Scientific paper

2-Dimensional Quantitative Structure-Activity Relationship Modeling Study of Glycine/ N-methyl-D-aspartate Antagonist Inhibition: Genetic Function Approximation Vis-à-vis Multiple Linear Regression Methods

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Abstract

A comparative study of genetic function approximation (GFA) and multiple linear regression analysis(MLR) techniques for understanding 2D quantitative structure-activity relationship (2D-QSAR) on N-methyl-D-aspartate (NMDA) inhibitors was conducted using distance and connectivity based topological indices (Wiener, Balaban and Randic Indices). Models generated were used to predict the inhibitory activity for a set of test compounds. The results indicated that the GFA method proved to be superior of the two in developing 2D QSAR model in all the cases (Uni- as well as multi-variate). Individual topological indices have also been studied to understand their correlation potential. In all the cases (Wiener, Balaban and Randic), the results gave a high value of correlation ($R^2 > 0.80$, $Q^2 > 0.79$) for the GFA method while the MLR method yielded poor correlation ($R^2 < 0.60$ and $Q^2 < 0.55$). Among the three indices, Randic connectivity index proved to be the best in describing the 2D-QSAR for this series of NMDA inhibitors ($R^2 = 0.893$, $Q^2 = 0.880$, F-ratio = 216.393)

Keywords: QSAR, NMDA, GFA, MLR, Wiener index, Randic index, Balaban index

1. Introduction

Distance and connectivity based topological indices, their correlation potential and applications in understanding the quantitative structure-activity relationship (QSAR) has been a matter of great interest to the chemistry community for the past decade or so.[1–7] The beauty of these indices is their easy understandability and applicability. Actual applications of topological indices do not limit to small-sized molecules only, but have crossed the traditional frontiers and have been successfully applied to bigger molecules, such as proteins and RNAs.[8,9] Some recent works studied the similarities and relationships between different topological indices and justified in principle, the selection of a group of arbitrary topological indices (e.g. W, J, χ, or M1) for evaluation of a model without using all the known indices.[10] Use of topological indices has been well illustrated in the literature.[11–18] Use of topological indices in understanding the Glycine/NMDA receptor inhibition has not been reported so far.

It has been observed that N-methyl-D-aspartate (NMDA) receptor play a key role in several abnormal brain processes such as Alzheimer's disease, Huntington's disease, epilepsy, and cerebral ischemia.[19–23] The NMDA receptor requires the occupation of two distinct recognition sites by glutamate and glycine, the latter at the so-called Gly-NMDA site for activation.[24,25] Glycine acts as an endogenous coagonist at its site.[26,27] Most of the selective receptor agonists available are based on NMDA, the diagnostic ligand for these receptors. NMDA itself is an

analogue of aspartate (can also act as a weak agonist at most glutamate receptors). Although this compound acts selectively at NMDA receptors, it cannot discriminate between receptor subtypes. A variety of potent and selective agonists to NMDA receptor are present. To mention a few; *trans*-ACBD,[28] *cis*-ACPD,[29] D-aspartic acid,[29] L-aspartic acid (endogenous NMDA agonist),[29] CCMQ,[30] D and L-glutamic acid (D is less active than the L isomer),[29,31] and homoquinolinic acid.[30]

Auerbach et al.[32] has suggested that the structural studies indicate that the binding of agonists causes a conformational change in the S1–S2 binding site domains of the protein. However, the details of the molecular events that constitute the global conformational change in the protein ("gating") remain unknown. Use of binding free energy/hydration free energy as an additional descriptor in performing SAR studies can be of immense importance in unraveling the chemistry of binding of molecules and can perhaps serve as a tool for distinguishing agonists from antagonists.[33–37] A reliable method of evaluating these free energies is by using Langevin dipoles.[38,39]

Some of the potent and competitive NMDA antagonists widely used are DL-AP5,[40] D-AP5,[40] DL-AP7(First generation phosphono NMDA antagonist),[41] CGP 37849,[42] SDZ 220–581.[43] With the discovery of the stimulatory action of glycine on the NMDA receptor, it was found that these effects of glycine were blocked by kynurenic acid KA, a weak and nonselective NMDA antagonist.[44,45] KA has a very weak affinity for the Gly-NMDA site and is not selective, having a similar potency as that of an antagonist at both NMDA and non-NMDA receptors, kainate and AMPA. KA on chemical modifications, however, has produced compounds with very high affinity.[46–50] Recently, a structure-activity study of 5- and 7-substituted KA derivatives was presented.[47] The biological property analyzed was the functional antagonist potency assessed by the determination of the apparent dissociation constants for the antagonism of the depolarization induced by NMDA. The remarkably important properties of these compounds require more research on their structure-activity relationships (SAR).This article reports results of comparative 2D-QSAR study using two statistical techniques namely MLR and GFA. Connectivity and distance based graph theoretical indices are used to perform correlations with the inhibitory activity of NMDA derivatives.

2. Molecular Modeling Methods

A series of 55 NMDA inhibitors[51] with their inhibition data is taken to perform 2D-QSAR studies. In an attempt to have a precise and detailed understanding of QSAR, graph theoretical descriptors namely Wiener (W), Randic ($^1\chi_R$) and Balaban (J) were used to describe 2D QSAR for the aforementioned series of NMDA inhibitors. In developing QSAR, $\log IC_{50}$ value was used as the dependent variable. MLR and GFA methods are used for performing correlation analysis.

Transformation of the chemical structures of these NMDA inhibitors into a mathematical graph makes it possible to express their chemical structures by a single numerical index. As it is well known, such a numerical index characterizing a molecule (or a corresponding molecular graph) is called a topological index.[12–15] Therefore; a topological index expresses topological information for a given chemical structure. The advantage of the topological indices is that they may be directly used as single molecular descriptors in QSAR as well as QSPR studies. These relationships are mathematical models that enable the prediction of activity or properties from their structural parameters. The structures for the compounds were generated and energy minimization procedures were carried out using Sybyl 6.9[52] while Gasteiger Marsili charges were assigned using Tripos force field. Cerius2®[53] was used to calculate the topological descriptors as well as to perform Multiple Linear Regression (MLR) and Genetic Function Approximation (GFA) analysis for the 2D QSAR studies on Silicon Graphics® Octane2 duel processor workstation.

2. 1. 2D-QSAR: Topological Indices Used

All the three topological indices, namely Wiener index (W), Randic ($^1\chi_R$) and Balaban (J) are well presented in the literature.[14,15] Therefore, they will be described here rather briefly.

2. 1. 1. The Wiener Index (W)

In 1947 Wiener[16] developed a number: Wiener number (W) that could characterize molecular branching. Wiener himself correlated a number of properties with W including boiling points and various thermodynamic parameters. Stiel and Thodos[54] used W to predict critical constant. Rouvray and Crafford[55] correlated W with density, viscosity and surface tension. Popazova and Bonchev[56] correlated W with chromatographic retention times. The index has also been used in the prediction of antibacterial activity.[57]

The Wiener index, W=W (G), of a graph is defined as the half the sum of the elements of the distance matrix

$$W = \frac{1}{2}\left(\sum_{i=1}^{n}\sum_{j=1}^{n} d_{ij}\right) \quad (1)$$

where (d_{ij}) is the *ij*th element of the distance matrix D, which denotes the shortest graph theoretical distance between vertices *i* and *j* in G. All the graphs are hydrogen suppressed.

2. 1. 2. The Randic Connectivity Index ($^1\chi_R$)

In 1975 Randic proposed a topological index,[17] that has most wide utility in both QSPR and QSAR studies. It makes use of vertices present in the chemical graph and is therefore sensitive to the shape of the chemical cluster. This is also known as molecular connectivity index. Molecular connectivity has been extensively employed in the QSPR and QSAR studies, by Keir and Hall. [12,56]

The connectivity index $\chi = \chi(G)$, of G is defined[17] as

$$^1\chi_R = \sum[\delta_i\delta_j]^{-0.5} \quad (2)$$

where δ_i and δ_j are the valences of the vertices *i* and *j*, equal to the number of bonds connected to the atoms *i* and *j* in G, representing the graph of a compound.

2. 1. 3. The Balaban Index (J)

The topological index of Balaban is based on the distance matrix of the graph G and is known as averaged distance sum connectivity index.[10]

The Balaban index J = J (G) of G is defined as:

$$J = [b/(\mu+1)]\sum_{i-k}(\delta_i\delta_k)^{-1/2} \quad (3)$$

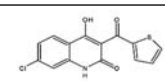
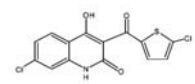
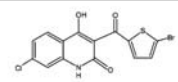
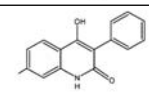
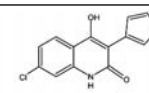
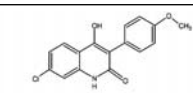
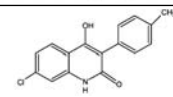
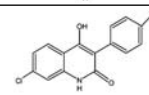
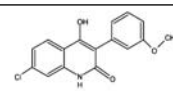
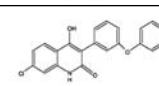
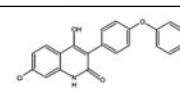
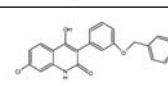
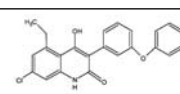
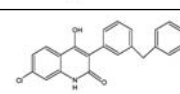
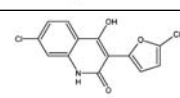
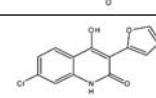
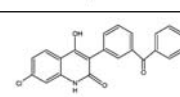
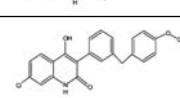
where *b* is the number of bonds in G, is the cyclomatic number of G and d_i and d_k (i or j = 1,2,3....N the number of vertices in G) are the distance sums. Balaban Index has been successfully used in the various QSAR and QSPR studies.[59,60]

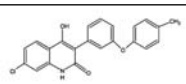
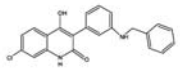
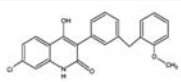
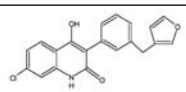
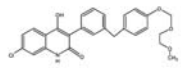
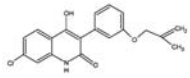
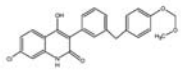
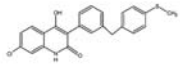
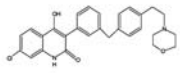
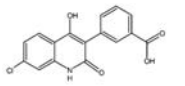
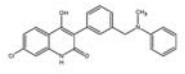
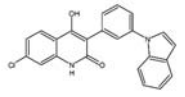
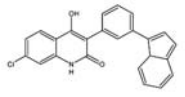
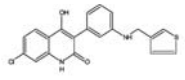
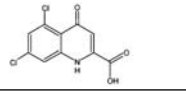
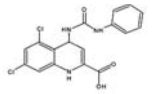
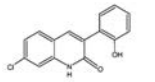
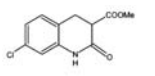
For understanding the quantitative structure-activity relationships, statistical analysis using uni- as well as multi-variate correlations were performed using multiple linear regression (MLR) and genetic function approximation (GFA) techniques and the results were then compared. First, a correlation matrix was derived, and then regression parameters were obtained. The results were summarized for comparison. In the case of GFA analysis linear, spline, quadratic, offset-quadratic and quadratic-spline terms were used, with a population size of 100 and number of generations as 10000. The value of add-new term was kept at 25, keeping all the other values as default with the initial length of equation at 4.

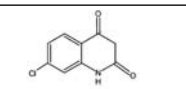
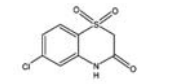
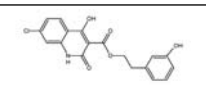
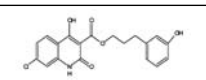
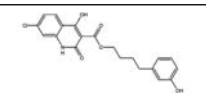
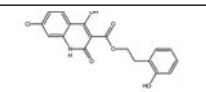
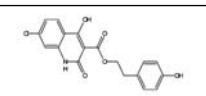
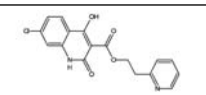
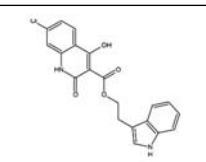
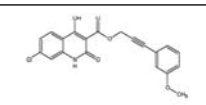
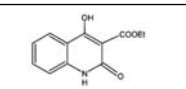
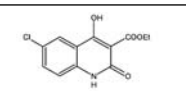
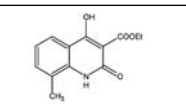
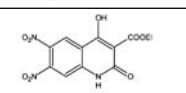
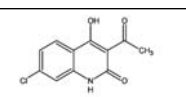
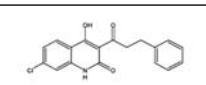
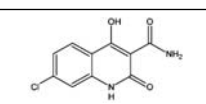
3. Results and Discussion

The structural descriptors (namely W, $^1\chi_R$, and J) for the NMDA inhibitors (training set) are given in Table 1-A. It also records their biological inhibitory activities, expressed as $\log IC_{50}$. Table1-B reports the biological activity and the graph theoretical indices of the test set.

Table 1-A: Topological Indices and Biological (Inhibitory) Activity of NMDA Inhibitors (Training set).

No.	COMPOUND	$\log IC_{50}$	W	J	$^1\chi_R$
01		3.037	761.0	2.0674	9.5754
02		3.182	881.0	2.0394	9.9692
03		2.980	881.0	2.0424	9.9692
04		2.236	658.0	2.1633	9.1647
05		2.547	559.0	2.1538	8.6647
06		2.624	908.0	2.0693	10.0966
07		2.592	773.0	2.1359	9.5586
08		2.818	773.0	2.1244	9.5586
09		2.310	882.0	2.1160	10.0966
10		0.301	1699.0	1.7016	12.6142
11		1.083	1790.0	1.6286	12.6142
12		1.086	1956.0	1.6115	13.1140
13		0.290	2036.0	1.7484	13.5629
14		0.602	1699.0	1.7168	12.6142
15		2.682	657.0	2.1308	9.0586
16		2.873	559.0	2.1472	8.6647
17		0.556	1842.0	1.7592	13.0417
18		0.653	2160.0	1.6523	13.5460

No.	COMPOUND	$\log IC_{50}$	W	J	$^1\chi_R$
19		0.892	1916.0	1.6780	13.0080
20		0.982	1956.0	1.6181	13.1142
21		0.903	2080.0	1.6988	13.5629
22		0.949	1505.0	1.7231	12.6142
23		0.556	3820.0	1.4348	16.0460
24		1.037	1357.0	1.9716	11.4524
25		0.342	2432.0	1.6148	14.0460
26		0.380	2160.0	1.6539	13.5460
27		0.954	4071.0	1.2735	16.5637
28		1.879	1006.0	2.1265	10.4693
29		1.068	2120.0	1.6419	13.5249
30		1.009	1997.0	1.6255	13.6142
31		0.778	1997.0	1.5811	13.6142
32		0.519	1738.0	1.6308	12.6142
33		1.806	403.0	2.4711	7.4861
34		0.602	1504.0	1.7732	11.9356
35		2.751	674.0	1.9440	9.1479
36		2.004	423.0	2.2261	7.6134

No.	COMPOUND	$\log IC_{50}$	W	J	$^1\chi_R$
37		2.004	226.0	2.4656	6.1647
38		2.004	269.0	2.5180	6.4880
39		0.260	1640.0	1.5886	11.9524
40		0.422	1900.0	1.5800	12.4524
41		0.418	2186.0	1.5065	12.9524
42		0.852	1622.0	1.6791	11.9692
43		0.467	1658.0	1.6540	11.9524
44		1.439	1456.0	1.6747	11.5586
45		–0.367	2051.0	1.4227	13.0249
46		–0.569	2132.0	1.6572	12.9904
47		2.004	488.0	2.4093	8.1471
48		2.004	572.0	2.4331	8.5409
49		2.004	566.0	2.4692	8.5577
50		1.021	1122.0	2.5847	10.7730
51		2.004	400.0	2.5770	7.5029
52		2.004	1242.0	1.8045	11.0586
53		2.004	400.0	2.5693	7.5029

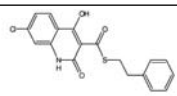
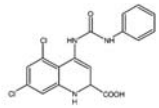
No.	COMPOUND	$logIC_{50}$	W	J	$^1\chi_R$
54		1.041	1456.0	1.6852	11.5585
55		0.602	1504.0	1.8140	11.9356

Table 1-B: Structure and Experimental logIC50 values of NMDA Inhibitors (Test Set).

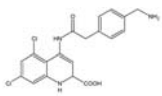
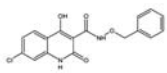
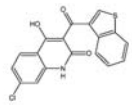
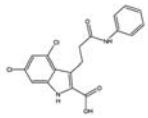
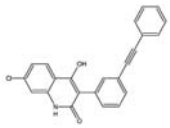
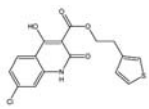
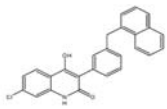
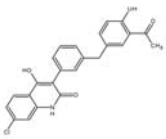
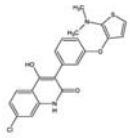
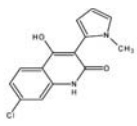
No.	**COMPOUND**	**$logIC_{50}$**	**W**	**J**	**$^1\chi_R$**
01		1.585	1930	1.7385	11.9356
02		2.004	1456	1.6734	11.5586
03		3.348	1261	1.8248	11.5586
04		1.561	1568	1.7981	11.9524
05		1.535	1956	1.7249	13.1142
06		3.477	1275	1.6921	11.0585
07		1.446	2509	1.534	14.5974
08		1.630	2574	1.675	14.3294
09		1.513	2078	1.6368	13.4356
10		2.913	644	2.171	9.0754

Table 2 summarizes the comparison of uni- and multivariate analysis using GFA and MLR methods. The bivariate results have not shown any significant improvement in the correlation coefficient and thus are excluded from the table.

Table 2: Regression parameters, Quality of correlation of $logIC_{50}$) with the Structural Descriptors for NMDA Inhibitors.

Index	**Correlation Parameter**	**MLR**	**GFA**
W	R^2	0.537	0.891
	Q^2	0.459	0.887
	F-ratio	61.593	154.289
$^1\chi_R$	R^2	0.565	0.893
	Q^2	0.527	0.880
	F-ratio	68.722	216.393
J	R^2	0.461	0.818
	Q^2	0.419	0.796
	F-ratio	45.271	117.103
W, $^1\chi_R$,J	R^2	0.566	0.932
	Q^2	0.429	0.923
	F-ratio	22.197	233.431

The $logIC_{50}$ for the NMDA inhibitors were estimated using the best correlation obtained from both MLR as well as GFA techniques, and such estimated $logIC_{50}$ values are recorded in Table- 3 for both MLR and GFA. The residuals demonstrate the quality of correlations, i.e. difference between the observed and estimated $logIC_{50}$ values and are given in Table-3. Table-4 presents the results obtained for the test set. Also, it records the regression parameters estimated for the test set. The correlation parameters obtained also indicate that GFA performs better as compared to MLR. In the training set, the prediction power of GFA was very high and also it performed better in estimating the activity values for the test set. As seen in equation 2, the spline terms used in the case of GFA are truncated power splines and are denoted by angle brackets (<, >).

Table 3: Observed and Estimated $logIC_{50}$ values of NMDA Inhibitors (training set) from the regression equations (1) (MLR) and (2) (GFA)

(MLR) $logIC_{50}$= 8.43042 – 0.00025036W – 1.24785J – 0.377459($^1\chi_R$) **(1)**

(GFA) $logIC_{50}$= 0.668898 + 0.011932 <1505 – W> + 6.90507<J – 2.11598>2 – 0.010232<1250 – W> – 5.69173<J-1.77322> **(2)**

		Linear		**GFA**	
No.	**$logIC_{50}$ (Obs)**	**$logIC_{50}$ (Pred)**	**Resd.**	**$logIC_{50}$ (Pred)**	**Resd.**
01	3.04	1.89	1.15	2.78	0.26
02	3.18	1.78	1.41	2.85	0.33
03	2.98	1.78	1.20	2.85	0.13

		Linear		GFA	
No.	$logIC_{50}$ (Obs)	$logIC_{50}$ (Pred)	Resd.	$logIC_{50}$ (Pred)	Resd.
04	2.24	2.00	0.24	2.60	–0.36
05	2.55	2.14	0.41	2.57	–0.03
06	2.62	1.74	0.88	2.64	–0.02
07	2.59	1.89	0.71	2.67	–0.08
08	2.82	1.89	0.93	2.69	0.13
09	2.31	1.74	0.57	2.57	–0.26
10	0.30	1.03	–0.73	0.66	–0.36
11	1.08	1.02	0.06	0.66	0.42
12	1.09	0.88	0.21	0.66	0.42
13	0.29	0.74	–0.45	0.66	–0.37
14	0.60	1.03	–0.43	0.66	–0.06
15	2.68	2.03	0.66	2.64	0.04
16	2.87	2.14	0.74	2.59	0.29
17	0.56	0.90	–0.34	0.66	–0.11
18	0.65	0.74	–0.08	0.66	–0.01
19	0.89	0.90	–0.01	0.66	0.23
20	0.98	0.88	0.11	0.66	0.32
21	0.80	0.74	0.06	0.66	0.14
22	0.95	1.18	–0.23	0.66	0.29
23	0.56	–0.12	0.67	0.66	–0.11
24	1.04	1.35	–0.31	1.03	0.01
25	0.34	0.57	–0.23	0.66	–0.32
26	0.38	0.74	–0.36	0.66	–0.28
27	0.95	–0.27	1.22	0.66	0.29
28	1.88	1.63	0.25	2.07	–0.19
29	1.07	0.75	0.32	0.66	0.40
30	1.01	0.75	0.26	0.66	0.35
31	0.78	0.75	0.03	0.66	0.11
32	0.52	1.03	–0.51	0.66	–0.14
33	1.81	2.42	–0.62	1.99	–0.18
34	0.60	1.22	–0.62	0.66	–0.06
35	2.75	2.02	0.73	2.94	–0.19
36	2.00	2.41	–0.40	2.38	–0.38
37	2.00	2.77	–0.77	1.90	0.11
38	2.00	2.68	–0.68	1.84	0.16
39	0.26	1.21	–0.95	0.66	–0.40
40	0.42	1.05	–0.63	0.66	–0.24
41	0.42	0.89	–0.47	0.66	–0.25
42	0.85	1.20	–0.35	0.66	0.19
43	0.47	1.20	–0.74	0.66	–0.20
44	1.44	1.33	0.11	1.15	0.29
45	0.37	0.90	–0.53	0.66	–0.30
46	0.57	0.88	–0.31	0.66	–0.09
47	2.00	2.25	–0.25	2.14	–0.13
48	2.00	2.14	–0.14	2.13	–0.13
49	2.00	2.14	–0.13	2.08	–0.07
50	1.02	1.50	–0.48	0.96	0.06
51	2.00	2.41	–0.41	1.83	0.18
52	2.00	1.47	0.53	1.80	0.20
53	2.00	2.41	–0.41	1.84	0.17
54	1.04	1.33	–0.29	1.15	–0.11
55	0.60	1.22	–0.62	0.65	–0.05

Table 4: Observed and Estimated log(1/C) values of NMDA Inhibitors (Test Set) from the regression equations EQ1(MLR) and EQ2 (GFA)

		Linear		GFA	
No.	$logIC_{50}$ (Obs)	$logIC_{50}$ (Calc)	Residuals	$logIC_{50}$ (Calc)	Residuals
01	1.59	1.91	–0.32	1.57	0.02
02	2.00	2.40	–0.40	1.98	0.03
03	3.35	2.42	0.93	3.39	–0.05
04	1.56	2.25	–0.69	1.47	0.09
05	1.54	1.83	–0.29	1.57	–0.03
06	3.48	2.58	0.89	3.48	0.00
07	1.45	1.29	0.15	1.57	–0.12
08	1.63	1.35	0.28	1.57	0.06
09	1.51	1.72	–0.21	1.57	–0.06
10	2.91	3.26	–0.34	2.84	0.07
		Linear		GFA	
	R^2	0.544		0.993	
	Q^2	0.318		0.990	

4. Conclusions

The present 2D-QSAR study related to NMDA inhibitors leads us to make the following conclusions:

(i) Of the two methods of correlations, namely MLR and GFA, GFA proved to be better in its predicting ability.

(ii) In MLR as well as GFA case of uni-variate analysis, Randic index ($^1\chi_R$) showed the best correlation, even though its predicting power was comparatively very poor in MLR.

(iii) The best correlation was obtained with the multivariate correlation, i.e. all the indices combined together, where the prediction power was very high for GFA ($R^2 = 0.932$ and $Q^2 = 0.923$) but was comparatively lower in the case of MLR ($R^2 = 0.566$, $Q^2 = 0.429$).

(iv) The results of the test set support the findings.

On the basis of the results obtained from these studies, it is evident that GFA should be used in preference to MLR for performing statistical analysis which will help in predicting the properties of novel molecules and thus novel molecules could be designed possessing better biological/inhibitory activity.

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6. References

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Povzetek

Opravljena je bila primerjalna raziskava uporabe dvodimenzionalnega modeliranja povezav med kemijsko strukturo in biološko aktivnostjo (2D-QSAR) na primeru N-metil-D-aspartatnih (NMDA) inhibitorjev. V študiji smo primerjali modeliranje z uporabo genetske funkcijske aproksimacije (GFA) in multiple linearne regresije (MLR). Za opis kemijske struktur smo uporabili topološke povezovalne indekse in indekse razdalj (Wienerjev, Balabanov, in Randićev indeks). Z izdelanimi modeli smo napovedovali inhibicijske sposobnosti testnega podatkovnega seta. GFA metoda generira boljše 2D QSAR modele tako pri modeliranju ob uporabi ene kot tudi večih spremenljivk. V študiji smo primerjali tudi modelirne sposobnosti posameznih indeksov. V vseh primerih (Wienerjev, Balabanov, Randićev indeks) smo dobili dobre korelacijske parametre ($R^2 > 0.80$, $Q^2 > 0.79$) ob uporabi GFA tehnike, medtem ko je MLR tehnika dala slabše korelacije ($R^2 < 0.60$, $Q^2 < 0.55$). Med tremi indeksi je najboljši 2D-QSAR model za napovedovanje aktvnosti NMDA inhibitorjev dal Randićev indeks ($R^2 = 0.89$, $Q^2 = 0.88$, F-ratio = 216).