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Spectral and structural studies of the anti-cancer drug Flutamide by density functional theoretical method

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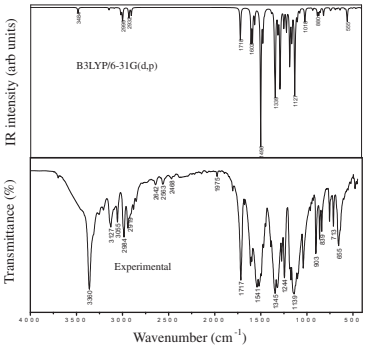
HIGHLIGHTS

- The FTIR and FT-Raman spectra of Flutamide were recorded.
- The vibrational frequencies were calculated by DFT method and compared.
- UV–Vis spectra were recorded and compared with calculated ones.
- NMR and NBO analysis were also carried out.

GRAPHICAL ABSTRACT



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ABSTRACT

A comprehensive screening of the more recent DFT theoretical approach to structural analysis is presented in this section of theoretical structural analysis. The chemical name of 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]-propanamide is usually called as Flutamide (In the present study it is abbreviated as FLT) and is an important and efficacious drug in the treatment of anti-cancer resistant. The molecular geometry, vibrational spectra, electronic and NMR spectral interpretation of Flutamide have been studied with the aid of density functional theory method (DFT). The vibrational assignments of the normal modes were performed on the basis of the PED calculations using the VEDA 4 program. Comparison of computational results with X-ray diffraction results of Flutamide allowed the evaluation of structure predictions and confirmed B3LYP/6-31G(d,p) as accurate for structure determination. Application of scaling factors for IR and Raman frequency predictions showed good agreement with experimental values. This is supported the assignment of the major contributors of the vibration modes of the title compound. Stability of the molecule arising from hyperconjugative interactions leading to its bioactivity, charge delocalization have been analyzed using natural bond orbital (NBO) analysis. NMR chemical shifts of the molecule were calculated using the gauge independent atomic orbital (GIAO) method. The comparison of measured FTIR, FT-Raman, and UV–Visible data to calculated values allowed assignment of major spectral features of the title molecule. Besides, Frontier molecular orbital analyze was also investigated using theoretical calculations.

Introduction

Flutamide (FLT) is an unusual example of an antiandrogenic drug lacking a steroidal structure. Flutamide, a widely used nonsteroidal antiandrogen drug for the treatment of prostate cancer, has been associated with rare incidences of hepatotoxicity in patients. It is believed that bioactivation of FLT and subsequent covalent binding to cellular proteins is responsible for its toxicity. It is used increasingly as part of total androgen ablation therapy and in neoadjuvant treatment before radical prostatectomy [1]. Although very useful and almost indispensable, it can produce

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adverse biological effects such as clinical photosensitization which has been recognized to result from FLT [2]. FLT can cross the placental barrier and thus can have an impact on fetal development [3]. The capabilities of DFT method to reproduce the structural features of benzamides, particularly in relation with intramolecular and intermolecular C–H----O hydrogen bonds, were also evaluated.

Crystal and molecular structure analysis of FLT and then bifurcated helicoidal C–H...O hydrogen bonds have been analyzed by Cense et al. [4]. Vargas et al. [5] have investigated photochemistry and phototoxicity studies of Flutamide, a phototoxic anti-cancer drug. Payen et al. [6] studied synthesis and biological activity of ferrocenyl derivatives of the non-steroidal antiandrogens Flutamide and bicalutamide. A comparison between two doses of Flutamide (250 mg/d and 500 mg/d) in the treatment of hirsutism have analyzed by Muderris et al. [7]. The detailed study and an electrochemical evidence of free radicals formation from Flutamide and its reactivity with endo/xenobiotics of pharmacological relevance investigated by Vergara et al. [8].

In the present study, we have used the density functional theory approach which was preferred in order to include exchange correlation functions and to obtain an accurate electron density from the Kohn–Sham equations [9,10]. FTIR and FT-Raman spectroscopy have been established as a useful technique to obtain information about the influence of structural analysis of certain molecule in the solid-state. The experimental wave numbers of both FTIR and FT-Raman were reproduced fairly well by DFT calculations at the B3LYP/6-31G(d,p) level. In addition to the theoretical vibrational spectrum, density functional methods have also been used to calculate the molecular geometry, the atomic charges and some other molecular properties. Furthermore, the combination of DFT calculations of chemical shifts and harmonic vibrations with nuclear magnetic resonance (NMR), FTIR and FT-Raman experimental parameters, have become an accepted technique to gather insight into the molecular structure.

Experimental details

The compound Flutamide (solid state, light yellow crystalline powder) was obtained from Sigma–Aldrich Chemical Company with a stated purity 99% and used as such without any further purification. The FTIR spectrum of the sample was carried out between 400 and 4000 cm^{-1} on a JASCO FT-IR-6300, spectrometer. The FT-Raman spectrum of the sample recorded using 1064 nm line of an Nd–YAG laser as the excitation wavelength in the region of 50–3500 cm^{-1} on a Bruker RFS 100/S FT-Raman spectrometer. The detector is a liquid nitrogen cooled Ge detector. Five hundred scans were accumulated at 1 cm^{-1} resolution using a laser power of 100 mW. The UV absorption spectrum of FLT molecule dissolved in Methanol and Ethanol is examined in the range 200–800 nm using Shimadzu UV-1800 PC, UV–Vis recording spectrometer. Data were analyzed by UV PC personal spectroscopy software, version 3.91. The experimental FT-IR and FT-Raman spectra along with the theoretically simulated IR and Raman spectra using DFT/B3LYP/6-31G(d,p) level of calculations are shown in Figs. 1 and 2. The spectral measurements were carried out at Indian Institute of Technology, Chennai, India.

Computational details

Quantum chemical calculations were used for FLT to carry out the optimized geometry and vibrational wavenumbers with 03 version of the Gaussian program [11]. The vibrational modes were assigned by means of visual inspection using the Gauss View

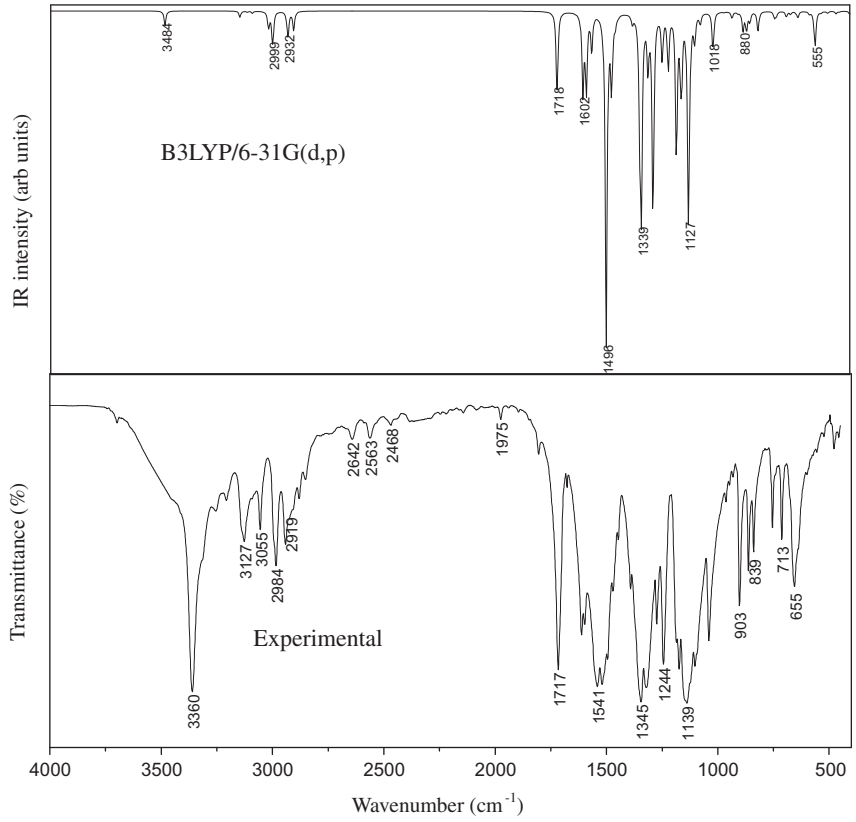

Fig. 1. Comparison of experimental and theoretical (B3LYP/6-31G(d,p)) FT-IR spectra for FLT.