



# Spectroscopic and electronic structure calculation of a potential chemotherapeutic agent 5-propyl-6-(*p*-tolylsulfanyl)pyrimidine-2,4(1*H*,3*H*)-dione using first principles



Monirah A. Al-Alshaikh<sup>a</sup>, Omar A. Al-Deeb<sup>b</sup>, Nourah Z. Alzoman<sup>b</sup>, Ali A. El-Emam<sup>b</sup>, Ruchi Srivastava<sup>c</sup>, Alok K. Sachan<sup>c</sup>, Onkar Prasad<sup>c</sup>, Leena Sinha<sup>c,\*</sup>

<sup>a</sup> Department of Chemistry, College of Sciences, King Saud University, Riyadh 11451, Saudi Arabia

<sup>b</sup> Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

<sup>c</sup> Department of Physics, University of Lucknow, 226007 Lucknow, India

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## ABSTRACT

Quantum chemical calculations of energy, geometrical structure and vibrational wavenumbers of a potential chemotherapeutic agent namely, 5-propyl-6-(*p*-tolylsulfanyl)pyrimidine-2,4(1*H*,3*H*)-dione were carried out, using DFT method. Comprehensive interpretation of the experimental FT-IR and FT-Raman spectra of the compound under study is based on potential energy distribution. The difference between the observed and scaled wavenumbers of most of the normal modes is very small with B3LYP/6-311 + +G(d,p) method. The UV–Vis spectrum of the compound was recorded and the electronic properties, such as frontier orbitals and band gap energies were calculated by the TD-DFT approach. The values of the electric dipole moment, polarizability and first static hyperpolarizability of the title compound have also been investigated. NBO analysis has been performed to explain the charge transfer within the molecule along with the calculation of different thermo-dynamical properties.

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## 1. Introduction

Due to multifarious pharmacological activities, pyrimidine and its related derivatives take up a key position in the field of chemotherapy. The chemotherapeutic efficacy of pyrimidine derivatives is related to their ability to inhibit vital enzymes responsible for DNA biosynthesis, such as dihydrofolate reductase, thymidylate synthetase, thymidine phosphorylase and reverse transcriptase. A broad set of pyrimidine drugs possesses a variety of curative properties. Several pyrimidine-based derivatives have been developed as anticancer agents [1–4], and antiviral agents against HIV [5–9], HBV [10,11], HCV [12], and HSV [13,14]. In addition, several pyrimidine derivatives have long been recognized as potent bactericidal [15–19], fungicidal [20,21] and antiprotozoal agents [22–25]. 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) and its related derivatives [26–30] were discovered as potent and selectively active agents against HIV-1 infections. In perpetuation to our pursuit in the structural and

pharmacological properties of pyrimidine and uracil derivatives [8,9,18,31–35], the title compound was synthesized as the more lipophilic 5-propyl HEPT analog for evaluation as potential chemotherapeutic agent [36], which is expected to endow better pharmacokinetic properties. In the present study, we present an in-depth investigation on the molecular structure, electronic properties and vibrational spectra of the title compound (Molecular formula C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S), with the aspiration that the results of present study may be decisive in the prognosis of its mechanism of biological activity.

The experimental FT-IR and FT-Raman spectra of the title compound have been recorded and the explicit assignment of spectral peaks has been done using normal coordinate analysis. The inversion dimer connected through pairs of strong N–H...O hydrogen bonds has been studied by DFT/B3LYP at the 6-31 + G(d,p) level. The UV–Vis spectrum of the title compound was recorded and electronic properties, such as frontier orbitals and band gap energies were calculated by the TD-DFT approach. The study also comprises of calculation of the non-linear optical parameters, 2D molecular electrostatic potential (MESP) contour map and 3D MESP surface map accompanied by DOS and PDOS analysis

\* Corresponding author.

E-mail address: [sinhaleena27@gmail.com](mailto:sinhaleena27@gmail.com) (L. Sinha).

of molecular orbitals. The Gauge-Including Atomic Orbital method has been used to calculate  $^1\text{H}$  nuclear magnetic resonance (NMR) chemical shifts of the compound and comparison has been made with observed experimental  $^1\text{H}$  NMR shifts. NBO analysis has been performed to explain the charge transfer within the molecule. Calculations of different thermo-dynamical properties have also been done.

## 2. Experimental details

The pure single colorless crystals of the title compound were synthesized in 72% yield via the reaction of 6-chloro-5-propyluracil with p-thiocresol in the presence of potassium hydroxide, and the structure was well established [36]. Perkin Elmer version 10.03.06 spectrophotometer was used for recording the FT-IR spectrum in the region  $4000\text{--}400\text{ cm}^{-1}$  using KBr pellet. The 532 nm laser light was used as the exciting wavelength for recording FT-Raman spectrum in the region  $4000\text{--}50\text{ cm}^{-1}$  using Planar RAME spectrometer. The UV absorption spectrum of the title compound was examined in the range  $500\text{--}200\text{ nm}$  using UV-VIS Varian Cary 50 Bio spectrophotometer. The UV pattern is taken from a  $10^{-5}\text{ M}$  solution, dissolved in methanol. All the experimental spectra were recorded at the Indian Institute of Technology, Kanpur, India.

## 3. Computational details

The molecular geometry was built from the X-ray diffraction data without any constraints [36]. The structures of monomer and dimer were optimized using gradient-corrected DFT with Becke 3 exchange [37] and Lee–Yang–Parr correlation functions (B3LYP) [38] with 6-311 ++ G(d,p) basis set. The vibrational wavenumbers under harmonic approximation were calculated at the same level of theory and basis set. The nonexistence of negative vibrational wavenumber in the Gaussian output shows the stability of the structure. The final optimized geometry for the monomer and dimer of the title compound, along with the numbering scheme of the atoms are shown in Fig. 1. The Counterpoise (CP) correction method of Boys and Bernardi was used, to shun the artificially lowered energy of the dimer as well as overblown strength of the hydrogen bonds due to the basis set superposition error (BSSE) [39]. The dipole moment  $\mu$ , mean polarizability  $\alpha$  and first static hyperpolarizability ( $\beta$ ) have been calculated using density functional theory method and Buckingham's definitions [40,41].

The  $\alpha$  and  $\beta$  values of Gaussian output are in atomic units (a.u.) so they have been converted into electrostatic units (esu) ( $\alpha$ ; 1 a.u. =  $0.1482 \times 10^{-24}$  esu,  $\beta$ ; 1 a.u. =  $8.6393 \times 10^{-33}$  esu.). The variation of thermodynamical properties such as heat capacity, entropy and enthalpy change with temperature have also been reckoned on the basis of vibrational analysis. Their correlation equations with temperature were fitted by quadratic formulas.

The  $^1\text{H}$  chemical shifts are calculated with the gauge-included atomic orbital (GIAO) approach [42,43] by applying the B3LYP/6-11 + G(d,p) method and compared with the experimental NMR spectrum [36]. The electronic properties such as HOMO and LUMO energies were determined by the TD-DFT approach. For analysis of molecular orbitals, density of state plots such as TDOS, PDOS have been drawn and analyzed. The 3D MESP and 2D contour map of title compound were drawn to access the most electron rich and electron deficient regions in the title compound. The theoretical UV–Vis spectrum has been computed by the TD-DFT method with 6-311++G(d,p) basis set for the gas phase and the solvent effect also has been taken into consideration by implementing IEFPCM model at the same level of theory. The natural bonding orbital (NBO) calculations [44] were accomplished using Gaussian 09 [45] package at the same level in order to figure out various second

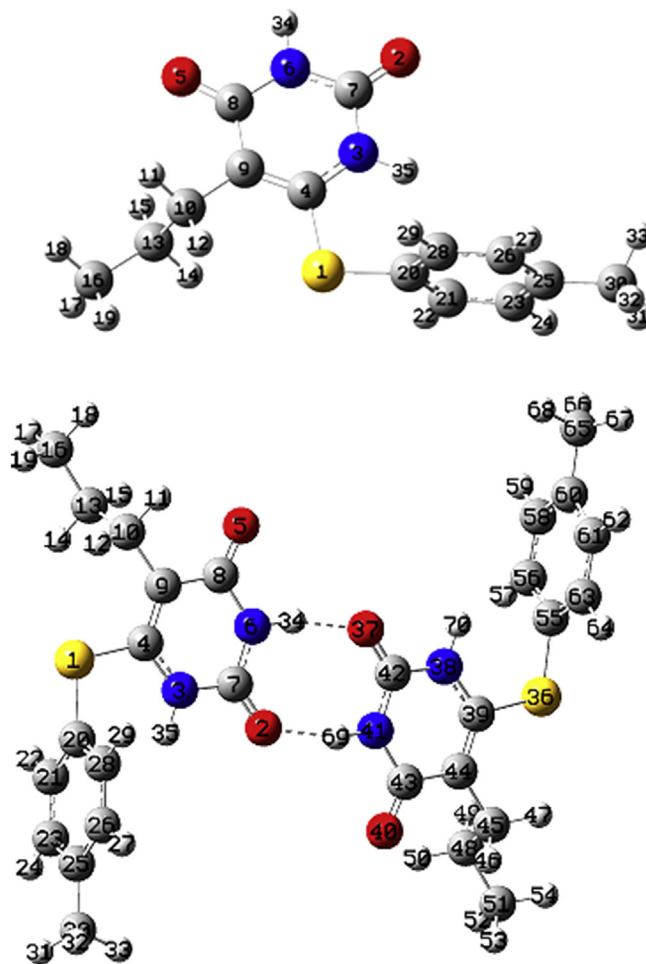


Fig. 1. Monomer and hydrogen bonded dimer of  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ .

order interactions between the filled orbitals of one subsystem and vacant orbitals of another subsystem, which enumerate the intra-molecular delocalization or hyper conjugation. The interactions result in a loss of occupancy from the localized NBO of the idealized Lewis structure (occupancy = 2) into an empty non-Lewis orbital. For each donor ( $i$ ) and acceptor ( $j$ ), the stabilization energy  $E^{(2)}$  associated with the delocalization  $i\text{--}j$  is estimated as

$$E^{(2)} = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\varepsilon_j - \varepsilon_i}$$

where  $q_i$  is the donor orbital occupancy,  $\varepsilon_i$  and  $\varepsilon_j$  are diagonal elements and  $F(i,j)$  is the off diagonal NBO Fock matrix element. The larger the  $E^{(2)}$  value the more intensive is the interaction between electron donors and acceptors i.e., the more donation tendency from electron donors to electron acceptor and greater the extent of conjugation of the whole system [46]. The NBO analysis allows us to analyze the charge-transfers and intra-molecular bond paths. The vibrational wavenumber assignments were carried out by combining the animation option of the Gauss view 5.08 program [47,48] and MOLVIB program (version V7.0-G77; written by T. Sundius) [49–51]. An empirical uniform scaling factor of 0.983 up to  $1700\text{ cm}^{-1}$  and 0.958 for greater than  $1700\text{ cm}^{-1}$  [52,53] was used to offset the systematic errors caused by the basis set incompleteness and vibrational anharmonicity [54] and, in general, a good agreement of the calculated modes with the experimental

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