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Intramolecular hydrogen bonds of two Teriflunomide analogues

Reihaneh Heidarian[1], Mansoureh Zahedi-Tabrizi[2,*]
[1] Department of Chemistry,Faculty of Physics & Chemistry , University of Alzahra , Tehran, Iran
Email address: r.heidarian@student.alzahra.ac.ir, telephone number: 09354039336
[2] Department of Chemistry,Faculty of Physics & Chemistry , University of Alzahra , Tehran, Iran
*corresponding author: zahedi@alzahra.ac.ir

ABSTRACT

*Leflunomide [N-{(4-trifluoromethyl)phenyl}-5-methylisoxazole-4-carboxamide] is one of the anti-inflammatory, anticancer, and antirheumatic drug.This therapeutic compound is transformed into its active metabolite, Teriflunomide [2-cyano-3-oxo-N-{(4-trifluoromethyl)phenyl}-2-butenamide] through isoxazole ring opening of Leflunomide. This metabolite is responsible for the biological activity of Leflunomide. In the present study, the structure and intramolecular hydrogen bonds of two active metabolites of leflunomide were inspected by density functional theory calculation at B3LYP/6-311++G** level of theory. The structure of the mentioned compounds was reported by X-ray crystallographic data in the literature. Topological parameters including Electronic charge density (ρ) and its Laplacian ($\nabla^2\rho$) at critical points of hydrogen bonds are computed for estimating the nature and the strength of intramolecular hydrogen bonds by QTAIM analysis. The hydrogen bond strength, natural charge distribution, steric effects, and electron delocalization were studied using NBO analysis. H-NMR chemical shifts of the hydrogen atoms in the hydrogen bond bridges were computed by GIAO method at the mentioned level of theory.*

Keywords: Leflunomide, Teriflunomide, Hydrogen Bond, DFT, H-NMR, AIM, NBO

1. INTRODUCTION

N-(3-chlorophenyl)-2-cyano-3-oxobutanamide (3-Cl-TFM) and N-(5-fluorophenyl) -2- cyano-3-oxobutanamide (5-F-TFM) are two active metabolite analogues of leflunomide. Leflunomide is a disease-modifying antirheumatic drug with anti-inflammatory and immunosuppressive activity used for the treatment of psoriatic and rheumatoid arthritis. It undergoes rapid metabolization to teriflunomide, a metabolite that plays a key role in pharmacological aspects of leflunomide [1] to [5]. X-ray crystallographic data of five active metabolite leflunomide has been reported by Ghosh et al. [6]. Sharma et al. [7] investigated the metabolic transformation of leflunomide to its active metabolite through isoxazole ring opening in vitro using steady state and time domain fluorescence spectroscopy and density functional theory (DFT). Conversion of leflunomide to its active metabolite can be both enzymatic and no enzymatic.The interaction of teriflunomide with dihydroorotate dehydrogenase enzyme has been the subject of many theoretical an experimental investigations [8] to [10].

The geometrical parameters, conformational analysis and intramolecular proton transfer of active metabolites of leflunomide using DFT calculations were performed by Panek et al.[11] Their conformational study displayed the intramolecular hydrogen bond stabilizes planar arrangement of the titled compounds. They showed that the CN and amide groups of these compounds are primary acceptors for external interactions. In view of the fact that the phenyl ring substituents play an important role in the intramolecular hydrogen bond strength, in the present study the structure and intramolecular hydrogen bonds of the titled active metabolite analogues of leflunomide were compared using density functional theory calculations. Considering the successful use of the quantum theory of atoms in molecules analysis (QTAIM) in investigating the strength of hydrogen bonds, we attempt to perform the study by AIM method, which will provide some deeper insights into the properties of the mentioned compounds. In order to get a clear understanding of the charge distributions and steric effects, we also performed the natural bond orbital (NBO) analysis.