CONFORMATIONAL ANALYSIS OF A THIOSEMICARBAZONE DERIVATIVE HAVING IN VITRO ANTIMICROBIAL ACTIVITY BY MOLECULAR MECHANICS AND AB INITIO METHODS

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ABSTRACT

Compounds having indoline-thiosemicarbazone moiety within their structure display biological activity against a wide range of biological targets, being used in clinical practice as anticancer and antiviral agents. The generation of low-energy conformers is extremely important for various computational chemistry applications, such as 3D QSAR, pharmacophore searches, ligand-receptor docking, and 3D database searching. This paper presents the study of the conformational space of 1-{[5-fluoro-2-oxo-1-(piperidin-1-ylmethyl)-2,3-dihydro-1H-indol-3-ylidene]amino}-3-(prop-2-en-1-yl)thiourea by molecular mechanics and ab initio calculations using the Omega (OMEGA (version 2.4.6), OpenEye Science Software, Santa Fe, USA, 2010), respectively the Gaussian 2009 (http://www.gaussian.com/) software. 219 *Z* and *E* isomers were generated by the MMFF94s force field included in the Omega program. They were further energy minimized by Restricted Hartree-Fock (RHF/3-21G) calculations. All optimized structures were characterized as true minima by frequency calculations (Nimag = 0 for each compound). The generated conformers have been compared by the root-mean-square-deviation (RMSD) overlay procedure with the X-ray structure of the compound. In both cases (molecular mechanics and *ab initio* calculations) the *Z* conformer with the lowest RMSD fit value was different from the lowest energy conformer. Also, a chair shape for the piperidine ring and a planar indole–thiosemicarbazone moiety was found by both methods. The formation of one intramolecular hydrogen bond has been noticed in both cases. The RMSD fit values were lower in case of Omega conformers and the difference between the highest and lowest energy conformer was smaller in case of *ab initio* calculations.

Keywords: conformational analysis, ab initio, molecular mechanics, thiosemicarbazone derivative

INTRODUCTION

Compounds having indoline-thiosemicarbazone moiety within their structure display biological activity against a wide range of biological targets, being used in clinical practice as anticancer [1, 2] and antiviral agents [3, 4]. Due to their multiple and diverse applications in clinical practice, it would be interesting to investigate and discover the conformations which are responsible for the biological activity of this class of compounds. Geometry models resulted from molecular mechanics or *ab initio* calculations can provide important information about active compounds. The generation of low-energy conformers is extremely important for various computational chemistry applications, such as 3D QSAR, pharmacophore searches, ligand-receptor docking, and 3D database searching.

This paper presents the study of the conformational space of 1-{[5-fluoro-2-oxo-1-(piperidin-1-ylmethyl)-2,3-dihydro-1H-indol-3-ylidene]amino}-3-(prop-2-en-1-yl)thiourea (1) by molecular mechanics and *ab initio* calculations using the Omega [5], respectively the Gaussian 2009 [6] software. The generated conformers were compared to the X-ray structure of the title compound [7] to assess the closest conformation to the experimental structure.

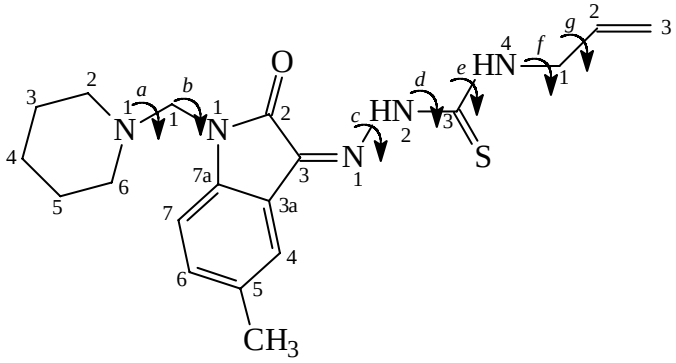


Figure 1. Structure of 1-{[5-fluoro-2-oxo-1-(piperidin-1-ylmethyl)-2,3-dihydro-1H-indol-3-ylidene]amino}-3-(prop-2-en-1-yl)thiourea

METHODS

Molecular mechanics calculations

Omega version 2.4.6 [5] was used to generate conformations of the title compound. It is a rule-based method which disassembles each molecule into fragments, whose conformations are either retrieved from a pre-generated library or constructed on-the-fly using distance constraints. These are used as starting points for a torsional search around rotatable bonds and finally the fragments are reassembled together to yield the conformations for the entire molecules. Conformers' generation was performed using the default parameters except the

maximum number of conformations to be generated that was set to 400. MMFF94s was used as force field. At the end, a library of 219 conformers was obtained.

Ab initio calculations

The conformers generated with Omega were further minimized by Restricted Hartree-Fock (RHF/3-21G) calculations performed by the Gaussian 2009 software [6]. Each optimized structure was characterized as true minima by frequency calculations (Nimag = 0 for each compound). The number of conformers obtained through RHF approach is lower than the number of conformers generated by Omega because several RHF conformers gave the same RMSD values when they have been compared to the experimental structure (Figure 2).

The RMSD procedure

The conformers generated using the above-mentioned methods, have been compared with the X-ray structure of the compound [7] by the root-mean-square-deviation (RMSD) overlay procedure, using the Vega ZZ software [8].

RESULTS AND DISCUSSION

The 219 *Z* and *E* conformers (with respect to the ylidene group attached to the indole ring) obtained by molecular mechanics, respectively *ab initio* methods were compared with the X-ray structure of the title compound. The distribution of the RMSD values computed from the superposition of the conformers generated by OMEGA and Gaussian programs with the experimental structure is displayed in Figure 2. Both methods indicated conformer with same number 9 as best pose conformer with respect to the experimental structure.

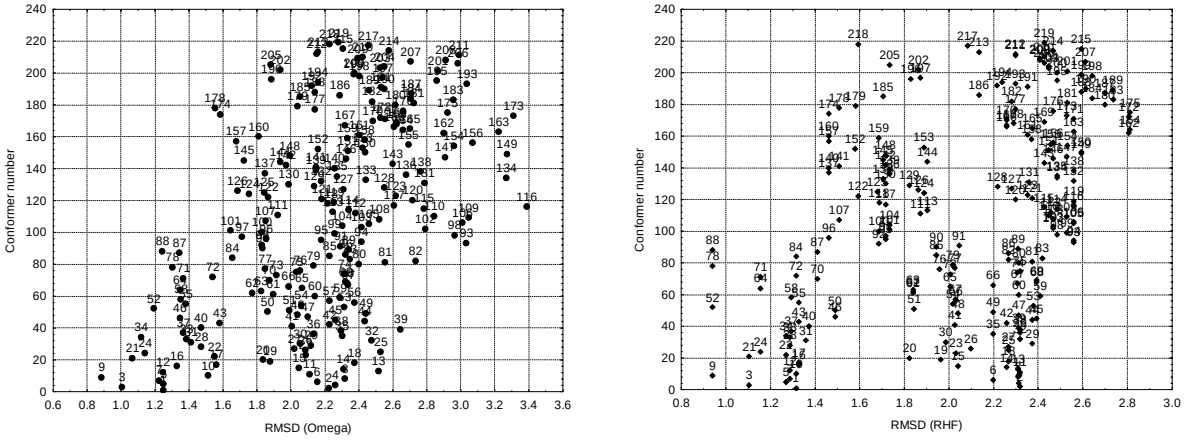


Figure 2. RMSD values (in Å) of all Omega (left) and Gaussian (right) conformers superimposed over the experimental X-ray structure

The torsion angles of X-ray structure and the best pose conformers resulted from both molecular mechanic and *ab initio* calculations are included in Table 1. Notably, the conformations presented in this table share several common features, like: one intramolecular hydrogen bond formed between one hydrazine nitrogen and a thiosemicarbazone hydrogen atom, a chair shape for the piperidine ring and a planar indole–thiosemicarbazone moiety.

Table 1. Torsion angles of the X-ray structure and of the best pose conformers of 1-{[5-fluoro-2-oxo-1-(piperidin-1-ylmethyl)-2,3-dihydro-1H-indol-3-ylidene]amino}-3-(prop-2-en-1-yl)thiourea obtained by the Omega and Gaussian programs

Structure	*a* (°)	*b* (°)	*c* (°)	*d* (°)	*e* (°)	*f* (°)	*g* (°)
Gaussian conformer	66.71	-120.84	179.75	16.58	124.9	-96.02	118.4
Omega conformer	76.3	-99.71	179.87	-0.005	-179.99	-89.59	119.04
X-ray structure	73.08	-106.2	178.2	3.86	-178.72	-99.07	137.35

The structures of the best pose conformers with respect to the X-ray structure are presented in Figure 3. Figure 4 includes these structures superimposed on the experimental one.

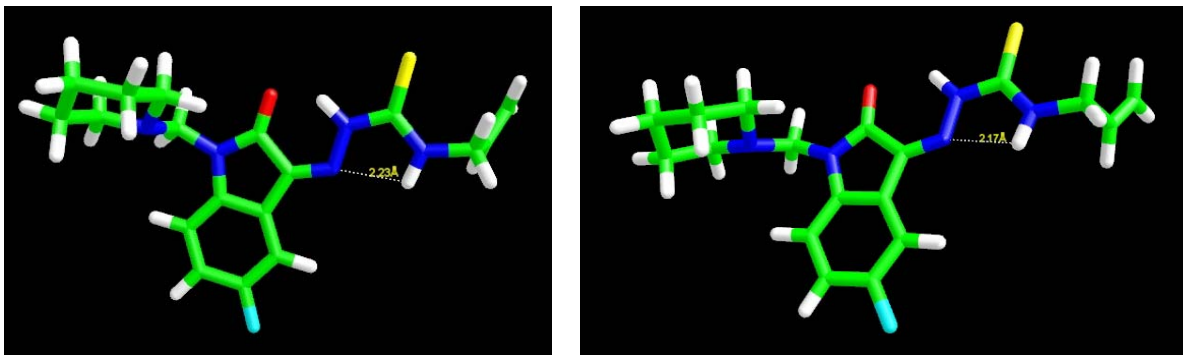
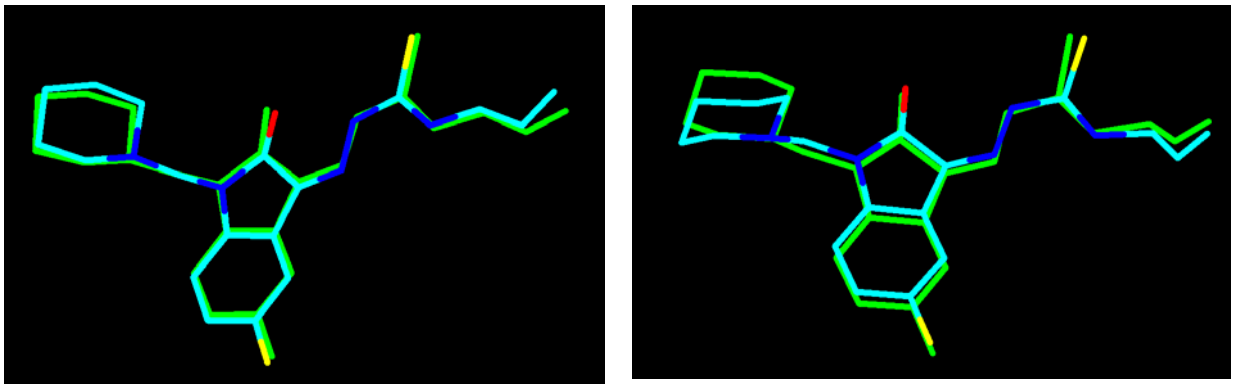


Figure 3. Best pose conformers obtained by molecular mechanics (left) and *ab initio* (right) methods

Two types (*Z* and *E*) of conformers (referred to the ylidene moiety attached in position 3 to the indole ring) were derived by both approaches. The *Z* conformer is more similar with the X-ray structure (Figure 4).



RMSD = 0.222 Å RMSD = 0.3621 Å

Figure 4. Superposition between the experimental structure (green highlighted) and the best pose conformer obtained by molecular mechanics (left) and *ab initio* (right) methods

If the allyl moiety was not considered in the superimposition procedure of the best pose conformer on the X-ray structure, better RMSD values were obtained: 0.16 Å for the Omega, respectively 0.349 Å for the Gaussian conformer. It can be concluded that both approaches gave acceptable pose conformers with respect to X-ray structure.

The range between the lowest and the best pose conformer energy is higher in the case of molecular mechanics (2.65 kcal/mol) compared to the RHF approach (0.016 kcal/mol).

The difference between the energy attributed to the lowest energy conformation and the energy of best pose conformation is very small in case of RHF approach, but the RMSD values of these conformers are very different (RMSD = 1.557 Å for the minimum energy conformer). In the case of Omega conformer, this RMSD difference was lower (RMSD = 0.712 Å for lowest energy conformation). The Omega conformer of minimum energy is closer to X-ray structure in comparison to the RHF minimum energy conformer.

The presence of the allyl group in the RHF conformers does not influence the RMSD values compared to the values obtained for the entire structure; smaller RMSD values were observed in case of Omega conformers in which the allyl group was not included. The allyl group is better parameterized with Omega software.

The Omega program proved to be effective at reproducing the X-ray conformation of the title compound, and provided an optimal balance between the speed of calculations (it ran a few minutes for all conformers in comparison to *ab initio* calculations which lasted more than 4 hours for one conformer) and performance.

CONCLUSIONS

The conformational analysis of 1-{[5-fluoro-2-oxo-1-(piperidin-1-ylmethyl)-2,3-dihydro-1H-indol-3-ylidene]amino}-3-(prop-2-en-1-yl)thiourea was performed by molecular mechanics (using the MMFF94s force field) and *ab initio* (RHF/3-21G) calculations and gave similar structural features: one intramolecular hydrogen bond between one hydrazine nitrogen and a thiosemicarbazone hydrogen atom, a chair shape for the piperidine ring, a planar indole–thiosemicarbazone moiety and *Z* conformer type of the best pose conformer with respect to the X-ray structure. The RMSD fit values were lower in case of Omega conformers and the difference between the highest and lowest conformer energy was smaller in case of *ab initio* calculations. Acceptable conformers with respect to the X-ray structure were found by both methods. The Omega software was found to be a suitable program to model the title compound, giving an optimal equilibrium between the speed of calculations and performance.

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