Supplementary data

Computational Molecular Modeling Studies of Some Mycobacterium Tuberculosis Alanine Racemase Inhibitors

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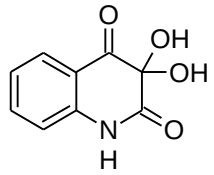
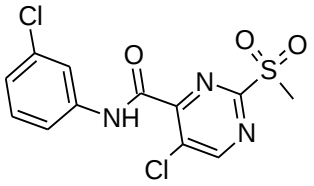
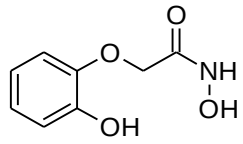
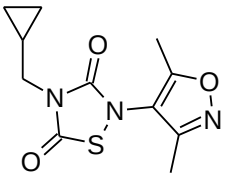
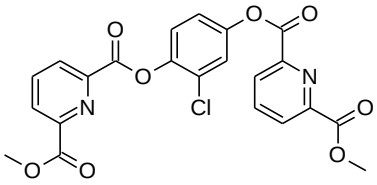
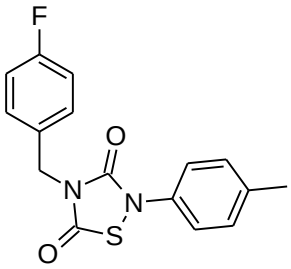
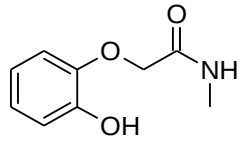
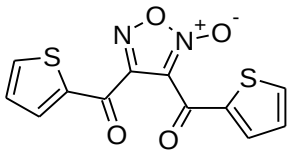
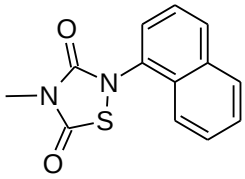
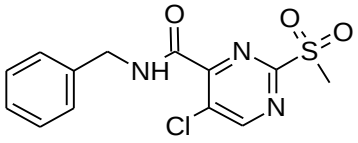
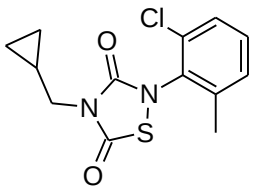
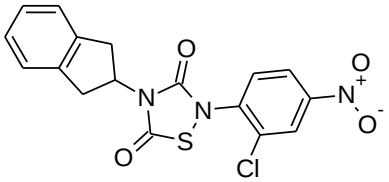
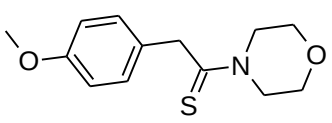
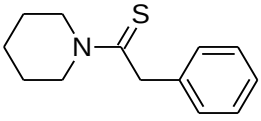
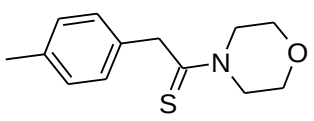
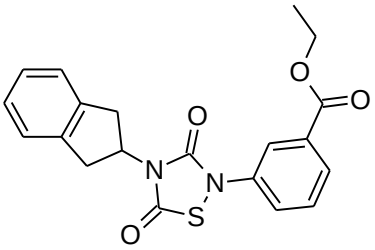
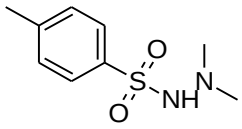
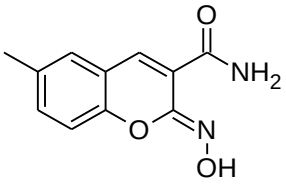
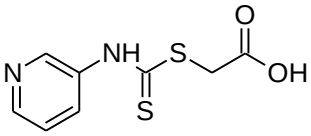
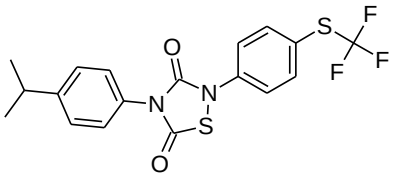
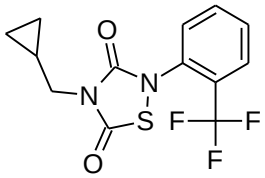
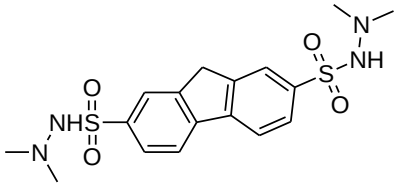
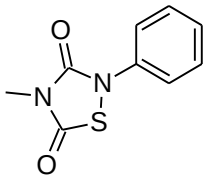
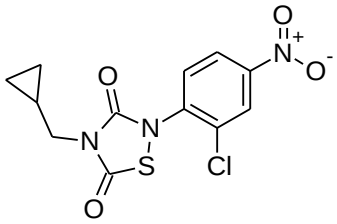
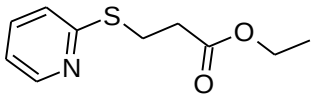
Table S1. Chemical structures of *Mycobacterium tuberculosis* AlaR inhibitors **1-25**.

Compd. No.	Chemical structures	Compd. No.	Chemical structures
1.		**14**	
2.		**15**	
3.		**16**	
4.		**17**	
5.		**18**	
6.		**19**	
7.		**20**	

8.		**21**	
9.		**22**	
10.		**23**	
11.		**24**	
12.		**25**	
13.			

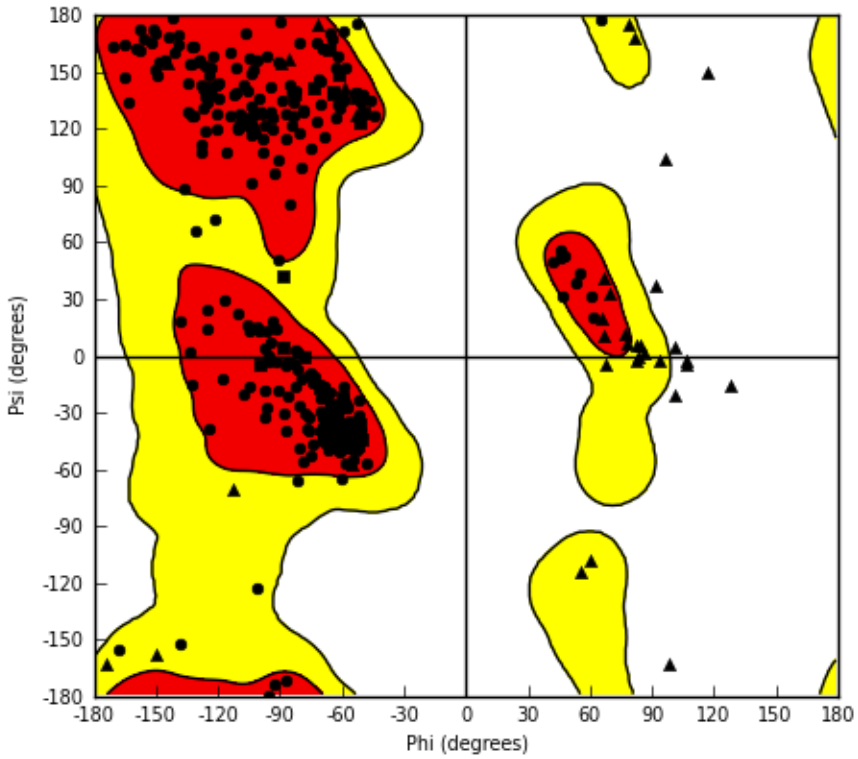


Figure S1. Ramachandran plot of *Mycobacterium tuberculosis* AlaR enzyme (PDB ID: 1XFC).

Table S2. Extra precision docking results with interacting amino acids in the catalytic pocket of 1XFC (kcal/mol).

Compd. No.	IC_{50} (µM)	Glide gscore	Glide evdw	Glide ecoul	Glide energy	Glide emodel	XP-HBond	Interacting amino acids	H-bonds
1.	5.2	-3.66	-16.87	-4.08	-20.96	-23.88	-1.41	Tyr46, Tyr175	1
2.	8.2	-3.57	-16.29	-9.78	-26.07	-29.28	-2.11	Lys42, Tyr46, His172, Tyr175, Tyr364,	3
3.	1.0	-4.34	-33.03	-7.39	-40.42	-67.20	-1.28	Lys42, Lys133, Arg140, His172, Tyr175	4
4.	5.7	-3.92	-16.54	-6.18	-22.72	-28.53	-1.54	Tyr46, Tyr175	2
5.	0.12	-3.81	-22.79	-2.48	-25.27	-32.19	-0.66	Tyr175	1
6.	4.48	-3.73	-22.43	-2.88	-25.32	-31.61	-0.70	Tyr175	1
7.	3.3	-3.34	-20.31	-5.24	-25.56	-32.20	-0.58	Tyr46, Arg140, His172, Tyr364	3
8.	6.5	-3.34	-17.29	-5.62	-22.92	-25.52	-0.74	Tyr46, Arg140, Hie172, Tyr364	1
9.	9.0	-3.33	-18.28	-1.88	-20.16	-22.08	-0.70	Lys42, Tyr46, His172	1
10.	13.1	-2.86	-19.90	-10.21	-30.12	-34.22	-0.81	Trp88, His172	2
11.	0.82	-3.10	-21.86	-0.99	-22.86	-31.80	0.00	Tyr46	-
12.	0.29	-3.10	-16.50	-2.97	-19.47	-24.46	-0.63	Tyr46, Arg140, Tyr364	1
13.	2.6	-2.97	-21.16	-4.34	-25.50	-29.57	-0.69	Lys42, Arg140, Tyr46	2
14.	8.2	-2.91	-27.88	-2.80	-30.69	-34.73	-0.17	Arg140	2
15.	1.46	-2.89	-26.26	-0.14	-26.40	-29.69	0.00	Tyr175	-
16.	0.13	-2.86	-24.01	-3.63	-27.65	-31.96	-0.39	Tyr46, Tyr175	-
17.	4.9	-2.84	-23.00	-1.94	-24.94	-32.28	-0.49	Tyr175, Tyr46	1
18.	6.8	-2.82	-28.74	-5.41	-34.15	-41.12	-0.35	Trp88,Arg140, Lys42, Tyr46	1
19.	0.05	-4.60	-31.45	-1.90	-33.35	-40.49	0.00	Tyr46, Asn141, His172, Tyr175	2
20.	6.0	-2.43	-20.06	0.19	-19.86	-23.98	0.00	Tyr46	-
21.	28.76	-2.15	-32.40	0.10	-32.30	-44.69	0.00	Lys42	-
22.	2.8	-2.11	-12.38	-10.50	-22.89	-31.22	-1.35	Lys42, Arg140, Tyr175	2
23.	0.17	-2.06	-28.04	-4.23	-32.28	-38.06	-0.71	Lys42,	1
24.	1.6	-1.90	-34.47	-2.70	-37.17	-48.33	0.00	Lys42, Lys133,	1
25.	0.03	-5.85	-23.05	-2.90	-25.95	-34.61	-0.33	His172, Met173, Tyr175,	2

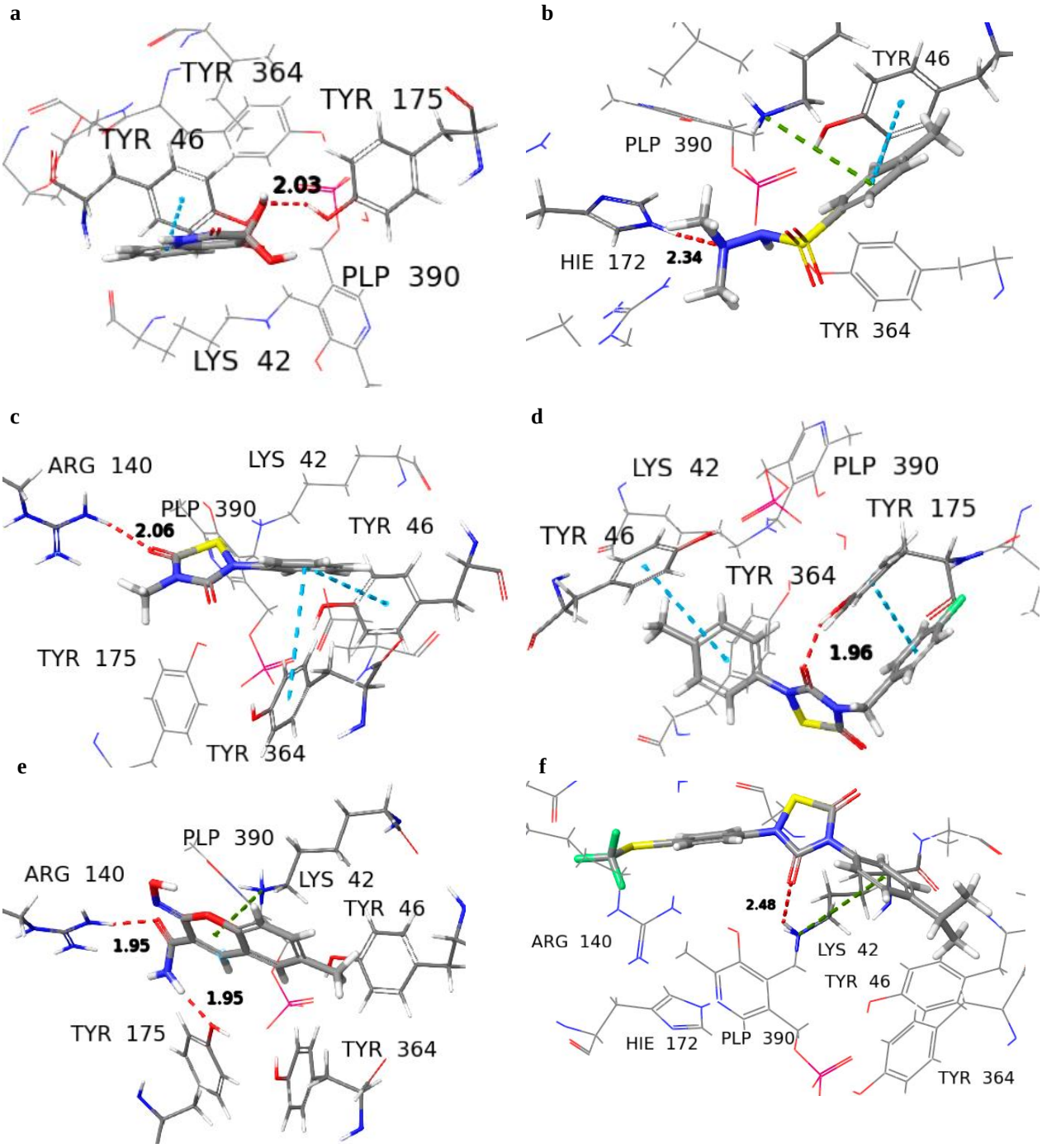


Figure S2. Binding mode of compounds (a) **1**, (b) **9**, (c) **12**, (d) **16**, (e) **22** and (f) **23** in the catalytic pocket of *Mycobacterium tuberculosis* AlaR enzyme (PDB ID: 1XFC).

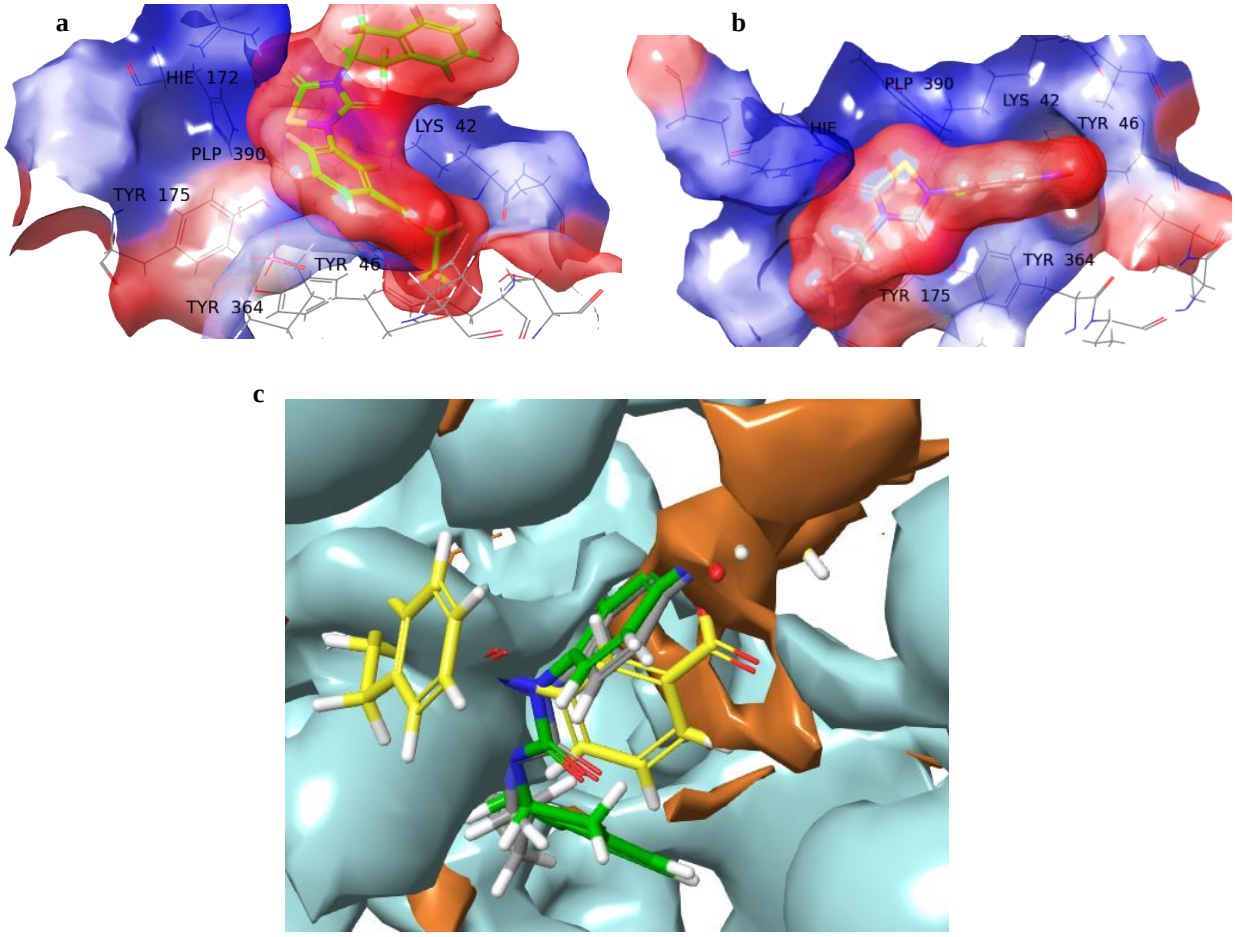


Figure S3. Surface electrostatic potential of inhibitors (a) Surface electrostatic potential of inhibitors **21** and (b) **25**. (c) Hydrophobic and hydrophilic map of inhibitors **19** (green), **21** (yellow) and **25** (grey) generated into the binding pocket of *Mycobacterium tuberculosis* AlaR enzyme (PDB ID: 1XFC).

Table S3. Quantum chemical parameters of *Mt*AlaR inhibitors **1-25**.

Compd.	IC_{50} (µM)	E_{HOMO} (eV)	E_{LUMO} (eV)	Elec Sup Delo[a]	Nuc Sup Del[b]	Rad Sup Del[c]	ESP Mean[d] (Kcal/mol)
1	5.2	-9.374	-0.804	-3.826	-1.070	-2.448	1.49
2	8.2	-9.237	-0.038	-3.571	1.932	4.18	-0.03
3	1.0	-9.489	-1.229	-8.899	-18.574	-13.736	2.42
4	5.7	-8.987	0.172	-3.645	-27.033	-15.339	-0.62
5	0.12	-8.836	-0.785	-4.96	-41.201	-23.08	1.61
6	4.48	-9.366	-0.718	-5.375	-21.625	-13.500	1.11
7	3.3	-8.551	0.071	-4.794	-49.120	-26.957	1.35
8	6.5	-8.555	0.042	-4.49	-65.727	-35.108	1.36
9	9.0	-10.08	-0.656	-3.982	-21.236	-12.609	0.84
10	13.1	-4.895	1.810	-6.194	-8.571	-7.383	-71.79
11	0.82	-9.409	-0.931	-5.846	0.717	-2.564	1.47
12	0.29	-9.009	-0.791	-3.926	-52.875	-28.400	2.11
13	2.6	-8.760	-0.00069	-4.004	2868.22	1432.108	0.92
14	8.2	-9.251	-1.145	-5.953	11.043	2.545	0.050
15	1.46	-9.390	-0.936	-4.977	34.533	14.778	3.09
16	0.13	-8.931	-0.819	-6.044	-73.621	-39.833	1.95
17	4.9	-9.563	-1.029	-5.646	-1.515	-3.581	2.43
18	6.8	-9.876	-1.275	-5.861	-466.891	-236.376	3.28
19	0.05	-9.207	-1.555	-7.171	703.455	348.142	3.55
20	6.0	-8.446	0.187	-4.170	-32.305	-18.238	2.69
21	28.76	-8.805	0.681	-7.080	-79.090	-43.09	-0.12
22	2.8	-7.944	-0.929	-4.399	-26.251	-15.325	3.32
23	0.17	-9.289	-1.239	-7.535	-127.961	-67.748	2.22
24	1.6	-9.939	-1.557	-7.545	-1378.2	-692.872	3.9
25	0.03	-9.713	-1.630	-5.873	178.047	86.087	4.45

E_{HOMO}; HOMO energy; E_{LUMO}: LUMO energy; [a]Elec Sup Delo: Total Electrophilic superdelocalizibility; [b]Nuc Sup Delo: Total nucleophilic superdelocalizibility; [c]Rad Sup Delo: Total radical superdelocalizibility; [d]ESP Mean: Mean electrostatic potential.

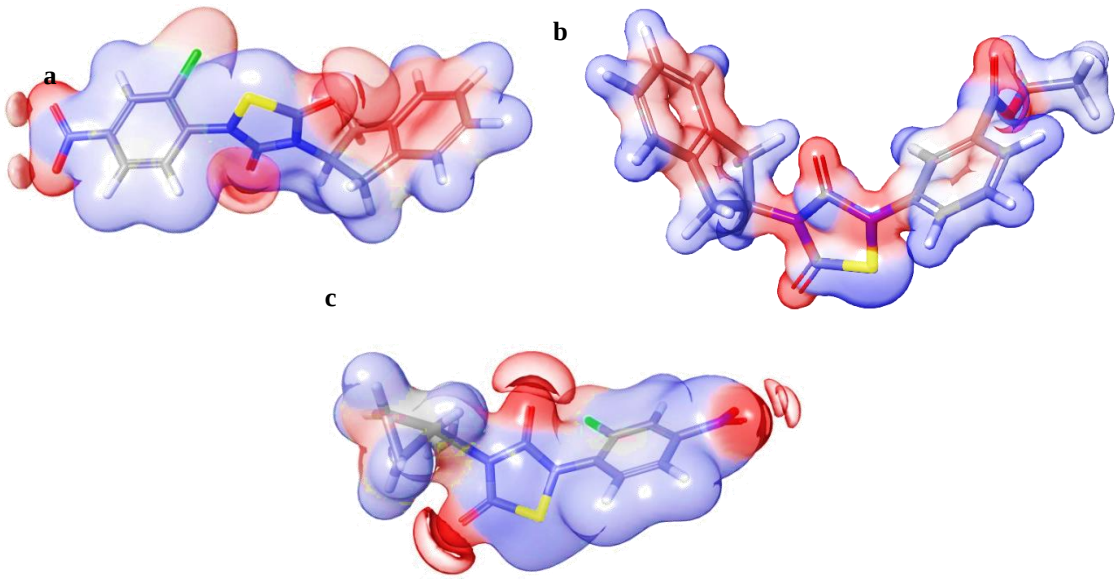


Figure S4. Surface electrostatic potential of inhibitors (a) **19** (b) **21** and (c) **25**.

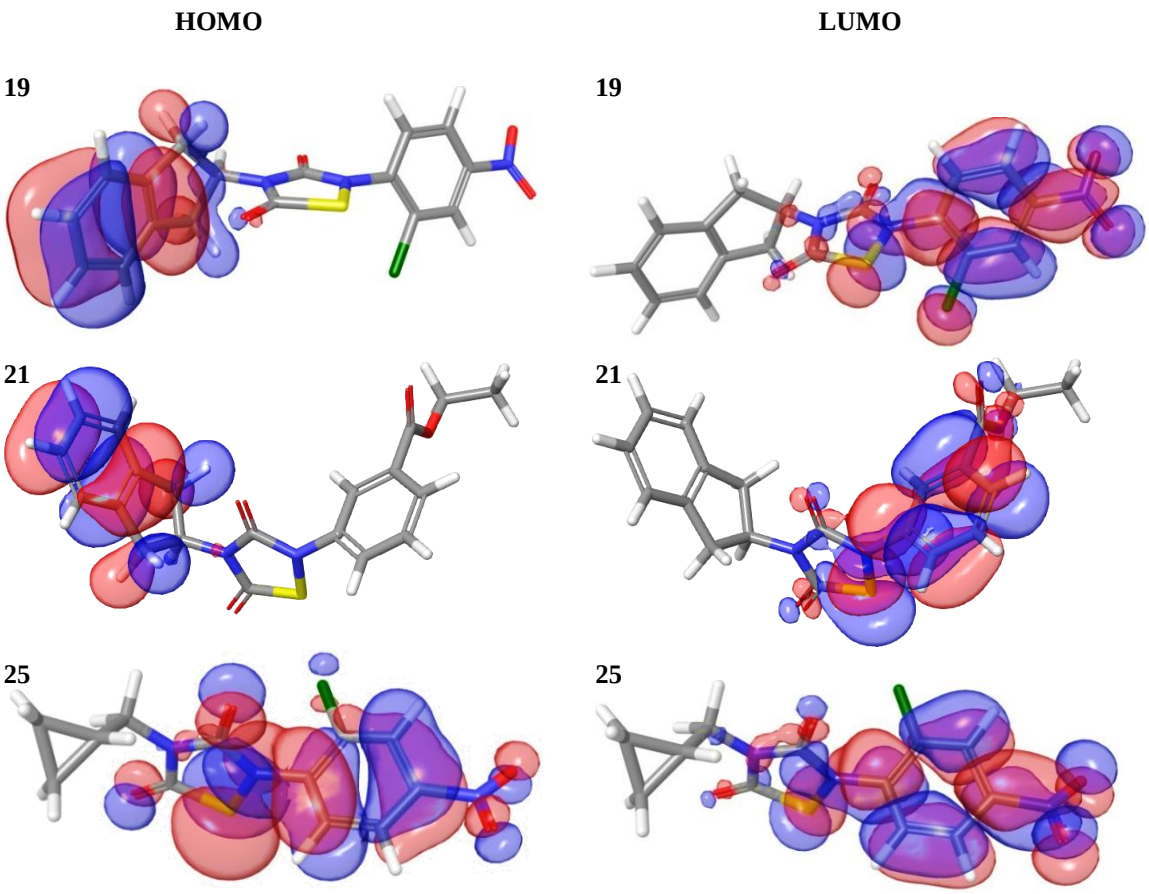


Figure S5. The orbital density distributions of compounds **19**, **21** and **25**.

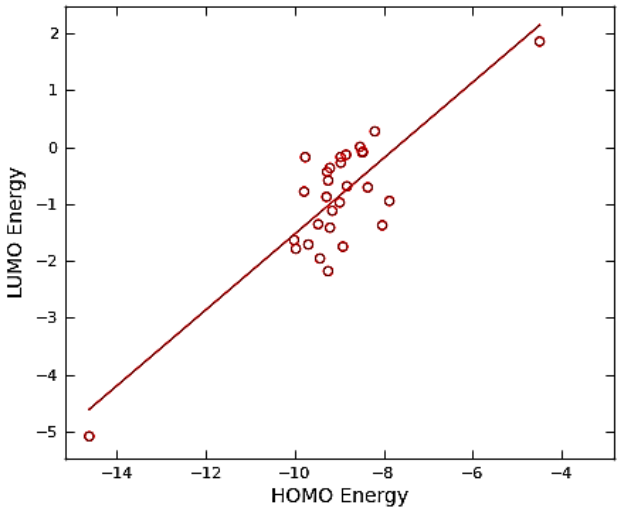


Figure S6. Plot represents HOMO vs LUMO energy, $y = 0.67x + 5.14$ ($R^2 = 0.71$).

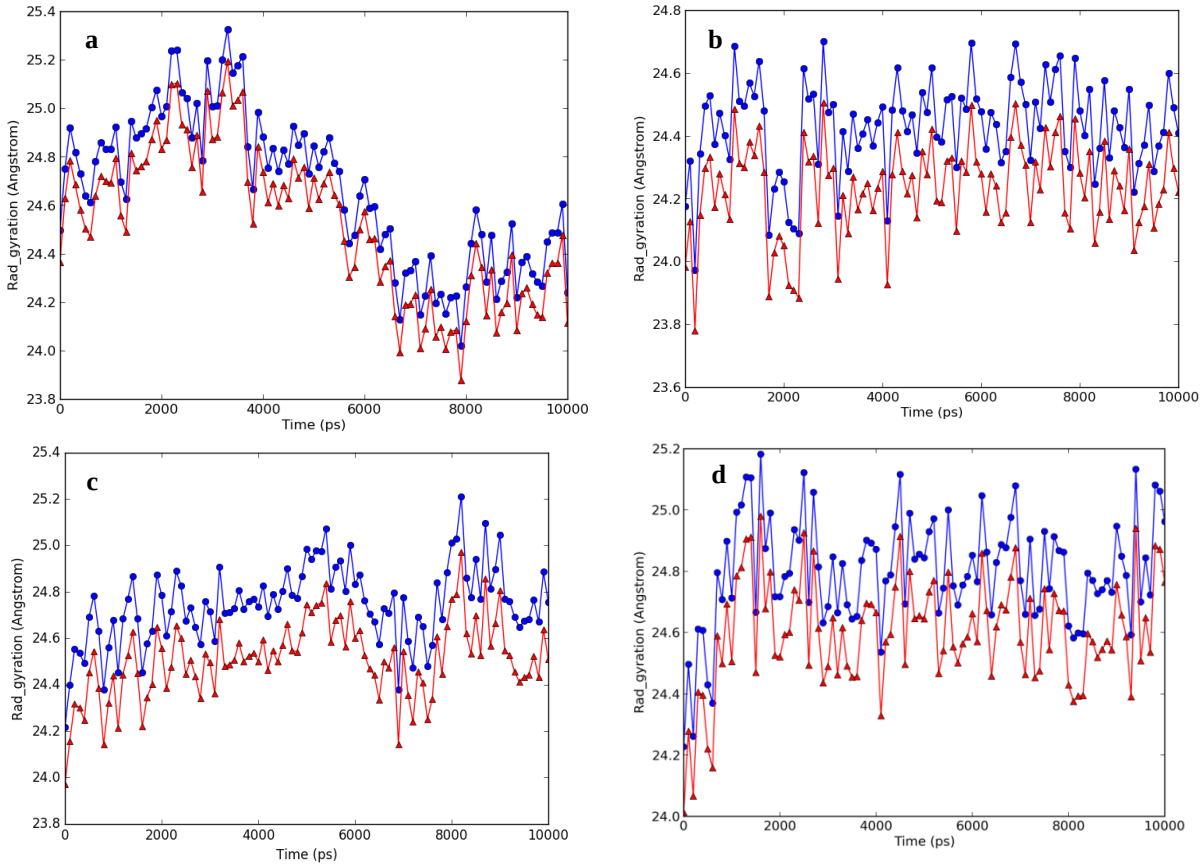
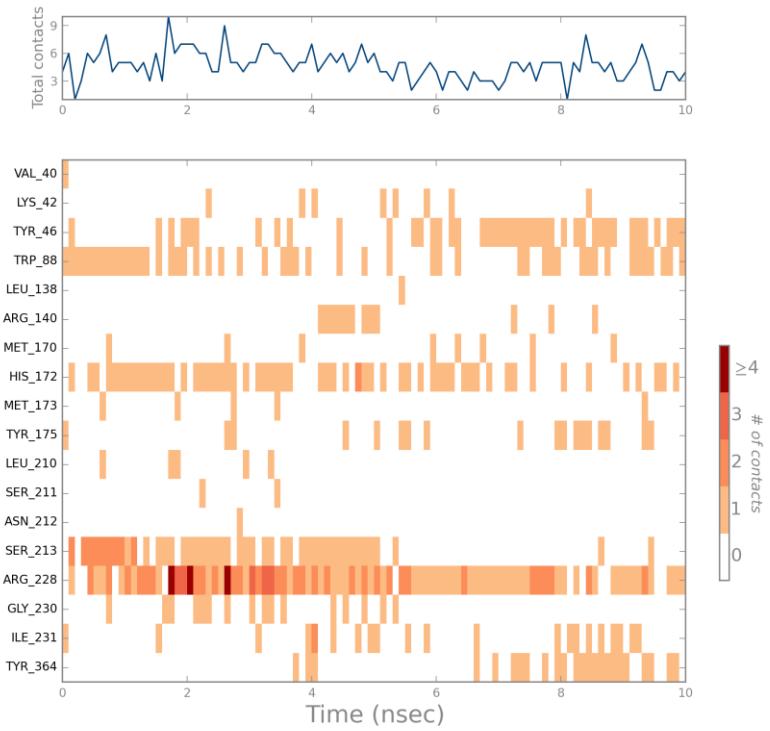


Figure S7. Radius of gyration of backbone (blue cirle) and C*α* atoms (red triangle) of (a) **10**, (b) **19**, (c) **21** and (d) **25**/1XFC complexes versus time at 300 K.

a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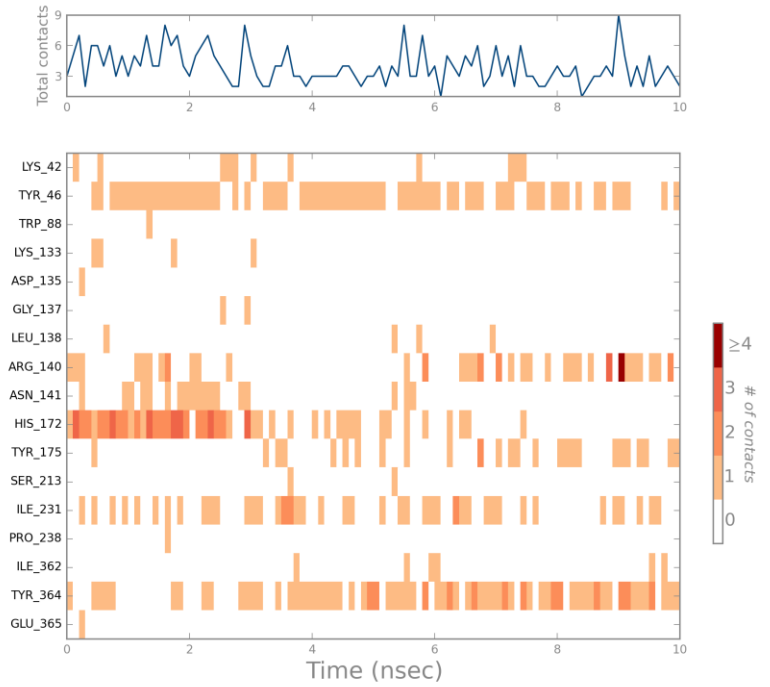
6
3
0
2
4
6
8
10
VAL_40
LYS_42
TYR_46
TRP_88
LEU_138
ARG_140
MET_170
HIS_172
MET_173
TYR_175
LEU_210
SER_211
ASN_212
SER_213
ARG_228
GLY_230
ILE_231
TYR_364
Time (nsec)
≥4
3
2
1
0
# of contacts

b


Total contacts
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3
0
2
4
6
8
10
LYS_42
TYR_46
TRP_88
LYS_133
ASP_135
GLY_137
LEU_138
ARG_140
ASN_141
HIS_172
TYR_175
SER_213
ILE_231
PRO_238
ILE_362
TYR_364
GLU_365
Time (nsec)
≥4
3
2
1
0
# of contacts

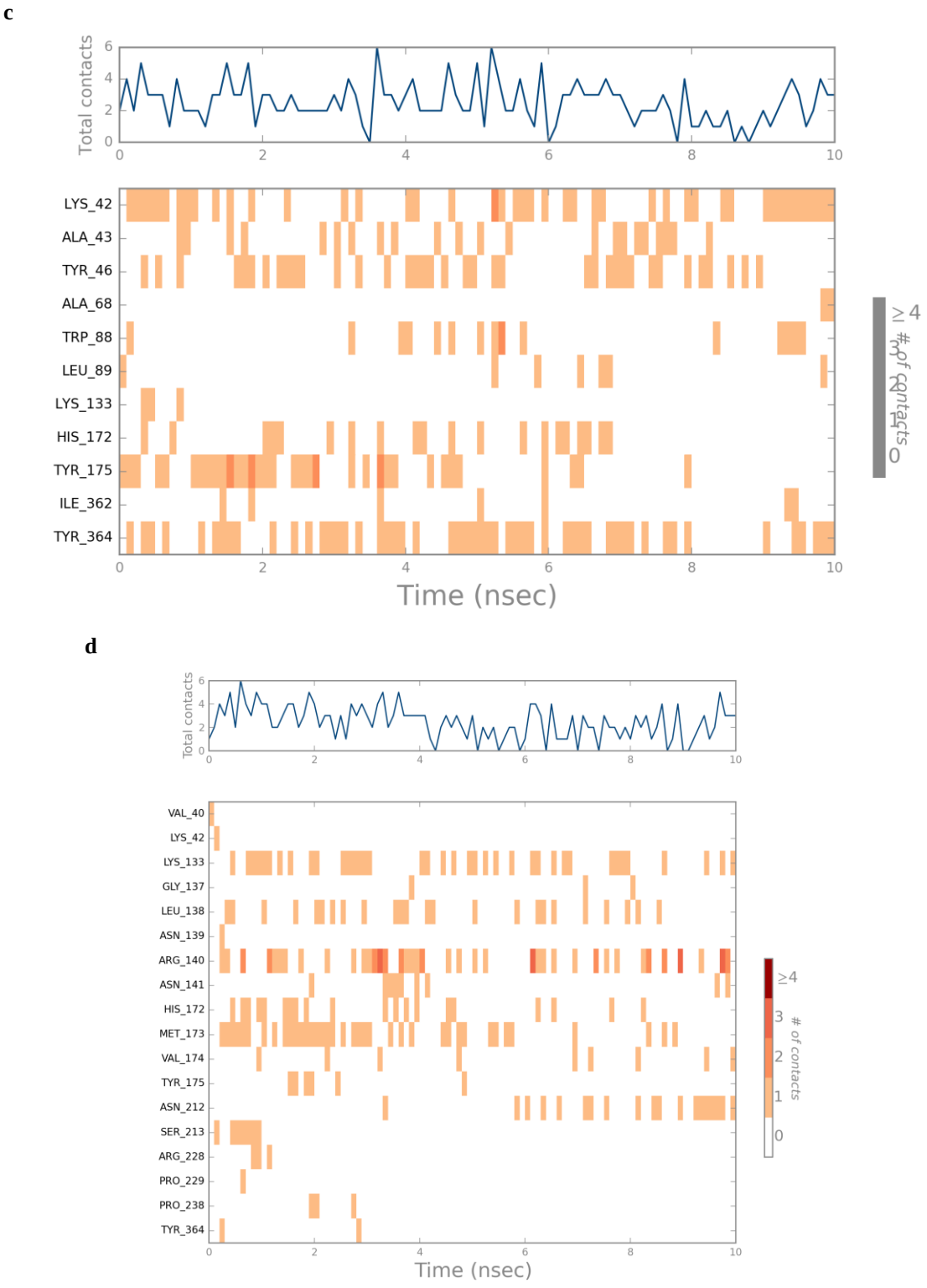


Figure S8. A timeline representation of the interactions and contacts of compounds (a) **10** (b) **19** (c) **21** and (d) **25** within the catalytic pocket of *M. tuberculosis* AlaR enzyme (PDB ID: 1XFC) during MD simulation.

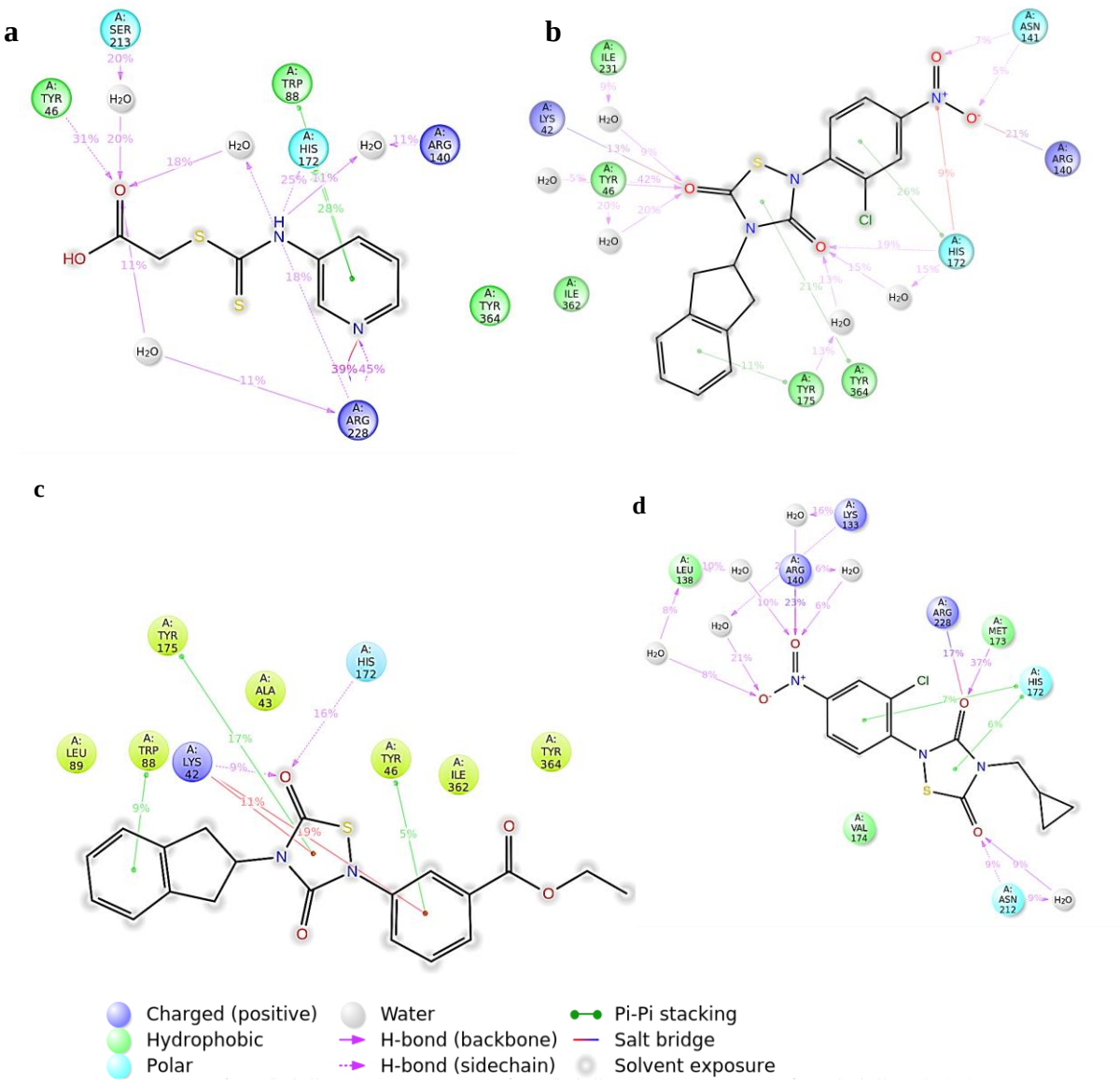


Figure S9. Two dimensional view of the binding interaction of compounds (a) **10** (b) **19** (c) **21** and (d) **25** within the *Mycobacterium tuberculosis* AlaR enzyme (PDB ID: 1XFC) throughout the simulation trajectory (0.00 through 10.00 ns).

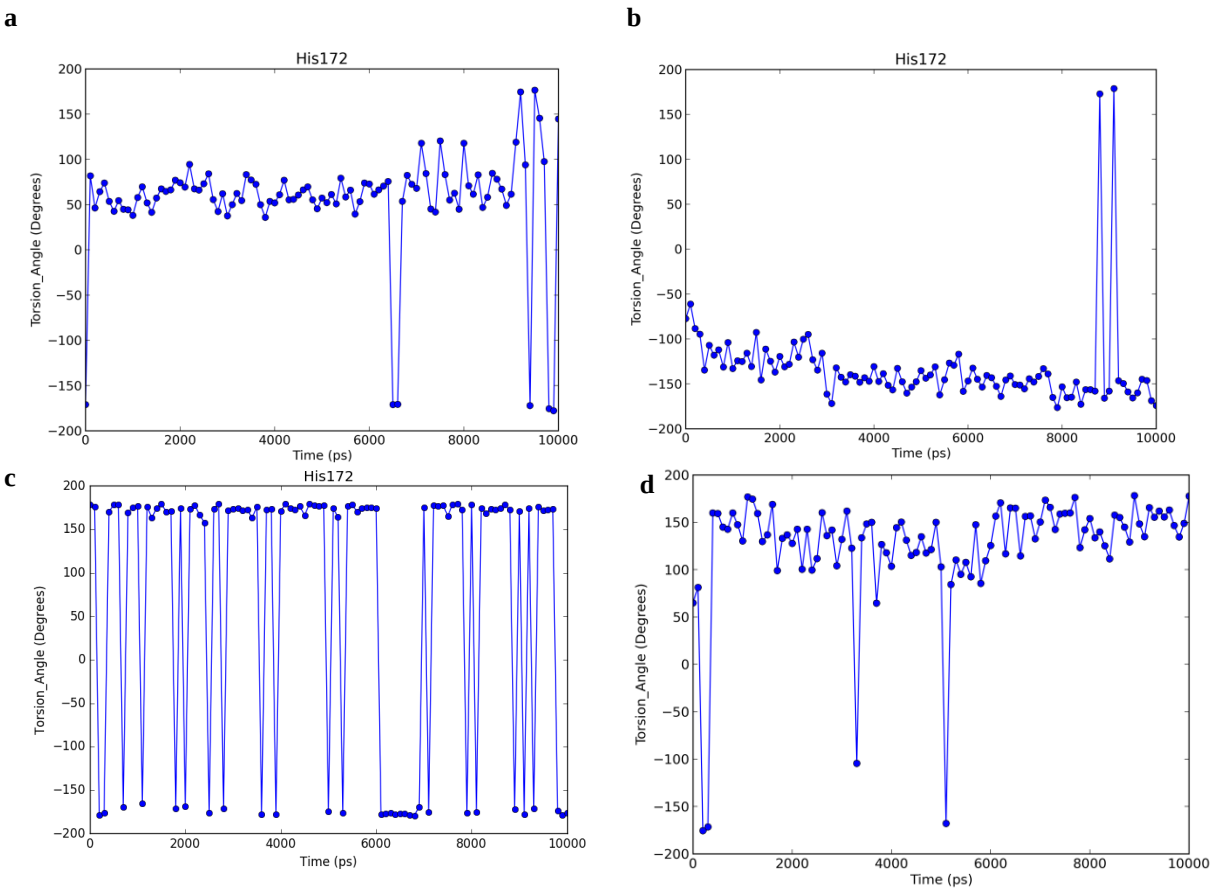


Figure S10. Torsion angles of His172 residue during MD simulations of (a) **10** (b) **19** (c) **21** and (d) **25**/1XFC complexes.

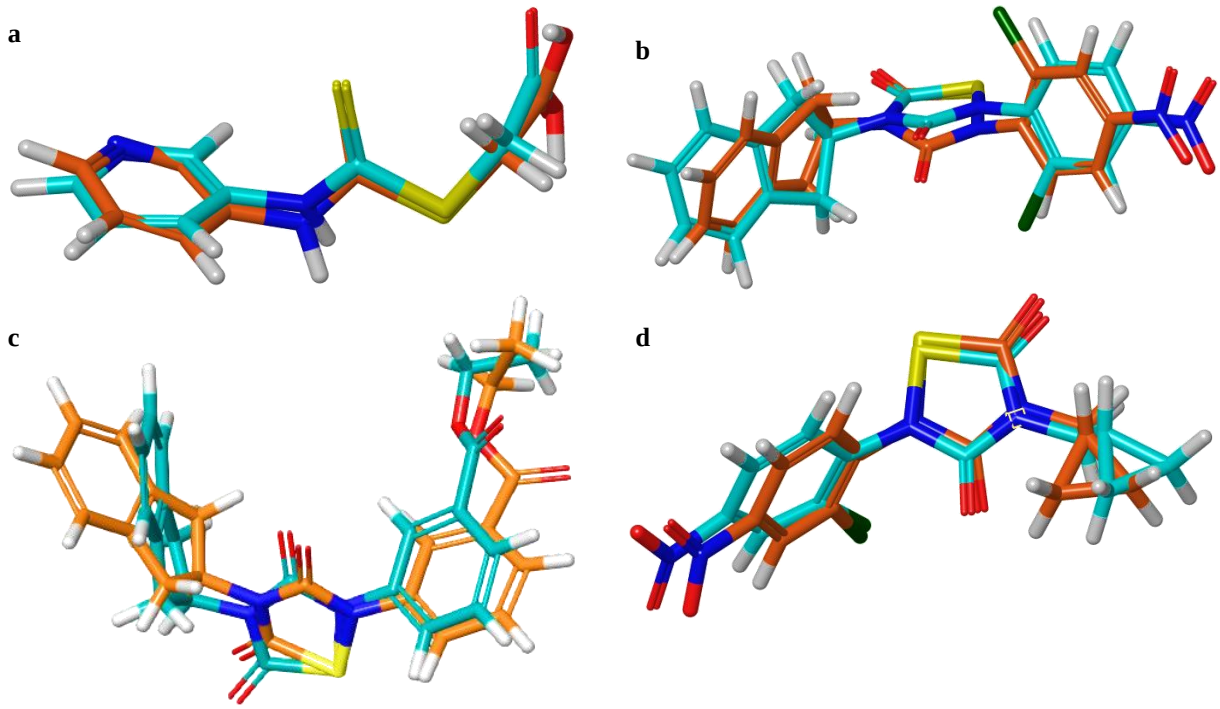
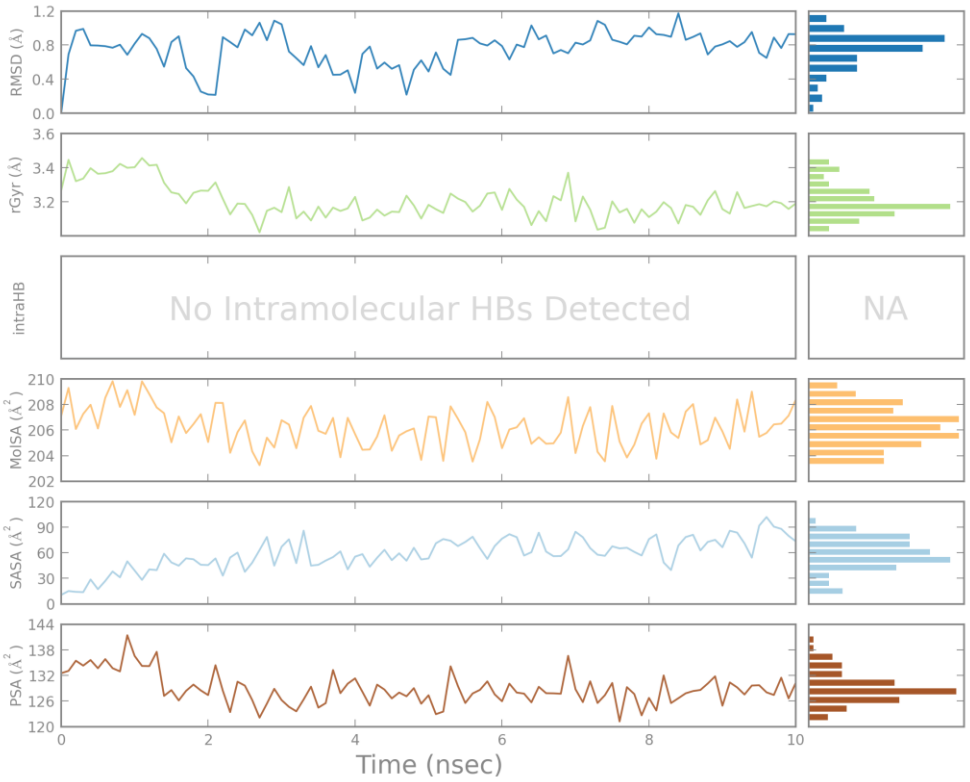


Figure S11. Superposition of conformations of (a) inhibitor **10** after MD simulation (orange) and best dock pose (turquoise) (RMSD: 1.23 Å) (b) inhibitor **19** after MD simulation (orange) and best dock pose (turquoise) (RMSD: 1.53 Å) (c) inhibitor **21** after MD simulation (orange) and best dock pose (turquoise) (RMSD: 1.35 Å) (d) inhibitor **25** after MD simulation (orange) and best dock pose (turquoise) (RMSD: 0.77 Å).

a


RMSD (Å)
rGyr (Å)
intraHB
No Intramolecular HBs Detected
NA
MolSA (Å²)
SASA (Å²)
PSA (Å²)
Time (nsec)

b


RMSD (Å)
rGyr (Å)
intraHB
No Intramolecular HBs Detected
NA
MolSA (Å²)
SASA (Å²)
PSA (Å²)
Time (nsec)

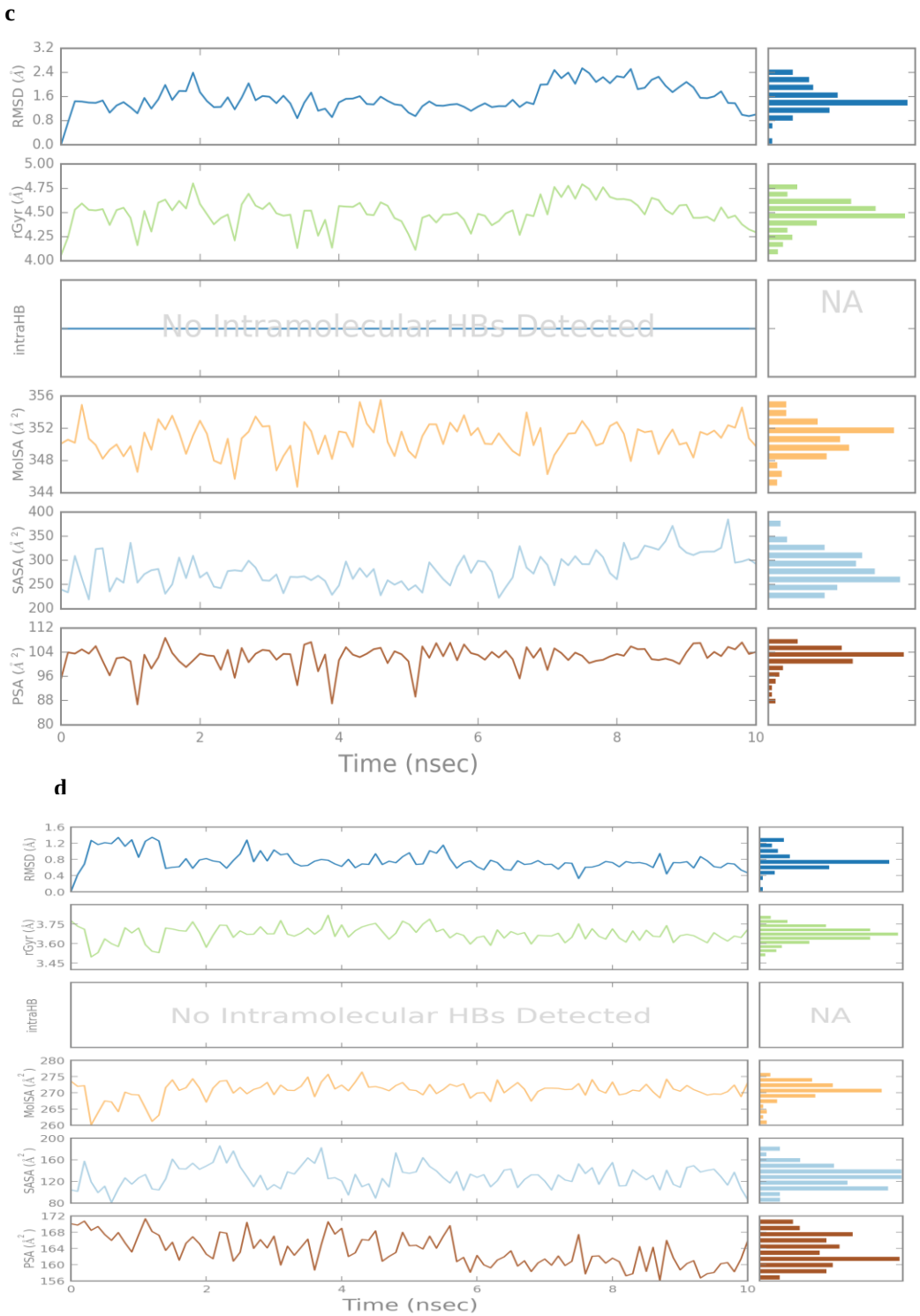


Figure S12. Ligand (a) **10** (b) **19** (c) **21** and (d) **25** properties during MD simulations (0.00 through 10.00 ns). RMSD: Root mean square deviation of a ligand with respect to the reference conformation; rGyr: Radius of Gyraion which measures the 'extendedness' of a ligand; intraHB: Intramolecular Hydrogen Bonds; MolSA: Molecular Surface Area; SASA: Solvent Accessible Surface Area; PSA: Polar Surface Area.