Journal of Molecular Structure 1127 (2017) 99–113

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Synthesis, stereochemistry determination, pharmacological studies and quantum chemical analyses of bisthiazolidinone derivative

Md. Mushtaque [a, *], Fernando Avecilla [b], Zubair Bin Hafeez [c, 1], Meriyam Jahan [a, 1], Md. Shahzad Khan [e, 1], M. Moshahid A. Rizvi [c, **], Mohd. Shahid Khan [d], Anurag Srivastava [e], Anwesha Mallik [f], Saurabh Verma [f]

[a] School of Physical and Molecular Sciences, Department of Chemistry, Al-Falah University, Dhauj, Faridabad, Haryana, 121004, India
[b] Departamento de Química Fundamental, Universidade da Coruña, Campus da Zapateira s/n, A Coruña, 15008, Spain
[c] Department of Biosciences, Jamia Millia Islamia, New Delhi, 110025, India
[d] Department of Physics, Jamia Millia Islamia, New Delhi, 110025, India
[e] Advanced Material Research Group, ABV-Indian Institute of Information Technology and Management, Gwalior, 474015, India
[f] National Institute of Pathology, Safdarjung Hospital Campus, New Delhi, 110029, India

ARTICLE INFO

Article history:
Received 17 June 2016
Received in revised form
17 July 2016
Accepted 20 July 2016
Available online 22 July 2016

Keywords:
Cytotoxicity
Cell cycle perturbation
DNA binding
Molecular docking and DFT studies

ABSTRACT

A new compound **(3)** bisthaizolidinone derivative was synthesized by Knoevenagel condensation reaction. The structure of synthesized compound was elucidated by different spectral techniques and X-ray diffraction studies. The stereochemistry of the compound **(3)** was determined by $^{1}H-^{1}H$ NOESY, $^{1}H-^{1}H$ NMR COSY and single crystal X-ray diffraction studies as *(Z, Z)*-configuration. The computational quantum chemical studies of compound(3) like, IR, UV, NBO analysis were performed by DFT with Becke-3-Lee-Yang-Parr (B3LYP) exchange-correlation functional in combination with 6−311++G(d,p) basis sets. The DNA-binding of compound **(3)** exhibited a moderate binding constant ($\mathbf{K_b = 1 \times 10^5\ Lmol^{-1}}$) with hypochromic shift. The molecular docking displayed good binding affinity **−7.18 kcal/mol**. The MTT assay of compound **(3)** was screened against different cancerous cell lines, HepG2, Siha, Hela and MCF-7. Studies against these cell lines depicted that the screened compound **(3)** showed potent inhibitory activity against HepG2 cell ($\mathbf{IC_{50} = 7.5\ \mu M}$) followed by MCF-7 ($\mathbf{IC_{50} = 52.0\ \mu M}$), Siha ($\mathbf{IC_{50} = 66.98\ \mu M}$), Hela ($\mathbf{IC_{50} = 74.83\ \mu M}$) cell lines, and non-toxic effect against non-cancerous HEK-293 cells ($\mathbf{IC_{50} = 287.89\ \mu M}$) at the concentration range (**0**−**300**) μM. Furthermore, cell cycle perturbation was performed on HepG2 & Siha cell lines and observed that cells were arrested in G2/M in HepG2, and G0/G1 in Siha cell lines with respect to untreated control. Hence, compound **(3)** possesses potent anti-cancerous activity against HepG2 cell line.

1. Introduction

Cancer is one of the deadliest diseases in human race ever seen [1]. According to world health organization (WHO), it is second most lethal disease causing deaths both in developing and developed countries [2]. All the developed, developing and under developed countries have constantly been afraid of this disease because it devastates both manpower as well as economy; thus creating havoc [3] for example, Asian countries like China and India along with Russia contribute more than half of the total cancer cases [4]. The current data of India show that every year, around 0.7 million people are losing their lives with one million new diagnosed cancer patients, which are estimated to be roughly doubled by the year 2035 [4]. Similarly, it is predicted that by 2030, approximately 20 million new cancer cases will be diagnosed worldwide and about 13 million cancer patients will die from this disease [3,5]. Indeed, many treatment modalities and drugs are available in the market to curb this terrifying disease like bio-alkylating (chloramethine) [6], anti-metabolic agents (fluorouracil) [7], anti-cancer antibiotics (doxorubicin) [8].

The anti-cancer drug development with less or no side effect is very important for chemotherapy of cancer. The necessity of such

** Corresponding author.
* Corresponding author.
E-mail addresses: mush.chem@gmail.com (Md. Mushtaque), rizvi_ma@yahoo.com (M.M.A. Rizvi).
[1] These authors contributed equally.

http://dx.doi.org/10.1016/j.molstruc.2016.07.089
0022-2860/

potent anti-cancer therapeutic agents has led to discovery of small synthetic molecules which have anti-cancer activity with lesser side effects. Thiazolidone molecular scaffold is of great importance in modern medicinal chemistry, and is known to exhibit a diverse range of pharmacological activities like anti-cancer [9–12], anti-bacterial [13–15] Fig. 1(a&b), anti-fungal [16–18], anti-viral [19–22], and anti-HIV [23,24].

Previous studies on this class of molecule report excellent anti-amoebic activity with a high cytotoxicity [25]. In the view of versatile pharmacological importance, we herein, report the synthesis, characterization, DNA binding, molecular docking and DNA, cell cycle perturbation, and cytotoxicity. Also, a DFT study was carried out for evaluation of its biological potency of compound **(3).**

2. Results and discussion

2.1. Chemistry

The presented compound **(3)** (2Z, 2′Z, 5Z, 5′Z)-5,5′-(1,4-phenylenebis (methanylylidene)) bis(3-isopropyl-2-(phenylimino) thiazolidin-4-one), was synthesized by reported method [26]. The compound **(3)** was prepared in absolute ethanol using terephthaladehyde and thiazolidinone by Knoevenagel condensation reaction as shown in Scheme 1. The compound **(3)** is stable at room temperature and well characterized by different spectroscopic techniques; CHNS analysis, FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The stereochemistry of compound **(3)** was determined by ^{1}H–^{1}H COSY-NMR and ^{1}H–^{1}H NOESY-NMR. Furthermore, stereochemistry was confirmed by X-ray single crystal structure.

The appearance and disappearance of the characteristic bands confirmed the formation of the compounds. In FT-IR, the appearance of the significant bands at 3265.14 cm^{-1} and 1240.83 cm^{-1} due to –NH and C═S confirmed the formation of compound (**1**). In ^{1}H NMR, the chemical shifts appeared at 8.267 ppm and 5.783 ppm due to presence of –NH protons, confirmed the formation of compound **(1).** Additionally, the compound **(1)** was confirmed by ^{13}C NMR. The presence of significant peak at 178.94 ppm was assigned to C═S, indicated the formation of compound **(1).** In case of intermediate compound **(2),** in IR, the appearance of characteristic bands at 1715.24 cm^{-1} and 1627.65 cm^{-1} due to –C═O and –C═N confirmed the formation of compound **(2).** In ^{1}H NMR, the presence of singlet at chemical shift 3.701 ppm due to the presence of-S–CH_2–C═O proton showed the formation of compound **(2).** The lead compound **(3)** was also confirmed by same spectroscopic techniques along with mass spectrometry and X-ray single crystal structure. In FT-IR, the presence of characteristic bands at 1704 cm^{-1} and 1629 cm^{-1} due to C═O and C═C confirmed the formation of compound**(3).** In ^{1}H NMR, the presence of characteristic peak resonated at high chemical shift at 7.631 ppm due to methylene (H–C═C-) proton confirmed the formation of compound **(3).** In ^{13}C NMR, the appearance of significant peaks due to C═O and C═C at 166.56 ppm and 148 ppm chemical shifts confirmed the formation of compound **(3)**. In mass spectrometry, the presence of $[M+H]^+$, $[M+2H]^+$ and $[M+3H]^+$ peaks at 567.18, 568.19 and 569.18 showed the formation of compound **(3).** Additionally, the structure of the compound **(3)** was confirmed by X-ray single crystal structure.

2.2. Stereochemistry and conformational properties

The determination of *E* or *Z*-configuration is important for compound **(3)** due to the presence of exocyclic C═N and C═C bonds. The configuration of compound **(3)** was determined by 2D-^{1}H–^{1}H COSY-NMR and ^{1}H–^{1}H NOESY-NMR. In ^{1}H–^{1}H COSY-NMR, the strong interactions were observed along off-diagonal peaks. The doublet due to methyl group at the range of 1.623–1.051 (ppm) chemical shift interacted with multiplet of CH at the range of 5.051–4.982 (ppm) chemical shift. But no off-diagonal peaks are present in the region of the aliphatic protons attached to the nitrogen of thiazolidinone ring and aromatic protons substituted at exocyclic nitrogen which could show correlation among them, indicating that the position of aromatic moiety adopted *Z*-configuration. Furthermore, there are strong interactions among the protons of exocyclic nitrogen substituted aromatic ring at chemical shifts range 7.432–7.349 ppm and 5-arylidene aromatic protons at chemical shift 6.990 ppm which confirms *Z*-configuration of exocyclic 5-arylidene. A *Z*-configuration of aromatic ring attached to exocyclic C═C bond of thiazolidinone derivative was further confirmed by a methine proton signal which resonated at a higher chemical shift 7.632 ppm as a singlet in ^{1}H NMR spectrum. The downfield chemical shift of the methine proton was due to deshielding effect of carbonyl group. Studies on *E*-configuration suggest the upfield resonance at chemical shift 6.6 ppm or less than δ 6.6 (ppm) [25–28]. In 2D NOESY ^{1}H NMR, the C═N imino and the C═C exocyclic double bond exhibited strong NOE signals at chemical shifts 7.432–7.349 ppm and 6.990 ppm due to the interaction of protons of two aromatic rings attached to imine (C═N) and 5-arylidene, indicating *Z*-configuration. No NOE signals were observed for exocyclic *N*-substituted aromatic protons and aliphatic (chain attached to the *N*-of thiazolidinone) protons which suggest that the molecule adopted Z-configuration. Additionally, a study of X-ray single crystal structure confirmed (*Z, Z*)-configuration Fig. 2.

2.2.1. Discussion of crystal structure

ORTEP diagram for the compound **(3)** (2Z,2′Z,5Z,5′Z)-5,5′-(1,4-Phenylene bis(methanylylidene))bis(3-isopropyl-2-(phenylimino) thiazolidin-4-one), was shown in Fig. 3. The asymmetric unit of **1**

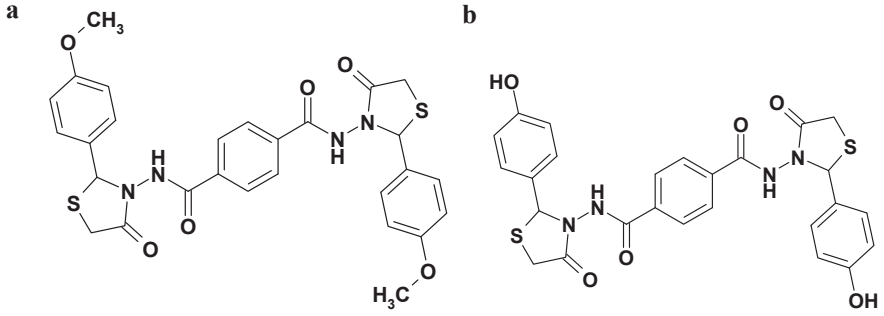

Fig. 1. (a–b): 4-Thaizolidinone derivatives (1 a & b) showing anti-bacterial.