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QSAR and Molecular Interaction Study of Piperine Analogues for Antitubercular Activity

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Abstract

In the present work QSAR and molecular docking studies have been performed to explore the binding affinity of 70 novel piperine analogues and 23 reported compounds against *Mycobacterium tuberculosis* (strain ATCC 25618 / H37Rv). Molecular docking studies for training and test compounds were done against protein Dev R (Uniprot ID: P9WMF8). The DevR-DosR works on two component regulatory system and was concerned in dormancy response of *Mycobacterium tuberculosis*. The best model from the training set showed r^2 value 0.8760 and q^2 value 0.7516. The validation of best QSAR model of each series was done by predicting the activity of the test set compounds. We have found that the reported compounds interacted with protein with a range of binding energy from -2.31 k cal/mol to -4.941 kcal/molby formation of one hydrogen bond to four hydrogen bond whereas predicted compounds interacted with binding energy ranges from -2.36 kcal/mol to -5.90kcal/molby forming one hydrogen bond to five hydrogen bonds.Similar pharmacophores containing molecules were designed and their activities were predicted using validated QSAR model and docking scores were also calculated. Some of predicted compounds showed improved binding affinity with the selected protein and some of them showed comparable affinity as compare to reported compounds.

Keywords: QSAR, Tuberculosis, *In Silico*, Piperine, Verapamil

Abbreviations: QSAR: Quantitative Structure Activity Relationship; TB: Tuberculosis; MDR-TB: Multi Drug Resistant Tuberculosis; XDR-TB: Extensively Drug Resistant Tuberculosis; WHO: World Health Organization; TRPV: Transient Receptor Potential Vanilloid

Introduction

Tuberculosis (TB) is a bacterial infection caused mainly by *Mycobacterium tuberculosis*, most commonly affects the lungs. According to WHO report an estimated 1.8 million people died from TB in 2015, of whom 0.4 million were co-infected with HIV. MDR-TB remains a public health crisis. Three countries carry the major burden of MDR-TB -India, China, and the Russian Federation. World Health Organization updated the estimate of incidence in India- that is, the number of new tuberculosis cases in a year - from 1.7 million cases to 2.8 million in 2015. In 2015, there were an estimated 10.4 million new (incident) TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children. Six countries accounted for 60% of the new cases: India, Indonesia, China, Nigeria, Pakistan and South Africa. Worldwide, the rate of decline in TB incidence remained at only 1.5% from 2014 to 2015 [1]. There were an estimated 1.4 million TB deaths in 2015, and an additional 0.4 million deaths resulting from TB disease among people living with HIV. There are nine drugs in advanced phases of clinical trials for the treatment of drug-susceptible TB, drug-resistant TB or LTBI. These are bedaquiline, delamanid, linezolid, PBTZ169, pretomanid, Q203, rifampicin (high-dose), rifapentine and sutezolid. There are 13 vaccine candidates in clinical trials, including candidates for prevention of TB infection and candidates for prevention of TB disease in people with LTBI.

The symptoms of active TB of the lung are coughing, sometimes with sputum or blood, chest pains, weakness, weight loss, fever, and night sweats [2]. The chemical composition of the mycobacterium cell wall and its unusual structurecreates major difficulty in TB treatment hence makes many antibiotics ineffective.Paleopathology and paleoepidemiology development in infectious diseases has proven the origin of this disease [3]. In 1993, the World Health Organization (WHO) declared TB to be a global emergency [4]. The exact cause of TB is unknown; it is thought that it could be because of the occurrence of HIV infection as well as MDR-TB due to inefficient management.

Isoniazid and Rifampicin are the two main drugs used in current first-line anti-TB chemotherapy. The therapy with existing TB drugs is exceedingly lengthy. Whereas MDR-TB and XDR-TB further complicates the world situation [5].

Poor activity of existing therapies and increasing drug resistance towards the latent stage of *Mycobacterium tuberculosis* has produced a clear need to develop novel therapeutics [6]. Natural products including plants, animals and minerals have been the basis of treatment of human diseases since from an ancient time. However, many effective medicines, including morphine, ephedrine, reserpine, aspirin, atropine and digitoxin were developed from natural products [7]. In our present work, we have focused on piperine, an alkaloid, major chemical constituent present in piper species. This alkaloid is responsible for pungency of black pepper. The pungency of piperine is because of activation of the heat and acidity sensing Transient receptor potential vanilloid (TRPV) ion channel TRPV1 on nociceptors [8].

Here *In silico* approach used as a strategy for designing and predicting activities of predicted compounds in comparison with some reported compounds. Verapamil analogues are derivatives of dimethoxy phenyl ring attached to a carbon chain have proven themselves as good anti-tubercular agents whereas piperine also having methylenedioxyphenyl ring attached to a carbon chain which is found to be essential structural requirement for its activity. Hence in present work we correlated these two compounds for same activity. QSAR is a methodology to design a rational molecule that meets the above-said requirement with not much effort, less time and lesser issues of environmental pollution. A QSAR equation correlates variety of physical or chemical parameters with biological activity [9-12]. There are many examples available in literature of successful screening of active compounds by QSAR methodology [13,14]. In our study, we predicted QSAR model from training compounds and further used that model for activity prediction of test compounds.

Materials and Methods

A total of 23 dimethoxyphenyl derivatives were selected from literature for QSAR and docking studies which have reported their activity against *Mycobacterium tuberculosis*. All the structures had the same pharmacophore with variable substitutions are which contributes to the difference in the observed anti tubercular activity.

QSAR studies

Around 800 descriptors for each of the compound were calculated using DRAGON and Chem office softwares. MLRA (Multiple Linear Regression Analysis) analysis was performed on each series to get best QSAR model using CODESSA®. Each series' best model was validated by predicting the activity of all training set compounds. The software enables evaluation of molecular descriptors and builds regression equation relating the best set of descriptors with the activity which can be used later for predicting activity of new molecules. The structures of the compounds were drawn and optimized by Chem Draw software. Eight hundred descriptors (Physico-chemical, Alignment Independent and Atom Type descriptors) were estimated. The data was divided into training and test sets randomly. Multiple linear regression analysis Method was used to identify the best model. Statistical parameters as r^2, q^2, S^2 and F were estimated for the regression equation to determine the quality of the data fit and the predictive capability for the model. Hence, we have designed 70 novel compounds by predicting their activities with the help of QSAR and docking results.

Docking Studies

The software used for studying the drug receptor interaction and designing new molecule was GLIDE module of Schrodinger 2016-1. Protein (3C3W) structure was obtained from www.rcsb.org and the protein was prepared using the module Protein Prep Wizard. The site mapping was done to get the binding cavity within the protein which is further used for the studies. Ligand structures were drawn by using 2D sketcher and optimized. Energy optimization was done using OPLS3. The pH of the simulated environment was maintained between 7±2. Molecular docking studies were done to find out the interactions between reported as well as predicted molecules. XP docking method was used in the GLIDE module to dock the ligands within the binding cavity of protein.

Results and Discussion

Table 1: QSAR model for antitubercular activity of dimethoxy phenyl derivatives.

Activity	Equation	R^2	F	S^2	Q^2
Antitubercular	A= = 3.6756e^3-6.0306e^3R1v+-5.6808e^3R8e^+ -8.6076e^3R3u$^+$-8.1775e^3R5m+2.0211e^4HATS7p	0.8760	22.60	23548.7441	0.7516
	A= = 2.3127e^3+1.2145e^3R1p-7.8508e^3R3u$^+$ -7.5687e^3R5m+1.6750e^4 HATS7p -1.0624e^4 R1v$^+$	0.8716	21.71	24390.8242	0.7320
	A= = 4.3766e^3-6.52272e^2R1p-9.7788e^3R3u$^+$ -9.3448e^3R5m+2.3631e^4 HATS7p-9.8759e^3 R8e^+	0.8561	19.04	27321.1855	0.6831
	A= = 3.2606e^3+4.2264e^2R1p-8.0711e^3R3u$^+$ -7.6948e^3R5m+1.5410e^4 HATS7p -8.5821e^3R1p$^+$	0.8545	18.79	27635.4238	0.7017
	A= 2.7295e^3-3.3894e^2R1p-1.0739e^4R3u$^+$ -5.4686e^3R5m+9.0903e^3R7u++5.7741e^3HATS8p	0.8527	18.52	27975.3555	0.7080

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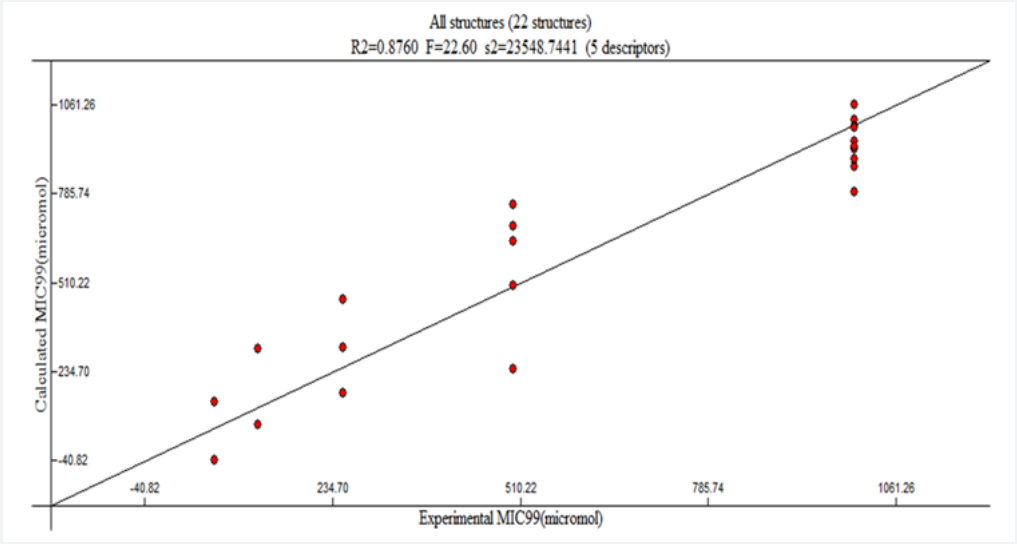
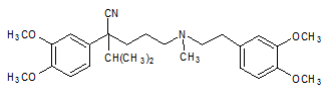
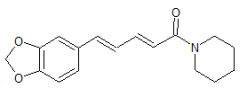
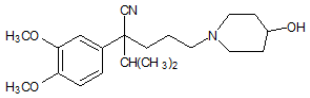
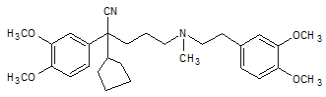


Figure 1: Correlation plot between calculated and experimental antitubercular activities of dimethoxyphenyl analogues.

Using 23 analogues bearing dimethoxy phenyl ring QSAR models were generated. The best fit model from QSAR studies for antitubercular activity showed r^2 value 0.8760 and q^2 value 0.7516, details are given in Table 1. The best equation shows that the anti TB activity is dependent on R1v (vander Waals volume), R8e+ (Sanderson electronegativity), and HATS7p (polarizability). Figure 1 is showing the correlation plot between calculated and experimental activities of antitubercular dimethoxy phenyl derivatives.

The molecular docking studies results in binding energy, binding affinity and interaction of ligands with the selected protein against *Mycobacterium tuberculosis*. The calculated and experimental activities, binding energies, hydrogen bond formed and interacting amino acids are given in Table 2 for reported compounds. Whereas calculated activity, binding energy, hydrogen bond formed and interacting amino acids for predicted compounds are given in Table 3. We have found that the reported compounds interacted with protein with a range of binding energy from -2.31 k cal/mol to -4.941 kcal/molby formation of one hydrogen bond to four hydrogen bond whereas predicted compounds interacted with binding energy ranges from -2.36 kcal/mol to -5.90kcal/mol to by forming one hydrogen bond to five hydrogen bonds. The Figure 2 (a-h) shows the docked molecules **sv10, sv20, p622, p1057 and p545** with good binding energy inside the binding cavity of protein. The amino acids majorly interacting with ligand at binding site of protein are GLN199, THR198, ALA200, VAL185, LEU57, PRO58, THR166, LEU165, VAL55, ARG56, LEU161, and GLY60. Schiff's bases were here proven to be good active compounds with better binding affinity against selected protein. In present study, electronegative atoms attached to Schiff's bases are contributing towards desired activity.

Table 2: Docking data of predicted compounds with 3C3W for anti-tubercular activity in decreasing order for their binding energies.

S.No.	Name	Structure	Calc. MIC99( )	Exp. MIC99 ( )	Binding Energy (kcal/mol)	H Bond	Interacting amino acid
1	Verapamil		682.5924	500.0000	-2.31	1H	ARG20
2	Piperine		241.8238	500.0000	-4.52	2H	TYR71, ARG232
3	**sv10**		502.2330	500.0000	**-4.941**	**3H**	ARG56, ASN167, GLU178
4	**sv20**		-40.8195	62.5000	**-4.724**	**2H**	ASP54, GLU195

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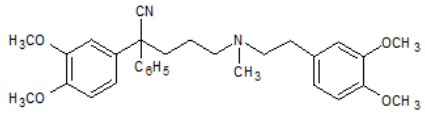
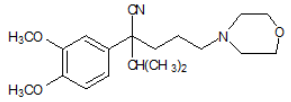
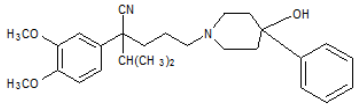
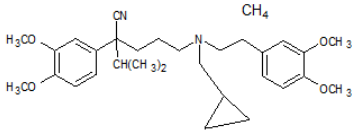
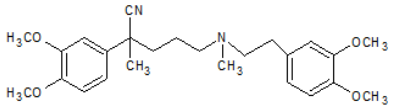
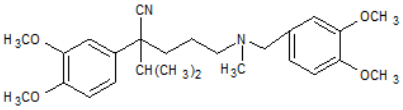
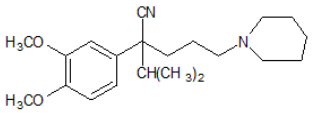
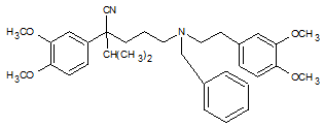
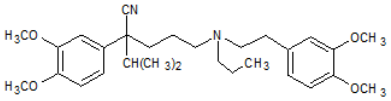
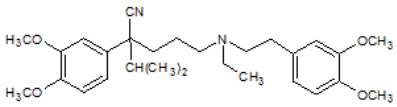
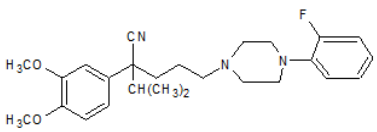
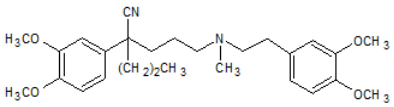
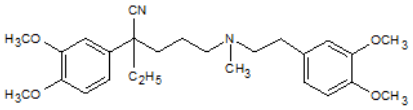
5	sv21		98.5675	125.000	-4.684	2H	ARG56, ASN167
6	sv9		932.7526	1000.0000	-4.495	2H	PRO58, LEU57, ASP9
7	sv12		307.0356	250.0000	-4.316	2H	ARG56, ASP54, PRO58
8	sv5		1.0138	1.0000	-4.163	1H	ARG56
9	sv17		990.1632	1000.0000	-4.133	1H	ASP9
10	sv7		995.1956	1000.0000	-4.052	2H	ASN167, ARG56
11	sv8		945.3430	1000.0000	-4.029	2H	ARG56, VAL55
12	sv4		71.2385	125.0000	-4.003	2H	LEU57, PRO58, ARG56
13	sv3		788.9936	1000.0000	-3.950	2H	LYS182, ARG56
14	sv2		749.4834	500.0000	-3.868	3H	LYS182, ASN167, ILE80, ALA190
15	sv15		891.3334	1000.0000	-3.876	1H	LEU57
16	sv19		305.6104	125.0000	-3.826	4H	ARG56, VAL36, ASN167, GLY60, THR82
17	sv18		635.9094	500.0000	-3.771	1H	ARG56

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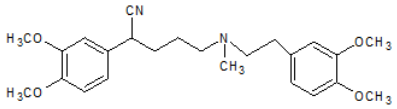
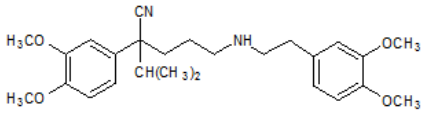
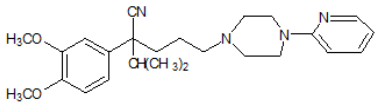
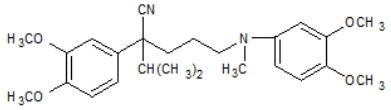
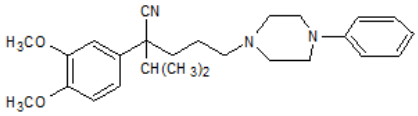
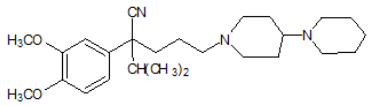
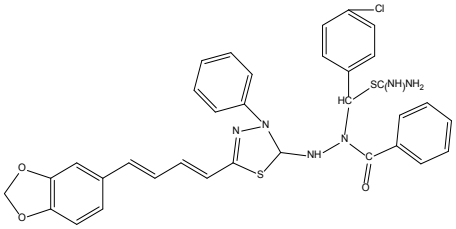
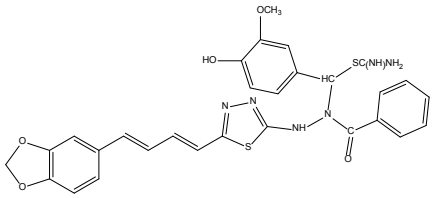
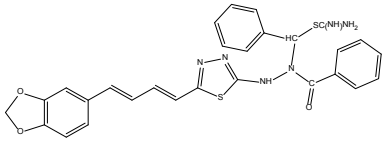
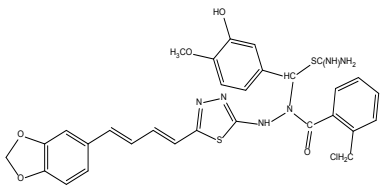
18	sv16		1.0613	1.0000	-3.763	2H	ARG56, GLN199
19	sv1		866.6174	1000.0000	-3.726	2H	LYS182, ARG56
20	sv14		138.8275	62.5000	-3.466	3H	ARG56, ASN167, LYS182
21	sv6		922.5297	1000.0000	-3.281	2H	ARG56, GLN199
22	sv13		455.6360	250.0000	-3.265	3H	GLN199, ARG56, ASP54
23	sv11		167.4232	250.0000	-3.011	2H	ARG56, ASN167, LYS182

Table 3: Docking data of predicted compounds with 3C3W for anti-tubercular activity in decreasing order for their binding energies.

S.No.	Code	Structure	Antitubercular Activity (calculated)	Binding Energy (kcal/mol)	H Bonds	Interacting Amino acid
1	P1057		966.0475	-5.90	3H	GLN199, ARG56, GLU195, ILE80
2	P622		919.7906	-5.833	5H	ARG56, LYS182, ASP54, GLU195, VAL55, LEU189
3	P545		718.5436	-5.775	3H	LEU57, PRO58, MET194
4	P725		797.1695	-5.403	3H	VAL185, MET194, LEU189

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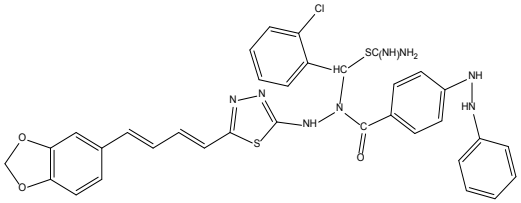
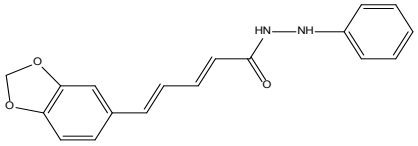
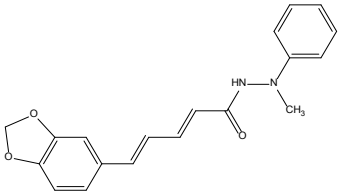
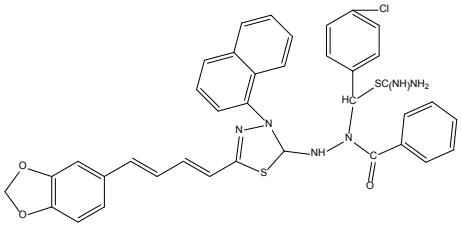
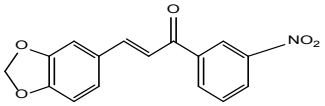
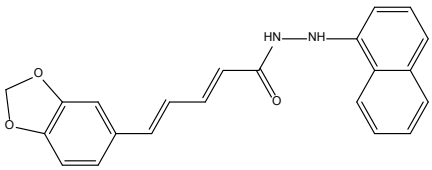
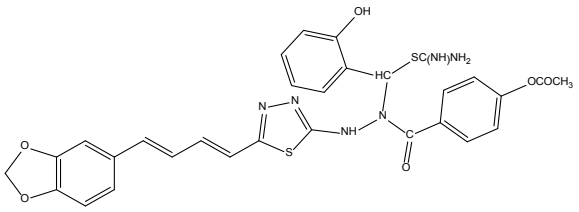
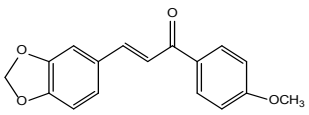
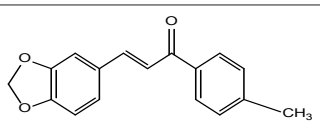
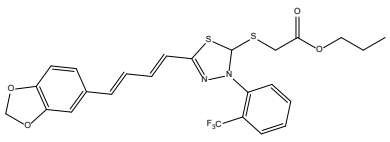
5	P557		776.4566	-5.309	2H	LEU165, ILE170, LEU57
6	P2		459.8483	-5.281	1H	LEU189, VAL55
7	P4		420.1175	-5.024	2H	MET194, VAL55, LEU189
8	P1045		770.9423	-4.983	2H	MET194, VAL185
9	P1090		479.1393	-4.936	2H	MET194, VAL55,
10	P8		456.4909	-4.822	1H	LEU165, LEU161
11	P594		514.3045	-4.890	3H	LEU189, VAL55, LEU57
12	P1087		797.1695	-4.856	1H	VAL185
13	P1088		574.5070	-4.856	1H	LEU57
14	P28		567.9867	-4.816	2H	MET194, VAL55, LEU189

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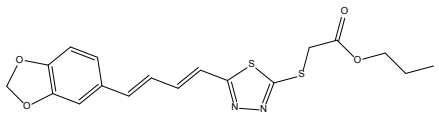
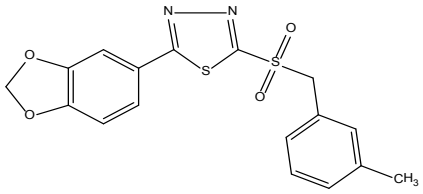
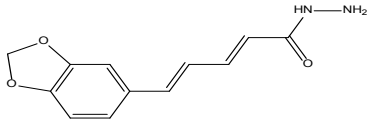
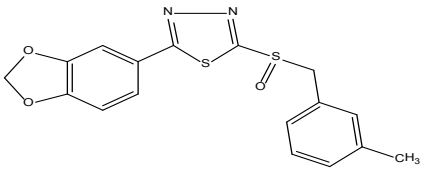
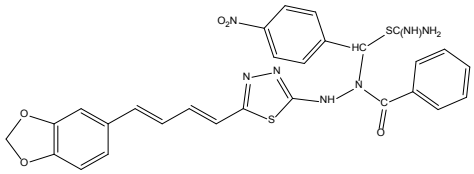
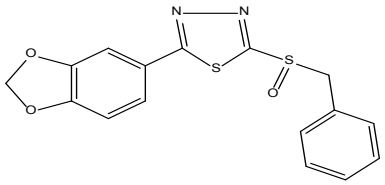
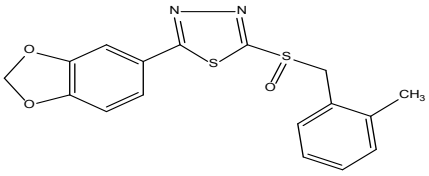
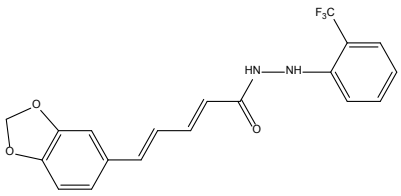
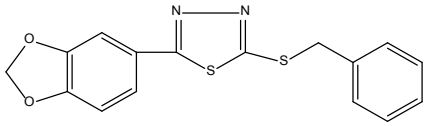
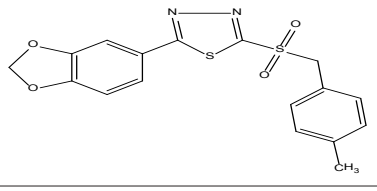
15	P12		231.3851	-4.795	2H	ALA200, LEU57
16	P1118		872.3487	-4.792	3H	VAL181, VAL185, VAL55, LEU189
17	P1		325.1452	-4.740	2H	GLU195, LEU189, VAL55
18	P1122		320.5677	-4.736	1H	ARG56
19	P677		460.0638	-4.730	2H	ASN167, ARG56, LEU161
20	P1120		750.3675	-4.723	1H	ARG56
21	P1121		432.3547	-4.689	1H	ARG56
22	P6		319.3465	-4.619	2H	ARG56, VAL185, LEU57
23	P1112		366.3680	-4.554	1H	ARG56
24	P1119		679.9823	-4.539	3H	ARG56, GLU195, GLN199, ILE170

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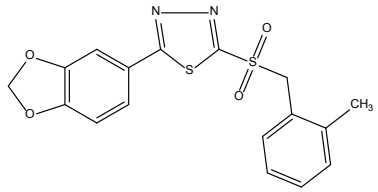
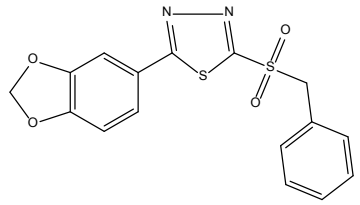
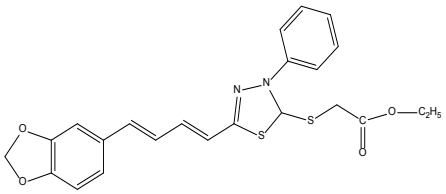
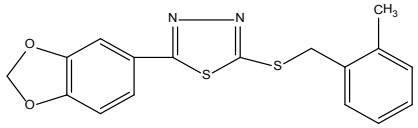
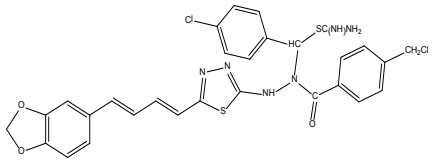
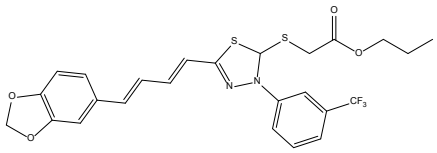
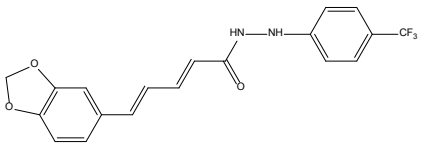
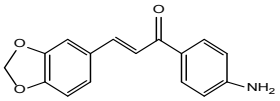
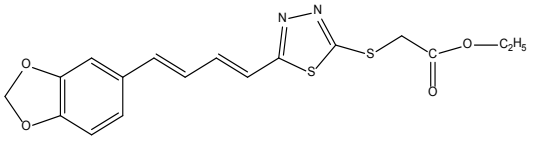
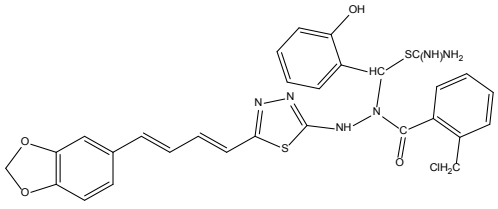
25	P1117		754.8769	-4.521	3H	ARG56, GLN199, VAL36, LEU57
26	P1116		657.8745	-4.515	3H	GLN199, ARG56, ILE80
27	P1070		213.8737	-4.515	1H	TYR184
28	P1114		239.6910	-4.508	1H	ARG56
29	P569		620.7211	-4.496	2H	ARG56, ASN167, VAL181
30	P32		-1.4363e^{3}	-4.491	No H Bond	
31	P5		312.1324	-4.488	2H	GLY60, ASN164
32	P1084		321.3975	-4.474	1H	GLN199
33	P1069		77.8940	-4.454	1H	ASN167
34	P593		529.3857	-4.428	2H	ARG56, GLU195

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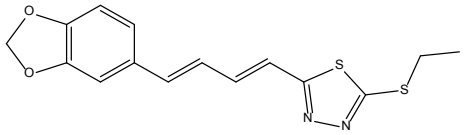
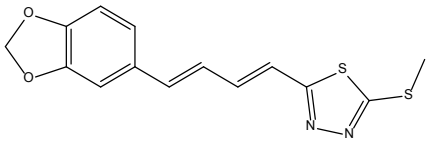
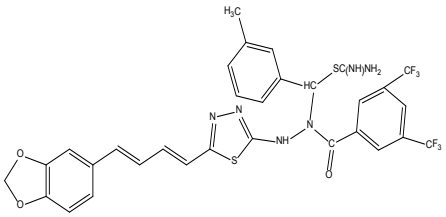
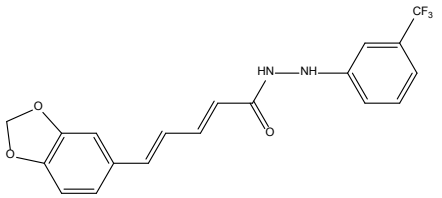
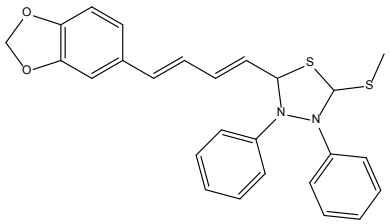
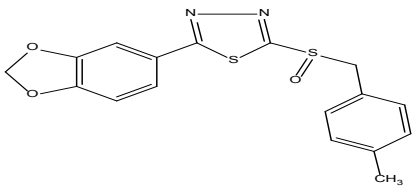
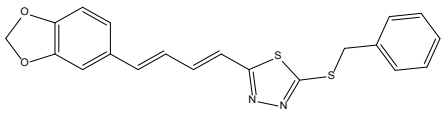
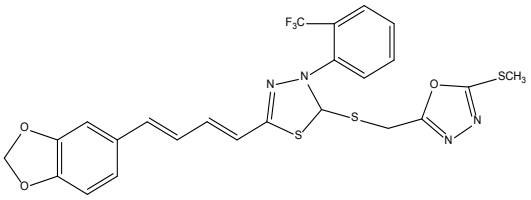
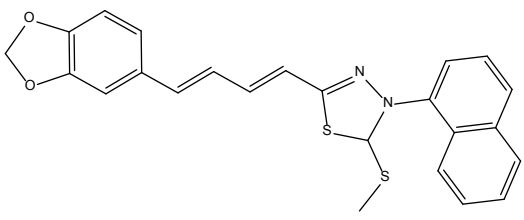
35	P10		111.6122	-4.415	No H Bond	
36	P9		$1.2751e^{3}$	-4.378	No H Bond	
37	P665		622.5968	-4.371	4H	GLY164, ASN167, VAL36, LEU165, LEU57
38	P7		256.7654	-4.326	1H	GLY60
39	P17		470.2918	-4.245	1H	ASN167
40	P1123		-230.4756	-4.243	No H Bond	
41	P11		45.2474	-4.202	No H Bond	
42	P1080		184.5850	-4.134	No H Bond	
43	P33		645.7685	-4.104	No H Bond	

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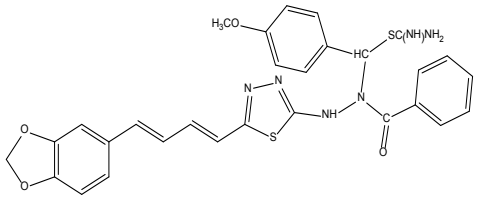
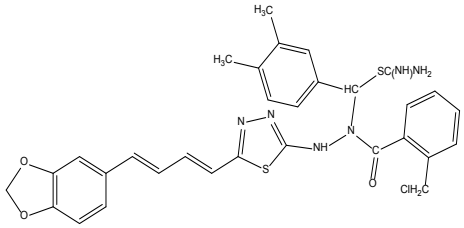
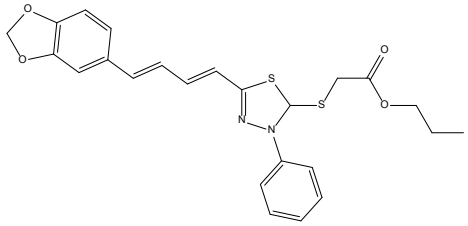
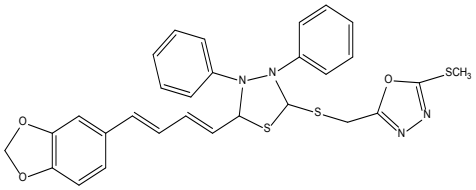
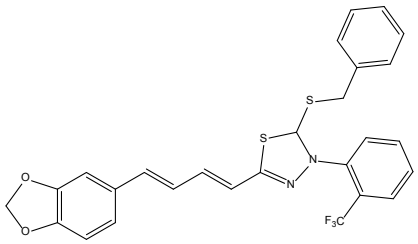
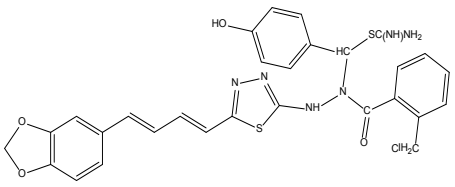
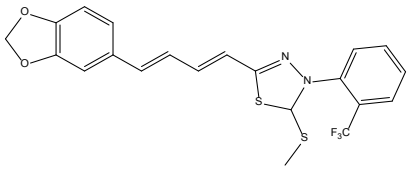
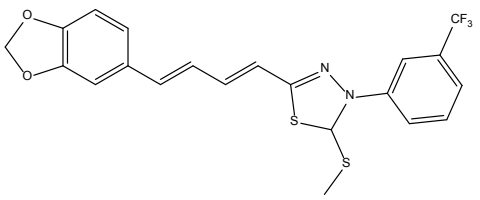
44	P743		876.9814	-4.001	2H	LEU57, GLU178
45	P743		456.3546	-3.976	No H Bond	
46	P16		704.6708	-3.904	1H	ASN167
47	P1078		59.3895	-3.874	No H Bond	
48	P27		$-1.6259e^{3}$	-3.836	No H Bond	
49	P604		$-1.5054e^{3}$	-3.795	2H	ARG56, GLN199
50	P25		$-2.2236e^{3}$	-3.700	No H Bond	
51	P29		367.5704	-3.700	No H Bond	

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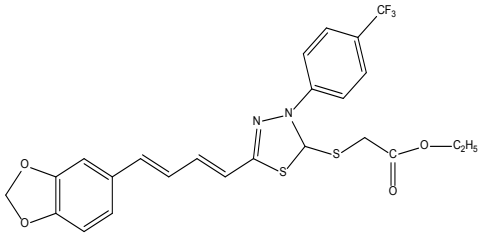
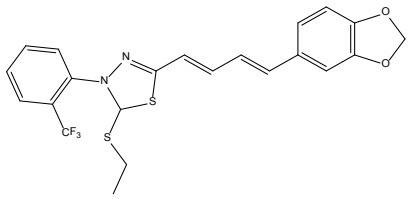
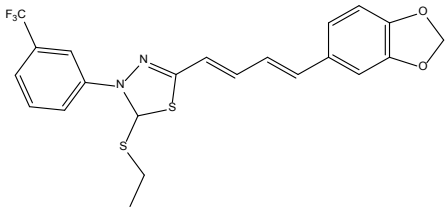
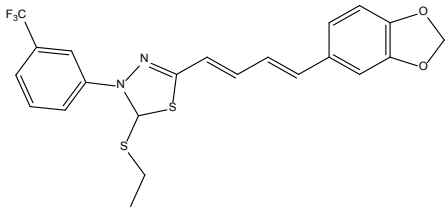
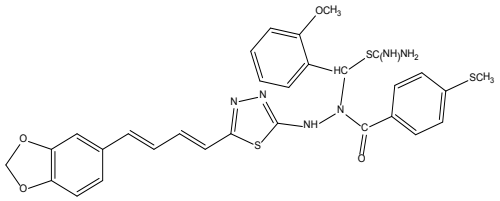
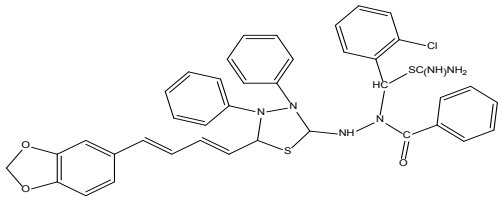
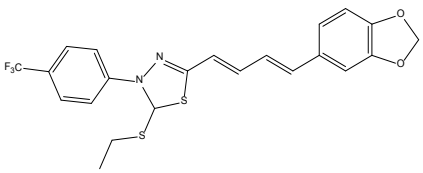
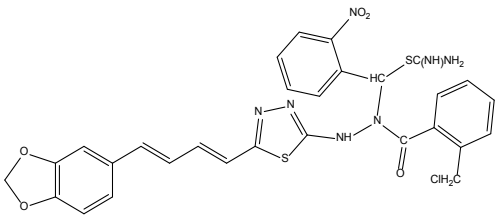
52	P1073		314.3073	-3.666	3H	GLN199, ARG56,THR82
53	P26		-1.5649e^{3}	-3.660	No H Bond	
54	P30		-147.6679	-3.590	No H Bond	
55	P30		-147.6679	-3.590	No H Bond	
56	P707		68.3878	-3.589	No H Bond	
57	P752		-560.3380	-3.56	No H Bond	
58	P22		-211.7911	-3.462	No H Bond	
59	P670		590.5082	-3.443	2H	ASP59, LEU165, VAL36

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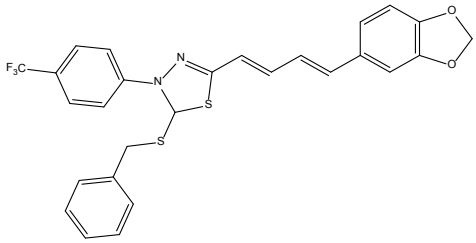
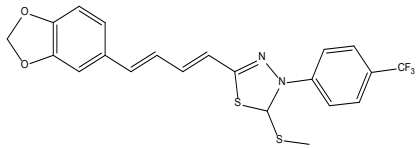
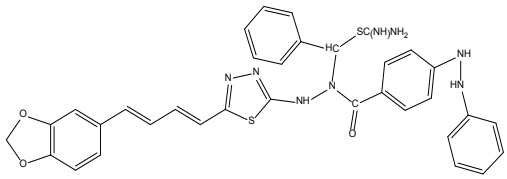
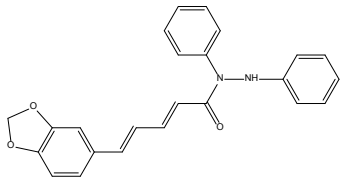
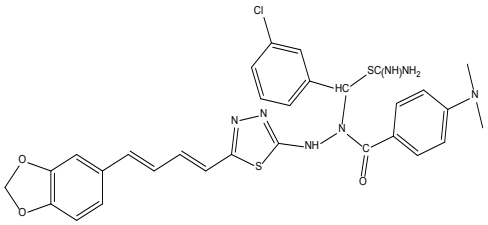
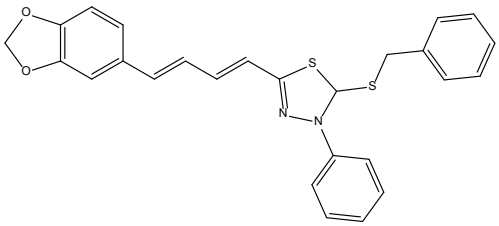
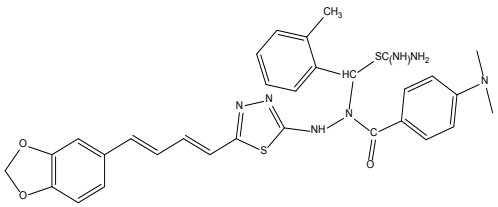
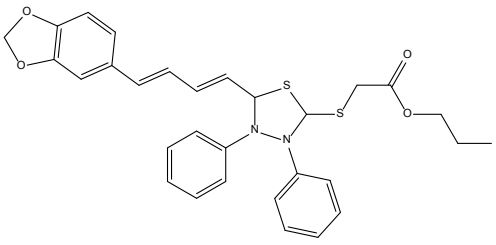
60	P23		491.5344	-3.429	1H	GLN199
61	P21		-109.2089	-3.372	1H	ARG56
62	P546		39.7419	-3.362	No H Bond	
63	P3		1.0967e3	-3.194	No H Bond	
64	P581		467.1514	-3.168	2H	LEU57, HIS10, ASP9
65	P15		14.1380	-3.080	No H Bond	
66	P636		408.7414	-2.991	1H	ARG56
67	P20		-195.5363	-2.699	No H Bond	

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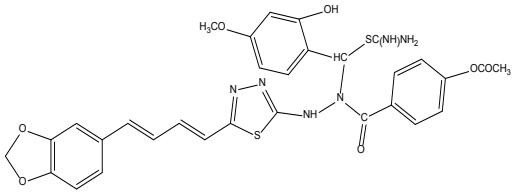
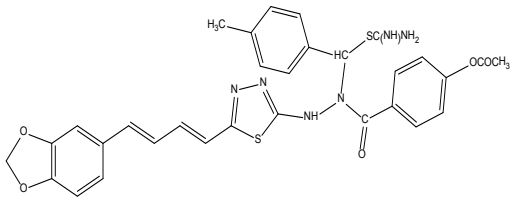
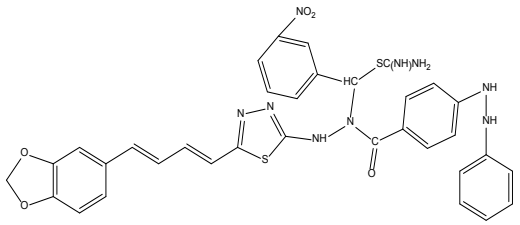
68	P737		-1.0726e^{3}	-2.67	No H Bond	
69	P649		-1.7930e^{3}	-2.47	No H Bond	
70	P689		-1.0038e+03	-2.36	No H Bond	

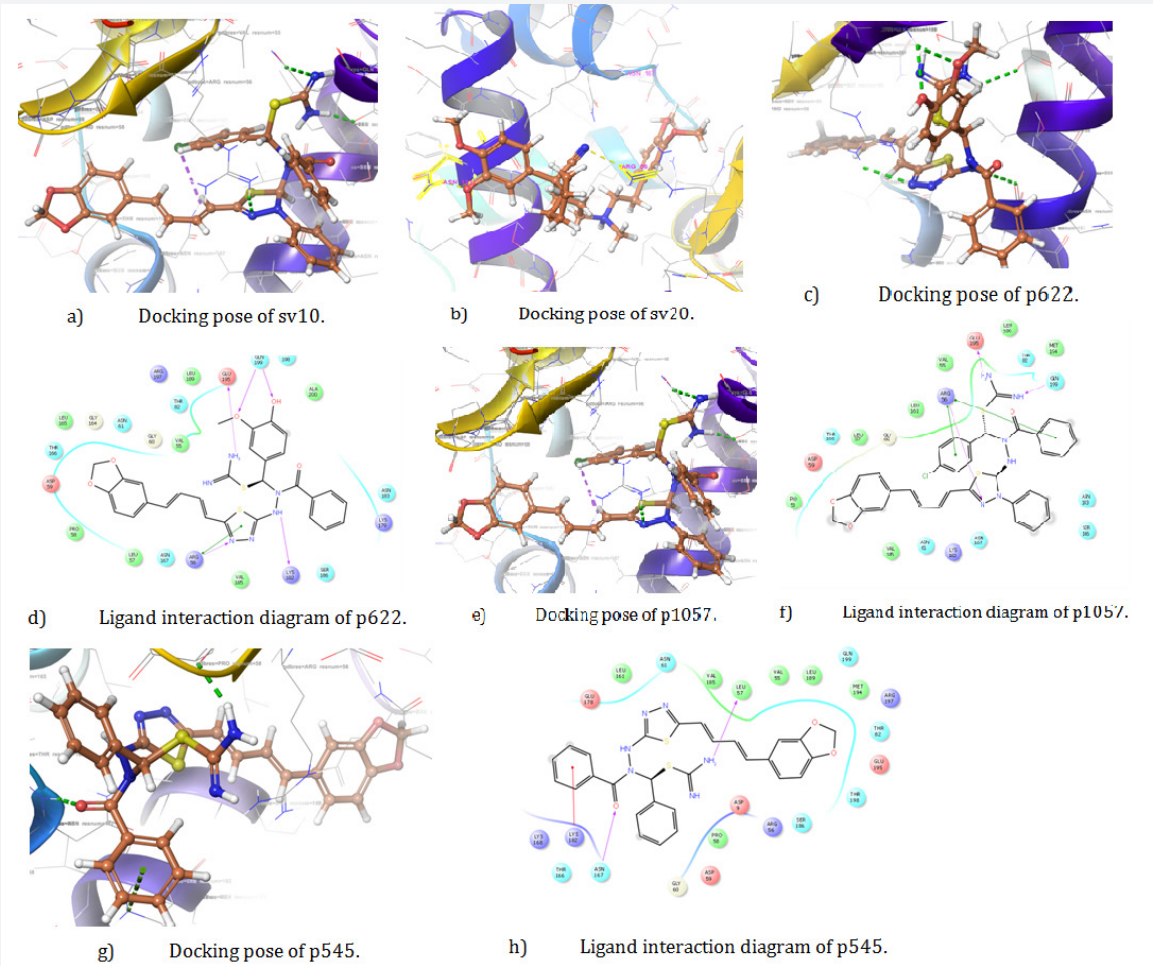


Figure 2: Docking poses and ligand interaction diagram of compounds showing best binding energies.

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Conclusion

Based on QSAR and molecular docking studies performed on 23 reported including reference compounds and 70 predicted compounds for antitubercular activity showed that binding energies for reported compounds with 3C3W protein ranges from -2.31 k cal/mol to-4.941 kcal/mol with one hydrogen bond to four hydrogen bonds. Whereas binding energies for predicted compounds with one hydrogen bond to five hydrogen bonds ranges from -2.36 kcal/mol to -5.90 kcal/mol. Some of the predicted compounds have shown good binding affinity as compared to reference drugs. Thus, we can be concluded that the QSAR models generated are good as the docking scores are comparable these models can be used to predict anti TB activity of the new compounds.

Conflict of Interest

Authors do not hold any economic interest in this work, and they do not hold any conflict of interest in the work presented.

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