Antimicrobial activity of novel synthesized substituted thiazolo[5,4-d]thiazole

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Abstract: The titled substituted thiazolo[5,4-d]thiazole have been synthesized from formylcoumarins and rubeanic acid. Some of the compounds evaluated for antimicrobial activity against *E. Coli* and *S. Typhi*.

Key Words Rubeanic acid, bis-benzothiazoles and antimicrobial activity.

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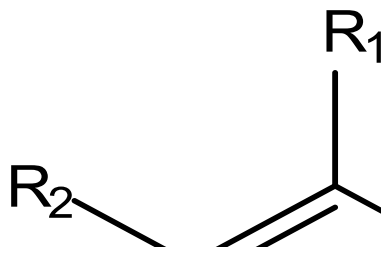
INTRODUCTION

Benzothiazoles are heterocyclic compounds with multiple application and although they have been known from long ago to be biologically active.[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 **7-12, 16-18.** These compounds were synthesized from formylcoumarins[7] and rubeanic acid is depicted in **Scheme I .**



EXPERIMENTAL

The melting points were determined in open capillary and are uncorrected . ^{1}H spectra were run on a Brucker AM 300 instrument using TMS as an internal standard. IR spectra were recorded on KBr,on an Shimadzu FTIR-4200 Spectrometerand mass [Micromass-Q-Tofmicro(YA-105)].

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 mmol) and rubeanic acid (0.69 gm, 0.0055 mmol) were dissolved in 20 mL of dimethylformamide in a 50 mL round bottomed flask with condenser. The reaction was heated to reflux for 5hrs. 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). GC-

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 **11**, 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 **12,** 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** (1.23g, 0.005 mol) and rubeanic acid (0.69 g, 0.0055 mol) in dimethylformide following the above protocol gave **13** , 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 (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 **15,** 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 **16**, 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 **20**, 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).

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.

Sr.No.	Compds	% yield	M.P °K	Elemental analysis found(calc. %)			
				%C	%H	%N	%S
1	**7**	49	411(Dec.)	62.99	3.28	6.29	13.88
2	**8**	58	422(Dec.)	58.97	2.98	5.91	13.29
3	**9**	51	>573	57.34	2.77	5.21	11.87
4	**10**	47	>573	58.67	3.31	4.99	11.34
5	**11**	51	>573	59.99	3.88	4.76	10.81
6	**12**	49	>573	64.57	2.96	4.31	9.66
7	**16**	48	428(Dec.)	67.78	2.69	5.38	12.29
8	**17**	43	398(Dec.)	60.34	3.65	5.55	12.37
9	**18**	48	410(Dec.)	68.92	3.45	5.21	11.78

Antimicrobial Screening[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 gram negative *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 (0.1ml of the test organism strain which contains 10^6bacilli/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).

CONCLUSION

Compounds **7-12, 16-18** were evaluated for their anti microbial activity by Using concentration level of 200 µg/ml to 800 µg/mL. The test organism employed were *S.aureus* and *E.coli*. The Minimum Inhibitory Concentration at which compound showed on growth are as follows.

Compound No.	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

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