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Conformational analysis of molecules with potential antileishmania activity

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Abstract: Leishmaniasis are a set of endemic protozooses present in 88 countries, being able to manifest in cutaneous, mucocutaneous and visceral forms[1]. In Brazil, *L. amazonensis* and *L. braziliensis* species are the main cause of leishmaniasis occurrences[2]. Since there is no effective treatment against the different species of *Leishmania* a lot of drugs have been developed to improve the treatment as well as attenuate the side effects of those existing. A possible target for the development for new drugs are the enzymes of topoisomerase family[3]. The overall mechanism of action, however, still not known. In these sense, an experimental group in UNIFEI has synthesized some new compounds with potential antileishmania activity. Thus, the overall aim of the project is to make a structural, electronic, thermodynamics and kinetics analysis of these new molecules and their process involved on mechanism of action through topoisomerase interactions using computational tools. In this work, the conformational analyses of the first compounds which are presented in figure 1, are studied as well as their substituent. The conformational freedom is an important feature to describe key interactions with biomolecular targets. All calculation have been performed using the Gaussian 09 program, through DFT calculations, with M06-2X functional and 6-31g(d,p) basis set for geometry optimization, followed by vibrational analysis which confirm the initial guesses as local minima and also for conformers search, as can by the multiple rotation of two dihedrals angles as represented in Figure 2.

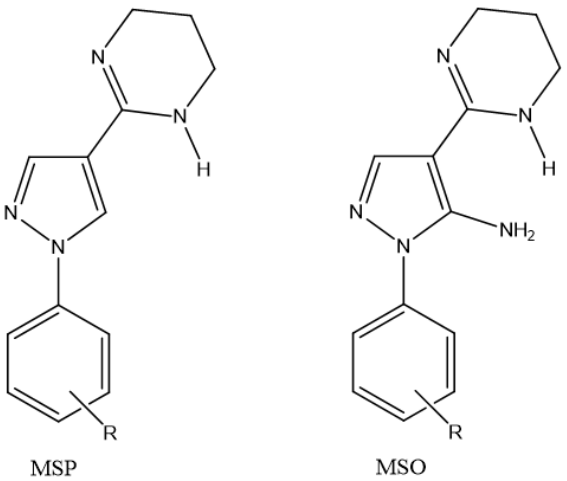

Figure 1: Structural Representation of basic compounds studied in this work. For ***MSP***: **01**: R=H; **02**: R=3–Cl; **04**: R=3,5–diCl; **07**: R=4–Cl; **10**: R=4–F; **13**: R=4–Br; **20**: R=4–OCH_3. For ***MSO***:**01**: R=H; **02**: R=3–Cl; **04**: R=3,5–diCl; **05**: R=3,4–diCl; **07**: R=4–Cl; **10**: R=4–F; **13**: R=4–Br; **14**: R=3–Br; **20**: R=4–OCH_3.

After analyzed the optimized 16 molecules structures, scan calculations were performed. There are centers of free rotation in these molecules, so changing the angles over these centers will make the

energy of the compound changes too. Scan calculation run over 36 steps, varying 10 degrees rotation in each step for both dihedrals θ and φ as presented in Figure 2. Since there are two possible dihedrals, 1296 conformations were evaluated. As example, Figure 2 shows the optimized structure of MSP04, with the two dihedral represented and Table 1 shows the highest energy conformation for the same molecule, indicated at 0 kcal/mol, and also the five most stable conformations from this calculation. The number of conformation is only an arbitrary number as structures identifier over the scan run.

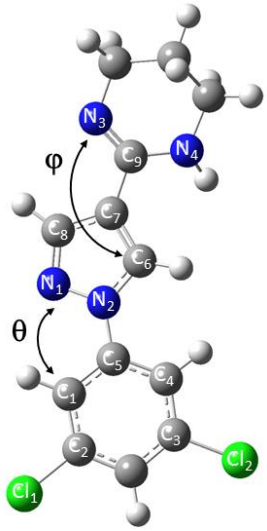

Figure 2: Optimized structure of MSP04.

Table 1: The energy values which vary according the dihedral values of the molecule MSP04.

Conformer	θ (º)	φ (º)	ΔE (kcal/mol)
948	93,50	99,17	0
36	333,50	199,17	-10,67
684	333,50	19,17	-10,70
2	353,50	199,17	-10,75
649	343,50	19,17	-10,82
1	343,50	199,17	-10,85 (global minimum)

Analyzing the results for MSP04, the minimum of energy for possible conformations was of the initial structure optimized and the maximum of energy occurred when the dihedral θ modified 110º from the local minimum and the dihedral φ modified 260º. For the most stable conformations the angles for the dihedral θ are closer to each other and for the dihedral φ they stay the same or rotate 180 degrees. This behavior suggests that the intramolecular forces between nitrogen (N_3 and N_4) and the hydrogens of the middle ring will be practically the same in both angle, increasing the molecule stability.
However, in a general analysis of the scan for this molecule, 95 conformations have energy in average close to 1 kcal/mol from global minimum. It is a too tight variation and these energy values of conformations would also be an energy minimum in solvent effect were included. A perspective for this work is optimize these others conformations to observe if the optimized structure will converge to the global minimum conformation or not. With global minimum defined, atomic charges calculation can be done, followed by docking analysis with the enzymes of topoisomerase family.

Key-words: Leishmaniasis, Conformational analysis, DFT
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