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A topological sub-structural approach of the mutagenic activity in dental monomers. 1. Aromatic epoxides

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Abstract

The topological sub-structural molecular design (TOPS-MODE) approach has been introduced for the study of mutagenic properties. The mutagenicity of 16 dental monomers was studied with this approach, obtaining a good quantitative structure–toxicity model. For comparison, four different weights were involved in the diagonal entries of the bond matrix for selecting the best TOPS-MODE model. TOPS-MODE was used to derive the contribution of different fragments to the toxicity of studied compounds.

Keywords: Aromatic Epoxides; Quantitative structure–activity relationships; Mutagenicity

1. Introduction

The activity of a chemical towards living organisms depends upon the physical or chemical action on biological tissues, and the nature of such action will depend ultimately on the molecular structure of the chemical. This was recognized over 100 years ago, and since then, but especially in the last two decades, many attempts have been made to relate the biological activity to molecular structure in a quantitative or qualitative way [1]. On the other hand, much effort is expended toward improving the quality and durability of polymer-based dental restoratives. These materials when prepared in situ may risk leaching of chemicals and the polymerization could not be ideal. Because substance such as monomers, initiators, and polymerization sensitizers must be reactive, there is also risk of interaction with genetic bio-molecules and therefore the possibility for inducing mutagenicity [2]. Mutagenicity is obviously a very important likely toxic effect and a number of in vitro genotoxicity studies using micro-organisms and cultured mammalian cell lines have been designed to measure a number of different genetic target points. Of these studies, those designed to measure the induction gene mutations, chromosomal aberration and genome alterations are of the utmost importance as they provide an insight into the factors contributing to the induction of human genetic disease. One of the most commonly used of such assays is the bacterial assay known as the Ames test [3].

The experimental determination of mutagenicity is difficult and expensive, to simplify the laboratory process, it would be suitable to use a model based on a dataset of published results to predict mutagenicity, of previously untested chemicals.

Thus, quantitative structure–activity relationships (QSAR) have great potential to facilitate the design of new dental resins that will posses favorable biocompatibility profiles. The method is somewhat new in dental materials research, but QSARs were found to be widely applied to rational drug design and successfully used to predict the structures of novel compounds [4].

In the context of in silico methods for modeling toxicological and biological properties of chemicals, the

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topological sub-structural molecular design (TOPS-MODE) approach has been introduced. The TOPS-MODE has been applied to the description of toxicological and biological properties of organic compounds [5–9]. The successful application of this theoretical approach to the modeling of toxicological and neurotoxicological properties [6,8] has inspired us to perform an exhaustive study in order to test and/or validate TOPS-MODE applicability in assessing discoveries about the human mutagenic impact. We will show here how TOPS-MODE is able to produce good QSAR models that permit easy structural interpretation of the results in terms of group contributions to mutagenicity.

2. Materials and methods

2.1. TOPS-MODE approach

TOPS-MODE is based on the computation of the spectral moments of the bond matrix, whose mathematical basis was described in previous reports by Estrada [10–12]. The TOPS-MODE approach has been recently reviewed in the literature [13], given a methodological explanation of how to use it as well as a software description [14].

According to Estrada, the application of the TOPS-MODE approach to the study of QSAR can be resumed in the following set of steps:

1. To draw the hydrogen-depleted molecular graphs for each molecule of the data set.
2. To use appropriated bond weights in order to differentiate the molecular bonds, e.g. bond distance, bond dipoles, bond polarizabilities, etc.
3. To compute the spectral moments of the bond matrix with the appropriated weights for each molecule in the data set, generating a table in which rows correspond to the compounds and columns correspond to the spectral moments of the bond matrix. Spectral moments are defined as the trace of the different powers of the bond matrix.
4. To find a QSAR by using any appropriated linear or non-linear multivariate statistical technique, such as multi-linear regression analysis (MRA), etc.:

$$P = a_0\mu_0 + a_1\mu_1 + a_2\mu_2 + a_3\mu_3 + \cdots + a_k\mu_k + b \quad (1)$$

where P is the property measurement, μ_k is the kth spectral moment, and a_ks are the coefficients obtained by the MRA.

5. To test the predictive capability of the QSAR model by using cross-validation techniques.
6. To compute the contributions of different groups of interest in order to determine their quantitative contribution to the activity of molecules under study.

The computation of fragment contributions to the mutagenic property under study is probably the most important advance of the TOPS-MODE approach to the study of toxicological variables compared to the traditional QSAR and QSPR methods. The procedure involves the calculation of the spectral moment for all the fragments contained in a given substructure, and by the difference of these moments we obtain the contribution of the substructure. The general algorithm for this computational approach is as follows:

First, we select the substructure whose contribution to the moments we would like to determine. Then, we generate all the fragments, which are contained in the corresponding substructure, and calculate the spectral moments for both, the substructure and all their fragments. The contribution of the substructure to the spectral moments is finally obtained as the difference between the spectral moments of the substructure and all those from their fragments. Once, the contributions of the different structural fragments are obtained, we only need to substitute these contributions into the quantitative model developed to describe the property studied.

2.2. Data set and computational strategies

In this study, we have selected a data set of 16 aromatic epoxides for the mutagenicity data reported by Yourtee et al. [15]. The mutagenic parameter studied here is the slopes of revertants vs. nanomoles of test chemical in the *Salmonella* test strain TA100 with the natural logarithm of the slopes (ln(TAs100)) used in the QSARs models. The names, smiles notation and experimental mutagenic activity are listed in Table 1.

TOPS-MODE computer software [16] was employed to calculate molecular descriptors. The standard dipole moments, hydrophobicity, molar refractivity and atomic radius of van der Waals were used as bond weightings for making differentiation of heteroatoms [11]. The selection of only these types of descriptors from the whole pool of 10 types included in TOPS-MODE methodology was carried out for the sake of simplicity and on the criteria that polarity and hydrophobicity parameters influence the mutagenicity of many compounds [2,15]. Therefore, four sets of spectral moments were obtained, one for each used bond weightings. A brief descriptions of these schemes used in the current work are given in Table 2.

In general, 15 spectral moments were calculated for each of the studied schemes, which make a total number of 60 descriptors. We also used multiplication of spectral moments as independent variables for describing mutagenicity on these monomers. In this case, we multiplied μ_0 and μ_1 for the first six spectral moments obtaining 12 new variables. However, we develop the QSAR models with each independent scheme and not with all the calculated descriptors at a time. All statistical analysis and data exploration was carry out using the Statistic 6.0 [18]. The most significance parameters were identified from the dataset using forward stepwise regression methods [19],

Table 1
Experimental and predicted values of mutagenic toxicity in Ames test of aromatic epoxides

No.	Compound	Smile notation	ln TA100	
			Exp.	Cal.
1	4-Methoxyphenyl glycidyl ether	COC1=CC=C(OCC2CO2)C=C1	0.115	0.377
2	4-Methylphenyl glycidyl ether	CC1=CC=C(OCC2CO2)C=C1	0.860	0.996
3	4-*t*-Butylphenyl glycidyl ether	CC(C1=CC=C(OCC2CO2)C=C1)(C)C	−0.362	−0.499
4	*m*,*p*-Dimethoxyphenyl propylene oxide	COC1=CC=C(CC2CO2)C=C1OC	−0.930	−0.820
5	*o*-Methoxyphenylpropylene oxide	COC1=CC=CC=C1CC2CO2	−0.576	−0.760
6	*p*-Benzylphenylpropylene oxide	C1(CC2=CC=C(CC3=CC=CC=C3)C=C2)CO1	−1.080	−1.134
7	*p*-Biphenylpropylene oxide	C1(C3=CC=CC=C3) = CC=CC=C1CC2CO2	0.620	0.793
8	*R*-Glycidyl alcohol	OC[C@@H]1CO1	−0.514	0.039
9	Phenylpropylene oxide	C1(CC2=CC=CC=C2)CO1	−0.536	−1.047
10	*p*-Hydroxy-*m*-methoxyphenyl propylene oxide	COC1=CC(CC2CO2) = CC=C1O	−1.060	−0.412
11	*p*-Methoxyphenylpropylene oxide	COC1=CC=C(CC2CO2)C=C1	−0.896	−0.883
12	*p*-Methylphenylpropylene oxide	CC1=CC=C(CC2CO2)C=C1	−0.111	−0.231
13	Phenoxypropylene oxide	C1(COC2=CC=CC=C2)CO1	0.172	−0.697
14	*R*-Naphthyl glycidyl ether	[C@@H]3(CO3)COC2=C1C=CC=CC1=CC=C2	2.230	1.984
15	*S*-Glycidyl alcohol	OC[C@H]1CO1	−1.040	−0.697
16	*S*-Naphthyl glycidyl ether	[C@H]3(CO3)COC2=C1C=CC=CC1=CC=C2	2.100	1.984

where the independent variables are individually added or deleted from the model at each step of the regression depending on the Fisher ratio values selected to enter and to remove until the 'best' model is obtained. In addition to the models considering one specific family of descriptors, mixed model with the entire pool of descriptors was seeked. In this experiment, feature selection was carried out by means of genetic algorithm. All the parameters such as population size mutation probabilities, *cross-over* probabilities, smoothing and so on were fixed at their default values [29].

Examination of the regression coefficient, the standard deviation, the significance and the number of variables in the equation determined the quality of the model.

In addition, the regression models obtained were validated by calculating q^2 values. The q^2 is obtained from 'leave-one-out' (LOO) testing, also known as cross-validation. A data point is removed from the set, and the regression recalculated; the predicted value for that point is then compared to its actual value. This is repeated until each datum has been omitted once; the sum of squares of these deletion residuals can then be used to calculate q^2, an equivalent statistic to R^2. The q^2 values can be considered as a measure of the predictive power of a regression equation, whereas R^2 can always be increased artificially by adding more parameters (descriptors), q^2 decreases if a model is overparameterized [19], and is therefore a more meaningful summary statistic for QSAR models. Analysis of residuals from the regression equations was used to identify outliers, which were removed to aid analysis.

Table 2
Definition of the different weighting bonds used in the current work

Weighting bonds	Definition[a]
Dipole	Standard dipole moments
Hidrophobicity	Bond parameters computed with the atomic hydrophobicity
Molar refractivity	Bond parameters computed with the molecular refractivity
Radius of van der Waals	Bond parameters computed with the atomic radius

[a] Consulting Ref. [17] for more complete definition of bond parameters.

3. Results and discussion

3.1. Quantitative structure association constant relations

In this work, the model selection was subjected to the principle of parsimony [22]. Then, we choose a function with higher statistical signification but having very fewer parameters as possible. Statistical parameters of the linear regression models obtained by using TOPS-MODE to describe mutagenicity are given in Table 3.

The order of spectral moments that are included in such models varies from one model to another. It is due to the fact that the structural information encoded by the different weighting schemes used here is different and they have different influences on the description of the variable studied. As can be seen, these models are statistically significant because of their $p < 0.05$. This confirms that all variables conforming the models are significant and essentially all of them could be used for predicting the studied property of this set of compounds. Furthermore, all models have the same number of significant variables and in all of them the same training set was used which was formed by 16 compounds as it is listed in Table 1. However, there are remarkable differences related to the explanation of the experimental variance and their (R^2) are also different. It can

Table 3
Statistical parameters of the lineal regression models for mutagenicity obtained for the four kinds of descriptors and the mixed of these kinds

Weighting bonds	Spectral moments	N	S	R^2	R^2_{adj}	F	p	q^2	S_{cv}
Hidrophobicity	μ_2, $\mu_0 \times \mu_6$, $\mu_1 \times \mu_4$	16	0.66	0.680	0.661	8.504	0.00	0.51	0.90
Dipole	$\mu_0 \times \mu_2$, $\mu_0 \times \mu_3$, $\mu_0 \times \mu_4$	16	0.45	0.852	0.835	23.056	0.00	0.79	0.81
Molar refractivity	$\mu_1 \times \mu_1$, $\mu_1 \times \mu_4$, $\mu_1 \times \mu_5$	16	0.30	0.932	0.908	54.943	0.00	0.89	0.48
Radius of van der Waals	μ_4, $\mu_0 \times \mu_0$, $\mu_0 \times \mu_1$	16	0.59	0.743	0.714	11.61	0.00	0.59	0.94
Mixed model	$\mu_1 \times \mu_1^{MR}$, $\mu_1 \times \mu_4^{MR}$, $\mu_1 \times \mu_5^{MR}$	16	0.30	0.932	0.908	54.943	0.00	0.89	0.48

be seen that models obtained using the weighting spectral moments with molar refractivity explains more than 93% of mutagenicity data variability. Thus, in our opinion, it is in fact a determining factor at the time of selecting the best model to be used later (Table 3), besides it presents a greater F of Fischer ($F = 54.94$) and minor standard deviation of data ($S = 0.30$) which confirms the former selection. Predicted and observed values for all compounds in training series are listed in Table 1. Fig. 1 shows immediately the predicted values against the observed mutagenicity.

Since a cross-validation of LOO type was developed, it was possible to confirm that the model obtained using molar refractivity for the bond weightings had a greater coefficient of correlation (q^2) and showed a minor standard deviation (S_{cv}) for this test (Table 3). In addition, from the statistical point of view this model is a robust one as can be seen from the statistical parameters of the cross-validation.

Equation of the model obtained by this bond weight is as follows:

$$\begin{aligned}\ln \mathrm{TA100} = {} & -1.773(\pm 0.256) + 0.073(\pm 0.007)\mu_1\mu_1^{MR} \\ & - 0.003(\pm 0.0002)\mu_1\mu_4^{MR} \\ & + 0.0004(\pm 0.00001)\mu_1\mu_5^{MR} \end{aligned} \quad (2)$$

In this equation, $\mu_1\mu_1$ is the square of the sum of molar refractivity in the molecule, the $\mu_1\mu_4$ and $\mu_1\mu_5$ are the multiplication of the respective spectral moment in the molecule according to selected case.

The structural significance of this model will be a steady

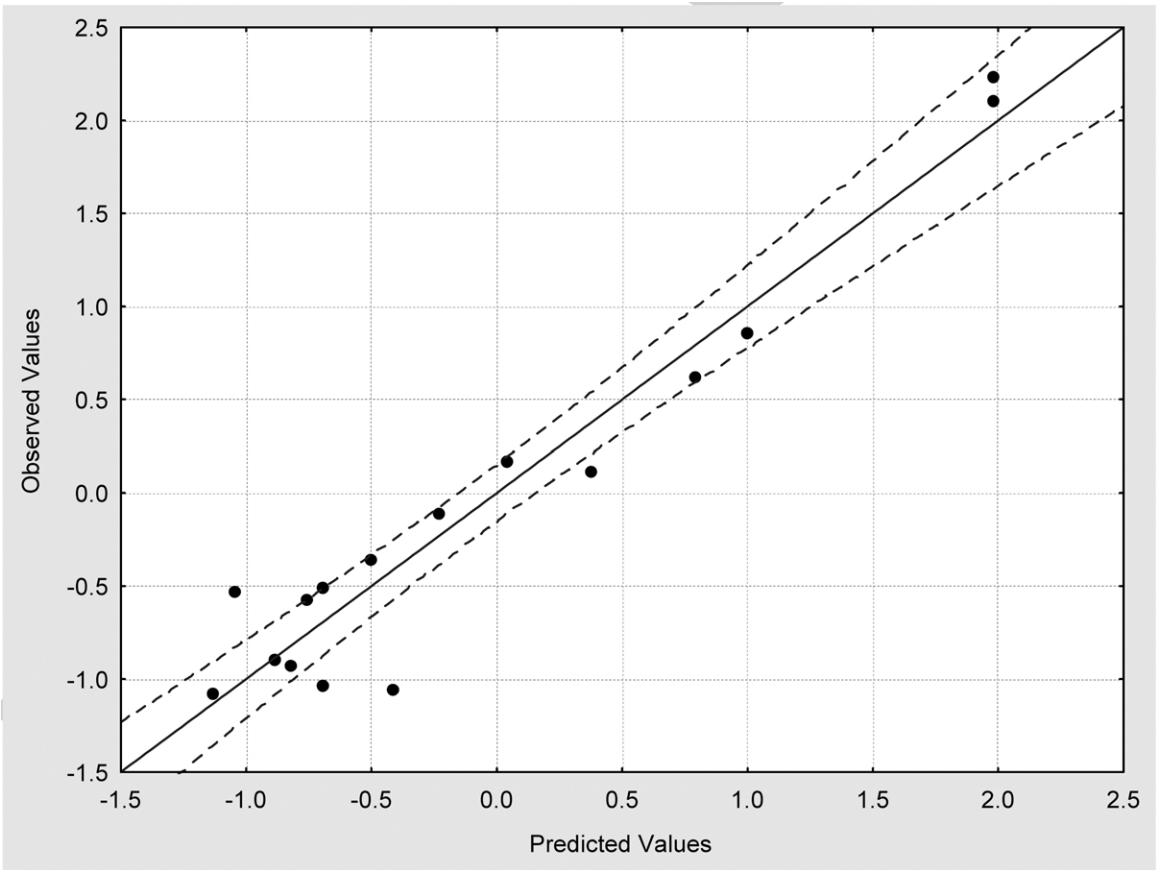

Fig. 1. The linear relation between observed and predicted mutagenicity in aromatic epoxides for Eq. (2).

support later when we analyze the contribution of the different structural fragments to mutagenic property.

Consideration of the outliers removed from a QSAR is essential. An outlier to a QSAR is identified normally by having a large standard residual [20] and can indicate the limits of applicability of a QSAR models. There are several reasons for their occurrence in QSAR studies, e.g. chemicals might be acting by a mechanism different from that of the majority of the data set. It is also likely that outliers might be a result of random experimental error that might be significant when analyzing large data sets. Although it is acceptable to remove a small number of outliers from QSAR [21] it is noted that it is not acceptable to remove the outlier repeatedly from a QSAR analysis simply to improve a correlation. In the current work, the compound 10 present a large residual and should be consider as an outlier. At removal of this compound from the training set the following equation is obtained:

$$\ln \mathrm{TA100} = -1.652(\pm 0.210) + 0.070(\pm 0.006)\mu_1\mu_1^{\mathrm{MR}} - 0.003(\pm 0.0002)\mu_1\mu_4^{\mathrm{MR}} + 0.0004(\pm 0.00003)\mu_1\mu_5^{\mathrm{MR}} \quad (3)$$

$$N = 15, \qquad R^2 = 0.951, \qquad S = 0.256, \qquad p = 0.000$$

Removal of the outlier improved the explanation of experimental variance of Eq. (2) when compared to Eq. (3). Nevertheless, the regression coefficient of the model represented by Eq. (3) does not improve significantly when this compound is removed from the model ($R^2 = 0.951$). For this reason, here any compound was considered as a potential outlier.

On the other hand, in all previous studies we only considered models with a specified family of molecular descriptors. Thence, in order to complete the demonstration of the potentialities of TOPS-MODE over the remnant ones mixed models considering all the molecular descriptors at the same time must be developed (Table 3). The total number of molecular descriptors considered here is higher than 185. Thus, a strategy for feature selection is necessary. In this sense, we performed a genetic algorithm previous to forward stepwise regression analysis. Anyhow, in our opinion the most interesting result is that the best model found coincides with the one reported in Eq. (2). This result has shown that the molar refractivity is a very important factor determining the capability of induced mutagenicity by aromatic epoxides.

3.2. Comparison with other approach

Certainly, there are several reports previously published: a QSAR on mutagenic activity that involve dental monomers, in special aromatic epoxides [15]. In this paper, Yourtee et al. used the following equation in order to describe the mutagenicity on the aromatic epoxides

$$\ln \mathrm{TA100} = 62.88 - 1.904\varepsilon_{\mathrm{LUMO}} + 330.00Q_{\min} - 0.083YZ_{\mathrm{shad}} + 497.20\bar{R}_{1\mathrm{eC}} + 36.08R_{1\mathrm{eC}}^{\min} \quad (4)$$

$$N = 16, \qquad R^2 = 0.9682, \qquad R^2_{\mathrm{CV}} = 0.8954,$$

$$F = 60.81$$

The descriptors for the aromatic set were the minimum atomic partial charge, $Q_{\min}$ (related to the electrostatic of the molecule); YZ_{shad} related to the two-dimensional shape of the molecule; and the reactivity descriptors: the LUMO energy, $\varepsilon_{\mathrm{LUMO}}$; and average and minimum one-electron reactivity indices for a carbon atom, $\bar{R}_{1\mathrm{eC}}$ and $R_{1\mathrm{eC}}^{\min}$, respectively.

Apparently, this model seems to be an excellent correlation among the descriptors and the mutagenicity of these dental monomers. However, exit several points that should be discussed.

Comparing Eq. (4) with our better model represented in Eq. (2) we note that this shows a better R^2 (0.968 vs. 0.932). Although, this difference is not marked from statistical point of view, the model presented by Yourtee et al. showed five variables in their equation with only three in our model. In addition, also the ratio between the number of cases vs. the number of adjustable parameters in the model, $\rho =$ (no. of data points)/(no. of adjustable parameters) should be considered here. This statistical parameter should be $\rho \geq 4$ [28]. The model reported in Eq. (4) presented $\rho = 2.67$ meanwhile our model reported $\rho = 4$. For that reason we feel that the model is overfitting. Along these years, much have been discussed about the problem of overfitting in the QSAR models, a clear example published recently showed that models that include unneeded predictors lead to worse decisions. In drug discovery, for example, a mistaken decision to add irrelevant predictors can make predictions worse because the coefficients fitted to them add random variation to the subsequent predictions [22]. In addition, this experimental measurement possesses a high error and therefore the models of mutagenicity where there are too many fittings is where a statistical point of view run the risk of an overfitting of the model. Therefore, it is not justified considerably to increase the complex of the model with the simple objective of increasing R^2. On the other hand, should be taking into account that the use of physicochemical descriptors is subject to a number of statistical criteria such that a minimum of five observations is required per variable (descriptor) at the equation in QSAR models [23]. This statistical criterion violated by Yourtee et al. (16 cases/five variables) contribute without a doubt to model overfitting.

3.3. Study of group's contribution to mutagenic property

In these years, individual QSARs have been developed for mutagenic endpoint. This has typically been for

individual class of compounds with the purpose guarantied the same action mechanism. For instance, Debnath et al. [24] describe that the prediction of the mutagenic to *Salmonella typhimurium* TA100 of aromatic and hetero-aromatic compounds prove that the hydrophobicity and molecular orbital properties are of vital importance for the modeling of this property. Confirming this, Tuppurainen [25] has reviewed the use of molecular orbital calculations and hydrophobicity in the prediction of mutagenicity and found E_{LUMO} to be useful for the prediction of the mutagenic potency of hydroxyhydrofuranones. In contrast, Franke et al. [26] demonstrated that on describing mutagenic potency in amines within the active compounds no log P term appears in these functions, so that hydrophobicity does not appear to be a key factor in class separation. Furthermore, Garg et al. [27] showed that in aminobenzene compounds can have rather similar values of log P but quite different mutagenic activities.

On the other hand, we find that for the case of the aromatic epoxides the best correlation with the mutagenicity is obtained when the molar refractivity is used as bond weights. This shows an interesting behavior if taken into account that the molar refractivity is the molecular volume corrected with the refraction index of the molecule. Thence may be concluding that the action mechanism of the different families of compounds depends on their molecular structure.

As we previously explained, the TOPS-MODE approach is able to compute the contribution of any structural fragment (real or hypothetical) to the biological property or activity studied. In the present case, we can find the positive and negative contributions of such fragments to the development of the mutagenicity activity. These fragments will be named here as active and inactive, respectively. The presence of active fragments does not presuppose the development of the mutagenicity activity per se, because it is well known that the activity is the consequence of the sum of contributions of all fragments in the molecule. In Table 4 and Fig. 2 we show the fragments and their contributions to the mutagenicity calculated from Eq. (2).

The analysis of the fragments F_{16} and F_{17} point out to the positive contribution of them to molecular mutagenic. The mutagenic character of these cyclic esters (epoxides) obeys to their vast reactivity so that the high torsion spanning of the three-member ring leads steady to the ring cleave. The internal bond angles of the ring around 60° are far away from the 109.5° expected for a tetrahedral arrangement at carbon atom or to the divalent oxygen bonded to the carbon atoms in acyclic ethers. Since the atoms are not enough close in order to allow the maximal overlapping of the orbitals, thence the bonds are not so strong like current ether and it is more reactive. The arrangement of the three atoms is normally accepted to look like a banana shape bond. Essentially, epoxides are electrophilic, reactive chemicals may form DNA–protein cross-links and induce mutagenesis. However, these one chemical properties of the epoxides convert them into potential precursor of dental resins. When these monomers are photo-excited a polymerization process takes place that leads to the building of resins. This process is encouraged by the presence of amino groups and hydroxyl groups bonding to aromatic and aliphatic chains. In this sense if we compare the moieties F_1 and F_8, we steady confirm that the former increases positively the property, while the latter supply a negative donation to the property. The mutagenic property could be decreased by epoxides, monomers where phenolic rests were involved.

Table 4
The contribution of different fragments to the mutagenic activity of the aromatic epoxides under study

Studied fragments	Fragment contribution	Studied fragments	Fragment contribution
F_1	0.604	F_{10}	−0.840
F_2	0.963	F_{11}	−0.186
F_3	0.508	F_{12}	−0.997
F_4	0.937	F_{13}	−3.212
F_5	1.486	F_{14}	−0.946
F_6	0.967	F_{15}	0.376
F_7	−0.114	F_{16}	0.458
F_8	−0.658	F_{17}	0.503
F_9	−0.789		

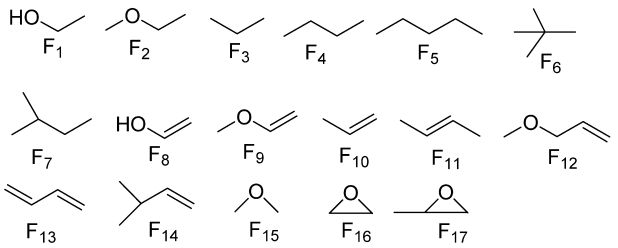

Fig. 2. Structures of selected fragments for which their contributions to the mutagenic activity was calculated.

On the other hand, an analysis on the results of this research show that an increase in the carbon lineal chain leads to an increase in the mutagenic activity.

This affirmation is based on the analysis of the set of fragment from F_3 to F_5 where an increase in methyl group in each fragment increase the contribution to the property from 0.508 to 1.486.

Nevertheless, when the branching of the fragments is increased, the contribution to the mutagenic property is minor as was observed in the fragments F_6 and F_7 where the contribution diminishes from 0.967 to −0.114. This type of contribution associate to the ramification or branching of the carbon chain is in relation with the target point of each dental monomer in special [2].

As have been observed there are sudden decreases in the activity by ramification of the groups of the lineal aliphatic chain, each one of these fragments (F_5, F_6, F_7) having the

same number of carbons (almost of the same hydrophobicity), but their contributions are extremely different, but if we compare aliphatic groups with difference in ramification and different number of methyl groups we would be able to appreciate higher changes in their contributions. In this case, an increase in the hydrophobicity leads to enlarge the analyzed property.

4. Concluding remarks

Despite some criticisms, there is an increase in the necessity of topological-indices-based QSAR models in order to rationalize the drug discovery process. In this sense, the TOPS-MODE approach has been extended not only to the discovery of novel leads but also to the study of the physicochemical, absorption properties and toxicology properties of drugs. In the present paper, the TOPS-MODE approach has been probed to generate good predictive linear models in order to account for mutagenic activity. Thence, we can assert that the TOPS-MODE approach may be used as an efficient alternative to screening of mutagenic activity of dental monomers.

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