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Synthesis and structure investigation of novel pyrimidine-2,4,6-trione derivatives of highly potential biological activity as anti-diabetic agent

Assem Barakat [a, b, *], Saied M. Soliman [b], Abdullah Mohammed Al-Majid [a], Gehad Lotfy [c], Hazem A. Ghabbour [d], Hoong-Kun Fun [d, e], Sammer Yousuf [f], M. Iqbal Choudhary [a, f], Abdul Wadood [g]

[a] Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia
[b] Department of Chemistry, Faculty of Science, Alexandria University, P.O. Box 426, Ibrahimia, Alexandria 21321, Egypt
[c] Organic Chemistry Department, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt
[d] Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia
[e] X-Ray Crystallography Unit, School of Physics, Universiti Sains Malaysia, Penang 11800, Malaysia
[f] H.E.J. Research Institute of Chemistry, International Center for Chemical Sciences, University of Karachi, Karachi 75270, Pakistan
[g] Department of Biochemistry, Abdul Wali Khan University Mardan, Mardan 23200, Pakistan

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ABSTRACT

Synthesis of (±)-1,3-dimethyl-5-(1-(3-nitrophenyl)-3-oxo-3-phenylpropyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3**) is reported. The structure of compound **3** was deduced by using spectroscopic methods, X-ray crystallography, and DFT calculations. The calculated geometric parameters were found to be in good agreement with the experimental data obtained from the X-ray structure. The NBO calculations were performed to predict the natural atomic charges at the different atomic sites and to study the different intramolecular charge transfer (ICT) interactions. The high LP(3)O6 →z BD*(2)O5–N3 ICT interaction energy (165.36 kcal/mol) indicated very strong n → π* electron delocalization while the small LP(2) O → BD*(1)C–H ICT interaction energies indicated that the C–H … O intramolecular interactions are weak. The ^{1}H and ^{13}C NMR chemical shifts calculated using GIAO method showed good agreement with the experimental data. The calculated electronic spectra of the studied compound using TD-DFT method showed intense electronic transition band at 243.9 nm (f = 0.2319) and a shoulder at 260.2 nm (f = 0.1483) which were due to H-4/H-2/H-1/H → L+2 and H-5 → L electronic excitations, respectively. Compound **3** (IC_{50} = 305 ± 3.8 μM) was identified as a potent inhibitor of α-glucosidase *in vitro* and showed several fold more inhibition than the standard drug acarbose (IC_{50} = 841 ± 1.73 μM). Molecular docking of the synthesized compound was discussed.

1. Introduction

Nitrogen-containing compounds are privileged heterocyclic scaffold due to their biological and pharmaceutical activities [1]. For example, pyrimidine-2,4,6-trione derivatives are known to have as anti-hypertensive [2], anti-cancer [3], anti-convulsant [4] anti-inflammatory [5], and anti-psychotic properties [6]. Because of the biological activities of these compounds, pyrimidine-2,4,6-triones (PYT) are widely used as a synthons in the design of antitumor agents. They have high efficacy to form hydrogen-bonding with drug targets (1–4, Fig. 1) [7–10]. Singh et al. have evaluated a series of new *N*-benzyl indole-pyrimidine-2,4,6-trione hybrid molecules against a panel of 60 human tumor cell lines. Several of these analogs are also inhibitors of DNA repair and replication stress response polymerases [11]. Recently, Barakat et al. [12], synthesized and evaluated some novel zwitterionic adduct derived from pyrimidine-2,4,6-trione (*e.g.*, compound **5**, Fig. 1) possess anti-oxidant properties.

Named after Arthur Michael, the conjugate addition of nucleophiles to acceptor activated alkene and alkyne substrates is a recognized strategy for an efficient and versatile construction of C–C bonds. The reaction produces a large variety of the conjugate addition products based on a broad range of the Michael donors

* Corresponding author. Department of Chemistry, College of Science, King Saud University, P. O. Box 2455, Riyadh 11451, Saudi Arabia.
E-mail address: ambarakat@ksu.edu.sa (A. Barakat).

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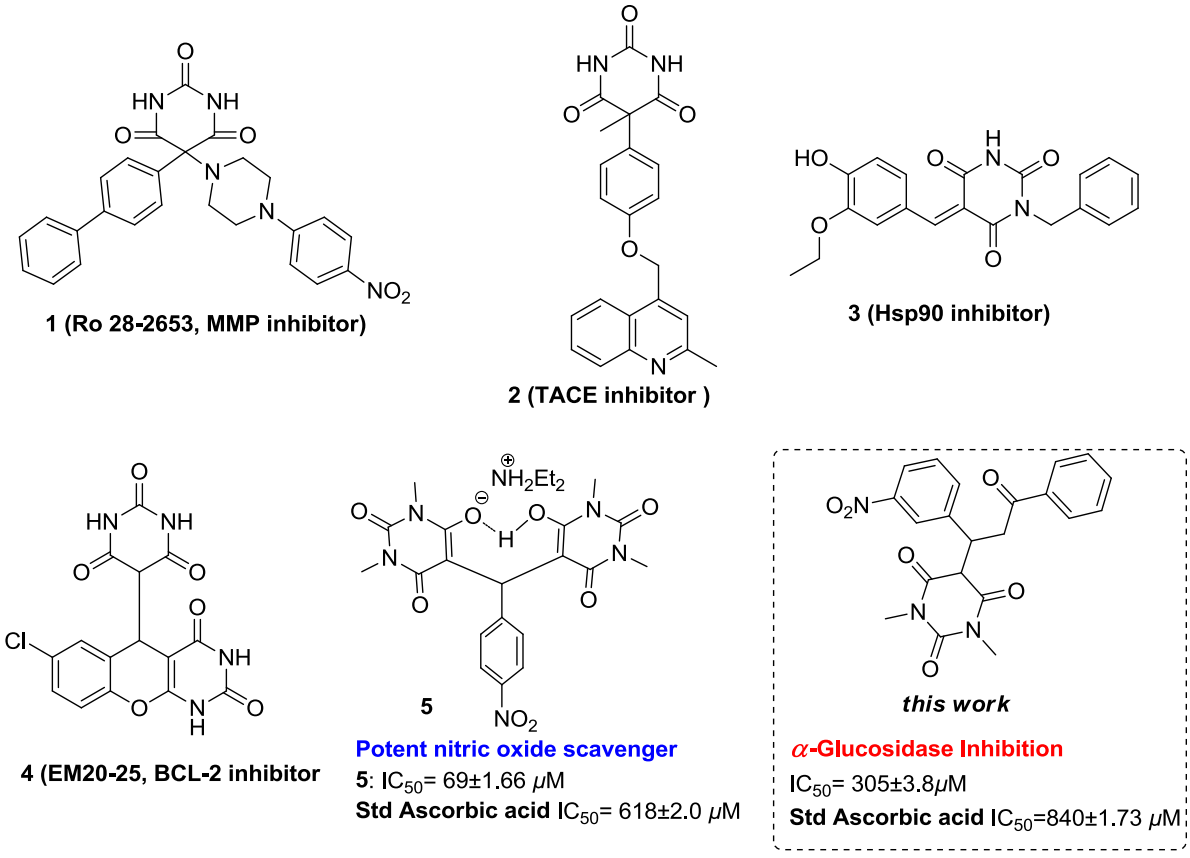

Fig. 1. Anticancer agents and anti-oxidant bearing pyrimidine-2,4,6-trione moiety.

and acceptor. Depending upon the nature of the nucleophile, many of its variants, in the form of hetero-Michael reactions, whose recent examples include, the sulpha-Michael, aza-Michael, oxo-Michael and phospha-Michael have been developed. The classical Michael additions are typically base catalyzed that also promotes Michael adducts efficiently [13–26].

In view of these reports and our interest in the synthesis of bioactive heterocyclic compounds [27–32], we report here an efficient synthesis of 1,3-dimethyl-5-(1-(3-nitrophenyl)-3-oxo-3-phenylpropyl)pyrimidine 2,4,6(1*H*,3*H*,5*H*)–trione. DFT/B3LYP calculations have also been performed to study the molecular structure characteristics of the studied compound. The electronic and spectroscopic properties of the compound have been predicted using the same level of theory. The TD-DFT calculations were used to predict and assign the electronic spectra of the studied compound. NBO calculations were performed to predict the natural atomic charges, and to study the different intramolecular charge transfer (ICT) interactions occurring in the studied system. The NMR chemical shifts were calculated using the gauge including atomic orbital (GIAO) method and used to assign the experimental results.

2. Experimental

2.1. General remarks

All the glassware was oven–dried before use, and the reactions were conducted under inert atmosphere. The progress of the reaction was monitored by TLC (Merck Silica Gel 60 F–254 thin layer plates). The chemicals were purchased from Aldrich, and Fluka etc, and were used without further purification, unless otherwise stated. Petroleum ether (PE), hexane, and ethyl acetate were distilled prior to use, especially for column chromatography. All the major solvents were dried by using slandered drying techniques mentioned in the literature. Melting points were measured on a Gallen-kamp 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 spectrometric analysis was conducted by using ESI mode on AGILENT Technologies 6410–triple quad LC/MS instrument. Elemental analysis was carried out on Elmer 2400 Elemental Analyzer, CHN mode. The X-ray diffraction measurement of compound **3** 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, UV/Vis spectrophotometer.

3 (Ethanol): 205 nm, 243 nm and 266 nm (sh).

2.2. 1,3-Dimethyl-5-(1-(3-nitrophenyl)-3-oxo-3-phenylpropyl) pyrimidine-2,4,6- (1H,3H,5H)-trione (**3**)

A solution of *N*,*N*-dimethyl barbituric acid **1** (1.5 mmol) and enone derivatives **2** (1.5 mmol) in 2 mL of dry CH_2Cl_2 were charged into a 50 mL round bottom flask under inert atmosphere. The Et_2NH (1.5 mmol) was then added to the reaction mixture and stirred at room temperature for up to 1.5–2 h, until TLC showed complete consumption of both the reactants. After the completion of