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Studies on 4-Thiazolidinones—Part I: Synthesis and Antimicrobial Activity of 1,4 Bis (2′-Aryl-5′-methyl/ carboxymethyl-4′-thiazolidinon-3′-ylamino) phthalazines

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Some new 4-thiazolidinones have been prepared bearing phthalazine moiety by the condensation of Schiff's bases from 1,4-dihydrazino phthalazine with thiolactic acid thiomalic acid. The structure of the product has been characterised by ir and PMR spectral studies. The products have been screened for antimicrobial activity. Most of the compounds showed moderate activity.

INTRODUCTION

4-Thiazolidinones have been found to be associated with diverse biological activities and numerous reports have appeared in the literature which highlight their chemistry and uses[1-3]. Phthalazine derivatives also possess wide therapeutic activity[4] like antiinflammatory, anaesthetic, antiepileptic, antipyretic, analgestic, antirheumatic, tuberoulostatic, etc. Dihydralazine is a potent antihypertensive agent[4].

With a view to obtain better therapeutic agents, we have synthesised different 4-thiazolidinones of type 3 by the action of thiolatic and thiomalic acid on Schiff's bases obtained by condensing 1,4-dihydrazino phthalazine with different aryl aldehydes. The structures have been confirmed by ir, mass and PMR spectral studies. The products have been screened for antimicrobial activity.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. ir spectra were recorded on a Shimazdu IR 435 spectrophotometer and PMR on Varian XL-400 and Mass (70 ev) on a Jeol, JMS-D 300 Spectrophotometer.

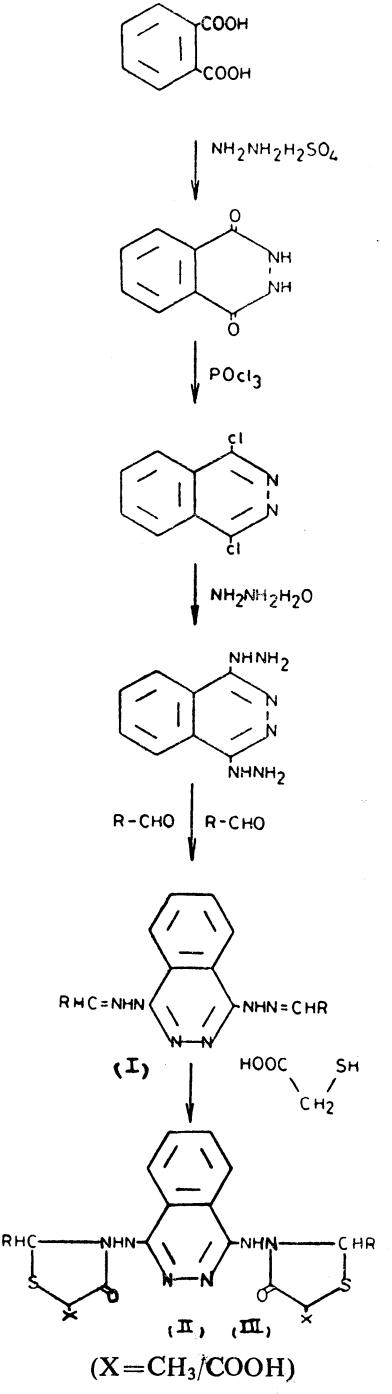
1,4-Bis (substituted benzal hydrazino) phthalazine (Type I)

The mixture of 1,4-dihydrazino phthalazine (1.9 gm, 0.01 M) and 3,4-dimethoxy benzaldehyde (3.32 gm, 0.02 M) was dissolved in methanol and refluxed for 15 min on waterbath. Poured the mixture into crushed ice and washed with sodium bisulphite. This was then dried and crystallised from methanol. $C_{26}H_{26}N_6O_4$; yield 54%; M.Pt. 184°C (Found: C, 68.70; N, 17.04; requires: C, 68.83; N, 17.72%).

λ_{max}(KBr) (R = 3,4-dimethoxy phenyl)

3300 (–NH str.); 1660 (C=N str.); 810 cm^{-1} (ring skeletal)

Mass: M/e : 263, 237, 213, 184, 160, 159, 129, 115 (base peak), 101, 89, 77, 65.



(X=CH_3/COOH)

Similarly other Schiff's bases were prepared (Table 1). All compounds gave correct nitrogen analysis.

TABLE 1

ANALYTICAL AND PHYSICAL DATA OF COMPOUNDS

Sl. No.	R	4-Thiazolidinones of type (II)		4-Thiazolidinones of type (III)	
		M.pt. °C	N % found/Calc.	M.pt. °C	N % found/Calc.
1.	Phenyl	low M.P.	15.20 (15.50)	197(d)	12.19 (12.77)
2.	2-Chlorophenyl	124(d)	13.45 (13.75)	300	11.23 (11.55)
3.	4-Chlorophenyl	140(d)	13.51 (13.75)	210	11.26 (11.55)
4.	2,6-Dichlorophenyl	310(d)	12.12 (12.35)	224	10.25 (10.55)
5.	3,4-Dichlorophenyl	130(d)	12.05 (12.35)	235(d)	10.30 (10.55)
6.	3-Amino phenyl	310(d)	14.35 (14.60)	300	16.11 (16.28)
7.	4-Amino phenyl	360	14.23 (14.69)	340	16.25 (16.28)
8.	2-Hydroxy phenyl	205	14.25 (14.63)	280	12.11 (12.17)
9.	4-Hydroxy phenyl	242(d)	14.31 (14.63)	360	12.07 (12.17)
10.	2-Methoxy phenyl	120	13.7 (13.95)	360	11.60 (11.70)
11.	4-Methoxy phenyl	135(d)	13.75 (13.95)	355(d)	11.65 (11.70)
12.	3,4-Dimethoxy phenyl	206	12.48 (12.69)	213	10.71 (10.80)
13.	3-Methoxy-4-Hydroxy phenyl	340	13.01 (13.25)	216(d)	11.02 (11.20)
14.	3-Nitro phenyl	140(d)	17.51 (17.72)	360	14.11 (14.29)
15.	Cinnamyl	139	14.01 (14.14)	175	11.65 (11.83)
16.	4-Dimethylamino phenyl	180	13.61 (17.83)	249	14.91 (15.05)

1,4-Bis (2'-aryl-5'-methyl/carboxymethyl-4'-thiazolidinon-3'-ylamino) phthalazine: (Type II)

A mixture of thiolactic acid (0.01 mole) and 1,4-bis (substituted benzal hydrazino) phthalazine (0.01 mole) was refluxed for 10 hrs on an oil bath at 110°–120°C. This was then cooled and washed with sodium bicarbonate. The product so obtained was filtered and dried. Recrystallised from methanol: dioxane (1 : 1); $C_{30}H_{30}N_6O_6S_2$; Yield 52%; M.Pt. 130°C (Found: C, 56.70; N, 13.19; S, 9.94; requires: C, 56.78; N, 13.25; S, 10.09).

IR (KBr) (R = 3,4-dimethoxy phenyl)

3250 (N—H str.); 1680 (C=0 str.); 650 cm^{-1} (C–S–C str.)

PMR ($CDCl_3$)

3.7 (6H, d, s-*CH*CH_3), 5.85 (2H, Q, s-*CH*CH_3),

3.98 (6H, s, OCH_3), 3.90 (6H, s, OCH_3),

7.3 (2H. s, N*CH*S), 6.6–7.2 (10H, C, Aromatic),

9.8 (2H, Br, -NH-).

Mass: M/e : 260, 259, 241, 233, 204, 130 (base peak), 129, 116, 115, 102, 90, 75, 65.

Similarly, other 4-thiazolidinone derivatives of type (III) were prepared (Table 1). All compounds gave correct nitrogen analysis.

1,4-Bis (2'-aryl-5'-carboxymethyl-4'-thiazolidinon-3'-ylamino) phthalazines: (Type III)

1,4-Bis (substituted benzal hydrazino) phthalazine (4.86 gm, 0.01 M) and thiomalic acid (3.0 gm, 0.02 M), were mixed in r.b.f. and heated on oil bath for 2 hrs. at 160°C and ½ hr. at 180°C. Then cooled and taken it in sodium bicarbonate. Then the sodium bicarbonate solution was acidified with diluted HCl to give the product, filtered and dried. Recrystallised from methanol-dioxane $C_{36}H_{38}N_6O_{10}S_2$, Yield 44% (Found: C, 55.35; N, 10.71; S, 8.01; requires: C, 55.52; N, 10.80; S, 8.2%).

RESULTS AND DISCUSSION

From the experimental data, it has been observed that all the 4-thiazolidinone derivatives of type (II) showed good activity against *Pseudomonas floures*. The products were moderately active against *E. coli* and *A. flavus*. However, comparatively significant activity was observed in compounds having R = 2-chlorophenyl, 4-aminophenyl, 4-methoxyphenyl, against *Pseudomonas floures* and R = 4-chlorophenyl, 2-methoxyphenyl against *S. citrus* and thiazolidinones of type (III) show significant activity having R = phenyl, 2,6-dichlorophenyl against *P. floures*.

TABLE 2

ANTIMICROBIAL ACTIVITY OF COMPOUNDS

Sl. No.	4-Thiazolidinones of type-II Zone of inhibition in mm.						4-Thiazolidinones of type-III Zone of inhibition in mm.					
	E.C.	A.F.	S.A.	C.A.	P.F.	S.C.	E.C.	A.F.	S.A.	C.A.	P.F.	S.C.
	1	2	3	4	5	6	7	8	9	10	11	12
1.	15	15	16	17	23	17	12	13	14	19	18	15
2.	12	16	16	17	22	13	12	15	15	22	21	16
3.	13	15	16	20	16	19	14	12	13	19	18	12
4.	15	18	14	21	15	11	12	11	14	19	17	14
5.	14	19	14	18	18	14	14	14	12	22	23	12
6.	10	17	16	17	22	11	12	19	15	20	20	13
7.	10	14	14	17	25	12	13	14	16	19	18	14
8.	14	12	17	20	18	13	12	11	16	19	16	13
9.	14	11	16	18	20	11	13	11	13	19	15	11
10.	12	11	13	18	21	17	11	12	11	19	19	10
11.	12	15	16	21	22	14	13	18	17	22	22	13
12.	12	11	16	16	16	11	12	14	15	20	20	14
13.	10	11	15	16	17	10	12	13	17	22	19	17
14.	12	11	15	20	19	13	10	11	16	21	20	15
15.	10	17	18	18	23	16	10	15	17	17	22	13
16.	12	11	15	19	18	12	12	11	15	20	19	14

E.C. = Escherichia coli, A.F. = Aspergillus flavus,
S.A. = Staphylococcus aureus, S.C. = Staphylococcus citrus,
C.A. = Candida albicans, P.F. = Pseudomonas floures.

Antifungal Activity

The compounds having R = 2,6-dichlorophenyl against *A. flavus* and R = 4-chlorophenyl, 2-hydroxyphenyl, 4-methoxyphenyl against *C. albicans* and for type (III) R = 3,4-dichlorophenyl, 4-methoxyphenyl, 3-methoxy-4-hydroxyphenyl against *C. albicans*; R = 3, aminophenyl, 4-methoxyphenyl against *A. flavus*.

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