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Original Research Paper

QSAR STUDIES OF FabH INHIBITORS USING GRAPH THEORETICAL & QUANTUM CHEMICAL DESCRIPTORS

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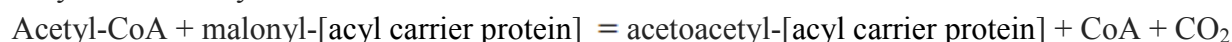
ABSTRACT

FabH plays a regulatory role for the whole pathway of fab cycle. FabH has also been found to be essential for an organism's survival and it is present in a wide number of important human pathogens. Regression model developed in this work may be essential step for further development in designing and synthesis of good FabH inhibitors as antibacterial agents.

Keywords: Antibacterial resistance, Drug designing, FabH inhibitors, Graph theoretical indices, Quantum chemical indices, Regression model, Docking.

INTRODUCTION

Resistance to known antimicrobial therapies for bacteria poses an enormous threat to public health. An increasing fraction of bacterial isolates would show a reduced susceptibility to our most trusted antibiotics. One of the keys to overcome this menace is to expand the bioactivity of the prevalent drugs and identify antibacterial agents with a novel mode of action toward a new target enzyme.¹ The bacterial fatty acid biosynthesis (fab) pathway has been shown to be essential for cell growth²⁻⁶ and may provide us with one such target in antibiotic research. This biosynthetic pathway has been studied primarily in *Escherichia coli*.^{7,8} Many gram positive organisms such as *bacilli*, *staphylo-cocci*, *streptomyces*, produce odd-and even-carbon number branched chain fatty acid. These branched chain fatty acid structures have either iso or anteiso-methyl branches.⁹⁻¹² In bacteria, plants, and animals, fatty acid biosynthesis is carried out by the ubiquitous fatty acid synthase (FAS) I system. It is an essential and universal process for generation of cell membrane and maintenance.^{13,14} The key enzyme responsible for initiation of bacterial fatty acid biosynthesis cycle is β -ketoacyl-[acyl-carrier-protein] synthase III, commonly known as FabH enzyme that catalyzes the chemical reaction:



FabH plays a regulatory role for the whole pathway of fab cycle.

FabH has also been found to be essential for an organism's survival and it is present in a wide number of important human pathogens. In humans, a single multifunctional enzyme carries out fatty acids synthesis, whereas in bacteria the pathway involves various enzymes, which can be separately considered to be putative targets.¹⁵ This major difference between bacterial and mammalian fatty acids synthesis pathways make this enzyme an excellent target for selective inhibition of bacterial growth and has been considerable interest in development of FabH inhibitors as antibacterial agents. The most active inhibitor of *Mycobacterium tuberculosis* and *E. coli* FabH enzymes is disulfide.¹⁴ These compounds exert their activity by capping an active site cysteinethiol by silylation, thus destroying the catalytic function of

enzyme. FabHs from different bacterial species show different substrate specificity for the acyl-CoA primer: the *E. coli* and *M. tuberculosis* enzymes (ecFabH and mtFabH respectively) are specific for acetyl-CoA and lauroyl-CoA, respectively.¹⁶ This specificity is conferred by the size and shape of the acyl binding pockets of these enzymes, which have been determined from crystal structures.¹⁷ 2-Tosyl-naphthalene-1-4-diol was identified as potent inhibitor of plasmodium falciparum FabH (PfFabH) through a virtual screening using a pharmacophore. Based on thiolactomycin¹⁸, it was developed. A further study on 2-Tosyl-naphthalene-1-4-diol, a series of more potent Sulfonylnaphthalene-1-4-diol inhibitors has been developed. The naphthalene-1-4-idol portion has been identified for activity against all three FabH enzymes. In this article, 35 inhibitors had been considered for quantitative structure activity relationship (QSAR) and it was found that the geometry of the structure is important for activity rather than the quantum chemical property. *M. tuberculosis*, the cause of tuberculosis, evades effective immune clearance through encapsulation, especially with mycolic acids that are particularly resistant to the normal degradative processes of macrophages. Furthermore, this capsule inhibits entry of antibiotics. The enzymes involved in mycolate biosynthesis are essential for survival and pathogenesis, and thus, as such represent excellent drug targets.

In *M. tuberculosis*, the beta-ketoacyl-[acyl-carrier-protein] synthase III enzyme is designated as mtFabH and is a crucial link between the fatty acid synthase-I and the fatty acid synthase-II pathways producing mycolic acids. FAS-I is involved in the synthesis of C₁₆ and C₂₆ fatty acids. The C₁₆ acyl-CoA product acts as a substrate for the synthesis of meromycolic acid by FAS-II, whereas the C₂₆ fatty acid constitutes the alpha branch of the final mycolic acid. MtFabH has been proposed to be the link between FAS-I and FAS-II by converting C₁₄-CoA generated by FAS-I to C₁₆-AcpM, which is channeled into the FAS-II cycle.¹⁹ According to *in silico* flux balance analyses²⁰, mtFabH is essential but not according to transposon site hybridization analysis.²¹ Unlike the enzymes in FAS-I, the enzymes of FAS-II, including mtFabH, are not found in mammals, suggesting that the inhibitors of these enzymes are suitable choices for a possible drug development endeavour.

In this work, we intend to find a correlation between pharmacological activity and different molecular descriptors of chemicals by constructing regression model for activity. In our study, the molecular docking simulation was carried out to predict the strength of association or binding affinity of ligands with protein. AutoDock has been bench-marked for a fast as well as an accurate prediction of bound conformations and binding energies of ligands with protein. This study also aims to enhance the path to the development of a new generation of FabH inhibitors.

MATERIAL AND METHODS

Calculation of Indices

Chemical structure of 44 compounds of β -ketoacyl-[acyl-carrier-protein] synthaseIII (FabH) inhibitors and their biological activity in IC₅₀²² in nM unit of derivatives has been collected from the site Binding db (www.bindingdb.org).²³⁻²⁵ The next step in developing a model is generation of the numerical descriptors of molecular structures. Calculations of molecular descriptors like HOMO energy, LUMO energy, Dipole moment²⁶⁻²⁸ and polarisability²⁹⁻³⁰ of FabH inhibitors are performed by DFT/B3LYP calculation using the Gamess³¹ suite and the basis set, namely, 6-31G (d) was used. The one lipophilic parameters logP³² is calculated by Mervine LogP³³ calculator and another parameter, Molar Volume (MV) was calculated using ACDLABS 10.0.³⁴ The graph theoretical indices like Wiener index³⁵, Harary index³⁶, Randic³⁷ connectivity index and Balaban³⁸ index were calculated by utilising our own code written in F77, after suitable modifications made for this purpose.

Docking Study

We have performed docking study with the ligand of the enzyme 3IL9 (β -ketoacyl-[acyl-carrier-protein] synthaseIII) (FabH) by using Autodock 4. The amino acid residues 209ASN, 203PHE, 303PHE, 248ARG

lies within the 3Å⁰ range from the binding site of 3IL9. All the amino acid residues within 3Å range are initially taken as flexible residue and docking was performed with compound 35. The lowest binding energy was obtained for 209ASN. (-8.03 kcal/mol) which also lies within 2.5Å⁰ from the binding site. Thus, we consider 209ASN as the flexible residue in this docking study. We have obtained the binding energy of docking of 35 compounds (compound no. 1 to 35) given in Table 1. Here we represent two docked images; compound 15 and compound 24 with their nearest neighbours. Figure 1 represents the docked image of compound 15, which binds to the region of the enzyme involving 82Ser, 508Asn, 83Ala, 509Ala, 81Thr, 510Asp, 50Thr, 48Asn and 47Pro. It has single hydrogen bonds with 47Pro, which also lies well inside the protein. Figure 2 presents docked image of compound 24 which binds to the region of enzyme involving 511Arg, 83Ala, 84Thr, 512Val, 85Thr, 513Asn, 510Asp. It has two hydrogen bond with 510Asp and 513Asn.

RESULTS

We have applied a Multiple Linear Regression technique to develop the QSAR model and to predict the inhibition of the selected compounds in the present study. Thirty-five inhibitors have been taken as the training set. The graph theoretical and quantum chemical indices of 35 training compounds are given in Table 1. Chemical structure of 35 training compounds are presented in table 2 and that of test set in table 3. Quantum chemical and graph theoretical parameters of test compounds are presented in table 4

DISCUSSION

To see the effect of binding energy on their activity we constructed Model 1.

Model 1: Regression model with binding energy

$$\ln IC_{50} = 7.533845 + (-0.1433)BE$$

$$R=0.044, F= 0.032$$

This model shows a very lower correlation coefficient and F value. Thus only binding energy can not specify the cytotoxic activity of these set compounds clearly. So there must be other factor which we have to incorporate with binding energy for getting better model.

In our stepwise regression analysis we have also developed two different models with quantum chemical descriptors (model 2) and geometrical descriptors (model 3). It shows that the model with graph theoretical (geometrical) descriptors have a better correlation and F value than that of the quantum chemical descriptors. The models are given below.

Model 2: Regression model with quantum chemical descriptors

$$\ln IC_{50} = 15.3435 + (-0.8373)HOMO + 56.7803LUMO + (-1.0451)DM + (0.2202) \log P$$

$$R= 0.65, F=11.89$$

Model 3: Regression model with graph theoretical descriptors

$$\ln IC_{50} = -44.7298 + 40.3309MV + (-14.9121) \ln \chi^0 + (-8.2253)J + (-27.6590) \ln H + 0.8919 \ln W$$

$$R= 0.77, F= 21.5568$$

Finally, we combined these three aspects and constructed Model 4, which shows a better correlation than that of the other three models.

$$\begin{aligned} \ln IC_{50} = & -97.75009 + 22.0908HOMO + 97.8535LUMO + (-0.4514)DM + (-1.9098) \log P + \\ & 53.8173MV + (-1.9810)BE + (-35.6588) \ln \chi^0 + (-3.2256)J + (-30.4665) \ln H + \\ \text{Model 4: } & 7.5841 \ln W \end{aligned}$$

$$R= 0.89, F= 61.52$$

To judge the credibility of the regression model, we have performed a cross validation test with loo (Leave one out) scheme. The obtained value was 0.52. Predicted activity according to model 4 and the

corresponding experimental values of the activity are given in table 5. The correlation graph is presented in figure 1.

CONCLUSIONS

In this study, by observing different regression models by choosing the different number and types of parameters, it was found that there is a lower correlation coefficient with binding energy. Graph theoretical descriptors has better correlation and F value than that of the quantum chemical descriptors. By combining these three aspects, best result has been found. Therefore, it would be advantageous to use all types of molecular descriptors.

ACKNOWLEDGEMENTS

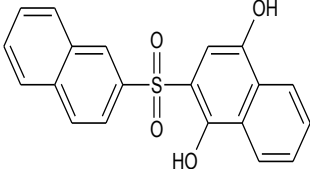
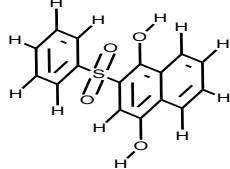
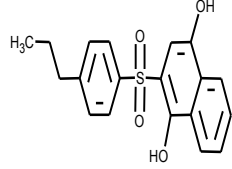
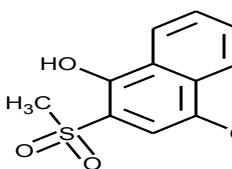
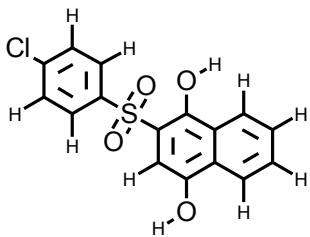
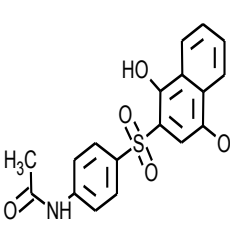
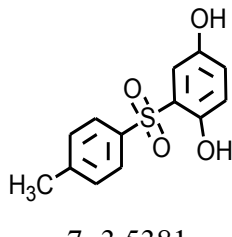
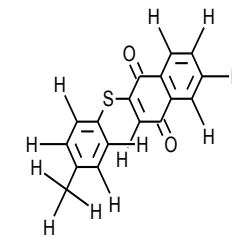
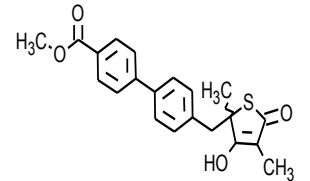
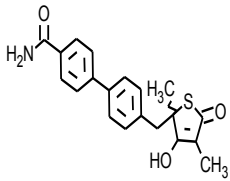
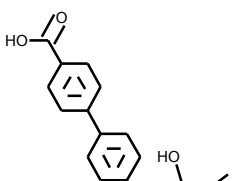
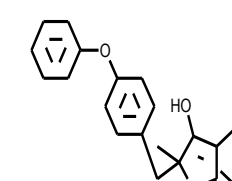
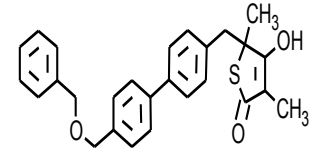
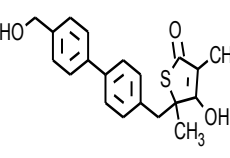
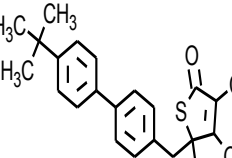
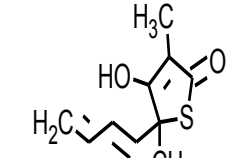
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Table 1: Graph theoretical and quantum chemical parameters of 35 compounds under study

S. No.	HOMO	LUMO	DM	LogP	MV	BE	LnR	J	LnH	LnW	LnIC ₅₀
1	-0.261	-0.1248	5.2518	2.75	5.4116	-8.91	2.7053	1.74	4.3766	6.8875	0.6881
2	-0.2039	-0.0545	6.2755	3.96	5.3408	-7.16	2.7245	1.54	4.313	6.7405	0.6881
3	-0.2019	-0.0544	7.7402	5.36	5.5529	-8.14	2.9423	1.54	4.4845	7.1815	1.1281
4	-0.2112	-0.0582	7.8786	1.85	5.0882	-6.11	2.4697	1.91	3.908	5.9635	1.2613
5	-0.2094	-0.0607	5.5847	4.56	5.3968	-8.03	2.7245	1.74	4.3766	6.8875	1.2837
6	-0.2119	-0.0605	7.5871	3.2	5.4881	-8.46	2.9058	1.47	4.539	7.3105	1.3244
7	-0.2227	-0.0389	7.05	3.48	5.2517	-6.15	2.6128	1.9301	4.0561	6.3595	3.5381
8	-0.2129	-0.1059	1.0448	3.77	5.3645	-8.76	2.6825	1.4431	4.205	6.7019	4.7185
9	-0.2256	-0.051	5.8703	4.71	5.6726	-8.86	3.0258	1.4377	4.5502	7.5496	8.0064
10	-0.2222	-0.0429	7.4879	3.58	5.6043	-7.95	2.9876	1.2891	4.4992	7.4277	8.294
11	-0.2302	-0.0527	6.1905	4.38	5.5812	-7.22	2.9686	1.2891	4.4992	7.4277	8.8537
12	-0.223	-0.0263	6.2056	4.56	5.5537	-8.11	2.9177	1.3802	4.3754	7.1929	9.6158
13	-0.161	-0.0257	5.7195	6.31	5.8659	-8.35	3.243	0.9885	4.7706	8.1303	9.741
14	-0.2095	-0.0264	5.7249	3.94	5.5861	-7.78	2.9851	1.3457	4.4421	7.3058	9.8522
15	-0.2032	-0.0291	5.134	6.25	5.767	-9.17	3.1345	1.4525	4.5585	7.5374	10.1266
16	-0.2235	-0.0317	4.3998	2.3	5.0549	-6.44	2.4091	2.3842	3.5424	5.4806	10.1266
17	-0.229	-0.0224	4.2568	4.6	5.5385	-7.78	2.9088	1.8984	4.1931	6.731	10.669
18	-0.1833	-0.1833	1.8677	3.77	5.2369	-12.3	2.6061	2.4189	3.7521	5.8971	10.8198
19	-0.22	-0.0255	5.52	4.71	5.5329	-7.92	2.8929	1.4932	4.3269	7.0299	10.8396
20	-0.2203	-0.0267	6.1228	5.22	5.5954	-8.14	2.9563	1.4187	4.3877	7.1685	10.859
21	-0.2175	-0.0256	6.3232	4.56	5.5537	-8.58	2.9177	1.4586	4.3877	7.1388	10.859
22	-0.2234	-0.0486	6.3966	4.26	5.6503	-8.79	3.0026	1.2891	4.4992	7.4277	10.8967
23	-0.2111	-0.0278	1.8877	7.13	5.7365	-7.3	3.1112	2.0708	4.1745	7.0544	11.0821
24	-0.207	-0.0387	4.5991	6.35	5.7626	-9.57	3.1205	1.1676	4.6601	7.7676	11.1273

25	-0.1627	-0.0356	3.6996	3.38	5.1538	-6.05	2.5124	2.6558	3.661	5.6698	11.2239
26	-0.211	-0.0266	1.731	6.24	5.624	-6.71	2.9931	2.1839	4.053	6.7068	11.2252
27	-0.2107	-0.0267	1.5782	8.1	5.8435	-6.92	3.2168	1.8364	4.2556	7.4324	11.2898
28	-0.2054	-0.026	4.7445	5.13	5.5556	-8.03	2.8842	1.4975	4.3291	7.029	11.3621
29	-0.2057	-0.0338	1.8643	3.38	5.1538	-6.01	2.5124	2.6558	3.661	5.6698	11.3737
30	-0.2206	-0.0272	4.6576	4.85	5.5494	-6.94	2.8912	1.4187	4.3877	7.1685	11.5617
31	-0.2269	-0.025	5.7561	3.57	5.3176	-7.25	2.68	1.9366	3.9603	6.2422	11.6263
32	-0.2083	-0.0314	4.8546	4.78	5.6559	-9.01	3.0468	1.47	4.5537	7.5267	11.6869
33	-0.2267	-0.0383	4.9203	5.31	5.5793	-8.29	2.8912	1.4187	4.3877	7.1685	11.7753
34	-0.2269	-0.0357	5.0976	4.99	5.5656	-7.22	2.8912	1.3888	4.4543	7.271	11.813
35	-0.2246	-0.0454	5.6575	4.26	5.6503	-7.73	3.0026	1.3245	4.5067	7.3987	11.9184

Table 2: Chemical structures of 35 training compounds

 1=6.811	 2=6.811	 3=1.1281	 4=1.2613
 5=1.2837	 6=1.3244	 7=3.5381	 8=4.7185
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 13=9.7410	 14=9.8522	 15=10.1266	 16=10.1266

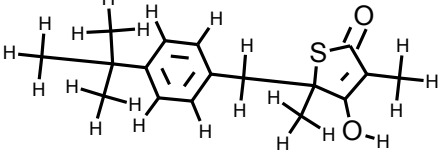
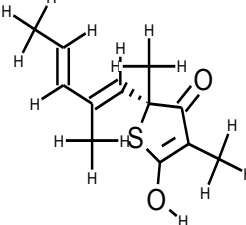
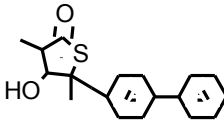
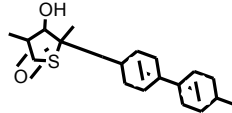
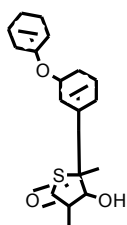
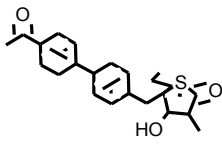
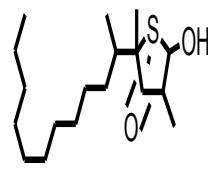
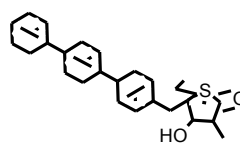
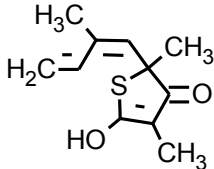
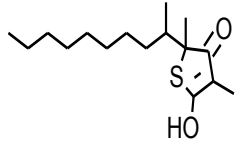
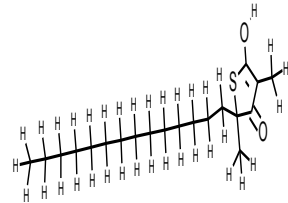
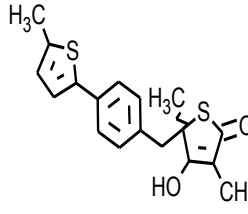
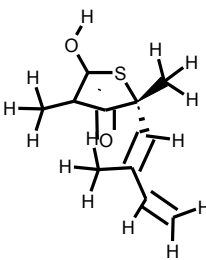
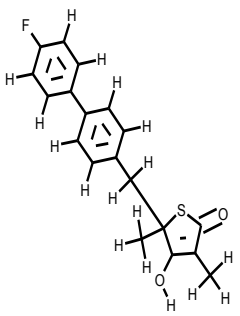
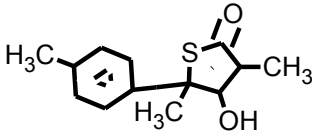
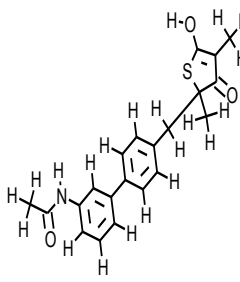
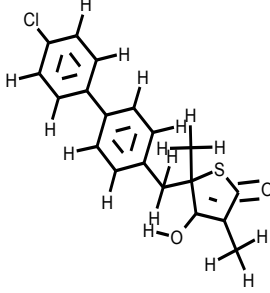
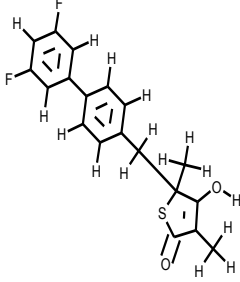
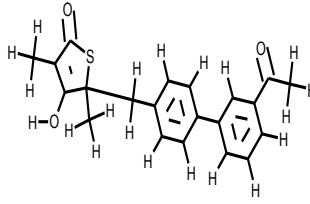
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 29=11.3737	 30=11.5617	 31=11.6263	 32=11.6869
 33=11.7753	 34=11.8130	 35=11.9184	

Table 3: Chemical structures of nine test compounds

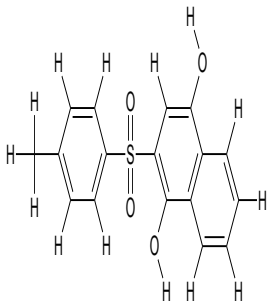
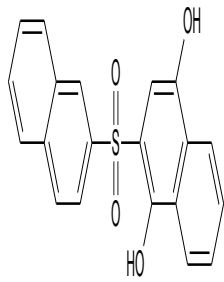
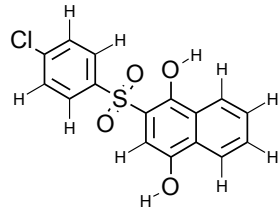
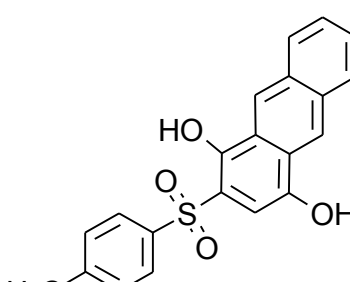
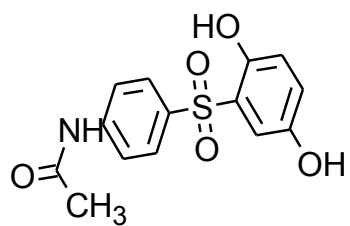
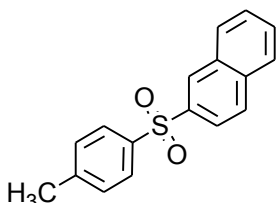
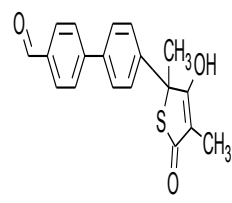
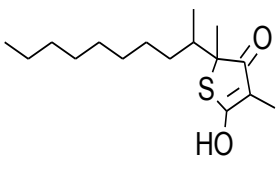
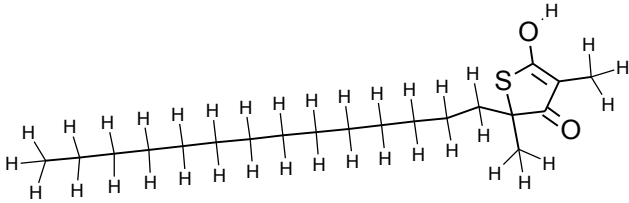
 1=-0.4943	 2=0.3987	 3=1.2753	 4=2.1365
 5=3.4468	 6=4.9780	 7=10.2751	 8=11.2252
 9=11.2898			

Table 4: Graph theoretical and quantum chemical parameters of nine test compounds

S.No.	HOMO	LUMO	DM	LogP	MV	BE	LnR	J	LnH	LnW	LnIC ₅₀
1b	-0.2017	-0.0521	4.8224	4.47	5.4161	-7.5	2.8009	1.7436	4.3766	6.8875	-0.4943
2b	-0.2108	-0.0609	8.489	4.95	5.4922	-9.32	2.8942	1.3278	4.5705	7.247	0.3987
3b	-0.2244	-0.0686	10.287	1.71	5.2459	-6.04	2.6775	2.07	4.1551	6.6567	1.2753
4b	-0.1925	-0.0754	6.345	5.46	5.5572	-9.14	2.959	1.29	4.6279	7.3562	2.1365
5b	-0.2221	-0.0481	6.8842	2.21	5.336	-8.56	2.7382	1.8487	4.2589	6.8606	3.4468
6b	-0.2233	-0.0596	6.2811	4.43	5.4297	-8.34	2.7332	1.4722	4.2148	6.6833	4.978
7b	-0.2271	-0.0537	5.037	4.42	5.5782	-7.35	2.9406	1.3457	4.4421	7.3058	10.2751
8b	-0.209	-0.0384	3.9288	3.38	5.1538	-6.38	2.5124	2.6558	3.661	5.6698	11.2252
9b	-0.2096	-0.0259	1.8067	7.65	5.7945	-7.09	3.1654	1.9539	4.2008	7.2848	11.2898

Table 5: Predicted and experimental activity using model 4

Compound no.	Predicted activity (LnIC ₅₀)	Experimental activity (LnIC ₅₀)
1	2.353394	0.69
2	1.227181	0.69
3	1.65538	1.1281
4	2.67408	1.2613
5	2.93428	1.2837
6	3.023674	1.3244
7	3.771637	3.5381
8	7.975639	4.7185
9	9.560753	8.006401
10	8.848732	8.294
11	4.759071	8.8537
12	10.94615	9.6158
13	11.26162	9.741001
14	10.25762	9.8522
15	11.01511	10.1266
16	12.67554	10.1266
17	11.2236	10.669
18	8.101242	10.8198
19	10.37917	10.8396
20	9.986764	10.859
21	10.97622	10.859
22	11.06315	10.8967
23	12.27911	11.0821
24	10.66647	11.1273
25	9.702431	11.2239
26	11.85791	11.2252
27	13.07494	11.2898
28	11.86285	11.3621
29	9.677895	11.3737
30	8.76783	11.5617
31	10.78869	11.6263
32	10.45075	11.6869
33	10.83329	11.7753
34	7.60218	11.813
35	9.020943	11.9184

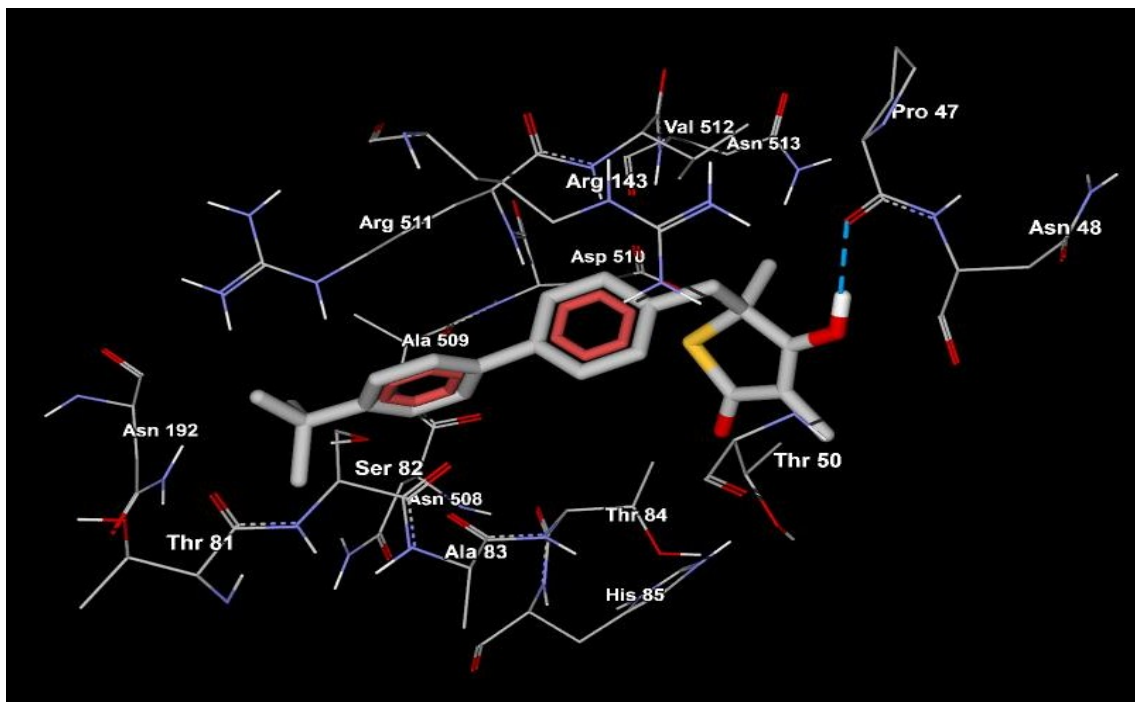


Figure 1: Docked image of compound 15

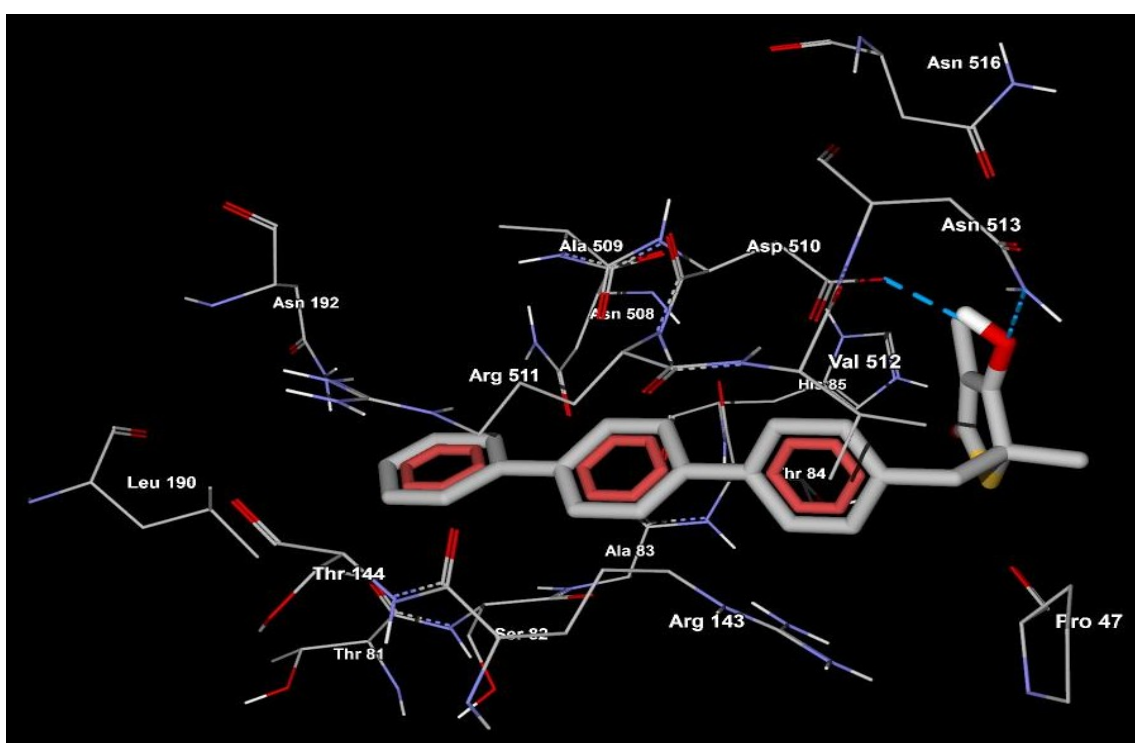


Figure 2: Docked image of compound 24

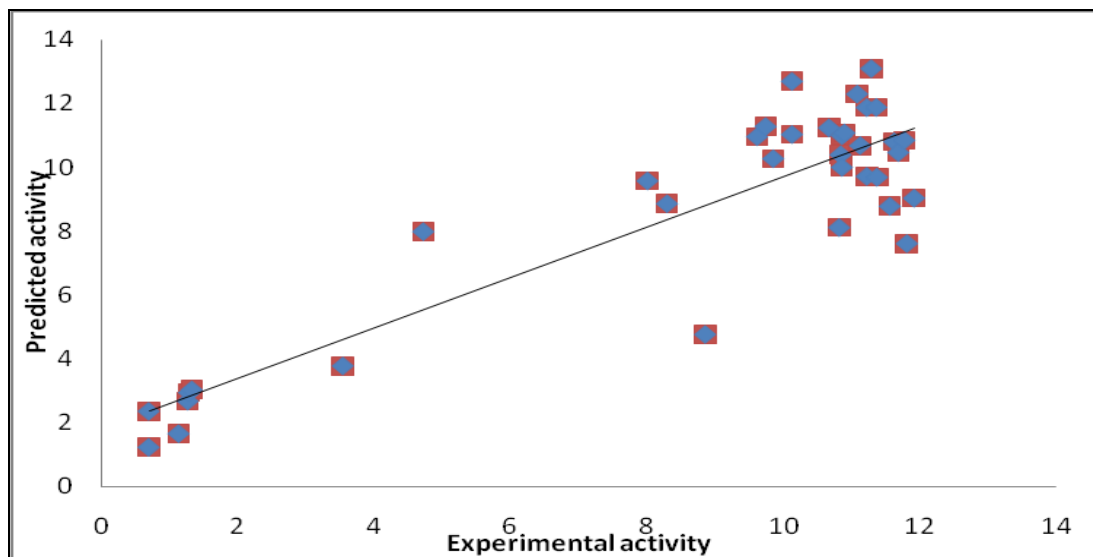


Figure 3: Correlation graph between experimental and predicted activity

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