



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].

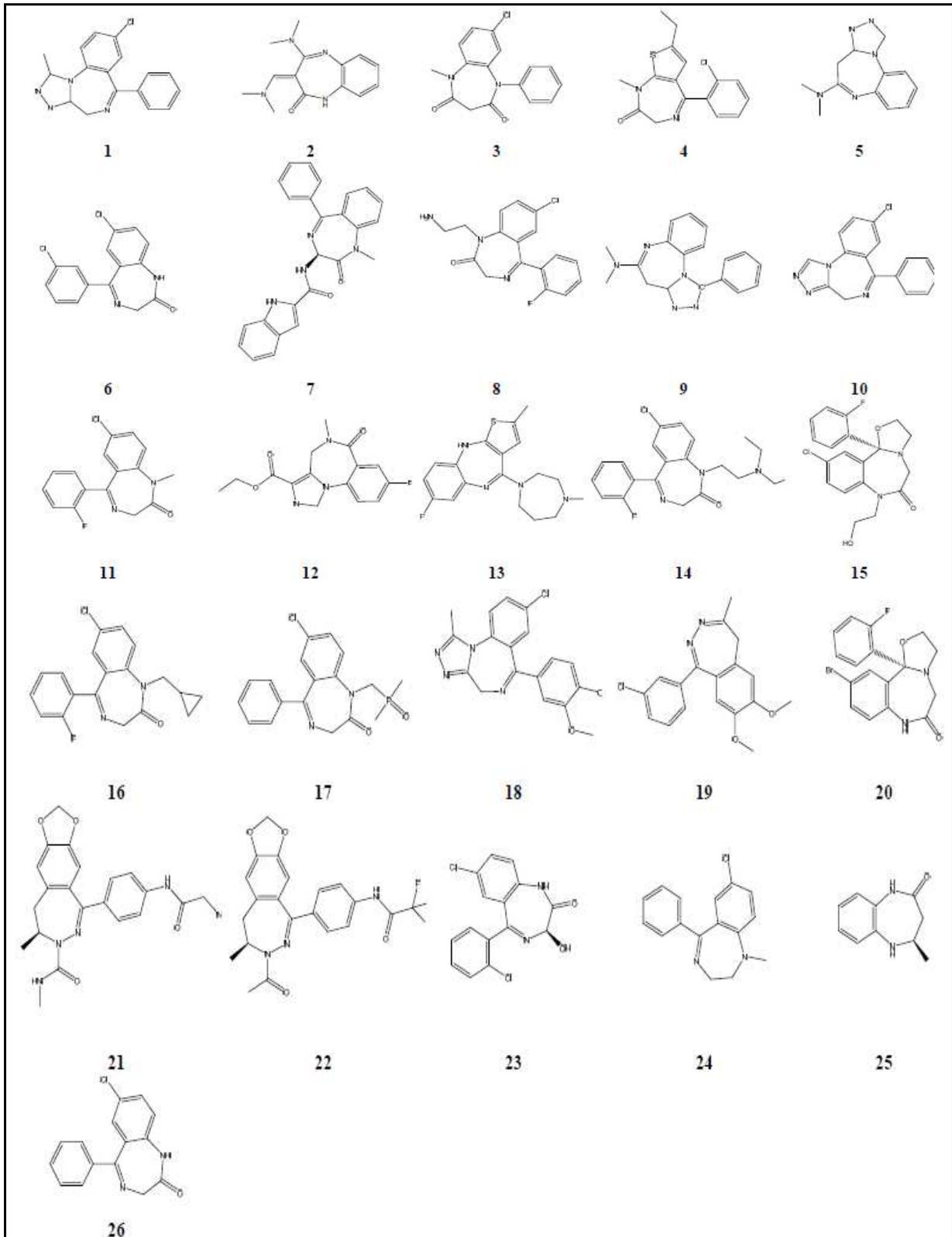
Quantitative structure – activity relationships (QSAR) have been widely used to correlate toxic activities of various chemical and biochemical compounds with computed observables [5,6]. In this regard several QSAR studies have explored the action of BDZs, including their mutual recognition and interaction 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 $\log\text{LD}_{50}$ 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, ϵ_{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-parameter 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 found 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 4-parameter | 1. WNSA-1 Weighted PNSA (PNSA1*TMSA/1000) [Q-Chem PC] 2. HOMO-1 energy 3. Image of the Onsager-Kirkwood solvation energy 4. Min valency of a C atom | D_{1Q} D_{2Q} D_{5Q} D_{6Q} | $R^2=0.7965$ $R^2_c=0.3815$ $F=20.55$ $s^2=0.1147$ |
| | 1. WNSA-1 Weighted PNSA (PNSA1*TMSA/1000) [Q-Chem PC] 2. HOMO-1 energy 3. Tot point-charge comp. of the molecular dipole 4. PPSA-2 Total charge weighted PPSA [Q-Chem PC] 5. RNCG Relative negative charge (QMNEG/QTMINUS) [Q-ChemPC] | D_{1Q} D_{2Q} D_{3Q} D_{4Q} D_{5Q} | $R^2=0.8388$ $R^2_{cv}=0.5184$ $F=20.82$ $s^2=0.0954$ |
| Electrostatic 4-parameter | 1. Topographic electronic index (all pairs) [Zefirov's PC] 2. Min partial charge (Qmin) 3. WNSA-1 Weighted PNSA (PNSA1*TMSA/1000) [Zefirov's PC] 4. PPSA-1 Partial positive surface area [Zefirov's PC] | D_{1E} D_{2E} D_{3E} D_{4E} | $R^2=0.6355$ $R^2_{cv}=0.3207$ $F=9.15$ $s^2=0.2054$ |
| | 1. Topographic electronic index (all pairs) [Zefirov's PC] 2. Min partial charge (Qmin) 3. WNSA-1 Weighted PNSA (PNSA1*TMSA/1000) [Zefirov's PC] 4. PPSA-1 Partial positive surface area [Zefirov's PC] 5. RNCG Relative negative charge (QMNEG/QTMINUS) [Zefirov's PC] | D_{1E} D_{2E} D_{3E} D_{4E} D_{5E} | $R^2=0.6587$ $R^2_{cv}=0.3016$ $F=7.72$ $s^2=0.2020$ |

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 | D_{4G} | $R^2=0.7603$ $R^2_{cv}=0.2003$ $F=9.01$ $s^2=0.1820$ |
| | 2. Moment of inertia B | D_{6G} | |
| 4-parameter | 3. XY Shadow | D_{7G} | $R^2=0.6925$ $R^2_{cv}=0.1216$ $F=9.01$ $s^2=0.1820$ |
| | 4. ZX Shadow / ZX Rectangle | D_{3G} | |
| 5-parameter | 1. Molecular volume / XYZ Box | D_{1G} | $R^2=0.7676$ $R^2_{cv}=0.4188$ $F=13.21$ $s^2=0.1376$ |
| | 2. YZ Shadow / YZ Rectangle | D_{2G} | |
| Topological | 3. ZX Shadow / ZX Rectangle | D_{3G} | $R^2=0.6369$ $R^2_{cv}=0.1555$ $F=9.21$ $s^2=0.2047$ |
| | 4. YZ Shadow | D_{4G} | |
| 4-parameter | 1. ZX Shadow | D_{5G} | $R^2=0.6751$ $R^2_{cv}=0.1988$ $F=8.31$ $s^2=0.1923$ |
| | 2. Randic index (order 0) | D_{1T} | |
| 5-parameter | 3. Average Information content (order 0) | D_{2T} | $R^2=0.7690$ $R^2_{cv}=0.4787$ $F=17.48$ $s^2=0.1302$ |
| | 4. Average Structural Information content (order 1) | D_{5T} | |
| Constitutional | 5. Complementary Information content (order 2) | D_{6T} | $R^2=0.6751$ $R^2_{cv}=0.1988$ $F=8.31$ $s^2=0.1923$ |
| | 1. Number of C atoms | D_{1C} | |
| 4-parameter | 2. Number of Cl atoms | D_{2C} | $R^2=0.6751$ $R^2_{cv}=0.1988$ $F=8.31$ $s^2=0.1923$ |
| | 3. Number of single bonds | D_{3C} | |
| 5-parameter | 4. Number of rings | D_{4C} | $R^2=0.6751$ $R^2_{cv}=0.1988$ $F=8.31$ $s^2=0.1923$ |
| | 1. Number of C atoms | D_{1C} | |
| 4-parameter | 2. Number of Cl atoms | D_{2C} | $R^2=0.6751$ $R^2_{cv}=0.1988$ $F=8.31$ $s^2=0.1923$ |
| | 3. Number of single bonds | D_{3C} | |
| 5-parameter | 4. Number of rings | D_{4C} | $R^2=0.6751$ $R^2_{cv}=0.1988$ $F=8.31$ $s^2=0.1923$ |
| | 5. Number of benzene rings | 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 $\log LD_{50}$ values and thus their increases enhance the toxicity.

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

| BDZ | $\log LD_{50}$ | D_{1Q} | D_{2Q} | D_{3Q} | D_{4Q} | D_{5Q} | D_{6Q} | D_{7Q} | D_{8Q} | D_{9Q} |
|-----|----------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| 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 |

D_{1Q} : WNSA-1 Weighted PNSA ($PNSA1 * TMSA / 1000$) [Quantum-Chemical PC]; D_{2Q} : HOMO-1 energy; D_{3Q} : Tot point-charge comp. of the molecular dipole; D_{4Q} : PPSA-2 Total charge weighted PPSA [Quantum-Chemical PC]; D_{5Q} : RNCG Relative negative charge (QMNEG/QTMINUS) [Quantum-Chemical PC]; D_{6Q} : Image of the Onsager-Kirkwood solvation energy; D_{7Q} : Min valency of a C atom. D_{8Q} : FNSA-2 Fractional PNSA ($PNSA-2 / TMSA$) [Quantum-Chemical PC]; D_{9Q} : PNSA-1 Partial negative surface area [Quantum-Chemical PC].

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

| <i>BDZ</i> | 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 (Q_{min}); 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 (Q_{min})* (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 ($\log LD_{50}$) 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 ($R^2=0.769$, $R^2_{cv}=0.479$ and $R^2=0.768$, $R^2_{cv}=0.419$). 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^2_{cv} in the two models respectively; $R^2=0.675$, $R^2_{cv}=0.199$ and $R^2=0.637$, $R^2_{cv}=0.156$. 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 $\log LD_{50}$. 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):

| <i>BDZ</i> | 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):

| <i>BDZ</i> | 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} : Number 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 (logLD₅₀) 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 | | | | |
| | Average Information content (order 0) | D _{2T} | 12.12 | | | | |
| | FNSA-2 Fractional PNSA (PNSA-2/TMSA) [Q-Chem PC] | D _{8Q} | 6.32 | 0.932 | 0.840 | 72.20 | 0.038 |
| | Number of benzene rings | D _{5C} | -3.83 | | | | |
| Eq. 2 | YZ Shadow | D _{4G} | -2.89 | | | | |
| | Average Information content (order 0) | D _{2T} | 12.12 | | | | |
| | Number of Cl atoms | D _{2C} | 2.406 | 0.959 | 0.901 | 93.87 | 0.024 |
| | 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 constitutinals *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.

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

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

In 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 logLD₅₀ 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.

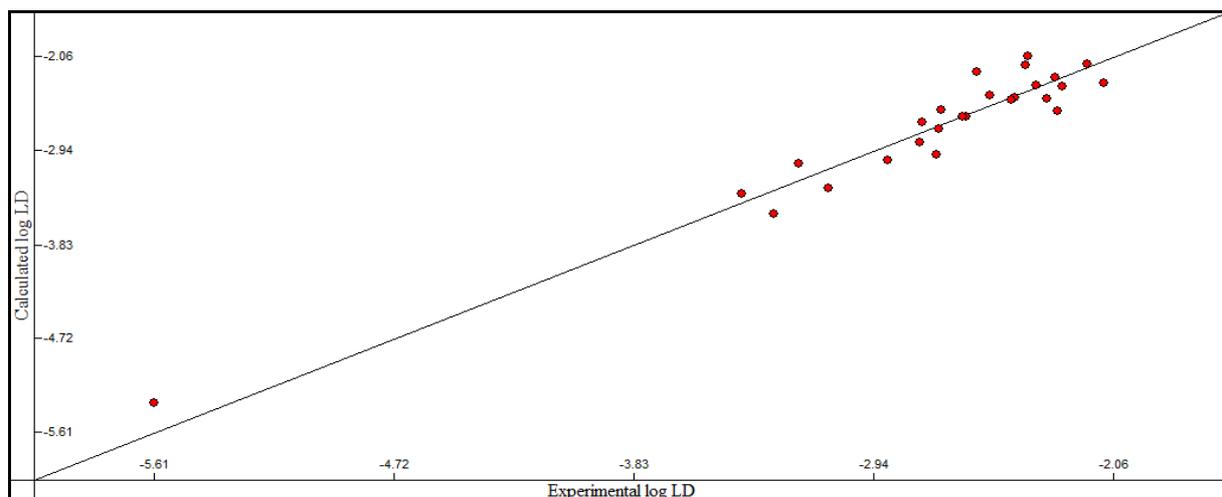


Fig. 1: Comparison of experimental and calculated toxicity of BDZs drugs from the regression analysis in eq. (1). $R^2 = 0.932$; $R^2_{cv} = 0.840$; $F=72.20$; $s^2 = 0.077$ for 26 BDZs.

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.

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

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

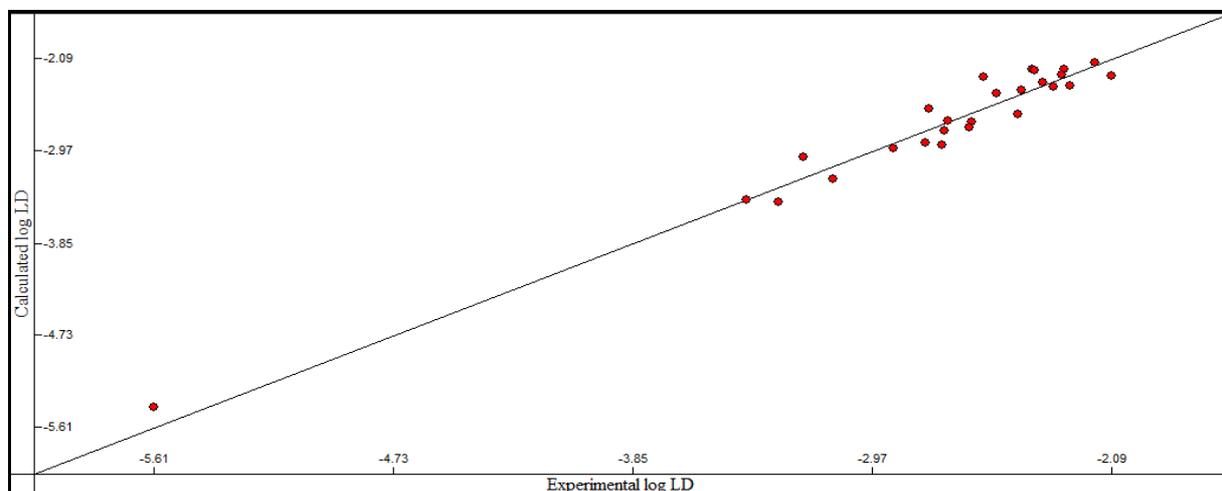


Fig. 2: Comparison of experimental and calculated toxicity of BDZs drugs from the regression analysis in eq. (2). $R^2 = 0.959$; $R^2_{cv} = 0.901$; $F=93.87$; $s^2 = 0.024$ for 26 BDZs

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.

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