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Geometry optimization of antimuscarinic, antichloenergic and antispasmodic aprophen hydrochloride

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Abstract: Aprophen hydrochloride extensively used as anticholenergic, antimuscarinnin and antispasmodic agent. Structure based drug designed is based on the firm understanding of molecular recognition between active site group and interacting molecules ,it is strategy that become as integral part of modern drug discovery. The aim of present study is find out the minimum potential energy for aprophen hydrochloride. The potential energy of the molecule in molecular mechanics calculated by using force field concept. Potential energy effect the inter action of drug molecule with receptor these properties could be use to synthesize new drug candidates with improve pharmacological and therapeutic activity.

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INTRODUCTION

Aprophen hydrochloride is structurally relayed to other anticholinergic azaprophen, atropine hydrochloride, adiphenine hydrochloride and qunuclidinyl benzilate hydrochloride[1]. All of pyridophen analogues were potent antagonist of the muscarinic receptor than aprophen[2]. Aprophen hydrochloride act as potent antimuscarinic and noncompetitive nicotinic antagonist activities these properties make it best choice for the treatment of poisoning by organophosphate and anticholinesterase agent. Benactazyine and adephenine hydrochloride are approximately 2-3 and 30 times less active as compare to aprophen hydrochloride respectively[1-2].

The major purpose of present study is to find out the minimum energy conformation of drug molecule this process is known as energy minimization s, geometry optimization or conformational analysis of drugs molecules. The minimum energy containing molecule is obtained by calculated lowest potential energy from the crystallography data[3]. The system makes many changes in the atom position through rotation and calculates energy in every position. This process repeated several times to find best position with minimum potential energy[4].

The one complete round of an atom rotation is called minimization step or iteration. By applying conformational analysis on molecule is based on molecular mechanics, it is method for calculation of molecular structures, conformational potential energy and other molecular properties using concept from classical mechanics' molecule is considered as a collection of atoms held together by classical forces are described by potential energy function of structural features like bond angle, bond length and torsion angles etc. The energy (E) of the molecule as a sum of term in equation: E = E (stretching) + E (bending) + E (torsion) + E (Vander Waals) + E (electrostatic) + E (hydrogen bond) + cross term.

These terms are of importance for the accurate calculation of geometric properties of molecules. The set of energy function and the corresponding parameters are called a force field[4-5]. By applying force field, the minimum energy of a molecule is its stable conformation can be calculated, which is always taken as negative derivative of the energy function with respect to the coordinates of the atoms[6]. Present work describes the geometric optimization (active conformation) of drug molecule.

MATERIALS AND METHODS

The crystallography data were used to draw different projection, prospective view; electron density cloud and lowest potential energy of aprophen hydrochloride molecule by method as reported by[7-9].Potential energy were calculated for lower limit (k2)[10].

RESULTS

Figure 1 shows 000 projection, figure 2 shows prospective view, figure 3 shows potential energy contour map and figure 4 shows electron density clouds of aprophen hydrochloride molecule. All properties of molecule are given in table 1.

DISCUSSION

The three dimensional quantitative structure activity relationships (3D-QSAR) give valuable information about the shape of receptors[11-14].

Different projection and drug molecule draw by using coordinates of atoms obtained by crystallography data. Figure 1 shows the (000) projection of molecule. Projection chose to select different pair for calculating potential energy of different pair individual pairs. Total potential energy obtained by sum of all individual pairs.

Table 1: Properties of all molecules

Name	2-Diethylaminoethyl 2,2-diphenylpropionate hydrochloride
Molecular Formula	= $C_{21}H_{28}ClNO_2$
Formula Weight	= 361.90552
Composition	= C(69.69%) H(7.80%) Cl(9.80%) N(3.87%) O(8.84%)
Molar Refractivity	= Not available
Monoisotopic Mass	= 361.180857 Da
Nominal Mass	= 361 Da
Average Mass	= 361.9055 Da
M+	= 361.180308 Da
M-	= 361.181405 Da
[M+H]+	= 362.188133 Da
[M+H]-	= 362.18923 Da
[M-H]+	= 360.172483 Da
[M-H]-	= 360.17358 Da

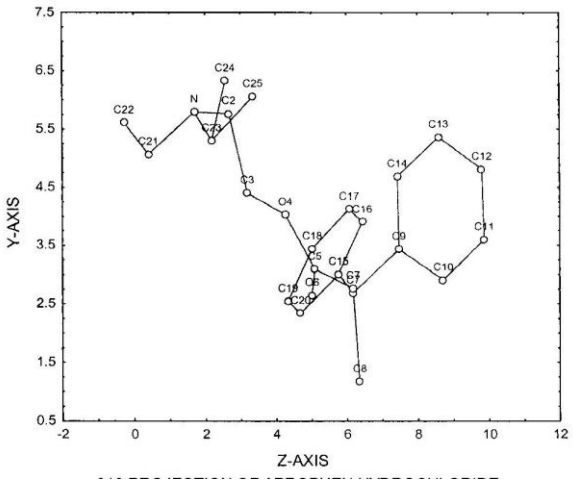

Figure 1: projection (100) of 2-Diethylaminoethyl 2, 2-diphenylpropionate hydrochloride.

Figure 2 shows the electron density map of aprophen hydrochloride by ACDLABS-3D viewer software. The electrostatic potential of drug caused by charged side chains and bound ions plays a role in recognition of active site of specific receptor.

The counter map in figure 3 shows total potential energy of drug. Lowest energy containing portion is denote by negative (-) sing while positive (+) mark show maximum energy containing area of drug molecule.

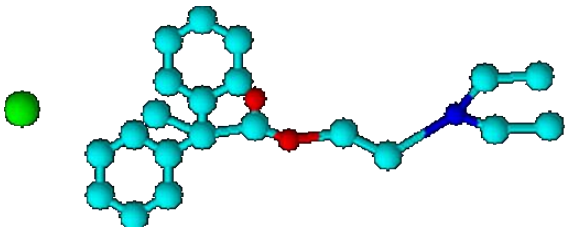

Figure 2: Prospective view of active conformation of 2-Diethylaminoethyl 2, 2-diphenylpropionate hydrochloride.

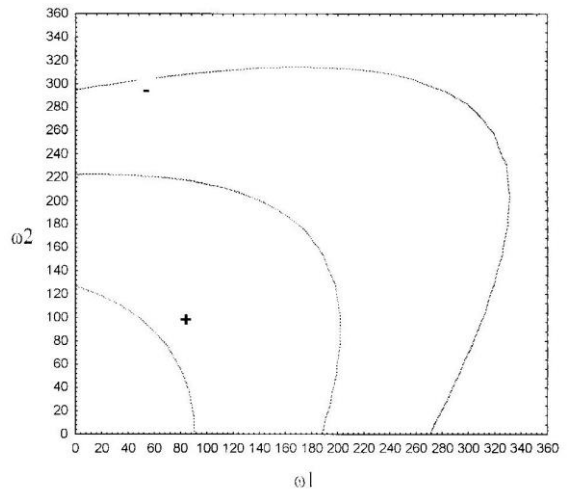

Figure 3: Contour map showing minimum total potential energy of 2-Diethylaminoethyl 2, 2-diphenylpropionate hydrochloride.

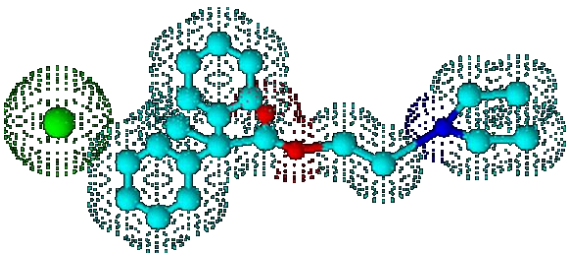

Figure 4: Electrons density clouds of 2-Diethylaminoethyl 2, 2-diphenylpropionate hydrochloride generates by ACD Labs.3D viewer.

The allowed region i.e., region in which drug can bind with their receptor .the area outside the zero line is allowed region. It is possible that drug in this conformations interact with receptor .the result indicate that it can only exist at one stable conformation and stable conformation exist at minimum potential energy. As describe by previous researchers[15-17].The minimum potential energy is found to be -0000000 k.cal/mol at w1= 00 and w2=000 (Figure 3) .The drug molecule has many three dimensional structure but only one or few of them conformation mathch with receptor structure

and bind to it. Potential energy value strongly related to the interaction of drug molecule with its specific receptor. These information could be use full to designed new drug molecule with improve anitcholenergic agent.

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