ISSN: 0974 - 7516 Volume 7 Issue 2

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 7(2), 2011 [90-95]

QSAR study on non-benzodiazepine GABA receptor compounds using quantum chemical descriptors

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Received: 15th August, 2010 ; Accepted: 25th August, 2010

ABSTRACT

QSAR models of 29 derivatives of 7,12-dihydropyrido[3,2-b] [5,4b] diindoles as non-BDZ_S compounds bunding to GABA receptors have been developed using quantum chemical descriptors dipole moment, electronegativity, total energy, HOMO energy, LUMO energy, absolute hardness and chemical potential in different combinations. Best QSAR model possesses the value regression coefficient 0.936862 and the value of correlation coefficient 0.857329. Descriptors used in the best QSAR model are dipole moment, total energy, HOMO energy and chemical potential. Prediction of activity of non- benzodiazepine compounds can also be done with the help of single descriptor HOMO energy because the QSAR model developed using HOMO energy has the value of regression coefficient 0.92486 and the value of correlation coefficient 0.906237.

KEYWORDS

Non-benzodiazepine;
GABA receptor;
Quantum chemical descriptors;
QSAR models;
Diindole of derivatives.

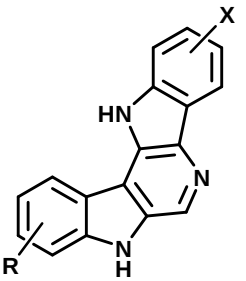
INTRODUCTION

Benzodiazepines (BDZs) are drugs used as centrally acting muscle relaxant for premeditation and as inducing agents in anesthesiology. They act via benzodiazepine receptor site (BzR) on the gamma-amino butyric acid receptor ($GABA_A$) family.

$GABA_A$ receptors are the major inhibitory neurotrans-mitter receptors in the brain, in the site of action of many clinically important drugs, and are important drug target representing the site of action of benzodiazepines, barbiturates and neurosteroids.

At synapses $GABA_A$ receptors[1] are activated by a brief non-equilibrium exposure to high concentration s of GABA. When BDZs bind to their receptors, they appear to induce a conformational change leading to an increase in the availability of $GABA_A$ receptor for GABA, leading to higher chloride influx and hyper-polarization. BDZ_S interact with two classes of recognition sites: central and peripheral types.

The central receptors located in the neuronal tis-



7,12-dihidropyrido [3,2-b] [5,4-b] diindole

sues[2] are functionally linked to a $GABA_A$ receptor chloride ionosphere complex[3] and are apparently located on synaptic membranes[4]. Central BDZ receptors mediate classical pharmacological properties of the clinically widely used BDZ_S[2] (anxiolytic, anti-convulsants, sedative and muscle relaxants).

All compounds that bind to the BzR should have certain common characteristics that allow for recognition by the receptors regardless of the type (in vivo) activity. Many types of compounds have been shown to bind at the BzR although; they are neither the benzodiazepine nor their derivatives. Such compounds are called non-benzo-diazepines (Non-BDZ_S). 7,12-Dihydropyrido[3,2-b] [5,4b] diindoles belong to non-BDZ_S series , acting as inverse agonists[5-9] in vitro and are believed to bind to sites associated with $GABA_A$ receptor. We propose to make QSAR study of some 7,12-dihydropyrido[3,2-b] [5,4-b] diindoles[10,11] whose binding affinity (in terms of inhibition of [3H]-diazepam and [3H] flunitrazepam] binding to the BzR) is reported, is presented in this paper.

MATERIAL AND METHOD

7,12-dihydropyrido [3,2-b][5,4-b] diindole, which are non-BDZ molecules , that bind to $GABA_A$/BDZ receptors, have been chosen for study. These derivatives are included in TABLE 1[10,11] QSAR studies of binding affinities of these derivatives have been made with the help of following descriptors:

Dipole moment	= α
Electronegativity	= χ
Total energy	= β
HOMO energy	= εHOMO
LUMO energy	= εLUMO
Absolute hardness	= η
Chemical potential	= μ

Descriptors in different combination have been used for multilinear regression analysis (MLR). The predicted activities obtained by regression equation have been examined for selecting QSAR models, which have high degree of predictive power. The correlation coefficient and cross validation coefficient of all the regression equations have been evaluated and listed in decreasing order of their predictive power.

The best QSAR Model, and the combination descriptors providing that model has also been identified. On the basis of such models new derivatives can be proposed which may have better binding affinity and may prove a better drug for anxiety and related disorder.

In TABLE 1, 29 derivaives of parent compound 7,12-dihidropyrido [3,2-b] [5,4-b] diindoles, as non-benzodiazepine molecules, binding to $GABA_A$/ BDZ receptors are presented.

The QSAR study has been made on these derivatives. The 3D modeling and geometry optimization[12,13] of all the compounds of TABLE 1 have been done with the help of Cache software using PM3 method. There after the values of descriptors have been evaluated with the help of same software. The QSAR models have been developed using the values of descriptors in all possible combinations. The principles on which the values of descriptors are derived are described below.

Dipole moment

It is the sum of dipole moment of all the atoms of the compound.

Electronegativity and chemical potential

Parr et al. have shown that the electronegativity[15,16] (χ) of any chemical species is equal to the negative value of chemical potential μ Indeed it follows rigorously that,

$$\chi = -\mu = \tfrac{1}{2}(I+A) \qquad (2)$$

Where A and I are ionization potential and electron affinity[17-25] of molecule.

Total energy:[26-28]

The total energy (sum of kinetic energy and potential energy), in eV, obtained by the addition of the electronic and nuclear terms, is partitioned into mono- and bi-centric contributions, and these contributions in turn are divided into nuclear and one- and two-electron terms.

Eigen value of HOMO

It is represented by the symbol εHOMO and is the energy of high-occupied molecular orbital.

Eigen value of LUMO

It is represented by the symbol εLUMO and is the energy of low unoccupied molecular orbital.

Absolute hardness

The absolute hardness η is defined as[24],

TABLE 1 : IC_{50} Inhibition of 10-substituted 7,12-ddihydropyridodiindoles against [3H] diazepam binding to the benzodiazepine receptors

Comp. No.	Substituents		Obsd. log $1/IC_{50}$
	R	X	
1	H	H	8.400
2	H	3-F	8.220
3	H	3-Cl	5.670
4	H	3-Br	6.130
5	H	3-CH_3	6.650
6	H	3-OCH_3	6.050
7	H	3-$OCH_2.C_6H_5$	5.800
8	H	3-OH	6.940
9	H	1-F	7.920
10	H	1-Cl	7.100
11	H	1-Br	7.550
12	H	1- CH_3	7.080
13	H	2-F	8.160
14	H	2-Cl	8.000
15	H	2-Br	7.720
16	H	2-CH_3	8.090
17	H	2-OCH_3	8.090
18	H	2-OH	8.220
19	H	2-$OCOCF_3$	6.700
20	H	4-Cl	6.150
21	H	4-OCH_3	6.600
22	H	4-OH	6.240
23	NO_2	H	8.400
24	NO_2	3-Cl	5.930
25	NO_2	2-Cl	6.900
26	NO_2	H	7.360
27	NO_2	2-Cl	7.010
28	Br	H	8.220
29	Cl	1-Cl	6.510

$$\eta = \tfrac{1}{2}(\delta\mu/\delta N)\nu(r) = \tfrac{1}{2}(\delta^2E/\delta N^2)\nu(r) \quad (5)$$

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

RESULT AND DISCUSSION

Values of the quantum chemical descriptors viz. dipole moment, electronegativity, total energy, HOMO energy, LUMO energy, absolute hardness and chemical potential of the compounds have been evaluated with the help of PM3 method using Cache software and the values are shown in the TABLE 2. With the help of these values in different combinations, several MLR equations have been developed and the values of regression coefficients obtained. Eight equations were found to have same value of regression coefficient above 0.9. They are PA1-PA8 and are given below:

PA1=-0.0966274*α+0.000955067 *β+ 236.091*εHOMO-57.7688*μ +1717.4

PA2=-0.0966274*α+57.7688*χ+ 0.000955067 *β+236.091 *εHOMO+ 1717.4

PA3=-0.0966274*α-414.414*χ+ 0.000955067 *β-236.091* εLUMO +1717.4

PA4=-0.0966274*α-178.323*χ+ 0.000955067*β-236.091 *η+1717.4

PA5=-0.0966274*α+0.000955067 *β+ 207.207*εHOMO-28.8844 *εLUMO +1717.4

PA6=-0.0966274*α+0.000955067*β+178.323*εHOMO-57.7688*η+1717.4

PA7=-0.0966274*α+0.000955067*β+178.323*εLUMO-414.414* η+1717.4

PA8=-0.0966274*α+0.000955067*β- 236.091*εLUMO +414.414*μ +1717.4

Each of the above QSAR model has the value of regression coefficient 0.936862 and the value of correlation coefficient 0.857329. These values of regression and correlation coefficients indicate that these QSAR models are most reliable and can be used to predict the activity of any compound. The values of predicted activities from the models PA1 to PA8 are the same and shown in the Table-3. Descriptors used in the development of these QSAR models are given below:

PA1 =Dipole Moment, Total Energy, HOMO Energy, Chemical Potential

PA2 =Dipole Moment, Electronegativity, Total Energy, HOMO Energy

PA3 =Dipole Moment, Electronegativity, Total Energy, LUMO Energy

PA4 =Dipole Moment, Electronegativity, Total Energy, Absolute Hardness

PA5 =Dipole Moment, Total Energy, HOMO Energy, LUMO Energy

PA6 =Dipole Moment, Total Energy, HOMO Energy, Absolute Hardness

PA7 =Dipole Moment, Total Energy, LUMO Energy, Absolute Hardness

PA8 =Dipole Moment, Total Energy, LUMO Energy, Chemical Potential

Graph of predicted activities PA1 to PA8 and ob-

TABLE 2 : Values of quantum chemical descriptors and activity of the compounds under study

Comp.	Dipole moment (debye)	Electro-negativity	Total energy (Hartree)	HOMO energy (eV)	LUMO energy (eV)	Absolute hardness	Chemical potential	Activity
1	2.892	4.653	-128.226	-8.376	-0.930	3.723	-4.653	8.400
2	4.449	4.656	-144.138	-8.377	-0.935	3.721	-4.656	8.220
3	3.980	4.661	-139.994	-8.389	-0.933	3.728	-4.661	5.670
4	4.026	4.660	-138.118	-8.386	-0.934	3.726	-4.660	6.130
5	2.660	4.659	-135.412	-8.384	-0.934	3.725	-4.659	6.650
6	2.744	4.660	-147.599	-8.387	-0.934	3.727	-4.660	6.050
7	2.574	4.661	-183.760	-8.388	-0.934	3.727	-4.661	5.800
8	2.773	4.660	-140.447	-8.383	-0.937	3.723	-4.660	6.940
9	2.768	4.657	-144.189	-8.378	-0.935	3.722	-4.657	7.920
10	2.760	4.660	-139.999	-8.382	-0.938	3.722	-4.660	7.100
11	2.806	4.657	-138.121	-8.380	-0.935	3.723	-4.657	7.550
12	2.977	4.658	-135.413	-8.382	-0.934	3.724	-4.658	7.080
13	3.993	4.656	-144.141	-8.377	-0.935	3.721	-4.656	8.160
14	3.522	4.656	-139.996	-8.378	-0.935	3.721	-4.656	8.000
15	3.531	4.657	-138.118	-8.379	-0.935	3.722	-4.657	7.720
16	2.355	4.656	-135.414	-8.377	-0.935	3.721	-4.656	8.090
17	3.382	4.657	-147.601	-8.378	-0.935	3.721	-4.657	8.090
18	3.787	4.658	-140.450	-8.379	-0.937	3.721	-4.658	8.220
19	4.982	4.659	-212.805	-8.384	-0.934	3.725	-4.659	6.700
20	3.450	4.661	-139.999	-8.386	-0.936	3.725	-4.661	6.150
21	1.464	4.662	-147.607	-8.389	-0.934	3.727	-4.662	6.600
22	2.291	4.659	-140.458	-8.386	-0.932	3.727	-4.659	6.240
23	5.010	4.656	-159.957	-8.376	-0.935	3.720	-4.656	8.400
24	4.851	4.663	-171.696	-8.387	-0.938	3.725	-4.663	5.930
25	4.165	4.657	-171.696	-8.380	-0.934	3.723	-4.657	6.900
26	4.185	4.658	-171.726	-8.381	-0.935	3.723	-4.658	7.360
27	2.285	4.658	-155.913	-8.382	-0.934	3.724	-4.658	7.010
28	2.452	4.657	-138.120	-8.378	-0.935	3.721	-4.657	8.220
29	2.150	4.659	-151.769	-8.385	-0.934	3.725	-4.659	6.510

served activities of the compounds of this series is shown in the graph 1.

Second best QSAR models are PA9 to PA16 whose MLR equations are given below:

PA9=-0.106448*α+58.9587*χ +238.11*εHOMO+1728.67

PA10=-0.106448*α-417.262*χ-238.11 *εLUMO+1728.67

PA11=-0.106448*α-179.152*χ-238.11 *η +1728.67

PA12=-0.106448*α+208.631 *εHOMO-29.4793 *εLUMO+ 1728.67

PA13=-0.106448*α+179.152* εHOMO-58.9587*η+1728.67

PA14=-0.106448*α+179.152* εLUMO -417.262 *η+1728.67

PA15=-0.106448*α-238.11*εLUMO +417.262 * μ+1728.67

TABLE 3 : Values of predicted activities PA1 to PA20

Comp.	PA1 to PA8	PA9 to PA16	PA17	PA19	PA19	PA20
1	8.315	8.304	9.089	8.379	7.376	9.089
2	8.127	8.119	7.996	8.208	8.150	7.996
3	5.679	5.653	6.194	5.792	5.750	6.194
4	6.127	6.102	6.519	6.228	6.183	6.519
5	6.771	6.760	6.887	6.721	6.672	6.887
6	6.163	6.159	6.463	6.152	6.107	6.463
7	5.900	5.931	6.286	5.916	5.872	6.286
8	7.117	7.114	6.607	6.996	7.419	6.607
9	7.996	8.002	7.784	7.924	7.868	7.784
10	7.301	7.299	6.560	7.147	7.726	6.560
11	7.636	7.633	7.523	7.574	7.519	7.523
12	7.161	7.151	7.191	7.128	7.077	7.191
13	8.113	8.108	7.954	8.151	8.094	7.954
14	8.005	8.001	7.841	8.000	7.943	7.841
15	7.732	7.723	7.643	7.735	7.679	7.643
16	8.211	8.214	7.904	8.085	8.028	7.904
17	7.959	7.962	7.782	7.946	7.908	7.782
18	7.774	7.766	7.264	7.741	8.061	7.264
19	6.521	6.562	6.922	6.768	6.719	6.922
20	6.265	6.249	6.127	6.247	6.598	6.127
21	5.835	5.840	5.988	5.694	5.782	5.988
22	6.348	6.342	6.924	6.332	5.966	6.924
23	8.234	8.237	8.123	8.379	8.319	8.123
24	5.946	5.947	5.583	6.039	6.771	5.583
25	7.422	7.437	7.574	7.537	7.406	7.574
26	7.284	7.299	7.388	7.394	7.341	7.388
27	7.140	7.155	7.141	7.062	7.011	7.141
28	8.061	8.064	7.765	7.946	7.924	7.765
29	6.667	6.677	6.788	6.588	6.540	6.788

PA16=-0.106448*α-238.11*η +179.152 *μ+1728.67

rCV^2=0.859051

r^2=0.936604

Each of the above QSAR model has the value of regression coefficient 0.936604 and the value of correlation coefficient 0.859051. These values of regression and correlation coefficients indicate that these QSAR models are also very reliable and can be used to predict the activity of any compound. The values of predicted activities from the models PA9 to PA16 are the same and shown in the TABLE 3. Descriptors used in the development of the QSAR models are given below:

PA9 = Dipole moment, Electronegativity, HOMO energy

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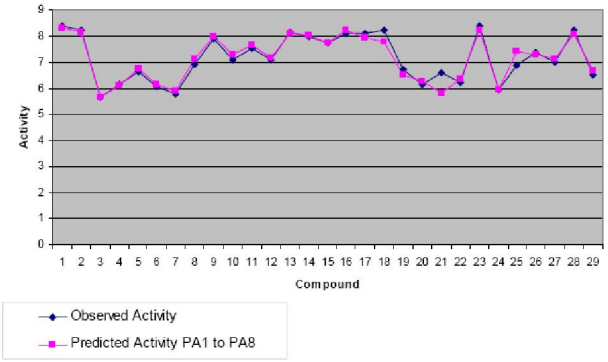
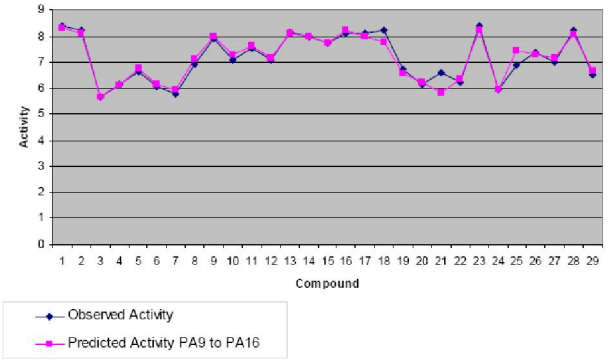


Graph 1 : Values of observed and predicted activities obtained from QSAR models PA1 to PA8



Graph 2 : Values of observed and predicted activities obtained from QSAR models PA9 to PA16

PA10 = Dipole moment, Electronegativity, LUMO energy

PA11 = Dipole moment, Electronegativity, Absolute hardness

PA12 = Dipole moment, HOMO energy, LUMO energy

PA13 = Dipole moment, HOMO energy, Absolute hardness

PA14 = Dipole moment, LUMO energy, Absolute hardness

PA15 = Dipole moment, LUMO energy, Chemical potential

PA16 = Dipole moment, Absolute hardness, Chemical potential

Graph of predicted activities PA9 to PA16 and observed activities of the compounds of this series is shown in the graph 2.

QSAR models using electronegativity as single descriptor

QSAR model PA17 using electronegativity as descriptor possesses the MLR equation,

PA17=-360.894*χ+1688.31

rCV^2=0.734848

r^2=0.781983

The value of regression coefficient is 0.781983 and the value of correlation coefficient is 0.734848 which indicate that the single descriptor electronegativity is itself sufficient to predict the activity of any compound of the series. Values of the predicted activities of the compounds predicted by QSAR model PA17 is given in the TABLE 3.

QSAR models using HOMO energy as single descriptor

QSAR model PA18 using HOMO energy as descriptor possesses the MLR equation,

PA18=204.696*εHOMO+1722.89

rCV^2=0.906237

r^2=0.92486

The value of regression coefficient is 0.92486 and the value of correlation coefficient is 0.906237 which indicate that the single descriptor HOMO energy is itself sufficient to predict the activity of any compound of the series. Values of the predicted activities of the compounds predicted by QSAR model PA18 is given in the TABLE 3.

QSAR models using absolute hardness as single descriptor

QSAR model PA19 using absolute hardness as descriptor possesses the MLR equation,

PA19=-352.569*η+1319.97

rCV^2=0.821518

r^2=0.829041

The value of regression coefficient is 0.829041 and the value of correlation coefficient is 0.821518 which indicate that the single descriptor absolute hardness is itself sufficient to predict the activity of any compound of the series. Values of the predicted activities of the compounds predicted by QSAR model PA19 is given in the TABLE 3.

QSAR models using chemical potential as single descriptor

QSAR model PA20 using chemical potential as descriptor possesses the MLR equation,

PA20=360.894*μ+1688.31

rCV^2=0.734848

r^2=0.781983

The value of regression coefficient is 0.781983 and the value of correlation coefficient is 0.734848 which indicate that the single descriptor chemical potential is itself sufficient to predict the activity of any compound of the series. Values of the predicted activities of the

compounds predicted by QSAR model PA20 is given in the TABLE 3.

CONCLUSION

Best descriptor of activity is any combination of descriptors in which dipole moment is present. The descriptors electronegativity, HOMO energy, absolute hardness and chemical potential alone are capable to predict the activity of the compounds. QSAR model using the single descriptor HOMO energy has the value of regression coefficient above 0.9 indicating its good predictive power.

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