ASIAN JOURNAL
ISSN: 0976-3376

Available Online at http://www.journalajst.com

ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

Asian Journal of Science and Technology
Vol. 6, pp.110-112, October, 2010

RESEARCH ARTICLE

QUANTUM CHEMICAL INVESTIGATION OF 4-ACETYLAMINO-5-AMINO-3-(1-ETHYL-PROPOXY)-2-[5-(5-OXO-5-PIPERIDIN-1-yl-PENTA-1, 3-DIENYL) BENZO [1,3] DIOXOL-2-yl]-CYCLOHEX-1-ENECARBOXYLIC ACID ETHYL ESTER MOLECULE

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Received 7th July, 2010; Received in revised form; 25th August, 2010; Accepted 27thSeptember, 2010; Published online 1st October, 2010

The structural and electronic properties of the 4-acetylamino-5-amino-3-(1-ethyl-propoxy) - 2- [5 - (5 - oxo - 5-piperidin –1 – yl – penta -1,3-dienyl)-benzo[1,3]dioxol-2-yl] -cyclohex -1-enecarboxylic acid ethyl ester (ARZK) molecule have been investigated theoretically by performing semi empirical molecular orbital theory. The structures of molecules are optimized at the level of PM3 and MNDO3 theory. The electronic properties and relative energies of the molecules are obtained.

Key words: Tami flu, Structure-activity-relationship, Piperine, semi empirical PM3 and MNDO3 methods

INTRODUCTION

The potential for a worldwide influenza pandemic caused by bird flu has heightened public interest regarding the availability and affordability of influenza antiviral medications such as Tamiflu (Yeh, 2005). Tamiflu is the first and only antiviral pill available for the treatment and prevention of all common strains of influenza A and B (Rossi, 2006). The compound has been shown to be active in animal models against avian flu, also known as the H5N1 strain of the virus. The H5N1 virus is alarming because, if it mutates into a form that easily infects many humans, it has the potential to cause a deadly "pandemic," or a global disease outbreak in humans (De Jong *et al.*, 2005). Tamiflu is not a vaccine, but is perhaps the most efficient antiviral treatment for influenza. The drug eases flu symptoms by preventing the influenza virus from spreading inside the human body. Some research studies have shown that Tamiflu is effective against the H5N1 avian and human virus strains (Word *et al.*, 2005).

Tamiflu is trade name of oselamivir, the IUPAC name of tamiflu is (3*R*,4*R*,5*S*)-4-acetylamino-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid ethyl ester, its formula $C_{16}H_{28}N_2O_4$, the molecular weight 312.4 g mol^{-1}, and the chemical structure is shown in Figure 1 (Cong and Yao, 2006).

As with other antiviral, resistance to the agent was expected with widespread use of oseltamivir. So, my suggestion in this work, is to produce anti virus more effect than tamiflu by inseartion of piperine in to tamiflu antivirus. .The piperine's pungency is used in treatment of many illnesses such as cancer, malaria, cholera, and it may kill virus (Epstein *et al.*, 1993). The chemical name of piperine (Figure 1) is 1-[(2E, 4E)-5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl], and the chemical formula is C_{17} H_{19} N O_3. Piperine can be isolated in good yield from ground black pepper, which is made up of 5-9% of alkaloids that also include piperidine, piperettine and piperanine and comes from the dried fruit of aschanti (Epstein *et al.*, 1993). The Biochemical Classification Committee determined that piperine is classified as a biochemical pesticide due to its non-toxic mode of action.

The IUPAC name of the studied molecule is 4-acetylamino-5-amino-3-(1-ethyl-propoxy)-2-[5-(5-oxo-5-piperidin-1-yl-penta-1,3-dienyl)-benzo[1,3]dioxol-2-yl]-cyclohex-1-enecarboxylic acid ethyl ester (ARZK), and its chemical formula is $C_{27}H_{31}N_3O_7$. The chemical structure is shown in Figure 2. Because of the biological and medical importance of the ARZH molecule, I have investigated the structural features and electronic properties theoretically in this work, and in the future, I will prepare the studied molecule practically.

Method of calculation

Geometry optimization is carried out by using a conjugate gradient method (Polak-Ribiere algorithm) (Fletcher, 1990), then the electronic structure of ARZK is calculated by applying the semi-empirical molecular orbital (MO) theory at the level of PM3 (Stewart, 1989), and MNDO3

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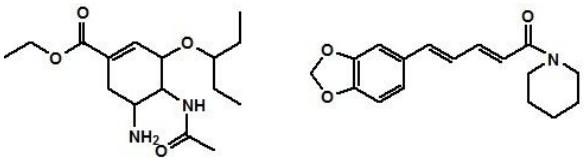
(Binghan *et al.*, 1975) within the restricted Hartree-Fock (RHF) (Roothaan, 1951). The convergence is set to 0.001 kcal mol^{-1}. All semi-empirical methods are done on hyperchem release 7.5 for Widows Molecular Modeling System running on Windows XP Workstation in Pentium IV PC (Hyperchem ^{TM} Release 7.52).



(a) **(b)**

Fig. 1. The chemical structure of (a) Tamiflu (b) Piperine

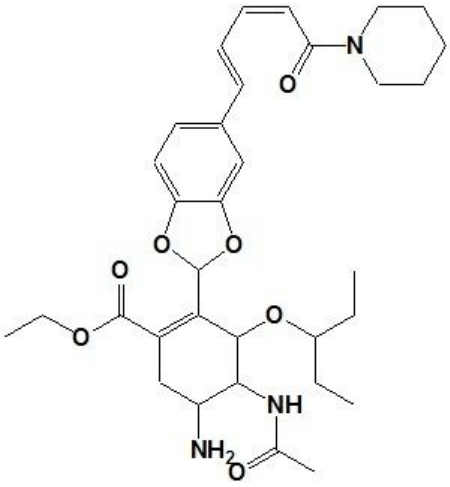


Fig. 2. The chemical structure of ARZK

RESULTS AND DISCUSSION

Some molecular information about the system considered are given in Table 1 .The PM3 and MNDO3 geometry optimization yields a non planar structure as the stable form of the ARZK.

Table 1. Some molecular information about the ARZK

Quantity	Method	
	PM3	MNDO3
No. of electrons	234	234
No. of dobly occupied levels	117	117
No. of total orbitals	217	217

Table 2 show the PM3 and MNDO3 calculated energies, the highest occupied and the lowest unoccupied MO (HOMO and LUMO respectively) energies and the interfrontier MO energy gap (LUMO – HOMO energy difference, ΔE) with the lowest and highest level energy values. The ARZK molecule has a binding energy value of about 86123.34 kcal mol^{-1} (PM3) and 104016.74 kcal mol^{-1} (MNDO3). On the other hand , the heat of formation of the system studied is endothermic and has the value of about 94863.22 kcal mol^{-1} (PM3) and 112756.61 kcal mol^{-1} (MNDO3) .The LUMO – HOMO gap of the ARZK is about 10 eV according to PM3 and MNDO3 methods. The resultant dipole moment of the ARZK molecule is about 7.7 and 6.7 Debyes by PM3 and MNDO3 methods respectively .This value of dipole moment may be considered as large for such a molecule (Erkoc *et al.*, 2002). According to the present calculated dipole moment value, ARZK molecule seems to be polar (hydrophilic).This property of ARZK makes it an active molecule with its environment, that is ARZK molecule may interacts with its environment strongly in solution (Erkoc and Erkoc, 2005).

Table 2. The energy values (in kcal mol^{-1}), the MO energy of HOMO, LUMO levels, ΔE (in eV), and dipole moment μ (in Debyes) for ARZK which is calculated by PM3 and MNDO3 methods

Quantity	Method	
	PM3	MNDO3
Total energy	-69702.38	-62420.37
Binding energy	86123.34	104016.74
Isolated atomic energy	-155825.73	-166437.12
Electronic energy	-88472.21	-94135.05
Core-core interaction	18769.82	31714.67
Heat of formation	94863.22	112756.61
Lowest level	-70.98	-95.66
Highest level	28.22	31.22
HOMO	-9.574	-9.827
LUMO	-0.105	0.614
ΔE	9.469	10.441
μ	7.7	6.7

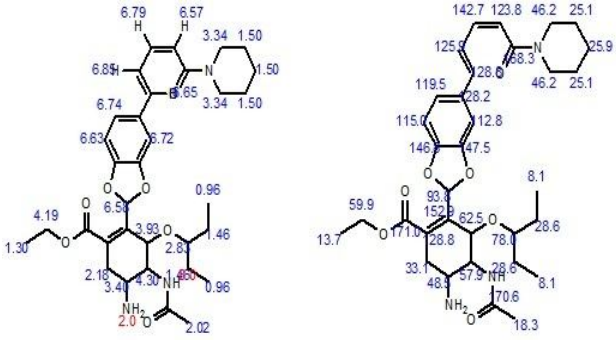


Fig. 3. Spectra of ARZK in ppm (a) ^{1}H NMR (b) ^{13}C NMR

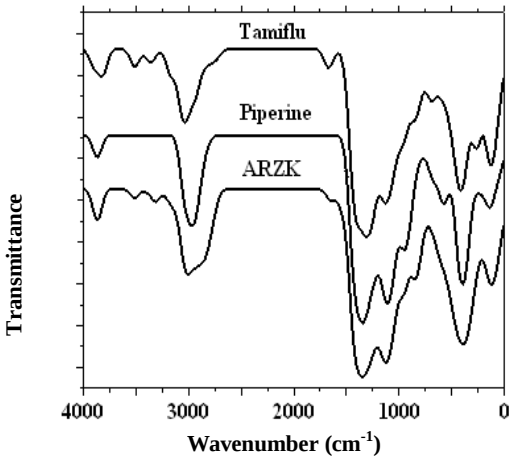


Fig. 4. Calculated infrared bands for the studied structures.

Table 3. Band assignment(cm^{-1})for the calculated structures.

Vibration	Molecules		
	Tamiflu	**Pipperin**	**ARZK**
OH	3817, 416	3870	3873-3863, 388
NH_2	3514 -3380, 1669, 262		3516-3385 1649, 126
NH	3345, 674		3363
CH_3	3161, 1130		3137, 1117
CH	3051, 3031, 3015	2977-2946	2974-2943, 947
CH_2	125	3012, 2961, 1113-1103, 948	1123, 947, 853
CH_2+ CO		1347-1342, 130, 118	
Ring		1121, 948	
Pyr. Ring		575	
C-O + N-H	1317	387	1365

The ^{1}H NMR and ^{13}C NMR spectra of the ARZK are shown in Figure 3 (Chem.Draw Ltra ®). The ranges of the protons absorbed vary between 1 to 9 ppm. The aromatic and vinyl protons chemical shifts are absorbed in the region 6.5 - 6.9 ppm while the other protons are absorbed in the region 0.9 - 4.2 ppm. In ^{13}C NMR spectra, the ranges of the carbon atoms are absorbed between 8–171 ppm .The absorption peak of aromatic and vinyl carbon atoms vary between 112–146 ppm, while the aliphatic carbon atoms are absorbed in the region 8–60 ppm. Finally the absorption peaks at range 167–171 ppm belong to carbon of carbonyl groups.

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