

QSAR study for diarylguanidines, noncompetitive NMDA receptor antagonists. A new topological index A_{Ad} derived from local invariants of the chemical graphs of diarylguanidines

Adrian Beteringhe,^{*a} Petru Filip,^{*b} and Laszlo Tarko^b

^a *Institute of Physical Chemistry "I. G. Murgulescu" of the Romanian Academy, Splaiul
Independentei 202, 77208 Bucharest, Romania*

^b *Institute of Organic Chemistry "C. D. Nenitzescu" of the Romanian Academy, Splaiul
Independentei*

202B, 77208 Bucharest, Romania

E-mail: chemworks2003@yahoo.com; pfilip@cco.ro

Dedicated to Alexandru Balaban on his 75th Anniversary

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Abstract

The binding affinities for NMDA receptor ion channel and σ receptor sites of four classes of diarylguanidines have been correlated with values of molecular descriptors implemented in CODESSA and PRECLAV programs: twenty-one derivatives of N, N' - diphenylguanidines type (1), eight N, N' - dinaphthylguanidines type (2), eighteen N - naphthyl - N' - phenylguanidines type (3) and two miscellaneous guanidines (4). A new topological index A_{Ad} based on local invariants of the chemical graphs has been defined and used in QSAR studies generating an increasing of correlation coefficient value r .

Keywords: Diarylguanidines, NMDA receptor ion channel site, σ receptors, molecular descriptors, CODESSA, PRECLAV, QSAR

Introduction

L-Glutamate is an excitatory amino acid (EAA) of the central nervous system (CNS), which is stored in presynaptic vesicles.¹⁻⁵ Postsynaptic glutamate receptors divide into two major classes: i) metabotropic receptors and ii) ionotropic receptors. Ionotropic receptors are ligand-gated ion channels mediating rapid changes in postsynaptic membrane sodium or calcium permeability. It is well known that these receptors are divided⁶ into *N*-methyl-D-aspartate (NMDA)^{1,7-12} and α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)^{5,13-15} receptors. AMPA is mediating Kainic acid (KA) effects so that most studies refer to AMPA/KA receptor.^{5,13-15}

The NMDA receptor ion channel site is the most studied because of its availability for both competitive and noncompetitive antagonists series.^{1,7-12} Through excessive long-term stimulation this receptor seems to be implicated in progressive neuronal losses such as epilepsy¹, Alzheimer's¹⁶⁻¹⁹ and Huntington's^{14-18,20} diseases, nerve cell death in stroke^{1,5}, amyotrophic lateral sclerosis²². Many ligands that interact at NMDA receptor ion channel site^{10, 23-29} also bind to σ receptors (N,N'-di-o-tolylguanidine, DTG)^{9,29}. σ Receptors do not appear to be associated with the NMDA receptor ion channel site and their physiological function is still unknown.⁷

Diarylguanidines represent a new class of compounds proven to be noncompetitive antagonists for NMDA receptor ion channel site in electrophysiological experiments blocking the response of this receptor. Some of these compounds are neuroprotective agents with therapeutic value in patients suffering from stroke, brain or spinal cord trauma and hypoglycemia.^{7,9,30,31}

The present QSAR study includes forty-nine diarylguanidines belonging to four classes: twenty-one compounds of the N, N' - Diphenylguanidines type (**1**), eight compounds of the N, N' - Dinaphthylguanidines type (**2**), eighteen compounds of the N - Naphthyl - N' - phenylguanidines type (**3**) and two miscellaneous guanidines of type (**4**). The binding affinity of these diarylguanidines for NMDA receptor ion channel and σ receptor was correlated with a variety of molecular descriptors implemented in CODESSA and PRECLAV programs and with a new topological index A_{Ad} derived from local invariants of the chemical graphs.

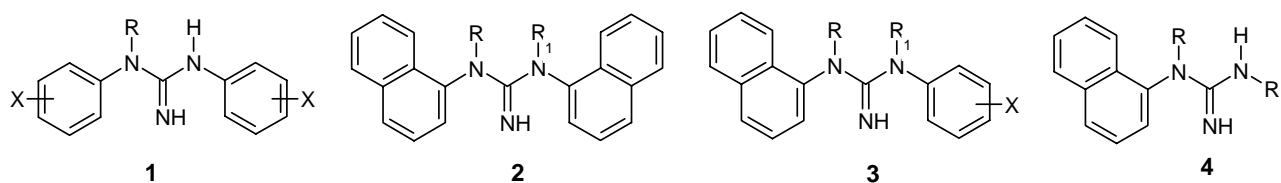


Figure 1. Structure of diarylguanidine derivatives.

QSAR results

In this study, the biological activity for forty-nine diarylguanidines was calculated using equation 1. Experimental values for IC_{50} were determined by Keana and coworkers.⁷

$$A = \log (383000/ IC_{50}) \quad 1$$

QSAR studies for NMDA receptor ion channel site interaction with the specific radioligand [³H]-(+)-5(S)-methyl-10(R),11-dihydro-5H-dibenzo[a,b]cyclohepten-5,10-imine (MK-801, **5**) and the σ receptor-specific radioligand [³H]-di-o-tolylguanidine (DTG, **6**) interaction were

obtained using CODESSA and PRECLAV programs, cross-validation being made by the "leave-one-out" method in both cases.

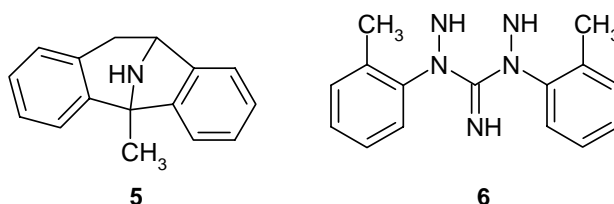


Figure 2. Structure for NMDA receptor ion channel site interaction with the specific radioligand [³H]-(+)-5(S)-methyl-10(R),11-dihydro-5H-dibenzo[a,b]cyclohepten-5,10-imine (MK801, **5**) and the σ receptor-specific radioligand [³H]-di-o-tolylguanidine (DTG, **6**).

The main differences between the CODESSA and PRECLAV programs are:

- a) Fifty per cent of molecular descriptors calculated and taken into account by these programs are different.
- b) The PRECLAV program calculates and use grid-field descriptors while the CODESSA program does not use such descriptors.
- c) For the selection of descriptors the PRECLAV program uses CLASS function instead of the criteria used by CODESSA program (only when it is working with testing sets); due to the use of CLASS functions PRECLAV program generates different QSAR equations for different testing sets.
- d) In the case of PRECLAV the main selection criterion of QSAR equations is the value of a cross-validation function while CODESSA does not use this criterion.
- e) The PRECLAV program uses only BMLR (Best MultiLinear Regression) while CODESSA allow the use of a wide range of statistical methods (Heuristic, PLS, PCA)

Results obtained with CODESSA program

The first set of QSAR correlations were done using the CODESSA program developed by Katritzky, Karelson and Lobanov.³²⁻³⁴

For [³H]-**5** (MK-801) the regression equation has the form:

$$\log A = a_0 + \sum a_i x_{ai} \quad 2$$

Values of coefficients obtained with the CODESSA program and definition of variables are given in Table 1. In Figure 3 the experimental versus estimated log A data correlation is presented.

Table 1. Coefficients and variables in equation 2

i	a_i	x_{ai}	Definition of x_{ai}
0	2.882		
1	-5.377	NBO_{Avg}	- Average bond order of a N atom
2	-38.58	MI_A	- Principal moment of inertia A
3	0.121	$NASE_{Min}$	- Minimum atomic state energy for a N atom
4	-91.43	FHDCA / HDCA	- FHDCA Fractional HDCA (HDCA/TMSA) [Quantum-Chemical PC]
5	-26.95	$CERI_{Max}$	- Maximum electrophilic reactivity index for a C atom
6	-83.72	CPC_{Min}	- Minimum partial charge for a C atom [Zefirov's PC]
7	-11.30	FNSA-2 / PNS A	- FNSA-2 Fractional PNSA (PNSA-2/TMSA) [Zefirov's PC]
8	$-9.751 \cdot 10^{-4}$	WPSA-2 / PPSA	- WPSA-2 Weighted PPSA (PPSA2*TMSA/1000) [Quantum-Chemical PC]
9	3.644	$SIGMA-PI_{Max BO}$	- Maximum SIGMA-PI bond order
10	6.147	RNDB	- Relative number of double bonds

The statistical parameters of the fit are:

$$N=49 \quad r=0.880 \quad s=0.451 \quad F=13.05 \quad Q=1.951 \quad R^2=0.774 \quad \text{cross validated} \\ R^2=0.672$$

where N is the number of data points, R and R^2 denote correlation coefficients, s is the standard deviation of the fit, F is the Fisher test and Q is the quality factor.

Results obtained with the PRECLAV program

The second set of QSAR correlations was obtained using the PRECLAV program developed by L. Tarko.^{35,36}

Results with PRECLAV program for [³H]-5 (MK-801)

$$\log A = b_0 + \sum b_i x_{bi} \quad 3$$

Values of coefficients obtained with the PRECLAV program and definition of variables are given in Table 2. In Figure 4 the experimental versus estimated log A data correlation is presented.

Table 2. Coefficients and variables in equation 3

i	b _i	x _{bi}	Definition of x _{bi}
0	2.674		
1	121.6	nhs	Number of NH single or faint bonds / Number of bonds
2	- 34.74	F 63	Resultant electrostatic force on probe atom 63
3	16.27	lhd	E(lumo+1) - E(homo-1) gap
4	- 3.769	M 36	Average chemical bonds parallax for probe atom 36
5	-1.319	zgg	Zagreb topologic index / Heavy atoms number
6	13.62	R 29	Rejection force sum on probe atom 29
7	-13.72	A 109	Attraction force sum on probe atom 109
8	32.30	A 60	Attraction force sum on probe atom 60
9	- 1.377	P 26	Maximum chemical bonds parallax for probe atom 26
10	2.138	P 97	Maximum chemical bonds parallax for probe atom 97

The statistical parameters of the fit are:

$$N=49 \quad r=0.932 \quad s = 0.308 \quad F = 25.56 \quad Q = 3.026 \quad R^2 = 0.868 \quad \text{cross validated} \\ R^2 = 0.802$$

where N is the number of data points, R and R² denote correlation coefficients, s is the standard deviation of the fit, F is the Fisher test and Q is the quality factor.

In Table 3 are listed the experimental and estimated biological activities of diarylguanidines obtained with CODESSA program (eq.2) and PRECLAV program (eq.3) for NMDA receptor ion channel.

Table 3. Experimental vs. estimated biological activity of diarylguanidines for NMDA receptor ion channel site obtained with CODESSA program (eq.2) and PRECLAV program (eq.3)

No.	Structure	X	R	R ₁	logA ⁷ (obs.)	logA (calc.) eq.2	logA (calc.) eq.3
1		2-CH ₃	H	-	1.623	2.181	1.319
2		H	H	-	2.054	1.599	1.931
3	1	2-C ₂ H ₅	H	-	2.669	2.586	3.018
4		2-CH(CH ₃) ₂	H	-	3.247	3.187	3.268
5		2-C(CH ₃) ₃	H	-	1.000	0.906	1.098
6		2-I	H	-	3.225	2.658	3.144
7		2-OCH ₃	H	-	2.379	2.508	2.487
8		2-C ₆ H ₅	H	-	1.583	2.166	1.115

Table 3. Continued

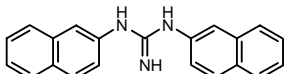
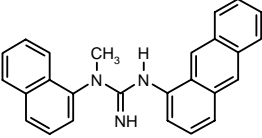
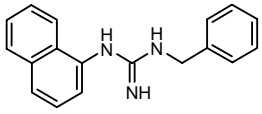
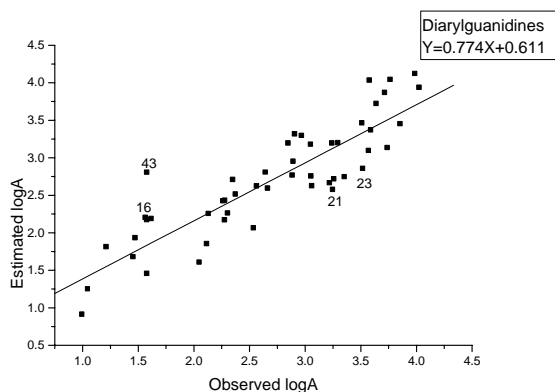
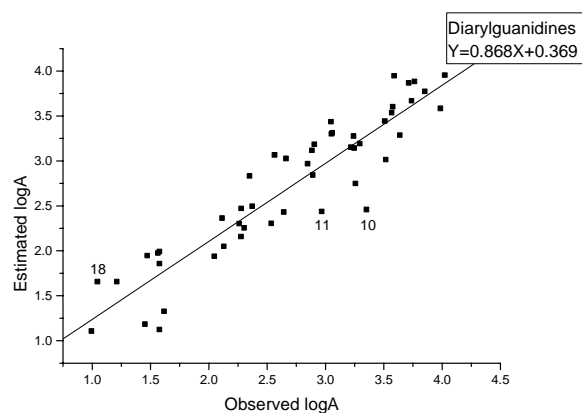
No.	Structure	X	R	R1	logA7 (obs.)	logA (calc.) eq.2	logA (calc.) eq.3
9		3-CH ₃	H	-	3.058	2.748	3.293
10		3-C ₂ H ₅	H	-	3.358	2.739	2.451
11		3-CH(CH ₃) ₂	H	-	2.974	3.288	2.430
12		3- (CH ₂) ₂ CH ₃	H	-	2.282	2.164	2.150
13		3-I	H	-	2.542	2.057	2.296
14		3-OCH ₃	H	-	2.890	2.760	3.110
15		4-CH ₃	H	-	1.459	1.673	1.174
16		4-C ₂ H ₅	H	-	1.570	2.196	1.966
17		4-CH(CH ₃) ₂	H	-	1.218	1.806	1.649
18		4-Br	H	-	1.052	1.244	1.648
19		2-CH ₃	CH ₃	-	1.583	1.450	1.848
20		3-CH ₃	CH ₃	-	2.284	2.426	2.463
21		3-C ₂ H ₅	CH ₃	-	3.253	2.568	3.135
22		-	H	H	3.065	2.617	3.304
23		-	H	CH ₃	3.523	2.850	3.006
24		-	H	C ₂ H ₅	3.515	3.457	3.435
25		-	H	C ₆ H ₅	2.898	2.943	2.834
26	2	-	CH ₃	CH ₃	3.744	3.127	3.661
27		-	CH ₃	C ₂ H ₅	3.859	3.445	3.766
28		-	CH ₃	C ₆ H ₅	2.911	3.309	3.177
29					1.479	1.926	1.938
30		3-C ₂ H ₅	H	H	3.992	4.114	3.576
31		2-CH(CH ₃) ₂	H	H	3.575	3.089	3.528
32		2-I	H	H	3.263	2.710	2.740
33	3	3-CH ₃	H	H	3.300	3.192	3.184
34		3-C ₂ H ₅	H	CH ₃	4.030	3.930	3.947
35		3-C ₂ H ₅	H	C ₂ H ₅	3.720	3.862	3.860
36		3-C ₂ H ₅	CH ₃	H	2.853	3.186	2.961
37		2-CH(CH ₃) ₂	CH ₃	H	2.649	2.799	2.423
38		3-CH ₃	H	CH ₃	3.054	3.171	3.428
39		3-NO ₃	H	CH ₃	3.644	3.714	3.279
40		3-NH ₂	H	CH ₃	2.267	2.417	2.293

Table 3. Continued

No.	Structure	X	R	R1	logA7 (obs.)	logA (calc.) eq.2	logA (calc.) eq.3
41		3-N ₃	H	CH ₃	3.770	4.035	3.876
42		3-NO ₃	CH ₃	H	2.136	2.248	2.041
43		3-NH ₂	CH ₃	H	1.583	2.798	1.983
44		3-N ₃	CH ₃	H	2.355	2.702	2.826
45		H	H	CH ₃	2.570	2.616	3.059
46		3-C ₂ H ₅	CH ₃	CH ₃	3.583	4.026	3.595
47		3-C ₂ H ₅	C ₂ H ₅	CH ₃	3.596	3.363	3.939
48	4				2.309	2.254	2.247
49					2.121	1.847	2.356

**Figure 3.** Experimental vs. estimated biological activity of diarylguanidines for NMDA receptor ion channel site obtained with CODESSA.**Figure 4.** Experimental vs. estimated biological activity of diarylguanidines for NMDA receptor ion channel site obtained with PRECLAV.

Results with CODESSA program for [³H]-6 (DTG)

For [³H]-6 (DTG) the regression equation has the form:

$$\log A = c_0 + \sum c_i x_{ci}$$

4

Values of coefficients obtained with the CODESSA program and definition of variables are given in Table 4. In Figure 5 the experimental versus estimated log *A* data correlation is presented.

Table 4. Coefficients and variables in equation 4

i	c_i	x_{ci}	Definition of x_{ci}
0	0.799		
1	103.3	HDCA-2/SQRT	- HA dependent HDCA-2/SQRT(TMSA) [Zefirov's PC]
2	2.935	FNSA-2/PNSA	- FNSA-2 Fractional PNSA (PNSA-2/TMSA) [Quantum-Chemical PC]
3	-5.732	SIGMA-PI _{Max BO}	- Maximum SIGMA-PI bond order
4	-329.4	FPSA-3 / PPSA	- FPSA-3 Fractional PPSA (PPSA-3/TMSA) [Zefirov's PC]
5	-0.093	HDSA-2	- HA dependent HDSA-2 [Quantum-Chemical PC]
6	4.522	TEI	- Topographic electronic index (all bonds) [Zefirov's PC]
7	80.13	NPCA _{Min}	- Minimum partial charge for a N atom [Zefirov's PC]
8	5.125	CBO _{Avg}	- Average bond order of a C atom
9	-0.127	KSI	- Kier shape index (order 1)
10	2.437	NVA _{Avg}	- Average valence of a N atom

The statistical parameters of the fit are:

$$N=49 \quad r=0.914 \quad s = 0.423 \quad F = 19.32 \quad Q = 2.160 \quad R^2 = 0.836 \quad \text{cross validated} \\ R^2 = 0.737$$

where *N* is the number of data points, *R* and *R*² denote correlation coefficients, *s* is the standard deviation of the fit, *F* is the Fisher test and *Q* is the quality factor.

Results with PRECLAV program for [³H]- 6 (DTG)

$$\log A = d_0 + \sum d_i x_{di} \quad 5$$

Values of coefficients obtained with the PRECLAV program and definition of variables are given in Table 5. In Figure 6 the experimental versus estimated log *A* data correlation is presented.

Table 5. Coefficients and variables in equation 5

i	d_i	x_{di}	Definition of x_{di}
0	8.593		
1	-15.98	cns	Number of CN single or faint bonds / Number of bonds
2	-2060	F 60	Resultant electrostatic force on probe atom 60
3	-1.810	P 87	Maximum chemical bonds parallax for probe atom 87
4	-0.122	lga	Number of aromatic bonds
5	-187.6	R 40	Rejection force sum on probe atom 40
6	-17.46	R 58	Rejection force sum on probe atom 58
7	-0.427	nri	Number of I atoms
8	5.436	P 7	Maximum chemical bonds parallax for probe atom 7
9	-1.509	lup	E(lumo+1) energy
10	0.394	cna	Percent of carbon · Minimum charge for C atoms

The statistical parameters of the fit are:

$$N=49 \quad r=0.938 \quad s = 0.319 \quad F = 28.45 \quad Q = 2.940 \quad R^2 = 0.880 \quad \text{cross validated} \\ R^2 = 0.814$$

where N is the number of data points, R and R^2 denote correlation coefficients, s is the standard deviation of the fit, F is the Fisher test and Q is the quality factor.

In Table 6 are listed the experimental and estimated biological activities of diarylguanidines obtained with CODESSA program (eq.4) and PRECLAV program (eq.5) for σ receptor.

Table 6. Experimental vs. estimated biological activity of diarylguanidines for σ receptor obtained with CODESSA program (eq.4) and PRECLAV program (eq.5)

No	Com pounds	X	R	R_1	$\log A^7$ (obs.)	$\log A$ (calc.) eq.4	$\log A$ (calc.) eq.5
1		2-CH ₃	H	-	4.091	3.626	2.742
2		H	H	-	2.984	3.151	3.222
3		2-C ₂ H ₅	H	-	4.437	4.080	4.285
4		2-CH(CH ₃) ₂	H	-	3.638	3.573	3.232
5	1	2-C(CH ₃) ₃	H	-	3.031	2.623	2.832
6		2-I	H	-	4.469	4.159	4.410
7		2-OCH ₃	H	-	2.284	3.069	2.377
8		2-C ₆ H ₅	H	-	1.674	1.942	1.720
9		3-CH ₃	H	-	3.949	3.086	4.290

Table 6. Continued

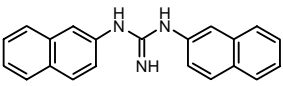
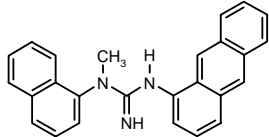
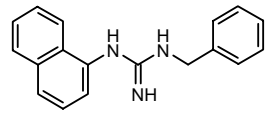
No	Com pounds	X	R	R1	logA7 (obs.)	logA (calc.) eq.4	logA (calc.) eq.5
10		3-C ₂ H ₅	H	-	4.680	3.885	4.110
11		3-CH(CH ₃) ₂	H	-	3.600	3.957	3.941
12		3- (CH ₂) ₂ CH ₃	H	-	3.959	3.828	4.072
13		3-I	H	-	3.486	4.129	3.676
14		3-OCH ₃	H	-	3.037	2.904	3.245
15		4-CH ₃	H	-	2.854	3.607	3.368
16		4-C ₂ H ₅	H	-	3.194	2.983	3.060
17		4-CH(CH ₃) ₂	H	-	3.199	3.426	3.334
18		4-Br	H	-	4.064	3.971	3.979
19		2-CH ₃	CH ₃	-	1.785	2.064	2.323
20		3-CH ₃	CH ₃	-	3.190	2.862	2.988
21		3-C ₂ H ₅	CH ₃	-	3.669	3.618	3.416
22		-	H	H	3.365	2.948	3.153
23		-	H	CH ₃	1.902	2.030	1.595
24	2	-	H	C ₂ H ₅	1.795	2.400	2.053
25		-	H	C ₆ H ₅	1.683	1.498	1.668
26		-	CH ₃	CH ₃	1.553	1.223	1.647
27		-	CH ₃	C ₂ H ₅	1.654	1.616	1.293
28		-	CH ₃	C ₆ H ₅	1.541	1.074	1.256
29						3.619	2.980
30		3-C ₂ H ₅	H	H	3.850	4.048	4.101
31		2-CH(CH ₃) ₂	H	H	3.624	3.508	3.147
32		2-I	H	H	3.981	3.567	3.719
33		3-CH ₃	H	H	3.708	3.788	3.705
34		3-C ₂ H ₅	H	CH ₃	2.178	2.718	2.323
35	3	3-C ₂ H ₅	H	C ₂ H ₅	2.242	2.161	2.539
36		3-C ₂ H ₅	CH ₃	H	2.583	2.724	2.643
37		2-CH(CH ₃) ₂	CH ₃	H	1.722	1.947	2.247
38		3-CH ₃	H	CH ₃	2.313	2.533	2.418
39		3-NO ₃	H	CH ₃	1.786	2.037	2.027
40		3-NH ₂	H	CH ₃	2.151	2.533	1.961
41		3-N ₃	H	CH ₃	2.103	2.037	1.765

Table 6. Continued

42		3-NO3	CH3	H	2.161	2.437	2.100
43		3-NH2	CH3	H	1.469	1.944	2.369
44	3	3-N3	CH3	H	2.145	2.053	2.179
45		H	H	CH3	2.120	1.706	2.635
46		3-C ₂ H ₅	CH ₃	CH ₃	2.500	1.994	2.482
47		3-C ₂ H ₅	C ₂ H ₅	CH ₃	2.223	2.590	2.245
48					2.261	2.381	2.340
	4						
49					3.437	3.763	3.396

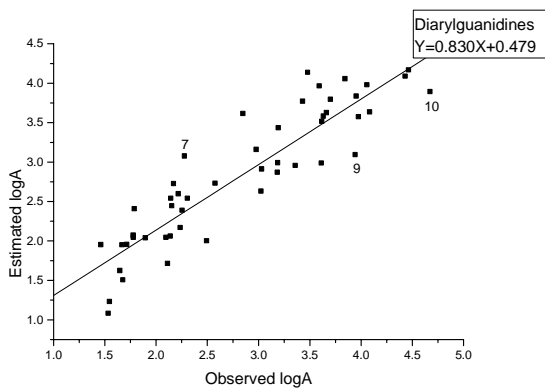


Figure 5. Experimental vs. estimated biological activity of diarylguanidines for σ receptor obtained with CODESSA.

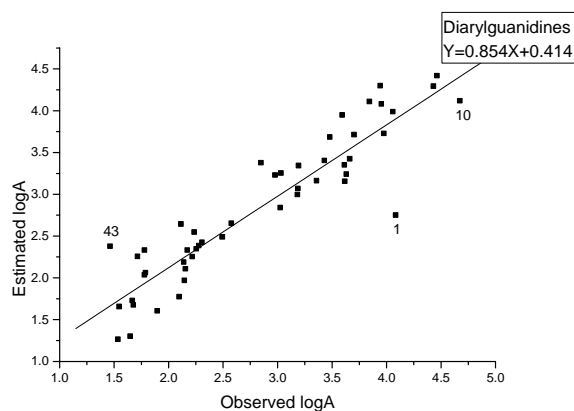


Figure 6. Experimental vs. estimated biological activity of diarylguanidines for σ receptor obtained with PRECLAV.

New topological index A_{Ad} derived from local invariants

A graph is a pair $G = (V, E)$ of sets satisfying $E \subseteq [V]^2$; thus the elements of E are 2-element subsets of V . The elements V are the vertices and E are the edges of the graph G . When V represents the atoms of a molecule and elements of E symbolize covalent bonds between pairs of atoms, then G becomes a *molecular graph*.³⁷ A graph invariant is a topological property that is conserved by molecular isomorphism. An inclusive graph invariant is one, which is the same for two or more graphs (i. e. molecules) and represents a degree of molecular similarity.^{38-41,43}

To obtain a local invariant set X one method is to solve a linear system of equations:

$$Q \cdot X = R \quad 6$$

where Q is a matrix derived from the adjacency matrix, R is a column vector and X is the column vector of local invariants x_i .^{42,43}

In the present QSAR study, we considered the distance matrix (D) obtained using MOPAC program as Q matrix, the diagonal terms being replaced with the value of the topological index J (Balaban)^{39,40,44-47} for the considered molecule. Column vector R was obtained multiplying the adjacency matrix (A) corresponding to the chemical graph with a column vector Z whose elements are the atomic numbers z_i . The equations (eq. 7) becomes:

$$D \cdot X = A \cdot Z \quad 7$$

Using the local invariant set X we built a new topological index A_{Ad} named Beteringhe-Filip-Tarko index, defined in equation 8, which has been included in the QSAR study of the interaction of diarylguanidines with the two types of receptors:

$$A_{Ad} = (q / q + N) \sum \log(x_i)^2 \quad 8$$

where q is the number of edges in the molecular graph, N is the number of vertices in the molecular graph and x_i are the local vertex invariants.

A better correlation of binding affinity ($\log A$) of diarylguanidines for σ receptor was observed including the new Beteringhe-Filip-Tarko topological index A_{Ad} in the QSAR equation.

Results with CODESSA program for [³H]-6 (DTG) including A_{Ad} in the correlation

$$\log A = e_0 + \sum e_i x_{ei} \quad 9$$

Values of coefficients and definition of variables are given in Table 7. In Table 8 are listed the experimental and estimated biological activities of diarylguanidines for σ receptor. In Figure 7 the experimental versus estimate $\log A$ data correlation is presented.

Table 7. Coefficients and variables in equation 9

i	e_i	x_{ei}	Definition of x_{ei}
0	31.56		
1	129.9	HDCA-2 / SQRT	HA dependent HDCA-2/SQRT(TMSA) [Zefirov's PC]
2	2.332	FNSA-2 / PNSA	FNSA-2 Fractional PNSA (PNSA-2/TMSA) [Quantum-Chemical PC]
3	-.023	HDSA-1	HA dependent HDSA-1 [Quantum-Chemical PC]
4	-262.5	FPSA-3 / PPSA	FPSA-3 Fractional PPSA (PPSA-3/TMSA) [Zefirov's PC]
5	2.596	TEI	Topographic electronic index (all bonds) [Zefirov's PC]
6	0.130	Min n-nR _{C-C}	Minimum n-n repulsion for a C-C bond
7	3.613	CBO _{Avg}	Average bond order of a C atom
8	-0.179	A_{Ad}	Beteringhe-Filip-Tarko topological index
9	-0.246	NASE _{Max}	Maximum atomic state energy for a N atom
10	-6.633	FHDSA / HDSA	FHDSA Fractional HDSA (HDSA/TMSA) [Quantum-Chemical PC]

The statistical parameters of the fit are:

$N=49$ $r=0.942$ $s=0.412$ $F=24.4$ $Q=2.286$ $R^2=0.887$ cross validated $R^2=0.795$
 where N is the number of data points, R and R^2 denote correlation coefficients, s is the standard deviation of the fit, F is the Fisher test and Q is the quality factor.

Table 8. Values of topological index A_{Ad} and experimental vs. estimated biological activity of diarylguanidines for σ receptor

No.	Compounds	X	R	R_1	A_{Ad}	LogA ⁷ (obs.)	logA (calc.)
1		2-CH ₃	H	-	-0.205	4.091	4.073
2		H	H	-	0.515	2.984	3.359
3		2-C ₂ H ₅	H	-	0.264	4.437	3.902
4		2-CH(CH ₃) ₂	H	-	0.229	3.638	3.342
5		2-C(CH ₃) ₃	H	-	0.127	3.031	2.910
6	1	2-I	H	-	1.214	4.469	4.243
7		2-OCH ₃	H	-	0.646	2.284	2.857
8		2-C ₆ H ₅	H	-	2.002	1.674	2.138
9		3-CH ₃	H	-	0.881	3.949	3.475
10		3-C ₂ H ₅	H	-	0.667	4.680	4.268
11		3-CH(CH ₃) ₂	H	-	1.870	3.600	4.014

Table 8. Continued

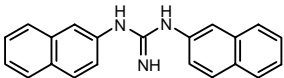
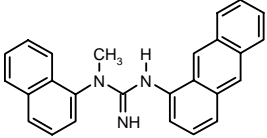
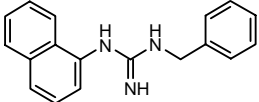
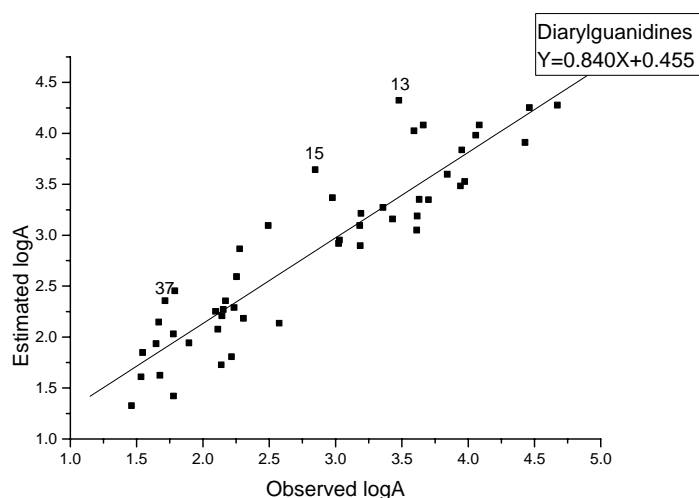
No.	Compounds	X	R	R1	AAd	LogA7 (obs.)	logA (calc.)
12		3-(CH ₂) ₂ CH ₃	H	-	-1.199	3.959	3.828
13		3-I	H	-	0.134	3.486	4.315
14		3-OCH ₃	H	-	-0.072	3.037	2.944
15		4-CH ₃	H	-	1.644	2.854	3.634
16		4-C ₂ H ₅	H	-	0.369	3.194	2.888
17		4-CH(CH ₃) ₂	H	-	1.468	3.199	3.205
18		4-Br	H	-	1.028	4.064	3.972
19		2-CH ₃	CH ₃	-	-0.228	1.785	2.022
20		3-CH ₃	CH ₃	-	1.274	3.190	3.085
21		3-C ₂ H ₅	CH ₃	-	0.579	3.669	4.072
22		-	H	H	0.717	3.365	3.263
23		-	H	CH ₃	0.654	1.902	1.933
24		-	H	C ₂ H ₅	0.653	1.795	2.445
25		-	H	C ₆ H ₅	1.436	1.683	1.615
26	2	-	CH ₃	CH ₃	0.752	1.553	1.839
27		-	CH ₃	C ₂ H ₅	0.157	1.654	1.926
28		-	CH ₃	C ₆ H ₅	0.456	1.541	1.601
29					0.653	3.619	3.041
30		3-C ₂ H ₅	H	H	0.239	3.850	3.589
31		2-CH(CH ₃) ₂	H	H	0.451	3.624	3.179
32		2-I	H	H	1.074	3.981	3.517
33		3-CH ₃	H	H	1.539	3.708	3.339
34		3-C ₂ H ₅	H	CH ₃	2.204	2.178	2.346
35		3-C ₂ H ₅	H	C ₂ H ₅	2.642	2.242	2.280
36		3-C ₂ H ₅	CH ₃	H	2.042	2.583	2.126
37		2-CH(CH ₃) ₂	CH ₃	H	1.212	1.722	2.348
38	3	3-CH ₃	H	CH ₃	2.234	2.313	2.175
39		3-NO ₃	H	CH ₃	1.657	1.786	1.412
40		3-NH ₂	H	CH ₃	-0.002	2.151	2.199
41		3-N ₃	H	CH ₃	1.593	2.103	2.242
42		3-NO ₃	CH ₃	H	0.865	2.161	2.262
43		3-NH ₂	CH ₃	H	1.811	1.469	1.316
44		3-N ₃	CH ₃	H	1.291	2.145	1.719
45		H	H	CH ₃	2.956	2.120	2.067
46		3-C ₂ H ₅	CH ₃	CH ₃	1.146	2.500	3.086

Table 8. Continued

No.	Compounds	X	R	R1	AAd	LogA7 (obs.)	logA (calc.)
47		3-C ₂ H ₅	C ₂ H ₅	CH ₃	2.148	2.223	1.797
48	4				0.608	2.261	2.584
49					-0.081	3.437	3.150

**Figure 7.** Experimental vs. estimated biological activity of diarylguanidines for σ receptor when in the QSAR equation A_{Ad} is used.

Discussion

In Tables 1-8 QSAR correlation equations are presented, either with experimental and calculated values for the binding affinity (log A) of forty-nine diarylguanidines for the NMDA receptor ion channel site and the σ receptor. The diagrams presented in Figures 3-7 show a linear dependence between experimental and calculated values of binding affinity (log A), the corresponding linear correlation equation is also presented. Comparing the values of correlation coefficient r obtained using the CODESSA and PRECLAV programs for the same number of descriptors, somewhat higher values were obtained when using PRECLAV program ($r = 0.932$ in case of NMDA

receptor ion channel site and 0.938 in case of σ receptor) than when CODESSA program was used ($r = 0.880$ in case of NMDA receptor ion channel site and 0.914 in case of σ receptor).

In the study performed with CODESSA, quantum-chemical descriptors (NBOAvg - Average bond order of a N atom - being retained as specific descriptor in the models for both receptors) have the highest weight in QSAR models for both receptors while in the study performed with PRECLAV, grid-field descriptors have the highest weight.

Grid electrostatic descriptors are resultant forces (F), repulsive (R) and attractive (A), between net atomic charges of the studied molecules and probe atoms placed in the evenly distributed points of a virtual network. Forces F, R and A represent a measure of the interaction of the molecule with the active site of the receptor in a certain zone of space.

Grid geometric descriptors are the parallaxes of atom pairs meaning the angle under which can be seen that pair of atoms from a point of the virtual network; for every network point the parallaxes are calculated for all atom pairs, then maximum parallaxes (P) and average parallaxes (M); the parallaxes are a measure of the section area of the molecule seen from a certain point of space.

The fact that in the final QSAR equations obtained with PRECLAV more grid descriptors are included than global descriptors, shows that electrostatic interactions and host-guest like interactions of the molecules with the active site are more important than other molecular characteristics (molecular mass, number of atoms of a certain type, type of chemical bonds).

When the new Beteringhe-Filip-Tarko topological index A_{Ad} , derived from local invariants of the chemical graphs of the diarylguanidines, is used an increase of the correlation coefficient ($r = 0.942$) is observed in the QSAR model corresponding to the σ receptor done using CODESSA, leading to the idea that a better structural characterization of diarylguanidines is represented in this new index. This is accountable to the fact that the new Beteringhe-Filip-Tarko index A_{Ad} was devised using the geometric characteristics of the molecule.

Conclusions

In this study the binding affinities for the NMDA receptor ion channel and σ receptor sites of four classes of diarylguanidines have been correlated with values of molecular descriptors implemented in CODESSA and PRECLAV programs: twenty-one derivatives of N, N' - Diphenylguanidines type (1), eight N, N' - Dinaphthylguanidines type (2), eighteen N - Naphthyl - N' - phenylguanidines type (3) and two miscellaneous guanidines (4).

Correlation coefficient, r , has a higher value when the PRECLAV program is used for building the QSAR model for the NMDA receptor ion channel site and σ receptor, due to the use of grid/field descriptors which show that electrostatic/host-guest interactions of the molecules with a certain site are more important than other molecular specific features.

Introduction of the new Beteringhe-Filip-Tarko topological index A_{Ad} in QSAR model for σ receptor increased the predictive value of the model.

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