Supplementary Materials

Molecular Modelling Study of c-KIT/PDGFRα Dual Inhibitors for the Treatment of Gastrointestinal Stromal Tumors

Seketoulie Keretsu[1], Suparna Ghosh[1], Seung Joo Cho[1,2,*]

[1]*Department of Biomedical Sciences, College of Medicine, Chosun University, Gwangju 501-759, Republic of Korea; keretsu@chosun.kr(S.K); s.ghosh@chosun.kr (S.G);* chosj@chosun.ac.kr (S.J.C)

[2] *Department of Cellular Molecular Medicine, College of Medicine, Chosun University, Gwangju 501-759, Republic of Korea*

Table **S1**. The experimental/actual and predicted pIC_{50} values with their residuals for the CoMFA and CoMSIA for c-KIT.

Compound	Experimental pIC_{50}	c-KIT CoMFA		c-KIT CoMSIA	
		Predicted pIC_{50}	Residual	Predicted pIC_{50}	Residual
1	8.62	8.27	-0.35	8.27	0.35
2	8.43	8.61	0.17	9.10	-0.67
5	8.41	8.58	0.17	8.13	0.28
6*	4.96	5.80	0.84	5.96	-0.99
7	5.74	5.91	0.17	6.73	-0.99
8	5.32	5.26	-0.06	5.86	-0.54
9	5.62	5.51	-0.11	5.51	0.11
10*	6.70	7.21	-0.52	7.33	-0.63
11	7.72	7.62	-0.10	7.57	0.15
12	5.71	5.87	0.16	5.88	-0.17
13	8.14	8.16	0.02	8.18	-0.04
14	8.62	8.68	0.06	8.27	0.35
15*	5.65	6.55	-0.90	6.60	-0.95
16	5.34	5.17	-0.17	5.16	0.18
17	6.40	6.12	-0.28	6.07	0.33
18	5.19	5.50	0.31	5.35	-0.16
19	7.92	7.97	0.05	8.26	-0.34
20*	7.92	7.62	0.30	8.90	-0.98
21	8.59	8.71	0.13	8.41	0.17
22	8.03	7.86	-0.17	7.78	0.25
23*	4.66	5.58	-0.93	5.60	-0.94
26	4.69	4.73	0.04	5.31	-0.62
27	8.46	8.37	-0.09	8.51	-0.05
28*	8.85	8.09	0.77	8.44	0.42
29	6.49	6.41	-0.08	5.88	0.62
30	5.85	6.10	0.25	5.82	0.03
31	6.26	6.18	-0.08	5.93	0.32
32*	6.50	6.46	0.03	6.30	0.20

33	6.84	6.94	0.10	7.08	-0.24
35*	7.29	8.10	-0.81	7.92	-0.62
36	7.59	7.48	-0.10	7.45	0.14
37*	7.11	6.11	1.00	6.47	0.64
39	8.43	8.57	0.14	8.37	0.06
40	8.77	9.02	0.25	8.88	-0.11
41	8.21	8.32	0.11	8.71	-0.51
42*	8.06	8.91	-0.85	8.68	-0.62
43	6.92	6.98	0.06	7.15	-0.23
44	7.70	7.75	0.05	7.75	-0.05
45*	7.85	6.92	0.94	7.62	0.23
46	8.72	8.37	-0.35	8.45	0.28
47*	7.70	8.42	-0.72	8.49	-0.79
48	8.44	8.14	-0.30	7.52	0.92

* Test set compounds

Table **S2**. The experimental/actual and predicted pIC_{50} values with their residuals for the CoMFA and CoMSIA for PDGFRα.

Compound	**Experimental pIC_{50}**	PDGFRα **CoMFA**		PDGFRα **CoMSIA**	
		Predicted pIC_{50}	**Residual**	**Predicted pIC_{50}**	**Residual**
1	7.06	7.14	-0.08	7.32	-0.26
2	7.49	7.49	0.01	7.45	0.04
5	7.66	7.54	0.12	7.23	0.43
6*	6.52	6.11	0.40	6.78	-0.27
7	7.19	6.98	0.21	6.99	0.20
8	6.58	6.55	0.03	6.81	-0.22
9	6.74	6.87	-0.13	7.05	-0.31
10*	4.67	3.85	0.82	5.56	-0.89
11	6.67	6.70	-0.03	6.57	0.09
12	5.75	5.57	0.18	5.25	0.50
13	6.90	7.00	-0.11	6.96	-0.06
14	8.14	7.98	0.16	7.96	0.18
15*	5.96	6.34	-0.38	6.65	-0.69
16	6.03	6.25	-0.22	5.50	0.53
17	4.72	4.66	0.06	5.30	-0.57
18	5.39	5.35	0.04	5.56	-0.17
19	6.87	6.89	-0.03	7.05	-0.19
20*	6.75	6.81	-0.06	7.04	-0.29
21	7.08	7.04	0.04	6.97	0.11
22	6.51	6.54	-0.03	6.86	-0.35
23*	5.34	5.99	-0.66	6.17	-0.83
26	4.36	4.33	0.03	4.59	-0.23
27	6.79	6.86	-0.07	6.80	-0.01
28*	7.57	6.94	0.63	6.90	0.67
29	5.95	5.96	-0.01	5.78	0.17
30	5.83	6.09	-0.25	5.90	-0.07
31	5.95	5.91	0.04	6.00	-0.06

32*	6.14	5.88	0.26	5.80	0.34
33	6.24	6.20	0.04	5.73	0.51
35*	6.41	6.88	-0.46	6.18	0.23
36	6.80	6.80	0.00	6.47	0.34
37*	6.33	6.86	-0.53	6.27	0.05
39	7.09	7.08	0.01	7.45	-0.36
40	7.62	7.66	-0.04	7.33	0.29
41	6.87	7.05	-0.18	6.90	-0.03
42*	7.08	7.54	-0.46	6.97	0.11
43	6.39	6.29	0.10	6.16	0.23
44	6.40	6.41	-0.01	6.43	-0.03
45*	6.50	6.29	0.22	6.03	0.47
46	7.66	7.57	0.09	7.50	0.16
47*	6.91	6.21	0.70	6.61	0.30
48	7.01	6.99	0.03	6.43	0.58

* Test set compounds

Table S3: The predicted ADMET values and synthetic accessibility values for the 8 designed compounds.

Compounds	Absorption	Distribution	Metabolism							Excretion	Toxicity	Synthetic Accessibility
	Intestinal absorption (human)	VDss (human)	CYP							Total Clearance	AMES toxicity	
			2D6 substrate	**3A4** substrate	**1A2** inhibitor	**2C19** inhibitor	**2C9** inhibitor	**2D6** inhibitor	**3A4** inhibitor			
	Numeric (% Absorbed)	Numeric (log L/kg)	Categorical (Yes/No)							Numeric (log ml/min/kg)	Categorical (Yes/No)	
D18	89	0.2	Yes	Yes	No	Yes	Yes	No	Yes	0.9	No	3.8
D23	98	-0.5	Yes	Yes	Yes	Yes	No	Yes	No	0.8	No	4.4
D25	87	-0.4	Yes	Yes	No	No	No	No	No	0.8	No	4.0
D28	92	-0.7	Yes	Yes	Yes	Yes	Yes	No	Yes	0.8	No	3.9
D32	93	-0.8	Yes	Yes	Yes	Yes	Yes	No	No	0.6	No	3.8
D39	88	-1.2	Yes	Yes	Yes	Yes	No	No	No	0.5	Yes	3.5
D44	87	0.1	Yes	Yes	Yes	Yes	Yes	No	No	0.8	No	3.5
D45	86	0.2	Yes	Yes	Yes	Yes	Yes	No	Yes	0.9	No	3.6

Figure S1. Showing the H-bond interactions of **imatinib** and **compound 14** with c-KIT and PDGFRα from the molecular docking studies. H-bond interactions were represented by yellow dotted lines and residues forming H-bonds were shown in purple color. **(a)** Binding interactions between imatinib (green) and c-KIT. The overlap between the docked pose (green) and the crystal ligand (salmon) is shown in inset **(b)** Binding interactions between imatinib (magenta) and PDGFRα. The overlap between the docked pose (magenta) and the crystal ligand (salmon) is shown in inset **(c)** Binding interactions between compound 14 (cyan) and c-KIT. **(d)** Binding interactions between compound 14 (yellow) and PDGFRα.

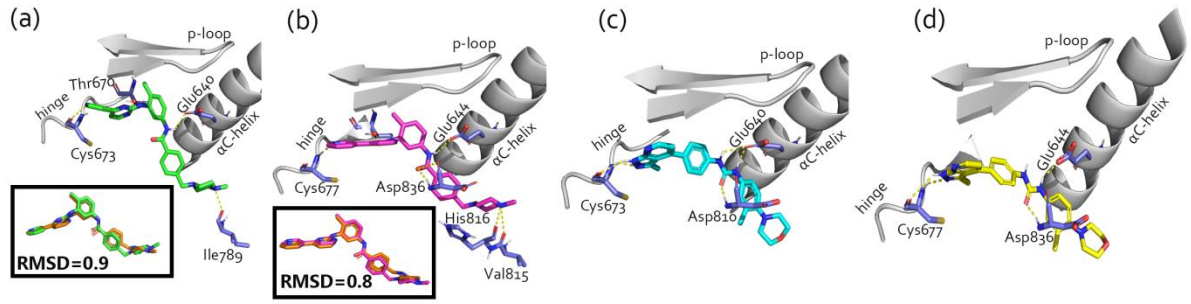

Figure S2. Showing the hydrophobic interactions of the inhibitors with c-KIT and PDGFRα. Hydrophobic interactions were represented in red dotted lines. Residues that showed Hydrophobic and H-bond interactions were given in green and black label respectively. **(a) Compound 14**-c-KIT **(b) Compound 31**-c-KIT **(c) D39**-c-KIT **(d) compound D39**-PDGFRα.

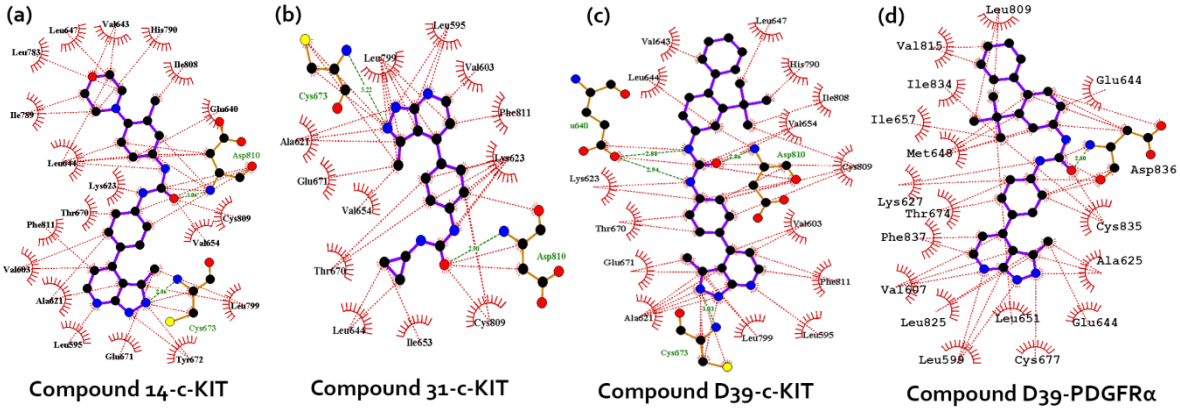

Figure S3. Scatter plot for the CoMFA and CoMSIA models. Scatter plot for **(a)** c-KIT CoMFA model **(b)** c-KIT CoMSIA model **(c)** PDGFRα CoMFA model **(d)** PDGFRα CoMSIA model. The values on the x-axis and y-axis represent the predicted pIC_{50} values and the experimental/actual pIC_{50} values respectively.

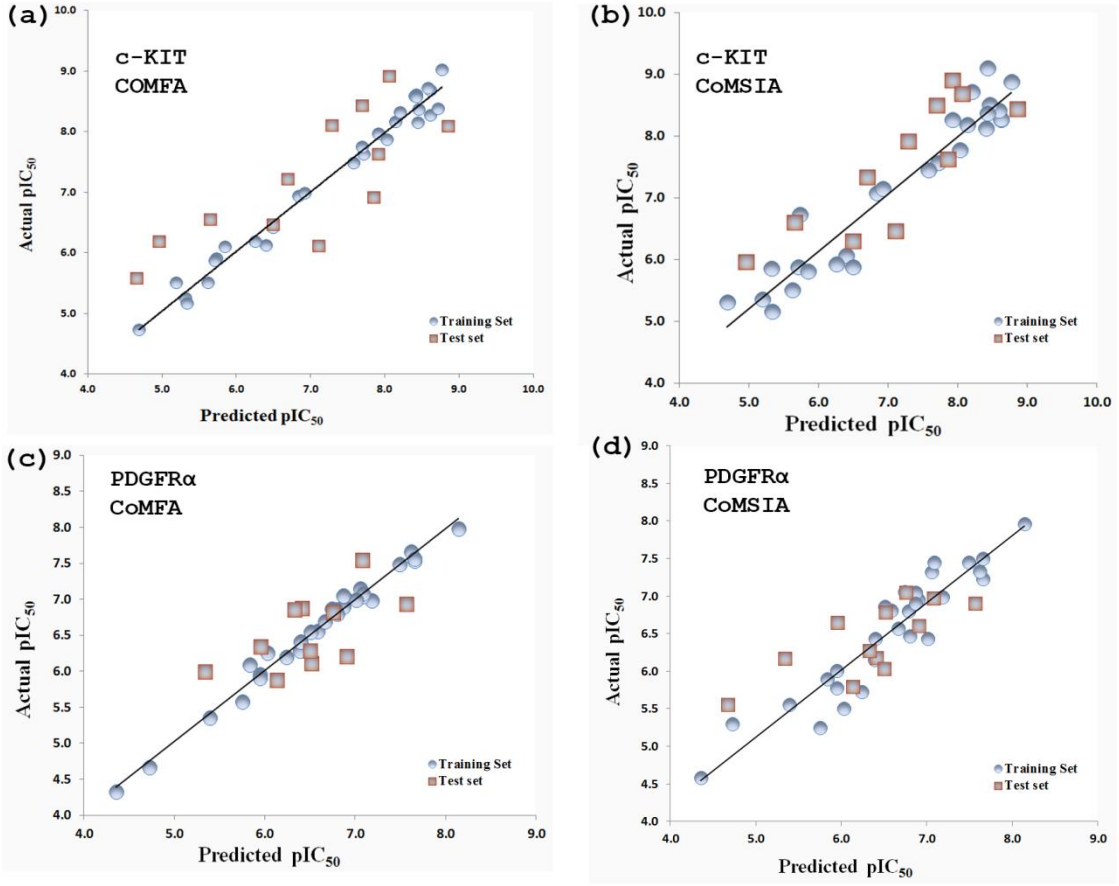

Figure S4. The ligand RMSD plots from the MD simulations. **(a)** Imatinib-c-KIT **(b)** Compound 14-c-KIT **(c)** Compound 31-c-KIT **(d)** D18-c-KIT **(e)** D23-c-KIT **(f)** D25-c-KIT **(g)** D28-c-KIT **(h)** D32-c-KIT **(i)** D39-c-KIT **(j)** D44-c-KIT **(k)** D45-c-KIT **(l)** Imatinib-c-KIT/T670I **(m)** Imatinib-PDGFRα **(n)** Compound 14- PDGFRα **(o)** Compound 31- PDGFRα **(p)** D18-PDGFRα **(q)** D23-PDGFRα **(r)** D25-PDGFRα **(s)** D28-PDGFRα **(t)** D32-PDGFRα **(u)** D39-PDGFRα **(v)** D44-PDGFRα **(w)** D45-PDGFRα **(x)** Imatinib-PDGFRα/T674I **(y)** Compound 14-c-KITα/T670I **(z)** Compound 14- PDGFRα/T674I

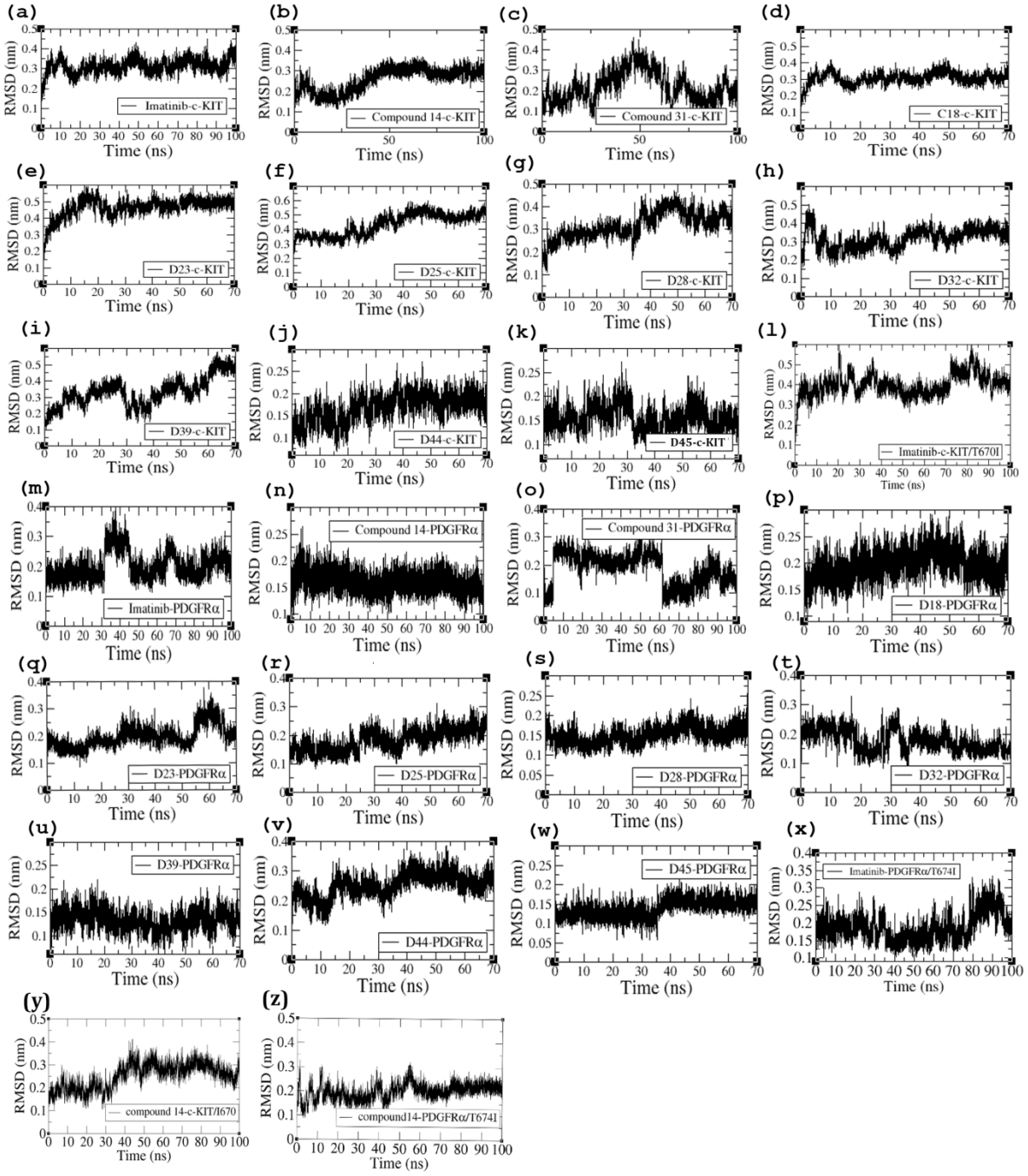

Figure S5. Hydrophobic surface of c-KIT and the binding interactions of compound 31 with the receptors. **(a)** The hydrophobic surface of the c-KIT binding site residues; Hydrophobic residues from the αC-helix and the catalytic loops are shown in stick representation **(b)** Binding interactions between **compound 31** and c-KIT. **(c)** Binding interactions between **compound 31** and PDGFRα.