11th International Conference
on Advanced Materials

ICAM2009

Rio de Janeiro Brazil
September 20 - 25

Theoretical Study on the Electronic Properties Responsible for the Interaction between Some Substances and PPAR receptor

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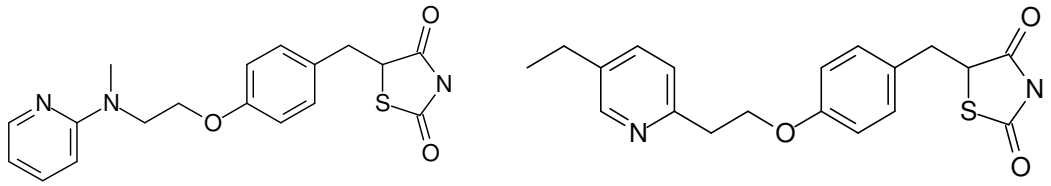
Diabetes mellitus (DM) is a disease characterized as a chronic disorder of the metabolism of carbohydrates, lipids and proteins. DM is the major cause of renal failure, amputation of lower members, blindness and cardiovascular disease. Peroxissome proliferator activated receptors (PPARs) are related to the regulation of various metabolic processes and can be considered attractive therapeutic targets for the treatment of DM. So, the main objective of this study is to evaluate the behavior of two substances employed as drugs to treat *diabetes mellitus* (DM) by using theoretical methods that characterize the molecular and electronic structure of these substances, providing information on possible mechanisms of interaction with the biological receptor (PPAR). The substances studied in this work were rosiglitazone and pioglitazone, which are two drugs used to treat DM and are marketed currently. The molecular structure of these substances, along with the biological property (EC_{50}), is shown in Figure 1.



Rosiglitazone
(EC_{50} = 31 nM)

Pioglitazone
(EC_{50} = 1200 nM)

Figure 1: Molecular structure of the studied compounds.

Geometry optimization and the calculation of electronic properties (total energy and energy of the frontier orbitals) were performed using the Density Functional Theory (DFT), with the functional B3LYP and dgdzvp basis set, as implemented in the computational package Gaussian03. We calculated the properties in vacuum, as well as in several solvents (water, ether and acetone). The solvents were chosen in order to analyse the behavior of the molecular geometry and the properties of each substance. From the overlap of the optimized geometries in different environments, it is possible to observe that both molecules maintained a very similar geometry in all environments and showed no significant variations. Analyzing the electronic properties, we can verify that the compounds studied have similar values of total energy and, therefore, have similar chemical stability. From the E_{HOMO} and E_{LUMO} values, we can observe the electron-donating and/or electron-acceptor characteristics of substances studied in this work. From the calculated values, it was possible to see that the studied compounds have very similar E_{LUMO} values in all environments used. Regarding E_{HOMO} values for both molecules, we can verify some important differences. Comparing the E_{HOMO} values of rosiglitazone and pioglitazone, it can be verified that rosiglitazone has a higher value than pioglitazone in all environments studied and this indicates that rosiglitazone has a more electron-donor character than pioglitazone, and this can be related to the biological potency of each compound, since rosiglitazone is the most potent compound (EC_{50} = 31nM) and has the highest electron-donor character. Therefore, we can notice that electronic properties obtained from theoretical methods have high correlation with the biological activity presented experimentally by two drugs marketed for the treatment of DM.

FAPESP, CNPq