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Synthesis and Antimycobacterial Activity of Thiazole Derivatives - Part-VI

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Tuberculosis is alarming due to multi drug resistance. Inhibition of an enzyme *RmlC* by the thiazole derivatives especially with carbonyl group scaffold has prompted us to synthesize a series of thiazole derivatives. Here the work done is presented and antimicrobial and antimycobacterial activities are discussed. Many of these compounds have shown better antimicrobial and antimycobacterial 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 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 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 agent with a different mode of action. A *de novo* structural design has demonstrated that the thiazole derivatives especially with carbonyl group scaffold inhibit an enzyme *RmlC*, which is an essential component for the biosynthesis of dTDP-rhamnose[4]. This prompted us to communicate our findings in this manuscript.

The required precursors 4-hydroxy-2-substituted-thiazole-5-carbaldehydes (**2**) were prepared from 2-substituted-thiazol-4-ols (**1**) according to reported procedure[5,6]. Reaction of 4-hydroxy-2-acetylamino-thiazole-5-carbaldehyde (**2a**) with chloroacetone in presence of potassium

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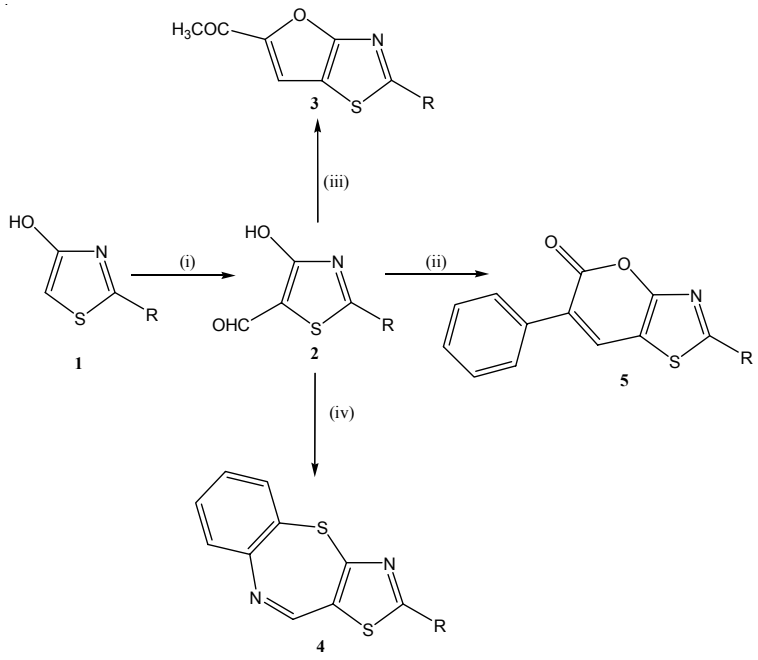
carbonate in dry acetone afforded 1-(2- acetylamino -furo[2,3-d]thiazol-5-yl)ethanone (**3a**). The product 2-acetylamino-1,4-dithia-3,9-diaza-benzo[f]-azulene (**4a**) was obtained by the treatment of **2a** with *o*-aminothiophenol in glacial acetic acid. Further we have carried out the reaction of **2a** with phenyl acetic acid in acetic anhydride at 120 ºC to achieve the product 2-(4-methylphenyl)-6-phenyl-pyrano[2,3-d]thiazol-5-one **5a**. Similarly, **2b-5b** and **2c-5c** have been prepared as per the procedure described (**Scheme-I**). The structures of the compounds **2**-**5** have been established on the basis of their ^{1}H NMR and elemental analysis (Tables 1 and 2).



1-5 a: R= -NHCOCH$_3$
b: R=-NHCOC$_6$H$_5$
c: R= -NHCOCH$_2$Cl

(i) Zn(CN)$_2$, dry ether, dry HCl; (ii) Phenyl acetic acid, acetic anhydride;

(iii)CH$_3$COCH$_2$Cl, K$_2$CO$_3$, dry acetone; (iv) *o*-aminothiophenol, AcOH.

Scheme-I

EXPERIMENTAL

The melting points were recorded on 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). The required precursors (**1**) and (**2**) were prepared according to the literature[7].

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), 9.2 (s, 1H, NH), 9.61 (s, 1H, CHO).
2b	5.0 (s, 1H, OH), 7.32-7.57 (m, 5H, ArH), 9.2 (s, 1H, NH), 9.61 (s, 1H, CHO).
2c	4.27 (s, 2H, CH_3), 5.0 (s, 1H, OH), 9.2 (s, 1H, NH), 9.61 (s, 1H, CHO).
3a	2.37 (s, 6H, CH_3), 7.1 (s, 1H, CH of furan), 9.20 (s, 1H, NH),
3b	2.14 (s, 3H, CH_3), 6.92 (s, 1H, CH of furan), 7.41-7.60 (m, 5H, ArH), 9.12 (s, 1H, NH).
3c	2.11 (s, 3H, CH_3), 4.16 (s, 2H, CH_2), 6.92 (s, 1H, CH of furan), 9.22 (s, 1H, NH),
4a	2.32 (s, 3H, CH_3), 5.1 (s, 1H, CH of thiazepin), 6.97-7.23 (m, 4H, ArH), 9.31 (bs, 1H, NH).
4b	5.16 (s, 1H, CH of thiazepin), 6.97-7.54 (m, 9H, ArH), 9.13 (bs, 1H, NH).
4c	4.17 (s, 2H, CH_2), 5.25 (s, 1H, CH of thiazepin), 6.76-7.36 (m, 4H, ArH), 9.09 (bs, 1H, NH).
5a	2.33 (s, 3H, CH_3), 7.0 (s, 1H, CH of pyran), 7.1-7.63 (m, 5H, ArH), 8.91 (bs, 1H, NH).
5b	6.94 (s, 1H, CH of pyran), 7.17-7.87 (m, 10H, ArH), 9.11 (bs, 1H, NH).
5c	4.33 (s, 2H, CH), 7.0 (s, 1H, CH of pyran), 7.1-7.63 (m, 5H, ArH), 8.91 (bs, 1H, NH).

1-(2-Acetylamino-furo[2,3-d]thiazol-5-yl)-ethanone (3a): A mixture consisting of 4-hydroxy-2-acetylamino-thiazole-5-carbaldehyde (**2a**) (0.001 mol), chloroacetone (0.001 mol) and K_2CO_3 (1 g) in dry acetone (10 mL) was refluxed for 1 h on water bath. Then the cooled reaction mixture was filtered and washed with excess acetone. This filtrate was then concentrated and poured into ice. Solid thus separated out was extracted with solvent, washed with water successively and dried over anhydrous sodium sulphate. 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 similar manner using **2b** and **2c** as starting material, respectively.

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

Compd.	m.p. (ºC)	Yield (%)	m.f. (mw.)	Elemental analysis %: Found (Calcd.)		
				C	H	N
3a	229-33	89	$C_9H_8N_2O_3S$ (224)	48.21 (48.55)	03.60 (03.86)	12.49 (12.75)
3b	237-42	87	$C_{14}H_{10}N_2O_3S$ (286)	58.73 (58.38)	03.52 (03.61)	09.78 (09.97)
3c	244-49	82	$C_9H_7N_2O_3SCl$ (259)	41.79 (41.64)	02.73 (02.57)	10.83 (10.59)
4a	226-31	61	$C_{12}H_9N_3OS_2$ (275)	52.34 (52.14)	03.29 (03.03)	15.26 (15.12)
4b	247-52	47	$C_{17}H_{11}N_3OS_2$ (337)	60.51 (60.77)	03.29 (03.47)	12.45 (12.62)
4c	239-43	49	$C_{12}H_8N_3OS_2Cl$ (310)	46.52 (46.23)	02.60 (02.24)	13.56 (13.81)
5a	221-26	91	$C_{14}H_{10}N_2O_3S$ (286)	58.73 (58.55)	03.52 (03.70)	09.78 (09.76)
5b	261-65	82	$C_{19}H_{12}N_2O_3S$ (348)	65.51 (65.36)	03.47 (03.28)	08.04 (08.34)
5c	254-59	79	$C_{14}H_9N_2O_3SCl$ (320)	52.42 (52.21)	02.83 (02.79)	08.73 (08.56)

2-Acetylamino-1,4-dithia-3,9-diaza-benzo[f]azulene(4a): 4-Hydroxy -2-acetylamino-thiazole-5-carbaldehyde (**2a**) (0.001 mol) was refluxed for 5 h at 140 ºC 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. 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 similar manner using **2b** and **2c** as starting material, respectively.

2-Acetylamino-6-phenyl-pyrano[2,3-d]thiazol-5-one(5a): 4-Hydroxy -2-acetylamino-thiazole-5-carbaldehyde (**2a**) (0.001 mol) was treated with phenylacetic acid (0.01 mol) in acetic anhydride (5 mL) at 120 ºC for 5 h. The resulting reaction mixture was then poured into crushed ice. The product separated was extracted with chloroform (3 × 10 mL), washed with water and dried over anhydrous sodium sulphate. Excess of solvent was removed under reduced pressure, which gave the crude product. 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 similar manner using **2b** and **2c** as starting material, respectively.

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* H37Rv. 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 has been retested at lower concentration against *M. tuberculosis* H37Rv 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* H37Rv (> 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* H37Rv strain (> 50 % inhibition).

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