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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF 2-ARYL-3-SUBSTITUTED THIAZOLIDYL-1, 3-THIAZOLIDIN-4-ONES FROM ARYL KETONES

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ABSTRACT

Substituted Schiff's bases **(VIIa-f)** prepared by the treatment of 2-amino-4-phenyl thiazole with different aldehydes on cyclocondensation with thioglycollic acid (mercapto acetic acid) in dry benzene furnished a new series of 2-(substituted phenyl)-N-(substituted-4-phenyl thiazolyl)-4-thiazolidinones **(IXa-f)**. The structure of the compounds have been assigned on the basis of elemental analysis and spectral data. The products were evaluated for their *in vitro* growth inhibiting activity against several microbes. Some of the compounds showed significant anthelmintic activity.

Key words: Thiazoles, Aryl 4-thiazolidinones, Antimicrobial activity, Anthelmintic activity.

INTRODUCTION

A large number of 4-thiazolidinone analogues have been developed for the treatment of many infectious diseases. These were found to possess various biological activities like antibacterial[1], antifungal[2,3], antiviral[4], anthelmintic[5-7], antitubercular[8,9], insecticidal[10] and anti-AIDS[11] properties. It was also found that they possess analgesic[12], anti-inflammatory[13], antithyroid[14], anticonvulsant[15] and antiparkinsonian[16] activities. We report herein the synthesis and biological activity studies of some new aryl substituted-4-thiazolidinones that constitute an important class of compounds. The chemistry and biological potencies of 4-thiazolidinones have been widely investigated and extensively renewed in the past years. However, little is known about aryl substituted-4- thiazolidinones having N-substituted aryl thiazole moiety. We have now synthesized a number of aryl substituted-4- thiazolidinones and evaluated them for biological activity.

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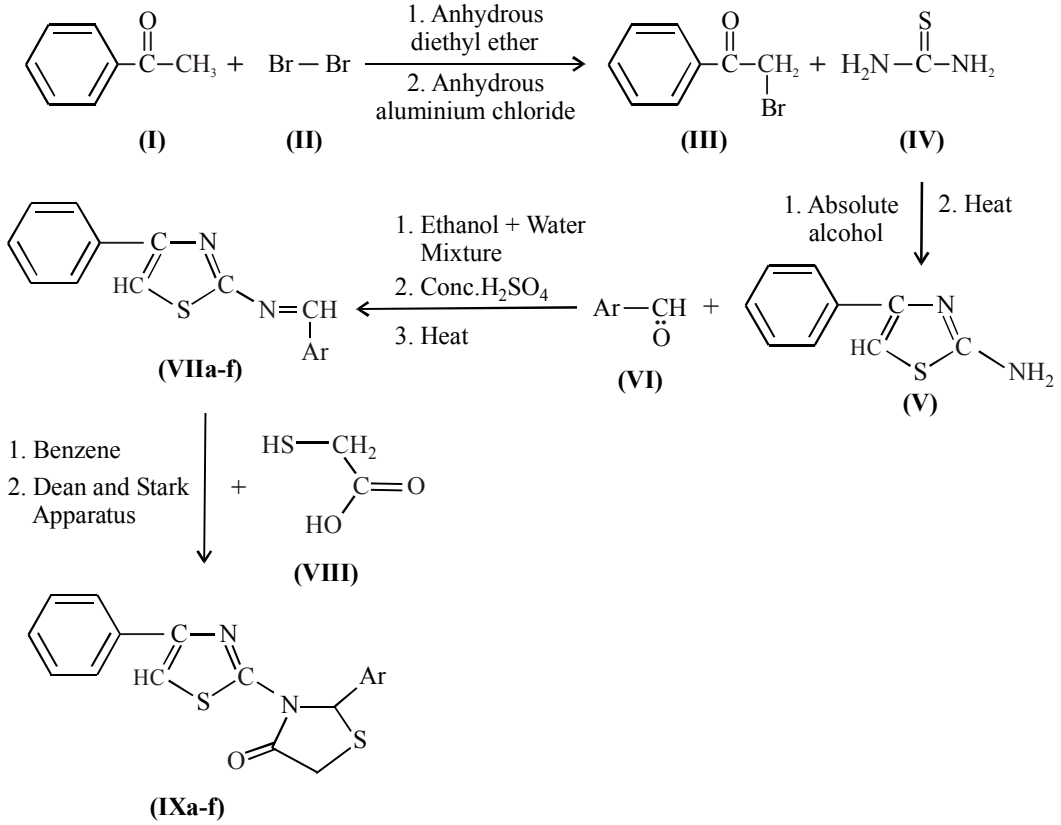
EXPERIMENTAL

All the reactions were carried out under prescribed laboratory conditions. The products were purified by recrystallization and melting points were determined in open capillaries and are uncorrected. All the final compounds were characterized by their elementary analysis, IR, mass and PMR spectra.

FT-IR spectra were recorded on Shimadzu 8201 PC, IR Spectro-photometer using a thin film supported on KBr pellets. PMR spectra were recorded on Bruker AC 300 (300 MHz), NMR spectrometer using TMS as internal standard, FAB mass spectra were recorded on JEOL SX 102 (DA-6000 mass spectrometer) Data system using Argon Xenon (6KV.10MA) as the FAB gas. The purity of the compounds was checked on silica gel coated plates (Merck).

General procedure for the preparation of aryl-4-thiazolidinones (IXa-f)

Synthesis of aryl-4- thiazolidinones involves four steps.



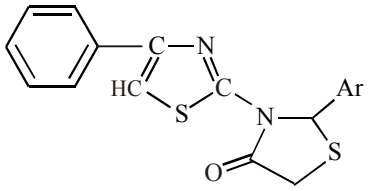
In the first step, acetophenone **(I)** in pure and anhydrous diethyl ether was treated with bromine **(II)** in presence of anhydrous aluminium chloride. Then phenacyl bromide **(III)** precipitates out. Second step consists of reaction of phenacyl bromide **(III)** in 100 mL of absolute alcohol and thiourea **(IV)**, which yields the desired 2-amino-4-phenyl thiazole **(V)**. **(V)** was then condensed with appropriate aldehydes **(VI)** in presence of ethanol-water mixture. Then two drops of conc. H_2SO_4 were added and refluxed for 4-5 hours in the third step and solid of Schiff's bases **(VIIa-f)** separates out. In the final step, the resulting Schiff's bases in benzene were refluxed with thioglycollic acid (mercapto acetic acid) using Dean and Stark apparatus till the clear distillate was formed. Resulting mixture was cooled to 0^oC. The solid separated out, was washed with 5% NaOH solution to give aryl substituted -4-thiazolidinones **(IXa-f)**. The molecules were synthesized as per the procedure and the outline is described in the **Scheme 1**. Physical and spectral data of final products are given in Tables 1 and 2.

Table 1: Physical data of compounds

S. No.	Compd. No.	Aldehyde	Physical state	M. P. (^oC)	Yield (%)	Mol. formula[a] (Mol. Wt.)
1	**IXa**	3,4,5-Trimethoxy benzaldehyde	Dark red crystals	161	73	$C_{21}H_{20}N_2O_4S_2$ (428.527)
2	**IXb**	p-Dimethyl-amino-benzaldehyde	Red crystals	191	71	$C_{20}H_{19}N3OS_2$ (381.316)
3	**IXc**	Vanillin	Pale yellow crystals	174	68	$C_{19}H_{16}N_2O_2S_2$ (368.475)
4	**IXd**	4-Chloro-benzaldehyde	Yellow crystals	184	70	$C_{18}H_{13}N_2OS_2$ (372.893)
5	**IXe**	4-Nitro-benzaldehyde	Orange crystals	164	71	$C_{18}H_{13}N_3O_3S_2$ (383.0)
6	**IXf**	2,4-Dihydroxy-benzaldehyde	Light orange crystals	172	72	$C_{18}H_{14}N_2O_3S_2$ (370.447)

[a]Elemental analyses for C, H, N are within ± 0.4% of the theoretical values

Table 2: Spectral data of the compounds (IXa-f)



(IX{a-f})

Compd.	IR (KBr, cm^{-1})	^1H NMR ($CDCl_3$,ppm)[a]	MS (m/z M^+)
IXa	3053.9 (Ar-CH), 1646.4 (-CO), 1635.3 (-N=C), 1525.1 (C= C) , 1100 (C-C), 1200 (O-CH_3)	δ 3.72 (S, 3H, -OCH_3), δ 5.24 (S, 1H, -SCH), δ 5.58 (S, 2H, -SCH_2), δ 7.24 -7.82 (m, 8H, Ar-H), δ 7.18 (S, 1H, thiazole)	428.5, (calculated 428.527)
IXb	3036.4 (Ar-CH), 1633.3 (-CO), 1615.2 (-N=C), 1535.1 (C=C), 1265 (N-$(CH_3)_2$), 1122 (C-C)	δ 7.68 (d, Ar-N $[CH_3]_2$), δ 7.08-7.58 (m, 8H, Ar-H), δ 7.21 (s, 1H, thiazole), 6.41 (2H, s, O-H), δ 5.61(s, 2H,-SCH_2), δ 5.28 (s, 1H, -SCH), δ 2.98 (s, 6H, N $(CH_3)_2$).	381.1, (calculated 428.527)
IXc	3043.9 (Ar-CH), 1666.4 (-CO), 1625.3 (-NCH), 1515.1 (C=C), 1230 (O-CH_3)	7.24 (s, 1H, thiazole), δ 7.02-7.6 (m, 8H, Ar-H), 6.38 (2H, s, O-H), δ 5.6 (s, 2H, -SCH_2), δ 5.26 (s, 1H, -SCH), δ 3.99 (S, 3H, -OCH_3).	368.1, (calculated 368.475)
IXd	3063.4 (Ar-CH), 1700 (-CO), 1605.8 (-NCH), 1545 (C=C)	Δ 7.89 (d, 2H, m-H), δ7.23 (s, 1H, thiazole), δ 7.04-7.52 (m, 8H, Ar-H), 6.43 (2H, s, O-H), δ 5.63 (s, 2H, -SCH_2), δ 5.26 (s, 1H, -SCH).	372.5, (calculated 372.893)
IXe	3058 (Ar-CH), 1646.3 (-CO), 1625 (-NCH), 1617	7.21 (s, 1H, thiazole), δ 7.05-7.54 (m, 8H, Ar-H), δ7.64 (d, 2H, m-H), δ 5.65 (s, 2H, -SCH_2), δ 5.27 (s, 1H, -SCH).	383.1, (calculated 383.0)
IXf	3260 (-OH) 3042 (Ar-CH), 1726 (-CO), 1621 (-NCH), 1618(Ar C=N) 1554(C=C). Ar C=N) 1518(C=C)	7.20 (s, 1H, thiazole), δ 7.02-7.8 (m, 8H, Ar-H), 7.42 (s, 2H, Ar-OH), δ 7.38 (S, 2H, m-H), δ7 .39 (s, 1H, -OH), δ 5.61 (s, 2H, -SCH_2), δ 5.26 (s, 1H, -SCH).	370.5, (calculated 370.447)

[a]s, singlet; d, doublet; m, multiplet

Biological activity

All the synthesized compounds were screened for their antibacterial activity against both gram-positive and gram-negative bacteria and also for their antifungal activity against *C. albicans* and *A. niger* and these were found active. The antibacterial and antifungal activities were carried out by the disk diffusion method. The data for anti microbial activities of synthesized compounds are given in Table 3.

Table 3: Antibacterial and antifungal activities of the synthesized compounds

S. No.	Compd. No.	Diameter of zone of inhibition (mm)					
		Ps. auregenosa	***E. coli***	***B. subtilis***	***S. aureus***	***C. albicans***	***A. niger***
1	**IXa**	11	09	11	12	08	09
2	**IXb**	13	10	12	13	11	11
3	**IXc**	14	10	10	11	13	14
4	**IXd**	15	11	11	14	09	10
5	**IXe**	13	11	10	12	12	13
6	**IXf**	16	12	13	15	10	09
7	**Amoxycillin**	21	20	20	22	-	-
8	**Griseofulvin**	-	-	-	-	16	18
9	**DMF**	-	-	-	-	-	-

- Indicates no inhibition

Anthelmintic activity studies were also carried out against *Pheritime posthuma* and *Eudrilus sp* by Garg's method[17]. Piperazine citrate was used as standard anthelmintic drug to compare the anthelmintic activity of synthesized compounds. The results of anthelmintic activity are given in Tables 4 and 5.

Table 4: Anthelmintic activity of the synthesized compounds against *Pheritime posthuma*

S. No.	compound	Conc. of compd. (mg)	Mean paralyzing time (min)+S.E.	Mean death time (min)+S.E.
1	**Control**	-	-	-
2	**Piperazine citrate**	200	14.26 ± 1.22	26.02 ± 1.5
3	**Mebendazole**	200	20.12 ± 1.16	31.06 ± 1.19
4	**IXa**	200	29.22 ± 1.16	48.17 ± 1.24
5	**IXb**	200	24.34 ± 1.26	39.01 ± 1.16
6	**IXc**	200	26.06 ± 1.24	41.46 ± 0.17
7	**IXd**	200	29.34 ± 1.17	48.27 ± 1.24
8	**IXe**	200	28.49 ± 1.31	45.36 ± 1.21
9	**IXf**	200	22.54 ± 1.02	37.14 ± 1.18

Table 5: Anthelmintic activity of the synthesized compounds against *Eudrilus sp*

S. No.	Compd.	Conc. of compd. (mg)	Mean paralyzing time (min)+S.E.	Mean death time (min)+S.E.
1	**control**	-	-	-
2	**Piperazine citrate**	200	13.48 ± 1.16	24.46 ± 1.07
3	**Mebendazole**	200	29.11 ± 1.18	38.23 ± 1.01
4	**IXa**	200	30.32 ± 0.54	50.12 ± 1.18
5	**IXb**	200	24.12 ± 1.22	40.13 ± 1.16
6	**IXc**	200	25.48 ± 1.26	42.09 ± 0.14
7	**IXd**	200	28.36 ± 0.28	47.43 ± 1.14
8	**IXe**	200	27.36 ± 1.15	44.52 ± 1.21
9	**IXf**	200	21.43 ± 1.13	35.46 ± 0.26

RESULTS AND DISCUSSION

IR spectra of all synthesized aryl-4-thiazolidinones revealed the important functional groups. ^{1}H NMR spectra of the products indicate the formation of the 4-thiazolidinone derivatives having substituents at position 3 and having different aryl groups at position 2.

The mass spectral data indicated stable molecular ion peak for all the synthesized final products. All the synthesized compounds gave satisfactory elemental analysis data.

It is concluded that aryl substituted 4-thiazolidinones can be synthesized successfully in the laboratory. The results from antimicrobial activity studies showed that some of the aryl substituted 4-thiazolidinones (**IXd**, **IXf**) possess good antibacterial activities and compounds (**IXb**, **IXc**, **IXe**) showed moderate to good activities, when compared to the standard drug amoxicillin whereas compounds (**IXc**, **IXe**,) showed good antifungal activities and compounds (**IXb**, **IXd**, **IXf**) showed moderate to good activities, when compared to the standard drug griseofulvin. The results from anthelmintic activity studies showed that all the synthesized compounds found to exhibit anthelmintic activity.

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REFERENCES

1. A. E. R. Abdul, A. M. Mohmoud, G. M. Elnaggar and H. A. Elsharief, Pharmazie, **38**, 589 (1983).
2. T. H. Pieter and B. S. Webb, Chem. Abstr., **100**, 139089 (1984).
3. R. H. Moizzoni and P. O. Esman, J. Am. Chem. Soc., **80**, 3471 (1958).
4. A. K. Sheinkman, Microbial. Zh., **33**, 89 (1971).
5. Copper Tinslay Laboratories Inc., Chem. Abstr., **63**, 112686 (1965).
6. S. E. Loland Jr., J. N. King and L. Wallace, J. Parasitol., **53**, 20 (1967).
7. M. I. Hussain and S. K. Agarwal, Indain J. Pharm., **37**, 89 (1975).
8. N. M. Turkevich, L. Y. Ladnaya, I. V. Pleshnev and O. L. Grom, Khim. Issled. Farm, 64 (1970).

9. Chem. Abstr., **76**, 34154 (1972).

10. B. C. Dash and G. N. Mahapatra, J. Indian Chem. Soc., **44**, 939 (1967).

11. J. J. Bhatt, B. R. Shah, H. P. Shah, P. B. Trivedi, N. K. Undavia and N. C. Desai, Indian J. Chem., **33B**,189 (1994).

12. Chem. Abstr., **58**, 12569 (1963).

13. W. Coyne, Medicinal Chemistry, Vol. II, A. Burger (Ed.), Wiley-Interscience, New York, (1970) p. 953.

14. S. N. Golubova, Ukr. Bickhim. Zh., **25**, 325 (1953) .

15. S. K. Srivastava, S. L. Srivastava and S. D. Srivastava, J. Indian Chem. Soc., **77**, 104 (2000).

16. P. Kumar, C. Nath, K. P. Bhargava and K. Shanker, Indian J. Chem., **21B**, 1128 (1982).

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