A PRELIMINARY THEORETICAL STUDY OF ANTIEPILEPTIC DRUGS

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Dedicated to Prof. Imre G. Csizmadia on the occasion of his 75th birthday

Abstract

This work is aimed to investigate the structural characteristics of several open chain enaminones, a group of organic compounds containing the conjugated system N-C=C-C=O, with the assumption that they possess two main characteristics: transportability through biological membranes and pharmacological effects as antiepileptics by binding to the voltage-gated sodium ion channel. To explore this possibility, density functional calculations were used to find the minimum energy conformations of nine candidate molecules. The conformational analysis was carried out by comparing the characteristics of the structures based on graphical and superposition techniques.

Resumen

Las enaminonas son un grupo de compuestos orgánicos que contienen el sistema conjugado N-C=C-C=O. Las enaminonas de cadena abierta han probado ser excelentes pro-drogas de aminas primarias fundamentalmente por su capacidad de transporte a través de las membranas biológicas, mientras que algunas enaminonas cíclicas resultan agentes antiepilépticos efectivos actuando como bloqueadores de la conducción del canal de sodio en células nerviosas. En el presente trabajo se investigan las características estructurales de algunas enaminonas de cadena abierta con la suposición de que estos compuestos reúnen ambas características. En este estudio preliminar, se realizaron cálculos DFT para encontrar las conformaciones de mínima energía de nueve moléculas candidatas. El análisis conformacional fue realizado a través de la comparación de las características de las estructuras basándose en técnicas gráficas y de superposición.

Introduction

Epilepsy is an heterogeneous disorder that affects approximately 0.5-1% of the world population [1]. Symptoms arise from disturbances of electrical activity in the brain and most of individuals with epilepsy continue to have seizures, even while being treated with anticonvulsant drugs [2]. In the antiepileptic drug development, a 50% decrease in seizure frequency is often accepted as evidence of clinical efficacy [3]. At the end of the past century, approximately 70% of newly diagnosed epilepsy cases were treated with one or more of the following drugs (figure 1):

a) Carbamazepine (CBZ), b) Phenytoin (PHYT), c) Clobazam or d) Phenylbarbital (PHEN). One of the three areas in which the mechanisms of antiepileptic drug action have been categorized, is that of 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.

Several structurally diverse vasodilating drugs are known to stimulate the opening of potassium channels in smooth muscle and the heart [4]. The only 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 [5].

Recently, several enaminones, a group of organic compounds containing the conjugated system N-C=C-C=O (figure 2**),** has been cited in the literature as antiepileptic agents [6, 7]. Comparing fig.1 and fig.2, there are structural similarities among the known antiepileptics and enaminones proposed as anticonvulsant drugs. Still more, their activity at the binding sites of voltage-dependent sodium channels are comparable to that of class 1 anticonvulsants CBZ and PHYT [7-9]. 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 [10-12].

In the process of drug discovery, the relationship among 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 allow drug molecules to cross membranes [13].

This paper is aimed to investigate the structural characteristics of a group of open chain enaminones with the assumption that they possess both characteristics: transportability through biological membranes and pharmacological effects by binding to the voltage-gated sodium ion channel. To explore this possibility, density functional calculations were used to find the minimum energy conformations of nine candidate molecules (Figure 3) selected because of their bioactivity as reported in recent bibliography. Particular attention was paid to the distance between the centre of the phenyl 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 the phenol of tyrosine 1771 on the α-subunit, while the carbonyl oxygen is hypothesized to form a hydrogen bond at the receptor site [14] as shown in Scheme 1 for anticonvulsants as well as for local anesthetics.

Molecular Computations

Density functional calculations were performed using the GAUSSIAN 03 computational program [15]. The B3LYP hybrid functional was employed at the 6-31G* level of theory [16, 17]. 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 open ring enaminones [18]. For comparative purpose, the molecule of DM5 (figure 2), a cyclic enaminone, recently reported as an effective antiepileptic drug [6] was calculated in the same sequence. In all cases, the geometry parameters were completely relaxed during further optimizations.

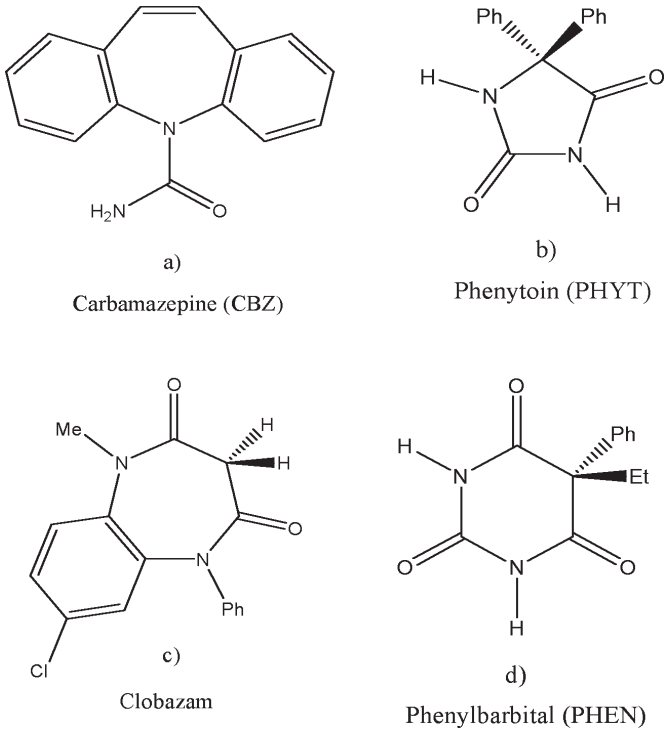
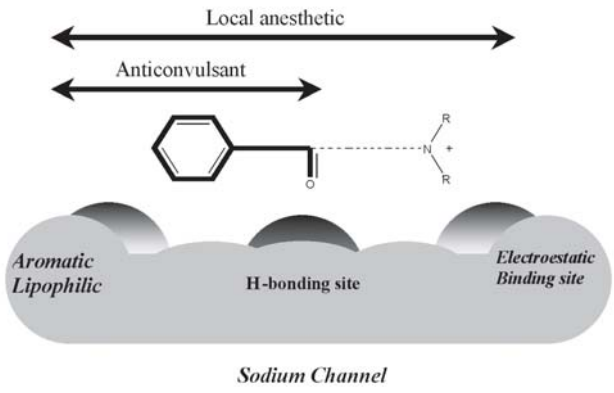
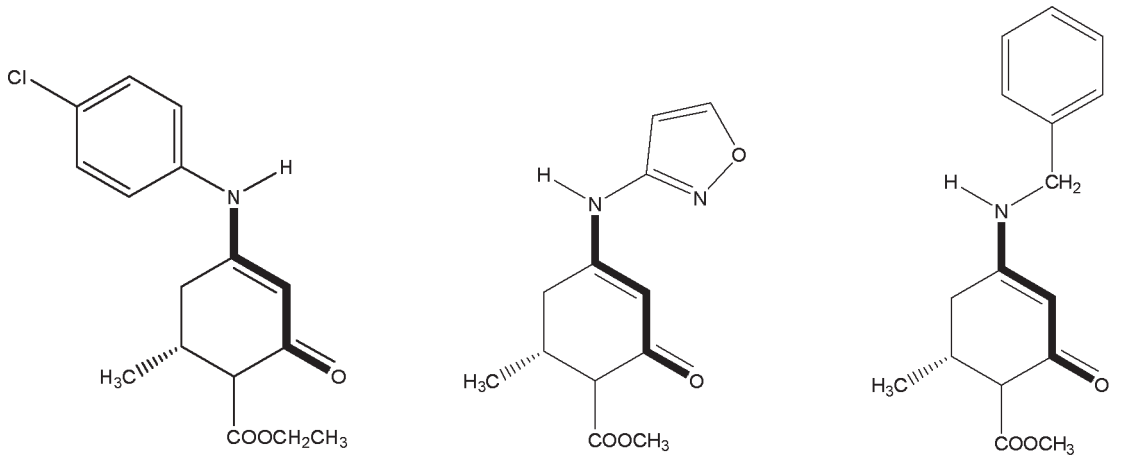


Figure 1. *Structure of four known anticonvulsants.*



Scheme 1. *Proposed binding of anticonvulsants to the sodium channel.*



Aniline Enaminone

DM5

Isoxazol Enaminone

Benzylaminol Enaminone

Figure 2. *Enaminones cited in the literature as antiepileptic agents.*

Results and discussion

To search for structural similarities in the pharmacophore, necessary for sodium channel binding, the conformational analysis of compounds was carried out by comparison of the characteristics of the structures. Full optimization of molecular geometry was done starting from the oxo tautomeric form of all molecules. Given the rotating angles $\phi_1 = \phi$ (OC-CC), $\phi_2 = \phi$ (CC-CN), $\phi_3 = \phi$ (CC-NH), four stable conformers were found for each one. On the other side, for DM5, where the enaminone characteristic group (N-C=C-C=O) is part of a ring, only one conformer was found possible.

Results of molecular geometry optimization, at two levels of theory, for the most stable structures are summarized in Table 1 including torsional angles, hydrogen bond distances and the distance between the centre of the phenyl ring and carbonyl oxygen of the enaminone group.

We can assume that these molecules are stabilized through the formation of an hydrogen bond between the hydrogen of the amino group and the oxygen of the carbonyl group close to a six member ring.

The average distance between the centre of the phenyl ring and carbonyl oxygen of the enaminone group is 4.48 $\pm$ 0.4 Å for open ring enaminones and 5.05 Å in DM5. The obtained results are in agreement with reported values of this distance in traditional antiepileptics as CBZ or PHEN [14] (Table 2).

The conformational analysis was done by comparison of the characteristics of the structures by means of a similarity analysis looking for portions shared by all the members of this set of open chain enaminones, based on graphical and superposition techniques (Figure 4).

In summary, the approximation in the results obtained at both levels of theory, HF and DFT, is reasonable.

Except for compound II, this set of open chain enaminones can be considered in pharmacological assays for antiepileptic agents, considering their flexible structures. The superposition analysis, as well as any quantitative structure-activity relationship (QSAR) study,

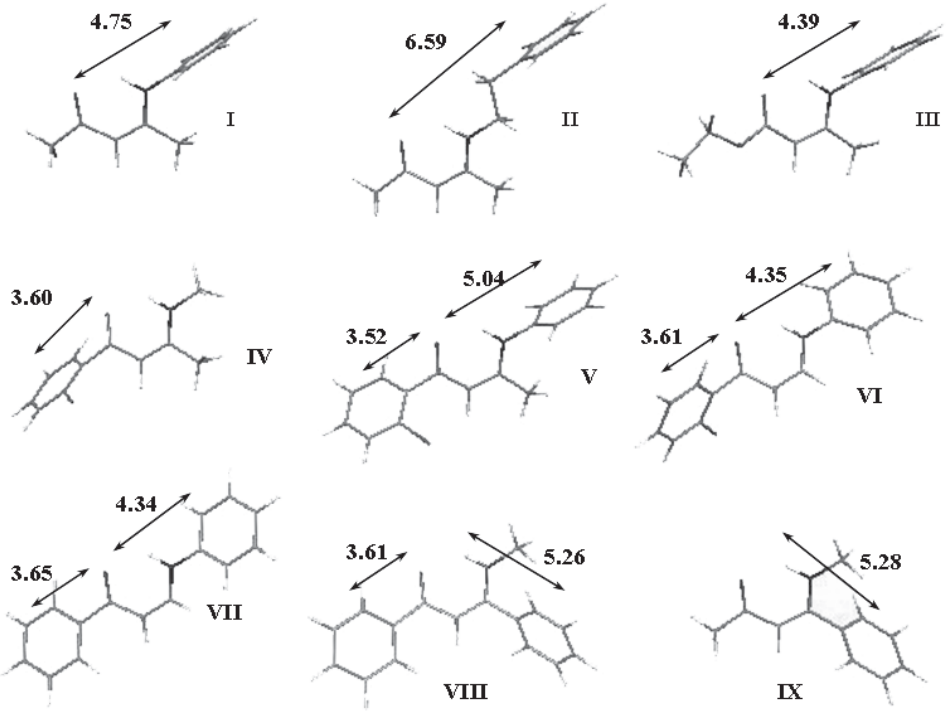


Figure 3.

cannot be based in the unique consideration of the conformation of lower energy of each compound, as there are four stable conformers for each very close in energy ($\Delta E \approx 10$ kcal/mol). Because of their flexibility, these closely located conformations are able to accommodate the requirements needed for the interaction with the receptor site, which define the active conformation. In this case, the active and rigid molecule of DM5 has been included in order to help identify the active conformation of the flexible compounds.

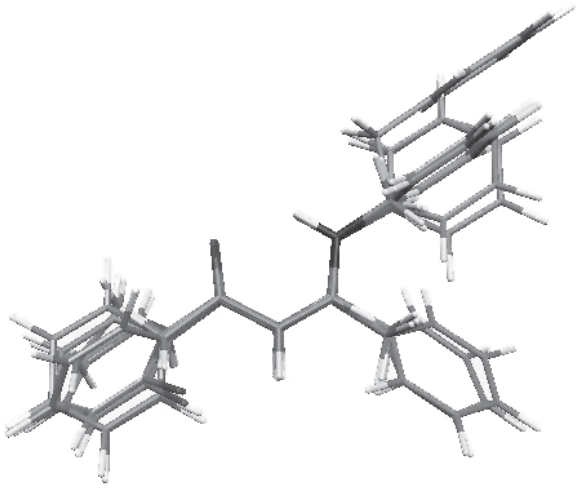


Figure 4. *Superposition of the compounds studied.*

Table 1: *Results of molecular geometry optimization.*

	ϕ_1	ϕ_2	ϕ_3	Energy (Hartree)	O-Phenyl Separation Å	H-Bonding Å
HF/6-31G*						
I	-0.01	-0.076	0.036	-553.4316	4.83	1.83
II	-0.046	0.011	-0.09	-631.5009	6.66	1.95
III	-0.027	0.009	-0.012	-667.3441	4.86	1.98
IV	2.27	0.37	-0.349	-1012.3219	3.51	1.95
V	2.63	0.15	-0.57	-1202.8358	4.80	1.94
VI	-0.323	-1.084	-2.852	-1163.8195	4.56/3.50	2.01
VII	3.95	0.484	-4.873	-704.9088	4.52/3.59	1.99
VIII	4.36	-2.13	-0.776	-743.9387	5.23/3.59	1.93
IX	1.205	-1.09	-2.25	-553.2132	5.12	1.92
DM5	176.03	178.56	172.39	-1315.8395	5.15	
B3LYP/6-31G*						
I	-0.05	0.031	-0.057	-556.9772	4.75	1.802
II	-0.154	0.092	0.033	-635.6047	6.59	1.829
III	1.46	0.244	-4.559	-671.5272	4.39	1.852
IV	1.57	0.693	-0.592	-1016.5675	3.60	1.81
V	3.03	0.514	-4.480	-1208.3079	5.04	1.775
VI	-2.07	-0.79	2.59	-116.9926	4.35/3.61	1.85
VII	1.62	-0.07	-1.68	-709.4038	4.34/3.65	183
VIII	3.22	-2.36	-0.57	-748.7131	5.26/3.64	1.79
IX	1.418	-2.305	-0.1	-5569736	5.285	1.80
DM5	178.42	177.75	167.10	-1321.8512	5.05	

Table 2: *Distance between the center of the phenyl ring and oxygen in anticonvulsants.*

Anticonvulsants	O-PhenylSeparation Å
Carbamezepine	4.10
Fenytoin	4.27
Fenylbarbital	3.98
Difeniloxazolidinedione	4.31
Fensuximide	4.26

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