ANTIMICROBIAL ACTIVITY OF SYNTHESIZED 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, ^{1}H NMR and mass spectrometric data. Some of the compounds evaluated for antimicrobial activity against *E. Coli* and *S. Typhi*.

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

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I. INTRODUCTION

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

The condensation of dithio-oxamide with aromatic aldehyde was described by Ephraim.[5] More recently, Johnson and Ketcham[6] 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[7] and rubeanic acid depicted in **Scheme I** and elemental analysis of synthesized compounds is summarized in **Table I.**

II. EXPERIMENTAL

Rubeanic acid was purchased from sigma aldrich chemical company. ^{1}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.

III. RESULT 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^{-1}-3074,1724, 1603,1560, 1451, 1364, 1257, 1170, 1110 and 819. ^{1}H-NMR (CF_3COOOD) 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^{-1}-3094, 1716, 1613, 1509, 1471, 1384, 1293, 1208, 1150, 1028, 989, 817 and 635. ^{1}H-NMR (CF_3COOD) δ- 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-acetyloxycoumarin-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°k, yield (51%), IR CM^{-1} - 3431, 2921, 1715, 1611, 1558, 1378, 1201, 1132, 1016 and 857. ^{1}H-NMR (D_2SO_4) δ-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-propanoyloxycoumarin-4-carboxaldehyde,**4** (1.23 g, 0.005 mol) and rubeanic acid (0.69 g, 0.0055 mol) in dimethylformide following the above protocol gave **10** , m.p. >573 °K yield (45%), IR CM^{-1}- 3045, 1771, 1720, 1611, 1378, 1266, 1142, 1140, 998 and 887 . ^{1}H-NMR (D_2SO_4) δ-1.70 (6H, t, *J* = 7.5 Hz), 2.57-3.8 (m, 4H), 7.66

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(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-butanoyloxycoumarin-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 °K yield (51%), IR CM^{-1}- 3016, 1756, 1717, 1616, 1553, 1377, 1223, 1199, 1159, 1117 and 1006[1]. ^{1}H-NMR (D_2SO_4) δ- 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* = 2.1Hz), 8.19 (2H, d, *J* = 8.9Hz).

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

7-benzoyloxycoumarin-4-carboxaldehyde,**6** (1.47 g, 0.005 mol) and rubeanic acid (0.69 g, 0.0055 mol) in dimethylformide. following the above protocol gave **12,** m.p. >573 °K yield (49%), IR CM^{-1}- 3067, 1731, 1615, 1557, 1443, 1377, 1255, 1146, 1115, 1068, 999, 882 and 776. ^{1}H-NMR (D_2SO_4) δ- 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 °K(char), yield(48%), IR CM^{-1}- 3094, 1716, 1613, 1509, 1384, 1246, 1150, 1028, 838 and 635. ^{1}H-NMR (D_2SO_4) δ- 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 dimethylformide following the above protocol gave **17**, m.p.418 °K(char) yield(43%), IR CM^{-1}- 3069, 2862, 1732, 1617, 1413, 1385, 1240, 1151, 1056, 995, 885, 732 and 648 . ^{1}H-NMR (D_2SO_4) δ- 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** (1.19 g, 0.005 mol) and Rubeanic acid (0.69 g, 0.0055 mol) in dimethylformamide following the above protocol gave **18**, m.p.418 °K(char) yield(48%), IR CM^{-1}- 3780, 1765, 1605, 1501, 1450, 1373, 1314, 1722, 1085, 937, 874, 774 and 650. ^{1}H-NMR (D_2SO_4) δ-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).

Scheme 1

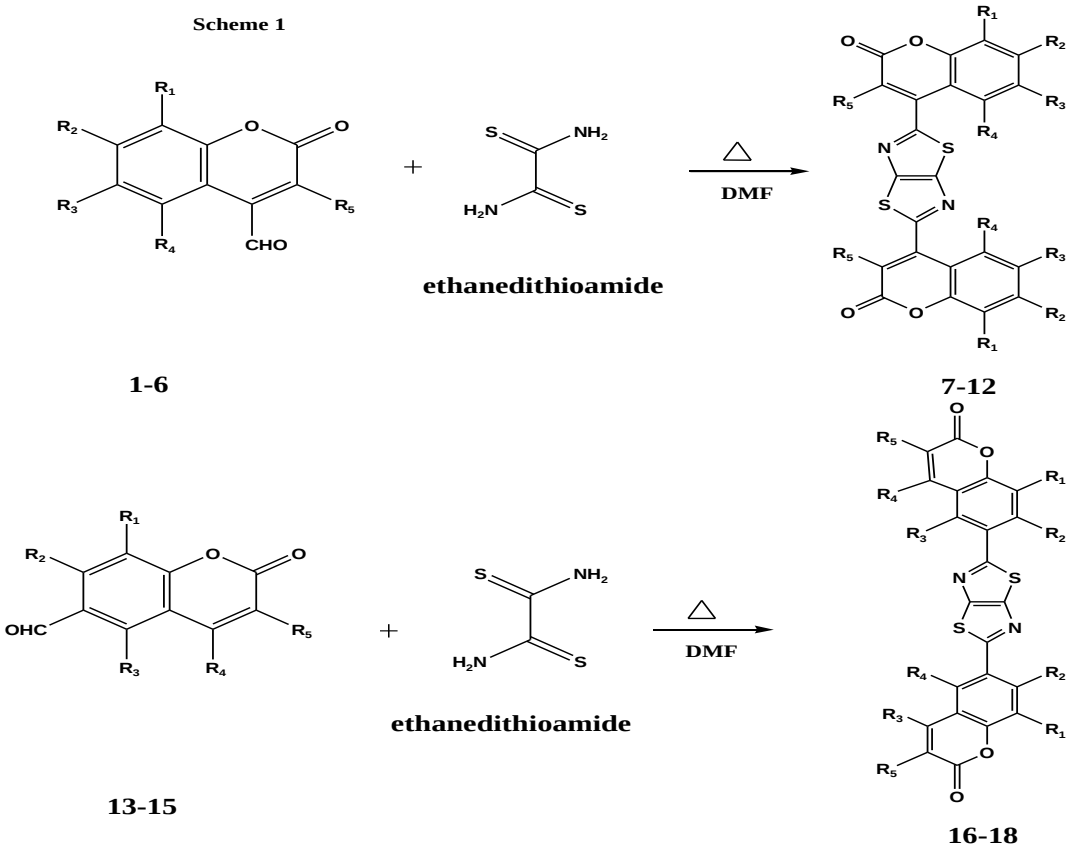

Table 1: The substituents, yields, solvent of crystallization and melting points of 2,5-Di(2H-1-benzo/naphthopyran-2-one-4-yl)thizolo[5,4-d]thiazoles 8-14, 17-18.

Compds	% 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

ANTIMICROBIAL ACTIVITY[7]

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. Innoculam of standard suspention (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.

Compound	Minimum inhibitory concencentration against (µg/mL)	
	S.aureus	*E.Coli*
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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