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Molecular docking, spectroscopic studies and quantum calculations on nootropic drug

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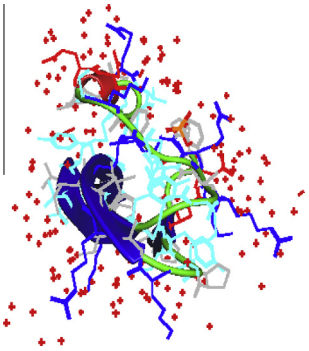
HIGHLIGHTS

- Piracetam is one of the groups of racetams.
- Description of the molecular geometry and molecular vibrational of the piracetam.
- Docking using Q-site finder and target protein is geometrically optimized.
- The values of β and μ suggest the possibility of technological (NLO) applications.

GRAPHICAL ABSTRACT

Piracetam improves the function of the neurotransmitter acetylcholine muscarinic cholinergic receptors, which are implicated in memory process. Among the possible therapeutic interventions, 2-pyrrolidine derivatives such as piracetam and related nootropics are currently used for their facilitatory effects in learning and memory in animal models.



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ABSTRACT

A systematic vibrational spectroscopic assignment and analysis of piracetam [(2-oxo-1-pyrrolidineacetamide)] have been carried out using FT-IR and FT-Raman spectral data. The vibrational analysis was aided by an electronic structure calculation based on the hybrid density functional method B3LYP using a 6-311G++(d,p) basis set. Molecular equilibrium geometries, electronic energies, IR and Raman intensities, and harmonic vibrational frequencies have been computed. The assignments are based on the experimental IR and Raman spectra, and a complete assignment of the observed spectra has been proposed. The UV–visible spectrum of the compound was recorded and the electronic properties, such as HOMO and LUMO energies and the maximum absorption wavelengths λ_{max} were determined by the time-dependent DFT (TD-DFT) method. The geometrical parameters, vibrational frequencies and absorption wavelengths were compared with the experimental data. The complete vibrational assignments are performed on the basis of the potential energy distributions (PED) of the vibrational modes in terms of natural internal coordinates. The simulated FT-IR, FT-Raman, and UV spectra of the title compound have been constructed. Molecular docking studies have been carried out in the active site of piracetam by using Argus Lab. In addition, the potential energy surface, HOMO and LUMO energies, first-order hyperpolarizability and the molecular electrostatic potential have been computed.

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Introduction

Piracetam (2-oxo-1-pyrrolidineacetamide) is a cyclic derivative of GABA and in the groups of racetams. Numerous positive individual studies supported the use of piracetam in people suffering from a wide range of cognitive disorders [1]. Piracetam has been studied in an extensive number of clinical experiments, and has shown positive results in the treatment of post-stroke aphasia, epilepsy, congnitive decline following heart and brain surgery, dementia and myoclones [2,3]. Piracetam improves the function of the neurotransmitter acetylcholine muscarinic cholinergic receptors, which are implicated in memory processes. Among the possible therapeutic interventions, 2-pyrrolidine derivatives such as piracetam and related nootropics are currently used for their facilitatory effects in learning and memory in animal models [4]. There is evidence that piracetam and piracetam-like nootropics might alter presynaptic cholinergic functions, possibly by enhancing high-affinity neuronal uptake of choline, and elevate muscarinic receptor density in the frontal cortex of aged mice [5,6]. The discovery of the nootropic properties of piracetam was the reason for the synthesis of some other nootropic drugs-oxiracetam, aniracetam, pramiracetam, and nefiracetam [7]. Its crystal structure was determined from X-ray powder diffraction in combination with the minimization of the crystal-lattice potential energy [8]. A molecular conformation study of piracetam in the gas phase was performed by Ksenafontov et al. [9].

The spectroscopic properties of Piracetam were studied by vibrational spectroscopy (FT-IR, FT-Raman) and electronic spectroscopy (UV–visible), and additionally the structure and vibrational frequencies of the piracetam molecule were calculated by the DFT method. Based on the molecular orbital analysis and the time dependent DFT (TD-DFT) calculations, we have discussed the electronic structure and the assignment of the absorption bands in the electronic spectra of piracetam. A literature survey reveals that to the best of our knowledge no theoretical or computational vibrational spectroscopic study on piracetam exists. Therefore, the present study aims to give a complete description of the molecular geometry and vibrations of piracetam. In the present work, a complete vibrational analysis, and a study of the potential energy surface and other molecular properties has been performed on the basis of DFT theory and we also attempt a theoretical study by docking using the Q-site finder.

Experimental

The compound piracetam in the solid form was procured from the Sigma–Aldrich Chemical Company, (USA) with a stated purity of 98% and used without further purification. The FT-Raman spectrum of piracetam is recorded in the region 4000–50 cm^{-1} in pure mode using a Nd:YAG laser of 100 mW with 2 cm^{-1} resolution on a BRUKER RFS 27 at SAIF, IIT Madras, India. The FT-IR spectrum of the sample is recorded in the region 4000–450 cm^{-1} in evacuation mode using KBr pellet technique on a PERKIN ELMER FTIR spectrophotometer at SAIF, IIT Madras, India. The observed experimental and simulated FT-IR and FT-Raman spectra are shown in Figs. 1 and 2, respectively. We think that the reported wavenumbers are accurate to within ±1 cm^{-1}.

Computational method

The entire set of calculations was performed at the density functional theory (DFT) level on a (personal computer) PC by energy optimization [10], using the GAUSSIAN 03W [11] program package. The optimized structural parameters and vibrational wavenumbers for the piracetam molecule were calculated using the B3LYP functional and the 6-311++G(d,p) basis set. The potential energy surface was also studied at the same level. All the parameters were allowed to relax and the calculations converged to an optimized geometry which corresponds to a true minimum, as seen from the lack of imaginary wavenumbers. The Cartesian representation of the theoretical force constants has been computed at the fully optimized geometry. Transformation of the force field, the subsequent normal coordinate analysis and calculation of the potential energy distribution (PED) were done on a PC with the MOLVIB program (version V 7.0) written by Sundius [12,13]. The structure of the protein Interleukin-13 with the PDB ID was retrieved from the Protein Data Bank. After obtaining the structure from Protein Data Bank, the possible binding sites of Protein Interleukin-13 were searched using Q-site Finder. These include pockets located on protein surfaces and voids buried in the interior of proteins. Q-site Finder includes a graphical user interface, flexible

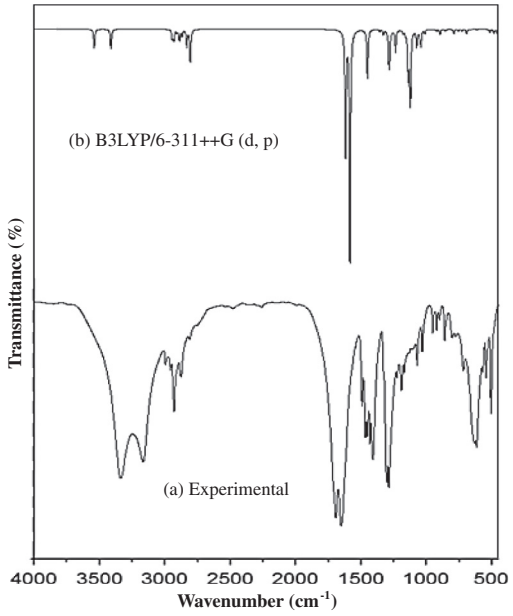

Fig. 1. FT-IR spectra of piracetam (Experimental, B3LYP/6-311++G(d,p)).

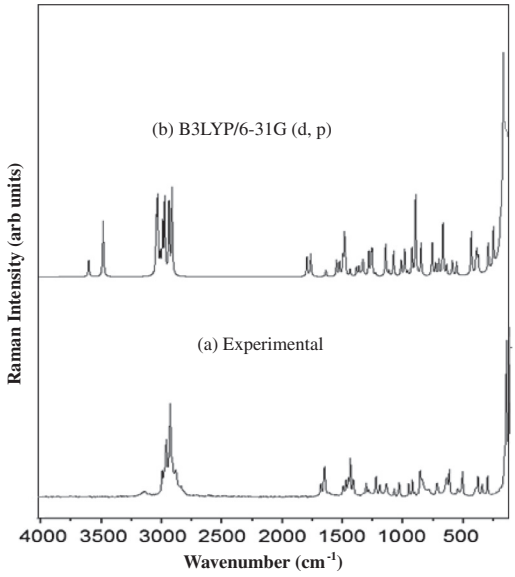

Fig. 2. FT-Raman spectra of piracetam (Experimental, B3LYP/6-311++G(d,p)).