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2D-QSAR STUDY OF SUBSTITUTED THIOPHENE CARBOXAMIDE DERIVATIVES:AN APPROACH TO DESIGNANTI-TUBERCULAR AGENT.

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Introduction

Tuberculosis is the leading cause of death by infectious disease with one-third of the world population infected[1]. *Mycobacterium tuberculosis*, the leading causative agent of tuberculosis (TB), is responsible for the morbidity and mortality of a large population worldwide. According to a WHO report, by 2020 AD, nearly one billion more people will be infected, 200 million population will get sick, and 70 million will die from tuberculosis if proper steps are not taken to control it[2,3]. TB is the world's second most cause of death due to infectious disease, after acquired immune deficiency syndrome (AIDS)[4]. No new antibiotics against TB have been developed in the last 30 years. There are three frontline antibiotics, isoniazide, rifampin and pyrazinamide, and several second line antibiotics including ethionamide, streptomycin, and *para*-aminosalicylic acid[5]. The situation with multidrug resistant (MDR) tuberculosis (TB) today worries the health authorities of the whole world, mainly chiefly in the developing countries, where the situation is more severe[6]. The response of patients with MDR-TB to treatment with expensive and toxic second-line drugs is poor and the mortality rate is about 50%. Thus, the developments of potent new antitubercular drugs, which are active against resistant strains and latent forms and reduce the treatment period, are urgently needed to combat this disease.

Materials and method

Computational method

Computational studies were performed on an HP with Windows 7 Home Basic running on an Intel® core pro- cessor. The molecular structures of the compounds in the data set were sketched using the V-life MDS (Molec- ular Design Suite)^{TM} 4.6 software supplied by V-life Sciences

Technologies [17]. Analogues 2,6-disubstituted 4,5,6,7-tetrahydrothieno[2,3-c] pyridine-3-3carboxamide and ten of 2-substituted 4,5,6,7,8,9-hexa hydrocycloocta [b]thiophene-3-carboxamide derivatives reported to have potent and selective with minimum inhibitory activity against M. tuberculosis H37Rv (MTB) were taken from the literature [18]. The biological assay used to test the activity of all of the molecules was the same, and hence, the inhibition values indicated by IC_{50} are comparable. The biological activities represented by IC_{50} were converted into the corresponding pIC_{50} values ($-\log IC_{50}$), which were used as dependent variables in the QSAR analysis. For this study, a total of 30 2,6-disubstituted 4,5,6,7-tetrahydrothieno[2,3-c] pyridine-3-3carboxamide and ten of 2-substituted 4,5,6,7,8,9-hexahydrocycloocta[b]thiophene-3-carboxamide derivatives were divided into training and test sets consisting of twenty-three and seven compounds (Table 1), respectively. The sphere exclusion method [19] was adopted to divide the training and test data set comprising of twenty-three and seven compounds, respectively, with a dissimilarity value of 8.6, where the dissimilarity value gives the sphere exclusion radius. This algorithm allows the construction of training sets covering all descriptor space areas occupied by representative points. Eight compounds, were used as the test set, while the remaining molecules were used as the training set. Initially, the data set was split into training (70%) and test sets (30%) using the MDS software. Care was taken to achieve an even distribution of activities in both sets (training and test).

To perform the QSAR analysis, the structures of the compounds in the data set were sketched in chem draw software, and the physicochemical descriptors of the molecules were cal- culated using the V-life MDS (molecular design suite) software. All of the compounds were batch optimized to minimize energies and optimize the geometry using Merck molecular force fields, followed by considering the distance-dependent dielectric constant of 1.0, the convergence criterion or root mean square (RMS) gradi- ent of 0.01 kcal/mol Å and the iteration limit of 10,000 [20].

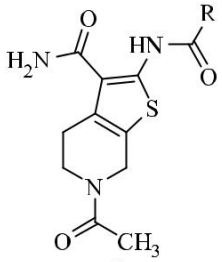
Two-dimensional QSAR

A large number of theoretical descriptors, such as SA Most Hydrophilic (most hydrophilic value on the vdW surface), SA Most Hydrophobic–Hydrophilic Distance (distance between most hydrophobic and hydrophilic point on the vdW surface), SA Hydrophilic Area (vdW surface descriptor showing hydrophilic surface area) and SK Most Hydrophilic, the radius of gyration, Wiener's index, moment of inertia, semi-empirical descriptors, HUMOEnergy (highest occupied molecular orbital), heat of formation and ionization potential, as well as constitutional, physicochemical, electrostatic, topologi- cal and semi-empirical descriptors have been computed from chemical structures with a view to developing the structure-activity relationships of 2,6-disubstituted 4,5,6,7-tetrahydrothieno[2,3-c] pyridine-3-3carboxamide and ten of 2-substituted 4,5,6,7,8,9-hexahydrocycloocta[b]thiophene-3-carboxamide compounds, which would, in turn, predict their biological activity.

The independent variables (*i.e.*, descriptors) were pre- processed by removing the invariable values (constant column), which resulted in a total of 280 descriptors for use in QSAR analysis. Descriptors with the same value or almost the + same value or that were highly correlated with

other descriptors were removed initially.data set of 24 compound was taken from the published series as reported. The anti TB activity of compound was reported in MIC value. The structure and anti TB activity data was listed in table no. 2.

Table no. 1 basic moiety for substitution series:



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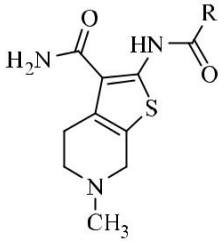

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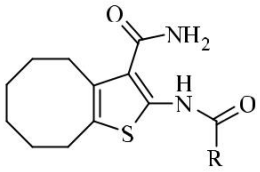

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table no . 2 biological activities of compound:

Compound No.	Compound	MIC (µM)	pMIC
7a	Methyl	88.6	4.052
7b	Phenyl	72.65	4.138
7c	2-Methoxyphenyl	66.84	4.174
7d	3-Nitrophenyl	64.26	4.192
7e	4-Tolyl	69.80	4.156
7f	4-Phenoxyphenyl	57.30	4.241
7g	1-Napthyl	63.45	4.197
7h	Cyclopropyl	81.15	4.090
7i	Cyclopentyl	74.40	4.128
7j	Cyclohexyl	71.40	4.146
8a	Methyl	39.43	4.404
8b	Phenyl	37.87	4.421
8c	2-Methoxyphenyl	36.12	4.442
8d	3-Nitrophenyl	34.62	4.460
8e	4-Tolyl	37.87	4.421
8f	4-Phenoxyphenyl	30.60	4.513
8g	1-Napthyl	17.07	4.767
8h	Cyclopropyl	5.57	5.254
8i	Cyclopentyl	5.06	5.295
8j	Cyclohexyl	7.76	5.110
12a	Methyl	18.72	4.727
12b	Phenyl	15.19	4.818
12c	2-Methoxyphenyl	13.92	4.856
12d	3-Nitrophenyl	16.71	4.777
12e	4-Tolyl	4.54	5.342
12f	4-Phenoxyphenyl	3.70	5.431
12g	1-Napthyl	13.19	4.879
12h	Cyclopropyl	17.06	4.768
12i	Cyclopentyl	9.73	5.011
12j	Cyclohexyl	9.33	5.030

Statistical computation

To calculate q^2, each molecule in the training set was sequentially removed, the model refit using the same descriptors, and the biological activity of the removed molecule predicted using the refit model [21]. The value of q^2 was calculated using the following equation:

where y_i, $\hat{y}_i$ are the actual and predicted activity of the *i*th molecule in the training set, respectively, and y_{mean} is the average activity of all molecules in the training set. For external validation, the activity of each molecule in the test set was predicted using the model generated from the training set. The pred r^2 value is calculated as follows (Eq. (2)):

where y_i, $\hat{y}_i$ are the actual and predicted activity of the *i*th molecule in the test set, respectively, and y_{mean} is the average activity of all molecules in the training set.
The developed quantitative model was evaluated using the following statistical measures: *N*, number of observations (molecules) in the training set; q^2, cross- validated r^2 (by leave one out), which is a relative measure of the quality of fit; pred r^2, r^2 for the exter- nal test set; q^2 se, standard error of cross-validation; and pred r^2 se, the standard error of the external test set prediction. The low standard error of pred r^2 se and q^2 se show the obsolete quality of fitness of the model. The high pred r^2 and low pred r^2 se show the high predictive ability of the model. The q^2 and pred r^2 values were used as deciding factors in selecting the optimal models.

Results and discussion

In this study, the training and test sets were generated using the sphere selection method followed by the partial least squares regression analysis. Several 2D QSAR models were constructed, and the best one regression equations obtained were as follows:

$$pIC_{50} = 0.7145(\pm 0.0896)SsNH2E\text{-}index + 0.0463(\pm 0.0114)SdOE\text{-}index - 0.1758(\pm 0.0522)T\_T\_N\_6 + 0.2537(\pm 0.1199)T\_T\_N\_7$$

Degrees of Freedom = 20, $N_{training}$ = 24, N_{test} = 6, r^2 = 0.8319, q^2 = 0.7950, *F* test = 43.148, r^2 se = 0.1772, q^2 se = 0.1888, pred r^2 = 0.7983, pred r^2se = 0.1832, Z_{Score} Q^2 = 1.971, Best Rand Q^2 = 0.58238

For qsar analysis, regression was performed using MIC value as adependent variable and calculated parameter as aindependent variable. In any investigation of the effect, of molecular properties, it is essentially proves that the result result stastically valid shown in figure 1 ,

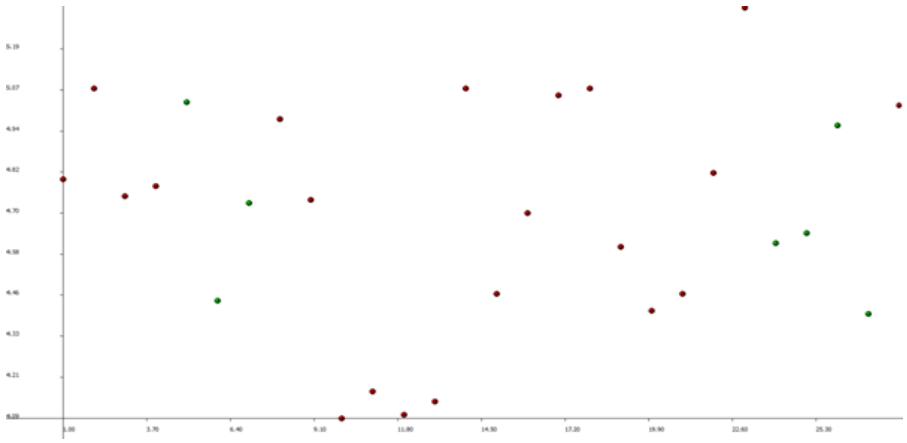

Figure no. 1 :distribution chart , model : all test set covered by the traning set

Contribution chart (figure 2) signifies that the descriptor below the zero line have negative contribution and above the line have positive contribution. In 2d QSAR SsNH2E-index, SdOE-index and T_T_N_7 shows positive contribution and T_C_N_6 .

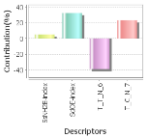

Figure no. 2 : contribution chart

- SsNH2E-index: Electrotopological state indices for no of –NH2 group connected with one single bond.
- SdOE-index : Electrotopological state indices for no of Oxygen atom connected with one double bond.
- T_T_N_7 :It determines the distance between nitrogen atom by 7 bond.
- T_C_N_6 :It determines the distance between nitrogen atom by 6 bond.

Unicolon stastitics support the suitability of selection of test set and training set and average should always more than the sum (table 3). Figure 3 shows that the test and training set lie in the plan fitness plot these compound have better predicted activity.

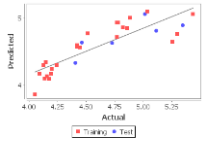

Figure no 3: fitness plot (blue colour spot for test set and red colour spot for training set)

	Column name	Average (mean)	Max*	Min*	Std Dev	Sum
Training set	pEC_{50}	4.3800	5.0700	4.100	0.3395	38.2400
Test set	pEC_{50}	4.6871	5.0300	4.400	0.2400	32.8100

Table no .3 unicolon stastics

From 24 analogues used for QSAR studies were found the most potent compound with minimum residual activity.

Compound	Observed activity	Predicted activity	Residual activity
1)7a	4.052	3.865122	0.1868
2)7b	4.138	4.104836	0.0331
3)7c	4.174	4.09659	0.0774
4)7d	4.192	4.171099	0.0209
5)7e	4.156	4.135246	0.0207
6)7f	4.241	4.304482	-0.0634
7)7g	4.197	4.24881	-0.0518
8)7h	4.090	4.176157	-0.0861
9)7i	4.128	4.30115	-0.1731
10)7j	4.146	4.34455	-0.1985
11)8a	4.404	4.333411	0.0705
12)8b	4.421	4.573125	-0.1521
13)8c	4.442	4.564879	-0.1228
14)8d	4.460	4.639389	-0.1793
15)8e	4.421	4.603535	-0.1825
16)8f	4.513	4.772772	-0.2597
17)8g	4.767	4.717099	0.0499
18)8h	5.254	4.644447	0.6095

19)8i	5.295	4.769439	0.5255
20)8j	5.110	4.81284	0.2971
12a	4.727	4.628856	0.0981
12b	4.818	4.86857	-0.0505
12c	4.856	4.860324	-0.0043
12d	4.777	4.934833	-0.1578
12e	5.342	4.89898	0.4430
12f	5.431	5.068216	0.3627
12g	4.879	5.012544	-0.1335
12h	4.768	4.939891	-0.1718
12i	5.011	5.064884	-0.0538
12j	5.030	5.108284	-0.0782

Table:-Observed and Predicted activity of the training set and test set molecules using 2D,SA-MLR Method.

Conclusion:

In this investigation qsar analysis was performed on data set consisting of structurally diverse compound to investigate the role of structural feature on their anti TB activity. The result indicated that the topological, electronic and spatial parameter significantly influences the activity. Thye result obtained from this study importance of SsNH2E-index, SdOE-index, T_T_N_6 and T_C_N_7 in determining the binding affinity for the anti TB receptors. These investigation will help in rationalizing the design of anti TB drug.

Aknowledgement:

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