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Research Article

K NEAREST NEIGHBOR AND 3D QSAR ANALYSIS OF THIAZOLIDINONE DERIVATIVES AS ANTITUBERCULAR AGENTS

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Abstract :

Purpose : The present research communication describes development of kNN and 3D QSAR models for identification of structural features which are responsible for antimycobacterial activity of Thiazolidinone.

Methodology/ Approach : In the present work, two predictiveof kNN and 3D QSAR models were developed via utilization of multiple linear regression analysis. MLR analysis was carried out on reported dataset of thiazolidinone as Antimycobacterial. Vlife MDS 4.4 is utilized for development of kNN and 3D QSAR models which were validated via internal test set.

Findings : Two different kNN and 3D QSAR models developed for dataset of thiazolidinone molecules as antimycobacterial. The Model A and Model B describes the best selected 3D QSAR model predicting antimycobacterial activity of the thiazolidinone derivatives. 3D QSAR model A is best selected model which indicates steric interaction fields needs to be minimized while electrostatic interaction field needs to be improved for potential increase in antimycobacterial activity. The Model C and D are two selected kNN models for anti-mycobacterial activity of the thiazolidinone derivatives. Model D is better fitted kNN model describing negative contribution of the electrostatic interaction fields and positive contribution of the steric interaction field.

Original Value : The review of literature revealed QSAR analysis plays vital role in the development of the novel drug like candidates. Thiazolidinone derivatives were reported for their antimycobacterial potential but their quantitative measures were not reported. These facts prompted us to for development of QSAR models which will be utilized for development of potent and selective antimycobacterial agents.

Conclusion : The study revealed that 3DQSAR model A and kNN model D better describes the antimycobacterial potential of the thiazolidinone derivatives. Substitution of the smaller groups on the aromatic ring bearing thiazolidinone nucleus will increase the antimycobacterial potential of the thiazolidinone derivatives.

Keywords : *Thiazolidinone derivatives, Antimycobacterial, 3D QSAR, kNN-MFA.*

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Introduction

Mycobacterium tuberculosisis a gram negative intracellular pathogen and causative agent of Tuberculosis. Tuberculosis is one of major killers of human being in current decade, and it accounts for three millions people around the world. Combination of the HIV and tuberculosis is making

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most lethal more than 30 % death of the HIV are due to the tuberculosis infection[1]. The Emergence of the MDR and XDR tuberculosis making the problem of the tuberculosis more and more critical. MDR and XDR are the resistant form of the tuberculosis in which Mycobacterium tuberculosis become resistant towards majority of the antitubercular drugs in the clinical use[2]. Number of chemical structures were reported for antimycobacterial potential but no single of them is come in to the clinical use due to their pharmacokinetic and pharmacodynamics limitations. Bedaquiline is first antimycobacterial agent approved in last decade, which indicates there is increasing need of the rational development of the novel antimycobacterial agents[3-4]. Computational methodologies like QSAR, Pharmacophore modelling and molecular docking have proved their efficiencies in development of novel NCE with desirable biological activity. Quantitative structure activity relationship (QSAR) analysis is correlative analysis between biological activity and structural properties of the molecules, which are utilized to identify the fundamental structural properties responsible for biological effect of the molecules. In 3D QSAR analysis 3D co-ordinates of the molecules in terms of the 3D interaction field which are contributors of the drug receptors interactions are calculated and correlated with biological activity[5-6]. These interaction fields are steric, hydrophilic and electrostatic interaction fields. K-nearest neighbor Molecular Field Analysis (kNN MFA) analysis is a pattern recognition method[7-9].In this method, an unknown pattern is classified according to the majority of the class memberships of its k nearest neighbors in the training set. Here we are reporting 3DQSAR and kNN MFA analysis on the series of thiazolidinone as antimycobacterial. The model derived from this investigation having good predictive ability will be utilized for development of novel antimycobacterial agents.

EXPERIMENTAL

Dataset Creation :

Molecular dataset of 24 molecules for thiazolidinone derivatives were taken from the published literature by Malipeddiet. al[10]. 2D structures of the molecules were drawn in the 2D molecular builder of Vlife MDS 4.4. 2D structures were optimized via converting into 3D structures via 3D converter. 3D converted structures were further optimized andminimized using the standard Merck molecular force field (MMFF) with distance dependent dielectric function and energy gradient of 0.001 kcal/mol.

Molecular alignment :

Alignment of the molecules is important requirement of 3D QSAR analysis. Optimized molecules were aligned using template based techniques. The alignment of all the molecules on the template is shown in figure. No 1.

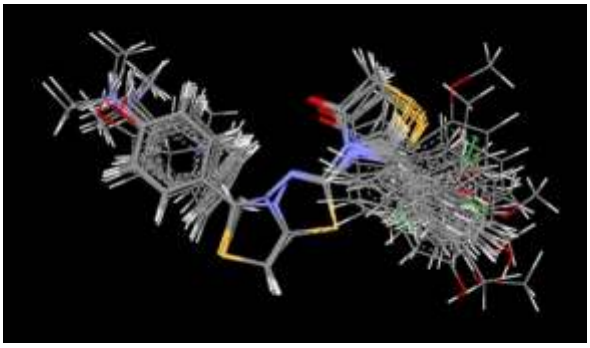


Figure 1: Figure showing alignment of molecules

Selection of Data set :

The structures and activity of the selected molecules are reported in table No 1. Selected molecules were randomly divided in to the training set of 16 molecules and test set 08 molecules. Training set of 16 molecules was utilized for construction of QSAR models while test set is utilized to validate the constructed model.

Descriptor Calculation :

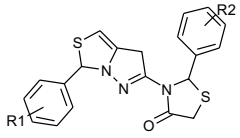
Molecular properties in term of descriptors were calculated by using QSAR module of Vlife MDS 4.4. Molecular descriptor is nothing but the hydrophilic, steric and electrostatic interaction energies which are computed at the lattice points of the grid using a CH_3probe of charge +1.

QSAR studies using Partial Least Square Regression :

Establishment of relationship between independent and dependent variables were done by multiple linear regression analysis. Linear regression is achieved by fitting straight line to the data. The QSAR models having correlation coefficients above 0.7 were selected for statistical analysis. The selected models were further scrutinized for their other

statistical parameters like q^2, and F test, r^2 pred. The selected models were shown in table No 2.

Table 1: Table showing Molecules under Study



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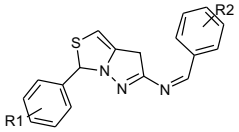

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S.no	R1	R2	Observed activity	Predicted activity (Model A)	Predicted activity (Model D)
1.	H	H	0.911	1.01	1.10
2.	H	2-Cl	1.25	1.21	1.07
3.	H	4-Cl	1.25	1.27	1.10
4. #	4-CH3	H	0.91	0.94	1.02
5. #	4-CH3	2-CH3	1.25	1.02	0.97
6.	4-CH3	4-CH3	2.02	2.21	1.09
7.	4-OH	H	0.911	0.921	1.10
8.	4-OH	2-OH	2.02	2.02	1.96
9. #	4-OH	4-OH	2.02	2.02	1.98
10. #	4-N(CH3)2	H	1.25	1.27	1.25
11.	4-N(CH3)2	2-OH3	1.25	1.29	1.25
12.	4-N(CH3)2	4-OH3	1.25	1.27	1.10
13.	H	H	1.25	1.22	1.02
14.	H	2-Cl	2.02	2.01	2.01
15.	H	4-Cl	2.02	2.012	2.02
16.	4-CH3	H	1.25	1.23	1.27
17.	4-CH3	2-CH3	2.02	2.01	2.02
18.	4-CH3	4-CH3	4.89	4.89	4.91
19. #	4-OH	H	1.25	1.23	1.23
20. #	4-OH	2-OH	2.02	2.12	2.00
21.	4-OH	4-OH	4.89	4.80	4.81
22.	4-N(CH3)2	H	1.25	1.25	1.27
23. #	4-N(CH3)2	2-OH3	2.02	2.21	2.21
24. #	4-N(CH3)2	4-OH3	2.02	2.203	2.21

#: Test set Molecules

Table 2 : Table showing the selected PLS 3D QSAR equations along with statistical parameters employed for model selection.

Model No.	QSAR model	N	r2	q2	F value	Pred r2
A	pMIC= 1.8819+2.0359 S_1000 +0.4699 S_602-0.0243 E_1122	24	0.90	0.80	110	0.78
B	pMIC= 0.0154+57.3881 S_979 +31.5191 S_1102+ E_486	24	0.87	0.72	52	0.69
C	pMIC= 0.3872+6.2517S_980 +0.1344E_1105-0.0997 E_427	24	0.81	0.65	58	0.44
D	pMIC= 4.4295-0.0629E_805 +0.1782S_1086-0.0943E_523	24	0.85	0.73	37	0.42
E	pMIC= 5.4024+0.0470S_989 +0.4348S_141+ 0.0760E_444	24	0.83	0.62	24	0.45
F	pMIC= 7.1982-0.0652 S_517-0.1793 S_141+ 0.1915E_902	24	0.81	0.71	78	0.51

RESULTS AND DISCUSSION

In present research communication congeneric series of 24 thiazolidinone derivatives with regularly distributed antitubercular activity are utilized to derive 3DQSAR and kNN MFA models. The training set of 16 molecules and test set of 8 molecules was utilized, for development QSAR models which are given in table No 2.

Interpretation of 3DQSAR Models :

The 3D structural requirement of thiazolidinone derivatives to act as antitubercular agents were obtained in the form of 3D QSAR model A and B. Model A is more significant than model B in terms of various statistical parameters. Regression coefficient (r^2) of QSAR model A was 0.90 and for model B is 0.87 Contributing descriptors for model A are steric interaction energies at lattice point S_1000, S_602 and electrostatic interaction energy at lattice point E_1122 as shown in figure 2 and figure 6. The steric interaction energies at lattice point S_1000 and S_602 are positively contributing towards antitubercular activity of thiazolidinone derivatives which indicates increase in size of the ring around R_2 substitution will potentiate the antitubercular activity. Substitutions of bicyclic rings like naphthalene, quinoline and isoquinoline will lead to development of potent molecules. Electrostatic interaction at E_1122 is negatively contributing for biological activity, which indicates substitution of electron withdrawing groups at R_1 will lead to increase biological activity. Substitutions like NO_2, OCH_3 in R_1 ring will lead to more potent antitubercular derivatives. 3D QSAR model B is another selected model for identification of structural requirement of thiazolidinone derivatives for antitubercular activity. Contributing descriptor for QSAR model B are S_979, S_1102 and E_486 as shown in figure No 3. Steric interactions at S_979, S_1102 are negatively contributing while electrostatic interactions at E_486 are positively contributing towards antitubercular activity.

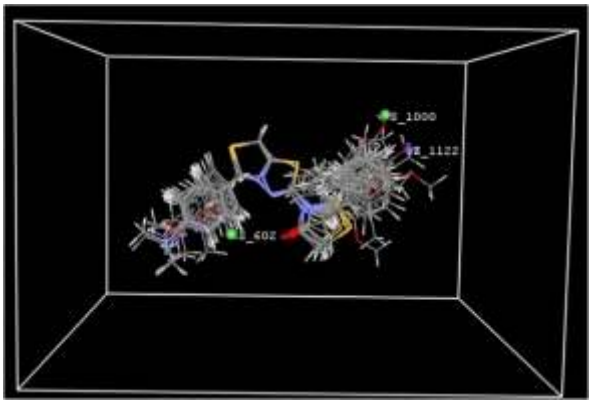

Figure 2: Figure showing grind point of selected 3D QSAR model A

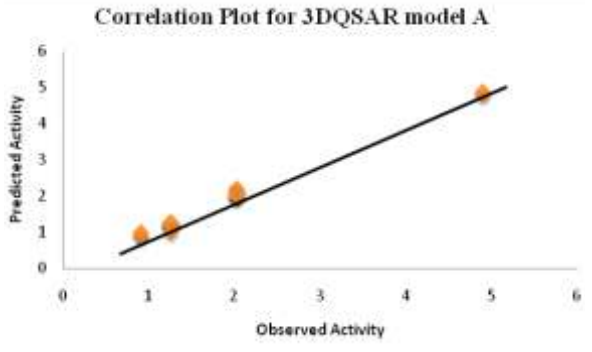

Figure 6: Figure showing Correlation plot for 3D QSAR model A.

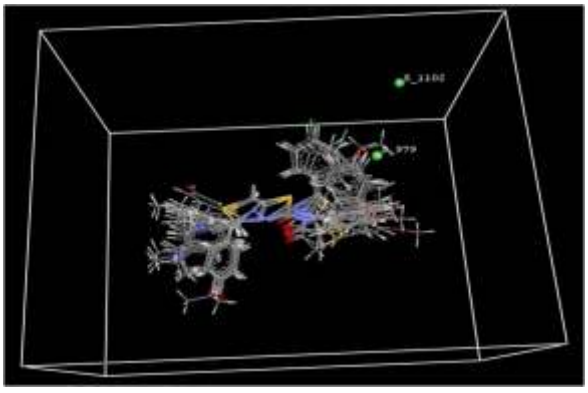

Figure 3: Figure showing grind point of selected 3D QSAR model B

Interpretation of k-Nearest neighbor Molecular Field Analysis (kNN-MFA) models:

We report two 3D QSAR kNN-MFA models generated via Stepwise (SW) Forward Backward selectionmethod. From all the developed models, two of them models C and D are having good q^2 & pred r^2 values, one of which was selected having good internal and external predictivity. The summary of the selected model D can be given as: k = 2; q^2= 0.97; pred_r^2 = 0.71; descriptor range: E_619 -8.9062 3.0863; E_280 -0.8034 0.4151; S_727 2.159916.7323 as shown in figure No. 4, 7 and table No. 3. Descriptor range for the selected model D elaborates that thiazolidinone ring is essential for

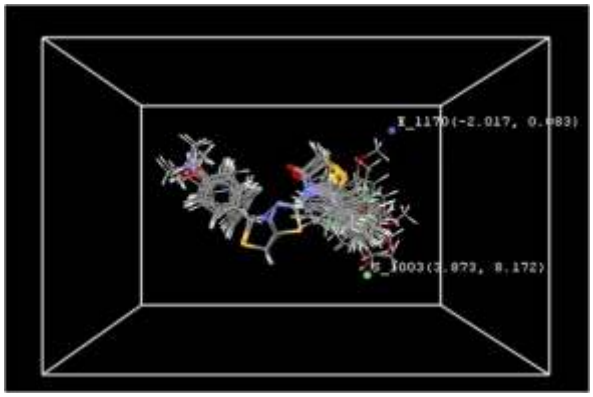

Figure 4: Figure showing grind point of selected 3D QSAR model C

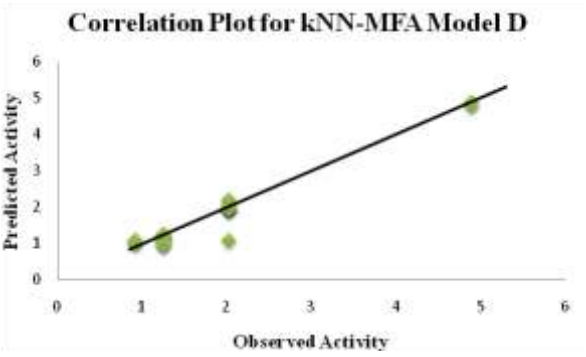

Figure 7: Figure showing Correlation plot for kNN-MFA model D.

Table 3 : Table showing the selectedkNN-MFA QSAR model along with statistical parameters employed for model selection.

Model No.	Descriptor Range	N	k Nearest Neighbors	q2	Pred r2
A	S_750-0.05700.4527 S_9890.1915 0.4527	24	02	0.78	0.69
B	E_9010.5872 14.233 E_805 0.8912 18.234	24	02	0.69	0.57
C	S_1003 3.8735 8.1725 E_1170 -2.0173 0.0834	24	02	0.81	0.59
D	S_727 2.1599 16.7323 E_619 -8.9062 3.0863 E_280 -0.8034 0.4151	24	02	0.97	0.71
E	S_989 0.4044 0.5632 S_1410.5623 18.230 S_980 -8.234 2.351	24	02	0.80	0.65
F	E_9020.26550.8132 E_910-0.1849 0.5630 S_141-0.02250.0433	24	02	0.81	0.69

antitubercular activity; negative range of electronic field indicates that electronegativesubstituent would be favorable for the activity. Positiverange of steric field indicates that substitution of the less bulky groups will lead to the increase in antitubercular activity of the thiazolidinone derivatives. Model C is also another selected 3D kNN-MFA model summary of the selected model C can be given as: k = 2; q^2= 0.9636; pred_r^2 = 0.6948; descriptor rangeS_1003 3.8735 8.1725; E_1170 -2.0173 0.0834 as shown in figure no 5.

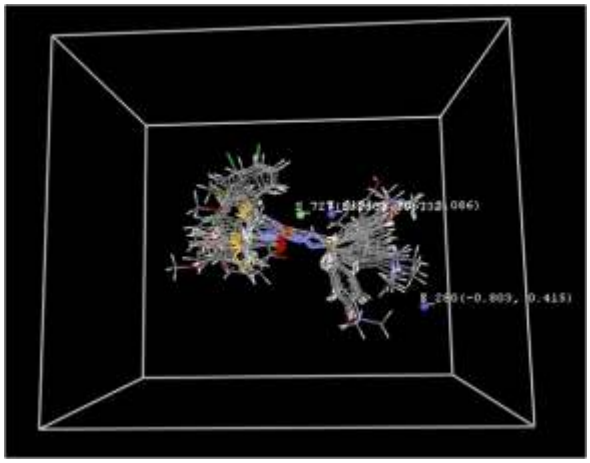

Figure 5: Figure showing grind point of selected 3D QSAR model D

CONCLUSION :

The results of 3DQSAR and 3D kNN-MFA study has shown that less electronegative substituent and bulkier substituents on the thiazolidinone nucleus would be favorable for antitubercular potential. Hence the future molecules should be designed with increase in the size of substituents on the R_2 position and substitution of electron withdrawing groups in R_1 position will lead to potent antitubercular agents.

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