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# Anticonvulsant Activity of Ringed Enaminones: A QSAR Study

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**Abstract**
The formalism of the QSAR Theory is employed to establish mathematical relationships that link the molecular structure of ringed enaminones to their observed antiepileptic activity. The design of predictive linear regression models, solely based on the available experimental information, involved the simultaneous analysis of 1312 theoretical descriptors calculated with Dragon software. This QSAR study that is based both on classic antiepileptics and second-generation anticonvulsant drugs, including compounds of the enaminone type, allowed the proposal of novel ringed enaminone derivatives as possible antiepileptic agents, posing a similar or even better predicted biological activity when compared to other commonly used drugs.

## 1 Introduction

Epilepsy is one of the most common neurological disorders. One percent of the world's population suffers this chronic disease and this percentage is doubled in children and adolescents [1]. In 1912, Hauptmann introduced into the market the first synthetic organic compound posing anticonvulsant activity, the phenobarbital [2]. In 1938, experimenting on animals, Merrit and Putnam showed the pharmacological activity of the anticonvulsant phenytoin [3]. During 1960–1974, only one compound, diazepam, was adopted as the optimal drug for the treatment of epilepsy. It has been since the 70s that many drugs with antiepileptic action were synthesized and are so-called second generation drugs [4].

Enaminones are organic compounds containing the characteristic conjugated group N–C=C–C=O, which become of popular interest for treating neurological diseases in recent years [5–10]. Recent studies indicated the great biological potential of this sort of compounds as anticonvulsive drugs acting on sodium ionic voltage dependent channels. Their structural similarity to classic and second generation antiepileptic drugs would allow the proposal of novel enaminones displaying a similar biological action.

Among the available in silico methods for searching semiempirical relationships between the molecular structure of a chemical compound and its experimental biological activity appear Quantitative Structure–Activity Relationships (QSAR) [11]. The various formulations of this theory suggest models capable of estimating biological properties, especially when the experimental information is not available. Such studies assume that the chemical structure of a compound is responsible for the exhibited activity or property. Therefore, the molecular structure is translated into numerical variables which characterize it (molecular descriptors), defined through mathematical equations obtained from different theories, such as the Chemical Graph Theory, the Information Theory, Quantum Mechanics, etc.[12–14]. There are thousands of descriptors in the literature, and the problem to be solved consists on selecting those which are most representative for the property under consideration.

The purpose of present work is the design of a QSAR model that is capable of predicting the antiepileptic activity for a group of enaminones of the closed- and opened-chain types, and therefore to facilitate the development of new antiepileptic drugs. As there exist no previous studies from the literature that were developed to the study of anticonvulsant activity on ringed enaminones, we hope this analysis provides new structural information on this family of molecules and guide the rational synthesis of new compounds.

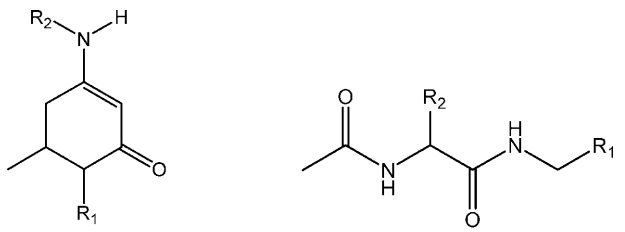
**Table 1.** Experimental and QSAR predicted antiepileptic activity for the enaminone derivatives analyzed.

| No. | Chemical Name | $\log_{10}ED_{50}$ | | |
|---|---|---|---|---|
| | | Exp. | Pred. | $res_i$ |
| | **Calibration Set** | | | |
| 1 | Ethyl 6-methyl-4-(5-methylisoxazol-3-ylamino)-2-oxocyclohex-3-enecarboxylate | 1.835[5] | 1.815 | 0.020 |
| 2 | Methyl 4-(4-cyanophenylamino)-6-methyl-2-oxocyclohex-3-enecarboxylate | 2.395[5] | 2.229 | 0.166 |
| 3 | Methyl 4-(4-chlorophenylamino)-6-methyl-2-oxocyclohex-3-enecarboxylate | 1.418[5] | 1.509 | −0.091 |
| 4 | 2-Acetamido-*N*-benzylpropanamide | 1.883[6] | 1.716 | 0.167 |
| 5 | 2-Acetamido-*N*-(3-fluorobenzyl)propanamide | 1.888[6] | 1.945 | −0.056 |
| 6 | 2-Acetamido-*N*-(2-fluorobenzyl)-2-(furan-2-yl)acetamida | 1.602[6] | 1.215 | 0.386 |
| 7 | 2-Acetamido-*N*-(3-fluorobenzyl)-2-(furan-2-yl)acetamida | 1.123[6] | 1.132 | −0.009 |
| 8 | 2-Acetamido-*N*-(4-fluorobenzyl)-2-(furan-2-yl)acetamida | 1.103[6] | 1.302 | −0.199 |
| 9 | 2-Acetamido-*N*-(2,5-difluorobenzyl)-2-(furan-2-yl)acetamida | 1.376[6] | 1.577 | −0.200 |
| 10 | 2-Acetamido-*N*-(2,6-difluorobenzyl)-2-(furan-2-yl)acetamida | 1.799[6] | 1.604 | 0.194 |
| 11 | 2-Acetamido-*N*-benzylpent-4-enamide | 1.526[6] | 1.653 | −0.126 |
| 12 | 2-Acetamido-*N*-benzyl-2-(tetrahydrofuran-2-yl)acetamida | 1.713[6] | 1.770 | −0.057 |
| 13 | 2-Acetamido-*N*-benzyl-2-(furan-2-yl)acetamide | 1.012[6] | 1.383 | −0.370 |
| 14 | 2-Acetamido-*N*-benzyl-2-(5-methylfuran-2-yl)acetamide | 1.283[6] | 1.450 | −0.166 |
| 15 | 2-Acetamido-*N*-benzyl-2-(*1H*-pyrrol-2-yl)acetamide | 1.206[6] | 1.486 | −0.279 |
| 16 | 2-Acetamido-*N*-benzyl-2-(5-methyl-*1H*-pyrrol-2-yl)acetamida | 1.562[6] | 1.530 | 0.031 |
| 17 | 2-Acetamido-*N*-benzyl-2-(thiophen-2-yl)acetamide | 1.651[6] | 1.388 | 0.262 |
| 18 | 2-Acetamido-*N*-benzyl-2-(thiophen-3-yl)acetamide | 1.943[6] | 1.783 | 0.160 |
| 19 | 2-Acetamido-*N*-benzyl-2-(1*H*-pyrrol-1-yl)acetamide | 1.904[6] | 1.572 | 0.332 |
| 20 | 2-Acetamido-*N*-benzyl-2-(1*H*-pyrazol-1-yl)acetamide | 1.217[6] | 1.249 | −0.032 |
| 21 | 2-Acetamido-*N*-benzyl-2-(pyridin-2-yl)acetamide | 1.033[6] | 0.880 | 0.153 |
| 22 | 2-Acetamido-3-amino-*N*-benzyl-3-thioxopropanamide | 1.937[6] | 1.550 | 0.386 |
| 23 | 2-Acetamido-*N*-benzyl-2-(ethylamino)acetamide | 1.627[6] | 1.525 | 0.102 |
| 24 | 2-Acetamido-*N*-benzyl-2-(hydroxy(methyl)amino)acetamide | 1.477[6] | 1.465 | 0.011 |
| 25 | 2-Acetamido-*N*-benzyl-2-(1-phenylhydrazinyl)acetamide | 1.631[6] | 1.524 | 0.107 |
| 26 | 2-Acetamido-*N*-benzyl-2-ethoxyacetamide | 1.792[6] | 1.795 | −0.003 |
| 27 | 2-Acetamido-*N*-benzyl-3-methoxypropanamide | 0.919[6] | 0.954 | −0.035 |
| 28 | 2-Acetamido-*N*-benzyl-3-ethoxypropanamide | 1.230[6] | 1.232 | −0.002 |
| 29 | 2-Acetamido-*N*-benzyl-2-(pyrazin-2-yl)acetamide | 1.170[6] | 0.929 | 0.240 |
| 30 | 2-Acetamido-*N*-benzyl-2-(pyrimidin-2-yl)acetamide | 0.908[6] | 1.151 | −0.243 |
| 31 | 2-Acetamido-*N*-benzyl-2-(oxazol-5-yl)acetamide | 1.021[6] | 0.998 | 0.022 |
| 32 | 2-Acetamido-*N*-benzyl-2-(thiazol-5-yl)acetamide | 1.079[6] | 1.417 | −0.337 |
| 33 | 2-Acetamido-2-(3-aminophenylamino)-*N*-benzylacetamide | 1.993[6] | 2.102 | −0.108 |
| 34 | 2-Acetamido-*N*-benzyl-2-(furan-2-yl)acetamide | 1.264[6] | 1.396 | −0.131 |
| 35 | Ethyl 4-(4-chlorophenylamino)-6-methyl-2-oxo-3-cyclohexene-1-carboxylate | 1.222[7] | 1.085 | 0.137 |
| 36 | Ethyl 4-(4-bromophenylamino)-6-methyl-2-oxo-3-cyclohexene-1-carboxylate | 0.897[7] | 1.259 | −0.362 |
| 37 | Ethyl 6-methyl-2-oxo-4-(4-(trifluoromethoxy)phenylamino)cyclohex-3-enecarboxylate | 1.569[7] | 1.708 | −0.139 |
| 38 | Ethyl 4-(4-cianophenylamino)-6-methyl-2-oxo-3-cyclohexene-1-carboxylate | 1.800[7] | 1.852 | −0.052 |
| 39 | 3-(4-Chlorophenylamino)-5-methyl-2-cyclohexenone | 1.606[7] | 1.804 | −0.198 |
| 40 | 3-(4-Iodophenylamino)-5-methyl-2-cyclohexenone | 1.886[7] | 1.924 | −0.038 |
| 41 | Methyl 6-methyl-4-(5-methylisoxazol-3-ylamino)-2-oxocyclohex-3-cyclohexene-1-carboxylate | 2.174[8] | 1.867 | 0.306 |
| 42 | *tert*-Butyl 6-methyl-4-(5-methylisoxazol-3-ylamino)-2-oxocyclohex-3-cyclohexene-1-carboxylate | 2.078[8] | 1.974 | 0.104 |
| 43 | Methyl 4-(benzylamino)-6-methyl-2-oxocyclohex-3-cyclohexene-1-carboxylate | 1.810[9] | 2.005 | −0.194 |
| 44 | Methyl 4-(4-fluorobenzylamino)-6-methyl-2-oxocyclohex-3-cyclohexene-1-carboxylate | 2.201[9] | 2.030 | 0.171 |
| 45 | 3-(Benzylamino)-5,5-dimethylcyclohex-2-cyclohexenone | 1.724[9] | 1.633 | 0.091 |
| 46 | Methyl 4-(benzylamino)-6,6-dimethyl-2-oxocyclohex-3-enecarboxylate | 2.120[10] | 2.219 | −0.099 |
| | **Validation set** | | | |
| 47 | Methyl 6-methyl-4-(4-nitrophenylamino)-2-oxocyclohex-3-enecarboxylate | 2.477[5] | 2.441 | 0.035 |
| 48 | 2-Acetamido-*N*-benzyl-2-phenylacetamide | 1.307[7] | 1.505 | −0.197 |
| 49 | 2-Acetamido-*N*-benzyl-2-(dimethylamino)acetamida | 1.656[7] | 1.413 | 0.242 |
| 50 | 2-Acetamido-2-(furan-2-yl)-*N*-(pyridin-3-ylmethyl)acetamida | 1.477[7] | 1.396 | 0.080 |
| 51 | 5,5-Dimethyl-3-(phenylamino)cyclohex-2-enone | 2.038[10] | 1.812 | 0.226 |

## 2 Experimental Data and Methodology

The experimental antiepileptic activities are obtained from various scientific publications [5–10, 15], while it is to be noted that reference 15 deals with the phthalimide structure. The analyzed set of compounds involved ringed enaminones, and also the family of benzyl-acetamide with no ring and ring substituents, as shown in Figure 1. Table 1




**Enaminone** **Bencilacetamide**

**Figure 1.** Molecular structures of studied compounds.

shows the members from the training and validation sets. The activity $ED_{50}$ represents the dose of chemical compound for which 50% of the individuals reach the desired effect. This is generally obtained in the 'Anticonvulsant Screening Project' (ASP) by the 'Maximal Electroshock Seizure' (MES) experimental method [16]. For modeling purposes, we used $\log_{10}ED_{50}$ to get a more standardized property. The structures of all the compounds examined here are optimized with the Semiempirical Method PM3 (Parametric Method-3) included in the HyperChem 6.03 software [17]. As some compounds of Table 1 are constituents of racemic (R/S) mixtures, we draw them in their S configuration as a model for the molecular structure.

The Dragon software [18] enabled us to calculate 1307 theoretical molecular descriptors, which included: 0D: Constitutional Descriptors; 1D: Functional Groups, Empiricals, Atom Centered Fragments; 2D: Topologicals, Molecular Walk Counts, Galvez Topological Charge Indices, BCUT; 3D: Charge, Aromatic Indices, Randic Molecular Profiles, Geometricals, Radial Distribution Functions, 3D-MoRSE, WHIM, and GATEWAY. In addition, 5 descriptors obtained from the semiempirical calculation were added: total energy, molecular dipole moment, energy of the HOMO and LUMO orbitals, and the HOMO-LUMO gap. Therefore, the pool of descriptors resulted in $D=$ 1312 numerical variables.

We used the program Matlab 7.0 in all our calculations [19]. Our interest is to find from the pool of descriptors D, containing $D$ descriptors, a subset d with $d \ll D$ ones with minimum standard deviation ($S$). This is accomplished with the Replacement Method (RM) [20–22], and the standard deviation optimization function is defined as follows:

$$S = \frac{1}{(N-d-1)} \sum_{i=1}^{N} res_i^2 \tag{1}$$

where $N$ is the number of molecules in the calibration set CC (molecular set used for calibrating the model), and $res_i$ is the residue of molecule $i$ (difference between the experimental and predicted activity for $i$).

Although the QSAR Theory searches for the best predictions for a considered activity, it is adopted as a rule in practice that linear models should be simple and involve seven molecules per descriptor to achieve satisfactory results, which is known as 'Rule of Thumb' [23]. Therefore, the maximum number of allowed descriptors ($d_{nm}$) in a linear model is calculated with the following equation:

$$d_{nm} = N/7 \tag{2}$$

On the other hand, the Kubinyi function *FIT* [24] is used to calculate the optimum number of descriptors ($d_{opt}$) to be included in each linear regression model established:

$$FIT = \frac{R^2(N-d-1)}{(N+d^2)(1-R^2)} \tag{3}$$

Here, $R$ is the model's correlation coefficient. The *FIT* function achieves a maximum value ($d_{max}$) deduced from the plot of *FIT* as a function of $d$. We adopted the following criterion for obtaining $d_{opt}$:

1) if $d_{max} \leq d_{nm}$, then $d_{max} = d_{opt}$

2) if $d_{max} > d_{nm}$, then:

a) calculate $d_1 = [d_{max}/2] + 1$ , where notation $[x]$ stands for 'the integer value'.

b) then, if the slope of *FIT* at $d_1$ is greater than in $d_1 + 1$, them $d_1 = d_{opt}$.

c) if this is not true (b), then $d_{opt} = d_1 + 1$.

By means of this criterion we expect to obtain a $d_{opt}$ value that reflects a 'breaking point' beyond which the *FIT* improvement can be considered negligible. We think that this is a very effective method for obtaining the optimal number of descriptors of a particular model [22, 25].

A next step of this study is to verify that the so established QSAR relationships on the training set of chemical structures behave not only as correlative, but also function similarly well on new chemical structures that did not participate in the training of each model and that conform the validation set. The validation process is very important and enables one to analyze the predictive performance of the designed models, so the standard deviation of validation *Sval* is calculated in this step. As the main purpose of this work relies on the prediction of $ED_{50}$ in a family of ringed enaminones, we defined two different types of standard deviations of validation (*Se* and *Slooe*):

*Se*: standard deviation for enaminones of the external validation set. It is calculated in the same manner as *Sval* (which is calculated involving all the validation compounds) but considers only the residues of the enaminones molecules. Low values in *Se* and high values in *Sval* indicate that the model has a good predictive power on enaminones but a modest predictive capability on the rest of

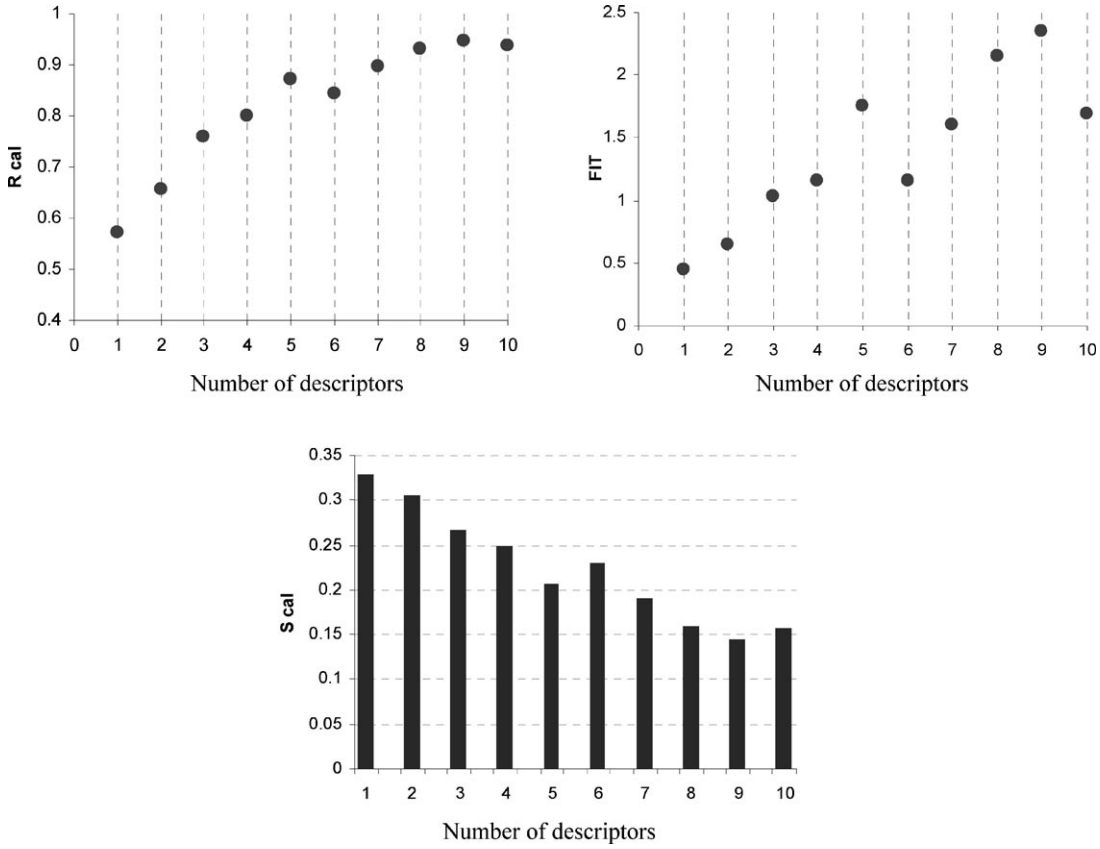



**Figure 2.** Statistical parameters of calibration as a function of the number of descriptors.

compounds. Low values in *Se* and *Sval* indicate that the model could be used for predicting any type of molecule from the calibration set. Models with high *Se* values are not valid for our present purposes.

*Slooe*: standard deviation for the Leave-One-Out (LOO) Cross Validation technique [26], calculated using only the residues of the enaminones from calibration set. As it is known, *Sloo* indicates the efficiency in the prediction of $ED_{50}$ in each molecule of the calibration set when this is not taken into account during calibration. Instead, *Slooe* is calculated in the same manner as *Sloo* but only 'leaving out' the enaminones compounds. Models with low *Slooe* are excellent for the purpose of this work.

## 3 Results

A calibration set consisting on 46 antiepileptic organic compounds is used to establish the QSAR model. The external validation set is composed of 5 molecules selected in such a way that they share similar structural characteristics to the calibration molecules. According to Equation 2, the maximum number of descriptors that the structure-activity should contain is 6. Figure 2 plots *S*, correlation coefficient *R* and *FIT* parameter as a function of the number of descriptors, for the linear regression models found by searching the pool D ($D=1312$ descriptors). According to the *FIT* criterion, $d_{opt}=5$ is obtained, as this plot demonstrates that this $d_{opt}$ is a maximum of the curve. Therefore, these criterions suggest that our QSAR model involves five optimal descriptors.

The validation set includes only 2 enaminone molecules. Figure 3 plots *Sval* versus *d* and, for the case of our five descriptors-QSAR, the validation parameters are $Sval=0.198$, $Rval=0.925$. In addition, the cross validation parameters for this model are $Sloo=0.232$ and $Rloo=0.835$, while the *Se* and *Slooe* values are 0.229 and 0.222, respectively. Therefore, the QSAR equation designed for predicting the anticonvulsant activity is:

$$\log_{10}ED_{50}=-3.310\ (\pm0.6)+3.712\ (\pm0.7)\ BELe6-2.338\ (\pm0.4)\ BELp8+0.128\ (\pm0.02)\ RDF025v+0.667\ (\pm0.1)\ Mor15e+33.683\ (\pm5)\ R4e^{+} \quad (4)$$

$N=46$, $N/d=9.2$, $R=0.870$, $S=0.206$, $FIT=1.751$

Table 1 includes the experimental and predicted values of $\log_{10}ED_{50}$ for the QSAR model of Equation 4, together with the associated residuals for each molecule. It can be noted from Figure 4 that the enaminones of the validation set are very well predicted. Finally, a more robust Cross Validation process leads to the parameters $Rl\text{-}10\text{-}o=0.730$

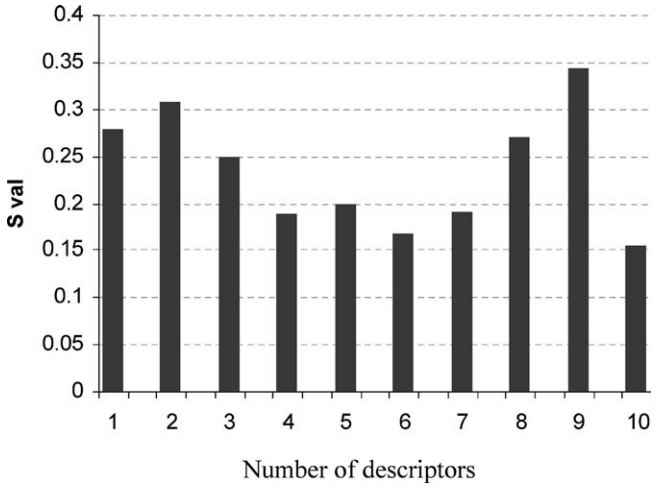



**Figure 3.** Standard deviation of validation versus the number of descriptors.

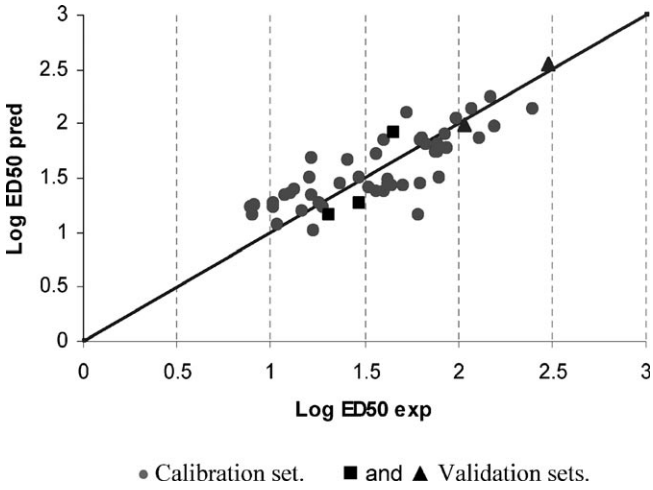



**Figure 4.** Experimental and predicted $\log_{10}ED_{50}$ values.

**Table 2.** Correlation matrix for theoretical descriptors participating in the designed QSAR of Equation 4.

| | *BELe6* | *BELp8* | *RDF025v* | *Mor15e* | *R4e*$^+$ |
|---|---|---|---|---|---|
| *BELe6* | 1 | 0.733 | 0.528 | 0.022 | 0.355 |
| *BELp8* | | 1 | 0.445 | 0.150 | 0.432 |
| *RDF025v* | | | 1 | 0.514 | 0.227 |
| *Mor15e* | | | | 1 | 0.284 |
| *R4e*$^+$ | | | | | 1 |

and *Sl-10-o* = 0.322, which confirm once again that Equation 4 is stable upon the removal of compounds from the training set. The descriptors involved in this QSAR are: 2D: BCUT descriptors, *BELe6:* lowest eigenvalue No. 6 of Burden matrix/weighted by atomic Sanderson electronegativities and *BELp8*: lowest eigenvalue No. 8 of Burden matrix/ weighted by atomic polarizativities; 3D: RDF descriptors, *RDF025v:* Radial Distribution Function −2.5 weighted by atomic van der Waals volumes; 3D-MoRSE descriptors: *Mor15e:* 3D-MoRSE-signal 15/weighted by

**Table 3.** Root mean square error achieved in different test sets of five compounds.

| Model | *RMS* training set | *RMS* test set | Molecular descriptors |
|---|---|---|---|
| Equation 4 | 0.190 | 0.178 | *BELe6*, *BELp8*, *RDF025v*, *Mor15e*, *R4e*$^+$ |
| M2 | 0.196 | 0.176 | *G(O…Cl)*, *RDF025m*, *RDF115m*, *R4e*$^+$, $\Delta_{\text{homo-lumo}}$ |
| M3 | 0.212 | 0.199 | *X0v*, *G(O..I)*, *RDF025m*, *Mor20e*, *R2v*$^+$ |
| M4 | 0.196 | 0.222 | *SNar*, *G(N..Br)*, *RDF025m*, *Mor20e*, *Mor15p* |
| M5 | 0.195 | 0.243 | *BEHe5*, *BELe6*, *RDF025*, *R4e*$^+$, *C-030* |
| M6 | 0.215 | 0.187 | *G(N..Br)*, *G1u*, *H4e*, *R4e*$^+$, *nCs* |

**Table 4.** Experimental and predicted $\log_{10}ED_{50}$ values for different test sets of five compounds according to descriptors of Table 3.

| Test Set 1 | Exp. | Pred. Eq. 4 | Test Set 2 | Exp. | Pred. M2 | Test Set 3 | Exp. | Pred. M3 |
|---|---|---|---|---|---|---|---|---|
| **47** | 2.477 | 2.441 | **34** | 1.265 | 1.289 | **4** | 1.884 | 1.828 |
| **48** | 1.307 | 1.505 | **41** | 2.174 | 1.974 | **3** | 1.418 | 1.705 |
| **49** | 1.656 | 1.413 | **26** | 1.792 | 1.947 | **14** | 1.283 | 1.030 |
| **50** | 1.477 | 1.396 | **17** | 1.651 | 1.610 | **25** | 1.631 | 1.782 |
| **51** | 2.038 | 1.812 | **42** | 2.079 | 1.783 | **21** | 1.033 | 1.193 |
| Test Set 4 | Exp. | Pred. M4 | Test Set 5 | Exp. | Pred. M5 | Test Set 6 | Exp. | Pred. M6 |
| **8** | 1.104 | 1.214 | **47** | 2.477 | 2.338 | **40** | 1.887 | 1.559 |
| **13** | 1.013 | 1.255 | **32** | 1.079 | 1.455 | **43** | 1.811 | 1.885 |
| **17** | 1.651 | 1.376 | **33** | 1.994 | 1.959 | **11** | 1.526 | 1.665 |
| **15** | 1.207 | 1.381 | **21** | 1.033 | 1.062 | **28** | 1.231 | 1.302 |
| **44** | 2.201 | 1.938 | **19** | 1.904 | 1.540 | **25** | 1.631 | 1.435 |

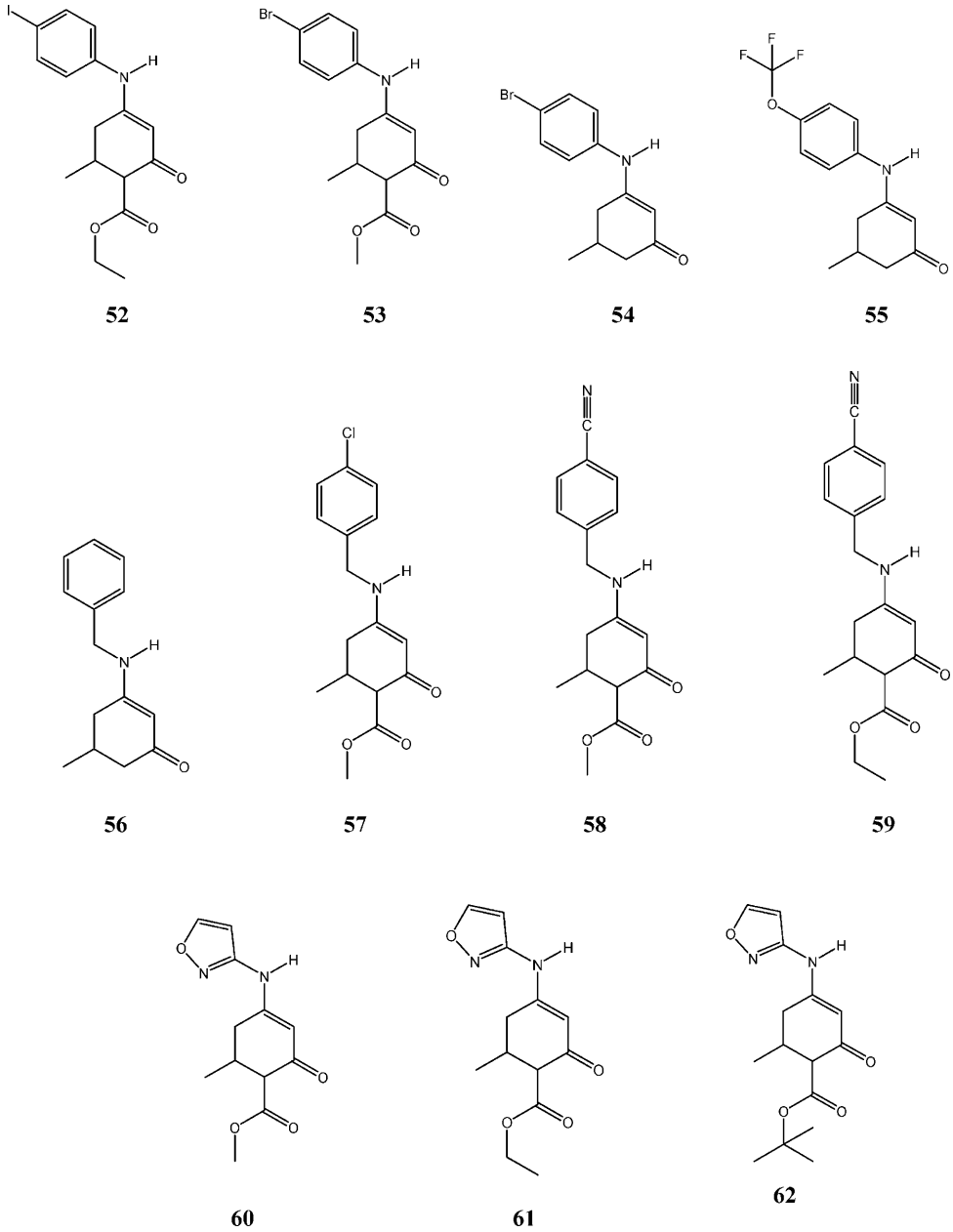



**Figure 5.** Ringed enaminones classified by the ASP as anticonvulsant molecules.

atomic Sanderson electronegativities; GATEWAY: $R4e^{+}$: R maximal autocorrelation of lag 4/weighted by atomic Sanderson electronegativities. Table 2 indicates that the highest inter-correlation between descriptors is 0.733. These values suggest that the structural information represented by each descriptor can be considered independent. In general, inter-correlations lower than 0.98 are generally accepted in QSAR models, but it is possible to eliminate such interdependencies among descriptors by employing the orthogonalization process [27].

**Table 5.** Ringed enaminone derivatives classified by the Anticonvulsant Screening Project and their $ED_{50}$ activity (mg kg$^{-1}$) predicted through QSAR.

| No. | ASP | $ED_{50}$ | Ref. |
|---|---|---|---|
| 52 | 1 | 17.87 | [6] |
| 53 | 1 | 49.30 | [5] |
| 54 | 1 | 104.23 | [6] |
| 55 | 1 | 18.82 | [6] |
| 56 | 1 | 56.20 | [5] |
| 57 | 2 | 142.28 | [5] |
| 58 | 3 | 332.08 | [5] |
| 59 | 3 | 505.23 | [5] |
| 60 | 2 | 200.33 | [15] |
| 61 | 2 | 138.47 | [15] |
| 62 | 1 | 53.83 | [15] |

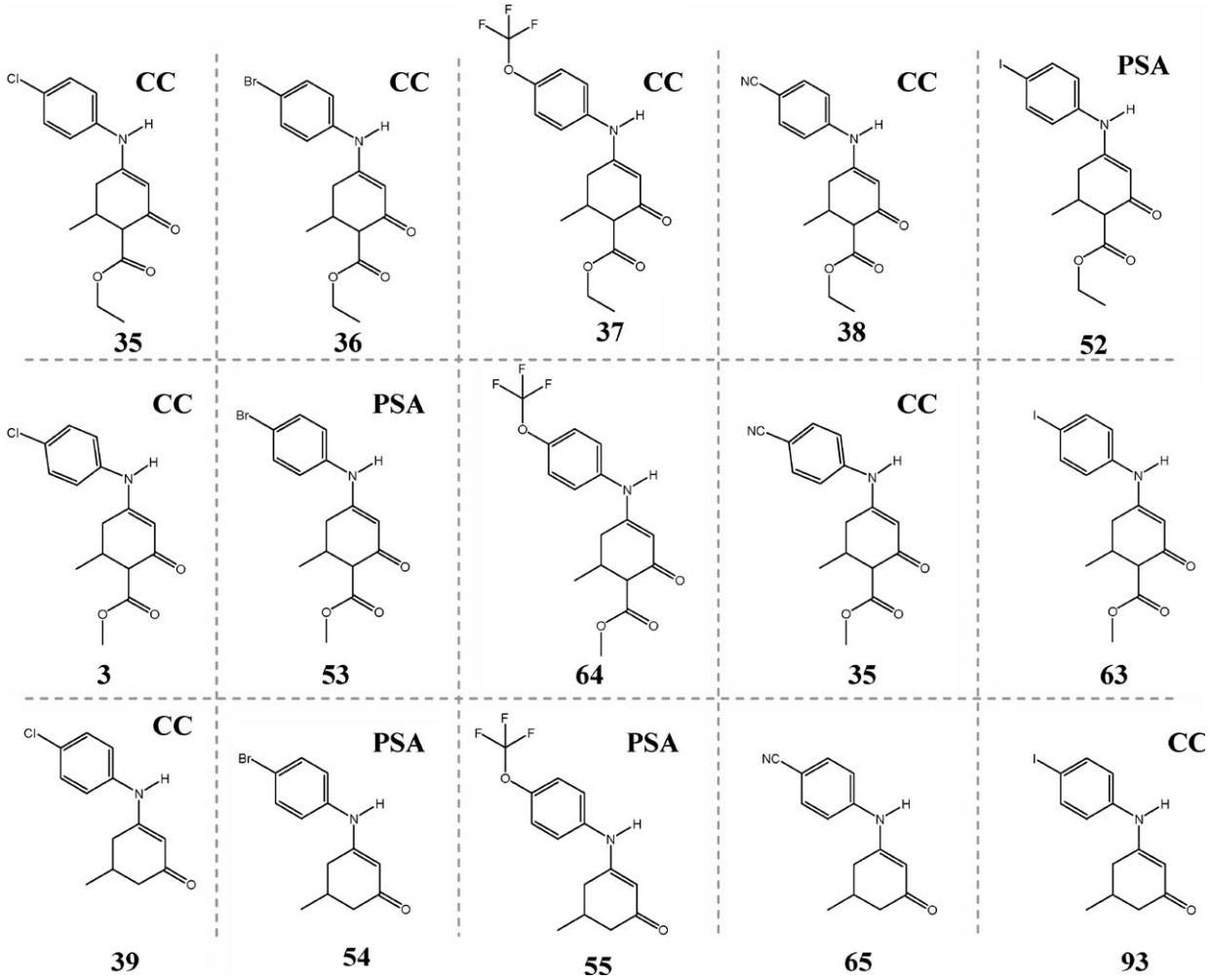



**Figure 6.** Aniline enaminone derivatives selected for the prediction of the anticonvulsant activity. (CC) calibration set, (ASP) Anticonvulsant Screening Project. **63–65** are unknown molecules chosen for prediction.

As the test set of compounds used involved only five compounds, we decided to perform a repetitive partitioning of the entire set into training and test sets, in order to demonstrate that the selection procedure leads to stable test set predictions. Table 3 includes the root mean square error (*RMS*) achieved on six different training and test sets, selected at random, while Table 4 includes the predictions achieved by the models on these test sets. As can be appreciated from both tables, the predictions are stable thus justifying the selection of Equation 4 as a valid QSAR model.

Figure 5 includes another external validation set of ringed enaminones. This is extracted from the literature [5–10], and the antiepileptic activities of these compounds are now predicted by using the QSAR model established. Experimental values of $ED_{50}$ are not known for this molecular set, but these are classified as anticonvulsants of Class 1, 2 and 3 by the ASP [16]: Class 1: activity at 100 mg kg$^{-1}$ or less; Class 2: activity between 100 mg kg$^{-1}$ and 300 mg kg$^{-1}$; Class 3: exceeding 300 mg kg$^{-1}$ or no-activity. Classifications according to the ASP and the activity values predicted by the QSAR of Equation 4 are shown in Table 5. This table reveals the excellent classification achieved through the predictions of our proposed QSAR. Only molecule **54** does not fit in the classification Class 1 (activity at 100 mg kg$^{-1}$ or less), but the predicted value 104.23 mg kg$^{-1}$ results very close. The excellent correlation achieved here between the ASP classification and the predicted values for the $ED_{50}$ activity suggest that our QSAR could be used to predict the $ED_{50}$ parameter for new enaminones as potential anticonvulsants.

Finally, the QSAR model designed is used to predict $ED_{50}$ values in a series of 10 ringed enaminones. The compounds that are analyzed as possible active molecules are structurally related to the enaminones previously employed for establishing our QSAR equation. The 15 ringed enaminones from CC and the 11 enaminones classified by the ASP [9] were separated in families and substituents. By means of this set of compounds, different organizing diagrams are elaborated as follows: Figure 6 (aniline enami-

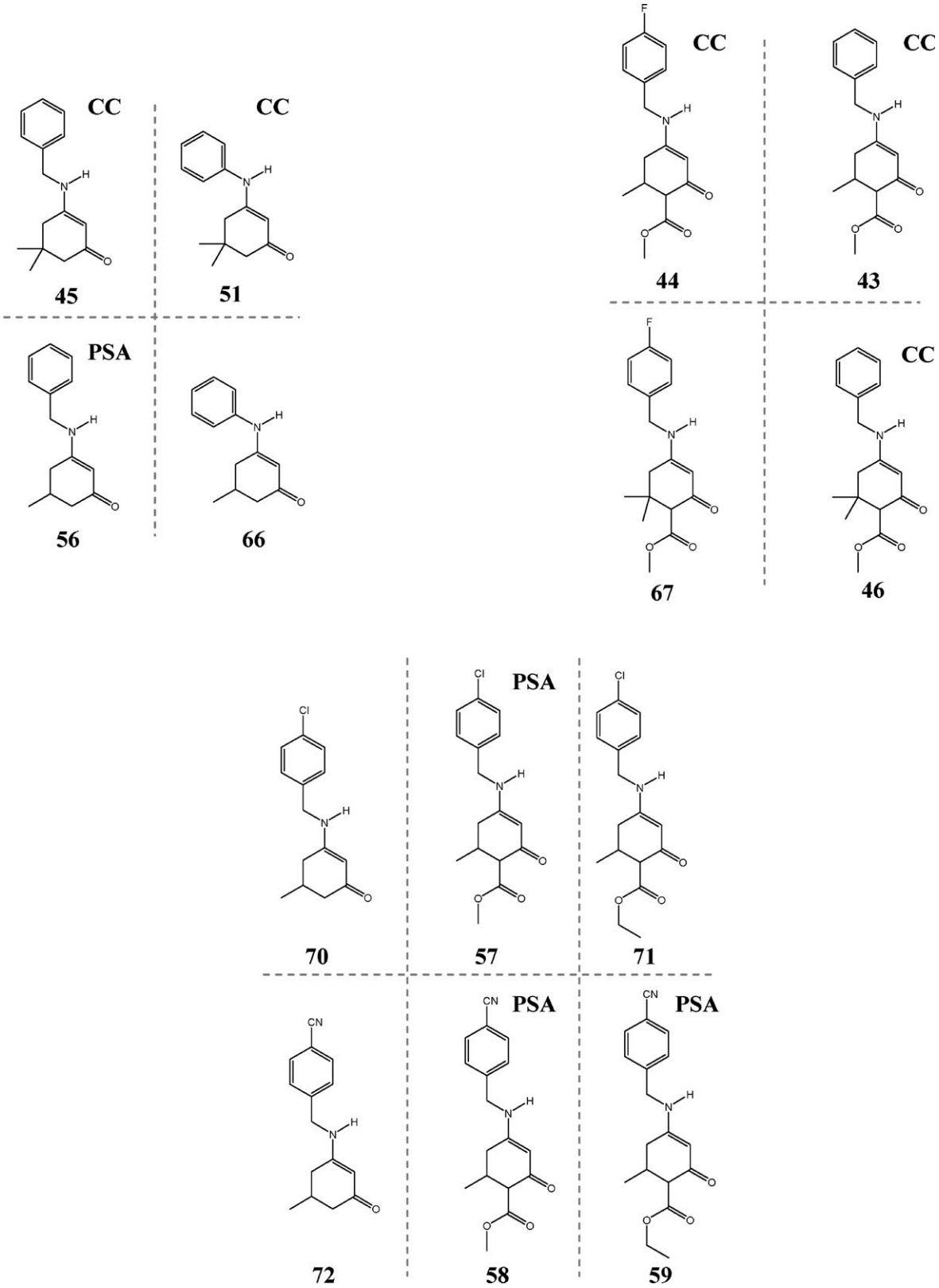



**Figure 7.** Benzylamine enaminone derivatives selected for the prediction of the anticonvulsant activity. (CC) calibration set, (ASP) Anti-convulsant Screening Project. **66**, **67**, **70**–**72** are unknown molecules chosen for prediction.

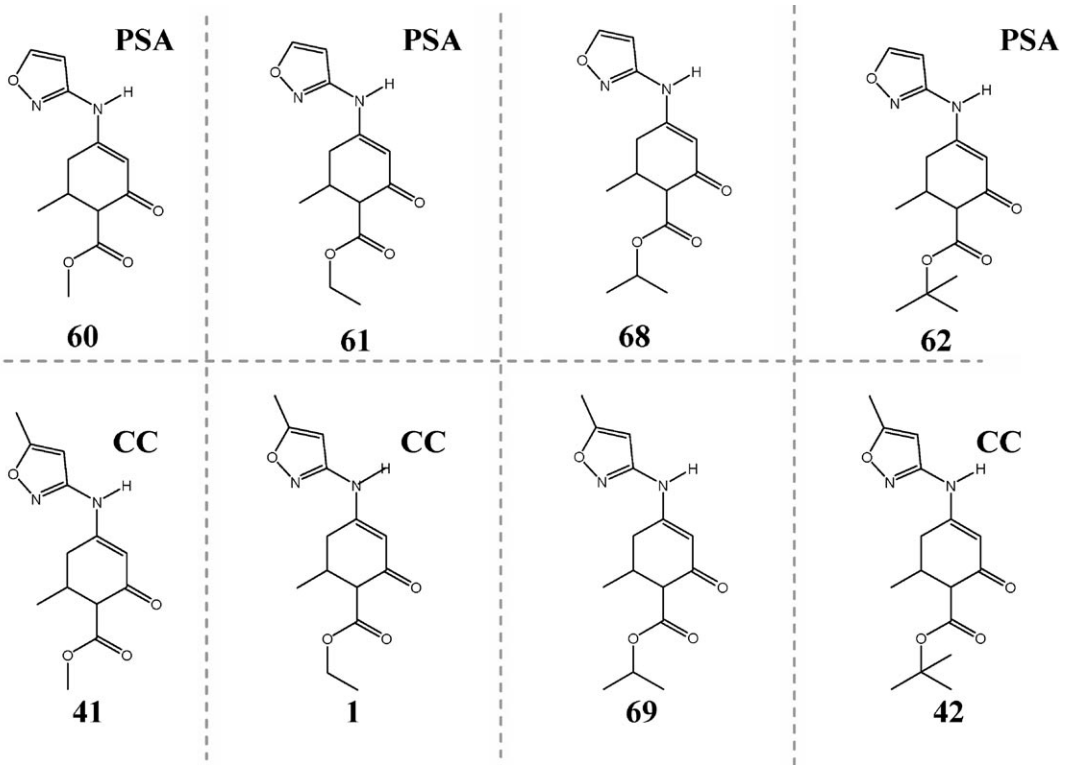



**Figure 8.** Isoxasol enaminone derivatives selected for the prediction of the anticonvulsant activity. (CC) calibration set, (ASP) Anticonvulsant Screening Project. **68**, **69** are unknown molecules chosen for prediction.

**Table 6.** QSAR predictions of $ED_{50}$ activity values (in mg kg$^{-1}$) for 10 new ringed enaminone derivatives.

| Molecule | $ED_{50}$ |
|---|---|
| 63 | 39.250 |
| 64 | 101.980 |
| 65 | 82.240 |
| 66 | 69.870 |
| 67 | 243.640 |
| 68 | 44.100 |
| 69 | 65.790 |
| 70 | 58.820 |
| 71 | 157.360 |
| 72 | 39.480 |

none derivatives), Figure 7 (benzylamine enaminone derivatives) and Figure 8 (isoxasol enaminone derivatives).

Enaminones **63**–**65** in Figure 6 do not belong to CC nor ASP. Then, the $ED_{50}$ activity of these aniline derivatives is predicted by the QSAR model. Figure 7 (benzylamine derivative enaminones) is divided into 3 parts, and **66**, **67**, **70**–**72** are also predicted through the model. Molecule **66** is an aniline enaminone derivative, but this molecule shows the relationship between the two families, aniline and benzylamine derivatives. Figure 8 reveals that **68** and **69** are predicted with the model. Table 6 reports the predicted $ED_{50}$ for the 10 ringed enaminones that emerged from the previous structural analysis. As shown by this table, the predicted potency by the QSAR model is in very good agreement with the ASP classification. Molecules **63** (aniline derivative), **68** (isoxasol derivative) and **72** (benzylamine derivative) display the greatest predicted activity for ringed enaminones. Instead, the **67** and **71** are classified as Class 2 by ASP with activities over 200 and 100 mg kg$^{-1}$.

## 4 Conclusions

This QSAR study established a predictive quantitative model based on experimental information and that is capable of predicting the anticonvulsant activity in several ringed enaminones. It is expected that, throughout the predictions done with the structures proposed in this paper, it results possible to guide the synthesis of future new drugs of structural similarity to the molecule tested during the calibration of the model. It is of real value the design of structure-activity relationships for the study of the biological activity exhibited by compounds with scarce experimental information. The methodology based on the simultaneous exploration of thousands of descriptors through multivariable linear regression analyzes allows establishing such kind of predictive models, so our research group would continue developing this line of investigation in the forecoming future.

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