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Synthesis characterization and biological screening of some novel substituted thaizine derivatives

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ABSTRACT

Research in Pharmaceutical Chemistry renders a vital role in the discovery of newer therapeutic agents. Thiazines constitute an interesting class of heterocyclic compounds with diverse biological and pharmaceutical profiles such as antimicrobial, anticonvulsant, anthelmintic, antiviral, herbicidal, pesticidal, analgesic and anti-inflammatory activities. Moreover thiazine nucleus is a pharmacophore of cephalosporin's that occupy a very important place in the field of antibiotics. Search for new molecules continues because of fast development of microbial resistance towards existing molecules and therefore new thiazines derivatives were synthesized with an aim to get potent antimicrobial agents. Acetyl acetone on Claisen-Schmidt condensation with various aromatic aldehydes in presence of dilute sodium hydroxide afforded the corresponding chalcones derivatives. Further these compounds were subjected to cyclocondensation with thiourea, catalyzed by aqueous potassium hydroxide to form 2-imino-3,6-dihydro-2H- 1,3-thiazine derivatives. Characterization of the synthesized compounds was done by using spectral techniques UV, IR, ^{1}H NMR & MASS. Antibacterial and antifungal screening was performed by cup plate method using the standards Ciprofloxacin and fluconazole respectively.

Key words: Synthesis, chalcones, thiazines, anticonvulsant, antimicrobial activity.

INTRODUCTION

Thiazines constitute an interesting class of heterocyclic compounds with diverse biological and pharmaceutical profiles such as antimicrobial, anticonvulsant, anthelmintic, antiviral, herbicidal, pesticidal, analgesic and anti-inflammatory activities. Moreover thiazine nucleus is a pharmacophore of cephalosporin's that occupy a very important place in the field of antibiotics. Search for new molecules continues because of fast development of microbial resistance towards existing molecules and therefore new thiazines derivatives were synthesized with an aim to get potent antimicrobial agents. Although a number of drugs are available in the market, the search for new molecules continues because of fast development of microbial resistance towards existing molecules.

In the present study, 2-imino-3,6-dihydro-2H- 1,3-thiazine derivatives **4a-j** were prepared by reacting acetyl acetone on Claisen-Schmidt condensation with various aromatic aldehydes in presence of dilute sodium hydroxide in ethyl alcohol afforded the corresponding chalcones (**3a-j)** derivatives. Further these compounds were subjected to cyclocondensation with thiourea, catalyzed by in ethanolic potassium hydroxide for about 14-hrs, the product **4a-j** were produced. **(Scheme-I)**

MATERIALS AND METHODS

The melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by TLC. The IR spectra were recorded on Shimadzu FTIR spectrophotometer using KBr pellets disc method. The ^{1}HNMR spectra were taken on Bruker 400 MHZ AVENCE spectrophotometer using CDCl3 using tetramethylsilane as internal reference. The chemical shifts are reported in parts per million downfield from tetramethylsilane. Mass spectra were recorded on LC-MS Schimadzu 2010A using dimethyl sulfoxide as solvent. The elemental analysis was carried out using Finnegan analyzer.

All the compounds gave satisfactory chemical analysis the homogencity of the compounds was checked by TLC on aluminum foil packed precoated silica gel plates using n- Hexane and ethyl acetate (8:2) as mobile phase and visualized non specific method by iodine vapors. The results are in table 1.

General Procedure:

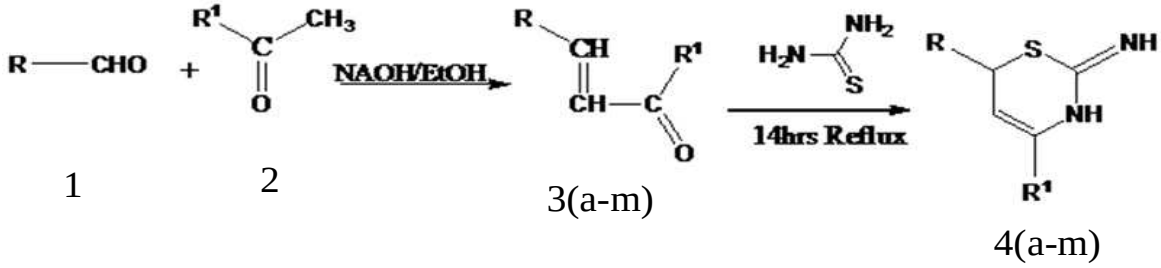
A) Synthesis of chalcones(a-j):

1a) An equimolar quantities of various aromatic aldehyde (0.01mol) and acetyl acetone (0.01mol) were dissolved in minimum amount of absolute ethanol (15ml).Sodium hydroxide solution (0.02mol) was added slowly and the mixture stirred for 2hrs until the entire mixture becomes very cloudy. Then the mixture was poured slowly in to 250ml of ice cold water with constant stirring and kept in refregirator for 24hrs.The yellow solid than obtained was filtered, dried and recrystalized from ethanol.

B) Synthesis of 2-imino-3,6-dihydro-2H- 1,3-thiazine derivatives(a-j):

1a) A mixture of Benzilidine acetyl acetone (0.01mol) and thiourea (0.01mol) were dissolved in ethanolic potassium hydroxide (15ml). The reaction mixture was refluxed for 14hrs.The mixture was then poured in to 200ml of ice cold water and stirring was continued for about 1hr and kept overnight in refrigerator. The precipitate obtained was filtered, washed with water and recrystalized with ethanol. The completion of reaction as monitored by TLC.

Methodology



Scheme-I

The physical data of the synthesized compounds is given in the below table 1.

Table 1: PHYSICOCHEMICAL PARAMETERS

S.NO	R	Mol. formula	% Yield	Melting Point (^{0}C)	R_f value
a	H	$C_{12}H_{13}N_2SO$	84%	120-122^{0}C	0.54
b	4-(N-CH3)$_2$	$C_{12}H_{12}N_2SFO$	81%	180-182^{0}C	0.56
c	3-Cl	$C_{12}H_{12}N_2SOCL$	67%	150-152^{0}C	0.81
d	4-Cl	$C_{12}H_{12}N_2SOCL$	69%	150-152^{0}C	0.64
e	3,4-(OCH$_3$)$_2$	$C_{15}H_{19}N_2O_4S$	84%	87-89^{0}C	0.91
f	3,4,5-(OCH$_3$)$_3$	$C_{14}H_{17}N_2O_3S$	80%	102-104^{0}C	0.62
g	4-F	$C_{14}H_{18}N_2OS$	74%	120-122^{0}C	0.54
h	2-NO$_2$	$C_{14}H_{17}N_3O_3S$	66	121-123^{0}C	0.81
i	3-NO$_2$	$C_{14}H_{17}N_3O_3S$	62	119-122^{0}C	0.86
j	4-NO$_2$	$C_{14}H_{17}N_3O_3S$	72	120-123^{0}C	0.79

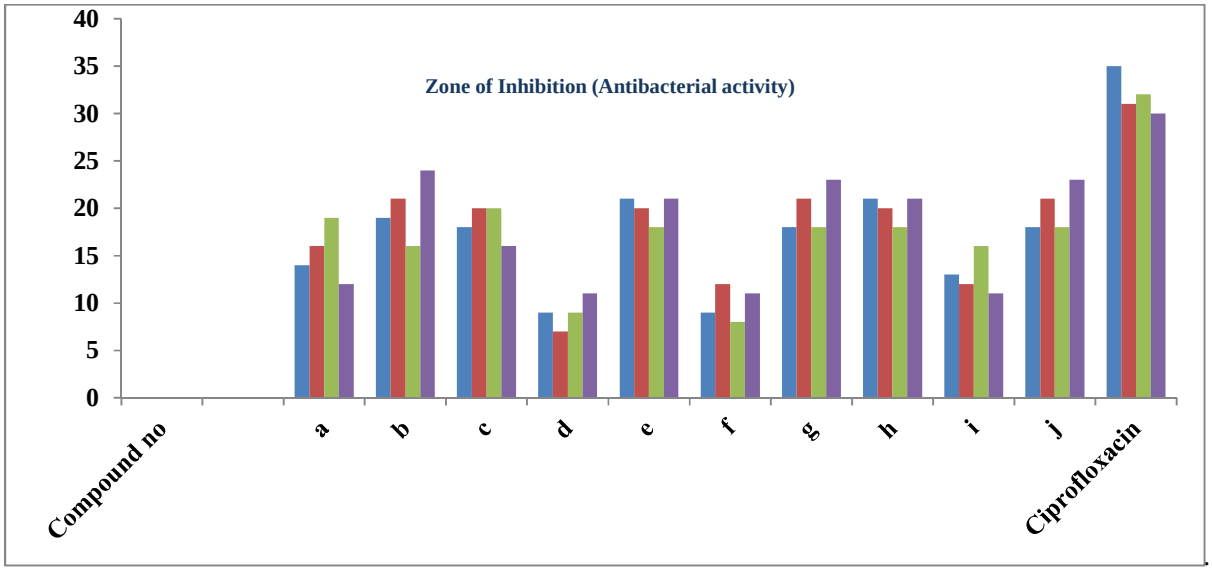
Antimicrobial Activity:

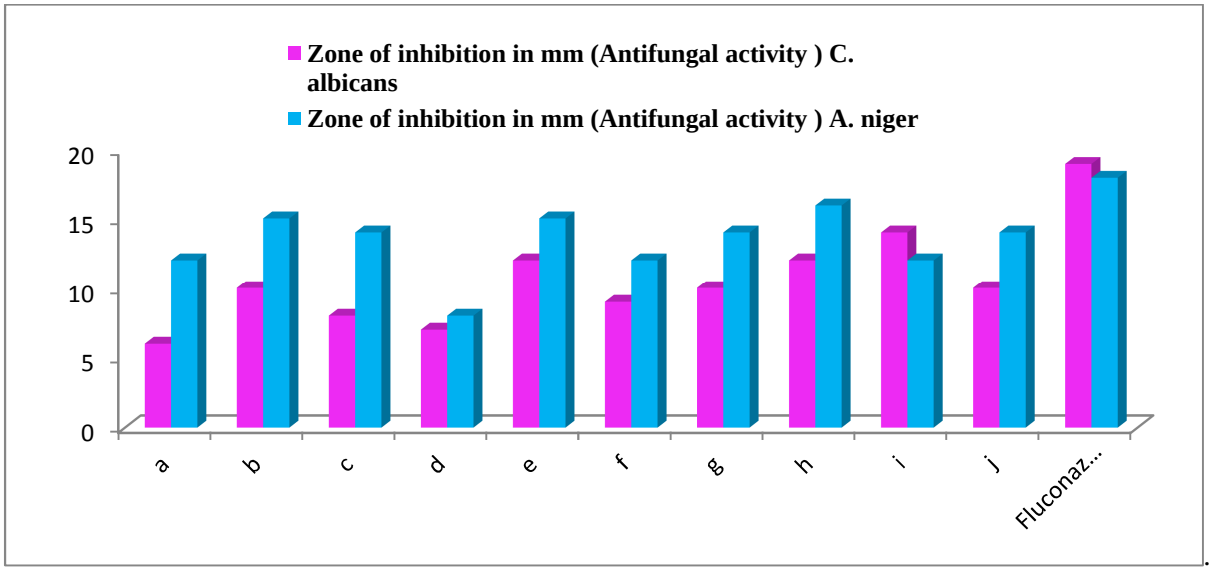
All the synthesized compounds were evaluated for their in vitro antibacterial activity against two Gram positive (*Staphylococcus aureus* and *Bacillus subtilis)* and two Gram negative (*Escherichia coli* and *Klebisiella pneumonia),two antifungal strains A. niger C. albicans*, at concentration of 150 micrograms/ml using cup plate method and MIC was determined by agar streak dilution method. Ciprofloxacin at a concentration of 10µ/ml was used as standard for antibacterial activity and fluconazole at a concentration of 20µ/ml was used as standard for antifungal activity. The zone of inhibition was measured in mm for all the synthesized compounds are presented in Table 2.

TABLE 2: Antimicrobial Activity of synthesized compounds 4a-j

Compound NO	Zone of inhibition in mm				Zone of inhibition in mm	
	Antibacterial activity				Antifungal activity	
	S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*	*C. albicans*	*A. niger*
a	14	16	19	12	6	12
b	19	21	16	24	10	15
c	18	20	20	16	8	14
d	9	7	9	11	7	8
e	21	20	18	21	12	15
f	9	12	8	11	9	12
g	18	21	18	23	10	14
h	21	20	18	21	12	16
i	13	12	16	11	14	12
j	18	21	18	23	10	14
Ciprofloxacin	35	31	32	30	-	-
Fluconazole	-	-	-	-	19	18

Graphical representation of biological activity





RESULTS AND DISCUSSION

The structures of new compounds prepared during the present investigation have been authentically established by their UV, IR, NMR, Mass spectral studies and elemental analysis. In the following section the spectral studies of some selected compounds have been dealt. The compound phenylhex-5-ene-2,4-dione I[S1] has been prepared by condensing one mole of acetyl acetone with one mole of benzaldehyde. The formation I[S1] has been indicated by its UV spectrum. The starting material acetyl acetone exhibited λmax at 258.5 nm. The compound I [S1] exhibited λmax at 324 nm. This clearly indicate that the bathochromic shift is attributed because of =CH-Ar chromophore. The formation of I [S1] has been indicated by its IR spectrum. The starting material, exhibited characteristic absorption band at 166o cm^{-1} due to C=O group. The compound II [S1] exhibited characteristic absorption band at 1652 cm^{-1} due to C=O group. The appearance of a characteristic band at C=O is mainly due to α,β- unsaturation. This clearly indicated the formation of IIA [S1]. Similarly the formations of compounds II [S. 2-6] have also been indicated by their IR spectra. The formation of II [S2] has also been indicated by its ^{1}H NMR spectrum. The presence of δ2.54 (s, 1H,CH), δ3.56 (s, 3H, CH_3), δ3.58 (s, 2H, CH_2), δ3.74 (s, 6H, $N(CH_3)_2$),651(s,1H, NH), 6.69-6.68(m,5H, Ar H) clearly indicated the formation of II[S2]. The formation of phenylhex-5-ene-2,4-dione [IIS (4)] has been confirmed by its mass spectrum. The molecular ion peak of II[S (6)] has been observed at 202.6, which is equal to (m+1) peak in positive mode. The formation of phenylhex-5-ene-2,4-dione [IIS (4)] has been indicated by its elemental (C, H, N) analysis. The calculated and observed % values are within ±0.5 limits. The compound 2-imino-3,6-dihydro-2H- 1,3-thiazine [IIIK (1)] has been prepared by cyclocondensation of phenylhex-5-ene-2,4-dione IIS (1) with thiourea in presence of potassium hydroxide. The formation IIIK (1) has been indicated by its UV spectrum. The compound IIS (1) exhibited λmax at 324 nm. The compound IIIK (1) exhibited λmax at 296 nm. This clearly indicates that the hypsochromic shift is attributed because of cyclocondensation. The formation of IIIK (1) has been indicated by its IR spectrum. The compound IIS (1) exhibited characteristic absorption band at 1660 cm^{-1} due to C=O group. The absence of 1649 cm^{-1} and the appearance of 3411.46 cm^{-1} (=NH) and 3085.55 cm^{-1} (cyclic NH) clearly indicated the formation of IIIK (1). Similarly the formation of compounds IIB (2, 3, 5 and 7) has been indicated by their IR spectra. The formation of IIIK [2] has also been indicated by its ^{1}H NMR spectrum. The presence of δ2.54 (s, 1H,CH), δ3.56 (s, 3H, CH_3), δ3.58 (s, 2H, CH_2), δ3.74 (s, 6H, $N(CH_3)_2$),651(s,1H, NH), 6.69-6.68(m,5H, Ar H) clearly indicated the formation of III[K2]. The formation of IIIK (1) has been confirmed by its mass spectrum. The molecular ion peak of IIIK (1) has been observed at m/z 288, which is equal to (M+1) peak in positive mode.

CONCLUSION

All the synthesized compounds were screened for their antibacterial and antifungal activity against, human pathogenic gram-positive and gram-negative microorganisms using ciprofloxacin and fluconazole as standard references. All the compounds were active against the entire tested microorganism compared to standard and the

MIC value of 150µ/ml against *Escherichia coli, Staphylococcus aures, Pseudomonas aeruginosa, Klebisiella pneamoniae and Asperigillus niger, Candida albicans.* Among all the compounds **4a-j** showed potent antimicrobial activity.

The newly compounds were synthesized by using Claisen–Schmidt condensation and Michael addition. The structures of newly synthesized compounds are authentically established on the basis of UV, IR, ^{1}H NMR, Mass spectral data and elemental analysis.

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