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A Multivariate QSAR Study on the Anticonvulsant Activity of Acetamido-N-Benzylacetamide Derivatives. Influence of Different Molecular Descriptors

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Abstract

A quantitative structure activity relationship analysis was applied to a library of 51 benzylacetamide derivatives with anticonvulsant activity. The molecular structures of 51 compounds were optimized with the Semiempirical Method PM6 (Parametric Method-6) included in the MOPAC2009 software. The optimized structures of all the examined compounds were represented by 1497 DRAGON-type descriptors. Using multiple linear regression (MLR), the influence of constitutional, topological, electronic, physicochemical and quantum molecular descriptors on the activity was investigated. The validation of models were performed through the leave-one-out cross technique in conjunction with external validation. From different types of molecular descriptors, six new QSAR models were developed. The models using 0D descriptors (constitutional descriptors) and quantum descriptors do not have high statistical quality. The combination of 2D and 3D descriptors produce a model of high predictive quality (Rcal= 0.888; Scal= 0.195; Rval= 0.814; Sval=0.431; Rloo=0.867; Sloo=0.212). Results show the important role of electronic and topologic features of molecules on their anticonvulsant activity in relative to constitutional parameters.

1. Introduction

The search for safe and more potent anticonvulsant remains a drug design priority and a wide variety of compound has been synthesized for this purpose. Previous comparisons of the structural characteristics of anticonvulsant drug have identified a common pattern defined by a nitrogen heteroatomic system, at least one carbonyl group, together with two or one phenyl group [1-3]. On the other hand, the role of hydrogen bond in the docking process has been largely discussed, although in spite of the efforts no correlation has been found [3].

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Quantitative structure-activity relationship (QSAR) studies have received widespread attention as a powerful tool to better direct the rational synthesis of new drugs with anticonvulsant activity [4-6].

We developed some structure-activity relationship studies on compounds with antiepileptic activity [4,7,8]. In 2005, Jin et al [9] used QSAR methodology to elucidate the structure correlates of anticonvulsant activity in the series of 35 benzylacetamide derivatives shown by Kohn et al [10]. Using the method of partial least-squares regression (PLSR) in conjunction with leave-one-out cross-validation, the influence of 31 topological, electronic, physicochemical, and structural molecular descriptors on anticonvulsant activity was investigated. A QSAR model of the $\log ED_{50}$ in the MES test (maximal electroshock seizure) was established as a function of the following seven molecular descriptors: the Wiener index on distance code (Wmean), the mean information index on atomic composition (rIac), the partial charge at the C-terminal carbonyl carbon (qCC), the sum of partial charge in the α substituent (qαtotal), the number of hydrogen bond donor and acceptor in the α substituent (Hdα and Haα), and the calculated value of squared n-octanol/water partition coefficient, with Rcal=0.77 and Rval=0.63. This model provided statistical support for the validity of the proposed anticonvulsant pharmacophore. From a structural perspective, favorable bioactivity was correlated with: highly branched, cyclic α substituents (indicated by Wmean and rIac); the presence of α substituents hydrogen-bond acceptors (from Haα); the absence of hydrogen-bond donor (Hdα); and, the presence of electron-withdrawing substituents at either the α-position or the benzyl moiety (from the qCC term).

Recently, others acetamido-N-benzylacetamide derivatives were shown to be a promising novel anticonvulsant class [11-14]. The putative benzylacetamide anticonvulsant pharmacophore (Fig. 1) consists of: a vicinal diamine linked; an oxygen atom on the ethylene chain bridging two amino groups; and an aromatic ring one carbon removed from an amine group.

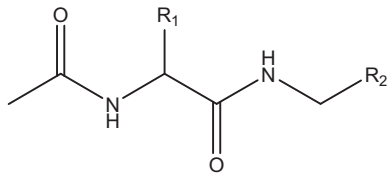


Figure 1: Pharmacophoric pattern for α-substituents acetamido-N-benzylacetamide compounds.

This paper proposes new QSAR models to elucidate the structural correlates of anticonvulsant activity in a serie of 51 α-substituents acetamido-N-benzylacetamide compounds [9-14]. In order to obtain the effects of the structural parameters on the activity, QSAR analysis with different type of molecular descriptors was operated.

The search for the best structure – activity models is carried out by means of the replacement method (RM) [15-17] variable subset selection technique and multiple linear regression (MLR).

2. Material and methods

2.1 Experimental data

All acetamido-N-benzylacetamide compounds of this study were synthesized and the racemates were pharmacologically evaluated as previously described [9,10]. The parameter of activity (ED_{50} in mg/kg) represents the dose at which 50% of individuals reach the desired effect. This is generally obtained in the "Anticonvulsant Selection Project" (ASP) by the experimental method "Maximal electroshock seizure" (MES) [18]. For modeling purposes, we use $\log_{10}ED_{50}$ to get a more standardized property.

2.2 Geometry optimization and molecular descriptors calculation

The structures of all the examined compounds are optimized with the Semiempirical Method PM6 (Parametric Method-6) [19] included in the MOPAC2009 software [20]. By means of the software Dragon [21] we calculate a set of 1497 molecular descriptors [22-25] (Table 1). Additionally, some quantum chemical descriptors obtained from a semiempirical molecular modeling study were added to the classical descriptors.

Table 1: Classification of molecular descriptors calculated by Dragon.

Type of Descriptors	Numbers of descriptors	Classification
Constitutional Descriptors	47	0D
Functional Groups	121	
Atom Centred Fragments	120	1D
Empirics Descriptors	3	
Properties	3	
Descriptors topological	266	2D
Molecular walk counts	21	

BCUT Descriptors	64	
Galvez Charge Index	21	
2D autocorrelation	96	
Descriptors of Charge	14	
Aromatic index	4	
Molecular profiles of Randic	41	
Geometry Descriptors	70	3D
RDF Descriptors	150	
3D-Morse Descriptors	160	
WHIM descriptors	99	
GATEWAY Descriptors	197	

Quantum: Heat of formation, Energy of the HOMO, LUMO and HOMO-LUMO difference, Molecular area, Electronic energy, Total energy, Ionization potential, Core-core repulsion and Molecular volume.

Molecular descriptors were then removed to reduce the number of highly correlation. Therefore, the set of descriptors contains D =1239 variables.

2.3 Model Development

To establish a predictive structure–activity relationship, it is necessary to search for a subset with the best molecular descriptors that reflect the structural features of compounds that best correlate with the biological activity under study. The QSAR models established are obtained via search of molecular descriptors by MLR using RM.

The RM is a powerful variable subset selection approach [15-17] and an efficient optimization tool that generates multi-parametric linear regression-based QSAR by searching the set d of D descriptors for an optimal subset d of d << D descriptors with minimum model's standard deviation (S). We used the computer Matlab 7.0 [26] system for all of our calculations by multivariable linear regression.

On the other hand, the Kubinyi function *FIT* [27-29] is used to get the optimum number of descriptors (d_{opt}) of each linear regression established. *FIT* function achieves a maximum value ($d_{\max}$) deduced from the plot of the *FIT* vs. *d*.

2.4 Validation techniques

A next step of current analysis is to verify the validation (predictive capability) of the QSAR relationships established on a calibration set of chemical structures. One would be able to verify that the linear relationships established behave correlatively and would also function well for the prediction of new data, not contemplated during the training stage of the model.

The predictive power of the models is explored using the Leave-One-Out (loo) Cross-Validation procedures [30,31]. Also, the models are then subjected to a more realistic external validation using a test set containing some new compounds that have not been contemplated during the model development; these structures are selected in such a way that they share chemical functional groups that are similar to the training set molecules.

3. Results and discussion

The chemical structure and biological activity of the molecules used in this study are shown in the Table 2. As it shown, the molecules possess a wide variety of substituent with different hydrophobic and electronic properties and their biological activity log ED_{50} is varied between 0.544 and 1.994. The most active compound has a CH_2OCH_3 group at R_1 and a *para*-$CH_2{=}CH_2$ group on the phenyl ring. The least active one is containing a N(H)Ph(3-NH_2) at R_1.

Table 2: Experimental and predicted by QSAR models anticonvulsant activity.

				$Log_{10}ED_{50}$ Pred					
ID	**R1**	**R2**	**$Log_{10}ED_{50}$ Exp** [b]	**Eq. 1**	**Eq. 2**	**Eq. 3**	**Eq. 4**	**Eq. 5**	**Eq. 6**
1	CH_3	Ph	1.884	1.568	1.597	1.729	1.416	1.556	1.732
2	CH_3	Ph-*m*-F	1.889	1.568	1.597	1.674	1.892	1.492	1.819
3	2-Furanyl	Ph-*o*-F	1.602	1.256	1.408	1.440	1.612	1.221	1.394
4[a]	2-Furanyl	Ph-*m*-F	1.124	1.256	1.408	1.404	1.482	1.166	1.349
5	2-Furanyl	Ph-*p*-F	1.104	1.256	1.408	1.279	1.422	1.157	1.200
6	2-Furanyl	2,5-$F_2C_6H_3$	1.377	1.256	1.408	1.230	1.480	1.205	1.130
7	2-Furanyl	2,6-$F_2C_6H_3$	1.799	1.256	1.408	1.500	1.515	1.152	1.474
8	3-Allyl	Ph	1.526	1.392	1.389	1.225	1.360	1.324	1.303
9	2-Tetrahydrofuranyl	Ph	1.713	1.785	1.805	1.521	1.755	1.259	1.792
10	Ph	Ph	1.308	1.594	0.973	1.115	1.296	1.139	1.398
11[a]	2-Furanyl	Ph	1.013	1.256	1.408	1.381	1.072	1.274	1.306
12	Furanyl-5-CH_3	Ph	1.283	1.256	1.597	1.091	1.122	1.302	1.218
13	2-Pyrrolyl	Ph	1.207	1.618	1.408	1.607	1.300	1.530	1.589

14	2-Pyrrolyl-5-CH_3	Ph	1.562	1.618	1.597	1.296	1.026	1.575	1.462
15[a]	2-Thienyl	Ph	1.651	1.618	1.408	1.699	1.504	1.263	1.551
16	3-Thienyl	Ph	1.943	1.618	1.843	1.839	1.864	1.331	1.540
17	1-Pyrrole	Ph	1.904	1.618	1.843	1.707	1.583	1.479	1.565
18	1-Pyrazole	Ph	1.217	1.618	1.408	1.406	1.283	1.320	1.354
19	2-Pyridyl	Ph	1.033	1.088	0.973	1.000	1.231	1.157	1.192
20	$C(S)NH_2$	Ph	1.937	1.392	1.965	1.843	1.781	1.695	1.896
21	$NHCH_2CH_3$	Ph	1.627	1.568	1.597	1.440	1.648	1.396	1.551
22	$N(CH_3)_2$	Ph	1.656	1.568	0.973	1.879	1.766	1.611	1.852
23	$N(CH_3)OH$	Ph	1.477	1.206	1.687	1.728	1.620	1.400	1.511
24	$NPhNH_2$	Ph	1.631	1.594	0.973	1.741	1.510	1.197	1.824
25	OH	Ph	1.898	1.206	1.687	1.894	1.757	1.537	2.128
26[a]	OCH_2CH_3	Ph	1.792	1.206	1.597	1.443	1.977	1.332	1.465
27	CH_2OCH_3	Ph	0.919	1.206	0.973	0.842	1.357	1.329	1.137
28	$CH_2OCH_2CH_3$	Ph	1.230	1.206	1.597	1.128	1.091	1.243	1.238
29	2-Pyrazinyl	Ph	1.170	1.088	0.973	0.927	1.350	1.181	1.185
30	2-Pyrimidyl	Ph	0.908	1.088	0.973	0.936	1.069	1.259	0.880
31	2-Oxazole	Ph	1.021	1.256	0.973	1.308	1.145	1.186	1.131
32	2-Thiazole	Ph	1.079	1.618	0.973	1.629	1.326	1.178	1.363
33	$N(H)Ph(3\text{-}NH_2)$	Ph	1.994	1.594	1.965	1.706	1.674	1.480	1.895
34	2-Furanyl	5-Pyridyl	1.477	1.256	1.408	1.381	1.149	1.250	1.326
35	CH_2OCH_3	Ph-*m*-F	0.839	1.206	0.973	0.865	0.695	1.325	0.679
36	CH_2OCH_3	Ph-*p*-F	0.623	1.206	0.973	0.741	0.610	1.351	0.569
37	CH_2OCH_3	Ph-*p*-OCF_3	0.556	0.844	0.973	0.577	0.550	1.010	0.640
38[a]	CH_2OCH_3	Ph-*p*-CH_2OCF_3	1.041	0.844	0.973	0.923	1.121	1.161	0.907
39	CH_2OCH_3	Ph-*p*-$CH_2CH_2CH_3$	0.929	1.206	0.973	0.991	1.137	1.172	0.922
40	CH_2OCH_3	Ph-*p*-CH_3	0.863	1.206	0.973	0.834	1.022	1.439	0.865
41	CH_2OCH_3	Ph-*p*-$CH_2CH_2CH_2OCH_3$	1.301	0.844	1.389	1.396	1.049	0.940	1.191
42	CH_2OCH_3	Ph-*p*-$CH_2{=}CH_2$	0.544	0.853	0.973	0.665	0.821	1.351	0.911
43	CH_2OCH_3	Ph-*p*-C_6H_5	0.903	1.055	0.973	1.129	1.196	1.051	1.017
44	CH_2OCH_3	Ph-*p*-$CCCH_2\ OCH_3$	1.000	0.667	0.973	1.243	0.957	1.042	1.014
45[a]	CH_2OCH_3	Ph-*p*-Cl	0.699	1.206	0.973	0.861	0.590	1.324	0.842
46	CH_2OCH_3	Ph-*p*-Br	0.940	1.206	0.973	0.967	1.110	1.278	0.827
47	CH_2OCH_3	Ph-*p*-I	1.204	1.206	0.973	1.169	1.120	1.256	1.209
48	$NHOCH_3$	Ph	0.792	1.206	0.973	0.883	0.817	1.379	0.844
49	NCH_3OCH_3	Ph	0.826	1.206	0.973	1.004	0.789	1.453	0.855
50[a]	2-Furanyl	Ph-p-CH_3	1.639	1.256	1.408	1.255	1.500	1.320	1.358
51	2-Furanyl	Ph-p-CF_3	1.358	1.256	1.408	1.548	1.496	0.991	1.617

[a] Compound used as external test set.
[b] Dates experimental previously published by other authors [9-14]

3.1 MLR analysis

MLR analysis was employed to model the structure-activity relationship with different set of descriptors. The resulted regression equations are summarized in Table 3. The first equation (eq. 1) was derived by using the 0D descriptors (constitutional descriptors). This equation which does not have high statistical quality (Rcal=0.606 and Scal=0.338), however, describes that number of multiple bonds (nBM), number of rings (nCIC), number of oxygen atoms (nO) and number of benzene (nBnz) affect on the anticonvulsant activity acetamido-N-benzylacetamide compounds..

The second equation (eq. 2) shows that the 1D descriptors could explain the structure-anticonvulsant activity relationship better than that of constitutional descriptors (Rcal=0.794 and Scal=0.258). The number of hydrogen attached to a carbon sp3, sp2, sp (H-048), number of hydrogen attached to a heteroatom (H-050), number of oxygen alcohol (O-056) and number of Ar-NH_2 or X-NH_2 (N-069) are the parameters of the equation. Some of these 0D and 1D descriptors (nO, nBnz, H-050 and N-069) are present to the common pattern previously showed.

According to the statistical parameters of eq. 3, the 2D descriptors are able to characterize better the anticonvulsant activities of compounds. This four-parametric equation has correlation coefficient and deviation standard equal to 0.855 and 0.220 respectively. The notation for de molecular descriptors involved in the QSAR models is shown in Table 4. The model obtained with 3D descriptors, eq. 4, has similar statistical parameters than eq. 3 (Rcal=0.860 and Scal=0.216). This also is a four-parametric equation and the molecular descriptors participating are: a RDF descriptors (RDF070m), a WHIM descriptors (G1u) and two GATEWAY type of descriptors (HATS8u and R3e), Table 4.

The eq. 5 was obtained from 11 quantum molecular descriptors. The high deviation standard and low regression coefficient of this equation reveal that the activity is not affected for these parameters. The two-parametric equation indicated the poor dependence of the activity on the ionization Potential, molecular volume and the others quantum descriptors.

Finally, the best statistical parameters were obtained when all type of molecular descriptors were used to build the QSAR model, eq. 6. The four descriptors from two different types of descriptors were used in this equation, three 2D descriptors and one from 3D family. This equation, which has high statistical quality (Rcal=0.888 and Scal=0.195), demonstrates that characteristic 2D and 3D of the molecules are major factors controlling the binding of the

acetamido-N-benzylacetamide derivative to the receptors. It is noted, that the constitutional and functional groups descriptors were not appeared in the final QSAR model. It can be explained compared the equation 3 and 4 with the equations 1 and 2. The correlation between the constitutional (0D descriptors) and functional groups (1D descriptors) is not as high as topological (2D descriptors) and Gateway (3D descriptors). The QSAR model proposed by Jin at al. (Rcal=0.77 and Rval=0.63) could be compared in quality with the model of 1D descriptors (eq. 2). However, the model obtained from 2D and 3D descriptors have higher quality and a more predicted power.

Table 3: MLR-QSAR models results.

Eq.	Model and Statistical Parameters	
1	**$\log_{10}ED_{50}$=2.621 (0.419) -0.176 (0.054) 'nBM' + 0.579 (0.190) 'nCIC' -0.362 (0.087) 'nO'+ 0.505 (0.242) 'nBnz'** N= 51 Rcal= 0.606 Scal= 0.338 Rval= 0.425 Sval=0.657 Rloo=0.511 Sloo= 0.368	**0D**
2	**$\log_{10}ED_{50}$=0.972 (0.052) + 0.435 (0.071) 'H-048' + 0.208 (0.032) 'H-052' + 0.714 (0.190) 'O-056' + 0.992 (0.190) 'N-069'** N= 51 Rcal= 0.794 Scal= 0.258 Rval= 0.761 Sval= 0.483 Rloo= 0.747 Sloo=0.283	**1D**
3	**$\log_{10}ED_{50}$=9.774 (0.802) -39.058 (7.642) 'PW5' - 2.510 (0.397) 'BEHv7' + 0.091 (0.012) 'ATS7p' -1.2474 (0.255) 'GATS7v'** N= 51 Rcal= 0.855 Scal= 0.220 Rval= 0.695 Sval=0.513 Rloo= 0.823 Sloo= 0.241	**2D**
4	**$\log_{10}ED_{50}$=-7.350 (1.213) + 0.073 (0.018) 'RDF070m' + 37.469 (5.872) 'G1u' - 3.395 (0.546) 'HATS8u' + 2.275 (0.327) 'R3e'** N= 51 Rcal= 0.860 Scal= 0.216 Rval= 0.903 Sval= 0.335 Rloo= 0.833 Sloo= 0.235	**3D**
5	**$\log_{10}ED_{50}$=8.282 (2.576) -0.518 (0.224) 'Pioniz' -0.006 (0.002) 'Vol'** N= 51 Rcal= 0.401 Scal= 0.381 Rval= 0.318 Sval=0.484 Rloo= 0.405 Sloo= 0.267	**Quantum**
6	**$\log_{10}ED_{50}$=3.152 (0.665) - 50.488 (6.699) 'PW5' + 0.066 (0.009) 'ATS7p' -1.073 (0.231) 'GATS7v' + 5.028 (0.631) 'HATS3u'** N= 51 Rcal= 0.888 Scal= 0.195 Rval= 0.814 Sval=0.431 Rloo=0.867 Sloo=0.212	**All**

Table 4: Notation for molecular descriptors involved in the QSAR models.

Descriptors	Classification [a]	Type	Brief description
nBM	0D	Constitutional Descriptors	Number of multiple bonds
nCIC			Number of rings
nO			Number of oxygen atoms
nBnz			Number of benzene
H-048	1D	Atom-center fragments	number of hydrogen attached to a carbon sp3, sp2, sp
H-052			H attached to CO (sp3) with 1X attached to next C.
O-056			alcohol
N-069			Ar-NH2 / X-NH2
PW5	2D	Topologic descriptors	Path/walk 5 –Randic shape index.
BEHv7		BCUT descriptors	Highest eigenvalues n. 7 of Burner matrix / weighted by atomic Van der Waals.
ATS7p		2D Autocorrelation	Broto-Moreau autocorrelation of a topological structure - lag 7 / weighted by atomic polarizabilities.
GATS7v			Geary autocorrelation - lag 7 / weighted by atomic Van der Waals volumes.
RDF070m	3D	Radial distribution Funtion	Radial Distribution Function - 7.0 / weighted by atomic masses.
G1u		WHIM descriptors	1st component symmetry directional WHIM index / unweighted.
HATS8u		GATEWAY	Leverage-weighted autocorrelation of lag 8 / unweighted.
R3e			R autocorrelation of lag 3 / weighted by atomic sanderson electronegativities.
HATS3u			Leverage-weighted autocorrelation of lag 3 / unweighted.
Pioniz		Quantum	Ionization Potential
Vol			Molecular Volume

[a] Classification given by the software Dragon

The correlation coefficient between the descriptors is listed in Table 5. All the non-diagonal elements were less than 0.83, indicating that the co-linear situation between different descriptors and redundant information included in the set of descriptors are low.

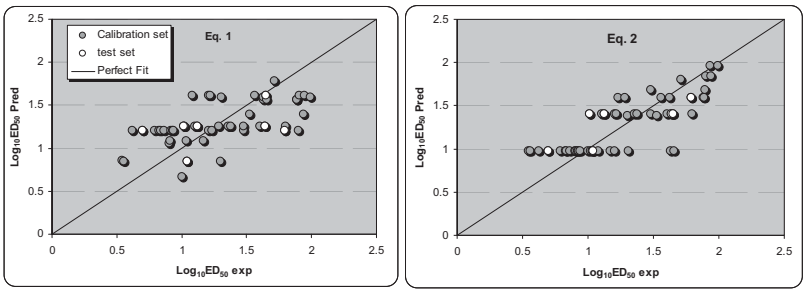
Table 5: Correlation matrix for descriptors of the QSAR models.

Eq.		nBM	nCIC	nO	nBnz
1	nBM	1.000	0.831	0.428	0.584
	nCIC		1.000	0.348	0.286
	nO			1.000	0.220
	nBnz				1.000
		H-048	H-052	O-056	N-069
2	H-048	1.000	0.280	0.117	0.117
	H-052		1.000	0.098	0.098
	O-056			1.000	0.041

	N-069				1.000
3		PW5	BEHv7	ATS7p	GATS7v
	PW5	1.000	0.649	0.729	0.078
	BEHv7		1.000	0.824	0.155
	ATS7p			1.000	0.025
	GATS7v				1.000
4		RDF070m	G1u	HATS8u	R3e
	RDF070m	1.000	0.339	0.067	0.080
	G1u		1.000	0.096	0.093
	HATS8u			1.000	0.215
	R3e				1.000
5		Pioniz	Vol		
	Pioniz	1.000	0.487		
	Vol		1.000		
6		PW5	ATS7p	GATS7v	HATS3u
	PW5	1.000	0.729	0.078	0.296
	ATS7p		1.000	0.025	0.487
	GATS7v			1.000	0.324
	HATS3u				1.000

3.2 Validation of generated QSAR models

To test the ability of the model for predicting $\log_{10}$ED50 values of a set of molecules, the leave-one-out cross validation and external validation were performed. To the external validation a subset was used as a test set. Thus, seven molecules (13.7%) out of the 51 data set of molecules were used to test the model. The statistical parameters of the different model (Table 3) indicate that the eq. 4 and eq. 6 QSAR models have stable predictive power within the current experimental data set, see Fig 2.



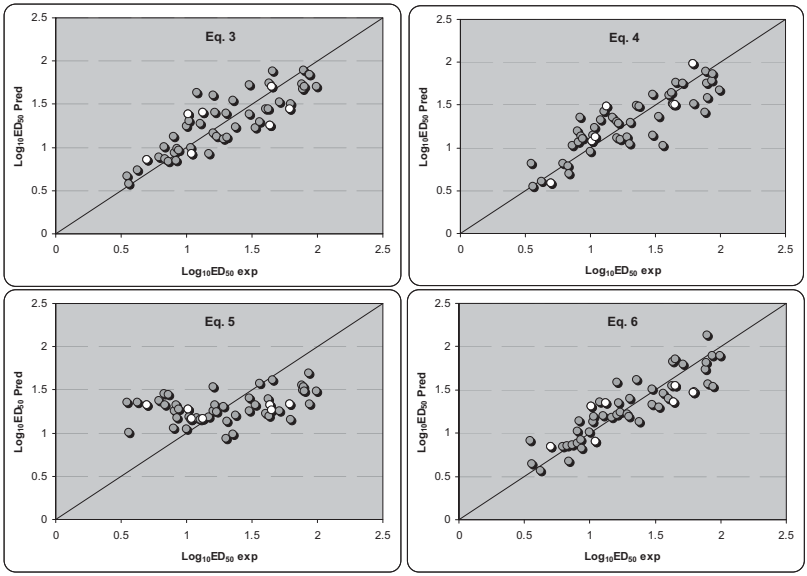


Figure 2: Experimental versus predicted anticonvulsant activity for the six QSAR models.

3.3 Descriptor contribution analysis

Descriptors used in the generated of different QSAR models were classified in tables 4 and 5. The contributions of each descriptor (standardized regression coefficients) in the MLR models were determined, and are provided in Table 6. The significance of the descriptors involved in each model decreases in the following order:

Equation 1:

nBM (0.926) >nCIC (0.715) > nO (0.540) > nBnz (0.335)

Equation 2:

H-052 (0.604) > H-048 (0.582) > N-069 (0.476) > O-056 (0.342)

Equation 3:

ATS7p (1.085) > BEHv7 (0.906) > PW5 (0.579) > GATS7v (0.395)

Equation 4:

R3e (0.537) > G1u (0.516) > HATS8u (0.480) > RDF070m (0.316)

Equation 5:

Vol (0.431) > Pioniz (0.349)

Equation 6:

ATS7p (0.789) > PW5 (0.748) > HATS3u (0.669) > GATS7v (0.340)

Table 6: Standardized regression coefficients for descriptors of QSAR models.

Eq.				
1	**nBM**	**nCIC**	**nO**	**nBnz**
	0.926	0.715	0.540	0.335
2	**H-048**	**H-052**	**O-056**	**N-069**
	0.582	0.604	0.342	0.476
3	**PW5**	**BEHv7**	**ATS7p**	**GATS7v**
	0.579	0.906	1.085	0.395
4	**RDF070m**	**G1u**	**HATS8u**	**R3e**
	0.316	0.516	0.480	0.537
5	**Pioniz**	**Vol**		
	0.349	0.431		
6	**PW5**	**ATS7p**	**GATS7v**	**HATS3u**
	0.748	0.789	0.340	0.669

For the case of eq. 1 *nBM* is the most important variable of this model. *nBM* represents the number of multiple bonds in the molecules. The signs of the regression coefficients suggest that the presence the rings like benzene and decreasing the number multiple bonds are favorable to the activity.

In the eqs. (2, 3, 4, 5) the most important descriptors are *H-052, ATS7p, R3e, Vol* respectively. The positive signs of the regression coefficients of *H-052, ATS7p, R3e* indicate that increasing in their values would lead to lower predicted ED_{50} values.

The descriptor *ATS7p* is the most important variable in the eqs. 3 and 6. The *ATS7p* is 2D autocorrelation descriptors and represent Broto-Moreau autocorrelation of a topological structure-lag 7 / weighted by atomic polarizabilities. *PW5* is a topological descriptor related to molecular shape. It is other important variable descriptor in eq.6 and belongs to 2D descriptors to. The presence of three 2D descriptors in de model (*ATS7p, PW5* and *GATS7v)* suggests that these types of descriptors are able to characterize better the anticonvulsant activities of compounds.

It should be noted from Table 6 that the difference in descriptor contribution between the descriptors in each models is not significant, indicating that all descriptors are indispensable in generating the different predictive models.

4. Conclusions

A QSAR analysis has been applied to a data set of 51 acetamido-N-benzylacetamide derivatives. Six QSAR models were performed used different families of molecular descriptors. The results suggest that of quantum descriptors used in the model has a poor correlation with the activity. The models obtained with constitutional descriptors present an acceptable correlation with the anticonvulsant activity, while the models with 2D and 3D descriptors are of higher quality. Finality, the combination of 2D and 3D descriptors produce a better model to predict the anticonvulsant activity on this family of compounds. The QSAR results found are able to achieve a higher quality model when compared to models obtained by other authors. Also, this study demonstrated the more important role of electronic and topologic features of molecules on their anticonvulsant activity in relative to constitutional parameters.

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References

[1] B. Hemmateenejad, R. Miri, M. Tabarzad, M. Jafarpour, F. Zand, Molecular modeling and QSAR análisis of the anticonculsant activity of some N-phenyl-N'-(4-pyridinyl)-urea derivatives, *J. Mol. Struct. (Theochem)* **684** (2004) 43–49.

[2] S. M. Tassoa, L. E. Bruno-Blanch, S. C. Moon, G. L. Estiú, Pharmacophore searching and QSAR analysis in the design of anticonvulsant drugs, *J. Mol. Struct. (Theochem)* **504** (2000) 229–240.

[3] M. D. Carter, V. C. Stephenson, D. F. Weaver, Are anticonvulsants 'two thirds' of local anesthetics? A quantum pharmacology study, *J. Mol. Struct. (Theochem)* **638** (2003) 57–62.

[4] J. C. Garro Martinez, P. R. Duchowicz, M. R. Estrada, G. N. Zamarbide, E. A. Castro, Anticonvulsant activity of ringed enaminones: A QSAR study, *QSAR Comb. Sci.* **28** (2009) 1376–1385.

[5] S. Thareja, S. Aggarwal, A. Verma, T. R. Bhardwaj, M. Kumar, 3D QSAR studies on 1, 3, 4-thiadiazole derivatives: An approach to design novel anticonvulsants, *Med. Chem.* **6** (2010) 233–238.

[6] N. D. Amnerkar, K. P. Bhusari, Synthesis, anticonvulsant activity and 3D-QSAR study of some prop-2-eneamido and 1-acetyl-pyrazolin derivatives of aminobenzothiazole, *Eur. J. Med. Chem.* **45** (2010) 149–159.

[7] J. C. Garro Martínez, M. F. Andrada, M. R. Estrada, G. N. Zamarbide, E. A. Castro, A preliminary theoretical study of antiepileptic drugs, *J. Arg. Chem. Soc.* **94** (2006) 121–127.

[8] J. C. Garro Martinez, M. F. Andrada, M. R. Estrada, E. A. Castro, G. N. Zamarbide, Z. Mucsi, I. G. Csizmadia, An exploratory study to investigate possible simple descriptors in order to predict relative activity of antiepileptic enaminones, *J. Phys. Org. Chem.* **21** (2008) 409–418.

[9] A. Y. Jin, H. Kohn, C. Béguin, S. V. Andurkar, J. P. Stables, D. F. Weaver, A quantitative structure-activity relationship study for α-substituted acetamido-N-benzylacetamide derivatives – A novel anticonvulsant drug class, *Can. J. Chem.* **83** (2005) 37–45.

[10] H. Kohn, J. D. Conley, J. D. Leander, Marked stereospecificity in a new class of anticonvulsants, *Barin. Res.* **457** (1988) 371–375.
[11] C. Salomé, E. Salomé-Grosjean, K. D. Park, P. Morieux, R. Swendiman, E. DeMarco, J. P. Stables, H. Kohn, Synthesis and anticonvulsant activities of (R)-N-(4′-substituted) benzyl 2-acetamido-3-methoxypropionamides, *J. Med. Chem.* **53** (2010) 1288–1305.
[12] C. Béguin, A. LeTiran, J. P. Stables, R. D. Voyksner, H. Kohn, N-Substituted amino acid N′-benzylamides: Synthesis, anticonvulsant, and metabolic activities, *Bioorg. Med. Chem.* **12** (2004) 3079–3096.
[13] S. V. Andurkar, J. P. Stables, H. Kohn, The anticonvulsant activities of N-benzyl 3-methoxypropionamides, *Bioorg. Med. Chem.* **7** (1999) 2381–2389.
[14] D. Choi, J. P. Stables, H. Kohn, Synthesis and anticonvulsant activities of N-benzyl-2-acetamidopropionamide derivatives, *J. Med. Chem.* **39** (1996) 1907–1916.
[15] P. R. Duchowicz, E. A. Castro, F. M. Fernández, M. P. González, A new search algorithm for QSPR/QSAR theories: Normal boiling points of some organic molecules, *Chem. Phys. Lett.* **412** (2005) 376–380.
[16] P. R. Duchowicz, E. A. Castro, F. M. Fernández, Alternative algorithm for the search of an optimal set of descriptors in QSAR-QSPR studies, *MATCH Commun. Math. Comput. Chem.* **55** (2006) 179–192.
[17] P. R. Duchowicz, A. G. Mercader, F. M Fernández, E. A. Castro, Prediction of aqueous toxicity for heterogeneous phenol derivatives by QSAR, *Chemom. Intell. Lab. Syst.* **90** (2008) 97–107.
[18] Anticonvulsant Screening Project, Antiepileptic Drug Development Program, National Institutes of Health (1978) DHEW Publ (NIH) (U.S.) NIH 78-1093.
[19] J. J. P. Stewart, Optimization of parameters for semiempirical methods V: Modification of NDDO approximations and application to 70 elements, *J. Mol. Model.* **13** (2007) 1173–1213.
[20] MOPAC2009, J.J.P. Stewart, 2008, Stewart Computational Chemistry, Colorado Springs, CO, USA, HTTP://OpenMOPAC.net.
[21] E-Dragon Software for Molecular Descriptor Calculations, http://michem.disat.unimib.it/chm
[22] N. Trinajstić, *Computational Chemical Graph Theory: Characterization, Enumeration, and Generation of Chemical Structures by Computer Methods*, CRC Press, Boca Raton, 1992.
[23] R. Todeschini, V. Consonni, *Handbook of Molecular Descriptors*, Wiley–VCH, Weinheim, 2000.
[24] R. Todeschini, V. Consonni, *Molecular Descriptors for Chemoinformatics*, Wiley–VCH, Weinheim, 2009.
[25] A. R. Katritzky, V. S. Lobanov, M. Karelson, QSPR: The correlation and quantitative prediction of chemical and physical properties from structure, *Chem. Soc. Rev.* **24** (1995) 279–287.
[26] Matlab 7.0, 2004, The MathWorks Inc.
[27] T. A. Andrea, H. Kalayeh, Applications of neural networks in quantitative structure-activity relationships of dihydrofolate reductase inhibitors, *J. Med. Chem.* **34** (1991) 2824–2836.
[28] H. Kubinyi, Variable selection in QSAR studies: II – A highly efficient combination of systematic search and evolution, *Quant. Struct. Act. Relat.* **13** (1994) 393–401.
[29] H. Kubinyi, Variable selection in QSAR studies. I. An evolutionary algorithm, Quant. Struct. Act. Relat. **13** (1994) 285-294.
[30] D. M. Hawkins, S. C. Basak, D. Mills, Assessing model fit by cross-validation, *J. Chem. Inf. Comp. Sci.* **43** (2003) 579–586.
[31] S. Wold, L. Eriksson, *Chemometrics Methods in Molecular Design*, Wiley–VCH, Weinheim, 1995.