CBPF-NF-066/97

The Antiepileptic Lamotrigine and its Analogues; Comparative Theoretical Electronic Properties

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Abstract

Electronic properties of lamotrigine (LTG) and two analogues (A1 and A2) are compared through MOPAC-AM1 calculations. A second conformer of LTG should exist. In the three compounds and the two conformers for each of them, the more favourable protonation sites are N_2 and N_4; these should then be the sites appropriate for interaction with a receptor and group valence reinforces the supposition. The molecular electrostatic potentials show that a region between the two chlorine atoms in LTG could be the site for an electrostatic interaction with a corresponding site in the receptor. The fluorine atom in A1 would play an equivalent role. A simple model for LTG-receptor interaction is proposed. A2 would have lesser agonist efficacy. Multicenter bond indices are related to aromaticity.

Key-words: Lamotrigine and analogues; Molecular electrostatic potentials; Receptor binding sites.

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1. Introduction

Epilepsy is known to be an acquired or hereditary neurological disorder, manifested through recurrent crises or attacks which may have different components [1]. Epidemiological studies report overall prevalences of 5 to 8 persons per 1000, suggesting a nearly uniform prevalence of epilepsy in most parts of the world [2]. Several drugs are used for the different kinds of epilepsy, between them benzodiazepines (BDZ) and their mechanism of action are extensively studied, both experimentally [3] and theoretically [4]. Most patients are significantly relieved by the available drugs. As, however, adverse side effects are also most frequent, there is actually a need for new antiepileptic drugs and research in this sense is in course [5]. Some of these drugs are used in clinical treatment and, independently from the huge commercial interest that they raise, they show a beneficial effect on seizure prevention. One of these widely investigated substances is a phenyl triazine, lamotrigine (LTG), namely 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine [6].

LTG is chemically not related with previously used antiepileptic drugs; its pharmacological profile is similar to that of phenytoin and carbamazepine. It has been suggested that its therapeutic effect may be due to blockade of voltage-sensitive sodium channels to stabilize neuronal membranes and inhibit transmitter release, mainly glutamate [7]. The knowledge of LTG crystallographic structure [8] encourages theoretical approaches. In fact, a few papers focusing electronic and structural properties of LTG have appeared [9, 10]. Somes analogues of LTG, closely similar in structure, have been synthesized and their X-ray structure is known [11–13].

Until some years ago, the carbonyl group found in antiepileptic drugs appeared to be essential for anticonvulsant activity [9, 14, 15]. In BDZs, the most important active sites are the imine nitrogen atom and the carbonyl group in the seven-membered ring [14]. It is then worthwhile to study electronic properties of antiepileptic drugs such as LTG, without any carbonyl group. Here, we consider LTG and the analogues 3,5-diamino-6-(2-fluorophenyl)-1,2,4-triazine [11] and 3,5-diamino-6-(2-methylphenyl)-1,2,4-triazine [12], named henceforth A1 and A2 respectively. To our knowledge there are still no experimental studies of their theurapeutical action. The triazine moiety of LTG and its analogues (Fig. 1) involves three σ electron pairs of the azine cycle and two π pairs from the amino N atoms, which could be significant to the effect of characteristic features. We complement in this work previous structural studies [9, 10]. We discuss some geometrical characteristics in LTG and its analogous. Two Cl substituents in the position ortho on the benzene ring in derivatives of phenyl triazol pyridazines seem to increase the anticonvulsant actitivity [9]. As LTG has instead a Cl in the ortho and another one in the meta position, we explore here whether this circumstance has any influence. We investigate the active sites of the agonists through protonation heats and molecular

electrostatic potentials. We propose a molecular model for LTG-receptor interaction. We calculate group valence and multicenter bond indices, which have been successfully applied to other kind of systems [16, 17].

2. Geometry and calculation procedure

We have reported in Fig. 1 the labelling for LTG, A1 and A2. For our calculations, we have used the MOPAC package [18]. Despite the known shortcomings of these methods [10], we have chosen the AM1 Hamiltonian, which predicts the existence of two conformers for each analogue, in agreement with experiment [11, 12]. Let us remark that MNDO, instead, leads incorrecly to a single conformer in each case, defined by the torsion angle $C'_2-C'_1-C_6-C_5$; MNDO yields 87^0 for Al and 91^0 for A2. We have also used HYPERCHEM [19] for the molecular electrostatic potentials.

Table 1 shows the torsion angles obtained. For LTG, the theoretical angle is around 15^0 less than the experimental one. The electrostatic attraction undergone by a hydrogen of the amino N_3 group towards the two chlorine atoms (see in Fig. 3b the local minimum between them) renders our predicted torsion of 66.7^0 between the rings quite credible. We have found a second conformer at 115.3^0 (see next section); a second form has indeed been crystallized, being relatively unstable to X-rays [8]. The analogues may be considered in reasonable agreement between theoretical and experimental values. Let us remark that the experimental angle of 61.7^0 for A2 would give a distance of 1.92Å between a hydrogen of the amino nitrogen N_3 and one of the hydrogens of the methyl group in the phenyl ring; this distance is too short, while the corresponding distance for our results is 2.70Å, more satisfactory taking into account the repulsion between both hydrogens. We have also carried out calculations for the molecule 3,5-diamino-6-phenyl-1,2,4-triazine, that is with no substituent in the phenyl ring. The results points at two energetic minima for the torsional angles 57^0 and 123^0, in fair agreement with the theoretical and experimental ones for the conformers of the analogues.

Fig. 2 shows a superimposition of LTG, A1C1 and A2C2, according to the experimental results of Refs. [8, 11, 12], in Fig. 2a and after optimization in Fig. 2b. Fig. 2a exhibits significant differences in the torsional angle τ between the phenyl and triazine rings; after optimization (Fig. 2b), the structures become well superimposed on each other for a torsional angle aroung 60^0. Some theoretical approaches intend to reproduce experimental structures [10, 20]. However, it has been argued that, due to the inherent difficulties in the determination of crystal structure through X-diffraction, optimized geometries are preferable for a more reasonable comparison of electronic structures in analogues [4, 21]. As the intermolecular interactions present in a crystal packing do not appear at low molecular concentrations [22], it happens for instance that one finds

optimized distances longer than those obtained experimentally from structural studies [10, 23].

3. Heats of protonation and molecular electrostatic potentials

Several molecular properties offer indicators related to the ligand-receptor interaction [21]; we shall return to this subject in the next section. One of these properties is the protonating ability of the various sites in the system.

Table 1 shows the heats of protonation at competing sites of the molecules, calculated as in Ref. [21], namely the difference between the heat of formation of the protonated and unprotonated form of each molecule. In all of them, N_2 and N_4 are the most favourable proton-accepting sites, those of A2 being slightly more favoured. N_1 comes next, with about 7-8 kcal/mol more than the previous cases. The amino nitrogens (not shown in the table) follow with 4-5 kcal/mol more than the N_1 case. That is, in LTG the amino groups do not seem to play an important role in protonation. The Cl atoms of LTG cannot protonate; rather, as well shall see right away from the potentials, a proton would go midway between both chlorines. LTG2 has practically the same energy and heats of protonation than LTG1. Strikingly, when protonating N_4, the torsion angle goes back to $\sim 66^0$, practically the same value that the optimized one obtained for LTG1.

The molecular electrostatic potential (MEP) distribution constitutes a powerful tool in theoretical chemistry concerning intermolecular interaction predictions, since it is directly related to the electrostatic energy [24] and has also been widely used in theoretical molecular biological studies [25, 26]. MEPs have been extensively used in connection with neurological problems. There are several works concerning GABA or GABA agonists/antagonists, focusing their interaction with receptor sites [27]. Loew and co-workers [4, 28] have analyzed MEPs of BDZ and BDZ antagonists, considering the effects due to different substituents in a certain position. We use here the AM1 MEPs of the HYPERCHEM package [19], which take into account the nuclear and continuous molecular electron density contributions to the electrostatic potential expression. Despite the fact that AM1 involves the NDDO approximation (neglect of diatomic differential overlap), the generated MEPs have proven to give results that are good enough for our purposes.

The obtained maps manifest the described features of protonation heats. In Fig. 3a, electrostatic potential contours generated in the triazine ring plane of LTG are displayed. The negative regions corresponding to the N_1, N_2 and N_4 atoms are clearly seen. It is worth to remark that a single negative potential zone is associated with nitrogens N_1 and N_2, but the latter atom zone appears enhanced in relation to the former, since a local minimum is obtained close to N_2. As expected, electrostatic potential positive regions are generated by the amino hydrogens of the N_3 and N_5 atoms in the triazine ring plane.

In Fig. 3b, the MEP map distribution in the phenyl ring plane is drawn, showing large positive potential zones around the ring and two local minima; one lies between the two chlorine atoms Cl_1 and Cl_2 and the other one is associated with the lone pair of the N_3 amino atom. The last one is visible due to the triazine ring tilt.

Considering that the obtained isopotential contours for the A1C1 and A2C1 compounds in the triazine ring are very similar to those displayed for the LTG molecule, we present for these analogues only the MEPs determined in the phenyl ring plane. The corresponding MEP for A1C1 appears in Fig. 4a and clearly indicates the local minima associated with the two lone pairs of fluorine, as well as the local minimum near the N_3 atom. Finally, Fig. 4b displays what happens when, in A2C1, Cl_1 is replaced by a methyl group and Cl_2 by a hydrogen atom. This Figure is quite similar to Fig. 3b; as the torsional angle of triazine with regard to the phenyl ring (117.5^0) is inverted in relation to the C_3–N_3 axis, the local minimum near the amino nitrogen N_3 is also inverted. A large positive potential zone around the methyl group is manifest in Fig. 4b.

Despite the fact that the above discussion of the MEP representation has been carried out qualitatively, it is expected that lower negative potentials will be found in the neighbourhood of the N_2 and N_4 nitrogens compared with those of the nitrogen N_1 region. As we have reported in all molecules, N_2 and N_4 are the most favourable proton-accepting sites. For LTG and Al, the phenyl ring includes halogen atoms substituents, the corresponding local minima of electrostatic potential detected could be rather associated to electrostatic interaction with cationic species of the receptor sites. Instead, the phenyl ring of the A2C1 compound does not present any local miminum; the electrostatic distribution obtained is depicted by large positive zones around the methyl group. This feature enhances the hydrophobic character of the phenyl ring in this lamotrigine analogue. The global aspects related to the electronic strucure of LTG and its analogues provides a basis to build an active site model for those systems, as we shall see next.

4. Molecular model for LTG-receptor interaction

Several molecular models have been proposed for BDZ receptors (BZR) up to 1990 [29]. In one of them, applied to BDZs, pyrazoloquinolines and a certain β-carboline derivative [30], the active domain of the BZR interacts with two high electronic density sites (proton acceptors) in the agonist pharmacophore. In BDZs, the two proton acceptors would be the oxygen in the carbonyl group and N_4 (Fig. 5a). A third interaction seems significant for the agonist efficacy; it takes place between a substituent on the ligand in position 7 (Cl in diazepam DZ) and an electrostatic interaction site ε^+ on the receptor [30]. In addition, for BDZ and the β-carboline derivative, a lipophilic pocket has been indicated, allowing for the entrance of the phenyl group as a requirement for full agonist

efficacy (Fig. 5b) [30]. In Ref. [31], dealing with several families of compounds – among which BDZs – six critical zones are described. One of them involves a π-electron rich aromatic region (PAR), usually occupied by a bicyclic heterocycle. Another one has two electron-rich regions, δ_1 and δ_2, placed at a certain distance from a reference centroid λ in the PAR (Fig. 5c). The model of Ref. [32] locates the centroid in ring A (Fig. 5a) and the interpretation is founded upon the distance from this centroid to atom O (region π_1 in the original text), which is 4.91Å. We shall try here to sketch a model for the interaction between LTG and a receptor, following the model of Ref. [30] and having in mind those of Refs. [31] and [32].

As it is well known, the last years have seen significant advance in the study of the structure of GABA receptors, $GABA_A$ and $GABA_B$, specially the first one [33]. BDZ and other anticonvulsionants act through the $GABA_A$ receptor formed by the combination of $\alpha, \beta, \gamma, \delta$ and ρ subunits [34]. Based on their affinity for imidazopyridine zolpidem, it has been possible to identify different types of BZR in rat brain; type I having high affinity, II_M with medium and II_L having low affinity [35]. Despite all the progress achieved, little is known about the composition and stoichiometry of the $GABA_A$ receptor subunits [36, 37]. On the other hand, studies about the mechanism of action of LTG on the central nervous system (CNS) and ion channels (using primary neuroglial cultures from rat cortex) show, through electrophysiological recordings, that LTG at 100 μM did not elicit diazepam-like modulatory responses [38].

As, in light of these experimental results, LTG does not mimic DZ at the $GABA_A$ receptor, let us return to the above mentioned classical BZR model [30] trying to fit it to LTG and its analogues. The adaptation is not straightforward as, for instance, LTG does not have a fused ring. Moreover, in LTG neither of the two Cl atoms (in ortho or meta position) is preferred for the electrostatic interaction with the receptor site ε^+. This site $\ominus$ (see Fig. 6a) is attracted towards the center of the negative local minimum of Fig. 3b. For the distance $[\ominus - \varepsilon^+]$ we take that of the ionic Cl^-Na^+ crystal, 2.8Å [39]. The distances of the present model (Figs. 6a,b) appear in Table 2.

The $H_2-\varepsilon^+$, $H_4-\varepsilon^+$ and H_2-H_4 distances are in excellent agreement with the average distances of Ref. [30] (Fig. 5b) and so may be considered the distances from N_2 and N_4 to $\ominus$, when compared with $\delta_1 - X$ and $\delta_2 - X$ (Fig. 5b). The distances from N_2 and N_4 to λ are satisfactorily close to those of Refs. [31] (see Fig. 5c) and to those of Ref. [32]. In the model of Ref. [32], the $O-\lambda$ distance must be less than 6Å, as a requirement fulfilled by an agonist.

As the models of Figs. 5b and 5c are intended for average intersite distances for a variety of compounds, some of the differences between them and our own in the table are self-explained. Let us mention, for instance, the short N_2-N_4 distance in LTG; the equivalent distances in Figs. 5b and 5c (3.5 and 3.2Å respectively) refer to more distant

atoms.

In A1C1 and A1C2 the distances disagree with the corresponding ones of Fig. 5b. If the fluorine atom substituted hydrogen in $C_{3'}$ (instead of $C_{2'}$), the agreement would be better, for $N_2{-}F$ and $N_4{-}F$ would become respectively (6.8; 6.6) in A1C1 and (6.3; 6.9) in A1C2.

It is not possible to apply the model to A2, due to the absence of an electrostatic interaction. Although the methyl group would enhance the hydrophobic effect of the phenyl ring, as we mentioned in section 3, the lack of electrostatic interaction would lead to decrease the agonist efficacy of A2. There are, to our knowledge, no experimental works about the therapeutical effects of the A1 and A2 analogues. There is instead evidence of the LTG efficacy, where the electrostatic interaction with the receptor does exist; the potency and duration of action of LTG is even superior to those of currently available antiepileptic drugs [40]. The models here considered, as other ones appearing in the literature, are too rigid as to allow an eventual flexibility acquired by the molecule when facing the receptor.

The authors of Ref. [9] have studied structural analogies between LTG and 3-amino-7-(2,6-dichlorobenzyl)-6-methyltriazolo-[4,3-b]-pyridazine (Fig. 7). This last compound has two electron-rich regions, the first one (δ_1) in the amino nitrogen N_3 and the second one (δ_2) between N_1 and N_2 [9]. The heats of protonation that we obtained for the three positions are, accordingly, 148.9 for N_1, 149.9 for N_2 and 160.1 kcal/mol for N_3; let us remark that N_5 has a protonation heat of 170 kcal/mol. The authors have found distances of 5.2Å and 4.1Å respectively from point λ and δ_1, δ_2; as to the $\delta_1{-}\delta_2$ distance, it turns to be 3.0Å (see Fig. 5c). Note that Ref. [9] places λ in position 7 of Fig. 7.

In short , it is possible to propose a model for the LTG-receptor interaction, within the geometrical features, somewhat similar to the classical models for the interaction between a receptor and BDZs or other agonists.

5. Dipole moments and frontier orbitals

Table 3 shows the AM1 dipole moments μ and frontier orbital levels for the studied compounds. The most different dipole moments are, strikingly, those of the first analogue conformers. As A1C1 has the lowest dipole moment, this may indicate more affinity towards nonpolar environment; similarly A1C2, which has the highest μ, would prefer the aqueous solution [21]. In BDz, the activity of analogues seems to be inversely relationed to the dipole moment [4]. It could be then hypothesized that the first conformer has a preferential binding to the receptor when compared to the second one.

The gaps between the HOMOs (highest occupied molecular orbitals) and the LUMOs (lowest unoccupied molecular orbitals) are quite similar for the three compounds and their

conformers. HOMO and LUMO are, besides, qualitatively similar to each other. The HOMO involves nearly all the atoms, leaving out C_3 and N_4; in LUMO the atoms having negligible contributions are C_3 and (N_2,N_5) instead of N_4. The Cl atoms of lamotrigine and F or methyl C of the analogues are excluded from the frontier orbitals, as well as the hydrogen atoms. The orbitals' nature is π only for the phenyl ring, the azine being mostly σ. Thus, no potential difference between lamotrigine and its analogues can be ascribed to the frontier orbitals.

6. Group valence and multicenter bond indices

An "affinity index" has recently been proposed, representing the global affinity between a ligand and a biomacromolecular receptor; it is determined as the slope of the linear relations between the relaxation rate of the ligand in the presence of a macromolecule and the macromolecular receptor concentration. This method was applied to the calculation of the lamotrigine-albumin affinity index using ^{1}H$-$NMR relaxation measurements [41]. The bond indices which concern us here allow a description of the bonds features involved in a certain molecular region. Let us briefly introduce the pertinent definitions.

Denoting by 2Π the density matrix for closed-shell systems, the idempotency of Π allows us to define a bond index I_{AB} between atoms A and B [42, 43]:

$$I_{AB} = 4 \sum_{\substack{a \in A \\ b \in B}} \Pi_{ab} \Pi_{ba} \tag{1}$$

where

$$\Pi_{ab} = \sum_{ic} x_{ia} x_{ic} S_{cb} \tag{2}$$

S is the overlap and x_{ia} are the coefficients of the a-th atomic orbital. In non-orthogonal bases, I_{AB} is the generalization of the Wiberg bond index [44]. As valence V_A of atom A is defined as [45]

$$V_A = \sum_{B \neq A} I_{AB} \tag{3}$$

The charge q_A of atom A may be written under the form [42, 43]

$$q_A = \left(I_{AA} + V_A \right) / 2 \tag{4}$$

Let us consider a group G in a molecule, involving the atoms $A, B, \cdots L$; the corresponding group valence V_G [16] is

$$V_G = \sum_{\substack{A \in G \\ B \notin G}} I_{AB} \tag{5}$$

Since the idempotency of Π holds for any power, in closed-shell problems a multicenter bond index may be defined as [17, 46]

$$I_{ABC\cdots L} = 2^L \sum_{\substack{a\in A \\ b\in B \\ \vdots \\ l\in L}} \Pi_{ab}\Pi_{bc}\cdots\Pi_{la} \tag{6}$$

For $L = 3$, the I_{ABC} index has been shown to be particularly suitable as a measure of hydrogen bonds [17]. For $L = 6$ in monosubstituted benzenes and some other six-ring typical systems, I(ring) may be related to aromaticity [46].

We show in Table 4 some V_G values for different groups in the corresponding molecules. For the analogues, in this case the distinction between conformers is immaterial. The group valence shows clearly the conjugation in each region; for example, the valences of groups 2, 3 and 4 manifest that conjugation involves the amino nitrogens with the respective π electron pairs. There is also a certain contribution ($\sim$0.07) from the secondary bonds N_2–N_3, N_3–N_4 and N_4–N_5. The involvement of the amino nitrogens in the ring conjugation makes them more difficult to protonate, as we have mentioned in section 3. This feature contributes to enhance the electronic cloud around N_2 and N_4. The negative potentials in these regions are hence increased, in agreement with the heats of protonation behavior. The valence of group 5 would be rather 2 than 3 if the triazine ring were not conjugated. The valence of G_8 is decidedly closer to 1 than that of G_3 or G_4, as expected; there is a certain degree of hyperconjugation with the phenyl ring, apparently less than in toluene [16].

Table 5 reports multicenter bonds indices [17, 46]. It is well known that secondary bonds are most important in multicenter bonds [17, 47]. The lack of secondary interactions between the hydrogen atoms of the amino groups G_3 and G_4 leads to small I_{ABC} values. The expressive six-center index of G_1, is related, instead, to the aromaticity of the phenyl ring [46]. The six-center index of the triazine G_2 is around 60% of $I(G_1)$, describing hence weaker aromaticity.

7. Conclusions

– Another conformer of LTG should exist.
– In the three compounds, the most favourable protonation sites are N_2 and N_4; group valences agree with this feature.
– A region between the two chlorine atoms of LTG may be appropriate for an electrostatic interaction with a receptor site. The fluorine atom in A1 would play an equivalent role.
– A2 would be less active.
– The six-center index of the triazine ring is around 60% of the one corresponding to the phenyl ring, indicating thus a weaker aromaticity.

Acknowledgements

The authors wish to acknowledge the assistance given by Dr. Sergio Barbosa Duarte in the course of this work and the helpful discussions carried out with Drs. Kleber Mundim and Javier Magnin.

Table 1. Torsion angle $\tau(C'_2{-}C'_1{-}C_6{-}C_5)$ between the rings (see Fig. 1) and heats of protonation ΔH at different sites. ΔH(kcal/mol)·$\tau_{\rm exp}$ from Refs. [8, 11, 12] (C1 and C2 denote conformers).

			ΔH			
	τ (this work)	$\tau_{\rm exp}$	N_1	N_2	N_4	R_1
LTG1	66.7^0	80.6^0	159.47	150.89	151.70	198.33
LTG2	115.3^0	–	158.55	150.85	151.25	195.45
A1C1	59.8^0	50.8^0	158.14	149.71	150.40	169.42
A1C2	119.9^0	125.0^0	156.71	149.37	150.77	164.77
A2C1	117.5^0	100.8^0	155.57	148.19	149.59	
A2C2	80.4^0	61.7^0	155.37	147.82	149.44	

Table 2. Intersite distances (in Å) involved in the LTG receptor model (see Figs. 6a, b). F denotes the fluorine atom in A1 and (C1, C2) are the two conformers of A1.

	$\ominus$	ε^+	N_4	H_4	λ	F(C1)	F(C2)
N_2	7.0		2.5		4.9	4.8	4.1
N_4	6.4				5.1	4.3	4.8
H_2		9.8		5.7			
H_4		9.0					

Table 3. Dipole moment μ and frontier orbital levels (HOMO and LUMO, in $-eV$) for lamotrigine, analogues and respective conformers.

	μ (Debyes)	HOMO	LUMO
LTG1	2.88	8.92	0.37
LTG2	3.32	8.91	0.38
A1C1	2.54	8.77	0.31
A1C2	3.88	8.77	0.29
A2C1	3.23	8.71	0.14
A2C2	3.45	8.85	0.01

Table 4. Atomic group valences V_G. Definition of groups as follows (see Fig. 1): G_1, 1' to 6' ring; G_2, 1 to 6 ring; G_3, amino N_3; G_4, amino N_5; G_5, AB bond, $A = N_1$, $B = N_2$; G_6, AB bond, $A = 2'$, B =heavy atom in R_1; G_7, AB bond, $A = 1'$, $B = 6$; G_8, R_1.

	V_G		
Group	LTG	A1C1	A2C1
G_1	6.23	6.15	6.11
G_2	3.96	3.96	3.93
G_3	1.44	1.43	1.42
G_4	1.43	1.42	1.42
G_5	2.97	2.97	3.01
G_6	3.03	3.01	5.88
G_7	5.86	5.85	5.87
G_8			1.09

Table 5. Multicenter bond indices $I_{ABC\cdots L}$ for the atomic groups defined in table 4.

	$I_{ABC\cdots L}$		
Group	LTG	A1C1	A2C1
G_1	0.0786	0.0795	0.0821
G_2	0.0454	0.0459	0.0472
G_3	0.0059	0.0057	0.0064
G_4	0.0067	0.0066	0.0062
G_5	1.5505	1.5490	1.5296
G_6	1.0031	1.0097	1.0007
G_7	0.9857	0.9909	0.9840

Figure captions

Fig. 1 - Labelling of lamotrigine (LTG), analogue 1 (A1) and analogue 2 (A2).

Fig. 2 - Superimposition of LTG, A1C1 and A2C2.
(a) experimental structures [8, 11, 12].
(b) theoretical AM1 structures.

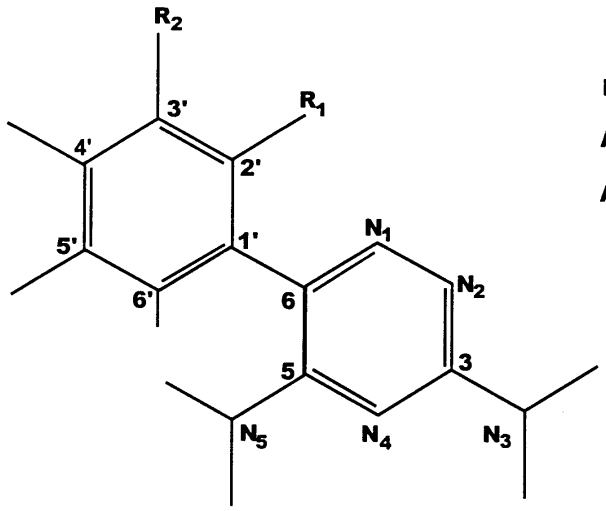
Fig. 3 - MEPs of AM1 conformation of LTG, $\tau(C'_2{-}C'_1{-}C_6{-}C_5) = 66.7^0$. The isoenergetic contours are drawn at intervals of 5 kcal/mole.
(a) in the triazine ring plane (z = 0.0).
(b) in the phenyl ring plane (z = 0.0).

Fig. 4 - MEPs of LTG analogues in the phenyl ring plane (z = 0.0). The isoenergetic contours are drawn at intervals of 5 kcal/mol.
(a) A1C1, AM1 conformation, $\tau(C'_2{-}C'_1{-}C_6{-}C_5)=59.8^0$.
(b) A2C1, AM1 conformation, $\tau(C'_2{-}C'_1{-}C_6{-}C_5)=117.5^0$.

Fig. 5 - (a) A benzodiazepine (BDZ); X = Cl,R1 = CH_3, diazepam (DZ).
(b) Average intersite distances in the agonists BZR interactions.
(c) The pharmacophore model of Ref. [31].

Fig. 6 - Molecular model for LTG-receptor interaction.
(a) This figure corresponds to Fig. 5(b) in our model.
(b) Our reference centroid λ. The two other positions indicated are the most favourable protonation sites.

Fig. 7 - A compound studies in Ref. [9], which is compared with LTG.



	R_1	R_2
LTG	Cl	Cl
A_1	F	H
A_2	CH_3	H

Figure 1

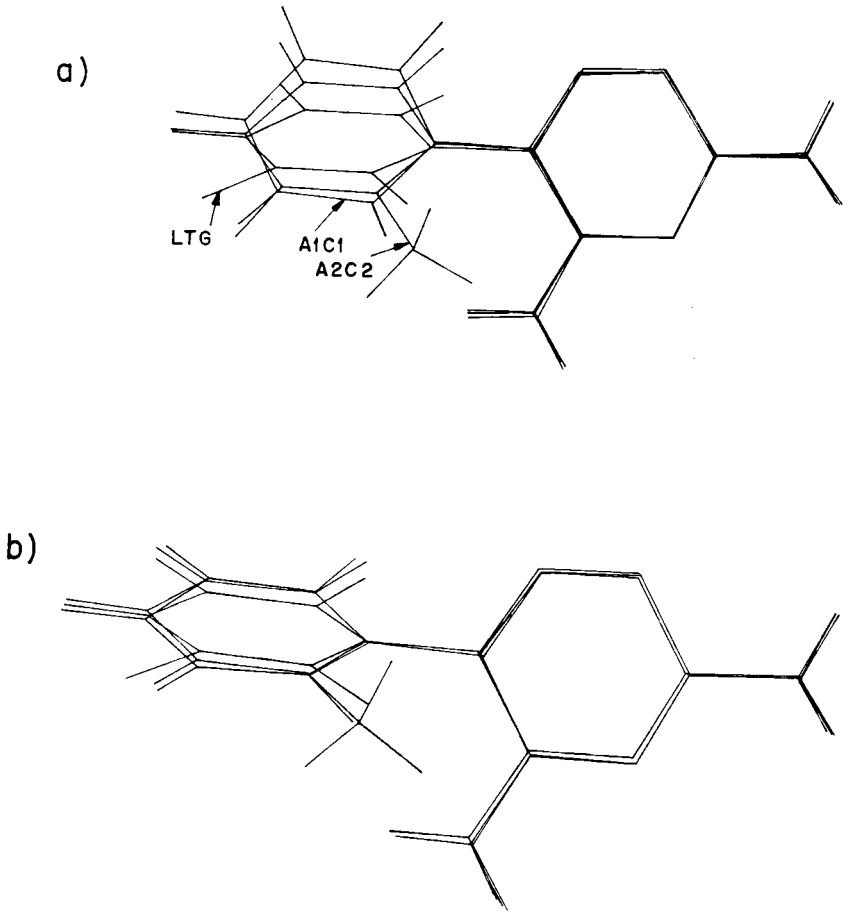


Figure 2

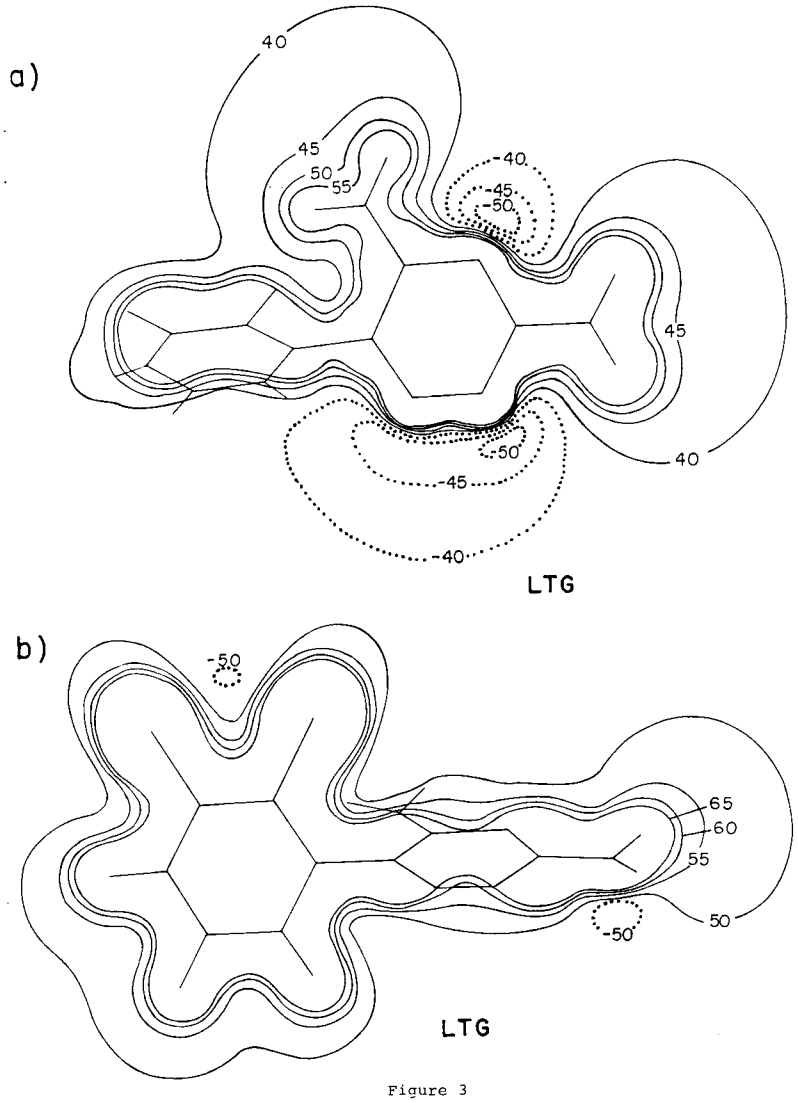


Figure 3

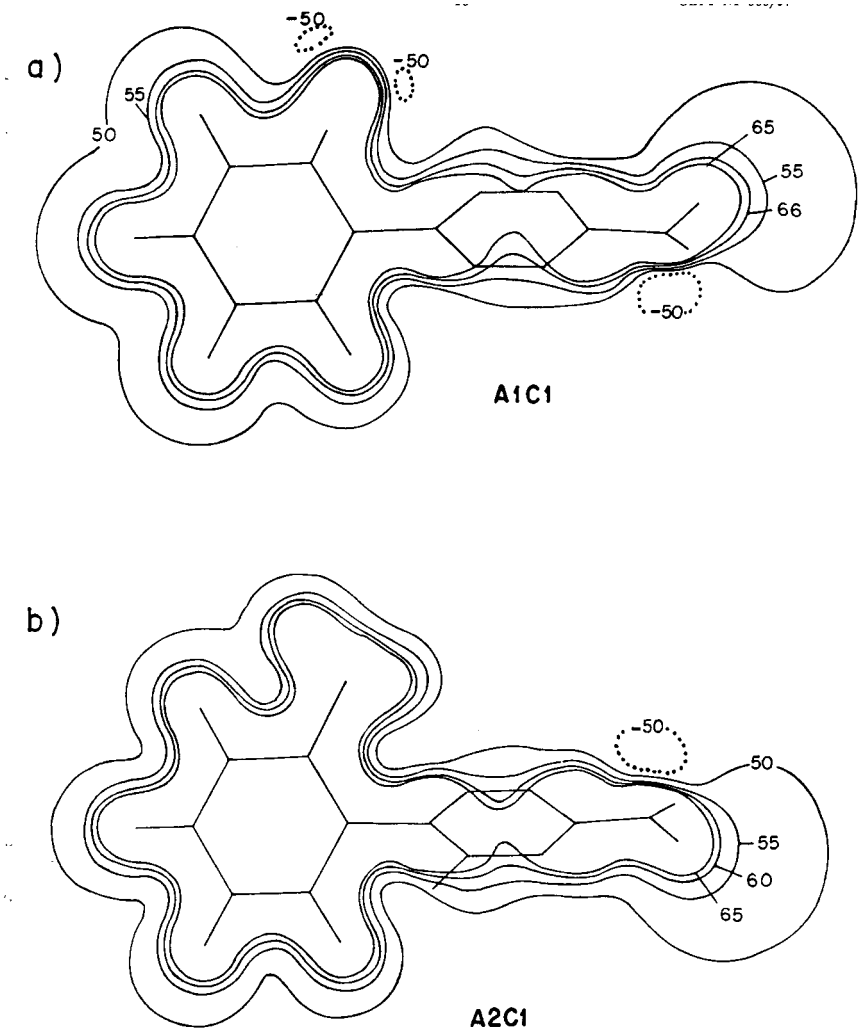


Figure 4

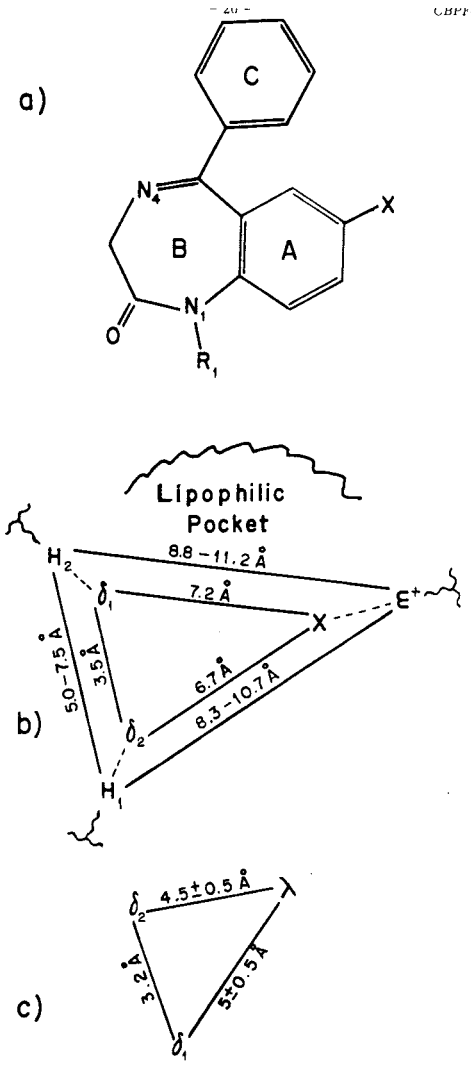

a)
C
N4
X
B
A
N1
O
R1
b)
Lipophilic
Pocket
H2
8.8 – 11.2 Å
δ1
7.2 Å
E+
X
5.0 – 7.5 Å
3.5 Å
6.7 Å
8.3 – 10.7 Å
δ2
H1
c)
δ2
4.5 ± 0.5 Å
λ
3.2 Å
5 ± 0.5 Å
δ1

Figure 5

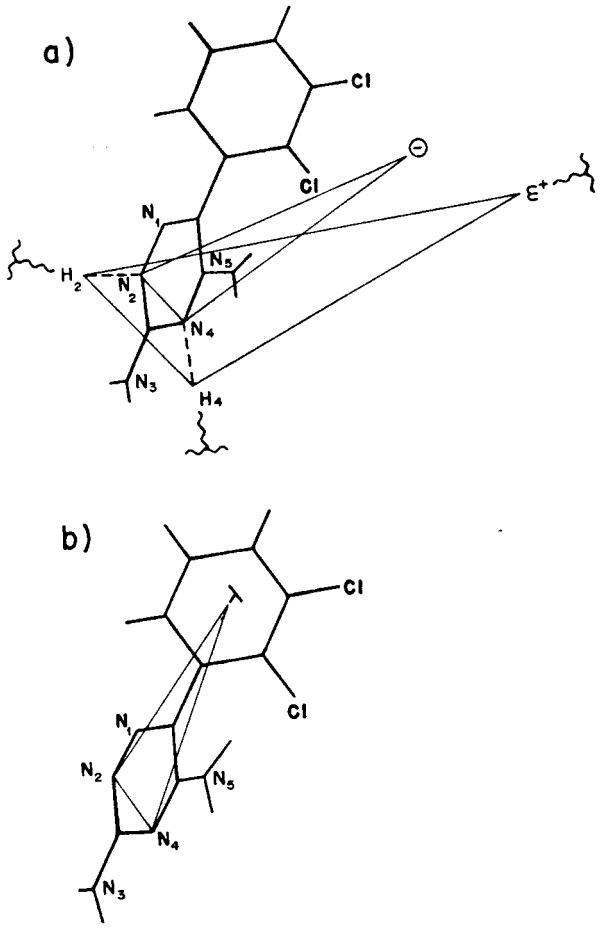


Figure 6

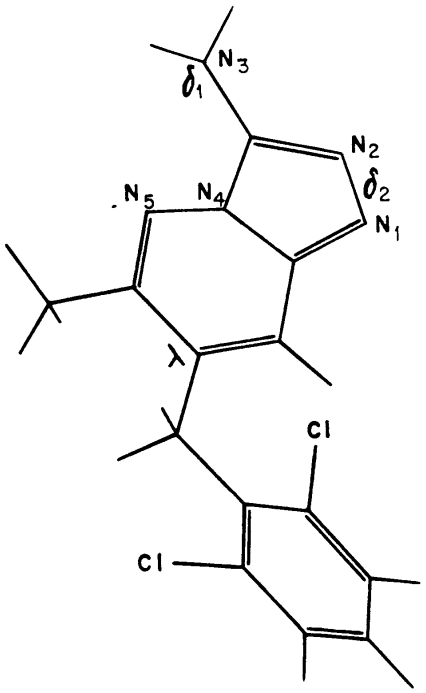


Figure 7

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