Electronic structure calculations toward new potentially AChE inhibitors

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Abstract

The main purpose of this study was the use of natural non-isoprenoid phenolic lipid of cashew nut shell liquid from Anacardium occidentale as lead material for generating new potentially candidates of acetylcholinesterase inhibitors. Therefore, we studied the electronic structure of 15 molecules derivatives from the cardanol using the following groups: methyl, acetyl, N,N-dimethylcarbamoyl, N,N-dimethylamine, N,N-diethylamine, piperidine, pyrrolidine, and N-benzylamine. The calculations were performed at RHF level using 6-31G, 6-31G(d), 6-31+G(d) and 6-311G(d,p) basis functions. Among the proposed compounds we found that the structures with substitution by acetyl, N,N-dimethylcarbamoyl, N,N-dimethylamine, and pyrrolidine groups were better correlated to rivastigmine indicating possible activity.

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1. Introduction

Alzheimer’s disease (AD) is one of the most common causes of mental deterioration and is increasing with the number of elderly population. AD is a progressive neurodegenerative disorder being the fourth leading cause of death in people over 65 years old [1]. Furthermore, this disease is related to about 50–60% of the overall cases of dementia among persons over 65 years of age. Given the overwhelming damage caused by AD not only to the patients, but also to their relatives, and the increasing cost required for health assistance, it is important to look for new active treatments for this disease [2,3].

The neocortex and hippocampus brains regions are those most affected by the characteristic pathology of AD. This includes the neuritic plaques (consisting mainly of extra cellular deposits of β-amyloid aggregates covered by dead neurons), intracellular formation of neurofibrillary tangles (paired helical filaments), and loss of neuronal synapses and pyramidal neurons [4]. As a result the typical symptomology of AD is characterized by the gross and progressive impairments of cognitive function [3].

The causes of AD have not been completely elucidated. The most successful approach for the symptomatic treatment of AD is the cholinergic hypothesis [5–7], where the cognitive deficit is a consequence of deficiency in acetylcholine (ACh) and consequently decreasing of cholinergic neurotransmission. The activity of the neurotransmitter ACh is determined by the acetylcholinesterase (AChE) which is involved in the regulation of signal transmission at cholinergic synapses [8,9]. Recent studies have shown that AD could also be associated to the reduction of the quantity of presynaptic nicotinic [10] and muscarinic (M2) receptors of acetylcholine, with retention of postsynaptic muscarinic receptors (M1 and M3) [11]. At the cellular level, there is a marked reduction in the levels of...
neurotransmitters, e.g. acetylcholine, serotonin, noradrenaline, dopamine, glutamate and substance P \[8,9\]. Therefore, inhibition of AChE appears to be a natural therapeutic strategy to attenuate the cognitive deficit in AD \[6,7,12\].

AChE is characterized by a deep and narrow ‘gorge’, which contains the catalytic site formed mainly by fourteen aromatic residues presumably involved in the diffusion of acetylcholine \[13\]. Among these residues several functional amino acids were identified including the catalytic triad [Ser203(200), His447(400), Glu334(327)] \[13,14\], the acyl pocket [Phe295(288) and Phe297(290)] \[15\] and the triad [Ser203(200), His447(400), Glu334(327)] \[13,14\], the aromatic amino acids were identified including the catalytic site formed mainly by fourteen aromatic residues presumably involved in the diffusion of acetylcholine \[13\]. Among these residues several functional amino acids were identified including the catalytic triad [Ser203(200), His447(400), Glu334(327)] \[13,14\], the acyl pocket [Phe295(288) and Phe297(290)] \[15\] and the ‘hydrophobic subunit’. The latter accommodates the alcoholic portion of the covalent adduct (tetrahedral intermediate) and may include residues Trp86(84), Tyr133(130), Tyr330(337) and Phe331(338). These last residues operate through non-polar and/or \(\pi\) stacking interactions, depending on the substrate \[15,16\]. Ariel et al. \[16\] suggested that the aromatic side chains of Trp86, Tyr123 and Tyr337 residues form together a continuous ‘aromatic path’ allowing for the accommodation of the different ligands through multiple modes of interaction.

Tacrine, donepezil and derivative/analogs substances have shown AChEI activity for AD treatment. Recently, rivastigmine was approved by FDA. Rivastigmine is a parasympathomimetic and a reversible cholinesterase inhibitor. This carbamate inhibits AChE by carbamoylating the serine residue of the catalytic triad in a pseudoirreversible manner.

In searching for new compounds useful for AD treatment, we have employed non-isoprenoid phenolic lipids from Anacardium occidentale as starting material to obtain new candidates of AChE enzyme inhibitor. The cashew nut shell liquid (CNSL) is one of most important source of non-isoprenoid phenolic lipids, e.g. anacardic acids, cardols, cardanol and maticardols \[17–19\].

The target compounds species were modeled using a substitution of hydrogen from the phenolic group of cardanol (R1 in Fig. 1) by groups such as (a) methyl, (b) acetyl, and (c) \(N,N\)-dimethylcarbamoyl, as well as the substitutions at the benzylic carbon from the side chain (R2 in the Fig. 1) by secondary amines, e.g. (1) \(N,N\)-dimethylamine, (2) \(N,N\)-diethyamine (3) pyrrolidine, (4) piperidine, and (5) \(N\)-benzylamine. These variations yielded a total of 15 structures.

We have optimized the geometries of rivastigmine (Fig. 2) and cardanol derivatives using the semi-empirical AM1 and PM3 methods. The calculations were performed using the MOPAC computational program \[20\]. The procedure used to optimize the set of molecules obtained through substitutions of cardanol in the positions of R1 and R2 (Fig. 1) are as follows: first, it was performed a pre-optimization and conformational analysis of 15 modeled structures. Fig. 3 depicts the potential energy surface map of the substitution of R1 group by \(N,N\)-dimethylcarbamoyl and the R2 group by the piperidine group. This map was done varying two dihedral angles using a step of 15° up to complete the cycle. The first dihedral angle (dihedral-1) refers to the plane formed by the group R1 and the plane of oxygen and carbon 2 and 3 of aromatic ring (Fig. 1). The second dihedral angle (dihedral-2) is formed by one of the two carbons of R2 bonded to nitrogen and the plane formed by the nitrogen of R2 and the carbons 7 and 6 of aromatic ring (Fig. 1). Potential energy

![Fig. 1. Schematic representation and notation used for the compound series obtained from the cardanol pattern with substitution of R1 and R2 groups.](image-url)
surface map was used in order to select the conformation of minimum energy and then this minimum structure was fully optimized. Additionally, this structure was used for calculation of single point electronic properties, e.g. highest occupied molecular orbital (HOMO), HOMO – 1, lowest unoccupied molecular orbital (LUMO), and LUMO + 1. The RHF method at 6-31G, 6-31G(d), 6-31+G(d) and 6-311G(d,p) basis sets were used. The same procedure was performed for the remaining structures. From these electronic data we have derived the GAP (LUMO/C0HOMO), GAP + 1 (LUMO + 1/C0HOMO + 1), DH/C01 (HOMO/C0HOMO + 1) and DL + 1 (LUMO + 1/C0LUMO) properties. These calculations were carried out using the GAUSSIAN 98 computational program [21].

In order to compare the electronic properties obtained from the 15 cardanol derivatives compounds with rivastigmine, we have used the Principal Components Analysis (PCA), as a multivariate statistical method [22]. This method reduces the initial parameter number (electronic properties) for the most relevant structure in this analysis, i.e. closer to rivastigmine. The PCA data were auto scaled using the average values of each electronic property as zero and the related standard deviation as unit. This procedure was used for eliminating artificial effects where some electronic properties with a large value could dominate the analysis. In the next step, each property of 15 molecules was analyzed in relation to the corresponding rivastigmine value in order to achieve variables with the best separation. We have also analyzed the electronic properties relationships. Fig. 4 shows the contribution for the difference of GAP + 1 versus LUMO + 1 for the cardanol derivatives and rivastigmine. Therefore, this analysis is important to yield the most relevant pair of variables. From these preliminary data the electronic variables used for the PCA calculation were modified and then classified in the principal components (PCs) in order of significance. The first component is a linear combination of electronic properties with larger variance from the original set.

3. Results and discussion

The HOMO orbital of rivastigmine at RHF/6-311G(d,p) level at the AM1 optimized geometry is depicted in Fig. 2. The HOMO orbital of rivastigmine shows a contribution of aromatic ring π orbital. The same contribution is found for all calculated compounds, i.e. it is mainly centered in the rivastigmine fragment for all compounds.

The results of the C7-R2 and O-R1 interatomic distances and C6-C7-R2 and C2-O-R1 angles for the 15 compounds at the AM1 optimized geometries are shown in Table 1. The interatomic distances showed no significant variation among the optimized compounds. The same trend is found for the above angles. The calculated root mean square deviations (RMSD) for the optimized structures compared to the rivastigmine have large values for the CA_{a_5}, CA_{c_1}, CA_{c_2}, CA_{c_3}, and CA_{c_5} compounds. Therefore, the N-benzylamine R2 and the R1 N,N-dimethylcarbamoyl groups have the largest influence on the optimized geometry.

The results for the 15 studied structures show that for all basis sets considered the values are significantly similar. Therefore, the electronic properties used to select the struc-
The systematic study was performed considering the variance and weight of the four calculated electronic properties (Table 2) and four derived values for both binary analysis and PCs (Fig. 5). Moreover, it was possible to identify the following set as the most significant for the selection of structures: HOMO\$/C0\$/1, LUMO + 1, GAP and D\$/H\$/C0\$/1 Using these properties to the PCA it was build the PCs (Table 3), which present the reasonable variance with the following contribution: first principal component (PC1)(78.93%), second principal component (PC2)(16.36%) and third principal component (PC3)(4.71%). The structures 6(CA_b_1), 8(CA_b_3), 11(CA_c_1) and 13(CA_c_3) were identified from the PCs as the best correlated to rivastigmine (16, Fig. 5). These results indicate that these substituents are promising candidates in order to produce a potential active inhibitor for the treatment of AD from cardanol.

4. Conclusions

In this work we presented electronic structure calculations regarding 15 cardanol derivatives. The main objective of this work was the use of non-isoprenoid phenolic lipids of cashew nut shell liquid as the start material for generating new candidates of AChE enzyme inhibitors. Therefore, we have used RHF method as the 6-31G, 6-31G(d), 6-31+G(d) and 6-311G(d,p) basis functions. In order to calculate the final results we have used the extended 6-311G(d,p) basis set. From the proposed structures we have performed a binary analysis of electronic properties. The large correlation with rivastigmine was found for the structures (6), (8), (11) and (13). This correlation occurs for the properties when analyzed by pairs. Furthermore, the PCs were calculated to select the structures that are better correlated to rivastigmine. From both performed analysis it was possible to devise that structures (6), (8), (11) and (13) are better correlated to rivastigmine indicating a possible activity for them.

Acknowledgements

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