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QSAR study on selective high-affinity 5-HT$_4$ receptor ligands as prospective imaging probes for positron emission tomography (PET)

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ABSTRACT

The 5-HT$_4$ receptor binding affinities of the radioligands based on SB 207710 have been quantitatively analyzed in terms of Dragon descriptors. In order to improve the 5-HT$_4$ receptor binding affinity of a compound, more number of halogen atoms (X) on aromatic ring and donor atoms (nitrogen and oxygen) for H-bonds in a molecule are recommended by descriptors nPhX and nHDon. Atomic properties (mass and van der Waals volume) have shown prevalence in terms of associations of masses to the lowest eigenvalues n.1, 6 and 8 of Burden matrix (BELm1, BELm6 and BELm8) and van der Waals volume to path length 1 of Moran autocorrelation (MATS1v). A lower values of descriptors MATS1v and BELm1 and higher values of descriptors BELm6 and BELm8 would be beneficiary to the activity. The derived models and participating descriptors in them have suggested that the SB 207710 moiety have sufficient scope for further modification.

Key words: QSAR, SB 207710, 5-HT$_4$ receptor ligands, binding affinity, combinatorial protocol in multiple linear regression (CP-MLR).

INTRODUCTION

Radioligands are important clinical research tools [1] as they offer a unique means for measuring brain neurotransmitter receptor concentrations in living subjects on application with molecular imaging techniques like positron emission tomography (PET) or single photon emission computed tomography (SPECT). Radioligands are also helpful in drug discovery and development because with the help of imaging techniques the receptor binding of unlabeled ligands *in vivo* may be assessed [2]. Serotonin (5-HT) is an important neurotransmitter which is known to act on at least 14 receptors in seven major subclasses. 5-HT receptors become important targets for deep biomedical investigation, drug discovery and development programs due to implications in neuropsychiatric disorders.

The effective radioligands for the *in vivo* imaging of the 5-HT$_4$ receptor subtypes are not yet well explored. The 5-HT$_4$ receptor which exists abundantly in brain (particularly in limbic and striatonigral regions) [3] is a well-characterized G-protein coupled receptor. It is implicated in dopamine, serotonin, acetylcholine release and neuropsychiatric disorders like Alzheimer's disease, anxiety, and depression [4-6].

The wide array of properties which must ideally be found in any candidate such as high target receptor affinity, high selectivity, generally moderate lipophilicity [7], appropriate intrinsic activity, ability to cross the blood-brain barrier [8], absence of troublesome radiometabolites [8] and amenability to labeling with a suitable radioisotope [9,10] is the reason behind the relatively slow development of 5-HT$_4$ PET radioligands. Carbon-11 or fluorine-18 and iodine-123 are the suitable radioisotopes for PET and SPECT, respectively. [^{123}I]SB 207710 ((1-Butylpiperidin-4-yl)methyl

8-amino-7-iodo-2,3-dihydrobenzo[*b*][1,4]dioxine-5-carboxylate) is an exceptionally high-affinity 5-HT_4 receptor antagonist [11,12] which provided the first demonstration of 5-HT_4 receptor imaging in primate brain in vivo [13]. The analogs of SB 207710, labeled with either carbon-11 or fluorine-18 in the terminal N-alkyl group, has shown promise for PET imaging in animal [14] and human subjects [15,16].

A synthetic study has been carried out by Xu *et al.* with the aim to develop prospective PET radioligands for the imaging of brain 5-HT_4 receptor incorporating structural modifications to the high-affinity 5-HT_4 antagonist SB 207710 and these analogs were evaluated for 5-HT_4 receptor binding [17]. The modifications were made mainly on the aryl side of the ester bond to permit possible rapid labeling of the carboxylic acid component with a positron emitter, either carbon-11 or fluorine-18, and included replacement of the aryl halo group and/or alkylation of the aryl amino group, opening of the dioxan ring, and manipulation of the N-alkyl chain length. In view of the importance of 5-HT_4 receptor ligands in the clinical management of several disorders, a quantitative structure–activity relationship is attempted on the binding affinities of these novel 5-HT_4 ligands. The present study is aimed at rationalizing the substituent variations of these analogues to provide insight for the future endeavours.

EXPERIMENTAL SECTION

Chemical structure database and biological activity

This study comprises a chemical structure database of reported eighteen SB 207710 analogs. The binding affinities of these compounds were determined in binding assays against human recombinant 5-HT_4 receptors (h5-HT_4) expressed in HEK293T cells. The structural variations and the binding affinities of titled compounds have been given in Table 1. The reported activity data has been used for subsequent QSAR analyses as the response variables. For the purpose of modeling all 18 analogs have been divided into training and test sets. Out of the 18 analogs, nearly one third compounds (05) have been placed in the test set for the validation of derived models. The training and test set compounds are also listed in Table 1.

Theoretical molecular descriptors

The structures of the compounds under study have been drawn in 2D ChemDraw [18]. The drawn structures were then converted into 3D modules using the default conversion procedure implemented in the CS Chem3D Ultra. The energy of these 3D-structures was minimized in the MOPAC module using the AM1 procedure for closed shell systems. This will ensure a well defined conformer relationship among the compounds of the study. All these energy minimized structures of respective compounds have been ported to DRAGON software [19] for the computation of descriptors for the titled compounds (Table 1). This software offers several hundreds of descriptors from different perspectives corresponding to 0D-, 1D-, and 2D-descriptor modules. The outlined modules comprised of ten different classes, namely, the constitutional (CONST), the topological (TOPO), the molecular walk counts (MWC), the BCUT descriptors (BCUT), the Galvez topological charge indices (GALVEZ), the 2D autocorrelations (2D-AUTO), the functional groups (FUNC), the atom-centered fragments (ACF), the empirical descriptors (EMP), and the properties describing descriptors (PROP). For each of these classes the DRAGON software computes a large number of descriptors which are characteristic to the molecules under multi-descriptor environment. The definition and scope of these descriptor's classes is given in Table 2. The combinatorial protocol in multiple linear regression [20] procedure has been used in the present work for developing QSAR models. Before the application of CP-MLR procedure, all those descriptors which are intercorrelated beyond 0.90 and showing a correlation of less than 0.1 with the biological endpoints (descriptor vs. activity, $r < 0.1$) were excluded. This has reduced the total dataset of the compounds from 468 to 64 descriptors as relevant ones for the binding activity. A brief description of the computational procedure is given below.

Model development

The combinatorial protocol in multiple linear regression (CP-MLR) is a 'filter' based variable selection procedure for model development in QSAR studies. It involves selected subset regressions. In this procedure a combinatorial strategy with appropriately placed 'filters' has been interfaced with MLR to result in the extraction of diverse structure-activity models, each having unique combination of descriptors from the dataset under study. In this, the contents and number of variables to be evaluated are mixed according to the predefined confines. Here the 'filters' are significance evaluators of the variables in regression at different stages of model development. Of these, filter-1 is set in terms of inter-parameter correlation cutoff criteria for variables to stay as a subset (filter-1, default value 0.3 and upper limit ≤ 0.79). In this, if two variables are correlated higher than a predefined cutoff value the respective variable combination is forbidden and will be rejected. The second filter is in terms of t-values of regression

coefficients of variables associated with a subset (filter-2, default value 2.0). Here, if the ratio of regression coefficient and associated standard error of any variable is less than a predefined cutoff value then the variable combination will be rejected. Since successive additions of variables to multiple regression equation will increase successive multiple correlation coefficient (r) values, square-root of adjusted multiple correlation coefficient of regression equation, r-bar, has been used to compare the internal explanatory power of models with different number of variables. Accordingly, a filter has been set in terms of predefined threshold level of r-bar (filter-3, default value 0.71) to decide the variables' 'merit' in the model formation. Finally, to exclude false or artificial correlations, the external consistency of the variables of the model have been addressed in terms of cross-validated R^2 or Q^2 criteria from the leave-one-out (LOO) cross-validation procedure as default option (filter-4, default threshold value $0.3 \leq Q^2 \leq 1.0$). All these filters make the variable selection process efficient and lead to unique solution. In order to collect the descriptors with higher information content and explanatory power, the threshold of filter-3 was successively incremented with increasing number of descriptors (per equation) by considering the r-bar value of the preceding optimum model as the new threshold for next generation.

Model validation

In this study, the data set is divided into training set for model development and test set for external prediction. Goodness of fit of the models was assessed by examining the multiple correlation coefficient (r), the standard deviation (s), the F-ratio between the variances of calculated and observed activities (F). A number of additional statistical parameters such as the Akaike's information criterion, AIC [21,22], the Kubinyi function, FIT [23,24], and the Friedman's lack of fit, LOF [25] (Eqs. 1-3) have also been derived to evaluate the best model.

$$\mathrm{AIC} = \frac{\mathrm{RSS} \times (n + p')}{(n - p')^2} \tag{1}$$

$$\mathrm{FIT} = \frac{r^2 \times (n - k - 1)}{(n + k^2) \times (1 - r^2)} \tag{2}$$

$$\mathrm{LOF} = \frac{\mathrm{RSS}/n}{\left[1 - \frac{k(d+1)}{n}\right]^2} \tag{3}$$

where, RSS is the sum of the squared differences between the observed and the estimated activity values, k is the number of variables in the model, p' is the number of adjustable parameters in the model, and d is the smoothing parameter. The AIC takes into account the statistical goodness of fit and the number of parameters that have to be estimated to achieve that degree of fit. The FIT, closely related to the F-value (Fisher ratio), was proved to be a useful parameter for assessing the quality of the models. The main disadvantage of the F-value is its sensitivity to changes in k (the number of variables in the equation, which describe the model), if k is small, and its lower sensitivity if k is large. The FIT criterion has a low sensitivity toward changes in k-values, as long as they are small numbers, and a substantially increasing sensitivity for large k-values. The model that produces the minimum value of AIC and the highest value of FIT is considered potentially the most useful and the best. The LOF takes into account the number of terms used in the equation and is not biased, as are other indicators, toward large numbers of parameters. A minimum LOF value infers that the derived model is statistically sound.

The internal validation of derived model was ascertained through the cross-validated index, Q^2, from leave-one-out and leave-five-out procedures. The LOO method creates a number of modified data sets by taking away one compound from the parent data set in such a way that each observation has been removed once only. Then one model is developed for each reduced data set, and the response values of the deleted observations are predicted from these models. The squared differences between predicted and actual values are added to give the predictive residual sum of squares, PRESS. In this way, PRESS will contain one contribution from each observation. The cross-validated Q^2_{LOO} value may further be calculated as

$$Q^2_{LOO} = 1 - \mathrm{PRESS}/\mathrm{SSY} \tag{4}$$

where, SSY represents the variance of the observed activities of molecules around the mean value. In leave-five-out procedure, a group of five compounds is randomly kept outside the analysis each time in such a way that all the compounds, for once, become the part of the predictive groups. A value greater than 0.5 of Q^2-index hints toward a reasonable robust model.

The external validation or predictive power of derived model is based on test set compounds. The squared correlation coefficient between the observed and predicted values of compounds from test set, r^2_{Test}, has been calculated as

$$r^2_{Test} = 1 - \frac{\sum (Y_{Pred(Test)} - Y_{(Test)})^2}{\sum (Y_{(Test)} - \overline{Y}_{(Training)})^2} \quad (5)$$

where, $Y_{Pred(Test)}$ and $Y_{(Test)}$ indicate predicted and observed activity values, respectively of the test-set compounds, and $\overline{Y}_{(Training)}$) indicate mean activity value of the training set. r^2_{Test} is the squared correlation coefficient between the observed and predicted data of the test-set. A value greater than 0.5 of r^2_{Test} suggests that the model obtained from training set has a reliable predictive power.

Y-randomization

Chance correlations, if any, associated with the CP-MLR models were recognized in randomization test [26,27] by repeated scrambling of the biological response. The data sets with scrambled response vector have been reassessed by multiple regression analysis (MRA). The resulting regression equations, if any, with correlation coefficients better than or equal to the one corresponding to the unscrambled response data were counted. Every model has been subjected to 100 such simulation runs. This has been used as a measure to express the percent chance correlation of the model under scrutiny.

RESULTS AND DISCUSSION

In multi-descriptor class environment, exploring for best model equation(s) along the descriptor class provides an opportunity to unravel the phenomenon under investigation. In other words, the concepts embedded in the descriptor classes relate the biological actions revealed by the compounds. For the purpose of modeling study, 05 compounds have been included in the test set for the validation of the models derived from 13 training set compounds. A total number of 64 significant descriptors from 0D-, 1D- and 2D-classes have been subjected to CP-MLR analysis with default 'filters' set in it. Statistical models in two and three descriptor(s) have been derived successively to achieve the best relationship correlating 5-HT_{2A} binding affinity. These models (with 64 descriptors) were identified in CP-MLR by successively incrementing the filter-3 with increasing number of descriptors (per equation). For this the optimum r-bar value of the preceding level model has been used as the new threshold of filter-3 for the next generation. Only three models in three descriptors with r^2_{Test} greater than 0.5 were obtained and these are presented below.

pK_i = –2.428(0.709)MATS1v + 0.901(0.292)nPhX + 2.066(0.396)nHDon + 6.713
n = 13, r = 0.916, s = 0.444, F = 15.823, FIT = 2.157, LOF = 0.471, AIC = 0.372,
Q^2_{LOO} = 0.584, Q^2_{L3O} = 0.718, r^2_{randY}(sd) = 0.278(0.237), r^2_{Test} = 0.594 (6)

pK_i = 1.646(0.496)BELm6 + 0.724(0.303)nPhX + 2.797(0.475)nHDon + 4.609
n = 13, r = 0.913, s = 0.451, F = 15.192, FIT = 2.071, LOF = 0.487, AIC = 0.385,
Q^2_{LOO} = 0.551, Q^2_{L3O} = 0.512, r^2_{randY}(sd) = 0.194(0.147), r^2_{Test} = 0.615 (7)

pK_i = –1.488(0.528)BELm1 + 1.460(0.555)BELm8 + 2.069(0.522)nHDon + 5.952
n = 13, r = 0.893, s = 0.500, F = 11.858, FIT = 1.617, LOF = 0.597, AIC = 0.472,
Q^2_{LOO} = 0.582, Q^2_{L3O} = 0.639, r^2_{randY}(sd) = 0.239(0.204), r^2_{Test} = 0.627 (8)

In above regression equations, the values given in the parentheses are the standard errors of the regression coefficients. The r^2_{randY}(sd) is the mean random squared multiple correlation coefficient of the regressions in the activity (Y) randomization study with its standard deviation from 100 simulations. In the randomization study (100

simulations per model), none of the identified models has shown any chance correlation. The signs of the regression coefficients suggest the direction of influence of explanatory variables in the models.

The descriptor, MATS1v, in above models is lone representative of 2D-AUTO class of Dragon descriptors. The 2D-AUTO descriptors have their origin in autocorrelation of topological structure of Broto-Moreau (ATS), of Moran (MATS) and of Geary (GATS). The computation of these descriptors involves the summation of different autocorrelation functions corresponding to the different fragment lengths and lead to different autocorrelation vectors corresponding to the lengths of the structural fragments. Also a weighting component in terms of a physicochemical property has been embedded in these descriptors. As a result, these descriptors address the topology of the structure or parts thereof in association with a selected physicochemical property. In these descriptors' nomenclature, the penultimate character, a number, indicates the number of consecutively connected edges considered in its computation and is called as the autocorrelation vector of lag k (corresponding to the number of edges in the unit fragment). The very last character of the descriptor's nomenclature indicates the physicochemical property considered in the weighting component for its computation. The participated descriptor, MATS1v, is the Moran autocorrelation of lag 1 weighted by atomic van der Waals volumes and it correlates negatively to the activity. The negative correlation suggest the unfavorable conditions associated with lag 1 weighted by atomic van der Waals volumes.

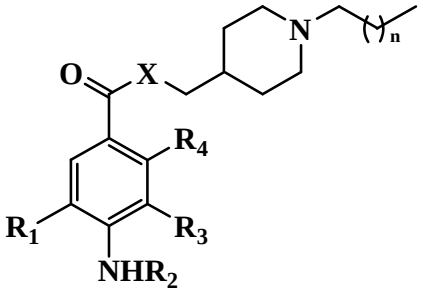
Descriptors BELm1, BELm6 and BELm8 are BCUT class descriptors. The BCUT descriptors are the first 8 highest and the lowest absolute eigenvalues, BEHwk and BELwk, respectively, for the modified Burden adjacency matrix. Here w refers to the atomic property and k to the eigenvalue rank. The ordered sequence of the highest and the lowest eigen values reflect upon the relevant aspects of molecular structure, useful for similarity searching.

All the emerged descriptors, BELm1, BELm6 and BELm8, represent the atomic masses weighted lowest eigenvalues n.1, 6 and 8, respectively of Burden matrix. The descriptor BELm1 have shown negative correlation and BELm6 and BELm8 positive correlation to the binding activity advocating that a lower of descriptor BELm1 and higher values of descriptors BELm6 and BELm8 would be favorable to the activity.

The remaining participated descriptors, nPhX and nHDon in above models belong to FUNC class. The functional class descriptors are molecular descriptors based on the counting of the chemical functional groups. The descriptor nPhX represents number of halogen atoms (X) on aromatic ring. Descriptor nHDon accounts for the number of donor atoms (nitrogen and oxygen) for H-bonds. The positive contribution of both of these descriptors, nPhX and nHDon, to the activity recommends more number of halogen atoms (X) on aromatic ring and donor atoms (nitrogen and oxygen) for H-bonds in a molecule for elevated binding affinity of titled compounds.

The three descriptor models discussed above have accounted for up to 83.90 percent variance in the observed activities. The values greater than 0.5 of Q^2-index is in accordance to a reasonable robust QSAR model. The pK_i values of training set compounds calculated using Equations (6) to (8) have been included in Table 1. These models are validated with an external test set of five compounds listed in Table 1. The predictions of the test set compounds based on external validation are found to be satisfactory as reflected in the test set r^2 (r^2_{Test}) values and the predicted activity values are also reported in Table 1. The plot showing goodness of fit between observed and calculated activities for the training and test set compounds is given in Figure 1.

Table 1: Structures[a] and observed and modeled binding activities of new 5-HT_4 receptor ligands



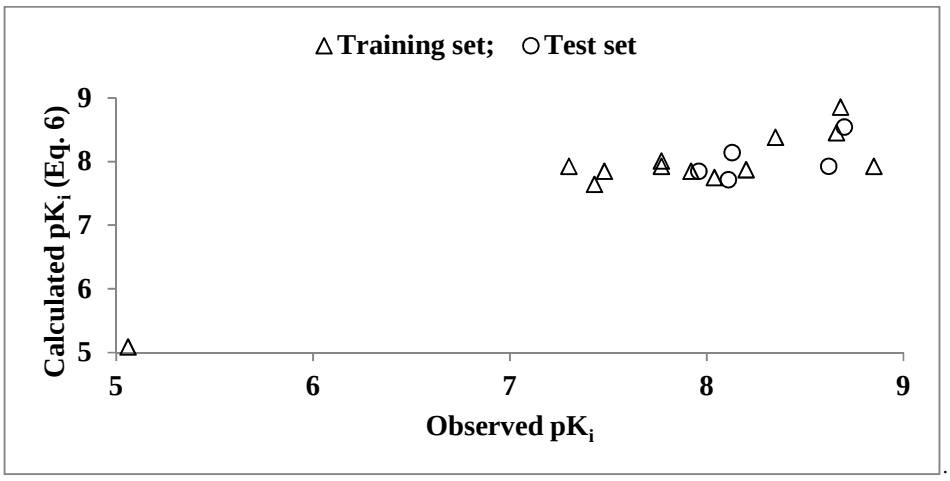
Cpd.	R_1	R_2	R_3	R_4	X	n	pK_i			
							Obsd[a].	Calc.		
								Eq. (6)	Eq. (7)	Eq. (8)
1[b]	I	H	OCH_2	OCH_2	O	2	8.66	8.45	8.68	8.62
2	H	H	OCH_2	OCH_2	O	2	8.85	7.93	7.95	8.07
3	CN	H	OCH_2	OCH_2	O	2	7.48	7.85	7.95	8.11
4	H	CH_3	OCH_2	OCH_2	O	2	8.04	7.75	7.64	7.67
5	CH_3	H	OCH_2	OCH_2	O	2	8.20	7.87	8.21	7.85
6[c]	Cl	CH_3	OCH_2	OCH_2	O	2	8.70	8.54	8.34	8.21
7	Br	CH_3	OCH_2	OCH_2	O	2	8.35	8.38	8.34	8.27
8[c]	I	CH_3	OCH_2	OCH_2	O	2	8.13	8.14	8.32	8.27
9	CN	CH_3	OCH_2	OCH_2	O	2	7.43	7.64	7.65	7.70
10	H	H	H	OCH_3	O	2	7.30	7.93	7.95	8.08
11[c]	H	H	OCH_3	H	O	2	8.62	7.93	7.95	8.03
12	H	H	OCH_3	H	N	2	5.06	5.09	5.15	5.15
13	H	H	OCH_3	H	O	1	7.77	8.01	7.95	7.41
14	H	H	OCH_3	H	O	3	7.92	7.85	7.95	8.14
15	F	H	OCH_2	OCH_2	O	2	8.68	8.85	8.68	8.43
16	H	H	OCH_2F	H	O	2	7.77	7.93	7.41	8.00
17[c]	H	H	$O(CH_2)_2F$	H	O	2	7.96	7.85	7.95	8.04
18[c]	NO_2	H	OCH_2	OCH_2	O	2	8.11	7.71	7.95	8.22

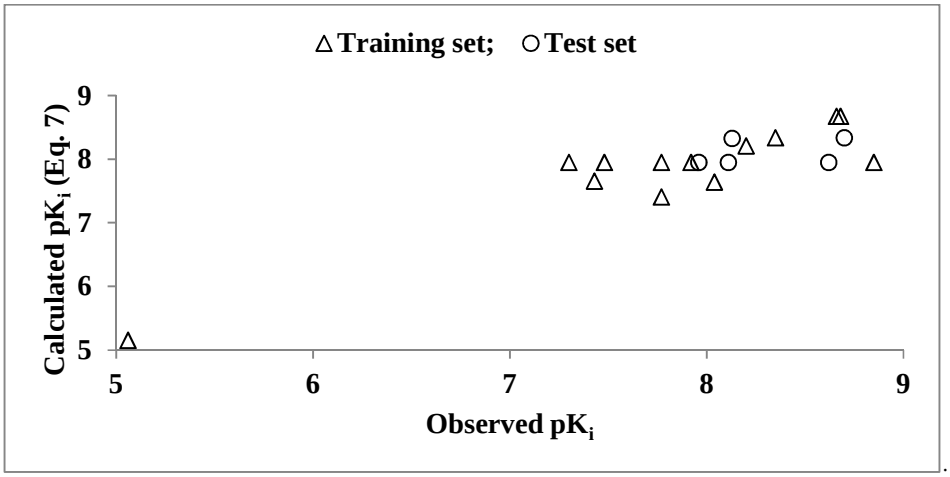
[a]Reference [17], [b]SB 207710, [c]Compounds included in test set.

Table 2: Dragon descriptor classes[a] used along with their definition and scope for modeling the binding affinity

Descriptor class (acronyms)	Definition and scope
Constitutional (CONST)	Dimensionless or 0D descriptors; independent from molecular connectivity and conformations
Topological (TOPO)	2D-descriptor from molecular graphs and independent conformations
Molecular walk counts (MWC)	2D-descriptors representing self-returning walks counts of different lengths
Modified Burden eigenvalues (BCUT)	2D-descriptors representing positive and negative eigenvalues of the adjacency matrix, weights the diagonal elements and atoms
Galvez topological charge indices (GALVEZ)	2D-descriptors representing the first 10 eigenvalues of corrected adjacency matrix
2D-autocorrelations (2D-AUTO)	Molecular descriptors calculated from the molecular graphs by summing the products of atom weights of the terminal atoms of all the paths of the considered path length (the lag)
Functional groups (FUNC)	Molecular descriptors based on the counting of the chemical functional groups
Atom centered fragments (ACF)	Molecular descriptors based on the counting of 120 atom centered fragments, as defined by Ghose-Crippen
Empirical (EMP)	1D-descriptors represent the counts of non-single bonds, hydrophilic groups and ratio of the number of aromatic bonds and total bonds in an H-depleted molecule
Properties (PROP)	1D-descriptors representing molecular properties of a molecule

[a]Reference [19].





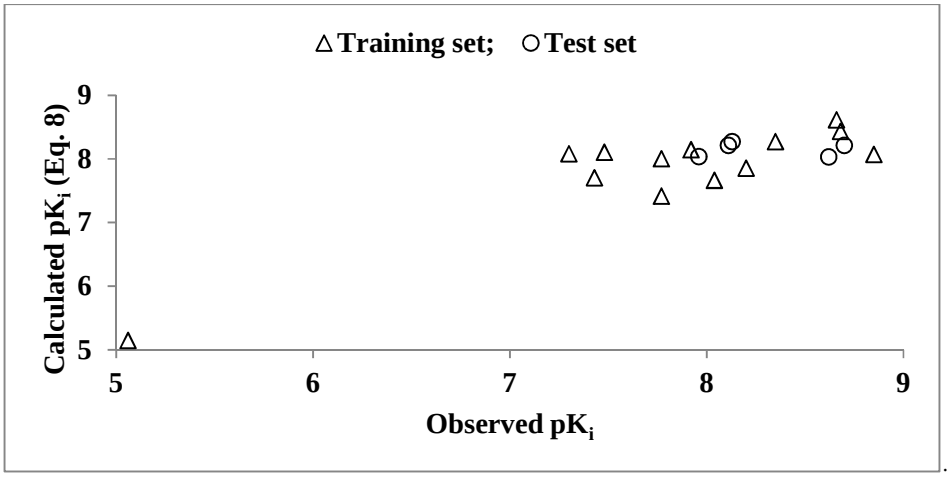


Fig. 1: Plot of observed versus calculated pK$_i$ values of the 5-HT$_4$ receptor radioligands

CONCLUSION

In conclusion, the present study has provided structure–activity relationships of the binding affinities of radioligands to 5-HT$_4$ receptor in terms of structural requirements. The binding affinity has, therefore become the function of the cumulative effect of different structural features which were identified in terms of individual descriptors.

In order to improve the 5-HT$_4$ receptor binding affinity of a compound, more number of halogen atoms (X) on aromatic ring and donor atoms (nitrogen and oxygen) for H-bonds in a molecule are recommended by descriptors nPhX and nHDon. Atomic properties (mass and van der Waals volume) have shown prevalence in terms of associations of masses to the lowest eigenvalues n.1, 6 and 8 of Burden matrix (BELm1, BELm6 and BELm8) and van der Waals volume to path length 1 of Moran autocorrelation (MATS1v). A lower values of descriptors MATS1v and BELm1 and higher values of descriptors BELm6 and BELm8 would be beneficiary to the activity. The derived models and participating descriptors in them have suggested that the ligands based on SB 207710 have sufficient scope for further modification.

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