WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 11, 1052-1059. Research Article ISSN 2277– 7105

2D-QSAR IN N-[(3S)-PYRROLIDIN-3-YL] BENZAMIDE DERIVATIVES AS NOVEL SEROTONIN REUPTAKE INHIBITORS

[1]*Neerja Shukla

[1]Department of Chemistry, University of Allahabad, Allahabad – 211003, U. P., India.

Article Received on
30 July 2017,
Revised on 20 August 2017,
Accepted on 10 Sept. 2017
DOI: 10.20959/wjpr201711-9745

***Corresponding Author**
Dr. Neerja Shukla
Department of Chemistry,
University of Allahabad,
Allahabad – 211003, U.P.,
India.

ABSTRACT

QSAR studies were performed on a series of N-[(3S)-Pyrrolidin-3-yl]benzamide derivatives as novel serotonin reuptake inhibitors. N-[(3S)-Pyrrolidin-3-yl]benzamide derivatives have been analyzed in relation to their physicochemical and molecular properties. The activities of the compounds were found to be significantly correlated with the physicochemical parameters such as molar refractivity (Mr), balaban centric index (BAC), molecular weight (MW), wiener index (W), equalized electro-negativity (Xeq). It was found that the presence of group 2-Me, 3-Cl at R_2 position was conducive and the presence of group 2-i-Propyl at R_2 position was unfavourable for the inhibitory activity. The results are critically discussed on the basis of regression data and cross validation techniques. Poglani factor Q and the results of LOO (leave one out) method confirms the reliability and predictability of the proposed models.

KEYWORDS: QSAR; serotonin reuptake inhibitors; physicochemical property; regression analysis.

INTRODUCTION

Serotonin (5-hydroxytryptamine or 5-HT) is a monamine neurotransmitter synthesized in serotonertig neurons in the central nervous system (CNS) and enterochromaffin cells in the gastrointestinal tract of animals including humans. Serotonin is also found in many mushrooms and plants, including fruits and vegetables. In the central nervous system, serotonin plays an important role as a neurotransmitter in the modulation of anger, aggression, body temperature, mood, sleep, sexuality, appetite, and metabolism, as well as stimulating vomiting. 5-hydroxytryptamine (Serotonin) receptor 5A, also known as HTR5A, is a protein which in humans is encoded by the HTR5A gene. The current study represents

the QSAR analysis of a series of N-[(3S)-Pyrrolidin-3-yl]benzamide derivatives as novel serotonin reuptake inhibitors using a number of structural parameters along with different indicator parameters at the respective substitution sites.

Experimental

QSAR Studies have been done on the series of 25 compounds of N-[(3S)-Pyrrolidin-3-yl]benzamide derivatives **(**Wakenhut et al., 2009**).** The 2D structures of the molecules were drawn using Chem. Sketch software (ACD-LAB). The following physicochemical parameters were used in the present study:

1. Molecular weight(MW): Molecular weight descriptor has been used in systems such as transport studies where diffusion is the mode of operation. It is an important variable in QSAR studies pertaining to cross resistance of various drugs in multi-drug resistant cell lines.[2]

2. Molar Refractivity(Mr): Molar Refractivity is generally considered to be a measure of overall bulk and is related to London dispersion forces as follows:

$$Mr = 4\pi N\alpha\backslash 3$$

Where N is Avogadros number and α is the polarizability of the molecule. It gives no information about shape and is generally scaled 0.1 and has been used in QSAR.

3. Equalized Electro-negativity (Xeq) (Srivastava et al., 2005, 2006, 2008)

Electro negativity was first defined by Pauling the power of an atom in a molecule to attract electrons to itself. Gord Pritchard and Skinner reviewed the relation to the effective nuclear charge and computed an electro-negativity scale using Slater's methods.

Charge conservation equation leads to general expression for equalized electro-negativity as shown below

$$Xeq = \frac{N}{\sum (v/x)} \qquad (1)$$

Where N= Σn total number of atoms in the species. V is the number of atoms of a particular element in the species an X is the electron negativity of that element.

The group negativity is defined as

$$Xn = \frac{No}{(v/x)} \qquad (2)$$

Where N_0 is the number of atoms in the group formula. The groups are fundamentally different from atoms in their ability to donate or withdraw charge. The important difference between atom and a group groups have the ability to dissipate the charge over several atoms increasingly with increasing N (G). A group can be treated as pseudo atoms in electro-negativity discussion because a polyatomic group can be considered as a reservoir of enhance charge capacity potentially able or withdraw considerable amount of charge with only small variation in electro- negativity.

4. Balaban Centric Index (BAC): BAC is topological parameter and is calculated with the help of DRAGON software (DRAGON Software).

5. Wiener Index (W)

The Wiener index (W) is a widely used topological index. It is based on the vertex-distances of the respective molecular graph. The Wiener index (W) was proposed in 1947 by H. Wiener (Leukovits, 1990, 1995; Senda et al., 1991; Zhu et al., 1996) and is defined as the sum over all bonds of the product of the number of vertices on each side of the bond.

6. Indicator Variables: Indicator variables (parameters), sometimes called dummy variables, are used in multiple linear regression analysis to account for certain features which cannot be described by continuous variables. The indicator parameters (variables) are generally assigned only two values zero and one. It is taken as 1 (one) for that particular group or substituent and at a specific site in the molecule and 0 (zero) for all such cases where that group or substituent is absent (Recantint et al., 1986).

These parameters were found to be useful earlier in a number of QSAR based drug modeling (Singh et al., 2008, 2008; Srivastava et al., 2008, 2008, 2008, 2008, 2009, 2009, 2010, 2010, 2011, 2011.2011).

Regression Analysis- The regression analysis is done using SPSS 7.5 version software.

RESULTS AND DISCUSSION

QSAR was performed on the series of 25 compounds of N-[(3S)-Pyrrolidin-3-yl]benzamide derivatives as novel serotonin reuptake inhibitors using the physicochemical parameters

which are given in Table-1. The QSAR multiple regression analysis were performed with SPSS 7.5 version of the software. The activity data and the physicochemical parameters evaluated are listed in Table 2. The biological activity (**pKi**) is a measure of inhibitory In order to study the role of different substituents at different positions indicator parameters I_1 and I_2 for 2-Me,3-Cl and 2-i-Propyl groups respectively present at the R_2 position were introduced and are also listed in Table- 1.

The aim of current study is mainly to study the different physicochemical parameters linear models and their stepwise regression analysis by using indicator variable and different parameters (According to correlation matrix). In this series, some significant QSAR models have been obtained which are given below:

pKi = 0.002 (±0.012) BAC + 0.058 (±0.043) MR − 0.005 (±0.010)MW + 0.397 (±0.688) I_1 − 2.538 (±0.809) I_2+ 4.724 **-------1**

n = 25, R = 0.873, R^2 = 0.762, R^2_A = 0.699, SE = 0.301, $F_{(5, 19)}$ = 12.138, Q = 2.900

pKi = 0.0004 (±0.013) BAC + 0.039 (±0.034) MR − 1.623 (±4.553)Xeq + 0.453 (±0.681) I_1 − 2.408 (±0.738) I_2+ 8.530 **-------2**

n = 25, R = 0.869, R^2 = 0.754, R^2_A = 0.690, SE = 0.305, $F_{(5, 19)}$ = 11.672, Q = 2.849

pKi = 0.001 (±0.015) BAC + 0.050 (±0.043) MR − 0.0005 (±0.001) W + 0.482 (±0.670) I_1 − 2.339 (±0.693) I_2+ 4.156 **-------3**

n = 25, R = 0.867, R^2 = 0.752, R^2_A = 0.687, SE = 0.307, $F_{(5, 19)}$ = 11.527, Q = 2.824

Where n is the number of data points , R is correlation coefficient of determination, SE is the standard error of estimate, R^2A represents adjusted R^2 or explained variance, F is variance ratio (Diudea, 2000) between observed and calculated activity. Q is the quality of fit (Pogliani, 1994, 1996) and data within parenthesis are for the 95% confidence intervals.

The negative coefficients of parameters MW, W in above Models indicate that these parameters have negative influence in determining the activity and less bulkier groups are preferable for the activity. The coefficient of Xeq is negative and therefore it may be suggested that less electronegative groups should be preferred for the drug modeling. The coefficient of MR is positive which suggests that denser should have positive influence on the 5-HT binding.

The positive sign of coefficient of **I_1** makes it that the presence of 2-Me,3-Cl at R_2 position is beneficial for the activity, while negative coefficient of **I_2** explains that 2-i-Propyl group at R_2 position may be avoided in the future drug modeling in this series.

In order to examine the relative potential of models, predictive correlation coefficient (R^2Pred) were estimated by plotting graphs between observed **pKi** versus predicted **pKi** values obtained with the help of model no.1. Is shown in graph (fig. 1) and the predicted R^2 was found to be fairly large.

The comparison between observed and predicted activities is listed in Table-3. Such correlations are shown in the plot. From the plot R^2Pred values obtained for equation 1 is 0.762 and this is fairly high indicating the quality of the models.

In this equation the F ratio value is much higher than theoretical F value [$F_{(5, 19)} = 2.74$] indicating the statistical significance of this equation. Predicted values are the activities calculated by the equation **(1)** and the residual values are the difference between the observed biological activities and the calculated activities and were found to be low.

Cross Validation

The cross validation analysis was performed using leave one out (LOO) method (Carmer et al., 1988; Podloga, 2000) in which one compound is removed from the data set and the activity is correlated using the rest of the data set. The cross-validated R^2 in each case was found to be very close to the value of R^2 for the entire data set and hence these models can be termed as statistically significant.

Cross validation provides the values of PRESS (Predicted residual Sum of Squares), SSY (Sum of the Squares of the response) and R^2_{cv} (Overall Predicted ability) and PSE (Predicted Squares error) from which we can test the predictive power of the proposed model. It is argued that PRESS, is a good estimate of the real predictive error of the model and if it is smaller than SSY the model predicts better than chance and can be considered statistically significant. Furthermore, the ratio PRESS/SSY can be used to calculate approximate confidence intervals of prediction of new compound. To be a reasonable QSAR model PRESS/SSY should be smaller than 0.4. Also, if PRESS value is transformed in a dimension less term by relating it to the initial sum of squares, we obtain R^2_{cv} i.e. the complement to the traces on of unexplained variance over the total variance. The PRESS and R^2_{cv} have good

properties. However, for practical purposes of end users the use of square root of PRESS/N, which is called predictive square error (PSE), is more directly related to the uncertainty of the predictions. The PSE values also support our results. The calculated cross-validated parameters confirm the validity of the models. All the requirements for an ideal model have been fulfilled by model no. 1.

R^2_A takes into account the adjusted R^2. R^2_A is a measure of the percentage explained variation in the dependent variable that takes into account the relationship between the number of cases and the number of independent variables in the regression model, whereas R^2 will always increase when an independent variable is added. R^2_A will decrease if the added variable doesn't reduce the unexplained variable enough to offset the loss of decrease of freedom.

Predictive Error of Coefficient Of Correlation (PE)

The predictive error of coefficient of correlation (PE) (Chatterjee et al., 2000) is yet another parameter used to decide the predictive power of the proposed models. We have calculated PE value of all the proposed models and they are reported in Table 4. It is argued that of

(a) R < PE, then correlation is not significant;

(b) R > PE; several times (at least three times), then correlation is indicated; and if,

(c) R > 6PE, then the correlation is definitely good.

For all the models developed the condition R > 6PE is satisfied and hence they can be said to have a good predictive power.

CONCLUSIONS

From the results and discussion made above, it may be concluded that:

1) Less bulkier and less electronegative groups should be used in future modeling.
2) The presence of group 2-Me, 3-Cl at R_2 position is beneficial for the activity.
3) 2-i-Propyl group at R_2 position should be avoided in the future drug modeling.

REFERENCES

1. Acd-Lab software for calculating the referred physicochemicalparameters. Chemsketch.<www.acdlabs.com/acdlabs-rss-feed.xml >.
2. Carmer III, R.D., Bunce, J. D., Patterson, D.E., Frank, I.E., 1988. *Quant. Struct. Act. Relat.*, 7, 18.

3. Chatterjee, S., Hadi, A. S. and Price, B., 2000. Regression analysis by example, 3rd Edn, Wiley VCH New York.
4. Diudea, M.V., 2000. ”QSPR/QSAR studies for molecular descriptors“, Eds., Nova Science, Huntingclon, New York.
5. DRAGON Software for calculation of topological indices: www.disat unimib. it.
6. Lucovits, I., "Weiner Indices and Partition Coefficients of Unsaturated Hydrocarbon", Quant. Struct. Act. Relat., 1990; 9: 227.
7. Lukovits, I., "Decomposition of the Weiner Topological Index for Cycle Containing Structures", J. Chem. Inf. Comput. Sci., 1995; 35: 1.
8. Podloga, B. L., Ferguson, D.M., *Drug Des. Discov*, 2000; 17: 4.
9. Pogliani, L., Structural property relationships of amine acids and some Peptides, Amino Acids, 1994; 6: 141.
10. Pogliani, L., Modeling with special descriptors derived from a medium size set of connectivity indices, *J. Phys. Chem*., 1996; 100: 18065.
11. Recantint, M., Klein, T. K., Yang, C. Z., McCarlin, J., Langridge, R., Hansch, C., Mol. Pharmacol, 1986; 29: 436.
12. Senda, M., Fujita, T., Chem Pharma. Bull, 1991; 39: 1736.
13. Singh, J., Dubey, V.K., Agarwal, V.K., Khadikar, P.V., QSAR study on octanol- water partitioning: Dominting role of equalized electronegativity, *Oxidation Communication*, 2008; 31(1): 27-43.
14. Singh, J., Agarwal, V.K., Singh, S., Khadikar, P.V., Use of topological as well as Quantum Chemical parameters in modeling Antimalarial activity of 2,4- Diamino -6- Quinazoline sulphonamides, *Oxidation Communication*, 2008; 31(1): 17-26.
15. Srivastava, A.K., Khan, A.A., Tripathi, A.and Chaurasia, S., *J. Saudi Chem.*, 2005; 9(3): 571-574.
16. Srivastava, A.K., Varma, A.and Khan, A.A., *Oxidation Comm*, 2006; 29(1): 8-11.
17. Srivastava, A.K., Chaurasia, S., Nath, A. and Archana, *Proc. Nat. Acad. Sci. India*, Sect. A., 2008; 78: Pt-1.
18. Srivastava, A.K., Srivastava, A., Archana, Jaiswal, M., Role of Physico-chemical parameters in Quantitative Structure-Activity Relationship based modeling of CYP26A1 inhibitory activity, *J. Indian Chem. Soc*., 2008; 85: 721-727.
19. Srivastava, A.K., Archana, Jaiswal, M., Quantitative Structure-Activity Relationshipstudies of ρ- Arylthiocinnamides as Antagonists of Biochemical ICAM- 1/ LFA-1 Interaction in relation to Antiinflammatory Activity., *Oxidation Communication*, 2008; 31: 44-51.

20. Srivastava, A.K., Jaiswal, M., Archana, QSAR studies on Indole substituted potent Human Histamine H_4 Antagonists: Role of physicochemical & statistical parameters, J. Saudi Chem. Soc., 2008; 12: 221-226.
21. Srivastava, A.K., Archana, Jaiswal, M., Exploring QSAR of selective PDE_4 inhibitors as 8-substituted analogues of 3- (3-cyclopentyloxy-4-methoxy-benzyl)-8 isopropyl Adenine, *J. Saudi Chem. Soc.*, 2008; 12: 227-232.
22. Srivastava, A.K. Jaiswal, M.,Archana, Srivastava, A., QSAR modelling of selective CC Chemokine receptor 3 (CCR3) Antagonists using physicochemical Parameters, Oxidation Communication., 2009; 32: 55-61.
23. Srivastava, A.K., Archana, Jaiswal, M., Srivastava, A., QSAR Modelling of selective CC Chemokine Receptor 3 (CCR3) antagonists using physicochemical Parameters, *Oxidation Communication,* 2009; 32: 55-61.
24. Srivastava, A.K., Pandey, A., Srivastava, A., QSAR based modeling on a series of a-hydroxy amides as a novel class of bradykinin B1 selective antagonists. Journal of Saudi Chemical Society, 2010. doi:10.1016/j.jscs.2010.09.001 (Article in press).
25. Srivastava, A. K., Shukla, N and Pathak, V. K., December. Quantitative structure activity relationship (QSAR) studies on a series of offtarget ion channel selective diltiazem sodium derivatives, J. Indian Chem. Soc., 2010; 87: 1-7.
26. Srivastava, A.K., Pandey, A., Srivastava, A., Shukla, N., QSAR based modeling of hepatitis C virus NS5B inhibitors , *Journal of Saudi Chemical Society*, 2011; 15: 25–28.
27. Srivastava, A.K., Shukla, N., Quantitative Structure Activity Relationship (QSAR) Studies on a series of imidazole derivatives as novel Orl1 receptor antagonists, Journal of Saudi Chemical Society, 2011. doi: 10.1016/j.jscs.2011.04.014 (Article in press).
28. Srivastava, A.K., Shukla, N., QSAR based modeling on a series of lactam fused chroman derivatives as selective 5-HT transporters. *Journal of Saudi Chemical Society*, 2011. doi:10.1016/j.jscs.2011.02.010 (Article in press).
29. Wakenhut, H., Allan, G. A., Fish, P. V., Fray, M. J., Harrison A. C., McCoy, R., Phillips, S. C., Stobie, A., Westbrook, D., Westbrook, S. L., Whitlock, G. A., N-[(3S)-Pyrrolidin-3-yl]benzamides as novel dual serotonin and noradrenaline reuptake inhibitors: Impact of small structural modifications on P-gp recognition and CNS penetration, *Bioorganic and Medicinal Chemistry Letters*, 2009; 20: 2017-2020.
30. Zhu H. Y., Klein D. J. and Lukovits I., "Extensions of the Wiener Number" J. Chem. Inf. Comput. Sci., 1996; 36: 420.