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Theoretical Raman and IR spectra of tegafur and comparison of molecular electrostatic potential surfaces, polarizability and hyerpolarizability of tegafur with 5-fluoro-uracil by density functional theory

Onkar Prasad*, Leena Sinha, and Naveen Kumar

Department of Physics, University of Lucknow, Lucknow, Pin Code - 226007, India

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Abstract. The 5-fluoro-1-(tetrahydrofuran-2-yl) pyrimidine-2,4 (1H,3H)-dione, also known as tegafur, is an important component of Tegafur-uracil (UFUR), a chemotherapy drug used in the treatment of cancer. The equilibrium geometries of "Tegafur" and 5-fluoro-uracil (5-FU) have been determined and analyzed at DFT level employing the basis set 6-311+G(d, p). The molecular electrostatic potential surface which displays the activity centres of a molecule, has been used along with frontier orbital energy gap, electric moments, first static hyperpolarizability, to interpret the better selectivity of prodrug tegafur over the drug 5-FU. The harmonic frequencies of prodrug tegafur have also been calculated to understand its complete vibrational dynamics. In general, a good agreement between experimental and calculated normal modes of vibrations has been observed.

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Key words: prodrug, polarizability, hyperpolarizability, frontier orbital energy gap, molecular electrostatic potential surface.

1 Introduction

The use of a prodrug strategy increases the selectivity and thus results in improved bioavailability of the drug for its intended target. In case of chemotherapy treatments, the reduction of adverse effects is always of paramount importance. The prodrug which is used to target the cancer cell has a low cytotoxicity, prior to its activation into cytotoxic form in the cell and hence there is a markedly lower chance of it "attacking" the healthy

*Corresponding author. *Email address:* prasad_onkar@lkouniv.ac.in (O. Prasad)

non-cancerous cells and thus reducing the side-effects associated with the chemotherapeutic agents. Tegafur, a prodrug and chemically known as 5-fluoro-1-(tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione, is an important component of 'Tegafur-uracil' (UFUR), a chemotherapy drug used in the treatment of cancer, primarily bowel cancer. UFUR is a first generation Dihydro-Pyrimidine-Dehydrogenase (DPD) inhibitory Flouropyrimidine drug. UFUR is an oral agent which combines uracil, a competitive inhibitor of DPD, with the 5-FU prodrug tegafur in a 4:1 molar ratio. Excess uracil competes with 5-FU for DPD, thus inhibiting 5-FU catabolism. The tegafur is taken up by the cancer cells and breaks down into 5-FU, a substance that kills tumor cells. The uracil causes higher amounts of 5-FU to stay inside the cells and kill them [1–4].

The present communication deals with the investigation of the structural, electronic and vibrational properties of tegafur due to its biological and medical importance in field of cancer treatment. The structure and harmonic frequencies have been determined and analyzed at DFT level employing the basis set 6-311+G(d,p). The optimized geometry of tegafur and 5-FU and their molecular properties such as equilibrium energy, frontier orbital energy gap, molecular electrostatic potential energy map, dipole moment, polarizability, first static hyperpolarizability have also been used to understand the properties and activity of the drug and prodrug. The normal mode analysis has also been carried out for better understanding of the vibrational dynamics of the molecule under investigation.

2 Computational details

Geometry optimization is one of the most important steps in the theoretical calculations. The X-ray diffraction data of the tegafur monohydrate and the drug 5-FU, obtained from Cambridge Crystallographic Data Center (CCDC) were used to generate the initial coordinates of the prodrug tegafur and drug 5-FU to optimize the structures. The Becke's three parameter hybrid exchange functionals [5] with Lee-Yang-Parr correlation functionals (B3LYP) [6,7] of the density functional theory [8] and 6-311+G(d, p) basis set were chosen. All the calculations were performed using the Gaussian 03 program [9]. The

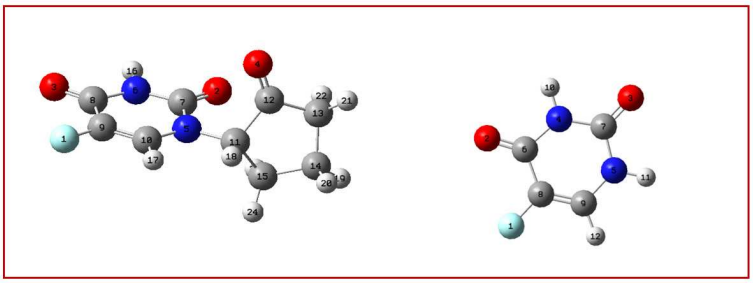

Figure 1: Optimized structure of Tegafur and 5-fluoro-uracil at B3LYP/6-311+G (d,p).