2D QSAR STUDY OF FUSED 5,6-BICYCLIC HETEROCYCLES AS ANTI ALZHEIMER'S AGENTS USING TOPOLOGICAL PARAMETERS

S.K. MISRA[*#], *PRITI SINGH*[*], *R.K. SINGH*[**], *G.K. SRIVASTAV*[***]

[*]Department of Chemistry, K.S. Saket P.G. College, Ayodhya, U.P., India,
[#]e-mail: pandit543sanjay@gmail.com
[**]Department of Chemistry, M.L.K. P.G. College, Balrampur, U.P., India
[***]Department of Chemistry, Shri Lal Bahadur Shastri Degree College, Gonda, U.P., India

Abstract. Alzheimer's disease (AD) is a degrading and irreversible neurodegenerative disorder associated with loss of brain functions. It is manifested clinically into psychological symptoms that collectively form cognitive dysfunction and the loss of thinking skills through the progressive degeneration of central nervous system neurons. Over the last decade, γ-secretase emerged as a promising target for the treatment of Alzheimer's disease. The γ-secretase modulator compounds would be good candidates for AD therapeutics. In previous years, a series fused 5,6-bicyclic heterocycles were investigated as γ-secretase modulators or anti Alzheimer's agents. In the present study, a quantitative structure activity relationship (QSAR) study of twenty-eight derivatives of fused 5,6-bicyclic heterocycles has been made with the help of topological parameters. The descriptors that have been used are solvent accessible surface area, valence connectivity indices of order 0, 1 and 2 and shape indices of order 1, 2 and 3. The best QSAR model for this set of derivatives has been obtained by using solvent accessible surface area as first descriptor, valence connectivity index (order-0) as second descriptor, valence connectivity index (order-1) as third descriptor and shape index (order-3) as fourth descriptor. The correlation coefficient (r^2) and cross validation coefficient (rCV^2) for this model are 0.773037 and 0.688568, respectively.

Key words: Anti Alzheimer's agents, solvent accessible surface area (*SASA*), valence connectivity indices, shape indices.

INTRODUCTION

In QSAR study, topological parameters gained much importance in recent years [15, 20, 23]. Topological descriptors take into account the internal atomic arrangement of compounds. They encode the information about molecular size, shape, branching, presence of heteroatom, multiple bonds etc. in numerical form [8]. Topological descriptors were successfully used in the QSAR study of various set of compounds [6, 7, 27, 32, 33, 38]. In this paper, topological descriptors have been used for the QSAR

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study of twenty-eight derivatives of fused 5,6-bicyclic heterocycles as anti Alzheimer's agents. Alzheimer's disease is a neurodegenerative disease that usually starts slowly and progressively worsens through the progressive degeneration of central nervous system neurons. As the disease advances, symptoms can include dementia, delusions, cognitive dysfunction, failure of thinking skills, disorientation (including easily getting lost), mood swings, loss of motivation, self-neglect, and behavioral issues [10, 11, 16, 25, 29, 31, 36,]. The disease process is largely associated with amyloid plaques, neurofibrillary tangles, and loss of neuronal connections in the brain [5, 9, 18, 26, 34]. Over the last decade, γ-secretase emerged as a promising target for the treatment of Alzheimer's disease [37]. γ-secretase modulation is more desirable than inhibition from a medical perspective and may reduce the risk of mechanism-based toxicities [21]. The γ-secretase modulator compounds would be good candidates for AD therapeutics [17]. In previous years, a series of fused 5,6-bicyclic heterocycles were investigated as γ-secretase modulators or anti Alzheimer's agents [3, 12]. An interest is created to understand the structural features of fused 5,6-bicyclic heterocycles responsible for their biological activity as anti Alzheimer's agents which can be helpful for designing potent novel derivatives. Quantitative structure activity relationship (QSAR) studies leading to models in terms of chemical structures and their biological activities produce useful information for drug design [35]. The QSAR methods provide information that how to improve performance by altering chemical structures of ligands [1, 28].

In the research work of K.S. Bhadoriya *et al.*, a 3D QSAR study of fused 5,6-bicyclic heterocycles were successfully made by using *k*-nearest neighbor molecular field (kNN-MFA) analysis [3]. In another research work by Boukarai *et al.*, a QSAR study of 5, 6-bicyclic heterocycles analogues have been made by using the statistical analysis methods [4]. They have calculated the descriptors molecular weight, molar refractivity, molar volume, parachor, refractive index, surface tension, density, polarizability, etc. for their study.

In the present study, a 2D QSAR study of twenty-eight derivatives of fused 5,6-bicyclic heterocycles has been made with the help of topological parameters. The descriptors that have been used are solvent accessible surface area (*SASA*), valence connectivity indices of order 0, 1 and 2 and shape indices of order 1, 2 and 3. In the present work, the predicted activities obtained from developed QSAR models were found close to reported observed activities. The developed QSAR models will provide guidance to design and synthesize novel anti Alzheimer's agents with increased biological activity than the reported compounds.

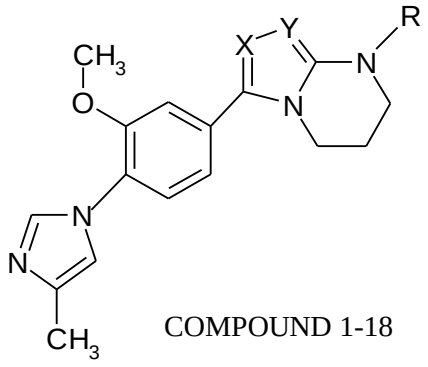
MATERIALS AND METHODS

Twenty-eight derivatives of fused 5,6-bicyclic heterocycles, listed in Table 1, are used as study material. Their observed biological activity is in terms of $A\beta_{42}$

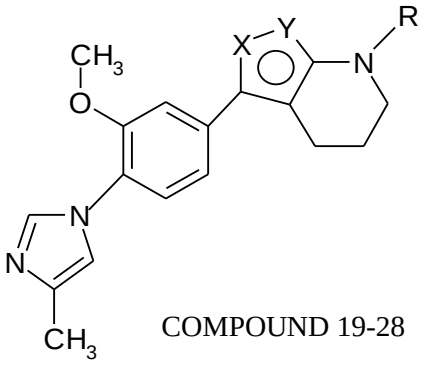
inhibitory activity ($A\beta_{42}pIC_{50}$). The geometry optimization of all the compounds has been done with the help of CAChe Pro software developed by Fujitsu Corporation of Japan, using density functional theory [22] method. Evaluation of values of descriptors has been done with the help of same software. The QSAR models have been developed by multi linear regression (MLR) analysis with the help of Project Leader program associated with CAChe Pro. The descriptors that have been used are described below.

Table 1

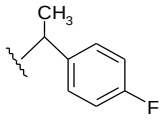
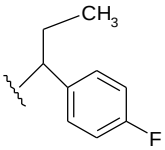
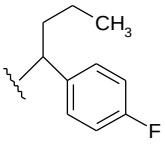
Chemical structures of fused 5,6-bicyclic heterocycles as γ-secretase modulators with $A\beta_{42}$ inhibitory activities

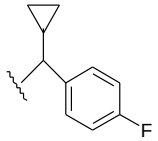
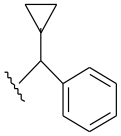
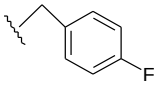
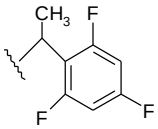
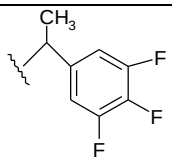
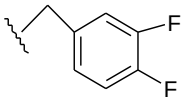
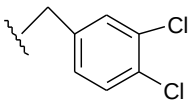
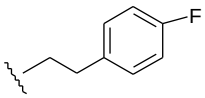
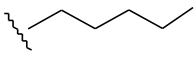
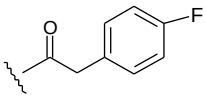


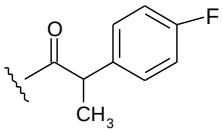
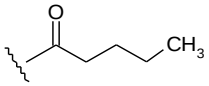
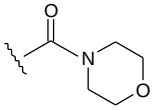
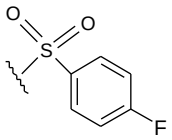
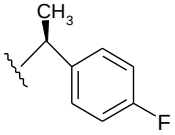
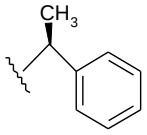
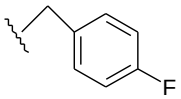
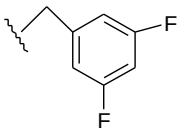
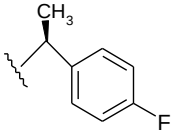
COMPOUND 1-18

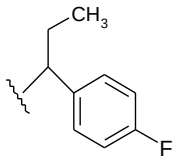
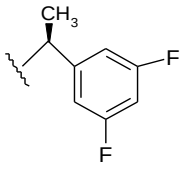
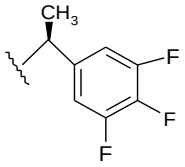
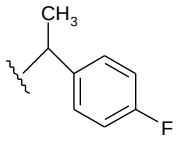
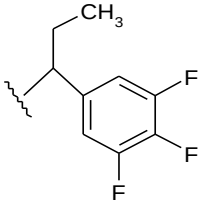


COMPOUND 19-28

Compound No.	R	X	Y	Observed activity ($A\beta_{42}pIC_{50}$) (nM)
1	H	N	N	4.70
2		N	N	6.29
3		N	N	6.81
4		N	N	6.84

5		N	N	4.79
6		N	N	4.70
7		N	N	6.19
8		N	N	6.47
9		N	N	6.94
10		N	N	6.26
11		N	N	6.90
12		N	N	6.21
13		N	N	5.85
14		N	N	5.72

15		N	N	6.31
16		N	N	5.68
17		N	N	4.70
18		N	N	5.65
19		O	N	6.33
20		O	N	6.27
21		O	N	6.45
22		O	N	6.36
23		N	O	6. 35

24		N	O	6.06
25		N	O	6.03
26		N	O	6.27
27		N	NH	6.79
28		N	NH	6.70

R is a group attached to nitrogen of cyclohexane ring, X and Y are heteroatoms, and $A\beta_{42}$ pIC_{50} is the negative logarithm of half maximal inhibitory concentration (IC_{50}) for amyloid β_{42}.

SOLVENT ACCESSIBLE SURFACE AREA (*SASA*)

Solvent accessible surface area is a measure of how much of the area of a molecule is available to the solvent. Solvent accessible surface area is designated as the region of the molecule surface exposed enough to be able to interact with solvent molecules. Lee and Richards first described the solvent accessible surface area of a molecular surface [19]. *SASA* is generally calculated by using the "rolling ball"

algorithm developed by Sharke and Rupley [2, 30]. This algorithm uses a sphere of solvent of a particular radius to probe the surface of the molecule. Using a smaller probe radius detects more surface details. Generally, the probe radius value used is 1.4 Å, which is approximately the radius of a water molecule.

VALENCE CONNECTIVITY INDICES

Valence connectivity indices are calculated as follows [24]:

$$^{m}\chi^{v} = \sum_{i=1}^{N_s} \prod_{k=1}^{m+1} \left[\frac{1}{\delta_k^v}\right]^{1/2} \quad (1)$$

where $\delta_k^v = \frac{Z_k^v - H_k}{Z_k - Z_k^v - 1}$ is the valence connectivity for the *k*-th atom in the molecular graph, Z_k = the total number of electrons in the *k*-th atom, Z_k^v = the number of valence electrons in the *k*-th atom, H_k = the number of hydrogen atoms directly attached to the *k*-th non-hydrogen atom, *m* = 0 - atomic valence connectivity indices (called order-0), *m* = 1 - one bond path valence connectivity indices (called order-1), *m* = 2 - two bond fragment valence connectivity indices (called order-2).

SHAPE INDICES [13, 14]

The first order shape index (κ_1) is given by:

$$\kappa_1 = \frac{A(A-1)^2}{(^1P)^2} \quad (2)$$

where, ^iP = length of paths of bond length *i* in the hydrogen suppressed molecule and *A* is the number of non hydrogen atoms in the molecule.

The second order kappa shape index (κ_2) is given by:

$$\kappa_2 = \frac{(A-1)(A-2)^2}{(^2P)^2} \quad (3)$$

The third order kappa shape index (κ_3) is given by:

$$\kappa_3 = \frac{(A-1)(A-3)^2}{(^3P)^2} \text{ if } A \text{ is odd} \quad (4a)$$

$$\kappa_3 = \frac{(A-3)(A-2)^2}{(^3P)^2} \text{ if } A \text{ is even} \quad (4b)$$

RESULTS

Twenty-eight fused 5,6-bicyclic heterocycles are given in Table 1 along with their biological activity in terms of pIC_{50}. The values of calculated seven descriptors are given in Table 2. Different combinations of descriptors have been used in the multi linear regression (MLR) analysis for the development of QSAR models. In the development of QSAR models the values of pIC_{50} of the compounds were taken as dependent variable and the seven descriptors were taken as independent variables. Compound numbers 14, 17 and 27 are outliers in the MLR analysis. Various QSAR models, with reliable predictive power, have been developed but only best five models are reported here.

Table 2

Values of descriptors and experimental activity of fused 5,6-bicyclic heterocycles

C. No.	*SASA* (Å^2)	$^0\chi$	$^1\chi$	$^2\chi$	κ_1	κ_2	κ_3	Bio act. (nM)
1	329.646	13.152	7.625	5.588	16.467	7.0870	3.254	4.70
2	443.813	18.364	10.696	8.059	23.728	10.318	4.898	6.29
3	458.497	19.071	11.234	8.307	24.684	10.948	5.120	6.81
4	472.687	19.779	11.734	8.687	25.641	11.588	5.496	6.84
5	460.421	19.356	11.768	9.165	24.343	10.401	4.721	4.79
6	454.346	19.055	11.669	9.024	23.402	10.166	4.500	4.70
7	428.223	17.494	10.242	7.686	22.776	10.092	4.940	6.19
8	453.394	18.966	10.907	8.290	25.641	10.776	5.086	6.47
9	456.376	18.966	10.907	8.306	25.641	10.776	5.086	6.94
10	437.309	17.795	10.347	7.808	23.728	10.318	5.035	6.26
11	457.409	19.307	11.103	8.622	23.728	10.318	5.035	6.90
12	450.084	18.201	10.742	8.001	23.728	10.727	5.327	6.21
13	425.583	16.928	10.085	7.332	21.240	9.871	4.694	5.85
14	451.391	18.402	10.707	7.986	24.684	10.948	5.404	5.72
15	466.108	19.273	11.154	8.401	25.641	11.171	5.354	6.31
16	425.442	17.129	10.050	7.287	22.203	10.080	4.769	5.68
17	427.218	17.692	10.423	7.671	22.776	10.092	4.666	4.70
18	445.122	18.828	11.732	9.531	24.684	10.166	4.857	5.65
19	444.268	18.378	10.749	8.147	23.728	10.318	4.898	6.33
20	436.011	18.078	10.649	8.006	22.776	10.092	4.666	6.27
21	431.808	17.508	10.295	7.774	22.776	10.092	4.940	6.45

22	439.385	17.809	10.394	7.926	23.728	10.318	5.178	6.36
23	441.263	18.378	10.749	8.148	23.728	10.318	4.898	6.35
24	453.458	19.085	11.287	8.396	24.684	10.948	5.120	6.06
25	451.147	18.679	10.849	8.300	24.684	10.546	5.120	6.03
26	457.090	18.979	10.960	8.395	25.641	10.776	5.086	6.27
27	443.298	18.470	10.836	8.233	23.728	10.318	4.898	6.79
28	471.304	19.778	11.585	8.728	26.601	11.396	5.307	6.70

where: ${}^0\chi$ = valence connectivity index (order-0), ${}^1\chi$ = valence connectivity index (order-1), ${}^2\chi$ = valence connectivity index (order-2), κ_1 = shape index (order-1), κ_2 = shape index (order-2), κ_3 = shape index (order-3), biological activity is $A\beta_{42}pIC_{50}$.

FIRST BEST QSAR MODEL

The best QSAR model is obtained by using *SASA* as first descriptor, valence connectivity index (order-0) as second descriptor, valence connectivity index (order-1) as third descriptor and shape index (order-3) as fourth descriptor. This QSAR model is given by the following regression equation.

$$PA1 = -0.0366132 \times SASA + 1.24061 \times {}^0\chi - 1.17597 \times {}^1\chi + 1.64332 \times \kappa_3 + 4.2007$$
$$r^2 = 0.773037, rCV^2 = 0.688568, SEE = 0.3052, P - Value = 0 \quad (5)$$

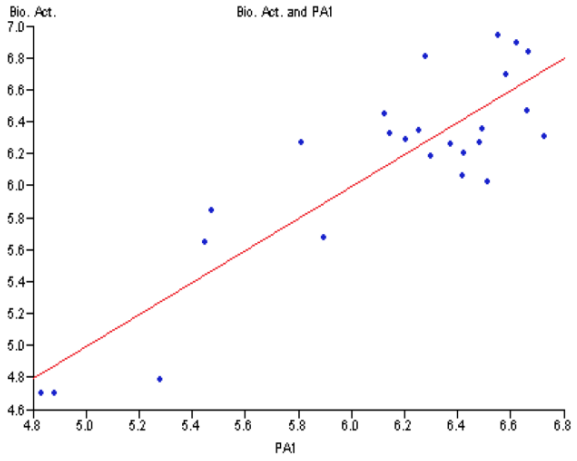


Fig. 1. Trend of observed activity and predicted activity *PA*1 of fused 5,6-bicyclic heterocycles.

In the regression equation (5), r^2 is the correlation coefficient, rCV^2 is the cross-validation coefficient, and *SEE* is the standard error of estimate. The value of r^2 is sufficiently higher than 0.5 which is the essential condition for the validity of a QSAR model. Values of correlation coefficient and cross validation coefficient indicate that this model has excellent predictive power. The predicted activities (*PA1*) obtained from above MLR equation are given in Table 3. The trend of observed activity versus predicted activity (*PA1*) is illustrated in Figure 1.

SECOND BEST QSAR MODEL

The second best QSAR model is obtained by following regression equation,

$$PA2 = -0.0557385 \times SASA + 1.26073 \times {}^{0}\chi - 0.805412 \times {}^{2}\chi + 1.88556 \times \kappa_3 + 5.01234$$
$$r^2 = 0.773037, rCV^2 = 0.688568, SEE = 0.3052, P - Value = 0 \quad (6)$$

The above QSAR model is obtained by using *SASA* as first descriptor, valence connectivity index (order-0) as second descriptor, valence connectivity index (order-2) as third descriptor and shape index (order-3) as fourth descriptor. Values of r^2 and rCV^2 for this QSAR model are high, which indicate that this regression model has good predictive power. The values of predicted activities (*PA*2) obtained from above regression equation are given in Table 3.

THIRD BEST QSAR MODEL

The third best QSAR model is obtained by following regression equation,

$$PA3 = 0.80755 \times {}^{0}\chi - 1.30203 \times {}^{1}\chi - 0.233064 \times \kappa_2 + 1.28386 \times \kappa_3 + 1.45156$$
$$r^2 = 0.741231, rCV^2 = 0.640239, SEE = 0.3257, P - value = 0 \quad (7)$$

The above QSAR model is obtained by descriptors valence connectivity index (order-0), valence connectivity index (order-1), shape index (order-2) and shape index (order-3). Values of r^2 and rCV^2 for this QSAR model indicate that this regression model has good predictive power. The predicted activities (*PA*3) obtained from above MLR equation are given in Table 3.

FOURTH BEST QSAR MODEL

The fourth best QSAR model is obtained by using valence connectivity index (order-0) as first descriptor, valence connectivity index (order-1) as second descriptor,

shape index (order-1) as third descriptor and shape index (order-3) as fourth descriptor. This QSAR is obtained by following regression equation,

$$PA4 = 0.845512 \times {}^{0}\chi - 1.35222 \times {}^{1}\chi - 0.0651019 \times \kappa_1 + 1.09922 \times \kappa_3 + 1.33886$$
$$r^2 = 0.741051, rCV^2 = 0.523271, SEE = 0.3259, P - Value = 0 \quad (8)$$

Values of correlation coefficient and cross validation coefficient indicate that this model has good predictive power. The predicted activities (*PA*4) obtained from above MLR equation are given in Table 3.

FIFTH BEST QSAR MODEL

The fifth best QSAR model is obtained by following regression equation,

$$PA5 = 0.744291 \times {}^{0}\chi - 1.30263 \times {}^{1}\chi + 1.02035 \times \kappa_3 + 1.4981$$
$$r^2 = 0.738063, rCV^2 = 0.63017, SEE = 0.3278, P - Value = 0 \quad (9)$$

The above QSAR model is obtained by using valence connectivity index (order-0) as first descriptor, valence connectivity index (order-1) as second descriptor, and shape index (order-3) as third descriptor. The values of predicted activities (*PA*5) obtained from above regression equation are given in Table 3.

Table 3

Observed and predicted activities of fused 5,6-bicyclic heterocycles

C. No.	Bio. Act. (nM)	*PA*1 (nM)	*PA*2 (nM)	*PA*3 (nM)	*PA*4 (nM)	*PA*5 (nM)
1	4.70	4.828	4.854	4.670	4.653	4.675
2	6.29	6.205	6.172	6.239	6.242	6.231
3	6.81	6.276	6.463	6.247	6.294	6.283
4	6.84	6.665	6.968	6.501	6.567	6.542
5	4.79	5.276	5.272	5.397	5.396	5.392
6	4.70	4.878	4.928	5.054	5.094	5.072
7	6.19	6.299	6.323	6.234	6.228	6.218
8	6.47	6.662	6.565	6.585	6.547	6.596
9	6.94	6.552	6.386	6.585	6.547	6.596
10	6.26	6.372	6.277	6.409	6.383	6.402
11	6.90	6.623	6.407	6.646	6.639	6.543
12	6.21	6.424	6.472	6.502	6.513	6.488
13	5.85	5.474	5.578	5.717	5.791	5.750
15	6.31	6.727	6.659	6.763	6.768	6.776
16	5.68	5.893	6.017	5.972	6.028	6.022
18	5.65	5.447	5.421	5.247	5.126	5.185
19	6.33	6.143	6.093	6.181	6.182	6.172

20	6.27	5.810	5.851	5.824	5.870	5.843
21	6.45	6.123	6.070	6.176	6.168	6.159
22	6.36	6.494	6.354	6.543	6.489	6.497
23	6.35	6.253	6.260	6.181	6.182	6.172
24	6.06	6.416	6.690	6.189	6.234	6.224
25	6.03	6.512	6.384	6.526	6.483	6.493
26	6.27	6.480	6.291	6.526	6.487	6.537
28	6.70	6.579	6.654	6.497	6.498	6.543

DISCUSSIONS

All the top five developed QSAR models are reliable with excellent predictive power. All these models have the value of correlation coefficient (r^2) greater than 0.7. The maximum variable count in these models is four i.e. in MLR equations the maximum number of descriptor used is four. From our study, we can conclude that the anti Alzheimer's activity of fused 5,6-bicyclic heterocycles can be successfully modeled by the combination of three and four calculated topological descriptors. In the previous QSAR studies performed on the same set of compounds [4], the value of correlation coefficient (r^2) is greater than 0.8 using variable count seven i.e., in their work seven descriptors were used to built MLR equation. Also, in all of the top five QSAR models the descriptors valence connectivity index (order-0) and shape index (order-3) are present with positive contribution which means an increase in the value of either of descriptors increases the value of biological activity.

CONCLUSIONS

It is clear from the above study that the best combination of topological descriptors is *SASA*, valence connectivity index (order-0), valence connectivity index (order-1) and shape index (order-3) for the QSAR study of fused 5,6-bicyclic heterocycles as anti Alzheimer's agents. This model, due to its high predictive power, can be used to find the activity of any new derivative of this class of compound. Also, in all of the top five QSAR models the descriptors valence connectivity index (order-0) and shape index (order-3) are present with positive contribution.

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