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# THEORETICAL STUDY OF THE OPIOID RECEPTOR SELECTIVITY OF SOME 7-ARYLIDENENALTREXONES

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## SUMMARY

A ZINDO/1 quantum-chemical structure-affinity relationship study is presented for the interaction of a group of 7-arylidenenaltrexones with μ, κ and δ opioid receptors. From this work it is concluded that:

1. The internal occupied molecular orbitals are extremely important to regulate receptor affinity and, in the case of the drug-receptor interaction, they seem to play a fundamental role in receptor affinity and selectivity.

2. Receptor selectivity seems to be regulated by subtle electronic differences, sometimes at the same atomic center.

3. In 7-arylidenenaltrexones, phenyl ring D is important for the interaction with all three receptors. Here, atoms 4 and/or 17 are possible targets for modifying receptor selectivity and/or affinity.

4. Reactivity indices of a given atom are affected by substituents placed on atoms that may be very far from it. It is suggested that this may be one of the main reasons to treat the drug-receptor interaction quantum-mechanically.

***KEYWORDS***: ZINDO/1, mu receptor, kappa receptor, delta receptor, KPG model, quantum pharmacology.

## INTRODUCTION

Molecular recognition processes control almost all the aspects of life on Earth [1]. The ability of molecules to recognize a certain atomic distribution pattern and not another is central to gene regulation, catalysis, drug effects, chemical reactivity, etc. [1]. Concerning the recognition by a drug of one or more receptors, this is a phenomena that need to be still fully understood to design new agonists or antagonists for a given receptor(s). We know now that not only the frontier molecular orbitals (HOMO and LUMO) are important in the drug-receptor interaction but also the lowest virtual and occupied MOs seem to play a central role. Note that the importance of the occupied molecular orbitals located just below the HOMO has been known for a long time [2-4]

One of the most interesting problems of the drug-receptor interaction is the following: how a given molecule can recognize two or more receptors and display a different affinity for them? Among the molecules having this interesting property we may cite dopaminergic, serotoninergic and opioid compounds. In the following we shall focus on the latter.

Regarding opiods there is abundant evidence for the existence of three major classes of receptors in the central nervous system (CNS), designated μ, κ and δ, as well as subtypes within each class. Each class has distinct selectivity profiles and unique distribution within the CNS [5]. Most of the opioids used clinically bind preferentially to μ receptors, reflecting their similarity to morphine. Drugs that are relatively selective at standard doses will interact with additional receptor subtypes when given at sufficiently high doses, although some drugs interact with more than one receptor class at clinical doses [5]. Several of the opioid peptides, such as β-endorphin, dynorphin A and the enkephalins, and also morphine, bind to μ receptors. Dynorphin A is the endogenous ligand for the κ1 receptor, and the enkephalins are the endogenous ligands for δ receptors [5].

Recently [6], a series of 7-arylidenenaltrexones related to 7-benzylidenenaltrexone (a $\delta_1$ selective antagonist) were synthesized. These molecules (Fig. 1) display different affinities for all three opioid receptors. The only difference among these molecules resides in the substituents on the phenyl group of the benzylidene moiety. Also, this is a typical case in which we have two aromatic portions without conjugation among them with substituents attached to only one of these portions.

The great medical importance of these and similar molecular systems requires more quantum-chemical research on their quantitative structure-

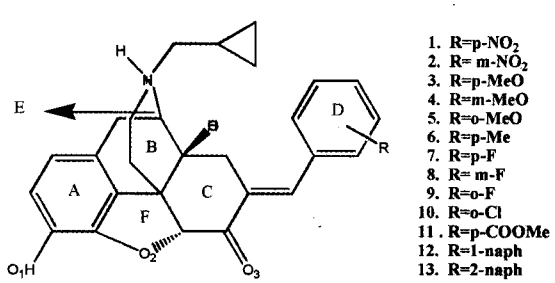


**Figure 1.** 7-Arylidenenaltrexones.

activity relationships (QSAR) in order to improve our knowledge about how receptor selectivity is achieved. Here we present QSAR results for the above molecules togheter with an hypothesis explaining how they display different affinities by the three opioid receptors. Note that this is the first time that this kind of problem is addressed.

## METHODS, MODELS AND CALCULATIONS

As the method has been discussed thoroughly elsewhere [7-13], we shall present a very general sketch. Briefly, the equilibrium constant K can be expressed as:

$$\log K = a + b\log M_D + c\log\sigma_D + d\log(I_1 I_2 I_3) + e\Delta E \quad (1)$$

where a,b,c,d and e are constants, D refers to the drug molecule, σ is the symmetry number, M the drug's molecular mass, $I_1 I_2 I_3$ is the product of the three moments of inertia about the three principal axes of rotation, and $\Delta E$ is the drug-receptor interaction energy.

The interaction energy is evaluated through the Klopman-Peradejordi-Gómez (KPG) approach as [7]:

$$\Delta E = W + \sum_i \left[E_i Q_i + F_i S_i^E + G_i S_i^N\right] + \sum_i \sum_m \left[H_i(m) D_i(m) + J_i(m) S_i^E(m)\right]$$

$$+ \sum_i \sum_{m'} \left[R_i(m') D_i(m') + T_i(m') S_i^N(m')\right] \quad (2)$$

where W, E, F, G, H, J, R $Q_i S_i^E$ and $S_i^N$ T are constants, are, respectively, the net charge, the electrophilic superdelocalizability and the nucleophilic superdelocalizability of atom i. The index m (m') refers to the contribution to the above properties of occupied (virtual) molecular orbital m (m'). $D_i(m)$ is the electronic density of atom i at MO m (or m'). Eq.(2) was derived assuming that the only important component of $\Delta E$ is the change in electronic energy. Only 7-arylidenenaltrexones-related terms appear in Eq. (2).

Inserting Eq. (2) into Eq. (1), we obtain the equation expressing the relationship between receptor affinity and reactivity parameters of the drug molecules only.

When employed within a CNDO/2 level of parametrization, this approach produced excellent QSAR results for very different biologically active molecules [9, 10, 12-16 and references therein].

The selected molecules are shown in Fig.1. The values for experimental receptor affinities were taken from the literature [6], and converted to equilibrium constants, $\log K_i$, accordingly to [13]:

$$\log K_i = \log(0.294 IC_{50} - 0.0147) \quad (3)$$

The molecules were studied in their protonated form. The geometry optimization and the calculation of the wave function were carried out by using the Hyperchem package [14] running on a Pentium II PC with 128 Mb of RAM. For full geometry optimization the AM1 semiempirical methodology was employed [15, Footnote 1]. The method selected for calculating the wave function was Zerner's ZINDO/1 [16, 17, Footnote 2]. Nevertheless, in the Hyperchem package constant orbital exponents are used for all the available elements, as recommended [14]. The choice on this semiempirical method is fully justified because after AM1 geometry optimization ZINDO/1 is the only method producing positive nucleophilic superdelocalizabilities as required by the model [18]. This is so because other quantum-chemical methods like AM1, MNDO and PM3 provide some virtual orbitals with negative energy and the definition of the nucleophilic superdelocalizability requieres that all virtual orbital have positive energy. In Table I we show, as an example, the results of the calculation of the total atomic nucleophilic superdelocalizability in two 7-arylidenenaltrexones after full AM1 geometry optimization. ZINDO/1 is the only method showing internal consistency in the values (earlier CNDO/2 results are also reported in Ref. 18).

The statistical fitting of Eq. 1 was performed by means of a stepwise regression technique with the receptor affinities as the dependent variables and the static reactivity indices of the atoms belonging to a common skeleton as independent variables. The common skeleton is shown in Fig. 2.

Table I. Atomic nucleophilic superdelocalizabilities for the nitro group of molecules 1 and 2 of Figure 1

| Molecula | Atom | CNDO | INDO | MNDO | MINDO/3 | ZINDO/1 |
|---|---|---|---|---|---|---|
| 1 | N | -59.50 | 24.23 | -6.01 | 0.79 | 16.27 |
| 1 | O1 | 2.99 | 12.27 | 0.42 | -1.00 | 4.27 |
| 1 | O2 | 13.13 | 11.60 | -10.11 | 1.20 | 5.00 |
| 2 | N | -185.52 | 22.27 | -4.95 | 0.46 | 16.12 |
| 2 | O1 | -6.94 | 11.68 | 0.76 | -1.24 | 4.27 |
| 2 | O2 | 8.38 | 9.92 | 0.45 | 0.90 | 4.88 |

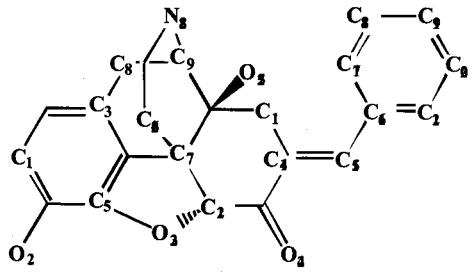

**Fig. 2.** Common skeleton numbering.

## RESULTS

### A. μ receptor affinity results.

The best equation is:

$$\log K_i = 0.33 + 10.59 Q_{11} - 3.50 S_{17}^E - 0.13 D_{21}(SHOMO) \quad (4)$$

with n=13, SD=0.10 and R=0.95. Here, $Q_{11}$ is the net charge of atom 11, $S_{17}^E$ is the total atomic electrophilic superdelocalizability of atom 17, and $D_{21}(SHOMO)$ is the electronic density of atom 21 at the third occupied molecular orbital (MO) (see Fig. 2). The analysis of variance of Eq. 4 gives F(3,9)= 34.51 (p<0.0005) showing that this equation is highly significant. The results of the Student's t-test for the significance of the variables are: t[$Q_{11}$]= 7.75 (p<0.0001), t[$S_{17}^E$]= -3.18 (p<0.01), and t[$D_{21}(SHOMO)$]= -4.93 (p<0.0001). The squares of the internal correlation coefficients are: $r^2$ [$Q_{11}$,$S_{17}^E$]=0.0001, $r^2$ [$Q_{11}$,$D_{21}(SHOMO)$]=0.004, and $r^2$ [$S_{17}^E$,$D_{21}(SHOMO)$]=0.08. We may appreciate that all the variables are significant and uncorrelated. The predicted $\log K_i$ are shown in Table II.

Table II. Experimental and calculated μ receptor affinities.

| Molecule | Exp. $\log K_i$ [a] | Calc. $\log K_i$ [b] |
|---|---|---|
| 1 | 0.11 | 0.27 |
| 2 | -0.49 | -0.47 |
| 3 | 0.04 | 0.05 |
| 4 | 0.27 | 0.20 |
| 5 | 0.39 | 0.46 |
| 6 | 0.31 | 0.35 |
| 7 | -0.19 | 0.03 |
| 8 | 0.36 | 0.36 |
| 9 | 0.05 | -0.05 |
| 10 | -0.42 | -0.31 |
| 11 | 0.04 | 0.07 |
| 12 | -0.46 | -0.38 |
| 13 | -0.02 | 0.12 |

a. Ref.2. b. With Eq. 4.

### B. κ receptor affinity results.

The best equation is:

$$\log K_i = 41.96 + 771.99 S_4^E + 4.30 Q_{12} - 0.37 D_{17}(SHOMO) \quad (5)$$

with n=13, SD=0.21 and R=0.87. Here, $S_4^E$ is the total atomic electrophilic superdelocalizability of atom 4, $Q_{12}$ is the net charge of atom 12, and $D_{17}(SHOMO)$ is the electronic density of atom 17 at the third occupied MO. The analysis of variance of Eq. 5 gives F(3,9)= 41.96 (p<0.0005) showing that this equation is highly significant. The results of the Student's t-test for the significance of the variables are: t[$S_4^E$]= 4.13 (p<0.002), t[$Q_{12}$]= 2.21 (p<0.05), and t[$D_{17}(SHOMO)$]= -5.34 (p<0.001). The squares of the internal correlation coefficients are: $r^2$ [$S_4^E$,$Q_{12}$]= 0.11, $r^2$ [$S_4^E$,$D_{17}(SHOMO)$]= 0.21, and $r^2$ [$Q_{12}$,$D_{17}(SHOMO)$]= 0.0001. All the variables are significant and uncorrelated. The predicted are shown in Table III.

Table III. Experimental and calculated κ receptor affinities.

| Molecule | Exp. $\log K_i$ [a] | Calc. $\log K_i$ [b] |
|---|---|---|
| 1 | -0.55 | -0.55 |
| 2 | -0.88 | -0.93 |
| 3 | -0.59 | -0.47 |
| 4 | -0.58 | -0.48 |
| 5 | -0.53 | -0.65 |
| 6 | -0.15 | -0.33 |
| 7 | -0.27 | -0.35 |
| 8 | -0.45 | -0.45 |
| 9 | -0.33 | -0.37 |
| 10 | -0.63 | -0.56 |
| 11 | -0.78 | -0.65 |
| 12 | -0.28 | -0.24 |
| 13 | -0.52 | -0.38 |

a. Ref. 2. b. With Eq. 5.

### C. δ receptor affinity results.

The best equation is:

$$\log K_i = -48.75 + 28.98 Q_4 - 964.18 S_4^E - 2.90 S_{16}^E(NHOMO) \quad (6)$$

with n=13, SD=0.23 and R=0.93. Here, $Q_4$ is the net charge of atom 4, $S_4^E$ is the total atomic electrophilic superdelocalizability of atom 4, and $S_{16}^E(NHOMO)$ is the contribution of atom 16 to the electrophilic superdelocalizability of the second occupied MO. The analysis of variance of Eq. 6 gives F(3,9)= 22.62 (p<0.0005) showing that this equation is highly significant. The results of the Student's t-test for the significance of the variables are: t[$S_4^E$]= -2.87 (p<0.02), t[$Q_4$]= 5.56 (p<0.001), and t[$S_{16}^E(NHOMO)$]= -3.74 (p<0.005). The squares of the internal correlation coefficients are: $r^2$ [$Q_4$, $S_4^E$]= 0.03,

$r^2[S_4^E, S_{16}^E(NHOMO)] = 0.11$, and $r^2$ [$Q_4$, $S_{16}^E(NHOMO)$ ]= 0.04. All the variables are significant and uncorrelated. The predicted $\log K_i$ are shown in Table IV.

Table IV. Experimental and calculated δ receptor affinities.

| Molecule | Exp. $\log K_i$ [a] | Calc. $\log K_i$ [b] |
|---|---|---|
| 1 | -0.26 | -0.34 |
| 2 | 0.18 | 0.31 |
| 3 | 0.21 | 0.49 |
| 4 | 0.72 | 0.86 |
| 5 | 1.55 | 1.49 |
| 6 | 0.82 | 0.75 |
| 7 | -0.24 | -0.11 |
| 8 | 0.68 | 0.91 |
| 9 | 0.70 | 0.49 |
| 10 | 1.58 | 1.37 |
| 11 | 0.63 | 0.24 |
| 12 | 0.57 | 0.74 |
| 13 | 0.53 | 0.43 |

a. Ref. 2. b. With Eq. 6.

## DISCUSSION

The location of the first three occupied MOs (i.e., HOMO, NHOMO and SHOMO) is not the same for all the molecules. In the case of the HOMO we have three situations:

a. The HOMO is centered on aromatic ring A (see Fig. 1) in molecules 1, 2 and 8-10,
b. The HOMO is centered on aromatic ring D of the benzylidene moiety in molecules 3-6, 12 and 13, and
c. The HOMO is centered on both rings, A and D, in molecules 7 and 11.

The NHOMO is located on both rings in all the molecules. The SHOMO shows three possibilities: centered on ring A (molecules 3 and 5), on ring D (molecules 1, 7 and 11) or on both (molecules 2, 4, 6, 8-10, 12 and 13). Analysis of the receptor affinites shows no relationship with the location of one or more MOs.

The above equations show that the variation of the μ, κ and δ receptor affinities is related to the variation of a definite set of molecular reactivity indices. This implies that, for each type of receptor, there is a common interaction mechanism for all the molecules analyzed. Before analyzing of the regression equations we must keep in mind that we are dealing with the **variation** of the reactivity indices. A contribution that remains constant through the family analyzed will not appear in the equations.

**a. μ receptor affinity**. Eq. 4 suggests that the following conditions are suitable for good receptor affinity (see Fig. 2): a negative value of $Q_{11}$, a low value of $S^E_{17}$ and a high value of $D_{21}(SHOMO)$.The appearance of $Q_{11}$ in Eq. 4 indicates that there is an electrostatic interaction of C-11 with an electron-deficient center of the μ receptor. The other two reactivity indices appearing in Eq. 4 belong to ring D of the benzylidene moiety. The appearance of might suggest a charge transfer from atom 17 to an electron-deficient center. Nevertheless, as optimal affinity requires a low electron-donating ability of atom 17, an electron-acceptor substituent attached to it seems reasonable. A high value of is needed for good receptor affinity. Given that the SHOMO is of π character, we suggest that there is a charge transfer from this atom toward the receptor. These results showed that the phenyl ring D of the benzylidene moiety also interacts with the receptor. It is interesting to note that in an earlier CNDO/2 study of the interaction of narcotics (morphine and benzomorphane derivatives) with the μ receptor [10], good affinity was related to good electron-accepting properties of atom 7, low electron-donating properties of atom 26, and a positively charged atom 4. The compatibility of these very different studies (CNDO/2 with standard geometry versus AM1-ZINDO/1) could indicate that certain sections of rings A-C, E and F are common *loci* for the interaction with μ receptors. The set of all these conditions define the interaction pharmacophore [19], which is shown in Fig. 3.

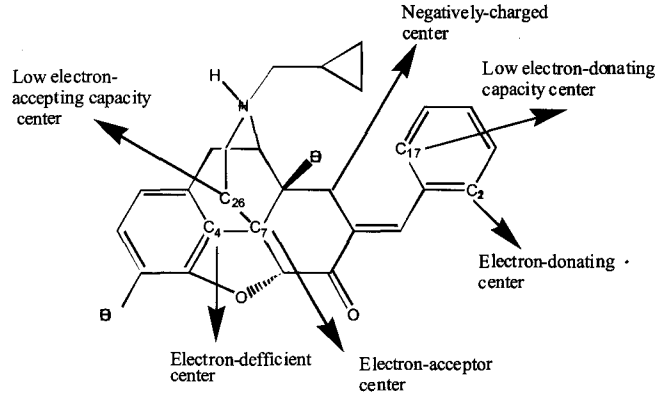


**Fig. 3**. Interaction pharmacophore for μ receptors.

**b. κ receptor affinity.** Eq. 5 shows that the following conditions are suitable for good receptor affinity: high values of $S^E_4$ and $D_{17}(SHOMO)$, and a negative value for $Q_{12}$. If atom 12 carries a negative net charge it will interact with a positive (or electron-deficient) center of the ( receptor. This interaction will probably involve the closer negatively-charged oxygen atoms (atoms 23 and 24 of Fig. 2). The requirement of a high value for suggests that the interaction with the ( receptor is through a charge transfer from atom 4 toward the receptor. This contrasts with ( receptor requirements, in which a positve net charge of atom 4 is demanded [10]. This is supported by the condition imposed on . A high value of this reactivity index is required, contrasting with the high electron-donating ability demanded for the interaction with the μ receptor. Note also the following coherence: here a negative charge on atom 12 is a requirement. Further, this atom is bonded to atom 7, that should have good electron-accepting properties to interact

with the μ receptors. We suggest here that this kind of subtle electronic differences is the basis of receptor selectivity.(see fig. 4)

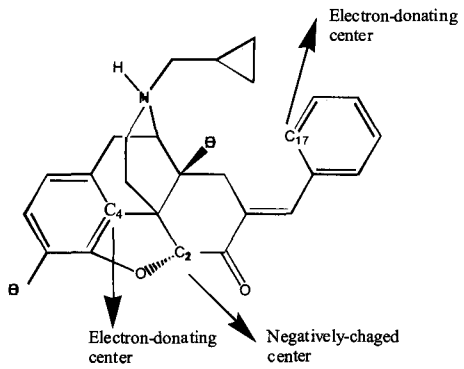


**Fig. 4.** Interaction pharmacophore for κ receptors.

**δ receptor affinity.** Eq. 6 suggests that the following conditions are optimal for $S^E_4$ good receptor affinity (see Fig. 2): a negative value for $Q_4$ and low values for $S^E_4$ and $S^E_{16}(NHOMO)$ . The requirement of a low value for $S^E_{16}(NHOMO)$ , which is coherent with a tendency to accept electrons, suggests that the interaction of atom 4 with the δ receptor is through a charge transfer from the latter. A low value for could indicate electron transfer from the receptor to atom 16. On the other hand, a negative value for is the best possibility for a high affinity.

As this requirement is contradictory with the condition imposed on , a balance must be struck between these two values. Our results indicate that the conditions for atom 4 seem to be intermediate between those for ( and ( receptors. This could be another fact pointing to the idea that small changes in the properties of some atomic centers may be the clue for receptor selectivity.

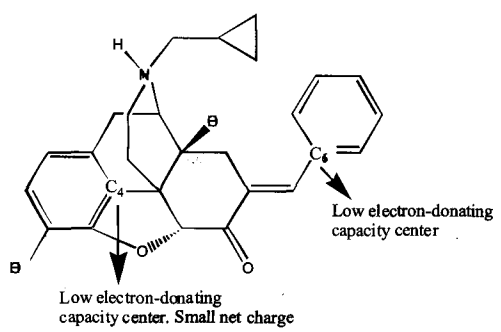


**Fig.5.** Interaction pharmacophore for δ receptors.

In conclusion we have shown, starting from a model-based method [19], the following facts:

1. The internal occupied molecular orbitals (NHOMO and SHOMO) are extremely important in regulating receptor affinity. The importance of these MOs is not new [3, 4, 20, 21] and, in the case of the drug-receptor interaction, they seem to play a fundamental role in receptor affinity and selectivity.

2. Receptor selectivity seems to be regulated by subtle electronic differences, sometimes at the same atomic center.

3. In 7-arylidenenaltrexones, phenyl ring D is important for the interaction with the three receptors.

4. Atoms 4 and/or 17 are possible targets for modifying receptor selectivity and/or afinity.

5. Reactivity indices of a given atom are affected by substituents placed on atoms that may be very far from it. This effect is explained as follows. When a substituent is added to one molecule, we are enlarging the atomic basis set. This produces a natural enlargement of the number of occupied molecular orbitals. This slightly modifies the energy and/or the location of other MOs, changing for example the value for the orbital electrophilic superdelocalizability or other indices. This indicates that the substituent effect does not only extend over the neighbouring atoms but must reach unexpected locations. Perhaps this is one of the main reasons for treating the drug-receptor quantum-mechanically.

## REFERENCES.


1. Delaage, M. Molecular Recognition Mechanisms, John Wiley & Sons,: New York, 1991.
2. Gómez-Jeria, J.S. Int.. J. Quant. Chem. 1983, 23, 1969.
3. Gómez-Jeria, J.S; Ojeda-Vergara, M. Int.J.Quant.Chem.1997, 61, 997.
4. Gómez-Jeria, J.S.; Lagos-Arancibia, L. Int. J. Quant. Chem. 1999, 71, 505.
5. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9/e, CD-ROM. Hardman, J.G. and Limbard, L.E. Editors-in-Chief. McGraw-Hill: New York, 1996.
6. Ohkawa, S.; Portoghese, P.S. J. Med. Chem. 1998, 41, 4177.
7. Gómez-Jeria, J.S., in Molecules in Physics, Chemistry and Biology, J.Maruani, Ed. (Kluwer, Dordrecht, 1989), Vol.4, pp.231-251.
8. Gómez-Jeria, J.S.; Morales-Lagos, D., in QSAR in Design of Bioactive Compounds, M.Kuchar, Ed. (J.R.Prous, Barcelona, 1984), pp. 145-1 73.
9. Gómez-Jeria, J.S.; Donoso-Espinoza, C.; Ojeda-Vergara, M. Mol. Engn. 1995, 5, 391.
10. Gómez-Jeria, J.S.; Sotomayor, P. J.Mol.Struct. (Theochem) 1988, 166, 493.
11. Gómez-Jeria, J.S.; Morales-Lagos, D.; Cassels, B.; Saavedra-Aguilar, J.C. Quant. Struct.Act. Relat. 1986, 5, 153.
12. Gómez-Jeria, J.S.; Cassels, B.; Saavedra-Aguilar, J.C. Eur.J. Med. Chem. 1987, 22, 433.
13. Gómez-Jeria. J.S. Farmaco 1985, 40, 299.

14. Hyperchem, V. 5.01. Hypercube Inc. 419 Phillip St., Waterloo, Ontario, Canada.
15. Dewar, M.J.S.; Zoebisch, E.G.; Hely, E.F.; Stewart, J.J.P. J. Am. Chem. Soc. 1985, 107, 3902.
16. Edwards, W.D.; Zerner, M.C. Theoret. Chim. Acta 1987, 72, 347.
17. Anderson, W.P.; Edwards, W.D.; Zerner, M.C. Inorg. Chem. 1986, 28, 2728.
18. Gómez-Jeria, J.S. J.Pharm.Sci. 1982, 71, 1423.
19. Martin, Y.C. Quantitative Drug Design; Dekker: New York, 1978.
20. Fleming, I. Frontier Orbitals and Organic Chemical Reactions. Wiley: New York, 1976.
21. Frontier Orbitals and Reaction Paths. Fukui, K.; Fujimoto, H., Eds.; World Scientific: Singapore, 1997.