Research Journal of Computer and Information Technology Sciences _____ISSN 2320 – 6527
Vol. **1(4),** 1-4, May **(2013)** *Res. J. Computer and IT Sci.*

QSAR Analysis of Anti T. B. Drug Isoniazide Based Azetidino-2-one Derivatives as Antimicrobial Agents

Patel Megha[1], Parmar Vijaykumar[2] and Shah Dipti[1]
[1]Department of Computer Science, Sardar Patel University, Vallabh Vidhyanagar-388120, INDIA
[2]Department of Pharmaceuticla Sciences, Sardar Patel University, Vallabh Vidhyanagar-388120, INDIA

Available online at: www.isca.in
Received 3rd April 2013, revised 17th April 2013, accepted 2nd May 2013

Abstract

QSAR model development of 20 azetidino-2-one derivatives was carried out to predict antimicrobial activity. Zone of inhibition for Bacillus subtilis was taken as biological activity. Physicochemical parameters were calculated using Dragon software, version 1.11. Stepwise multiple linear regression analysis was applied to derive QSAR model, which was further evaluated for statistical significance and predictive power by internal and external validation. The best quantitative structure activity relationship model was selected having a correlation coefficient (R^2) of 0.835, cross-validated correlation coefficient (Q^2) of 0780 and, R^2_{pred} of 0.830. The predictive ability of the selected model was also confirmed by leave one-out cross-validation. The QSAR model indicates that the descriptors (E3s, HATS6e) play an important bacterial inhibition. The information derived from the present study may be useful in the design of more potent Azetidino-2-one..

Keywords: QSAR, Azetidino-2-one, multiple linear regression, Bacillus subtilis.

Introduction

The use of antimicrobial agents is limited, due to rapidly developing drug resistance and unsatisfactory status of present treatment of bacterial and fungal infections and drug side effects[1]. Therefore the development of newer antimicrobial drugs is an important objective and much of research program efforts are directed towards the design of new agents. Recently Azetidine derivatives are reported to show a variety of antimicrobial[2-4], antitubercular[5], anticonvulsant[6], anti-inflammatory[7] and cardiovascular activities[8]. Pursuing these research consequences we have undertaken QSAR study on previously reported compounds. The aim of the study was to identify the molecular properties which increase the biological activity in analogous series.

Material and Methods

A total of 20 Azetidino-2-one derivatives reported as synthesized as Chemistry department, S. P. University, Vallabh vidyanagar were used as the data set in QSAR analysis (Table 1). These molecules have found to be active against *bacillus subtilis*. The zone of inhibitions (mm) was converted in to logarithmic for QSAR study.

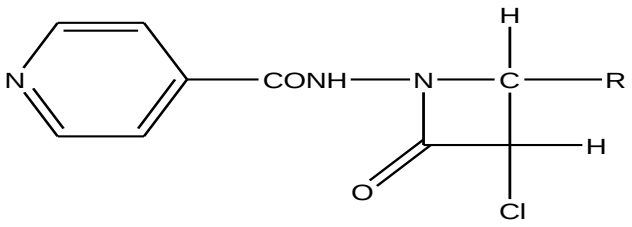

Table-1
Chemical and biological data of Azetidino-2-one derivatives

Compound no.	R	Zone of inhibition (mm)
1	4-bromophenyl	1.146
2	4-chlorophenyl	1.114
3	4-nitrorophenyl	1
4	2-diethylamino-4-hydroxyphenyl	1.146
5	furan-2-yl	1.079
6	5-bromofuran-2-yl	1.146
7	2,4-dichlopheny	1.176
8	2-chloro-4-fluoropheny	1.231
9	3-chloro-2,6-diflurophenyl	1.279
10	2,5-diflurophenyl	1.255
11	1*H*-pyrrol-2-yl	1.146
12	5-hydroxy-1*H*-pyrrol-2-yl	1.079
13	phenyl	0.954
14	4-methoxyphenyl	1.041
15	4-hydroxyphenyl	1.079
16	2-hydroxyphenyl	1.176
17	2-methylphenyl	0.778
18	Benzo[d]-1,3-dioxol-5-yl	1
19	4—hydroxy-3-methoxyphenyl	0.903
20	3,4-diethoxyphenyl	1.041

Molecules were divided into the training set (15 molecules) and test set (5 molecules) by random selection. The structures were drawn and transformed to 3D on software ChemOffice 2004[9]. The energy minimization was performed using molecular mechanics-2 (MM2) until the root mean square (RMS) gradient value became smaller than 0.100 kcal/mol Å and then molecules were subjected to re-optimization via MOPAC (Molecular Orbital Package) method until the RMS gradient attained a value smaller than 0.0001kcal/mol Å.

Various descriptors like electronic, steric, and thermodynamic were calculated on the Dragon software, version 1.11[10]. Stepwise multiple linear regression method was applied for generation of QSAR model using VALSTAT program[11]. For the validation of QSAR models "Leave-one-out (LOO)" method was used, the best model was selected on the basis of various statistical parameters such as correlation coefficient (R), square of correlation coefficient (R^2), sequential Fischer test (F). The quality of the each model was estimated from the cross-validated squared correlation coefficient (Q^2), standard deviation of prediction (S_{PRESS}), Standard deviation of error of prediction (S_{DEP}). Boot-strapping square correlation coefficient (R^2_{bt}) was calculated to confirm the robustness and applicability of QSAR equation. The derived QSAR models were used for the prediction of the activity compounds in the test set, R^2_{pred} was calculated.

The Z-score was calculated for the detection of outliers. Z-score can be defined as absolute difference between the value of the model and the activity field, divided by the square root of the mean square error of the data set. Any compound which shows a value of Z-score higher than 2.5, during generation of a particular QSAR model, was considered as outlier. Finally, the derived QSAR models were used for the prediction of the activity of the compounds in the test set and the external validation parameter, predictive R^2 (R^2_{pred}) was calculated for evaluating the predictive capacity of the model.

Results and Discussion

In present study authors tried to develop QSAR model to establish the correlation between physicochemical parameters and *bacillus subtilis* inhibitory activity. A reported data set of 20 indoyl aryl sulfones derivatives was used in present study.

When data set was subjected to sequential multiple linear regression analysis several equations were obtained. Out of these three most statistically significant equation was considered as significant.

BA= [0.721532(± 0.239799)] +E3s [1.00023(± 0.521482)] +HATS6e [0.154725(± 0.54056)]

Descriptors vales for the equation are shown in table 2. The statistical parameters for this model are shown in table 3**.** The inter correlation of descriptor s is shown in table 4.

Table-2
Calculated values of various descriptors for the set of compounds

Compound No.	E3s [a]	HATS6e [b]
1	0.238	0.56
2	0.244	0.546
3	0.371	0.52
4	0.33	0.531
5	0.307	0.584
6	0.299	0.615
7	0.412	0.598
8	0.387	0.606
9	0.444	0.661
10	0.448	0.654
11	0.279	0.574
12	0.28	0.564
13	0.256	0.562
14	0.207	0.469
15	0.219	0.517
16	0.331	0.614
17	0.245	0.438
18	0.276	0.483
19	0.14	0.528
20	0.261	0.332

[a]3rd component accessibility directional WHIM/weighted by atomic electrotopological states. [b]leverage –weighted autocorrelation of lag 6/weighted by atomic Saunderson electronagativity.

Table-3
QSAR statistics of significant equations[#]

Parameters	Values
N Train	15
N test	05
NV	2
R	0.871
R^2	0.759
Variance	0.004
Std	0.059
F	17.315
R^2_{bt}	0.824
Chance	<0.001
Q^2	0.666
S_{PRESS}	0.069
S_{DEP}	0.061
R^2_{pred}	0.897

#N Train= number of training set, N Test= number of test set, NV= number of variables, R= coefficient of correlation, R^2= squared correlation coefficient, Std= standard deviation of estimation, F= Fischer's value, R^2_{bt}= boot-strapping square correlation coefficient, Q^2=cross-validated squared correlation coefficient, SPRESS= predictive residual sum of square, S_{DEP} =

standard error of prediction. R^2 = predicted coefficient of correlation.

Table-4
Correlation matrix for the inter-correlation of structural descriptors and their correlation with the activity

Parameters	Zone of inhibition	E3s	HATS6e
Zone of inhibition	1	0.680	0.675
E3s	0.680	1	0.583
HATS6e	0.675	0.583	1

Model shows a good correlation coefficient (R) of 0.871 between the descriptors of E3s and HATS6e and zone of inhibition. The R^2 of 0.759 explains 75.9 % of the variance in biological activity. This model also shows significance, with a low standard deviation of estimation 0.059, manifest of accuracy of the model. The stability of model- judged by leave-one-out procedure is good (Q^2= 0.666) suggesting that the models will be useful for meaningful predictions. The robustness of model was shown by magnitude of the R^2_{bt} (0.824), which was near to conventional R^2 (0.759). Further support in this regard is obtained from the low values of the cross-validation parameters S_{PRESS} and S_{DEP}. The predicted R^2 value of the test set was 0.897, indicating excellent predictive ability of model. The observed, calculated and predicted values activities are shown in table 5 and table 6. The correlation between observed and predicted activity (LOO) of training set is shown in figure 1. The correlation between observed and predicted activity of training test set is shown in figure 2. Positive contribution of E3s and HATS6e in biological activity indicates increased value of this parameter increases the antibacterial activity.

Table-5
Activity of training set for QSAR Model

Compound No.	Observed activity	Calculated activity	Predicted activity
6	1.146	1.120	1.116
9	1.279	1.275	1.274
5	1.079	1.113	1.117
10	1.255	1.276	1.286
4	1.146	1.111	1.107
20	1.041	0.957	0.810
8	1.231	1.197	1.191
15	1.079	1.002	0.991
13	0.954	1.056	1.068
14	1.041	0.969	0.957
18	1	1.039	1.044
17	0.778	0.990	1.034
12	1.079	1.080	1.080
19	0.903	0.933	0.952
1	1.146	1.039	1.022

Table-6
Observed and predicted activity of test compounds

Compound No.	Observed activity	Predicted activity
7	1.176	1.217
2	1.114	1.038
3	1	1.1441
11	1.146	1.083
16	1.1761	1.149

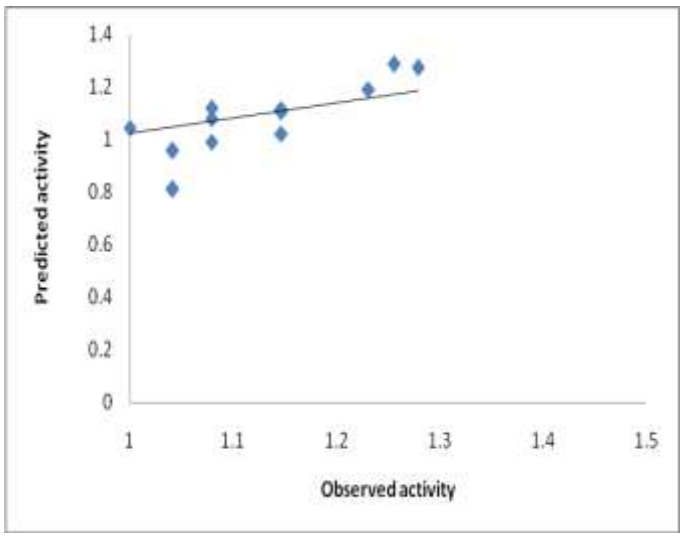

Figure-1
Graphs of actual versus predicted activity (zone of inhibition) of the training sets

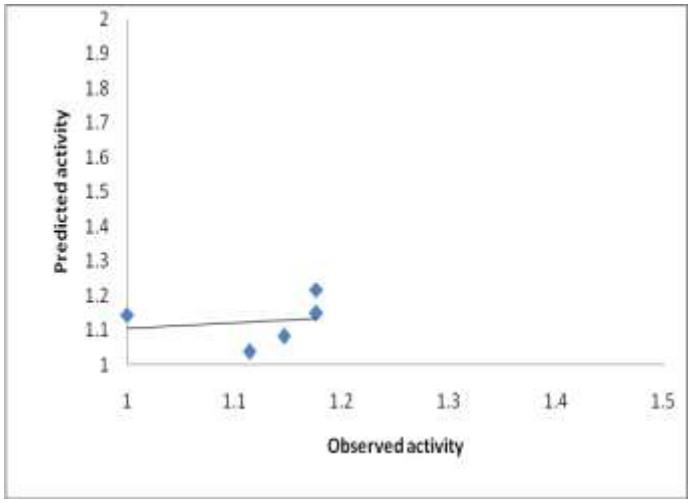

Figure-2
Graphs of actual versus predicted activity (zone of inhibition) of the test for

Conclusion

It can be concluded, by increasing parameters E3s and HATS6e, inhibition capacity of towards *bacillus subtilis* can be increased. The equation will help to develop new compounds in indoyl aryl sulfones series with high potency.

References

1. Fiddler D.F., Legal issues associated with antimicrobial drug resistance, *Emerge. Infect. Dis.*, **4**, 169-177 **(1998)**

2. Srivastava S.K., Dua R., Srivastava S.D., Synthesis and antimicrobial activity of [N1-(N-substituted-arylidene-hydrazino)-acetyl]-2-methyl-imidazoles and [N1-(4-substitutedaryl-3-chloro-2-oxo-1azetidinyl-amino)-acetyl]-2-methyl-imidazoles, *Proc.Nat. Acad. Sci. India, Sec A:Phys. Sci.*, **80**, 117-121 **(2010)**

3. Trivedi P.B., Undavia N.K., Dave A.M., Bhatt K.N., Desai N.C., Synthesis and antimicrobial activity of 4-oxothiazolidines, Azetidino-2-ones, malonanilic acid hydrazines and pyrazoline derivatives of phenothiazine, *Indian J. Chem.*, **32B (7),** 760-765 **(1993)**

4. Panwar H., Verma R.S., Srivastava V.K., Kumar A., Synthesis of some substituted Azetidinonyl and thiazolidinonyl-1,3,4-thiadiazino[6,5-b] indoles as prospective antimicrobial agents, *Indian J. Chem.*, **45B**, 2099-2104 **(2006)**

5. Patel R.B., Desai P.S., Desai K.R., Chikhalia K.H., Synthesis of pyrimidine based thiazolidinones and azetidinones: antimicrobial and antitubercular agents, *Indian J. Chem.*, **45B**, 773-778 **(2006)**

6. Siddiqui N., Rana A., Khan S.A., Haque S.E., Alam M.S., Ahsan W., Arshada M.F., Anticonvulsant and Toxicity Evaluation of Newly Synthesized 1-2-(3,4-disubstitutedphenyl)-3-chloro4-oxoazetidin-1-yl-3-(6-substituted-1,3-benzothiazol-2-yl) ureas, *Acta Chim. Slov.*, **56**, 462–469 **(2009)**

7. Srivastava S.K., Srivastava S.L., Srivastava S.D., Synthesis of new 2-chloro phenothiadiazol-2-oxoazetidines-antimicrobial and anti-inflammatory agents, *Indian J. Chem.*, **39B**, 464-467 **(2000)**

8. Kumar A. and Gurtu S., Agarwal J.C., Sinha J.N., Bhargava K.P., Shanker K., Synthesis and cardiovascular activity of substituted 4-azetidinones, *J. Indian Chem. Soc.*, **60**, 608-610 **(1983)**

9. CS Chem Office, Version 8.0, Cambridge Soft Corporation, Software Publishers Association, 1730 M Street, NW, Suite 700, Washington, D.C. **(2003)**

10. Todeschini R, Consonni V, Dragon software (version 1.11), Milano Chemometrics and QSAR Group, Milano, Italy, **(2001)**

11. Gupta A.K., Arockia B.M., Kaskhedikar S.G., VALSTAT: Validation Program for Quantitative Structure Activity Relationship Studies, *Ind. J. Pharm. Sci.*, **66**, 396-402 **(2004)**