Journal of Molecular Structure 1159 (2018) 83–95

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Probing vibrational activities, electronic properties, molecular docking and Hirshfeld surfaces analysis of 4-chlorophenyl ({[(1*E*)-3-(1*H*-imidazol-1-yl)-1-phenylpropylidene]amino}oxy)methanone: A promising anti-*Candida* agent

K. Jayasheela [a], Lamya H. Al-Wahaibi [b], S. Periandy [a], Hanan M. Hassan [c, d], S. Sebastian [e], S. Xavier [e], Joseph C. Daniel [f], Ali A. El-Emam [g, h], Mohamed I. Attia [g, i, *]

[a] Department of Physics, Kanchi Mamunivar Center for Post Graduate Studies and Research, Lawspet, Puducherry, 605 008, India
[b] Department of Chemistry, College of Sciences, Princess Nourah Bint Abdulrahman University, Riyadh, 11671, Saudi Arabia
[c] Department of Pharmaceutical Sciences, College of Pharmacy, Princess Nourah Bint Abdulrahman University, Riyadh, 11671, Saudi Arabia
[d] Department of Pharmacology and Biochemistry, College of Pharmacy, Delta University for Science and Technology, Mansoura, Egypt
[e] Department of Physics, St. Joseph's College of Arts & Science (Autonomous), Cuddalore, Tamilnadu, 607 001, India
[f] Department of Microbiology, St.Joseph's College of Arts & Science (Autonomous), Cuddalore, Tamilnadu, 607 001, India
[g] Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, 11451, Saudi Arabia
[h] Department of Medicinal Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura, 35516, Egypt
[i] Medicinal and Pharmaceutical Chemistry Department, Pharmaceutical and Drug Industries Research Division, National Research Centre (ID: 60014618), El Bohooth Street, Dokki, Giza, 12622, Egypt

ARTICLE INFO

Article history:
Received 8 November 2017
Received in revised form
16 January 2018
Accepted 16 January 2018

Keywords:
Candida albicans
Vibrational spectra
Molecular docking
RDG
NBO
Hirshfeld surfaces

ABSTRACT

The promising anti-*Candida* agent, 4-chlorophenyl ({[1*E*-3(1*H*-imidazole-1-yl)-1-phenylpropylidene} oxy)methanone (4-CPIPM) was comprehensively characterized by FT-IR, FT-Raman, UV, as well as ^{1}H and ^{13}C spectroscopic techniques. The theoretical calculations in the current study utilized Gaussian 09 W software with DFT approach of the B3LYP/6-311++G(d,p) method. The experimental X-ray diffraction data of the 4-CPIPM molecule were compared with the optimized structure and showed well agreement. Intermolecular electronic interactions and their stabilization energies have been analyzed by natural bond orbital method. Potential energy distribution confirmed the normal fundamental mode of vibration with the aid of MOLVIB software. The chemical shift values of the ^{1}H and ^{13}C spectra of the title compound were computed using gauge independent atomic orbital and the results were compared with the experimental values. The time-dependent density function theory method was used to predict the electronic, absorption wavelength and frontier molecular orbital energies. The HOMO-LUMO plots proved the charge transfer in the molecular system of the title compound through conjugated paths. The molecular electrostatic potential analysis provided the electrophilic and nucleophilic reactive sites in the title molecule which have been analyzed using Hirshfeld surface and two dimensions fingerprint plots. Non covalent interactions were also studied using reduced density gradient analysis and color filled electron density diagram. Molecular docking studies of the ligand-protein interactions along with their binding energies were carried out aiming to explain the potent anti-*Candida* activity of the title molecule.

1. Introduction

Fungal infections represent a global serious health problem particularly with immunocomprimised individuals. Anticancer chemotherapeutic agents or immunosupressants gave the opportunity for opportunistic fungi to cause life-threatening fungal infections [1]. *Candida albicans* (*C. albicans*) is a prevalent invasive fungal pathogen that is linked to high mortality rates worldwide [2]. Significant side effects and resistance to the first-line antifungal durgs persuaded the search for new potent and safe antifungal agents.

* Corresponding author. Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, 11451, Saudi Arabia.
E-mail address: msamabd@yahoo.com (M.I. Attia).

https://doi.org/10.1016/j.molstruc.2018.01.042
0022-2860/

Azole antifungal drugs are widely used in clinic to eradicate systemic candidiasis through inhibition of fungal lanosterol 14α-demethylase (CYP51) leading to depletion of ergosterol with subsequent death of the fungal cells [3]. The nitrogen atom in the azole moiety coordinates with the iron of the heme present in the binding pocket of CYP51 resulting in competitive inhibition of the lanosterol 14α-demethylase enzyme [4]. The title compound, namely (4-chlorophenyl) ({[(1*E*)-3(1*H*-imidazol-1-yl)-1-phenylpropylidene]amino}oxy)methanone (4-CPIPM) is a potent imidazole-bearing anti-*C. albicans* agent. It exhibited MIC value of 0.0054 μmol/mL being about 300-fold and 3.5-fold more potent than the reference antifungal drugs, fluconazole and miconazole, respectively [5].

Screening the literature exposed that the density functional theory (DFT) computations on the promising anti-*C. albicans* agent, 4-CPIPM molecule, have not yet explored. Therefore, the vibrational properties, molecular geometry, inter/intra-molecular iterations and orbital's energy analysis of the 4-CPIPM molecule have been thoroughly investigated. In addition, the natural bond orbital (NBO) analysis has been performed in order to gain insight into the possible intermolecular delocalization or hyper-conjugation for the 4-CPIPM molecule. While the HOMO and LUMO molecular orbital's investigations were carried out to show the possible intermolecular interactions such as the interaction of the 4-CPIPM molecule with the amino acid residues in the binding pocket of its target protein. Also, Hirshfeld analysis provided a valuable graphical image for deep studying the intermolecular interactions of the 4-CPIPM molecule. The non covalent interactions of the title molecule were studied using reduced density gradient (RDG) analysis and color filled electron density diagram. Furthermore, molecular docking studies were exploited to show the possible binding mode of the 4-CPIPM molecule with its target protein aiming to explain its potent anti-*Candida* activity.

2. Experimental details

2.1. Synthesis

A solution containing 4-chlorobenzoic acid (10.0 mmol), ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI·HCl, 10.4 mmol) and 4-dimethylaminopyridine (DMAP, 0.4 g) in methylene chloride (80 mL) was stirred for 10 min at ambient temperature. Compound **4** (9.9 mmol) was added to the reaction mixture and stirring was continued for 18 h at room temperature. Thereafter, the reaction mixture was washed successively with water (2 × 25 mL), 10% $NaHCO_3$ solution (2 × 20 mL), and water (2 × 20 mL). The organic phase was separated, dried (Na_2SO_4) and evaporated under vacuum. The residue was re-crystallized from isopropyl alcohol to furnish the title compound 4-CPIPM (**5**) in 54% yield m.p. 399–401 K. The spectral data of compound **5** are consistent with the previously reported ones [5].

2.2. Spectral characterization

The FT-IR spectrum of the 4-CPIPM molecule was recorded using IFS66V spectrophotometer in 4000–500 cm^{-1} region using KBr pellet technique. The FT-Raman spectrum was recorded using Nerus 670 spectrophotometer supported by Nd-YAG laser as excitation source in the region of 3500–50 cm^{-1}. The NMR (^{13}C and ^{1}H) spectra of the 4-CPIPM molecule were recorded in $CDCl_3$ on Bruker NMR spectrometer (Bruker, Reinstetten, Germany) at 500 MHz for ^{1}H and 125.76 MHz for ^{13}C at the Research Center, College of Pharmacy, King Saud University, Saudi Arabia. The ultraviolet absorption spectrum of the 4-CPIPM molecule was examined in chloroform in the region 200–600 nm using Shimadzu UV-1650 PC, UV–Vis recording spectrophotometer.

2.3. Quantum computation methods

The optimized geometry of the 4-CPIPM molecule in the gas and chloroform phases was confirmed to be at the local true minima on the potential energy surface (PES). It lacks any imaginary frequencies in the vibrational mode by the use of Gaussian 09 W software [6] using density functional theory (DFT) with Becke 3-Parameters (exchange) Lee-Yang-Parr (B3LYP) correlation function with 6–311++G(d,p) basis set. The harmonic vibrational wavenumbers were scaled down by 0.967 [7]. The other parameters were performed using Gaussian 09 W and visualized by GaussView program [8]. The vibrational modes for the 4-CPIPM molecule were predicted using MOLVIB software [9,10] with Potential energy distribution (PED) contribution for each normal mode of vibration.

The natural bond orbital (NBO) calculations were carried out using NBO 3.1 program implemented in Gaussian 09 W [6]. The ^{13}C and ^{1}H NMR isotropic chemical shifts were computed by gauge independent atomic orbital (GIAO) method [11] using the optimized structure in the gas and chloroform phases. The time-dependent density function theory (TD-DFT) method was used to calculate excitation energy, oscillator strength and absorption wavelengths. In the TD-DFT computations, the solvent effects were incorporated using integral equation formalism-polarizable continuum model (IEF-PCM) [12]. GaussSum 3.0 [13] was used to plot the density of state (DOS) spectrum of the title compound in the gas and chloroform phases. The obtained graphs convoluted the molecular orbital with Gaussian curve of unit height of full width half maximum (FWHM) of 0.3 eV. Multiwfn software [14] was used to plot the reduced density gradients (RDG) and VMD 9.1 Program [15] was used to plot electrostatic potential (ESP).

3. Results and discussion

3.1. Synthesis

Scheme 1 illustrates the chemical pathway to achieve the title molecule **5**. Thus, Mannich reaction was carried out on acetophenone (**1**) to furnish the Mannich base **2** which was elaborated to the ketone **3** using imidazole as a nucleophile. The oxime **4** was obtained from compound **3** and was subsequently esterified with 4-chlorobenzoic acid to furnish the title molecule **5**.

3.2. Molecular geometry

The crystal structure of the 4-CPIPM molecule belongs to the monoclinic of P_{21}/n space group with cell parameter a = 16.3185(4) Å, b = 8.1333 (2) Å, C = 14.2996(4) Å, β = 114.317(1) and Z = 4 [16]. The optimized molecular structure of the 4-CPIPM molecule by B3LYP/6-311++G(d,p) method was shown in Fig. 1. The computed optimized structure showed C1 point group symmetry with ground state energy of −1508.813845 a.u. and dipole moment of 4.0101 Debye. The computed geometrical parameters along with the XRD values are presented in Table S1. The recorded XRD showed that O3–N4 is a pure single bond character at a distance of 1.4354(17) Å which is correlated with computed bond lengths of 1.419 and 1.423 Å by the B3LYP/6-311++G(d,p) method in the gas and chloroform phases, respectively. On the other hand, the N4=C5 has a double bond character as it is evident from the computed bond lengths of 1.285 and 1.286 Å in the gas and chloroform phases, respectively, which is in a well agreement with the XRD value (1.285 Å). The two phenyl rings appear to be planar as evident from their dihedral angles (O2–C1–C19–C20 = −172.006° and O2–C1–C19–C24 = 6.741°) for the chloro substituted phenyl ring