International Journal of
Medicinal Chemistry & Analysis
e ISSN 2249 – 7587
Print ISSN 2249 - 7595
www.ijmca.com
Research Article

2-D QSAR STUDY OF 5-ARYL BENZIMIDAZOLONE AND OXINDOLE BASED AMPA RECEPTOR MODULATORS SELECTIVE FOR TARP γ-8 FOR ANTI-EPILEPTIC ACTIVITY

Sweta N.Desai, Ghanshyam Sanghani, Nishadh Solanki, Vineet Jain.

Bhagwan Mahavir College of Pharmacy, Surat, Gujarat, India.

ABSTRACT

Quantitative Structure Activity Relationship (QSAR) represents an attempt to correlate 2D and 3D properties (descriptors) of compounds with activity. In order to understand the structural requirements for AMPA receptor antagonism. QSAR study for the anti-epileptic activity of 18new15-Aryl Benzimidazolone and Oxindole- Based AMPA Receptor Modulators Selective for TARP γ-8 was established. With the PaDEL-Descriptorprogram, more than 1000 different Molecular descriptors were calculated. Bias-Variance Estimator using Bootstrapping method did re-sampling of descriptors.For Regression, analysis dataset division was performed by Kennard stone method. Partial least squares regression (PLS regression) generated model from 12 molecule training set and 6 molecule test set revealed that polarity of the molecules is governing factor for anti-epileptic activity. The best model with 4 descriptor was selected which has r^2 = 0.96251, q^2 = 0.91389.

Keywords: QSAR, benimidazolone, oxindole, anti-epileptic acitivty.

Corresponding Author: - **Sweta N. Desai** Email: 13swets@gmail.com

INTRODUCTION

Quantitative structure-activity relationships are mathematical relationships linking chemical structure and pharmacological activity in a quantitative manner for a series of compounds. Methods which can be used in QSAR include various regression and pattern recognition techniques.A receptor is a molecule or a polymeric structure in or on a cell that specifically recognizes and binds a compound acting as a molecular messenger (neurotransmitter, hormone, lymphokine, lectin, drug, etc.).Fast excitatory transmission in the central nervous system (CNS) is mediated primarily by glutamate-gated ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. In the endoplasmic reticulum, AMPA receptors (AMPARs) are formed as tetrameric assemblies of subunits (GluA1-GluA4) and then trafficked to the synaptic membrane where they play an integral role in regulating synaptic strength.

Access this article online

Home page: http://ijmca.com/

DOI: http://dx.doi.org/10.21276/ijmca.2020.10.1.1

Quick Response code

Received:21.08.19 | **Revised**:12.09.19 | **Accepted**:18.09.19

MATERIALS AND METHODS

The data set of total 20 compounds was taken from published literature (ACS Med Chem Lett. 2018 Jul 13;9(8):821-826. Ravula S, Savall BM, Wu N) in which authors had reported anti-epileptic activity of 5-Aryl Benzimidazolone and Oxindole Based AMPA Receptor Modulators Selective for TARP γ-8 .The general structure of the analogs is shown in Fig. (1). All the values of biological data shown via pIC50 vale measured in a FLIPR assay using HEK-293 cells expressing a human GluA1o-γ-8 fusion construct.

Molecular modeling studies were performed using CS Chem office, 2015 molecular modeling software

ver. 9.0, supplied by Cambridge Software Company. Energy minimized geometry was used for calculation of various thermodynamic, steric and electronic descriptors.

By using the PaDEL-Descriptor program, more than 1000 different Molecular descriptors were calculated. For Regression, analysis dataset division was performed by Kennard stone method using Dataset Division GUI v1.2. In order to explore the predictive power of the selected descriptors, the data set of 5-Aryl Benzimidazolone and Oxindole was divided into training set (16 compounds) and test set (10 compounds). Test and training set compounds were chosen manually such that low, moderate, and high activity compounds were present in approximately equal proportions in both sets. Partial least squares regression (PLS regression) method was use to QSAR generated model having 3 variables. The model was evaluated by various statistical measures for evaluation of the significance of the model. Statistical quality of the models was judged by degree of freedom, squared correlation coefficient (r^2), pred_r^2 for external test set, Standard Error of Estimate (SEE), F-test for statistical significance of the model (Fischers Value - F), Alpha error probability (F_prob), Z score calculated by the randomization test (Zscore), highest q^2 value in the randomization test (best_ran_q^2), highest r^2 value in the randomization test (best_ran_ r^2), statistical significance parameter by randomization test (alpha). r^2 is the relative measure of quality of fit of the model; F represents the F-ratio between the variance of calculated and observed activity.

RESULTS AND DISCUSSION

Partial least squares regression (PLS regression) generated model analysis and cross validation by leave-one-out resulted in MATS7i, AMR and GATS4vas the most significant descriptors (Table 3). Model represents the linear QSAR model from a complete set of 18, 5-Aryl Benzimidazolone and Oxindole derivatives. The most significant QSAR models with three descriptors is selected.

Model

pIC50 = -4.6864(+/-3.0863)+1.6184(+/-0.9291) MATS7i +0.2544(+/-0.0254) AMR -7.3172(+/-1.7762) GATS4v

Description about selected variables

MATS7i(Dragon; 2D autocorrelations): Moran autocorrelation of lag 7 weighted by ionization potential AMR(Dragon; Molecular properties): Ghose-Crippen molar refractivity (molar refractivity is a measure the overall polarity of a molecule.

The molar refractivity (AMR) is calculated according to the Ghose-Crippen model, based on a group contribution method.

GATS4v(Dragon; 2D autocorrelations): Geary autocorrelation of lag 4 weighted by van der Waals volume

Validation Parameters

n = 18, r^2 = 0.96251, r^2adj = 0.88459, q^2 = 0.91389, Standard Error = 0.05216, F test = 13.2088, F-tab = 5.20, ZScore R^2 = 0.67237ZScore Q^2 = 0.72128 Best Rand R^2 = 0.04272 Best Rand Q^2 = 0.15230, Degree of freedom = 13.

where, n is the number of data points, r^2 is squared correlation coefficient which explains variance in activity, SEE is the standard error of estimate or standard deviation; it is an absolute measure of quality of fit, lesser the value of SEE, higher will be the accuracy with which the expected activity of a new molecule may be predicted. q^2 is cross-validated squared correlation coefficient which indicates internal predictivity of the model. F-value is the measure of level of statistical significance of regression model. Fcal is the calculated F value and Ftab is the tabulated F value. It indicates statistical validity of the equation at specific significance level (0.01); hereFcal value exceeds Ftab, it indicates that correlation is not by chance but a true relationship exists

Model shows a good squared correlation coefficient (r^2 = 0.96251) between descriptors such as MATS7i, AMR and GATS4vpIC50 vale measured in a FLIPR assay.A descriptor coefficient magnitude shows its relative contribution with respect to other descriptors and sign indicates whether it is directly (+) or inversely (-) proportional to the activity. The orthogonality of descriptors in the selected correlations was confirmed by the calculation of overall correlation matrix as shown in Table. 2. Calculated values of all the descriptor in the selected model are shown in Table 3.

The squared correlation coefficient (r^2) of 0.96251 explains 96.2% of the variance in the biological activity. F-statistics proves it to be statistically highly significant (more than 99.9 %) as the calculated Fischer value (F) exceeds the Tabulated F value and low Standard Error of Estimate.The cross validated squared correlation coefficient of the model was 0.676, showing good internal predictivity of the model.

The low r^2 and q^2 values from the Y-randomization test (Best Rand R^2 = 0.48523 Best Rand Q^2 = 0.15230), indicate that the good results of the developed QSAR model are not due to chance correlation of structural dependency of the training set. The low value of alpha (<0.01), suggests that the model is having statistical significance.

The results of the cross-validation for model are shown in Table 4. A graph of observed and predicted antibacterial activity against *E coli* indicates the efficient predictive ability of model 3 as shown in Fig. (2).

A brief explanation of the descriptors utilized to generate the statistical QSAR model

The ionization potential alone and in combination with the molar refractivity and van der Waals volumedependable variables for QSARmodels. The study indicates that ionization potential appears an

important descriptor for 5-Aryl Benzimidazolone and Oxindole derivatives, The molar refractivity reflects arrangements of the electron shells of ions in molecules and yields information about the electronic polarization of ions. Usual characterization of molecular size and packing characteristic of molecule.

Table 2. Correlation matrix for descriptors in the selected models

	GATS4v	AMR	MATS7i
GATS4v	1		
AMR	0.456	1	
MATS7i	0.151	-0.171	1

Table. 3. Descriptors contributing to pIC50 vale measured in a FLIPR assay 5-Aryl Benzimidazolone and Oxindole derivatives.

Name	MATS7i	AMR	GATS4v
10	-0.02875	74.0074	0.995317
11	-0.10644	77.7641	1.031967
12	-0.09614	82.3133	1.053358
13	-0.09679	79.4291	1.07894
14	-0.12944	79.3903	1.140048
15	-0.05849	85.8336	1.113658
16	-0.10181	82.0404	1.065081
17	-0.14828	82.1682	1.027592
18	-0.09285	86.3224	0.9941
19	-0.18394	82.828	1.004048
20	-0.17559	81.7228	0.998438
3	-0.15631	80.5401	1.104187
4	0.063691	73.8517	1.142296
5	-0.41756	78.1337	1.100753
6	-0.04056	76.6334	1.131391
7	-0.07267	77.0676	1.073546
8	-0.10564	83.2719	1.059705
9	-0.13956	77.5018	1.026477

Table 4. Observed and predicted activities of the molecules

Compound	Observed activity	Predicted activity
11	6.9	7.49884
12	8.4	8.24327
13	7.1	7.34467
14	6.6	6.65874
15	8.9	8.34894
16	8	8.05493
18	10	9.7523
20	8.3	8.69549
4	5.6	5.49985
5	6.4	6.73935
6	6.8	6.18684
8	8.4	8.37679
10	6.8	6.77572
17	8.9	8.34278
19	8.6	8.62364
3	7.5	7.28514
7	7.2	6.82878
9	7.3	7.17283

Fig 1. General structure of 5-Aryl Benzimidazolone and Oxindole.

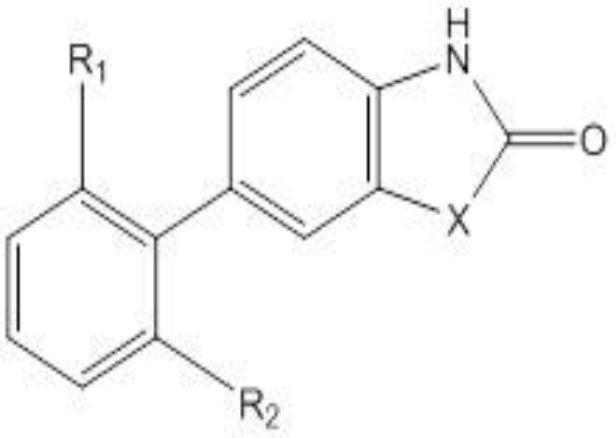
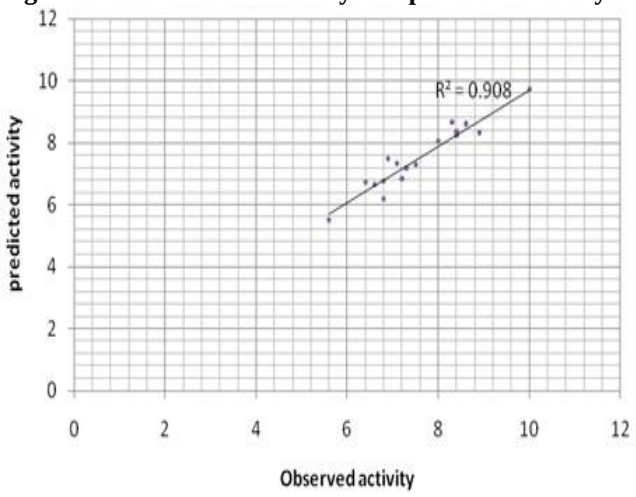


Fig 2. Plot of Observed activity and predicted activity



CONCLUSION

The ionization potential combination with the molar refractivity and van der Waals volume dependable variables for QSAR models. The study indicates that ionization potential appears plays a role because it is important for drug-receptor interactions. The molar refractivity reflects arrangements of the electron shells of ions in molecules and yields information about the overall polarity of a molecule. Van der Waals volume indicates usual characterization of molecular size and packing characteristic of molecule.

AKNOWLEDGEMENT

Nil

CONFLICT OF INTEREST

Nil

REFERENCES

1. Ravula S, *et al*. Lead Optimization of 5-Aryl Benzimidazolone- and Oxindole-Based AMPA Receptor Modulators Selective for TARP γ-8. *ACS Med Chem Lett*, 9(8), 2018, 821-826.
2. http://teqip.jdvu.ac.in/QSAR_Tools