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

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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] and antiviral agents [2].**

- **Geometry models resulted from molecular mechanics or *ab initio* calculations can provide important information about active compounds.**

[1]. M.D. Hall, N.K. Salam, J.L. Hellawell, H.M. Fales, C.B. Kensler, J.A. Ludwig, G. Szakács, D.E. Hibbs, M.M. Gottesman, *J. Med. Chem.,* 2009, *52*, 3191-3204.

[2]. H. Zhang, L. Vrang, K. Bäckbro, P. Lind, C. Sahlberg, T. Unge, B. Öberg, *Antiviral Res.*, 1995, *28*, 331-342.

AIM:

- **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) was studied by molecular mechanics and *ab initio* calculations.**
- **The generated conformers were compared to the X-ray structure of the title compound [3] to assess the closest conformation to the experimental structure.**

[3]. The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (available at: http://www.ccdc.cam.ac.uk/)

METHODS

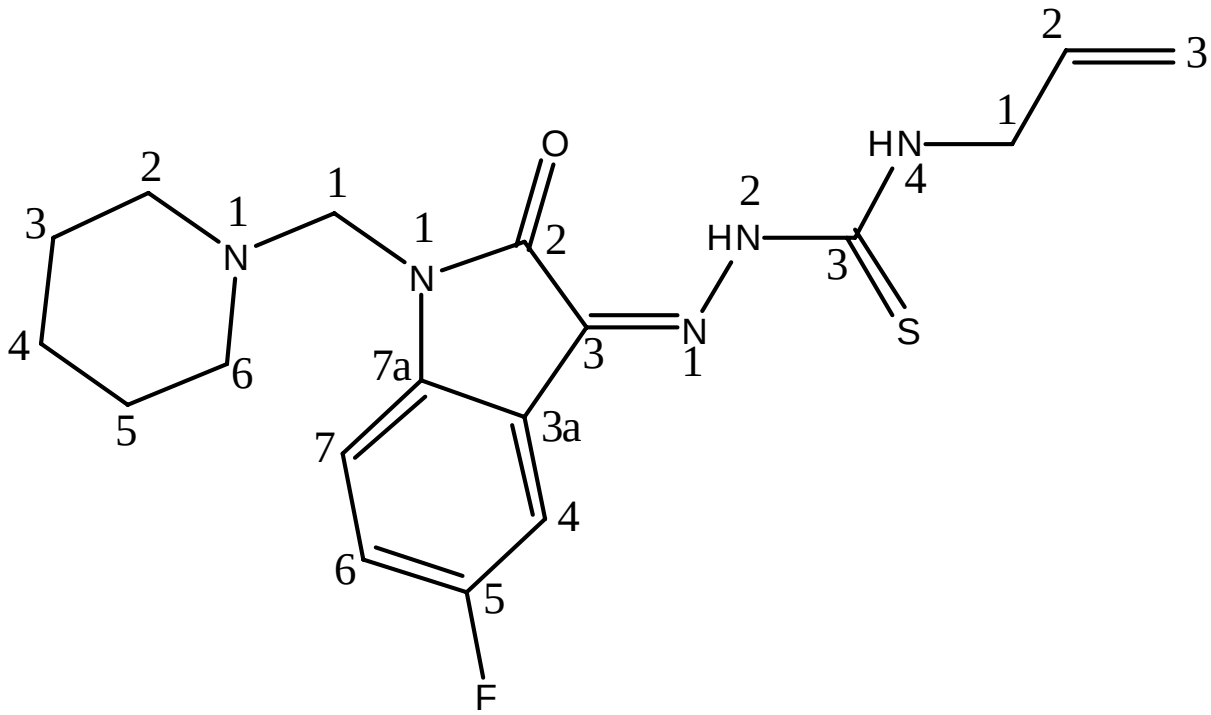


Figure 1. Structure of 1-{[5-fluoro-2-oxo-1-(piperidin-1-ylmethyl)-2,3-dihydro-1H-indol-3-ylidene]amino}-3-(prop-2-en-1-yl)thiourea

METHODS

- ***Molecular mechanics calculations***

- **Omega version 2.4.6 [4] was used to generate conformations of the title compound.**
- **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.**
- **A library of 219 conformers was obtained.**

[4]. OMEGA (version 2.4.6), OpenEye Science Software, Santa Fe, USA, 2010)

METHODS

- ***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 [5]**
- **Each optimized structure was characterized as true minima by frequency calculations (Nimag = 0 for each compound).**

[5]. Gaussian 2009 , http://www.gaussian.com/

METHODS

- ***The RMSD procedure***

- **The conformers generated using the above-mentioned methods, have been compared with the X-ray structure of the compound [3] by the root-mean-square-deviation (RMSD) overlay procedure, using the Vega ZZ software [6].**

[6]. Vega ZZ version 2.4.0.25, Dipartimento di Scienze Farmaceutiche "Pietro Pratesi ", the University of Milan, Italy, http://www.vegazz.net/

RESULTS AND DISCUSSION

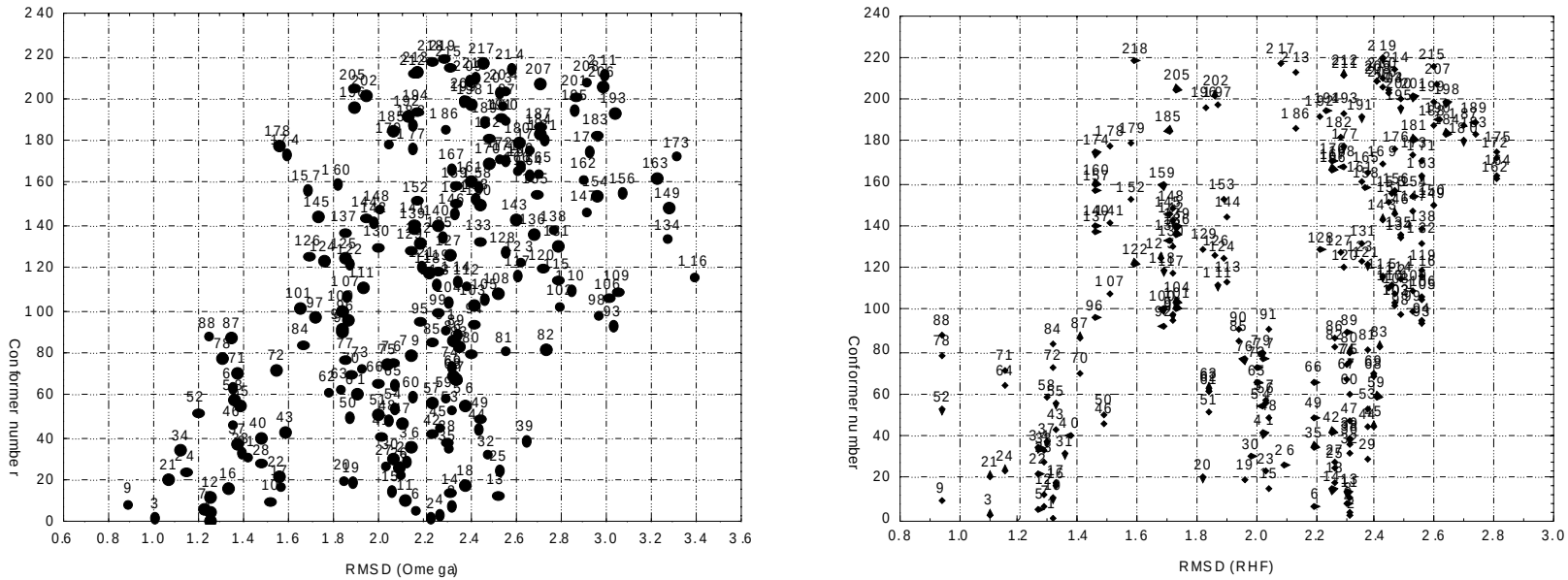


Figure 2. RMSD values (in Å) of all Omega (left) and Gaussian (right) conformers superimposed over the experimental X-ray structure

- **Both methods indicated conformer with same number 9 as best pose conformer with respect to the experimental structure.**

RESULTS AND DISCUSSION

- **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**
- **The best pose conformers 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.**

RESULTS AND DISCUSSION

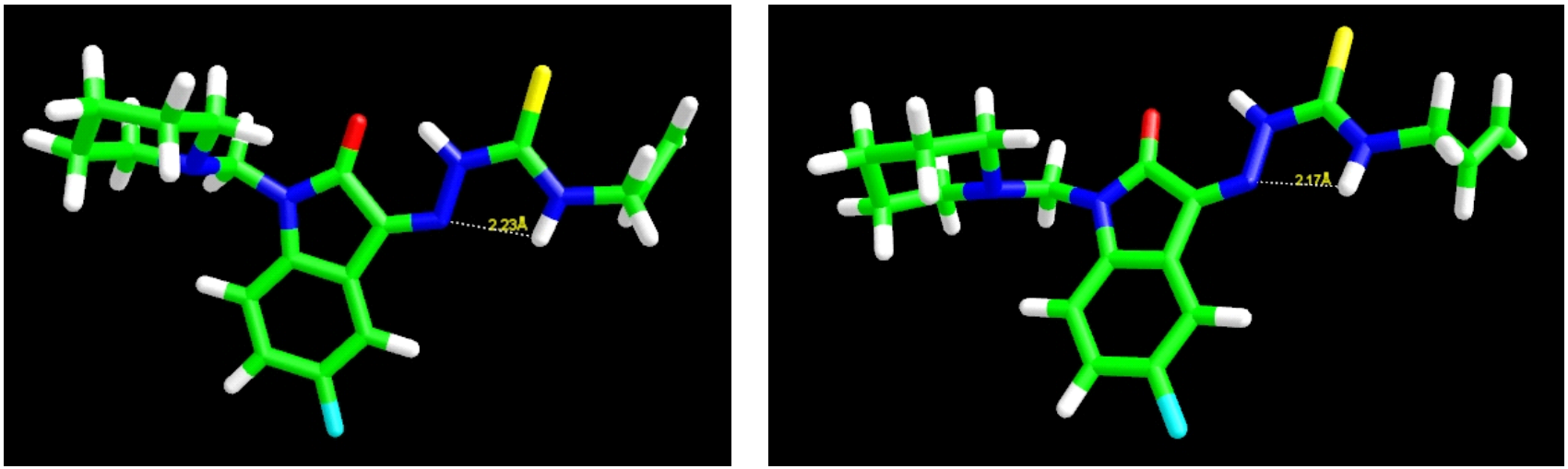
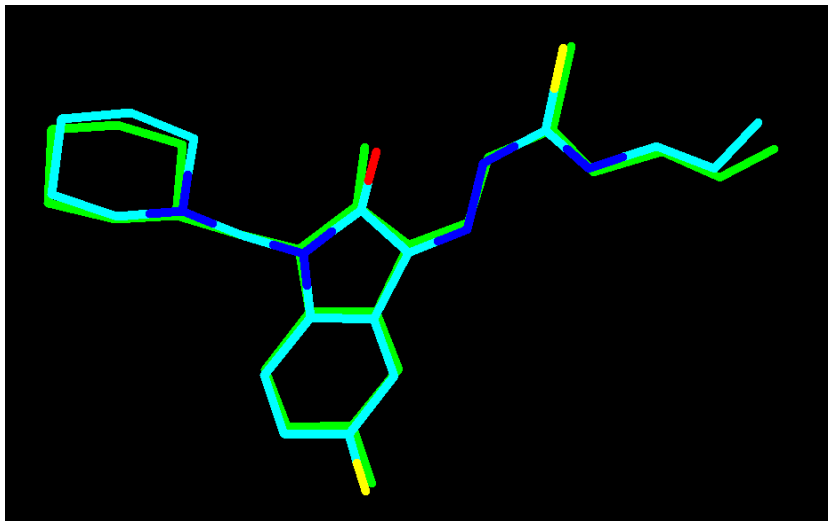
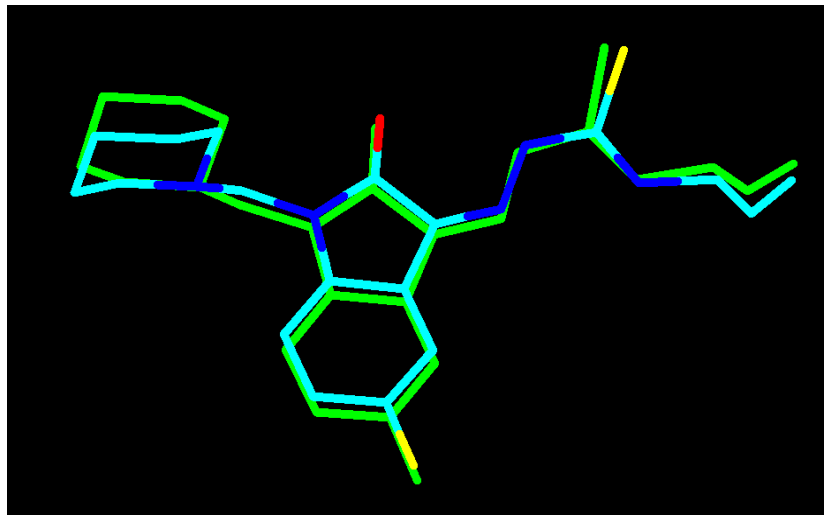


Figure 3. Best pose conformers obtained by molecular mechanics (left) and *ab initio* (right) methods

RESULTS AND DISCUSSION



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

RESULTS AND DISCUSSION

- **Two types of *Z* and *E* 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.**
- **Both molecular mechanics and *ab initio* methods gave acceptable pose conformers with respect to the X-ray structure.**
- **The Omega conformer of minimum energy is closer to X-ray structure in comparison to the RHF minimum energy conformer.**

CONCLUSIONS

- **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 were derived for the best pose conformer with respect to the X-ray structure by molecular mechanics and *ab initio* calculations.**
- **Acceptable conformers compared to the X-ray structure were found by both methods.**
- **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.**
- **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.**

ACKNOWLEDGEMENTS

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