Supporting Information

Discovery of novel antimyeloma agents targeting TRIP13 by molecular modeling and bioassay

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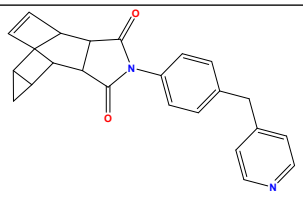
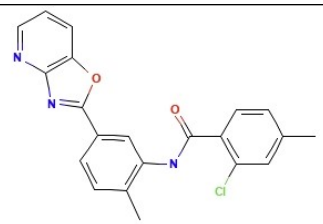
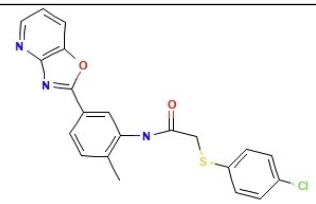
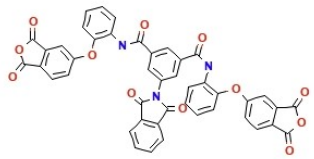
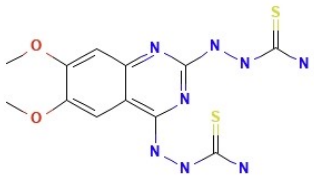
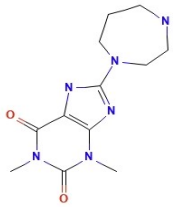
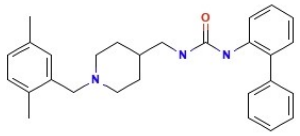
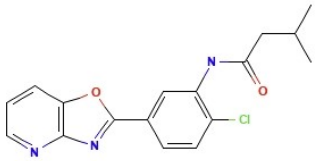
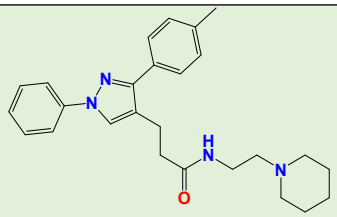
Table S1. Molecules obtained from virtual screening and purchased from the vendor.

(DCZ0415 was used as a positive control; crystal structure (PDB ID: 6LK0) was used for docking)

S/N	Molecule ID	Molecule Structure	Molecular Formula	Molecular Weight	LogS	LogP	Docking Score (kcal/mol)
	DCZ0415		$C_{23}H_{20}N_2O_2$	368.15	-4.65	3.0	-7.97

1.	4410-4309		$C_{21}H_{16}ClN_3O_2$	377.83	-3.64	5.01	-8.63
2.	4907-0005		$C_{21}H_{16}ClN_3O_2S$	409.896	-4.51	4.92	-8.5
3.	8004-8698		$C_{44}H_{23}N_3O_{12}$	785.68	-6.25	4.70	-9.56
4.	8014-9790		$C_{12}H_{16}N_8O_2S_2$	368.443	-3.60	0.18	-8.43
5.	8019-3544		$C_{12}H_{18}N_6O_2$	278.31	2.12	0.65	-8.31
6.	D264-1047		$C_{28}H_{33}N_3O$	427.59	-2.90	5.71	-8.28
7.	D725-0108		$C_{17}H_{16}ClN_3O_2$	329.78	-4.44	3.75	-8.21
8.	F368-0090		$C_{26}H_{32}N_4O$	416.566	-4.60	4.69	-8.24

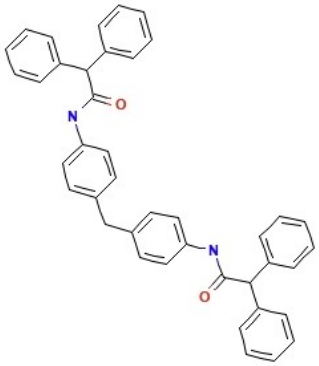
9.	Y503-0843		$C_{41}H_{34}N_2O_2$	586.733	-8.88	7.30	-8.25

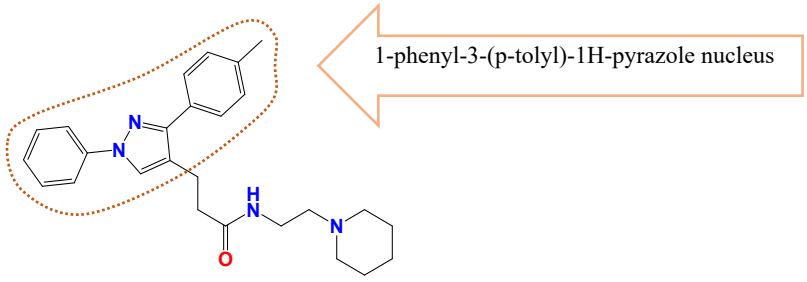
Table S2: Bioassay result of the high-affinity molecules from virtual screening

Molecule Name	Molecular Weight	ARP-1 (Inhibition rate at 25μM)	NCI-H929 (Inhibition rate at 25μM)
DCZ0415	368.44	67.4%±4.6%	76.1%±6.6%
F368-0090	416.57	73.1%±0.5%	85.2%±15.4%
4907-0005	409.9	1.4%±1.8%	7.9%±6.2%
8014-9790	368.44	0.6%±6.5%	-1.1%±5.1%
8019-3544	278.31	8.2%±1.6%	-6.7%±1.8%
D264-1047	427.59	97.6%±1.2%	97.2%±2.0%
Y503-0843	586.73	-1.5%±4.0%	-7.2%±1.9%
4410-4309	377.83	15.1%±5.9%	4.0%±9.6%
D725-0108	329.78	11.3%±4.4%	-0.2%±2.3%
8004-8698	785.68	0.4%±5.1%	-3.0%±2.3%

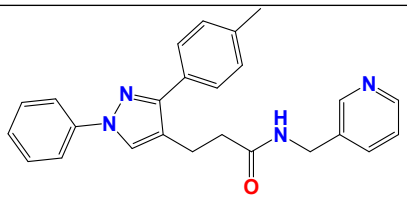
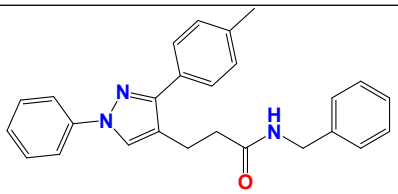
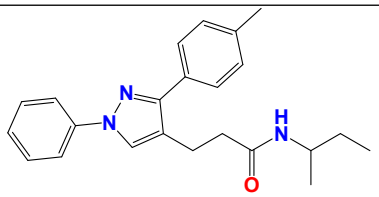
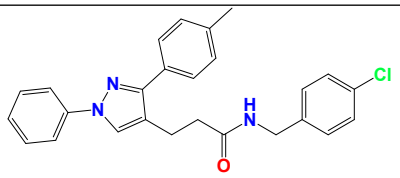
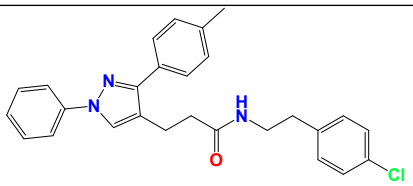
ARP-1 and H929: Multiple myeloma cell lines

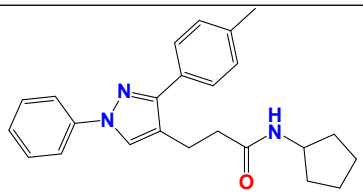
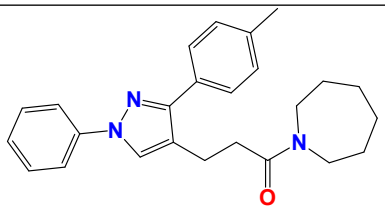
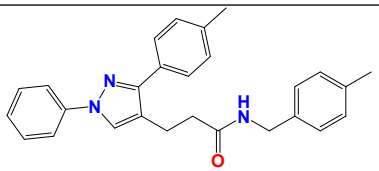
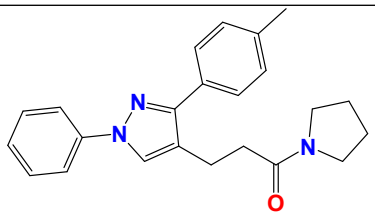
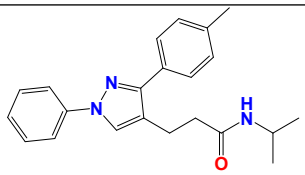
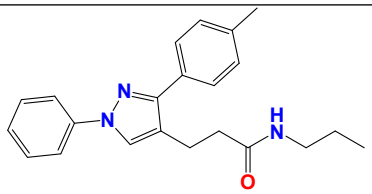
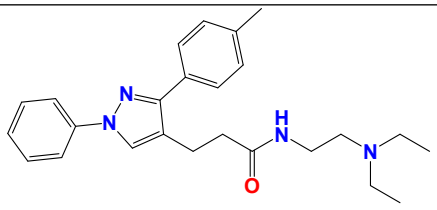
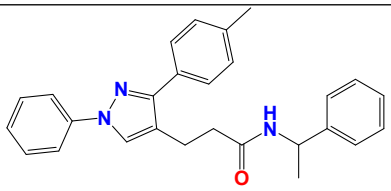
SD: Standard deviation

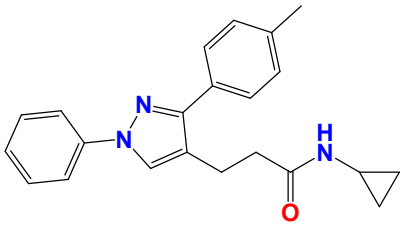
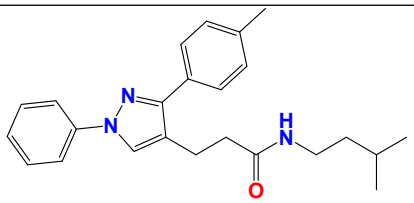
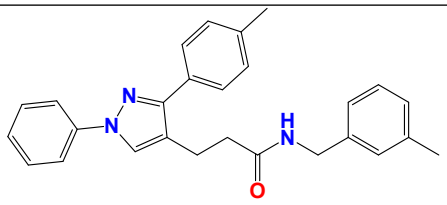
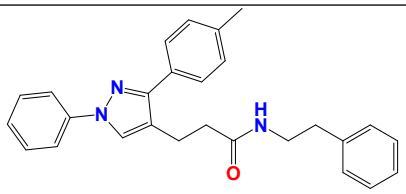
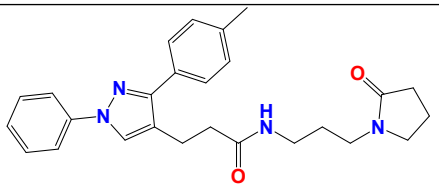
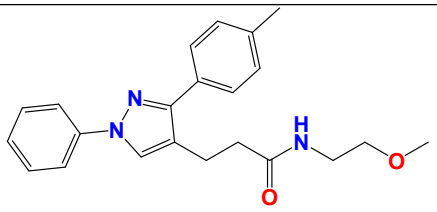
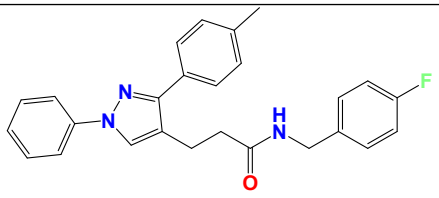
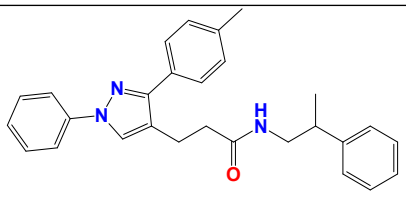
Supporting Information Table S3. Similarity Search of molecule F368-0090 and molecules that bioassay was conducted. Molecular docking was performed with PDB ID: 6LK0.

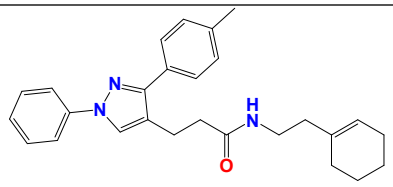
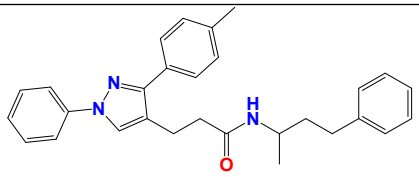
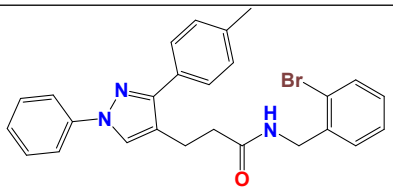
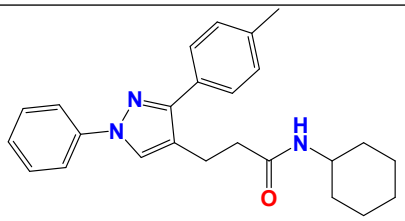
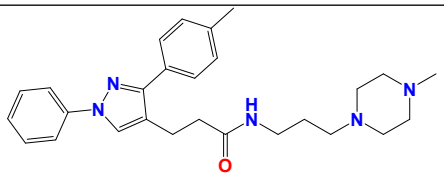
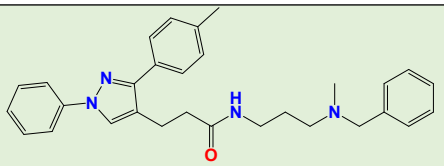
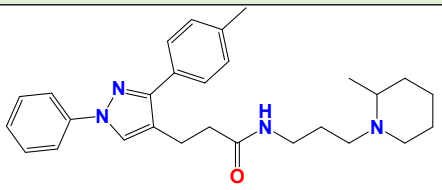
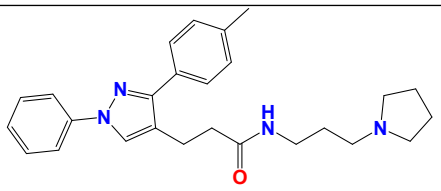
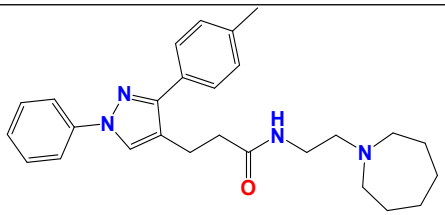


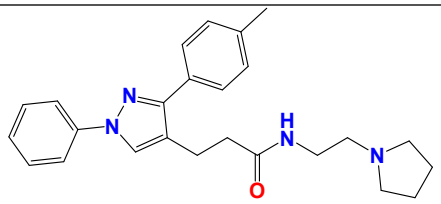
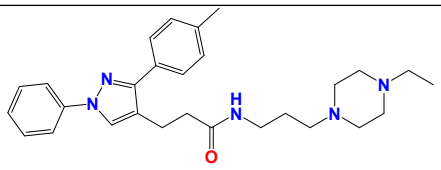
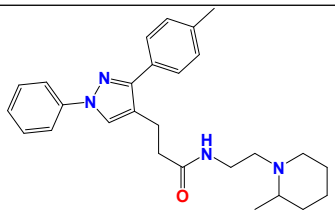
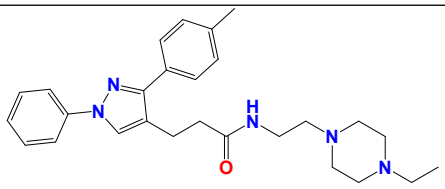
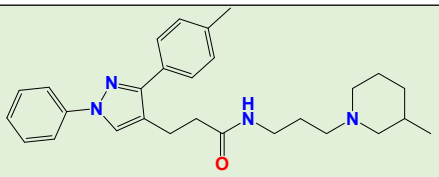
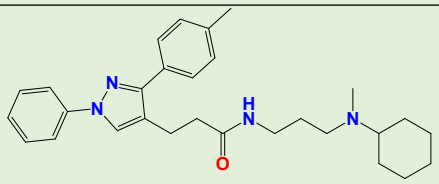
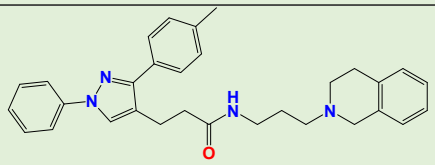
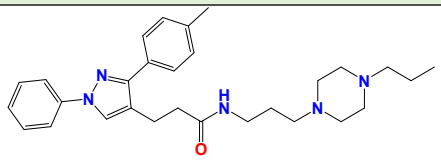
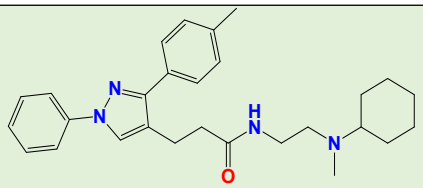
Molecule ID: F368-0090

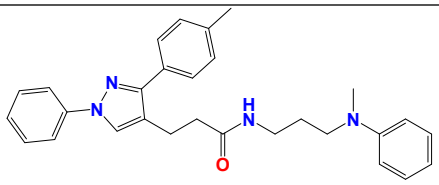
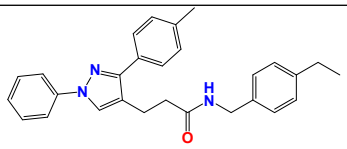
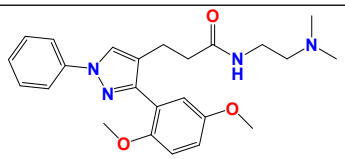
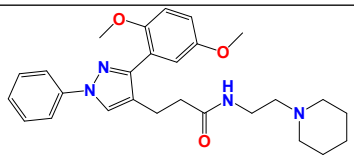
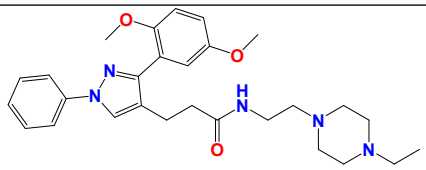
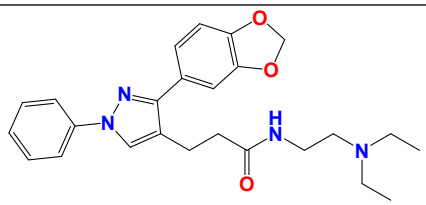
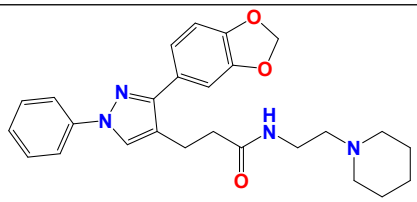
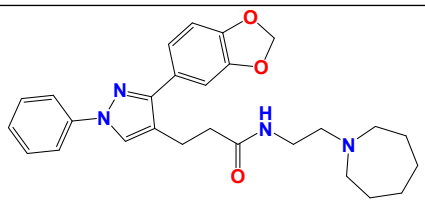
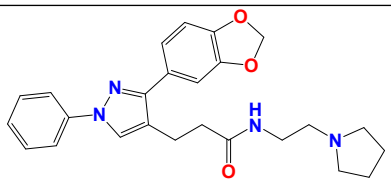
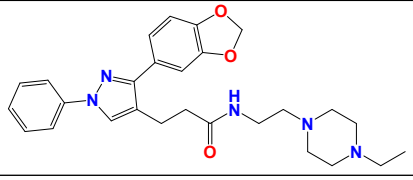
S/N	Molecule ID (ChemDiv)	Molecule Structure	Molecular Formula	Molecular Weight	LogS	LogP	Docking Score (kcal/mol)
1.	F368-0008		$C_{25}H_{24}N_4O$	396.49	-3.72	3.77	-8.60
2.	F368-0012		$C_{26}H_{25}N_3O$	395.50	-4.53	4.99	-8.35
3.	F368-0014		$C_{23}H_{27}N_3O$	361.49	-4.22	4.59	-8.06
4.	F368-0019		$C_{26}H_{24}ClN_3O$	429.95	-5.97	5.59	-8.35
5.	F368-0023		$C_{27}H_{26}ClN_3O$	443.98	-5.97	5.36	-8.26

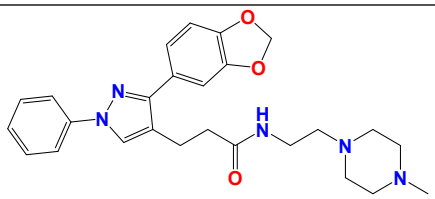
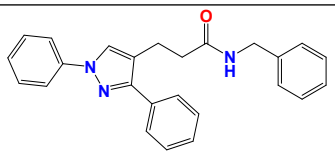
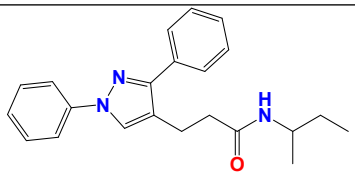
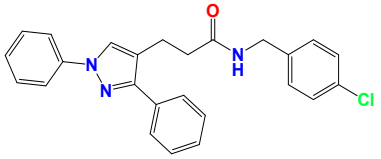
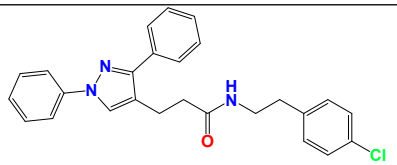
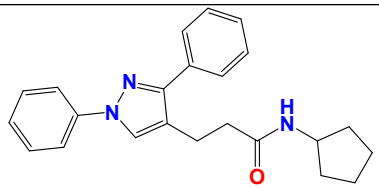
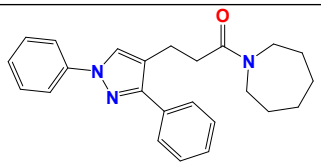
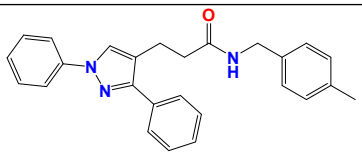
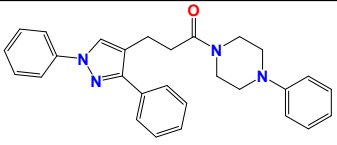
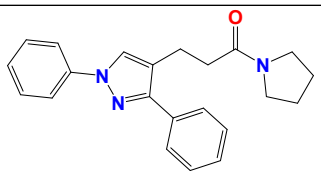
6.	F368-0025		$C_{26}H_{31}N_3O$	401.55	-5.31	5.83	-7.65
7.	F368-0026		$C_{24}H_{27}N_3O$	373.50	-4.41	4.88	-6.90
8.	F368-0043		$C_{25}H_{29}N_3O$	387.52	-4.65	5.08	-7.66
9.	F368-0047		$C_{27}H_{27}N_3O$	409.53	-5.31	5.42	-7.45
10.	F368-0053		$C_{23}H_{25}N_3O$	359.47	-4.16	4.37	-8.35
11.	F368-0068		$C_{22}H_{25}N_3O$	347.46	-4.15	4.20	-8.22
12.	F368-0069		$C_{22}H_{25}N_3O$	347.46	-3.95	4.06	-7.03
13.	F368-0070		$C_{25}H_{32}N_4O$	404.55	-3.91	4.05	-7.00
14.	F368-0073		$C_{27}H_{27}N_3O$	409.53	-5.29	5.35	-7.26

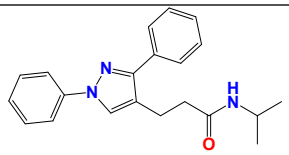
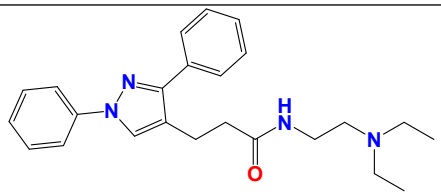
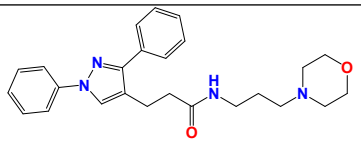
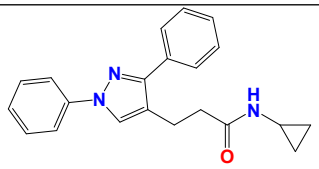
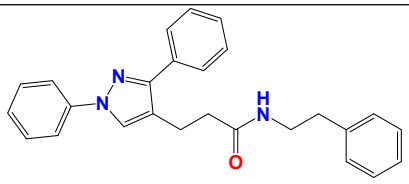
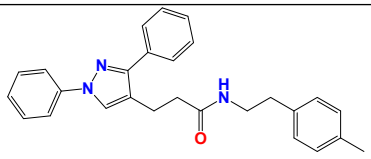
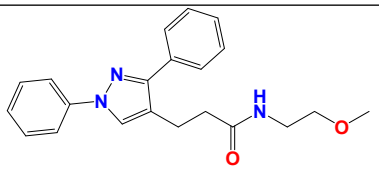
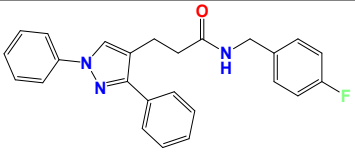
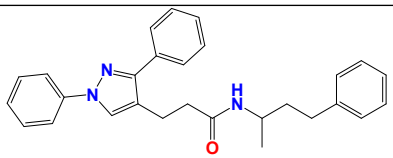
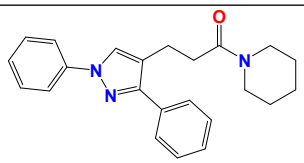
15.	F368-0077		$C_{22}H_{23}N_3O$	345.44	-4.10	4.01	-7.23
16.	F368-0079		$C_{24}H_{29}N_3O$	375.51	-4.33	4.86	-8.37
17.	F368-0080		$C_{27}H_{27}N_3O$	409.53	-5.36	5.68	-8.01
18.	F368-0081		$C_{27}H_{27}N_3O$	409.53	-4.43	4.77	-6.84
19.	F368-0086		$C_{26}H_{30}N_4O_2$	430.55	-2.94	2.66	-6.79
20.	F368-0093		$C_{22}H_{25}N_3O_2$	363.46	-3.41	3.33	-8.14
21.	F368-0102		$C_{26}H_{24}FN_3O$	413.49	-4.51	5.02	-7.73
22.	F368-0106		$C_{28}H_{29}N_3O$	423.56	-5.51	5.84	-7.67

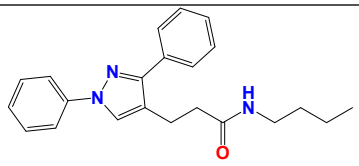
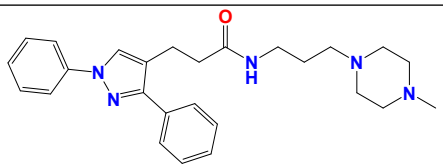
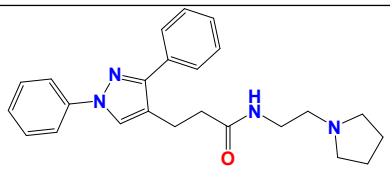
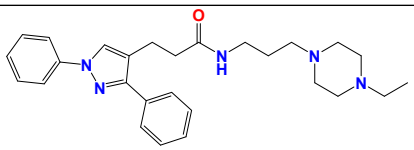
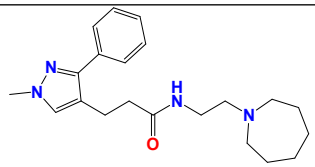
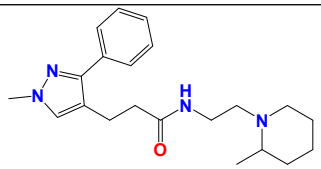
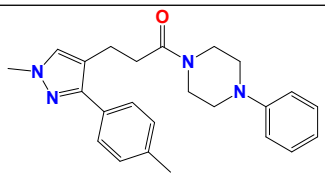
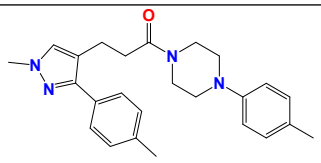
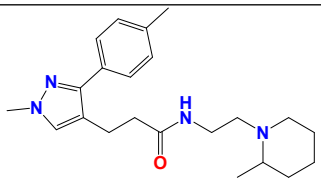
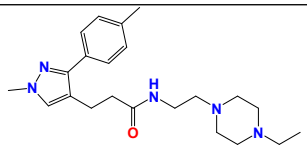
23.	F368-0118		$C_{27}H_{31}N_3O$	413.56	-4.81	5.14	-7.31
24.	F368-0124		$C_{29}H_{31}N3O$	437.58	-5.46	6.07	-7.55
25.	F368-0141		$C_{26}H_{24}BrN_3O$	474.40	-5.50	5.87	-6.86
26.	F368-0143		$C_{25}H_{29}N_3O$	387.52	-5.05	5.34	-8.35
27.	F368-0166		$C_{27}H_{35}N_5O$	445.61	-3.22	2.94	-8.13
28.	F368-0168		$C_{30}H_{34}N_4O$	466.63	-4.26	4.73	-7.31
29.	F368-0171		$C_{28}H_{36}N_4O$	444.62	-4.00	4.29	-6.88
30.	F368-0172		$C_{26}H_{32}N_4O$	416.57	-3.76	3.77	-8.24
31.	F368-0173		$C_{27}H_{34}N_4O$	430.59	-3.91	4.51	-8.16

32.	F368-0174		$C_{25}H_{30}N_4O$	402.54	-3.65	3.65	-7.84
33.	F368-0176		$C_{28}H_{37}N_5O$	459.63	-3.23	3.29	-7.81
34.	F368-0177		$C_{27}H_{34}N_4O$	430.59	-3.96	4.07	-8.28
35.	F368-0178		$C_{27}H_{35}N_5O$	445.61	-3.11	3.17	-7.57
36.	F368-0182		$C_{28}H_{36}N_4O$	444.62	-3.97	4.43	-8.14
37.	F368-0183		$C_{29}H_{38}N_4O$	458.65	-4.23	4.89	-8.11
38.	F368-0185		$C_{31}H_{34}N_4O$	478.64	-4.56	5.09	-8.28
39.	F368-0186		$C_{29}H_{39}N_5O$	473.66	-3.67	3.76	-8.16
40.	F368-0188		$C_{28}H_{36}N_4O$	444.62	-4.17	4.76	-8.19

41.	F368-0200		$C_{29}H_{32}N_4O$	452.60	-4.10	4.68	-7.86
42.	F368-0235		$C_{28}H_{29}N_3O$	423.56	-5.45	5.93	-8.55
43.	F368-0263		$C_{24}H_{30}N_4O_3$	422.53	-3.44	2.74	-8.29
44.	F368-0301		$C_{27}H_{34}N_4O_3$	462.59	-3.72	3.58	-8.46
45.	F368-0339		$C_{28}H_{37}N_5O_3$	491.63	-3.32	2.73	-7.75
46.	F368-0407		$C_{25}H_{30}N_4O_3$	434.54	-3.67	3.64	-7.28
47.	F368-0426		$C_{26}H_{30}N_4O_3$	446.55	-3.56	3.60	-7.48
48.	F368-0496		$C_{27}H_{32}N_4O_3$	460.58	-4.06	4.10	-7.28
49.	F368-0497		$C_{25}H_{28}N_4O_3$	432.52	-3.34	3.24	-7.79
50.	F368-0501		$C_{27}H_{33}N_5O_3$	475.59	-3.20	2.75	-7.58

51.	F368-0505		$C_{26}H_{31}N_5O_3$	461.56	-2.98	2.41	-6.78
52.	F368-0551		$C_{25}H_{23}N_3O$	381.48	-4.39	4.47	-8.19
53.	F368-0553		$C_{22}H_{25}N_3O$	347.46	-3.97	4.06	-8.15
54.	F368-0558		$C_{25}H_{22}ClN_3O$	415.92	-5.36	5.06	-8.16
55.	F368-0562		$C_{26}H_{24}ClN_3O$	429.95	-5.01	4.84	-7.75
56.	F368-0565		$C_{23}H_{25}N_3O$	359.47	-4.26	4.36	-6.81
57.	F368-0582		$C_{24}H_{27}N_3O$	373.50	-4.29	4.56	-6.80
58.	F368-0586		$C_{26}H_{25}N_3O$	395.50	-4.45	4.89	-7.80
59.	F368-0589		$C_{28}H_{28}N_4O$	436.56	-4.53	4.69	-7.62
60.	F368-0592		$C_{22}H_{23}N_3O$	345.44	-3.90	3.84	-7.47

61.	F368-0607		$C_{21}H_{23}N_3O$	333.43	-3.74	3.67	-7.41
62.	F368-0609		$C_{24}H_{30}N_4O$	390.53	-3.33	3.52	-8.17
63.	F368-0613		$C_{25}H_{30}N_4O_2$	418.54	-2.68	2.50	-8.02
64.	F368-0616		$C_{21}H_{21}N_3O$	331.42	-3.42	3.48	-7.56
65.	F368-0620		$C_{26}H_{25}N_3O$	395.50	-4.29	4.24	-7.38
66.	F368-0622		$C_{27}H_{27}N_3O$	409.53	-4.24	4.66	-7.78
67.	F368-0632		$C_{21}H_{23}N_3O_2$	349.43	-3.15	2.80	-7.84
68.	F368-0641		$C_{25}H_{22}FN_3O$	399.47	-4.37	4.50	-8.26
69.	F368-0664		$C_{28}H_{29}N_3O$	423.56	-5.42	5.54	-8.81
70.	F368-0684		$C_{23}H_{25}N_3O$	359.47	-4.03	4.06	-8.76

71.	F368-0686		$C_{22}H_{25}N_3O$	347.46	-3.97	4.12	-8.50
72.	F368-0706		$C_{26}H_{33}N_5O$	431.58	-2.70	2.42	-8.41
73.	F368-0714		$C_{24}H_{28}N_4O$	388.51	-3.19	3.12	-7.30
74.	F368-0716		$C_{27}H_{35}N_5O$	445.61	-2.98	2.76	-8.02
75.	F368-1150		$C_{21}H_{30}N_4O$	354.49	-2.47	2.24	-7.73
76.	F368-1153		$C_{21}H_{30}N_4O$	354.49	-2.07	1.80	-8.10
77.	F368-1333		$C_{24}H_{28}N_4O$	388.51	-3.38	3.48	-6.93
78.	F368-1346		$C_{25}H_{30}N_4O$	402.54	-3.98	4.03	-6.53
79.	F368-1385		$C_{22}H_{32}N_4O$	368.52	-2.63	2.33	-7.73
80.	F368-1387		$C_{22}H_{33}N_5O$	383.54	-1.95	1.43	-7.92

Supporting Information Table S4: The in vitro anti-proliferative assay (antimyeloma) bioactivity of all the compounds was obtained via a similarity search at different concentrations of the test compounds over 72 hours.

S/N	Compound ID	In vitro anti-proliferative bioassay (72hr)					
		(25µM)		(10µM)		(5µM)	
		ARP-1 (%)	H929 (%)	ARP-1 (%)	H929 (%)	ARP-1 (%)	H929 (%)
Control	**DCZ0415**	**67.4**	**76.1**	**58.6**	**62.1**	**44.3**	**36.3**
	VEL	**99.5 (20nM)**	**96.9 (20nM)**	**98.1(10nM)**	**96.5(10nM)**	**34.4(5nM)**	**46.8(5nM)**
	F368-0090	**73.1**	**99.0**	**16.4**	**53.0**	**17.1**	**27.9**
1	F368-0008	7.73	41.40	ND	ND	ND	ND
2	F368-0012	6.53	0.83	ND	ND	ND	ND
3	F368-0014	9.57	37.37	ND	ND	ND	ND
4	F368-0019	8.80	42.73	ND	ND	ND	ND
5	F368-0023	15.67	43.77	ND	ND	ND	ND
6	F368-0025	4.97	-1.07	ND	ND	ND	ND
7	F368-0026	16.13	33.17	ND	ND	ND	ND
8	F368-0043	27.30	84.53	17.3	16.4	-5.2	-14.6
9	**F368-0047***	**7.23**	**7.20**	**ND**	**ND**	**ND**	**ND**
10	F368-0053	29.47	73.27	39.0	34.0	12.0	3.6
11	F368-0068	11.20	26.50	ND	ND	ND	ND
12	F368-0069	10.97	23.37	ND	ND	ND	ND
13	F368-0070	27.73	93.73	26.6	54.4	0.0	10.0
14	F368-0073	12.97	29.43	ND	ND	ND	ND
15	F368-0077	21.27	31.03	17.1	8.3	0.7	-11.2
16	F368-0079	14.37	28.60	ND	ND	ND	ND
17	F368-0080	8.33	24.33	ND	ND	ND	ND
18	F368-0081	32.07	65.53	22.5	23.4	4.3	-3.5
19	F368-0086	12.67	20.50	ND	ND	ND	ND
20	F368-0093	13.60	32.40	ND	ND	ND	ND
21	F368-0102	2.35	10.77	ND	ND	ND	ND
22	F368-0106	10.30	57.00	20.5	40.4	6.3	1.8
23	F368-0118	21.20	17.27	ND	ND	ND	ND
24	F368-0124	16.95	33.80	ND	ND	ND	ND
25	F368-0141	53.65	10.83	ND	ND	ND	ND
26	F368-0143	12.30	2.00	ND	ND	ND	ND
27	F368-0166	36.75	88.97	16.6	24.6	1.2	5.2
28	**F368-0168****	**96.05**	**92.95**	**75.3**	**94.3**	**4.9**	**18.8**
29	F368-0171	97.50	95.30	21.1	52.7	0.7	5.1
30	F368-0172	85.35	82.93	18.0	29.8	-0.2	-5.8

31	F368-0173	95.15	97.55	20.9	35.5	7.0	-2.3
32	F368-0174	96.20	98.85	20.6	30.6	11.4	6.4
33	F368-0176	82.00	92.88	20.5	27.5	1.4	10.6
34	F368-0177	99.70	98.13	25.9	55.1	8.1	14.6
35	F368-0178	32.30	99.0	18.8	27.8	7.1	5.8
36	**F368-0182****	**100.20**	**78.50**	**45.1**	**79.4**	**5.1**	**26.8**
37	**F368-0183****	**87.85**	**99.15**	**98.5**	**99.5**	**12.7**	**34.7**
38	**F368-0185****	**99.55**	**99.20**	**85.0**	**98.1**	**0.1**	**24.7**
39	F368-0186	55.95	97.55	13.7	28.9	-7.1	0.7
40	**F368-0188****	**100.25**	**99.37**	**90.7**	**99.3**	**7.5**	**26.7**
41	F368-0200	66.60	79.65	21.2	38.8	12.0	-1.8
42	F368-0235	23.95	17.70	ND	ND	ND	ND
43	F368-0263	27.10	19.10	ND	ND	ND	ND
44	F368-0301	43.50	67.00	13.6	5.1	4.1	-4.5
45	F368-0339	34.45	36.80	ND	ND	ND	ND
46	F368-0407	69.85	58.48	12.5	20.6	7.5	-1.1
47	F368-0426	60.70	61.10	10.8	23.5	3.9	1.2
48	F368-0496	55.55	27.83	ND	ND	ND	ND
49	F368-0497	71.85	83.57	11.2	28.8	7.2	6.3
50	F368-0501	16.10	3.28	ND	ND	ND	ND
51	F368-0505	23.7	28.48	ND	ND	ND	ND
52	F368-0551	78.87	94.05	10.8	11.5	21.9	21.0
53	F368-0553	27.30	48.25	ND	ND	ND	ND
54	F368-0558	87.98	95.62	5.4	21.1	25.3	24.9
55	F368-0562	92.28	98.23	11.3	27.2	29.1	36.4
56	F368-0565	28.69	50.35	ND	ND	ND	ND
57	F368-0582	98.66	100.13	24.2	35.2	33.7	28.8
58	F368-0586	9.27	57.55	3.7	8.3	21.5	30.7
59	F368-0589	76.22	93.31	5.7	13.3	20.6	25.1
60	F368-0592	38.52	40.84	ND	ND	ND	ND
61	F368-0607	51.39	49.27	ND	ND	ND	ND
62	F368-0609	47.41	70.67	7.6	11.5	23.	24.2
63	F368-0613	37.38	30.21	ND	ND	ND	ND
64	F368-0616	35.60	42.87	ND	ND	ND	ND
65	F368-0620	87.97	96.55	21.8	27.0	0.1	7.1
66	F368-0622	70.47	80.52	14.7	25.6	25.3	26.1
67	F368-0632	56.24	29.06	ND	ND	ND	ND
68	F368-0641	91.60	95.22	12.7	21.2	25.3	22.2
69	F368-0664	96.72	97.92	19.4	31.5	24.5	33.2
70	F368-0684	88.46	68.48	18.6	20.4	3.9	6.6
71	F368-0686	59.04	60.47	16.4	21.8	-1.0	7.2

72	F368-0706	37.16	35.24	ND	ND	ND	ND
73	F368-0714	37.08	32.33	ND	ND	ND	ND
74	F368-0716	30.00	28.55	ND	ND	ND	ND
75	F368-1150	26.75	12.19	ND	ND	ND	ND
76	F368-1153	20.18	12.51	ND	ND	ND	ND
77	F368-1333	38.34	50.57	ND	ND	ND	ND
78	F368-1346	40.30	65.52	13.5	21.4	1.5	-2.2
79	F368-1385	22.93	18.17	ND	ND	ND	ND
80	F368-1387	21.89	16.00	ND	ND	ND	ND

ND = Not Determined because the inhibition rate was lower than 50% at 25µM.

**Compound(s) with best IC_{50}

*Negative control

VEL - Bortezomib

Table S5: ATPase inhibitory bioassay of five active compounds, positive and negative control at 150 μM.

Compound ID	Percentage ATPase inhibitory (%)		Mean (%)	SD (%)
	1st Test	2nd Test		
DCZ0415	30.74	29.05	29.90	1.20
F368-0090	46.18	46.35	46.26	0.12
F368-0188	95.18	95.72	95.45	0.38
F368-0182	56.69	56.61	56.65	0.06
F368-00168	50.11	51.06	50.58	0.67
F368-0183	20.27	20.74	20.51	0.34
F368-0185	18.87	20.12	19.49	0.89
F368-0047	-4.01	-4.21	-4.11	0.14

SD – Standard deviation.

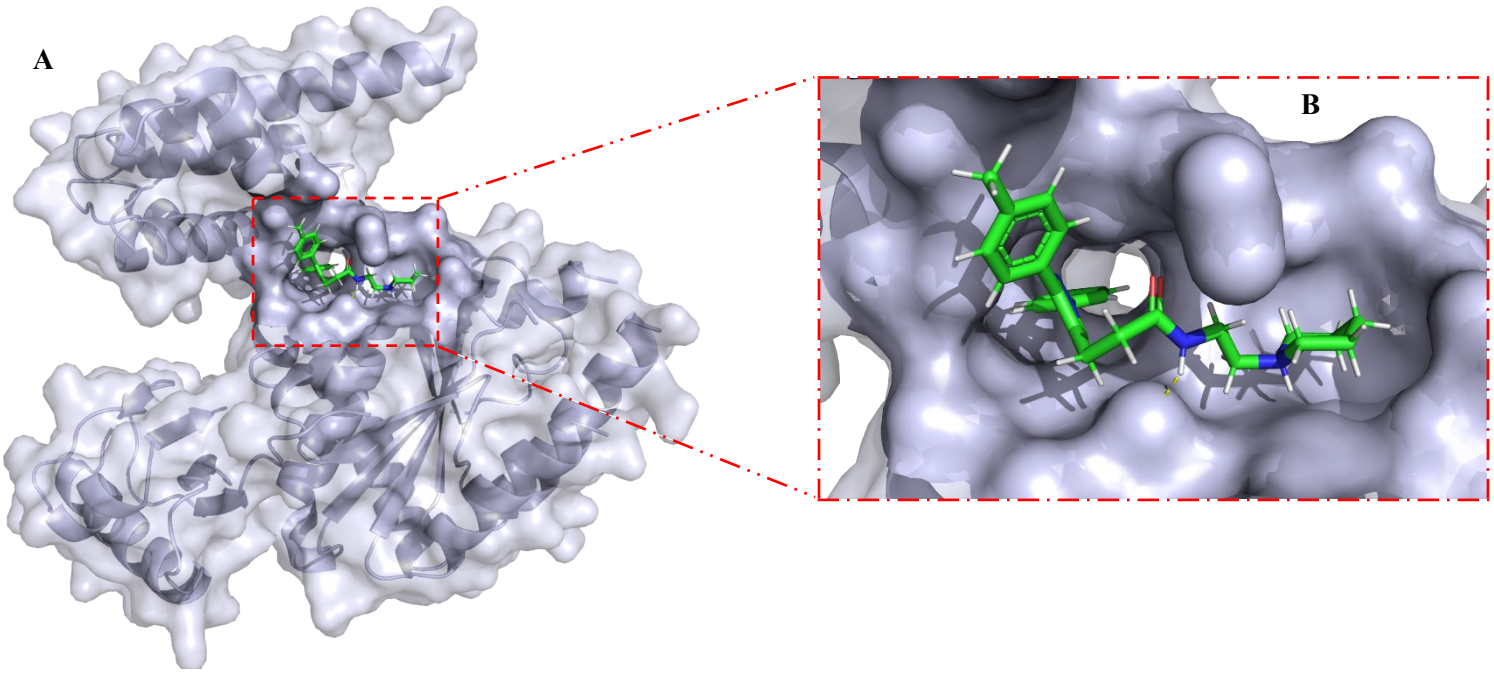


Fig. S1 F368-0090 was observed to fit into the TRIP13 pocket (The ATP binding site); PDB: 6LKO. (A) whole protein and ligand, (B) ligand binding pose and pocket in TRI13 protein.

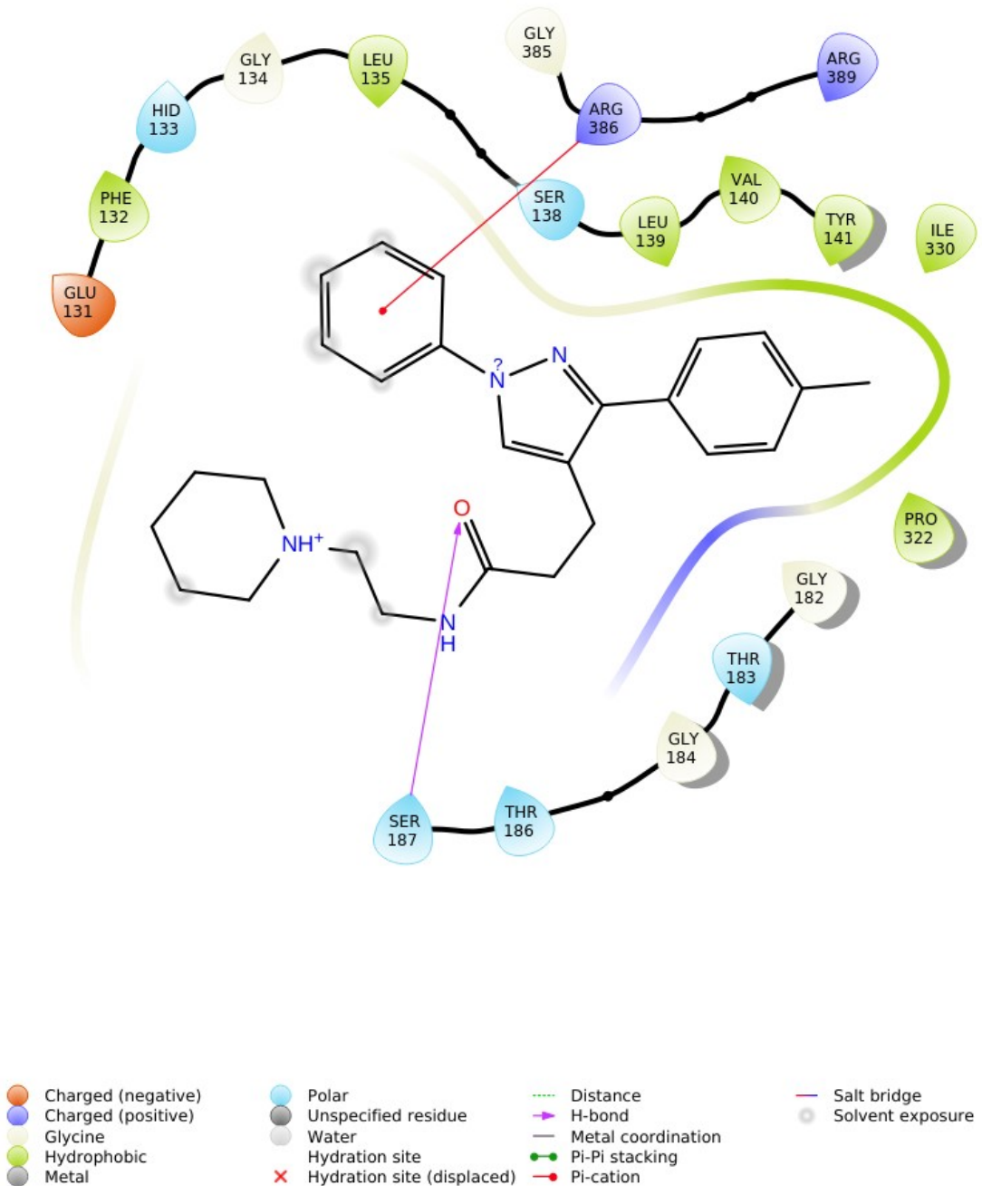


Fig. S2 F368-0090 – TRIP13 molecular interactions revealed by molecular docking

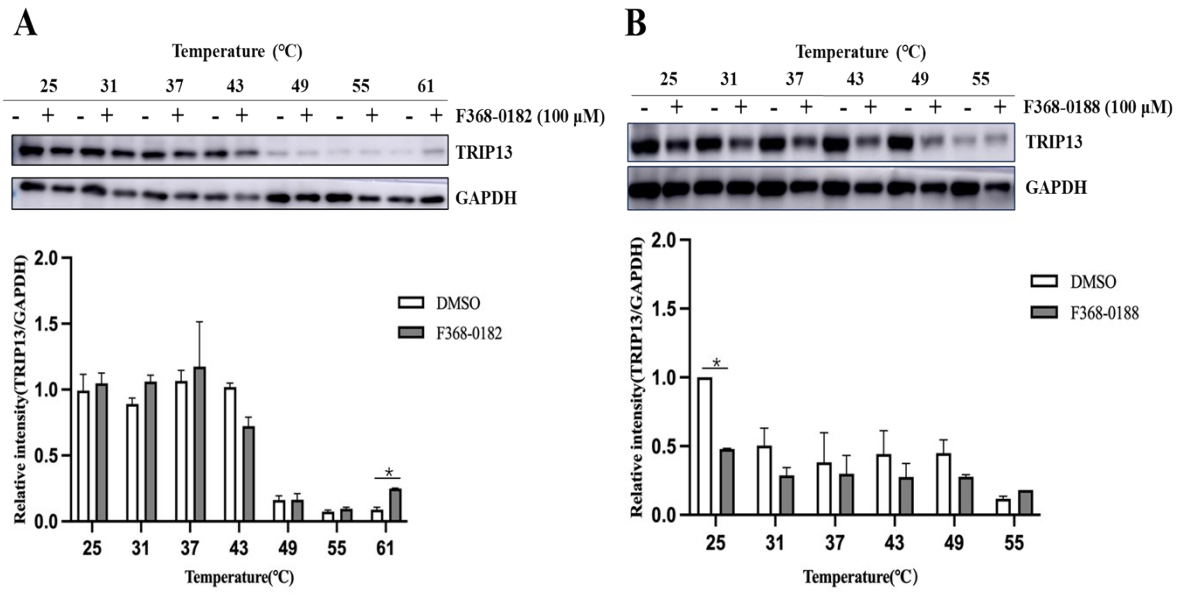


Fig. S3 Identification of F368-0182 (A) and F368-0188 (B) binding to TRIP13 using cellular thermal shift assay (CETSA). The supernatants were subjected to SDS-PAGE and western blot analysis (top). The relative levels of soluble TRIP13 were measured and compared to GAPDH and plotted as a function of temperature (bottom). All results are expressed as mean ± SD of three independent experiments and *p≤0.01, * Comparable activity with control.

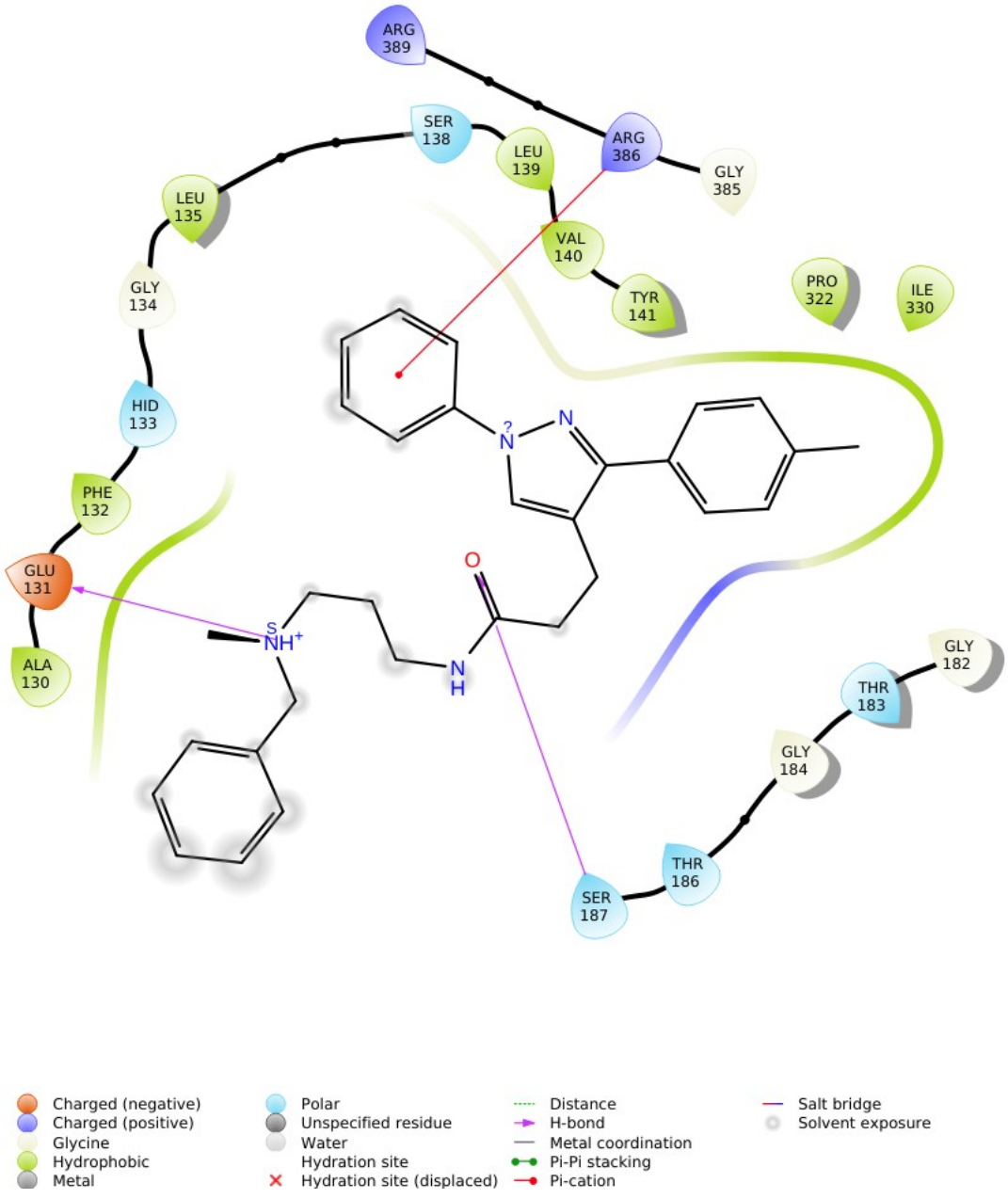


Fig. S4 2D Protein-Ligand Interaction of TRIP13 and F368-0168

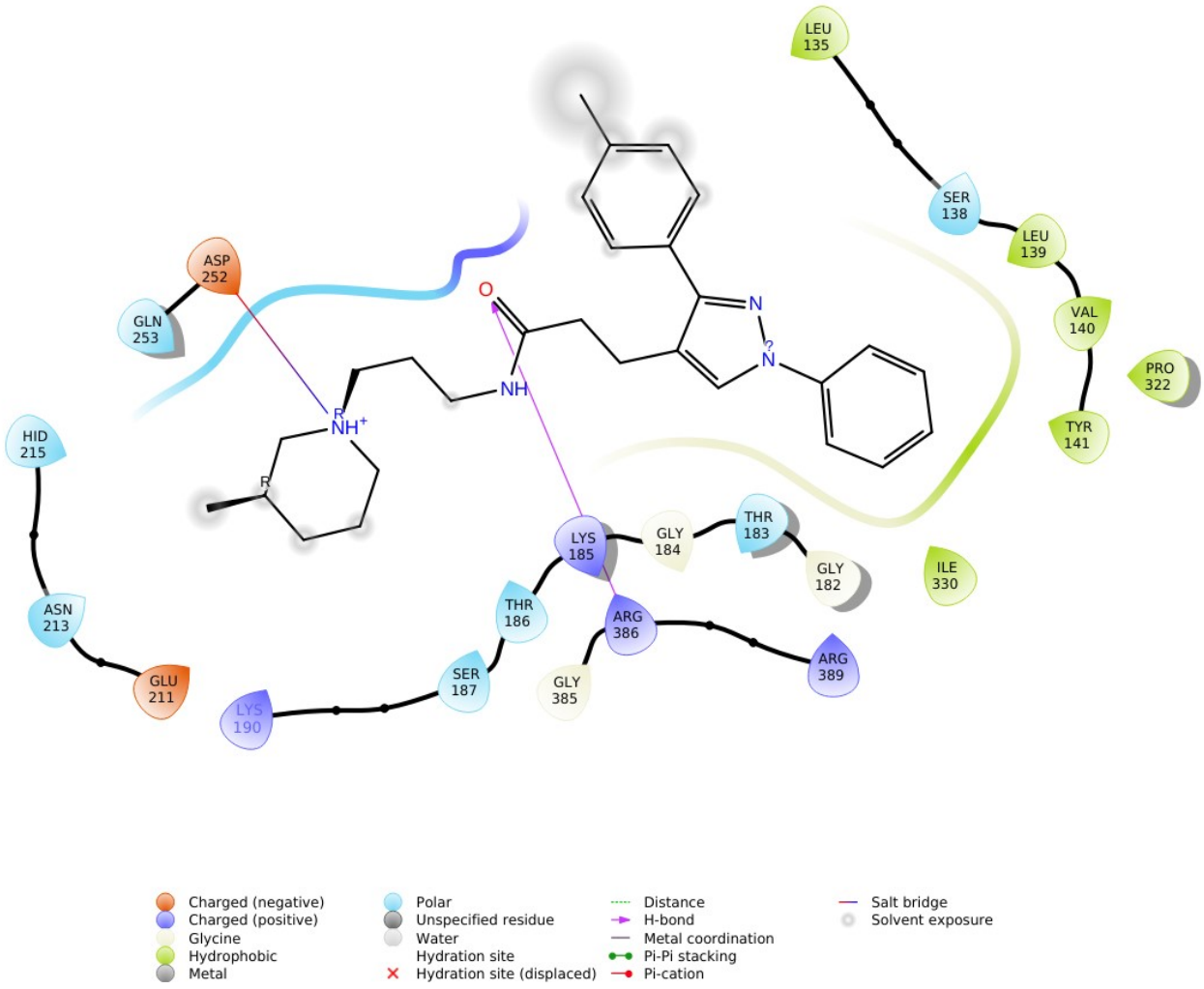


Fig. S5 2D Protein-Ligand Interaction of TRIP13 and F368-0182

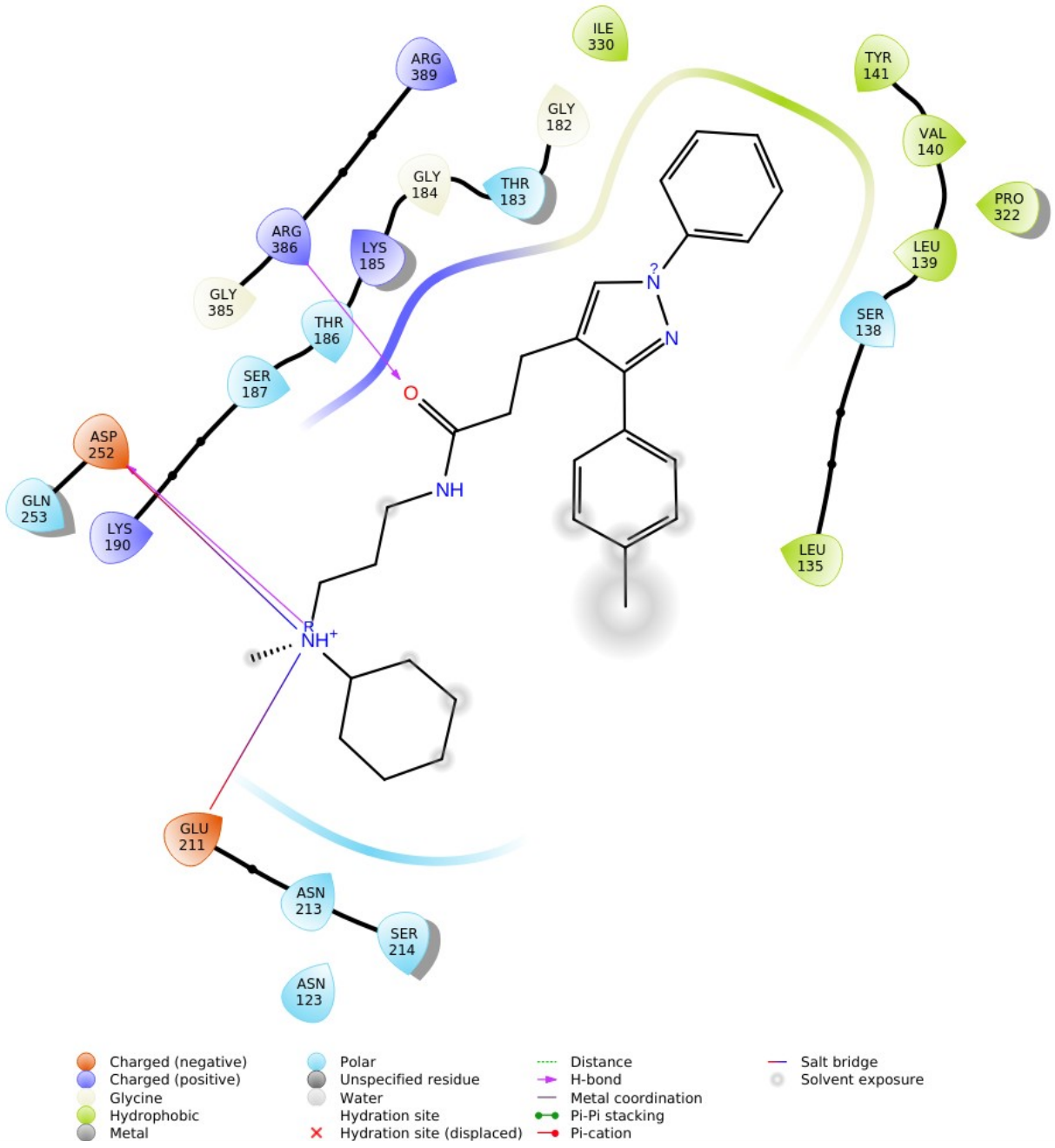


Fig. S6 2D Protein-Ligand Interaction of TRIP13 and F368-0183

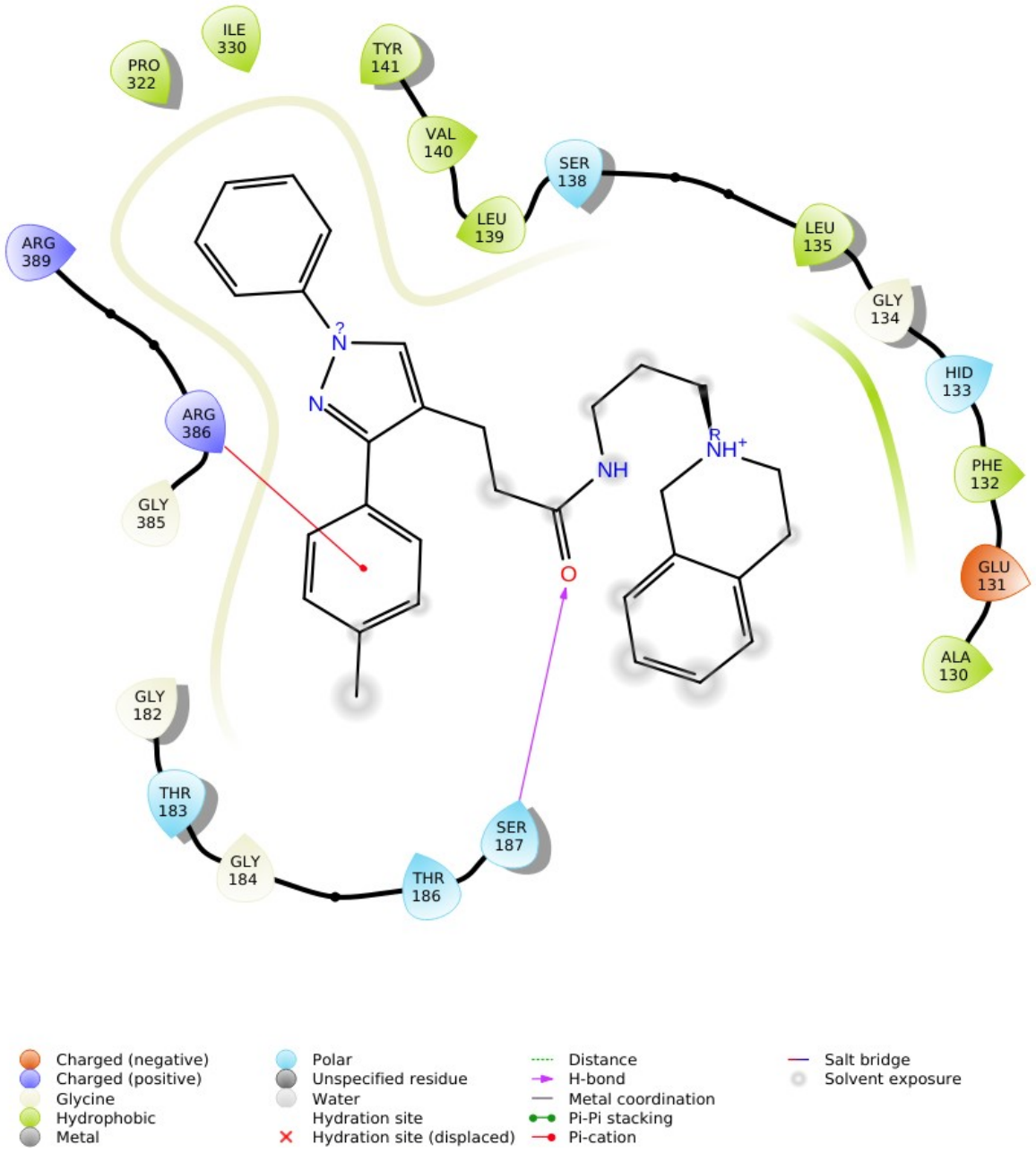


Fig. S7 2D Protein-Ligand Interaction of TRIP13 and F368-0185

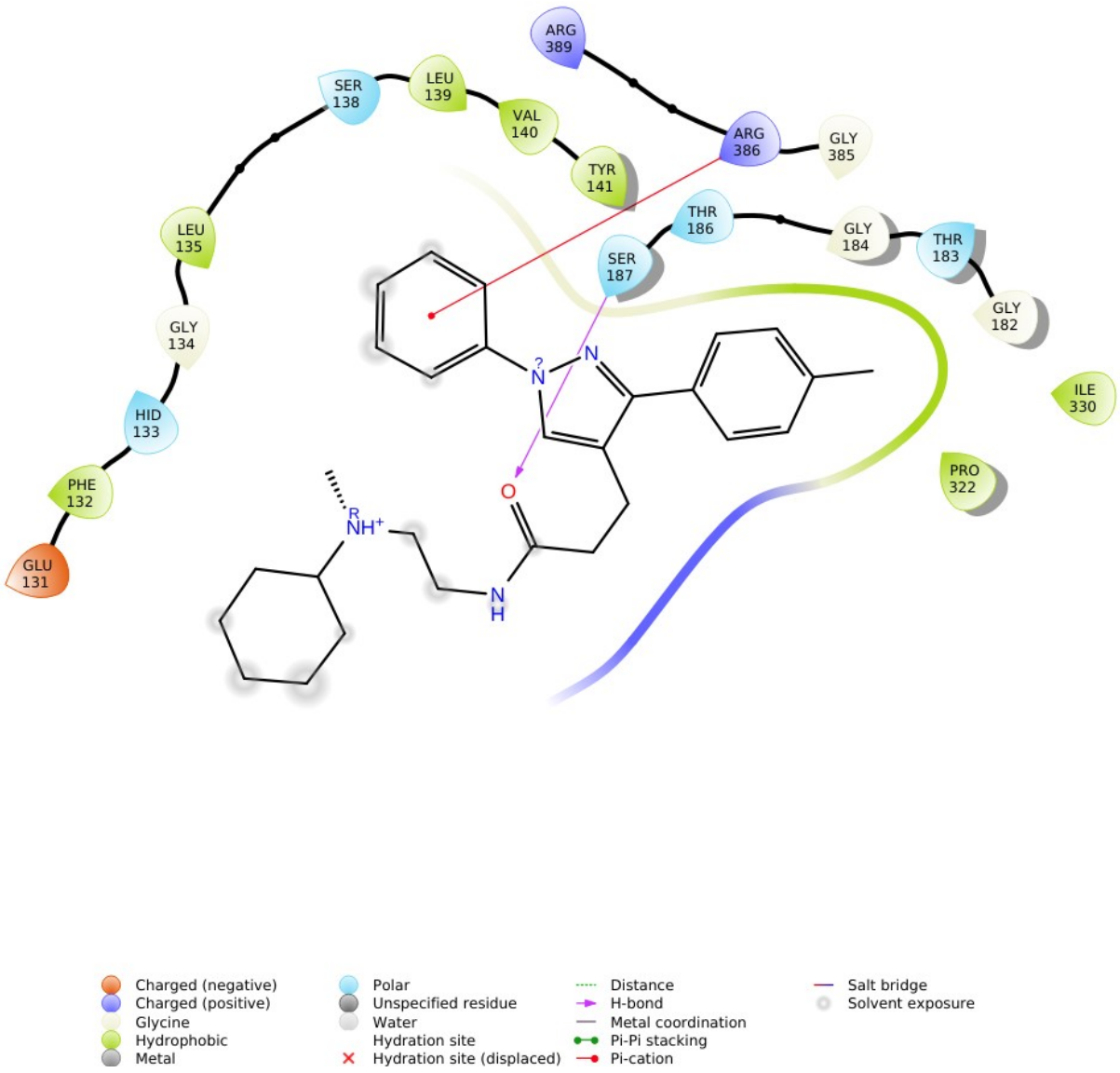


Fig. S8 2D Protein-Ligand Interaction of TRIP13 and F368-0188

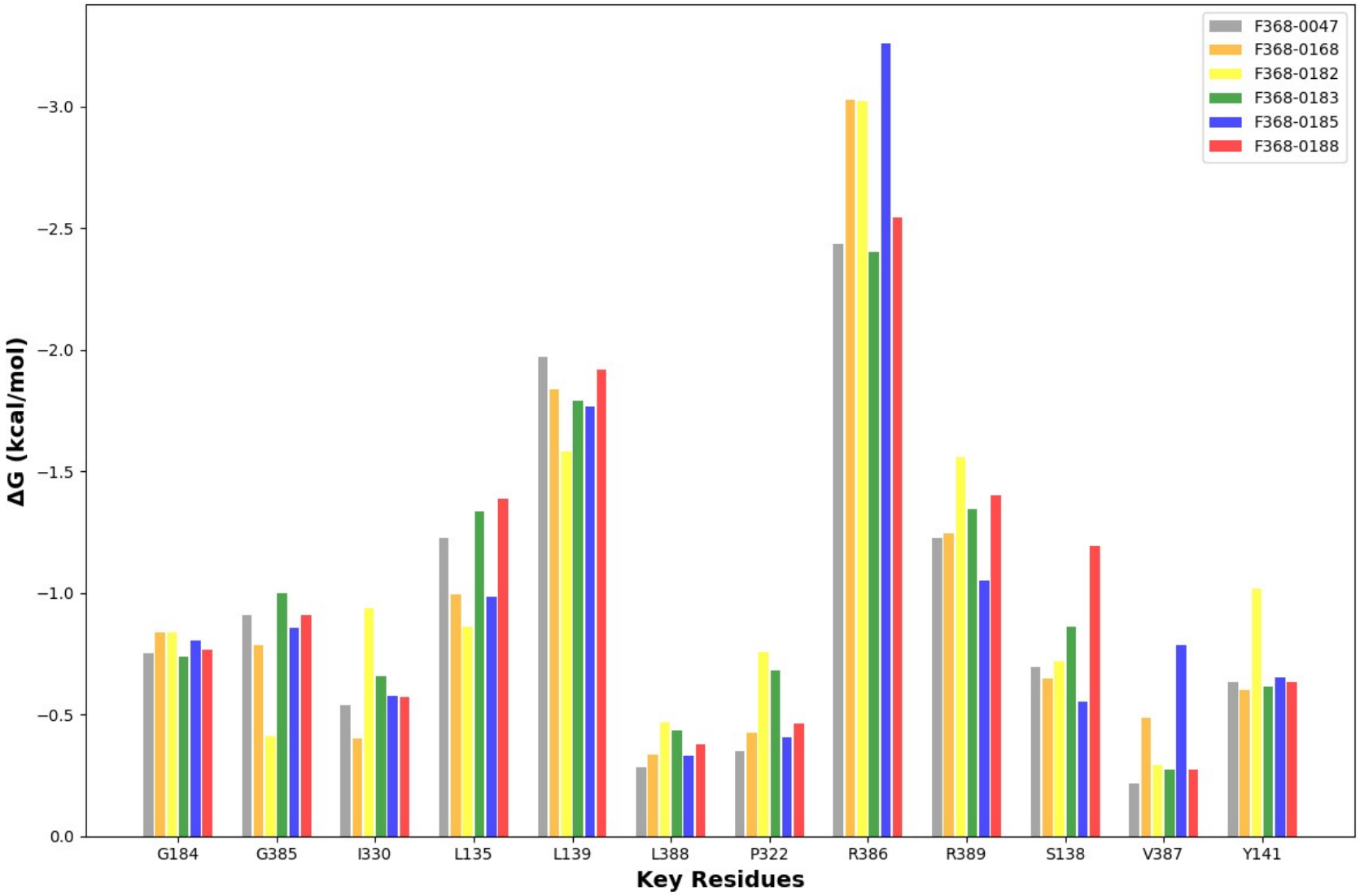


Fig. S9 The binding free energy decomposition of novel TRIP13 inhibitors with key residues

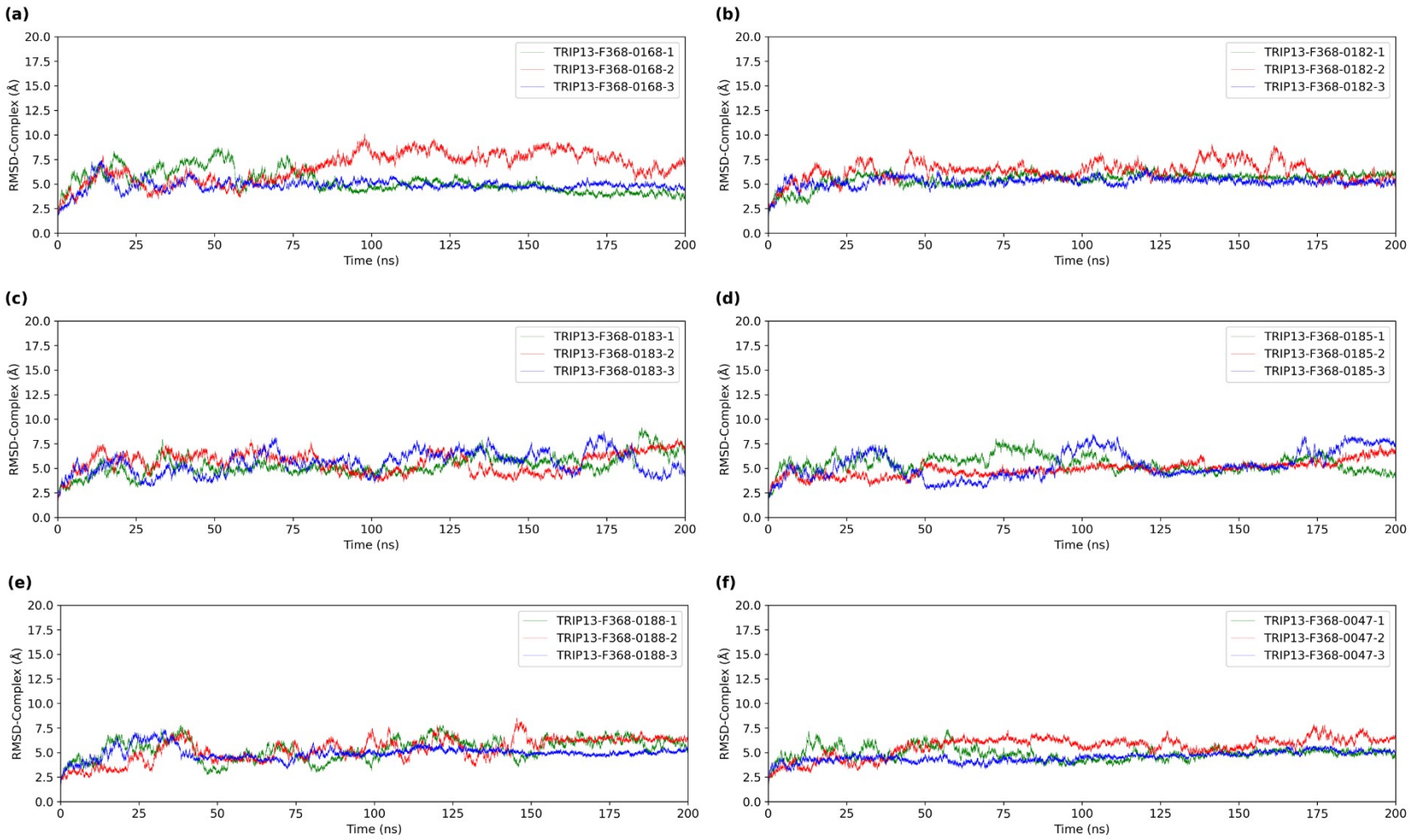


Fig. S10 Time dependence of the system RMSD during 200 ns MD simulation of the novel TRIP13 inhibitors.

1. **a-e:** systems formed by active compounds and TRIP13 protein (PDB ID: 6LK0).
2. **f:** system formed by the inactive compound and TRIP13 protein (PDB ID: 6LK0).

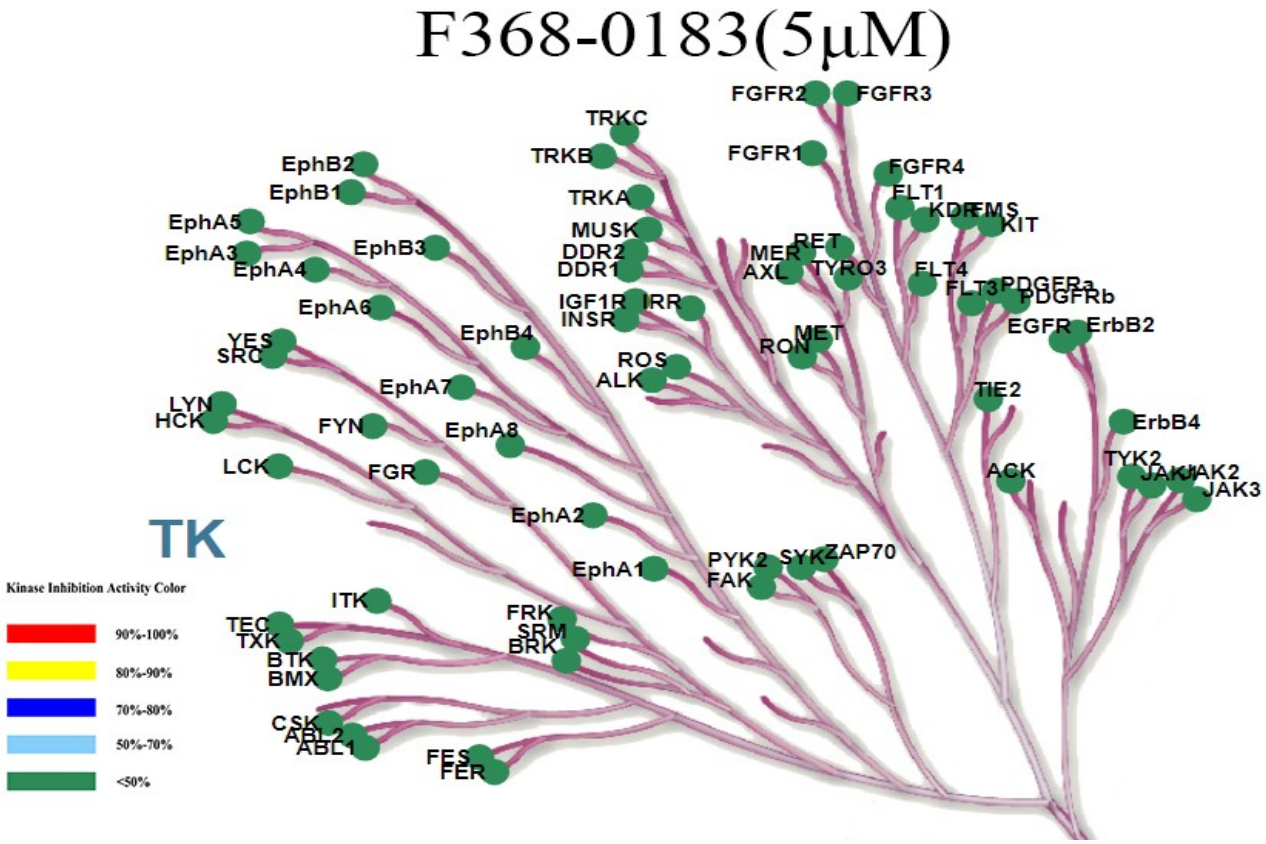


Fig. S11 Kinase panel report of F368-0813**.** Kinase phylogenetic tree (KT), kinome, a comprehensive family of kinases. Green circles highlight specific kinases that interacted with F368-0183. The Heatmap represented (right side) shows % inhibition of kinases by F368-0183 at 5 μM. The color scale (right bar) transitions from green (low inhibition) to red (high inhibition), suggesting minimal inhibition at this concentration.