Journal of Saudi Chemical Society (2013) **xxx**, xxx–xxx

King Saud University

Journal of Saudi Chemical Society

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Synthesis, characterization and biological evaluation of 4-oxo-thiazolidine compounds

Dinesh R. Godhani [a,*], Anand A. Jogel [a], Purvesh B. Dobariya [a], Anil M. Sanghani [b]

[a] *Department of Chemistry, DST-FIST Sponsored, Mahatma Gandhi Campus, Maharaja Krishnakumarsinhji Bhavnagar University, Bhavnagar 364022, Gujarat, India*
[b] *Chemistry Department, Sir P.P. Institute of Science, Bhavnagar 364002, Gujarat, India*

Received 8 February 2013; accepted 26 March 2013

KEYWORDS

4-Oxo-thiazolidine;
Antibacterial activity;
Antifungal activity;
Antitubercular activity

Abstract A series of compounds 4-oxo-thiazolidine derivatives $\mathbf{AJ5_{a-j}}$ were synthesized by condensation reactions. The structure of synthesized compounds was characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The present paper deals with newly synthesized thiazolidine compounds $\mathbf{AJ5_a}$–$\mathbf{AJ5_j}$ that were screened for their antimicrobial activity against different strains of bacteria and fungi using serial broth dilution method (Mueller–Hinton broth dilution method). *In vitro* antitubercular activity of compounds $\mathbf{AJ5_{a-j}}$ was carried out against *Mycobacterium tuberculosis* H_{37}Rv. Compounds $\mathbf{AJ5_a}$, $\mathbf{AJ5_d}$, $\mathbf{AJ5_e}$, $\mathbf{AJ5_f}$ and $\mathbf{AJ5_g}$ were found most active against selected bacterial strains (MIC = **62.5** μg/mL) and compounds $\mathbf{AJ5_{a-j}}$ were found moderately active against *M. tuberculosis*.

1. Introduction

Tuberculosis is an infection that caregivers in poor countries face every day. Its treatment does not essentially require a vertical programme and should be a part of regular medical activities, even when the number of patients is limited. According to the WHO, eight to ten million new tuberculosis cases are reported worldwide, and two million people die due to tuberculosis sickness. The growing problem of struggle against tuberculosis drugs (half a million new cases of multi drug resistance TB annually) has further made tuberculosis management a difficult task (Balasco et al., 2010; WHO, 2006). The nucleus of 4-oxo-thiazolidine derivatives has occupied a unique place in the field of medicinal chemistry due to a wide range of biological activities (Joshi et al., 2001). They have interesting activity profiles mainly cox-1 inhibitors, inhibitors of bacterial enzyme, non nucleoside inhibitors of HIV Type 1 Reverse Transcriptase (HIVRT) and antihistaminic agent (Diurno and Vittnsia, 1999). 4-Oxo-thiazolidines are derivatives of thiazolidinone with a carbonyl group at the 4th position formed by the attack of sulphur nucleophile on imine carbon followed by

* Corresponding author. Tel.: +91 9687615488.
E-mail address: drgodhani@yahoo.com (D.R. Godhani).
Peer review under responsibility of King Saud University

Production and hosting by Elsevier

1319-6103 © 2013 Production and hosting by Elsevier B.V. on behalf of King Saud University.
http://dx.doi.org/10.1016/j.jscs.2013.03.002

intramolecular cyclization with elimination of water. Recent studies on molecular modification of the later 1*H*, 3*H*-thiazolo [3,4-a] benzimidazoles (TBZs) revealed that, dismantling of the imidazole nucleus leading to the design of new 4-oxo-thiazolidine derivatives, maintained the molecular requirements for enzyme inhibition. A literature search revealed that 4-oxo-thiazolidine derivatives may exhibit anti-HIV (Rawal et al., 2005) enzyme murB (Andres et al., 2000), antimicrobial activity (Srivastava and Srivastava, 2002), antituberclousis (Babaoglu et al., 2003; Govindarajan et al., 2003) antiproliferative agent (Ottanà et al., 2005), CNS activity (Basu et al., 2008), cytotoxic agent (Gududuru et al., 2005), anticonvulsant activity (Archana et al., 2002), antibacterial activity (Bonde and Gaikwad, 2004; Sayyed et al., 2006), analgesic agent (Moustfa et al., 1989), antiinflammetry agent (Vigorita et al., 2001; Goel et al., 1999), antihypertensive agent (El-subbagh, 1999), and hypolipidemic agent (Lohary et al., 1999) properties.

2. Synthetic aspects

Syntheses of 4-oxo-thiazolidines have been reported either by cyclization of acyclic compound or by interconversion among appropriately substituted 4-oxo-thiazolidine derivatives. Mane et al. (2001) have synthesized 4-oxo-thiazolidine bearing 2-mercapto-4-methylimidazoles moiety. Mogilaiah et al. (1999) have synthesized 2-aryl-3-(2-trifluromethyl-1,8-naphthyridine-3-carbonylamino)-4-thiazolidinones. Synthesis of 4-oxo-thiazolidine has been reported by the microwave irradiation (Abdel et al., 1994). Parikh et al. (1980) have synthesized a variety of 4-oxo-thiazolidine bearing diphenyl sulphone, substituted aryl arsanilic acid, 2-aryl-1,3,4-thiadiazole,γ-picolinylamino, sulphonamido benzoylamino, phthalazine-1-yl-amino, aryl substituted hydroxyaryl, β-β-dichloroethylaminophenyl and 8-hydroxy-quinolinyl moieties. 4-Oxo-thiazolidines have been reported as potent antimicrobial agents.

In view of above findings and continuation of our research programme to find effective new antimicrobial and antitubercular agents for the treatment of infectious diseases, the present study focused on the synthesis and biological evaluation of some 4-oxo-thiazolidine derivatives **AJ5$_{a–j}$** by modified protocols.

3. Experimental

Melting points are determined on a Gallenkemp melting point apparatus and are uncorrected. Completion of reaction and purity of synthesized compounds are checked on aluminium-coated TLC plates 60 F_{245} (E. Merck) using benzene:ethyl acetate (8:2 V/V) as mobile phase and visualized under ultraviolet (UV) light or iodine vapour. All compounds were purified by combi flash chromatography using ethylacetate:hexane as eluent. Elemental analysis (% C, H, N) is carried out by a Perkin–Elmer 2400 CHN analyser. IR spectra of compounds have been recorded on Thermo-Nicolet FT-IR-200 spectrophotometer in KBr disc (cm^{-1}). ^1H NMR and ^{13}C NMR spectra are recorded on Bruker DRX (200 MHz) spectrometer using $CDCl_3$ as a solvent and TMS as an internal standard. Chemical shifts are reported in parts per million (δ_{ppm}). Mass spectra of synthesized compounds (**AJ5$_{a–j}$**) were carried out using the shimadzu GC–MS (Shimadzu 2010 plus) direct probe method. Compounds (**AJ5$_{a–j}$**) were synthesized by using Random synthesizer Syrris IKA-RCA with safety control.

3.1. Preparation of (E)-N′-(4-chlorobenzylidene)-2-(3-(4-fluorophenyl)-4-oxo-3,4-dihydroquinazolin-2-ylthio) acetohydrazide (4_a)

A mixture of compound **(3)** (0.01 mol) and 4-chlorobenzaldehyde (0.01 mol) in ethanol was refluxed. During the refluxing period 2–3 drops of acetic acid was added and the reaction mixture was refluxed for 8 h. The product was filtered and washing with sodium bicarbonate solution was carried out to remove excess of acidity. The intermediate product was crystallized from methanol and chloroform (1:1, v/v) mixture to yield compound (**4$_a$**). Similarly, compound (**4$_{b–j}$**) is also prepared using a similar method.

3.2. General procedure for synthesis of N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-2-((3-(4-fluorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio)acetamide (AJ5$_{a–j}$)

A mixture of compound **4$_{a–j}$** (0.01 mol) in dioxan and mercapto acetic acid (0.01 mol) with a pinch of $ZnCl_2$ was refluxed for about 10 h. The separated solid was crystallized from ethanol to get compounds (**AJ5$_{a–j}$**).

3.3. Elemental and characterization data of 3-(4-fluorophenyl)-2-mercaptoquinazolin-4(3H)-one (1)

This was prepared according to the literature method (Sanja et al., 2007).

Yield: 75%. M. p.-263 °C. IR (KBr): 1193 cm^{-1} (–C–O stretching), 1310 cm^{-1} (Ar–C–H bending of $–CH_2$), 835 cm^{-1} (p-substituted benzene ring), 653 cm^{-1} (C–S stretching), 1730 cm^{-1}(C═O stretching of benzene ring), 1490 cm^{-1} (Ar–C═C aromatic stretching band), 968 cm^{-1} (–C–F stretching in benzene ring), 1632 cm^{-1} (C═N stretching in quinoline). ^1H NMR ($CDCl_3$, 200 MHz): δ 6.612–7.165 ppm (s, 8H, –Ar–H), δ 2.440 ppm (s, 1H, –SH of thiole). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 115.7–162.9 ppm (Ar–C, 8C benzene ring), δ 160.6 ppm (Ar–C═O, 1C of quinoline), δ 146.9, 128.3 ppm (Ar–C–N, 2C of quinoline), δ 159.3 ppm (Ar–C–SH, 1C of thiole), δ 162.9 ppm (Ar–C–F, 1C of aniline), δ 120.9 ppm (Ar–C–C, 1C of benzene ring). MS: *m*/z (relative intensity %), (73%) M^+224 amu Anal Calcd (%) for $C_{14}H_9FN_2OS$: C. 61.75; H, 3.33 N. 10.29; Found: C. 61.74; H, 3.32; N. 10.29.

3.4. Elemental and characterization data of ethyl 2-(3-(4-fluorophenyl)-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetate (2)

The equimolar solution of compound **1** (0.1 mol) and ethyl chloro acetate (0.1 mol) in dry acetone (35 mL) in the presence of K_2CO_3 (0.15 mol) was refluxed on a water bath for about 12 h. The reaction mixture was poured on ice to get a solid product, and was washed with methanol. Compound **(2)** is crystallized in ethanol to get compound **(2)**.

Yield: 73%. M. p.- 186 °C. IR (KBr): 1194 cm^{-1} (–C–O stretching), 1312 cm^{-1} (Ar–C–H bending) 833 cm^{-1} (p-substituted benzene ring), 656 cm^{-1} (C–S stretching), 1732 cm^{-1}(C═O stretching of benzene ring), 1492 cm^{-1} (Ar–C═C aromatic stretching band), 966 cm^{-1} (–C–F stretching in benzene ring), 1634 cm^{-1} (C═N stretching of quinoline), 2930 cm^{-1} (–CH stretching $–CH_3$ & $–CH_2$). ^1H NMR ($CDCl_3$, 200 MHz): δ 6.614–7.167 ppm (s, 8H, –Ar–H), δ 2.440 ppm (s, 1H, –SH of thiole), δ 4.123 ppm (s, 3H, $–CH_3$ of ester) δ

Please cite this article in press as: Godhani, D.R. et al., Synthesis, characterization and biological evaluation of 4-oxo-thiazolidine compounds. Journal of Saudi Chemical Society (2013), http://dx.doi.org/10.1016/j.jscs.2013.03.002