DENSITY FUNCTIONAL THEORY-BASED STUDY OF FUSED 5, 6-BICYCLIC HETEROCYCLES AS ANTI-ALZHEIMER'S AGENTS USING QUANTUM MECHANICAL DESCRIPTORS

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Abstract. Alzheimer's disease (AD) is a neurodegenerative disease which starts slowly and gradually worsens by the progressive degeneration of central nervous system neurons. As the disease advances, symptoms appear such as dementia, delusions, failure of thinking skills, cognitive dysfunction, mood swings, self-neglect, loss of motivation and behavioral issues. The γ-secretase modulator compounds emerged as better option for the treatment of Alzheimer's disease in recent years. In our study, density functional theory (DFT) based quantum mechanical descriptors have been used for the quantitative structure activity relationship (QSAR) study of twenty-eight derivatives of fused 5,6-bicyclic heterocycles as anti-Alzheimer's agents. The descriptors dipole moment, total energy, conformation minimum energy, ionization potential, electron affinity, heat of formation and electrophilicity index were used in our study. The value of the coefficient of determination (r^2) and cross validation coefficient (rCV^2) for the best QSAR model of this set of compounds is 0.846104 and 0.734673 respectively. The best QSAR model has been obtained by using descriptors dipole moment, total energy, conformation minimum energy and ionization potential.

Key words: Anti-Alzheimer's agents, DFT, dipole moment, total energy, ionization potential.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease which progressively degenerates central nervous system neurons. AD develops many psychological and behavioral problems such as dementia, delusions, failure of thinking skills, cognitive dysfunction, mood swings, self-neglect, loss of motivation, etc. [2, 4, 6, 7, 13, 19, 30]. AD is mainly related with amyloid plaques, neurofibrillary tangles, and loss of neuronal connections in the brain [8, 9, 10, 28, 29, 33]. The γ-secretase modulator compounds emerged as better option for the treatment of AD in recent years [15, 18, 31, 32]. The γ-secretase modulator compounds are better than inhibitory compounds

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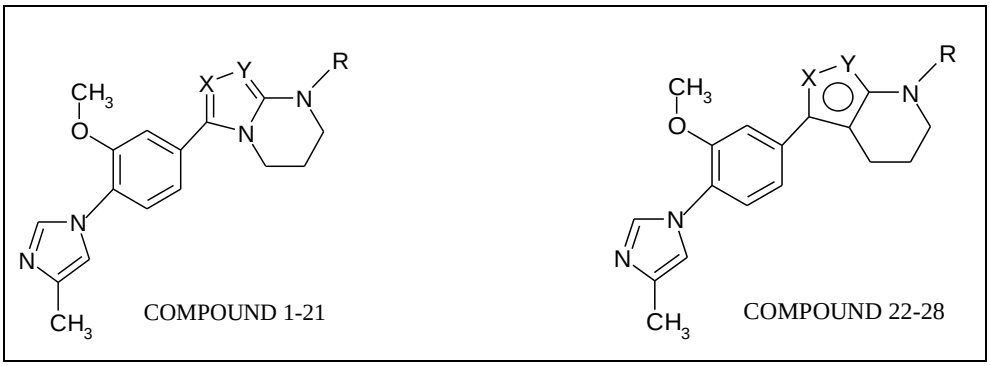
as they reduce the risk of toxicities [11, 16, 23]. In previous years, a series of fused 5, 6-bicyclic heterocycles as γ-secretase modulators or anti-Alzheimer's agents were investigated [3, 12]. The structural features of fused 5,6-bicyclic heterocycles responsible for their biological activity as anti-Alzheimer's agents can be understood with the help of Quantitative Structure Activity Relationship (QSAR) studies. QSAR study provides models in terms of chemical structures and their biological activities. These models produce useful information for drug design [22]. The QSAR methods provide information about how we can improve the biological activity of a series of compounds by altering their chemical structures [1, 27].

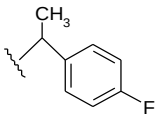
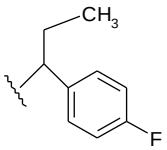
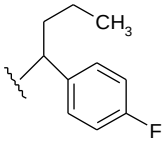
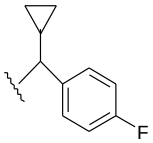
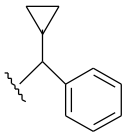
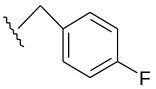
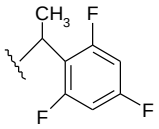
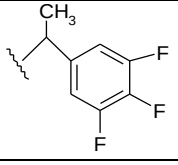
In our previous work [21], a 2D QSAR study has been made with the help of topological parameters for the twenty-eight derivatives of fused 5,6-bicyclic heterocycles as anti-Alzheimer's agents. In that study, the solvent accessible surface area (SASA), valence connectivity indices of order 0, 1 and 2 and shape indices of order 1, 2 and 3 were used as descriptors.

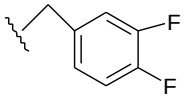
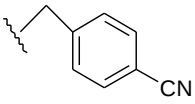
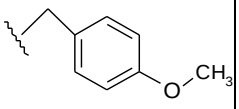
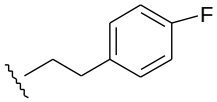
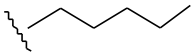
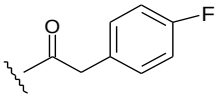
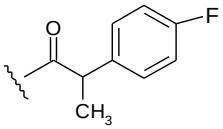
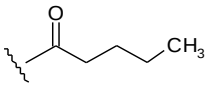
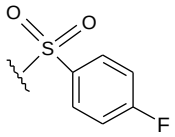
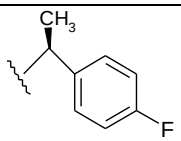
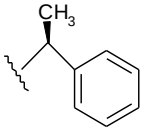
In the present work, DFT based quantum mechanical descriptors have been used for the 2D QSAR study of twenty-eight derivatives of fused 5,6-bicyclic heterocycles as anti-Alzheimer's agents. Quantum mechanical descriptors were successfully used in the QSAR study of various sets of compounds [14, 17, 20, 24]. The descriptors that have been calculated in the present work are the following: the dipole moment, total energy, conformation minimum energy, ionization potential, electron affinity, heat of formation and electrophilicity index. The predicted activities obtained from the developed QSAR models were found close to the observed biological activities. The developed QSAR models will help to design and synthesize novel 5,6-bicyclic heterocycles as anti-Alzheimer's agents with better biological activity.

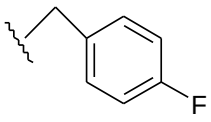
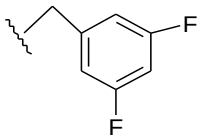
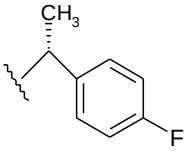
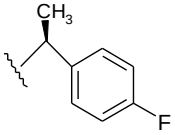
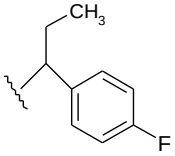
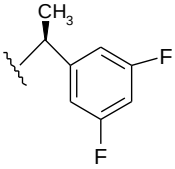
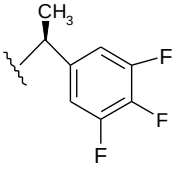
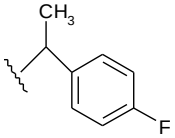
Table 1

Structures of fused 5,6-bicyclic heterocycles as anti-Alzheimer's agents with observed biological activities in terms of $A\beta_{42}pIC_{50}$



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	5.60
12		N	N	5.85
13		N	N	6.21
14		N	N	5.85
15		N	N	5.72
16		N	N	6.31
17		N	N	5.68
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	5.86
24		N	O	6. 35
25		N	O	6.06
26		N	O	6.03
27		N	O	6.27
28		N	NH	6.79

where R, X and Y represent the different functional groups or atoms in the general basic skeleton of the set of compounds under study.

MATERIALS AND METHODS

Twenty-eight derivatives of fused 5,6-bicyclic heterocycles, with $A\beta_{42}$ inhibitory activity, are used as study material. These derivatives are listed in Table 1 with their observed biological activity in terms of $A\beta_{42}$ inhibitory activity ($A\beta_{42}pIC_{50}$). The geometry optimization of all the compounds has been done by DFT method with the help of CAChe Pro software developed by Fujitsu Corporation of Japan. The values of descriptors have also been evaluated with the help of the same software using DFT-B88-LYP method with DZVP basis set. The density functional theory (DFT) is a quantum mechanical method based on electron density rather than the wave function. The B88-LYP functional is a GGA (generalized gradient approximation) functional made by combining Becke's 1988 exchange functional and Lee-Yang-Parr correlation functional. The double zeta valence polarized (DZVP) basis set ensures a balanced description of valence electron density and polarization effects. Multi linear regression (MLR) analysis has been performed to develop QSAR models with the help of Project Leader program of CAChe Pro software. The descriptors used are described below.

DESCRIPTOR DEFINITIONS

Dipole moment: A molecule consists of several atoms. Each pair of atoms will have a bond dipole moment due to chemical bonding, represented by magnitude and direction. The overall dipole moment of a molecule will depend upon the magnitude and direction of the individual bond dipole moments. Therefore, the net dipole moment is the vector addition of the individual moments,

$$\boldsymbol{\mu} = \sum q_i \cdot \boldsymbol{r}_i \tag{1}$$

where, $\boldsymbol{\mu}$ is dipole moment of the molecule, q_i is the charge on i^{th} atom and $\boldsymbol{r}_i$ is the position vector representing the position of the i^{th} atom.

Total energy, TE, of a molecular system is the sum of the total electronic energy, E_{ee}, and the energy of inter nuclear repulsion, E_{nr} [25].

$$TE = E_{\text{ee}} + E_{\text{nr}} \tag{2}$$

The total electronic energy of the system is given by

$$E_{\text{ee}} = \frac{1}{2\,\boldsymbol{P}(\boldsymbol{H}+\boldsymbol{F})} \tag{3}$$

where $\boldsymbol{P}$ is the density matrix, $\boldsymbol{H}$ is the one-electron matrix, and $\boldsymbol{F}$ is the Fock matrix.

The heat of formation is defined as:

$$\Delta H_{\text{f}} = E_{\text{elect}} + E_{\text{nuc}} - E_{\text{isol}} + E_{\text{atom}} \tag{4}$$

where E_{elect} is the electronic energy, E_{nuc} is the nuclear-nuclear repulsion energy, E_{isol} is the energy required to strip all the valence electrons of all the atoms in the system and E_{atom} is the total heat of atomization of all the atoms in the system [5].

The conformation minimum energy (*CME*) is the energy calculated for an optimized conformation of the chemical sample.

The ionization potential (*IP*) is the energy required to remove an electron from a molecule in its ground state.

The electron affinity (*EA*) is the change in the total energy of a molecule when an electron is added.

Parr *et al*. introduced the electrophilicity index (ω) in terms of the chemical potential (μ_c) and hardness (η) [26]. The operational definition of the electrophilicity index is given by:

$$\omega = \frac{\mu_c^2}{2 \cdot \eta}. \tag{5}$$

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 the corresponding calculated descriptors are given in Table 2. Different combinations of descriptors have been used in the multiple 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 variables and the seven descriptors were taken as independent variables. Various QSAR models, with reliable predictive power, have been developed but only the best five models are reported here.

Table 2

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

C. No.	μ (debye)	*TE* (hartree)	ΔH_f (kcal/mol)	*CME* (eV)	*IP* (eV)	*EA* (eV)	ω (eV)	Bio. act. (nM)
1	8.392	–166.185	68.399	2.153	4.641	1.779	7.201	4.70
2	7.363	–232.549	46.684	–9.495	4.547	1.786	7.268	6.29
3	7.120	–239.698	40.245	–7.919	4.570	1.793	7.290	6.81
4	7.461	–246.867	37.372	–8.940	4.498	1.766	7.181	6.84
5	7.460	–245.312	76.602	261.607	4.504	1.776	7.228	4.79

6	8.221	–229.397	119.163	261.939	4.455	1.770	7.211	4.70
7	7.653	–225.381	49.962	–10.238	4.501	1.788	7.289	6.19
8	7.395	–264.361	–34.789	–27.008	4.557	1.825	7.454	6.47
9	5.537	–264.376	–39.123	–1.854	4.646	1.896	7.781	6.94
10	8.222	–241.307	7.810	–4.998	4.558	1.822	7.439	6.26
11	7.048	–222.273	129.998	–9.701	4.754	2.364	10.600	5.60
12	9.049	–228.861	56.682	–9.755	4.513	1.742	7.055	5.85
13	7.811	–232.556	45.542	–7.859	4.522	1.795	7.316	6.21
14	8.021	–201.939	45.234	1.934	4.412	1.717	6.970	5.85
15	9.450	–242.872	16.521	–20.227	4.795	1.966	82.084	5.72
16	9.208	–250.053	11.342	–17.059	4.790	2.039	8.482	6.31
17	10.207	–212.276	11.119	–12.307	4.830	2.026	8.382	5.68
18	10.566	–252.069	–2.906	5.464	4.704	2.549	12.215	5.65
19	3.111	–233.061	24.424	7.205	4.871	1.987	8.154	6.33
20	4.524	–217.149	67.952	7.379	4.834	1.950	7.979	6.27
21	3.830	–225.909	28.125	6.787	4.816	2.047	8.506	6.45
22	3.615	–241.821	–13.802	4.468	4.888	2.030	8.373	6.36
23	6.865	–233.062	25.757	6.408	4.646	1.835	7.466	6.35
24	6.918	–240.216	21.663	6.765	4.598	1.821	7.414	6.06
25	6.872	–248.972	–17.257	5.419	4.753	1.905	7.782	6.03
26	6.665	–264.878	–59.203	14.090	4.808	1.938	7.928	6.27
27	7.098	–230.437	38.455	–9.701	4.418	1.499	5.993	6.79
28	5.281	–269.419	–51.414	–1.715	4.532	1.619	6.490	6.70

where, μ = dipole moment, TE = total energy, ΔH_f = heat of formation, *CME* = conformation minimum energy, *IP* = ionization potential, EA = electron affinity, ω = electrophilicity index.

FIRST BEST QSAR MODEL

The best QSAR model is obtained by using dipole moment as first descriptor, total energy as second descriptor, conformation minimum energy as third descriptor and ionization potential as fourth descriptor. This QSAR model is given by the following regression equation:

$$PA_1 = -0.141971 \times \mu - 0.0130116 \times TE - 0.00598068 \times CME - 1.2103 \times IP + 9.74867$$

$$r^2 = 0.846104 \qquad rCV^2 = 0.734673 \qquad (6)$$

In the above regression equation, r^2 is the coefficient of determination and $rCV^2$is the cross-validation coefficient. The value of r^2 is sufficiently higher than 0.5, which is the essential condition for the validity of a QSAR model. The values of the coefficient of determination and cross validation coefficient indicate that this model has excellent predictive power. The predicted activities (PA_1) obtained from the above MLR equation are given in Table 3.

SECOND BEST QSAR MODEL

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

$$PA_2 = -0.102092 \times \mu - 0.0136645 \times TE - 0.00563633 \times CME - 0.7591 \times EA + 5.11785$$

$$r^2 = 0.838147 \qquad rCV^2 = 0.723063 \qquad (7)$$

The above QSAR model is obtained by using dipole moment as first descriptor, total energy as second descriptor, *CME* as third descriptor, and electron affinity as fourth descriptor. The values of r^2 and rCV^2 for this QSAR model are high, which indicates that this regression model has good predictive power. The values of predicted activities (PA_2) obtained from the above regression equation are given in Table 3.

THIRD BEST QSAR MODEL

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

$$PA_3 = -0.114908 \times \mu - 0.0155383 \times TE - 0.00187416 \times \Delta H_f - 0.00584311 \times CME + 3.28863$$

$$r^2 = 0.780576 \qquad rCV^2 = 0.679165 \qquad (8)$$

The above QSAR model is obtained by descriptors dipole moment, total energy, heat of formation and *CME*. The 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 the above MLR equation are given in Table 3.

FOURTH BEST QSAR MODEL

The fourth best QSAR model is obtained by using dipole moment as first descriptor, total energy as second descriptor and *CME* as third descriptor. This QSAR model is obtained by the following regression equation:

$$PA_4 = -0.112217 \times \mu - 0.0130099 \times TE - 0.00532995 \times CME - 3.90788$$

$$r^2 = 0.772461 \qquad rCV^2 = 0.661753 \qquad (9)$$

The values of the coefficient of determination and the cross-validation coefficient indicate that this model has good predictive power. The predicted activities (PA_4) obtained from the above MLR equation are given in Table 3.

FIFTH BEST QSAR MODEL

The fifth best QSAR model is obtained by the following regression equation:

$$PA_5 = -0.0150879 \times TE - 0.00574047 \times CME - 0.153912 \times \omega + 3.82$$

$$r^2 = 0.746344 \qquad rCV^2 = 0.621314 \qquad (10)$$

The above QSAR model is obtained by using total energy as first descriptor, *CME* as second descriptor and electrophilicity index as third descriptor. The values of the predicted activities (PA_5) obtained from the above regression equation are given in Table 3.

DISCUSSION

All the above discussed QSAR models have excellent predictive power. The best two QSAR models have the value of the coefficient of determination (r^2) greater than 0.8 and all the top five developed models have the r^2 value greater than 0.74. In our previous work on the same set of compounds using topological descriptors the best QSAR model has the r^2 value 0.77 [21]. Thus, the anti-Alzheimer's activity of fused 5,6-bicyclic heterocycles can be better modeled by the combination of quantum mechanical descriptors. The total energy and conformation minimum energy appear to be important descriptors in the QSAR study of this set of compounds since both are present in all the top five QSAR models.

Table 3

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

Compound No.	Bio. act. (nM)	PA_1 (nM)	PA_2 (nM)	PA_3 (nM)	PA_4 (nM)	PA_5 (nM)
1	4.70	5.090	5.169	5.022	5.117	5.207
2	6.29	6.283	6.242	6.199	6.158	6.265
3	6.81	6.373	6.350	6.317	6.270	6.360
4	6.84	6.511	6.439	6.389	6.330	6.491
5	4.79	4.866	4.886	4.858	4.868	4.907
6	4.70	4.608	4.593	4.601	4.574	4.668
7	6.19	6.208	6.117	6.065	6.036	6.157
8	6.47	6.785	6.742	6.639	6.661	6.816
9	6.94	6.791	6.736	6.698	6.736	6.622
10	6.26	6.235	6.221	6.137	6.151	6.345
11	5.60	5.944	5.696	6.233	6.060	5.598
12	5.85	6.038	6.054	5.968	5.922	6.243
13	6.21	6.240	6.180	6.136	6.099	6.248
14	5.85	5.886	5.744	5.578	5.625	5.783
15	5.72	5.885	6.093	6.126	6.115	6.356
16	6.31	6.000	6.143	6.237	6.219	6.385
17	5.68	5.289	5.508	5.507	5.590	5.803
18	5.65	5.802	5.518	5.954	5.972	5.712
19	6.33	6.401	6.436	6.556	6.552	6.040
20	6.27	6.037	6.101	6.227	6.186	5.826
21	6.45	6.275	6.222	6.372	6.381	5.880
22	6.36	6.439	6.487	6.579	6.624	6.154
23	6.35	6.145	6.173	6.132	6.135	6.151
24	6.06	6.287	6.274	6.227	6.221	6.264
25	6.03	6.228	6.342	6.304	6.347	6.348
26	6.27	6.346	6.506	6.445	6.531	6.515
27	6.79	6.450	6.459	6.182	6.161	6.430
28	6.70	7.030	7.041	6.782	6.830	6.896

CONCLUSIONS

The above study indicates that the best combination of quantum mechanical descriptors is dipole moment as first descriptor, total energy as second descriptor, conformation minimum energy as third descriptor and ionization potential as fourth descriptor for the QSAR study of fused 5,6-bicyclic heterocycles as anti-Alzheimer's agents. This model has high predictive power and can be used to find the activity of any new derivative of this class of compounds. Also, two descriptors, the total energy and conformation minimum energy, are present with negative contribution in all the top five QSAR models.

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