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A QSAR Study of the Activity of Some Fluorinated Anesthetics

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Abstract

The density functional B3LYP was used to computationally investigate the anesthetic activity of 19 different fluorinated anesthetics. The structures were optimized at 6-311G** basis set and subsequent quantitative structure–activity relationship investigation using CODESSA package was employed to correlate the molecular anesthetic activities with several computed descriptors. In the computed models, the activity was mainly attributed to both quantum mechanical and electrostatic observables. Statistically, the most significant correlation was a four- parameter equation with good statistical parameters; correlation coefficients, R^2= 0.985, cross-validated correlation coefficients, R^2_{CV} = 0.972, F = 225.096, and S^2 = 0.227. The obtained model is good enough to be used to estimate the activities of the fluorinated anesthetics.

Keywords: anesthetic; flouro-compounds; B3LYP; CODESSA; QSAR.

Introduction

Quantitative structure – activity/property relationships (QSAR/QSPR) have been widely used to correlate pharmacological activities of various chemical compounds with computed related observables [1, 2]. A primary step in constructing the QSAR/QSPR models is finding one or more molecular descriptors that represent variation in the structural property of the molecules. The concluded mathematical equations relate the computed structural features to the molecular therapeutic or biological activities. Usually, these equations provide vital information for further development of the drugs design and enhance the capacity to estimate the property of other molecules or to find the parameters affecting the potency.

CODESSA has been successfully employed in several QSAR studies [3,4]. The main advantage of CODESSA over other packages in these applications is the easy generation of a large number of theoretical descriptors which code the chemical structure in numerical format. For such analysis, quantum-chemical methods are used to calculate physicochemical parameters that

represent the structural features. In this regard, *ab initio* method has been successfully applied to study some drugs [5].

The most recent enhancement of the computer technology and electronic structure software allow calculating quantum chemical descriptors at first-principle levels with higher accuracy including some effective consideration of electron correlation effects. Also, the evolution and the subsequent development of density functional theory (DFT) have been inspiring researchers to further use in both chemical and biological applications. The theory's major features of relatively low computational costs and realistic accuracy have been motivating this trend of research [6].

Several types of molecules produce some extent of anesthesia indicating that the property is not linked to some particular features of chemical composition or structure [7]. As a common example of potent anesthetics widely used in medical applications are fluorinated anesthetics such as alkanols [8]. The diversity of molecular structures of anesthetics made it hard for early researchers to attribute the general anesthetics act to a specific manner. Hence, their action on neuronal membrane was thought to be global rather than site-specific interaction [9].

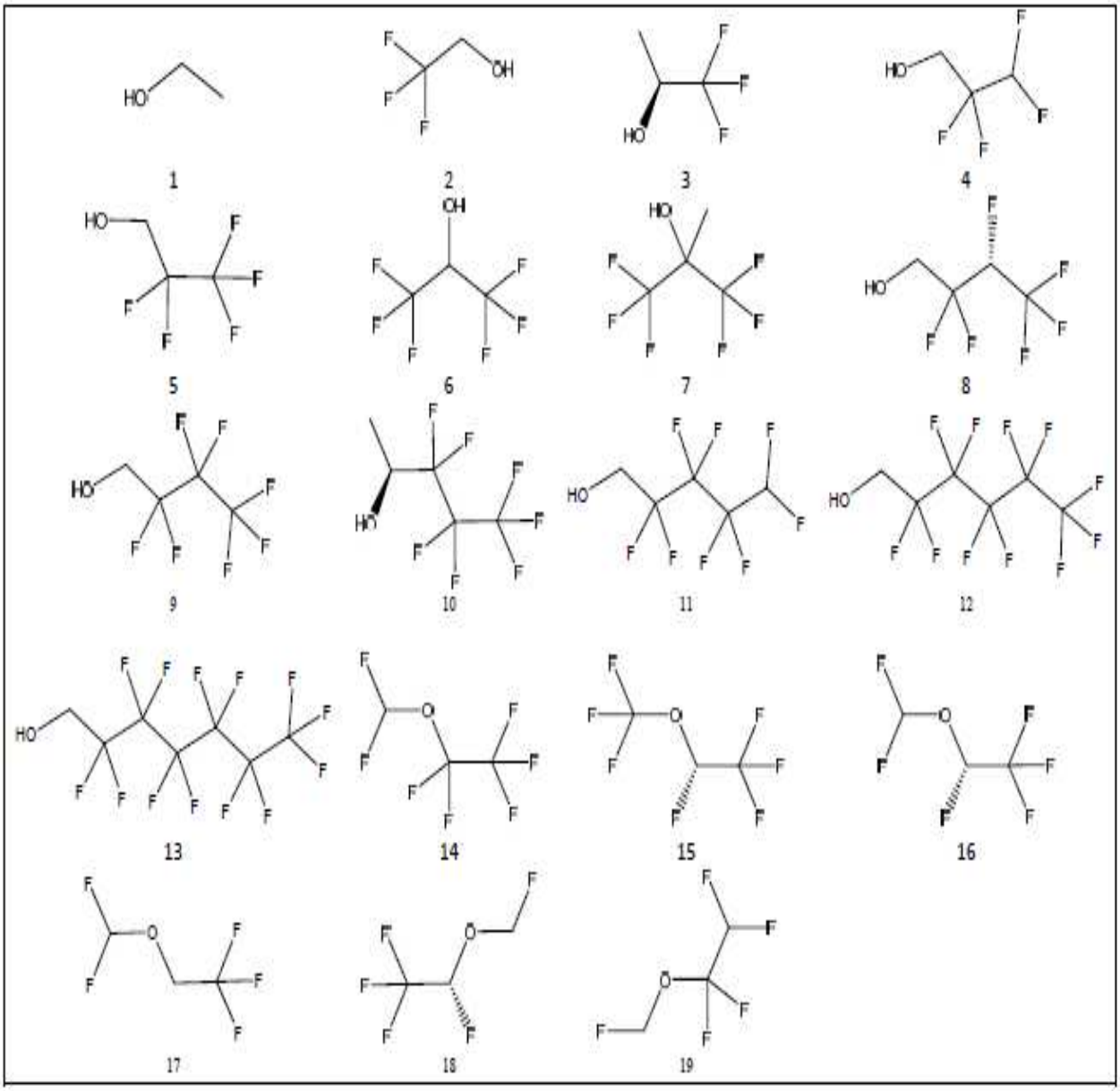
Two fundamentally different approaches have been used in order to characterize interactions between anesthetics and their targets; thermodynamic and molecular descriptions [10]. Thermodynamic descriptions consider averages over many individual interactions, while molecular descriptions attempt to measure directly individual interactions between anesthetic molecules and their molecular targets. The thermodynamic approach has been largely replaced by molecular approaches while more revised molecular methods have become available. Attempts have been made to identify the contributions of hydrophobic and weak polar interactions by using multiple linear regression analysis on thermodynamic parameters [11]. The desired function requires that the interactions be weak and readily reversible such as van der Waals intermolecular association [12]. Also, both polarity and nonpolarity appear to be vital factors implying that the sites of anesthetic activity must be able to accommodate both types of interactions [13].

Equations have been used to quantify the relative contributions of various physical properties of an anesthetic such as its ability to donate or accept a hydrogen bond, its dipolarity and polarizability, and its size, to the magnitude of partition coefficients or concentrations of anesthetic endpoints [14].

In this study, the anesthetic activity of several fluorinated anesthetics reported in the literature as potent and anesthetics agents are investigated by QSAR [2,8,12]. We aimed to study the effect of various fluorine substitutions on the anesthetic potency. Anesthetic activity is commonly measured by the minimum alveolar anesthetic concentration (MAC), which is the least amount needed to produce no response in rats to electrical stimulation [15]. The lower the MAC, the more powerful is the anesthetic. For numeral simplicity, researchers may also express the anesthetic activity as pMAC (-log MAC).

Computational Methodology

The molecular geometries of the investigated fluorinated anesthetics (**1-19**) in scheme 1 were fully optimized with DFT method at the hybrid functional B3LYP (Becke's three-parameter functional employing the Lee, Yang, and Parr correlation functional) and the medium-size basis set 6-311G(d,p) level [16]. The full optimization was carried out at the solvent-phase with both the Gaussian 2003 for windows (G03W) without any applied molecular symmetry constraint [17]. The route command used in G03W was appropriate to use the output file in CODESSA based QSAR calculations [18]. The optimized structures were properly attributed to their local minima where the matrices of the energy second derivatives were checked at the same level of theory to have zero imaginary values. Local charges, local charges at each atom, dipole moment, HOMO and LUMO energies were calculated for each of the compounds.



Scheme 1: Fluorinated anesthetics (1-19) used in the study

For CODESSA part, about 300 constitutional, topological, geometrical, electrostatic, and quantum mechanical descriptors were computed for the geometrical features of the fluorinated anesthetics (**1-19**). Similarly to our previous studies, the heuristic method (HM) was then applied to the whole dataset of the compounds to select the rough starting regression models. As in our previous studies, the maximum number of descriptors used was set to 5 to keep the recommended ratio between the number of descriptor exploited and the available known molecules reported in the literature when employing multiple linear regressions (MLR) [19]. Quality of the expected correlation was identified through both the more or less significant descriptors from the standpoint of a single-parameter correlation, and then the highly inter-correlated descriptors. Descriptors for which values could not be calculated and/or descriptors of low variance in each dataset were discarded. A stepwise addition of descriptors is employed to reach the best multi-parameter regression models with optimal values of the statistical parameters including highest values of regression factor R^2, the cross-validated R^2_{cv}, Fisher F-criterion value and s^2, and the standard deviation of the regression.

Results and Discussion

The anesthetic activities are listed in Table 1 along with several significant computed descriptors. Employing HM of CODESSA-based QSAR analysis in the study, three types of descriptors has evicted in the reached models; two quantum mechanical, two electrostatic, and one constitutional. Namely, the descriptors are *Average bond order of a H atom* (**D_1**) and *minimum nucleophilic reaction index for a O atom* (**D_4**) are quantum-chemical descriptors; *WPSA-3 Weighted PPSA (PPSA3*TMSA/1000) {Zefirov's PC}* (**D_3**) and *maximum partial charge for a H atom [Zefirov's PC]* (**D_5**) are electrostatic descriptors; and n*umber of H atoms* (**D_2**) is a constitutional descriptor.

Quantum-chemical descriptors add important information to the conventional descriptors. They provide information about the internal electronic properties of molecules that is not available by other means. Karelson *et al*. have reviewed the utilization of quantum chemical descriptors in the provision of QSPRs with a wide variety of biological and physicochemical properties [20].

Electrostatic descriptors 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 [21], which takes molecular electronegativity as a geometric mean of atomic electronegativities, or by the widely used Gasteiger–Marsili method, which involves iterative partial equalization of orbital electronegativity [22].

Constitutional descriptors reflect only the molecular composition of the compound without using the topology, geometry or electronic structure of the molecule.

Table 1: Calculated CODESSA-based descriptors of the fluorinated anesthetics (1-19):

Sys.	pMAC	D_1	D_2	D_3	D_4	D_5	D_6	D_7	D_8	D_9	D_{10}	D_{11}
1	3.000	0.916	6	1.181	0.047	0.082	-	-	-	0.445	-	-
2	3.150	0.877	3	1.287	0.045	0.093	0.879	-0.099	-0.358	0.458	-0.099	1.87E-04
3	3.280	0.900	5	1.308	0.044	0.092	0.877	-0.099	-0.356	0.456	-0.099	8.59E-05
4	4.240	0.888	4	1.874	0.045	0.099	0.873	-0.118	-0.353	0.463	-0.117	5.83E-05
5	3.280	0.874	3	1.411	0.044	0.092	0.879	-0.108	-0.339	0.461	-0.085	8.22E-05
6	4.350	0.832	2	1.023	0.040	0.103	0.886	-0.091	-0.345	0.471	-0.091	5.97E-05
7	3.640	0.888	4	1.034	0.037	0.102	0.880	-0.092	-0.355	0.467	-0.092	8.19E-04
8	4.350	0.882	4	1.739	0.042	0.091	0.869	-0.126	-0.345	0.457	-0.090	2.65E-05
9	3.400	0.870	3	1.026	0.039	0.092	0.877	-0.111	-0.333	0.464	-0.081	7.09E-05
10	3.300	0.899	5	1.533	0.044	0.091	0.878	-0.111	-0.340	0.458	-0.081	3.06E-06
11	4.700	0.885	4	2.188	0.043	0.104	0.869	-0.113	-0.340	0.462	-0.100	3.95E-06
12	3.340	0.872	3	1.549	0.042	0.092	0.879	-0.112	-0.337	0.457	-0.080	1.24E-06
13	3.370	0.872	3	1.746	0.040	0.092	0.878	-0.112	-0.338	0.457	-0.080	2.06E-06
14	-4.942	0.929	1	0.598	0.028	0.110	0.888	-0.107	-0.338	0.138	-0.079	1.20E-04
15	-5.604	0.921	1	0.407	0.010	0.101	0.890	-0.116	-0.329	0.176	-0.076	2.54E-04
16	-2.515	0.921	2	1.365	0.019	0.106	0.878	-0.119	-0.344	0.175	-0.088	1.42E-03
17	-0.343	0.924	3	1.521	0.036	0.103	0.877	-0.114	-0.347	0.199	-0.097	9.73E-05
18	-2.693	0.934	3	1.695	0.025	0.095	0.874	-0.146	-0.343	0.157	-0.089	1.44E-04
19	-2.536	0.933	3	1.579	0.018	0.104	0.866	-0.143	-0.343	0.163	-0.099	2.35E-03

pMAC: *anesthetic activity;* ***D_1:*** *Avg bond order of a H atom;* ***D_2:*** *Number of H atoms;* ***D_3:*** *WPSA-3 Weighted PPSA (PPSA3*TMSA/1000) [Zefirov's PC];* ***D_4:*** *Min nucleoph. react. index for a O atom;* ***D_5:*** *Max partial charge for a H atom [Zefirov's PC];* ***D_6:*** *Avg bond order of a F atom;* ***D_7:*** *Avg bond order of a H atom;* ***D_8:*** *Max net atomic charge for a F atom;* ***D_9:*** *Avg valency of a F atom;* ***D_4:*** *HOMO - LUMO energy gap;* ***D_5:*** *HOMO energy;* ***D_6:*** *LUMO energy;* ***D_7:*** *Max partial charge for a F atom [Zefirov's PC]; Max net atomic charge for a F atom;* ***D_8:*** *Max net atomic charge for a H atom;* ***D_9:*** *Max net atomic charge for a H atom;* ***D_{10}:*** *Max partial charge for a F atom [Zefirov's PC];* ***D_{11}:*** *Min nucleoph. react. index for a F atom.*

Table 1 (continued): Calculated CODESSA-based descriptors of the fluorinated anesthetics (1-19):

Sys.	D_{12}	D_{13}	D_{14}	D_{15}	D_{16}	D_{17}	D_{18}	D_{19}	D_{20}	D_{21}	D_{22}	D_{23}
1	67.241	52.994	46.068	0.263	1.607	8.353	-7.348	1.006	169.676	166.995	40.423	43.104
2	82.722	68.787	100.039	0.338	3.383	8.719	-8.313	0.406	78.158	76.818	149.981	151.321
3	99.322	85.710	114.066	0.338	3.449	8.657	-8.190	0.467	110.217	110.217	150.033	150.033
4	99.842	89.863	132.056	0.305	3.304	8.487	-8.134	0.353	93.142	91.802	173.480	174.820
5	104.802	96.286	150.046	0.368	3.450	8.684	-8.425	0.259	71.285	70.615	204.684	205.354
6	111.522	101.348	168.036	0.332	2.505	9.352	-9.054	0.297	38.566	38.170	244.166	244.166
7	122.202	117.298	182.063	0.333	0.887	9.805	-8.949	0.856	80.453	72.524	209.985	218.028
8	130.842	117.830	182.063	0.360	1.668	8.725	-8.335	0.391	75.875	72.524	239.595	242.946
9	131.482	123.265	200.053	0.376	1.928	8.964	-8.495	0.469	52.109	50.099	254.266	256.277
10	149.079	139.800	214.080	0.377	3.447	8.568	-8.244	0.324	98.289	98.289	236.576	236.576
11	142.480	145.385	232.070	0.338	4.342	8.506	-8.453	0.053	80.453	79.113	264.735	266.075
12	184.553	177.671	300.067	0.379	1.674	8.440	-8.486	-0.046	56.312	52.961	336.780	340.131
13	208.309	204.852	350.074	0.379	1.710	8.362	-8.478	-0.116	59.266	57.256	365.628	367.638
14	122.122	106.678	186.026	0.327	1.309	11.770	-10.561	1.210	17.370	17.370	291.658	291.658
15	120.802	106.466	186.026	0.339	1.255	11.579	-10.515	1.064	13.360	13.360	286.977	286.977
16	114.442	101.568	168.036	0.320	1.637	11.383	-10.097	1.285	43.521	43.521	252.278	252.278
17	112.922	96.498	150.046	0.300	2.577	9.944	-9.232	0.712	62.038	60.698	237.521	238.861
18	110.922	96.414	150.046	0.344	2.974	10.394	-9.661	0.733	74.648	74.648	218.082	218.082
19	107.802	96.266	150.046	0.321	2.897	10.505	-9.476	1.028	68.729	68.729	211.092	211.092

D_{12}: *Molecular surface area;* ***D_{13}:*** *Molecular volume;* ***D_{14}:*** *Molecular weight;* ***D_{15}:*** *Polarity parameter (Qmax-Qmin);* ***D_{16}:*** *Tot dipole of the molecule;* ***D_{17}:*** *HOMO - LUMO energy gap;* ***D_{18}:*** *HOMO energy;* ***D_{19}:*** *LUMO energy;* ***D_{20}:*** *PPSA-1 Partial positive surface area [Zefirov's PC];* ***D_{21}:*** *PPSA-1 Partial positive surface area [Quantum-Chemical PC];* ***D_{22}:*** *PNSA-1 Partial negative surface area [Zefirov's PC];* ***D_{23}:*** *PNSA-1 Partial negative surface area [Quantum-Chemical PC].*

Three correlated equations of the best three-, four-, and five- parameters were selected as QSAR models are summarized in Table 2, and expressed mathematically in Eqs. (**1-3**). In each of these models, N is the number of compounds, the correlation coefficient, R^2, measures the fit of the regression equation, while, R^2_{CV} is the 'leave one out' (LOO) cross-validated coefficient. F, the Fisher test value which reflects the ratio of the variance explained by the model and the variance due to the error in it. s^2 is the standard deviation of the regression.
The HM based three-parameter regression expression is as in eq. (1), where:

$$\text{pMAC} = -(90.278 \pm 4.8320)\, \boldsymbol{D_1} + (1.3932 \pm 0.1169)\, \boldsymbol{D_2} + (1.1517 \pm 0.3498)\, \boldsymbol{D_3} + (76.244 \pm 4.4052) \quad \textbf{(1)}$$
$$N = 19;\ R^2 = 0.9776;\ R^2_{cv} = 0.9595;\ F = 220.44;\ s^2 = 0.4574$$

In the above equation, the quantum mechanical descriptor $\boldsymbol{D_1}$ has a negative sign while the electrostatic descriptor $\boldsymbol{D_3}$ has a positive-sign coefficient, implying that both descriptors have opposite impacts on the activity of the fluorinated anesthetics (**1-19**). It may be significant to conclude that the anesthetic potency is enhanced by the increase of an electrostatic factor. Similarly, the activity is increased by increasing the constitutional descriptor $\boldsymbol{D_2}$.

Among the obtained four-parameter models, the best one is as shown below:

$$\text{pMAC} = -(77.518 \pm 6.5006)\, \boldsymbol{D_1} + (1.0924 \pm 0.1549)\, \boldsymbol{D_2} + (1.0853 \pm 0.3005)\, \boldsymbol{D_3} + (57.467 \pm 22.586)\, \boldsymbol{D_4} + (63.808 \pm 6.1733) \quad \textbf{(2)}$$
$$N = 19;\ R^2 = 0.9847;\ R^2_{cv} = 0.9715;\ F = 225.0959;\ s^2 = 0.2285$$

The descriptors $\boldsymbol{D_1}$, $\boldsymbol{D_2}$, and $\boldsymbol{D_3}$ have the same impact in this model as before in Eq. (**1**). $\boldsymbol{D_4}$ is a quantum chemical descriptor with a positive coefficient, which highlights an increase in the magnitude of $\boldsymbol{D_4}$ will favor more anesthesia by the fluorinated anesthetics.

Several five-parameter equations was obtained, where out of these equations, Eq. (**3**) in the model below consists of $\boldsymbol{D_5}$ along with the previously correlated descriptors. It is an electrostatic descriptor related to charge distribution which reflects the maximum partial charge for a H atom *{Zefirov's PC}*.

$$\text{pMAC} = -(79.174 \pm 5.8258)\, \boldsymbol{D_1} + (1.2451 \pm 0.15450)\, \boldsymbol{D_2} + (0.9531 \pm 0.27386)\, \boldsymbol{D_3} + (61.893 \pm 20.171)\, \boldsymbol{D_4} + (43.759 \pm 20.113)\, \boldsymbol{D_5} + (60.574 \pm 5.6829) \quad \textbf{(3)}$$
$$N = 19;\ R^2 = 0.9888;\ R^2_{CV} = 0.9672;\ F = 229.0471;\ s^2 = 0.1804.$$

In this model, the signs of coefficients are the same as in the previous models and thus they carry the same significance. The positive sign of $\mathbf{D_5}$ coefficient implies that the increase in its magnitude would be favorable for the exhibition of the anesthetic activity of the compounds.

Thus, according to the best match between R^2 and R^2_{cv} among Eqs. (**1-3**), the four-descriptor model (eq. 2), shown also in Table 2, is the best model with good statistical parameters; R^2= 0.985, R^2_{cv} = 0.972, s^2 = 0.229, F = 225.10. This indicates a significant correlation between the predicted and experimental pMAC values as shown in Fig. 1b. However, for comparative purposes Fig. 1a shows the correlation with the five-descriptor model Eq. (**3**), and Table 3 displays the numerical comparison between the experimental pMAC and the predicted ones according to each of the three models reached.

Table 2: statistical and Regression parameters of the correlations of the anesthetic activity of fluorinated anesthetics (pMAC) in the present study**:**

Models	**Descriptors involved**	**Symbol**	**t-test**	***B* (intercept)**	Statistical Parameters			
					R^2	**R^2_{cv}**	**F**	**S^2**
Eq. 1	Avg bond order of a H atom Number of H atoms WPSA-3 Weighted PPSA (PPSA3*TMSA/1000) [Zefirov's PC]	D_1 D_2 D_3	- 18.6835 11.9130 3.2924	17.3076	0.9776	0.9595	218.3080	0.3119
Eq. 2	Avg bond order of a H atom Number of H atoms WPSA-3 Weighted PPSA (PPSA3*TMSA/1000) [Zefirov's PC] Min nucleoph. react. index for a O atom	D_1 D_2 D_3 D_4	10.3361 - 11.9247 7.0520 3.6109	10.3361	0.9847	0.9715	225.10	0.2285
Eq. 3	Avg bond order of a H atom Number of H atoms WPSA-3 Weighted PPSA (PPSA3*TMSA/1000) [Zefirov's PC] Min nucleoph. react. index for a O atom Max partial charge for a H atom [Zefirov's PC]	D_1 D_2 D_3 D_4 D_5	- 13.5901 8.0589 3.4805 3.0684 2.1757	10.6589	0.9888	0.9672	229.0471	0.1804

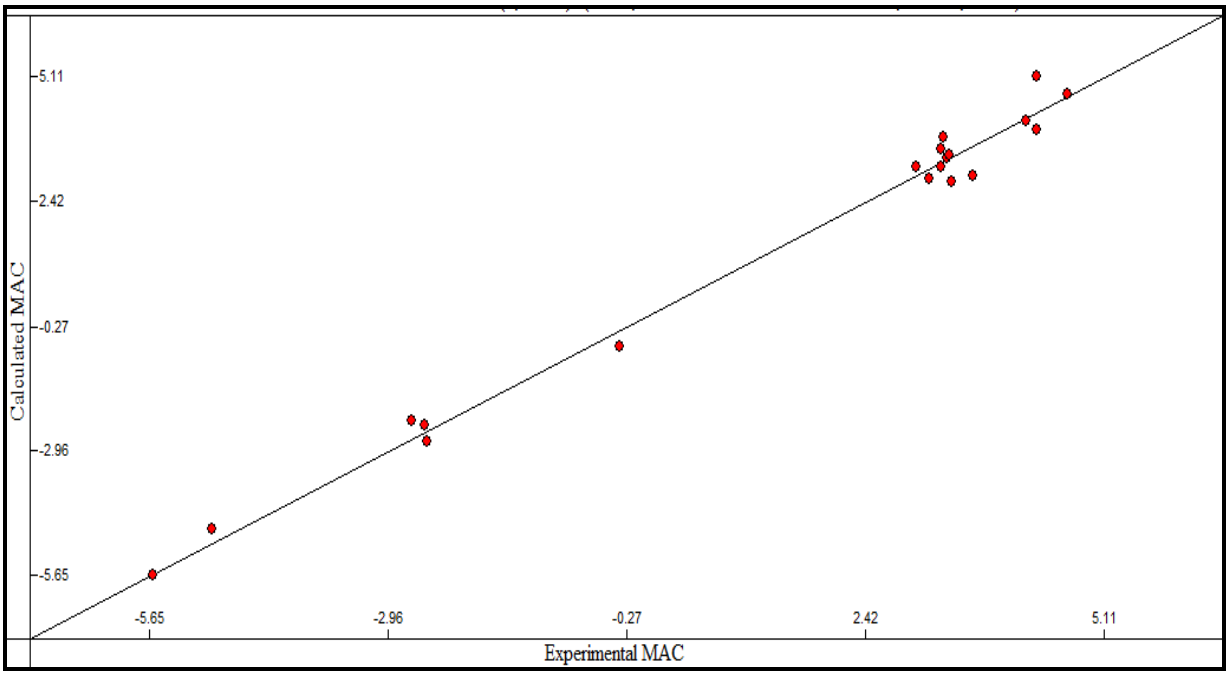


Fig. 1a: Comparison of experimental and calculated anesthetic activity from the regressional analysis in eq. (3). R^2=0.989; R^2_{CV}=0.967; F=229.047; s^2=0.180 for 19 fluorinated anesthetics.

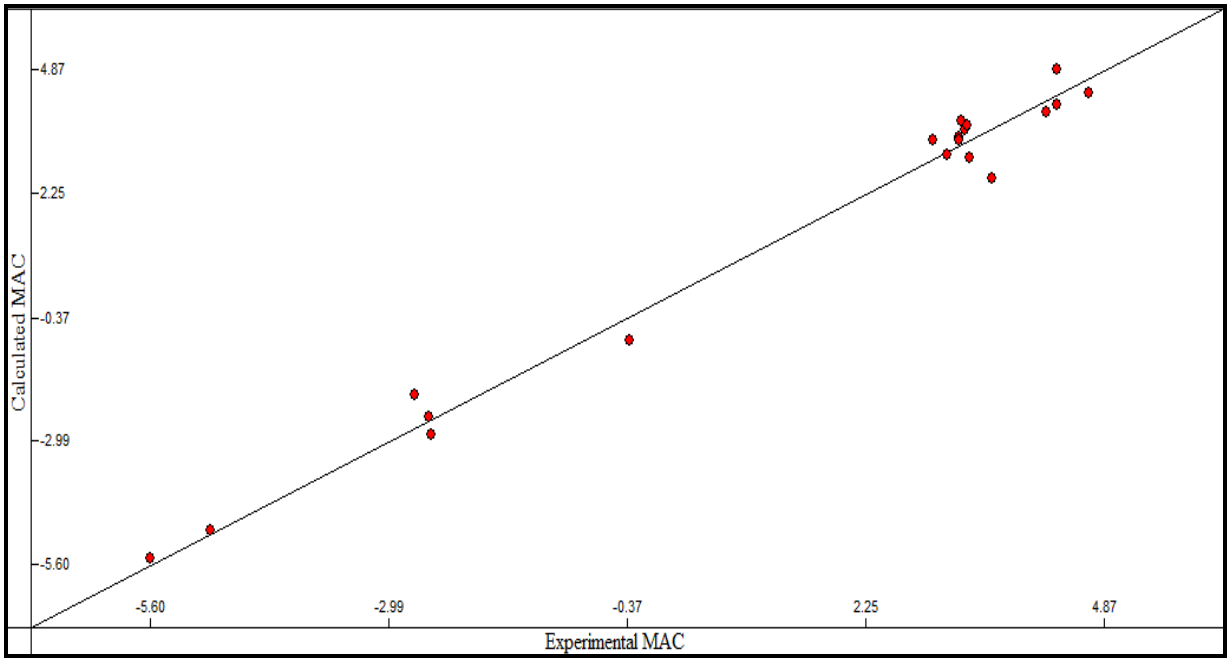


Fig. 1b: Comparison of experimental and calculated anesthetic activity from the regressional analysis in eq. (2). R^2 = 0.985; R^2_{cv} = 0.972; F=255.096; s^2 = 0.228 for 19 fluorinated anesthetics.

The significance of the descriptors included in the best concluded models in Eqs. (**1-3**) is ranked according to t-test criterion (as in table 2) as D1 >D2 >D3 >D4 >D5. Thus, the most significant descriptor is *Average bond order of a H atom* (**D_1**). It is a quantum-chemical observable related to the H atoms indicating the importance of electrostatic interactions in determining the activity of anesthetic compounds. It has a negative impact on the anesthetic activity in the three equations.

The next important descriptor is *Number of H atoms* (**D_2**). This Constitutional descriptor has a positive influence in the equations. An agreement may be reached from the tabulated data with what has been reported that a hydrogen or hydroxyl on a given carbon is rendered more potent if that carbon is surrounded by carbons having CF_3 groups [23]. This trend suggests that the surrounding CF_3 groups stabilize the position of the intervening carbon hydrogen or hydroxyl at the anesthetic site of action, possibly through increasing the acidity of the hydrogen proton. Also, the fact that the $CHF_2(CF_2)_nCH_2OH$ anesthetics are 10 times more active than fully fluorinated anesthetics indicates that the CHF_2 moiety adds significantly to potency. That is, the CHF_2- moiety must influence the anesthetic site of action in addition to the -CH_2OH moiety [14].

Increasing the chain length for $CHF_2(CF_2)_nCH_2OH$ anesthetics from three to five carbons significantly increases potency. However, a further increase in chain length for the $CHF_2(CF_2)_nCH_2OH$ anesthetics from five to seven carbons seems to reverse the process, and potency tends to decrease [14].

Table 3: Experimental and calculated anesthetic activity of fluorinated anesthetics using five-[1], four-[2] and three-[3] parameter correlations in eqs. (3), (2) and (1).

Sys	Exp. pMAC	Calc. pMAC[1]	Diff[1]	Calc. pMAC[2]	Diff[2]	Calc. pMAC [3]	Diff[3]
1	3.000	3.170	0.170	3.374	0.374	3.286	0.286
2	3.150	2.929	-0.221	3.060	-0.090	2.710	-0.440
3	3.280	3.561	0.281	3.453	0.173	3.452	0.172
4	4.240	4.149	-0.091	3.971	-0.269	3.844	-0.396
5	3.280	3.180	-0.100	3.374	0.094	3.149	-0.131
6	4.350	5.107	0.757	4.866	0.516	5.066	0.716
7	3.640	2.968	-0.672	2.575	-1.065	2.836	-0.804
8	4.350	3.986	-0.365	4.144	-0.206	4.223	-0.127
9	3.400	2.844	-0.556	3.014	-0.386	3.067	-0.333
10	3.300	3.808	0.508	3.784	0.484	3.810	0.510
11	4.700	4.735	0.035	4.393	-0.307	4.416	-0.284
12	3.340	3.363	0.023	3.599	0.259	3.534	0.194
13	3.370	3.426	0.056	3.694	0.324	3.706	0.336
14	-4.942	-4.655	0.287	-4.870	0.072	-5.542	-0.600
15	-5.604	-5.649	-0.044	-5.471	0.134	-5.031	0.573

16	-2.515	-2.763	-0.248	-2.854	-0.339	-2.567	-0.051
17	-0.343	-0.698	-0.355	-0.0843	-0.500	-1.269	-0.926
18	-2.693	-2.311	0.381	-2.017	0.676	-1.938	0.754
19	-2.536	-2.384	0.153	-2.480	0.057	-1.984	0.552
St. deviation*	0.1804			0.228		0.3119	

*The tiny standard deviations reflect the importance of both the two models in calculating anesthetic activity according to eqs. (1-3).

The third most important descriptor is the surface weighted charged partial positive surface area WPSA-3 Weighted PPSA (PPSA2*TMSA/1000) {Zefirov's PC}. This electrostatic descriptor is related to charge distribution and describes the positively charged surface areas of the Anesthetic calculated from empirical approach by Zefirov. The descriptor is directly dependent on the hydrogen bonding donor or acceptor ability of the molecule [24]. It has a positive influence in the equations and its values increase with the increase of molecular size.

The fourth important descriptor is the quantum chemical observable of the *Minimum nucleophilic reaction index for a O atom*. The values of this descriptor has a small positive influence in the equations of Table 2.

The last significant descriptor in the QSPR model of Table 3 is the maximum *partial charge for a H atom computed by Zefirov*. It is an electrostatic observable related to charge distribution which reflects the maximum partial charge for hydrogen calculated by Zefirov [24].

For further validation of our reached models, the correlation matrix for the inter-correlation of the five descriptor included in the correlation is displayed in Table 4.

Table 4: Correlation matrix for the inter-correlation of descriptors involved in the obtained models.

	D1	***D2***	***D3***	***D4***	***D5***
D1	1.0000	0.9415	0.1814	0.5748	-0.5029
D2		1.0000	0.0930	0.5766	-0.4466
D3			1.0000	0.2942	0.2174
D4				1.0000	-0.5370
D5					1.0000

The absence of geometrical descriptors from the reached models implies that shape seems of minimal relevance to the anesthetics activity of few-carbon fluoro- straight-chained compounds. Similarly, while only H and O related descriptors have emerged in the correlations, no observables related to F atoms have been selected in spite of its highest relative number in each of the structures. These findings may again point out to the importance of hydrogen bonding in determining the

potency of anesthetics [25]. Also, this may suggest that the anesthetic site of action is impacted by both polar and nonpolar characteristics, and that the -OH moiety enhances the potency by providing a higher affinity to the polar site [26].

Conclusion

In the present QSAR study, the descriptors of 19 optimized fluoro-anesthetics have been computed using CODESSA package and correlated with their reactivity (pMAC). Four-parameter equation consists mainly of quantum chemical and electrostatic observables has been reached with excellent statistical parameters; (R^2= 0.985, R^2_{CV} = 0.972, F = 225.096, and S^2=0.227). Namely the descriptors are (1) Average bond order of a H atom, (2) Number of H atoms, (3) WPSA-3 Weighted PPSA (PPSA3*TMSA/1000) {Zefirov's PC}, (4) Minimum nucleophilic reaction index for a O atom. The QSAR model as concluded from table 3 is working properly to predict the anesthetic activity of flouro- compounds.

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