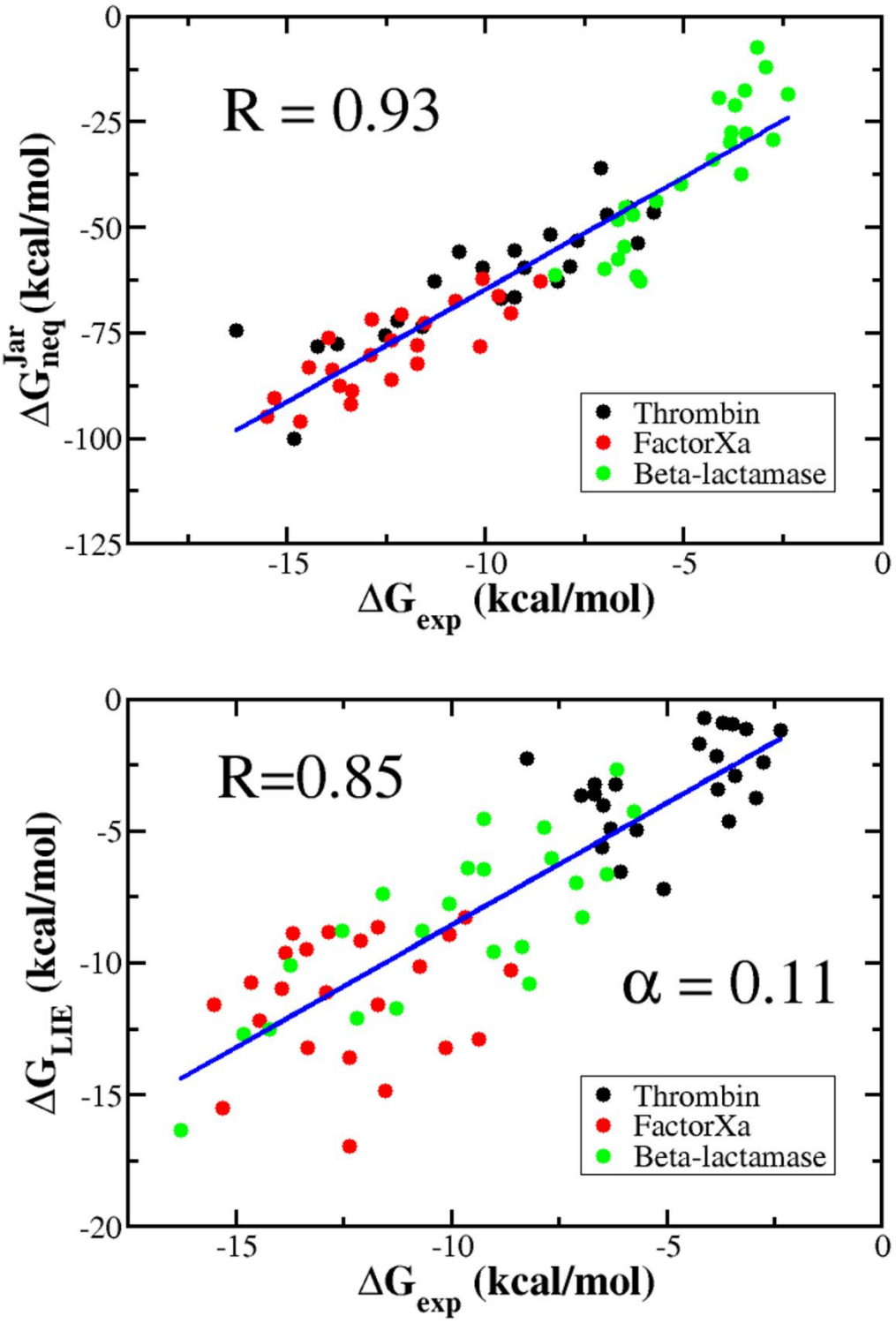


Figure S8. Correlation between the binding free energies of Jarzynski (upper panel) and LIE (lower panel) with the experimental binding free energy for 3 combined data sets including beta-lactamase, thrombin, and factor Xa. ΔG_{LIE} was obtained using α=0.11.

Reference

1. Young, M.B., et al., *Discovery and evaluation of potent P1 aryl heterocycle-based thrombin inhibitors.* J Med Chem, 2004. **47**(12): p. 2995-3008.
2. Krishnan, R., et al., *Structure of thrombin complexed with selective non-electrophilic inhibitors having cyclohexyl moieties at P1.* Acta Crystallogr D Biol Crystallogr, 2000. **56**(Pt 3): p. 294-303.
3. Baum, B., et al., *Think twice: understanding the high potency of bis(phenyl)methane inhibitors of thrombin.* J Mol Biol, 2009. **391**(3): p. 552-64.
4. Tucker, T.J., et al., *Design and synthesis of a series of potent and orally bioavailable noncovalent thrombin inhibitors that utilize nonbasic groups in the P1 position.* J Med Chem, 1998. **41**(17): p. 3210-9.
5. Nantermet, P.G., et al., *Design and synthesis of potent and selective macrocyclic thrombin inhibitors.* Bioorg Med Chem Lett, 2003. **13**(16): p. 2781-4.
6. Malley, M.F., et al., *Crystallographic determination of the structures of human alpha-thrombin complexed with BMS-186282 and BMS-189090.* Protein Sci, 1996. **5**(2): p. 221-8.
7. Brandstetter, H., et al., *Refined 2.3 A X-ray crystal structure of bovine thrombin complexes formed with the benzamidine and arginine-based thrombin inhibitors NAPAP, 4-TAPAP and MQPA. A starting point for improving antithrombotics.* J Mol Biol, 1992. **226**(4): p. 1085-99.
8. Senger, S., et al., *Sulfonamide-related conformational effects and their importance in structure-based design.* Bioorg Med Chem Lett, 2007. **17**(10): p. 2931-4.
9. Weir, M.P., et al., *Novel natural product 5,5-trans-lactone inhibitors of human alpha-thrombin: mechanism of action and structural studies.* Biochemistry, 1998. **37**(19): p. 6645-57.
10. Biela, A., et al., *Impact of ligand and protein desolvation on ligand binding to the S1 pocket of thrombin.* J Mol Biol, 2012. **418**(5): p. 350-66.
11. Gerlach, C., et al., *KNOBLE: a knowledge-based approach for the design and synthesis of readily accessible small-molecule chemical probes to test protein binding.* Angew Chem Int Ed Engl, 2007. **46**(47): p. 9105-9.
12. Ye, B., et al., *Thiophene-anthranilamides as highly potent and orally available factor Xa inhibitors.* J Med Chem, 2007. **50**(13): p. 2967-80.
13. Adler, M., et al., *Crystal structures of two potent nonamidine inhibitors bound to factor Xa.* Biochemistry, 2002. **41**(52): p. 15514-23.
14. Qiao, J.X., et al., *Achieving structural diversity using the perpendicular conformation of alpha-substituted phenylcyclopropanes to mimic the bioactive conformation of ortho-substituted biphenyl P4 moieties: discovery of novel, highly potent inhibitors of Factor Xa.* Bioorg Med Chem Lett, 2008. **18**(14): p. 4118-23.
15. Pinto, D.J., et al., *1-[3-Aminobenzisoxazol-5'-yl]-3-trifluoromethyl-6-[2'-(3-(R)-hydroxy-N-pyrrolidin yl)methyl-[1,1']-biphen-4-yl]-1,4,5,6-tetrahydropyrazolo-[3,4-c]-pyridin-7-one (BMS-740808) a highly potent, selective, efficacious, and orally bioavailable inhibitor of blood coagulation factor Xa.* Bioorg Med Chem Lett, 2006. **16**(15): p. 4141-7.
16. Nazare, M., et al., *Probing the subpockets of factor Xa reveals two binding modes for inhibitors based on a 2-carboxyindole scaffold: a study combining structure-activity relationship and X-ray crystallography.* J Med Chem, 2005. **48**(14): p. 4511-25.
17. Pinto, D.J., et al., *Discovery of 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H -pyrazolo[3,4-c]pyridine-3-carboxamide (apixaban, BMS-562247), a highly potent, selective, efficacious, and orally bioavailable inhibitor of blood coagulation factor Xa.* J Med Chem, 2007. **50**(22): p. 5339-56.
18. Adler, M., et al., *Preparation, characterization, and the crystal structure of the inhibitor ZK-807834 (CI-1031) complexed with factor Xa.* Biochemistry, 2000. **39**(41): p. 12534-42.
19. Pinto, D.J., et al., *Discovery of potent, efficacious, and orally bioavailable inhibitors of blood coagulation factor Xa with neutral P1 moieties.* Bioorg Med Chem Lett, 2006. **16**(21): p. 5584-9.
20. Quan, M.L., et al., *Discovery of 1-(3'-aminobenzisoxazol-5'-yl)-3-trifluoromethyl-N-[2-fluoro-4- [(2'-dimethylaminomethyl)imidazol-1-yl]phenyl]-1H-pyrazole-5-carboxyamide hydrochloride (razaxaban), a highly potent, selective, and orally bioavailable factor Xa inhibitor.* J Med Chem, 2005. **48**(6): p. 1729-44.
21. Roehrig, S., et al., *Discovery of the novel antithrombotic agent 5-chloro-N-({(5S)-2-oxo-3- [4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene- 2-carboxamide (BAY 59-7939): an oral, direct factor Xa inhibitor.* J Med Chem, 2005. **48**(19): p. 5900-8.
22. Qiao, J.X., et al., *SAR and X-ray structures of enantiopure 1,2-cis-(1R,2S)-cyclopentyldiamine and cyclohexyldiamine derivatives as inhibitors of coagulation Factor Xa.* Bioorg Med Chem Lett, 2007. **17**(16): p. 4419-27.
23. Young, R.J., et al., *Structure- and property-based design of factor Xa inhibitors: pyrrolidin-2-ones with acyclic alanyl amides as P4 motifs.* Bioorg Med Chem Lett, 2006. **16**(23): p. 5953-7.
24. Chan, C., et al., *Factor Xa inhibitors: S1 binding interactions of a series of N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}sulfon amides.* J Med Chem, 2007. **50**(7): p. 1546-57.
25. Senger, S., et al., *Arylsulfonamides: a study of the relationship between activity and conformational preferences for a series of factor Xa inhibitors.* Bioorg Med Chem Lett, 2006. **16**(22): p. 5731-5.
26. Brandstetter, H., et al., *X-ray structure of active site-inhibited clotting factor Xa. Implications for drug design and substrate recognition.* J Biol Chem, 1996. **271**(47): p. 29988-92.
27. Young, R.J., et al., *Selective and dual action orally active inhibitors of thrombin and factor Xa.* Bioorg Med Chem Lett, 2007. **17**(10): p. 2927-30.
28. Hosur, M.V., et al., *Influence of stereochemistry on activity and binding modes for C2 symmetry-based diol inhibitors of HIV-1 protease.* Journal of the American Chemical Society, 1994. **116**(3): p. 847-855.

29. Andersson, H.O., et al., *Optimization of P1-P3 groups in symmetric and asymmetric HIV-1 protease inhibitors.* Eur J Biochem, 2003. **270**(8): p. 1746-58.
30. Munshi, S., et al., *An alternate binding site for the P1-P3 group of a class of potent HIV-1 protease inhibitors as a result of concerted structural change in the 80s loop of the protease.* Acta Crystallogr D Biol Crystallogr, 2000. **56**(Pt 4): p. 381-8.
31. Munshi, S., et al., *Rapid X-ray diffraction analysis of HIV-1 protease-inhibitor complexes: inhibitor exchange in single crystals of the bound enzyme.* Acta Crystallogr D Biol Crystallogr, 1998. **54**(Pt 5): p. 1053-60.
32. Ekegren, J.K., et al., *Microwave-accelerated synthesis of P1'-extended HIV-1 protease inhibitors encompassing a tertiary alcohol in the transition-state mimicking scaffold.* J Med Chem, 2006. **49**(5): p. 1828-32.
33. Wu, X., et al., *Two-carbon-elongated HIV-1 protease inhibitors with a tertiary-alcohol-containing transition-state mimic.* J Med Chem, 2008. **51**(4): p. 1053-7.
34. Schaal, W., et al., *Synthesis and comparative molecular field analysis (CoMFA) of symmetric and nonsymmetric cyclic sulfamide HIV-1 protease inhibitors.* J Med Chem, 2001. **44**(2): p. 155-69.
35. Ekegren, J.K., et al., *A new class of HIV-1 protease inhibitors containing a tertiary alcohol in the transition-state mimicking scaffold.* J Med Chem, 2005. **48**(25): p. 8098-102.
36. Abdel-Meguid, S.S., et al., *An orally bioavailable HIV-1 protease inhibitor containing an imidazole-derived peptide bond replacement: crystallographic and pharmacokinetic analysis.* Biochemistry, 1994. **33**(39): p. 11671-7.
37. Thaisrivongs, S., et al., *Structure-based design of novel HIV protease inhibitors: carboxamide-containing 4-hydroxycoumarins and 4-hydroxy-2-pyrones as potent nonpeptidic inhibitors.* J Med Chem, 1995. **38**(18): p. 3624-37.
38. Blum, A., et al., *Structure-guided design of C2-symmetric HIV-1 protease inhibitors based on a pyrrolidine scaffold.* J Med Chem, 2008. **51**(7): p. 2078-87.
39. Hoog, S.S., et al., *A check on rational drug design: crystal structure of a complex of human immunodeficiency virus type 1 protease with a novel gamma-turn mimetic inhibitor.* J Med Chem, 1995. **38**(17): p. 3246-52.
40. Blum, A., et al., *Achiral oligoamines as versatile tool for the development of aspartic protease inhibitors.* Bioorg Med Chem, 2008. **16**(18): p. 8574-86.
41. Lee, T., et al., *Discovery of Potent Myeloid Cell Leukemia-1 (Mcl-1) Inhibitors That Demonstrate in Vivo Activity in Mouse Xenograft Models of Human Cancer.* J Med Chem, 2019. **62**(8): p. 3971-3988.
42. Caenepeel, S., et al., *AMG 176, a Selective MCL1 Inhibitor, Is Effective in Hematologic Cancer Models Alone and in Combination with Established Therapies.* Cancer Discov, 2018. **8**(12): p. 1582-1597.
43. Rescourio, G., et al., *Discovery and in Vivo Evaluation of Macrocyclic Mcl-1 Inhibitors Featuring an alpha-Hydroxy Phenylacetic Acid Pharmacophore or Bioisostere.* J Med Chem, 2019. **62**(22): p. 10258-10271.
44. Pelz, N.F., et al., *Discovery of 2-Indole-acylsulfonamide Myeloid Cell Leukemia 1 (Mcl-1) Inhibitors Using Fragment-Based Methods.* J Med Chem, 2016. **59**(5): p. 2054-66.
45. Shaw, S., et al., *Optimization of Potent and Selective Tricyclic Indole Diazepinone Myeloid Cell Leukemia-1 Inhibitors Using Structure-Based Design.* J Med Chem, 2018. **61**(6): p. 2410-2421.
46. Bruncko, M., et al., *Structure-guided design of a series of MCL-1 inhibitors with high affinity and selectivity.* J Med Chem, 2015. **58**(5): p. 2180-94.
47. Lee, T., et al., *Discovery and biological characterization of potent myeloid cell leukemia-1 inhibitors.* FEBS Lett, 2017. **591**(1): p. 240-251.
48. Szlavik, Z., et al., *Structure-Guided Discovery of a Selective Mcl-1 Inhibitor with Cellular Activity.* J Med Chem, 2019. **62**(15): p. 6913-6924.
49. Friberg, A., et al., *Discovery of potent myeloid cell leukemia 1 (Mcl-1) inhibitors using fragment-based methods and structure-based design.* J Med Chem, 2013. **56**(1): p. 15-30.
50. Burke, J.P., et al., *Discovery of tricyclic indoles that potently inhibit Mcl-1 using fragment-based methods and structure-based design.* J Med Chem, 2015. **58**(9): p. 3794-805.
51. Chu, X.J., et al., *Discovery of [4-Amino-2-(1-methanesulfonylpiperidin-4-ylamino)pyrimidin-5-yl](2,3-difluoro-6-methoxyphenyl)methanone (R547), a potent and selective cyclin-dependent kinase inhibitor with significant in vivo antitumor activity.* J Med Chem, 2006. **49**(22): p. 6549-60.
52. Hole, A.J., et al., *Comparative structural and functional studies of 4-(thiazol-5-yl)-2-(phenylamino)pyrimidine-5-carbonitrile CDK9 inhibitors suggest the basis for isotype selectivity.* J Med Chem, 2013. **56**(3): p. 660-70.
53. Moshinsky, D.J., et al., *SU9516: biochemical analysis of cdk inhibition and crystal structure in complex with cdk2.* Biochem Biophys Res Commun, 2003. **310**(3): p. 1026-31.
54. Misra, R.N., et al., *N-(cycloalkylamino)acyl-2-aminothiazole inhibitors of cyclin-dependent kinase 2. N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4- piperidinecarboxamide (BMS-387032), a highly efficacious and selective antitumor agent.* J Med Chem, 2004. **47**(7): p. 1719-28.
55. Wang, S., et al., *2-Anilino-4-(thiazol-5-yl)pyrimidine CDK inhibitors: synthesis, SAR analysis, X-ray crystallography, and biological activity.* J Med Chem, 2004. **47**(7): p. 1662-75.
56. Berg, S., et al., *Discovery of novel potent and highly selective glycogen synthase kinase-3beta (GSK3beta) inhibitors for Alzheimer's disease: design, synthesis, and characterization of pyrazines.* J Med Chem, 2012. **55**(21): p. 9107-19.
57. Wu, S.Y., et al., *Discovery of a novel family of CDK inhibitors with the program LIDAEUS: structural basis for ligand-induced disordering of the activation loop.* Structure, 2003. **11**(4): p. 399-410.
58. Hamdouchi, C., et al., *The discovery of a new structural class of cyclin-dependent kinase inhibitors, aminoimidazo[1,2-a]pyridines.* Mol Cancer Ther, 2004. **3**(1): p. 1-9.
59. Echalier, A., et al., *An integrated chemical biology approach provides insight into Cdk2 functional redundancy and inhibitor sensitivity.* Chem Biol, 2012. **19**(8): p. 1028-40.
60. Shao, H., et al., *Substituted 4-(thiazol-5-yl)-2-(phenylamino)pyrimidines are highly active CDK9 inhibitors: synthesis, X-ray crystal structures, structure-activity relationship, and anticancer activities.* J Med Chem, 2013. **56**(3): p. 640-59.

61. Arris, C.E., et al., *Identification of novel purine and pyrimidine cyclin-dependent kinase inhibitors with distinct molecular interactions and tumor cell growth inhibition profiles.* J Med Chem, 2000. **43**(15): p. 2797-804.
62. Clare, P.M., et al., *The cyclin-dependent kinases cdk2 and cdk5 act by a random, anticooperative kinetic mechanism.* J Biol Chem, 2001. **276**(51): p. 48292-9.
63. Sayle, K.L., et al., *Structure-based design of 2-arylamino-4-cyclohexylmethyl-5-nitroso-6-aminopyrimidine inhibitors of cyclin-dependent kinases 1 and 2.* Bioorg Med Chem Lett, 2003. **13**(18): p. 3079-82.
64. Beattie, J.F., et al., *Cyclin-dependent kinase 4 inhibitors as a treatment for cancer. Part 1: identification and optimisation of substituted 4,6-bis anilino pyrimidines.* Bioorg Med Chem Lett, 2003. **13**(18): p. 2955-60.