Research Article

Journal of Physical Organic Chemistry

Received: 29 August 2007, Revised: 14 December 2007, Accepted: 20 February 2008, Published online in Wiley InterScience: 2008

(www.interscience.wiley.com) DOI 10.1002/poc.1365

# An exploratory study to investigate possible simple descriptors in order to predict relative activity of antiepileptic enaminones

J. C. Garro Martinez[a*], M. F. Andrada[a], M. R. Estrada[a], E. A. Castro[b], G .N. Zamarbide[a], Z. Mucsi[c] and I. G. Csizmadia[a, c]

**A general structure, substituent and activity relationship of the following type has been fitted to the available $ED_{50}$ values of cyclic enaminone antiepileptic compounds: $ED_{50} = f[\text{structure}, \text{substituent}] = f[d, \sigma]$. In this relationship 'structure' was quantified by *d*, the distance measured between the carbonyl oxygen and the first atom of the aromatic ring. The 'substituent' was quantified by Hammett substituent constant: ($\sigma$). With the aid of the above function of two independent variables, a new molecular structure was predicted by extrapolation that has shown about two orders of magnitude greater activity than the most active molecule in the original set with measured $ED_{50}$ values. Copyright © 2008 John Wiley & Sons, Ltd.**

**Keywords:** enaminone; MO theory; structure and conformations; geometrical parameters; epileptic activity

## INTRODUCTION

Epilepsy is a heterogeneous disorder that affects nearly 1% of the world population.[1] Symptoms are due to disturbances of electrical activity of the brain and most of individuals with epilepsy continue to have seizures, even while being treated with anticonvulsant drugs.[2] In antiepileptic drug development, a 50% decrease in seizure frequency is often accepted as the evidence of clinical efficacy.[3] By the end of the past century, approximately 70% of newly diagnosed epilepsy cases were treated with one or more of the following drugs: (a) Carbamazepine (CBZ),[4] (b) Phenytoin (PHYT),[4] (c) Phenylbarbital (PHEN).[4] One of the three areas in which the mechanisms of antiepileptic drug action have been categorized is drugs that modify cell excitability by altering, either directly or indirectly, the activity of voltage-dependent ion channels that mediate cell firing and rhythmicity.[1,3] That is the proposed mechanism of action for CBZ and PHYT (Fig. 1).

Several structurally diverse vasodilating drugs are known to stimulate the opening of potassium channels in smooth muscle and the heart.[5] The compounds investigated in this category have been unable to penetrate the blood–brain barrier. The inability of these drugs to get to the site of action in the brain would be the major limitation to their use.[6]

Recently, several enaminones, a group of organic compounds containing the conjugated system N—C═C—C═O (Fig. 2), has been cited in the literature as antiepileptic agents.[7,8] Comparing Figs 1 and 2, there are some structural similarities among the known antiepileptics and enaminones proposed as anticonvulsant drugs. Still more than that, their activity at the voltage-dependent sodium channel-binding site are comparable to that of class 1 anticonvulsants CBZ and PHYT.[8–10] Interestingly enough, all of the above compounds have ring structures, while open-ring enaminones proved to be excellent prodrugs of model primary amines because of their transportability through biological membranes.[11–13]

In the process of drug discovery, the relationship between drug structure, drug receptor affinity and drug bio-availability plays a significant role in the viability of a drug candidate. An orally administered drug must possess not only intrinsic activity, but also favourable biopharmaceutical properties which will allow drug molecules to cross membranes.[14]

## SCOPE

The present paper aims to establish a kind of relationship between the anticonvulsant activity of a certain set of compounds (Fig. 3) and structural characteristics like distances, Taft steric constants (Es) and Hammett ($\sigma$) parameters. The compounds investigated are, consisting of two structural types,

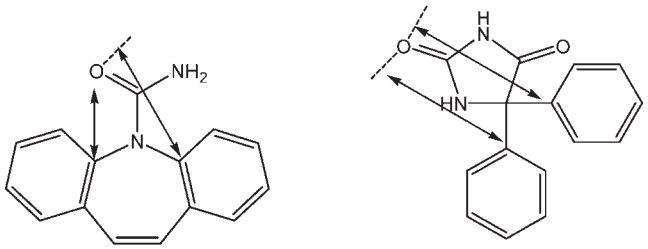
* *Departamento de Química, Universidad Nacional de San Luis, SAN LUIS 5700, Argentina.*
*E-mail: jcgarro@unsl.edu.ar*

a *J. C. G. Martinez, M. F. Andrada, M. R. Estrada, G .N. Zamarbide, I. G. Csizmadia*
*Departamento de Química, Universidad Nacional de San Luis, SAN LUIS 5700, Argentina*

b *E. A. Castro*
*INIFTA, División Química Teórica, Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, LA PLATA 1900, Argentina*

c *Z. Mucsi, I. Csizmadia*
*Department of Chemistry, University of Toronto, Toronto, Ontario, Canada, M5S 3HG*

| Antiepileptic | Distance | $ED_{50}$ Activity µmol/kg |
|---|---|---|
| Carbamezepine (CBZ) | 4,10 / 5,01 | 37 |
| Phenytoine (PHYT) | 4,44 / 4,69 | 38 |




**Carbamazepine** (CBZ) **Phenytoin** (PHYT)

**Figure 1.** Typical antiepileptics drugs and their biological activities, $ED_{50}$. Calculated[14] critical distances, *d*, in Å, are also shown

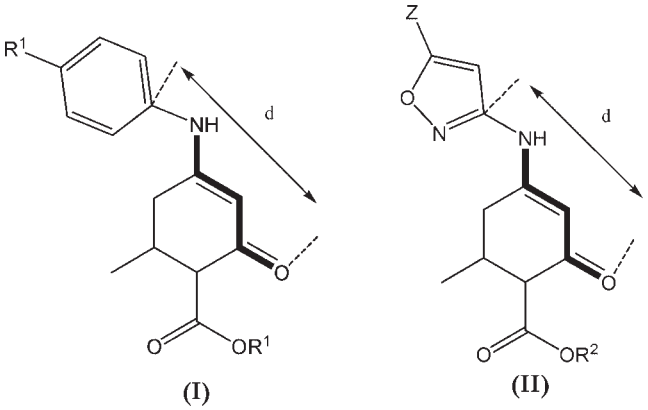



**Figure 3.** The two types of enaminones studied

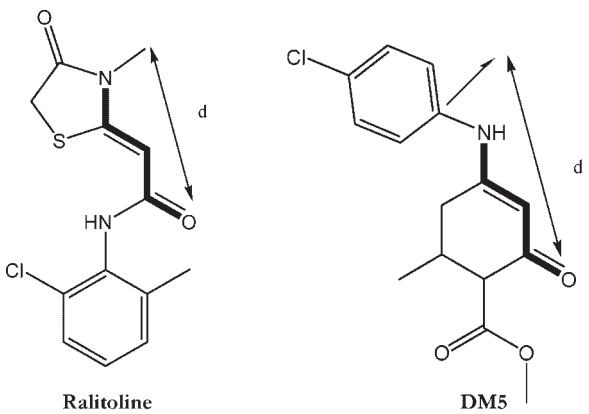
assumed to possess transportability through biological membranes and pharmacological effects by binding to the voltage-gated sodium ion channel. A few of the set of compounds have been studied experimentally and the $ED_{50}$ (µmol/kg) were measured.[7,9,13,14]

To explore this possibility, calculations were used to find the minimum energy conformations of 26 candidate molecules: 18 + 8 = 26 cyclic enaminones (Types **I** and **II**, respectively in Fig. 3). Particular attention was paid to the electron push and pull characteristics of the substituents for the compounds studied and to the distance *d* between the first atom of the aromatic ring and carbonyl oxygen of the enaminone group as both groups are thought to bind to the receptor site on the sodium channel. The phenyl group is believed to interact via π–π electron stacking with an aromatic group on the channel, possibly tyrosine 1771 on the α-subunit, while the carbonyl oxygen is hypothesized to form a hydrogen bond at the receptor site[4] as shown in Fig. 4 for anticonvulsants as well as for local anaesthetics.

In the drug discovery process, very often a million compounds must be subjected to a fast 'through-put' screening to reduce the original set of million molecules to a subset of considerably less than a thousand structures before synthesis, biological testing and QSAR investigation is to commence. The proposed method may become such a tool of the drug discovery projects at least for antiepileptic compounds. It should be emphasized that the scope of the present work was to explore the possibility to find an interatomic distance as a descriptor. No QSAR investigation was attempted, in view of the relatively few available experimental points, as it is done by many researchers in the field for better experimental data-sets.[15–21]

## MOLECULAR COMPUTATIONS

Calculations were performed using the GAUSSIAN 03 computational programme.[22] Cyclic enaminones of Family A in Figs. 5 and 6 with known $ED_{50}$ values, reported as antiepileptic drugs,[6] were optimized at AM1 semiempirical level. Cyclic enaminones of Family B (Fig. 7) with unknown $ED_{50}$ values were also geometry optimized at AM1 semiempirical level of theory.




**Ralitoline** **DM5**

| Antiepileptic | Distance | $ED_{50}$ Activity µmol/kg |
|---|---|---|
| Ralitoline | 5,19 | 9,51 |
| DM5 | 6,01 | 89,41 |

**Figure 2.** Typical enaminone-type antiepileptic drug and their biological activities, $ED_{50}$. Calculated[9,13] critical distances, in Å, are also shown

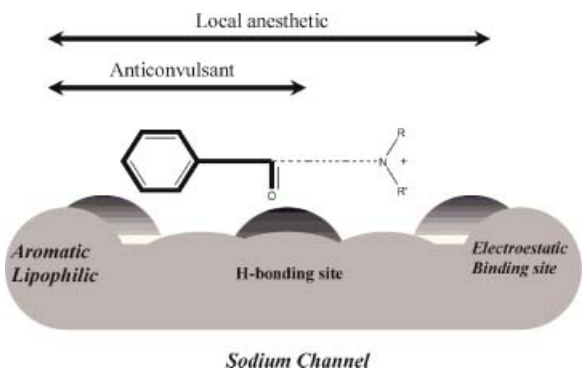



**Figure 4.** Proposed binding mechanism of anticonvulsants to the sodium channel

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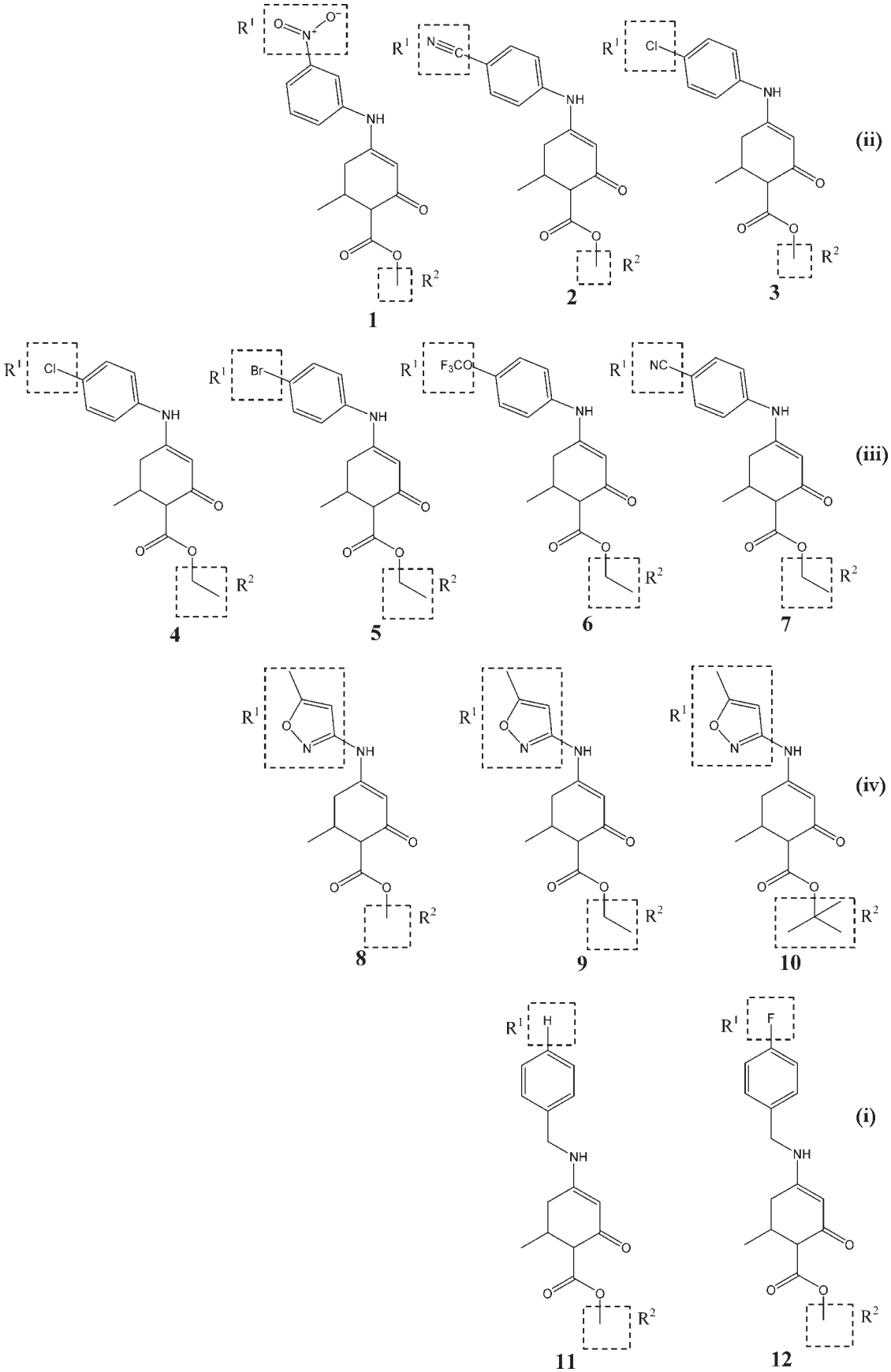


**Figure 5.** Semiempirical MO-optimized structures of selected bioactive enaminones (Family A) with $R^1$ and $R^2$ substituents. Subfamilies are labelled as (i), (ii), (iii) and (iv)



  

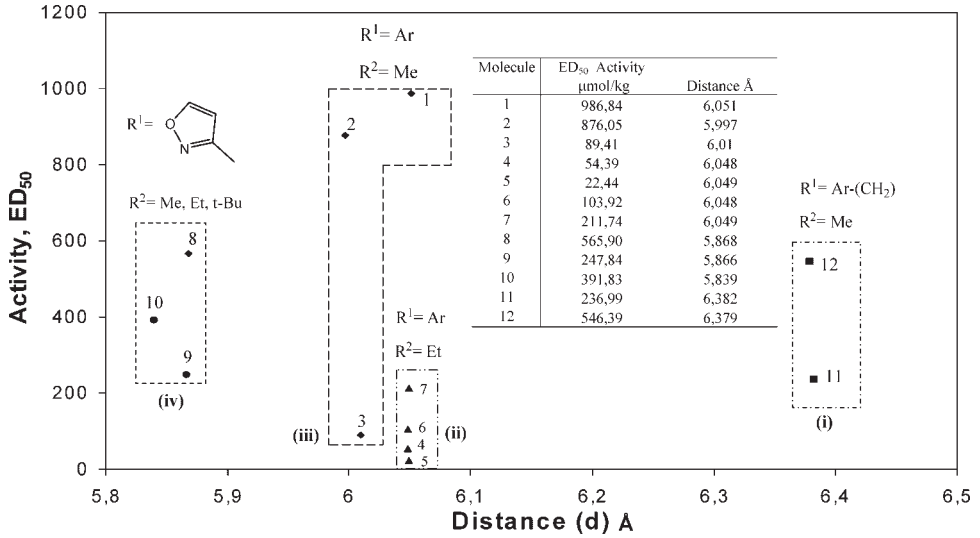


**Figure 6.** Bioactivity ($ED_{50}$) cluster pattern as a function of C–O distance (*d*) for compounds of Family A. Subfamilies are denoted as (i), (ii), (iii) and (iv)

Initial geometries were obtained from a previous exploratory study in the oxo tautomeric form of molecules, at HF/6-31G* level of theory, based on published results on geometrical isomerism of enaminones.[23,24]

## RESULTS AND DISCUSSION

### General background

We were seeking to establish a general correlation of the type:

$$ED_{50} = f[\text{structure, substituent}] \quad (1)$$

In this function the structure was quantified by *d* as a distance between the carbonyl oxygen and the first atom of the aromatic ring and the nature of the substituent was measured either by the Hammett ($\sigma$) or the Tafts steric (Es) substituent constant as was appropriate.

Two types of enaminones A and B were studied (Figs 5 and 7). Compounds from Family A came from Types **I** and **II** enaminones and they had not only structural and substituent parameters but their $ED_{50}$ values were also determined (Table 1). Family B also came from Types **I** and **II** enaminones, but their $ED_{50}$ values were not determined (Table 2).

Clearly, the number of measured biological activities of Types **I** and **II** is very small for a regular QSAR study. Consequently, exploratory analyses were made, in terms of single variable crossections, (2), (3), (4) and in terms of two independent variable surfaces (5), (6), in the hope that they may reveal some trend that may be useful in designing further investigations. Furthermore, it is also hoped that the structural parameter *d* may be a useful structural guide in designing bioactive enaminone structures.

$$ED_{50} = f_1(d) \quad (2)$$

$$ED_{50} = f_1'(\sigma) \quad (3)$$

$$ED_{50} = f_2(d, \sigma) \quad (4)$$

$$ED_{50} = f_1''(Es) \quad (5)$$

$$ED_{50} = f_2'(d, Es) \quad (6)$$

### Cyclic enaminones

Family A compounds consisting of 12 chemical structures, 9 of Type **I** and 3 of Type **II** are depicted in Fig. 5 and their $ED_{50}$ variations with *d*, according to Eqn (2) are seen in Fig. 6. As can be seen from Fig. 6 a total of four subfamilies, (i), (ii), (iii) and (iv), may be recognized within Family A. The fact that the points of each of these subfamilies are virtually above each other indicates that there must be a variation of the activity with the substituents. The upper part of Fig. 8 shows for the subfamilies (i), (ii) and (iii) of Family A, the structural variation according to the functional relationship (3) while the central part of Fig. 8 illustrates a structural variation of subfamily (iv) in Family A according to Eqn (4). The bottom part of Fig. 8 shows the variation of *d* with Taft Es parameter is also for the subfamily (iv).

The central part of Fig. 8 shows a very poor lineal correlation and the location of part suggests that there is a minimum values of the activity at about $Es = -1.5$ (broken line). In contrast to that the bottom part of Fig. 8 which shows the lineal dependence although the points are few.

Family B consists of compounds for which no $ED_{50}$ measurements were made (Fig. 7). Compounds **13**–**16** are of Type **II** enaminones, corresponding to subfamily (v) of Family B, while compounds **18**–**26** belong to Type **I** enaminones; corresponding to subfamilies of (vi), (vii) and (viii) of Family B. One-dimensional variations with substituent constants, according to (4) and (3), are

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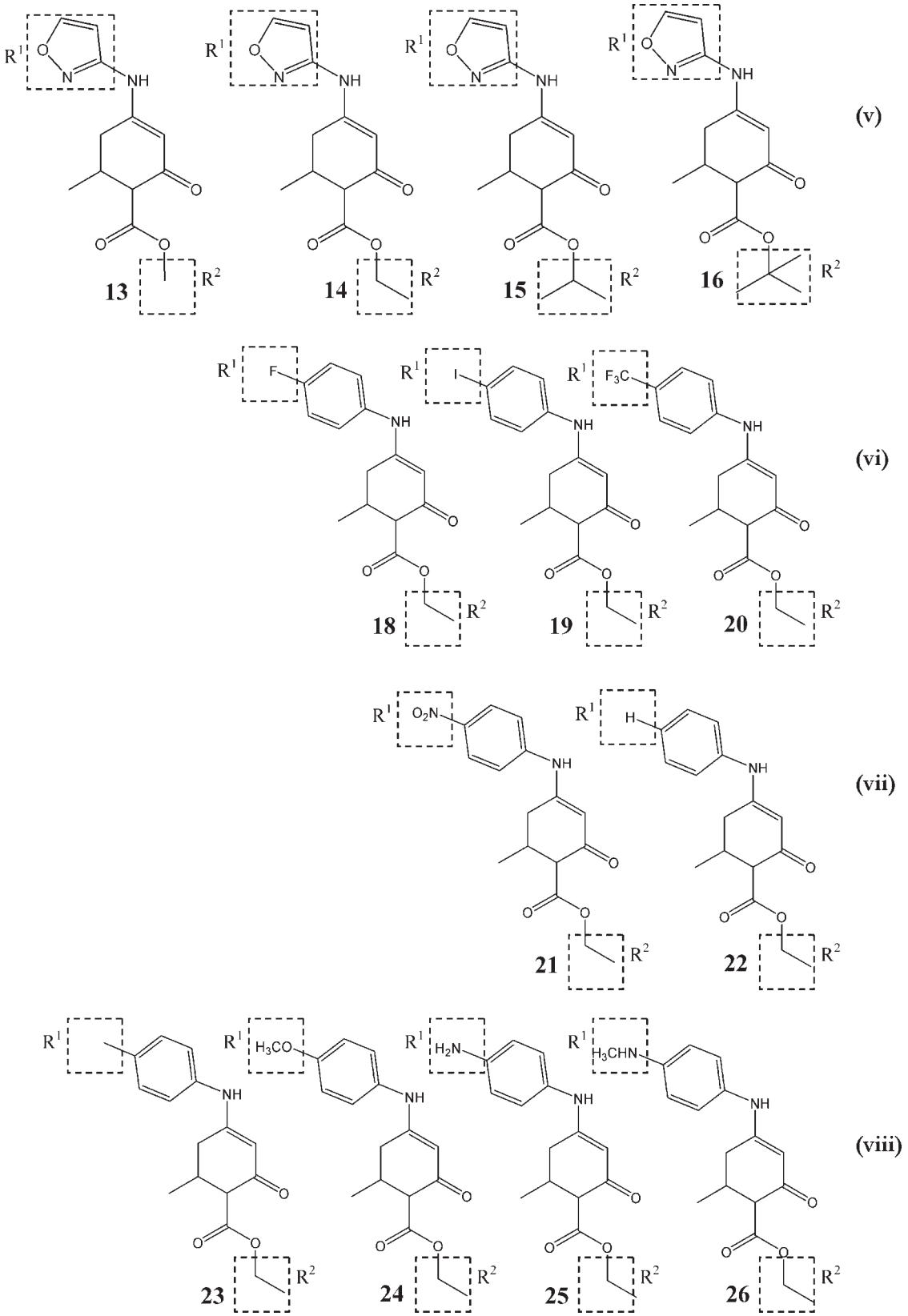


**Figure 7.** Semiempirical MO-optimized structures of selected bioactive enaminones with assumed bioactivity (Family B) with $R^1$ and $R^2$ substituents. Subfamilies are labelled as (v), (vi), (vii) and (viii)



  

**Table 1.** Bioactivity ($ED_{50}$) substituents and substituent constants for compounds of Family A

| Molecule | Activity | $R^1$ | Hammett sigma ($\sigma$) | $R^2$ | Taft size parameter (Es) | *d*/Å |
|---|---|---|---|---|---|---|
| 1 | 986.84 | $O_2N$ | 0.71 | $H_3C$ | | 6.051 |
| 2 | 876.05 | NC | 0.66 | $H_3C$ | | 5.997 |
| 3 | 89.41 | Cl | 0.227 | $H_3C$ | | 6.01 |
| 4 | 54.39 | Cl | 0.227 | $C_2H_5$ | | 6.048 |
| 5 | 22.44 | Br | 0.232 | $H_5C_2$ | | 6.049 |
| 6 | 103.92 | $F_3CO$ | 0.35 | $H_5C_2$ | | 6.048 |
| 7 | 211.74 | CN | 0.66 | $H_5C_2$ | | 6.049 |
| 8 | 565.9 | $H_3C$ | | $H_3C$ | −1.24 | 5.868 |
| 9 | 247.84 | $H_3C$ | | $H_5C_2$ | −1.31 | 5.866 |
| 10 | 391.83 | $H_3C$ | | t-$H_9C_4$ | −2.78 | 5.839 |
| 11 | 236.99 | H | 0 | $H_3C$ | | 6.382 |
| 12 | 546.39 | F | 0.062 | $H_3C$ | | 6.379 |

Critical distances, *d*, calculated by semiempirical MO are shown.

shown in Fig. 9 for subfamilies (v) as well as subfamilies (vi), (vii) and (viii), respectively.

According to Eqn (5), the topological clustering of the set of compounds associated with subfamilies (i), (ii), (iii), (vi), (vii) and (viii) is shown in Fig. 10. The two dimensional variation for subfamilies (i), (ii) and (iii) according to (5) is shown in Fig. 11. The topological clustering of subfamilies (iv) and (v) are shown in Fig. 12 and the surface for subfamily (iv) is presented in Fig. 13.

As far as structural and substituent effects are concerned, from Figs. 10 and 11 it is clear that most of the points fall within the range of $6.0\,\text{Å} \leq d \leq 6.1\,\text{Å}$ and the Hammett $\sigma$ values are varied in the range of $-0.9 \leq \sigma \leq +0.8$. Most of these structures contain *p*-substituted aniline moieties while the two points on the side (compounds **11** and **12**) are *p*-substituted benzylamines. It may also be noted that the $\pi$-electron withdrawing groups (like —$NO_2$ and —$CF_3$) are unfavourable, while $\pi$-electron donating groups (like —Cl and —Br) enhance biological activity resulting in lower $ED_{50}$ value. From Fig. 13 it is apparent that the larger the size of the alkyl group ($R^2$) in the carboxylic acid ester (—$COOR^2$), such as t-Bu, the less active is the molecule in contrast to the smaller sized $R^2$ group (e.g. Me and Et). The two best activities were observed with *p*-chloro phenyl and *p*-bromo phenyl groups (compounds **4** and **5** in Table 1, Figs 5, 6 and 11) combined with $R^2 = Et$, corresponding to 54.99 and 22.41 μmol/kg, respectively.

A 'spline' function fitted surfaces are not suitable for direct extrapolation. Consequently, some least square curve fitting may be in order. A simplified example, which also reveals the inaccuracy of the determined $ED_{50}$ data is shown in Fig. 14A.

**Table 2.** Substituents and substituent constants for compounds of Family B

| Molecule | $R^1$ | Hammett sigma ($\sigma$) | $R^2$ | Taft size parameter (Es) | *d*/Å |
|---|---|---|---|---|---|
| 13 | | | $H_3C$ | −1.24 | 5.852 |
| 14 | | | $H_5C_2$ | −1.31 | 5.848 |
| 15 | | | i-$H_7C_3$ | −1.71 | 5.850 |
| 16 | | | t-$H_9C_4$ | −2.78 | 5.847 |
| 18 | F | 0.06 | | | 6.038 |
| 19 | I | 0.18 | | | 6.039 |
| 20 | $F_3C$ | 0.54 | | | 6.041 |
| 21 | $O_2N$ | 0.78 | | | 6.050 |
| 22 | H | 0.00 | | | 6.047 |
| 23 | $H_3C$ | −0.17 | | | 6.048 |
| 24 | $H_2CO$ | −0.27 | | | 6.037 |
| 25 | $H_2N$ | −0.66 | | | 6.020 |
| 26 | $H_3CHN$ | −0.84 | | | 6.015 |

Critical distances, *d*, calculated by semiempirical MO are shown.

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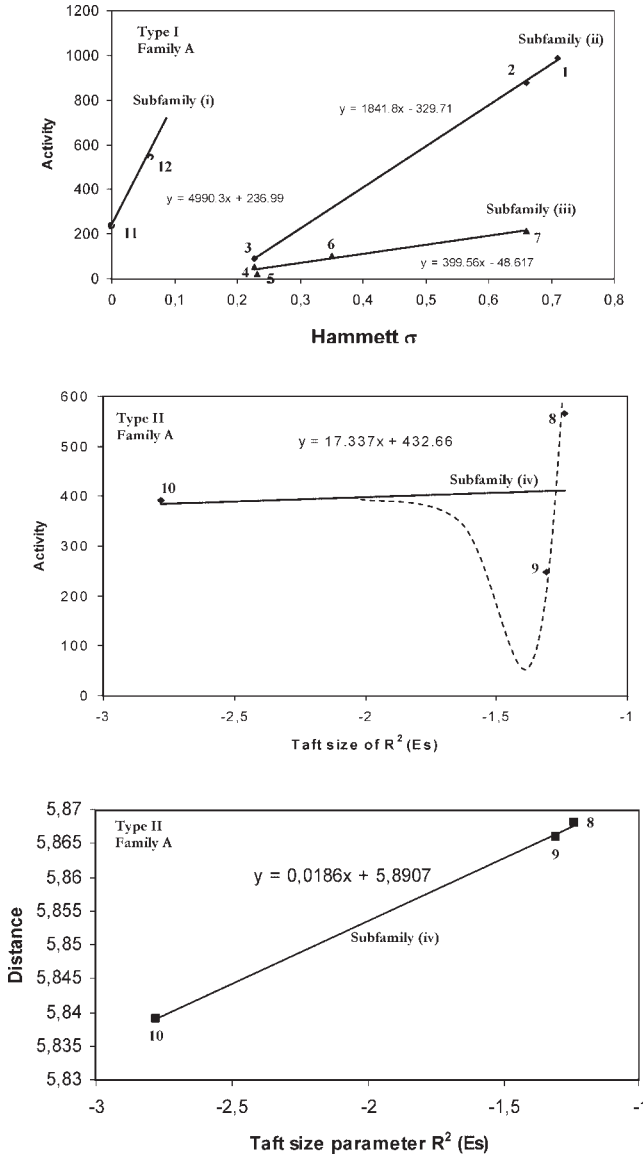


**Figure 8.** Bioactivities as function of substituents for subfamilies (i), (ii), (iii) and (iv) of Family A compounds. Top: variation of activity with Hammett substituent constant ($\sigma$) of subfamilies (i), (ii), (iii). Central: variation of activity with Taft size parameter (Es) of subfamily (iv). Bottom: variation of distance (d) with Taft size parameter (Es) of subfamily (iv)

The fitted logarithmic straight line had the following form:

$$\ln[ED_{50}] = m\sigma + \ln[ED_{50}]_0 = 5.541\sigma + 2.611 \quad (7)$$

and the fitted exponential form turned out to be

$$[ED_{50}] = [ED_{50}]_0 e^{m\sigma} = 13.61e^{5.541\sigma} \quad (8)$$

However, the direct exponential fit (8) is somewhat different from the logarithm (7).

Clearly, as can be seen from Fig. 14A, the linear fit has a slightly higher $R^2$ value (0.810) than the exponential fit (0.785). This method may be generalized further, if we interpolate between the experimental $ED_{50}$ values, using the $d = 6.045$ cross-section of

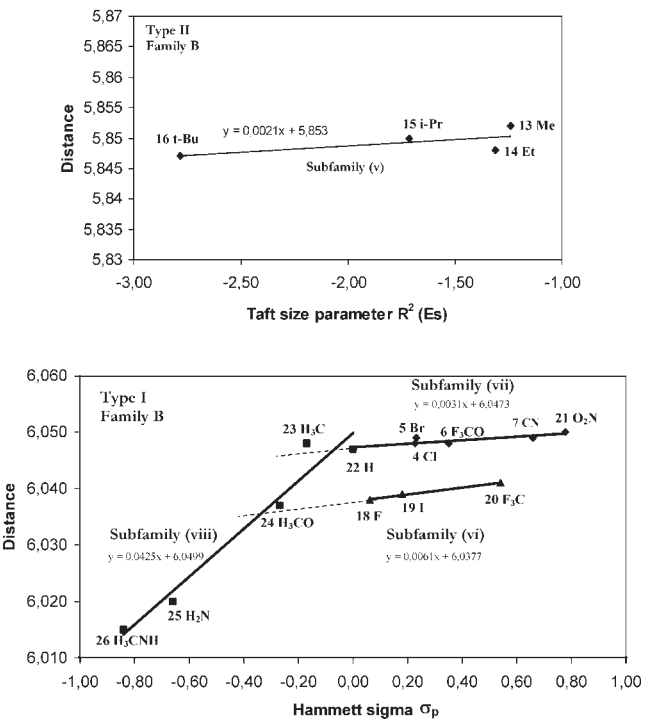


**Figure 9.** Calculated critical distances, in Å, for Family B compounds. Top: variation with Taft size parameter (Es) of subfamily (v). Bottom: variation with Hammett substituent constant (8) of subfamily (vi), (vii) and (viii)

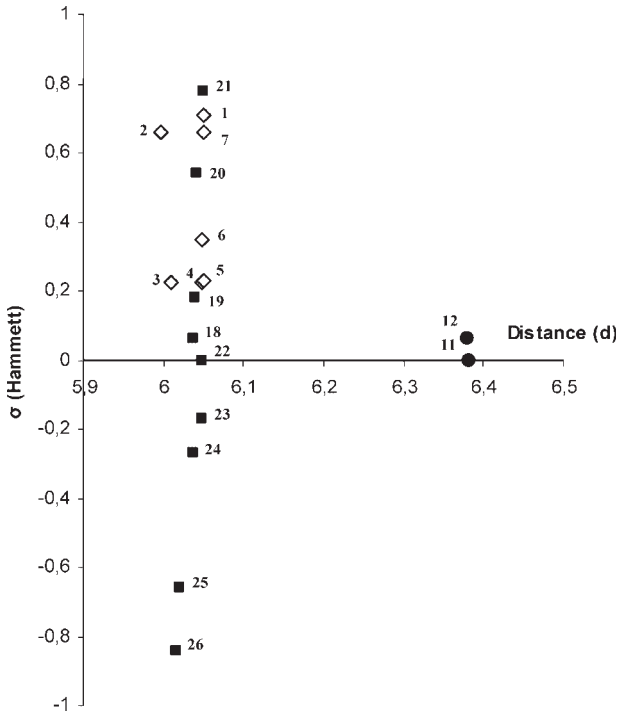


**Figure 10.** Topology of structures on a $ED_{50} = f_2$ ($d$, $\sigma$) surface



  

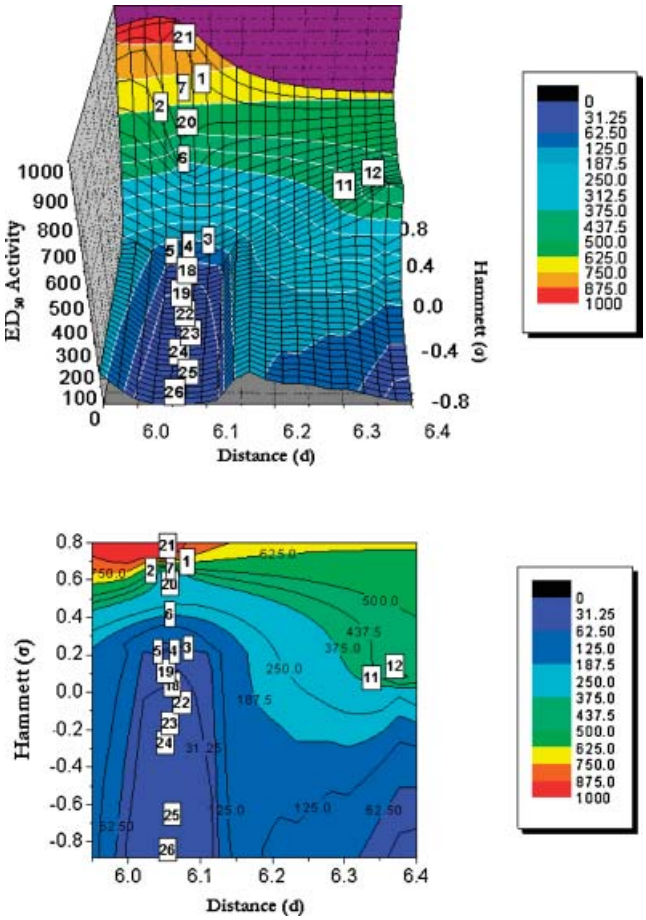


**Figure 11.** Graphical representation of the $ED_{50} = f_2$ ($d$, $\sigma$) surface

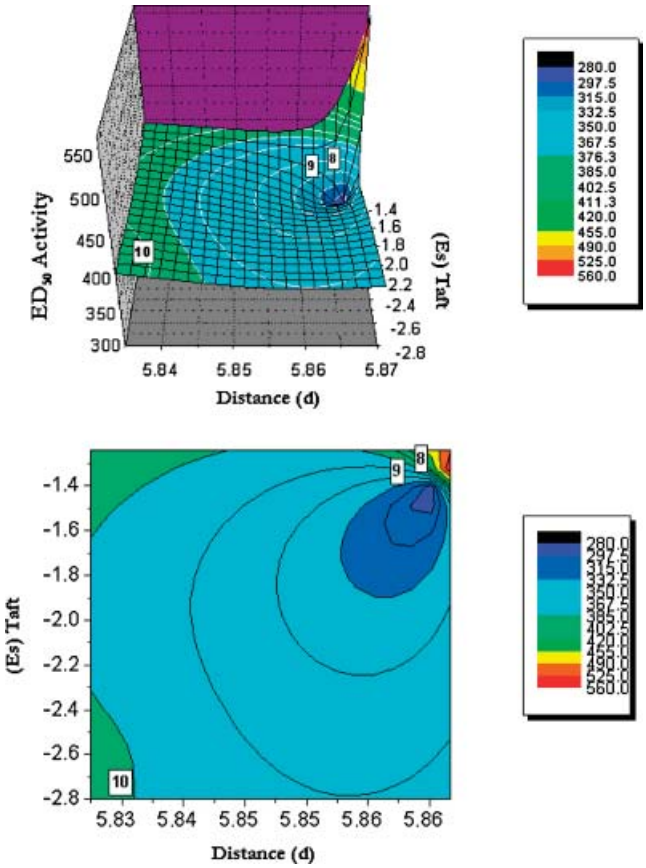


**Figure 13.** Graphical representation of the $ED_{50} = f'_2$ ($d$, Es) surface

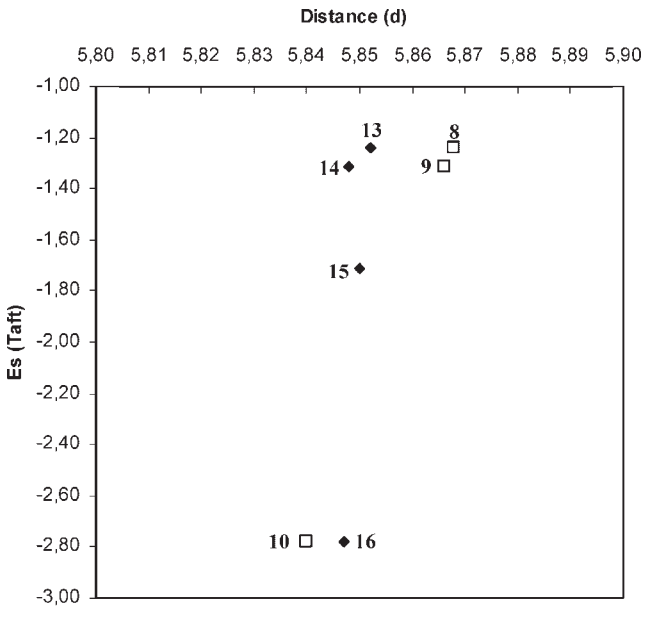


**Figure 12.** Topology of structures on the $ED_{50} = f'_2$ ($d$, Es) surface of subfamilies (iv) and (v)

the spline function fitted surface of Fig. 11. The result, for such an attempt, is shown in Fig. 14B. For the linear fit $R^2 = 0.955$ and for the exponential fit $R^2 = 0.931$; again the linear fit is slightly more accurate.

The logarithmic straight line, fitted to the interpolate points, had the following form:

$$\ln[ED_{50}] = m\sigma + \ln[ED_{50}]_0 = 5.209\sigma + 2.869 \quad (9)$$

and the fitted exponential form turned out to be

$$[ED_{50}] = [ED_{50}]_0 e^{m\sigma} = 17.62e^{5.869\sigma} \quad (10)$$

However, the direct exponential fit (10) is somewhat different again from the logarithm (9).

The comparison of the two linear fits (7) and (9) as shown in Fig. 15 is remarkable, in view of the fact, that originally we had only seven $ED_{50}$ measurements. On the basis of these Hammett-type analyses, the two types of approaches predict, at $\sigma = -0.84$, a relatively low $ED_{50}$ value corresponding to structure **26**, the *p-N*-methyl amine-substituted compound. The two values are $ED_{50} = 0.218$ μmol/kg, fitted to the Interpolated

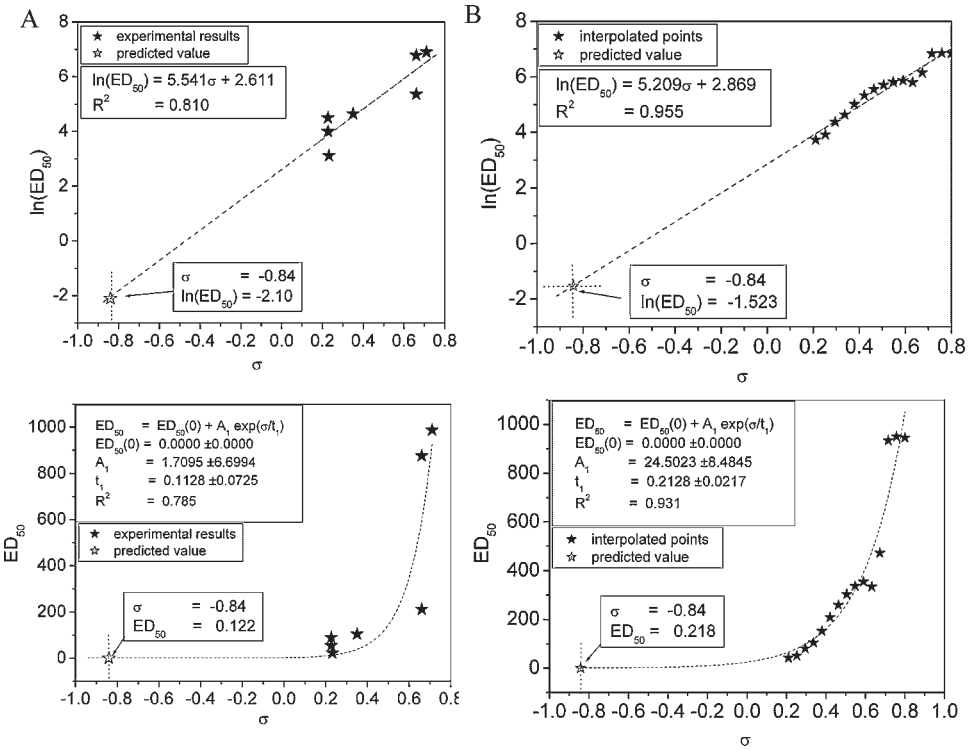


**Figure 14.** Extrapolation of ln ($ED_{50}$) versus $\sigma$ (top) and $ED_{50}$ versus $\sigma$ (Bottom) fitted function. A: Fitting was made to the anitable $ED_{50}$ points (compounds from **1** to **7** of Type **I**, Family A). B: Fitting was made to the interpolated $ED_{50}$ points along the line of $d = 6.045$Å of Fig. 11

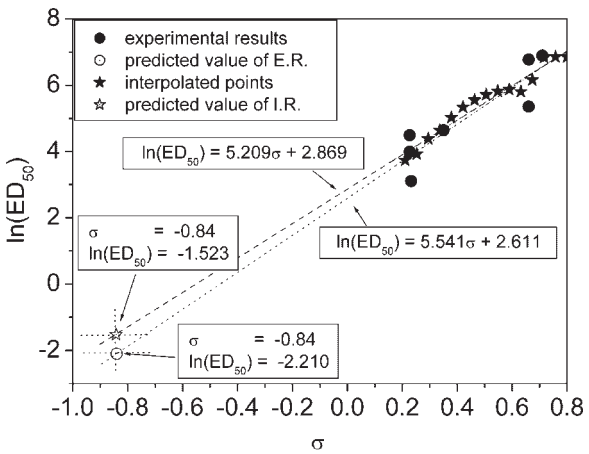


**Figure 15.** Comparison of linear fits orbital from experimental results (ER) and interpolation results (IR)

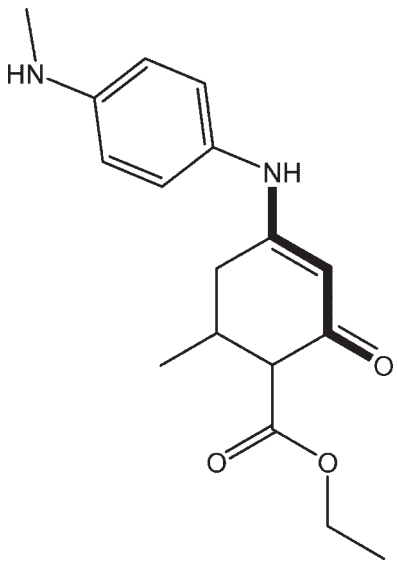


**Figure 16.** Predicted 'lead compound' as antiepileptic cyclic enaminone

Results (IR in Fig. 15), and $ED_{50} = 0.110$ μmol/kg, fitted to the Experimental Results (ER in Fig. 15). These values indicate a 100–200 times greater activity than the best measured activity (22.44 μmol/kg) for the *p*-bromo-substituted compound (corresponding to structure number **5** in Figs 5 and 6). As the predicted activity is of the order of 0.1 μmol/kg (or 100 nano-mole/kg) this compound may turn out to be a 'lead compound' (Fig. 16) worth-while to study experimentally in a the Drug Discovery process.

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