Preliminary results of a semi-empirical study on the structure and reactivity of the Paroxetine drug.

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Abstract

Paroxetine is a widely consumed drug with antidepressant and anxiolytic activity prescribed in the treatment of related disorders, such as obsessive-compulsive disorder, panic fits, social phobias and post-traumatic stress. Molecular modelling analyses show that both semi-empirical methods (PM3 and AM1) give us approximated the same values of heat of formation, Total energy, binding energy, nuclear energy, Dipole moment, HOMO and LUMO energies, etc. And the Paroxetine molecule has a large negative heat of formation indicating that it is a molecule thermodynamically stable.

Keywords: Paroxetine, Semi-empirical, PM3, AM1, HyperChem.

Introduction

Paroxetine (PXT) is a selective serotonin reuptake inhibitor (SSRI), with antidepressant and anxiolytic activity [1]. PXT is comparable to the tricyclic antidepressants in their clinical efficacy, however PXT is safer and has greater acceptance by the patients [2]. Consistent with its lipophilic amine character,

paroxetine is extensively distributed into tissues. Its plasma protein binding at therapeutically relevant concentrations is about 95%. Paroxetine is eliminated by metabolism involving oxidation, methylation, and conjugation [3]. It is also prescribed in the treatment of related disorders, such as obsessive-compulsive disorder, panic fits, social phobia, and post-traumatic stress, and it has been proved [4]. PXT is devoid of sedative effect and remarkably safe in overdose. PXT takes 5.2 hours to reach the peak, with extended half-life (21 hours) that allowed the introduction of formulations for once-daily dosing [5]. These combined qualities made PXT the most widely prescribed antidepressants [6].

This is the first study of paroxetine using molecular modeling analysis with the programs HyperChem 7.0 (HyperChem, 2002) to investigate the relative stability of paroxetine and be able to predict the behavior of this drug.

Computation Methods

The geometry of Paroxetine ((3*S*,4*R*)- 3-([benzo[*d*] [1,3]dioxol-5-yloxy] methyl)-4-(4-fluorophenyl) piperidine) has been optimized based on molecular mechanics and semi-empirical calculations, using the molecular modeling programs HyperChem 7.0. Molecular mechanics calculations were carried out using MM+ force field. Semi-empirical calculations were carried out using the routines AM1, PM3 and Polak-Ribiere conjugated gradient algorithm. For the optimized structure, single point calculations were carried to give molecular properties including electrostatic potential maps, HOMO/ LUMO energies, heat of formation, dipole moment, atom charges (Mulliken), total energy of the molecule, binding energy, electron energy and nuclear energy.

Results and Discussion

Some of the molecular propierties of the system considered are given in Table 1. Both methods (AM1 and PM3) gives similary energies and dipole moments. Paroxetine has a high and negative heat of formation (between -97 and -98 Kcal/mol) indicating that this is a thermodynamically stable molecule. The AM1 and PM3 gives a non planar structure as more stable for Paroxetine molecule, this non planar structure increase the molecular volume of the system. The optimized structures of the molecules are show in Fig. 1 with numbered atomic labels, and the excess charge on the atoms of the system considered are show on the atoms in Fig. 2.

Table 1. Some of the calculated energy and dipole moments of the Paroxetine molecule in the ground state.

	AM1	PM3
Total Energy (kcal/mol)	- 100.549	- 93204.563
Binding Energy (kcal/mol)	-4697.353	-4696.740
Heat of Formation (kcal/mol)	-97.836	-97.223
Electronic Energy (kcal/mol)	-708129.688	-692834.375
Nuclear Energy (kcal/mol)	607581.063	599629.813
HOMO (eV)	-8.62	-8.78
LUMO(eV)	-0.11	-0.22
LUMO-HOMO (eV)	8.51	8.56
DM (Debye)	1.72	1.59
μ_x (Debye)	1.02	0.64
μ_y (Debye)	-1.00	-1.16
μ_z (Debye)	0.94	0.87

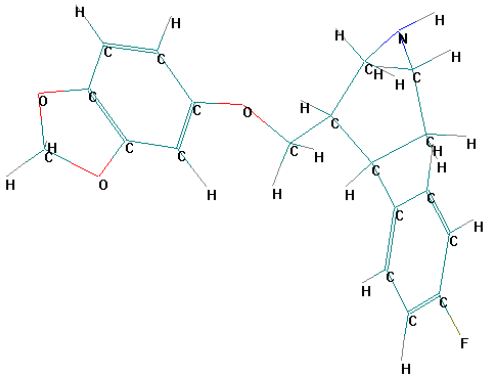

Fig 1. The optimized structure of Paroxetine molecule on the ground state.

As one expect, in the Paroxetine molecule, oxygen atoms have -0.198, -0.202 and -0.186 units of electron charges obtained with PM3 results and -0.216, -0.219 and -0.209 electron charges with AM1 respectively; these values indicates that oxygen atoms are attractive centers within the paroxetine molecule.

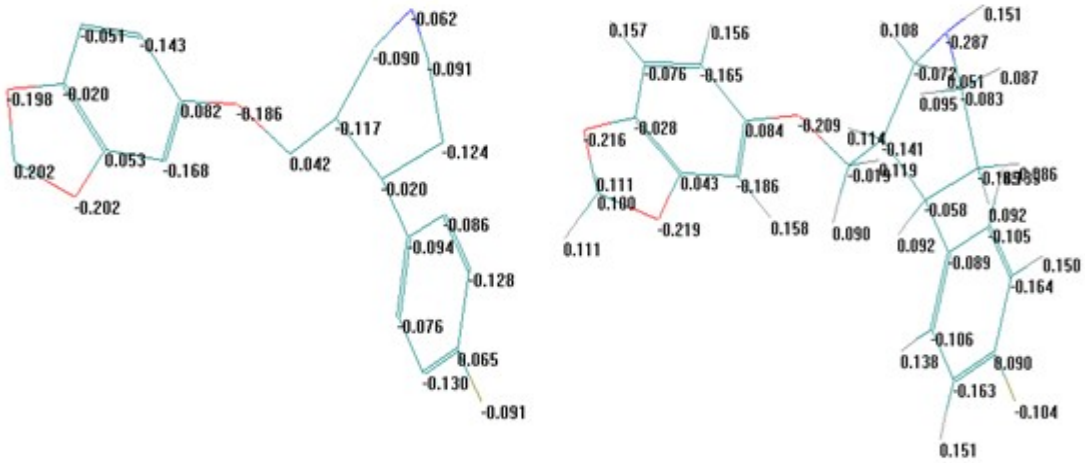

Fig 2. Excess charges on the atoms of Paroxetine molecule in the ground state; PM3 (left), AM1 (right) results.

The structure also give 2D contours of total electrostatic potential (Fig 3), The electrostatic potential give us a physical property of a molecule related to how a molecule is first seen or felt by another approaching species [7]. The pink contours over Oxygen atoms in the paroxetine molecule means negatives electrostatic potential, and in these sites are the portion of the molecule that could be susceptible to electrophilic attack, the more negatives the better. And finally the green contours are positive electrostatic potential.

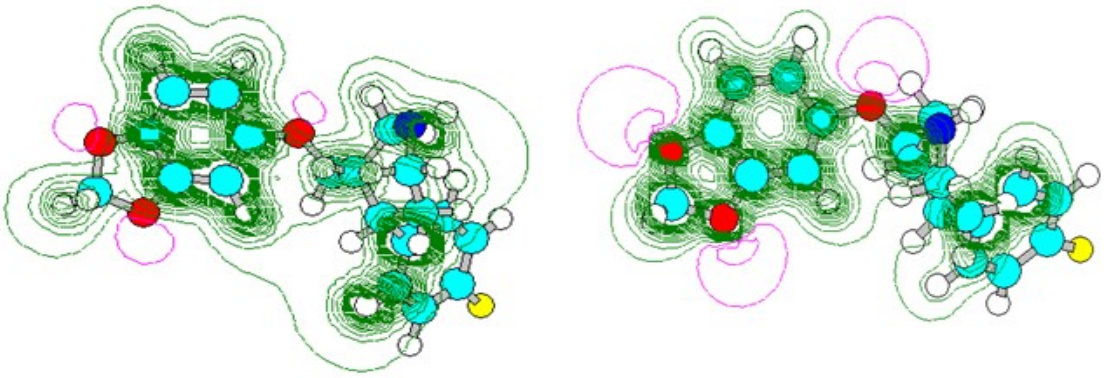

Fig 3.Structure of Paroxetine molecule in the ground state giving 2D contours of total electrostatic potential; PM3 (left), AM1 (right) results.

Conclusions

This is the first theoretical and semi-empirical analysis of the Paroxetine drug. This molecular modeling analysis show us that it has a large negative heat of formation indicating that is thermodynamically stable. Also we saw that Paroxetine is a polar molecule with a value between 1.59 and 1.72 Debyes. And finally with 2D contours of total electrostatic potential we can see graphically which sites could be susceptible to electrophilic attack.

References

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