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QSAR Studies on 4-thiazolidinones and 2-Azetidinones bearing Benzothiophene Nucleus as Potential Anti-Tubercular Agents

Abstract

Quantitative structure-activity relationships (QSAR) study 011 a series of (substituted I, 2-dihydro)4-thiazolidinones r and 2-azetidinones bearing benzothiophene nucleus with anti-tubercular activity has been carried out using a combination of various physicochemical descriptors. Several significam equations with good co-efficient of correlation (0.860) have been obtained. The two models are selected using internal predictive power discerned by cross-validated coefficient q^2. Both models highlight some common important feature, ie. bulky substitution and the high nucleophilicity nature of the molecules, favorable for anti-tubercular activity.

Keywords: Anti-tubercular activity, QSAR, benzothiaphenc. anti-tubercular agents.

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Introduction

Tuberculosis is a chronic grannulomatous disease'. It is estimated that today one-third to one-half of the world population is infected with tuberculosis leading to approximately 6% of all deaths worldwide. The causative moiety of the disease is Mycobacterium tuberculosis. Despite of the development of several types of synthetic anti-tubercular agents, the incidences of tuberculosis is still increasing in large parts of the world due to the development of resistance in Mycobacterium to the available drugs.

Thus, there is I am urgent need for novel anti-tubercular agents. With modes of action and chemical structures different from the currently used compounds, it is planned to study the quantitative structure activity.[5-6] And relationships 4-thiazolidinones[7-9] (QSAR), of some 10-12 which have played an 2-azetidinones, important role in medicinal chemistry. Moreover, they have been studied extensively because of their ready accessibility, diverse chemical reactivity and broad spectrum of biological activity.

Aim of the Study

The focus of the present investigations is the QSAR analysis of thiazolidinones and azetidinones nucleus as potent anti- tubercular agents.

Materials and Methods

The Dataset and Parameters Quantitative structure activity relationship (QSAR) studies of anti- tubercular activity of newly reported thiazolidinones and azetidinones derivatives against *Alycobacterium tuberculosis* reported by Joshi et al13 performed using linear free energy relation of Hansch. Some of the were compounds reported in the original paper were excluded in the present study because of their non-graded quantitative activity datil or non- availability of parametric values. Antilubercular activity of remaining compounds are given in Table I. The biological activity values [HA] reported in the literature were converted to molar units and then further to - log scale and subsequently used as the response variable for the QSAR analysis. Th: molar anti-tubercular activities were then subjected to multiple regression analysis on different physicochemical parameters and indicator variables (QSAR). The relationships between the activities were also studied to explore the selectivity in terms of structural requirements. The congeneric series possesses one region of structural variation. Figure 1 shows effect of R substitution on 2-(substitutedbenzal- hydrazinocarbony 1)-3,5-chlorobenzo(b)thio-phene, Figure 2 shows effect of R substitution on 2ary 1-5H-3-(3',5-dichloro-2'-bcnzo(b)thiophenylamino)4-thiazolidin- ones and Figure 3 shows effect of R substitution on the 4-aryJ-3-chloro-l- (3',5' -

dichloro2'-benzo(b)-thiophenylamino)-2- azetidinones.

Table 1

All the computations in the present study performed on PIV were workstation. The molecular structures of the training set were sketched using Chem Draw Ultra module of CS Chem Office 2001 molecular modeling software ver. 6.0, supplied by Cambridge Software Company[14]. The sketched structures were exported to Chem3D module in order to create its 3D model. Each model was "cleaned up" and energy minimization was perfonned using Allinger's MM2 force field by fixing Root Mean Square Gradient (RMS) to 0.1 Kcal/molA°. Further, geometry optimization was done using semiemperical AMI (Austin Model) Hamiltonian method, closed shell restricted wave function available in the MOPAC module until the RMS value becomes smaller than 0.001 Kcal/molA. The low energy confortfi'ers obtained from the aforementioned procedure was used for the calculation of the descriptors. The descriptors include physicochemical, thermodynamic, electronic and spatial descriptors available in the 'Analyze' option of the Chem. 3D package Table II). The descriptors calculated for the present study accounts for four important properties of the molecules: physicochemical, thermodynamic,

Figure 3

electronic and steric, as they represent the possible molecular interactions between the receptor and thiadiazinoacridines.

7
Henry's Law Constant (HCL)
Thermodynamic
Ideal Gas Thermal Capacity (IGTC)
Thermodynamic
9
Log P
Thermodynamic
Melting Point (MP)
10
Thermodynamic
Molar Refractivity (MR)
11
Thermodynamic
Standard Gibbs Free Energy (SGFE)
12
Thermodynamic
Connolly Accessible Area (CAA)
13
Steric
Connolly Molecular Area (CMA)
14
Steric
15 Connolly
Solvent-Excluded
Volume Steric
(CSEV)
16 Ovality (OVA)
Steric
Principal Moment of Inertia - X(PMI-X)
Steric
17
Steric
Principal Moment of Inertia -Y (PMI-Y)
18
Principal Moment of Inertia -Z (PMI-Z)
Steric
19
Electronic
Dipole Moment (D)
20
Electronic
Dipole Moment X Axis (DX)
21
Electronic
Dipole Moment Y Axis (DY)
Electronic
23
Dipole Moment Y Axis (DZ)
Electronic
Electronic Energy (EE)
24
Electronic
HOMO Energy (HOMO)
Electronic
LUMO Energy (LUMO)
26
228

Electronic
27
Rupulsion Energy (RE)
Bend Energy (Eb)
Thermodynamic
28
Thermodynamic
Charge-Charge Energy (CCE)
29
Thermodynamic
Charge-Dipole Energy (CDE)
30
Thermodynamic
Dipole-Dipole Energy (DDE)
31
Thermodynamic
Non-1, 4 VDW Energy (E,)
32
Thermodynamic
33 Stretch Energy (SE)
Thermodynamic
Stretch-Bend Energy (SBE)
34
Thermodynamic
Torsion Energy (Et)
35
Thermodynamic
Total Energy (E)
36
Thermodynamic
Van der Waals e 1, 4 Energy (VDWE)
37
Thermodynamic
VDW 1, 4 Energy (VDWE)
38
Thermodynamic
39 Partition coefficient

and corresponding regression equation is found out to calculate predicted activity value and predicted residual (press) of deleted compound. The PRESS (predicted residual sum of squares) statistics provides the relations between the observed activity and calculated value (according to PRESS equation). The

Table III- Calculated descriptor values for the given series of compounds

E1
HOMO
Compd
PMI-X
D
-5.2672
2730.62
-8.7059
la
2.4079

3g
3224.63
5.5351
-8.9489

-1.2288
3h
2523.64
6.2512
-8.6158
3.63627
31
3644.38
4.2893
-8.7998
6.50846

stability and predictive capacity of the equation were cross validated from PRESS statistics obtained by running V ALST A T16 programs using "leave-one-out" technique.

Results and Discussion

Biological activity data and various physicochemical parameters were taken as dependent and independent variables, respectively, and correlations were established using sequential multiple regression analysis. The descriptors selected for modeling antitubercular activity of thiazolidinones and azetidinones derivatives are summarized in Table III. The quarter parametric models were obtained and these models are significant for anti-tubercular activity.

Model I
0.00018139(0.000147211)
4.48858(+:: 2.70123)
-10gB A
PMI-X
0.0606539(0.05596'19) D 0.453772(0.305151)
HOMO-
0.0246623(+0.014462) E
n -22, R-0.860104, Variance 0.0183792, SD 0.13557, F -12.0823

Model II
-logBA
4.45369(2.67143)
+0.000217417(0.000135005)
PMX- 0.0646233(0.0528988) D 0.458231 (0.301616)HOME-
0.0232831 (+0.014025) El
n 24, 'R -0.854129, variance-0.0183422, SD 0.135433, F - 12.8125

The study of model I and model II revels those thermodynamic parameters like torsion energy (El), steric parameters like principal moment of inertia Xaxis (PMI-X) and electronic parameters like dipole moment (D) and highest occupied molecular orbit (HOMO) are associated with anti-tumor activity.

In model I, dipole moment, an electronic parameter and is important in case when dipole dipole interactions are involved in ligand-receptor interaction; and torsion energy (E) is the thermodynamic parameter, which represents the energy associated with deforming torsion angles in the molecules from their ideal values. The negative coefficients of descriptors suggest presence of conjugation and bulky substituents tolerable for activity, whereas principal moment of inertia, X-axis is a spatial descriptor, which explains the significance of orientation and conformation rigidity of the molecule. The positive coefficient of these descriptor suggest the presence of bulky substituents oriented towards X-axis of the molecules will give better activity and highest occupied molecular orbital. HOMO is

significance of the model as follows. Bootstrapping r = 0.777145, q Q.586244, Spress 0.167511, SpEP 0.149044

The correlation matrix shows model II to be more significant than model 1. In model I, all independent parameters (PMI-X, D, E and expected HOMO) have poor (independent) correlation with each other as in QSAR analyses but in model-II independent parameters (PMI-X, D, E and HOMO) have dependent ,correlation. The correlation matrix and predicted activity data for model 1 and model II are shown in Table IV, V and Table VI, VII, respectively. Figure 4 and Figure 5 show a plot of observed vs predicted activities of compounds of model 1 and model II, respectively. The comparison of significant than model I, model 1 and model II, the model II was more having good correlation coefficient (R), crossvalidated (q) value (reflects predictive power of model) bootstrapping (r) value (reflect accuracy of the model), and independent correlation between

Table IV - Correlation matrix for parameters in model I

E
HOMO
Parameters
PMI-X
PMI-X
1.000000
1.000000
D
0.055336
1.000000
0.170548
HOMO
0.077995

Et
0.256476
0.222781
0.402842
1.000000

Table V - Correlation matrix for parameters in Model II

Parameters
PMI-X
HOMO
E
D
PM I-X
1.000000
0.014297
1.000000
HOMO
1.000000
0.208958
0.090494
1.000000
0.4059 I 2
Et
0.319568
0.247327

Table VI
Predicted activity data of model I
Compd Observed-
log BA
Calculated
Predicted
-10gB A
-logBA
1.01723
la
1.12
0.991225
0.865298
1b
0.881516
0.78
0.794575
0.717722
lc
1.06
0.983557
1.05483
Id
0.86
1.13694
1.09521
le
1.19
1.14194
1.15091
1.12
1f
0.684136
0.692616
2a
0.6
0.735515
0.733646
2b
0.75
0.602833
0.597315
0.65
2d
0.851327
0.842528
0.95
2e
0.864789
0.856629
0.9
2f
0.827379
0.855464
0.65
2g
1.19375
1.19709
1.]9
2h
0.720402
0.74133
0.6
2i
0.624585
0.625229
0.62
3a
0.372207
0.31487
3b
0.45
0.67239
0.702978
0.41
3d
0.597353
0.588495
3e
0.65
0.692664
0.658391
3f
0.75
0.707332
0.754452
3g 0.6

3h
0.54
0.575164
0.567922
3i
0.95
0.735868
0.643861
Compd 2e and 3e are outlier
Table VII Predicted activity data of Model II
Calculated
Compd Observed
Predicted -logBA
-10gB A
-log BA
1.02507
1.00262
la
1.12
0.848092
lb

0.78
0.860242
0.77437
le
1.06
0.698692
0.961711
1.01338
1d
0.86
1.14472
1.11086
le
1.19
1.125559
1f
1.12
1.12779
0.703618
2a
0.6
0.604477
0.741783
2b
0.75
0.742706
2c
1.99
0.595105
0.870313
2d
0.65
0.864143
0.87649]
2e
0.95
0.871481
0.822645
2f
0.9
0.84961
1.2154
2g
0.65
1.23674
0.752844
2h
1.19
0.772968
0.648548
2i
0.6
0.651867
0.354963
3a
0.62
0.289744
0.696674

3b
0.45
0.723234
0.5926
3e
0.41
0.583873
0.705752
3d
1.69
0.684702
0.72504
3e
0.65
0.565729
0.776434
3f
0.78498
0.75
0.57102
0.565729
3g
0.6
0.735432
0.78498
0.57102
3h
0.54
0.870313
0.735432
3i
0.95
1.2
1
0.8
0.6
0.4
0.2
0 .
O
0.5
1
1.5
Observed activity
Figure 4-Graph between observed activity and predicted
activity of model I
1.4
1.2
1
0.8
0.6 -
0.4
0.2 -
0
0
0.5
1.5
Observed activity
Figure 5-Graph between observed activity and predicted
activity of model II
Predicted activi
Predicted activity

Figure 5- Graph between observed activity and predicted activity of model II parameters as expected in QSAR analyses. These results show that such

models can be helpful for theoretical prediction of anti-tubercular activity of new molecules

Conclusion

IQSAR analysis was performed on a series of antitubercular activity of thiazolidinones and azetidinones derivatives using molecular modeling program Chemoffice 2001. QSAR models were proposed for anti-tubercular activity of the thiazolidinones and azetidinones using descriptors employing sequential multiple regression analysis method. The predictive power of each model was estimated with bootstrapping method and leave one out cross validation method. It was observed from the selected models that biological activity of thiazolidinones and azetidinones derivatives is governed by thennodynamic and steric properties of the molecules. The models also provide valuable insight into the mechanism of action of these compounds. The result of the study suggests involvement of partition coefficient in the mechanism of anti- tubercular action of thiazolidinones and azetidinones. The study will be helpful in the design of better anti-tubercular analogs of thiazolidinones and azetidinones derivatives for anti-tubercular activity.

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