QSAR Studies on Chalcones and Flavonoids as Anti-tuberculosis Agents Using Genetic Function Approximation (GFA) Method

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Design of compounds having good anti-tubercular activity is gaining much importance in the field of tuberculosis research due to reemergence of antibiotic resistance strains. In this paper quantitative structure activity relationships (QSAR) were developed on chalcones, chalcone-like compounds, flavones and flavanones to understand the relationship between biological activity and structural features. Genetic function approximation (GFA) method was used to identify the descriptors that would lead to good regression equations. The best molecular descriptors identified were Jurs descriptors (Jurs charged partial surface area), hydrogen bond donor, principal moment of inertia, molecular energy, dipole magnetic, molecular area, absorption, distribution, metabolism and excretion (ADME) properties and Chi indices (Kier & Hall chi connectivity indices). Excellent statistically significant models were developed by this approach (r^2=0.8—0.97) for the four groups of compounds. The cross validated r^2 (XV r^2) which is an indication of the predictive capability of the model for all the cases was also very good (=0.79—0.94).

Key words quantitative structure activity relationship; genetic function approximation; anti-tuberculosis agent; highest occupied molecular orbital.

Tuberculosis is an infection caused by *Mycobacterium tuberculosis*, which commonly affects the respiratory tract, *i.e.* lungs.[1] It is termed as "a global health emergency" by world health organization (WHO) in 1993 as it affects 1.7 billion people per year, that is equal to one-third of the entire world population. The first line of drugs used in the treatment of tuberculosis (TB) is a combination of isoniazid, rifampicin, pyrazinamide and ethambutol. The high concentration of lipids in the cell wall of *M. tuberculosis* has been attributed to its resistant to antibiotics. The lipid fraction of cell wall consists of three major components mycolic acids, cord factor and wax-D. Isoniazid is known to inhibit the synthesis of mycolic acid. Ethambutol is known to inhibit the incorporation of mycolic acid into the cell wall. Rifampicin acts by binding to DNA-dependent RNA polymerase and inhibits initiation of RNA synthesis. Pyrazinoic acid, the active form of pyrazinamide, is reported by Zhang Y., *et al.* to inhibit *M. tuberculosis* membrane transport function and disrupt membrane energetics.[2] It is expected that the disease can be completely eliminated with the help of combination therapy, but these hopes were dashed with the advent of drug resistant strains. The development of drug resistant strains is due to point mutations in the bacterial chromosome, resulting in changes in the antibiotic target that renders the strain no longer susceptible to the drug.

Thus the increasing clinical importance of tuberculosis has lent additional urgency to researchers to identify new and effective antimycobacterial compounds. Literature survey reveals that chalcones, flavones and flavanones possess anti-inflammatory,[3] anticancer,[4] antileishmanial,[5] antimalarial,[6] antimicrobial and antioxidant[7] activities. It is reported that the chalcones and their derivatives are more effective against Gram-positive bacteria than against Gram-negative bacteria.[8] But it is interesting to note that they are also effective against this acid-fast bacillus which is neither Gram-positive nor negative. These compounds show very good activity against *H37Rv* strain. Understanding the effect of structural features on the activity would help the researchers to design new molecules that may exhibit higher activity. Quantitative structure activity relationship (QSAR) approach is better for designing new drugs when the target is not known or if there are multiple targets.

QSAR studies on heterocyclic analogues of salicylanilides performed through the combination of Free-Wilson and Hansch approach explains the influences of electronic and hydrophobic properties.[9] Gupta M. K., *et al.* have observed that topological descriptors are correlated with the anti-mycobacterial activity of nitro/acetamido alkenol and chloro/amino alkenol derivatives.[10] 3D-QSAR uses three-dimensional properties of the molecules (particularly steric and electrostatic factors) and correlates these descriptors with the biological activity. 3D-QSAR studies carried out by Shagufta, *et al.* on diaryloxy-methano-phenanthrene derivatives helped in optimizing the phenanthrene ring and its side chain.[11] Hydrophobicity of the molecule is found to play a major role in determining the antitubercular activity. Relationship between descriptors such as logP (hydrophobicity of the molecule) and dipole moment with toxicity of compounds is explained by Coleman M. D., *et al.*[12] Comparative molecular field analysis (CoMFA) and comparative molecular similarity index analysis (CoMSIA) techniques are applied on ring-substituted quinolines to arrive at relationship linking structure and activity. The study helped in elucidating the importance of the steric and electronic factors on the activity.[13] In the present paper QSARs are developed for four groups of compounds namely, chalcones, chalcone-like compounds, flavones and flavanones which have shown good anti-tuberculosis activity. Although QSAR studies for these compounds have not been reported in the literature similar analysis as listed above has been carried out for other anti-mycobacterial compounds.

Experimental

The structure and anti-tuberculosis inhibitory concentration of chalcones, chalcone-like compounds, flavones and flavanones was collected from the literature for developing the QSAR models.[14] The structure of various molecules, as shown in the Tables 1—4 was built and its energy was minimized

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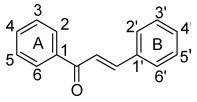
Table 1. Anti-tuberculosis Activity of Chalcones



S. No	Compounds	B-ring					A-ring			% inhibition at 12.5 μg/ml	
		2′	3′	4′	5′	6′	2	3	4	Data	Model
1	1	OH	—	OCH_3	—	—	—	—	—	78	58.65
2	2	OH	—	—	—	OCH_3	—	—	OCH_3	75	62.71
3	3	OH	—	—	Phenyl	—	—	—	—	68	54.86
4	4	—	—	NO_2	—	—	—	—	OCH_3	62	54.03
5	5	OH	—	—	—	—	—	—	—	61	60.99
6	6	OH	—	OCH_3	—	OCH_3	—	—	OCH_3	40	46.83
7	7	OH	—	OCH_3	—	—	—	—	OCH_3	32	39.55
8	8	OH	—	—	—	—	—	OH	—	18	41.44
9	9	OH	—	—	—	—	—	NH_2	—	11	7.25
10	10	OH	—	—	NH_2	—	—	—	—	6	2.88
11	11	—	—	NH_2	—	—	—	—	—	5	19.14
12	12	F	—	—	—	—	—	—	OCH_3	82	84.91
13	13	OH	—	—	—	F	—	—	OCH_3	66	62.42
14	14	OH	—	F	—	—	—	—	OCH_3	63	53.29
15	15	OH	—	—	—	—	—	Cl	—	90	85.73
16	16	OH	—	Cl	—	—	—	—	—	89	74.96
17	17	OH	—	—	Cl	—	—	—	—	67	77.67
18	18	OH	—	—	—	—	—	—	Cl	67	69.51
19	19	OH	—	Cl	—	—	—	—	OCH_3	57	57.32
20	20	OH	—	—	—	—	Br	—	—	83	102.06
21	21	OH	Br	—	—	—	—	—	—	79	74
22	22	OH	—	—	—	—	—	—	Br	70	49.06
23	23	OH	—	—	Br	—	—	—	—	68	66.08
24	24	OH	—	Br	—	—	—	—	—	57	58.85
25	25	OH	—	Br	—	—	—	—	OCH_3	25	32.74
26	26	OH	—	—	Br	—	—	—	OCH_3	23	36.71
27	27	OH	—	Br	—	—	NH_2	—	—	12	3.18
28	28	OH	—	—	Br	—	NH_2	—	—	8	10.13
29	29	OH	—	—	—	—	—	I	—	92	105.21
30	30	—	NH_2	—	—	—	I	—	—	88	72.8
31	31	OH	—	—	I	—	—	—	—	51	48.94
32	32	OH	—	I	—	—	—	—	—	21	37.26
33	33	OH	—	—	—	—	—	—	I	21	24.19

using the Consistent-Valence Force Field (CVFF) available in Cerius^2 software® (Accerlys Inc, U.S.A.). CVFF is commonly used for the minimization of small molecules and macromolecules.[15] Forty-eight descriptors that include topological indices, spatial, charge, geometrical, constitutive properties, quantum mechanical and thermodynamic were evaluated for all the compounds. Several literature references[16—18] give a detailed description of these descriptors. A GFA technique was used to select the best set of descriptors from the forty eight descriptors, so that it gives the most appropriate QSAR. The problem that is faced frequently by a researcher is that of a small number of observations (experiments) and a large number of molecular parameters in the descriptor pool. One has to select the best set of descriptors that represent the molecule from this large set. At times selecting the wrong set of descriptors could lead to chance correlations or incorrect understanding.

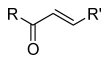
According to researchers the quality of a QSAR depends on two factors namely, the kind of molecular descriptors selected and the method used to extract the useful molecular information. These problems are addressed by the use of GFA. This is a useful technique for searching in a large parameter space when the data is small. This technique can be used together with standard regression analysis for constructing QSAR. This method provides multiple models that are created by evolving random initial models using different descriptors. Models are improved by performing a crossover operation to recombine terms of better scoring models. The GFA algorithm approach has a number of important advantages over other techniques such as, it builds multiple models rather than a single model and it automatically selects which features are to be used in the models *etc.* GFA has been used by other researchers as well to develop good QSAR models.[19,20]

The goodness of the regression fits are estimated using parameters such as, r^2 ($=1-$SSE/TSS), r^2_{adj} ($=1-(n-1)(1-r^2)/(n-p-1)$), XV r^2 (cross-validated $r^2=1-$PRESS/TSS), F ratio ($=(n-2)r^2/(1-r^2)$) and MSSE (=mean sum of square of error=SSE/n) where, TSS=total sum of squares and SSE=sum of squares, PRESS=predicted sum of squares based on leave-one-out method.[21] The quantity r, called the correlation coefficient, measures the strength and the direction of the relationship between two variables. In bootstrap validation, K n-dimensional groups are generated by a randomly repeated selection of n-objects from the original data set. Each group of data is always of n-dimension. The model obtained on the first selected objects is used to predict the values for the excluded sample. From each bootstrap sample the statistical parameter of interest is calculated. Bootstrap r^2 (BS r^2) is the average squared correlation coefficient calculated during the validation procedure.[22] The root mean square error (also known as the standard error of the estimate) is the square root of the residual mean square and it is an indication of the quality of the fit. It is the standard deviation of the data about the regression line, rather than about the sample mean. A large F indicates that the model fit is not a chance occurrence. If r^2, r^2_{adj}, and XV r^2 are above a value of 0.6 it indicates a good model fit.

Results and Discussion

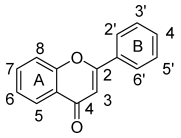
Table 5 lists the best QSAR models derived for the series of chalcones, chalcone-like compounds, flavones and flavanones using the reported biological activity. The descrip-

Table 2. Anti-tuberculosis Activity of Chalcone-Like Compounds



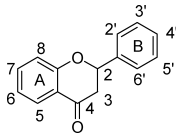
S. No	Compounds	R	R′	% inhibition at 12.5 μg/ml	
				Data	Model
34	34	4-Fluorophenyl	Pyridin-3-yl	98	77.53
35	35	3-Hydroxyphenyl-	Phenanthren-9-yl	97	76.63
36	36	Pyridin-3-yl	Phenanthren-9-yl	96	62.23
37	37	Furan-2-yl	3-Phenyl	96	120.26
38	38	Phenanthren-2-yl	2-Aminopyridino-3-yl	74	68.29
39	39	3-Flurenyl-	2-Aminopyridino-3-yl	53	75.63
40	40	Pyridin-2-yl	Pyridin-2-yl	42	39.47
41	41	Naphthalen-1-yl-	Phenyl-	37	23.64
42	42	Pyridin-2-yl	4-Dimethylaminophenyl-	16	35.86
43	43	4-Bromo-2-hydroxyphenyl-	Furan-2-yl	17	34.80
44	44	Pyridin-4-yl	Indol-2-yl	12	9.78
45	45	2-Hydroxy-4-methoxyphenyl-	Furan-2-yl	3	9.48
46	46	4-Aminophenyl	2-Aminopyridin-3-yl	7	10.39
47	47	Pyridin-4-yl	4-Dimethylaminophenyl-	1	5.009

Table 3. Anti-tuberculosis Activity of Flavones



S. No	Compounds	3	5	6	7	8	2′	3′	4′	% inhibition at 12.5 μg/ml	
										Data	Model
48	48	OH	—	I	—	—	—	—	—	64	47.46
49	49	OH	—	—	—	—	—	Br	—	60	50.56
50	50	OH	—	—	Cl	—	—	—	—	58	51.43
51	51	OH	—	Br	—	—	—	—	—	58	47.73
52	52	OH	—	—	Cl	—	—	—	—	52	51.43
53	53	OH	—	—	F	—	—	—	OCH_3	50	39.19
54	54	OH	—	Cl	—	—	—	—	OCH_3	48	33.29
55	55	OH	—	—	—	—	—	—	OCH_3	48	51.91
56	56	OCH_3	Br	—	—	—	—	—	—	44	50.10
57	57	OH	—	—	I	—	—	—	—	43	47.95
58	58	OH	—	—	—	—	—	—	—	38	47.28
59	59	—	—	—	—	—	—	—	OCH_3	29	36.09
60	60	OH	—	F	—	—	—	—	OCH_3	29	37.25
61	61	Br	—	—	—	—	—	—	OCH_3	28	43.90
62	62	—	—	—	—	—	—	—	Br	26	18.40
63	63	OH	—	Br	—	—	—	—	OCH_3	24	30.61
64	64	—	—	—	—		Br	—	—	23	18.29
65	65	—	—	—	—	—	I	—	—	22	14.90
66	66	—	—	—	—	—	—	I	—	22	13.19
67	67	—	—	—	I	—	—	—	—	20	23.37
68	68	Br	—	—	OCH_3	—	—	—	Cl	19	25.52
69	69	—	—	—	—	—	—	—	OH	18	6.24
70	70	—	—	—	F	—	—	—	—	15	18.87
71	71	—	—	—	Br	—	—	—	—	15	12.82
72	72	—	—	I	—	—	—	—	OCH_3	15	14.44
73	73	Benzoyl	—	—	Benzoyl	—	—	—	—	12	11.28
74	74	—	—	—	—	—	—	—	Cl	7	22.94
75	75	—	—	F	—	—	—	—	—	7	5.25
76	76	—	—	—	—	I	—	—	—	5	14.73
77	77	—	—	COOH	—	—	—	—	OCH_3	2	3.87
78	78	—	—	—	—	—	OH	—	—	1	11.75

Table 4. Anti-tuberculosis Activity of Flavanones



S. No	Compounds	3	5	6	7	8	3′	4′	5′	% inhibition at 12.5 μg/ml	
										Data	Model
79	79	OCH_3	—	—	—	Br	—	—	—	87	85.54
80	80	—	—	—	—	—	Br	—	—	73	78.30
81	81	OH	—	—	—	—	Cl	—	—	63	60.85
82	82	—	—	—	Br	—	—	—	—	53	43.63
83	83	—	—	—	OCH_3	—	—	—	—	48	48.63
84	84	—	—	Cl	—	—	—	—	—	30	31.53
85	85	—	—	I	—	—	—	—	—	27	32.04
86	86	Br_2	OCH_3	—	OCH_3	—	OCH_3	OCH_3	OCH_3	16	16.68
87	87	—	—	Br	—	—	—	—	—	8	7.81

Table 5. Regression Statistics for the Best QSAR Models

Model	Compounds	n	r	r^2	r^2_{adj}	F	XV r^2	BS r^2	PRESS	Error
1	Chalcone	33	0.92	0.85	0.83	39.49	0.79	0.85	5550.59	0.0016
2	Chalcone-like compounds	14	0.97	0.94	0.91	37.17	0.87	0.94	2499.84	0.0001
3	Flavone	31	0.92	0.86	0.83	38.90	0.81	0.86	1958.23	0.0019
4	Flavanone	9	0.99	0.97	0.96	61.20	0.94	0.97	342.08	0.0007

tors which gave the best models for all the four groups of compounds are Jurs descriptors surface-weighted charged partial surface (WNSA-3), atomic charge weighted negative surface area: sum of the product of solvent-accessible surface X partial charge for all negatively charged atoms (PNSA-3) and relative positive charge surface area: solvent-accessible surface area of the most positive atom divided by descriptor (RPCS), principal moments of inertia (PMI-mag), dipole-mag, Kier and Hall-molecular Connectivity index valence-modified CHI-2 (CHI-V-2), order 1 chi index, related to the number of edges and rings order: number of skeleton atoms in the subgraphs considered (CHI-1), valence-odified CHI-3_C, C: cluster (CHI-V-3_C), valence-modified CHI-3_P, V: valence-modified connectivity index (CHI-V-3_P), conformational energy (Energy), H-bond donor and HOMO. Blood Brain Barrier (BBB) permeation depends on multiple factors such as H-bonding capacity, local hydrophobicity, molecular size, and lipophilicity. It is observed that for all the models the data fit (r^2=0.8—0.97) and the predictive capability (XV r^2>0.79) is good. Other statistical measures such as r^2adj, F-value and PRESS for all the cases were found to be satisfactory. The QSAR models for the four different groups of compounds are shown below.

Model-1 is developed to predict the anti-tubercular activity of chalcone analogues. The statistically significant Eq. 1 shows a positive correlation with CHI-V-2 and negative correlation with H-bond donor, PMI-mag and Jurs WNSA-3 as shown below

$$\text{activity} = 3.45 + 38.14(\text{CHI-V-2}) - 31.93(\text{H-bond donor}) - 0.11(\text{PMI-mag}) - 1.11(\text{JursWNSA-3}) \quad (1)$$

The structural descriptor namely H-bond donor denotes the number of hydrogen-bond donors present in the compounds, the spatial descriptor PMI calculates the principal moments of inertia about the principal axes of a molecule and Jurs WNSA-3 represents the partial weighting of the surface accessible portions of the molecule. Valence-modified CHI-2 connectivity index (CHI-V-2) is a topological descriptor that gives information related to the connectivity of atoms namely, the number of bonds present in the atoms. This is an indication of size, degree of branching and flexibility. H-bond donor, flexibility and C logP are part of "Lipinski rule of 5" which describes the drug likeliness property and they play a major role in designing anti-tubercular drugs.[23] Moment of inertia is also an indication of the size and shape of the molecule.

Model-2 is developed to predict the anti-tubercular activity of chalcone-like compounds. The Eq. 2 shows a positive correlation with CHI-1 and conformational energy, negative correlation with Jurs PNSA-3 and CHI-V-3_C.

$$\text{activity} = 186.53 - 2.33(\text{Jurs PNSA-3}) - 2.62(\text{CHI-V-3\_C}) + 1.34(\text{energy}) + 17.85(\text{CHI-1}) \quad (2)$$

Conformational energy is the internal energy of the molecule, related to the stability and biological activity (lowest energy conformer will have highest biological activity) of the molecule. Jurs descriptor PNSA-3 is the atomic charge weighted negative surface area, namely sum of the product of solvent-accessible surface area and partial charge for all negatively charged atoms. Kier and Hall molecular connectivity indices CHI-V-3_C and CHI-1 give information regarding the connectivity of the various atoms in the compound. Con-

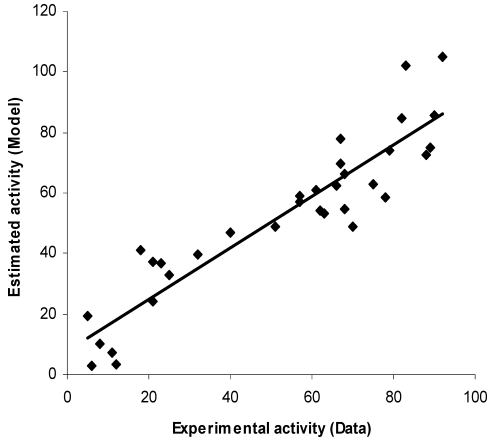


Fig. 1. Graph between Experimental and Estimated Activity of Chalcones

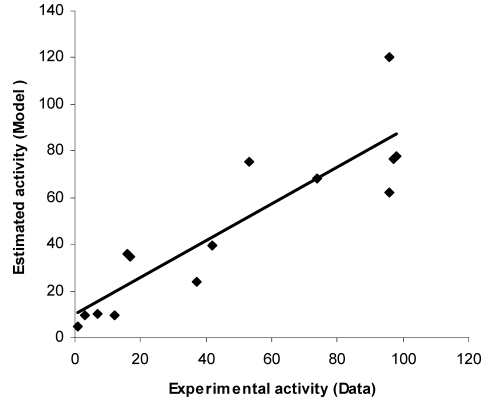


Fig. 2. Graph between Experimental and Estimated Activity of Chalcone-Like Compounds

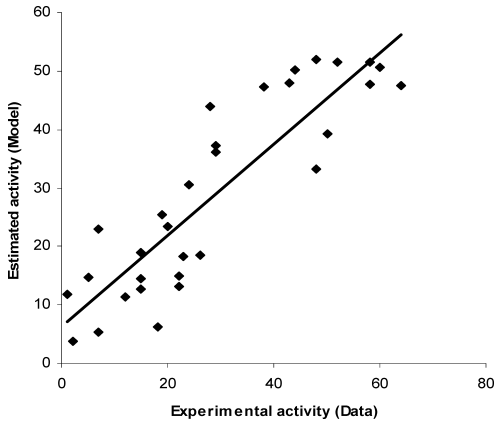


Fig. 3. Graph between Experimental and Estimated Activity of Flavones

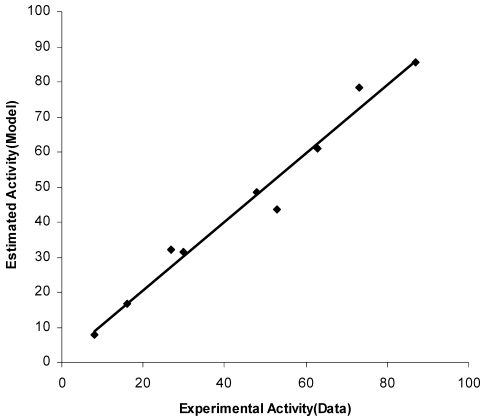


Fig. 4. Graph between Experimental and Estimated Activity of Flavanones

tributions of connectivity indices in QSAR in predicting activity against *Mycobacterium avium* has been reported by other researchers as well.[24)]

Model-3 is developed to predict the anti-tubercular activity of flavone analogues. The statistically significant Eq. 3 shows a positive correlation with Jurs RPCS and conformational energy, and negative correlation with CHI-V-3_P and ADME_BBB_Level_2D.

$$\text{activity} = 56.90 - 19.87(\text{ADME\_BBB\_Level\_2D}) + 7.81(\text{Jurs RPCS}) + 0.39(\text{energy}) - 11.13(\text{CHI-V-3\_P}) \quad (3)$$

Jurs RPCS is a measure of the relative positive surface charge of the molecule. ADME_BBB_Level_2D measures BBB permeation value of the compounds which is computed using actual solvent-accessible surface area using either 3-D or both 2-D and 3-D models of the molecule.

Model-4 is developed to predict the anti-tubercular activity of flavanone analogues. This Eq. 4 shows a negative correlation with Energy, HOMO and Dipole-mag.

$$\text{activity} = 190.16 - 0.91(\text{energy}) - 19.37(\text{dipole-mag}) - 2.70(\text{HOMO}) \quad (4)$$

Molecules with high HOMOs can donate electrons with ease and are hence relatively reactive, compared to molecules with low HOMOs. Thus HOMO measures the nucleophilicity of a molecule. Its importance has been previously reported by other researchers.[12,25)] The dipole mag descriptor is a 3D electronic descriptor that indicates the strength and orientation behavior of a molecule in an electrostatic field measured in Debyes units. Previous contribution lists dipole-mag, as an important descriptor in antitubercular activity.[26)]

Figures 1 to 4 compare the experimental and the predicted anti-tubercular activities for all the four cases. The graphs clearly show the goodness of the model fit.

Our recent research work related to the synthesis, anti-mycobacterial evaluation and QSAR studies of twenty three analogues of chalcones with methylthio, dimethylamino, methoxy substitutions at 2-, 3-, 4-, and 5-position in the A- and B-rings also showed the importance of ADME_BBB_Level_2D, CHI-V-1, PMI-mag and H-bond donor descriptors (paper in communication). The models developed there were similar to the ones reported in this paper.

Conclusion

QSARs were developed for the reported anti-tuberculosis activity of chalcones, chalcone-like compounds, flavones and flavanones using a robust statistical technique such as GFA. The generated equations in each model were analyzed, for the goodness of fit and their predictive capability. Jurs descriptors, Kier and Hall molecular connectivity indices, dipole-mag and conformational energy have contributed significantly to the observed activity. The analysis also points out to the importance of the presence of hydrogen bond donor, PMI-mag and HOMO. This study indicates that these re-

ported compounds are more lipophilic in nature and hence, as expected exhibit good activity since *M. tuberculosis* has a high concentration of lipid layer. These reported models could be explored further to design potent, newer compounds having better antimycobacterial activity.

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