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3D QSAR study of quinoline derivatives for potent antitubercular activity

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ABSTRACT

The present communication deals with 3D QSAR analysis on series of quinoline derivatives for the designing of DNA Gyrase inhibitors with antitubercular activity by using k-NN MFA. The 3D QSAR models are generated using data set of 35 molecules as DNA Gyrase inhibitors from literature studies. Alignment of the 3D optimized structures was done by template based alignment method by taking quinoline as the template. The 3D QSAR result gives insights for understanding of the relationship between structural features of substituted quinoline derivatives and their activities which should be useful to design newer potential antitubercular agents. The best model showed q^2 value = 0.6422 and predicted r^2 of 0.6198 with three descriptors namely S_1046, S_517, and S_926. k, number of nearest neighbors were observed 2 for this model.

Keywords: 3D QSAR, k-NN, *DNA Gyrase*, Quinoline derivatives, Antitubercular, Alignment.

INTRODUCTION

Tuberculosis (TB) is one of the first identified infectious diseases and remains a major health problem with two million deaths and eight million new cases annually [1-3]. Due to multi-drug resistant (MDR) strains of mycobacterium and to a high prevalence of tuberculosis in patients who have acquired human-immunodeficiency syndrome (AIDS) the number of patients infected with the disease is increasing worldwide [4-6]. The clinical management of TB has relied heavily on a limited number of drugs such as Isonicotinic acid, Hydrazide, Rifampicin, Ethambutal, Streptomycin, Ethionamide, Pyrazinamide, Fluroquinolones etc.[7,8]. No new antibiotics against

TB has been developed in the last 30 years. Currently, patients require 6-9 months of treatment. This long period leads to the lack of compliance, which in turn, can be responsible for the relapse and emergence of resistant strains [9]. There are several reasons that justify the need to search for new drugs for TB, like improvement of current treatment by shortening its duration, to achieve efficient treatment for MDR TB and to eradicate the latent infection. So, the improvement of new drugs for shortening the duration of the treatment and to fight against multidrug resistant tuberculosis strains is urgent [10].

Quinoline is an important scaffold due to variety of pharmacological properties associated with the derivatives bearing this heterocycle [6]. We chose to search for quinoline derivatives displaying significant antitubercular properties, considering the possible affinity of such molecular scaffold for *DNA Gyrase* which is bacterial targets of prime strategic importance for the future development of new antitubercular drug-compounds.

The present 3D QSAR study has been done by VLife MDS software by using various regression methods on a series of compounds, as novel quinoline derivatives for their potent antitubercular activity, reported by P. Senthilkumar *et al.* and M. Dinakarana *et al.* [11, 12]. Regression methods were used to build a QSAR model in the form of a numerical equation. Explains variation of one or more dependent variables in terms of independent variables by this equation. The QSAR models can be used to predict activities for screening a large set of molecules and for new molecules whose activities are not known and the result can lead to design and synthesis of new compounds.

MATERIALS AND METHODS

Data Set

A data set of 35 molecules reported by P. Senthilkumar *et al.* and M. Dinakarana *et al.* published in journal *Bioorganic and Medicinal Chemistry* available online at www.sciencedirect.com. All the series were reported to have antitubercular activity. The series has a basic quinoline moiety on which different substitutions were done at R and R_1 positions (Fig. 1a & 1b). The antitubercular activity was expressed in terms of MIC. All the biological activity data was converted to negative logarithmic form to reduce skewness of data set. The structures and antitubercular activity data of compounds are listed in Table 1.

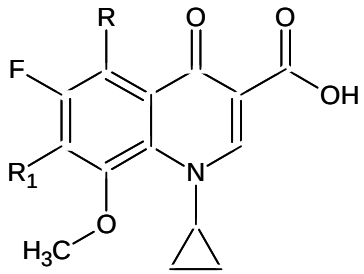


Fig. 1a: Basic Moiety (1)

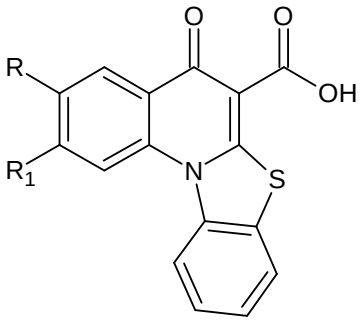
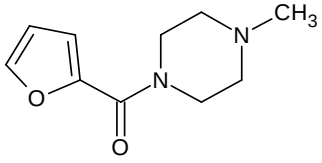
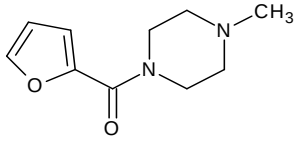
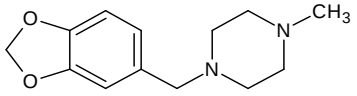
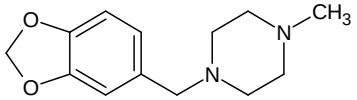
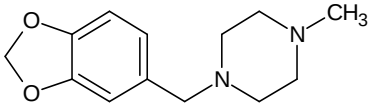
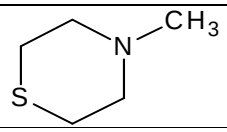
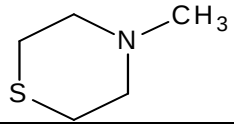
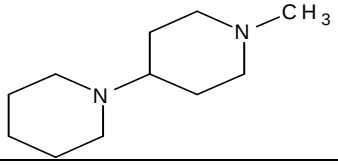
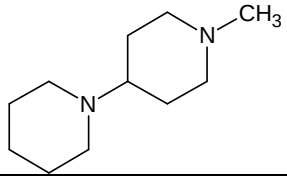
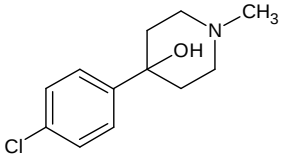
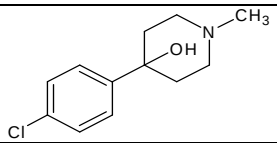
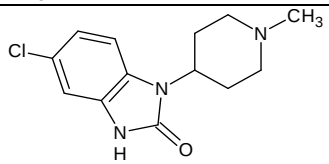
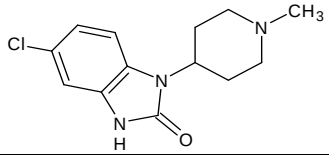
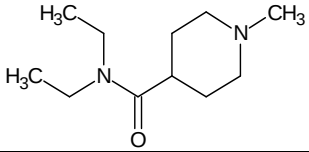
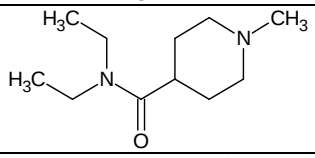
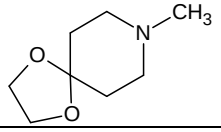
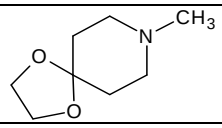
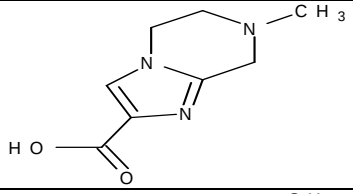
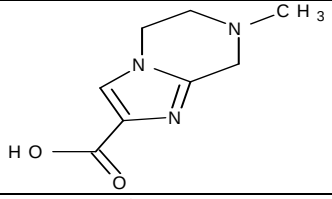
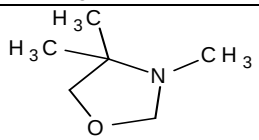
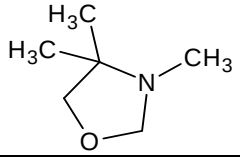
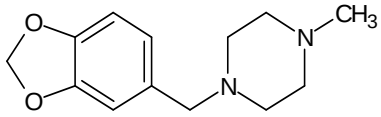
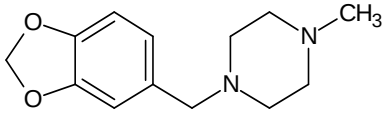
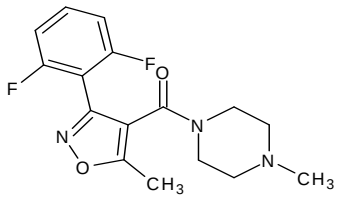
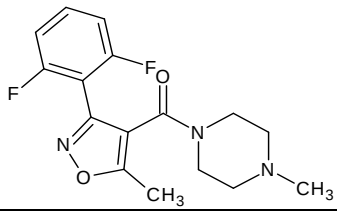
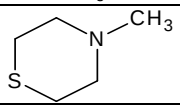
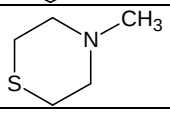


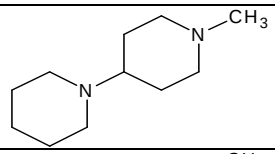
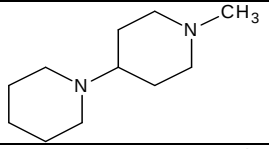
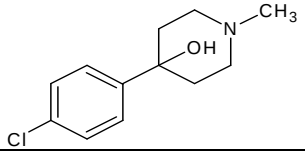
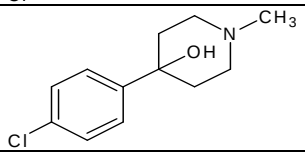
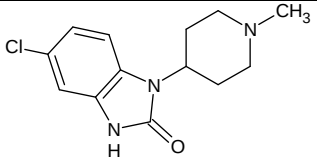
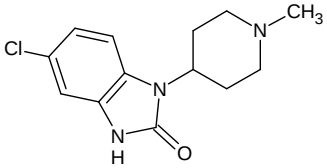
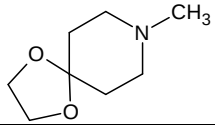
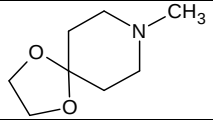
Fig. 1b: Basic Moiety (2)

Table 1: List of Compounds used for QSAR studies having Antitubercular Activity

S. No.	R	R_1	MIC	pMIC
1.	H		13.72	-1.1373
2.	NO_2		6.25	-0.7958
3.	H		1.57	-0.1958
4.	NO_2		0.35	0.4559
5.	NH_2		3.06	-0.4857

6.	H		2.06	-0.3138
7.	NO_2		1.84	-0.2648
8.	H		7.06	-0.8488
9.	NO_2		6.41	-0.8068
10.	H		6.43	-0.8082
11.	NO_2		5.88	-0.7693
12.	H		5.94	-0.7737
13.	NO_2		5.47	-0.7379
14.	H		1.69	-0.2278
15.	NO_2		1.55	-0.1903
16.	H		0.93	0.0315

17.	NO_2		0.84	0.0757
18.	H		3.53	-0.5477
19.	NO_2		3.120	-0.4941
20.	H		4.14	-0.6170
21.	NO_2		1.85	-0.2671
22	F		1.47	-0.1673
23	NO_2		5.60	-0.7481
24	F		2.52	-0.4014
25	NO_2		4.85	-0.6857
26	F		3.76	-0.5751
27	NO_2		7.09	-0.8506

28	F		0.39	0.4089
29	NO_2		3.08	-0.4885
30	F		0.36	0.4436
31	NO_2		2.84	-0.4533
32	F		2.77	-0.4424
33	NO_2		5.31	-0.7250
34	F		0.86	+0.0655
35	NO_2		1.62	-0.2095

Molecular structure generation

Molecular modeling and correlation analysis were executed on the Vlife Molecular Design Suite (MDS) 3.5 version software. Structures were builded using 2D application tool and exported in 3D format. Energy minimization and batch optimization was carried out using Merck molecular force field method by fixing root mean square gradient to 0.01 kcal/mol, dielectric constant 1, number of cycles 1,00,000 and gradient type analytical. All the molecules were initially optimized and then used for the calculation of descriptors, regression analysis and model generation.

Alignment

Molecular alignment is a crucial step in 3D-QSAR study to obtain meaningful results. This technique is based on moving of molecules in 3D space and related to the conformational flexibility of molecules. The goal is to get optimal alignment between the molecular structures necessary for ligand-receptor interactions.

Alignment of optimized molecules was carried out using template based alignment method. Compound 7-methyl-4-dihydroquinoline-3-carboxylic acid was considered as reference molecule as template. The alignment of 35 molecules is shown in Fig. 3.

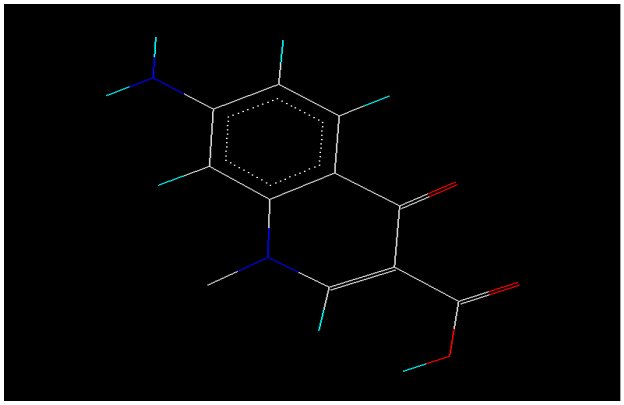


Figure 2: 7-methyl-4-dihydroquinoline-3-carboxylic acid (Template)

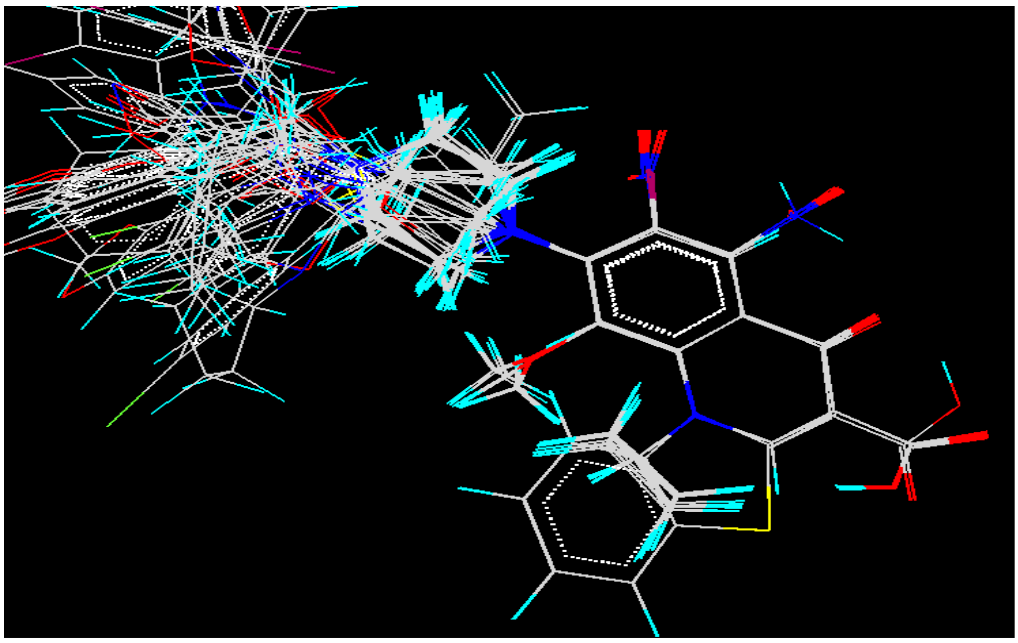


Figure 3: Template Based Alignment of all 35 Compounds

Calculation of Descriptors

All three fields electrostatic, hydrophobic and steric were computed at the lattice points of grid around aligned molecules in space and calculated using Gasteiger Marsilli charges. The values 10 kcal/mol and 30kcal/mol were used as cut-offs of electrostatic and steric respectively. Dielectric constant of medium was taken as 1. Methyl probe of charge +1.0 was used to compute interaction energies. At the end, it provided how descriptors govern binding of each molecule at the active site in the form of numbers.

Data selection

In numerical data of different variables, activity and all the other descriptors were considered as dependent and independent variables respectively. Data set was categorized in to two parts, test set and training set. Only training set is exclusively used for building QSAR model. Generated model is applied to predict activity of test set to evaluate its predicting ability. Sphere exclusion method was used to generate training set and test set.

3D QSAR Model Generation

For model generation the data set was divided into training set and test set. Regression was applied by using k-NN-MFA with stepwise forward backward variable selection method by fixing cross correlation limit: 0.5, term selection

criteria: q^2, F-Test in: 4.00, F-Test out: 3.99, variance cut off: 2.0, auto scaling, number of maximum neighbors: 5, number of minimum neighbors: 3, selection prediction method: distance based weight average and most active: positive. Models were validated by both internal (cross-validation, q^2) and external validation (predicted_r^2).

RESULTS AND DISCUSSION

For QSAR analysis, regression performed by using pMIC values as dependent variables and calculated descriptors as independent variables. The model generated by this method showed the q^2 value 0.6422 and Pred_r^2 value 0.6198. In the 3D map, the steric interaction fields are represented in green lattice points at S_1046, S_517, and S_926 (Fig. 4) implies that the steric interactions along these lattice points are required to be addressed. All the steric points showed positive contribution, so the compounds which have bulky substituents at the quinoline moiety can show the increased activity. Fitness plot between actual and predicted activity is shown in Fig. 4.

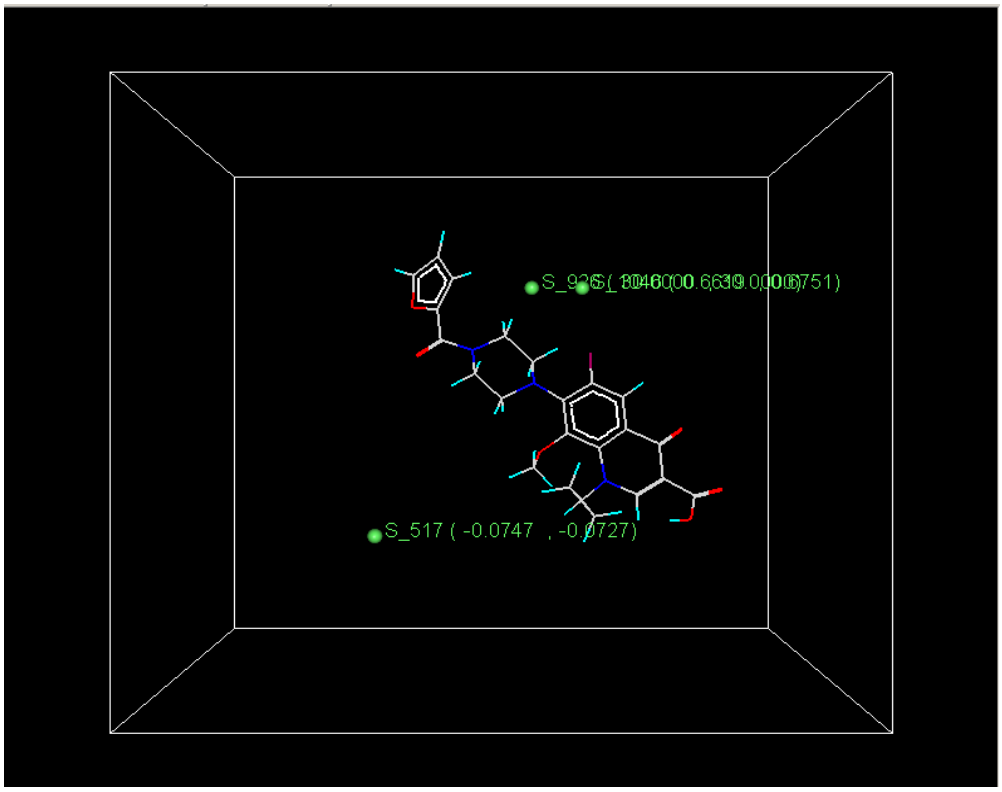


Figure 4: Show points (Descriptors with range)

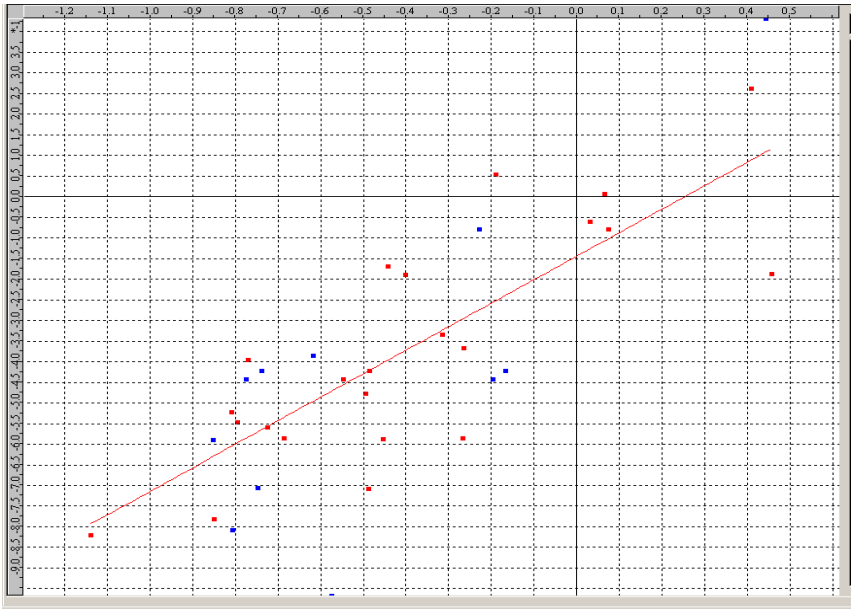


Fig. 5: Fitness Plot of between Actual and Predicted Activities of 3D QSAR Model [Training set (red spot) and Test set (blue spot)]

CONCLUSION

From the derived QSAR model, it is concluded that antitubercular activity of quinoline derivatives is strongly influenced by the steric interactions. The show point of 3D model with positive values suggested pattern of substitution to improve the biological activity of already existing compounds. This study has been found very helpful in development and optimization of this class of compounds as well as designing of new compounds with improved antitubercular activity.

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REFERENCES

[1] Bate AB, Kalin JH, Fooksman EM, Amorose EL, Price CM, Williams HM, Rodig MJ, Mitchell MO, Cho SH, Wang Y, Franzblauc SG, *Bioorg. Med. Chem. Lett*., **2007**, 17, 1346.
[2] Puratchikody A, Natarajan R, Jayapal M, Doble M, *Chem Biol Drug Des*, **2011**, 78, 988. [3] Vicente E, Pérez-Silanes S, Lima LM, Ancizu S, Burguete A, Solano B, Villar R, Aldana I, Monge A, *Bioorg. Med. Chem.*, **2009**, 17, 385.
[4] Shafii B, Amini M, Akbarzadeh T, Shafiee A, *J. Sci. I. R. Iran*, **2008**, 19, 323
[5] Upadhayaya RS, Vandavasi JK, Vasireddy NR, Sharma V, Dixit SS, Chattopadhyaya J, *Bioorg. Med. Chem.*, **2009**, 17, 2830.
[6] Savini L, Chiasserini L, Gaeta A, Pellerano C, *Bioorg. Med. Chem.*, **2002**, 10, 2193.
[7] Khadke AP, Patil AM, Jain BB, *Int. J. Pharm. Bio. Sci.*, **2011**, 1, 501.
[8] Goyal RK, Dureja H, Singh G, Madan AK, *Sci Pharm*, **2010**, 78, 791.
[9] Almasirad A, Samiee-Sadr S, Shafiee A, Iran. *J. Pharm. Res.*, **2011**, 10, 727.
[10] Higuchi CT, Sannomiya M, Pavan FR, Leite SRA, Sato DN, Franzblau SG, Sacramento LVS, Vilegas W, Leite CQF, *Evid. Based Complement. Alternat. Med.*, **2011**, 2011, Article ID 128349, doi:10.1093/ecam/nen077.
[11] Senthilkumar P, Dinakaran M, Bannered D, Devakaram RV, Yogeeswari P, China A, *Bioorg. Med. Chem.*, **2008**, 16, 2558.
[12] Dinakarana M, Senthilkumar P, *Bioorg. Med. Chem.*, **2008**, 16, 3408.