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The Role of Various Theoretical Descriptors in QSAR Investigations of Toxicity of Benzodiazepine Drugs

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Abstract

In this study the efficiency of each type of CODESSA descriptors to correlate with benzodiazepines toxicity was investigated. The AM1 semiempirical approach was used to computationally optimize 26 different benzodiazepine drugs. Subsequent QSAR investigations at HF/3-21G level using CODESSA package was employed to correlate the drugs' potency with quantum chemical, electrostatic, geometrical, topological and constitutional descriptors related to each of the structures. The concluded QSAR models reflected that the drugs toxicity was mainly attributed to both geometrical and topological descriptors without any electrostatic contribution. Statistically, the most significant overall correlation was a five-parameter equation with good statistical parameters; correlation coefficient, R^2= 0.959, cross-validated correlation coefficient, R^2_{CV} = 0.901, Fisher F-criterion, F = 93.87, and the standard deviation of the regression, S^2 = 0.0242. The obtained model is good enough to be used to estimate the activities of the benzodiazepines drugs toxicity.

Keywords: benzodiazepine; toxicity; AM1; CODESSA; QSAR.

Introduction

Thousands of different benzodiazepines (BDZs) have been synthesized while only about thirty are in both therapeutic and diagnostic cases, including four of which are widely used in clinical anesthesia [1]. BDZs are widely prescribed anxiolytic drugs, which also possess immunomodulatory and anti-inflammatory properties. The main effects of benzodiazepines are sedation, hypnosis, decreased anxiety, anterograde amnesia, centrally mediated muscle relaxation and anti-convulsant activity. Practically these effects result from their actions on the central nervous system. At low doses the BDZs have anxiolytic and anti-convulsive effects. As the dose increases, the BDZs produce sedation, amnesia and finally sleep. Obviously, their effect

is dose-related but there seems to be a ceiling effect where increasing the dose does not increase the effect [2].

The fact that BDZs readily cross the blood brain barrier potentially gives them a major therapeutic advantage in the treatment of diseases characterized by production of neurotoxic immune mediators such as AIDS. Ideal therapeutic drugs for the treatment of AIDS dementia should not only readily cross the blood-brain barrier, but should also possess both direct antiviral as well as anti-inflammatory activities. Both of these properties have been demonstrated with BDZs [3]. The actions of BDZs have been believed due to the potentiation of the neural inhibition that is mediated by gamma-aminobutyric acid (GABA). GABA receptors are two pharmacologically distinct subtypes ("A" and "B") of membrane-bound proteins. The chemical structure of the each BDZ is closely linked to its receptor binding properties and also pharmacokinetics [4].

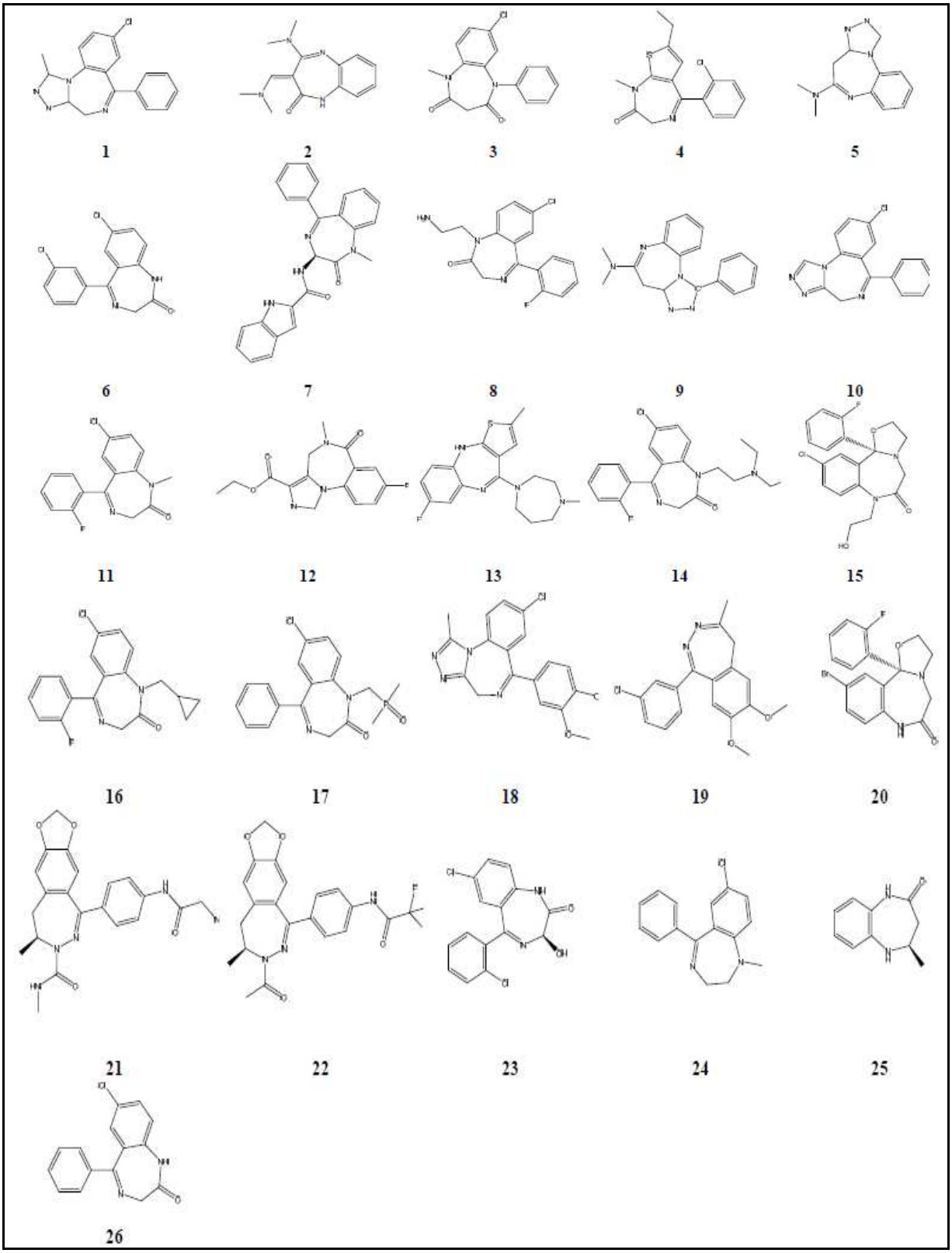
Quantitative structure – activity relationships (QSAR) have been widely used to correlate toxic activities of various chemical and biochemical compounds with computed observables [5,6]. In this regard several QSAR studies have explored the action of BDZs, including their mutual recognition and interaction with receptors [7,8]. The concluded models out of these studies included various descriptors including dipole moments, lipophilicity, ε_{HOMO}, ε_{LUMO}, molar refractivity, and local charges.

In this study, the toxic activity of several BDZs is investigated by QSAR using various types of descriptors in CODESSA [9]. We aimed to investigate the individual impact of each type of the descriptors in this type of applications. Toxic activity is commonly denoted as LD_{50}, which stands for "the logarithm of the lethal dose to 50% of a population". The higher the LD_{50}, the less toxic the material is. LD_{50}'s are expressed in mg/kg and provides a way to compare the toxicity of different substances. Here we use the $\log LD_{50}$ in Table 2 as a measure of toxicity [7].

CODESSA has been successfully employed in toxicity related investigations [10]. The package is very well known for its powerful capability of generating a large number of descriptors which describe the structural features in terms of numerical format. In such procedures, quantum-chemical methods including *ab initio* have been successfully used to calculate physicochemical parameters that represent the structural features [11].

Computational Work

The molecular geometries of the investigated BDZs (**1-26**) in scheme 1 were fully optimized with semiempirical AM1 method at the solvent-phase with the Gaussian 2003 for windows (G03W) without any applied molecular symmetry constraint [12,13]. The optimized structures were properly attributed to their local minima at the same level of theory with no imaginary frequencies. For QSAR calculations, a single point run was carried again for each of the previously optimized structures at Hartree Fock (HF/6-31G) level of theory in G03W using



Scheme 1: benzodiazepine drugs (1-26) used in the study

the route command appropriate for CODESSA version 2.10 input file. Local charges, local charges at each atom, dipole moment, $\varepsilon_{HOMO,}$ and ε_{LUMO} were calculated for each of the BDZs.

In CODESSA procedures, about 300 quantum chemical, electrostatic, geometrical, constitutional, and topological descriptors were computed for the optimized BDZs (**1-26**). Heuristic method (HM) was applied to the whole dataset of the BDZs, a pre-selection of descriptors occurs. Descriptors unavailable for some compounds are discarded altogether with the invariant descriptors and descriptors that correlate poorly. Additional descriptors are discarded when high inter-correlations between them are found. The remaining descriptors are then ranked according to their correlation coefficients. To decide whether a model generated is good or not is commonly defined by the square coefficient of fitting model (R^2), the square coefficient of cross validated (R^2_{cv}), Fisher F-criterion value which reflects the ratio of the variance explained by the model and the variance due to the error in it, and the standard deviation of the regression (s^2). Generally speaking, the values of R^2 and R^2_{cv} should approximate mutually for a good model. Correlations of all pairs of descriptors (2-parameter QSARs) are calculated, and the best combinations are saved as working sets. The 10 QSARs with the highest R^2 and the 10 with the highest F values are then saved in the program temporary library. Each working set is combined with the remaining descriptors to derive 3-paramteter QSARs. Again, the 10 QSARs with the highest R^2 and the 10 with the highest F values are saved. This method is repeated until the maximum number of parameters specified by the user is achieved.

Results and Discussion

HM of CODESSA was first employed individually with each of the five types of the descriptors included in the package. The statistical analyses of these models are displayed in Table 1 for the reached four-, and five-parameter QSAR models of each type. The mathematical description of each of the descriptors is not our immediate concern in this study, while it could be find in the literatures including CODESSA manual.

Quantum-chemical descriptors (QC) provide information about the internal electronic properties of molecules that is not available by other means. Thus they add important information to the conventional descriptors. Karelson *et al*. have reviewed the utilization of quantum chemical descriptors in the QSPRs applications in various biological and physicochemical properties [14]. With QC part of study, seven significant descriptors (D_{xQ}) were evicted in the reached models which are listed in table 1 while their numerical values are in Table 2. Namely they are; *WNSA-1 Weighted PNSA (PNSA1*TMSA/1000) [Quantum-Chemical PC]* (D_{1Q}), *HOMO-1 energy* (D_{2Q}), *Tot point-charge comp. of the molecular dipole* (D_{3Q}), *PPSA-2 Total charge weighted PPSA [Quantum-Chemical PC]* (D_{4Q}), *RNCG Relative negative charge (QMNEG/QTMINUS) [Quantum-Chemical PC]* (D_{5Q}), *Image of the Onsager-Kirkwood solvation energy* (D_{6Q}), *and Min valency of a C atom,*(D_{7Q}). As shown in Table 1, five-parameter model shows the best correlation with R^2 = 0.839, F=20.82, and s^2=0.0954. However, the big gap with the counterpart value of R^2_{CV} (0.302) presents a major drawback in this model. Obviously, the QC descriptors may have a relatively major role in explaining the toxicity of BDZs and may be relevant to their mechanism of action.

Table 1: QASR models for different types of descriptors in the correlation with BDZs toxicity.

Descriptors & Model	Descriptors involved	Symbol	Statistical Parameters
Quantum	1. WNSA-1 Weighted PNSA (PNSA1*TMSA/1000) [Q-Chem PC]	$\mathbf{D_{1Q}}$	
	2. HOMO-1 energy	$\mathbf{D_{2Q}}$	R^2=0.7965 R^2c =0.3815
	3. Image of the Onsager-Kirkwood solvation energy	$\mathbf{D_{5Q}}$	F=20.55 s^2=0.1147
4-parameter	4. Min valency of a C atom	$\mathbf{D_{6Q}}$	
	1. WNSA-1 Weighted PNSA (PNSA1*TMSA/1000) [Q-Chem PC]	$\mathbf{D_{1Q}}$	
	2. HOMO-1 energy	$\mathbf{D_{2Q}}$	
	3. Tot point-charge comp. of the molecular dipole	$\mathbf{D_{3Q}}$	R^2=0.8388 R^2cv=0.5184
5-parameter	4. PPSA-2 Total charge weighted PPSA [Q-Chem PC]	$\mathbf{D_{4Q}}$	F=20.82 s^2=0.0954
	5. RNCG Relative negative charge (QMNEG/QTMINUS) [Q-ChemPC]	$\mathbf{D_{5Q}}$	
Electrostatic	1. Topographic electronic index (all pairs) [Zefirov's PC]	$\mathbf{D_{1E}}$	
	2. Min partial charge (Qmin)	$\mathbf{D_{2E}}$	R^2=0.6355 R^2cv=0.3207
	3. WNSA-1 Weighted PNSA (PNSA1*TMSA/1000) [Zefirov's PC]	$\mathbf{D_{3E}}$	F=9.15 s^2=0.2054
4-parameter	4. PPSA-1 Partial positive surface area [Zefirov's PC]	$\mathbf{D_{4E}}$	
	1. Topographic electronic index (all pairs) [Zefirov's PC]	$\mathbf{D_{1E}}$	
	2. Min partial charge (Qmin)	$\mathbf{D_{2E}}$	
	3. WNSA-1 Weighted PNSA (PNSA1*TMSA/1000) [Zefirov's PC]	$\mathbf{D_{3E}}$	R^2=0.6587 R^2cv=0.3016
5-parameter	4. PPSA-1 Partial positive surface area [Zefirov's PC]	$\mathbf{D_{4E}}$	F=7.72 s^2=0.2020
	5. RNCG Relative negative charge (QMNEG/QTMINUS) [Zefirov's PC]	$\mathbf{D_{5E}}$	

Table 1 (continued): QASR models for different types of descriptors in the correlation with BDZs toxicity.

Descriptors & Model	Descriptors involved	Symbol	Statistical Parameters
Geometrical	1. YZ Shadow	$\mathbf{D_{4G}}$	R^2=0.7603 R^2cv=0.2003
	2. Moment of inertia B	$\mathbf{D_{6G}}$	
4-parameter	3. XY Shadow	$\mathbf{D_{7G}}$	F=9.01 s^2=0.1820
	4. ZX Shadow / ZX Rectangle	$\mathbf{D_{3G}}$	
	1. Molecular volume / XYZ Box	$\mathbf{D_{1G}}$	
	2. YZ Shadow / YZ Rectangle	$\mathbf{D_{2G}}$	R^2=0.6925 R^2cv=0.1216
5-parameter	3. ZX Shadow / ZX Rectangle	$\mathbf{D_{3G}}$	F=9.01 s^2=0.1820
	4. YZ Shadow	$\mathbf{D_{4G}}$	
	1. ZX Shadow	$\mathbf{D_{5G}}$	
Topological	2. Randic index (order 0)	$\mathbf{D_{1T}}$	
	3. Average Information content (order 0)	$\mathbf{D_{2T}}$	R^2=0.7690 R^2cv=0.4787
4-parameter	4. Average Structural Information content (order 1)	$\mathbf{D_{5T}}$	F=17.48 s^2=0.1302
	5. Complementary Information content (order 2)	$\mathbf{D_{6T}}$	
	1. Randic index (order 0)	$\mathbf{D_{1T}}$	
5-parameter	2. Average Information content (order 0)	$\mathbf{D_{2T}}$	R^2=0.7676 R^2cv=0.4188
	3. Average Structural Information content (order 1)	$\mathbf{D_{3T}}$	F=13.21 s^2=0.1376
	4. Complementary Information content (order 2)	$\mathbf{D_{4T}}$	
	5. Balaban index	$\mathbf{D_{5T}}$	
Constitutional	1. Number of C atoms	$\mathbf{D_{1C}}$	
	2. Number of Cl atoms	$\mathbf{D_{2C}}$	R^2=0.6369 R^2cv=0.1555
4-parameter	3. Number of single bonds	$\mathbf{D_{3C}}$	F=9.21 s^2=0.2047
	4. Number of rings	$\mathbf{D_{4C}}$	
	1. Number of C atoms	$\mathbf{D_{1C}}$	
5-parameter	2. Number of Cl atoms	$\mathbf{D_{2C}}$	R^2=0.6751 R^2cv=0.1988
	3. Number of single bonds	$\mathbf{D_{3C}}$	F=8.31 s^2=0.1923
	4. Number of rings	$\mathbf{D_{4C}}$	
	5. Number of benzene rings	$\mathbf{D_{5C}}$	

As t-test implies D_{2Q} is the most significant descriptor in the models followed by D_{1Q} and D_{3Q}. Quantitatively, the three descriptors are inversely proportional to $logLD_{50}$ values and thus their increases enhance the toxicity.

Table 2: Calculated quantum chemical (D_{xQ}) descriptors of the benzodiazepine drugs (1-26):

BDZ	*logLD₅₀*	*D₁Q*	*D₂Q*	*D₃Q*	*D₄Q*	*D₅Q*	*D₆Q*	*D₇Q*	*D₈Q*	*D₉Q*
1	-2.60	105.361	-9.146	7.281	1696.7	0.157	0.124	3.803	-1.667	192.073
2	-3.11	73.611	-8.558	4.758	2384.8	0.114	0.054	3.761	-1.740	142.101
3	-2.71	112.955	-9.199	7.880	1698.6	0.121	0.085	3.745	-2.312	216.563
4	-2.70	87.832	-9.220	8.598	2133.6	0.125	0.146	3.731	-1.582	159.550
5	-2.38	70.970	-9.278	4.614	1467.5	0.129	0.091	3.771	-1.578	153.512
6	-2.51	101.179	-9.281	5.437	1387.7	0.172	0.038	3.818	-1.566	193.692
7	-5.61	226.458	-8.418	13.286	2973.2	0.090	0.213	3.742	-3.709	324.620
8	-2.34	119.885	-9.470	8.456	2113.8	0.157	0.087	3.812	-2.216	211.416
9	-2.77	109.579	-8.458	4.206	2233.2	0.103	0.054	3.771	-2.055	193.695
10	-2.69	95.134	-9.413	7.219	1320.5	0.124	0.127	3.835	-1.440	184.894
11	-2.56	109.929	-9.369	7.518	1512.0	0.136	0.079	3.747	-2.037	212.480
12	-2.37	136.715	-9.942	6.012	2017.8	0.109	0.074	3.743	-2.837	245.123
13	-3.22	80.196	-8.409	7.425	3089.0	0.099	0.072	3.811	-1.745	140.007
14	-2.89	135.361	-9.346	7.214	3483.7	0.095	0.052	3.811	-2.266	202.533
15	-2.30	119.648	-9.151	3.661	2547.4	0.119	0.025	3.771	-2.392	205.618
16	-2.15	124.931	-9.331	7.377	2242.2	0.113	0.064	3.815	-2.171	212.782
17	-2.26	126.672	-9.092	8.451	3373.8	0.143	0.113	3.664	-2.858	207.727
18	-2.27	116.322	-9.184	8.327	2661.3	0.120	0.131	3.698	-1.901	188.603
19	-2.42	88.422	-8.703	4.798	2342.6	0.133	0.101	3.707	-1.418	151.801
20	-2.43	109.186	-9.182	6.394	2075.1	0.124	0.027	3.767	-2.098	197.760
21	-3.31	194.488	-8.539	7.928	4367.6	0.096	0.071	3.630	-3.468	266.967
22	-3.43	265.068	-8.920	1.794	2985.7	0.088	0.006	3.529	-4.651	373.142
23	-2.24	108.892	-9.442	8.474	1466.1	0.169	0.091	3.822	-1.808	207.002
24	-2.76	58.033	-8.672	2.966	1601.8	0.131	0.028	3.788	-0.997	117.010
25	-2.09	60.250	-8.918	5.159	1126.7	0.162	0.093	3.822	-1.683	150.241
26	-2.61	110.093	-9.064	5.825	1309.9	0.165	0.054	3.817	-1.858	215.165

D₁Q: *WNSA-1 Weighted PNSA (PNSA1*TMSA/1000) [Quantum-Chemical PC];* ***D₂Q:*** *HOMO-1 energy;* ***D₃Q:*** *Tot point-charge comp. of the molecular dipole;* ***D₄Q:*** *PPSA-2 Total charge weighted PPSA [Quantum-Chemical PC];* ***D₅Q:*** *RNCG Relative negative charge (QMNEG/QTMINUS) [Quantum-Chemical PC];* ***D₆Q:*** *Image of the Onsager-Kirkwood solvation energy;* ***D₇Q:*** *Min valency of a C atom.* ***D₈Q:*** FNSA-2 Fractional PNSA (PNSA-2/TMSA) [Quantum-Chemical PC]; ***D₉Q:*** *PNSA-1 Partial negative surface area [Quantum-Chemical PC].*

Table 3: Calculated electrostatic descriptors (D_{xE}) of the benzodiazepine drugs (1-26):

BDZ	D_{1E}	D_{2E}	D_{3E}	D_{4E}	D_{5E}
1	2.241	-0.1001	125.725	319.346	0.202
2	3.374	-0.1190	73.611	375.916	0.193
3	2.762	-0.1126	136.248	260.358	0.191
4	2.508	-0.1124	127.062	319.680	0.210
5	2.262	-0.1138	70.041	310.812	0.241
6	2.215	-0.1125	151.486	232.375	0.214
7	4.416	-0.1097	226.458	372.991	0.139
8	3.599	-0.1575	133.327	331.934	0.220
9	2.829	-0.1138	106.083	378.215	0.209
10	2.048	-0.1001	116.010	289.065	0.208
11	2.646	-0.1575	123.268	279.098	0.264
12	3.814	-0.1575	111.800	357.290	0.192
13	4.067	-0.1575	83.825	426.463	0.219
14	4.426	-0.1575	153.551	438.591	0.196
15	5.128	-0.1783	130.354	357.878	0.190
16	3.199	-0.1575	139.676	349.238	0.238
17	3.499	-0.1427	150.586	362.861	0.212
18	3.738	-0.1767	113.019	433.513	0.229
19	3.009	-0.1765	99.131	412.301	0.274
20	3.816	-0.1727	134.324	308.828	0.234
21	5.739	-0.1605	175.689	487.350	0.150
22	5.354	-0.1605	249.160	359.621	0.146
23	2.959	-0.1617	151.944	237.202	0.241
24	2.111	-0.1164	81.200	332.243	0.272
25	2.155	-0.1154	60.250	250.780	0.284
26	2.125	-0.1125	131.546	254.580	0.233

D_{1E}: *Topographic electronic index (all pairs) [Zefirov's PC];* ***D_{2E}:*** *Min partial charge (Qmin);* ***D_{3E}:*** *WNSA-1 Weighted PNSA (PNSA1*TMSA/1000) [Zefirov's PC];* ***D_{4E}:*** *PPSA-1 Partial positive surface area [Zefirov's PC];* ***D_{5E}:*** *RNCG Relative negative charge (QMNEG/QTMINUS) [Zefirov's PC]* Geometrical.

Electrostatic descriptors (D_{xE}) from the other side reflect the electrostatic structure of the molecules characterized by the partial charge distribution or the electronegativities of the atoms. The partial charges in the molecule can be calculated using the approach proposed either by Zefirov [15], which takes molecular electronegativity as a geometric mean of atomic electronegativities, or by the widely used Gasteiger–Marsili method [16], which involves iterative partial equalization of orbital electronegativity. With electrostatic descriptors (D_{xE}) in Tables 1 and 3, five significant descriptors were evicted in the reached models; *Topographic electronic index (all pairs) [Zefirov's PC]* (D_{1E}), *Min partial charge (Qmin)* (D_{2E}), *WNSA-1 Weighted PNSA (PNSA1*TMSA/1000) [Zefirov's PC]* (D_{3E}), *PPSA-1 Partial positive surface*

area [Zefirov's PC] (D_{4E}), and *RNCG Relative negative charge (QMNEG/QTMINUS) [Zefirov's PC]* (D_{5E}). As shown in Table 1, both four-, and five-parameter models show similarly low correlation with R^2 (0.636 and 0.659) with almost same differences with R^2_{CV} (0.302 and 0.321). Quantitatively, the negative coefficients of each of the descriptors here imply positive impacts on the toxicity of the structures, where their significance comes as $D_{2E} > D_{3E} > D_{4E}$. Obviously, the electrostatic descriptors may have limited contribution in explaining the toxicity of BDZs drugs.

Geometrical descriptors (D_{xG}) are derived from the information about the orientation of atoms in space. CODESSA calculates D_{xG} from the two-dimensional single values that describe the molecule's size, shape, relative position, and properties of space of molecules. Correlation of BDZs toxicity ($logLD_{50}$) with geometrical descriptors produced QSAR models with seven important descriptors (Tables 1 and 4). They are *Molecular volume/XYZ Box* (D_{1G}), *YZ Shadow/YZ Rectangle* (D_{2G}), *ZX Shadow/ZX Rectangle* (D_{3G}), *YZ Shadow* (D_{4G}), *ZX Shadow* (D_{5G}), *Moment of inertia B* (D_{6G}), and *XY Shadow* (D_{7G}). Both R^2 and R^2_{cv} in both four- and five-parameter models reflect a similar limited role to that of the electrostatic descriptors. (R^2=0.693, $R^2_{cv=}$0.122 and R^2=0.760, $R^2_{cv=}$0.200) respectively. The most important descriptor here as t-test reveals is D_{3G} followed by D_{4G} and D_{2G}.

Topological descriptors (D_{xT}) are widely utilized in modern QSAR/QSPR studies [17]. They are numerical indices based on the topology of the atoms and their bonds including the molecular connectivity, branching, and chemical conformation. The four- and five-parameter QSAR models reached in Tables 1 and 5 show that this type of descriptor is very important in correlating with the toxicity of BDZs drugs. Two models with consistent same topological descriptors were concluded with relatively good statistical parameters (R^2=0.769, R^2cv=0.479 and R^2=0.768, R^2cv=0.419). These values may reveal a greater role of the topological descriptors, compared with the other types of descriptors, in better understanding the toxic activity. These descriptors are *Randic index (order 0)* (D_{1T}), *Average Information content (order 0)* (D_{2T}), *Average Structural Information content (order 1)* (D_{3T}), *Complementary Information content (order 2)* (D_{4T}), and Balaban index (D_{5T}). While D_{2T} and D_{3T} are the most important descriptors in the model, they have opposite impact on the toxicity of BDZs.

Lastly, the constitutional descriptors (D_{xC}) reflect only the molecular composition of the compound without using the topology, geometry or electronic structure of the molecule. They consist of molecular descriptors such as molecular mass, molecular formula, formal charges, fraction of rotatable bonds; and number of rigid bonds, rings, charged groups, and so forth. An outcome of the HM of CODESSA, the best linear models with four and five parameters in Table 2 was obtained. However, the correlation was poor in terms of the large mismatching of R^2 and R^2cv in the two models respectively; R^2=0.675, R^2cv =0.199 and R^2=0.637, R^2cv =0.156. These descriptors concluded in the models are *Number of C atoms* (D_{1C}), *Number of Cl atoms* (D_{2C}), *Number of single bonds* (D_{3C}), *Number of rings* (D_{4C}), *and Number of benzene rings* (D_{5C}). According to the t-test, *Number of Cl atoms* is the most important constitutional descriptor affecting the toxic activity of the BDZs. Higher values of $D_{2C,}$ $D_{3C,}$ D_{4C} or D_{2C} would produce higher values of $logLD_{50}$. The computed values of the constitutional descriptors in the models are displayed in Table 5.

Table 4: Calculated geometrical descriptors (D_{xG}) of the benzodiazepine drugs (1-26):

BDZ	D_{1G}	D_{2G}	D_{3G}	D_{4G}	D_{5G}	D_{6G}	D_{7G}
1	0.285	0.666	0.679	51.781	66.841	7.381E-03	79.621
2	0.264	0.671	0.637	56.621	59.941	1.050E-02	75.501
3	0.281	0.655	0.712	55.161	55.161	9.466E-03	81.342
4	0.254	0.656	0.717	60.241	66.401	7.989E-03	82.302
5	0.307	0.644	0.648	38.361	47.921	1.500E-02	74.341
6	0.274	0.677	0.694	53.641	61.761	7.310E-03	74.781
7	0.221	0.696	0.563	85.122	92.802	3.485E-03	102.082
8	0.275	0.611	0.682	57.061	71.981	6.958E-03	78.121
9	0.281	0.671	0.663	48.921	66.381	6.436E-03	91.082
10	0.279	0.659	0.657	49.061	61.541	8.273E-03	76.581
11	0.254	0.603	0.676	52.381	65.041	8.458E-03	76.941
12	0.279	0.701	0.631	47.181	69.101	5.203E-03	91.662
13	0.278	0.699	0.663	60.141	63.361	6.095E-03	93.342
14	0.252	0.644	0.667	65.641	95.782	3.664E-03	88.022
15	0.286	0.682	0.630	64.021	76.001	5.927E-03	80.161
16	0.234	0.569	0.625	51.961	77.341	5.205E-03	88.842
17	0.288	0.665	0.661	53.621	75.541	4.574E-03	91.882
18	0.232	0.596	0.640	57.321	85.622	4.229E-03	83.342
19	0.228	0.625	0.644	55.201	68.981	5.043E-03	94.582
20	0.269	0.661	0.672	65.721	66.021	5.238E-03	75.521
21	0.232	0.685	0.711	68.721	84.762	2.915E-03	117.522
22	0.236	0.675	0.676	68.061	87.142	2.133E-03	108.322
23	0.276	0.695	0.703	59.421	61.801	8.467E-03	73.821
24	0.279	0.693	0.707	54.041	59.521	1.010E-02	73.321
25	0.375	0.704	0.642	33.600	40.621	2.170E-02	61.061
26	0.277	0.652	0.689	48.201	57.601	1.080E-02	75.641

D_{1G}: *Molecular volume/XYZ Box*, D_{2G}: *YZ Shadow/YZ Rectangle*, D_{3G}: *ZX Shadow/ZX Rectangle*, D_{4G}: *YZ Shadow*, D_{5G}: *ZX Shadow*, D_{6G}: *Moment of inertia B*, D_{7G}: *XY Shadow*.

Table 5: Calculated Topological (D_{xT}) and constitutional descriptors (D_{xC}) of the benzodiazepine drugs (1-26):

BDZ	D_{1T}	D_{2T}	D_{3T}	D_{4T}	D_{5T}	D_{6T}	D_{1C}	D_{2C}	D_{3C}	D_{4C}	D_{5C}
1	15.104	1.888	0.635	39.510	1.948	926	17	1	22	4	2
2	13.991	1.938	0.623	61.020	2.486	642	14	0	29	2	1
3	14.983	1.928	0.605	42.265	2.220	807	16	1	22	3	2
4	14.983	2.125	0.716	23.510	2.105	831	16	1	28	3	1
5	11.828	1.969	0.663	29.510	2.114	454	12	0	22	3	1
6	14.113	1.956	0.679	29.652	2.190	742	15	2	18	3	2
7	21.372	1.766	0.585	82.512	1.498	2572	25	0	33	5	3
8	16.397	2.125	0.695	33.652	2.209	1063	17	1	26	3	2
9	15.811	1.832	0.591	61.649	1.827	1066	18	0	27	4	2
10	14.234	1.831	0.634	32.755	1.944	822	16	1	19	4	2
11	14.983	2.065	0.682	28.406	2.255	819	16	1	21	3	2
12	15.853	2.299	0.742	18.265	2.075	956	15	0	28	3	1
13	16.681	2.054	0.657	40.265	1.734	1213	18	0	39	4	1
14	19.389	2.064	0.591	67.161	2.038	1747	21	1	38	3	2
15	18.311	2.217	0.673	39.652	2.019	1361	19	1	34	4	2
16	16.681	2.099	0.663	35.652	1.864	1197	19	1	29	4	2
17	17.320	2.098	0.624	52.265	2.153	1207	18	1	30	3	2
18	18.259	2.104	0.653	45.774	1.896	1520	19	1	30	4	2
19	16.397	1.952	0.638	43.774	2.202	1095	18	1	28	3	2
20	16.027	2.198	0.705	27.652	2.033	970	17	0	27	4	2
21	21.250	2.140	0.687	41.020	1.790	2386	21	0	41	4	2
22	22.336	2.351	0.695	43.774	1.747	2665	21	0	37	4	2
23	14.983	2.099	0.705	25.652	2.261	819	15	2	19	3	2
24	13.242	1.809	0.597	39.510	2.184	638	16	1	23	3	2
25	9.259	1.867	0.694	18.755	2.357	224	10	0	19	2	1
26	13.242	1.862	0.647	32.755	2.186	643	15	1	18	3	2

D_{1T}: *Randic index (order 0);* ***D_{2T}:*** *Average Information content (order 0);* ***D_{3T}:*** *Average Structural Information content (order 1);* ***D_{4T}:*** *Complementary Information content (order 2);* ***D_{5T}:*** *Balaban index;* ***D_{6T}:*** *Wiener index*
D_{1C}: *Number of C atoms;* ***D_{2C}:*** *Number of Cl atoms;* ***D_{3C}:*** *Number of single bonds;* ***D_{4C}:*** *Numbe of rings;* ***D_{5C}:*** *Number of benzene rings.*

The numerical values of the descriptors evicted in the preceding ten models are displayed in Tables 2-5 along with the toxic activities of the twenty six BDZs drugs in terms of $\log LD_{50}$. Though three rings are a key structural constituent in all structures and big similarity in their geometry, there are substantial differences in the listed properties. Employing HM of CODESSA seeking an all descriptors QSAR analysis, the produced four-, and five-parameter models in

Table 6 are rather amazing, where only four types of indices have been driven out. with no any electrostatic indices.

Table 6: Regression parameters and statistical quality of the correlations of the toxicity of BDZs ($logLD_{50}$) in the present study

Model	Descriptors involved		t-test	Statistical Parameters			
				R^2	R^2_{cv}	F	S^2
Eq. 1	YZ Shadow	D_{4G}	-2.89	0.932	0.840	72.20	0.038
	Average Information content (order 0)	D_{2T}	12.12				
	FNSA-2 Fractional PNSA (PNSA-2/TMSA) [Q-Chem PC]	D_{8Q}	6.32				
	Number of benzene rings	D_{5C}	-3.83				
Eq. 2	YZ Shadow	D_{4G}	-2.89	0.959	0.901	93.87	0.024
	Average Information content (order 0)	D_{2T}	12.12				
	Number of Cl atoms	D_{2C}	2.406				
	PNSA-1 Partial negative surface area [Q-Chem PC]	D_{9Q}	-7.32				
	Number of benzene rings	D_{5C}	5.24				

The five molecular descriptors (two constitutional, one quantum chemical, one geometrical, and one topological) involved in the five-parameter model are: the geometrical *YZ Shadow* (D_{4G}); the topological *Average Information content (order 0)* (D_{2T}); the constitutionals *Number of Cl atoms* (D_{2C}) and *Number of benzene rings* (D_{5C}); and the quantum-chemical *PNSA-1 Partial negative surface area [Quantum-Chemical PC]* (D_{9Q}). Unexpectedly, the four-parameter model excluded the quantum chemical D_{9Q} and replaced the constitutional (D_{2C}) with a new quantum-chemical descriptor; *FNSA-2 Fractional PNSA (PNSA-2/TMSA) [Quantum-Chemical PC]* (D_{8Q}). Obviously, each of these descriptors except the new joining one was of the most significant descriptors in the previous individual correlations.

In the models listed in Table 6 and plotted in Figs. 1 and 2, the HM based four-parameter regression expression is in eq. (1), where N everywhere is the number of compounds.

$$logLD_{50} = -(6.9686 \pm 6.5643e\text{-}1) - (5.3461e\text{-}2 \pm 5.4552e\text{-}3)\, D_{4G} + (3.6252 \pm 3.2416e\text{-}1)\, D_{2T} + (5.1733e\text{-}1 \pm 6.8261e\text{-}2)\, D_{8Q} + (5.6915e\text{-}1 \pm 1.0814e\text{-}1)\, D_{5C} \quad (1)$$

$$N = 26;\ R^2 = 0.932;\ R^2_{cv} = 0.840;\ F = 72.20;\ s^2 = 0.0773$$

n the above equation, the topological (D_{2T}) and constitutional descriptors (D_{2C}) have positive-sign coefficients, implying that an increase in their magnitude would favor an increase in $logLD_{50}$ of the BDZs drugs. According to the t-test, the most important descriptor in this model affecting the BDZs' toxicity is (D_{2T}) followed by (D_{4G}) and (D_{8Q}), indicating that the toxicity is impacted mainly by topological and geometrical but not any electrostatic descriptors.

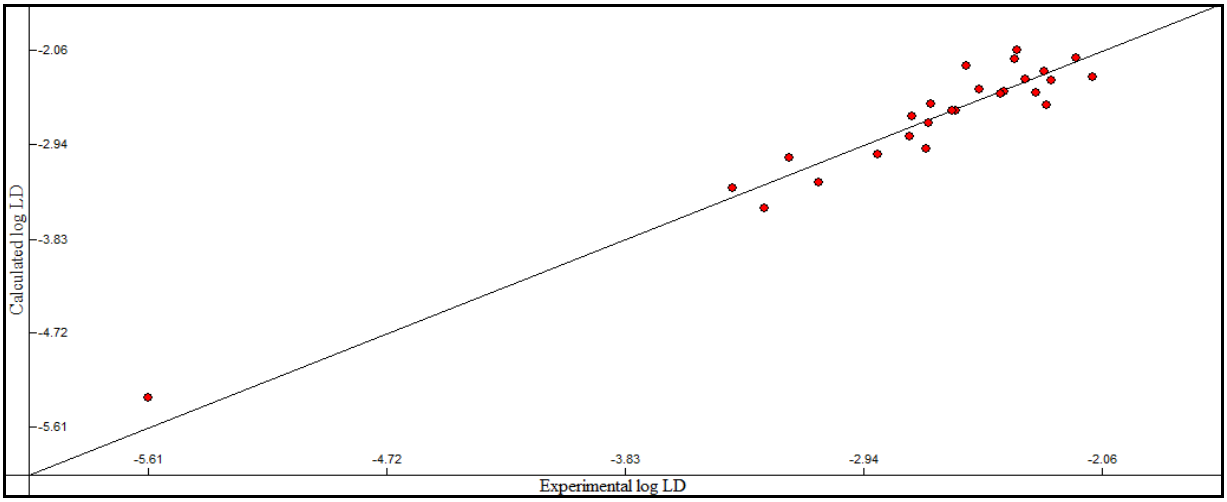


Fig. 1: Comparison of experimental and calculated toxicity of BDZs drugs from the regressional analysis in eq. (1). *R^2 = 0.932; R^2_{cv} = 0.840; F=72.20; s^2 = 0.077* for 26 BDZs.

Among the obtained five-parameter models, the best one is as shown in eq. (2). The model is summarized in Table 7 and plotted Fig. 2.

$$\log LD_{50} = - (6.3136 \pm 5.2607e\text{-}1) - (5.6120e\text{-}2 \pm 4.3527e\text{-}3)\, D_{4G} + (3.4034 \pm 2.8085e\text{-}1)\, D_{2T} + (1.5808e\text{-}1 \pm 6.5697e\text{-}2)\, D_{2C} - (6.9020e\text{-}3 \pm 9.4277e\text{-}4)\, D_{9Q} + (6.3380e\text{-}1 \pm 1.2095e\text{–}1)\, D_{5C} \quad (2)$$

$N = 26; R^2 = 0.959; R^2_{cv} = 0.901; F=93.87; s^2 = 0.0242$

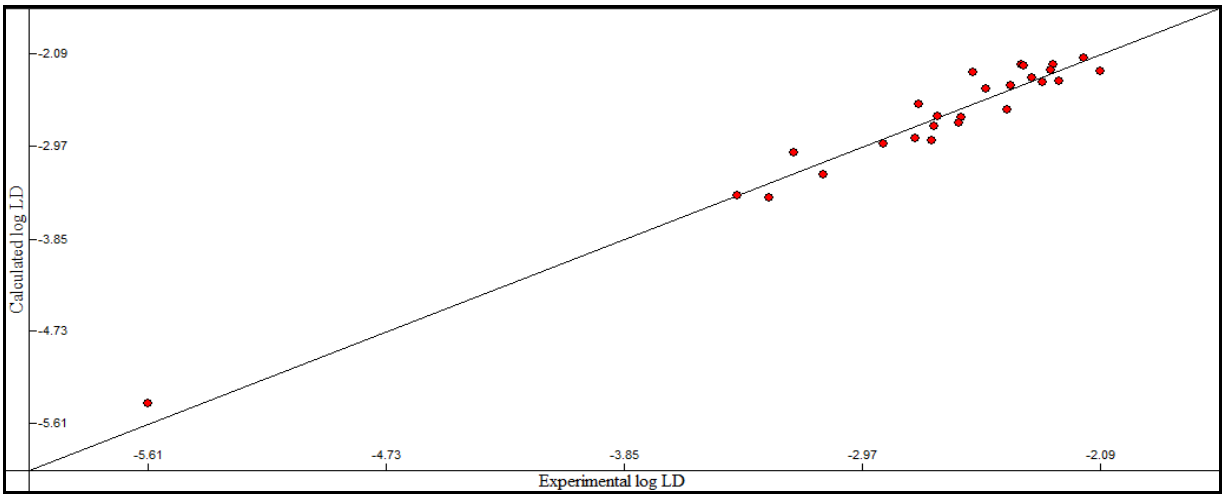


Fig. 2: Comparison of experimental and calculated toxicity of BDZs drugs from the regressional analysis in eq. (2). R^2= 0.959; R^2_{cv} = 0.901; F=93.87; s^2 = 0.024 for 26 BDZs

Similarly, in the previous model, the topological (D_{2T}) and both the constitutional descriptors (D_{2C}) and (D_{5C}) have positive-sign coefficients, implying that increasing their magnitude would favor the amount of $\log LD_{50}$ of the drugs. The most important descriptor affecting the toxicity as revealed by t-test that is (D_{2T}) followed by (D_{4G}) and (D_{9Q}), indicating that this model is

impacted mainly by topological geometrical, and quantum chemical descriptors, but not any electrostatic descriptors.

Conclusion

A comparative study for various types of descriptors in CODESSA including quantum chemical, electrostatic, geometrical, topological and constitutional was introduced to explore their significance in studying the toxicity of benzodiazepines drugs. All types except electrostatic descriptors showed specific extent of contribution in the developed QSAR models for 26 benzodiazepines. It was found that both topological and geometrical descriptors are the most significant components in the multilinear regression of toxicity of the drugs.

References

[1] K. T. Olkkola, J. Ahonen, Midazolam and Other Benzodiazepines; J. Schüttler and H. Schwilden (eds.) Modern Anesthetics. Handbook of Experimental Pharmacology 182, Springer-Verlag Berlin Heidelberg, **2008**.
[2] R.I. Hall; I.M. Schwieger; C.C. Hug; *Anesthesiology*, **1988**, 68, 862.
[3] J.R. Lokensgard; C.C. Chao; G. Gekker; S.Hu; P.K. Peterson, *Molecular Neurobiology*, 1998, 18, 23.
[4] D.R. Mould; T.M. DeFeo; S. Reele; G. Milla; R. Limjuco; T. Crews; N. Choma; I.H. Patel, *Clin. Pharmacol. Ther*, 1995, 58, 35.
[5] F.M. Abu Awwad, Islamic Univ. *J. (Nat. St. Eng)*, 2010, 18, 1.
[6] A.R. Katritzky; P. Oliferenko; A. Oliferenko; A. Lomaka; M. Karelson, *J. Phys. Org. Chem.*, 2003, 16, 811.
[7] S. Funar-Timofei; D. Ionescu; T. Suzuki; *Toxicology in Vitro*, 2010, 24, 184.
[8] D., Hadjipavlou-Litina; C. Hansch, *Chemical Reviews*, 1994, 94, 6, 1483.
[9] CODESSATM, V.2.7.10 (PC), Semichem, 7204 Mullen, Shawnee, KS, USA, Copyright Semichem and the University of Florida, **2002.**
[10] F.M. Abu-Awwad; *Int. J. ChemTech Res*, **2009**, 1, 3, 742.
[11] B. Hemmateenejad; MA. Safarpour; F. Taghavi; *THEOCHEM*, **2003**, 635,183.
[12] M. J.S. Dewar, E.G. Zoebisch, E.F. Healy, J.J.P. Stewart, *JACS*, **1985,** 107, 3902.
[13] M. J. Frisch, (1995) Gaussian (03W) **2003**, Gaussian, Inc., Pittsburgh, PA, USA.
[14] M. Karelson; V.S. Lobanov; A.R. Katritzky, *Chem Rev*, **1996**, 96, 1027.
[15] N.S. Zefirov; others, Doklady Akad. Nauk. *SSSR*, **1987**, 296, 883.
[16] J. Gasteiger; M. Marsili; *Tetrahedron*, **1980**, 36, 3219.
[17] F. Tiana; P. Zhoua; Z. Li; *J Molec Struct*, 2007, 830, 1-3, 106.