Spectroscopic and electronic structure calculation of a potential antibacterial agent incorporating pyrido-dipyrimidine-dione moiety using first principles

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ARTICLE INFO

ABSTRACT

Quantum chemical calculations of geometrical structure, energy and vibrational wavenumbers of a novel functionalized pyrido-pyrimidine compound (a prospective antibacterial agent), chemically known as 6-Methyl,13,14,15-Trihydro-14-(4-Nitrophenyl)pyrido[1,2-a:1′,2′-a′] pyrido[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione ($C_{24}H_{16}N_6O_4$), were carried out, using B3LYP/6311++G(d,p) method. Comprehensive interpretation of the infrared and Raman spectra of the compound under study is based on potential energy distribution. A good coherence between experimental and theoretical wavenumbers shows the preciseness of the assignments. NLO properties like the dipole moment, polarizability, first static hyperpolarizability and molecular electrostatic potential surface have been calculated to get a better cognizance of the properties of the title compound. Molecular docking results reveal that the title compound exhibit inhibitory activity against *Staphylococcus aureus*.

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1. Introduction

Pyrido [1, 2-a] pyrimidines are prominent nitrogen-bridged heterocyclic compounds and have occupied an important place not only in organic chemistry but also in medicinal chemistry. These compounds are known to possess numerous pharmacological activities, due to which significant attention has been focused on this class of heterocyclic compounds. Various biological activities possessed by Pyrido[1,2-a] pyrimidines are antitumor [1] antiallergic [2], antifolate, tyrosine kinase inhibitor, antimicrobial [3], calcium channel antagonist [4], antibacterial [5], anti-inflammatory, analgesic [6], antihypertensive [7], antileishmanial [8], tuberculostatic [9], anticonvulsant [10], diuretic potassium sparing [11] and antiaggressive activities [12].

A series of novel pyridopyrimidine derivatives was synthesized by one-pot four-component cyclocondensation of 2-Hydroxy-4-H-pyrido[1,2-a]pyrimidin-4-one, substituted aromatic aldehydes and ammonium acetate or methyl amine in dioxane as a solvent. The synthesized compounds were bio evaluated for their possible antimicrobial activity against a panel of gram-positive and gram-negative bacterial strains and fungal strains by known methods. Among the synthesized compounds, 6-Methyl,13,14,15-Trihydro-14-(4-Nitrophenyl)pyrido[1,2-a:1′,2′-a′] pyrido[2″,3″-d:6″,5″-d′] dipyrimidine-13,15-dione ($C_{24}H_{16}N_6O_4$) possesses pronounced antibacterial activity against *Staphyllococcus aureus* MTCC 96. In the present study, a comprehensive investigation on the molecular structure, electronic properties and vibrational spectra of this novel antibacterial compound (Molecular formula ($C_{24}N_6O_4H_{16}$) has been reported. The Fourier-transform infrared (FT-IR) and FT-Raman spectra of the title compound have been recorded. The work also includes calculation of non-linear optical properties along with 3D MESP surface map. The thermodynamic properties such as heat capacity, entropy and enthalpy change at various temperatures have also been calculated to reveal thermal characteristics of the title compound. As the title compound possesses pharmaceutically important moieties, molecular docking studies have also been reported.

2. Experimental section

2.1. Synthesis of 6-Methyl,13,14,15-Trihydro-14-(4-Nitrophenyl) pyrido[1,2-a:1′,2′-a′] pyrido[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione

A mixture of 2-Hydroxy-4-H-pyrido[1,2-a]pyrimidin-4-one (0.02 mol), 4-nitrobenzaldehyde (0.01 mol) and methylamine (0.02 mol) in dioxane was refluxed for about 6 h. The reaction mixture was cooled and poured onto crushed ice. The solid thus obtained was filtered and washed with water. The crude product was re-crystallized in acetone. The structure was established using NMR and FT-IR spectral analysis.

2.2. Spectroscopic observations

The synthesized compound in crystalline state was used for further experimental analysis. The FT-IR spectrum of title compound was recorded using Perkin Elmer Spectrum Two IR spectrometer in the region 4000-400 cm^{-1} using KBr pellet method. The FT Raman spectrum in the region 4000-200 cm^{-1} with a spectral resolution of 4 cm^{-1} was recorded on a SNOM/CONFOCAL/MICRRAMAN/WITec alpha 300 series microscope. Single longitudinal mode, diode-pumped solid state (SLM-DPSS) laser with 532 nm laser line was used as the exciting wavelength. UV absorption spectrum was recorded in ethanol solvent on JASCO-UV (V-670) spectrometer in the spectral region of 200–500 nm with resolution of 0.5 nm. The ^{1}H-NMR spectra was recorded on Bruker DRX 300 instrument. All the experimental spectra were recorded at IIT Kanpur.

3. Computational details

In order to provide a comprehensive information pertaining to the structural features of $C_{24}N_6O_4H_{16}$, the gradient-corrected DFT [13] using Becke 3-parameters exchange and Lee–Yang–Parr correlation functional (B3LYP) [14] has been employed. To investigate the most stable geometry for the title compound, 2D potential energy scan (PES) was performed by varying the C33–C32–C13–C12 dihedral angle at B3LYP/6-31 + G(d,p) level of theory. The PES showing the variation of dihedral angle, and corresponding energies are shown in Fig. 1(a). The two stable conformers corresponding to minima on PES at −62 and + 118.1° differ only by the rotation of NO$_2$ group with respect to phenyl ring and since the positions of two oxygen atoms of the nitro group are

equivalent, the conformer with C33–C32–C13–C12 = +118.1° was chosen without any distinction and further optimized at a higher basis set 6-311++G(d,p) shown in Fig. 1(b). The optimized structure has been used for calculation of various molecular properties like dipole moment, mean polarizability and first static hyperpolarizability. Theoretical calculations in this study have been performed with the Gaussian 09 program package [15] and results were analyzed with the Gaussview 5.0 molecular visualization program [16]. Due to unavailability of the x-ray crystallographic data of $C_{24}N_6O_4H_{16}$, it's optimized parameters have been compared with compounds having similar moieties [17,18]. Positive values of all the calculated vibrational wavenumbers confirm the stability of optimized geometry. Different scaling factors are used in the different spectral region (0.9567 (4000-2000 cm^{-1}), 0.9679 (2000-1200 cm^{-1}), 0.9879 (1200-700 cm^{-1}) and 0.9989 (below 700 cm^{-1})) to outweigh the systematic errors caused by basis set incompleteness and vibrational anharmonicity [19,20]. Theoretical vibrational assignment of the title compound was carried out by combining the animation option of the Gauss view 5.08 and the VEDA programs [21]. The Raman activities (S_i) calculated with the Gaussian 09 program were subsequently converted to relative Raman intensities (I_i) using the relationship derived from the basic theory of Raman scattering [22,23]. The calculated Raman and IR spectra were plotted using the pure Lorentzian band shape with FWHM equal to 4 cm^{-1}.

The theoretical UV–Vis spectrum has been computed by TD-DFT method with 6-311++G(d,p) basis set and solvent effect has been taken into consideration by implementing IEFPCM model. We have used the finite field approach to calculate analytically the dipole moment (μ), mean polarizability $<\alpha>$, and the total first static hyperpolarizability β [24–26]. The mathematical details used for the calculation of electric moments have been reported in our earlier publications [27,28]. The proton NMR chemical shifts of title compound were calculated with gage-included atomic orbital (GIAO) approach by applying B3LYP/6-311++G(d,p) method and compared with observed experimental proton-NMR spectrum.

4. Results and discussion

4.1. Molecular geometry

The ground state energy of the title compound optimized at the DFT/B3LYP/6-311++G (d,p) level is found to be −1553.956184 Hartree. The optimized structure with numbering of atoms and computed geometrical parameters are presented in Fig. 1(b) and
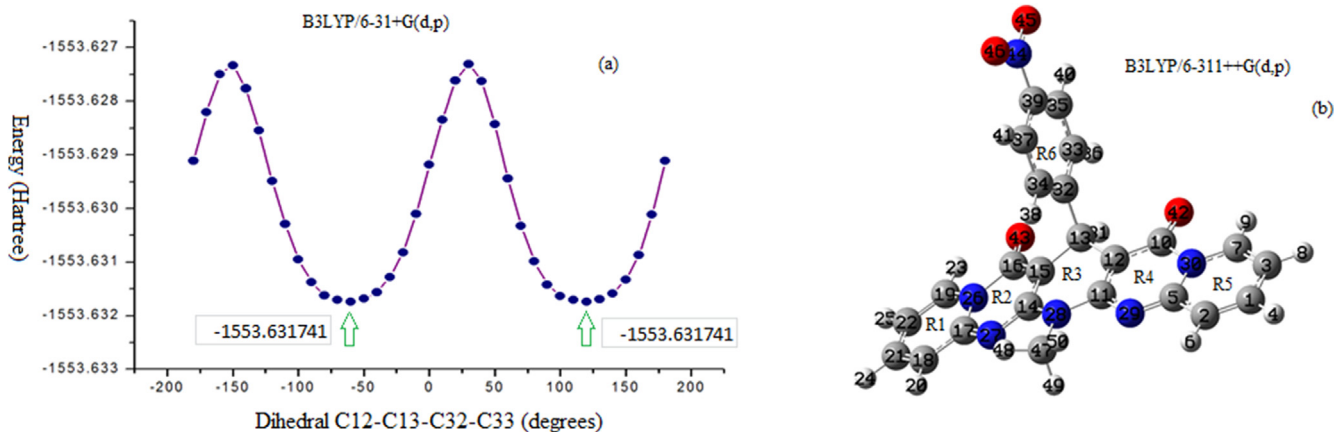

Fig. 1. The potential energy curves of $C_{24}N_6O_4H_{16}$ along the C12–C13–C32–C33 and optimized geometric structure for ground state with atoms numbering.