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Pharmacophoric Profile: Design of New Potential Drugs with PCA Analysis

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1. Introduction

Searching for the pharmacophoric profile based on the concepts of chemical and structural contribution of the receptor active sites as well as receptor ligand interactions are fundamental for the development of new potential drugs for several different diseases and body dysfunctions such as degenerative brains disorders, Alzheimer disease, Parkinson's, diabetes Mielittus, cancer and many others known sickness conditions.

Basically, a pharmacophore describes the main molecular features regarding the recognition of a ligand by a biological macromolecule. In accord to the IUPAC (International Union of Pure and Applied Chemistry) Pharmacophore can be considered as "the largest common denominator shared by a set of active molecules to specific biological target"(Wermuth et al., 1998).

A pharmacophore is defined by the pharmacophoric descriptors that are a set of electronic, structural, electrostatic and topological properties. Those descriptors can be obtained by experimental and theoretical studies. Experimental studies like X-ray crystallography, spectroscopic measurements are used to define some atomic properties of a molecule, but need a previous job – a synthesis of such molecule. Thus, in this way theoretical studies eliminate this previous job the *in silico* experiments or the theoretical studies are important tools to know a molecule before this one gets synthesized.

In modern computational chemistry, pharmacophores are used to define the essential features of one or more molecules with the same biological activity. In the past few years, it has been common that the drug discovery has a contribution from pharmacophore modeling to identify and develop new potential molecules with desired biological effect (Steindl et al., 2006).

Therefore, in order to enhance the insights to identify potential new medicinal drugs many computational strategies are widely used (Steindl et al., 2006; Tasso, 2005). Mathematics and chemical molecular modeling applied on bioinformatics are important examples of these strategies. Multivariate analysis (principal component analysis - PCA) and quantum chemistry calculations (density functional theory - DFT) are some of them, and can led to the identification of the main information required to describe the essential pharmacophore profile.

PCA has been used to find new potential molecules in a series of biological systems (Carotti et al., 2003; de Paula et al., 2009; Nascimento, et al., 2011). It is a method abundantly used in a lot of multivariate analysis (Jolliffe, 2002). This method has two main aims: to decrease variable sets in the problems of multivariate data and to select the best properties (linearly independents) that describe the system (principal components). According to Jolliffe (Jollife, 2002) the central idea of PCA analysis "is to reduce the dimensionality of a data set in which there are a large number of interrelated variables, while retaining as much as possible of the variation present in the data set. This reduction is achieved by transforming to a new set of variables, the principal components, which are uncorrelated, and which are ordered so that the first *few* retain most of the variation present in *all* of the original variables. Computation of the principal components reduces to the solution of an eigenvalue-eigenvector problem for a positive-semidefinite symmetric matrix".

Although it may seem a simple technique, PCA can be applied in a lot of problems with several variables, such as the problems involving the determination of the pharmacophoric profile of a particular class of molecules.

There are different pretreatment methods for the data analysis, e.g., mean-centering and autoscaling. This work covers the second method. The autoscaling is very similar to the mean-centering with additional paths.

First, it is calculated the mean of the data matrix **X**, where the columns correspond to the variables and the lines are the samples (or objects). The mean is the jth column vector of a data matrix:

$$\bar{x}_n = \frac{1}{M}\sum_{m=1}^{M} x_n \tag{1}$$

After mean-centering the standard deviation (Equation 2) for each column is calculated and the autoscaling is obtained by the division of standard deviation (Equation 3).

$$s_n^2 = \frac{1}{M-1}\sum_{m=1}^{M}(x_n - \bar{x}_n)^2 \tag{2}$$

$$\bar{x}_{ij} = \frac{x_{ij} - \bar{x}_i}{s_i} \tag{3}$$

Within the autoscaling all variables are adjusted to the same range, such that each variable has a zero mean, while the standard deviation is one. Therefore, autoscaling is important for data set where the variables have different units.

DFT is a method to investigate the electronic structure of many-body systems, like atoms and molecules (Cramer, 2004). This method can be used to calculate electronic and structural properties of molecules with biological activity like new drugs to treat a disease. Applying functional that are spatially dependent on the electronic density of multi-electronics systems.

The application of human and economic resources to improve life quality has promoted benefits and has led to the increasing on the number of diseases known as age-dependent.

Among these diseases the most frequently are the dementias, diabetes and cardiovascular disease. Among the several types of dementia existing and the most common incidents in the population over 60 years of age are Alzheimer's disease (AD), vascular dementia and Pick's disease. It is estimated that 45 million people worldwide have some kind of dementia, among these, 18 million have symptoms characteristic of Alzheimer's disease. AD is a disease that has no determined cause, and therefore their treatment is based on drugs that only treat the disease in order to remediate the cognitive functions and slow down the degenerative advance. (Sugimoto, 2002)

AD is a kind of dementia that affects neural cognitive function. Thus, one of the most widely used strategies for the treatment of this disease consists in blocking off the hydrolysis (Figure 1) of the neurotransmitter acetylcholine in cholinergic synapses of neurons, this strategy is called cholinergic hypothesis, nowadays a major target in the development of drugs that benefits and improves the chemical balance of the concentration of acetylcholine in patients with AD (Tezer, 2005; Camps, 2005; Costantino, 2008).

Some drugs act as inhibitors of AChE, among them, tacrine first drug approved by FDA for the treatment of AD (Sugimoto, 2002; Ul-haq, 2010), followed by donepezil (Sippl, 2001), rivastigmine (Sugimoto, 2002; Ul-haq, 2010) and galantamine (Sippl, 2001). Other drugs have been clinically studied and tested for use in the treatment of AD, such as physostigmine (Sippl, 2001; Ul-haq, 2010; Bartolucci, 2006). Some others are being tested and are promising candidates for the approval, including, Huperzine A (Patrick, 2005; Barak, 2005), metrifonate (Sippl, 2001) and phenserine (Sippl, 2001; Ul-haq, 2010). These drugs are indicated to treat mild to moderate stages of AD, when the patient still has independent cognitive activity.

Fig. 1. Hydrolysis of acetylcholine

Chemically, the inhibitors mentioned above have in common the inhibitory action of AChE, but have different structure and chemical nature. The geometries of some AChEIs are shown in Figure 2. Organophosphates, alkaloids and acridines, are some of the classes of drugs that inhibit acetylcholinesterase and are used in the treatment of AD. This raises the question: what are the electronic, structural, topological and chemical properties that correlate these different classes of drugs as inhibitors of the same biological target?

The brain is the most complex system of the human body and main focus of biochemical and neuromolecular studies of the twenty -first century. The research and development of drugs that act more effectively in the treatment and the study of brain's diseases mechanisms are subject to various areas of knowledge.

PCA have been used to find new potential molecules in a series of biological systems (Carotti, 2003, de Paula, 2009; de Paula, 2007; Li, 2009; Nascimento, 2011; Nascimento, 2008; Rocha, 2011; Steindl, 2005). A methodology based on PCA for the pharmacophore identification of the acetylcholinesterase inhibitors (AChEI) was recently used (de Paula, 2009; de Paula, 2007; Fang, 2011; Nascimento, 2011; Nascimento, 2008). In this chapter the electronic, structural, topological and chemical properties of studied molecules, were taken from the theoretical procedures and related to the activity by means of the multivariate analysis PCs that provides the pharmacophoric profile of these AChEIs.

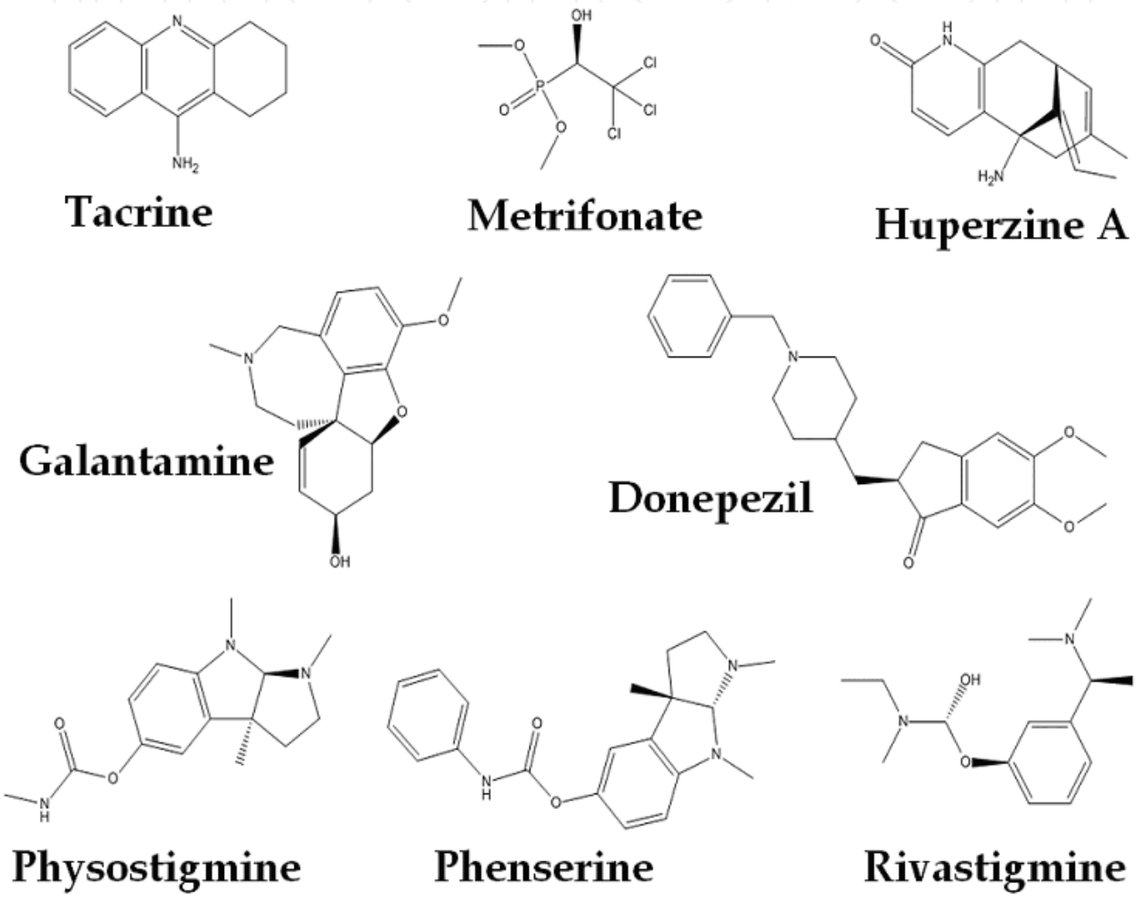

Fig. 2. Structures of some acetylcholinesterase inhibitors.

2. Mapping the pharmacophoric profile of acetylcholinesterase inhibitors

2.1 Acetylcholinesterase inhibitors, the AChEIs molecules

The cholinesterase inhibitors can be used for various purposes, as chemical warfare weapons such as sarin gas, in diseases treatment, e.g., the Alzheimer's disease treated with rivastigmine. There were used two different concepts to the rational design of inhibitors of this enzyme:

- drugs that have the molecular recognition in the catalytic site of AChE, doing preferably covalent bonds with the hydroxyl of the serine residue 200, this bond may be reversible or irreversible;
- drugs that are recognized by the to active site of the enzyme, which act by blocking the entry of the natural substrate, the neurotransmitter acetylcholine at the active site of AChE.

Some drugs that inhibit the function of the enzyme have also neuroprotective function, acting more effectively in the AD treatment. These drugs act in a negative way in the process of hyperphosphorylation of β-amyloid protein, inhibiting the breakdown of this protein and consequently the formation of amyloid plaques.

The inhibitors tacrine (THA), donepezil (E2020), rivastigmine (RIVA), galantamine (GALA), metrifonate (METRI), dichlorvos (DDVP), phenserine (PHEN), physostigmine (PHYSO), huperzine A (HUPE) and the tacrine dimer (DIMTHA) been studied theoretically by means of molecular modeling. From these studies, the mapping of pharmacophoric profile of these AChEIs was important to elucidate the correlation of such molecules as drugs to treating Alzheimer's disease.

2.2 Molecular modeling

Molecular modeling is one of the fields of theoretical chemistry that has been a great development in recent decades. The rational drug design is an area of application of molecular modeling of high relevance. Predict computationally a molecule with pharmacological activity and a drug candidate brings the expectation of reducing the search time and the cost in the molecular synthesis process and the clinical tests *in vitro* and *in vivo*.

The molecular modeling is characterized by applications of classical mechanics, quantum mechanics and stochastic methods like Monte Carlo in chemical and biochemical systems. One possibility is the prediction of spatial behavior and chemical interaction between a receptor and its biological substrate (ligand). Another is the calculation of molecular properties relevant to determining how this interaction takes place. Modeling the system receptor-ligand (RL) is possible to obtain important information about the interactions. These RL interactions establish the functionality of a given molecule. However, only the studies of interactions do not provide enough parameters to the development of new ligand.

The properties of a molecule can be obtained by theoretical calculations using classical mechanics and quantum mechanics. In the molecular mechanics approach, the classical mechanics deals with the problem without taking into account the electrons. Thus, electronic properties can only be treated by methods of electronic structure by means of quantum mechanical calculations. The main properties that describe a molecule are classified according to how it is defined spatially.

With the development of computational tools (hardware and software) it is possible today to treat complex molecular systems using approximate methods of quantum theory. Quantum mechanics considers that the energy of a molecule can be described as a sum of terms of energy resulting from electrostatic interactions between core and electrons (kinetic and potential energy). The fundamental postulate of quantum mechanics describes a wave function for each chemical system where a mathematical operator can be applied to this

function resulting in observable properties of such system. Equation 4 is the focus of the study of quantum methods for the description of chemical systems and is known as the Schrödinger equation, independent of time and without relativistic corrections;

$$H\Psi = E\Psi \tag{4}$$

where **H** is a mathematical operator that returns the energy eigenvalue of the system as an operator called the Hamiltonian. **Ψ** is the wave function that describes the system state from the coordinates of the positions of nuclei and electrons of the atoms in the molecule. **E** is the eigenvalue, and represents the total energy of the system.

2.2.1 Computational modeling of AChEIs

The theoretical studies of AChEIs were performed using the Gaussian03 program package (Frisch, 2004) in order to determine the best electronic and geometrical parameters of AChEIs molecules. Was have used DFT at the B3LYP hybrid functional level with 6-31+G(d,p) basis set. The geometries of the target drugs were first optimized using internal coordinates in order to minimize all geometric data.

AChEI structures were taken from Protein Data Bank (PDB). Specifically, the structure of AChEI complexed with AChE included the inhibitors tacrine (PDB code 1ACJ), galantamine (PDB code 1DX), donepezil (PDB code 1EVE), tacrine dimer (PDB code 2CKM), huperzine A (PDB code 1VOT) and rivastigmine (PDB code 1GQR). However, the three-dimensional structures of physostigmine, phenserine, metrifonate and dichlorvos were not found in a complex with AChE, and so the structures were modeled using the GaussView 4.1 program.

In order to analyze the activity of such AChEIs, we have computed the electronic and structural properties of those molecules: dipole, frontier molecular orbital energies Highest Occupied Molecular Orbital and Lowest Unoccupied Molecular Orbital (HOMO, HOMO-1, LUMO and LUMO+1), charge of heteroatoms, charge of most acid hydrogens, volume, distance between the most acid hydrogens – H-H, molecule size, LogP (partition coefficient/lipophilicity), LogS (solubility), number of H-bond acceptors, number of H-bond donors, number of aromatic rings, gap (HOMO-LUMO), and map of electrostatic potential (MEP). The charge used was from the ChelpG (i.e., the charge from electrostatic potentials using a grid-based method) population analysis.

2.3 Electronic structure of AChEI molecules

Table 1 shows the values for some calculated properties for the studied AChEIs. The values of the HOMO orbital energies are different when comparing the organophosphate DDVP and METRI (higher values) and other AChEIS. Thus, the values of the orbital HOMO-1 energy for these organophosphates are almost similar while the values of this energy for other AChEIS, structurally different, are between -6.04 and -6.75, indicating that this orbital may be important in process of interaction of these drugs with acetylcholinesterase.

Properties such as volume, size of the molecule, logP and dipole have different values for each AChEI. Although some of these molecules are of the same class, the calculated values for the same property changes sharply, as the volume between DDVP and METRI.

	DDVP	METRI	DIMTHA	THA	HUPE	GALA	E2020	PHYSO	RIVA	PHEN
Dipole (D)	3.04	2.93	2.09	3.51	6.08	1.67	2.48	1.08	2.53	1.85
Charge H^+ (ua)	0.070	0.438	0.260	0.339	0.365	0.371	0.136	0.333	0.103	0.281
Charge N (ua)	0	0	-0.320	-0.766	-1.013	-0.632	-0.484	-0.619	-0.378	-0.753
Charge O(ua)	-0.638	-0.639	0	0	-0.670	-0.685	-0.554	-0.659	-0.594	-0.505
HOMO (eV)	-6.86	-8.11	-5.90	-5.76	-5.90	-5.53	-5.95	-5.46	-5.79	-5.23
HOMO-1 eV)	-8.57	-8.30	-6.71	-6.56	-6.75	-6.04	-6.05	-6.08	-6.53	-6.43
LUMO (eV)	-0.54	-1.59	-1.47	-1.28	-1.30	-0.48	-1.53	-0.33	-0.43	0.52
LUMO+1(eV)	0.42	0.70	-0.58	-0.46	0.36	-0.14	-0.48	-0.07	0.21	0.51
GAP (eV)	6.32	6.52	4.47	4.49	4.60	5.53	4.41	5.12	5.36	5.75
H-H (Å)	1.796	2.307	1.998	1.683	1.625	2.373	2.342	2.324	2.460	2.250
Volume ($Å^3$)	185	207	606	236	286	329	454	321	312	332
Size (Å)	7.849	7.068	19.386	9.516	9.051	10.290	12.281	12.927	11.242	14.808
logP	1.66	0.80	3.88	3.13	2.60	1.39	4.14	1.94	2.86	2.99
logS	-1.44	-1.77	-4.98	-3.16	-2.47	-2.23	-4.93	-2.44	-1.89	-4.2
PSA($Å^2$)	44.8	55.8	58.5	38.9	58.9	41.9	38.8	44.8	32.8	44.9
H-donnor	0	1	4	2	2	1	0	1	0	1
H-acceptor	4	4	4	2	4	4	4	5	4	5
Aromatic ring	4	0	4	2	1	2	2	2	1	1

H^+: most acid hydrogen of the molecule. H-H: distance between the most acid hydrogens.

Table 1. Electronic and structural data of AChEIs from B3LYP/6-31+G(d,p) level of calculation.

The distribution of frontier orbitals in the molecule is important to determine which atoms are most relevant for the interaction between the ligand and the receptor, during the activity of such drug with the biological target. Figure 3 shows the regions of the frontier orbitals of RIVA. The LUMO of RIVA is located in an unusual region for orbitals poor in electrons, since the benzyl ring is by definition the region of high electronic density. RIVA have the HOMO and LUMO in the opposite region of carbamate moiety.

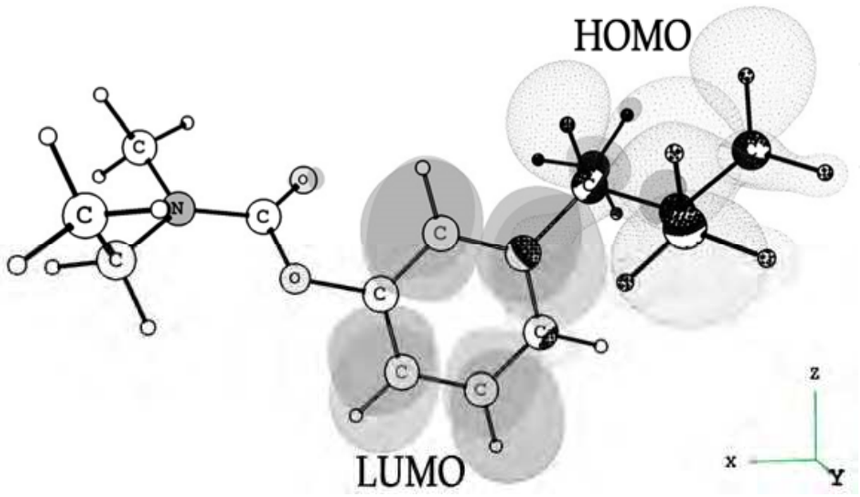

Fig. 3. HOMO and LUMO of RIVA calculated at B3LYP/6-31+G (d,p) level.

Figure 4 shows the MEP for all drugs studied. The maps indicate that all AChE have well-defined regions of high electron density (red) and low density (dark blue). These regions are likely points of interaction with AChE through electrostatic interactions like hydrogen bonding. Other electron density regions of AChE present mostly negative, indicating that these regions may have electrostatic interactions such as charge transfer, interactions with π–π systems of aromatic residues in the active site of AChE. According to the literature (2003; de Paula et al., 2009; Nascimento, et al., 2011) RIVA interacts with the Ser200 residue of the catalytic triad through the carbamoyl moiety.

The regions of highest electronic density are located under the oxygen atoms in DDVP, METRI, HUPE, GALA, E2020, PHYSO, RIVA suggesting that these oxygens are receptors of hydrogens that can share in interactions, such as hydrogen bonding with the residues of the AChE catalytic triad or promoting covalent bonds, with the hydroxyl group of Ser200 (Camps, 2002). The rivastigmine (Figure 4h) and donepezil (Figure 4f) have more regions with low electronic density than other drugs, which is important for the interaction with the receptor site. The molecular volume is an important descriptor for drug design, and it is shown that some inhibitors are more linear which should improve the binding to two or more parts of the enzyme.

2.4 Mapping of the pharmacophoric profile of AChEIs via PCA

The mapping of pharmacophoric profile of AChEIs was conducted by means of PCA analysis, using of the data set obtained from calculations of the properties obtained for each molecule. For the analysis of principal components the geometry optimizations were performed at the level B3LYP/6-31 + G (d, p). The properties amount is shown in Table 1.

PCA was used to correlate 18 properties of 10 AChEI molecules to reduce the initial parameter set and determine the most relevant data for the acetylcholinesterase inhibition. PCA was conducted using the autoscaling method because the structural and electronic properties have different dimensions.

Since the structural and electronic properties have very different dimensions, autoscaling method is required. This normalization method consists in moving and stretching axes, centering the data on average and divides them by their standard deviation. Thus, each variable present zero mean and variance equal 1, giving the same significance for all variables (Jolliffe, 2002).

The first PCA showed that 83.3% on average of the information set formed by 10 AChEIs and 18 properties, obtained through the calculation performed in this work can be represented by four principals components (38.3% variance to PC1; 59.2% cumulative variance to PC2, 73.2% cumulative variance to PC3, 83.3% cumulative variance to PC4).

In studies of systems of many variables with PCA, it is desirable the lowest possible number of principal components that properly represent over 90% of cumulative variance. Thus, to increase the accuracy and determine the principal components we have used all combinations of 18 properties for the 10 AChEIs studied. Then the PCA was taken from the most relevant properties in relation to the total variance with the lower number of principal components.

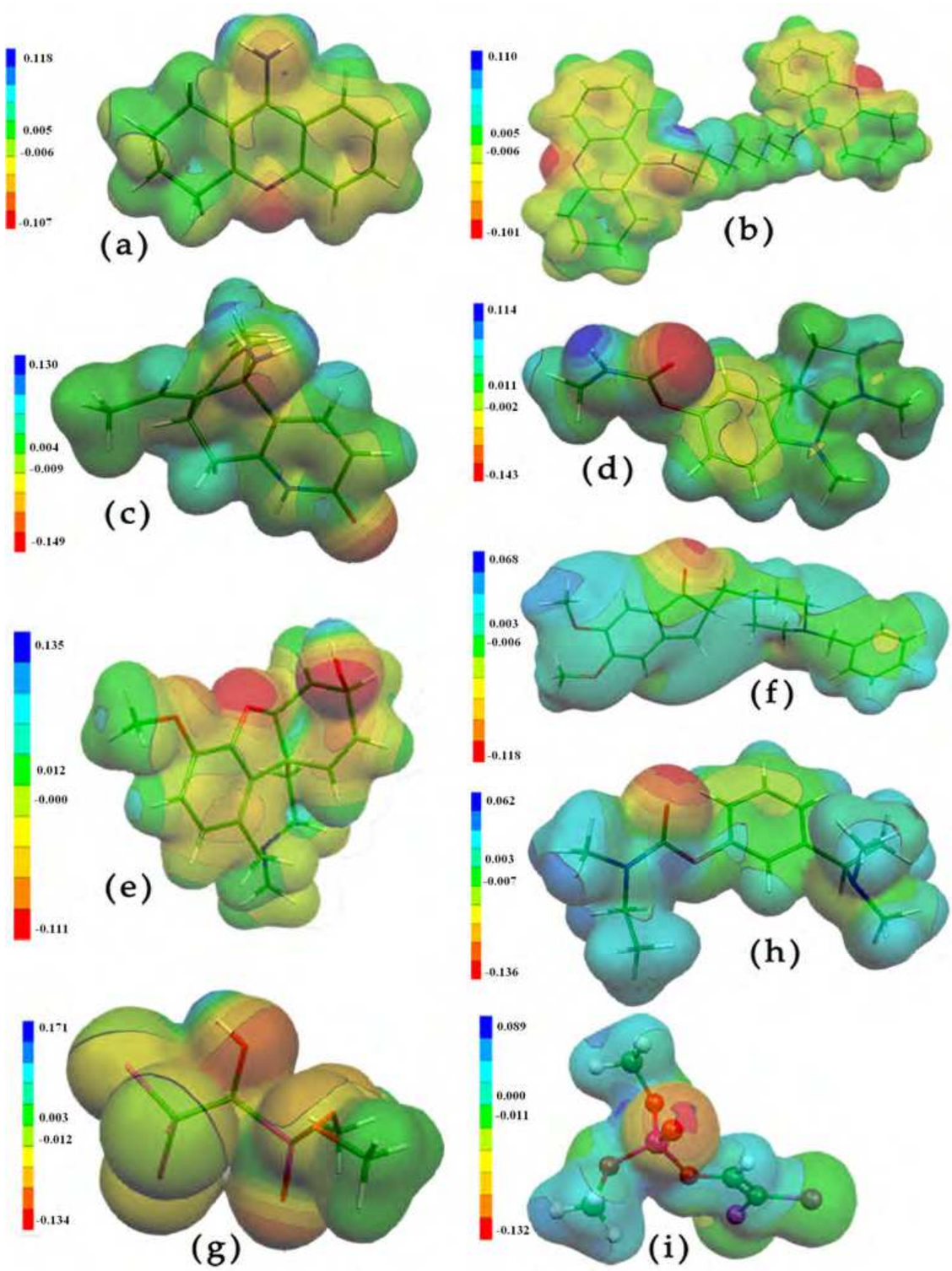

Fig. 4. Map of electrostatic potential of AChEIs calculated at B3LYP/6-31+G(d,p) level. (a) tacrine, (b) tacrine dimer, (c) huperzine A, (d) phenserine, (e) galantamine, (f) donepezil, (g) metrifonate, (h) rivastigmine, (i) dichlorvos.

In a second part, only 6 variables were used (shown below) with the 10 objects (AChEIs), these results in a 92% of total variance with information that characterizes these drugs in three principal components. Therefore, PCA (Figure 5) suggests that following properties are responsible for 92% of variance (63.5% for PC1 and 19.1% for PC2): volume, size of the molecule, distance between the two most acid hydrogens, energy of HOMO-1 frontier orbital, logP partition coefficient, and the number of aromatic rings (Table 2). In other words, these properties describes well the whole set of molecules data.

	PC1	PC2	PC3
B3LYP/6-31+G(d,p)	63.5 %	82.6%	91.7%

Table 2. Total cumulative variance (%) using 10 AChEIs and 6 properties

Equations 5, 6 and 7 show the scores of the PC1, PC2 and PC3. The PC1 is essentially the volume, size, partition coefficient- log P and number of aromatic rings of the drug (structural and electronic parameters), the PC2 represents the distance H-H (structural parameter) while the PC3 mainly represents the energy of the HOMO-1 orbital (electronic parameter).

$$PC1 = 0.48_{volume} + 0.46_{Size} + 0.13_{H\text{-}H} + 0.37_{HOMO\text{-}1} + 0.42_{logP} + 0.44_{Arom.} \quad (5)$$

$$PC2 = -0.01_{volume} + 0.02_{Size} + 0.88_{H\text{-}H} + 0.28_{HOMO\text{-}1} - 0.33_{logP} - 0.19_{Arom.} \quad (6)$$

$$PC3 = -0.38_{volume} - 0.40_{Size} - 0.16_{H\text{-}H} + 0.79_{HOMO\text{-}1} + 0.18_{logP} + 0.04_{Arom.} \quad (7)$$

Figure 5 shows that the molecules are grouped into some main groups in regard to PC1, one of these are the GALA, RIVA, PHEN and PHYSO which forms a cluster and these are the FDA approved drugs. HUPE, THA form other group with two potent inhibitors acetylcholinesterase. Therefore, volume, π–π systems and drug size are important parameters that correlate the AChEIs.

On other hand PC2 is dominated by the HH distance (score: +0.88), which separates compounds according to the distance between the two hydrogens more acidic in two groups: one that found them have H-H values smaller than 2.0 Å, and other group of objects that have values greater than those cited.

Figure 6 depicts the scores of PC1 versus PC3. In this case there are two standards in PC3 DDVP / METRO and GALA / PHYSO / RIVA / PHEN, this is reasonable, since PC3 represent the orbital energy of HOMO-1 (+0.79) (Equation 7), these AChEIs have values close to the HOMO-1 and the volume, as shown in Table 1. Figures 5 and 6, Equations (5, 6 and 7) generated in the PC indicates that the electronic parameters - orbital energy of HOMO-1 , log P and number of aromatic systems - and the structural parameters - volume, size of the drug and H-H- are the most significant properties of AChE in this multivariate analysis.

3. Applications of PCA from pharmacophoric profile of the AChEIs

From the pharmacophore profile determined by means of PCA and electronic structure calculations, other classes of molecules can be considered to be classified as AChEI. Therefore, it is important to note that, when added other objects, the new plotted PCs should have accumulative variance equal or larger than the original PCA (Table 3). That is, the original data set is the reference.

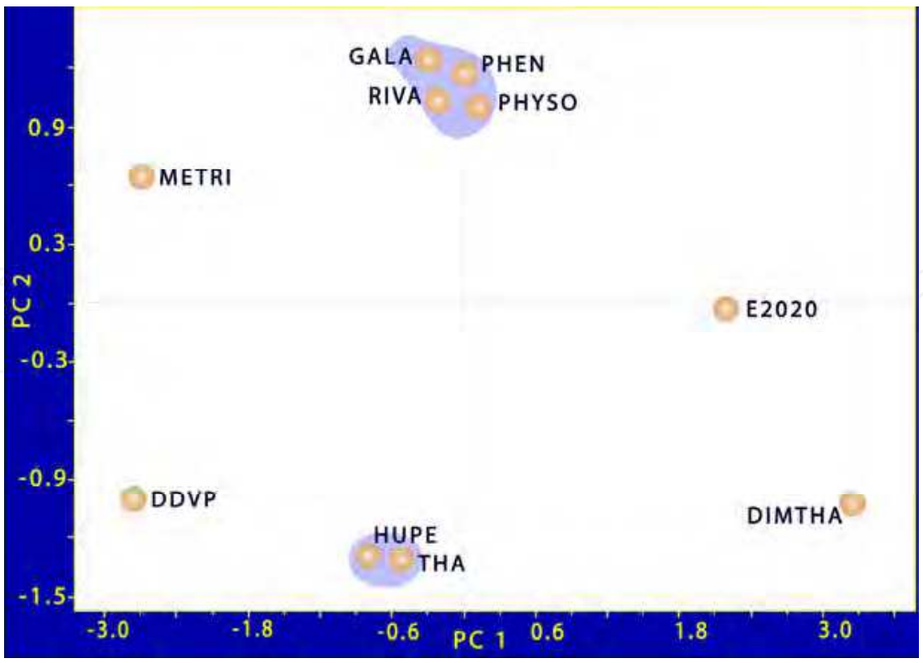

Fig. 5. PC1 versus PC2 scores from B3LYP/6-31+G(d,p) data.

	PC1	PC2	PC3
B3LYP/6-31+G(d,p)	71 %	86%	94%

Table 3. Total cumulative variance (%) using 10 AChEIs, 2 new molecules, 1 substrate and 6 properties.

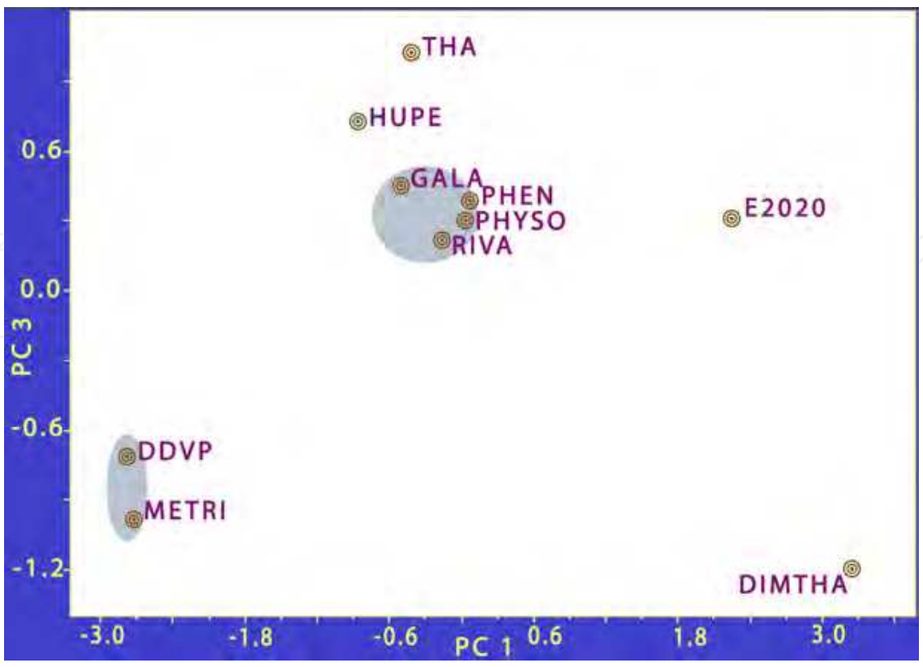

Fig. 6. PC1 versus PC3 scores from B3LYP/6-31+G(d,p) data.

The following are some applications explored. One possible application is the identification of dual biological activity of molecules. Another is the identification of activity against the function of acetylcholinesterase inhibitor, i.e., how behaves the natural substrate of the enzyme.

MOL1 and MOL2 with different biological activity from AChEIs were studied. We have also added another compound on the data set, acetylcholine (acetylcholinesterase substrate). Within these data from the properties obtained through electronic structure calculations, the new PCA was generated. These three objects were added to the 10 other objects of the first PCA which determined the pharmacophoric profile of AChEIs.

As shown in Figure 7, the natural substrate reorients the axis of the PCs and is completely opposed to the other (active) drugs. The acetylcholine is close to some of AChEIS by PC1, which have the properties of volume, size and number of aromatic rings with more high scores. Although acetylcholine is not an inhibitor it must have some properties correlated with the AChEIs. All molecules that are recognized by a protein have a certain set of properties that allows this recognition.

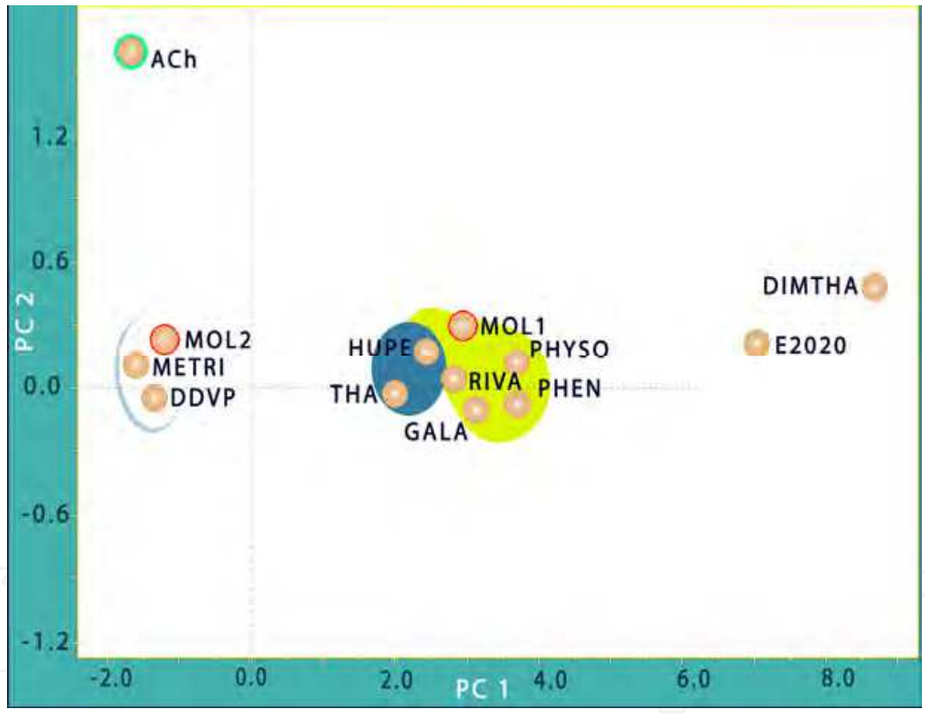

Fig. 7. PC1 versus PC2 scores from 10 AChEIs, 2 new molecules and ACh at B3LYP/6-31+G(d,p) level.

According to the PCA the two new drugs can be classified as AChEIs, although it is not possible to determine whether they have efficacy in the treatment of Alzheimer's disease. It is important to note that the effectiveness of a drug depends also on other factors that are difficult or much complex for modeling.

As shown in Figure 7, the natural substrate reorients the axis of the PCs and is completely opposed to the other (active) drugs. The acetylcholine is close to some of AChEIs by PC1,

which have the properties of volume, size and number of aromatic rings with large scores. Although acetylcholine is not an inhibitor it must have some properties correlated with the AChEIs.

All molecules that are recognized by a protein have a certain set of properties that allows this recognition. As shown in Figure 8, in the case of acetylcholinesterase specifically, molecular modeling studies showed that during the molecular recognition of acetylcholine, the quaternary nitrogen of the substrate has a strong ionic interaction with the carboxyl group of the residue Asp72. In addition, there is formation of hydrogen bonds between the amine and ester group of the residue Asn65 and Tyr130 (Patrick, 2005).

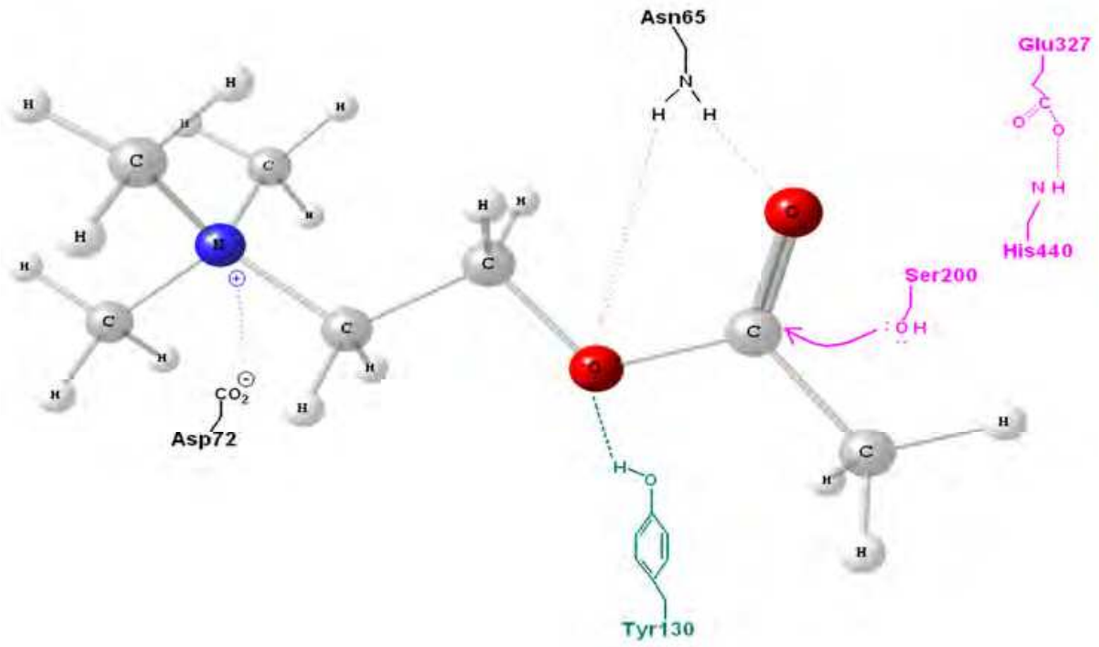

Fig. 8. PC1 Optimized structure of acetylcholine and main points of molecular recognition in acetylcholinesterase at B3LYP/6-31+G(d,p) level.

4. Conclusion

All studied AChE inhibitors are recognized as drugs that act effectively in the treatment of AD, even if some are not recommended due to unwanted side effects. From the computer modeling, applied by electronic structure calculations and PCA of known AChEIs with potential for the treatment of AD, it is possible to conclude that the properties relevant to the inhibitory activity are:

1. The HOMO-1 orbital is the most important property, characteristic of all drugs.
2. The study of the electrostatic potential map indicates that all AChEIs have well-defined regions of high and low electronic density, and these regions are the likely points of interaction with acetylcholinesterase, through electrostatic interactions such as hydrogen bonding. In some cases, such as dichlorvos, rivastigmine and physostigmine, it is possible to predict a bond with covalent character to the catalytic triad of the enzyme.

3. The H-H distance between 1.625-2.460Å, volume, and logP are also relevant for the pharmacophoric profile.
4. The electronic properties - orbital energy of the HOMO-1, log P and number of aromatic systems - and the structural parameters volume, size of the drug and H-H distance are the most significant properties in this study, the main components of the pharmacophore profile of AChEIs.
5. From the pharmacophore profile determined using PCA and electronic structure calculations, other classes of molecules can be considered to be classified as AChEI.

In addition to the structural and electronic properties mentioned above, an efficient inhibitor should have good bioavailability, cross the blood brain barrier with relative ease, to have high selectivity for acetylcholinesterase compared to butilcholinesterase; be able to form a complex reversible or pseudo-reversibly with AChE, be non-competitive compared to natural substrate. All these properties are jointly sharing in the profile of AChE pharmacophore studied in this work.

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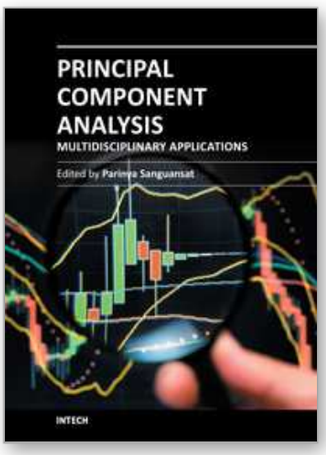

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This book is aimed at raising awareness of researchers, scientists and engineers on the benefits of Principal Component Analysis (PCA) in data analysis. In this book, the reader will find the applications of PCA in fields such as taxonomy, biology, pharmacy,finance, agriculture, ecology, health and architecture.

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