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STRUCTURE BASED MOLECULAR DOCKING STUDIES ON SOME 1,3-DISUBSTITUTED UREA DERIVATIVES AS ANTI-TUBERCULAR AGENTS

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Keywords:

Docking , Glide, H-bond interaction, Tuberculosis, Docking score, Epoxide hydrolase, 1,3-disubstituted urea derivatives

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ABSTRACT: Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex and is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets and plays an important role in the rational design of drugs. The present study has been focused on the Docking studies of 1,3-disubstituted ureas derivatives as anti-tubercular agents that can explore the binding affinity of ligands to that of the epoxide hydrolase with the help of Schrodinger molecular modelling software. The G-score of the ligand 6s was found to be -8.03 as comparable with the G-score of co-crystallized ligand i.e. -3.77. The carbonyl oxygen of urea moeity of the ligand 6s showed a H-bond interaction with the phenolic oxygen of TYR381 and TYR465 amino acid of the protein residue with distances 2.24Å and 1.67Å respectively and the carbonyl oxygen of urea moeity of the co-crystallized ligand also showed a H-bond interaction with the phenolic oxygen of TYR381 and TYR465 amino acid of the protein residue with distances 2.24Å and 1.74Å respectively.

INTRODUCTION: Tuberculosis (TB) is a major health issue, especially in developing countries, that account for 95% cases and deaths worldwide according to the World Health Organization (WHO) [1]. Although TB appears as a chronic disease with comparatively slow development multidrug- resistant strains can kill immune compromised patients in very short periods of time [2]. Approximately 98% of human TB cases are caused by *Mycobacterium tuberculosis*.

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M tuberculosis grows slowly in culture, requiring an average of 2 to 3 weeks of incubation before growth can be detected. [3]. Rates of tuberculosis in Central Asia are extremely high [4]. Central nervous system (CNS) involvement occurs in 5–10% of extra pulmonary tuberculosis cases. [5].

In 2012, WHO estimated that 450 000 new cases of multidrug resistant (MDR) tuberculosis—defined as *Mycobacterium tuberculosis* resistant to at least Isoniazid and rifampicin—occurred worldwide [6]. Epoxides are three atom cyclic ethers formed by the oxidation of olefins [7]. Soluble epoxide hydrolase (sEH) is a ubiquitous enzyme that catalyzes the conversion of epoxides into the corresponding vicinal diols by the addition of water [8]. Epoxide hydrolases are widely spread in

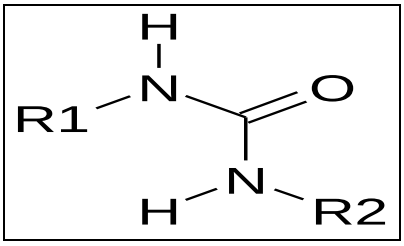
microorganisms. EHs are intracellular and constitutively expressed [7]. Based on the catalytic mechanism and structure of sEH 1,3-disubstituted ureas, amides and carbamate were found to be potent and stable competitive inhibitors of sEH [9]. Epoxide hydrolases are vital to many organisms by virtue of their roles in detoxification, metabolism and processing of signaling molecules [10]. The *Mycobacterium tuberculosis* genome encodes at least six epoxide hydrolases (EHs A to F) [11]. Suggesting that they might be of particular importance to these bacteria. [10].

Ligand-binding interactions are central to numerous biological processes signal transduction, physiological regulation, gene transcription and enzymatic reactions. These encompass both macromolecule complexes (e.g protein-protein and protein-DNA) and complexes of small molecules with macromolecules. A detailed understanding of interactions between small molecules and protein may therefore form the basis for a rational drug design strategy [12]. Molecular docking is playing an increasingly important role in lead discovery and design [13].

Protein–ligand docking is a key technology for in-silico screening and many protein–ligand docking programs have been reported [14]. Molecular docking is a structure-based computational technique is most commonly used in the field of drug design and docking may be applied to: hit identification, lead optimization and Bioremediation [15]. The docking algorithms suggest possible structures for molecular complexes. They are used to model biological function and to discover potential ligands [16].

The interaction of a drug molecule with its receptor protein is a complex event encompassing the interplay in entropy and enthalpy of many forces: conformational flexibility and electrostatic, hydrophobic, and van der Waals interactions [17]. Since the bioactive conformation of a bound ligand rarely corresponds to the isolated ligand X-ray structure, recent techniques have dealt with the issue of conformational flexibility [18]. Considering the importance of protein flexibility on ligand binding, recent research has explored ways of addressing the situation where the ligand and protein are flexible [19]. The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized [20, 21].

Molecular docking computationally screens thousands to millions of organic molecules against protein structures, looking for those with complementary fits [22]. Scoring functions are used to estimate the binding affinity of novel structures or an individual molecular fragment in a given position inside the receptor pocket [23]. In continuation of the research of molecular modelling, here in this paper we report the docking analysis of 1,3-disubstituted urea derivatives with epoxide hydrolase to explore favourable drug-receptor interaction.



MATERIAL AND METHODS:

Molecular Docking:

Selection of molecules and dataset:

A set of 40 molecules belonging to the class of urea derivatives reported by [24] was subjected to the docking analysis for their antitubercular activity. All docking studies were performed by the GLIDE module of Schrodinger Maestro 9.5 [25, 26]. The biological activity of the compounds was reported as IC50values (nM) and converted to pIC50 (LOG 1/ IC50) values. **Table 1** shows the structure of all 40 compounds along with their biological activity values.

Ligand preparation:

All the molecules of dataset were sketched in ISIS draw and saved in mol format. The set of molecules were then imported in the Ligprep workflow wizard. The energies of the molecules were the minimised using OPLS_2005.The ionisation was done with epik ioniser at pH 7.0 ± 2.0 and the conformers were generated. This is an automatic preparation process, performed with the LigPrep tool of the Schrödinger package.

Receptor preparation:

Epoxide hydrolase crystal structure was obtained from the protein data bank (PDB ID-1EK2) The PDB file was then imported into the protein preparation wizard. The PDB file was modified to include only chain A of the homodimer. The hydrogens were added and water molecules were deleted. The protein was then optimized and minimized under the refine section of the protein preparation wizard. All the parameters were set by default in the preparation wizard. The prepared protein file was then saved into the appropriate directory.

TABLE 1: STRUCTURE OF THE COMPOUNDS IN THE SERIES ALONG WITH THEIR BIOLOGICAL ACTIVITY

MOL	R1	R2	IC50	PIC50(nm)
1s	(2-Adamantyl)	(2,3,4-trifluorophenyl	0.4	9.397
2s	(1-Adamantyl)	(2,3,4-trifluorophenyl)	0.4	9.397
3s	(1-Adamantyl)methyl)	(2,3,4-trifluorophenyl	0.4	9.397
4s	Heptyl	(2,3,4-trifluorophenyl)	0.4	9.397
5s	(2,3,4-Trifluorophenyl)	(2,6,6-trimethylbicyclo[3.1.1]-heptan-3-yl	0.4	9.397
6s	((6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)methyl)	(2,3,4-trifluorophenyl)	0.4	9.397
7s	Cyclooctyl	(2,3,4-trifluorophenyl)	0.4	9.397
8s	Cyclohexyl	(2,3,4-trifluorophenyl)	1.2	8.920
9s	Cyclopentyl	(2,3,4-trifluorophenyl)	56.2	7.250
10s	(2-Adamantyl)	(4-cyanophenyl	1.1	8.958
11s	(2-Adamantyl)	phenethyl	4.5	8.346
12s	(3-Acetylphenyl)	(2-adamantyl)	0.5	9.301
13s	(2-Adamantyl)	benzyl	14.8	7.829
14s	(2-Adamantyl)	(3-chloro-2-methylphenyl)	4.5	8.346
15s	(2-Adamantyl)	isopropyl	84.4	7.073
16s	(2-Adamantyl)	tert-butyl	24.2	7.616
17s	(2-Adamantyl)	propyl	61.4	7.211
18s	(2-Adamantyl)	cyclohexyl	0.4	9.397
19s	(2-Adamantyl)	pentyl	6.4	8.193
20s	(2-Adamantyl)	hexyl	1.0	9.000
21s	(2-Adamantyl)	heptyl	0.5	9.301
22s	(1-(1-Adamantyl)methyl)	(3-chloro-4-methylphenyl)	0.4	9.397
23s	(3-Chloro-4-methylphenyl)	heptyl	1.6	8.795
24s	(3-Chloro-4-methylphenyl)	cyclooctyl	0.4	9.397
25s	(3-Chloro-4-methylphenyl)	(3-fluorobenzyl)	16.6	7.779
26s	(3-Chloro-4-methylphenyl)	(4-phenylbutan-2-yl)-	15.0	7.823
27s	(2-Fluoro-3-(trifluoromethyl)phenyl)	heptyl	0.4	9.397
28s	Cyclooctyl	(2-fluoro-3-(trifluoromethyl)phenyl)	0.4	9.397
29s	(2-Fluoro-3-(trifluoromethyl)phenyl)	(4-phenylbutan-2-yl)	1.9	8.721
30s	(3-Chlorobenzyl)	(2-fluoro-3-(trifluoromethyl)-phenyl)	3.7	8.431
31s	(2-Adamantyl)	(2,3,4-trifluorophenyl)thio	4.8	8.318
32s	Adamantyl	2,3,4-trifluorophenylcarbamate	463.8	6.333
33s	(2-Adamantyl)	methyl-3-(2,3,4-trifluorophenyl)	38.1	7.419
34s	(2-Adamantyl)-1,3-dimethyl	(2,3,4-trifluorophenyl)	1838.1	5.735 7.844
35s	(2-Adamantyl)	(4-methoxyphenyl)	14.3	8.920
36s	Methyl 4-(3-(1-adamantyl)ureido)	-2-hydroxybenzoate	1.2	6.280
37s	(1-Adamantyl)	(2-ethoxyethyl)	524.8	6.413
38s	(1-Adamantyl)	(3-methoxypropyl)	386.1	6.584
39s	(1-Adamantyl)	(2-isopropoxyethyl)	260.4	6.615
40s	(1-Adamantyl)	(2-propoxyethyl)	242.6	

Receptor grid generation:

Then receptor grid was generated around the binding site. For receptor grid generation, centroid of the workspace ligand was selected by picking and excluding the co-crystallized ligand from the binding site.

Ligand Docking:

Molecular docking experiments were carried out by means of the Glide, as implemented in the Schrodinger [7]. A cubing receptor grid was centered around the co-crystallized ligand where the active binding site is present. The XP (extra precision) scoring function of GLIDE 6.0 was used and lastly the docking job was run. The scoring function of GLIDE docking program is presented in the G-score form. G-score indicates the binding affinity of the designed compound to the receptor/enzyme.

G Score = 0.05*vdW + 0.15*Coul + Lipo + H bond + Metal + Rewards + RotB + Site.

where, vdW, Van der Waal energy; Coul, Coulomb energy; Lipo, lipophilic contact term; H Bond, hydrogen-bonding term; Metal, metal-binding term; Bury P, penalty for buried polar groups; Rot B, penalty for freezing rotatable bonds; Site, polar interactions at the active site [27].

RESULTS AND DISCUSSION:

Docking Studies:

The docking studies were carried out to explore the interaction between inhibitors and the receptor. The final evaluation is done with glide score (docking score) and best pose is generated as the output. The 3D view of epoxide hydrolase (EH) is shown in **Fig.1**.

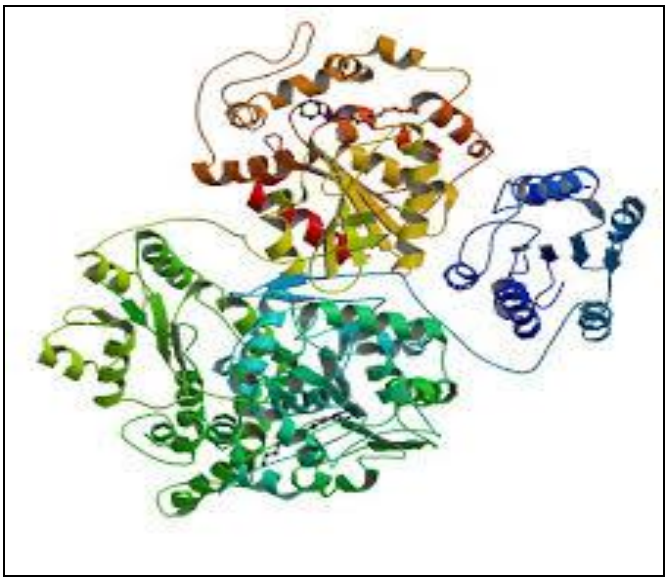


FIG. 1: 3D VIEW OF EPOXIDE HYDROLASE (PDB ID-1EK2)

The most active compound in the training set has scored a best docking score value of -8.03. It has formed an interaction with TYR381 and TYR465. The Glide scores and other solutions of protein-ligand complexes obtained from docking calculations for selected compound are listed in **Table 2**.

TABLE 2: DOCKING SCORES AND OTHER SOLUTIONS OBTAINED FOR THE MOST ACTIVE LIGAND4

Ligand	6s
GScore	-8.03
LipophilicEvdW	-2.94
PhobEn	-2.65
PhobEnHB	0
PhobEnPairHB	0
HBond	-1.12
Electro	-0.74
Sitemap	-0.53
PiCat	0
ClBr	0
LowMW	-0.41
Penalties	0.07
HBPenal	0
ExposPenal	0
RotPenal	0.3

The various Glide XP terms used can be described as:

G Score: Total Glide Score; sum of XP terms

Lipophilic EvdW: Lipophilic term derived from hydrophobic grid potential at the hydrophobic ligand atoms.

Phob En: Hydrophobic enclosure reward.

PhobEnHB: Reward for hydrophobically packed H-bond.

PhobEn Pair HB: Reward for hydrophobically packed correlated H-bonds.

H bond: Chem Score H-bond pair term.

Electro: Electrostatic rewards; includes Coulomb and metal terms.

Site Map: Site Map ligand-receptor non-H bonding polar-hydrophobic terms.

π Cat: Reward for pi-cation interactions.

ClBr: Reward for Cl or Br in a hydrophobic environment that pack against Asp or Glu.

Low MW: Reward for ligands with low molecular weight.

Penalties: Polar atom burial and desolvation penalties, and penalty for intra-ligand contacts.

HB Penal: Penalty for ligands with large hydrophobic contacts and low H-bond scores.

Expos Penal: Penalty for solvent-exposed ligand groups; cancels vander Waals terms.

Rot Penal: Rotatable bond penalty.

The ligand protein interaction in 2D view is shown in **Fig.2** and **Fig.4** shows the 3D view of docking of ligand into binding pockets of EH.

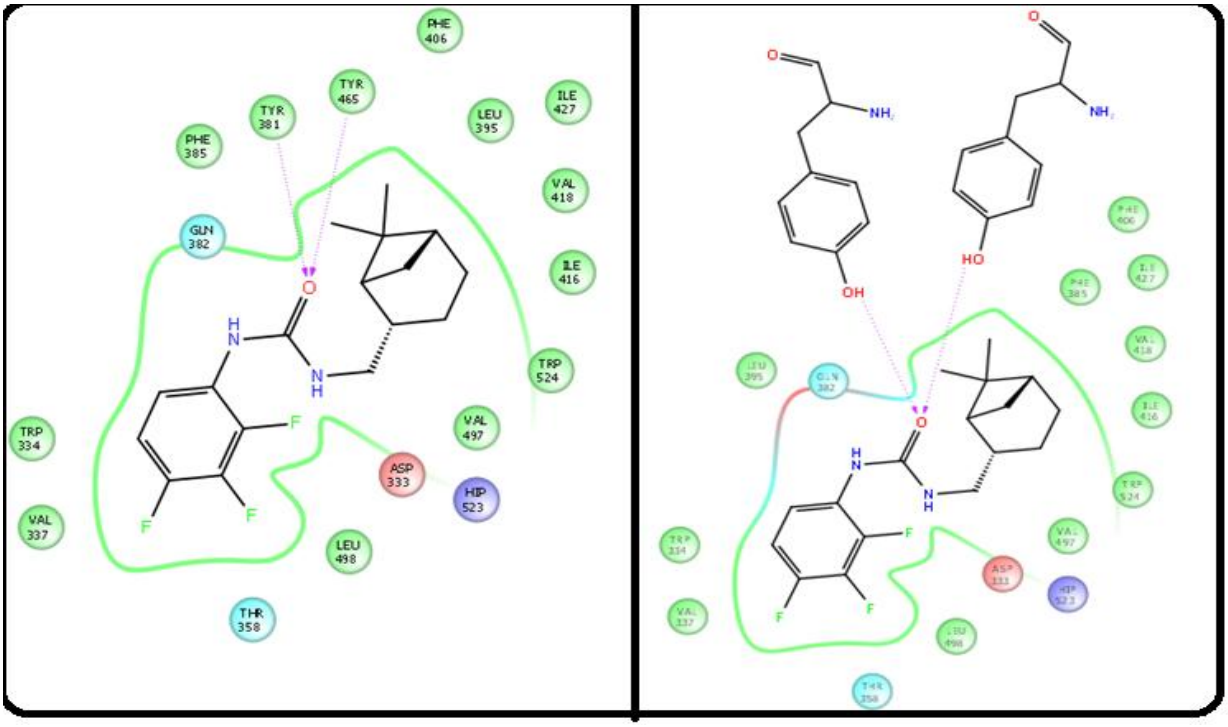


FIG. 2: DOCKING INTERACTION POSE OF MOST ACTIVE LIGAND (6S) WITH EPOXIDE HYDROLASE.

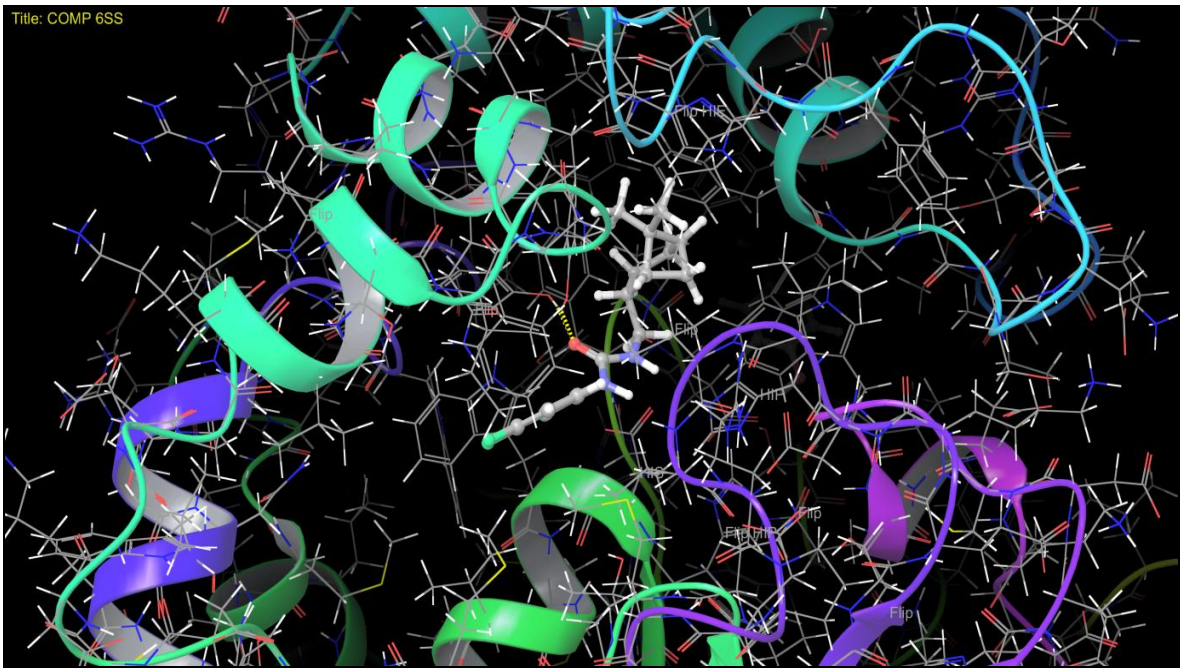


FIG. 4: THE BINDING POCKET OF EH (PDB ID: 1EK2) WITH THE MOST ACTIVE COMPOUND 6S.

To validate the docking protocol, co-crystallized ligand (CDU: N-CYCLOHEXYL-N'-DECYLUREA) itself was docked into the active site of epoxide hydrolase (1EK2). The Glide scores and other solutions of protein-ligand complexes obtained from docking calculations for selected compound are listed in **Table 3**.

TABLE 3: DOCKING SCORES AND OTHER SOLUTIONS OBTAINED FOR THE CO-CRYSTALLIZED LIGAND

Ligand	Reference
G Score	-3.7769
LipophilicEvdW	-2.275
PhobEn	-1.2
PhobEnHB	0
PhobEnPair HB	0
H Bond	-1.16354
Electro	-0.59854
Sitemap	0
Pi Cat	0
ClBr	0
Low MW	-0.5
Penalties	0.015702
HB Penal	0
Expos Penal	0.118857
Rot Penal	1.943855

The ligand protein interaction in 2D view is shown in **Fig.3** and **Fig.5** shows the 3D view of docking of co-crystallized ligand into binding pockets of EH.

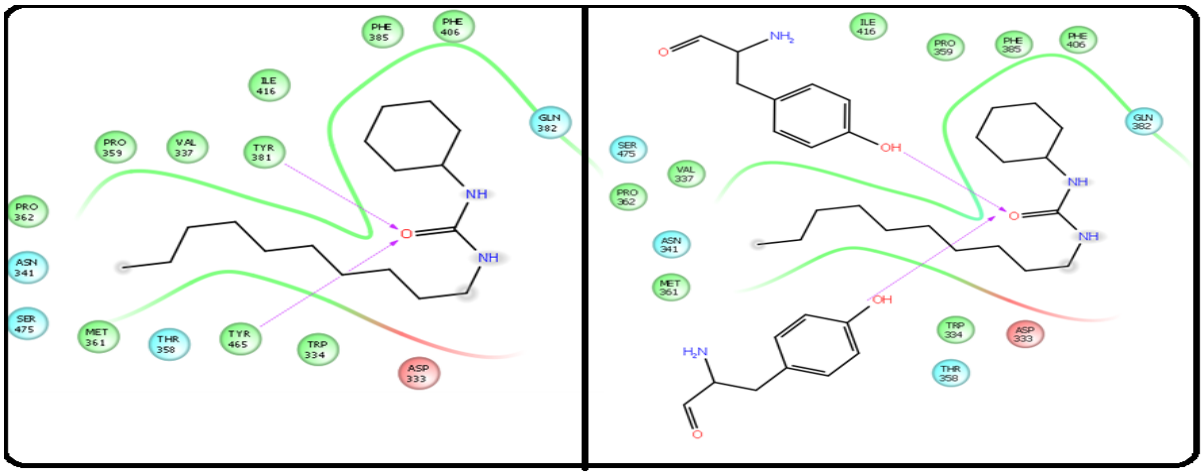


FIG. 3: DOCKING INTERACTION POSE OF CO-CRYSTALLIZED LIGAND WITH EPOXIDE HYDROLASE.

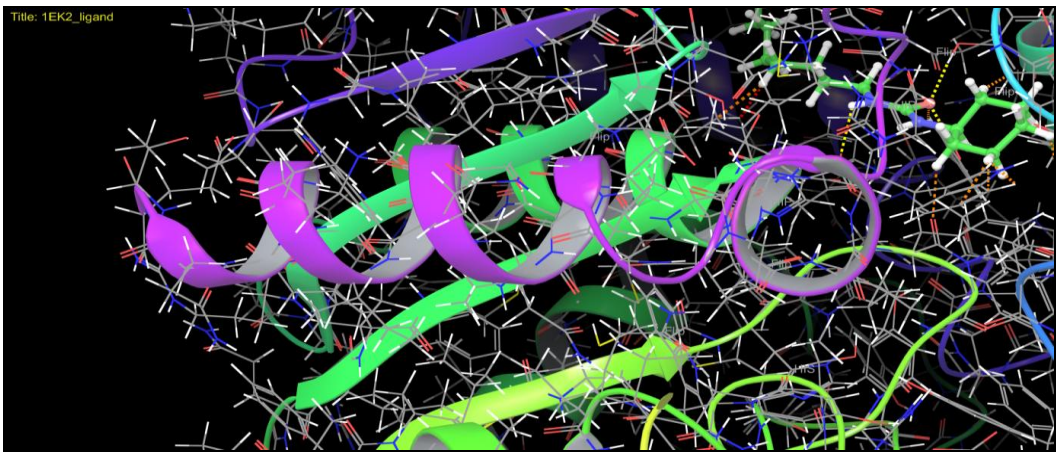


FIG.5: THE BINDING POCKET OF EH (PDB ID: 1EK2) WITH THE CO-CRYSTALLIZED LIGAND OF THE PROTEIN

Interactions in Docking:

A) Ligand 6s:

The carbonyl oxygen of urea moeity showed H-bond interaction (distance=2.24Å) with the phenolic oxygen of TYR381 amino acid of the protein residue. The carbonyl oxygen of urea moeity showed H-bond interaction (distance=1.67Å) with the phenolic oxygen of TYR465 amino acid of the protein residue. The lipophilic term (LipophilicEvdW) score, hydrophobic enclosure reward, electrostatic rewards were found to be -2.94,-2.65 and -0.74 respectively.

B) Co-crystallized Ligand:

The oxygen of carbonyl group of urea moeity showed a H-bond interaction (distance=2.2Å) with the phenolic oxygen of TYR381 amino acid of the protein residue. The carbonyl oxygen of urea moeity showed a H-bond interaction (distance=1.74Å) with the phenolic oxygen of TYR465 amino acid of the protein residue. The lipophilic term (LipophilicEvdW) score, hydrophobic enclosure reward, electrostatic rewards were found to be -2.275,-1.2 and -0.59854 respectively.

CONCLUSION: The binding interactions of the database epoxide hydrolase inhibitors in the active site were studied by molecular docking. The scoring function of GLIDE docking program is presented in the G-score form which indicates the binding affinity of the designed compound to the receptor/enzyme. The Gscore of the ligand 6s was found to be -8.03 as comparable with the G-score of reference drug i.e. -3.77. The present study aimed to develop ligand based pharmacophore hypothesis and a interaction pattern by docking. The carbonyl oxygen of urea moeity of ligand 6s interacts with and orients the carboxylate oxygen of the tyrosine381 residues and showed H-bond interaction (distance=2.24) while the carbonyl oxygen of urea moeity of co-crystallized ligand interacts with and orients the carboxylate oxygen of the tyrosine381 residues and showed H-bond interaction (distance=2.20).

Also the carbonyl oxygen of urea moeity of ligand 6s interacts with and orients the carboxylate oxygen of the tyrosine465 residues and showed H-bond interaction (distance=1.67) while the carbonyl oxygen of urea moeity of co-crystallized ligand interacts with and orients the carboxylate oxygen of the tyrosine 465 residues and showed a H-bond interaction (distance=1.74).

These studies have opened a path for the development of potent inhibitors with good pharmacokinetic profiles against all *Mycobacterium tuberculosis* EHs of the α/β type and provided crucial clues and guidance that can be used in the successful designing of novel highly active analogues against epoxide hydrolase enzyme which is widely spread in microorganism.

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