

Modeling of Pyrazine based Blockers of the Na_v 1.8 Sodium Channel for the Treatment of Neuropathic Pain using QSAR

Shraddha Srivastava¹, A.K. Srivastava¹, Neerja Shukla^{1*}, Prashant Mishra^{2*}

QSAR Research Laboratory, Department of Chemistry, University of Allahabad, Allahabad, U.P, India. ¹

Harish-Chandra Research Institute, Chhatnag Road, Jhusi, Allahabad, U.P, India²

*Corresponding authors.

* pm_kgp21@yahoo.com (P. Mishra); *neerjashuklaau2007@rediffmail.com (N. Shukla)

ABSTRACT: Quantitative structure–activity relationship has been performed on a series of pyrazine-based blockers of the Na_v 1.8 sodium channel, using different physicochemical parameters along with appropriate indicator variables. A large number of physicochemical parameters were calculated for the present series of compounds and multiple linear regression analysis (MLRA) was performed. Various regression models have been formulated and the statistical data indicate that some of the descriptors provide valuable information that can be used to predict activity of future derivatives. Different models that were generated were found to be associated with high values of R² and low values of PRESS/SSY ratio. The statistically significant equations were statistically tested by using leave one out (LOO) technique and other cross-validation methods.

KEYWORDS: Neuropathic Pain, DFT, Pyrazine, QSAR and Regression analysis.

I. INTRODUCTION

Antidepressant drugs have been widely used for many years to treat neuropathic pain, despite the rationale for their use being still unclear. We review recent insights into their mechanism of action, focusing on central and peripheral analgesic actions. Beside the traditional monoaminergic hypothesis, other pharmacological actions have been studied: antidepressants interfere with the opioid system, interact with the NMDA¹ receptors, and inhibit ion channel activity. Firm evidence from randomized controlled trials demonstrated that TCAs²⁻³ are the most effective drugs for treatment of different neuropathic pain conditions. They exhibit the lowest number needed to treat compare with all other drugs investigated. SSRIs⁴ failed to provide an adequate analgesia, due to their high selectivity. SSRIs are clearly less effective than TCAs supporting the hypothesis that a balanced inhibition of noradrenalin and serotonin reuptake is more effective in relieving pain⁵⁻⁶. On the basis of initial results Venlafaxine⁷ seems to be the most promising of the newer antidepressants. Newer antidepressants show a better side effects profile, but further investigation are warranted to clarify their potential role in the management of pain. Neuropathic pain remains a challenging condition to treat, as all currently available drugs fail to achieve adequate pain relief in a significant proportion of patients. TCAs should be currently considered the first choice in treatment of neuropathic pain and the gold standard against which to compare other potential new treatments.

Quantitative structure–activity relationships (QSAR) have been widely used in the field of drug design and presently most of the drugs are evolved using this technique. The motivation of such study is to identify the molecules with high binding affinity to the receptors in order to maximize biochemical activity of the drugs⁸. The fundamental principle of QSAR is that a macroscopic property of a molecule, such as binding affinity at a receptor and electronic properties are determined by its molecular structure. QSAR methods in fact attempt to capture the relationship between structural attributes of molecules and their biological activity.

Chronic pain comprises a breadth of heterogeneous symptoms that can be characterized as inflammatory or neuropathic pain, Neuropathic pain result from injury to the peripheral or central sensory pathways. Na_v1.8 (also known as PN3) is a

International Journal of Innovative Research in Science, Engineering and Technology

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tetrodotoxin-resistant (TTX-r) voltage-gated sodium channel (VGSC) that is highly expressed on small diameter sensory neurons. It has been implicated in the pathophysiology of inflammatory and neuropathic pain, and we envisioned that selective blockade of Na_v1.8 would be analgesic, while reducing adverse events typically associated with non-selective VGSC blocking therapeutic agents. In the present work we perform QSAR analysis on pyrazine based blockers of the Na_v1.8 sodium channel for the treatment of neuropathic pain.⁹

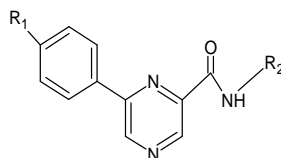
II. RELATED WORK

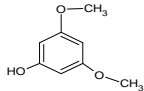
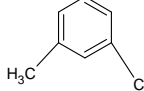
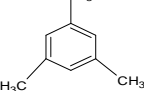
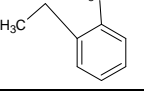
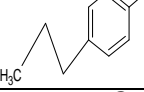
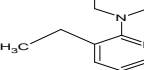
Method

Data set for analysis

On the basis of diversity between different substituents and reported biological activities, this series of compounds have been selected for QSAR analysis. In this series Na_v 1.8 channel blockers activity has been expressed as IC₅₀ value in nano molar units which represents the concentration of drug that inhibits 50 % of neuropathic pain. The values were converted to negative logarithms (pIC₅₀)¹⁰ in order to reduce the skewness of the data set and obtain a linear relationship in QSAR equations. The values of negative logarithms (pIC₅₀) and structural details of the compounds along with indicator parameters are summarized in Table 1.

Table 1: Structural detail and Biological activity for series of pyrazine derivatives with indicator parameter



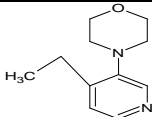
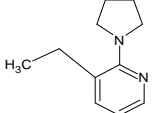
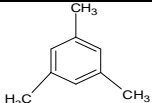
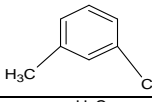
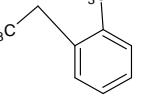
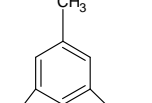
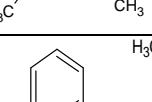
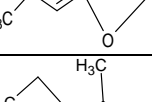
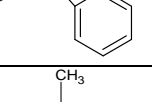
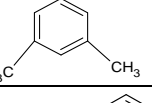
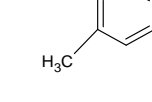
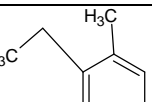
Sl. No.	R ₁	R ₂	I ₄	I ₁₄	I ₁₇	pIC ₅₀
1	-Cl		0	0	0	8.22
2	-Cl		0	0	0	8.22
3	-Cl		1	0	0	8.52
4	-CN		0	1	0	7.57
5	-Cl		0	0	0	7.72
6	-Cl		0	0	0	7.43

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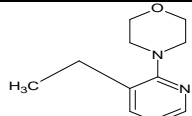
7	-Cl		0	0	0	6.49
8	-Cl		0	0	0	7.52
9	-Cl		1	0	0	8.70
10	-Cl		0	0	0	9.00
11	-Cl		0	0	0	7.08
12	-Cl		1	0	0	7.30
13	-CN		0	0	0	6.82
14	-CN		0	1	0	7.68
15	-Cl		1	0	0	8.30
16	--OCF ₃		0	0	0	7.74
17	-CN		0	1	0	7.00
18	-OCF ₃		0	0	1	7.07

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19	-OCF ₃		0	0	0	7.64
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III. COMPUTATIONAL DETAIL

Two dimensional (2D) structures of various derivatives of 6 aryl-pyrazine carboxamidy were drawn using ACD Lab Chem Sketch version 10 software¹¹ and some physio chemical and hydrophobic parameters such as molecular weight (Mw)¹² molecular volume (Mv)¹³ molar refractivity(Mr)¹⁴ parachor (Pc)¹⁵, index of refraction (IOR)¹⁶ surface tension (st)¹⁷ density (D)¹⁸, polarizability (Pz)¹⁹ and partition coefficient (LogP)¹⁹ were calculated with the help of this software. the topological parameters such as Balaban indices (J)²⁰, Wiener index (W), mean Wiener index (WA) Balaban centric index (BAC), and molecular connectivity (χ)²⁰. HOMO, LUMO, TE (total energy) , Dipole, Band gap were calculated by using discovery software. The topological parameters such as balaban indices (J), Wiener index (W), mean wiener index (WA), Balaban centric index (BAC), molecular connectivity (χ) and quantum chemical descriptors such as total energy (TE), softness (S), hardness (η), chemical potential (μ), binding or cohesive energy (BE), band gap (BG), highest occupied molecular orbital energy (HOMO) and lowest unoccupied molecular orbital energy (LUMO). were calculated with the help of Accelrys's Discovery Studio 3.5 program⁸. All species were fully optimized by density-functional theory at GGA-PW91 level in gas phase.

IV. EXPERIMENTAL RESULTS

In the present work physicochemical, topological & quantum chemical parameters were calculated however we found Balaban indices , moleculer connectivity, parachor (PC), molar refractivity (Mr), surface tension(St), dipole, band gap and LUMO most significant parameters for the modeling of activity of these derivatives. In order to study the role of different substituents at different positions, indicator parameters I₄ which represent -Cl group at R₁ position, I₁₄ which represent -CN group at R₁ position and I₁₇ which represent -OCF₃ group at R₁ position were introduced. Regression analysis was performed by using SPSS 7.5 version. The calculated value of significant parameters used in the present analysis is given in Table 2. In multiple regression analysis, the independent variables must be orthogonal, its value must be less than 0.5 and consequently the autocorrelation among the descriptors was checked and is given in the correlation matrix in Table 3. Statistically significant models were obtained when one of the parameters PC), (Mr), (St), (Dipole), (B gap), (LUMO),(Balaban indices) , (χ^3) is combined with the indicator parameter. The models obtained are reported as:

Table 2: Physicochemical topological and quantum chemical descriptors for series of derivatives

Compound no.	Pc	Mr	St	dipole	B gap	LUMO	Jx	χ^0	χ^3
1	757.70	99.85	53.60	1.75926	.075728	-.107552	1.77	14.94920	.65158
2	682.00	91.32	56.90	1.73441	.088066	-.111952	1.80	13.21010	.66895
3	719.70	96.14	54.70	1.72346	.076738	-.121100	1.78	13.34520	.56431
4	758.60	100.87	53.00	1.38768	.089273	.113245	1.76	14.83980	.78217
5	765.70	99.56	53.80	2.08691	.091131	-.112956	1.58	14.75820	.75927
6	862.50	109.93	59.30	2.08945	.008424	-.410626	1.58	15.95190	.67904
7	862.50	109.93	59.30	2.89765	.007416	-.413292	1.45	15.95190	.69359
8	842.10	108.32	60.50	.74053	.061851	-.113516	1.42	16.06270	.71631
9	780.20	102.56	50.20	1.21950	.088787	-.100463	1.68	16.06270	.54230
10	742.60	97.73	51.80	1.42599	.088733	-.101349	1.74	14.89860	.58150
11	787.40	101.36	48.00	1.05544	.091171	-.093880	1.68	15.35430	.54230

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12	811.70	102.37	72.60	3.68418	.080748	-.122104	1.66	15.00900	.81449
13	798.40	100.33	65.30	2.83999	.081715	-.119946	1.72	13.73050	.73387
14	740.00	93.98	67.60	2.78285	.083595	-.117157	1.70	15.04100	.59319
15	764.10	98.38	46.20	2.20400	.088809	-.110304	1.71	14.11830	.86265
16	726.40	93.56	47.50	2.17356	.088678	-.111346	1.70	14.82540	.69599
17	722.10	97.09	44.50	2.10341	.090922	-.107738	1.64	14.82540	.69238
18	764.50	95.25	49.80	2.66284	.090885	-.122067	1.63	14.82920	.67481
19	907.70	112.17	51.30	2.47270	.008957	-.410531	1.40	16.86020	.67258

pIC₅₀= activity, Jx= Balaban indices, Pc= parachor, Mr= Molar referactivity, Bgap= Band gap, LUMO= Lowest Unoccupied Molecular Orbital Energy, χ , χ^3 = Connectivity index

Table 3: Correlation matrix between different parameters.

Correlations	PAR	MF	ST	I ₄	DIPOLE	BGAP	LUMO	I ₁₄	JX	CHI ₃	CHI ₀	I ₁₇
ACTIVITY	1.000											
ACTIVITY	1.000											
PAR	-.560	1.000										
MF	-.406	-.953	1.000									
ST	-.453	.263	.177	1.000								
I ₄	-.018	-.236	-.094	-.295	1.000							
DIPOLE	-.630	.195	.000	.496	-.149	1.000						
BGAP	.466	-.814	-.818	-.211	.207	-.218	1.000					
LUMO	.413	-.705	-.652	-.141	.411	-.355	.406	1.000				
I ₁₄	-.150	-.231	-.230	-.111	.244	-.035	.296	.162	1.000			
JX	.561	-.824	-.789	-.085	.140	-.113	-.705	.466	-.012	1.000		
CHI ₃	-.403	.160	.113	.164	.227	.413	-.015	.079	-.198	-.148	1.000	
CHI ₀	-.319	-.778	-.784	-.023	-.055	-.075	-.608	-.518	.008	-.771	-.136	1.000
I ₁₇	-.180	-.247	-.201	-.125	-.664	-.161	.287	.395	-.683	.189	-.164	.020
												1.000

Modeling of pIC₅₀ using empirical parameters

In the present study we found that Pc, Mr and St most significant parameters. For this parametric equation, R² comes out to be 0.720. It is the best equation, obtained using empirical parameter.

$$pIC_{50} = -2.77 \pm (2.784) Pc + 0.211(\pm 0.129)Mr - 2.70 (\pm 2.698)St - 1.044 (\pm 1.34) I_4 + 9.628$$

$$n = 19, R = 0.849, R^2 = 0.720, R^2_A = 0.640, S.E. = 0.40, F_{(4-15)} = 8.99, Q = 2.13 \dots (1)$$

dipole, Band gap, LUMO has also been found to be an effective parameter in modeling of pIC₅₀. For this parametric equation, R² comes out to be 0.705. The equation is given below:

$$pIC_{50} = -631(\pm 9.46)dipole + 28.236(\pm 18.553)Bgap - 4.682(\pm 4.314)LUMO - 0.636(\pm 0.542)I_{14} + 6.368$$

$$n = 19, R = 0.840, R^2 = 0.705, R^2_A = 0.621, S.E. = 0.41, F_{(4-15)} = 8.361, Q = 2.05 \dots (2)$$

Connectivity index (χ^3) and (χ^0) parameter has also been found effective in modeling of pIC₅₀. For this equation, R² comes out to be 0.533. The equation is given below:

$$pIC_{50} = -4.317(\pm 3.85) Jx + 2.408(\pm 3.18) \chi^3 + 0.167(\pm 0.476) \chi^0 - 0.611(\pm 0.647)I_{17} - 0.181$$

$$n = 19, R = 0.744, R^2 = 0.553, R^2_A = 0.425, S.E. = 0.50, F_{(4-18)} = 4.328, Q = 1.46 \dots (3)$$

In the calculated model (1)–(3), we have used as the symbol n for the number of compounds in the data set, R for the correlation coefficient, R² for the coefficient of determination, R²_A for the adjusted R², SE for the standard error of estimate, F for the variance ratio²¹ and Q for the quality of fit¹⁵. The negative sign of coefficients of indicator parameter I₄, I₁₄ and I₁₇ shows that the -Cl, CN and OCF₃ group at R₁ has a negative influence on activity and should not be used at R₁ position in the future drug designing. The above equations show that the coefficient of zero and third order of molecular connectivity (χ^3 and χ^0) Mr and Bgap has positive coefficient and this indicates that bulkier substituents with more branching and high value of Bgap parameter should be preferred for future modeling. Negative coefficient of Pc, Di, St, LUMO and Jx indicates that these parameters contribute negatively towards activity. The high values of R, R² and low values of S.E. indicate the statistical significance of the proposed mentioned models.

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On the basis of calculated statistical parameter it is evident that model 1 is the best among all multiparametric models discussed above. The quality factor Q is the ratio of correlation coefficient to its standard error of estimation i.e. $Q = R/S.E.$ thus higher the value of R, the lower the S.E., the greater will be the Q. The predictive power as determined by the Pogliani Q parameter for the model expressed by Eq. (1) [$Q = 2.13$] confirms that this model has excellent statistics as well as excellent predictive power.

Predicted and residual activity values for model no. 1 are given in Table 4. Predicted values are the calculated activities obtained from model no. 1 and the residual values are the difference between the observed biological activities and calculated activities. The plot of observed pIC_{50} verses predicted pIC_{50} for Eq. (1) is shown in graph (Fig. 1) and the predicted R^2 was found to be fairly large.

Table 4: Comparison between observed and predicted activities and their residual values for the model 1

Sr. No.	Observed Activity	Predicted Activity	Residual Activity
1	8.22	8.27	-0.05
2	8.22	8.47	-0.25
3	8.52	8.51	0.07
4	7.57	7.43	0.13
5	7.72	7.98	-0.26
6	7.43	7.34	-0.08
7	6.49	7.34	-0.85
8	7.52	7.53	0.01
9	8.70	8.31	0.38
10	9.00	8.29	0.70
11	7.72	7.91	-0.19
12	7.08	6.79	0.28
13	7.30	6.92	0.37
14	6.82	7.14	-0.32
15	7.68	7.98	-0.30
16	8.30	7.97	0.32
17	7.74	7.87	0.13
18	7.00	7.21	-0.21
19	7.07	6.77	0.29

Cross validation

The cross validation analysis was performed using leave one out (LOO) method¹⁹ 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 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, SSY and R^2_{cv} and PSE 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 of PRESS/SSY can be used to calculate approximate confidence intervals of prediction of a new compound. To be a reasonable QSAR model PRESS/SSY should be smaller than 0.4 and for our best models the value of this ratio is 0.096. The calculated result revealed that this model is excellent. Also, if PRESS value is transformed into 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 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

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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, that's why, we have considered this models as the best model. R^2_A takes into account the adjustment of 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 does not 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)¹⁴ 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 5.

Table 5: Cross validated parameters and predictive error of coefficient of correlation (PE) for the model 1.

n	R	1-R ²	P.E	6PE	PRESS	SSY	PRESS/SSY	R ² _{cv}	PSE
19	0.849	0.272	0.092	0.556	0.12	1.26	0.096	0.904	2.33

It is argued that if the values $R < PE$, then such correlation is not significant; however if values are $R > PE$ in several times (at least three times), then values are correlated. However, if values are $R > 6PE$, then mathematically the correlation is unquestionably good. For all the models developed the condition $R > 6PE$ is satisfied and hence they can be said to have a good predictive power.

V. CONCLUSION

The obtained best QSAR model based on empirical parameter demonstrate that derivative having more molar refractivity and less parachor and surface tension value enhances the activity of the drugs towards the treatment of neuropathic pain. In reference of indicator parameter absence of chlorine at R₁ position may be beneficial for these derivatives towards the treatment of neuropathic pain.

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