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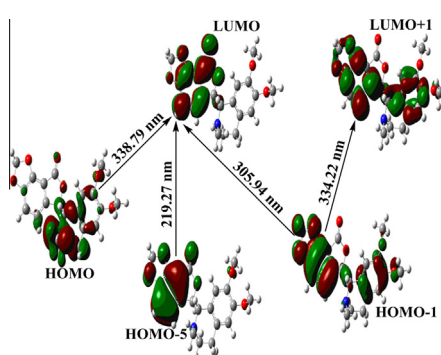
## Quantum chemical and experimental studies on the structure and vibrational spectra of an alkaloid–Corlumine

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## HIGHLIGHTS

- Spectral properties of alkaloid COR were revealed employing FT-IR and FT-Raman.
- Theoretical computations were performed and compared with experimental.
- The assignments of electronic excitations were done using TD-DFT/6-31G//IEF-PCM method.
- The chemical reactivity was explained by mapping molecular electrostatic potential.
- The charge transfer properties were elucidated by NBO analysis.

## GRAPHICAL ABSTRACT



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## ABSTRACT

The study concentrates on an important natural product, phthalide isoquinoline alkaloid Corlumine (COR) [(6R)-6-[(1S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinolin-1-yl] furo [3,4-e]-1,3-benzodioxol-8(6H)-one] well known to exhibit spasmolytic and GABA antagonist activity. It was fully characterized by a variety of experimental methods including vibrational spectroscopy (IR and Raman), thermal analysis (DSC), UV and SEM. For a better interpretation and analysis of the results quantum chemical calculations employing DFT were also performed. TD-DFT was employed to elucidate electronic properties for both gaseous and solvent environment using IEF-PCM model. Graphical representation of HOMO and LUMO would provide a valuable insight into the nature of reactivity and some of the structural and physical properties of the title molecule. The structure–activity relationship have been interpreted by mapping electrostatic potential surface (MEP), which is valuable information for the quality control of medicines and drug–receptor interactions. Stability of the molecule arising from hyper conjugative interactions, charge delocalisation has been analyzed using natural bond orbital (NBO) analysis. Computation of thermodynamical properties would help to have a deep insight into the molecule for further applications.

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## Introduction

Recently focus on plant research has increased all over the world and a large body of evidence has been collected to show im-

mense potential of medicinal plants used in various traditional systems [1–3]. Research into the use of plant-derived natural products alone in just the field of medicine covers a broad spectrum of activities [4–8]. The study of natural products would prove to be helpful for pharmaceutical scientists in identifying new lead structures, templates and scaffolds in the finite world of chemical diversity. Therefore to further aid that study isoquinoline alkaloid Corlumine (COR), isolated from the leaves and stems of *Corydalis*

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*meifolia* Wall (Papaveraceae) plant have been intensively investigated [9] in the present work. Isoquinoline alkaloids are of great importance to humanity because of their medicinal values and different structures. COR whose chemical structure is shown in Fig. 1 have spasmolytic and GABA antagonist activity. It is a more potent convulsant than adlumine because it does not affect blood pressure or heart action except in fatal doses. It produces marked respiratory stimulation in large subconvulsive doses, but the dose necessary is too near the convulsive dose for therapeutic purposes. Activity of the compound was assessed earlier by its ability to inhibit the contraction of the smooth muscles induced by various spasmogens, such as acetylcholine, histamine, serotonin and barium chloride [10]. It is a well known convulsant and in subconvulsive doses it has little effect on blood pressure. Subconvulsive doses of the base increase the depth and frequency of respiration [11].

Spectroscopic techniques when combined with quantum chemical calculations are emerging as one of the most powerful tools to study the dynamical behavior and to gain an insight into the electronic and molecular structures of natural products at microscopic level [12,13]. The density functional theory (DFT) [14] based theoretical calculations not only support the experimental studies in particular but also help in understanding molecular, electronic and vibrational properties in a better way. We have fully characterized COR experimentally by a variety of methods including vibrational spectroscopy (IR and Raman), thermal analysis (DSC), UV and SEM. Then utilizing quantum chemical methods we have performed a detailed conformational and vibrational analysis of COR. To obtain an understanding of energy distribution, the calculated vibrational spectra were analyzed on the basis of potential energy distribution (PED) of each vibrational mode. The molecular structure, vibrational frequencies and energies of the optimized geometries of COR were computed employing the DFT and HF methods using Gaussian 09 program package [15] and Becke's three parameter hybrid exchange functional with Lee–Yang–Parr correlation functional (B3LYP) [16–18] employing 6-311++G(d,p) basis set [19,20]. The structure–activity relationship was interpreted by mapping electrostatic potential surface (MEP), which is valuable information for the quality control of medicines and drug–receptor interactions. The time-dependent density functional theory (TD-DFT) [21,22] was employed for assignment of electronic excitations both in gaseous and solvent phase. The HOMO and LUMO energies were calculated and they show that charge transfer occurs within the molecule. The thermodynamic properties were also calculated at different temperatures revealing the correlation between the standard heat capacities ( $C$ ), entropies ( $S$ ), enthalpy changes ( $H$ ) and temperatures. Natural bond orbital (NBO) [23] analysis was performed to investigate stability of the molecule arising from intramolecular charge transfer interactions,

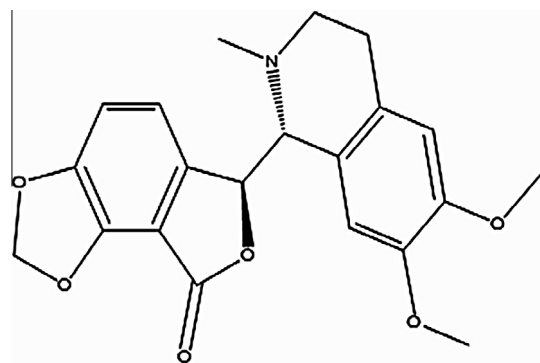


Fig. 1. Chemical structure of COR.

rehybridization and delocalization of electron density within the molecule.

## Experimental details

The air-dried leaves and stems of *C. meifolia* Wall (Papaveraceae) plant (2.5 kg) was powdered and percolated with ethanol (95%) ( $5 \times 2.5$  l) at room temperature. The combined percolate was concentrated under reduced pressure below  $40^\circ\text{C}$  to give a viscous mass (500 g). The viscous mass was then extracted with 5% aqueous hydrochloric acid ( $5 \times 150$  ml). The combined aqueous acidic extract was defatted with petroleum ether ( $5 \times 200$  ml), basified with  $\text{Na}_2\text{CO}_3$  (pH 8–8.5). The precipitate so formed was extracted with  $\text{CHCl}_3$  ( $5 \times 150$  ml), the combined  $\text{CHCl}_3$  layer washed with  $\text{H}_2\text{O}$ , dried (anhyd.  $\text{Na}_2\text{SO}_4$ ) and evaporated *in vacuo* to give a crude alkaloidal mixture (20 g). The crude alkaloidal mixture was subjected to chromatography over a column of  $\text{SiO}_2$  (80 g). The column was successively eluted from hexane, hexane–chloroform; v/v (99:1), (95:5), (90:10), (75:25), (50:50), (25:75); chloroform, chloroform–methanol (99:1), (95:5), (90:10), (75:25), and pure methanol, elution was monitored by TLC. The fractions were mixed on the basis of TLC, the fractions eluted from hexane–chloroform (25:75) mixed and the solvent removed. The crude product so obtained was subjected to preparative TLC (plates: silica gel, solvent:  $\text{CHCl}_3$ –MeOH, 97:3) to afford Corlumine (100 mg), mp.  $160^\circ$  [24].

Infrared spectra were recorded on a Bruker TENSOR 27 FT-IR spectrometer with a spectral resolution of  $4\text{ cm}^{-1}$  in the region  $300$ – $4000\text{ cm}^{-1}$ . KBr pellets of solid samples were prepared from mixtures of KBr and the sample in 200:1 ratio using a hydraulic press. Multi-tasking OPUS software was used for base line corrections.

FT-Raman spectra were recorded in the region  $100$ – $3500\text{ cm}^{-1}$  by using a Bruker MultiRAM spectrometer, equipped with Nd–YAG laser operating at  $1064\text{ nm}$  in backscattering. The laser was focused on the sample as an approximately  $100\text{ }\mu\text{m} \times 100\text{ }\mu\text{m}$  area and a liquid nitrogen-cooled germanium detector was used. About 512 scans with a resolution of  $4\text{ cm}^{-1}$  were averaged for each sample. Furthermore, GRAMS/AI 7.02 was used for correcting Raman spectra.

DSC thermogram of the powder sample of COR was recorded on Mettler Toledo system model DSC 1 STAR<sup>e</sup> with a heating rate of  $15^\circ\text{C}/\text{min}$  and nitrogen flow at the rate of  $30\text{ ml}/\text{min}$ .

The absorption spectrum of COR was recorded in ethanol (EtOH) solvent in the range  $200$ – $800\text{ nm}$  using a Varian – Cary 50, UV–visible spectrophotometer equipped with a  $10\text{-mm}$  quartz cell. The UV pattern was taken from a  $10^{-5}\text{ M}$  solution of COR, dissolved in EtOH at  $30^\circ\text{C}$ .

The scanning electron microscope LEO 430, Cambridge, utilizing the Polaron sputter coater sc7640 coating machine having the coating target made up of AuPd alloy was used for the study of surface morphology of COR.

## Computational details

The molecular structure, vibrational frequencies and energies of the COR were computed employing the DFT [14] method using Gaussian 09 program [15] package and Becke's three parameter (local, non-local, Hartree–Fock) hybrid exchange functional with Lee–Yang–Parr correlation functional (B3LYP) [16–18]. The split-valence basis set 6-311++G, augmented by 'd' polarization functions on heavy atoms and 'p' polarization functions on hydrogen atoms as well as diffuse functions for both hydrogen and heavy atoms were used [19,20]. The absolute Raman intensities and infrared absorption intensities were calculated in the harmonic approximation at the same level of theory as used for the

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