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QSAR modeling and molecular docking studies of 3, 7-disubstituted quinoline derivatives against mycobacterium tuberculosis (TB)

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Abstract
A quantitative structure-activity relationship (QSAR) study has been carried out for a set of 15 quinolone derivatives to correlate and predict the mycobacteria activity against mycobacterium tuberculosis (TB) using Molecular Operating Environment (MOE) program. The statistical regression expressions were obtained using partial least squares (PLS) method which can effectively establish a correlation model between the molecular descriptors and associated properties. A good QSAR model is generated by the training dataset with squared correlation coefficient (r^2) = 0.8228, cross validation coefficient (Q^2) = 0.9071, standard deviation (s) = 0.16457 and correlation coefficient (r) for the external dataset is 0.9892 while r^2 of predicted dataset (test set) is 0.9896. Model obtained was used to predicted the activity against mycobacterium tuberculosis (TB) for a set of 34 designed 3, 7-disubstituted quinolone derivatives. Finally, molecular docking analysis was carried out to better understand the interactions between (A) test, (B) designed compounds and the active site of the mycobacterium tuberculosis (TB) target site.

Keywords: QSAR; descriptors; validation; tuberculosis (T. B); biological activity; docking

Introduction
Tuberculosis (T.B), a contagious disease transmitted through the air, and caused by the mycobacterium tuberculosis is an important world-wide public health problem, which was declared a global health emergency in 1933 by the world health organization (WHO). According to statistics, one-third of the world's population is currently infected with TB bacillus, each year, 8 million people worldwide develop active TB and about 1.7 million dies (De Souza *et al.*, 2009) [3]. Mycobacterium tuberculosis is a bacterial species responsible for causing tuberculosis (TB). It mainly affects the lungs and other parts of the body such as spine, kidney, and brain unless urgent treatment is provided. Tuberculosis remains one of the most prevalent infectious bacterial diseases, resulting in the death of 1.4 million people worldwide (Adeniji *et al*., 2018). World Health Organization (WHO) has recommended standard strategy for the treatment of the tuberculosis by a program called DOTS (Directly observed treatment, short-course), which include six-month regimen of four first-line TB-drugs, Isoniazid, Rifampicin, Ethambutol and pyrazinamide (Nayak *et al*., 2016). In spite of the availability of these drugs, rapidly increasing multi drug resistant TB (MDR-TB) has resulted enormous difficulty in fighting against TB. In addition, the weak or no activity of the current drugs against extremely drug resistant TB (XDR-TB), particularly in HIV infected patients is a serious problem in TB control (Corbett *et al.*, 2003). However, due to the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis, this poses a big challenge towards the successful treatment of tuberculosis (Lamichhane *et al.*, 2011). This led to development of new therapeutics against diverse strains of m. tuberculosis due to high impact of MDR and recently XDR in TB treatment we urgently need new drugs and strategies to treat this disease efficiently (Organization 2017).
Quantitative structure-activity relationship (QSAR) is an essential tool in modern chemistry that is used to find a correlation between biological activities measured for a panel of compounds and molecular descriptors (Hadaji *et al*., 2017). QSAR plays a crucial part in novel drug design via a ligand-based approach (Panthananickal *et al*., 1979).
The key success of the QSAR method is the possibility to predict the properties of new chemical compounds without the need to synthesize and test them. This technique is broadly utilized for the prediction of physicochemical properties in the chemical, industrial, pharmaceutical, biological, and environmental spheres (Wong *et al*., 2014). Moreover, the application QSAR to molecular and drug design has led to the inclusion of tools developed in the field of computational chemistry using as tool to determine the quantitative correlation between structures and activity (Mansouri *et al.*, 2013).
In QSAR analysis, one or more molecular descriptors are related with the molecular activity by means of a statistical analysis. The main objective of this analysis is the creation of statistical models through which it is possible to predict the biological activity of novel compounds that have not been tested yet. Also, through a QSAR study one can give a mechanistic interpretation to the activity of a certain family of compounds and direct

their optimization. The main steps involved in the development of a QSAR model are the selection of the database of compounds with known biological activities (training set), the calculation of molecular descriptors, and the development of a statistical model that relates the activity with the calculated descriptors and, later, the evaluation of the generated model with a test set (Vilar *et al.*, 2008).

The aim of this study was to develop QSAR model to predict the activity of a series of quinoline derivatives as potent anti-mycobacterium tuberculosis compounds and to elucidate the interaction between the inhibitor molecules and mycobacterium tuberculosis target site. In this context, I collected summarize group of series quinoline derivatives with biological activity to QSAR study to obtain model, which were used to predict the biological activity of some designed compounds against TB treatment.

Experimental

QSAR Studies

A series of quinoline derivatives reported by (De Souza *et al.*, 2009) [3], was used to QSAR study. The experimental IC_{50} (IC_{50} in microgram per milliliter) values inhibition cell growth (TB) was converted to pIC_{50} using the equation (pIC_{50} = - log IC_{50}). The data set compounds were split in to training set and test set by employing Kennard and Stone's algorithm. The training set comprises 80% of the data set which was used to build the model, while the remaining 20% of the data set (test set) was used to validate the built model. The structures of all compounds training and test set along with their actual and predicted biological activities are showing in Table (1).

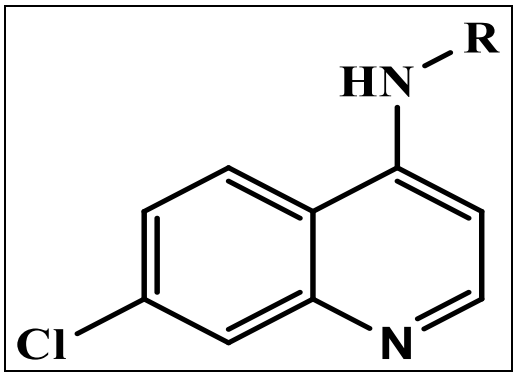


Fig 1

Table 1: Experimental IC_{50}, experimental pIC_{50}, predicted pIC_{50} and residual values of a series quinoline derivative using training and test sets for predict anti-mycobacterium tuberculosis reported by (De Souza *et al.*, 2009).

No	R	IC_{50}(µM) (Exp)	pIC_{50} (Exp)	pIC_{50} (predict)	Residual
1	CH_2CH_2Cl	12.50	4.900	4.3088	-0.0088
2	$CH_2CH_2N_3$ (LO)	50.00	4.300	……	……
3	CH_2CH_2NHBN T	50.00	4.300	4.232	0.0679
4	$(CH_2)_6NH_2$	25.00	4.600	4.8357	-0.2357
5	$(CH_2)_8NH_2$ T	6.250	5.200	5.1875	0.0125
6	$(CH_2)_{10}NH_2$	3.120	5.500	5.3636	0.1364
7	CH_2CH_2NHi-Pr	100.0	4.000	4.1370	0.1630
8	$CH_2CH_2CH_2CH_3$	12.50	4.900	4.5858	0.3172
9	$CH_2CH_2CH_2Cl$ (LO)	50.00	4.300	……	……
10	H	100.0	4.000	3.8393	0.1607
11	CH_2CH_2NHCyclohexyle	100.0	4.000	4.3608	0.3608
12	Propyl	50.00	4.300	3.9782	0.0218
13	i-Propyl	50.00	4.300	4.3353	-0.0353
14	CH_3	100.0	4.000	4.1585	-0.1585
15	$SCH_2CH(C_2H_5)$ CH_2Cl T	50.00	4.300	4.400	-0.1000

*T = test set. *LO = leave out.

Molecular Descriptors Calculation

The correlation matrix data was used to select the best subset of physicochemical properties (highly correlated chemical descriptors). The descriptors were selected by the ratio (5:1) from each five compounds in the training set one descriptor was selected (Dutta *et al*., 2007). The first were drawn all compounds of training and test set using ACD/Lab (version 12.01, Build 36726, 26 Feb 2010) freeware program and saved at''mol 2000'' file format. Then, was opened file by MOE 2009.1010 chemical computing group Inc., program and minimized energy. A total of 15 molecular descriptors were calculated by MOE program and decrease to nine depended of

high correlation matrix data between them and logP. Nine descriptors were left including log octanole/water partition (logP o/w), dipole moment (MNDO - dipole), electrostatic energy (E-ele), Absolute different in surface areas (DASA), Absolute different in charge-weighted areas (DCASA), potential energy (E), Non-bonded Energy (E-nb), Dipole moment (AM1-dipole), Dipole moment (MP3-dipole), the values of descriptors, named listed in Table (2) and Table (3) respectively and details of correlation matrix for chemical descriptors showed in figure (1).

Table 2: the values of descriptors calculated for training set compounds.

No	logP(o/w)	E-ele	DCASA	PM3-dipole	E	AM1-dipole	DASA	MNDO-dipole	E-nb
1	3.34	-7.05	27.36	3.77	37.92	4.68	12.07	4.49	26.4
2	1.57	-28.81	85.56	2.54	19.37	3.26	26.28	2.92	2.21
3	1.58	-28.81	102.27	2.55	19.37	3.27	31.41	2.47	2.20
4	3.39	-7.11	25.50	3.73	42.00	4.59	11.25	4.68	26.90
5	3.78	-7.05	25.61	3.67	37.71	4.73	11.30	4.50	27.52
6	2.06	-7.24	42.53	3.36	37.50	4.09	18.52	3.94	20.52
7	3.97	3.82	14.08	4.17	49.00	5.10	4.45	4.41	47.27
8	2.95	3.89	26.11	3.72	45.50	4.72	8.25	4.42	41.40
9	3.34	-7.04	28.19	3.77	37.92	4.65	12.44	4.50	26.39
10	2.38	-7.06	45.12	3.50	39.96	4.30	19.91	4.37	24.09

Table 3: List of some descriptors used in the QSAR optimization model.

No	Descriptor's symbol	Name of descriptor(s)	Class
1	log (o/w)	Log octanole/water partition coefficient	2D
2	E-ele	Electrostatic Energy	3D
3	DCASA	Absolute different in charge-weighted areas	3D
4	PM3-dipole	Dipole moment	3D
5	E	Potential Energy	3D
6	AM1-dipole	Dipole moment	3D
7	DASA	Absolute different in surface areas	3D
8	MNDO-dipole	Dipole moment	3D
9	E-nb	Non-bonded Energy	3D

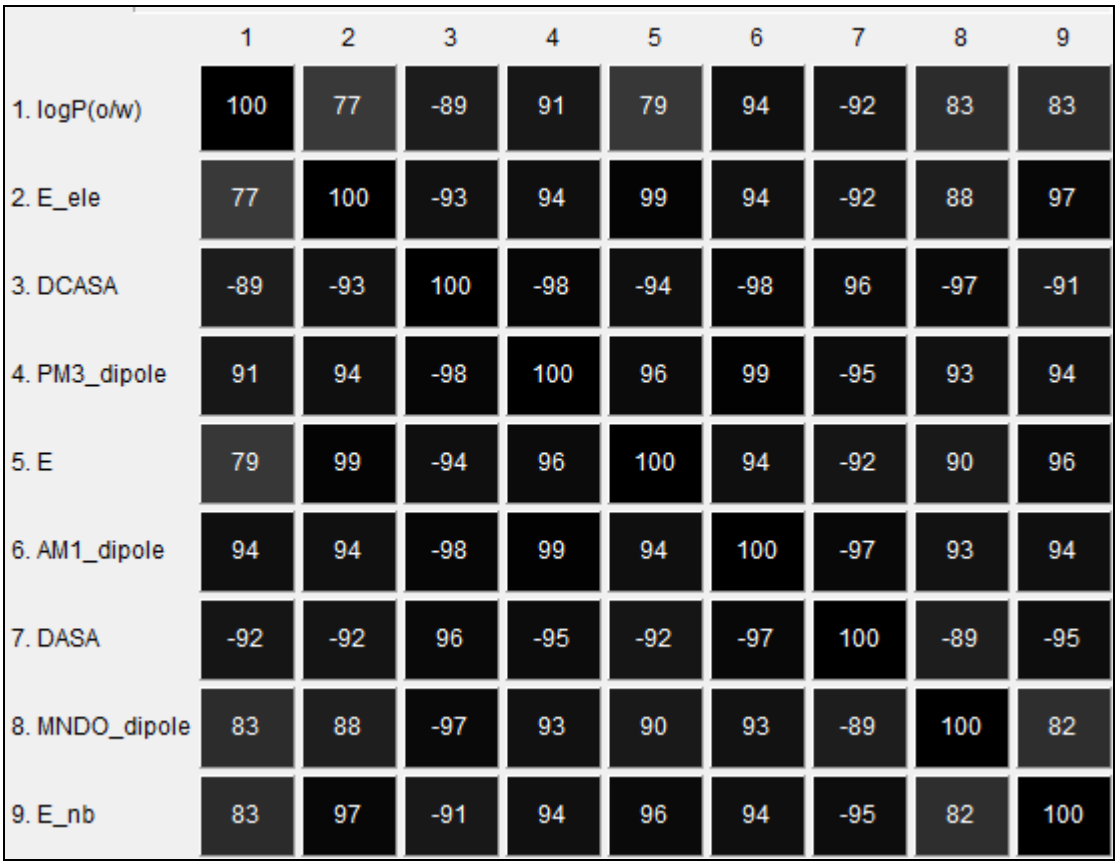


Fig 2: details of correlation matrix for chemical descriptors in training set.

QSAR model development

In this study, QSAR models were developed from the dataset using the methods MLR and PLS to screen potential leads against TB within a training dataset set. Therefore, to robust QSAR model equation was derived by MLR; irrelevant descriptors were removed through a forward stepwise method leading to a selection of two (2) descriptors (logP o/w, DCASA Absolute different in charge-weighted areas) in the final QSAR regression for 10 compounds of training set. A QSAR model equation was derived by using PLS statistical methods (Equations). The statistical quality of each regression model was evaluated using a square correlation coefficient ($r^2 > 0.8$), cross-validated (r^2 or $q^2 > 0.5$) and root mean square error (RMSE) (Xu *et al.,* 2015). The coefficient r^2 indicated how well the equation fits the data. The q^2 was considered as an indicator of the predictive performance and stability of a QSAR mode (Sharma *et al.,* 2010). Finally, to exclude false and justified regression equation used statistical parameter such as standard error estimate (s) and F- test values, the calculation of statistical parameters was carried out by using statistical program SPSS version 24.10

$pIC_{50} = 0.95860 + 0.74495 \times \log P\ (o/w) + 0.03159 \times DCASA$ (1)

The developed QSAR model equation showed a relationship between predicted pIC_{50} values (-log pIC_{50}) and correlated two chemical descriptors. It is evident from the model equation that the molecular descriptors namely DCASA (Absolute different in charge-weighted areas, and logP (log octanol/water partition coefficient are positively correlated.

Model validation

For the validation of the predictive power of a QSAR model, two basic principles (internal validation and external validation) used in this study to developed QSAR models by the following procedure (Yadav *et al*., 2014).

(i) Internal validation: in this step was carried out using leave more out (LMO) methods of cross validation (q^2). For calculation q^2, each molecule in the training set was eliminated once and the activity of the eliminated molecules was predicted by using the model developed by the remaining molecule.

(ii) External validation: in this step the predictive ability of the selected model was confirmed by external of test set compounds which is also denoted with predicted - r^2.

The observed activities and those provided by QSAR studies (Equation 1) for training and test set were presented in Tables (3) and (4) respectively. It should be noted that the predicated anti-tuberculosis activities by obtained QSAR model was close to those experimentally observed, indicating that these models can be safely applied.

Predict the activity of designed quinoline diazenyl compounds (1 - 34)

A set of designed quinoline diazenyl compounds (1 - 34) were sketched using the computer software chemo office program. These compounds were not used in the developed QSAR model, but sketched to predict their anti-mycobacterial activity against Tuberculosis (T.B) by using developed QSAR model (equation 1). The predict activity of all sketched structure were listed in table (4).

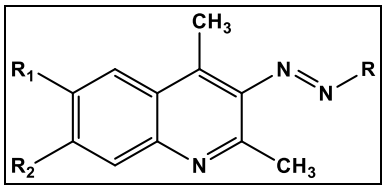
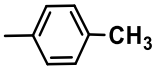
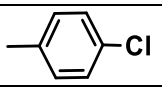
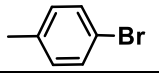
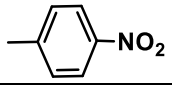
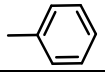
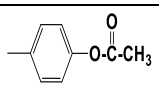
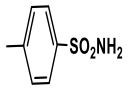
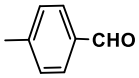
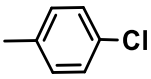
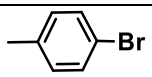
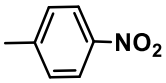
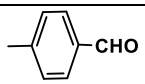
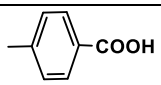
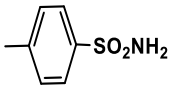
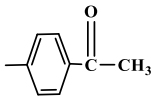
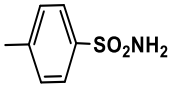
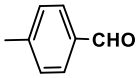
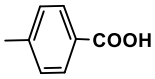
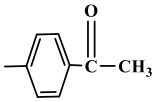
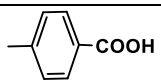
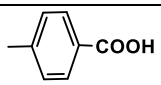
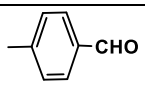
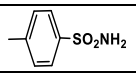
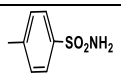
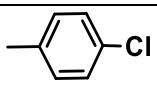
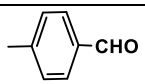
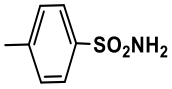
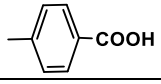
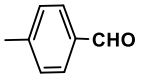
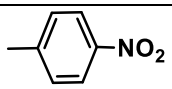
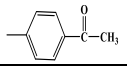


Fig 3

Table 4: Structures of some designed of 3,7- disubstituted quinoline derivatives with their predicted pIC_{50} values against mycobacterial tuberculosis (TB).

Comp. No	R	R_1	R_2	Molecular weight	Predicted pIC_{50}
1		$-CH_3$	-H	289.38	9.715
2		- Cl	-H	330.22	13.120
3		-Br	-H	419.12	16.904
4		$-NO_2$	-H	261.37	12.239
5		-H	-H	233.31	9.158
6		CH_3COO^-	-H	377.40	9.773

7		-SO_2NH_2	-H	363.42	4.785
8		-CHO	-H	261.28	11.077
9		-COOH	-H	293.28	11.653
10		-CH_3	-H	309.80	6.792
11		-CH_3	-H	354.25	8.208
12		-CH_3	-H	289.38	9.185
13		-CH_3	-H	303.37	10.204
14		-CH_3	-H	319.36	9.658
15		-CH_3	-H	354.43	7.233
16		-CH_3	-H	317.39	8.520
17		-Cl	-H	374.85	12.297
18		-Cl	-H	295.73	4.850
19		-Cl	H	339.78	8.606
20		-$COCH_3$	H	333.35	7.921
21		-CHO	-H	384.47	10.097
22		-SO_2NH_2	-H	368.47	5.140
23		-SO_2NH_2	-H	382.44	7,509
24		-$COCH_3$	-H	419.30	4.791
25		-Br	-H	330.22	14.981
26		-H	-Cl	317.35	12.580
27		-H	-CHO	374.85	11.448
28		-H	-Cl	349.35	11.410
29		-H	-COOH	333.25	8.761

30		-H	-COOH	289.32	11.066
31		-H	$-NO_2$	289.32	10.004
32		CH_3	H	275.63	8.6064
33		CH_3CO-	H	303.37	8.6067
34		CH_3CO-	H	345.40	7.5305

Statistical methods

To complete select of quality QSAR model were justified by statistical parameters such as the root mean square error (RMSE), correlation coefficient (r), square correlation coefficient (r^2), standard error of estimate (s) and F-test value (ratio between the variance of observed and calculated activities, F). Calculation of statistical parameters were carried out by using statistical program SPSS version 22, see table (5).

Table 5: statistical parameters used for statistical of model.

r	r^2	RMSE	Q^2	S	F	P value
0.907	0.823	0.219	0.801	0.164	37.43	0.0001

Docking study

Molecular docking is expedient tool used in the drug discovery field to investigate the binding compatibility of molecules (ligands)to target receptor (Hawkins *et al*., 2007).

In this's study 34 compounds of quinoline derivatives drawing by ACD/lab and saves as (mol file 2000) formats and opened in Molecular Operating Environment (MEO). The 3D proteins of structure compounds and hide hydrogen atoms from Linder then compute energy minimize and save all compounds in molecular data base as (mdb) file for run to dock. The *in vitro* structure of the receptor of mycobacterium tuberculosis (TB) $H_{37}Rv$ strain protein (PDB code = 6KGH) was download from protein data bank (pdb). The pdb file was reported from MEO program to prepared receptor and from sequins (SEQ) to deleted water molecules. To prepared ligand and validation select serve and map from compute and save file as pdb file. After that prepared data base for all design compounds one by one and save all files in specific folder after energy minimize. To run validation docked from newly design compounds done from compute simulation dock and insert the target compounds one by one as (mdb) file and run docking to validation hydrogen bonds with amino acid in the mycobacterium tuberculosis (TB) $H_{37}Rv$ strain protein.

Result and discussion

QSAR results

Quantitative structure activity relationship (QSAR) studies are useful tools in the rational search for bioactive molecules. The main success of the QSAR method is the possibility to estimate the characteristics of new chemical compounds without the need to synthesize and test them (Podunavac *et al*., 2009) [15].

Molecular descriptors can be defined as the essential information of a molecule in terms of its physicochemical properties such as constitutional, electronic, geometrical, hydrophobic, lipophilicity, solubility, steric, quantum chemical, and topological descriptor (Isarankura *et al.,* 2009) [7]. Molecular descriptors are mathematical values that describe physicochemical properties of a molecule (Adeniji *et al.,* 2018) [1].

Partial Least Squares (PLS) is a technique that reduces dimensionality in a regression context using orthogonal components (Opiyo and Moriyama 2007) [11]. Multiple Linear Regression (MLR) can be used in the prediction of values of the dependent variable based on a combination of independent variables, MLR analysis is based on the hypothesis that the dependent variable (in our case the biological activity) has a lineal relationship with the independent variables molecular descriptors (Pires and Rodrigues 2007) [14].

The QSAR studies in this work have been performed on some of 3, 7-disubstituted quinolone derivatives that acts using Molecular Operating Environment (MOE) by Partial Least Squares (PLS) and Multiple Linear Regression (MLR). The studies were carried out on 15 analogs, 12 used as training set and 3 as test set (see Table (2). All the compounds were drawn with the builder module of ACD/Lab and save file as mole 2000 and open file in MOE program. The compounds were then subjected to conformational analysis and energy minimization. Descriptors were calculated from the lowest energy conformer. By the nine descriptors means log octanole/water partition (logP o/w), dipole moment (MNDO - dipole), electrostatic energy (E-ele), Absolute different in surface areas (DASA), Absolute different in charge-weighted areas (DCASA), potential energy (E), Non-bonded Energy (E-nb), Dipole moment (AM1-dipole), Dipole moment (MP3-dipole). The correlation between the biological activity (pIC_{50}) and the descriptors were performed by stepwise regression analysis using QSAR easy software, on yielded the following equation:

$pIC_{50} = 0.95860 + 0.74495 \times \log P\ (o/w) + 0.03159 \times DCASA.$

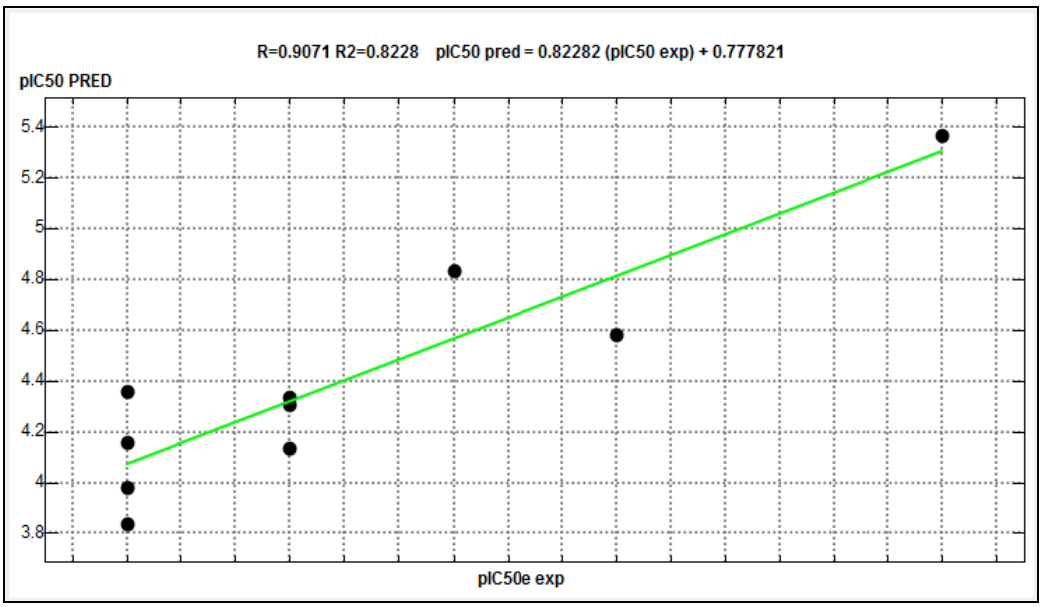


Fig 4: plots of predicted training set versus experimental p IC_{50} values against mycobacterium tuberculosis (TB).

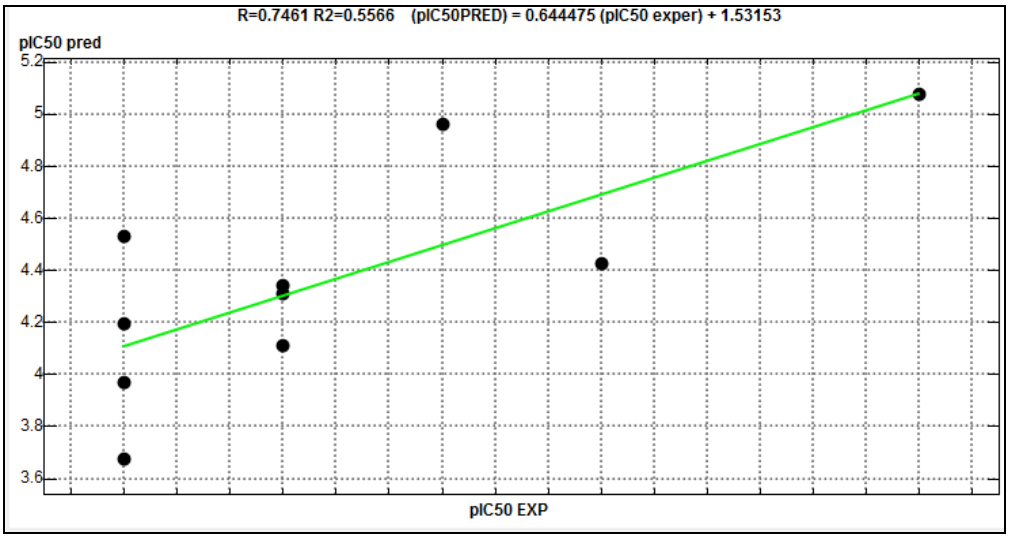


Fig 5: plots of cross validation prediction versus experimental pIC_{50} values against mycobacterium tuberculosis (TB).

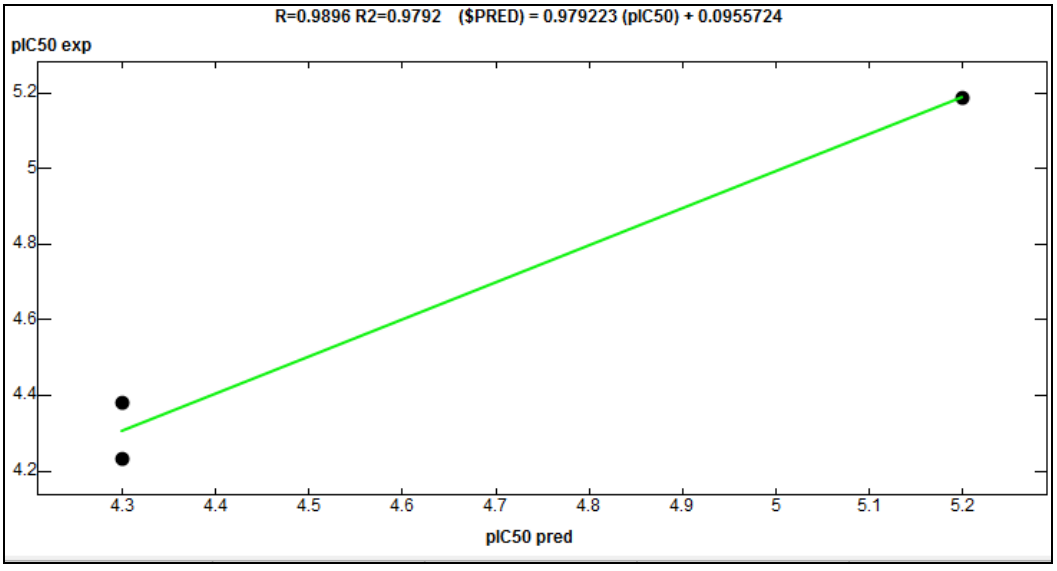


Fig 6: plots of predicted test set versus experimentally pIC_{50} values against mycobacterium tuberculosis (TB).

Docking results

The result of docking study for all designed compounds of some 3.7-disubstituted quinoline derivatives done by silico molecular docking, the results of these study divided in tow groups, one of them consist from compounds has active side and have ability interaction with amino acid, and second group consist from compounds have no active side and have no ability interaction with target amino acid. The good simulation docked of each new designed compound matured by maximum number of interactions with amino acid and lowest free energy bonds interaction. Molecular docking suggested that all of the designed quinoline derivatives were capable of forming a hydrogen bond with the amino acids and energy score (s), The result of docking studies of all designed and tested compounds conformations with active sites and details of docking result are tabulated in table (6) and table (7) respectively.

Observed the interaction between ligand and amino acid accomplish by the different type of interaction such as (H-bond acceptor, π interaction, N-diazinyl and phenyl interaction) this elucidation activity compounds against mycobacterium tuberculosis (TB) $H_{37}Rv$ strain protein. Mostly ligands showing strong tow oxygen atom in carboxylic group with hydrogen atom of amino acid in Arg564, also compounds 17 showed three different types of interaction with amino acid in sulphanilamide group ($-SO_2NH_2$) and N-diazinyl group as more interaction in one molecule (Pro431, Gln575 and Thr433) figure (4) and see also the π-interaction in figure (5). Also compounds number 4, 8 and 21 can be no interaction with amino acid because the structures have no polar group.

Conclusions

From the above presented results, I conclude that a series of quinolone derivatives are effective *in vitro* against the mycobacterium tuberculosis (TB). Molecular modeling and QSAR analysis were performed to find the quantitative effects of the molecular structure of the compounds on their antibacterial activity. An accurate mathematical model was developed for predicting the inhibitory activity of some a series of quinolone derivatives. The validity of the model has been established by the determination of suitable statistical parameters. The established model was used to predict the inhibitory activity of a series of quinolone derivatives investigated and close agreement between experimental and predicted values was obtained. The low residual activity and high cross-validated r^2 (CV = 0.9792) values obtained suggests a good predictive ability of the developed QSAR model. It indicates the antibacterial activity of a series of quinolone derivatives can be successfully modeled using various molecular descriptors. It can be concluded that the strong influence of the logP is important for the antibacterial activity and this parameter is usually related to inhibitory activity. The molecular docking study has been done for the better understanding of the ligand-receptor interaction. In the view of this study, further research can be carried out designed 3,7-disubstituted quinolone derivatives to investigated there in vitro antibacterial against to mycobacterium tuberculosis (TB).

Table 6: bonding score of amino acid interaction of the designed compounds (1 – 34).

Co. N	S. (Kcal/mol)	Amino acid	Interacting group	type of interacting	Length (Aº)
1	-17.8167	Thr433	N.deiazenyl	H-bond acceptor	2.15
2	-19.6877	Arg564	phenyl	π.interaction	-
3	-17.7075	Thr433	N.deiazenyl	H-bond acceptor	2.06
4	-19.0964	No interaction			
5	-15.7230	Thr433	N.deiazenyl	H-bond acceptor	2.23
6	-20.7435	Gln575	C=O	H-bond acceptor	2.21
7	-18.5165	Pro431 Gln575	NH_2 SO_2	H-bond acceptor H- bond acceptor	1.95 2.58
8	-17.036	No interaction			
9	-21.8094	Arg564	C=O	H-bond acceptor	2.26
10	-21.8046	Arg564	C=O	H-bond acceptor	2.90
		Arg564	C=O	H-bond acceptor	2.91
11	-18.3209	Thr433	phenyl	π.interaction	-
12	-17.1306	Thr433	N.deiazenyl	H-bond acceptor	2.96
13	-18.5967	Thr433	N.deiazenyl	H-bond acceptor	2.24
14	-17.999	Arg564	C=O	H-bond acceptor	2.84
15	-18.5967	Gln575	NH_2	H-bond acceptor H-	2.68
		Thr433	SO_2	bond acceptor	2.91
16	-20.5126	Thr433	phenyl	π.interaction	-
17	-19.1307	Gln575	SO_2	H-bond acceptor H-	3.90
		Pro431	NH_2	bond acceptor	2.93
		Thr433	N.deiazenyl	H-bond acceptor	2.90
18	-17.2369	Thr433	phenyl	π.interaction	-
19	-16.1915	Arg564 Thr433	C=O phenyl	H-bond acceptor π.interaction	3.04 -

20	-19.6866	Arg564	phenyl	π.interaction	-
21	-17.7461	No interaction			
22	-17.4285	Pro431	NH_2	H-bond acceptor H-	1.98
		Thr433	NH_2	bond acceptor H-bond	2.35
		Arg564	C=O	acceptor	2.03
23	-17.2346	Thr433	N.deiazenyl	H-bond acceptor	2.15
		Gln575	NH_2	H-bond acceptor	1.97
24	-17.8389	Thr433	N.deiazenyl	H-bond acceptor	2.88
		Thr435	NH_2	H-bond acceptor	2.59
		Gln575	SO_2	H-bond acceptor	2.31
25	-19.3230	Pro431	NH_2	H-bond acceptor	1.98
		Ala555	NH_2	H-bond acceptor	2.05
26	-18.9608	Thr433	N.phenyl	H-bond acceptor	1.87
27	-17.8260	Thr433	NH_2	H-bond acceptor	2.60
		Gln575	SO_2	H-bond acceptor	2.02
		Pro431	NH_2	H-bond acceptor	1.94
28	-18.3328	Arg564	SO_2	H-bond acceptor	2.97
		Pro431	NH_2	H-bond acceptor	2.88
29	-18.9448	Arg564	C=O	H-bond acceptor	2.11
30	-21.5289	Thr433	N.deiazenyl	H-bond acceptor H-	2.16
		Arg564	C=O	bond acceptor	2.89
31	-18.7960	Thr433	N.deiazenyl	H-bond acceptor	2.13
32	-16.9094	Thr433	N.deiazenyl	H-bond acceptor	2.54
33	-18.4047	Thr433	CH_3CO-	H-bond acceptor	3.11
34	-19.1323	Gln575	N.deiazenyl	H-bond acceptor	3.72
Rifampicin	-25.236	Gin575	C-O	H-bond acceptor	1.89
reference		Thr433	C=O	H-bond acceptor	2.09
drug		Pro431	NH_2	H-bond acceptor	1.83

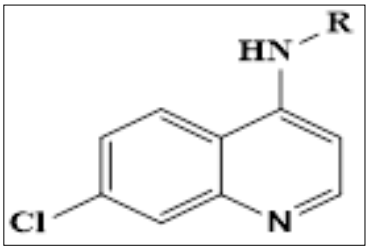


Fig 7

Table 7: docking resut of the training and test set compounds of a series quinoline derivative reported by (De Souza *et al*. 2009).

C.N	R	s- energy	amino acid	interaction group	type of interaction	Length (Aº)
1	$-CH_2CH_2Cl$	-15.57695	Th433	-NH	H-bond	2.87
2	$-CH_2CH_2NHBN^T$	-20.26943	Tyr574	phenyl	π-interaction	-
3	$-(CH_2)_6NH_2$	-14.89765	Pro431	-NH	H-bond	1.94
4	$-(CH_2)_8NH_2^T$	-19.64986	Lys440	-NH	H-bond	2.49
5	$-(CH_2)_{10}NH_2$	-19.22596	Arg569	$-NH_2$	H-bond	2.54
6	$-CH_2CH_2NH$i-Pr	-13.83842	no interaction			
7	$-CH_2CH_2CH_2CH_3$	-16.83704	no interaction			
8	-H	-13.82262	no interaction			
9	$-CH_2CH_2NH$ Cyclohexene	-15.50278	GIn575	$-NH_2$	H-bond	1.76
			Pro431	$-NH_2$	H-bond	1.84
			Th433	-NH	H-bond	2.31
10	$-CH_2CH_2CH_3$	-13.72923	Pro431	$-NH_2$	H-bond	1.87
			Gin575	$-NH_2$	H-bond	1.82
			GIn575	$-NH_2$	H-bond	1.91
11	$-CH_3$	-14.02032	no interaction			
12	$-SCH_2CH(C_2H_5)CH_2Cl^T$	-19.37063	GIn575	-NH	H-bond	2.35

*T = Test set

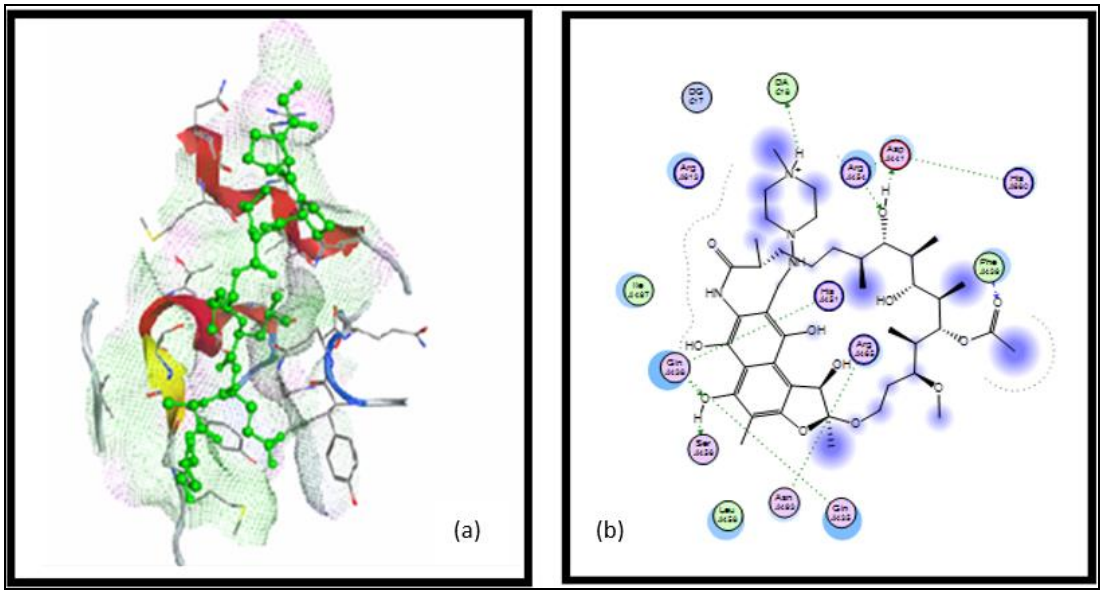


Fig 8: 3D model of active sites of bacteria 6KGH protein (a) with Rifampicin analog ligand and 2D model of ligand interaction with protein (b).

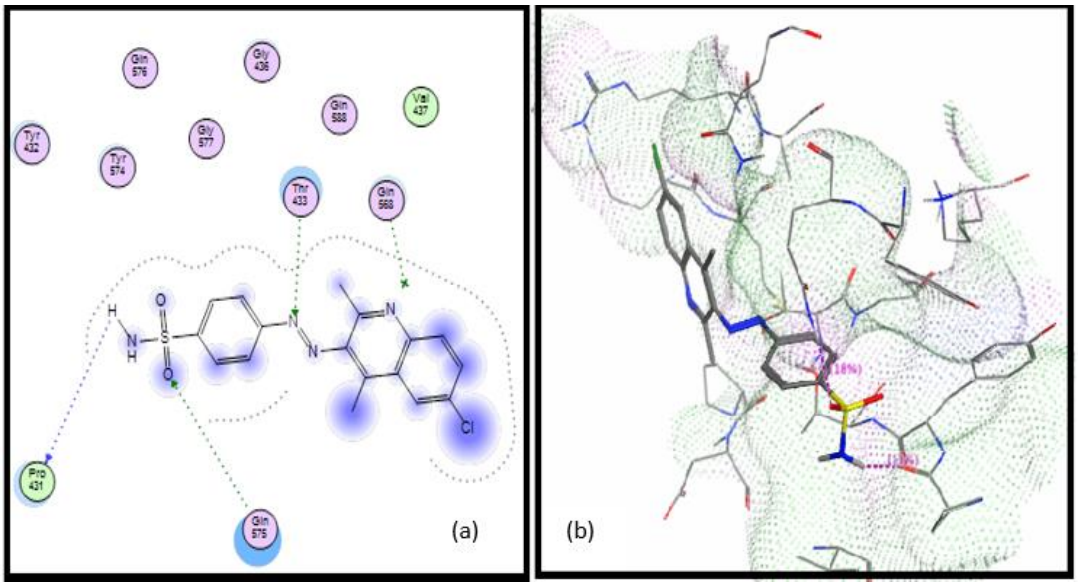


Fig 9: 2D Binding interaction (different type interaction) (a) and 3D structure of compound 17 active site (b).

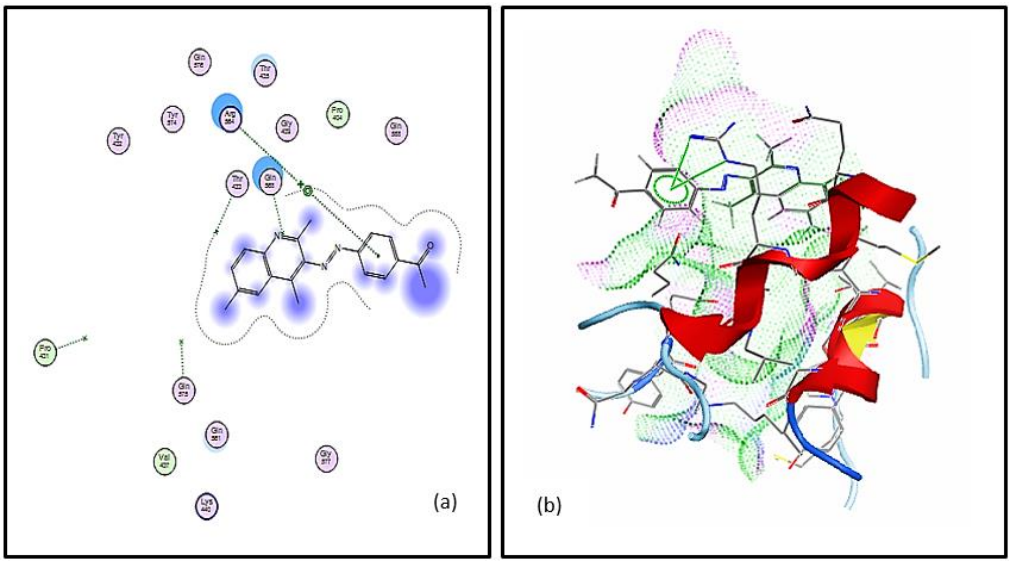


Fig 10: 2D Binding (π. interaction) with phenyl ring (a) and 3D structure of compound 16 active site (b).

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