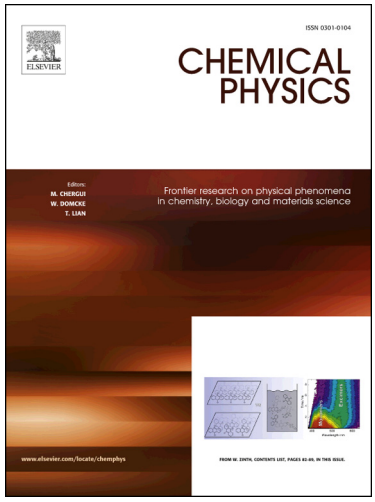

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M. Saeed Mirzaei, Avat Arman Taherpour

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Tautomeric Preferences of the *cis* and *trans* Isomers of Axitinib

M. Saeed Mirzaei[a] *and Avat Arman Taherpour**[a,b]

[a]Faculty of Chemistry, Razi University, P.O. Box: 67149-67346, Kermanshah, Iran.
[b]Medical Biology Research Centre, Kermanshah University of Medical Sciences, Kermanshah, Iran.
E-mail: avatarman.taherpour@gmail.com, Fax: +98 83 34274559; Tel: +98 83 34274559.

Abstract: The tautomeric preferences of axitinib, a potent anticancer drug, as tyrosin kinase inhibitor have been investigated using quantum chemical calculations and docking methods. The energy differences between the two tautomers of *trans*-isomer are around 4 and 3 kcal mol^{-1} in *vacuo* and water, respectively, and for its *cis*-isomer (major photochemical isomerization product) this equilibrium reversed completely in favour of the second tautomer (not considered previously), which is about 7-8 kcal mol^{-1} more stable in both gas and aqueous media. The results indicate a very high activation energy for proton exchange for both [1,2] and [1,5] H-shift (around 50 kcal mol^{-1}) in the gas phase, but inclusion of protic solvents (e.g. water) decrease this barrier to around 14 and 35 kcal mol^{-1} for the both hydrogen shift processes, respectively. In order to have better insight about the electronic structure of axitinib tautomers, the NBO, HOMO- LUMO, NICS and molecular electrostatic potential surfaces (MESP) calculations have been carried out. Docking investigations on the two more stable tautomers revealed that binding of the trans isomer of tautomer I to the active site of the receptor is the most favourable in the terms of energy and structure. This more stability could be attributed to the more hydrogen bonding of this tautomer with the protein residues in comparison to the second tautomer.

Keywords: Axitinib, Conformer, DFT, Hydration Effects, Isomer, Tautomer, Docking, Ligand, Receptor

1. Introduction

Tautomerism, a process with great importance in the field of organic and bioorganic chemistry, has been the subject of numerous studies by theoretical chemists.[1] The improved computational methods and their success in predicting and analysing the structure and properties of chemical and biological systems, have had the key role in expanding our knowledge of the molecules with different tautomeric structure. Axitinib, anticancer agent, as a tyrosin kinase inhibitor receives attention due to its pharmaceutical potential against several types of cancers including soft tissue sarcoma and thyroid cancer,[2-7] but it is mainly prescribing for patients who are suffering from renal cell carcinoma (advanced kidney cancer). This feature has been approved recently for treating this type of cancer. As a drug, axitinib, occupies the TK active site, leading to a decrease in activity of enzyme which in turn results in inhibition of protein tyrosine phosphorylation and Angiogenesis.[8]

Since the axitinib structure has several single bonds, it is conformationally flexible. Thus, as Pemovska and co-workers reported, this conformational flexibility has significant effect on drug-receptor interactions**.** Their study (Pemovska et al) divulged that the conformational changes of axitinib would lead to distinct binding interaction with the receptor (e.g. ABL1 instead of VEGFR2). This produce different results for patients with chronic myeloid leukemia.[1] Furthermore, about 71 different polymorphs of axitinib were identified by Campeta and co-workers, which this great number were attributed to the wide variety of stable conformers.[9] Five of them indicated the non-solvated structures and two of them show the hydrated forms.[10] Owing to this phenomenon, some computational works were performed to elucidate and predict the crystal structure of axitinib.[11,13]