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

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Abstract
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. Synthesized compounds screened against antibacterial activity.

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

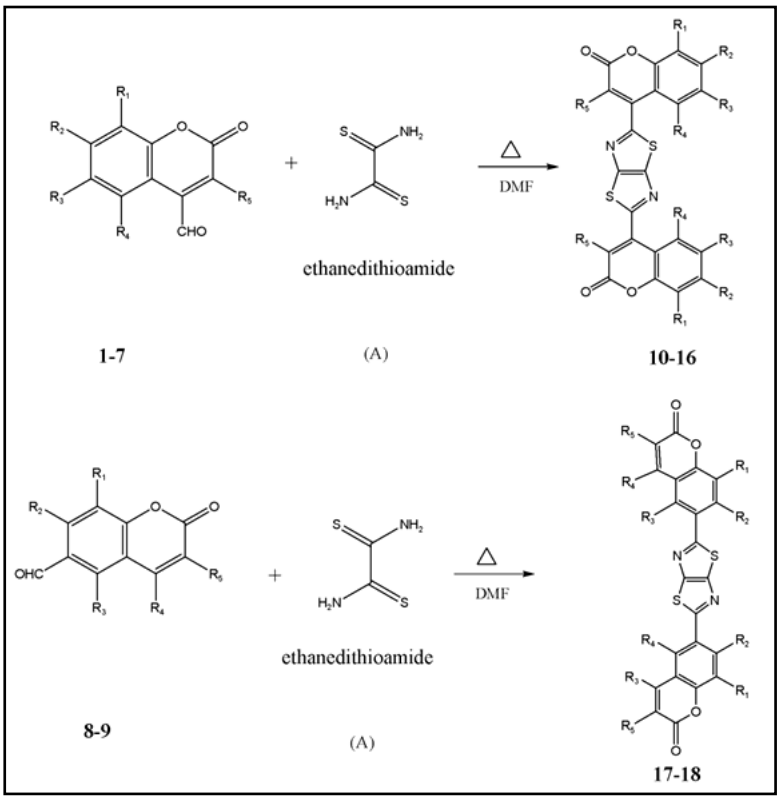
Inroduction

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 **1-9.** These compounds were synthesized from formylcoumarins[7] and rubeanic acid is depicted in **Scheme I .**

EXPERIMENTAL

Melting points are taken 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)].



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

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 dimethylformide 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 0.69 g (yield = 49%, M.P. = 138 °C). IR (KBr) : 3074,1724, 1603,1560, 1451, 1364, 1257, 1170, 1110 and 819 cm^{-1}. ^{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-MS : *m/z* = 459 (M^+).

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

7-methoxycoumarin-4-carboxaldehyde, **2** (1.02 g, 0.005 mol) and rubeanic acid (0.69 g, 0.0055 mol) in dimethyformide following the above protocol gave **II**b, 0.71 g (yield = 58%, M.P. = 145 char °C). IR (KBr): 3094, 1716, 1613, 1509, 1471, 1384, 1293, 1208, 1150, 1028, 989, 817 and 635 cm^{-1}. ^{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 12

7-acetyloxycoumarin-4-carboxaldehyde, **3**(1.16 g, 0.005 mol) and rubeanic acid (0.69 g, 0.0055 mol) in dimethylformide following the above protocol gave **IIc,** 0.70 g (yield = 51% , M.P. >300 °C). IR (KBr) : 3431, 2921, 1715, 1611, 1558, 1378, 1201, 1132, 1016 and 857 cm^{-1}. ^{1}H-NMR (D_2SO_4) : δ = 2.56 (s, 6H), 7.31-7.38 (m, 6H), 8.11 (2H, d, *J* = 9.5Hz).

Synthesis of 2,5-Di(7-propanoyloxy-2H-1-Benzopyran-2-one-4-yl)thiazolo[5,4-d] thiazole 13

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 **IId** , 0.65 g (yield = 45%, M.P. = >300 °C). IR (KBr) : 3045, 1771, 1720, 1611, 1378, 1266, 1142, 1140, 998 and 887 cm^{-1}. ^{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 14

7-butanoyloxycoumarin-4-carboxaldehyde, **5** (1.30 g, 0.005 mol) and Rubeanic acid (0.69 gm, 0.0055 mol) in dimethylformide following the above protocol gave **IIe**, 0.82 g (yield = 51%, M.P. = >300 °C). IR (KBr) : 3016, 1756, 1717, 1616, 1553, 1377, 1223, 1199, 1159, 1117 and 1006 cm^{-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 15

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 **6,** 0.79 g (yield= 47%, M.P. > 300C). IR (KBr) : 3067, 1731, 1615, 1557, 1443, 1377, 1255, 1146, 1115, 1068, 999, 882 and 776 cm^{-1}. ^{1}H-NMR (D_2SO_4) : δ 6.88 (s, 2H), 6.96 (s, 2H), 7.14 (4H, d, *J* = 7.7Hz), 7.44 (2H, d, *J* = 7.7Hz), 7.60 (s, 2H), 7.70 (4H, d, *J* = 10.7Hz), 7.75 (2H, d, *J* = 7.7Hz).

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, **7** (1.09 g, 0.005 mol) and rubeanic acid (0.69 g, 0.0055 mol) in dimethylformamide following the above protocol gave **7**, 0.62 g (yield = 48%, M.P. = 145 °C char). IR (KBr):-3094, 1716, 1613, 1509, 1384, 1246, 1150, 1028, 838 and 635 cm^{-1}. ^{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,**8** (1.12 g, 0.005 mol) and_Rubeanic acid (0.69 gm, 0.0055 mol) in dimethylformide following the above protocol gave **17**, 1.21 g (yield = 42%, M.P. = 125 °C char). IR (KBr):-3069, 2862, 1732, 1617, 1413, 1385, 1240, 1151, 1056, 995, 885, 732 and 648 cm^{-1}. ^{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* = 7.7Hz).

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, **I**i (1.19 g, 0.005 mol) and Rubeanic acid (0.69 g, 0.0055 mol) in dimethylformamide following the above protocol gave **18**, 0.65 g(yield = 45%, M.P. = 137 °C char). IR (KBr) : 3780, 1765, 1605, 1501, 1450, 1373, 1314, 1722, 1085, 937, 874, 774 and 650 cm^{-1}. ^{1}H-

NMR (D_2SO_4) : 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 Screening[7]

In the present study, compounds **10-18** 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.aureus* 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).

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 10-18

Sr.No.	compds	% yield	M.P °C	Elemental analysis found(calc. %)			
				%C	%H	%N	%S
1	**10**	49	138(Dec.)	62.99	3.28	6.29	13.88
2	**11**	58	149(Dec.)	58.97	2.98	5.91	13.29
3	**12**	51	>300	57.34	2.77	5.21	11.87
4	**13**	47	>300	58.67	3.31	4.99	11.34
5	**14**	51	>300	59.99	3.88	4.76	10.81
6	**15**	49	>300	64.57	2.96	4.31	9.66
7	**16**	48	145(Dec.)	67.78	2.69	5.38	12.29
8	**17**	43	125(Dec.)	60.34	3.65	5.55	12.37
9	**18**	48	137(Dec.)	68.92	3.45	5.21	11.78

Table 2

	Minimum inhibitory concencentration against (µg/mL)	
	S.aureus	*E.Coli*
10	500	500
11	400	500
12	500	400
13	500	500
14	500	400
15	400	400
16	600	500
17	400	400
18	600	500

Conclusion

Compounds **10-18** were evaluated for their anti microbial activity by Using concentration level of 200µg/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 in Table 2.

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