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Synthesis, Characterization and Evaluation of Some 1, 3 Thiazine Derivatives as Possible Antimicrobial Agents

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ABSTRACT

A series of [6-(p-substituted aminophenyl)-4-(p-substituted phenyl)—6H-1,3 thiazin-yl]-acetamides were synthesized via Claisen-Schmidt condensation. The titled compounds were characterized by IR, NMR analysis. The synthesized compounds were screened for their antibacterial and antifungal activity disc diffusion method. Among the synthesized compounds, T-2 was found to have a strong antibacterial and antifungal activity. Compounds T-1, T-3, T-4 and T-5 were found to have promising antimicrobial activity.

Keywords: Thiazines, Acetamides, Claisen-Schmidt Reaction, Antibacterial, Antifungal

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INTRODUCTION

Many heterocyclic analogous of chalcones have been synthesized and subsequently demonstrated to possess biological and pharmacological activities, which may possibly result in chemotherapeutic agents. Because of great potentiality the heterocyclic analogous of chalcones are most helpful synthons. In the view of the varied biological and pharmacological application, we synthesized some heterocyclic derivatives of chalcones[1]. In recent years, attention has increasingly been given to the synthesis of thiazine derivatives as a source of new antimicrobials. The synthesis of novel thiazine derivatives remain a main focus of medicinal research.

Thiazine derivatives have been reported to posses antifungal, antibacterial, anticonvulsant, antiviral, and analgesic activity. Thiazine derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis. Due to the rapid development of bacterial resistant to antibacterial agents, it is vital to discover novel scaffold for the design and synthesis of the new antibacterial agents to help in the battle against pathogenic microorganisms. Much research has been carried out with the aim to discover the therapeutic value of chalcones. The present methodology bears the merits of reduced worthwhile to synthesis the titled compounds, as they appeared to be highly promising.

MATERIALS AND METHODS

All the chemicals were of synthetic grade and commercially purchased from sigma aldrich Chemicals. Melting point was recorded on a open capillary melting point apparatus. IR spectra was recorded on Fourier Transform Infrared spectrophotometer, using KBr disc method. The 1H-NMR spectra was recorded in DMSO- d6 on Perkin Elmer NMR Spectrophotometer-300 MHz. using tetramethyl silane as an internal standard. Thin layer chromatography was performed on pre-coated silica gel plates.

Synthesis of chalcones[2]

Equal molar quantities (0.01mol) of substituted aromatic aldehydes and substituted acetanilide were mixed and dissolved in minimum amount of ethanol (30ml). Potassium hydroxide solution (0.02mol) was added slowly and the mixture was stirred for three hours using a magnetic stirrer. Then the reaction mixture was poured slowly into 400ml of ice cold water with constant stirring and kept it in refrigerator for overnight. The precipitate obtained was filtered, washed and dried. It was recrystallised from ethanol. The completion of reaction was monitored by TLC.

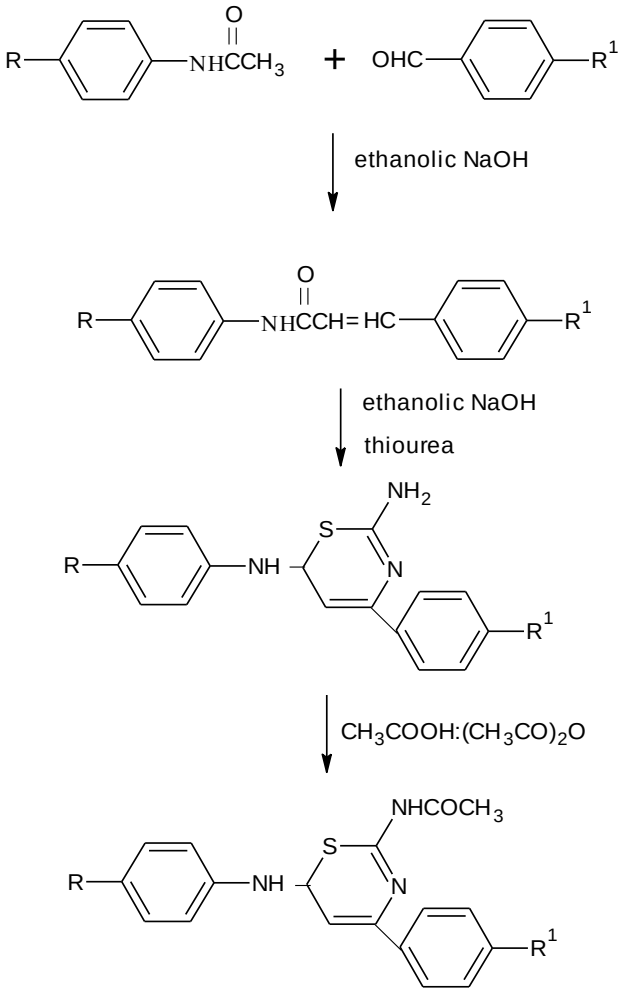
Synthesis of 1,3 thiazine derivatives[3-6]

Equal molar quantities (0.01mol) of chalcone derivatives, thiourea (0.01mol) and sodium acetate

in ethanol (25ml) were refluxed for six hours. Then the reaction mixture was cooled and poured slowly into ice-cold water with constant stirring. The precipitate obtained was filtered, washed and dried. It was recrystallised from ethanol. The completion of reaction was monitored by TLC.

Synthesis of 1,3 thiazinyl acetamide derivatives (T1 –T5):

A mixture of 1,3 thiazine derivatives (1 mol), acetic anhydride (1.2mol) and glacial acetic acid(1.2 mol) was refluxed for 10 mins. The hot mixture was poured into excess of cold water under stirring where acetamide precipitated out. The precipitate obtained was filtered, washed and dried. It was recrystallised from ethanol. The completion of reaction was monitored by TLC.



(T-1 – T-5)

[6-(p-substituted aminophenyl)-4-(p-substituted phenyl)—6H-1,3 thiazin-yl]-acetamide

Characterization of titled compounds[7]:

T-1: M.P. 110^0 C, Yield 48.38%, M.F. $C_{20}H_{22}N_4SO$, M.W. 366.29, IR- 2817.7 (Ar-H stretch) 1663.3 (C=O stretch) 3295.75 (NH stretch) 2713.35 (C-S-C stretch) 1163.83 (C-N stretch) 1597.73 (Ar C=C stretch), ^{1}NMR- 3.02 (s, 6H, $N(CH_3)_2$, 2.02 (d, 3H, CH_3), 9.66 (s, 1H, NH),

9.88 (s, 1H, NH), 6.98-7.68 (m,11H, Aromatic)

T-2: M.P. 140^0 C, Yield 31.18%, M.F. $C_{18}H_{15}N_4O_3SCl$, M.W. 402.22 IR- 2220.66 (Ar-H stretch) 1616.06 (C=O stretch) 3415.31 (NH stretch) 2848.35 (C-S-C stretch) 1095.37 (C-N stretch) 1492.63 (Ar C=C stretch), 1410.63 (Ar-NO_2 stretch), 755.95 (C-Cl stretch) ^{1}NMR- 2.32 (d, 3H, CH_3), 9.52 (s, 1H, NH), 9.76 (s, 1H, NH), 7.01-7.59 (m,10H, Aromatic)

T-3: M.P. 162^0 C, Yield 92.30%, M.F. $C_{18}H_{16}N_4O_3S$, M.W. 368.23, IR- 1616.06 (C=O stretch) 2918.73 (NH stretch) 2848.35 (C-S-C stretch) 1095.37 (C-N stretch) 1589.06 (Ar C=C stretch), 1432.63 (Ar-NO_2 stretch), ^{1}NMR- 2.06 (d, 3H, CH_3), 9.46 (s, 1H, NH), 9.78 (s, 1H, NH), 6.96-7.43 (m,11H, Aromatic)

T-4: M.P. 150^0 C, Yield 68.28%, M.F. $C_{19}H_{19}N_4O_4S$, M.W. 399.26, IR- 2815.7 (Ar-H stretch) 1664.27 (C=O stretch) 3134.72 (NH stretch) 2812.36 (C-S-C stretch) 1063.25 (C-N stretch) 1665.23 (Ar C=C stretch), 1452.63 (Ar-NO_2 stretch), ^{1}NMR- 2.13 (s, 3H, OCH_3), 2.12 (d, 3H, CH_3), 9.36 (s, 1H, NH), 9.54 (s, 1H, NH), 7.09-7.54 (m,11H, Aromatic)

T-5: M.P. 142^0 C, Yield 81.20%, M.F. $C_{18}H_{16}N_5O_5S$, M.W. 414.23,IR- 2615.32 (Ar-H stretch) 1653.3 (C=O stretch) 3187.75 (NH stretch) 2723.35 (C-S-C stretch) 1161.83 (C-N stretch) 1697.73 (Ar C=C stretch), 1424.63 (Ar-NO_2 stretch), ^{1}NMR- 2.51 (d, 3H, CH_3), 9.86 (s, 1H, NH), 9.56 (s, 1H, NH), 7.00-7.64 (m,11H, Aromatic)

Table : 1 List of synthesized thiazinyl acetamide derivatives

Compound code	R	R^1
T-1	H	$N(CH_3)_2$
T-2	NO_2	Cl
T-3	NO_2	H
T-4	NO_2	OCH_3
T-5	NO_2	NO_2

ANTIMICROBIAL ACTIVITY[8]

Antibacterial activity

Muller Hinton Agar medium was prepared and transferred into sterile petriplates, 200µl of the standardized bacterial inoculums was spread on agar medium using sterile cotton swab. The test impregnated discs were placed on the inoculated agar medium. Ciprofloxacin 10µg/ml capacity disc were used as positive reference standard to determine the sensitivity of each microbial species tested. All petriplates were incubated at 37ºC for 24hours. After incubation diameter of inhibition was measured.

Antifungal activity

Sabouraud dextrose agar medium was prepared and transferred into sterile petriplates. 200µl of the standardized fungal inoculums were spread on agar medium using cotton swab. The test

impregnated discs were placed on the inoculated agar medium. Cotrimazole 10µg/ml was used as positive reference standard to determine sensitivity of each microbial species tested. All petriplates were incubated at 27ºc for 72 hours. After the incubation diameter of zone of inhibition was measured.

RESULTS AND DISCUSSION

Chalcones were synthesized by Claisen-Schmidt condensation of various substituted acetanilides and substituted aromatic benzaldehydes. The synthesized chalcones were cyclised to their corresponding1,3 thiazine derivatives by condensation with thiourea and ethanolic sodium hydroxide. Thiazine derivatives were acetylated using acetic anhydride and glacial acetic acid to afford the target compounds. The titled compounds were screened for their antibacterial and antifungal activity. Among the compounds, T-2 exhibited a stronger antimicrobial activity comparable to other compounds. Compounds T-1, T-3, T-4 and T-5 exhibited a promising antibacterial and antifungal activity.

Antimicrobial activity

The synthesized compounds were screened for their antibacterial and antifungal activity against various strains of bacteria and fungi by disc diffusion method. The synthesized compounds were dissolved in dimethyl sulfoxide to a final concentration of 100µg/ml. The sterile discs (6mm in diameter) were impregnated with 10µg of the sample and test against microbial cultures. Ciprofloxacin and Co-trimoxazole of 10 µg/ml capacity were used as positive reference standard. Among the compounds synthesized, compound T-2 exhibited more pronounced antibacterial activity against all the bacterial microorganisms used for the study whereas compounds T-1 and T-2 exhibited a strong inhibition against the fungi used. All others compounds were found to have a promising activity against the microorganisms. Antibacterial and antifungal activity data is shown in Table 2.

Table 2: Antimicrobial activity data of titled compounds

Microorganisms	**Zone of inhibition in mm**					
	T-1	**T-2**	**T-3**	**T-4**	**T-5**	**Standard**
Bacillus subtilis	10	21	17	14	11	25
Staphylococcus albus	16	20	11	13	11	23
Staphylococcus aureus	13	18	10	17	14	26
Salmonella paratyphi	19	20	10	17	16	28
Escherichia coli	18	22	13	10	12	28
Klebsiella pneumonia	11	16	12	14	13	25
Candida albicans	15	14	10	11	12	15
Aspergillus niger	17	22	19	15	18	30

CONCLUSION

Substituted 1,3 thiazinyl acetamide derivatives were synthesized and screened for their antimicrobial activity. The titled compounds were characterized by IR and NMR analysis.The synthesized compounds were found to have a promising antibacterial activity and a more pronounced antifungal activity. The present work details on the broad spectrum of antibacterial and antifungal activity in comparison with a standard antibiotic. It will be worthwhile to investigate the effect of titled compounds on other biological activities such as antitumor, anti HIV, anti-malarial, antihypertensive etc., which can broaden the therapeutic utility for the compounds synthesized that will form part of a future study on titled compounds

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