



## Computer Added Drug Design of 1,3,4-oxadiazoles as antimycobacterial agents

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### Abstract

Recently several 1,3,4-oxadiazole derivatives were 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* H<sub>37</sub>Rv (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  $q^2$  and  $\text{pred}_r^2$  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 ( $q^2$ ) and cross validation ( $\text{pred}_r^2$ ) values of 0.5022 & 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

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### 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 & suffering world wide 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 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.

## Results and Discussion

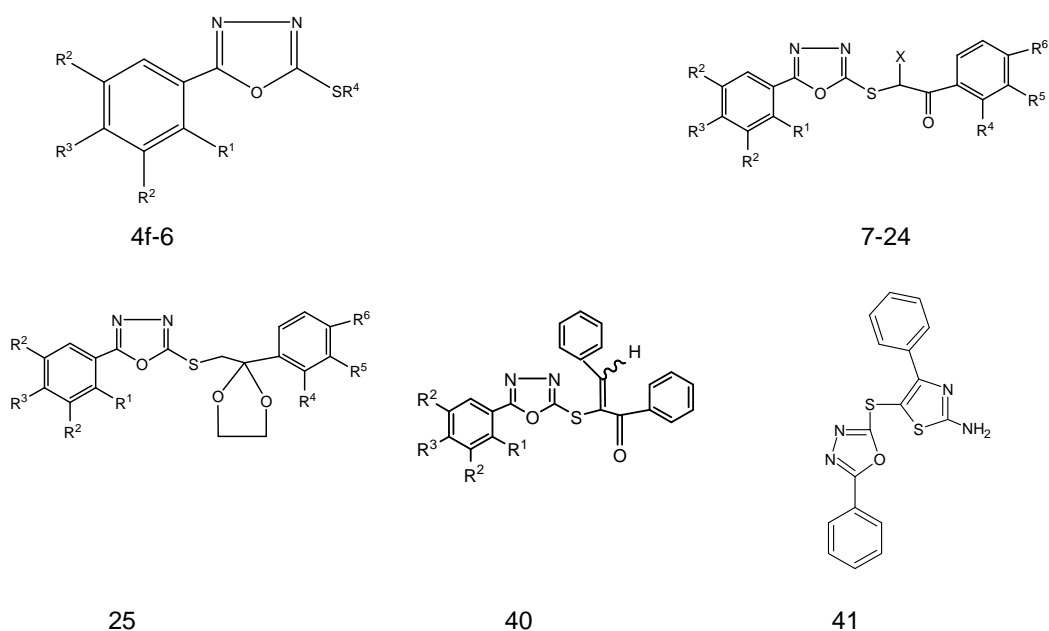
The importance and utility of the new 3D QSAR method discussed has been established by applying it to known sets of molecules as described above. We report that 52, 3D QSAR models were generated by kNN-MFA in conjunction with Simulated Annealing (SA), Genetic Algorithms & Stepwise (SW) Forward Backward selection method. From these models, two of them were having good  $q^2$  &  $\text{pred}_r^2$  values, one of which was selected having good internal & 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:  $k = 5$ ;  $q^2 = 0.5022$ ;  $\text{pred}_r^2 = 0.2898$ ; 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.

Training Set Size = 33
Test Set Size = 8
<b>Selected Descriptors:</b>
S_954
E_1177
S_1678
E_318
<b>Statistics:</b>
k Nearest Neighbour= 5
n = 33
Degree of freedom = 26
$q^2 = 0.5022$
$q^2_{se} = 11.4783$
$\text{Pred}_r^2 = 0.2898$
$\text{pred}_r^2 se = 23.2517$
<b>Table. 1: Model Summary</b>
<b>Descriptor Range:</b>
S_954 -0.4392 -0.2215
E_1177 -1.2670 -0.4091
S_1678 -0.0060 -0.0005
E_318 0.3709 0.9445

## Material and Methods

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]. 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].

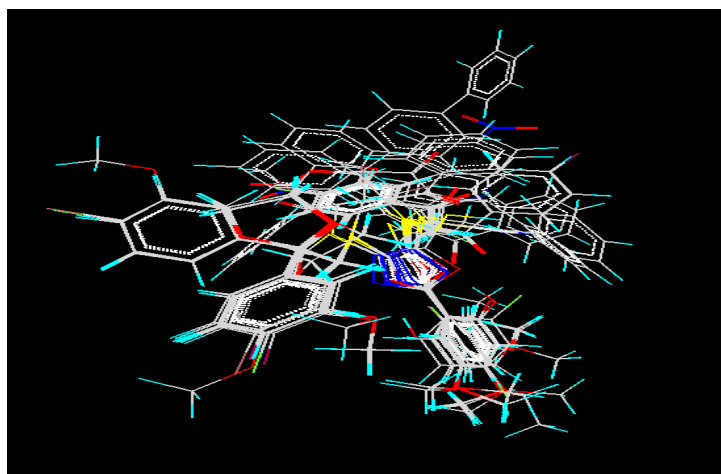
All the 41 molecules taken in the study (Fig.1) were drawn in Vlife QSAR Plus. They were optimized by using “Merck Molecular Force Field (MMFF)” and they were batch optimized also (as described in table.2). After this all the 41 molecules were aligned (Fig.2) using template based alignment method by choosing a minimum common structure as ‘*Template*’ (Fig.3) and the most effective one as the ‘*Reference Molecule*’ (Fig.4). From the 41 molecules taken in the study, a training set of 33 molecules & 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*’ (Fig.6).



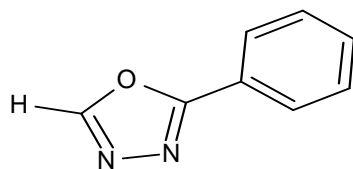
**Fig.1 Structures of the molecules for the series**

Table. 2

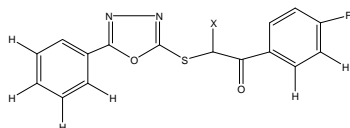
COMPOUND	R1	R2	R3	R4	R5	R6	Inhibition (%)
4f	Cl	H	Cl	H	—	—	20
4j	H	OMe	OMe	H	—	—	3
5b	OH	H	H	Me	—	—	30
5c	Br	H	H	Me	—	—	47
5f	H	OMe	OMe	Me	—	—	20
6	H	OMe	OMe	CH <sub>2</sub> Py	—	—	39
7	H	H	H	H	H	H	28
8	OH	H	H	H	H	H	45
9	Me	H	H	H	H	H	19
10	Cl	H	H	H	H	H	17
11	H	H	H	H	H	F	58
12	H	OMe	OMe	H	H	F	27
13	H	H	H	H	H	NO <sub>2</sub>	24
14	H	OMe	OMe	H	H	Br	22
15	H	OMe	OMe	Cl	H	Cl	12
16	H	OMe	OMe	H	OMe	H	17
17	H	OMe	OMe	H	H	Me	48
18	H	OMe	OMe	H	H	Phenyl	37
19	H	OMe	OMe	H	H	NO <sub>2</sub>	33
20	H	OMe	OMe	H	H	Cl	27
21	H	OMe	OMe	H	OMe	OMe	31
22	H	OMe	OMe	2-Naphthyl	39	31	-
23	H	OMe	OMe	H	H	H	19
24 <sup>a</sup>	H	H	H	H	H	H	33
25	OH	H	H	H	H	F	33
26	OH	H	H	2-Naphthyl	15	15	-
27	OH	H	H	H	H	Br	13
28	H	H	H	H	H	H	82
29	OH	H	H	H	H	H	55
30	H	H	OEt	H	H	H	-
31	H	H	OMe	H	OMe	H	-
32	H	H	OMe	H	H	Cl	15
33	H	H	OH	H	OMe	H	-
34	H	H	OH	H	OMe	OMe	3
35	H	OMe	OMe	H	H	F	6
36	H	OMe	OMe	H	H	Br	7
37	H	OMe	OMe	H	H	Cl	28
38	H	OMe	OMe	H	OMe	H	5
39	H	OMe	OMe	H	H	H	14
40	H	H	H	H	H	H	30
41	H	H	H	H	H	H	55



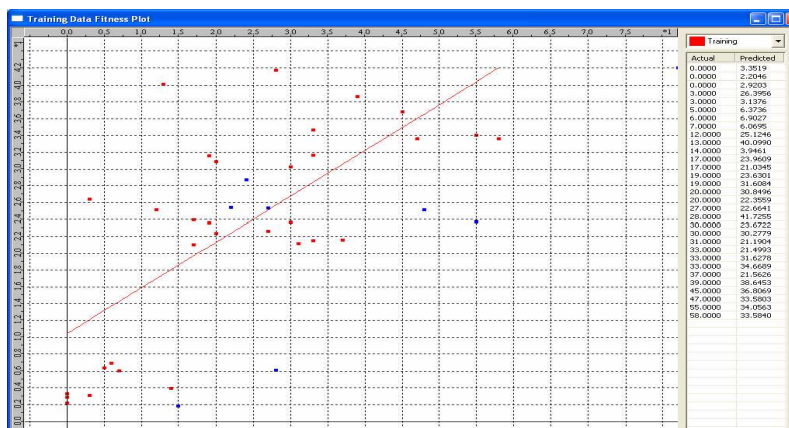
**Fig.2: Aligned molecules of the series**



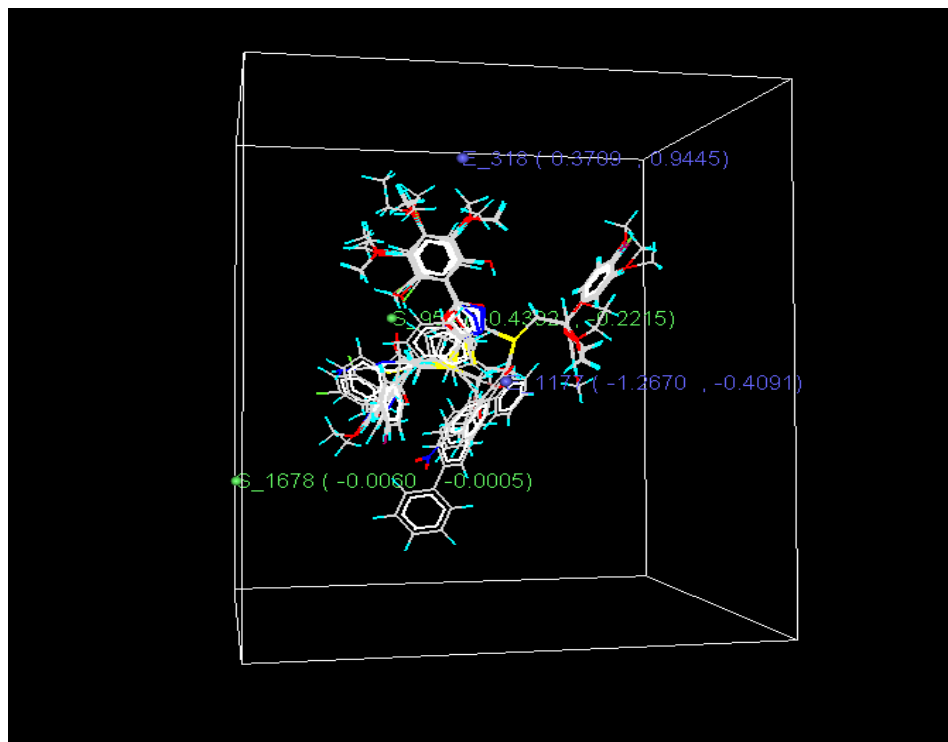
**Fig.3: Template**



**Fig.4: Reference Molecule**



**Fig.5: Training Data Fitness Plot**



**Fig.6: Show Point**

#### ***Evaluation of QSAR models***

The QSAR models were evaluated using following statistical measures: n-number of descriptors; k-number of nearest neighbors;  $q^2$  - cross validated  $r^2$  (by leave-one-out method);  $\text{pred}_r^2$  - predicted  $r^2$  for the external test.

#### **Conclusion**

The above investigations have revealed the synthesis of novel 1,3,4-oxadiazoles with less bulky groups on sulphur and more electronegative groups at  $R^6$  along with less bulkier substituents at  $R^2$  &  $R^3$  positions.

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