Supplementary Materials for:

Discovery of urea-based hit compound as novel inhibitor of transforming growth factor-β type 1 receptor: *In silico* and *in vitro* studies

Yaxin Li [a, b], Sisi Liu [b], Zhuoya Wang [c], Xiaoli Wang [a], Jiamin Xu [a], Keke Yao [a], Ranran Zhang [b], Chenxuan Lu [b], Zhigang Wu [b], and Liming Hu [a, *]

[a] *Beijing Key Laboratory of Environmental and Oncology, College of Chemistry and Life Science, Beijing University of Technology, Beijing 100124, China*

[b] *Hebei Key Laboratory of Neuropharmacology, School of Pharmacy, Hebei North University, Zhangjiakou 075000, China;*

[c] *Qingdao Marine Science and Technology Center, Qingdao 266237, China*

* Corresponding author. Prof. Hu, E-mail address: huliming@bjut.edu.cn;

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1. Figure S1-S10.
2. Table S1.

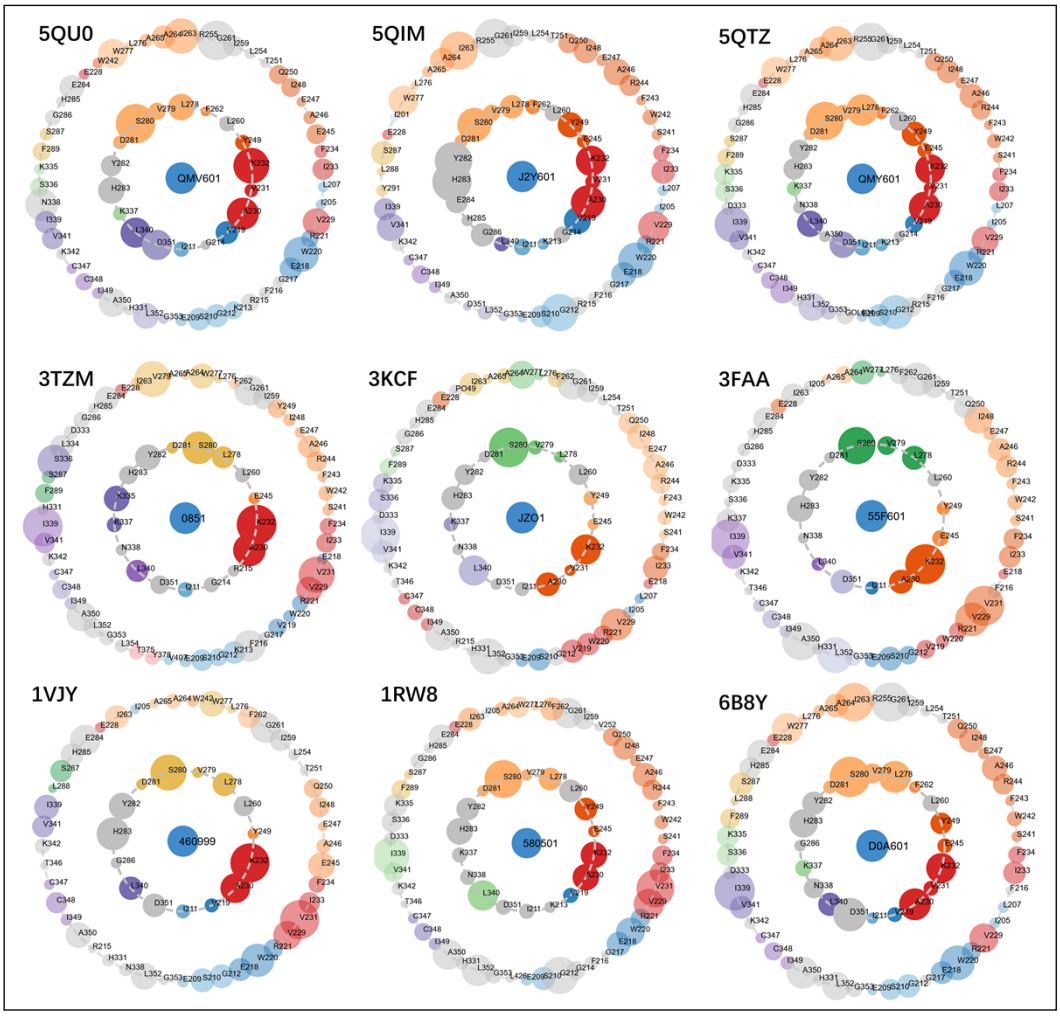

Figure S1. The results of the protein-ligand contact atlas and key residues interacting with the ligands in the crystal structures (S280, Y282, H283, A230, and K232).

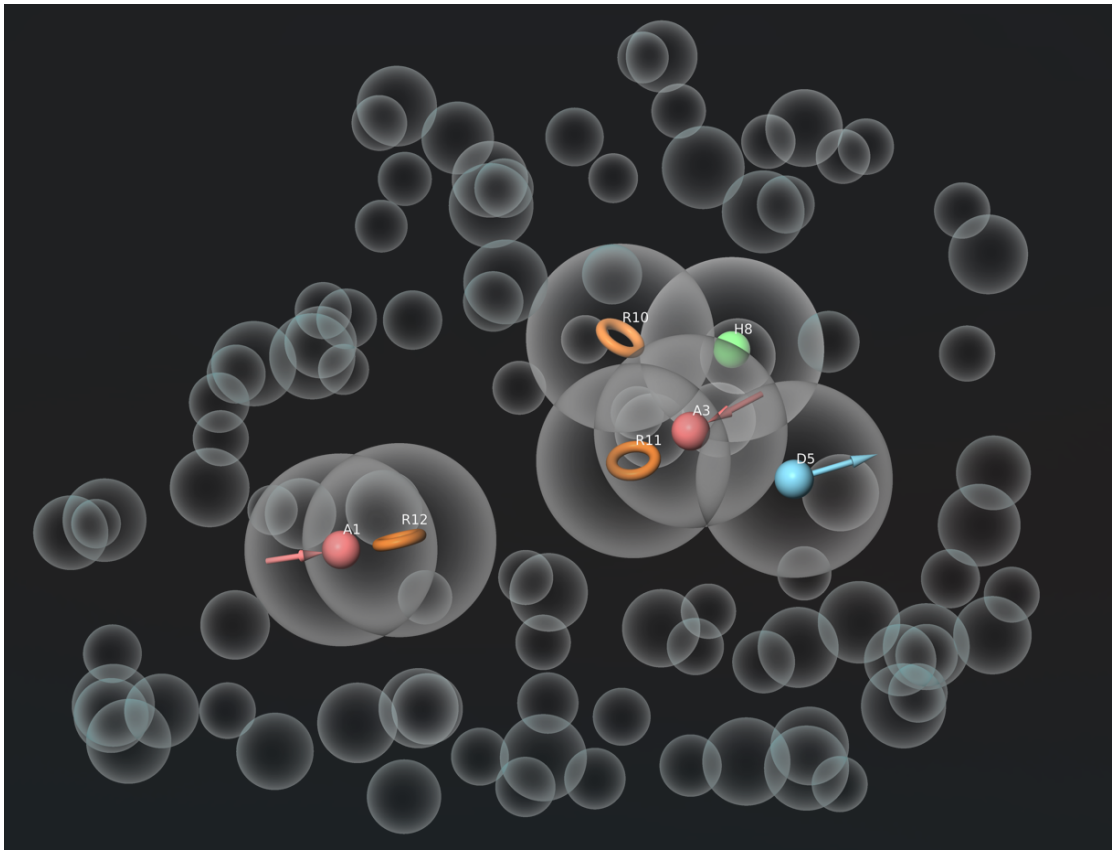

Figure S2. The common key pharmacophore features selected for virtual screening. The outer hollow blob indicates the excluded volume. A, D denote hydrogen bond acceptor and donor, respectively. R denotes an aromatic ring and H denotes a hydrophobic group.

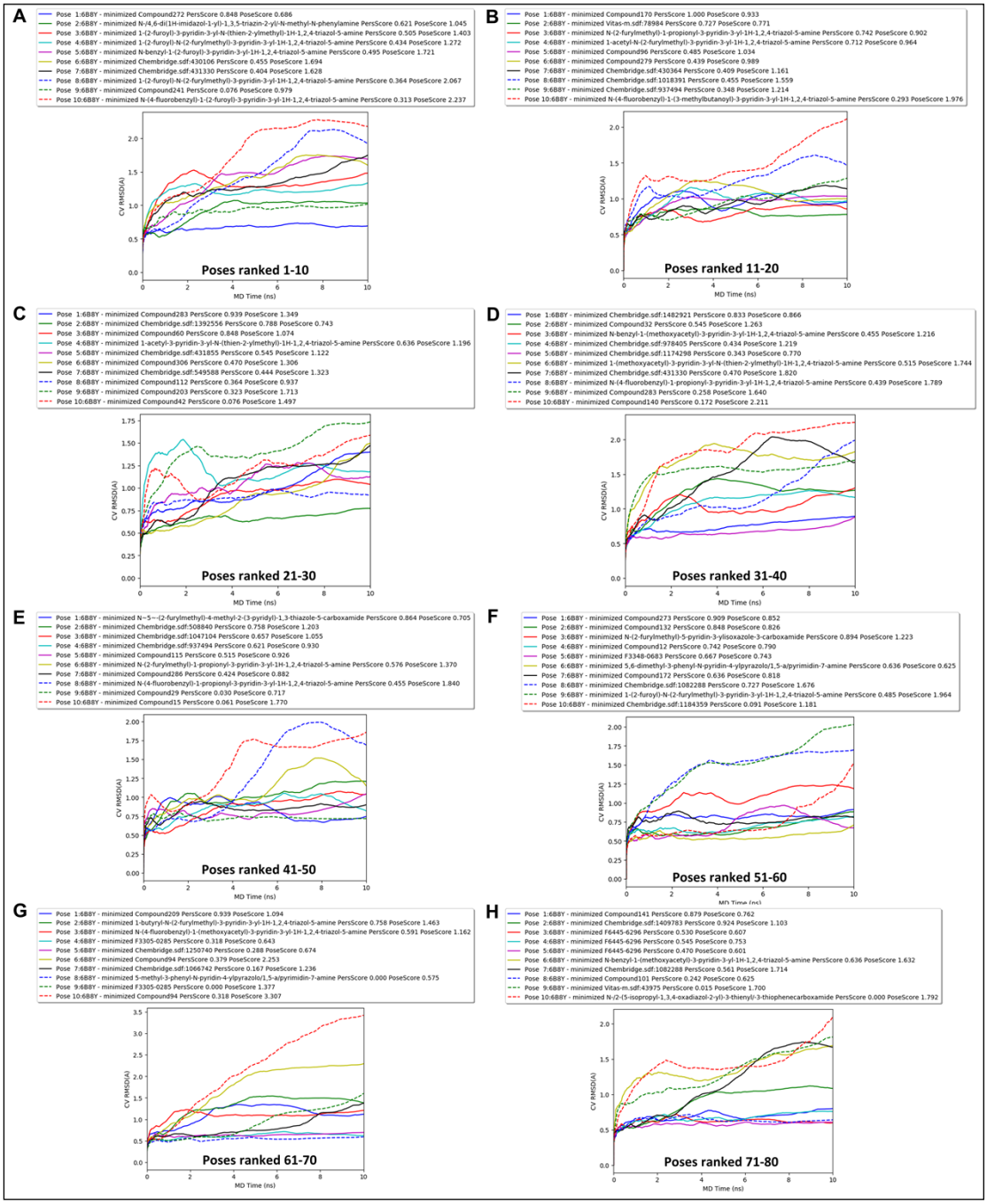

Figure S3. Average RMSD of ligands during the 10 × 10 ns binding pose metadynamics runs in TGFβR1 complexes.

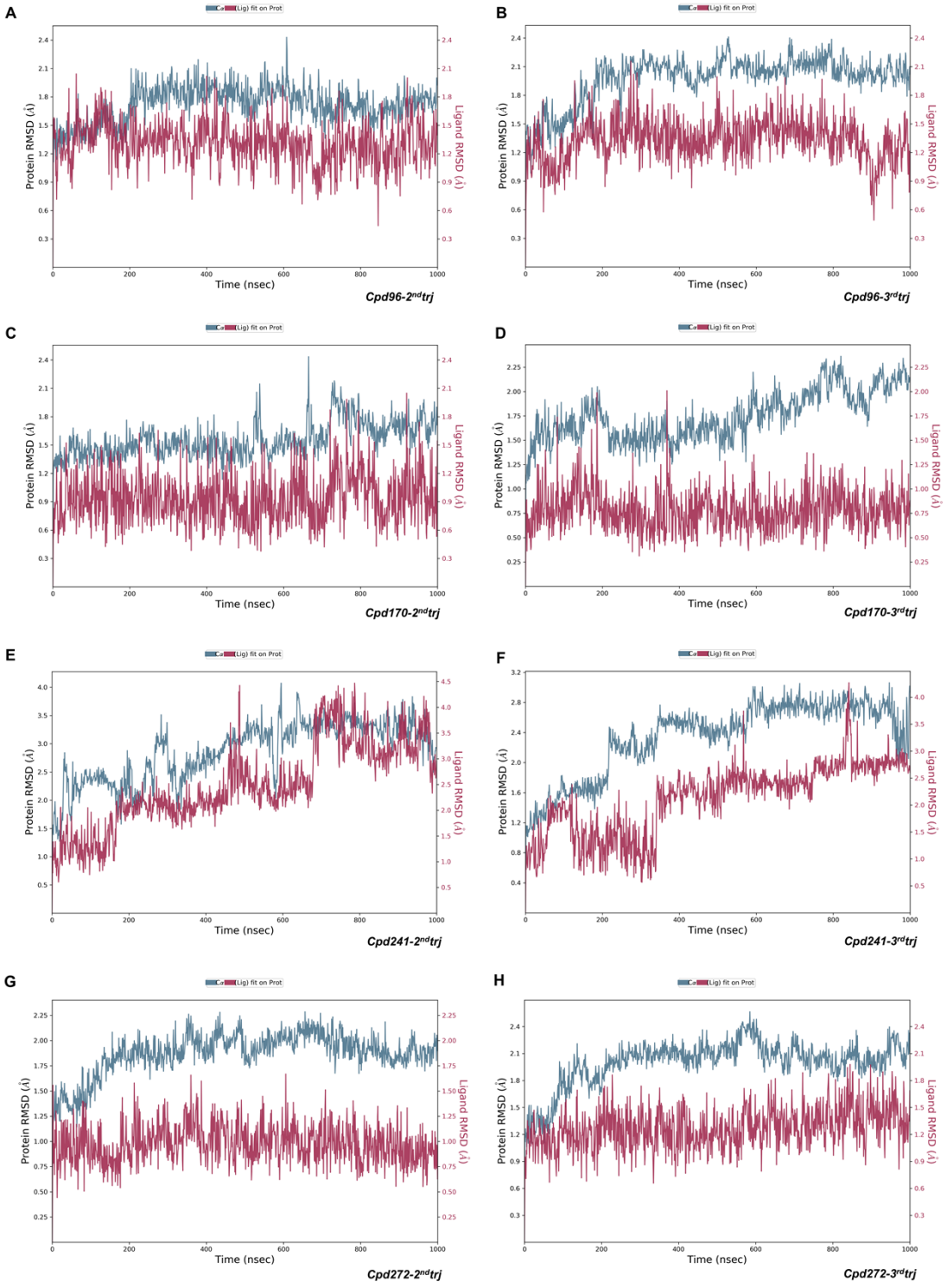

Figure S4. The RMSD values of the 'ligand-fit-protein' and Cα atoms of proteins monitored throughout the latter two replicates of the MD simulations.

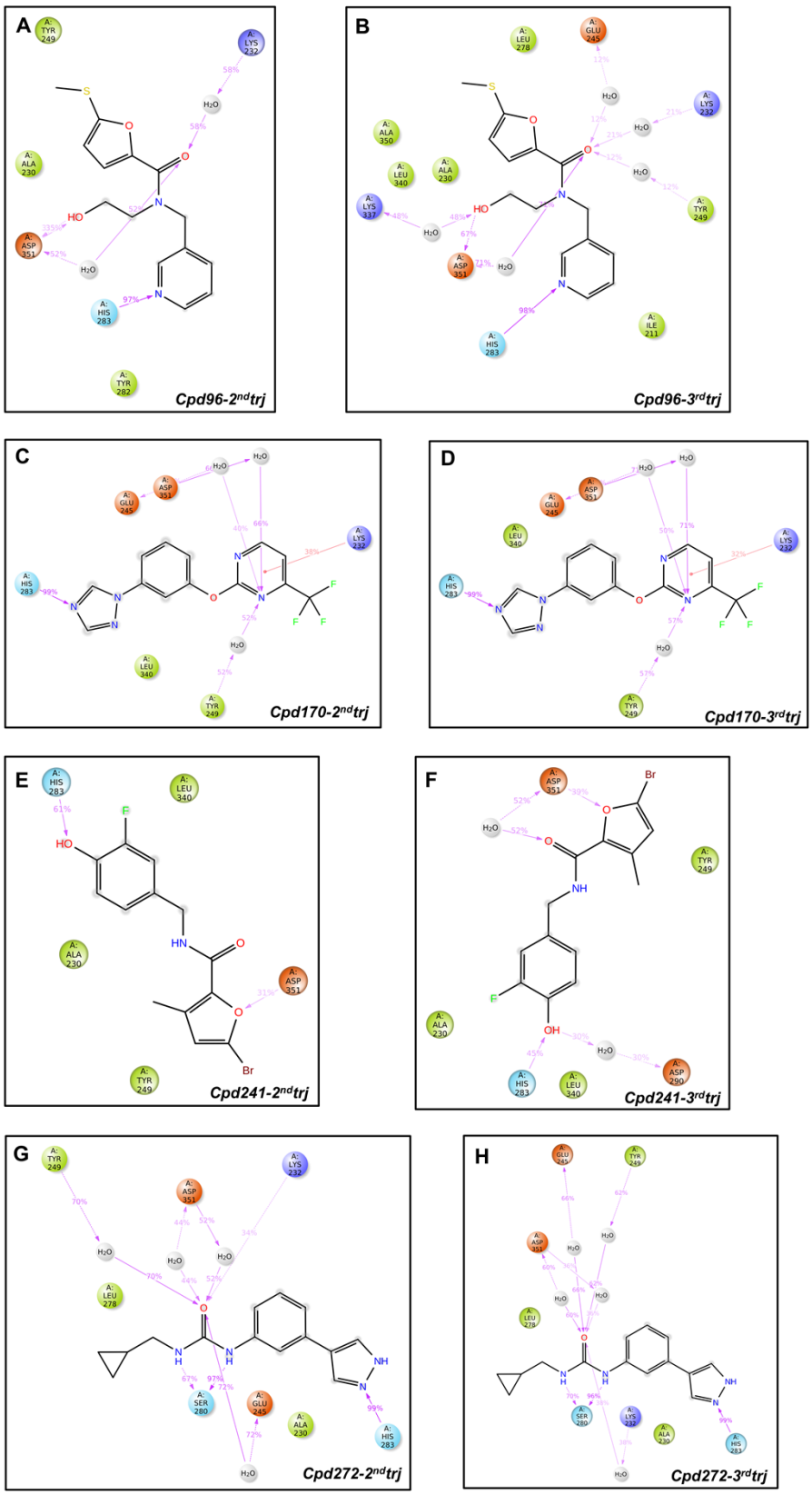

Figure S5. Non-covalent interactions between the protein and ligand monitored throughout the MD simulations. Purple arrows indicate hydrogen bonds, with the atom being pointed at serving as the hydrogen bond acceptor.

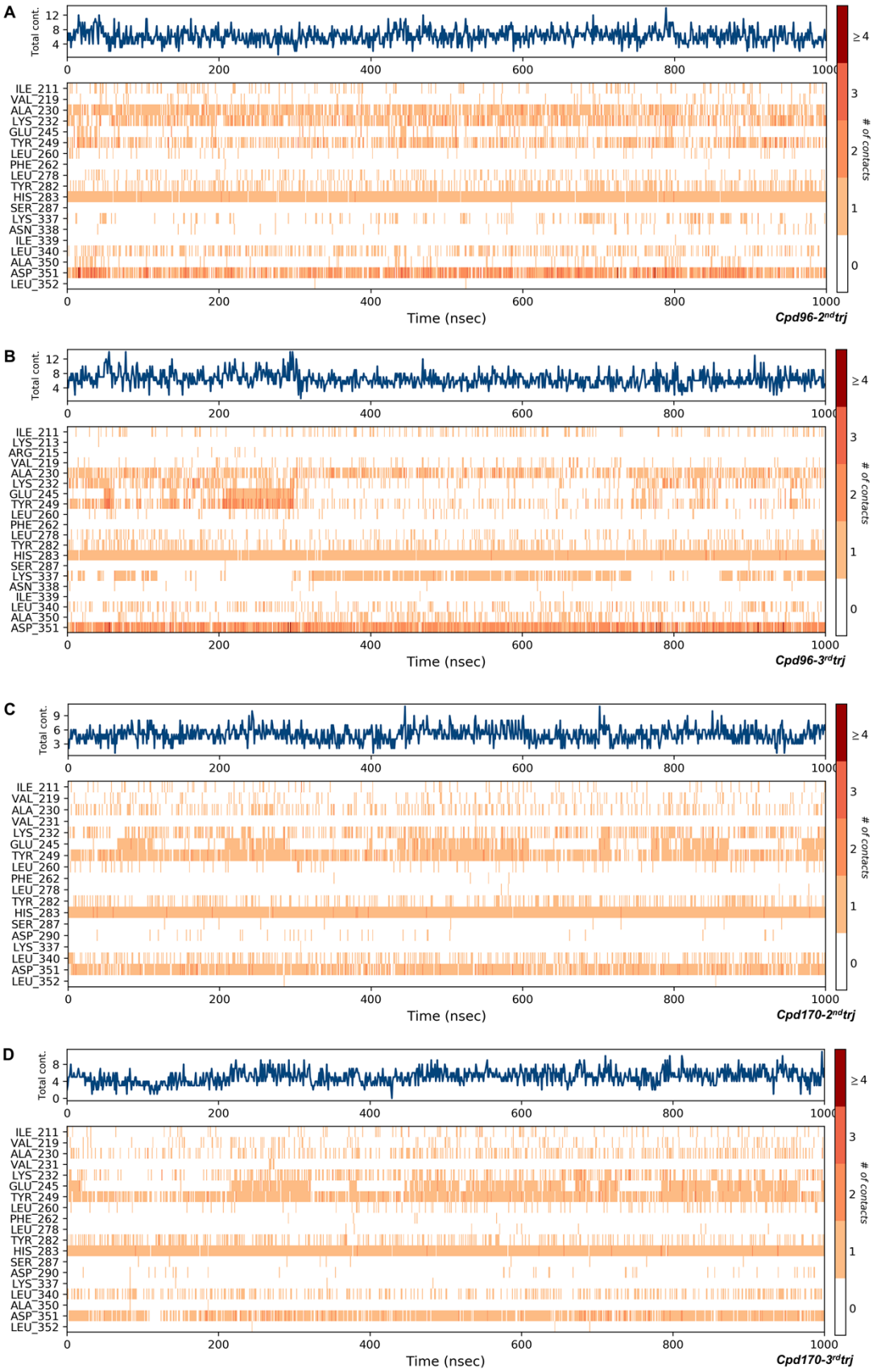

Figure S6. Non-covalent contacts between the protein and ligand monitored throughout the MD simulations (**Cpd96** & **Cpd170**).

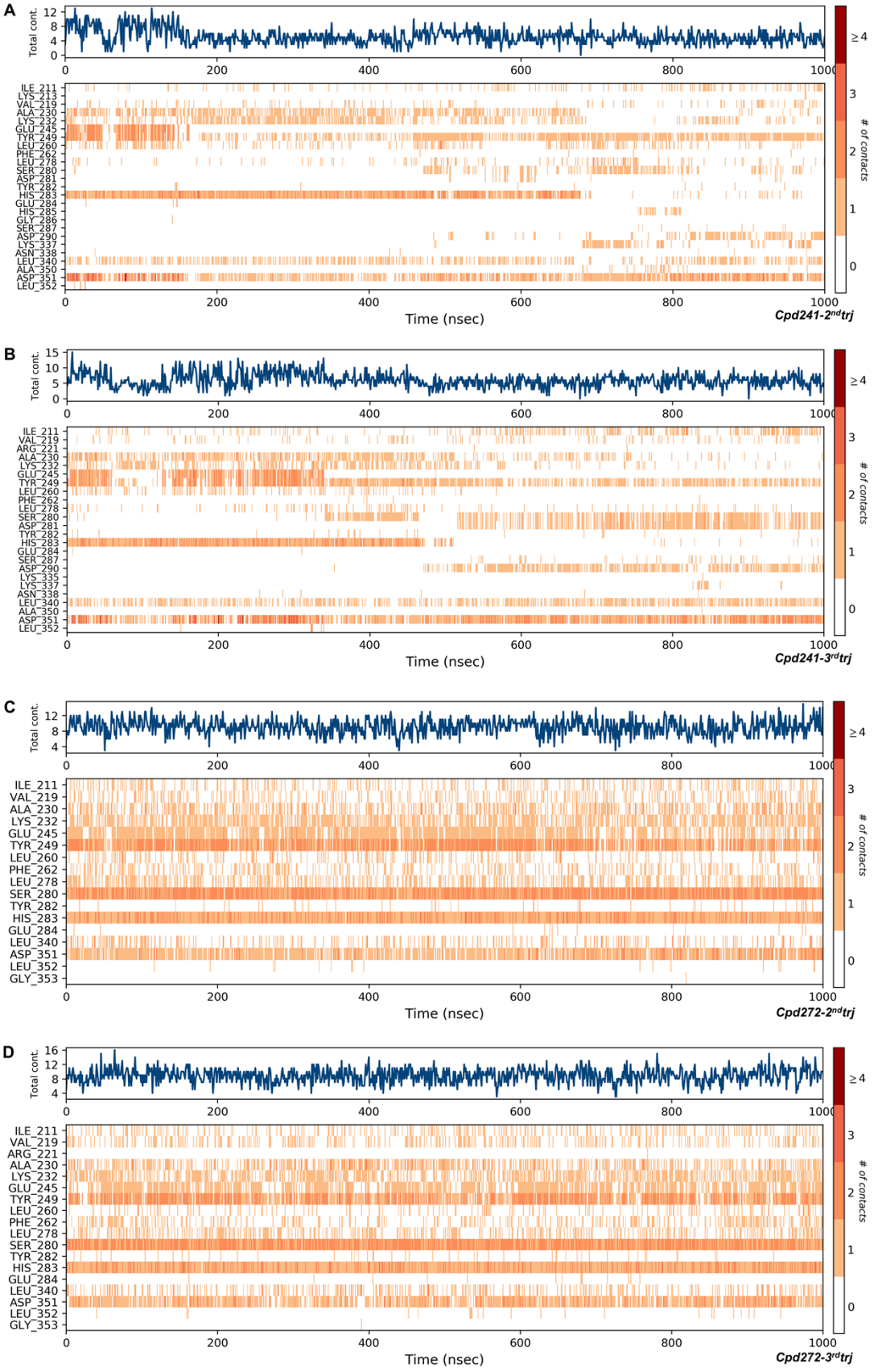

Figure S7. Non-covalent contacts between the protein and ligand monitored throughout the MD simulations (**Cpd241** & **Cpd272**).

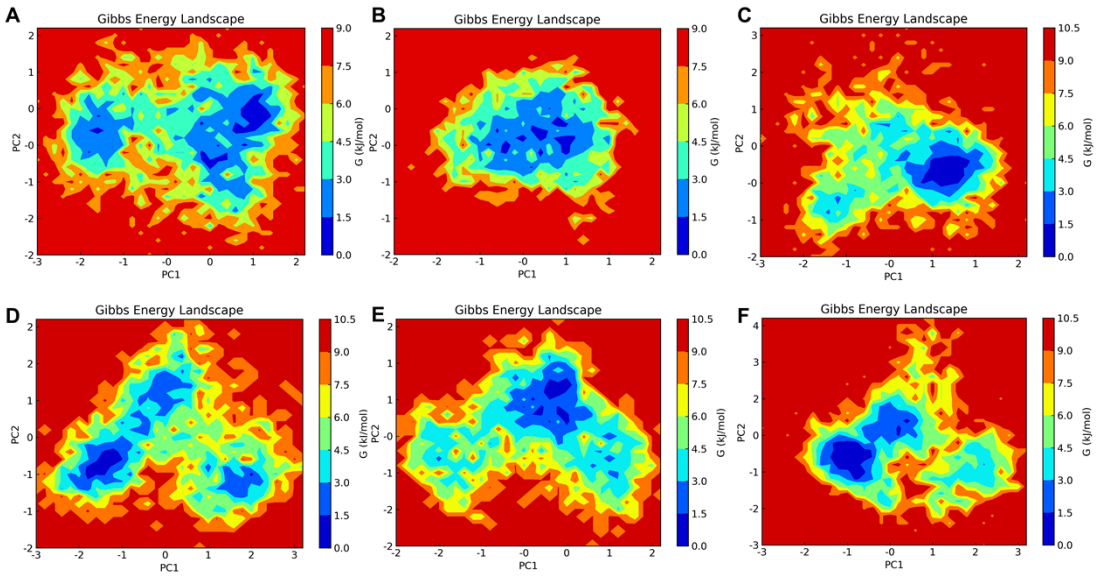

Figure S8. 2D free energy contour maps along the first two principal components (PCs) 1 and 2 for TGFβR1-apo (A), TGFβR1-**coligand** (B), TGFβR1-**cpd96** (C), TGFβR1-**cpd170** (D), TGFβR1-**cpd241** (E), and TGFβR1-**cpd272** (F).

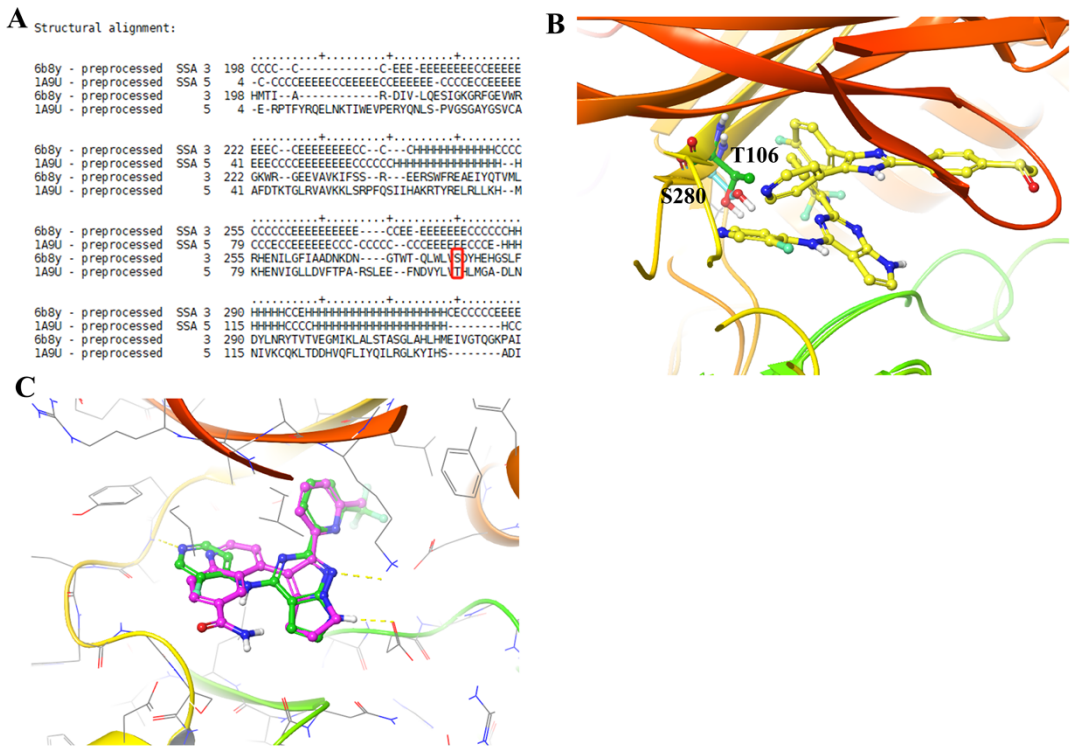

Figure S9. (A) Alignment of the crystal structure of TGFβR1 (PDB id 6B8Y) with that of p38α (PDB id 1A9U). (B) S280 in the crystal structure of TGFβR1 and T106 at the corresponding position in the crystal structure of p38α indicated in cyan and green, respectively. (C) Alignment of the docked pose of **LY2157299** (magenta) with the co-crystal structure of 6B8Y (green).

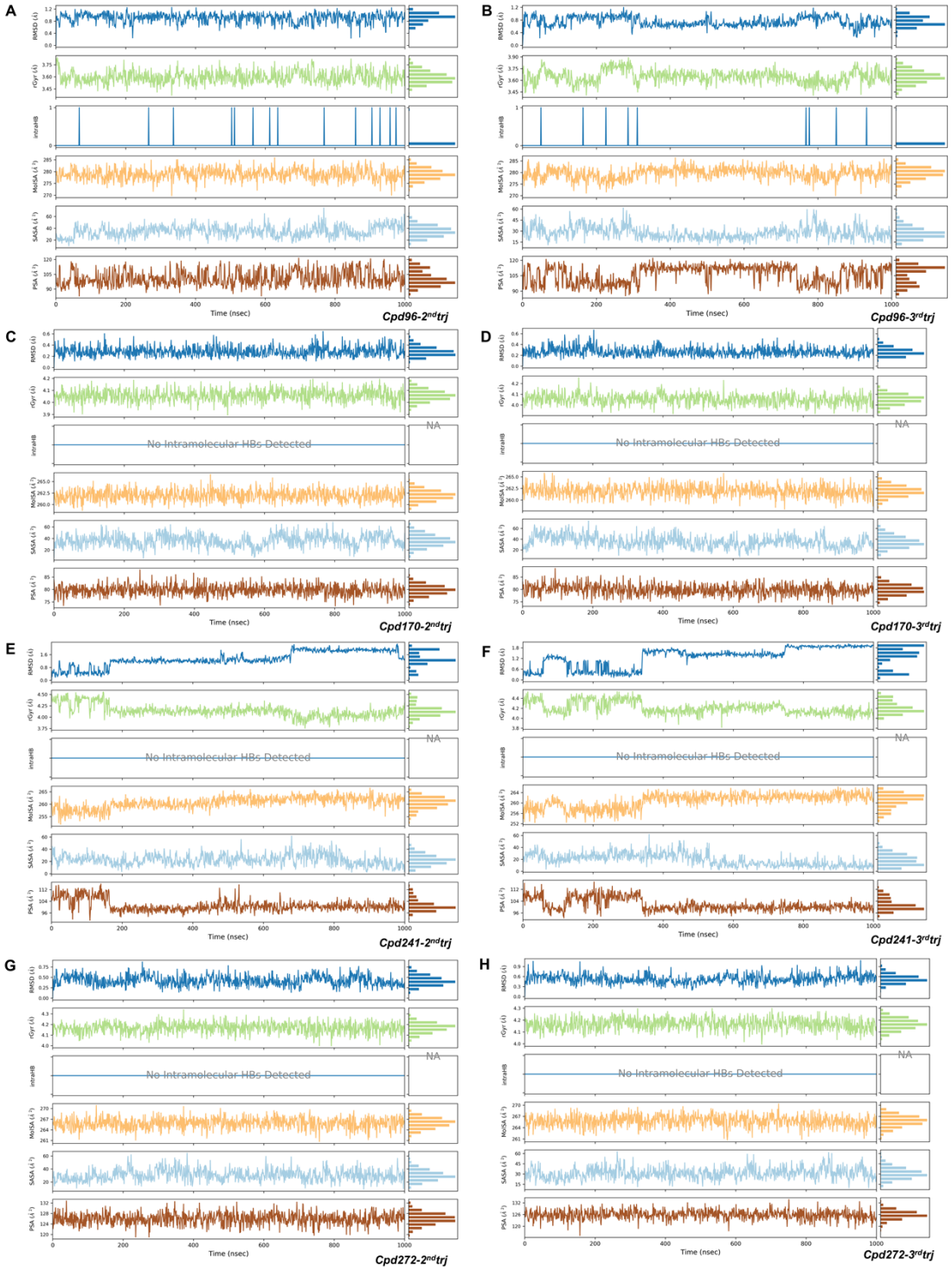

Figure S10. The properties of **Cpd96** (A&B), **Cpd170** (C&D), **Cpd241** (E&F), and **Cpd272** (G&H) monitored during the MD simulations.

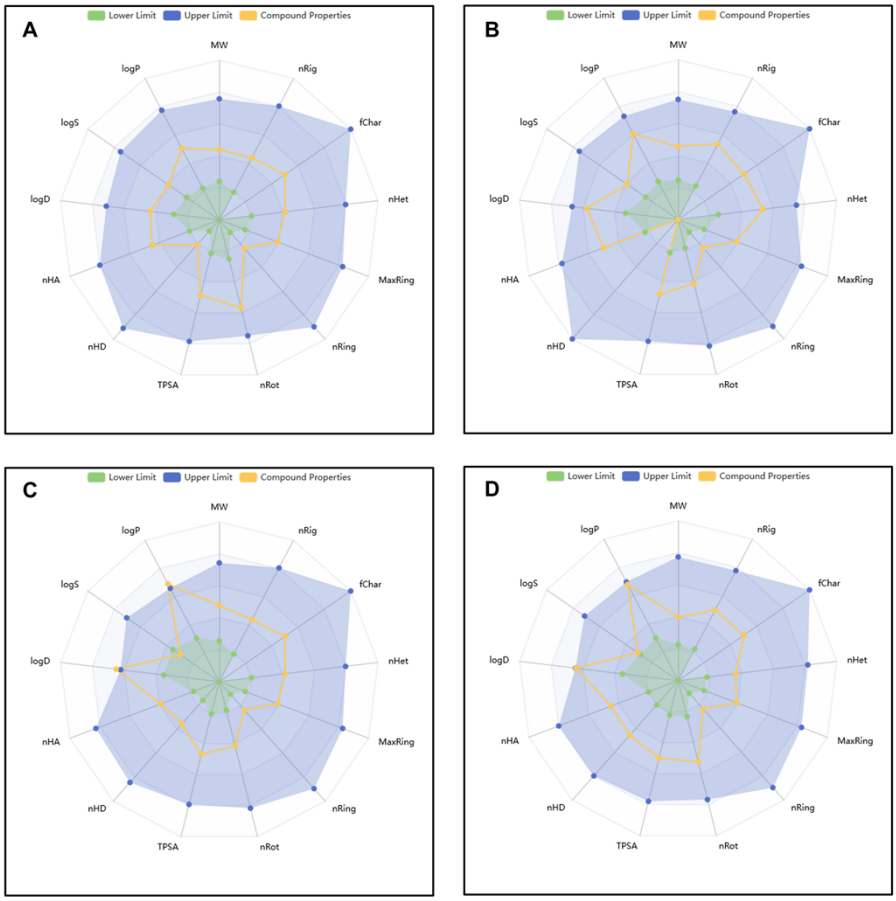

Figure S11. Physicochemical properties of **Cpd96** (A), **Cpd170** (B), **Cpd241** (C), and **Cpd272** (D).

Table S1. The XP Glide docking score, Prime MMGBSA binding free energies, Metadynamics Binding PersScore and PoseScore of the 80 promising compounds.

ScreenID	Name	XP Glide Docking Score	Prime MMGBSA $\Delta G_{binding}$ (kcal/mol)	Metadynamics Binding PersScore [a]	Metadynamics Binding PoseScore [b]
Chembridge:680279	-	-10.769	-65.9	0.404	1.628
ChemDiv:644201	N-benzyl-1-(2-furoyl)-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-11.463	-63.99	0.495	1.721
ChemDiv:644178	1-(2-furoyl)-N-(2-furylmethyl)-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-10.476	-63.28	0.434	1.272
Enamine:3519141	Compound241	-10.217	-63.27	0.076	0.979

ChemDiv:644178	1-(2-furoyl)-N-(2-furylmethyl)-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-10.9	-63.19	0.364	2.067
ChemDiv:644152	1-(2-furoyl)-3-pyridin-3-yl-N-(thien-2-ylmethyl)-1H-1,2,4-triazol-5-amine	-10.548	-62.09	0.505	1.403
Enamine:621869	Compound272	-9.53	-62.09	0.848	0.686
Chembridge:678291	-	-10.554	-62.07	0.455	1.694
ChemDiv:644247	N-(4-fluorobenzyl)-1-(2-furoyl)-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-11.58	-61.84	0.313	2.237
ChemDiv:403179	N-/4,6-di(1H-imidazol-1-yl)-1,3,5-triazin-2-yl/-N-methyl-N-phenylamine	-10.712	-60.66	0.621	1.045
Vitas-m:122996	-	-10.623	-60.64	0.727	0.771
ChemDiv:644167	N-(2-furylmethyl)-1-propionyl-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-9.733	-60.52	0.742	0.902
Enamine:3505736	Compound170	-10.347	-59.1	1	0.933
ChemDiv:644166	1-acetyl-N-(2-furylmethyl)-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-9.748	-59.12	0.712	0.964
Enamine:391660	Compound96	-10.041	-59.41	0.485	1.034
Enamine:3579058	Compound279	-10.917	-57.92	0.439	0.989
Chembridge:678724	-	-9.544	-59.13	0.409	1.161
Chembridge:1809682	-	-9.571	-58.83	0.455	1.559
Chembridge:1647975	-	-9.39	-58.02	0.348	1.214
ChemDiv:644249	N-(4-fluorobenzyl)-1-(3-methylbutanoyl)-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-11.432	-57.99	0.293	1.976
Enamine:676033	Compound283	-9.94	-56.44	0.939	1.349
Chembridge:2553615	-	-9.402	-56.54	0.788	0.743
Enamine:3699359	Compound60	-9.217	-56.49	0.848	1.074
ChemDiv:644138	1-acetyl-3-pyridin-3-yl-N-(thien-2-ylmethyl)-1H-1,2,4-triazol-5-amine	-9.475	-56.98	0.636	1.196
Chembridge:681123	-	-9.47	-57	0.545	1.122
Enamine:3504250	Compound306	-10.27	-57.74	0.47	1.306
Chembridge:867615	-	-9.375	-57.84	0.444	1.323
Enamine:2567468	Compound112	-9.309	-56.77	0.364	0.937
Enamine:3431977	Compound203	-9.795	-57.8	0.323	1.713
Enamine:3451714	Compound42	-9.069	-57.14	0.076	1.497
Chembridge:2700968	-	-11.886	-55.57	0.833	0.866
Enamine:199111	Compound32	-10.167	-55.99	0.545	1.263
ChemDiv:644190	N-benzyl-1-(methoxyacetyl)-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-10.202	-55.81	0.455	1.216
Chembridge:1730002	-	-9.306	-55.79	0.434	1.219
Chembridge:2128071	-	-9.594	-56.33	0.343	0.77
ChemDiv:644142	1-(methoxyacetyl)-3-pyridin-3-yl-N-(thien-2-ylmethyl)-1H-1,2,4-triazol-5-amine	-9.567	-55.21	0.515	1.744
Chembridge:680279	-	-10.23	-55.73	0.47	1.82
ChemDiv:644234	N-(4-fluorobenzyl)-1-propionyl-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-10.645	-55.67	0.439	1.789
Enamine:3589009	Compound283	-9.423	-56.28	0.258	1.64
Enamine:3823638	Compound140	-8.997	-55.99	0.172	2.211
ChemDiv:1401960	N~5~-(2-furylmethyl)-4-methyl-2-(3-pyridyl)-1,3-thiazole-5-carboxamide	-10.211	-54.61	0.864	0.705

Chembridge:801078	-	-10.151	-54.89	0.758	1.203
Chembridge:1869990	-	-10.054	-55.29	0.657	1.055
Chembridge:1647975	-	-10.218	-54.63	0.621	0.93
Enamine:3656534	Compound115	-9.026	-54.78	0.515	0.926
ChemDiv:644167	N-(2-furylmethyl)-1-propionyl-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-9.527	-54.81	0.576	1.37
Enamine:3171976	Compound286	-9.517	-54.61	0.424	0.882
ChemDiv:644234	N-(4-fluorobenzyl)-1-propionyl-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-10.195	-55.11	0.455	1.84
Enamine:106811	Compound29	-10.015	-54.9	0.03	0.717
Enamine:1486779	Compound15	-9.393	-55.09	0.061	1.77
Enamine:2449962	Compound273	-9.616	-54.28	0.909	0.852
Enamine:3465910	Compound132	-10.785	-54.54	0.848	0.826
ChemDiv:856890	N-(2-furylmethyl)-5-pyridin-3-ylisoxazole-3-carboxamide	-10.373	-54.36	0.894	1.223
Enamine:196657	Compound12	-10.02	-54.2	0.742	0.79
Lifechemical:404247	F3348-0683	-10.692	-54.49	0.667	0.743
ChemDiv:765946	5,6-dimethyl-3-phenyl-N-pyridin-4-ylpyrazolo/1,5-a/pyrimidin-7-amine	-10.794	-54.4	0.636	0.625
Enamine:111214	Compound172	-9.885	-54.25	0.636	0.818
Chembridge:1942426	-	-11.602	-54.52	0.727	1.676
ChemDiv:644178	1-(2-furoyl)-N-(2-furylmethyl)-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-10.415	-54.52	0.485	1.964
Chembridge:2146342	-	-9.813	-54.29	0.091	1.181
Enamine:3380163	Compound209	-9.851	-54.15	0.939	1.094
ChemDiv:644168	1-butyryl-N-(2-furylmethyl)-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-10.14	-54.11	0.758	1.463
ChemDiv:644237	N-(4-fluorobenzyl)-1-(methoxyacetyl)-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-10.277	-54.17	0.591	1.162
Lifechemical:398096	F3305-0285	-10.656	-54.13	0.318	0.643
Chembridge:2275924	-	-9.41	-54.19	0.288	0.674
Enamine:1850292	Compound94	-9.812	-54.11	0.379	2.253
Chembridge:1910833	-	-8.905	-54.2	0.167	1.236
ChemDiv:765334	5-methyl-3-phenyl-N-pyridin-4-ylpyrazolo/1,5-a/pyrimidin-7-amine	-10.643	-54.12	0	0.575
Lifechemical:398096	F3305-0285	-10.506	-54.18	0	1.377
Enamine:1850292	Compound94	-9.812	-54.15	0.318	3.307
Enamine:3329291	Compound141	-9.676	-54	0.879	0.762
Chembridge:2584925	-	-10.736	-53.46	0.924	1.103
Lifechemical:36906	F6445-6296 F6445-6296	-9.447	-53.9	0.53	0.607
Lifechemical:36906	F6445-6296 F6445-6296	-9.274	-53.94	0.545	0.753
Lifechemical:36906	F6445-6296 F6445-6296	-9.261	-54.09	0.47	0.601
ChemDiv:644190	N-benzyl-1-(methoxyacetyl)-3-pyridin-3-yl-1H-1,2,4-triazol-5-amine	-10.005	-53.53	0.636	1.632
Chembridge:1942426	-	-11.263	-53.95	0.561	1.714
Enamine:3250881	Compound101	-9.524	-53.34	0.242	0.625
Vitas-m:68117	-	-9.183	-53.65	0.015	1.7
ChemDiv:2265865	N-/2-(5-isopropyl-1,3,4-oxadiazol-2-yl)-3-thienyl/-3-thiophenecarboxamide	-9.048	-53.66	0	1.792

[a] PersScore ≥ 0.6, hydrogen bonds were kept good persistence

[b] PoseScore ≤ 2, binding pose of the compound was considered stable