Supplementary

Synthesis, molecular docking, binding free energy calculation and molecular dynamics simulation studies of benzothiazol-2-ylcarbamodithioates as *Staphylococcus aureus* MurD inhibitors

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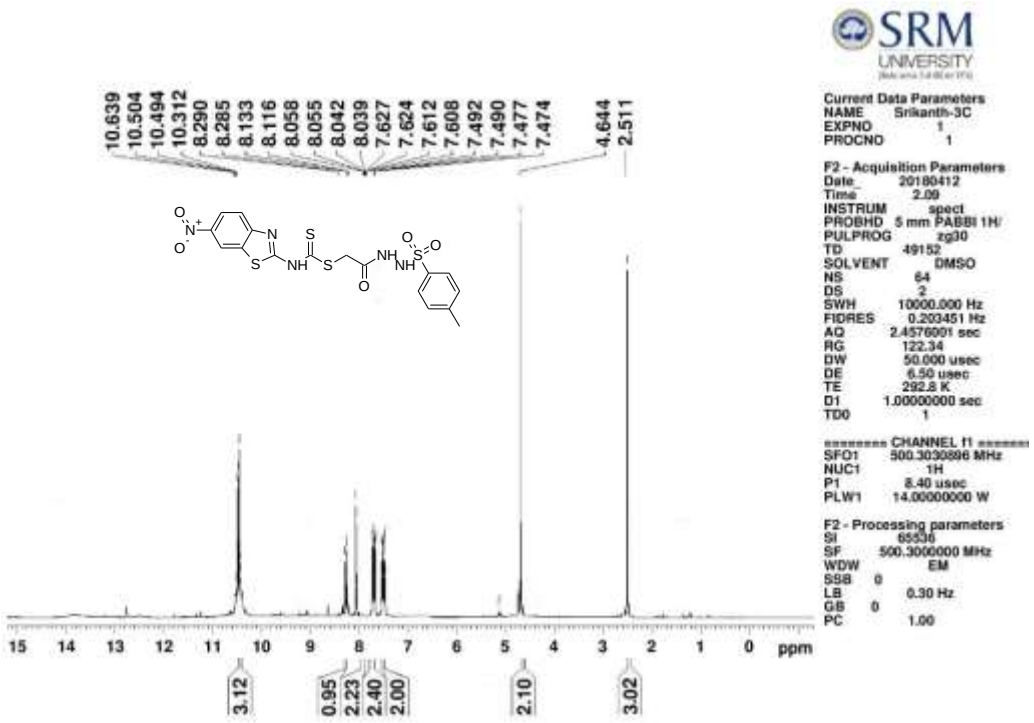


Figure S1a. [1]H-NMR spectrum of synthesized compound **5a**.

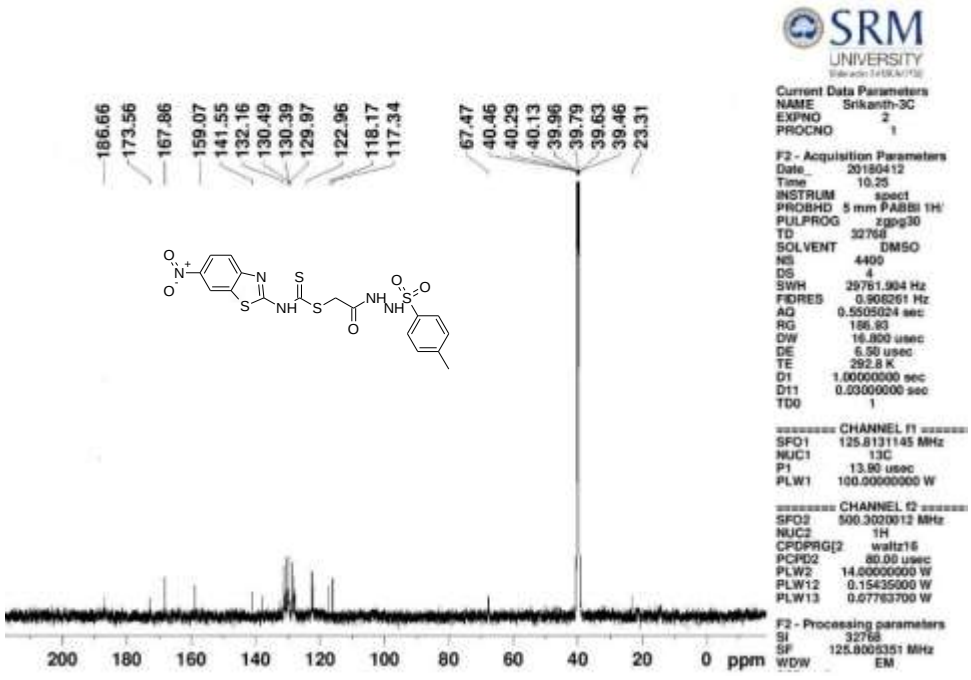


Figure S1b. [13]C-NMR spectrum of synthesized compound **5a**.

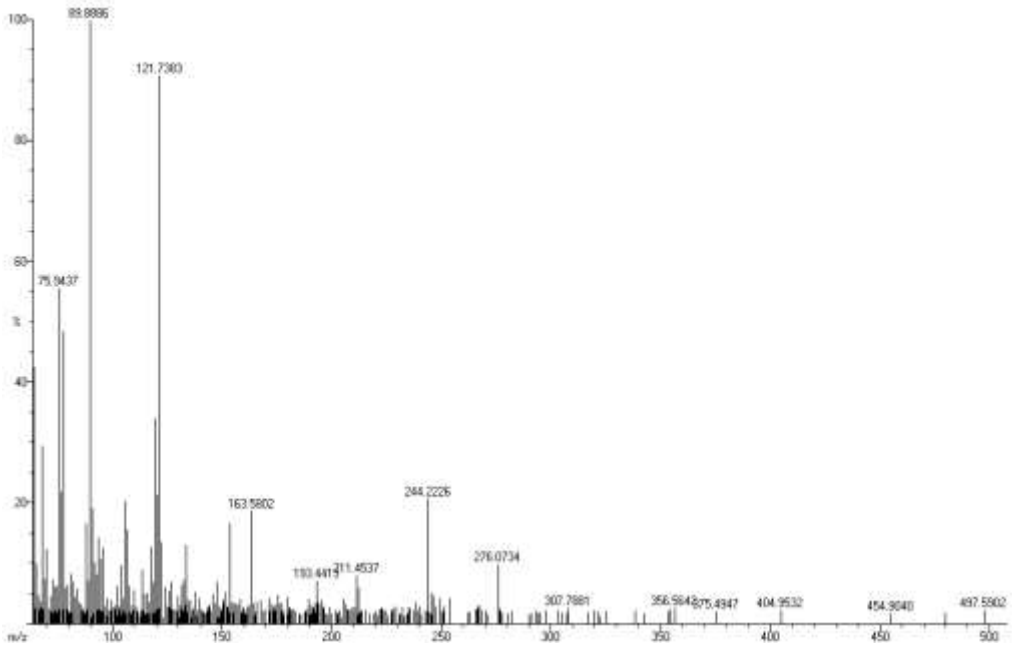


Figure S1c. Mass spectrum of synthesized compound **5a** (calculated mol. wt. 497.591).

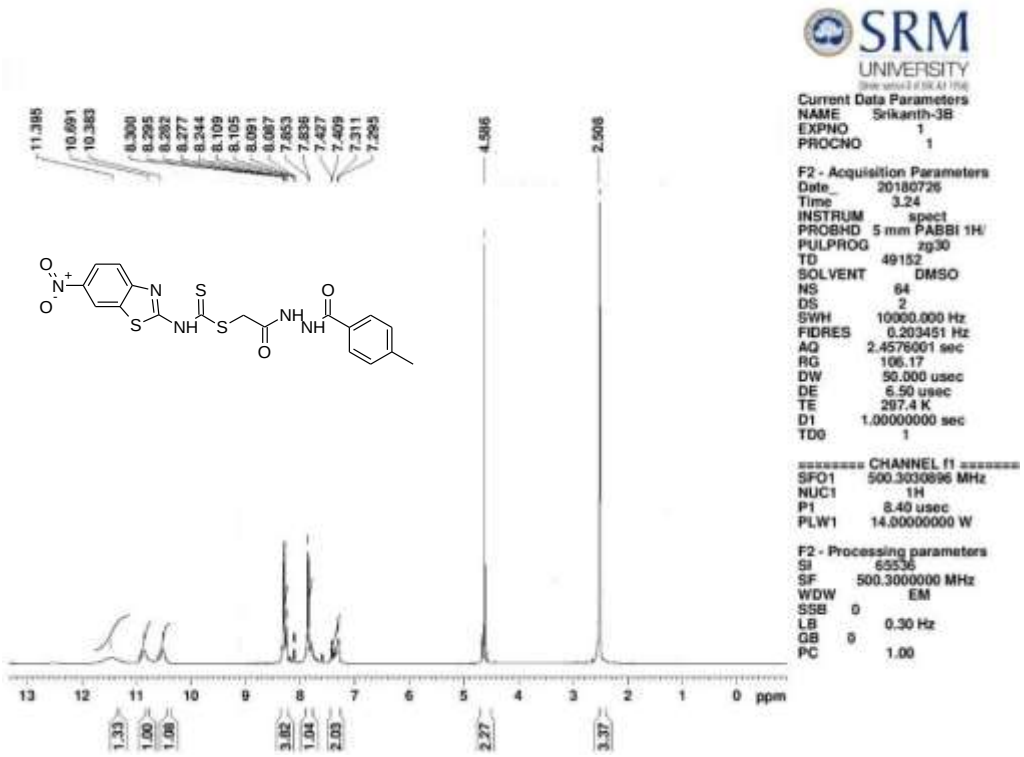


Figure S1d ^{1}H-NMR spectrum of synthesized compound **5b**.

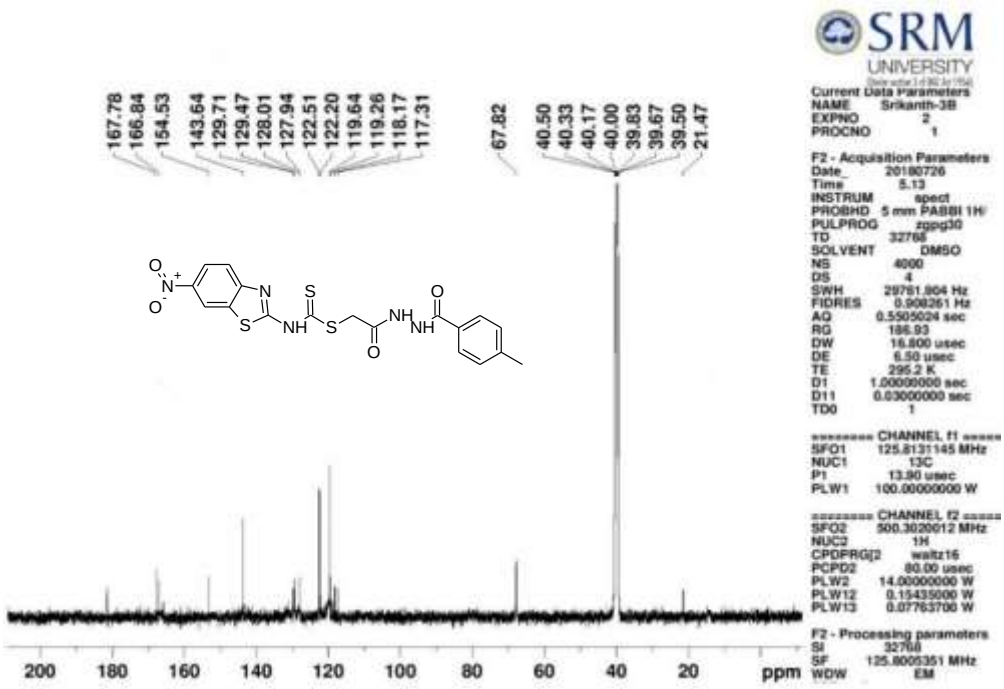


Figure S1e. ^{13}C-NMR spectrum of synthesized compound **5b**.

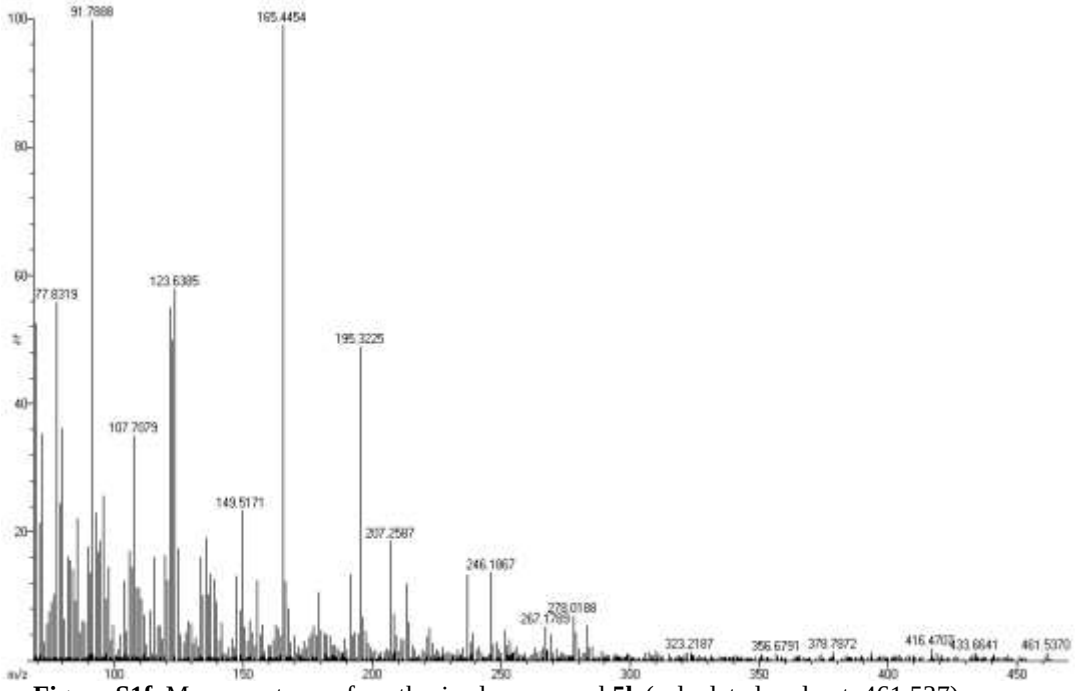


Figure S1f. Mass spectrum of synthesized compound **5b** (calculated mol. wt. 461.537).

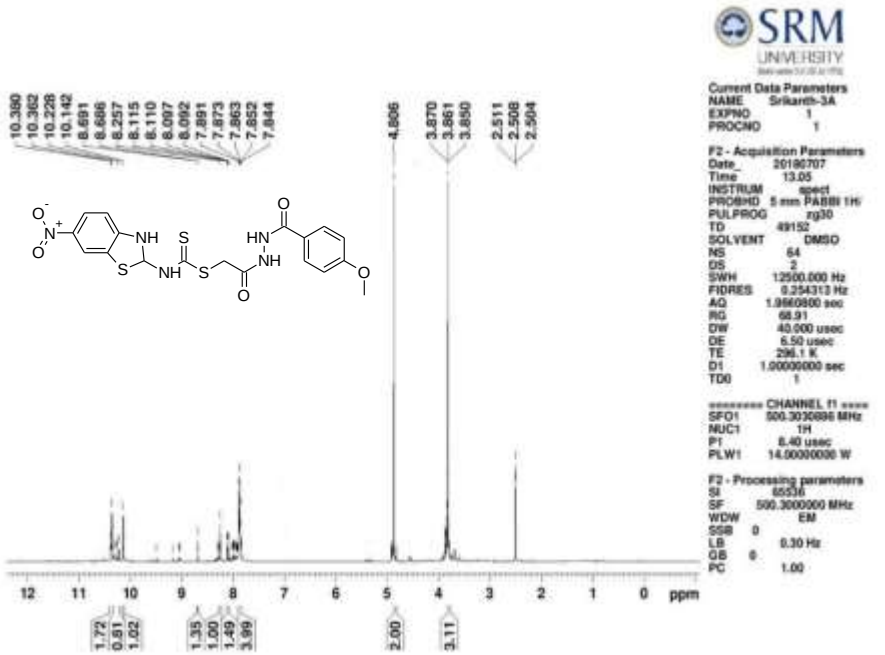


Figure S1g. [1]H-NMR spectrum of synthesized compound **5d**.

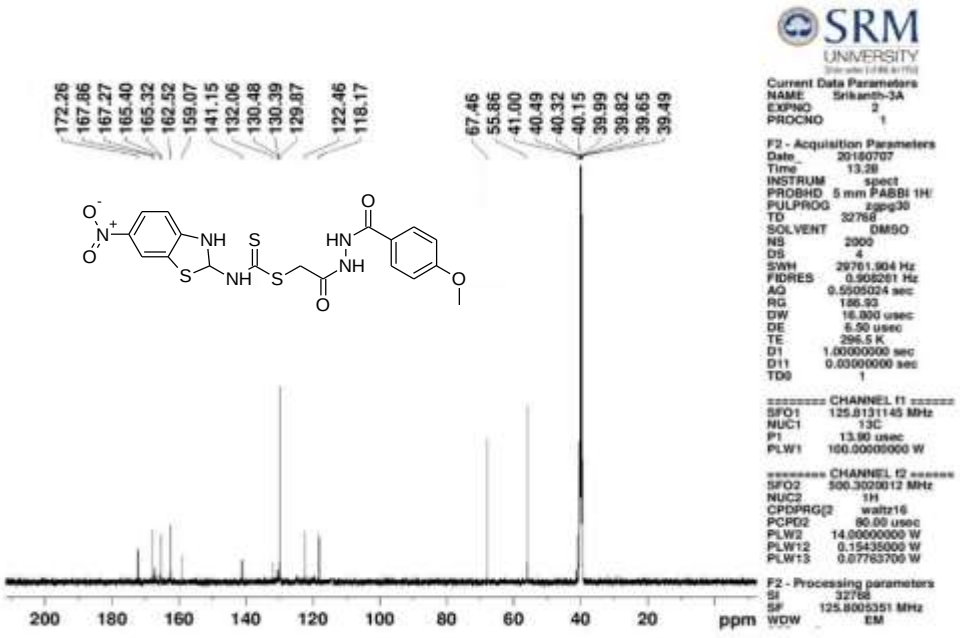


Figure S1h. [13]C-NMR spectrum of synthesized compound **5d**.

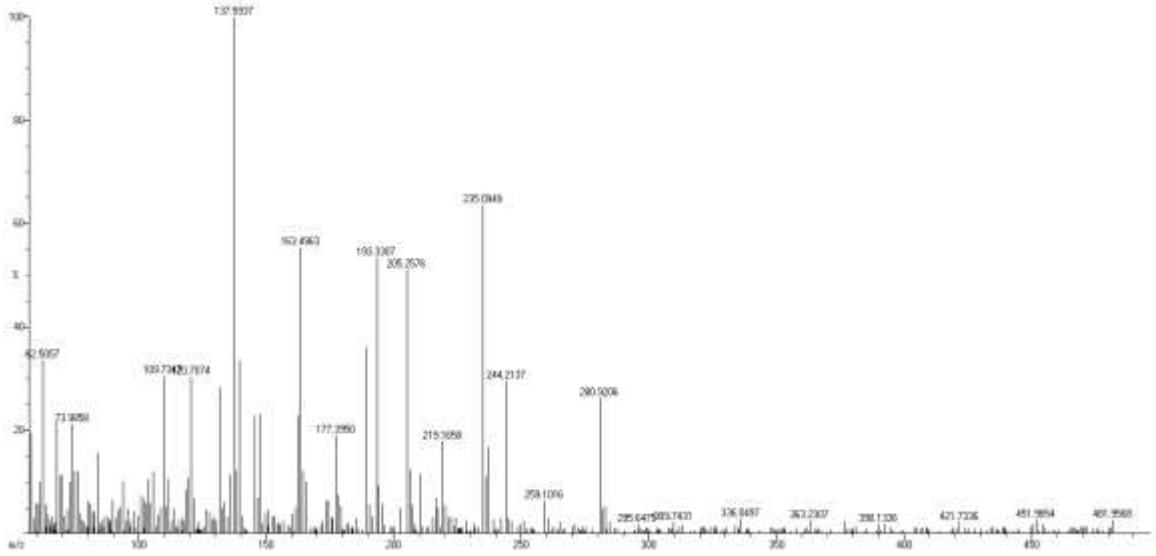
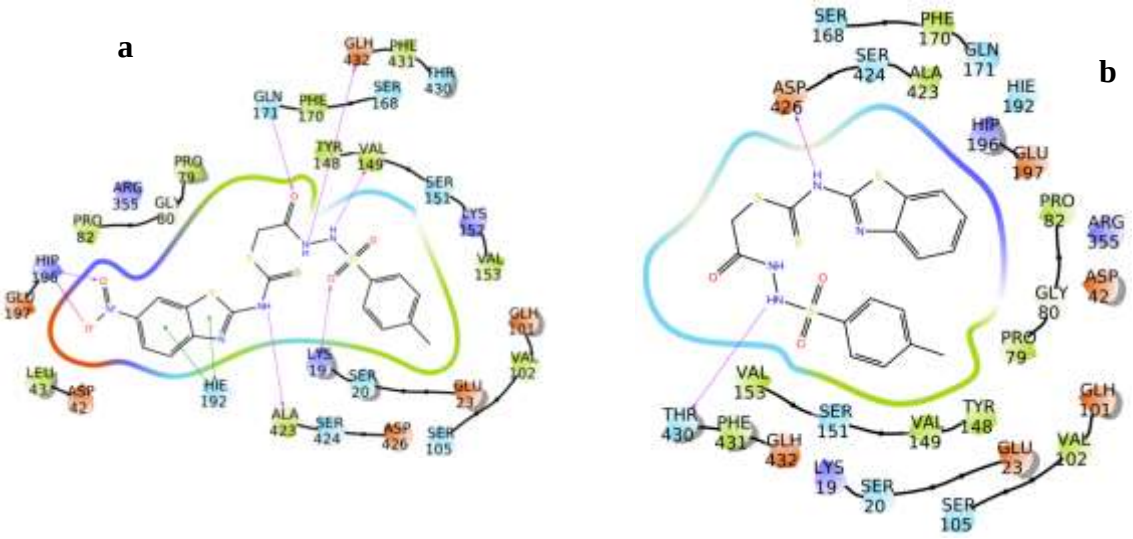


Figure S1i. Mass spectrum of synthesized compound **5d** (calculated mol. wt. 477.43).

Table S1. Number of hydrogen bonds and interacting residues for the designed ligands **5a-f** in the active site of modelled *S. aureus*MurD ligase enzyme.

Comp.	No of Hydrogen bonds	Interacting amino acid residues
5a	5	Ala18, Lys77, Gly80, Phe170$^{\$}$, His192$^{\#\$}$, Glu197*, Thr430, Glu432
5b	2	His192$^{\#}$, Glu197*, Asn331, Glu432
5c	5	Lys19, Val149, Glu171, His192$^{\$}$, His196, Ala423, Glu432
5d	5	Lys19, Ser20, Ser168, His192$^{\$}$, His196*, Asp426, Glu432
5e	2	Asp426,Thr430
5f	4	Lys19, Ser20, His192$^{\$}$, Asp426, Glu432

*Salt bridge, $^{\#}$π-Cation, $^{\$}$π-π



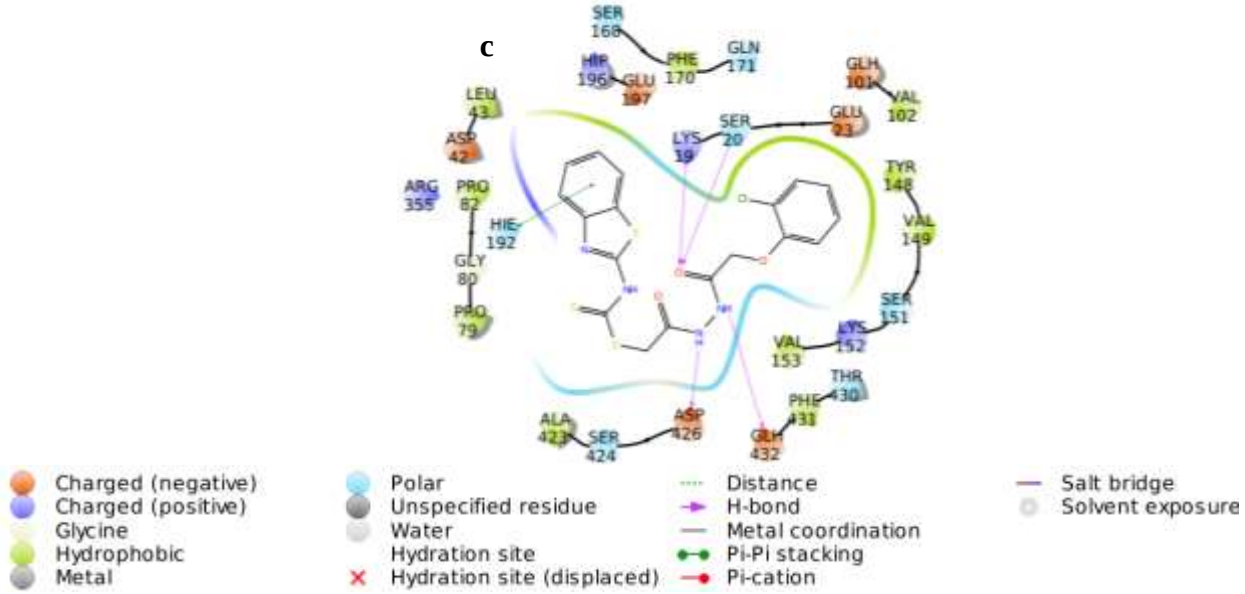


Figure S2. Represents extra-precision docking pose of compounds (a) **5c** (b) **5e** and (c) **5f** in the catalytic pocket of modelled *S. aureus* MurD protein.

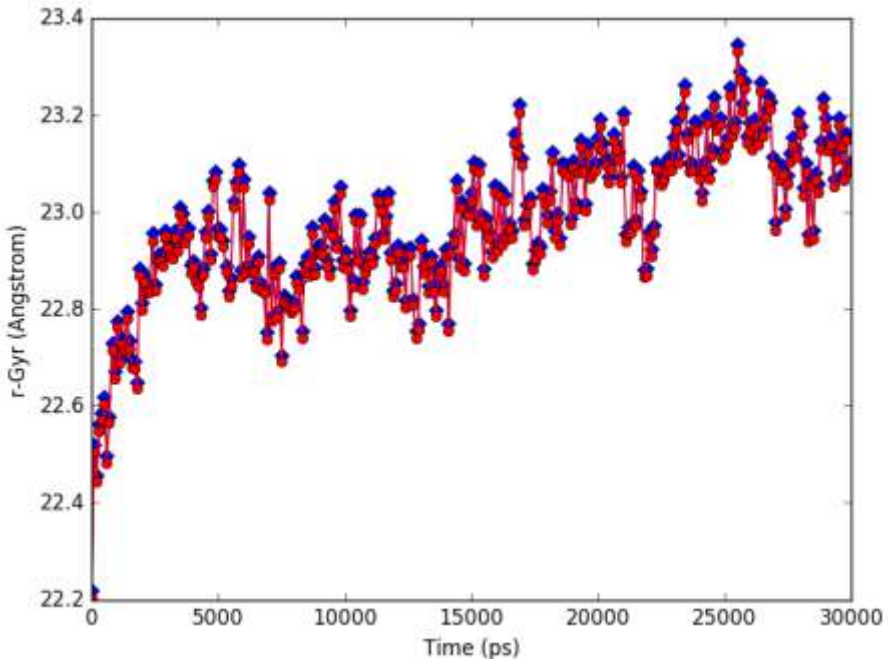


Figure S3. rGyr of modelled *S. aureus* MurD Cα and backbone atoms during MD simulation of **5d/** modelled *S. aureus* MurD complex.

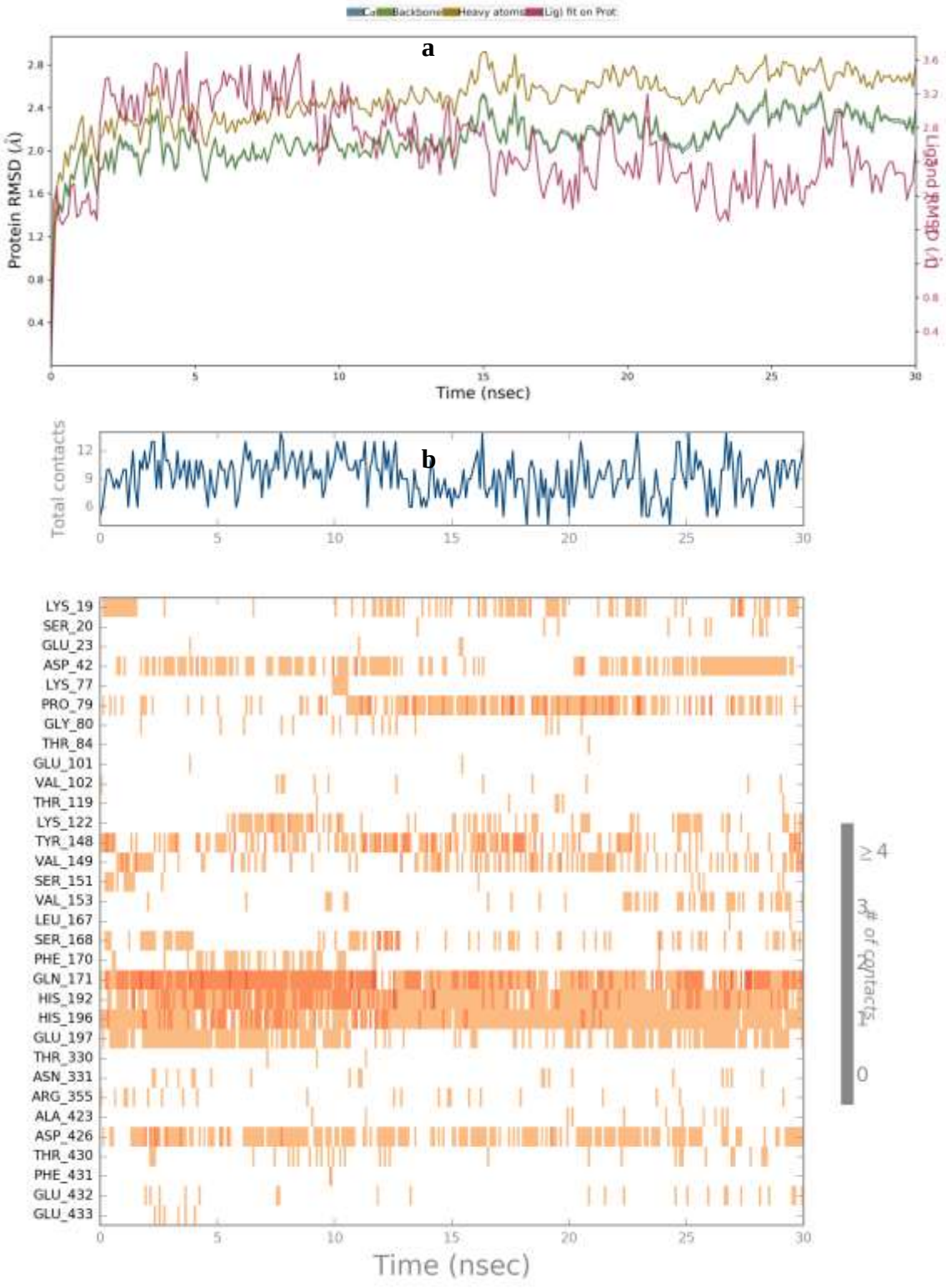


Figure S4. (a) Plot represent RMSD (Å) of the simulated positions of modelled *S. aureus* MurD protein Cα and backbone atoms and ligand from those in the initial structure. (b) Time line representation of inhibitor **5d** and modelled *S. aureus* MurD enzyme contacts during 30 ns simulation.

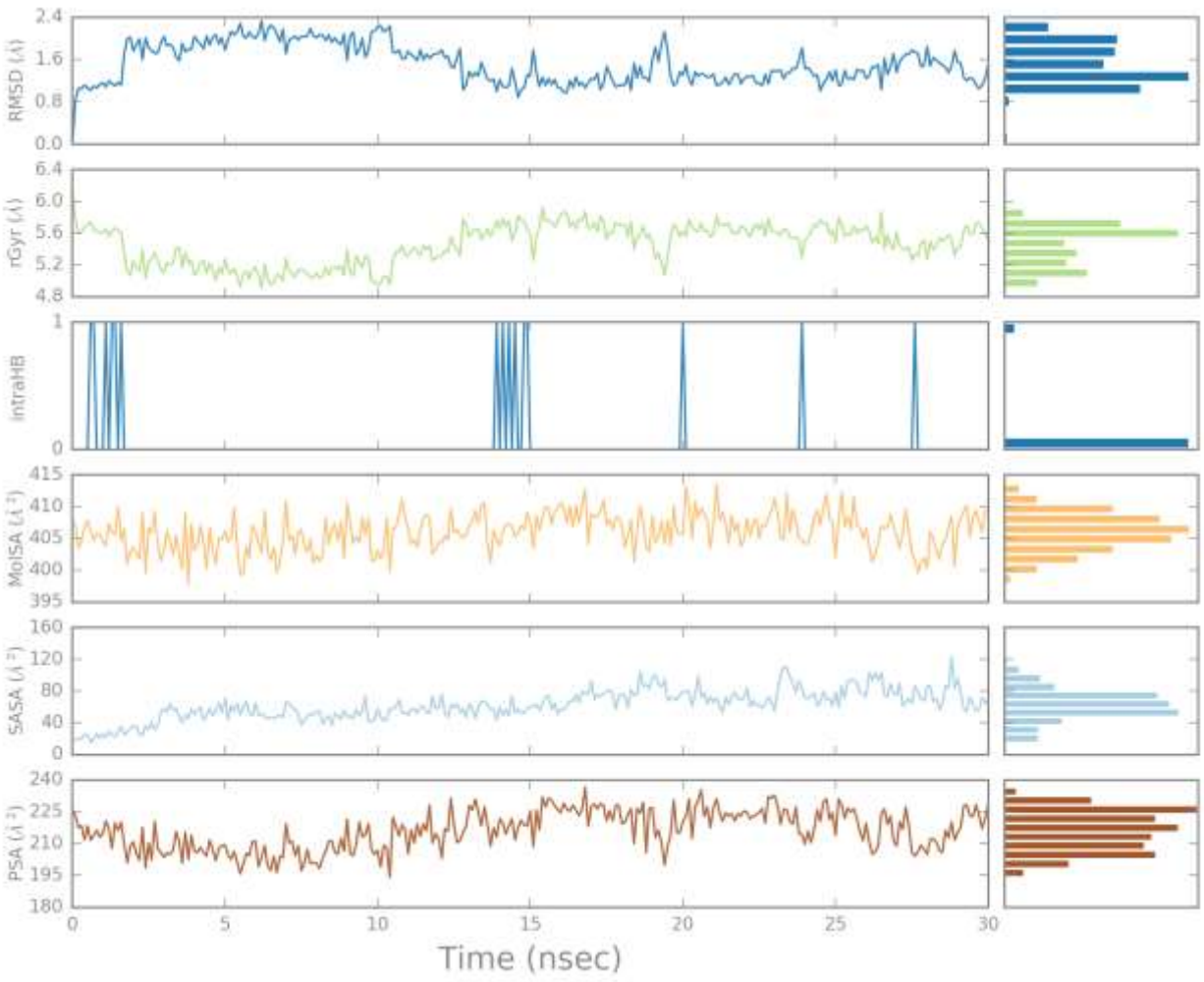


Figure S5. Represents ligand **5d** properties during MD simulations (0.00 through 30.00 ns). RMSD: root mean square deviation of a ligand with respect to the reference conformation; rGyr: radius of gyraion which measures the 'extendedness' of a ligand; intraHB: intramolecular hydrogen bonds; MolSA: molecular surface area; SASA: solvent accessible surface area; PSA: polar surface area.

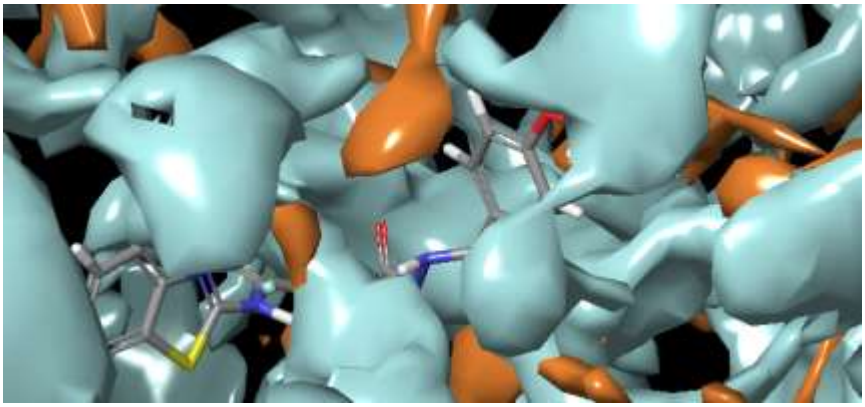


Figure S6. Hydrophilic-hydrophobic map generated for the average MD pose structure of **5d/**modelled *S. aureus* MurD protein complex.

Table S2. *In silico* ADMET properties of synthesized compounds **5a-d** predicted by QikProp.

Comp.	CNS	SASA	Donor HB	Accpt HB	QP logP o/w	QP log HERG	QPP Caco	PSA	Rule of 5
5a	-2	752.59	2.25	10.75	1.82	-4.25	92.93	167.1	0
5b	-2	773.95	1.5	8.0	3.34	-4.81	101.31	156.3	0
5c	-2	761.42	1.5	8.0	3.47	-2.84	53.05	156.8	0
5d	-2	778.62	1.5	8.75	3.10	-3.77	96.653	165.8	0
5e	-2	708.89	2.25	9.75	2.51	-4.30	208.98	120.3	0
5f	-2	777.24	1.5	7.75	4.41	-3.20	343.00	121.3	0

CNS: Predicted central nervous system activity (-2 to +2); SASA: Total solvent accessible surface area (300-1000); Donor HB: Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution (0.0-6.0); Acceptor HB: Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution (2.0-20.0); QP log P o/w: Predicted octanol/water partition coefficient (-2 to 6.5); QPlog HERG: Predicted IC_{50} value-blockage of HERG K^+ Channels (concern < -5); QPP Caco: Predicted Caco-2 cell permeability in nm/sec (<25 poor> 500 great); PSA (Polar Surface Area): Vander Waals SA of polar nitrogen and oxygen (7-200); Rule of 5: Number of violations of Lipinski's rule of five (Max 4).