ARTICLE

PM3 Method based QSAR Study of the Derivatives of Thiadiazole and Quinoxaline for Antiepileptic Activity using Quantum Mechanical and Energy Descriptors

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ABSTRACT

QSAR analysis of the derivatives of thiadiazole and quinoxaline has been made for antiepileptic activity (pED_{50}) using quantum mechanical and energy descriptors. The descriptors ionization potential, HOMO energy, LUMO energy, electron affinity, total energy, conformation minimum energy and log P have been used for QSAR analysis. The PM3 method has been employed for the calculation of descriptors. The best QSAR model has been obtained by using the descriptors electron affinity, total energy, conformation minimum energy and log P in which regression coefficient is 0.836651 and cross-validation coefficient is 0.761455. Also the single descriptor total energy is able to produce good QSAR model and hence the antiepileptic activity of any compound of the series can be predicted by calculating the value of total energy.

KEYWORDS

Descriptors, QSAR analysis, PM3 method, Antiepileptic activity, Regression coefficient, Cross-validation coefficient.

INTRODUCTION

Epilepsy that occurs as a result of other issues may be preventable [1]. Seizures are controllable with medication in about 69% of cases [2]; inexpensive anti-seizure medications are often available [1]. In those whose seizures do not respond to medication, surgery, neurostimulation or dietary changes [2-8] may then be considered. Not all cases of epilepsy are lifelong and many people improve to the point that treatment is no longer needed [1,9,11].

Today, biological activity is considered as a function of physico-chemical properties. With this concept, structure activity relationship (SAR) are developed when a set of physico-chemical properties of a group of congeners are found to explain variation in biological responses of those compounds. This resulted in discovery, examination and interpretation of SAR in a more systematic way, which led to the introduction of quantitative structure activity relationship (QSAR) studies. The QSAR study tries to explain the observed variations in biological activities of a group of congeners in terms of molecular variation caused by a change of the substituents [12-22].

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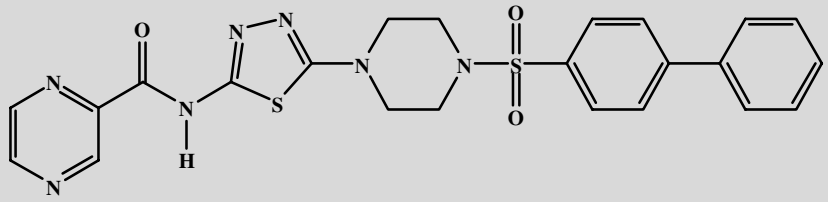
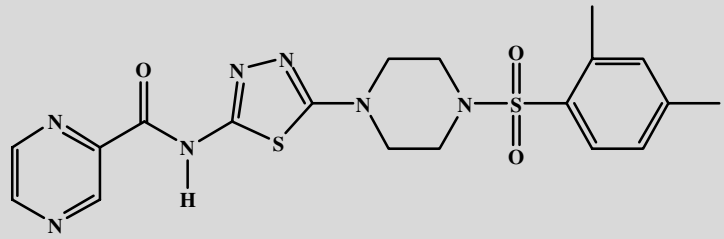
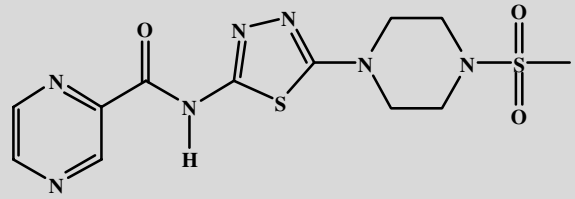
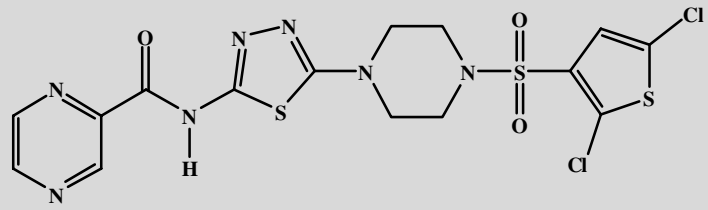
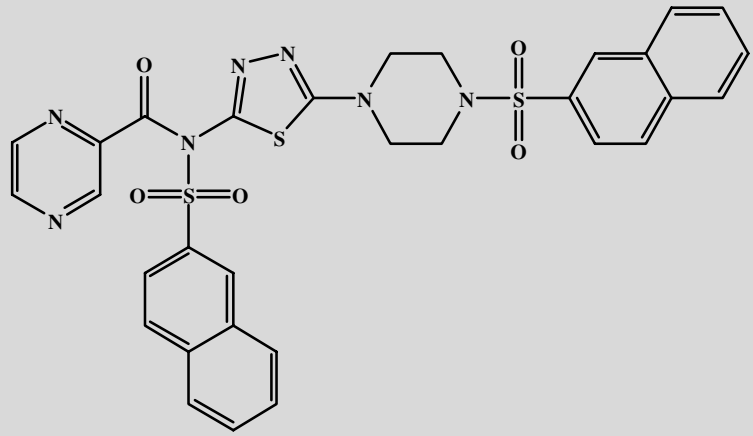
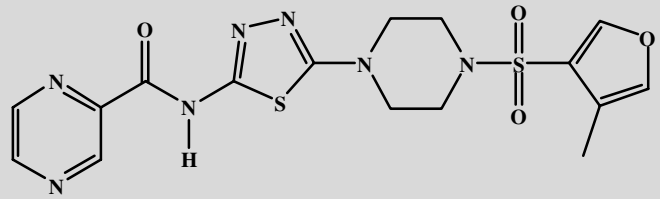
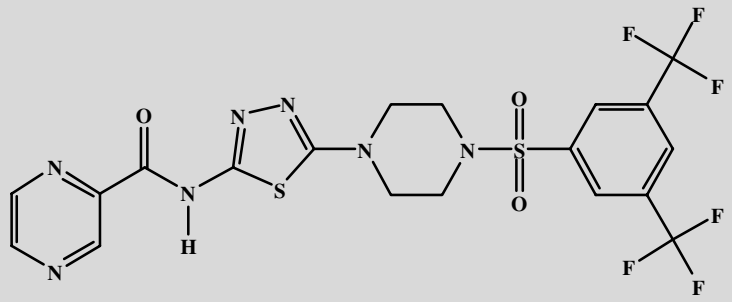
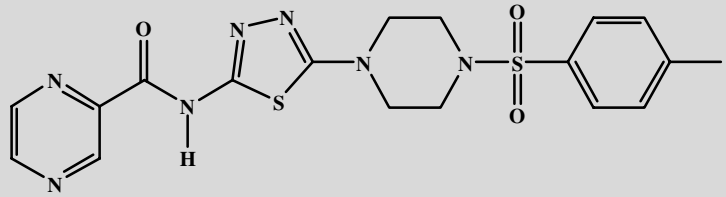
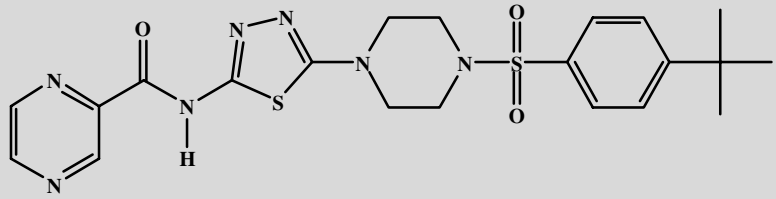
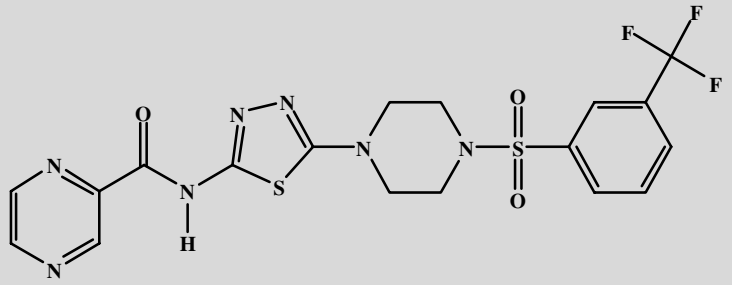
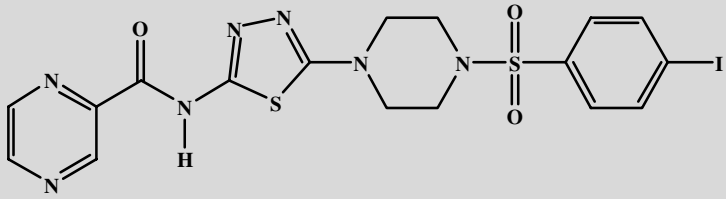
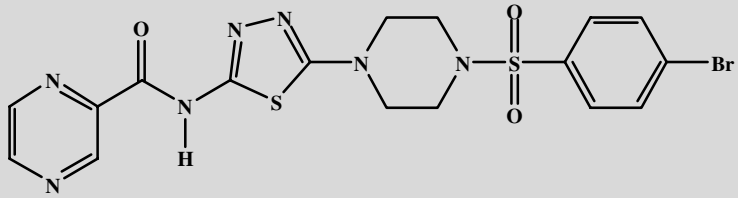
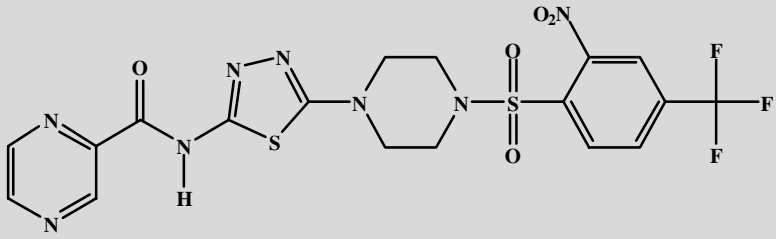
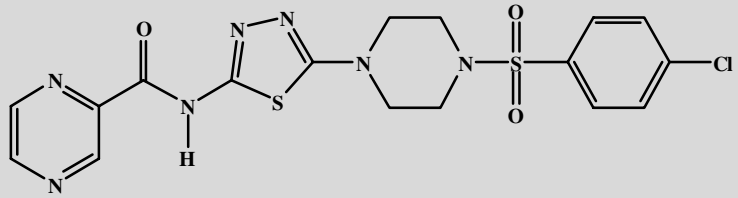
EXPERIMENTAL

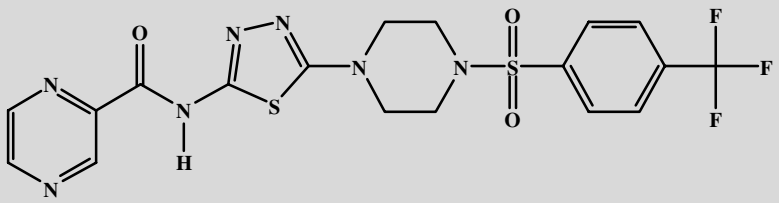
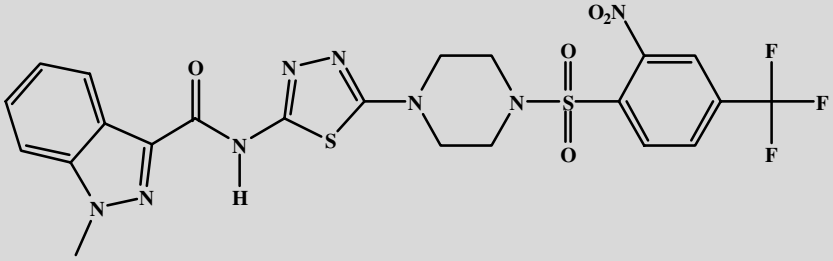
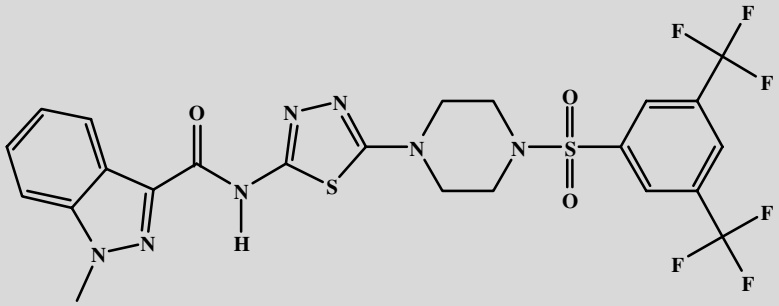
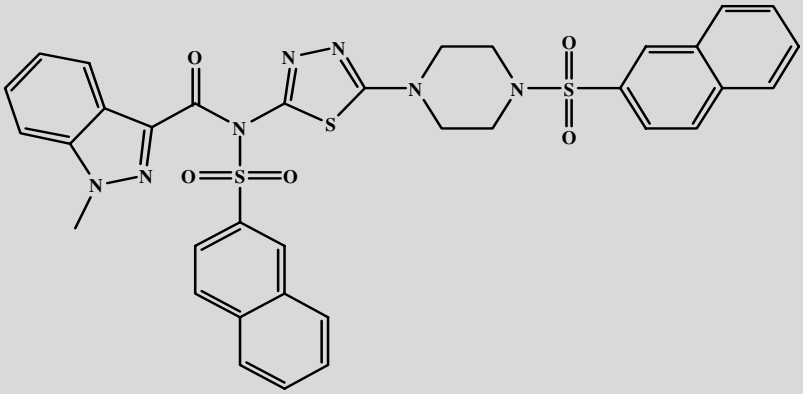
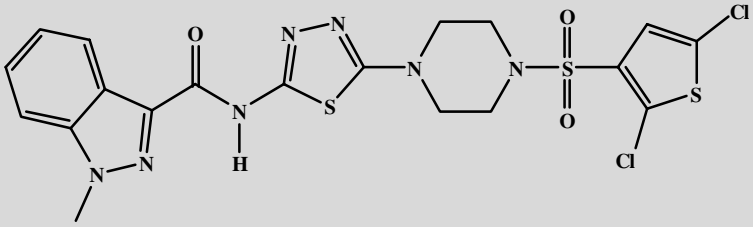
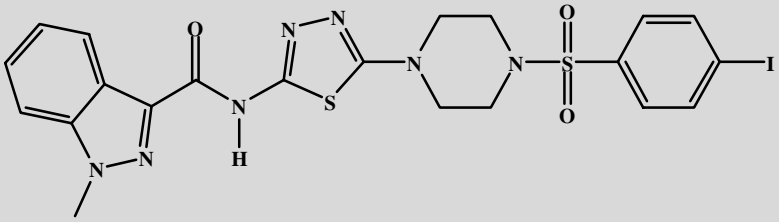
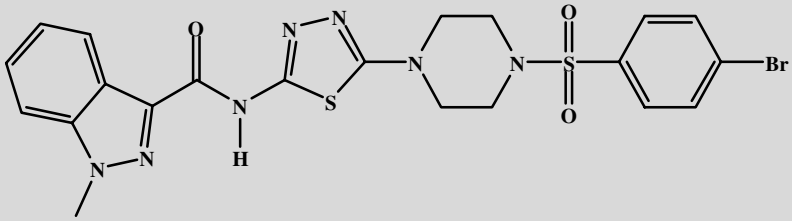
The studied materials are thiadiazole and quinoxaline derivatives along with their antiepileptic activities (pED_{50}) are presented in Table-1. For QSAR prediction, the 3D modeling and geometry optimization [23,24] of all the compounds have been done with the help of CAChe software using MOPAC2000. The values of descriptors used for QSAR models have been evaluated using the CAChe software by PM3 [25,26] methods.

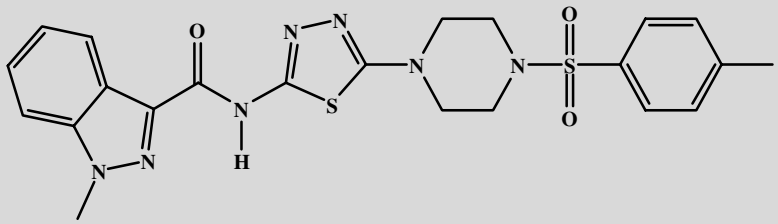
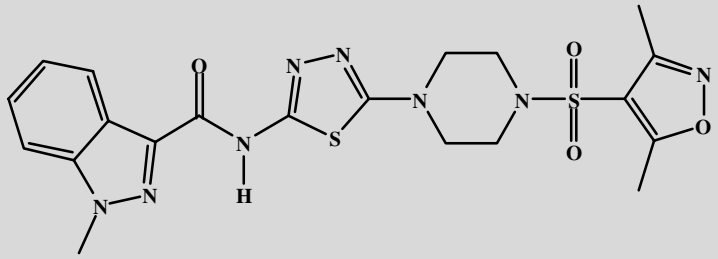
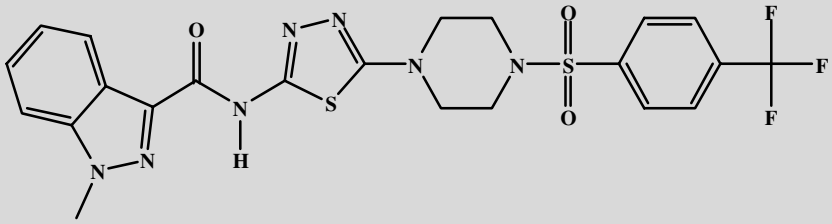
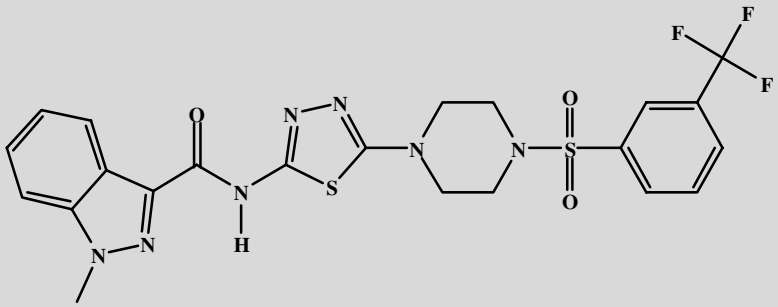
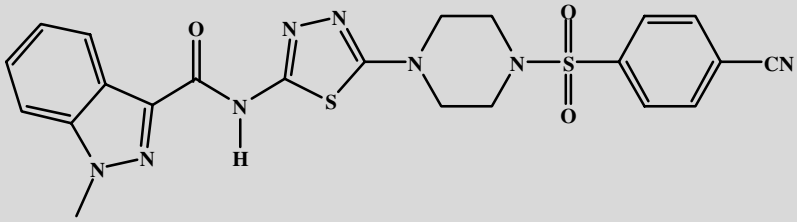
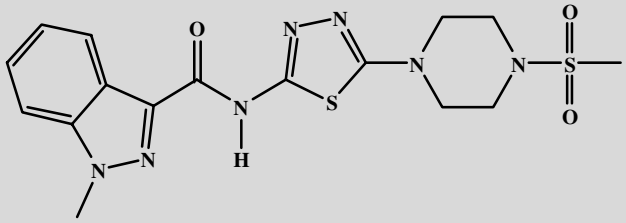
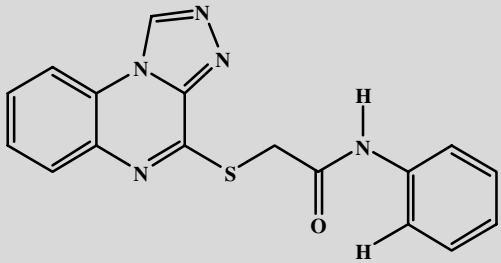
The values of descriptors *viz.*, ionization potential, HOMO and LUMO energies, electron affinity, total energy, conformational minimum energy and log P have been derived by solving the relevant equation given below:

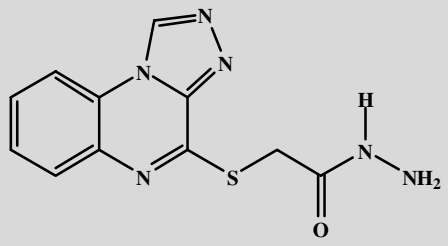
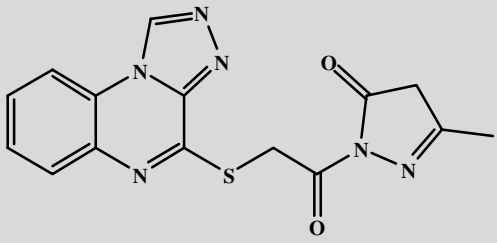
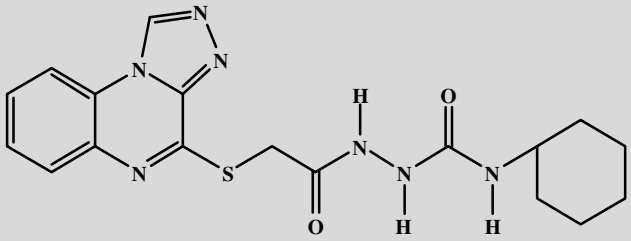
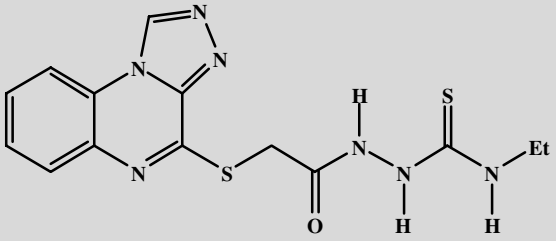
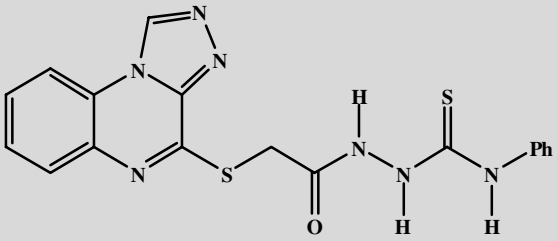
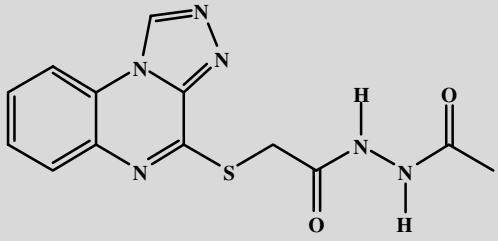
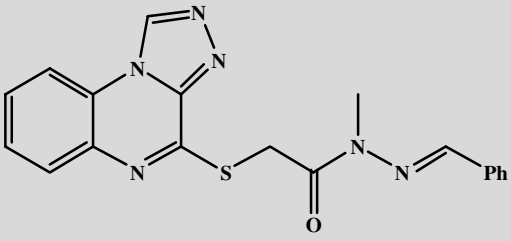
TABLE-1
ANTIEPILEPTIC ACTIVITIES (pED_{50}) OF THIADIAZOLES AND QUINOXALINE DERIVATIVES

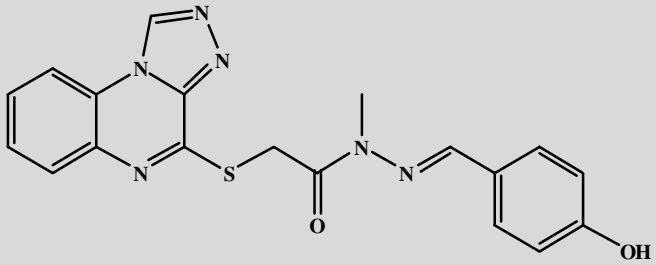
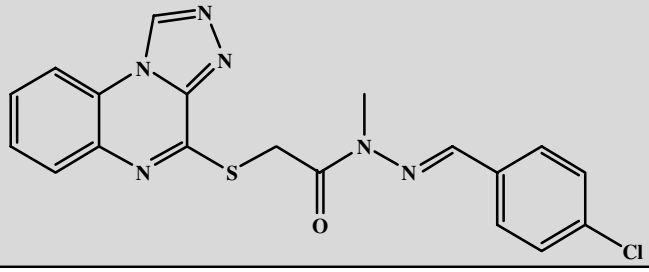
Compound	Compound structure	Antiepileptic activity (pED_{50})
TD 1		0.81
TD 2		0.87
TD 3		0.91
TD 4		0.30
TD 5		0.83
TD 6		0.54

TD 7		0.24
TD 8		0.90
TD 9		0.90
TD 10		0.40
TD 11		0.67
TD 12		0.91
TD 13		0.32
TD 14		0.65

TD 15		0.47
TD 16		0.33
TD 17		0.25
TD 18		0.81
TD 19		0.32
TD 20		0.80
TD 21		0.79

TD 22		0.84
TD 23		0.34
TD 24		0.47
TD 25		0.81
TD 26		0.74
TD 27		0.91
TD 28		1.60

TD 29		1.90
TD 30		1.60
TD 31		1.50
TD 32		1.50
TD 33		1.50
TD 34		1.50
TD 35		1.60

TD 36		1.60
TD 37		1.90

Parr *et al.* [27,27,28] defined electronegativity as the negative of chemical potential:

$$\chi = -\mu = -\left(\frac{\partial E}{\partial N}\right)_{v(r)} \quad (1)$$

The absolute hardness η is defined as [29]

$$\eta = \frac{1}{2}\left(\frac{\delta\mu}{\delta N}\right)_{v(r)} = \frac{1}{2}\left(\frac{\delta^2 E}{\delta N^2}\right)_{v(r)} \quad (2)$$

where E is the total energy, N the number of electrons of the chemical species and ν(r) the external potential.

The operational definition of absolute hardness and electronegativity [30] is defined as:

$$\eta = \frac{IP - EA}{2} \quad (3)$$

$$\chi = -\mu = -\left(\frac{IP}{EA}\right) \quad (4)$$

where IP and EA are the ionization potential and electron affinity respectively, of the chemical species.

According to the Koopman's theorem, the IP is simply the Eigen value of the HOMO with change of sign [31] and the EA is the Eigen value of the LUMO with change of sign hence the eqns. 3 and 4 can be written as:

$$\eta = \frac{\varepsilon_{LUMO} - \varepsilon_{HOMO}}{2} \quad (5)$$

$$\chi = \frac{\varepsilon_{LUMO} + \varepsilon_{HOMO}}{2} \quad (6)$$

The heat of formation is defined as:

$$\Delta H_f = E_{elect.} + E_{nuc.} - E_{isol.} + E_{atom} \quad (7)$$

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.

Total energy of a molecular system is the sum of the total electronic energy, E_{ee} and the energy of internuclear repulsion, E_{nr}.

RESULTS AND DISCUSSION

The QSAR studies of the compounds listed in Table-1 have been made with the help of quantum mechanical and energy descriptors in the different combinations of descriptors. PM3 calculation provides the valuable theoretical information useful for drug design and QSAR studies. The PM3 based calculations have been made to obtain the values of the descriptors with the help of MOPAC and CAChe software. The values of descriptors in different combination have been put to multi linear regression analysis (MLR) to obtain the predicted activity of the compounds listed in Table-1. The predicted activity has been compared with the observed activity and their qualities have been adjudged by the values of cross-validation and regression coefficients. Values of the descriptors of the compounds have been calculated using PM3 Hamiltonian by MOPAC 2000 software and these values of descriptors are represented in Table-2.

For the development of QSAR models, the predicted activities have been obtained in the ninety combinations of descriptors using MLR analysis with the help of the Project Leader software provided by Fijutsu Company of Japan. The outlier compounds are TD14, TD23 and TD37. The values of predicted activities PA1 to PA9 are said to form very good QSAR models. With the help of good QSAR models, the activity of any unknown compound of this series can be calculated and then synthesis may be done if the activity is found good. Nine MLR equations which form good QSAR models are given below:

1. PA1 = 0.321313 * Electron affinity + 0.0115923 * Total energy − 0.000503927 * Conformation minimum energy + 0.192599*log P + 2.8171

$rCV^2 = 0.761455$

$r^2 = 0.836651$

2. PA2=0.123795*HOMO energy - 0.350949 * LUMO energy + 0.0106094*Total energy + 0.158222 * log P+3.72732

$rCV^2 = 0.724236$

$r^2 = 0.833627$

TABLE-2
VALUES OF THE DESCRIPTORS OF THE COMPOUNDS UNDER STUDY WITH THEIR ANTIEPILEPTIC ACTIVITY IN TERMS OF (pED_{50})

Compound	Ionization potential (eV)	HOMO energy (eV)	LUMO energy (eV)	Electron affinity (eV)	Total energy (Hartree)	Conformation minimum energy (kcal/mol)	log P	Antiepileptic activity in terms of (pED_{50})
TD 1	9.120	-9.120	-1.287	1.287	-257.975	67.785	2.841	0.810
TD 2	8.993	-8.993	-1.164	1.164	-236.124	29.600	2.091	0.870
TD 3	8.816	-8.816	-0.940	0.940	-194.597	0.428	-0.042	0.910
TD 4	9.066	-9.066	-1.430	1.430	-241.972	48.643	1.775	0.300
TD 5	8.597	-8.597	-2.456	2.456	-338.684	91.328	5.809	0.830
TD 6	9.119	-9.119	-1.209	1.209	-230.637	47.286	-0.154	0.540
TD 7	9.147	-9.147	-1.711	1.711	-331.565	-267.966	2.922	0.240
TD 8	8.910	-8.910	-1.124	1.124	-228.953	33.931	1.624	0.900
TD 9	9.232	-9.232	-1.210	1.210	-214.194	1.284	0.309	0.900
TD 10	8.972	-8.972	-1.290	1.290	-276.666	-112.783	2.040	0.400
TD 11	8.934	-8.934	-1.132	1.132	-230.579	65.800	2.414	0.670
TD 12	8.970	-8.970	-1.149	1.149	-231.653	52.354	1.949	0.910
TD 13	9.436	-9.436	-2.155	2.155	-308.466	-108.368	1.993	0.320
TD 15	9.022	-9.022	-1.471	1.471	-276.664	-112.337	2.040	0.470
TD 16	9.091	-9.091	-2.095	2.095	-333.995	-84.290	3.957	0.330
TD 17	9.038	-9.038	-1.701	1.701	-357.098	-242.056	4.886	0.250
TD 18	8.429	-8.429	-1.542	1.542	-364.780	81.651	6.722	0.810
TD 19	8.909	-8.909	-1.385	1.385	-267.506	72.904	3.739	0.320
TD 20	8.894	-8.894	-0.983	0.983	-256.114	91.891	4.378	0.800
TD 21	8.897	-8.897	-1.066	1.066	-257.186	78.183	3.913	0.790
TD 22	8.842	-8.842	-0.875	0.875	-254.483	59.827	3.588	0.840
TD 24	8.935	-8.935	-1.429	1.429	-302.205	-87.482	4.004	0.470
TD 25	9.041	-9.041	-1.270	1.270	-302.202	-86.291	4.004	0.810
TD 26	8.974	-8.974	-1.491	1.491	-260.086	106.397	3.157	0.740
TD 27	8.926	-8.926	-0.949	0.949	-218.272	34.243	1.439	0.910
TD 28	8.958	-8.958	-1.449	1.449	-167.698	98.424	2.593	1.600
TD 29	9.300	-9.300	-1.542	1.542	-140.870	92.260	0.652	1.900
TD 30	9.056	-9.056	-1.371	1.371	-176.489	69.754	1.637	1.600
TD 31	9.120	-9.120	-1.405	1.405	-209.241	34.376	1.845	1.500
TD 32	9.096	-9.096	-1.313	1.313	-179.167	115.884	1.866	1.500
TD 33	8.979	-8.979	-1.418	1.418	-201.043	157.386	3.201	1.500
TD 34	9.139	-9.139	-1.436	1.436	-165.472	52.001	0.285	1.500
TD 35	9.114	-9.114	-1.442	1.442	-182.331	141.031	2.954	1.600
TD 36	9.049	-9.049	-1.460	1.460	-194.555	96.402	2.670	1.600

3. PA3=-0.123795*Ionization potential-0.350949* LUMO energy + 0.0106094* Total energy + 0.158222*log P + 3.72732

rCV^2 = 0.724236

r^2 = 0.833627

4. PA4=-0.123795*Ionization potential + 0.350949* Electron affinity + 0.0106094 *Total energy + 0.158222*log P +3 .72732

rCV^2 = 0.724236

r^2 = 0.833627

5. PA5=0.325529 *Electron affinity + 0.0106125*Total energy + 0.168698 * Log P + 2.62144

rCV^2 = 0.785363

r^2 = 0.832505

6. PA6 = -0.325529*LUMO energy + 0.0106125*Total energy + 0.168698*log P + 2.62144

rCV^2 = 0.785363

r^2 = 0.832505

7. PA7 = 0.010948*Total energy – 0.000568636* Conformation minimum energy + 0.200784*log P + 3.08551

rCV^2 = 0.752413

r^2 = 0.796076

8. PA8 = -0.192213*HOMO energy + 0.00993059 * Total energy + 0.189525*log P +1.12135

rCV^2 = 0.75204

r^2 = 0.794105

9. PA9=0.192213*Ionization potential + 0.00993059 * Total energy + 0.189525 * log P +1.12135

rCV^2 = = 0.75204

r^2 = 0.794105

On the basis of values of regression and cross-validation coefficients, the QSAR models have been arranged and quality of prediction has been decided. A QSAR model is said to have good predictive power if the regression coefficient (r^2) is greater than 0.5 provided that the value of cross-validation coefficient (rCV^2) is greater than or equal to 0.2. As the value of regression coefficient approaches to unity, the predictive power of the QSAR model increases. QSAR model is said to have 100% predictive power when regression coefficient (r^2) becomes unity. QSAR model has no predictive power if either the value of cross-validation coefficient (rCV^2) is less than 0.2 or the value regression coefficient (r^2) is less than 0.5. Predicted activities PA1-PA9 of the compounds have been calculated using above MLR equations and these are included in Table-3.

TABLE-3
VALUES OF THE PREDICTED ANTIEPILEPTIC ACTIVITIES FROM PA1 TO PA9

Compound	PA1	PA2	PA3	PA4	PA5	PA6	PA7	PA8	PA9
TD 1	0.753	0.763	0.763	0.763	0.782	0.782	0.793	0.851	0.851
TD 2	0.842	0.848	0.848	0.84 8	0.847	0.847	0.903	0.901	0.901
TD 3	0.855	0.895	0.895	0.895	0.855	0.855	0.946	0.875	0.875
TD 4	0.789	0.821	0.821	0.821	0.818	0.818	0.765	0.797	0.797
TD 5	0.753	0.851	0.851	0.851	0.807	0.807	0.492	0.511	0.511
TD 6	0.478	0.551	0.551	0.551	0.541	0.541	0.503	0.555	0.555
TD 7	0.221	0.140	0.140	0.140	0.153	0.153	0.195	0.141	0.141
TD 8	0.820	0.847	0.847	0.847	0.832	0.832	0.886	0.868	0.868
TD 9	0.782	0.786	0.786	0.786	0.794	0.794	0.802	0.827	0.827
TD 10	0.474	0.457	0.457	0.457	0.449	0.449	0.530	0.485	0.485
TD 11	0.940	0.954	0.954	0.954	0.950	0.950	1.008	1.006	1.006
TD 12	0.850	0.871	0.871	0.871	0.866	0.866	0.911	0.914	0.914
TD 13	0.372	0.358	0.358	0.358	0.386	0.386	0.170	0.250	0.250
TD 15	0.532	0.514	0.514	0.514	0.508	0.508	0.530	0.495	0.495
TD 16	0.423	0.420	0.420	0.420	0.426	0.426	0.271	0.302	0.302
TD 17	0.287	0.190	0.190	0.190	0.210	0.210	0.295	0.238	0.238
TD 18	0.337	0.418	0.418	0.418	0.386	0.386	0.395	0.393	0.393
TD 19	0.845	0.864	0.864	0.864	0.864	0.864	0.866	0.886	0.886
TD 20	0.961	0.947	0.947	0.947	0.962	0.962	1.108	1.117	1.117
TD 21	0.892	0.891	0.891	0.891	0.899	0.899	1.011	1.019	1.019
TD 22	0.809	0.808	0.808	0.808	0.811	0.811	0.986	0.974	0.974
TD 24	0.588	0.550	0.550	0.550	0.555	0.555	0.631	0.597	0.597
TD 25	0.537	0.481	0.481	0.481	0.503	0.503	0.630	0.617	0.617
TD 26	0.836	0.880	0.880	0.880	0.879	0.879	0.811	0.862	0.862
TD 27	0.852	0.867	0.867	0.867	0.857	0.857	0.965	0.942	0.942
TD 28	1.788	1.758	1.758	1.758	1.751	1.751	1.714	1.669	1.669
TD 29	1.759	1.726	1.726	1.726	1.738	1.738	1.622	1.634	1.634
TD 30	1.492	1.474	1.474	1.474	1.471	1.471	1.442	1.420	1.420
TD 31	1.181	1.163	1.163	1.163	1.169	1.169	1.146	1.146	1.146
TD 32	1.463	1.456	1.456	1.456	1.462	1.462	1.433	1.444	1.444
TD 33	1.479	1.487	1.487	1.487	1.489	1.489	1.438	1.457	1.457
TD 34	1.389	1.389	1.389	1.389	1.381	1.381	1.302	1.289	1.289
TD 35	1.665	1.638	1.638	1.638	1.654	1.654	1.602	1.622	1.622
TD 36	1.497	1.478	1.478	1.478	1.482	1.482	1.437	1.435	1.435

TABLE-4
NINE GOOD QSAR MODELS IN THE DECREASING ORDER OF PREDICTIVE ANTIEPILEPTIC ACTIVITIES ALONG WITH THE DESCRIPTORS USED

Predicted antiepileptic activity	Descriptors used in the predicted activity	Cross-validation coefficient (rCV^2)	Correlation coefficient (r^2)
PA1	Electron affinity, total energy, conformation minimum energy, log P	0.761455	0.836651
PA2	HOMO energy, LUMO energy, total energy, log P	0.724236	0.833627
PA3	Ionization potential, LUMO energy, total energy, log P	0.724236	0.833627
PA4	Ionization potential, electron affinity, total energy, log P	0.724236	0.833627
PA5	Electron affinity, total energy, log P	0.785363	0.832505
PA6	LUMO energy, total energy, log P	0.785363	0.832505
PA7	Total energy, conformation minimum energy, log P	0.752413	0.796076
PA8	HOMO energy, total energy, log P	0.75204	0.794105
PA9	Ionization potential, total energy, log P	0.75204	0.794105

Nine good QSAR models (r^2 <= 0.5 and rCV^2 > 0.2) in decreasing order of predicted antiepileptic activity are listed in Table-4 along with the descriptors used. These good QSAR models are PA1, PA2, PA3, PA4, PA5, PA6, PA7, PA8 and PA9 in the decreasing order of their predictive power.

Description of first two good QSAR models

Best QSAR model: QSAR model PA1 is the best QSAR model in which the descriptors are electron affinity, total energy, conformation minimum energy and log P. Multi-linear regression (MLR) equation is given below:

PA1=0.321313*Electron affinity+0.0115923*Total energy-0.000503927* Conformation minimum energy +0.192599*Log P+2.8171

rCV^2 = 0.761455

r^2 = 0.836651

The value of regression coefficient is 0.836651 and the value of cross-validation coefficient is 0.761455, which indicates that this QSAR model possesses very good predictive power and can be used successfully to predict the activity of any compound of this series. A releationship observed and predicted

activities is shown in Fig. 1, whereas the difference between the observed antiepileptic activity and predicted antiepileptic activity PA1 is shown in Fig. 2.

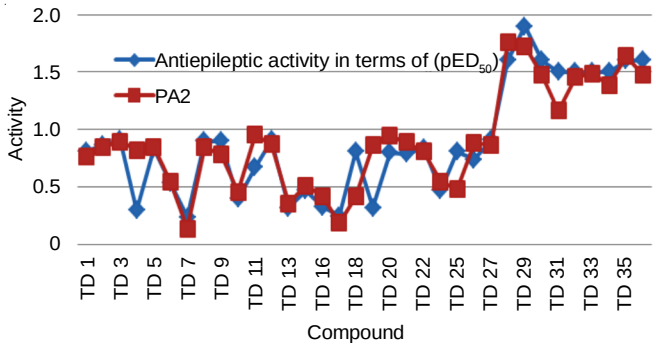


Fig. 1 Graph between observed activity and predicted activity PA1

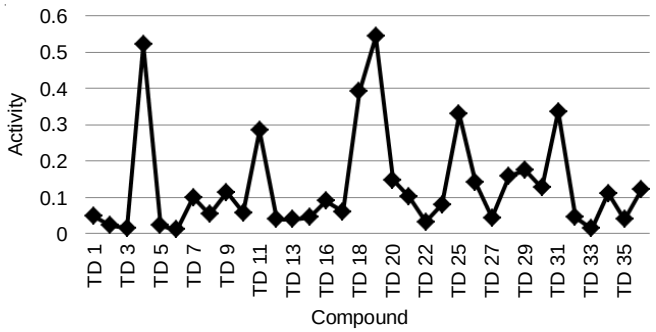


Fig. 2. Graph showing the difference between observed activity and predicted activity PA1

Second best QSAR model: QSAR model PA2 is the second best QSAR model in which the descriptors are HOMO energy, LUMO energy, total energy and log P. Multi-linear regression (MLR) equation is given below:

PA2 = 0.123795*HOMO energy-0.350949*LUMO energy + 0.0106094*Total energy+0.158222*log P+3.72732

The value of regression coefficient (r^2) is 0.833627 and the value of cross-validation coefficient (rCV^2) is 0.724236, which indicates that this QSAR model possesses very good predictive power and can be used successfully to predict the activity of any compound of this series. A relationship between observed and predicted activities is shown in Fig. 3. A difference between the observed antiepileptic activity and predicted antiepileptic activity PA2 is shown in Fig. 4. The QSAR models PA3 and PA4 have same predictive power.

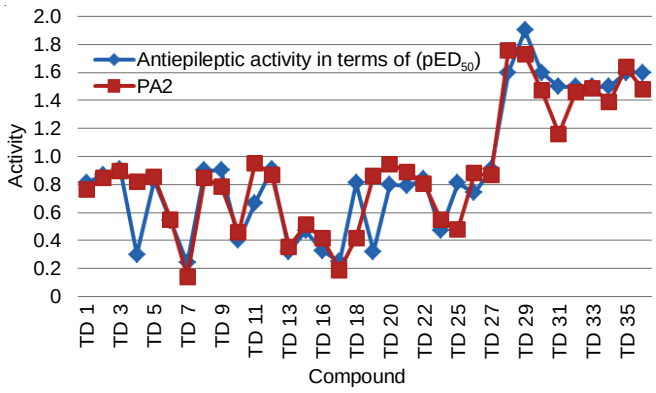


Fig. 3. Graph between observed activity and predicted activity PA2

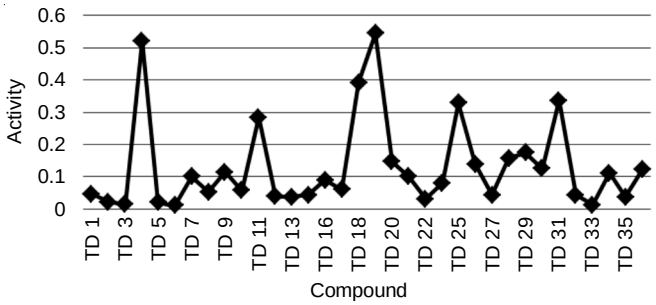


Fig. 4. Graph showing the difference between observed activity and predicted activity PA2

QSAR model developed with the help of single descriptor total energy: QSAR model PA10 is the QSAR model in which the descriptor is the total energy. Multi-Linear Regression (MLR) equation is given below:

PA10 = 0.006485*Total energy+2.49841

The value of regression coefficient (r^2) is 0.626803 and the value of cross-validation coefficient (rCV^2) is 0.622623, which indicates that this QSAR model possesses good predictive power and can be used to predict the activity of any compound of this series.

Conclusion

QSAR model PA1 in which the descriptors are electron affinity, total energy, conformation minimum energy and log P is the best QSAR model. In this QSAR model, the regression coefficient is 0.836651 and cross-validation coefficient is 0.761455, which indicate very good predictive power of this QSAR model. Total energy plays an important role in the prediction of activity of compounds since QSAR model developed using the single descriptor total energy has regression coefficient 0.626803 and the cross-validation coefficient 0.622623 which indicates that the QSAR model developed using total energy possesses good predictive power and can be used to predict the activity of any compound of this series.

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