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In silico study for the prediction of multiple pharmacological activities of novel hydrazone derivatives

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The present studies are aimed to predict multiple pharmacological activities of novel hydrazone derivatives. Molecular docking of compounds 1 to 51 have been performed in Small-Molecule Drug Discovery Suite of Schrödinger. Fifty one compounds have been targeted on seven enzymes *viz*. 2NSD and 2X22 involved in tuberculosis activity, 4COX and 3LN1 involved in inflammation, 4GCP and 4HL2 involved in bacterial infection and 4WMZ involved in fungal infection. The generated lower energy conformers of all ligands have been docked into generated grid of active site of enzymes by XP precision of docking inside Glide-v7.4. Molecular docking results suggest that the compounds 4, 5, 11, 18, 30, 34, 35, 37, 38, 42, 43, 44, 45, 46 and 47 have good docking score and are predicted to interact with all enzymes. In all fifteen novel hydrazone derivatives have been predicted for multiple pharmacological activities.

Keywords: Hydrazone, molecular docking, multiple pharmacological activities

In hydrazone, the nitrogen is attached to hydrogen; these hydrazone are stable enough for isolation. However, in some cases, especially with simple R group, they rapidly decompose or polymerize unless there is at least one aryl group on nitrogen or the carbon. When there is an aryl group the compound are quite stable and these compound called Schiff bases and the reaction is the best way to prepare them. The reaction is straightforward and proceeds in high yield[1].

Hydrazones with an azomethine −NHN=CH− proton constitute an important class of compounds for new drug development. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. These observations have been promoting and guiding the development of new hydrazones that possess multiple biological activities. Hopefully, this will allow the development of innovative new strategies for the development of novel compounds with different schemes, methods and materials[2].

The chemistry of these derivatives has been a fascinating field of investigation in medicinal chemistry. They have been found to exhibit enhanced biological profile. Hydrazones are known to exhibit a wide variety of biological activities. They are used as antibacterial agents, anti-tubercular agents, analgesics, anti-inflammatory agents, antiviral agents, antifungal agents, muscle relaxants and antihistamines, *etc*.[3]

The docking is a computational method to study the formation of intermolecular complexes and is a subject of intensive research. Drug exerts its biological activity by binding to the pocket of receptor molecule. In their binding conformations, the molecules exhibit geometric and chemical complementarily, both of which are essential for successful drug activity. The computational process of searching for a ligand that is able to fit both geometrically and energetically into the binding site of a protein is called molecular docking.

Molecular docking helps in studying drug/ ligand or receptor/ protein interactions by identifying the suitable active sites in protein, obtaining the best geometry of ligand - receptor complex and calculating the energy of interaction for different ligands to design more effective ligands. The target or receptor is either experimentally known or theoretically generated through knowledge based protein modeling or homology modeling. The molecular docking tool has been developed to obtain a preferred geometry of interaction of ligand - receptor complexes having minimum interaction energy based on different scoring functions. This utility allows one to screen a set of compounds for lead optimization or synthesis[4,5].

Experimental Section

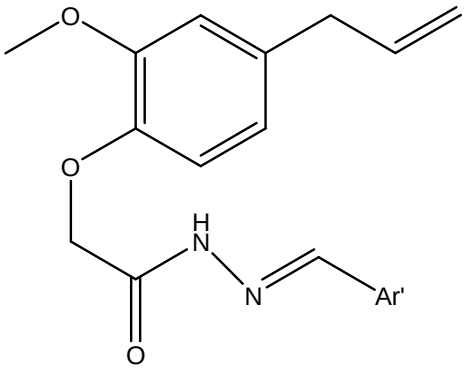
Molecular docking of 1 to 51 compounds was performed in Small-Molecule Drug Discovery Suite of Schrödinger. Fifty one compounds were targeted on 7 enzymes such as 2NSD and 2X22[13] involved in tuberculosis activity, 4COX[8,9] and 3LN1[6,7,10] involved in inflammation[11,12], 4GCP and 4HL2 involved in bacterial infection and 4WMZ involved in fungal infection. The generated lower energy conformers of all ligands were docked into generated grid of active site of enzymes by XP precision of docking inside Glide-v7.4.

Preparation of small molecule: A set of new 51 hydrazone derivatives (Table I) were compiled by us using ChemDraw. 3D structures which were constructed using Chem 3D ultra 12.0 software [Molecular Modeling and Analysis; Cambridge Soft Corporation, USA (2010)], and saved as MDL Mol File (* .mol).

Ligand preparation

The structure of each compound was cleaned and optimized using Ligprep. The clean-up and optimization process include conversion of structures from 2D to 3D, addition of hydrogen atoms, generation of possible ionization state at *p*H 7.0, generation of tautomers (if any), generation of all combinations of stereoisomers, and energy minimization. The low energy conformer of ligands was generated using OPLS3 force field. All structures were saved in 'maestro' output format.

Table I — List of compounds



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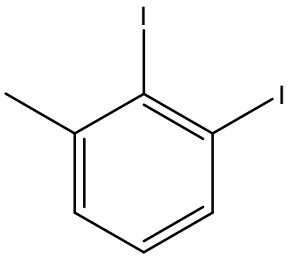
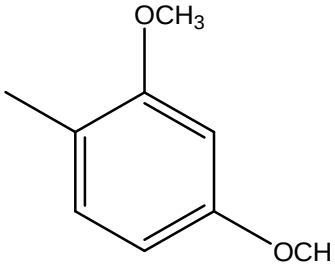
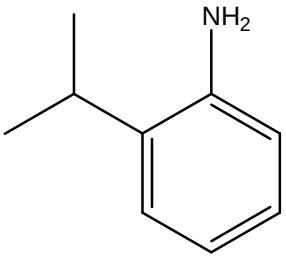
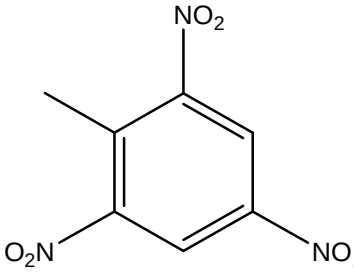
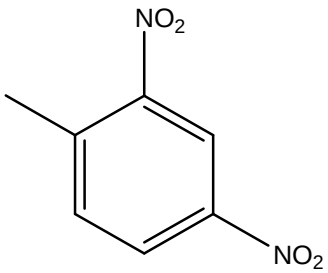
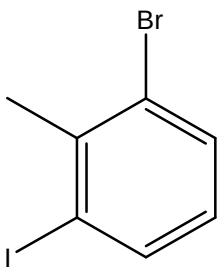
1		6		11	
2		7		12	

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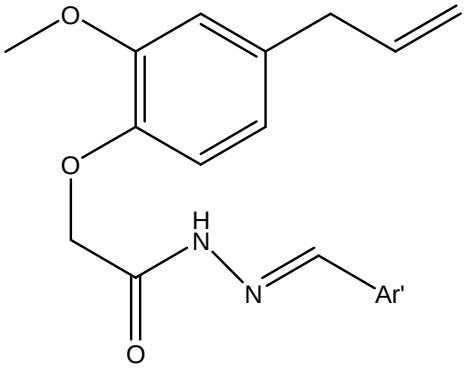
Table I — List of compounds (*Contd*.)



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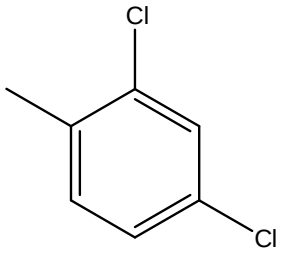
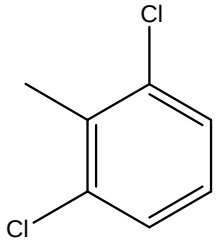
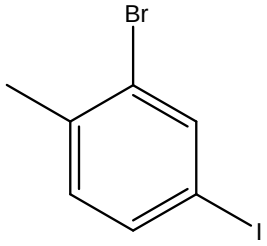
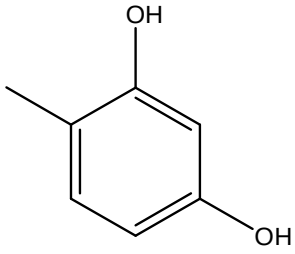
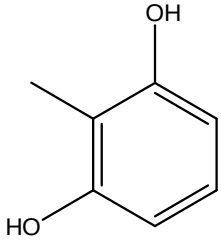
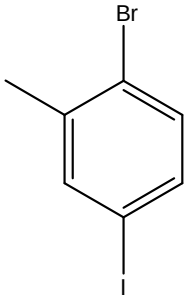
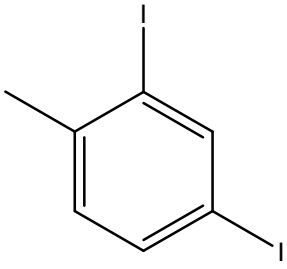
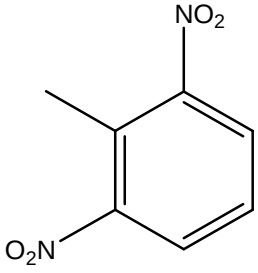
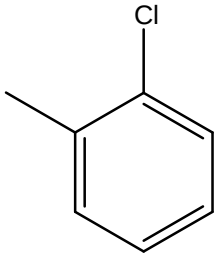
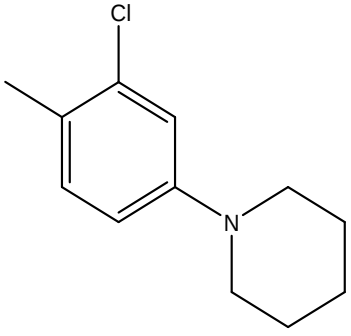
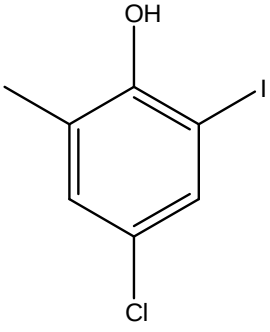
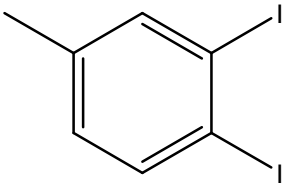
3		8		13	
4		9		14	
5		10		15	
16		21		26	

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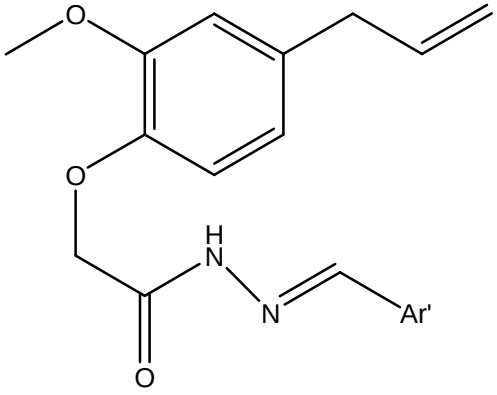
Table I — List of compounds (*Contd*.)



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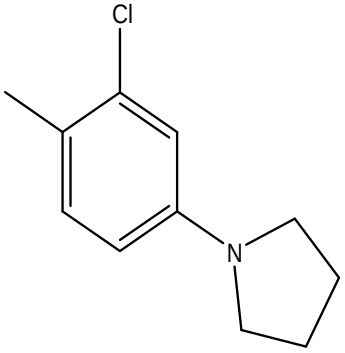
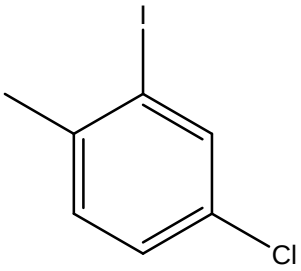
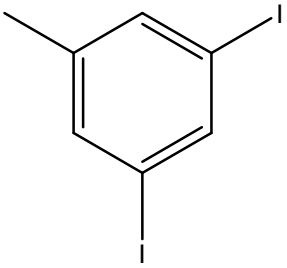
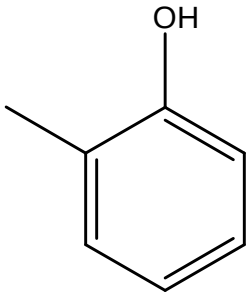
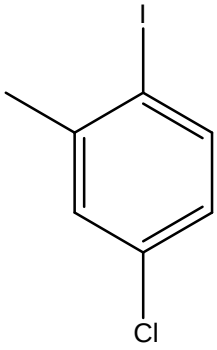
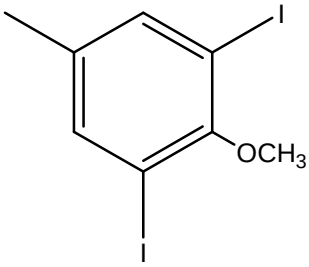
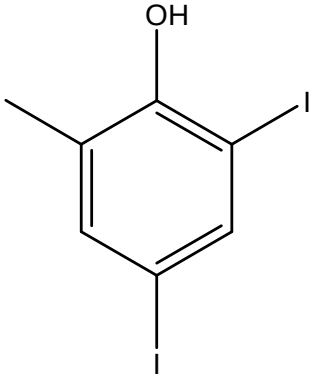
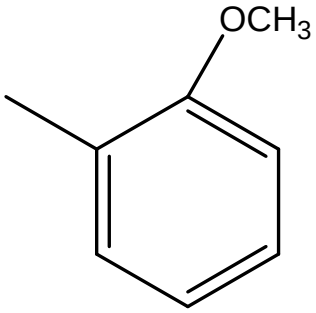
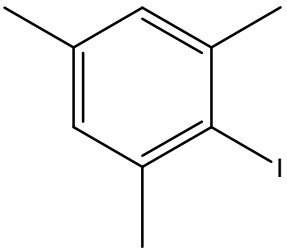
17		22		27	
18		23		28	
19		24		29	

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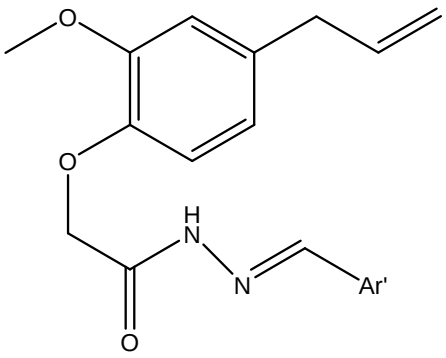
Table I — List of compounds (*Contd*.)



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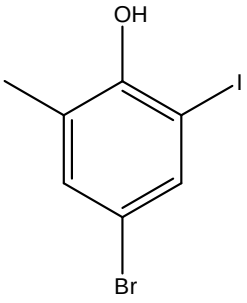
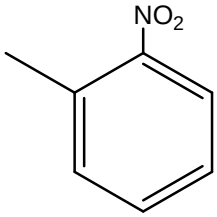
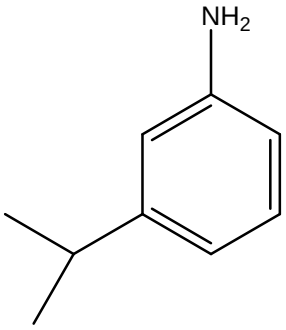
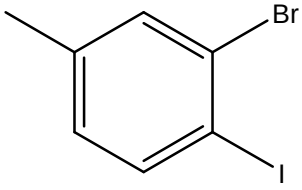
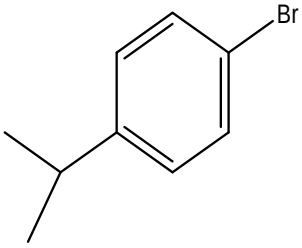
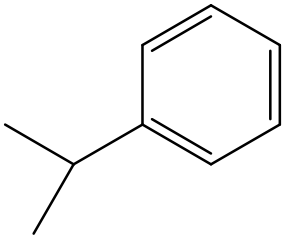
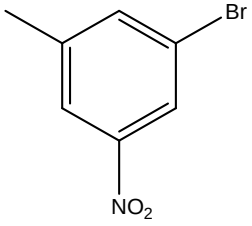
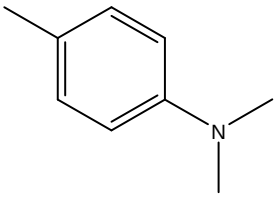
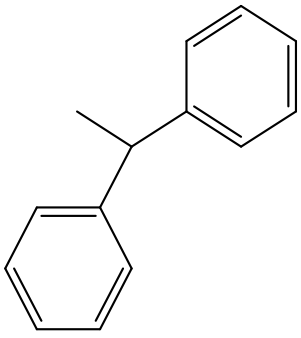
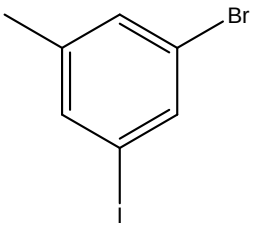
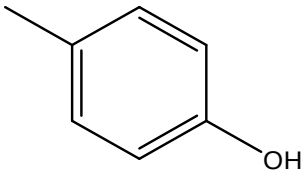
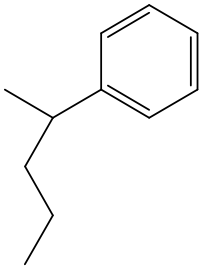
20		25		30	
31		38		45	
32		39		46	
33		40		47	

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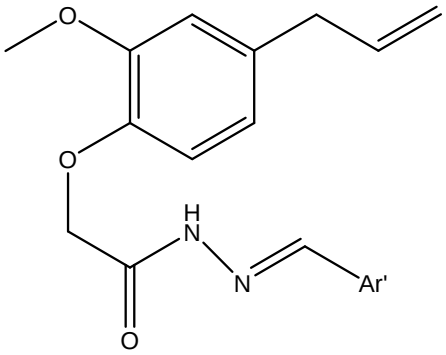
Table I — List of compounds (*Contd*.)



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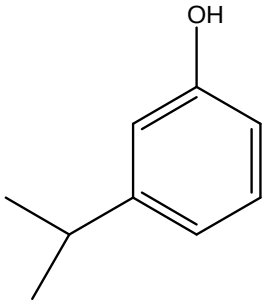
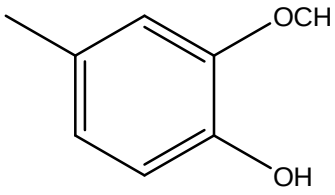
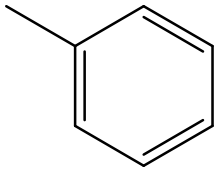
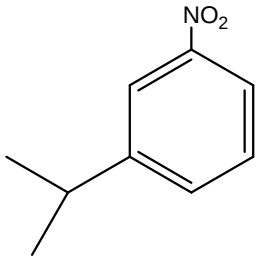
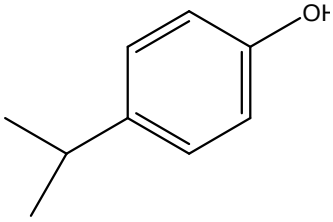
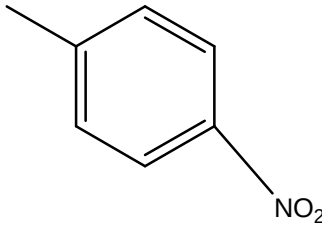
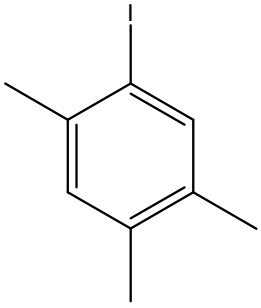
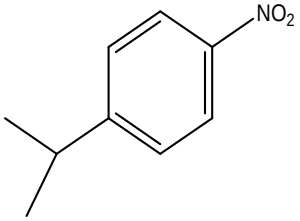
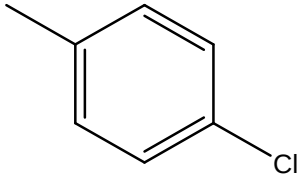
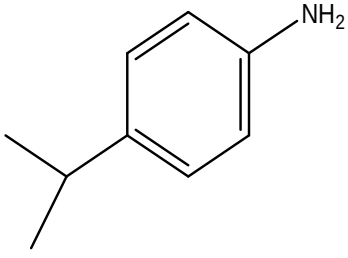
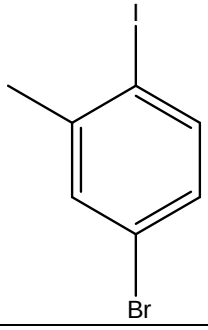
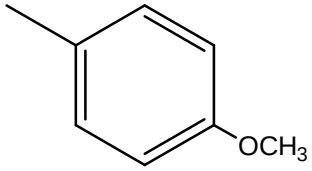
34		41		48	
35		42		49	
36		43		50	
37		44		51	

Protein preparation

The protein such as 2NSD, 2X22, 4COX, 3LN1, 4GCP, 4HL2 and 4WMZ download from protein data bank. All protein structures were prepared for docking using the ''protein preparation wizard'' in Maestro-v11.1. The protein preparation was carried out in two steps, preparation and refinement. Preparation steps involved assigning of bond order, addition hydrogen, removal of original hydrogen, creation of zero order bonds to metals, and filling of missing side chain an d loops using prime. All water molecules in the crystal structures were deleted, het states of bound ligands were generated using Epik at *p*H 7.0 and termini were capped by adding ACE and NMA residue. The refinement steps involved the optimization of hydrogen bonding network was by reorienting hydroxyl groups, and amide groups of Asn and Gln, and selecting appropriate states and orientations of the imidazole ring in His residues. The refinement steps also include a restrained impact minimization of the co-crystallized complex. It uses the OPLS3 force field for this purpose.

Grid Generation

Grid files represent the active sites of enzyme that are searched when attempting to dock a ligand. It was generated by Receptor Grid Generation panel of Glide-v7.4. Grids were defined by centering on the co-crystallized ligand in the crystal structure. It excludes co-crystallized ligand and thus determines the position and size of the active site. The size of grid box was fixed so that ligand with size of </= 20 Å can be docked. The van der Waals radius scaling factor of 0.7 for atoms with a partial atomic charge (absolute value) less than 0.25 was used to soften the potential for nonpolar parts of the receptor. The constraints were also defined as per various interactions visualized in PDB of co-crystallized ligands with respective enzyme. The rotatable groups like hydroxyl and thiol groups in enzymes were allowed to rotate.

Docking calculations

The generated lower energy conformers of all ligands were docked into generated grid of active site of enzymes by XP precision of docking inside Glide-v7.4. The ligand sampling was set up to be flexible which allow the sampling of ring conformation, nitrogen inversion and penalize the non planar conformation of amide groups. Some more settings were set like adding of epic state penalties to docking score, rewarding intramolecular hydrogen bonds, and enhancement of planarity of conjugated pi-groups. The constraints were selected as set in grid generation, must be satisfied for at least 1 interaction. All other advanced settings were set as defaults given in software.

Results and Discussion

The docking study was performed using Small-Molecule Drug Discovery Suite of Schrödinger Glide-v7.4. All novel hydrazone derivatives were docked into the active site of seven enzymes such as enoyl acyl carrier protein reductase inhA (PDB ID: 2NSD), *M. tuberculosis* inhA (PDB ID: 2X22), COX-2 (PDB ID: 4COX), COX-2 (PDB ID: 3LN1), *E. coli* OmpF porin (PDB ID: 4GCP), New delhi metallo-beta-lactamase-11.05 A (PDB ID: 4HL2) and *S. cerevisiae* CYP51 (PDB ID: 4WMZ) which showed better docking scores than the reference compounds (Table II). There are fifteen compounds which showed a fit interaction with enzymes (Figures 1-14) and predicted for multiple pharmacological activities (Table III).

Table II — Docking score of compounds

Compounds	Enoyl acyl carrier protein reductase inhA PDB ID: 2NSD	M. tuberculosis inhA PDB ID:2X22	COX-2 PDB ID:4COX	COX-2 PDB ID:3LN1	E.coli OmpF porin PDB ID: 4GCP	NDM beta-lactamase PDB ID:4HL2	S. cerevisiae CYP51 PDB ID: 4WMZ
Isoniazide	−3.682	−4.682	–	–	–	–	–
Indomethacin	–	–	−10.739	−6.157	–	–	–
Ampicillin	–	–	–	–	−5.547	−11.363	–
Fluconazole	–	–	–	–	–	–	−4.709
1	−8.747	−5.959	−8.383	–	–	−4.247	−4.732
2	−6.847	−4.009	–	–	−2.959	−4.665	−4.572
3	–	−8.007	−8.257	–	−1.63	−5.972	−6.508

(*Contd.*)

Table II — Docking score of compounds (*Contd.*)

Compounds	Enoyl acyl carrier protein reductase inhA PDB ID: 2NSD	M. tuberculosis inhA PDB ID:2X22	COX-2 PDB ID:4COX	COX-2 PDB ID:3LN1	E.coli OmpF porin PDB ID: 4GCP	NDM beta-lactamase PDB ID:4HL2	S. cerevisiae CYP51 PDB ID: 4WMZ
4	−10.393	−8.426	−9.265	−7.791	−4.511	−6.898	−8.428
5	−7.919	−6.09	−8.442	−6.428	−1.5	−4.423	−6.679
6	−7.247	–	−7.668	–	−2.714	−5.027	–
7	−7.179	−6.67	−5.952	–	–	−5.166	−6.291
8	−8.387	−5.981	−8.302	–	−2.187	−5.034	–
9	−8.525	−7.538	−7.875	−1.693	−3.142	−5.923	−6.864
10	−7.099	–	−6.187	–	−2.405	−4.581	−5.751
11	−9.5	−7.726	−8.955	–	−3.181	−5.374	−8.413
12	−6.942	−4.965	–	–	–	−4.264	−6.665
13	−8.921	–	−7.069	–	–	−4.427	–
14	−8.216	−8.073	−6.788	–	–	−4.68	−6.013
15	−7.428	−6.721	−7.81	–	–	−5.311	−4.785
16	−7.815	−2.124	−8.288	–	–	−4.998	–
17	−7.266	−6.04	−8.619	−4.222	–	−4.124	−6.796
18	−7.632	−6.625	−9.066	–	−2.803	−7.064	−6.546
19	−7.681	−5.954	−8.421	−4.79	−1.941	−6.277	−4.722
20	−7.466	−4.423	−8.086	–	−2.969	−7.064	−6.602
21	−6.799	−7.037	−8.669	−6.662	−3.806	−5.954	−7.407
22	−7.005	−5.353	−8.992	–	−1.627	−4.757	−6.903
23	−7.867	–	−8.302	–	−3.138	−5.497	−6.266
24	−7.883	−4.742	−7.439	−6.857	−3.146	−5.18	–
25	−8.657	−6.098	–	–	−1.774	−5.192	−6.006
26	−8.15	−4.74	–	–	–	−5.294	−7.637
27	−7.37	–	−8.443	−5.13	–	−4.478	−5.638
28	−8.101	−7.486	–	–	−2.672	−4.591	–
29	−6.097	−2.37	−8.057	–	−2.145	−4.536	−4
30	−9.021	−7.769	−8.387	−5.29	−4.511	−6.344	−7.069
31	−7.804	−6.092	−8.034	–	–	−4.533	−5.082
32	−6.384	−4.919	−7.632	−4.498	–	−3.956	−5.302
33	−6.955	−6.071	−6.671	–	−3.023	−4.951	−5.997
34	−10.13	−7.448	−8.813	−6.432	–	−5.596	−7.837
35	−9.813	−7.338	−7.143	−5.75	−3.408	−4.739	−5.981
36	−6.538	−6.226	−7.645	−4.353	−2.342	−3.919	–
37	−9.632	−9.092	−9.093	–	−3.923	−5.879	−7.368
38	−9.587	−7.932	−8.51	−5.06	−2.745	−4.878	−6.968
39	−6.818	−5.289	−7.305	−3.918	−3.266	−4.89	−5.633
40	−6.921	−7.674	−7.827	–	−3.537	−5.813	–
41	−6.98	–	–	−7.744	–	−5.297	−6.793
42	−9.747	−8.527	−9.213	−6.714	−4.075	−6.698	−8.273
43	−9.256	−6.551	−8.132	−7.166	−3.418	−5.93	−6.468
44	−8.898	−5.356	−7.439	–	−3.139	−5.436	−6.403
45	−9.049	−6.262	−9.028	–	−3.349	−5.752	−6.648
46	−9.593	−7.758	−8.239	−5.798	−3.107	−5.097	−7.65
47	−9.485	−7.556	−8.945	−5.585	−2.442	−6.18	−7.724
48	−6.469	−4.896	−7.119	–	−1.847	−5.637	−5.377
49	−8.072	−5.725	−7.728	–	−3.171	−5.141	–
50	−6.338	−6.666	−8.549	–	–	−5.029	−5.944
51	−6.175	−4.293	−8.001	–	−1.611	−4.306	−7.02

Table III — Docking score of compounds with multiple pharmacological activities

Compounds	Enoyl acyl carrier protein reductase inhA PDB ID: 2NSD	M. tuberculosis inhA PDB ID: 2X22	COX-2 PDB ID: 4COX	COX-2 PDB ID: 3LN1	E.coli OmpF porin PDB ID: 4GCP	NDM beta-lactamase PDB ID: 4HL2	S. cerevisiae CYP51 PDB ID: 4WMZ
Isoniazide	−3.682	−4.682					
Indomethacin			−10.739	−6.157			
Ampicillin					−5.547	−11.363	
Fluconazole							−4.709
4	−10.393	−8.426	−9.265	−7.791	−4.511	−6.898	−8.428
34	−10.13	−7.448	−8.813	−6.432	−5.78	−5.596	−7.837
42	−9.747	−8.527	−9.213	−6.714	−4.075	−6.698	−8.273
37	−9.632	−9.092	−9.093	–	−3.923	−5.879	−7.368
45	−9.049	−6.262	−9.028	–	−3.349	−5.752	−6.648
46	−9.593	−7.758	−8.239	−5.798	−3.107	−5.097	−7.65
38	−9.587	−7.932	−8.51	−5.06	−2.745	−4.878	−6.968
30	−9.021	−7.769	−8.387	−5.29	−4.511	−6.344	−7.069
11	−9.5	−7.726	−8.955	–	−3.181	−5.374	−8.413
18	−7.632	−6.625	−9.066	–	−2.803	−7.064	−6.546
47	−9.485	−7.556	−8.945	−5.585	−2.442	−6.18	−7.724
43	−9.256	−6.551	−8.132	−7.166	−3.418	−5.93	−6.468
44	−8.898	−5.356	−7.439	–	−3.139	−5.436	−6.403
5	−7.919	−6.09	−8.442	−6.428	−1.5	−4.423	−6.679
35	−9.813	−7.338	−7.143	−5.75	−3.408	−4.739	−5.981

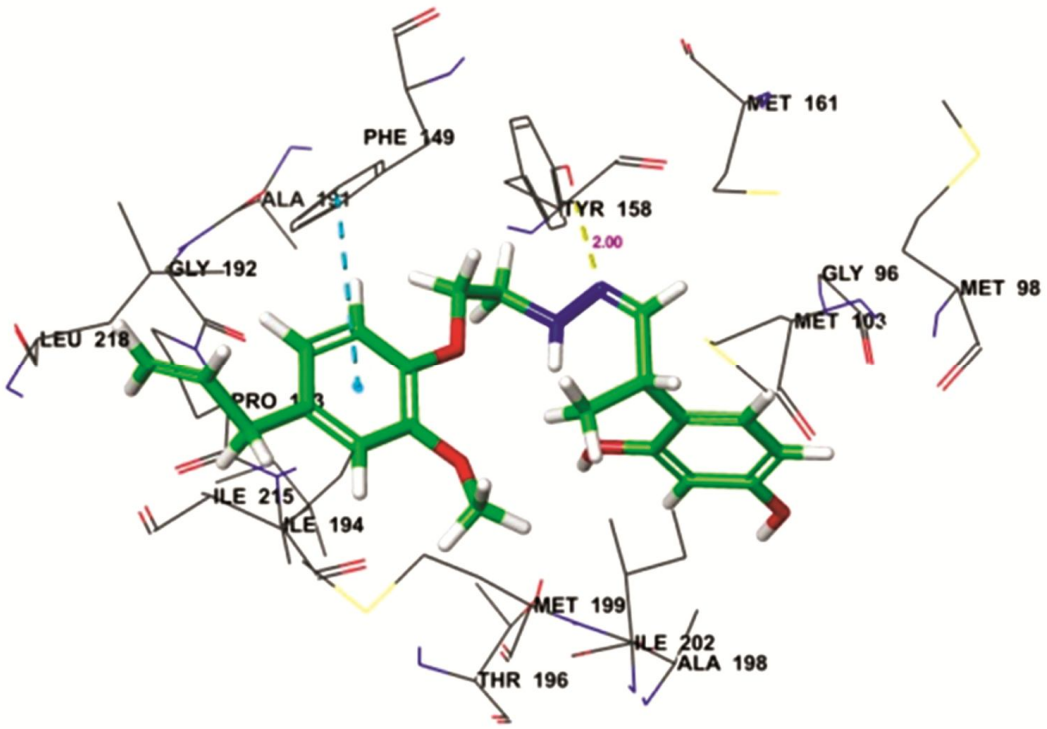


Figure 1 — The orientation of compound 4 in 2NSD enzyme

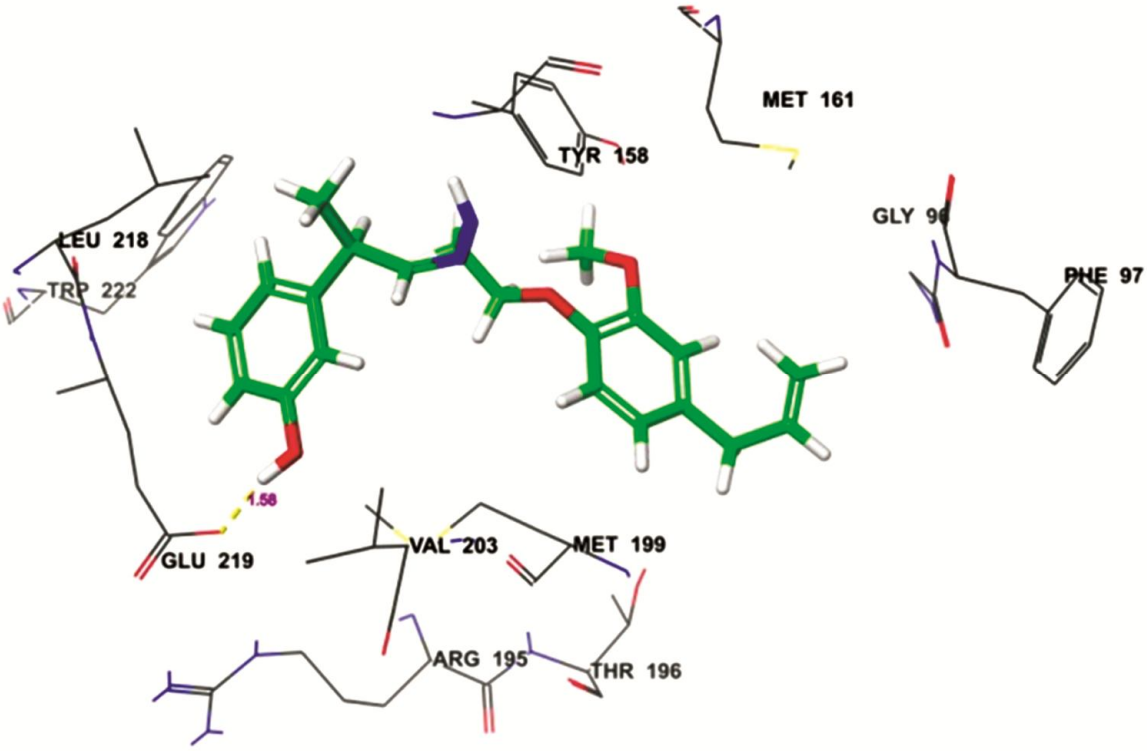


Figure 2 — The orientation of compound 34 in 2NSD enzyme

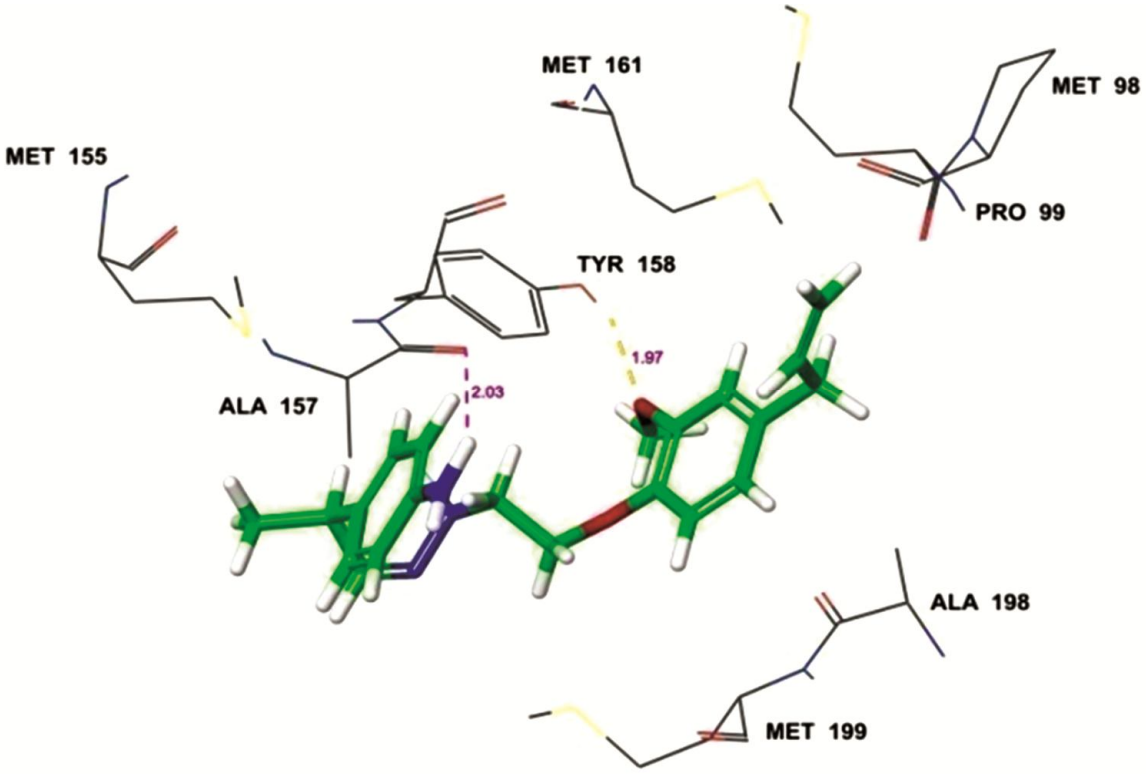


Figure 3 — The orientation of compound 37 in 2X22 enzyme

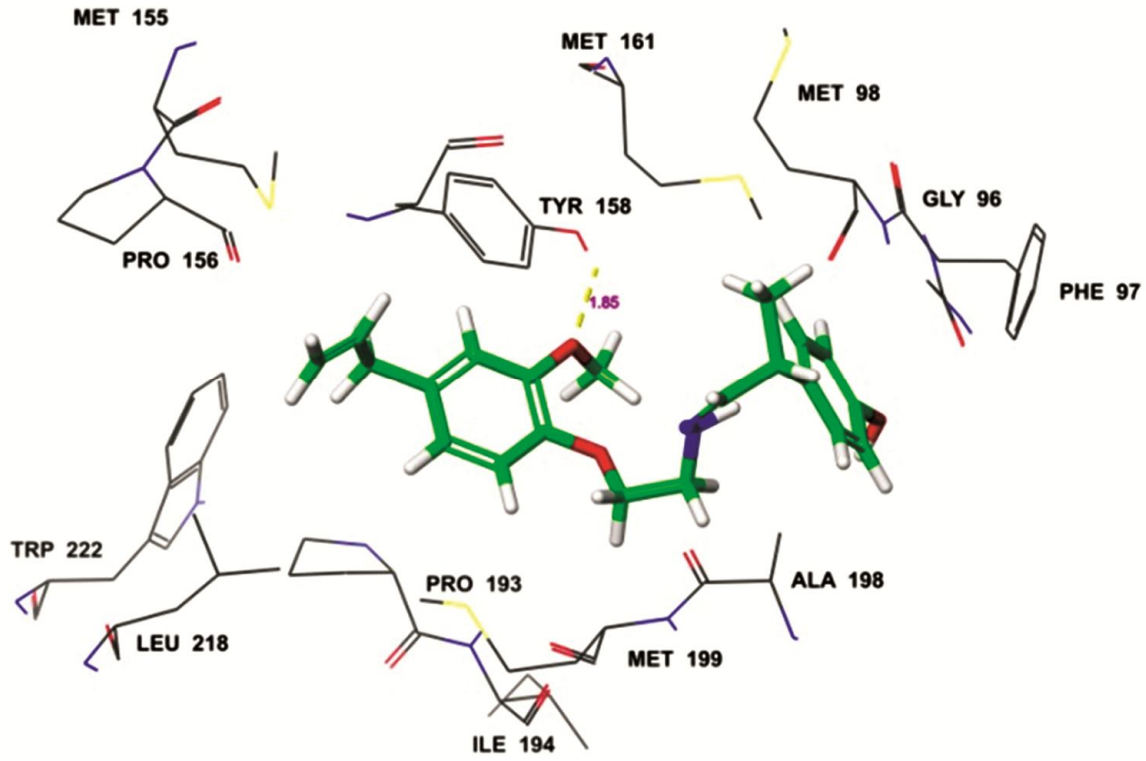


Figure 4 — The orientation of compound 42 in 2X22 enzyme

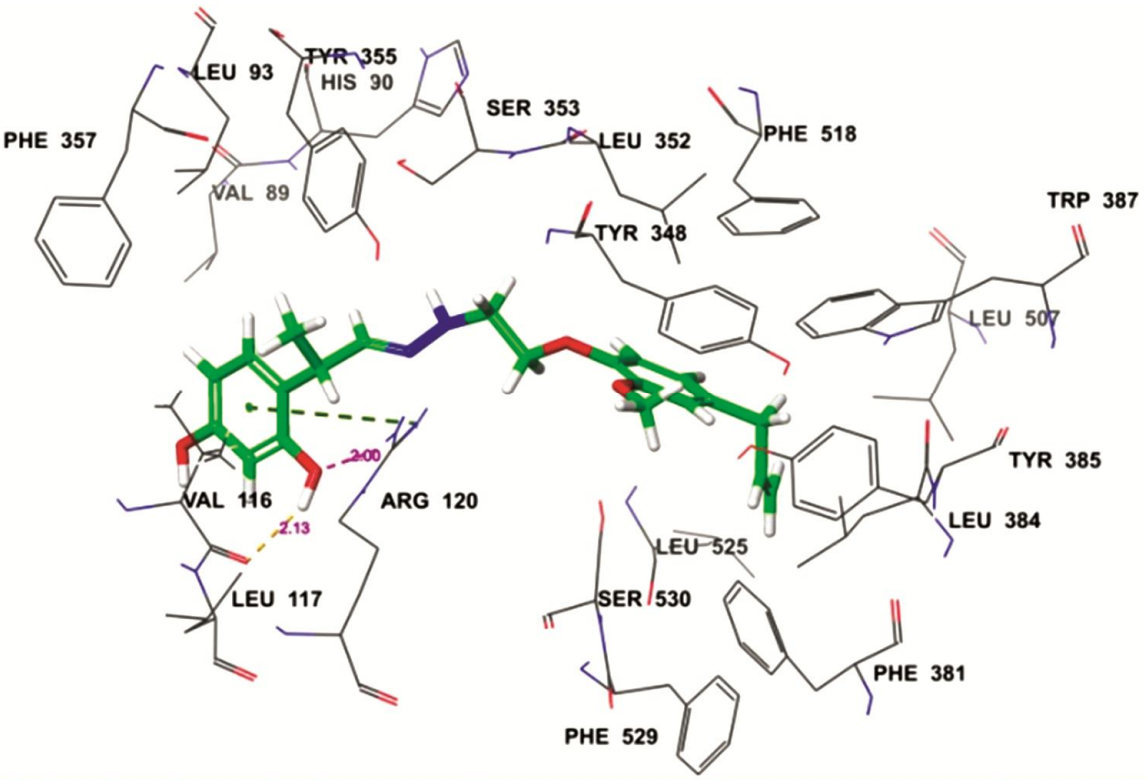


Figure 5 — The orientation of compound 4 in 4COX enzyme

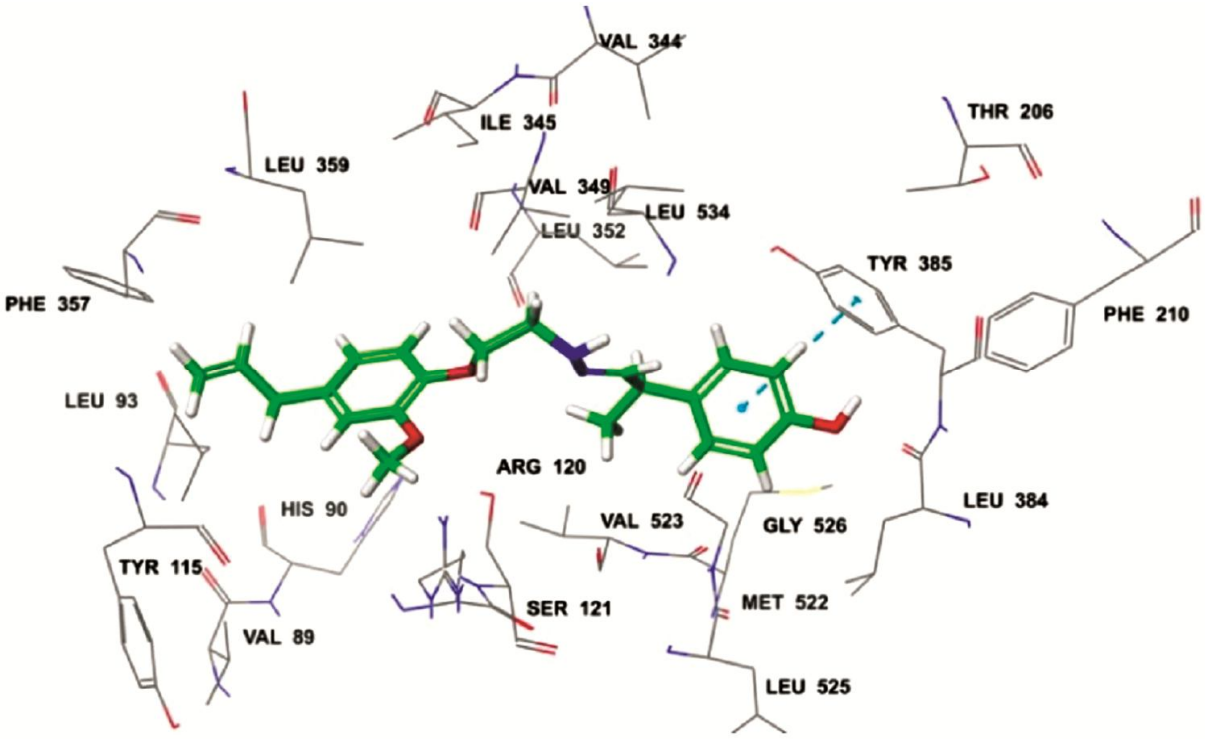


Figure 6 — The orientation of compound 42 in 4COX enzyme

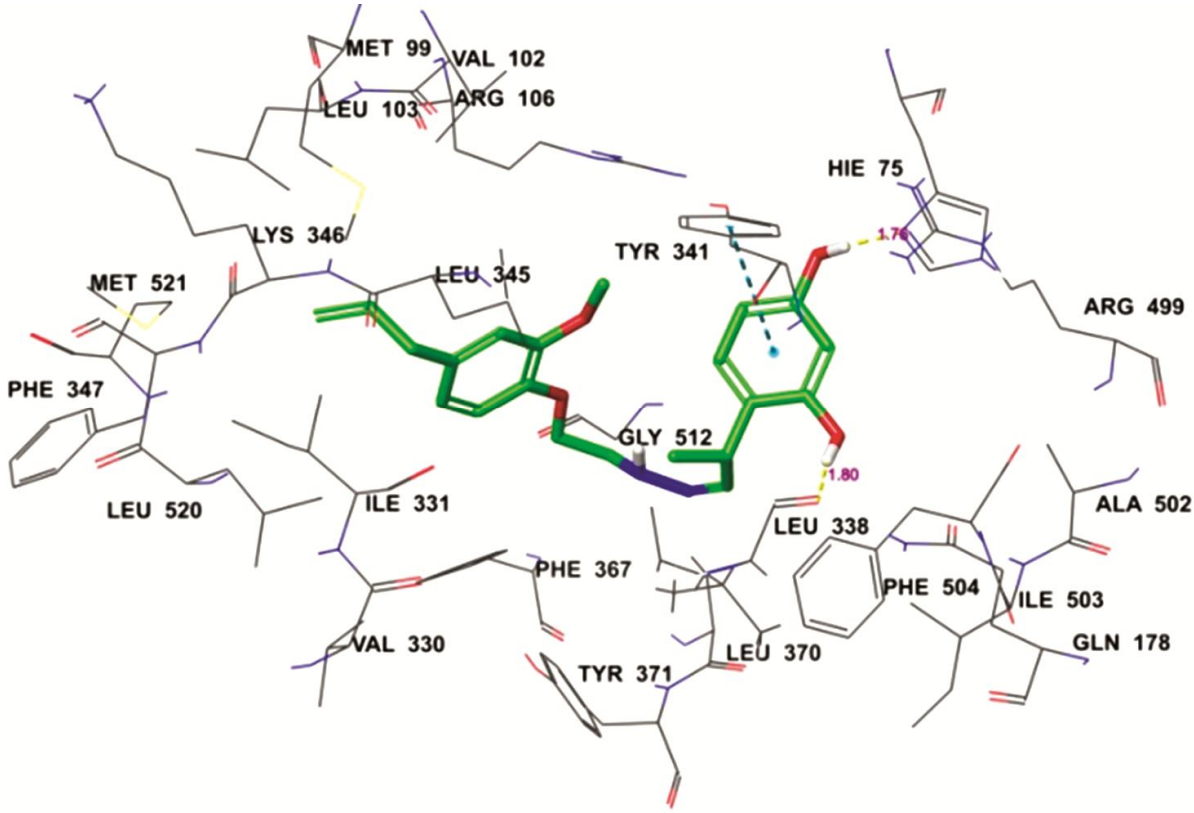


Figure 7 — The orientation of compound 4 in 3LN1 enzyme

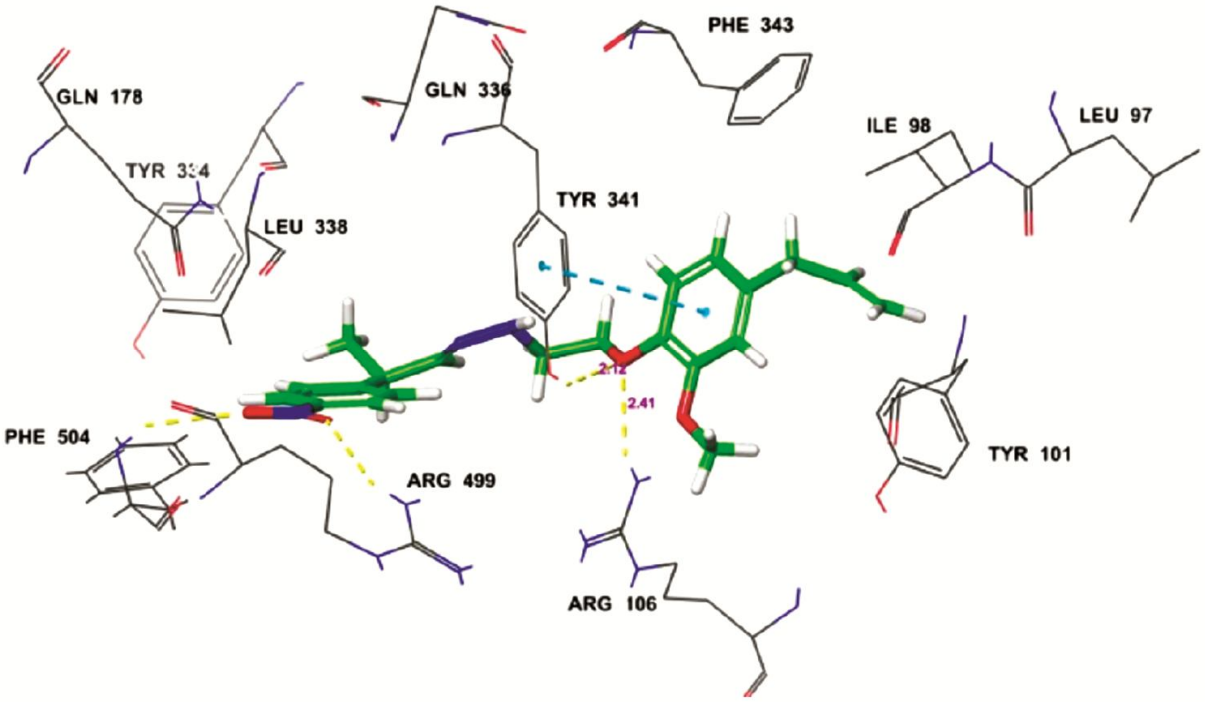


Figure 8 — The orientation of compound 43 in 3LN1 enzyme

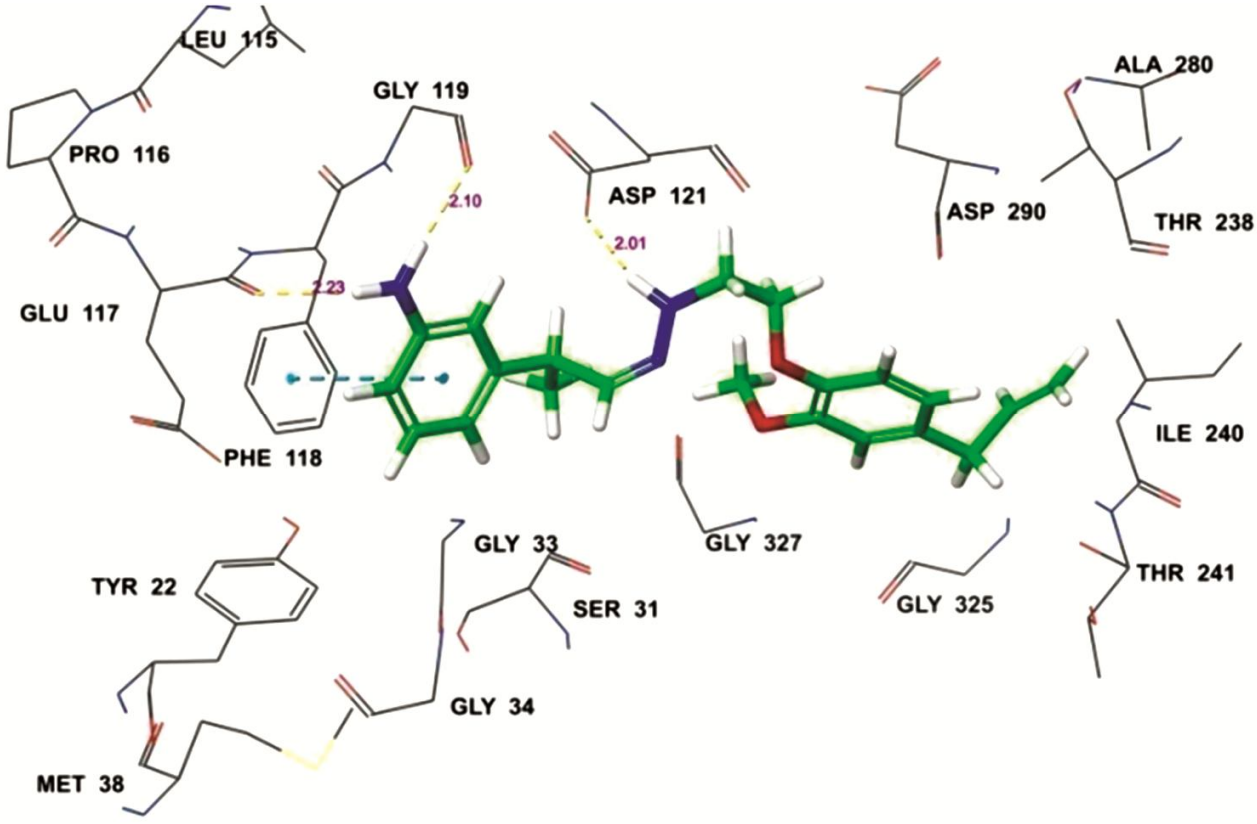


Figure 9 — The orientation of compound 30 in 4GCP enzyme

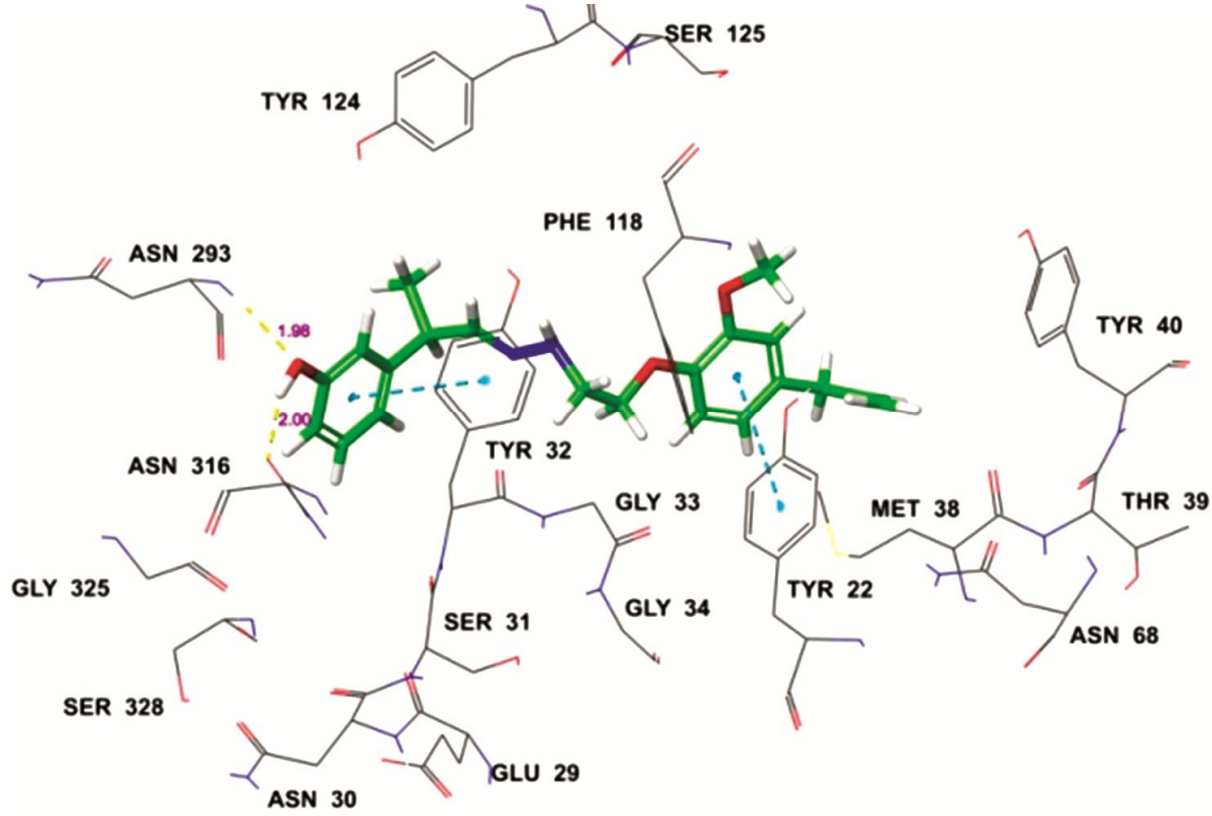


Figure 10 — The orientation of compound 34 in 4GCP enzyme

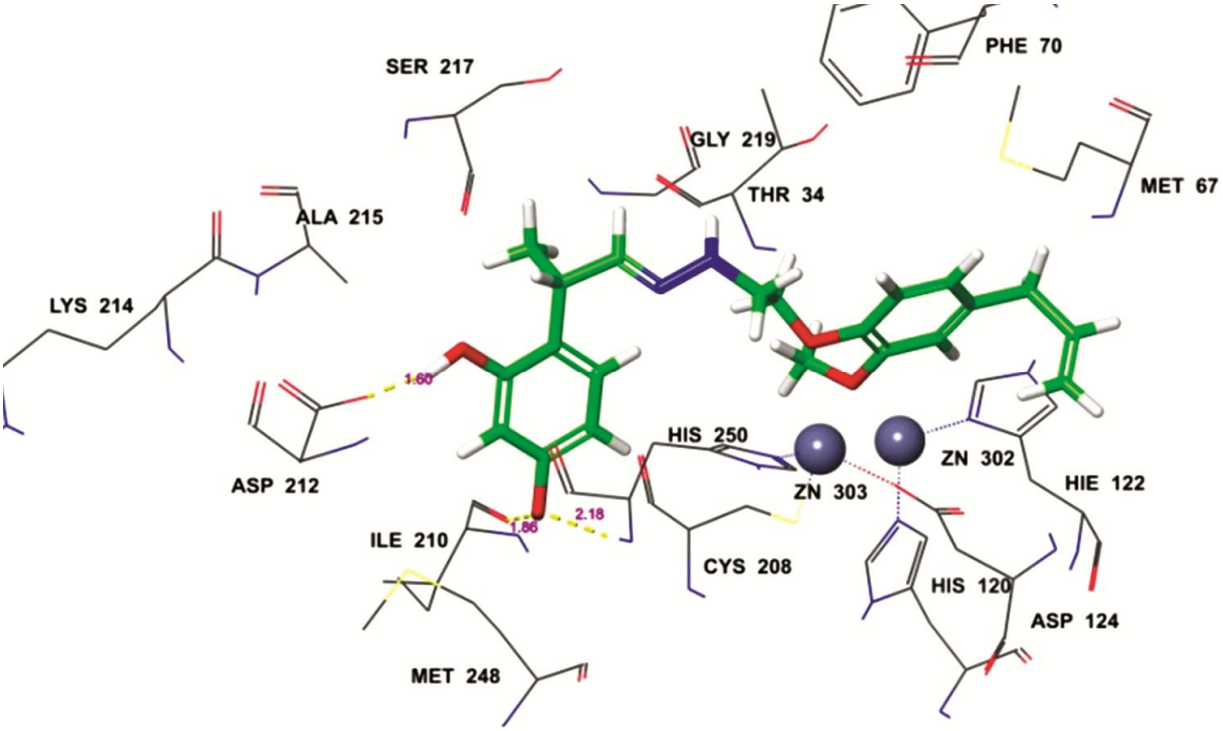


Figure 11 — The orientation of compound 4 in 4HL2 enzyme

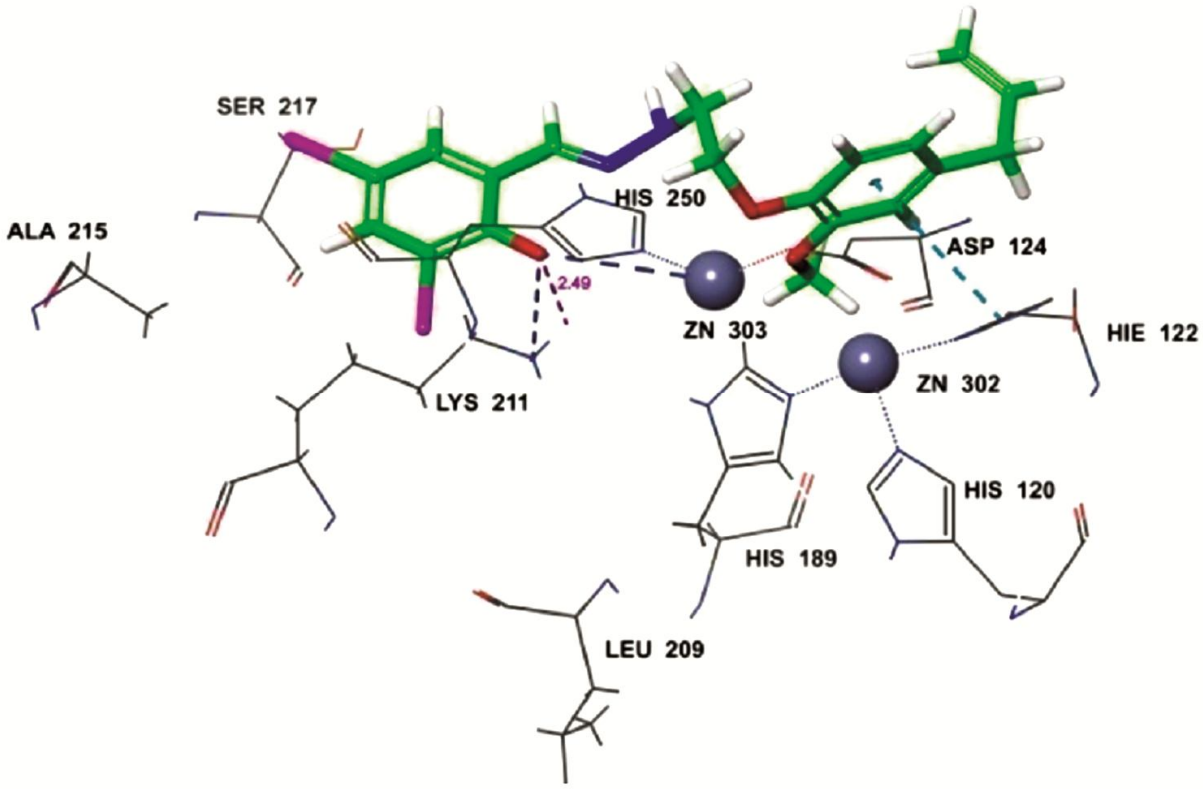


Figure 12 — The orientation of compound 18 in 4HL2 enzyme

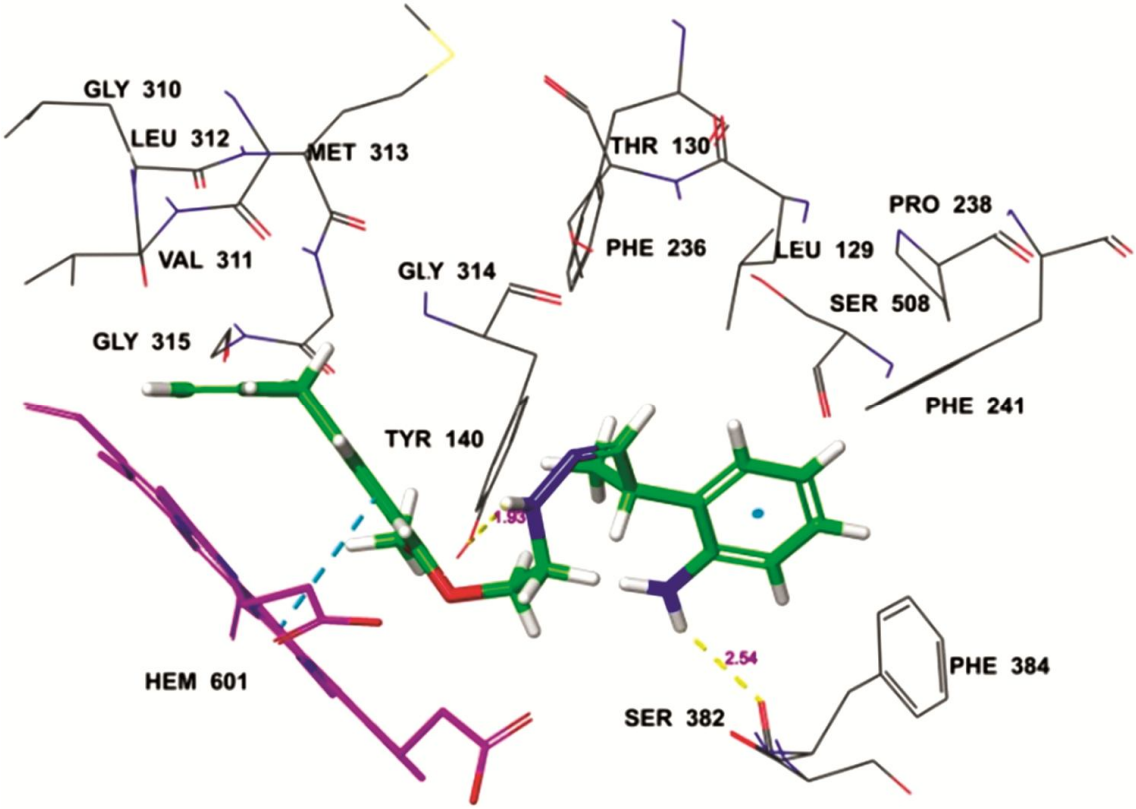


Figure 13 — The orientation of compound 11 in 4WMZ enzyme

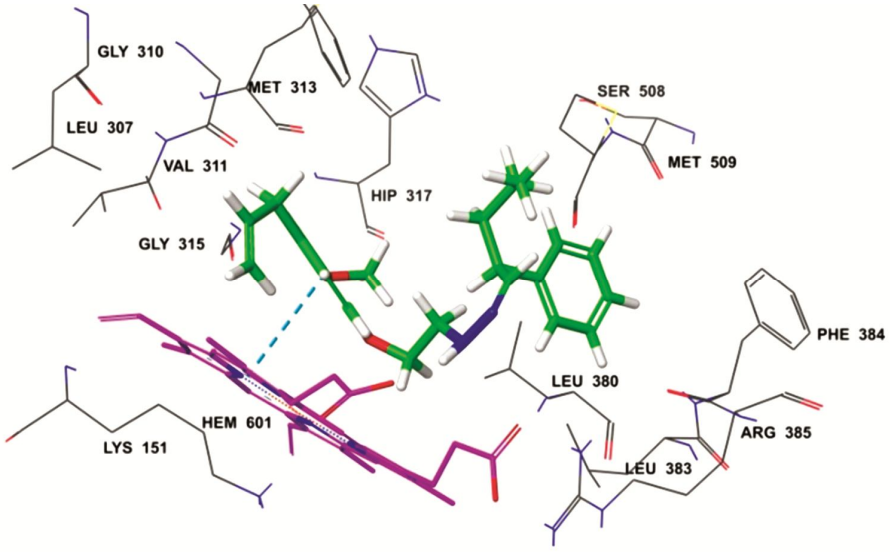


Figure 14 — The orientation of compound 47 in 4WMZ enzyme

Conclusion

Molecular docking has gaining consideration as an important tool for drug discovery. The molecular docking studies help in understanding the various interactions between the ligands and enzyme active sites in detail and thereby help to design novel hydrazones. The docking experiments were carried out for all the fiftyone compounds on seven enzymes and compared the docking score with reference compounds. The compounds 4, 5, 11, 18, 30, 34, 35, 37, 38, 42, 43, 44, 45, 46 and 47 showed higher binding score. These compounds are predicted for multiple pharmacological activities such as antitubercular, anti-inflammatory, antibacterial and antifungal.

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