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Research Article

SYNTHESIS OF A SERIES OF THIAZOLIDINONE DERIVATIVES AND EVALUATION OF THEIR ANTIMICROBIAL PROPERTIES

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ABSTRACT

A series of thiazolidinone derivatives with various aromatic aldehyde substitution were synthesized and characterized by physical (TLC and M.P.) and spectral data (IR, NMR and MASS). They were evaluated for antimicrobial potential against Gram positive *Staphylococcus aureus, Bacillus subtilis,* gram-negative *Escherichia coli, Pseudomonas aeuroginosa, Shigella* and fungi *Candida albicans* and *Aspergillus niger.* The initial screening using zones of inhibition at 50 µl concentration revealed that they are moderately active against the tested strains.

Keywords: Thiazolidinone, Acridin-9(10H)-one, Antimicrobial properties

INTRODUCTION

The main objective of the medicinal chemistry is to synthesize the compounds that show promising activity as therapeutic agents with lower toxicity.[1] Heterocycles bearing nitrogen and/or sulphur moieties constitute the core structure of number of biological interesting compounds.[2] The biological and therapeutic properties of thiazolidinone have greatly initiated the synthesis of immense derivatives of these moieties. The β-lactam ring is associated with a larger number of antibiotics such as penicillins and cephalosporins. Schiff's bases also show diverse biocidal activities by virtue of a toxopheric C=N linkage. This prompted us to construct a novel molecule containing both these structural features.[3] 4-Thiazolidinones are the derivatives of thiazolidine with a carbonyl group at the 4 position. Considerable interest has been shown in the field of thiazolidinone chemistry due to their wide range of therapeutic activities such as antimicrobial,[4-6] hypoglycaemic and hypolipidemic,[7-8] antitubercular,[9-11] diuretic,[12] analgesic,[13] anticonvulsant,[14-15] anthelminitic,[16-17] anti-inflammatory,[18] and pesticidal[19] activities. Acridone containing alkaloids have been isolated from the bark and leaves of several trees, for instance *Melicopoe fareana* & *Evodia xanthoxyloids*. These trees are found in forests of Queensland (Australia) and the important alkaloids are melicopicine, melicopidine and eroxanthine.[20] Acridone are reported to possess a wide spectrum of biological activities such as antileishmanial, antitumor, anti-HIV, antimicrobial etc. In addition, drug resistance and poor bioavailability are also associated with acridone.[21] Microbiological screening of the thiazolidinone derivatives are increasing in demand due to the prescribed agents show resistance to microbes. The numbers of methods are used to synthesize the newer drugs. We already described the synthesis and microbiological screening of newer 5-arylidene-3-(2-phenyl-4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one derivatives from acridinone and various aromatic aldehydes.[22] In this paper, we describe the synthesis, characterization and antimicrobial screening of a series of thiazolidinone derivatives bearing acridin-9-one moiety. The structures of newly synthesized compounds were confirmed from spectral data and were screened for microbiological screening.

MATERIALS AND METHODS

All the reagent was used as procured from Aldrich, Merck, Hi-media, Sigma and used without further purification. The melting point was determined in open capillaries and uncorrected. The reactions were monitored using TLC for completion and compounds were checked for purity by silica gel G. IR spectra were recorded by FTIR-8400S SHIMADZU and values are expressed in cm^{-1}. ^{1}HNMR spectral analysis were carried out using instrument amx-400 and the solvent used are deuterated chloroform and dimethyl sulfoxide. The mass spectral data were recorded from LCMS 2010A, SHIMADZU.

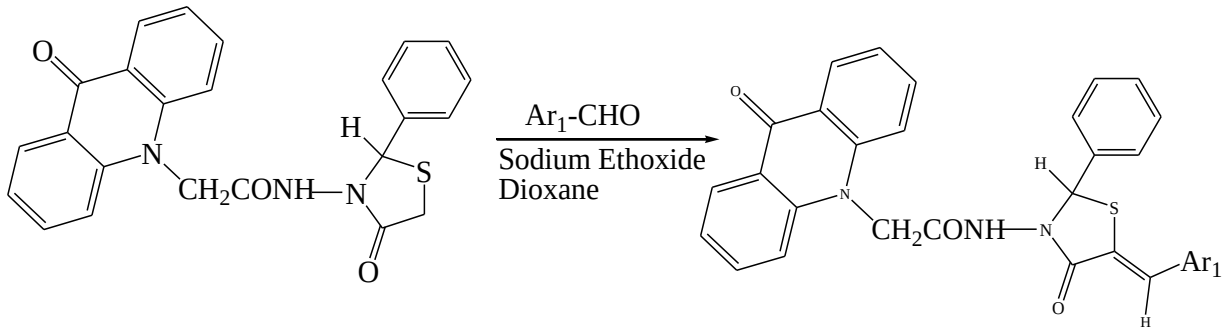
Procedure for synthesis of 3-(2-phenyl 4-oxo-1,3-thiazolidine) acetamido acridin-9-one (1): The required 3-(2-phenyl 4-oxo-1,3-thiazolidine) acetamido acridin-9-one was synthesized from acridin-9-one. The detailed synthetic procedure and their characterization data were given in our earlier publication.[22]

Synthesis of 5-benzylidene-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (2a): Equimolar 3-(2-phenyl 4-oxo-1,3-thiazolidine) acetamido acridin-9-one (0.05 mol 21.45gm) & benzaldehyde (0.05 mol 5.3ml) were taken in round bottom flask along with 50 ml dioxane in presence of four drops of sodium ethoxide and allowed to reflux for approximate 7 hours. Poured the mixture into 250 ml ice-cold water and stirred. Precipitate obtained was filtered, dried and recrystalized from chloroform.

Synthesis of 5-(2,4-dichlorobenzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (2b): Equimolar 3-(2-phenyl 4-oxo-1,3-thiazolidine) acetamido acridin-9-one (0.05 mol 21.45gm) & 2,4-dichlorobenzaldehyde (0.05 mol 8.75gm) were taken in round bottom flask along with 50 ml dioxane in presence of four drops of sodium ethoxide and allowed to reflux for approximate 8 hours. Poured the mixture into 250 ml ice-cold water and stirred. Precipitate obtained was filtered, dried and recrystalized from chloroform.

Synthesis of 5-(4-N,N-dimethylaminobenzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (2c): Equimolar 3-(2-phenyl 4-oxo-1,3-thiazolidine) acetamido acridin-9-one (0.05 mol 21.45gm) & 4-N,N-dimethylaminobenzaldehyde (0.05 mol 7.45gm) were taken in round bottom flask along with 50 ml dioxane in presence of four drops of sodium ethoxide and allowed to reflux for approximate 8 hours. Poured the mixture into 250 ml ice-cold water and stirred. Precipitate obtained was filtered, dried and recrystalized from chloroform.

Scheme



(1) **(2a-2e)**

Compound	Ar_1-CHO
2a	Benzaldehyde
2b	2,4-Dichlorobenzaldehyde
2c	4-N,N-Dimethylaminobenzaldehyde
2d	3-Methoxy-4-hydroxybenzaldehyde
2e	3,4-Dimethoxybenzaldehyde

Synthesis of 5-(3-methoxy-4-hydroxybenzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (2d): Equimolar 3-(2-phenyl 4-oxo-1,3-thiazolidine) acetamido acridin-9-one (0.05 mol 21.45gm) & 3-methoxy-4-hydroxybenzaldehyde (0.05 mol 7.6gm) were taken in round bottom flask along with 50 ml dioxane in presence of four drops of sodium ethoxide and allowed to reflux for approximate 8 hours. Poured the mixture into 250 ml ice-cold water and stirred. Precipitate obtained was filtered, dried and recrystalized from chloroform.

Synthesis of 5-(3,4-dimethoxybenzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (2e): Equimolar 3-(2-phenyl 4-oxo-1,3-thiazolidine) acetamido acridin-9-one (0.05 mol 21.45gm) & 3,4-dimethoxybenzaldehyde (0.05 mol 8.3gm) were taken in round bottom flask along with 50 ml dioxane in presence of four drops of sodium ethoxide and allowed to reflux for approximate 10 hours. Poured the mixture into 250 ml ice-cold water and stirred. Precipitate obtained was filtered, dried and recrystalized from chloroform.

Antimicrobial Activity[23]: The antimicrobial activity of synthesized compounds (2a-2e) was evaluated by cup-plate method. Working solution of test compounds is prepared in DMSO to a concentration of 50µg/ml and used for the microbial study. Zone of inhibition of the synthesized compounds was determined against the gram-positive organisms *Staphylococcus aureus, Bacillus subtilis* and gram-negative organisms *Escherichia coli, Pseudomonas aeuroginosa, Shigella*. The bacteria were subcultured on Nutrient Agar medium. The petridishes were incubated at 37ºC for 24hr. The antifungal activity of the synthesized compounds was tested against the fungi *Candida albicans* and *Aspergillus niger*. The fungi were subcultured in Sabouraud Dextrose Agar medium. The petridishes were incubated for 48hr at 25ºC. Ampicillin (10 mcg/disc)(Std.1), Ciprofloxacin(30mcg/disc)(Std.2) and Streptomycin (10mcg/disc)(Std.3) were used as antibacterial standards and Fluconazole (10 mcg/disc)(Std.1), Amphotericin B (100 units/disc)(Std.2), Clotrimazole (100 mcg/disc)(Std.3) and Griseofulvin (100mcg/disc)(std.4) as antifungal standards. The results are presented in Table 2.

RESULTS AND DISCUSSION

The newly synthesized compounds were confirmed by various physical and spectral data. These results are given as:

3-(2-Phenyl 4-oxo-1,3-thiazolidine) acetamido acridin-9-one (1): (m.p. 217°C), **IR (KBr), CM^{-1}:** 3033, 3097(C-H Ar str.), 3276, 3475(-NH str), 2866 (-N-CH_2-S str.), 1631 (CONH str.), 1596 (C=C Ar str.), 1265, 1290(N-CH_2 str.), 673 (-CH_2-S-CH); **1H NMR ($CDCl_3$)**: δ 7.1-8.4 (13H, Ar-H), δ 8.5 (1H, CONH), δ 6.1 (1H, N-CH-Ar), δ 3.1-3.4 (2H, N-CH_2), δ 3.6-4.0 (2H, S-CH_2); **MS: (m/z):** 429, 430 (M+1), 351.

5-Benzylidene-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (2a): (m.p. 232°C), **IR (KBr), CM^{-1}:** 2873 (-N-CH_2-S str.), 3070 (C-H Ar str.), 1685 (CONH str.), 1292, 1325 (N-CH_2 str.),1583 (C=C Ar str.), 659 (-CH_2-S-CH); **1H NMR ($CDCl_3$)**: δ 6.6-7.8 (18H, Ar-H), δ 8.4 (1H, CONH), δ 4.1 (1H, C=CH-Ar), δ 2.5-2.9 (2H, N-CH_2), δ 3.3(1H,S-CH-Ar); **MS: (m/z):** 517, 518 (M+1), 352.

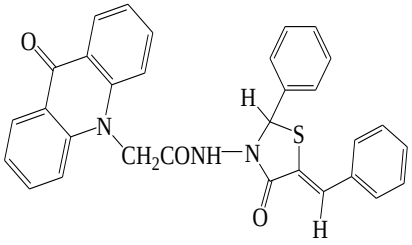
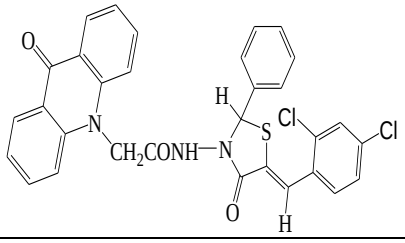
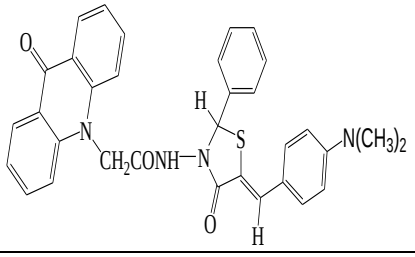
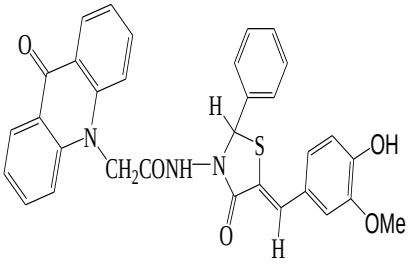
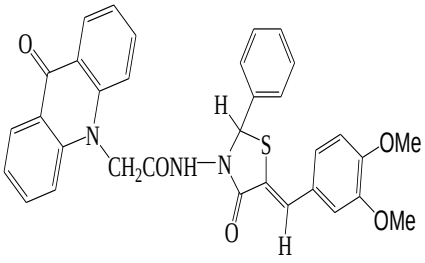
5-(2,4-Dichlorobenzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (2b): (m.p. 274°C), **IR (KBr), CM^{-1}:** 3066, 3087 (C-H str. aromatic), 2852 (-N-CH_2-S str.), 1731 (C=O cyclic), 1679 (CONH str.), 1558, 1587 (C=C str. aromatic), 1192, 1249 (N-CH_2 str.), 848, 823 (C-Cl Str.)

5-(4-N,N-Dimethylaminobenzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) aceto hydrazido acridin-9-one (2c): (m.p. 249°C), **IR (KBr), CM^{-1}:** 3310 (dialkyl –N-CH_3), 3087(C-H str. aromatic), 2852 (-N-CH_2-S str.), 1745 (C=O cyclic), 1650 (CONH str.), 1549, 1556 (C=C str. aromatic), 1232 (N-CH_2 str.), 630 (-CH_2-S-CH).

5-(3-Methoxy-4-hydroxybenzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) aceto hydrazido acridin-9-one (2d): (m.p. 262°C), **IR (KBr), CM^{-1}:** 3029, 3078 (C-H str. aromatic), 3342, 3442 (C-OH Aromatic phenol), 2852 (-N-CH_2-S str.), 1709 (C=O cyclic), 1645 (CONH str.), 1519, 1573 (C=C str. aromatic), 1274 (N-CH_2 str.), 640 (-CH_2-S-CH)

5-(3,4-Dimethoxybenzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (2e): (m.p. 260°C), **IR (KBr), CM^{-1}:** 3024, 3072 (C-H str. aromatic), 2829 (-N-CH_2-S str.), 1747 (C=O cyclic), 1683 (CONH str.), 1583 (C=C str. aromatic), 1292, 1325 (N-CH_2 str.), 657 (-CH_2-S-CH)

Table 1: Physical data of newly synthesized thiazolidinone derivatives

Comp. Code	Structure of compound	Molecular Formula	% Yield	Rf*	M.P.
2a		$C_{31}H_{23}O_3N_3S$	64.60%	0.49	232°C
2b		$C_{31}H_{21}O_3N_3SCl_2$	69.30%	0.70	274°C
2c		$C_{33}H_{28}O_3N_4S$	70.50%	0.77	249°C
2d		$C_{32}H_{25}O_5N_3S$	66.80%	0.67	262°C
2e		$C_{33}H_{27}O_5N_3S$	50.25%	0.55	260°C

*Stationary Phase: Silica Gel G, Mobile Phase: Chloroform: Acetone:: 9:1

Table 2: Biological Activity of newly synthesized thiazolidinone derivatives

Comp. Code	Zone of Inhibition (in mm)						
	B.subtilis	***S.aureus***	***E.coli***	***P.aeuroginosa***	***Shigella***	***C.albicans***	***A.niger***
	50 µg	50 µg	50 µg	50 µg	50 µg	50 µg	50 µg
2a	14	17	20	17	13	21	13
2b	17	22	19	20	17	17	12
2c	12	16	18	12	11	18	11
2d	16	17	20	20	11	11	12
2e	11	13	17	11	11	10	9
Std. 1	4	4	NI	8	6	23	19
Std. 2	32	38	30	29	39	29	18
Std. 3	26	29	20	17	21	17	21
Std. 4	--	--	--	--	--	28	19
Control	NI	NI	NI	NI	NI	NI	NI

Note: Average zone diameter in mm of triplicates, NI: No inhibition, Control: DMSO

CONCLUSION

Five newer substituted derivatives of thiazolidinone with various aromatic aldehyde were synthesized. The newly synthesized compounds were characterized by various spectral techniques and were screened for antibacterial and antifungal activity. All the synthesized compounds show mild to moderate antimicrobial activity against Gram positive, Gram negative and fungal organism. The derivatives of 5-(2,4-dichlorobenzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (2b) and 5-(3-methoxy-4-hydroxybenzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (2d) show potent antimicrobial activity against Gram positive, Gram negative and Fungal organism compare to other derivatives. So it is concluded that the electron withdrawal group substituted thiazolidinone derivatives show potent activity compare to others. Hence, with these encouraging results, the compounds can be further explored for detailed pharmacological and microbiological investigations.

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