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Quantitative Structure-activity Relationships (QSAR) and Docking Studies on Pyrimidine Derivatives for Antitubercular Activity against *M. tuberculosis* H37Rv

Kawkab Ali Hussain[1*], Sadiq M. H. Ismael[1] and Wisam A. Radhi[2]

[1]Department of Chemistry, College of Education Pure Science, Iraq.
[2]Department of Chemistry, Polymer Research Center, University of Basrah, Iraq.

Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: QSAR techniques and docking increase the probability of success and reduce time and coast in drug discovery process. The study presents QSAR investigation on 20 pyrimidine derivatives for antitubercular activity against *M. tuberculosis*.
Materials and Methods: The relationship analysis between compounds and physicochemical properties under study was done by two methods Multiple linear regression (MLR) and Step wise Selection of Terms (SW). The results show good models with six and five (SW) parameters linear equations. While the molecular docking simulation study of selected target Cytochrome P450 14alpha-sterol demethylases (CYP51) of *M. tuberculosis* H37Rv(1E9X) and ligands (active pyrimidine derivatives) as well as 4-Phenyl-1h-Imidazol for comparison was performed by using Autodock software.
Results: The best model predicted in this study was the eq. 1 (MLR) with excellent statistical fit as SE = 9.06234 R-Sq = 94.9% R-Sq (adj) = 92.1% and F=34.107, while the best model by (SW) was the eq. 2 with excellent statistical fit as SE= 8.89630 R-sq= 94.64% R-sq (adj)= 92.40%

**Corresponding author: E-mail: kawkabali@ymail.com;*

F=42.354. All the parameters showed insignificant role in the antitubercular activity. The molecular docking of ligands 3a-j with the cytochrome P450 14alpha-sterol demethylases (CYP51) of *M. tuberculosis* H37Rv was examined and the best docked pose was shown to have one hydrogen bond with PRO386. While the compound 4-Phenyl-1h-Imidazolshowed lower scores of docker energy.

Conclusion: Quantum chemical calculated parameters can be successfully used in the derived a designer QSAR. And the study indicated that predicted antitubercular activity values for pyrimidine derivative compounds can be modeled by two methods; stepwise (SW) and multiple linear regression (MLR), as well as the docking analysis showed that all compounds exhibited quite similar binding energy and compound 4 as best ligand which showed the highest binding energy and this agreement with experimental data. The most compounds understudy exhibit the best results comparison with the ligand 4-Phenyl-1h-Imidazol.All the rustles could potentially offer a new opportunity in the design of novel properties or extended to other compounds.

Keywords: Pyrimidine derivatives; antitubercular activity; M. tuberculosis; QASR anddocking.

1. INTRODUCTION

Tuberculosis (TB) is a lung infection caused primarily due to *Mycobacterium tuberculosis* (Mtb), is one of the world's most dangerous infectious agent. According to the World Health Organization (WHO) estimates TB kills more adults now than all other infectious diseases combined [1]. The single drug therapy of TB by potential drugs such as streptomycin [2], rifampicin [3], rifampetine [4], isoniazid (INZ) [5], and so on fails because of drug resistance after some time [3]. Presently, a combination of broad and narrow spectrum antimycobacterial drugs, namely PRISE, is being used for the treatment of TB [4] novel molecules such as chalcones, thiophene, pyrimidine derivatives was synthesis exhibit antimycobacterial activity against other species of Mycobacterium [6-9]. Despite the fact that death from TB is often preventable, the rapid increase of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis has resulted in an urgent need to develop new drug targets for *Mycobacterium tuberculosis* (Mtb) [10-11]. The discovery and development of new anti-TB therapeutics is widely recognized as one of the major global health emergencies, yet it is also a major pharmaceutical challenge. A theoretical technique such as quantum chemical descriptors have been extensively used in Quantitative Structure-Activity Relationship (QSAR) to predict the physiological and biological properties of compounds understudy. Whether these compounds (pyrimidine derivatives) provide structural precedence and may lead to the generation of novel anti-TB therapeutics. The major aim of QSAR study is to develop quantitative models to predict compounds' properties such as biological activity, and these models can contribute to reduction of the time of drug discovery [9-10]. This technique shall reduce the drug discovery cost, time and efforts [11-16]. Molecular modeling, docking is a method which predicts the preferred orientation ofone molecule to a second when bound to each other to forma stable complex. Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule [13-14].

1.1 Modeling and Geometry Optimization

The quantum chemical calculations were performed for 20 pyrimidine derivatives compounds understudy with the PCGAMESS program [17]. Geometry optimizations were carried out using Density Functional Theory (DFT) method at B3LYB/6-31G (d) level of theory. The experimental antitubercular activity data of 20 compounds under study have been taken from reference [18]. Structures of 20 compounds shown in Fig. 1.

2. MATERIALS AND METHODS

2.1 Quantitative Structure– activity Relationship QSAR

To screen out potential leads against *M. tuberculosis* H37Rv, 20 compounds (2a-j & 3a-j) as described in Ref [18] which used in the training setfor the development of a robust QSAR model by two methods Multiple linear Regression (MLR) and Stepwise Selection of Terms (SW), demonstrate the usefulness and focus of some of the parameters in deriving predictive QSAR Models [19-21]. The relation between the anti-TB therapeutics and quantum chemical calculated parameters, and identical molecular descriptors to calculate R, S and F. Linear regression

Sr. No	R=
2a	Phenyl
2b	2-Hydroxyphenyl
2c	4- Hydroxyphenyl
2d	2-Nitrophenyl
2e	3- Nitrophenyl
2f	2-Chlorophenyl
2g	4-Methoxyphenyl
2h	3-Methoxy-4-hydroxy-phenyl
2i	Styryl
2j	2-Furyl
3a	Phenyl
3b	2-Hydroxyphenyl
3c	4- Hydroxyphenyl
3d	2-Nitrophenyl
3e	3- Nitrophenyl
3f	2-Chlorophenyl
3g	4-Methoxyphenyl
3h	3-Methoxy-4-hydroxy-phenyl
3i	Styryl
3j	2-Furyl

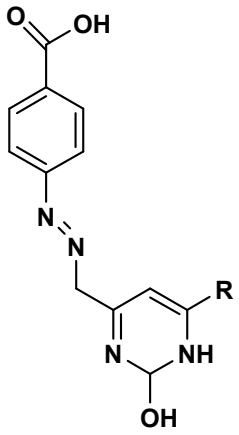

Fig. 1. Molecular structure of the compounds understudy

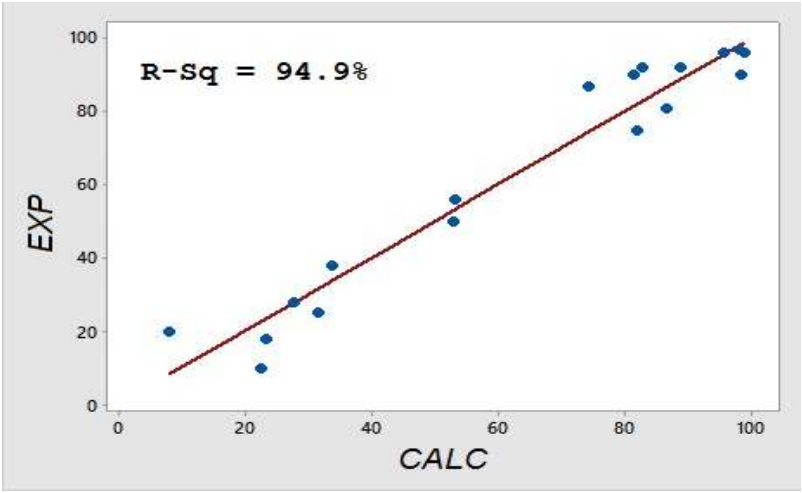

Fig. 2. Plot of antitubercular activity prediction versus antitubercular activity experimental using Eq. 1

analyses are performed to find the best correlation between various biological activity indices and the biological activities of the studied. A large number of molecular descriptors [20] were calculated which including, logP, Polarizability (pol), Hydration Energy (H.E), Refractivity (ref), ionization potential I, electron affinity A, hardness η, softness S, electrophilicity ω, dipole moment (μ), HOMO and LUMO energies, Energy Gap, Total energy, number of Nitrogen atoms and Oxygen atoms, number of OH,C-N, C=O, and C-O groups. A brief

description of the descriptors used in this study is represented in Table 1.

2.2 Molecular Docking

To find the bioactive conformation of active pyrimidine derivatives (Fig. 3), the molecular docking simulation study of selected target Cytochrome P450 14alpha-sterol demethylases (CYP51) of *M. tuberculosis* H37Rv and legends (active pyrimidine derivatives) were performed by using Autodock software. The 3D crystallographic structures of antituberculosis target protein of *M. tuberculosis* H37Rv (PDB entry: 1E9X. [22-24].

3. RESULTS AND DISCUSSION

In an attempt to determine the role of structural features of compounds, which appears to influence the antimycobacterial activity, QSAR models were generated. The structures of the studied compounds is shown in Fig. 1, and Table 1. In this study we used parameters in Table 2. to establish the statistical correlation, the physicochemical parameters were taken as independent variables and antitubercular activity as dependent variable. The best model was selected on the basis of statistical parameters viz observed with high coefficient of multiple (R-Sq), adjusted coefficient of multiple determination (R-Sq(adj)), sequential Fischer test (F) and low standard error of estimate (S). While the varine inflation factor (VIF) quantifies the severity of multicollinearity least squares regression analysis, were employed to judge the validity of regression equation and evaluate the obtained QSPR models [25,26]. For the development of QSAR equations, two different methods were used: (i) stepwise (SW) regression (ii) Multiple linear regression (MLR) was used for building the QSAR models. The SW-MLR analysis led to the derivation of one model, with five variables. It is described by the following equation:

The six- parameter correlations of the pyrimidine derivatives were given in Eq. (1), depicted in Fig. 2. The Eq. 1. of the antitubercular activity of pyrimidine derivatives compounds are best predicated by the depend on only six parameter gave good model with correlation coefficient R-Sq values for this model of 94.9%, and generated by multiple linear regression (MLR) method.

Exp = - 339 - 0.0156 T.E + 44.7 nC=O + 12.4 nC-O + 2.04 H.E - 79.9 μ + 6.95 Log P (1)

n=18 SE = 9.06234 R-Sq = 94.9% R-Sq(adj) = 92.1% F=34.107

The excellent relationship between the experimental data and predicted antibacterial activities. In this model depends on values of nC=O, nC-O, H.E, and log p suggest that the activity increases with increase values of these descriptorswhile it decreases with increasing values of both T. E and μ. Since they have a negative value in this equation. Fig. 2. Show the relationship between the experimental data.

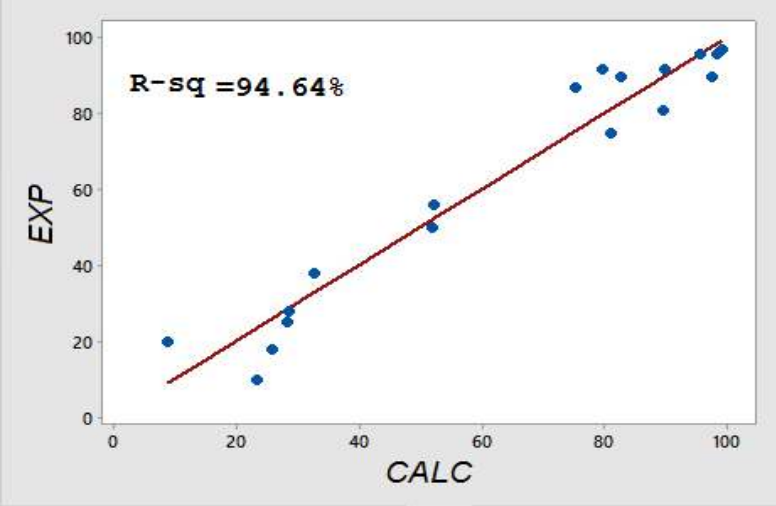

Fig. 3. Plot of antitubercular activity prediction versus antitubercular activity experimental using Eq. 2

Table 1. Descriptors as the independent variables used for QSAR analysis of compounds

*Exp	log P	pol.	H.E	Ref.	I	A	η	S	ω	μ	Homo	Lumo	E. GAP	T.E	No. N	No. O	No. OH	No C-N	No. C=O	No. C-O
10	3.74	36.48	-27.87	98.49	5.603	1.689	1.957	0.511	3.396	-3.646	-5.603	-1.689	3.913028	-1214.71	4	4	3	5	1	3
20	3.74	36.48	-29.07	98.49	5.366	1.624	1.871	0.534	3.264	-3.495	-5.366	-1.624	3.741595	-1214.71	4	4	3	5	1	3
56	3.97	37.68	-27	104.12	5.741	2.493	1.624	0.616	5.219	-4.117	-5.741	-2.493	3.249065	-1343.94	5	5	2	6	1	2
50	3.97	37.68	-26.99	104.12	5.736	2.492	1.622	0.617	5.217	-4.114	-5.736	-2.492	3.243623	-1343.95	5	5	2	6	1	2
25	4.54	37.77	-21.49	101.6	5.499	1.714	1.893	0.528	3.436	-3.607	-5.499	-1.714	3.785134	-1599.06	4	3	2	5	1	2
28	3.77	38.32	-23.86	103.26	5.323	1.701	1.811	0.552	3.578	-3.6	-5.323	-1.701	3.621864	-1253.99	4	4	2	5	1	3
38	3.48	38.95	-29.77	104.95	5.325	1.722	1.802	0.555	3.446	-3.524	-5.325	-1.722	3.602816	-1329.18	4	5	3	5	1	5
18	4.55	39.32	-23.13	107.11	5.393	1.845	1.774	0.564	3.691	-3.619	-5.393	-1.845	3.548393	-1216.87	4	3	2	5	1	2
90	2.65	35.71	-17.57	96.56	5.802	2.348	1.727	0.579	4.808	-4.075	-5.802	-2.348	3.453152	-1139.55	4	4	2	5	1	4
92	2.37	36.35	-21.31	98.25	5.956	2.4	1.778	0.562	4.909	-4.178	-5.956	-2.4	3.556556	-1214.74	4	3	1	6	2	1
87	2.37	36.35	-24.41	98.25	5.798	2.041	1.879	0.532	4.087	-3.919	-5.798	-2.041	3.757922	-1214.74	4	4	2	6	2	2
96	2.6	37.55	-19.43	103.88	5.913	2.119	1.897	0.527	4.251	-4.016	-5.913	-2.119	3.793297	-1343.95	4	4	2	6	2	2
96	2.6	37.55	-22.18	103.88	6.065	2.501	1.782	0.561	5.147	-4.283	-6.065	-2.501	3.56472	-1343.97	5	5	1	7	2	1
92	3.17	37.64	-16.74	101.36	5.812	1.869	1.972	0.507	3.741	-3.841	-5.812	-1.869	3.942961	-1599.08	4	3	1	6	2	1
97	2.4	38.18	-19.25	103.02	5.674	2.169	1.753	0.57	4.387	-3.922	-5.674	-2.169	3.504854	-1254.01	4	4	1	6	2	3
90	2.11	38.82	-25.05	104.71	5.744	2.112	1.816	0.551	4.248	-3.928	-5.744	-2.112	3.632749	-1329.2	4	5	2	6	2	4
81	3.18	39.19	-18.07	106.88	5.753	2.245	1.754	0.57	4.559	-3.999	-5.753	-2.245	3.507575	-1216.9	4	3	1	6	2	1
75	0.15	32.87	-19.28	91.55	5.867	2.012	1.928	0.519	4.024	-3.939	-5.867	-2.012	3.844999	-1137.35	4	4	1	6	2	3

**Experimental inhibition against Mycobacterium tuberculosis at 6.25 mg/mL*

While when using stepwise (SW). The five-parameter correlations of the pyrimidine derivatives were given in Eq. (2), depicted in Fig. 4. The Eq. 2. of the antitubercular activity of pyrimidine derivative compounds are best predicted by thedepend on only 5 parameter, Good model with R-sq= 94.64%.

Exp= -324.5 + 47.14 nC=O + 12.60 nC-O + 2.119 H.E - 79.5 μ + 8.66 Log p (2)

n=18 SE= 8.89630 R-sq= 94.64% R-sq(adj)= 92.40% F=42.354

As well as the excellent relationship between the experimental data in this model depends on values of nC=O, noC-O, H.E, μ and logp suggest that the activity increases with increase values of these descriptors. On the other hand the negative value of μ suggests the opposite. Fig 3. Show the relationship between the experimental data.

Table. 2 shows variance inflation factors of descriptors in eq. 1 and eq. 2. The VIF for the descriptors Log p and n. C=O are fairly large in both equations but eq. 2 have less VIF factors from eq. 1. VIF factors for descriptors in eq. 2 falls into the range 1.0-5.0 therefore eq. 2 is more acceptable from eq. 1.

Table 2. The varied inflation factor (VIF) quantifies the severity of multicollinearity least squares regression analysis

VIF coefficients of eq. 1	VIF coefficients of eq. 2
1.51T.E	4.22n.C=O
4.79n.C=O	2.76n.C-O
2.77n.C-O	1.64H.E
1.68H.E	1.84μ
1.85μ	4.31Log p
5.50Log P	-----

It could be seen from Table 3. The predicted of the antitubercular activity of pyrimidine derivatives compounds values obtain from Eq. 1-2 in this study and comparable with the experimental values in the Reference [18]. It is obvious from this Table 3. that the relations between descriptors which calculations in this study and experimental the antitubercular activity values are excellent.

3.1 Molecular Docking

Our primary aim in this study was to analyse ligand–protein interactions, based on Ref [18] just the last compounds 3a-j. To find the bioactive conformation of active pyrimidine derivatives (Fig. 3), the molecular docking simulation study of selected target protein of *M. tuberculosis* H37Rv and ligands (pyrimidine derivatives) was performed by using Autodock software. The 3D crystallographic structures of antituberculosis target protein of *M. tuberculosis* H37Rv (PDB entry: 1E9X. To examine the possible interactions between ligands (pyrimidine derivatives) and the active site of the Mycobacterium DNA. Molecular docking of the compound with the protein molecule was carried out using the program AutoDoCK4 [27]. A grid box of 110 x 110 x 100 with the grid spacing of 0.883 A^0 was chosen. The grid was automatically centered in the middle of the active site. The electrostatic and atomic interaction maps for all atom types of the ligand molecule were calculated using the module Autogrid of the Autodock program. The Lamarckian genetic algorithm (LGA) was employed for up to 100 runs for docking studies. The values and other parameters were taken as defaults in the docking program. The conformation of the docked ligand molecule was analyzed based on the binding energy values [28-30].

Table 3. Predicated experimental data depends on Eq. 1. & Eq. 2

No molecule	Calc by stepwise selection	Calc by (MLR)	Exp ref (18)
1	23.55	22.59	10
2	9	8.08	20
3	52.23	53.19	56
4	52.01	52.97	50
5	28.3	31.6	25
6	28.65	27.9	28
7	32.76	33.82	38
8	25.87	23.32	18
9	82.63	81.53	90
10	89.82	88.8	92
11	75.26	74.22	87
12	95.52	95.73	96
13	98.32	99.03	96
14	79.65	82.73	92
15	99.29	98.22	97
16	97.56	98.48	90
17	89.48	86.75	81
18	81.1	82.05	75
19*	-----	------	----
20**	------	------	----

**compound 2a(phenyl), ** compound 2j (furyl)*

3.2 Docking Analysis

The ligand-receptor interactions were studied for pyrimidine derivatives and 1E9X protein.

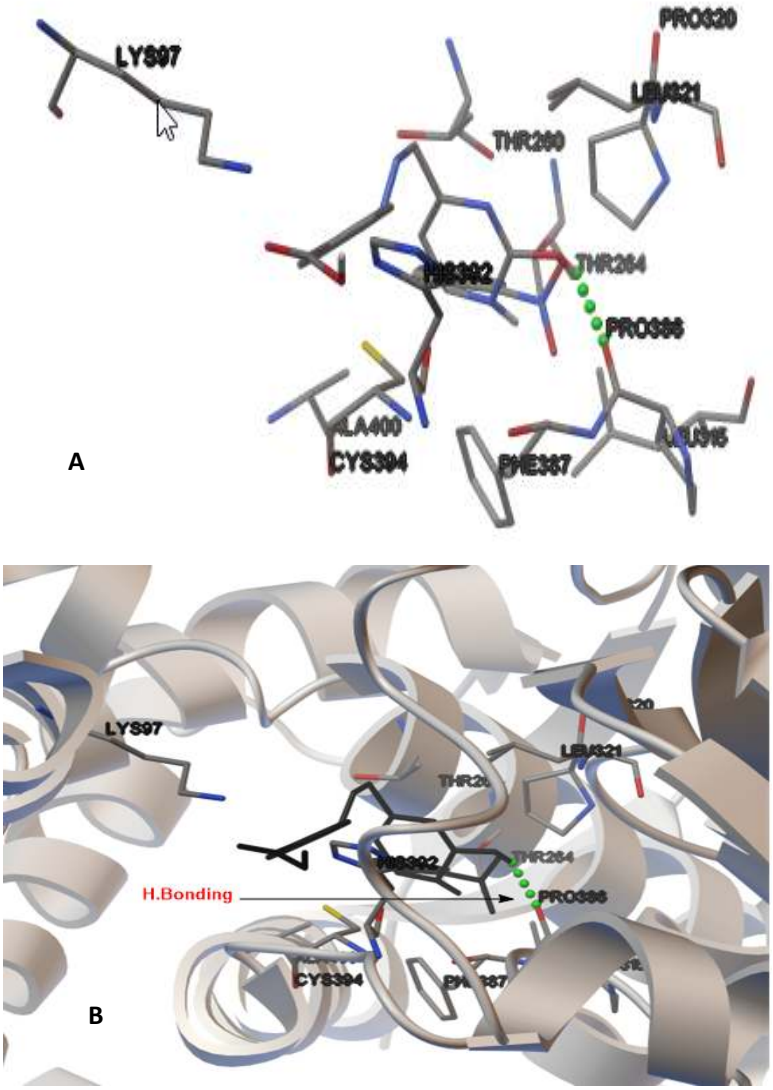

Fig. 4. (a) Docked conformation of compound 4 has been included in stickrepersentaion showing hydrogen bonding. (b) Hydrophobic interaction with LY897, LEU321, THR200, PRO320, HIS392, THR264, PRO386, CYS394, PHE387, LEU315 of 1E9X, residue (ribbon format)

Receptor 1E9X protein was docked with the all ligands like pyrimidine derivatives structure. Default parameters were used for the docking process and Energy values (E values, inhibition constant (Ki), Intermolecular Energy, Internal Energy, Torsional Energy, Unbound Extended energy) of each docking were obtained Table 4. The substituted group of the various compounds undergoes various types of bonded and non-bonded interaction with various residues depending on the type of the group present on designed of anti-tuberculosis. The molecular docking of different molecules shows that the predicted binding free energies are quite good, without any reparametrization (Table 3). Docking analysis showed that all compounds exhibited quite similar binding energy except the three compounds (No. 4, 5, 7) exhibited high binding energy Table 3. The docking results indicate that compound 4 (Fig. 4) as best ligand which showed highest score of docker energy (minimum free binding energy) and good interaction energy among all the compounds and this agreement with experimental data. This compound showed hydrogen bond interaction with PRO386 and electrostatic interaction as well

as showing hydrophobic interactions (due to non-polar residue interaction) with some hydrophobic amino acid residues with LY897, LEU321, THR200, PRO320, HIS392, THR264, PRO386, CYS394, PHE387, LEU315. Therefore the compound 4 may be suitable to overcome the drug resistance of *Mycobacterium tuberculosis* H37Rv. The molecular docking of 4-Phenyl-1h-Imidazol for comparison (used as the reference drug) with compounds understudy. The docking results indicate the compound 4-Phenyl-1h-Imidazol (Fig. 5) showed lower scores of docker energy. This compound showed hydrogen bond interaction with ILE323 as well as hydrophobic interactions with hydrophobic amino acid residues with PHE78, TYR76, MET433, LEU321, ILE322.

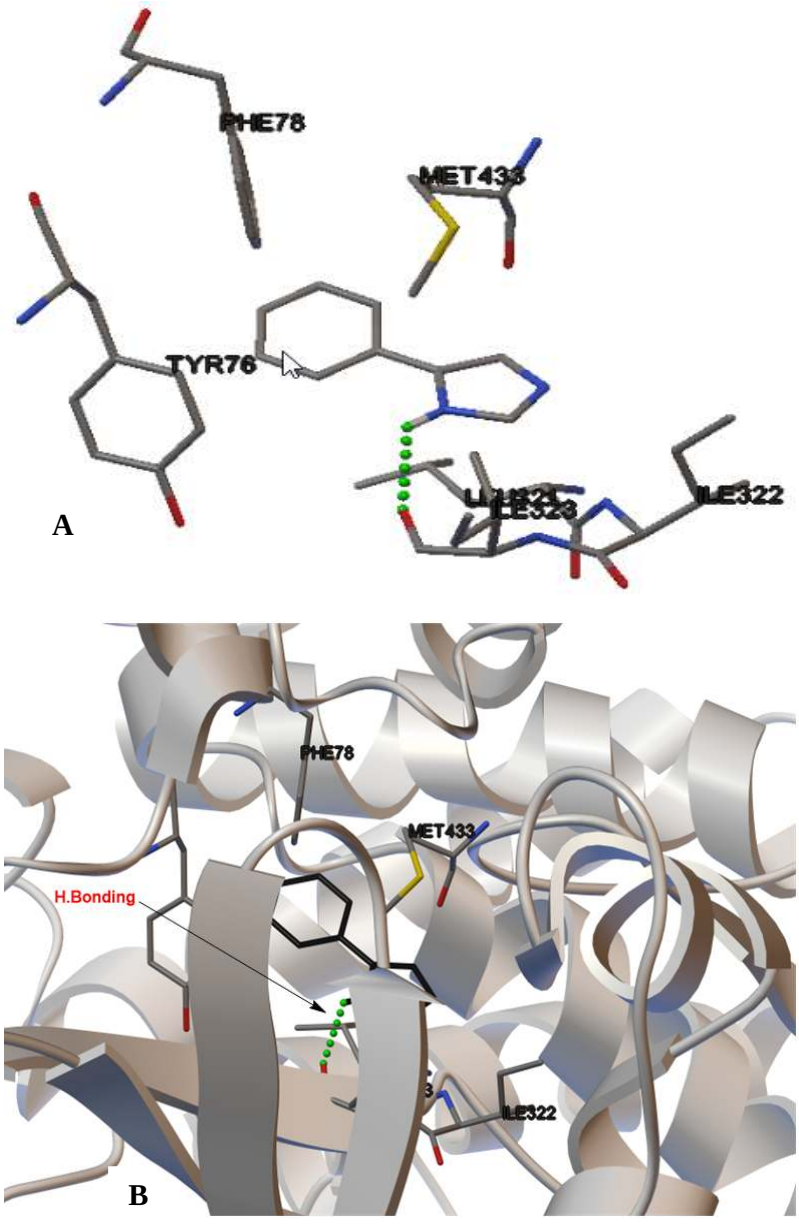

Fig. 5. (a) Docked conformation of compound 4 has been included in stickrepersentaion showing hydrogen bonding. (b) Hydrophobic interaction with hydrophobic amino acid residues with PHE78, TYR76, MET433, LEU321, ILE322. residue (ribbon format)

Table 4. Docking parameter for all ligands 3a-jandcytochrome P450 14alpha-sterol-demethylases (CYP51) of *M. tuberculosis* H37Rv. As well as with 4-Phenyl-1h-Imidazol

Properties	4-Phenyl-1h-Imidazol	Compounds									
		1	2	3	4	5	6	7	8	9	10
Binding energy	-5.59	-6.35	-6.07	-6.73	-8.63	-7.08	-6.99	-7.12	-5.86	-6.85	-5.92
Ki uM	80.31	22.07	35.65	11.58	474.92	6.46	7.52	6.04	50.76	9.45	45.44
Intermolecular energy	-5.89	-8.44	-8.45	-9.12	-11.01	-9.47	-9.08	-9.51	-8.54	-9.24	-8.01
vdW+Hbond+desolv energy	-5.72	-5.66	-5.25	-7.04	-8.59	-6.16	-6.85	-5.56	-6.23	-8.01	-4.74
Electrostatic energy	-0.01	-0.66	-0.06	-0.07	-0.36	-0.36	+0.02	-1.36	-0.26	+0.46	-0.97
Final total internal energy	-0.16	-0.80	-1.71	-0.76	-2.49	-0.66	-1.02	-0.74	-1.51	-1.54	-1.27
Torsional energy	0.30	2.09	2.39	2.39	2.39	2.39	2.09	2.39	2.68	2.39	2.09
Unbound system's energy	-0.16	-0.78	-1.08	-0.49	-2.3	-0.63	-0.89	-0.61	-1.54	-0.82	-1.18
Temperature (K)	298	298	298	298	298	298	298	298	298	298	298

From Table 4, the comparison between the compound understudy and the ligand 4-Phenyl-1h-Imidazol, showed the most compounds understudy exhibit the best results comparison with the ligand 4-Phenyl-1h-Imidazol. The results obtained will be helpful in designing a new series of drugs especially for the resistant tubercular bacteria. cytotoxicity must be taken into account for more studies for the compounds understudy.

4. CONCLUSION

Quantum chemical calculated parameters can be successfully used in the derived a designer QSAR capable of predicting the antitubercular activity values. The study indicated that predicted antitubercular activity values for pyrimidine derivatives compounds can be modeled by two methods stepwise (SW) and multiple linear regression (MLR),. The best equation which generated by the two methods was 1 eq and 2 eq with six and five parameters. The model depending on the eq. 1. (MLR) is the best produced model with very good statistical fit as evident SE = 9.06234 R-Sq = 94.9% R-Sq (adj) = 92.1% and F= 34.107, while the model depending on the Eq. 2. (SW) is the best produced model with very good statistical fit as evident SE= 8.89630 R-sq= 94.64% R-sq (adj) = 92.40% F=42.354. From the results the descriptors (T.E, nC=O, nC-O, H.F, μ, LogP) play an important role in effect on antitubercular activity properties of compounds, which allow chemists to elucidate and to understand how molecular structure influences properties.The docking study for the anti tuberculosis activity against *M. tuberculosis* H37Rv (PDB entry: 1E9X was done using Autodock software. The possible number of compounds interactions and the binding ability of the derivatives were predicted. The best docked pose was shown to have one hydrogen bond with PRO386. The molecular docking of 4-Phenyl-1h-Imidazol for comparison (used as the reference drug) with compounds understudy. The docking results indicate the compound 4-Phenyl-1h-Imidazol showed lower scores of docker energy. The most compounds understudy exhibit the best results comparison with the ligand 4-Phenyl-1h-Imidazol.

Modification and substitution on pyrimidine ring may lead to potential lead compounds for antimicrobial activity and good docking resulting. The results obtained will be helpful in designing of new series of drugs especially for the resistant tubercular bacteria. As well as Insilico approach helps in screening the appropriate molecules as drug targets. Hence, these compounds can be of lead importance in the development of pharmaceutical drugs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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