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Synthesis and Antimycobacterial Activity of Thiazole Derivatives

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In this paper, a series of thiazole derivative compounds were synthesized and their antimicrobial as well as antimycrobacterial activities are discussed. Many of these compounds have shown better antimicrobial and antimycrobacterial activities while others were inactive.

Key Words: Synthesis, Thiazole derivatives, Antimycobacterial.

INTRODUCTION

The synthesis of substituted thiazoles[1] has attracted considerable attention in recent years, as this class of compounds constitute an important place in therapeutics. Thiazole derivatives are reported to have an array of biological activities as antiinflammatory, antimicrobial, antitubercular, CNS depressant, anticancer, etc[2]. Tuberculosis remains the major cause of death over the world. Emergence of multi-drug resistant tuberculosis has made the condition most alarming. Up to 4% of all tuberculosis cases worldwide are resistant to more than one antitubercular drug because of incomplete or partial therapy[3]. Therefore, there is an urgent demand for a new class of antitubercular agents with a different mode of action. A *de novo* structural design has demonstrated that the thiazole derivatives especially with carbonyl group scaffold inhibits an enzyme *RmlC*, which is an essential component for the biosynthesis of *d*TDP-rhamnose[4]. This prompted us to communicate our findings in this manuscript.

EXPERIMENTAL

The melting points were recorded on an electrothermal apparatus and are uncorrected. IR Spectra were recorded in KBr on a Perkin-Elmer-983; ^{1}H NMR spectra on a Bruker Avance 300 MHz instrument using $CDCl_3$ as solvent (chemical shifts in δ ppm) using TMS as internal standard; mass spectra on a Finning LCQ mass spectrometer. Elemental analysis was performed on a Heracus CHN-rapid analyzer. The purity of the compounds was checked on silica gel coated Al plates (Merck).

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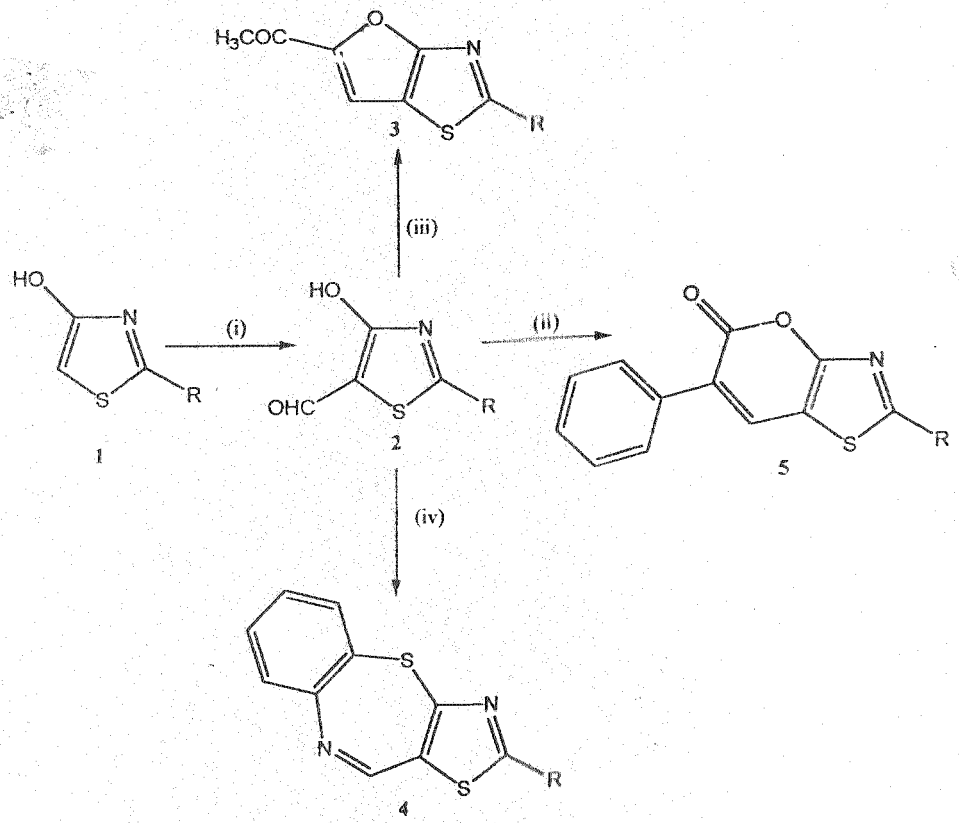
The required precursors 4-hydroxy-2-substituted-thiazole-5-carbaldehydes (2) were prepared from 2-substituted-thiazol-4-ols (1) according to reported procedure[5–7]. Reaction of 4-hydroxy-2-(4-methylphenyl)-thiazole-5-carbaldehyde (2a) with chloroacetone in presence of potassium carbonate in dry acetone afforded 1-(2-(4-methylphenyl)-furo[2,3-*d*]thiazol-5-yl)ethanone (3a). The product 2-(4-methylphenyl)-1,4-dithia-3,9-diaza-benzo[*f*]azulene (4a) was obtained by the treatment of 2a with *o*-aminothiophenol in glacial acetic acid. Further, the reaction of 2a with phenyl acetic acid in acetic anhydride at 120°C was carried out to achieve the product 2-(4-methylphenyl)-6-phenyl-pyrano[2,3-*d*]thiazol-5-one (5a) (Scheme-1).



(a) R = –4$CH_3C_6H_5$, (b) R = –4$C_2H_5C_6H_5$, (c) R = –4$C_3H_7C_6H_5$
(i) $Zn(CN)_2$, dry ether, dry HCl; (ii) Phenyl acetic acid, acetic anhydride;
(iii) H_3COCH_2Cl, K_2CO_3, dry acetone; (iv) *o*-aminothiophenol, AcOH

Scheme-1

1-(2-(4-Methylphenyl)-furo[2,3-*d*]thiazol-5-yl)-ethanone (3a)

A mixture consisting of 4-hydroxy-2-(4-methylphenyl)-thiazole-5-carbaldehyde (2a) (0.001 mol), chloroacetone (0.001 mole) and K_2CO_3 (1 g) in dry acetone (10 mL) was refluxed for 1 h on a water bath. Then the cooled reaction mixture was filtered and washed with excess acetone. This filtrate was then concentrated and poured into ice. The solid thus separated out was extracted with solvent, washed with water successively and dried over anhydrous sodium sulphate. The

solvent was then removed at reduced pressure, which gave crude product. Purification was done by passing the crude product through silica gel column and eluting with petroleum ether-ethyl acetate mixture (95 : 05). Compounds **3b** and **3c** were prepared in a similar manner using **2b** and **2c** as starting material respectively.

2-(4-Methylphenyl)-1,4-dithia-3,9-diaza-benzo[*f*]azulene (4a)

4-Hydroxy-2-(4-methylphenyl)-thiazole-5-carbaldehyde (**2a**) (0.001 mol) was refluxed for 5 h at 140°C with *o*-aminothiophenol (0.001 mol) in acetic acid. The resulting reaction mixture was then poured into crushed ice. The product separated was extracted with ethyl acetate, washed with water and dried over anhydrous sodium sulphate. Excess of solvent was removed under reduced pressure, which gave the crude product. The crude product was then purified by passing through silica gel column and eluting with petroleum ether-ethyl acetate mixture (90 : 10). Compounds **4b** and **4c** were prepared in a similar manner using **2b** and **2c** as starting materials respectively.

2-(4-Methylphenyl)-6-phenyl-pyrano[2,3-*d*]thiazol-5-one (5a)

4-Hydroxy-2-(4-methylphenyl)-thiazole-5-carbaldehyde (**2a**) (0.001 mol) was treated with phenylacetic acid (0.01 mol) in acetic anhydride (5 mL) at 120°C for 5 h. The resulting reaction mixture was then poured into crushed ice. The product separated was extracted with chloroform (3X mL), washed with water and dried over anhydrous sodium sulphate. Excess of solvent was removed under reduced pressure, which gave the crude product. The crude product was then purified by passing through silica gel column and eluting with petroleum ether-ethyl acetate mixture (95 : 05). Compounds **5b** and **5c** were prepared in a similar manner using **2b** and **2c** as starting material respectively.

RESULTS AND DISCUSSION

The structures **(2)–(5)** have been established on the basis of their ^{1}H NMR, IR, CHN analysis and physical data (Tables 1 and 2).

TABLE-1
^{1}H NMR DATA OF COMPOUNDS **2a–c, 3a–c, 4a–c** AND **5a–c**

Compd.	^{1}H NMR (δ ppm)
2a	2.35 (s, 3H, CH_3), 5.0 (s, 1H, OH), 7.16–7.32 (m, 4H, ArH), 9.61 (s, 1H, CHO).
2b	1.27 (t, 3H, CH_3, J = 7.2 Hz), 2.53 (q, 2H, CH_2, J = 7.2 Hz), 5.0 (s, 1H, OH), 7.16 = 7.32 (m, 4H, ArH), 9.61 (s, 1H, CHO).
2c	0.96 (t, 3H, CH_3, J = 8.3 Hz), 1.66 (m, 2H, CH2 J = 7.2 Hz), 2.55 (t, 2H, CH_2 J = 7.2 Hz), 5.0 (s, 1H, OH), 7.2–7.5 (m, 4H, ArH), 9.61 (s, 1H, CHO).
3a	2.37 (s, 3H, Acetyl CH_3), 2.74 (s, 3H, CH_3), 7.1 (s, 1H, CH of furan), 7.16–7.32 (m, 4H, ArH).
3b	1.44 (t, 3H, CH_3, J = 7.2 Hz), 2.39 (q, 2H, CH_2, J = 7.2 Hz), 2.72 (s, 3H, acetyl CH_3), 7.21 (s, 1H, CH of furan), 7.32–7.57 (m, 4H, ArH).

Compd.	^{1}H NMR (δ ppm)
3c	0.89 (t, 3H, CH_3, J = 9.3 Hz), 1.54 (m, 2H, CH_2, J = 7.2 Hz), 2.47 (t, 2H, CH_2, J = 7.2 Hz), 2.61 (s, 3H, acetyl CH_3), 7.14 (s, 1H, CH of furan), 7.2–7.5 (m, 4H, ArH).
4a	2.32 (s, 3H, CH_3), 6.97–7.52 (m, 9H, ArH).
4b	1.22 (t, 3H, CH_3 , J = 7.2 Hz), 2.67 (q, 2H, CH_2, J = 7.2 Hz), 6.97 (t, 4H, ArH, J = 8.08 Hz), 7.21 (d, 4H, ArH, J = 8.08 Hz), 7.52 (s, 1H, CH).
4c	0.94 (t, 3H, CH_3, 8.3 Hz), 1.69 (m, 2H, CH_2, J = 7.2 Hz), 2.51 (t, 2H, CH_2, J = 7.2 Hz), 4C 6.97 (t, 2H, ArH, J = 8.08 Hz), 7.11 (d, 2H, ArH, J = 8.08 Hz), 7.25-7.47 (m, 4H, ArH), 7.52 (s, 1H, CH).
5a	5a 2.33 (s, 3H, CH_3), 7.1–7.63 (m, 9H, ArH), 7.0 (s, 1H, CH).
5b	1.37 (t, 3H, CH_3, J = 7.2 Hz), 2.38 (q, 2H, CH_2, J = 7.2 Hz), 7.1—7.62 (m, 9H, ArH), 7.45 (s, 1H,CH).
5c	1.13 (t, 3H, CH_3, J = 8.3 Hz), 1.75 (m, 2H, CH_2, J = 7.2 Hz), 2.86 (t, 2H, CH_2, J = 7.2 Hz), 7.1–7.5 (m, 9H, ArH), 7.65 (s, 1H, CH).

TABLE-2
PHYSICAL AND ELEMENTAL ANALYSIS DATA OF COMPOUNDS
3a–c, 4a–c AND **5a–c**

Compd.	m.p. (°C)	Yield (%)	m.f. (m.w.)	Analysis (%), Found (Calcd.)		
				C	H	N
3a	229–33	89	$C_8H_7NO_2S$ (181)	52.76 (53.03)	03.58 (03.86)	07.51 (07.73)
3b	237–42	87	$C_9H_9NO_2S$ (195)	55.9 (55.38)	04.51 (04.61)	07.41 (07.17)
3c	244–49	82	$C_{10}H_{11}NO_2S$ (209)	57.76 (57.41)	05.03 (05.26)	06.46 (06.69)
4a	226–31	61	$C_{11}H_7N_2S_2$ (231)	57.41 (57.14)	03.21 (03.03)	12.35 (12.12)
4b	147–52	47	$C_{12}H_9N_2S_2$ (245)	58.44 (58.77)	03.54 (03.67)	11.49 (11.62)
4c	239–43	49	$C_{13}H_{11}N_2S_2$ (259)	59.96 (60.23)	04.37 (04.24)	10.53 (10.81)
5a	221–26	91	$C_{13}H_9NO_2S$ (243)	64.46 (64.19)	03.53 (03.70)	05.59 (05.76)
5b	261–65	82	$C_{14}H_{11}NO_2S$ (257)	65.03 (65.36)	04.16 (04.28)	05.12 (05.44)
5c	254–59	79	$C_{15}H_{13}NO_2S$ (271)	66.14 (66.42)	04.55 (04.79)	05.38 (05.16)

PE: Petroleum ether (60–80°C); EA: Ethyl acetate.

Antimicrobial activity

All the compounds were screened for antibacterial activity against *S. aureus* and *E. coli* by paper disc technique[8]. The concentration of the test compound used

was 100 μg. Gentamycin was used as standard. The antifungal activity of all the compounds was evaluated against *C. albicans* using the same technique. Nystatin was used as standard.

Antitubercular activity

The title compounds were tested *in vitro* for their antitubercular activity against *M. tuberculosis* $H^{37}Rv$. The antitubercular evaluation of compounds was carried out at Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF), USA. Primary screening of the compounds for antitubercular activity has been conducted using the BACTEC 460 radiometric system. Compounds demonstrating at least > 90% inhibition in the primary screening have been retested at lower concentration against *M. tuberculosis* $H^{37}Rv$ to determine the actual minimum inhibitory concentration (MIC) in BACTEC 460. The data was compared with the standard drug Rifampin at 0.03 μg/mL concentration, which showed 97% inhibition. Compounds **3c** and **4c** were most active against *M. tuberculosis* $H^{37}Rv$ (> 90% inhibition) that will be retested at lower concentration to determine the actual MIC. Other compounds *viz.* **3a**, **5b** and **4a** were moderately active against *M. tuberculosis* $H^{37}Rv$ strain (> 50% inhibition).

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