Electronic Supplementary Material (ESI) for RSC Advances.

Discovery of vascular endothelial growth factor receptor tyrosine kinase inhibitors by quantitative structure–activity relationships, molecular dynamics simulation and free energy calculation

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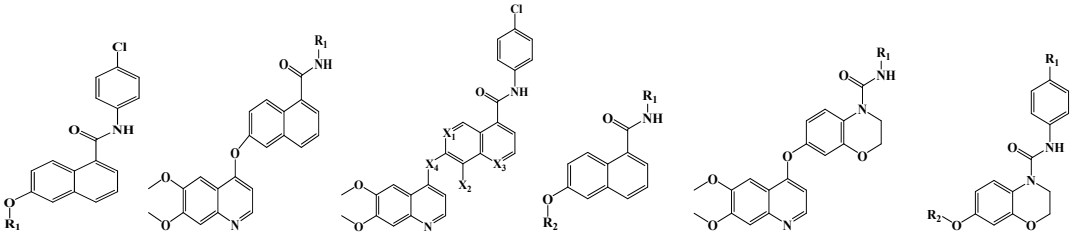
Supplementary Materials

Materials of contents

Table S1. Molecular Structures and Inhibitory Activities (pIC50) for KDR Inhibitors

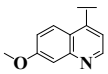
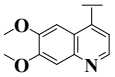
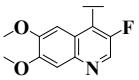
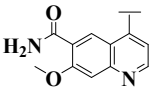
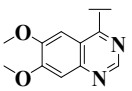


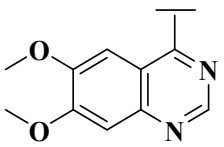
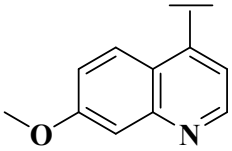
1-13 14-39, 44-51 40: X1=X3=CH, X2=F, X4=O 52-60 61-76 77-82

41: X1=CH, X2=H, X3=N, X4=O

42: X1=N, X2=H, X3= CH, X4=O

43: X1=X3=CH, X2=H, X4=NH

NO	R_1	R_2	Obsd[b]	Cald1[c]	Error
1			8.52	8.27	-0.25
2			7.74	7.20	-0.54
3*			8.15	7.75	-0.4
4			6.51	6.74	0.23
5			7.34	7.29	-0.05
6			7.70	7.25	-0.45
7*			7.55	7.56	0.01
8			8.40	9.04	0.64
9			9.00	8.83	-0.17
10			9.31	8.95	-0.36
11			7.70	7.95	0.25
12*			9.70	9.56	-0.14
13			8.70	8.50	-0.2
14	Ph		9.70	9.62	-0.08
15	2-F-Ph		8.70	8.48	-0.22
16*	3-F-Ph		9.22	8.48	-0.74

17*	4-F-Ph		9.00	8.87	-0.13
18*	3-Cl-Ph		9.52	9.12	-0.4
19	4-Me-Ph		9.30	9.43	0.13
20	3-CF3-Ph		9.30	8.87	-0.43
21*	4-CF3-Ph		9.30	9.27	-0.03
22*	4-t-Bu-Ph		9.15	8.61	-0.54
23	2,4-Cl-Ph		8.70	9.29	0.59
24	3,5-Cl-Ph		9.52	9.92	0.4
25	3-CF3-4-Cl-Ph		9.00	9.32	0.32
26	2-Pyridyl		9.10	9.21	0.11
27	3-Pyridyl		9.10	8.47	-0.63
28	4-Pyridyl		8.70	8.55	-0.15
29*	2-Thiazolyl		9.52	9.54	0.02
30	3-Isoxazole		9.70	10.20	0.5
31	5-Methyl-3-isoxazolyl		9.22	9.27	0.05
32	3-Methyl-5-isoxazolyl		9.00	9.01	0.01
33	5-tert-Butyl-3-isoxazolyl		9.10	8.90	-0.2
34	Cyclopropyl		9.22	8.89	-0.33
35	1-Methylcyclopropyl		7.82	8.28	0.46
36	Cyclobutyl		8.67	8.71	0.04
37	Cyclopentyl		7.92	8.34	0.42
38	Propyl		8.89	8.53	-0.36
39	Isopropyl		8.26	8.42	0.16
40			9.52	9.21	-0.31
41			7.66	8.49	0.83
42			7.64	8.51	0.87
43*			8.10	8.13	0.03
44*	Cyclopropylmethyl		7.96	8.11	0.15
45	Methyl		8.42	8.19	-0.23
46*	Ethyl		8.89	8.29	-0.60
47	t-Butyl		5.82	6.65	0.83
48	2-Trifluoroethyl		8.42	8.32	-0.1
49*	2-Methoxyethyl		7.92	7.66	-0.26
50	3-Methoxypropyl		8.38	8.29	-0.09
51*	H		9.05	9.01	-0.04
52	Cyclopropyl		8.54	8.40	-0.14
53	2-Methoxyethyl		6.50	6.98	0.48
54*	H		8.89	8.68	-0.21
55	Cyclopropyl		9.35	8.23	-1.12
56	2-Methoxyethyl		7.55	7.48	-0.07
57	H		8.92	8.48	-0.44

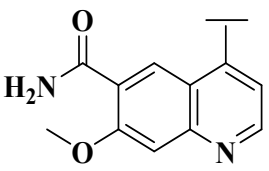
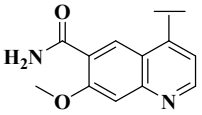
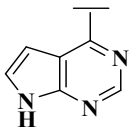
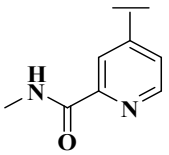
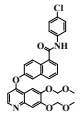
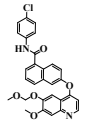
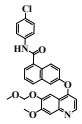
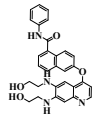
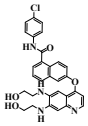
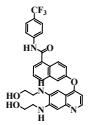
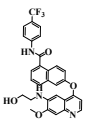
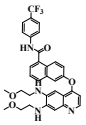
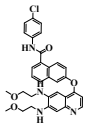
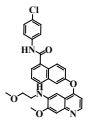
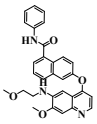
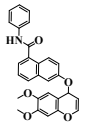
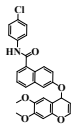
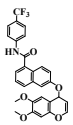
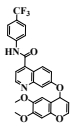
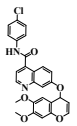
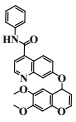
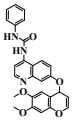
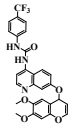
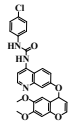
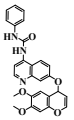
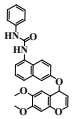
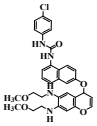
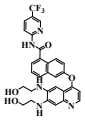
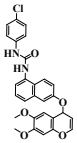
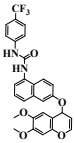
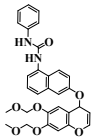
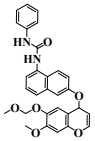
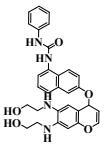
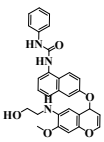
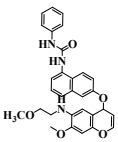
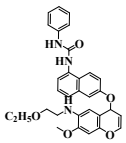
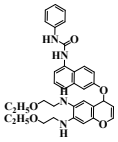
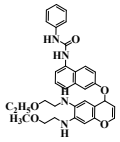
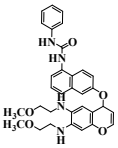
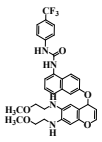
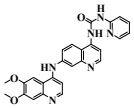
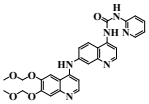
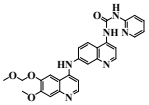
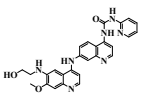
58	Cyclopropyl		9.43	9.59	0.16
59	2-Methoxyethyl		7.66	8.00	0.34
60	H		8.89	8.97	0.08
61*	Ph		9.00	8.87	-0.13
62	2-Me-Ph		9.00	8.79	-0.21
63	3-Me-Ph		9.00	8.51	-0.49
64	4-Me-Ph		9.70	8.79	-0.91
65	2-Cl-Ph		7.72	7.63	-0.09
66	3-Cl-Ph		9.00	9.09	0.09
67	4-Cl-Ph		9.30	9.08	-0.22
68	4-F-Ph		8.52	8.49	-0.03
69	H		7.24	7.25	0.01
70	Methyl		7.40	7.02	-0.38
71*	Ethyl		9.00	8.98	-0.02
72	i-Propyl		7.40	7.06	-0.34
73	Bn		7.28	7.65	0.37
74*	4-Me-Bn		7.59	7.89	0.3
75	(S)-Me-Bn		9.00	8.45	-0.55
76	(R)-Me-Bn		7.40	7.97	0.57
77	Cl		9.22	8.82	-0.4
78	Me		9.30	9.61	0.31
79	Cl		7.11	7.28	0.17
80	Me		7.59	7.75	0.16
81	Cl		7.02	7.70	0.68
82*	Me		7.21	7.66	0.45

Table S2 Ten Atomic Types and 55 Atomic Interactions in 3D-HoVAIF

No.	Atomic type	1	2	3	4	5	6	7	8	9	10
1	H	1-1	1-2	1-3	1-4	1-5	1-6	1-7	1-8	1-9	1-10
2	C(sp3)		2-2	2-3	2-4	2-5	2-6	2-7	2-8	2-9	2-10
3	C(sp2)			3-3	3-4	3-5	3-6	3-7	3-8	3-9	3-10
4	C(sp)				4-4	4-5	4-6	4-7	4-8	4-9	4-10
5	N(sp3), P(sp3)					5-5	5-6	5-7	5-8	5-9	5-10

6	N(sp2), P(sp2)	6-6	6-7	6-8	6-9	6-10
7	N(sp), P(sp)		7-7	7-8	7-9	7-10
8	O(sp3),S(sp3)			8-8	8-9	8-10
9	O(sp2), S(sp2)				9-9	9-10
10	F, Cl, Br, I					10-10

Table S3. Molecular Structures of Designed Analogs

NO	Compound	NO	Compound	NO	Compound	NO	Compound
1		2		3		4	
5		6		7		8	
9		10		11		12	
13		14		15		16	
17		18		19		20	
21		22		23		24	
25		26		27		28	
29		30		31		32	
33		34		35		36	
37		38		39		40	

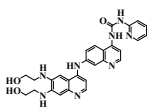
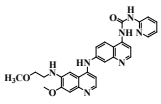
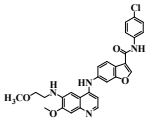
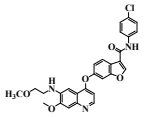
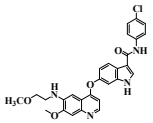
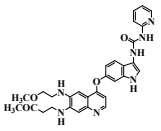
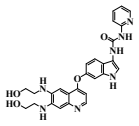
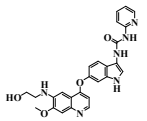
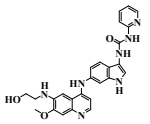
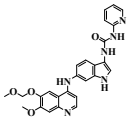
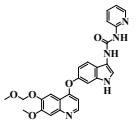
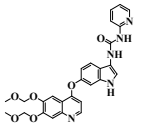
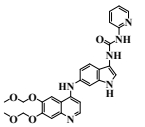
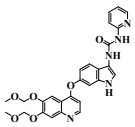
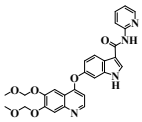
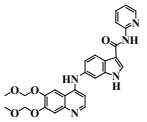
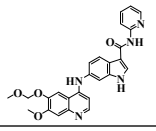
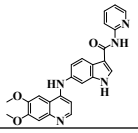
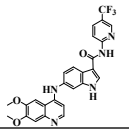
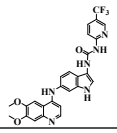
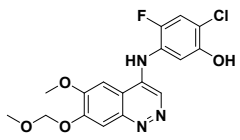
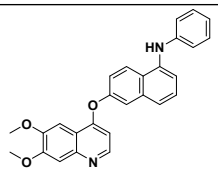
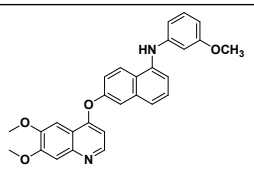
41		42		43		44	
45		46		47		48	
49		50		51		52	
53		54		55		56	
57		58		59		60	

Table S4. ADMET Properties Prediction of Designed Analogs

Compound	**Absorption**	**Solubility**	**BBB**	**CYD2D6**	**Hepatotoxicity**	PPB	AlogP98	PSA_2D
N3	**0(good)**	3(good)	**3(low)**	1(inhibitor)	1(toxic)	0(<90%)	1.65	78.95
N12	0	**1(possible)**	3	1	1	0	2.94	79.49
N13	0	**2(low）**	2	1	1	0	2.38	74.84
N15	0	1	2	1	1	0	2.22	76.70
N16	0	1	3	1	1	1(>90%)	2.78	79.33
N17	0	2	2	1	1	1	2.07	88.78
N18	0	2	3	1	1	0	1.71	79.33
N22	0	3	3	1	1	1	2.13	78.32

Table S5. Molecular Structures of Potent KDR Inhibitors with High Inhibitory Activity

Compound	IC50 (nM)	Compound	IC50 (nM)	Compound	IC50 (nM)
	4		2		1

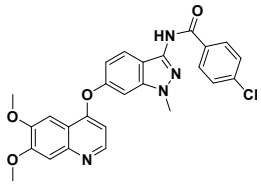
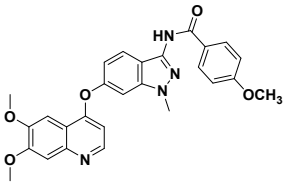
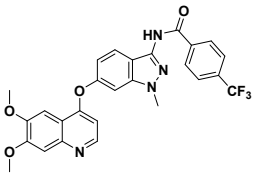
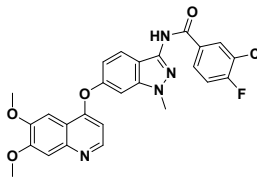
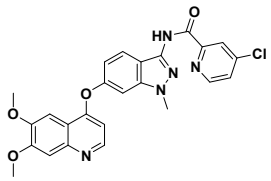
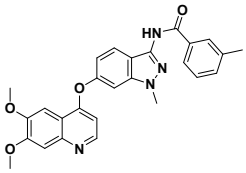
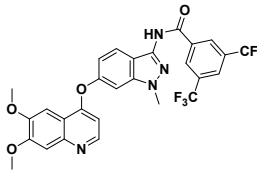
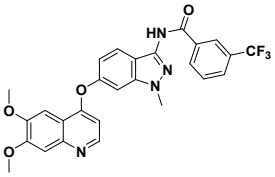
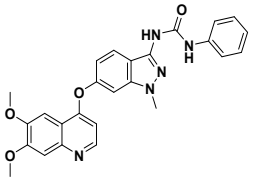
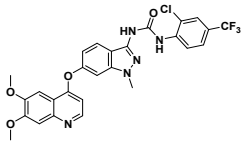
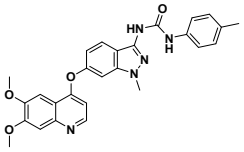
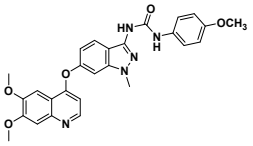
	5		3		3
	3		2		2
	2		1		2
	8		2		1

Table S6. The Primary Targets of Potent Inhibitors Identified from Reverse Screening Approaches

NO	1	2	3	4	5
10	Androgen receptor	Vascular endothelial growth factor receptor 2	Beta-secretase 1	Vascular endothelial growth factor receptor 2	Dihydroorotate dehydrogenase mitochondrial
12	Beta-secretase 1	Dihydroorotate dehydrogenase mitochondrial	Androgen receptor	Vascular endothelial growth factor receptor 2	Cathepsin K
14	Vitamin D3 receptor	Androgen receptor	Dihydroorotate dehydrogenase mitochondrial	Vascular endothelial growth factor receptor 2	Beta-secretase 1
30	Cellular retinoic acid-binding	Androgen receptor	transthyretin	Cell division protein kinase 2	GTPase HRas

	protein 2				
47	Androgen receptor	Beta-secretase 1	Neprilysin	Dihydroorotate dehydrogenase mitochondrial	Vascular endothelial growth factor receptor 2
64	Vascular endothelial growth factor receptor 2	Beta-secretase 1	Hepatocyte growth factor receptor	Basic fibroblast growth factor receptor 1	GTPase HRas
N3	Vascular endothelial growth factor receptor 2	Proto-oncogene tyrosine-protein kinase LCK	Beta-secretase 1	Mitogen-activated protein kinase 14	Dihydroorotate dehydrogenase mitochondrial
N12	Androgen receptor	Mitogen-activated protein kinase 14	Vascular endothelial growth factor receptor 2	Dihydroorotate dehydrogenase mitochondrial	Cell division protein kinase 2
N13	Vascular endothelial growth factor receptor 2	Beta-secretase 1	Mitogen-activated protein kinase 14	Cell division protein kinase 2	Proto-oncogene tyrosine-protein kinase LCK
N15	Methionine aminopeptidase 2	Proto-oncogene tyrosine-protein kinase LCK	Vascular endothelial growth factor receptor 2	Mitogen-activated protein kinase 14	Beta-secretase 1
N16	Beta-secretase 1	Vascular endothelial growth factor receptor 2	Proto-oncogene tyrosine-protein kinase LCK	Mitogen-activated protein kinase 14	Methionine aminopeptidase 2
N17	Vascular endothelial growth factor receptor 2	Dihydroorotate dehydrogenase mitochondrial	Methionine aminopeptidase 2	Beta-secretase 1	Cellular retinoic acid-binding protein 2
N18	Androgen receptor	Sex hormone-binding globulin	Cellular retinoic acid-binding protein 2	Peptidyl-prolyl cis-trans isomerase FKBP1A	Aldose reductase
N22	Androgen receptor	Cellular retinoic acid-binding protein 2	Cell division protein kinase 2	Aldo-keto reductase family 1 member C3	GTPase HRas

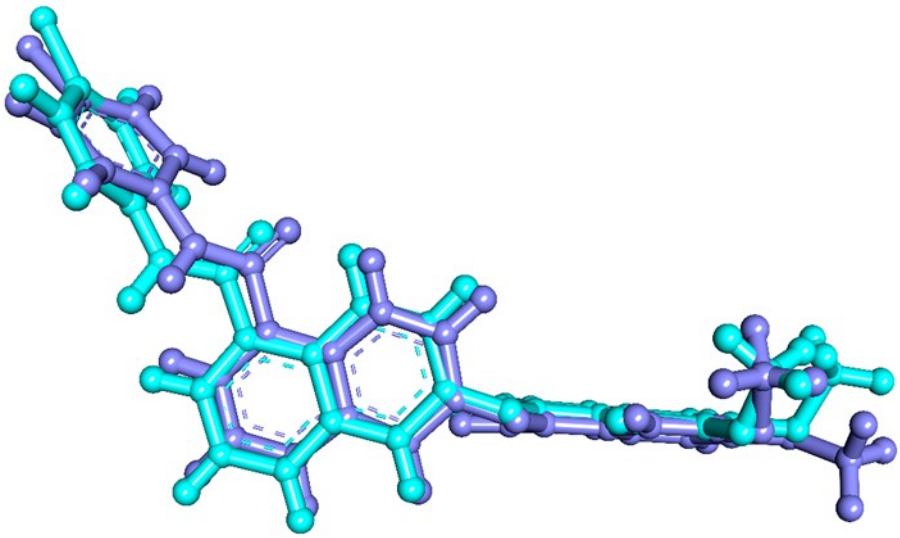


Fig S1. Binding conformations of compound 10 from MD simulated(purple) and the co-crystallized compound 10(cyan) at the active sites of KDR.

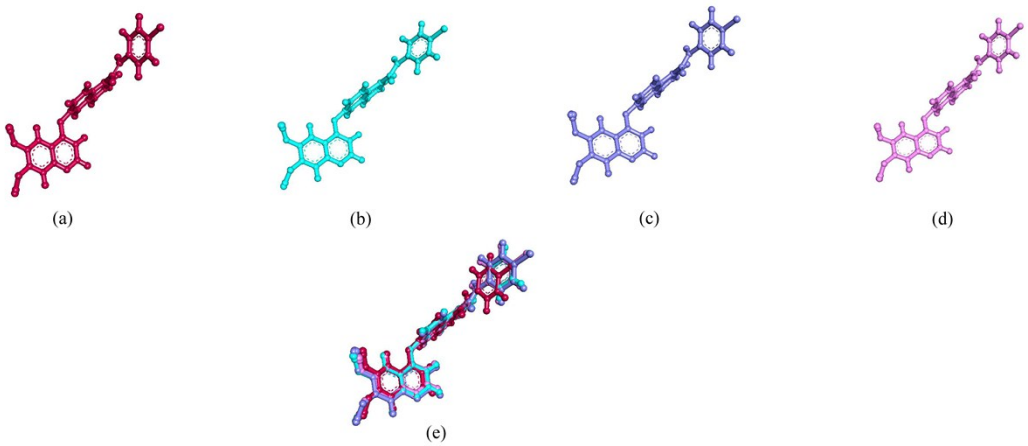
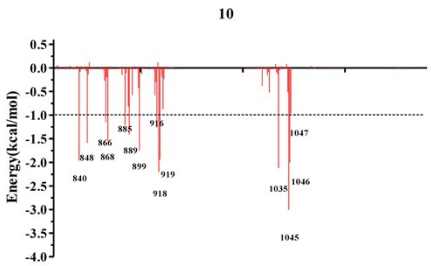


Fig S2. The average structures from 0 to 75ns(magenta, a) , 75 to 85 ns(cyan, b), 85 to 88 ns(purple, c) and 88 to 100 ns(pink, d) MD trajectories of compound 10. (e) Superimposition of the four average structures.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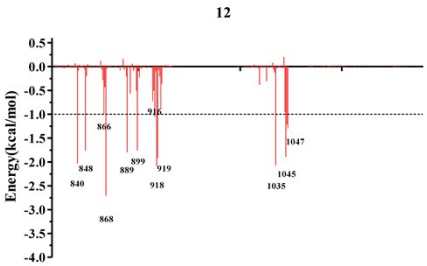
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
840
848
866
868
885
889
899
916
918
919
1035
1045
1046
1047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848
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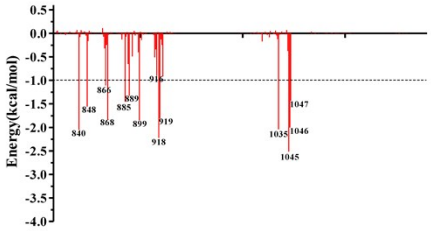
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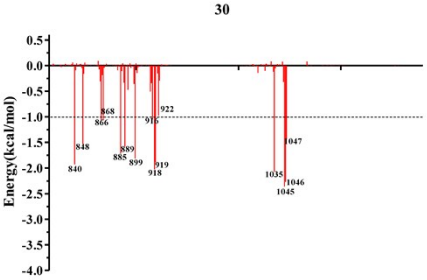
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918
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922
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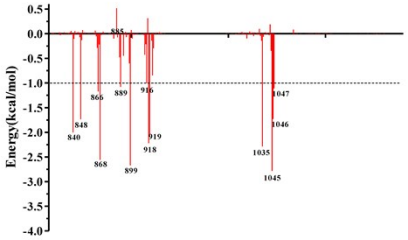
047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-3.0
-3.5
-4.0
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866
868
885
889
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918
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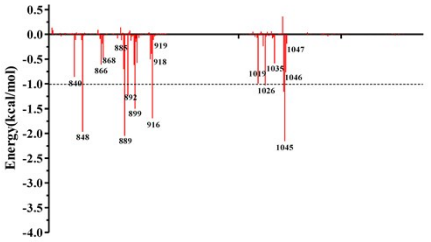
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-4.0
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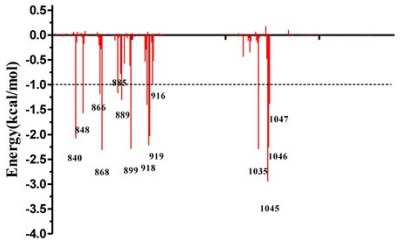
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-3.5
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868
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889
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918
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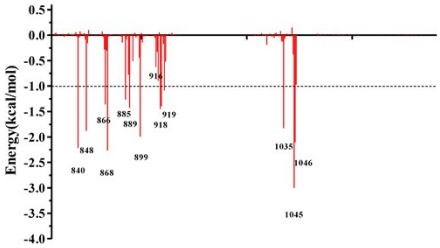
1047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848
866
868
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889
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916
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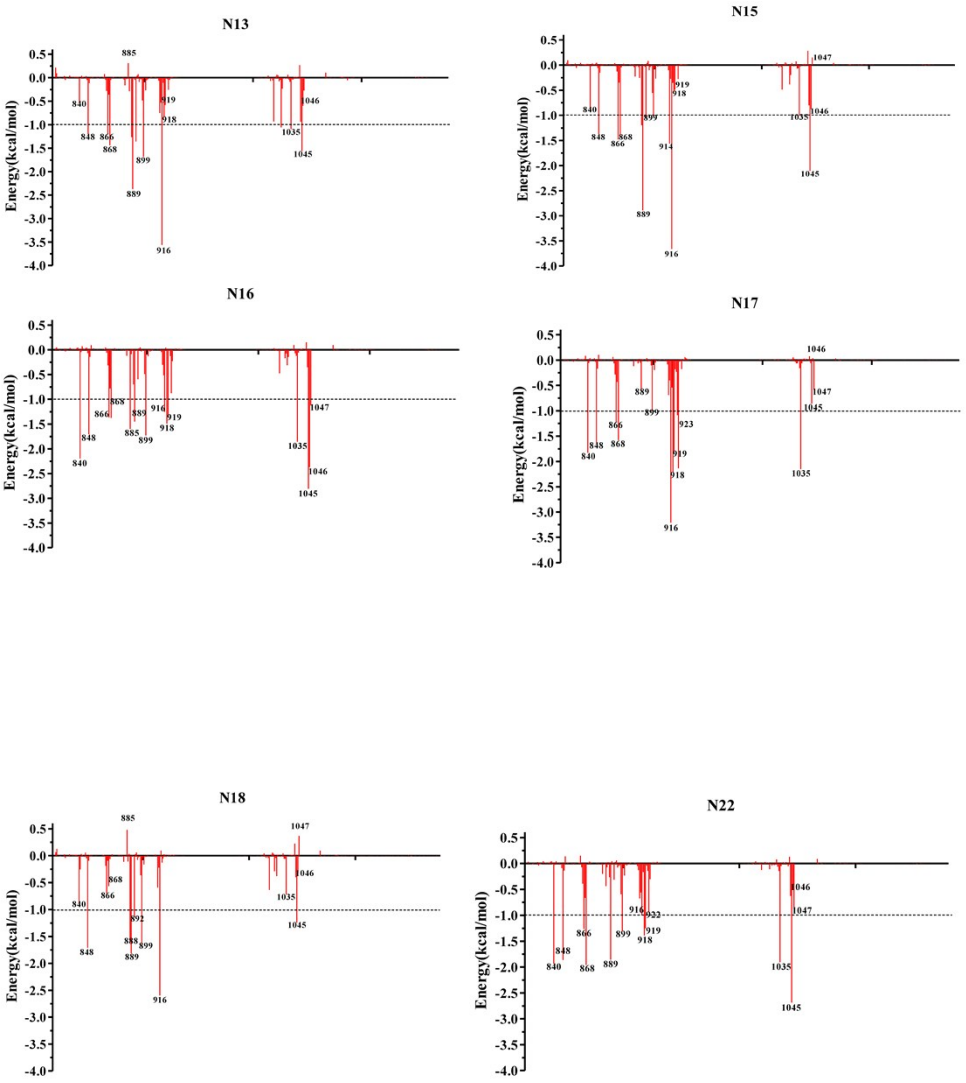

Fig S3. The residue interaction spectrum for potent KDR inhibitors.