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Synthesis, molecular structure investigations and antimicrobial activity of 2-thioxothiazolidin-4-one derivatives

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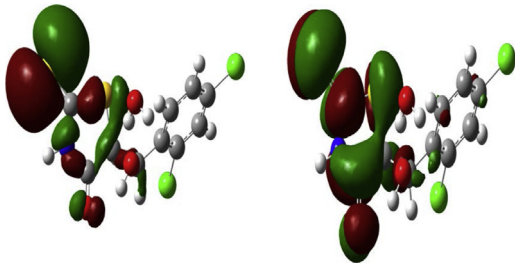
HIGHLIGHTS

- A series of 2-thioxothiazolidin-4-one derivatives have been synthesized.
- The structure for **3** was elucidated by X-ray diffraction.
- MEP, NBO and FMO were studied using DFT calculations.
- *In-vitro* evaluation of antibacterial and antifungal potencies were carried out.

GRAPHICAL ABSTRACT



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ABSTRACT

A variety of 2-thioxothiazolidin-4-one derivatives were prepared and their *in vitro* antimicrobial activities were studied. Most of these compounds showed significant antibacterial activity specifically against Gram-positive bacteria, among which compounds **4a**,**e**,**g**, **5b**,**e**,**g**,**h** and **6f** exhibit high levels of antimicrobial activity against *Bacillus subtilis* ATCC 10400 with Minimum Inhibitory Concentration (MIC) value of 16 μg/mL. All compounds have antifungal activity against *Candida albicans*. Unfortunately, however, none of the compounds were active against Gram-negative bacteria. The chemical structure of **3** was confirmed by X-ray single crystal diffraction technique. DFT calculations of **3** have been performed on the free $C_{10}H_7Cl_2NO_2S_2$, **3a** and the H-bonded complex, $C_{10}H_7Cl_2NO_2S_2{\cdot}H_2O$, **3b** to explore the effect of the H-bonding interactions on the geometric and electronic properties of the studied systems. A small increase in bond length was observed in the C12–O6 due to the H-bonding interactions between **3a** and water molecule. MEP study has been used to recognize the most reactive sites towards electrophilic and nucleophilic attacks as well as the possible sites for the H-bonding interactions. The TD-DFT calculations have been used to predict theoretically the electronic spectra of the studied compound. The most intense transition band is predicted at 283.9 nm due to the HOMO-2/HOMO-1 to LUMO

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transitions. NBO analyses were carried out to investigate the stabilization energy of the various intramolecular charge transfer interactions within the studied molecules.

Introduction

The treatment of infectious diseases still remains an important and challenging problem. The extensive search of novel antimicrobial agents is a current field of growing interest. Many compounds have been synthesized with this aim but their clinical use has been limited by their relatively high risk of toxicity, ineffectiveness, bacterial resistance and/or pharmacokinetic deficiencies. Infectious diseases are responsible for a significant proportion of deaths worldwide according to WHO. With all of these in mind, there is an urgent need for the discovery or optimization of novel antimicrobial agents that are active against these resistant strains [1]. The diversity in the biological response of 4-thiazolidinones has attracted the attention of many researchers to explore this framework for its potential. The 4-thiazolidinone ring system is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activity, such as antiviral, anti-inflammatory, anticonvulsant, anti-proliferative, anti-diabetic, cardiovascular, anti-tubercular, anti-hyperlipidemic, antibacterial, and antifungal properties. Compounds such as pioglitazone (hypoglycemic), etozoline (antihypertensive), ralitoline (anticonvulsant), and thiazolidomycin (activity against *streptomyces* species), based on this pharmacophore are already in the market (Fig. 1). In recent years, 4-thiazolidinone derivatives with antitumor activity on melanoma, leukemia, colon, lung, ovarian, CNS, renal, breast and prostate cancers cell lines have become a promising area of research. Different researchers have reviewed the progress on the scaffold from time to time, such as Jain et al. [2], Hamama et al. [3], Verma et al. [4], Abdel-Rahman et al. [5], Singh et al. [6], and our group has also been continuously involved in researching this nucleus through chemical modifications with encouraging results [7].

Indeed, 4-thiazolidinones have many interesting activity profiles including non-nucleoside inhibitors of HIV-RT [8], namely COX-1 inhibitors [9], antidiabetic [10], inhibitors of aldose reductase [11,12], inhibitors of the bacterial enzyme MurB which is a precursor acting during the biosynthesis of peptidoglycan and YycG histidine kinase [13,14]. Moreover derivatives of 4-thiazolidinones have been reported for anthelmintic, antitubercular and antifungal activities [2].

Thiazolidinones with C-2 and N-3 substituted positions possess diverse degrees of inhibition against bacteria and fungi. The SAR studies of thiazolidinone derivatives showed that they are more effective on Gram-negative bacteria as compared to Gram-positive bacteria. The search for new antimicrobial agents will continuously remain as an important and challenging task for medicinal chemists. With this in mind and as part of our ongoing studies towards the development of new antimicrobial agents, the various structural modifications in the series of synthesized compounds were evaluated against a variety of pathogens for their antibacterial and antifungal activity. DFT calculations have also been performed to simulate the effect of H-bonding interactions on the molecular structure and electronic properties of the investigated systems. TD-DFT calculations were used to predict the accurate electronic transitions and to draw the HOMO and LUMO levels. The natural bond orbital (NBO) calculations were used to predict the stabilization energies due to intramolecular charge transfer (ICT) within the studied systems.

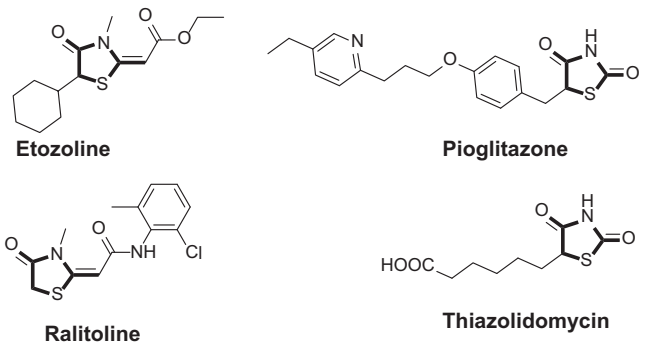

Fig. 1. Some biologically important thiazolidinone compounds.

Experimental

Materials and methods

All the chemicals were purchased from Sigma–Aldrich, Fluka etc., and were used without further purification, unless otherwise stated. Melting point was measured on a Gallenkamp melting point apparatus in open glass capillaries and is 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 dimethylsulfoxide (DMSO-d_6). Chemical shifts (δ) are referred in terms of ppm and *J*-coupling constants are given in Hz. Mass spectra were recorded on a Jeol of JMS-600 H. Elemental analysis was carried out on Elmer 2400 Elemental Analyzer; CHN mode.

*Synthesis of 5-((2,4-dichlorophenyl)(hydroxy)methyl)-2-thioxothiazolidin-4-one (**3**)*

A mixture of 2,4-dichlorobenzaldehyde (3 mmol, 525 mg), 2-thioxothiazolidin-4-one **1** (3 mmol, 400 mg), and diethylamine (3 mmol, 310 µl) in 3 mL of degassed H_2O was stirred at room temperature for 30 min, the crude product was extracted with mixture of DCM/EtOH, was with 10%HCl (2 × 10 mL), the organic phase was with brine and recrystallized from DCM/EtOH to afford **3** yellow crystalline material (0.8 g, 2.6 mmol, 87%). m.p: 80 °C; IR (KBr, cm^{-1}): 3450, 3015, 1744, 1350; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (bs, 1H, NH), 7.70(s, 1H, Ph), 7.60–7.25 (m, 4H, CH&CH& Ph); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 198.1, 177.8, 136.1, 134.9, 133.7, 131.6, 129.8, 128.2, 67.1, 65.1; LC/MS (ESI): 309 [M]$^{+}$; Anal. for $C_{10}H_7Cl_2NO_2S_2$; calcd: C, 38.97; H, 2.29; Cl, 23.01; N, 4.54; Found: C, 39.01; H, 2.31; Cl, 23.12; N, 4.57.

Antimicrobial activity

Chemical compounds were individually tested against a panel of gram positive and negative bacterial pathogens. Antimicrobial tests were carried out by the agar well diffusion method [15–17] using 100 mL of suspension containing 1 × 10^{8} CFU/mL of pathological tested bacteria, 1 × 10^{6} CFU/mL of yeast and 1 × 10^{4} spore/mL of fungi spread on nutrient agar (NA), Sabourand dextrose agar (SDA), and potato dextrose agar (PDA) medium respectively. After the media had cooled and solidified, wells (10 mm in diameter)