Electronic Supplementary Material (ESI) for Molecular BioSystems.

Supplementary Information

Insights into the structural basis of 3,5-diaminoindazoles as CDK2 inhibitors: Prediction of binding modes and potency by QM/MM interaction, MESP and MD simulation

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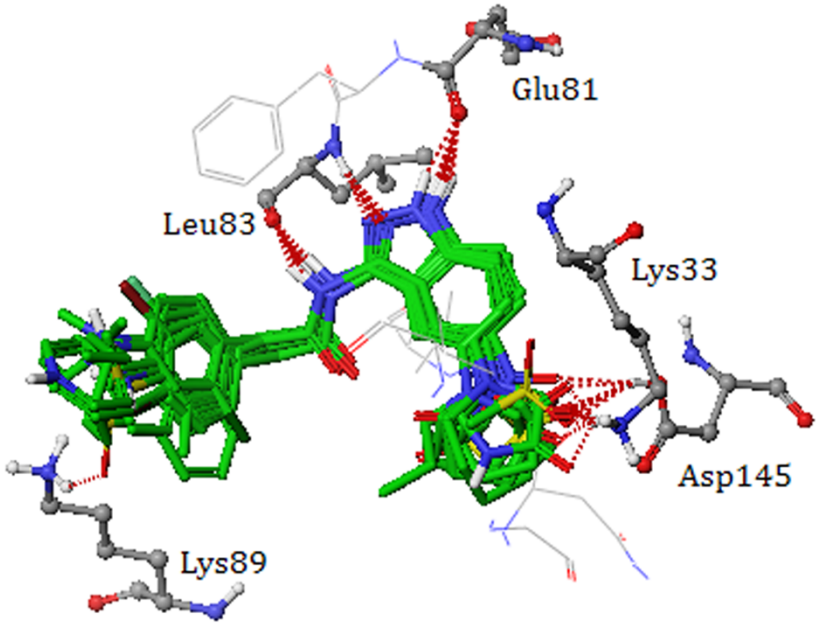


Fig. S1 Alignment of all compound (except compound **5**, due to not appropriate alignment) docked structures within the active site of CDK2. The main residues are identified with a three-letter representation.

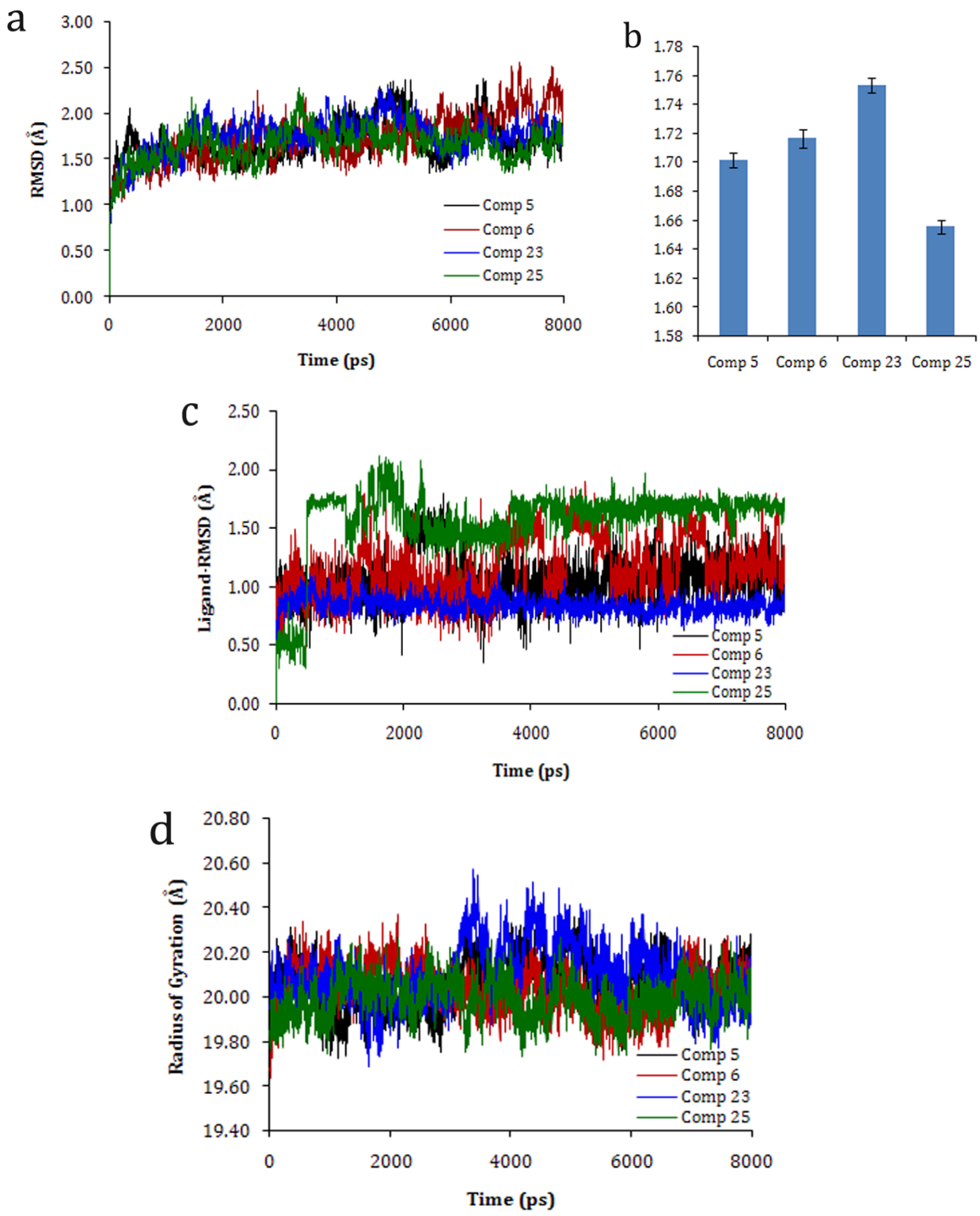
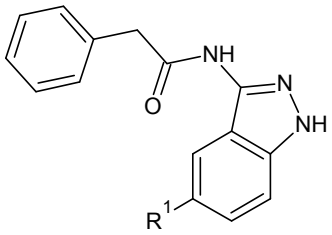
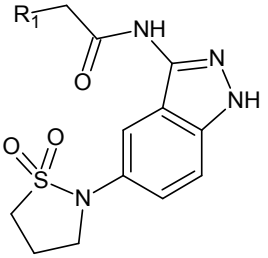


Fig. S2 The RMSD of backbone (with 12 Å cut-off for non-bonded interactions) atoms of the protein (a), the average means RMSD using bars, and the corresponding standard deviations are shown using error bars (b) and the heavy atoms in the ligand (c) time dependences of gyration radii for bound CDK2 (d) for the compound **5**, **6**, **23** and **25** bound CDK2 systems as a function of the simulation time.

Table S1. Structure of 3,5-diaminoindazoles series of CDK2 inhibitors (compounds **1-29**) along with biological activity.



Compound **1-9**



Compound **10-29**

Compounds	R1 Group	IC_{50} values (μM)	pIC_{50} values (μM)
1	NO_2	2.0	5.69
2	C_2H_5NH	0.5	6.30
3	$(C_2H_5)_2N$	0.2	6.69
4	$(n\text{-}C_3H_7)_2N$	1.8	5.74
5	$(n\text{-}C_4H_9)_2N$	100	4.00
6	$CO(CH_2)_3N$	0.17	6.76
7	$CO(CH_2)_4N$	7.1	5.14
8	$COCH_2NHCON$	2.0	5.69
9	$SO_2(CH_2)_3N$	0.036	7.44
10	$3\text{-}F\text{-}C_6H_4\text{-}$	0.01	8.00
11	$4\text{-}F\text{-}C_6H_4\text{-}$	0.02	7.69
12	$2\text{-}Cl\text{-}C_6H_4\text{-}$	0.024	7.61
13	$3\text{-}Cl\text{-}C_6H_4\text{-}$	0.01	8.00
14	$4\text{-}Cl\text{-}C_6H_4\text{-}$	0.01	8.00
15	$3\text{-}Br\text{-}C_6H_4\text{-}$	0.007	8.15
16	$4\text{-}Br\text{-}C_6H_4\text{-}$	0.007	8.15
17	$3\text{-}CH_3\text{-}C_6H_4\text{-}$	0.01	8.00
18	$4\text{-}CH_3\text{-}C_6H_4\text{-}$	0.007	8.15
19	$4\text{-}OH\text{-}C_6H_4\text{-}$	0.009	8.04
20	$4\text{-}NH_2\text{-}C_6H_4\text{-}$	0.016	7.79
21	$4\text{-}(CH_3)_2N\text{-}C_6H_4\text{-}$	0.01	8.00
22	$4\text{-}(C_2H_5)_2N\text{-}C_6H_4\text{-}$	0.04	7.39

23	4-(1-Piperidinyl)-C_6H_4-	0.03	7.52
24	4-CH_3S-C_6H_4-	0.01	8.00
25	4-CH_3SO_2-C_6H_4-	0.022	7.65
26	1-Naphthyl	0.02	7.69
27	2-Naphthyl	0.009	8.04
28	4-Biphenyl-	0.014	7.85
29	4-(4-Pyridyl)-C_6H_4-	0.03	7.52

Table S2. Simple linear regression for two variables by using biological activity and MM-GBSA calculated free energy of binding.

Compounds	Model Set	Experimental pIC_{50} value	Predicted pIC_{50} value
1	training	5.69	6.06
2	test	6.30	6.55
3	training	6.69	6.29
4	test	5.74	5.53
5	training	4.00	4.59
6	training	6.76	7.01
7	training	5.14	6.94
8	training	5.69	6.20
9	test	7.44	7.51
10	training	8.00	7.68
11	training	7.69	7.61
12	training	7.61	6.70
13	test	8.00	7.94
14	training	8.00	8.19
15	training	8.15	7.91
16	training	8.15	8.12
17	training	8.00	7.36
18	test	8.15	7.91
19	training	8.04	7.57
20	test	7.79	6.48
21	training	8.00	7.92
22	training	7.39	8.11
23	training	7.52	7.26
24	training	8.00	8.55
25	training	7.65	8.18
26	training	7.69	7.26
27	test	8.04	7.57
28	training	7.85	6.61
29	training	7.52	7.05

Table S3. Simple linear regression for two variables by using biological activity and QM/MM interaction energy

Compounds	Model Set	Experimental pIC_{50} value	Predicted pIC_{50} value
1	training	5.69	5.44
2	test	6.30	5.9
3	training	6.69	5.86
4	test	5.74	5.79
5	training	4.00	5.44
6	training	6.76	5.77
7	training	5.14	5.89
8	training	5.69	6.04
9	test	7.44	7.10
10	training	8.00	8.01
11	training	7.69	7.40
12	training	7.61	7.66
13	test	8.00	7.89
14	training	8.00	8.50
15	training	8.15	7.74
16	training	8.15	7.44
17	training	8.00	7.48
18	test	8.15	7.52
19	training	8.04	7.64
20	test	7.79	7.27
21	training	8.00	8.03
22	training	7.39	7.78
23	training	7.52	7.87
24	training	8.00	8.43
25	training	7.65	7.67
26	training	7.69	7.72
27	test	8.04	7.87
28	training	7.85	7.81
29	training	7.52	7.57

Table S4. Descriptive analyses of RMSD of the compounds in 8ns MD simulation with 12 Å cut-off for non-bonded interactions.

Complex	Mean	Standard error	Median	Standard deviation	Maximum	Confidence level (95.0%)
Compound **5**	1.70	0.003	1.67	0.216	2.37	0.005
Compound **6**	1.72	0.003	1.71	0.263	2.56	0.006
Compound **23**	1.75	0.002	1.77	0.200	2.28	0.004
Compound **25**	1.66	0.002	1.67	0.184	2.30	0.004

Table S5. Principle descriptors calculated for 3,5-diaminoindazoles series of CDK2 inhibitors.

Compounds	Molecular[a] Weight	Molecular[b] volume	VDW[c] PSA	HB[d] donors	HB[e] acceptors	Rotable[f] bonds
1	296.29	929.82	113.94	2	4	4
2	294.36	1010.50	79.16	3	4	5
3	322.41	1068.85	68.21	2	4	6
4	350.46	1173.06	68.49	2	4	8
5	378.52	1284.61	68.13	2	4	10
6	334.38	1082.43	96.44	2	6	3
7	348.40	1141.40	95.41	2	6	3
8	349.35	1038.86	141.61	3	7	3
9	370.43	1118.77	109.08	2	8	3
10	388.42	1100.95	108.83	2	8	3
11	388.42	1093.07	108.92	2	8	3
12	404.87	1131.61	107.62	2	8	3
13	404.87	1123.31	108.29	2	8	3
14	404.87	1109.94	108.89	2	8	3
15	449.32	1130.23	108.24	2	8	3
16	449.32	1117.4	108.89	2	8	3
17	384.45	1128.94	107.47	2	8	3
18	384.45	1122.91	107.52	2	8	3
19	386.43	1091.96	131.44	3	8	4
20	385.44	1099.91	135.26	3	9	4
21	413.49	1198.42	108.95	2	9	4
22	441.55	1291.85	107.07	2	9	6
23	453.56	1303.29	112.35	2	9	3
24	416.51	1173.24	107.18	2	8	4
25	448.51	1242.29	144.63	2	12	4
26	420.49	1179.81	102.86	2	8	3
27	420.49	1194.03	105.93	2	8	3
28	446.52	1277.78	105.77	2	8	4
29	447.51	1260.39	118.29	2	9	4

[a]Molecular weight of the molecule (accepted range: 130.0 - 725.0)

[b]Total solvent-accessible volume in cubic angstroms using a probe with a 1.4 Å radius (acceptable range: 500.0 - 2000.0)

[c]van der Waals surface area of polar nitrogen and oxygen atoms (accepted range: 7 - 200)

[d]Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution (range: 0.0 - 6.0)

[e]Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution (accepted range: 2.0 - 20.0)

[f]Number of non-trivial (not CX3), non-hindered (not alkene, amide, small ring) rotatable bonds (accepted range: 0.0 - 15)

Table S6. Physicochemical descriptors calculated for 3,5-diaminoindazoles series of CDK2 inhibitors.

Compounds	QPlogPo/w[a]	QP (%)[b]	QPlogHERG[c]	QPPCaco[d]	QPPMDCK[e]
1	2.31	78.47	-5.50	132.68	55.75
2	2.89	94.77	-5.83	699.66	336.27
3	3.52	100.00	-4.79	986.26	487.37
4	4.16	100.00	-5.04	1000.0	494.71
5	4.85	100.00	-5.27	1025.7	508.51
6	2.55	87.95	-5.57	375.06	171.40
7	2.94	91.35	-5.92	432.39	199.88
8	1.46	68.65	-5.25	71.35	28.51
9	1.99	79.63	-5.46	196.62	87.01
10	2.19	86.08	-4.80	386.74	263.05
11	2.17	86.31	-4.73	406.03	287.46
12	2.35	86.24	-5.13	349.15	236.59
13	2.38	87.47	-4.98	400.79	322.47
14	2.34	87.90	-4.68	435.25	376.61
15	2.44	87.88	-4.92	403.98	342.52
16	2.41	88.38	-4.77	441.18	403.19
17	2.26	87.22	-4.82	425.45	196.43
18	2.25	87.74	-4.69	459.50	213.46
19	1.41	75.96	-4.68	189.29	81.85
20	1.28	74.40	-4.77	171.36	73.50
21	2.34	89.34	-4.67	527.16	247.63
22	2.90	93.08	-4.63	557.62	263.13
23	2.57	81.57	-4.71	162.23	70.69
24	2.47	89.57	-4.76	490.04	329.48
25	1.83	66.32	-4.96	84.81	35.50
26	2.76	92.26	-5.08	557.13	262.89
27	2.82	91.87	-5.15	508.37	238.10
28	3.35	94.58	-5.60	481.86	224.71
29	2.45	85.02	-5.36	278.34	124.17

[a]Predicted octanol/water partition co-efficient log p (acceptable range: -2.0 to 6.5).

[b]Percentage of human oral absorption (acceptable range: <25% is poor and >80% is high).

[c]Predicted IC_{50} value for blockage of HERG K+ channels (concern below -5.0).

[d]Predicted Caco-2 cell permeability in nm/s (acceptable range: <25 is poor and >500 is great).

[e]Predicted apparent MDCK cell permeability in nm/s.