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ORIGINAL ARTICLE

Synthesis, structure combined with conformational analysis, biological activities and docking studies of bis benzylidene cyclohexanone derivatives

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Abstract We report the synthesis and biological evaluation of bis benzylidne cyclohexanone derivatives 2,6-di(4-fluorobenzylidene)cyclohexanone **3a** and (2E,6E)-2,6-bis({[4-(trifluoromethyl) phenyl]methylidene})cyclohexanone **3b**. Compound **3b** crystallized in the monoclinic space group $P2_1/n$ with unit cell parameters $a = 29.3527(12)$ Å, $b = 8.3147(3)$ Å, $c = 32.7452(14)$ Å, $\beta = 112.437(2)°$, and $V = 7386.8(5)$ Å^3, $Z = 16$, and $R_{int} = 0.072$ at $T = 100$ K. The asymmetric unit contains four independent molecules, each of which has slight differences in the bond lengths and angles. One non-classical C11D–H11F···F3A hydrogen bond connects the molecules. Density functional theory was used to optimize the structures and calculate the natural charges, dipole moments, frontier molecular orbitals, and NMR and UV–Vis spectroscopic properties, which are discussed and compared with the experimental data. The synthetic derivatives were evaluated for α-glucosidase inhibitory activity, and we found that compound **3a** ($IC_{50} = 96.3 \pm 0.51$ μM) is a potent α-glucosidase inhibitor, showing superior activity to the standard drug acarbose ($IC_{50} = 841 \pm 1.73$ μM). Compound **3b** ($IC_{50} = 7.92 \pm 1.3$ μg/mL) was found to be a potent antileishmanial compound, especially compared to the antileishmanial drugs pentamidine ($IC_{50} = 5.09 \pm 0.04$ μM) and amphotericine B ($IC_{50} = 0.29 \pm 0.05$ μg/mL). In addition, **3a** and

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3b have cytotoxic effects against PC3 (prostate cancer), HeLa (cervical cancer), and MCF-3 (breast cancer) cell lines. Docking study for compounds activity was performed with Openeye software in order to understanding their pose of interaction in the target receptors.

1. Introduction

Chalcones are privileged structures present in a broad range of biologically active molecules. Chalcones exhibit a range of pharmaceutical effects including anti-inflammatory, anti-infective, anti-oxidative, anti-malarial, and anti-cancer properties [1]. Recently; several excellent reviews have been published concerning the importance of fluorine compounds as pharmaceuticals targets [2–7]. Several studies revealed the influence of different substituents and linkers toward the biological activities [8,9]. There deduced electrostatic interactions, small size, and high electronegativity of fluorine atoms often conspire to effect substantial changes in the omniphobicity, lipophilicity, and electron density distribution of drugs containing fluorine [3].

α-Glucosidase is an enzyme responsible for the hydrolysis of polysaccharides to monosaccharides, which results in a rise in blood glucose levels after eating, clinically known as postprandial hyperglycemia. Many pathological conditions such as cataracts, retinopathy, neuropathy, nephropathy, atherosclerosis, and impaired wound healing are known to be associated with high blood glucose levels and result from the glycation of different proteins. Therefore, the use of α-glucosidase inhibitors is a strategy to control the onset of various health disorders resulting from hyperglycemia [10–13].

The toxicity of a substance toward a cell (cytotoxicity) is critical to the body's immune system and can be effectively used to kill unwanted or cancerous cells in a biological system. Low cytotoxicity to healthy cells and high cytotoxicity to cancerous cells is the ultimate goal of many anticancer drugs.

Leishmaniosis is a tropical disease caused by *Leishmania major* and known to be transmitted from animal hosts to humans via the bite of infected sand flies. The disease can be classified by its severity; visceral leishmaniosis is the most severe, where the internal organs have been infected, whereas cutaneous leishmaniosis, characterized by skin lesions on the face, arms, and other exposed body parts, is the least severe. In addition, disfiguration of the face on infection of the mucous membrane has also been observed in mucocutaneous leishmaniosis. The development of drug resistance of the *Leishmania* parasite and the adverse health effects of available drugs make the search for effective antileishmanial drugs vital to prevent an epidemic of leishmaniosis.

Among the wide range of synthesized compounds examined as potential anticancer agents, varieties of functionalities as Michael acceptor have attracted reasonable attention. A group of compounds containing Michael acceptor are conjugated enones or enone-like compounds such as chalcones and bis-chalcones. Chalcones are open-chain molecules where two aromatic rings flank a three-carbon enone fragment on either side. Curcumin is a naturally occurring bis-chalcone derivative from the powdered root of *Curcuma longa* L. [14].

Previous studies have shown that different chalcones have potent anti-cancer activity through inhibition for different enzymes as EGFR, glutathione transferase [15,3].

The interesting biological activities of chalcones have prompted us to synthesize and evaluate various chalcones for their activity against α-glucosidase enzymes, their antileishmanial activity, and their cytotoxic activity against PC-3 (prostate cancer), HeLa (cervical cancer), MCF-7 (breast cancer), and 3T3 (normal fibroblast) cell lines [16–21].

In this paper, the synthesis and investigation of the antiproliferative properties of structurally related chalcone hybrids containing a fluorine pharmacophore is reported. Conformational analysis of the studied compound combined with electronic and spectroscopic properties predictions were investigated using density functional theory (DFT) calculations. Many of the calculated electronic properties provide detailed information necessary for understanding the biological activities of these compounds.

2. Experimental

2.1. General remarks

"All the chemicals were reagent-grade, purchased from Sigma–Aldrich and Fluka, among others, and were used without further purification, unless otherwise stated. All melting points were measured on a Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR Spectra were measured as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer. The NMR spectra were recorded on a Jeol-400 NMR spectrometer. ^{1}H-NMR (400 MHz), and ^{13}C-NMR (100 MHz) were run in deuterated chloroform ($CDCl_3$). Chemical shifts (δ) are referred in terms of *ppm* and *J*-coupling constants are given in *Hz*. Mass spectra were recorded on a Jeol JMS-600 H. Elemental analysis was carried out on Elmer 2400 Elemental Analyzer in CHN mode. The X-ray diffraction measurement of compound **1** was collected by using Bruker SMART APEXII D8 Venture diffractometer. The thermal analysis of the studied compound has been carried out using TGA Q500 V20.10. The wt% loss has been measured from the ambient temperature up to 800 °C. The electronic spectrum of the studied compound is measured using Perkin Elmer, Lambda 35, spectrophotometer".

2.2. Preparation of *3a,b*

A mixture of cyclohexanone (6 mmol, 588 mg), and appropriate aldehyde (12 mmol, 1280 mg) in EtOH (20 mL; 95%). The reaction mixture was then stirred magnetically until both reagents dissolved. A solution of NaOH (560 mg, 14 mmol) in 20-mL of water–ethanol (1:1) was added dropwise (using a Pasteur pipet) into the reaction mixture and stirred magnetically. The reaction mixture turned yellow and solidified within