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MOLECULAR MODELLING OF 1,3,4-OXADIAZOLE DERIVATIVES AS ANTIMYCOBACTERIAL AGENTS

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Abstract

Recently several 1,3,4-oxadiazole derivatives have been identified as potentially active antimycobacterial agents. Various 5-aryl-2-thio-1,3,4-oxadiazoles have been reported having good antimycobacterial activity against Mycobacterium tuberculosis H37Rv (ATCC 27294). In this paper we report 3D QSAR studies for the 41 molecules of 1,3,4-oxadiazoles by using k-Nearest Neighbor Molecular Field Analysis (kNN-MFA) combined with various selection procedures. Using kNN-MFA approach 52 3D-QSAR models were generated; one of these models was selected on the basis of q2 and pred_r2 values. The selected model had shown good internal and external predictivity for the training set of 33 molecules and test set of 8 molecules with validation (q2) and cross validation (pred_r2) values of 0.5022 and 0.2898, respectively.

This model can be used for preliminary screening of large diversified compound libraries. The model has shown that presence of sulphur is must for activity, however the larger bulky substituents reduce the activity. The presence of halogen and other non-halogen groups have also contributed to the activity.

Hence the future schemes with smaller groups on sulphur and electronegative groups in the molecule would result in potentially active molecules.

Keywords: 1,3,4-oxadiazole; Antimycobacterial Activity; 3D QSAR; kNN-MFA.

Introduction

Recently W.H.O has reported a significant rise in drug resistant tuberculosis (1, 2). Tuberculosis (T B) is one of the leading causes of death and suffering worldwide among the infectious diseases. The ever increasing drug resistance, toxicity and side effect of currently used anti-tuberculosis drugs and the absence of their bactericidal activity highlight the need for new, safer and more effective antituberculosis drugs(3).

The computer-aided prediction of biological activity in relation to the chemical structure of a compound is now a commonly used technique in drug discovery (4-7). Modern drug discovery also relies on the interface of chemical and biological diversity through high throughput screening (8).Generation of functional molecular diversity for probing the biological activity space requires robust molecular scaffolds that are low in molecular weight and are easily modified to create a variety of chemically diverse, biologically active potential drugs. We do report our efforts to relate the dependence of the antimycobacterial activity of new compounds on the nature of

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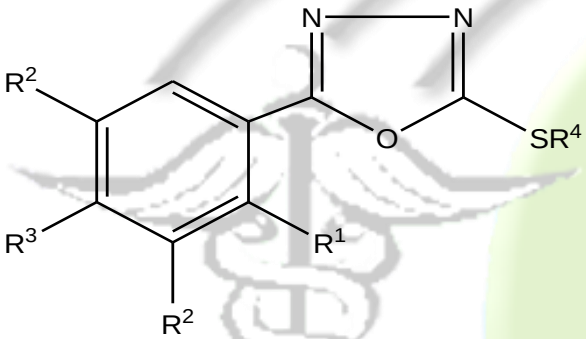
substitution in the 5-aryl-2-thio-1, 3, 4-oxadiazoles. The present 3D QSAR study was carried out by using k-Nearest Neighbor Molecular Field Analysis (K-NNMFA) method for predicting the antitubercular activity. The better the description of a molecule in terms of structural parameters representing its activity, the better the results of pattern recognition and separation of molecules by activity.

Figure 1. Structures of the molecules for the series



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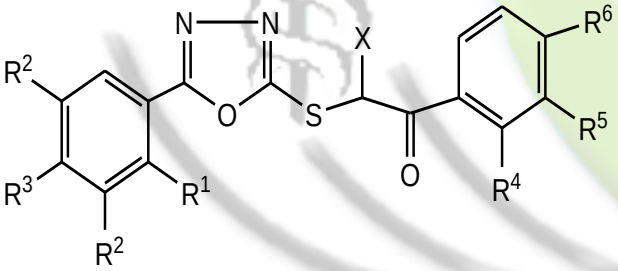

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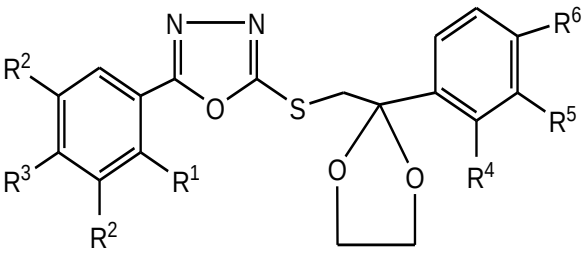

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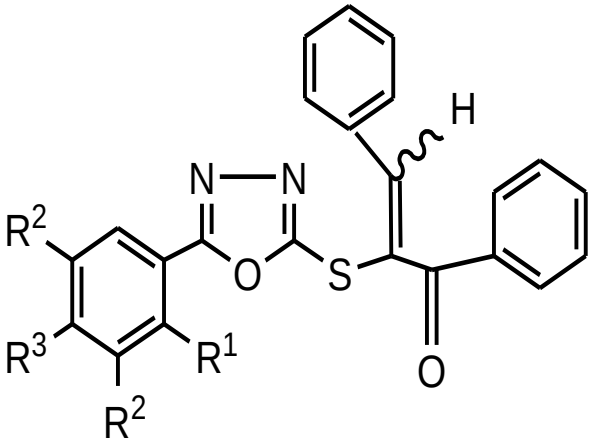

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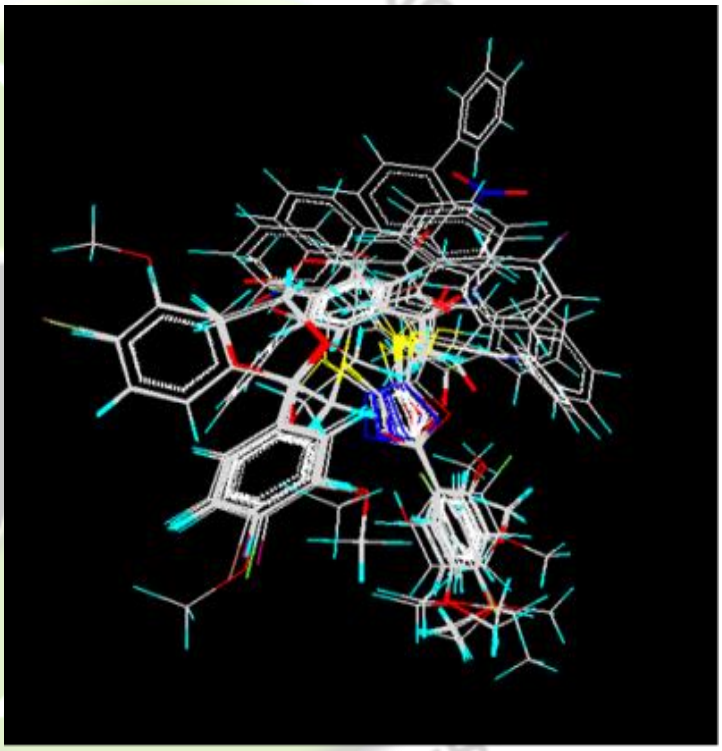
Figure 2- Aligned Molecules of Series



EXPERIMENTAL

METHODOLOGY

The in vitro percentage inhibition values for anti-mycobacterial activities of 5-aryl-2-thio-1, 3, 4-oxadiazoles against M . tuberculosis H37 Rv were taken from the literature (9).

Table 1. List of substituents for the series

COMPOUND	R^1	R^2	R^3	R^4	R^5	R^6
4F	Cl	H	Cl	H	—	—
4J	H	OMe	OMe	H	—	—
5B	OH	H	H	Me	—	—
5C	Br	H	H	Me	—	—
5F	H	OMe	OMe	Me	—	—
6	H	OMe	OMe	CH_2Py	—	—
7	H	H	H	H	H	H
8	OH	H	H	H	H	H
9	Me	H	H	H	H	H
10	Cl	H	H	H	H	H
11	H	H	H	H	H	F
12	H	OMe	OMe	H	H	F
13	H	H	H	H	H	NO_2
14	H	OMe	OMe	H	H	Br
15	H	OMe	OMe	Cl	H	Cl
16	H	OMe	OMe	H	OMe	H
16	H	OMe	OMe	H	H	Me
17	H	OMe	OMe	H	H	Phenyl
18	H	OMe	OMe	H	H	NO2
19	H	OMe	OMe	H	H	Cl
20	H	OMe	OMe	H	H	Cl
21	H	OMe	OMe	H	OMe	OMe
22	H	OMe	OMe	2-Naphthyl	39	31
23	H	OMe	OMe		H	H
24[a]	H	H	H	H	H	H
25	OH	H	H	H	H	F
26	OH	H	H	H	15	15
27	OH	H	H	2-Naphthyl	H	Br
28	H	H	H		H	H
29	OH	H	H	H	H	H
30	H	H	OEt	H	H	H
31	H	H	OMe	H	OMe	H
32	H	H	OMe	H	H	Cl
33	H	H	OH	H	OMe	H
34	H	H	OH	H	OMe	OMe
35	H	OMe	OMe	H	H	F
36	H	OMe	OMe	H	H	Br
37	H	OMe	OMe	H	H	Cl
38	H	OMe	OMe	H	OMe	H
39	H	OMe	OMe	H	H	H
40	H	H	H	H	H	H
41	H	H	H	H	H	H

To these values, we have applied one of the modest kNN-MFA with various variable selection methods. Similar to many 3D QSAR methods (10, 11) kNN-MFA requires suitable alignment of set of molecule. This is followed by generation of common rectangular grid around the molecules. The steric and electrostatic energies are computed at the lattice point of grid using methyl probe of charge +1, these interaction energy values at the grid point are considered for relationship generation using kNN method and utilized as descriptors to decide nearness between molecules (12).

All the 41 molecules taken in the study (Figure 1) were drawn in Vlife QSAR Plus. They were optimized by using "Merck Molecular Force Field (MMFF)" and were also batch optimized. After this all the 41 molecules were aligned (Figure 2) using template based alignment method by choosing a minimum common structure as 'Template' (Figure 3) and the most effective one as the 'Reference Molecule' (Figure 4). From the 41 molecules taken in the study, a training set of 33 molecules and test set of 8 molecules were generated using the various selection procedures. After the selection of the test and training sets, kNN methodology was applied to the descriptors generated over the grid as shown in the 'Show Point' (Figure 5).

Fig 3- Show Point

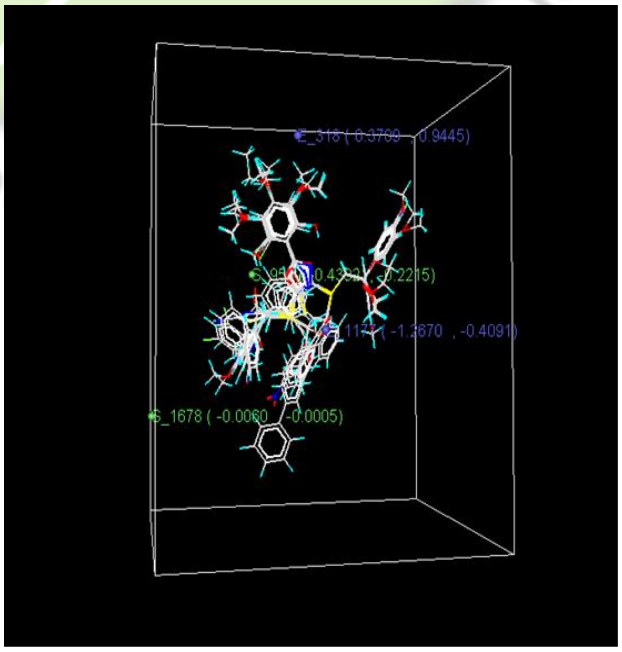


Table 2. Model summary

Training Set Size = 33

Test Set Size = 8

Selected Descriptors:

S_954

E_1177

S_1678

E_318

Statistics:

k Nearest Neighbour= 5

n = 33

Degree of freedom = 26

q2 = 0.5022

q2_se = 11.4783

Predr2 = 0.2898

pred_r2se = 23.2517

Descriptor Range:

S_954 -0.4392 -0.2215

E_1177 -1.2670 -0.4091

S_1678 -0.0060-0.0005

E_318 0.3709 0.9445

EVALUATION OF QSAR MODELS The QSAR models were evaluated using following statistical measures: n-number of descriptors; k-number of nearest neighbors; q2-cross validated r2 (by leave-one-out method); pred-r2 - predicted r2 for the external test.

RESULTS AND DISCUSSION

The importance and utility of the new 3D QSAR method discussed has been established by applying it to known sets of molecules as described above. We report that 52, 3D QSAR models were generated by kNN-MFA in conjunction with Simulated Annealing (SA), Genetic Algorithms and Stepwise (SW) Forward Backward selection methods. From these models, two of them were having good q2 and pred-r2 values, one of which was selected having good internal and external predictivity. For this model training and test sets were selected using random selection method and the descriptors were selected using simulated annealing method. The summary of the selected model (Table 1) can be given as: k=5; q2=0.5022; pred-r2 = 0.2898; Descriptor range: S-954 -0.4392 to -0.2215; E-1177 -1.267 to -0.4091; S-1678 -0.0060 to -0.0005; E-318 -0.3709 to 0.9445.

The selected model has shown good internal and external predictivity with q2=0.5022 and pred-r2=0.2898 for the training and test set molecules. The model had indicated that the presence of sulphur is required for optimum antimycobacterial activity, whereas the large bulky substituents on sulphur i.e. R4 reduces the activity, as indicated by increase in negative value of descriptor S-954. The presence of electronegative groups on R6 with less bulky substituents on other positions specifically R2 and R3 has shown better activity as indicated by increase in positive value of electronic descriptor E-318.

Thus, it would be worthwhile to synthesize a novel 1,3,4-oxadiazole analogue with less bulky groups on sulphur and more electronegative group at R6 along with less bulky substituents at R2 and R3 positions.

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