

# SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2,5-DI(2H-1-BENZO/NAPHTHOPYRAN-2-ONE-4-YL) THIAZOLO [5,4-d]THIAZOLE

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## ABSTRACT

The titled 2,5-Di(2H-1-benzo/naphthopyran-2-one-4-yl)thiazolo[5,4-d]thiazole have been synthesized from formylcoumarins and rubeanic acid. Compounds characterized on the basis of IR, <sup>1</sup>H NMR and mass spectrometric data. Some of the compounds evaluated for antimicrobial activity against *E. Coli* and *S. Typhi*.

**Keywords:** Rubeanic acid, thiazolo[5,4-d]thiazoles and antimicrobial activity.

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## INTRODUCTION

Benzothiazoles are heterocyclic compounds with multiple application and although they have been known from long ago to be biologically active.<sup>1-3</sup> Recently, Racane et al<sup>4</sup> have described the synthesis of bis-substituted amidinobenzothiazoles as potential anti-HIV agents.

The condensation of dithio-oxamide with aromatic aldehyde was described by Ephraim.<sup>5</sup> More recently, Johnson and Ketcham<sup>6</sup> studied the reaction and established the structure of the resulting parent heterocycles as thiazolo[5,4-d]thiazoles. Taking the advantage of thiazole as biological active, we also have attempted to explore the possibility of generation of antimicrobial activity in 2-(2H-1-benzopyran-2-one-4-yl)thiazolo[5,4-d]thiazoles (**7-12**, **16-18**). These compounds were synthesized from formylcoumarins<sup>7</sup> and rubeanic acid depicted in Scheme-1 and elemental analysis of synthesized compounds is summarized in Table-1.

## EXPERIMENTAL

Rubeanic acid was purchased from sigma aldrich chemical company. <sup>1</sup>H NMR spectra were recorded on a Mercury (300 MHz) spectrometer with TMS as internal standard. Mass spectra were obtained on a Micromass-Q-Tofmicro(YA-105) spectrometer. IR spectra were taken on a Bruker Vertex 80 infrared spectrophotometer. Melting points were measured with a SGW-X-4 microscopic melting point instrument and are uncorrected.

## RESULTS AND DISCUSSION

### Synthesis of 2,5-Di(7-methyl-2H-1-Benzopyran-2-one-4-yl)thiazolo[5,4-d]thiazole (7)

7-methylcoumarin-4-carboxaldehyde, **1** (0.94 gm, 0.005 mol) and rubeanic acid (0.69 gm, 0.0055 mol) were dissolved in 20 ml of dimethylformamide in a 50 ml round bottomed flask with condenser. The reaction was heated to reflux for 5 hours. The reaction mixture was cooled in cold water and the solid compound obtained was filtered, dried and recrystallized in ethanol, m.p. 411°k yield (49%), M+1 460, IR CM<sup>-1</sup>-3074,1724, 1603,1560, 1451, 1364, 1257, 1170, 1110 and 819. <sup>1</sup>H-NMR (CF<sub>3</sub>COOD) δ- 2.82 (s, 6H), 7.55 (s, 2 H), 7.91 (2H, d, J = 9.2 Hz), 8.06 (2H, d, J = 7.6 Hz), 8.47 (s, 2H).

### Synthesis of 2,5-Di(7-methoxybenzyl-2H-1-Benzopyran-2-one-4-yl)thiazolo[5,4-d] thiazole (8)

7-methoxycoumarin-4-carboxaldehyde, **2** (1.02 g, 0.005 mol) and rubeanic acid (0.69 g, 0.0055 mol) in dimethylformamide following the above protocol gave **8**, m.p. 418°k , yield (58%), IR CM<sup>-1</sup>-3094, 1716,

1613, 1509, 1471, 1384, 1293, 1208, 1150, 1028, 989, 817 and 635.  $^1\text{H-NMR}$  ( $\text{CF}_3\text{COOD}$ )  $\delta$ - 4.39 (s, 6H), 7.37 (s, 2H), 7.50 (s, 2H), 7.53 (s, 2H), 8.65 (s, 2H).

#### Synthesis of 2,5-Di(7-acetyloxy-2H-1-Benzopyran-2-one-4-yl)benzo[d] thiazole (9)

7-acetyloxy coumarin-4-carboxaldehyde, **3** (1.16 g, 0.005 mol) and rubeanic acid (0.69 g, 0.0055 mol) in dimethylformamide following the above protocol gave **9**, m.p.  $>573^\circ\text{K}$ , yield (51%), IR  $\text{CM}^{-1}$  - 3431, 2921, 1715, 1611, 1558, 1378, 1201, 1132, 1016 and 857.  $^1\text{H-NMR}$  ( $\text{D}_2\text{SO}_4$ )  $\delta$ -2.56 (s, 6H), 7.31-7.38 (m, 6H), 8.11 (2H, d,  $J = 9.5$  Hz).

#### Synthesis of 2,5-Di(7-propanoyloxy-2H-1-Benzopyran-2-one-4-yl)thiazolo[5,4-d] thiazole (10)

7-propanoyloxy coumarin-4-carboxaldehyde, **4** (1.23 g, 0.005 mol) and rubeanic acid (0.69 g, 0.0055 mol) in dimethylformamide following the above protocol gave **10**, m.p.  $>573^\circ\text{K}$  yield (45%), IR  $\text{CM}^{-1}$  - 3045, 1771, 1720, 1611, 1378, 1266, 1142, 1140, 998 and 887.  $^1\text{H-NMR}$  ( $\text{D}_2\text{SO}_4$ )  $\delta$ -1.70 (6H, t,  $J = 7.5$  Hz), 2.57-3.8 (m, 4H), 7.66 (2H, d,  $J = 1.8$  Hz), 7.69 (s, 2H), 7.77 (2H, d,  $J = 2.1$  Hz), 8.92 (2H, d,  $J = 8.9$  Hz).

#### Synthesis of 2,5-Di(7-butanoyloxy-2H-1-Benzopyran-2-one-4-yl)thiazolo[5,4-d]thiazole (11)

7-butanoyloxy coumarin-4-carboxaldehyde, **5** (1.30 g, 0.005 mol) and Rubeanic acid (0.69 gm, 0.0055 mol) in dimethylformamide following the above protocol gave **11**, m.p.  $>573^\circ\text{K}$  yield (51%), IR  $\text{CM}^{-1}$  - 3016, 1756, 1717, 1616, 1553, 1377, 1223, 1199, 1159, 1117 and 1006.  $^1\text{H-NMR}$  ( $\text{D}_2\text{SO}_4$ )  $\delta$ - 1.68 (s, 6H), 2.57-3.17 (m, 4H), 3.19 (s, 4H), 7.66 (s, 2H), 7.69 (2H, d,  $J = 2.1$  Hz), 7.77 (2H, d,  $J = 2.1$  Hz), 8.19 (2H, d,  $J = 8.9$  Hz).

#### Synthesis of 2,5-Di(7-benzoyloxy-2H-1-Benzopyran-2-one-4-yl)thiazolo[5,4-d]thiazole (12)

7-benzoyloxy coumarin-4-carboxaldehyde, **6** (1.47 g, 0.005 mol) and rubeanic acid (0.69 g, 0.0055 mol) in dimethylformamide following the above protocol gave **12**, m.p.  $>573^\circ\text{K}$  yield (49%), IR  $\text{CM}^{-1}$  - 3067, 1731, 1615, 1557, 1443, 1377, 1255, 1146, 1115, 1068, 999, 882 and 776.  $^1\text{H-NMR}$  ( $\text{D}_2\text{SO}_4$ )  $\delta$ - 6.88 (s, 2H), 6.96 (s, 2H), 7.14 (4H, d,  $J = 7.7$  Hz), 7.44 (2H, d,  $J = 7.7$  Hz), 7.60 (s, 2H), 7.70 (4H, d,  $J = 10.7$  Hz), 7.75 (2H, d,  $J = 7.7$  Hz).

#### Synthesis of 2,5-Di (7-methoxy-4-methyl-benzopyran-2-one-6-yl)thiazolo[5,4-d]thiazole (16)

7-methoxy-4-methyl-benzopyran-2-one-4-carboxaldehyde, **13** (1.09 g, 0.005 mol) and rubeanic acid (0.69 g, 0.0055 mol) in dimethylformamide following the above protocol gave **16**, m.p.  $418^\circ\text{K}$  (char), yield (48%), IR  $\text{CM}^{-1}$  - 3094, 1716, 1613, 1509, 1384, 1246, 1150, 1028, 838 and 635.  $^1\text{H-NMR}$  ( $\text{D}_2\text{SO}_4$ )  $\delta$ - 2.71 (s, 6H), 2.82 (s, 6H), 7.13 (s, 2H), 7.91 (s, 2H), 8.4 (s, 2H).

#### Synthesis of 2,5-Di(naphthopyran-2-one-6-yl) thiazolo[5,4-d]thiazole (17)

Naphthopyran-2-one-4-carboxaldehyde, **14** (1.12 g, 0.005 mol) and Rubeanic acid (0.69 gm, 0.0055 mol) in dimethylformamide following the above protocol gave **17**, m.p.  $418^\circ\text{K}$  (char) yield (43%), IR  $\text{CM}^{-1}$  - 3069, 2862, 1732, 1617, 1413, 1385, 1240, 1151, 1056, 995, 885, 732 and 648.  $^1\text{H-NMR}$  ( $\text{D}_2\text{SO}_4$ )  $\delta$ - 7.7 (s, 2H), 7.87-8.07 (m, 6H), 8.19 (2H, d,  $J = 8.8$  Hz), 8.66 (2H, d,  $J = 7.7$  Hz).

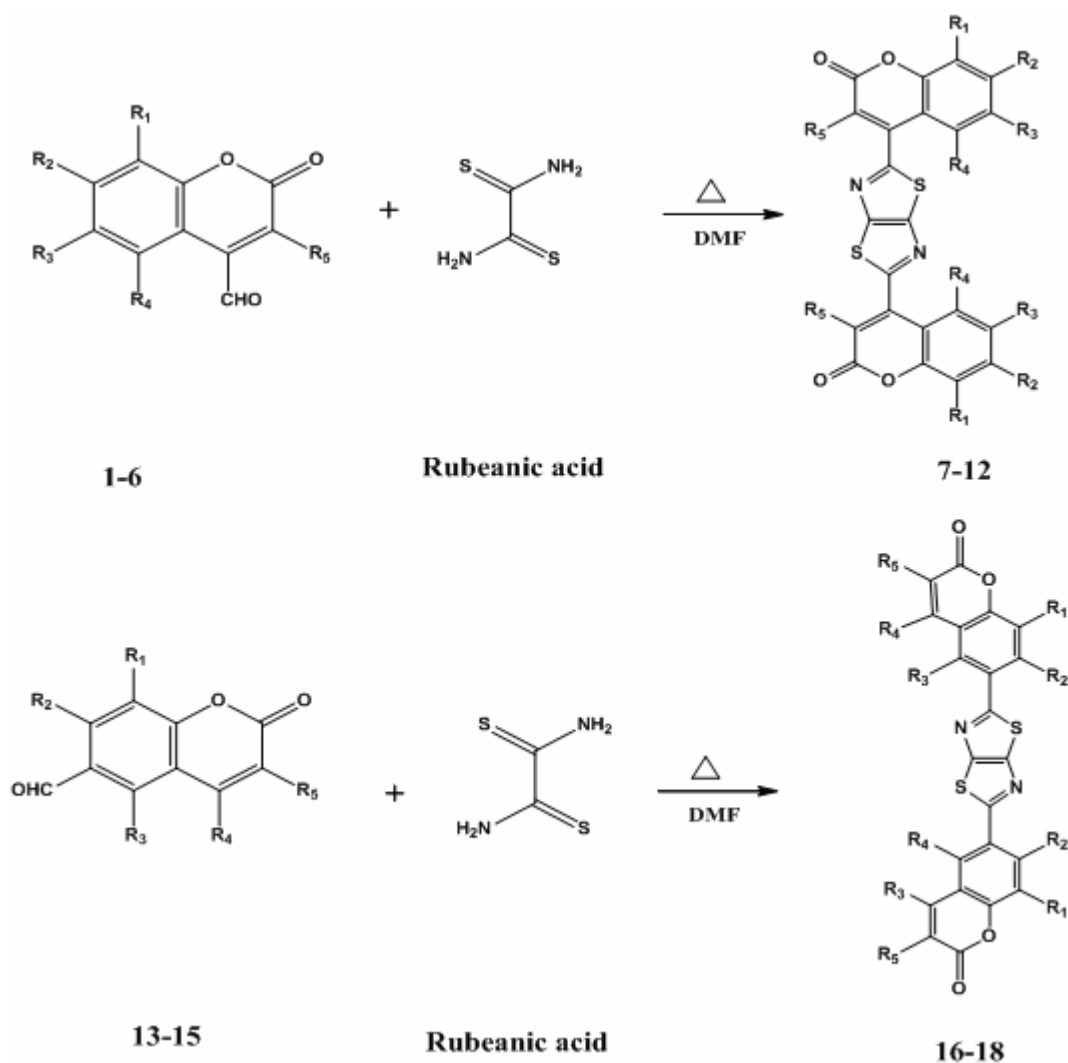
#### Synthesis of 2,5-Di(4-methyl-naphthopyran-2-one-6-yl)thiazolo[5,4-d]thiazole (18)

7-methoxy-naphthopyran-2-one-4-carboxaldehyde, **15** (1.19g, 0.005mol) and Rubeanic acid (0.69 g, 0.0055 mol) in dimethylformamide following the above protocol gave **18**, m.p.  $418^\circ\text{K}$  (char) yield (48%), IR  $\text{CM}^{-1}$  - 3780, 1765, 1605, 1501, 1450, 1373, 1314, 1722, 1085, 937, 874, 774 and 650.  $^1\text{H-NMR}$  ( $\text{D}_2\text{SO}_4$ )  $\delta$ -2.97 (s, 6H), 7.32 (s, 2H), 8.03-8.14 (m, 6H), 8.48 (s, 2H), 8.82 (2H, d,  $J = 5.9$  Hz).

#### Antimicrobial Activity<sup>7</sup>

In the present study, compounds **7-12**, **16-18** have been tested for their effect on the growth of microbial cultures. The test compounds have been subjected in *In vitro* screening against *S.Typhi* and *E.Coli* using tube dilution technique.

Meuller Hinton broth was used as a culture medium. Sterilized medium was dispensed in each borosilicate glass tube (150+20mm). The drug solution was added in order to attend final drug concentration as 200, 400, 600 and 800 µg/ml.etc. Inoculum of standard suspension (0.1 ml of the test organism strain which contains  $10^6$  bacilli/ml) was added. The tubes were incubate at 37°C for 48 hours and then examined for the presence or absence of growth of the organism. The lowest concentration, which showed no visible growth was taken as endpoint (MIC). Compounds **7-12**, **16-18** were evaluated for their anti microbial activity by Using concentration level of 200µg/ml to 800 µg/ml. The Minimum Inhibitory Concentration at which compound showed on growth are as follows(Table-2).



Scheme-1

Table-1: The substituents, yields, solvent of crystallization and melting points of 2,5-Di(2H-1-benzo/naphthopyran-2-one-4-yl)thiazolo[5,4-d]thiazoles 8-14, 17-18.

Comps	% yield	M.P. °K	Elemental analysis found(calc. %)			
			%C	%H	%N	%S
7	49	411(Dec.)	62.99	3.28	6.29	13.88
8	58	422(Dec.)	58.97	2.98	5.91	13.29

9	51	>573	57.34	2.77	5.21	11.87
10	47	>573	58.67	3.31	4.99	11.34
11	51	>573	59.99	3.88	4.76	10.81
12	49	>573	64.57	2.96	4.31	9.66
16	48	428(Dec.)	67.78	2.69	5.38	12.29
17	43	398(Dec.)	60.34	3.65	5.55	12.37
18	48	410(Dec.)	68.92	3.45	5.21	11.78

Table-2: The Minimum Inhibitory Concentration

Compound	Minimum inhibitory concentration against ( $\mu\text{g/mL}$ )	
	<i>S.aureus</i>	<i>E.Coli</i>
7	500	500
8	400	500
9	600	600
10	500	600
11	600	500
12	400	500
16	400	500
17	500	600
18	600	600

### CONCLUSION

Some of Synthesized compounds shows moderate activity against *S.aureus* and *E.coli*.

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