



SYNTHESIS AND ANTITUBERCULAR ACTIVITY OF NOVEL 2-ARYL N-(3,4,5-TRIHYDROXY BENZAMIDO)-4- THIAZOLIDINONE DERIVATIVES

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ABSTRACT

A series of novel 2-Aryl -N-(3,4,5-trihydroxy benzamido)-4-thiazolidinone derivatives (3a-f) were synthesized by reacting various Schiff bases of galloyl hydrazide 2(a-f) with thioglycolic acid in presence of dioxan. The newly synthesized compounds were characterized by IR, MS, ¹H NMR spectrum and elemental analysis. The compounds were evaluated for antitubercular activity against *Mycobacterium tuberculosis* H37Rv by Microplate Alamar Blue Assay (MABA) method. The experimental results revealed that compound 3f exhibited promising antitubercular activity.

Key words: Gallic acid; Thiazolidinone; Antitubercular.

INTRODUCTION

Tuberculosis (TB) is one of the most common infections caused by *Mycobacterium tuberculosis*. According to the World Health Organization (WHO), nearly 2 billion people, i.e. one third of the world's population have been exposed to the tuberculosis pathogen¹. Annually, 8 million people become ill with tuberculosis². The association of tuberculosis and HIV infections is so dramatic that in some cases, nearly two- third of the patients diagnosed with the tuberculosis are also HIV- seropositive³. There have been no new classes of TB drugs in 40 years. Isoniazid continues to be the drug of choice for TB⁴. Moreover there has been a recent and disturbing increase in the number of TB cases that are caused by organisms which are resistant to the first-line drugs such as Isoniazid, Rifampicin, Ethambutol, Streptomycin and Pyrazinamide⁵. On September 1, 2006, WHO announced that a deadly new strain of extensively drug-resistant tuberculosis (XDR-TB) had been detected in Tugela Ferry, a rural town in the South African province of KwaZulu-Natal, the epicentre of South Africa's HIV/AIDS epidemic. Of the 544 patients studied in the area in 2005, 221 had multi-drug-resistant tuberculosis (MDR-TB). Of these 221 cases, 53 were identified as XDR-TB⁶, i.e., MDR-TB plus resistance to at least three of the six classes of second-line agents⁷. The Global Alliance for TB Drug Development (GATB) was established to address this need⁸. Its top priority is the development of new agents that will shorten the duration of chemotherapy from the current 6–8 months to two months or less, although new drugs with activity against multidrug resistant tuberculosis and latent TB are also needed. Gallic acid is a naturally occurring antioxidant. It occurs along with tannins. It possesses various biological activities like analgesic,⁹ antineoplastic,¹⁰ antiproliferative¹¹ and anti-inflammatory¹². Keeping this in mind, a large number of gallic acid derivatives were prepared in our laboratory and screened for antimycotic activity.

EXPERIMENTAL

Reactions were monitored by thin layer chromatography (TLC) on pre coated silica gel plates obtained from E. Merck and Co. Melting points were determined in an Veego digital melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR Spectrophotometer. ¹H NMR spectra were measured with a Bruker Spectrophotometer [400 MHz] in CDCl₃ using TMS as an internal standard. Mass spectra were obtained with LC-MSD Trap- SL 2010 A-Shimadzu.

Synthesis of galloyl hydrazide, (1a)

A solution of propyl gallate (0.01 mol) in ethanol and hydrazine hydrate (0.01 mol) was refluxed for 6 hours. The excess solvent was distilled off under reduced pressure. The cooled residual mass was washed with distilled water. It was filtered and dried. The crude product was recrystallised from methanol to yield galloyl hydrazide **1a**.

Synthesis of N-substituted arylidene galloyl hydrazide, (2a-f)

Equimolar concentration of galloyl hydrazide **1a** and various aromatic aldehydes in ethanol were refluxed for 6 hours. The completion of reaction was monitored on silica gel G pre-coated TLC plates using ethylacetate and petroleum ether (1:1) as an eluent and observed under UV light. The resultant mixture was poured into ice cold water. The crude Schiff bases were washed, filtered, dried and recrystallised from ethanol.

Synthesis 2-Aryl -N-(3,4,5-trihydroxy benzamido)- 4-thiazolidinones, (3a-f)

Thioglycolic acid (0.05mole) was added to the solution of Schiff base (0.03 mole) in benzene and refluxed for 6 hours at a temperature of 45-50 °C. The solvent was removed and the reaction mixture was poured into ice cold water. The crude product was filtered and recrystallized from DMF.

2-(phenyl)-N-(3,4,5-trihydroxy benzamido)-4-thiazolidinone (3a)

Yield: 70 %, M.p.; 221 °C. IR (cm⁻¹): ν(Ar-OH) 3613; ν(N-H) 3467; ν(CH) 2977; ν(CO-NH) 1648; ν(CH-N) 1474; ν(C=O) 1744; ¹H NMR δ (ppm): 7.08- 7.44 (m, 7H, Ar-H), 2.33 (s, 3H, OH), 5.2 (s, 1H, CH-N) and 4.15 (s, 1H, NH). MS 388 [M⁺]

2-(2-hydroxy phenyl)-N-(3,4,5-trihydroxy benzamido)-4-thiazolidinone (3b)

Yield: 73 %, M.p.; 198 °C. IR (cm⁻¹): ν(Ar-OH) 3613; ν(N-H) 3467; ν(CH) 2977; ν(CONH) 1648; ν(CH-N) 1474; ν(C=O) 1755. ¹H NMR δ (ppm): 7.68-8.34 (m, 6H, Ar-H), 2.76 (s, 3H, OH), 5.43 (s, 1H, CH-N) and 4.75 (s, 1H, NH). MS 404 [M⁺]

2-(2-hydroxy 3-methoxyphenyl)-N-(3,4,5-trihydroxy benzamido)-4-thiazolidinone (3c)

Yield: 67%, M.p.; 217 °C. IR (cm⁻¹): ν(Ar-OH) 3614; ν(NH) 3458; ν(CH) 2985; ν(CONH) 1661; ν(CH-N) 1482; ν(C=O) 1743; ν(COC) 1268. ¹H NMR δ (ppm): 7.12- 8.44 (m, 5H, Ar-H), 3.48 (s, 3H, OH), 5.5 (s, 1H, CH-N), 4.4 (s, 1H, NH) and 3.9 (s, 3H, OCH₃). MS 418 [M⁺]

2-(3-hydroxy phenyl)-N-(3,4,5-trihydroxy benzamido)-4-thiazolidinone (3d)

Yield: 63 %, M.p.; 206 °C. IR (cm⁻¹): ν(Ar-OH) 3632; ν(NH) 3465; ν(CH) 2977; ν(CONH) 1667; ν(CN) 1458; ν(C=O) 1731. ¹H NMR δ (ppm): 7.52- 8.91 (m, 6H, Ar-H), 3.31 (s, 3H, OH), 7.48 (s, 1H, CH-Cl), 5.5 (s, 1H, CH-N) and 4.4 (s, 1H, NH). MS 418 [M⁺]

2-(4-hydroxy phenyl)-N-(3,4,5-trihydroxy benzamido)-4-thiazolidinone (3e)

Yield: 64 %, M.p.; 228 °C. IR (cm⁻¹): ν(Ar-OH) 3609; ν(NH) 3358; ν(CH) 2978; ν(CONH) 1653; ν(CN) 1483; ν(C=O) 1772. ¹H NMR δ (ppm) : 7.08- 8.58 (m, 6H, Ar-H), 2.78 (s, 3H, OH), 5.5 (s, 1H, CH-N) and 4.4 (s, 1H, NH). MS 404 [M⁺]

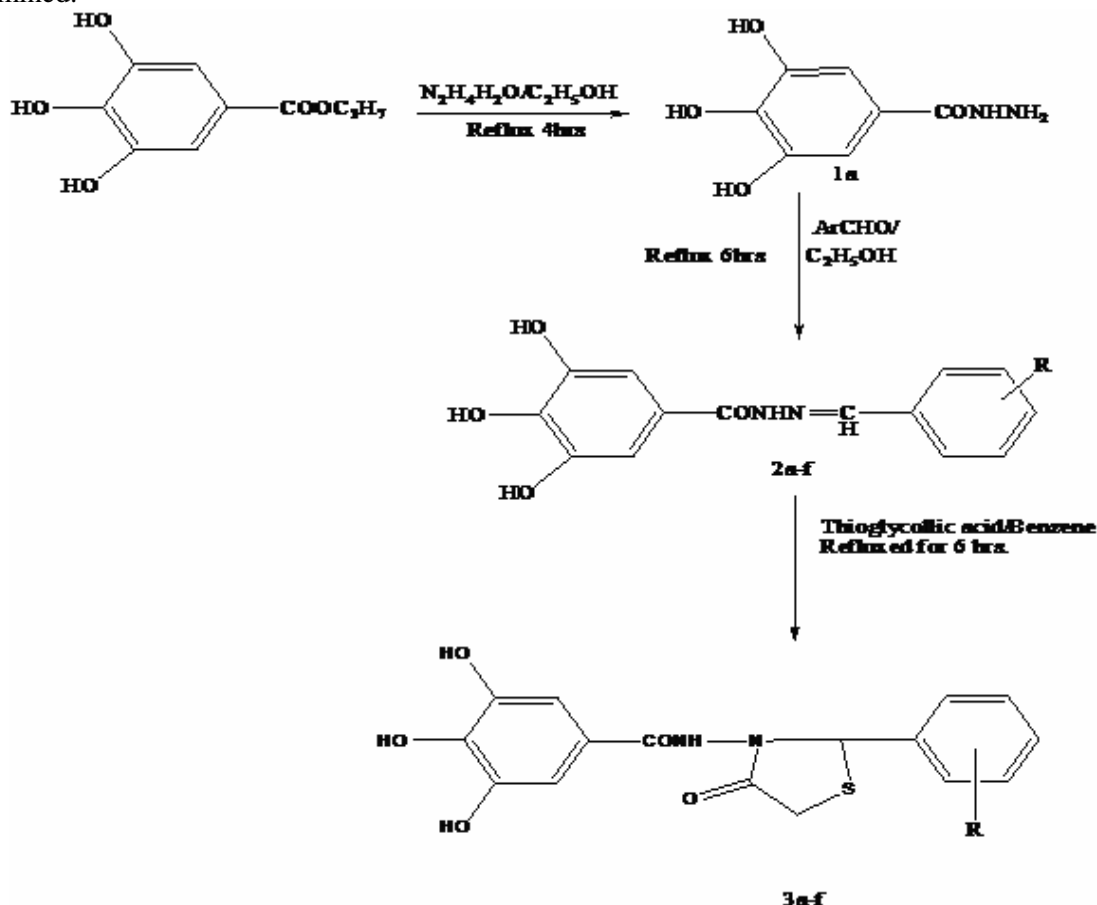
2-(2-chloro phenyl)-N-(3,4,5-trihydroxy benzamido)-4-thiazolidinone (3f)

Yield: 71%, M.p.; 243 °C. IR (cm⁻¹): ν(Ar-OH) 3790; ν(NH) 3330; ν(CONH) 1591; ν(C=O) 1726. ¹H NMR δ (ppm): 7.12-8.48 (m, 6H, Ar-H), 2.83 (s, 3H, OH), 7.7 (s, 1H, CH-Cl), 5.3 (s, 1H, CH-N) and 4.8 (s, 1H, NH). MS 422 [M⁺]

Antitubercular activity

Antitubercular activity was evaluated against *Mycobacterium tuberculosis* H37 Rv ATCC27294 using well known Microplate Alamar Blue Assay method. Antitubercular susceptibility testing was performed in black, clear-bottomed, 96-well microplates (black view plates; Packard Instrument Company, Meriden) in order to minimize background fluorescence. Initial drug dilutions were prepared in dimethylsulfoxide, and subsequent two fold dilutions were performed in 0.1 ml of 7H9GC media in the microplates. 100ml of 2000CFU/ml of *Mycobacterium tuberculosis* H37 Rv in 7H9GC were added to each well of 96 well microtitre plate containing test compounds. Three control well plates containing drug and medium, bacteria and medium and medium only were prepared and microtitre plates were incubated at 37°C. At day 7 of incubation Alamar Blue dye solution (20 µl Alamar Blue solution and 12.5 ml of 20% Tween 80)

were added to all the wells and plates were re-incubated at 37 °C. for 24 hours. Fluorescence was measured in a Victor II multilabel fluorometer (Perkin Elmer Life Sciences Inc., Boston) and MIC was determined.



Schem-1: Synthesis of novel thiazolidinone 3a-f of Gallic acid

RESULTS AND DISCUSSION

The results of *in vitro* antitubercular activity of the synthesized compounds **3a-f** against *M. tuberculosis* H37Rv were listed in Table 2. Compound **3f** showed MIC values equivalent to the standard drug Isoniazid. The substitution with chloro group in phenyl ring of thiazolidinone nucleus is highly active. This suggests that electron withdrawing groups enhances the activity. It is interesting to note that some of the existing drugs for the treatment of TB like Pyrazinamide, Isoniazid and Ethionamide also possess electron withdrawing groups. Further studies are going on in our laboratory to establish the quantitative structure activity relationship (QSAR) of the series.

Table-1: Physico chemical parameters of the synthesized compounds (3a-f).

Compound	R	Molecular Formula	Color	Mol. Wt.	%Yield
3a	H	C ₁₈ H ₃₁ N ₂ O ₅ S	Pale yellow	387.5	68
3b	2-OH	C ₁₈ H ₃₁ N ₂ O ₆ S	Pale yellow	403.5	72
3c	2-OH-3-OCH ₃	C ₂₀ H ₃₄ N ₂ O ₇ S	Pale yellow	417.5	69

3d	3-OH	C ₁₈ H ₃₁ N ₂ O ₆ S	Yellow	403.5	78
3e	4-OH	C ₁₈ H ₃₁ N ₂ O ₆ S	Yellow	403.5	73
3f	2-Cl	C ₁₈ H ₃₀ ClN ₂ O ₅ S	Brown	421.9	80

Table-2: Antitubercular activity of the synthesized compounds (3a-f).

Compound	R	Antitubercular activity(MIC in µg/ml)
3a	H	2.8
3b	2-OH	5.3
3c	2-OH-3-OCH ₃	3.7
3d	3-OH	5.8
3e	4-OH	9.7
3f	2-Cl	0.79
Isoniazid	-	0.56

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