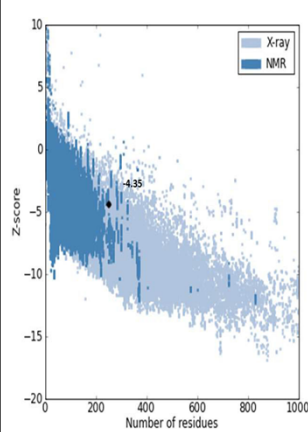
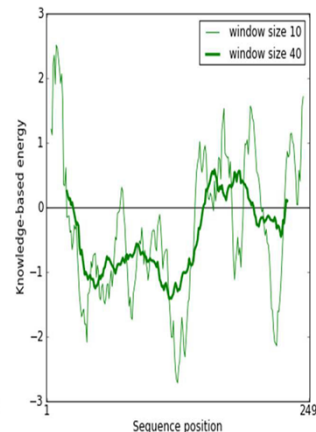


(a)



(b)



(c)

Figure S1: (a) Ramchandran plot of the modeled protein showed 97.7% residues in the allowed region, (b) The Z-score of -4.35 (c) The sequence position graph with a stretch of structure in the desired range.

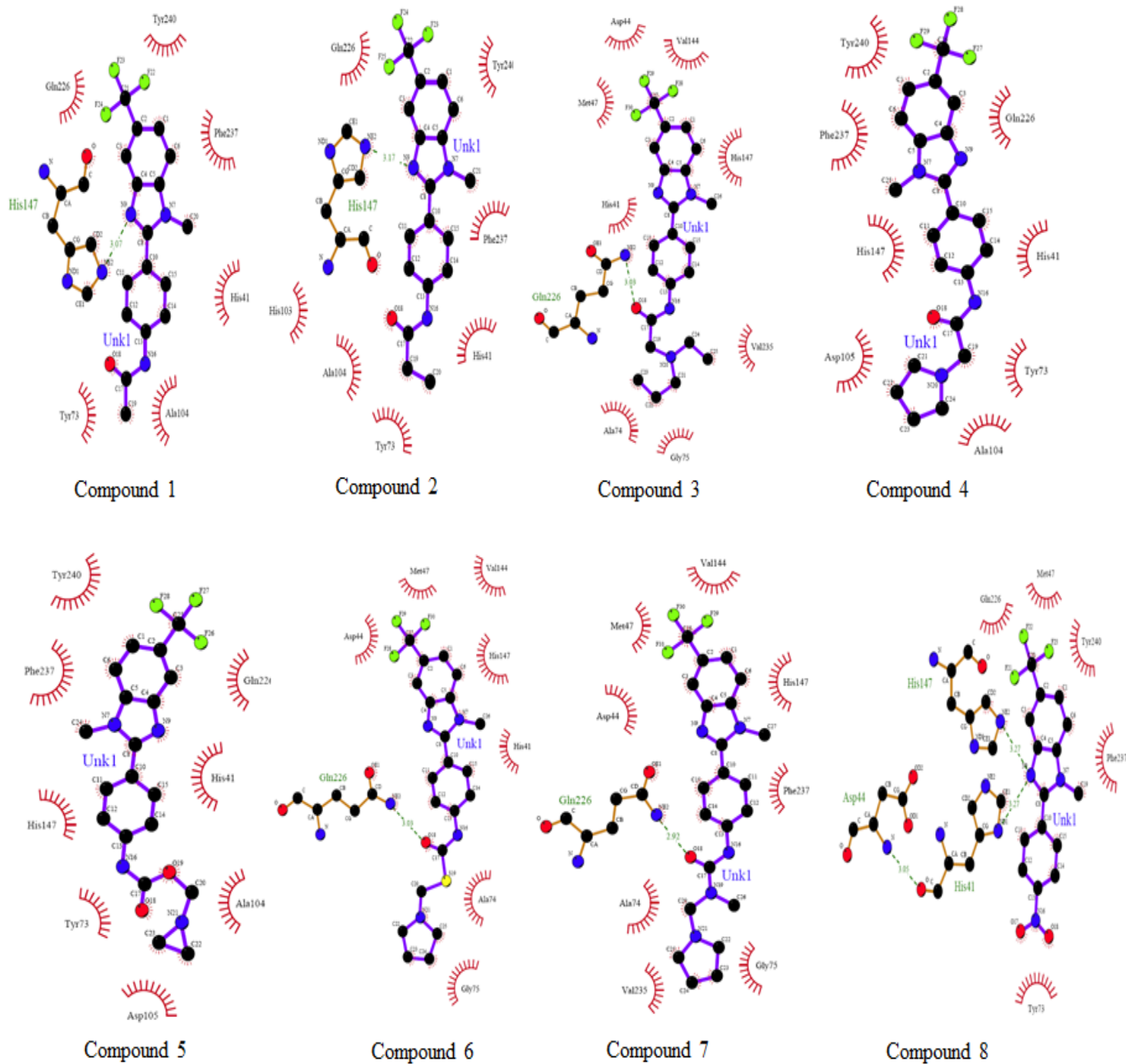


Figure S2 (a)-(h): Two dimensional plot of Protein-ligand interaction.

Supplementary Tables

Sr.no	aa residue	Entropy	Sr.no	aa residue	Entropy
1.	His ¹⁴	3.05	19.	Gly ⁶⁷	2.07
2.	Cys ⁴¹	3.26	20.	Asp ⁸⁶	2.57
3.	Glu ⁵⁸	3.32	21.	Thr ¹⁴⁰	2.72
4.	Trp ⁹²	3.79	22.	Phe ¹⁴¹	2.86
5.	His ¹⁴⁹	3.13	23.	Asp ¹⁴²	2.55
6.	His ¹⁵²	3.40	24.	Gly ¹⁴⁵	2.69
7.	Trp ²³⁴	3.44	25.	Ser ¹⁴⁷	2.19
8.	Ala ¹³	2.27	26.	Asn ¹⁵¹	2.75
9.	Pro ¹⁵	2.76	27.	Lys ¹⁷⁶	2.68
10.	Asp ¹⁶	2.69	28.	Tyr ¹⁷⁷	2.98
11.	Asp ¹⁷	2.73	29.	Met ²²⁴	2.82
12.	Glu ¹⁸	2.9	30.	His ²²⁸	2.37
13.	Met ²⁰	2.92	31.	Gln ²³¹	2.98
14.	Phe ²¹	2.49	32.	Phe ²³⁵	2.02
15.	Phe ²²	2.47	33.	Arg ²³⁶	2.15
16.	Pro ²⁴	2.63	34.	Tyr ²⁵⁴	2.61
17.	Gly ⁵²	2.34	35.	Asn ²⁴⁹	2.40
18.	Arg ⁵⁵	2.93			

Table S1: The co-evolving residues with >2.0 relative entropy lying within the active site and in the vicinity of the active site.

Target protein	PDB_ID	aa length	Fold	Resolution (Å)	Organism
Hypothetical protein Rv1170 (MshB)	1Q7T	328	A/B	1.90	<i>M. tuberculosis</i>
Hypothetical protein TT1542 (TT1542)	1UAN	227	A/B	2.00	<i>T. thermophilus</i>
LMBE-related protein (BcZBP)	2IXD	242	A/B	1.8	<i>B. cereus</i>
N-Acyl glm pseudo-teicoplanin deacetylase	2XAD	273	A/B/C/D	1.7	<i>A. teichomyceticus</i>
Pseudoaglycone deacetylase (Dbv21)	3DFI	270	A	2.10	<i>A. teichomyceticus</i>
Teicoplanin pseudoaglycone deacetylase orf2	3DFM	273	A	2.01	<i>A. teichomyceticus</i>
1D-myo-inositol 2-acetamido-2-deoxy-alpha-D-glucopyranoside Deacetylase (MshB)	1Q74	303	A/B/C/D	1.70	<i>M. tuberculosis</i>
deacetylase-bog complex	2X9L	273	A	1.73	<i>A. teichomyceticus</i>
Teicoplanin pseudoaglycone deacetylases Orf2	3DFF	273	A	1.60	<i>A. teichomyceticus</i>
Teicoplanin pseudoaglycone deacetylase Orf2	3DFK	273	A	1.60	<i>A. teichomyceticus</i>

Table S2: Crystal structures used in the experiment