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Research Article

Synthesis of New Chalcone Derivatives as Antibacterial Agents

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Abstract

The increase in antibiotic resistance due to multiple factors has encouraged the search for new compounds which are active against multidrug-resistant pathogens. In a wide search program towards new and efficient antimicrobial agent's two series of chalcone derivatives containing s-triazine and acetamido group were synthesized. Claisen-Schmidt condensation was used for synthesis of chalcone derivatives. The conventional procedure of Claisen-Schmidt condensation for synthesis of chalcone was optimized. All the synthesized compounds were characterized and tested for their antibacterial activity. All the synthesized compounds were found to be active against both Gram positive and Gram negative bacteria. Compound **6a** was found to show best activity.

1. INTRODUCTION

Due to the rapid development of resistance towards antibiotics, there is a constant need for the development of new antibacterial agents. There are many molecules containing ring such as imidazole, triazole, pyrazole, benzimidazole, benzotriazole, oxypurine, pyrimidinyl, naphtyl, 1, 3-dioxolane, thiosemicarbazone, pyridine, furan, thiophene which have shown antibacterial activity [1-4]. Use of various pharmacophore that are not common to micro-organisms or against which resistance has not been observed should be focused to develop novel antibacterial agents.

Chalcones are the aromatic ketones which belong to 1, 3-diaryl-2-propen-1-ones, which forms the central core for the synthesis of variety of important biologically active compounds. The compounds with the backbone of chalcone have been reported to exhibit a wide variety of pharmacological activity including antimalarial[5], antibacterial [6], antituberculosis [7], anticancer [8], anti-inflammatory [9], antifungal [10], antioxidant [11], antileishmanial [12].

During the last few years the potential of s-triazine derivatives in agrochemical and medicinal properties have been subjected to investigation. It is found that substituted s-triazine derivatives are an important class of compounds having antibacterial, anticancer, antitumor, antiviral, antifungal and antimalarial activities [13, 14]. Many acetamido derivatives have been synthesized and have showed antibacterial activity and other activities too[15].

Chalcones are a class of compounds that provides an option of developing inexpensive, easily synthetic and therapeutic antibacterial agents. The s-triazine [16-22] and acetamido [23-26] containing compounds have also been found as promising antibacterial agents and thus incorporation of these in chalcone backbone may results into compounds with significant antibacterial activity. Keeping this in view, the present work comprises of, synthesis of two series of compounds namely;

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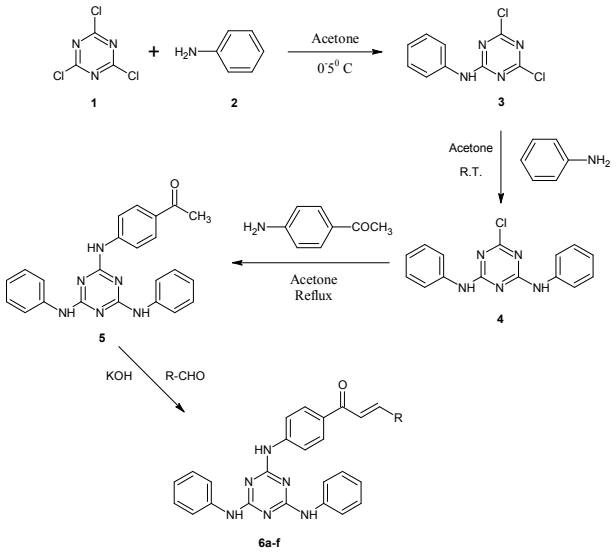
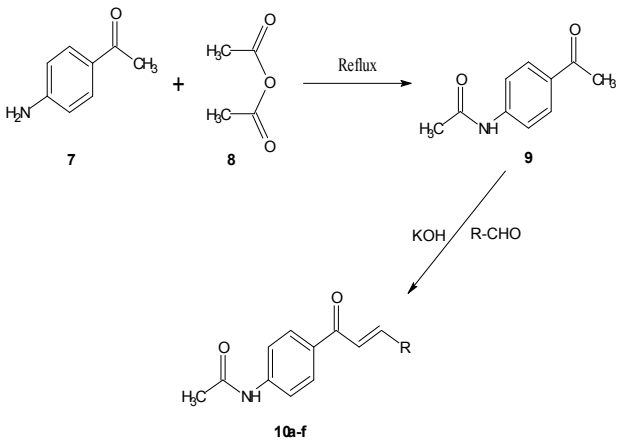
Series 1: S-Triazine containing Chalcone
Series 2: Acetamido containing Chalcone



Schematic procedure for synthesis of series-1 compounds

Compound No.	R
6a	5-methylfurfural
6b	3-nitrobenzaldehyde
6c	2-chlorobenzaldehyde
6d	2-bromobenzaldehyde
6e	3-bromobenzaldehyde
6f	4-bromobenzaldehyde



Schematic procedure for synthesis of series-2 compounds

Compound No.	R
10a	5-methylfurfural
10b	3-nitrobenzaldehyde
10c	2-chlorobenzaldehyde
10d	2-bromobenzaldehyde
10e	3-bromobenzaldehyde
10f	2-methoxybenzaldehyde

2. MATERIALS AND METHODS

Starting materials and solvents used for each reaction is of synthetic grade procured from S D Fine, and the products obtained were assessed for purity by physical constant determination, and Thin Layer Chromatography (TLC).

All the reactions were monitored using thin layer chromatography on pre- coated TLC plates (Silica gel 60-120#) using solvent system Benzene: Ethanol [8:2] for series-1 compounds and Dichloromethane: Ethyl acetate [9:1] for series-2 compounds. TLC was performed by ascending development in a chamber previously saturated with the solvent system. TLC plates were observed under long UV lamp in UV chamber for detection of spots. Final reactions were carried out on sonicator of Ultrasonic Cleaner Oscar Microclean-103.

The synthesized compounds were purified by recrystallization and their structures were characterized by Physical constant, IR and NMR. They have shown single spot on TLC plate when observed under UV light; Melting points were taken in open capillaries on melting point apparatus and were uncorrected. Infrared spectroscopy was carried out using potassium bromide (KBr) pellet method on the SHIMADZU IR Affinity-1. Nuclear Magnetic Resonance (NMR) spectroscopy was done by recording the spectra 1HNMR on Joel FT/NMR 300MHz analyzer. The characterization with IR and ^{1}HNMR spectra of the synthesized compounds, confirmed the anticipated structure. IUPAC names were confirmed with Chemdraw Ultra 8.0 (Chemoffice 2004, Cambridge Soft, Cambridge, USA).

Claisen-schmidt condensation reaction was used for synthesis of chalcones. The conventional procedure used was optimized and is given below;

2.1 Conventional procedure

Acetophenone (10 mmol) was dissolved in suitable solvent and aromatic aldehyde (10 mmol) was added with constant stirring at room temperature. Then KOH solution was added to reaction mixture which was stirred for 24 hrs at room temperature. Finally the reaction mixture was poured into crushed ice and neutralized with HCl. The product separated out, was filtered, washed with water, dried and recrystallized from alcohol to give chalcone.

2.2 Optimized procedure

A mixture of acetophenone (10 mmol), aromatic aldehyde (10 mmol), KOH and solvent were taken in a beaker and sonicated for 15–30 mins in the water bath of an ultrasonic cleaner bath. The progress of the reaction was monitored by TLC. The reaction mixture was then cooled in ice-water bath. The formed precipitate was filtered, washed with cool water, dried and recrystallized from alcohol to give chalcone.

This optimized procedure was used for the synthesis of compounds 6a-f and 10a-f.

1.4 -N-phenyl-, 6-dichloro 1, 3, 5-triazine-2-amine ***(3)***

Cyanuric chloride **1** (0.01 mole) was added to acetone (25 ml) at 0–5^{0}C, then Aniline **2** (0.01 mole) was added dropwise with constant stirring for 3 hrs. Sodium carbonate solution (10%) was added slowly to neutralize HCl evolved during the reaction. Finally, the contents were poured into crushed ice. The solid separated, was filtered, washed with water, dried and recrystallized from ethanol to give compound **3**. Yield 85.59%, M.p 198^{0}C. IR (KBr, cm^{-1}): 754.17 (C-Cl stretch), 806.25 (C-N stretch, s-triazine), 1388.75 (C-N stretch), 2999.31 (C-H stretch, aromatic), 3263.56 (N-H stretch).

2.6-chloro-N, N'-diphenyl-1, 3, 5-triazine-2, 4-diamine ***(4)***

Compound **3** (0.01 mole) was added to acetone (30 ml) at room temperature, then Aniline **2** (0.01 mole) was added dropwise with constant stirring for 3 hrs. Sodium carbonate solution (10%) was added slowly to neutralize HCl evolved during the reaction. Finally, the contents were poured into crushed ice. The solid separated, was filtered, washed with water, dried and recrystallized from ethanol to give compound **4**. Yield 78.87%, M.p 176^{0}C. IR (KBr, cm^{-1}): 754.17 (C-Cl stretch), 806.25 (C-N stretch, s-triazine), 1400.32 (C-N stretch), 3034.03 (C-H stretch, aromatic), 3267.41 (N-H stretch).

3.1-{4-[(4, 6-dianilino-1, 3, 5-triazin-2-yl) amino] phenyl} ethanone ***(5)***

Compound **4** (0.01 mole) and 4-Aminoacetophenone (0.01 mole) was added to acetone (40 ml). The reaction mixture was refluxed for 6 hrs. Sodium carbonate (10%) was added periodically and slowly to neutralize HCl evolved during the reaction. Finally, the reaction mixture was cooled and poured into crushed ice. The solid separated, was filtered, washed with water, dried and recrystallized from ethanol to give compound **5**. Yield 73.94 %, M.p 220^{0}C. IR (KBr, cm^{-1}): 810.10 (C-N stretch, s-triazine), 1363.67 (C-N stretch), 1683.86 (C=O stretch), 3053.32 (C-H stretch, aromatic), 3340.71 (N-H stretch).

4.1-{4-[(4, 6-dianilino-1, 3, 5-triazin-2-yl) amino] phenyl}-3-(5-methylfuran-2-yl) prop-2-en-1-one ***(6a)***

A mixture of compound **5** (10 mmol), 5-methyl-2-furaldehyde (10 mmol), KOH (2 mmol) and ethanol (4 ml) was sonicated for 15–30 mins in the water bath of an ultrasonic cleaner bath. The progress of the reaction was monitored by TLC. The reaction mixture was cooled in ice-water bath. The formed precipitate was filtered, washed with cool water, dried and recrystallized from ethanol to give compound **6a**. Yield 79.65%, M.p 152^{0}C. IR (KBr, cm^{-1}): 804.32 (C-N stretch, s-triazine), 1315.45 (C-N stretch), 1604.77 (C=C stretch), 1678.07 (C=O stretch), 3034.03 (C-H stretch, aromatic), 3265.49 (N-H stretch). ^{1}H NMR (DMSO, delta ppm): 10.07 (s, 3H), 7.91 (d, 1H), 7.77 (dd, 4H), 7.55 (d, 1H), 7.39 (d, 4H), 7.20 (m, 5H), 6.82 (t, 2H), 6.52 (d, 1H), 2.29 (s, 3H).

Similarly the remaining compounds **6b–f** were prepared.

5.N-(4-acetylphenyl) acetamide ***(9)***

A mixture of 4-aminoacetophenone **7** (0.025 mole) and acetic anhydride **8** (4 ml) was taken. The reaction mixture was then heated at reflux for 45 mins. The solution was cooled in an ice bath and the resulting solid obtained was washed with cool water, filtered, dried under vacuum and recrystallized from ethanol to get pure crystals of compound **9**. Yield 85.67%, M.p 170^{0}C. IR (KBr, cm^{-1}): 1674.21 (C=O stretch, amide), 1735.93 (C=O stretch), 3047.53 (C-H stretch, aromatic), 3296.35 (N-H stretch).

6.N-{4-[(2E)-3-(5-methyl-2-furyl) prop-2-enoyl] phenyl} acetamide ***(10a)***

A mixture of compound **9** (10 mmol), 5-methyl-2-furaldehyde (10 mmol), KOH (2 mmol) and ethanol (4 ml) was sonicated for 15–30 mins in the water bath of an ultrasonic cleaner bath. The progress of the reaction was monitored by TLC. The reaction mixture was cooled in ice-water bath. The formed precipitate was filtered, washed with cool water, dried and recrystallized from ethanol to

give compound **10a**. Yield 93.89%, M.p 162^{0}C. IR (KBr, cm^{-1}): 1600.92 (C=C stretch), 1647.21 (C=O stretch), 1683.86 (C=O stretch, amide), 3043.67 (C-H stretch, aromatic), 3296.35 (N-H stretch). 1H NMR (DMSO, delta ppm): 10.21 (s, 1H), 7.99 (d, 2H), 7.77 (d, 2H), 7.45 (d, 1H), 7.40 (d, 1H), 6.80 (d, 1H), 6.22 (d, 1H), 2.39 (s, 3H), 2.12 (s, 3H).
Similarly the remaining compounds **10b–f** were prepared.

3. RESULTS AND DISCUSSION

3.1 Chemistry

In Series-1, reaction of cyanuric chloride with substituted amine at 0 – 5^0 C gave monosubstituted triazine and then when again reacted with substituted amine at room temperature gave disubstituted triazine. This disubstituted triazine was then refluxed with 4-aminoacetophenone to give trisubstituted triazine containing acetyl group. This trisubstituted triazine with acetyl group when reacted with different aldehydes using appropriate base gave different chalcone derivatives.
In Series-2, 4-aminoacetophenone was acetylated using acetic anhydride and then reacted with different aldehydes using appropriate base to give different chalcone derivatives.

Different methods are reported for the synthesis of Chalcones compounds. But we have used claisen-schmidt condensation reaction for synthesis of chalcones[27-32]. The conventional procedure used for the synthesis of chalcones was optimized.
The conventional procedure was optimized by using the sonication technique. The conventional procedure takes about 24 hrs of stirring at room temperature for the synthesis of chalcone. But by the sonication technique chalcone was synthesized in 15-30 mins. Also less amount of solvent was required to carry out the reaction when compared with conventional procedure. The % yield of chalcone by conventional and optimized procedure was found to be approximately same.
Thus by observing that the consumption of time and solvent used was less unlike that of the conventional procedure; both the series (1 and 2) of chalcone were synthesized using the optimized procedure.

The physicochemical data and IR of synthesized compounds is shown in following table-1

Table-1: Physicochemical and IR data of synthesized compounds

Compound No.	R	M.P. (^{0}C)	Yield (%)	IR
6a	5-methylfurfural	152	79.65	804.32 (C-N stretch, s-triazine), 1315.45 (C-N stretch), 1604.77 (C=C stretch), 1678.07 (C=O stretch), 3034.03 (C-H stretch, aromatic), 3265.49 (N-H stretch)
6b	3-nitrobenzaldehyde	168	71.45	804.32 (C-N stretch, s-triazine), 1311.59 (C-N stretch), 1350.17 (C-NO_2 stretch), 1600.92 (C=C stretch), 1664.57 (C=O stretch), 3089.96 (C-H stretch, aromatic), 3263.56 (N-H stretch)
6c	2-chlorobenzaldehyde	160	80.64	754.17 (C-Cl stretch), 804.32 (C-N stretch, s-triazine), 1338.60 (C-N stretch), 1600.92 (C=C stretch), 1699.29 (C=O stretch), 3097.68 (C-H stretch, aromatic), 3259.70 (N-H stretch)
6d	2-bromobenzaldehyde	116	83.92	688.59 (C-Br stretch), 806.25 (C-N stretch, s-triazine), 1338.60 (C-N stretch), 1600.92 (C=C stretch), 1697.36 (C=O stretch), 3097.68 (C-H stretch, aromatic), 3263.56 (N-H stretch)
6e	3-bromobenzaldehyde	180	82.35	688.59 (C-Br stretch), 804.32 (C-N stretch, s-triazine), 1309.67 (C-N stretch), 1600.92 (C=C stretch), 1656.85 (C=O stretch), 3091.89 (C-H stretch, aromatic), 3263.56 (N-H stretch)
6f	4-bromobenzaldehyde	192	85.89	688.59 (C-Br stretch), 804.32 (C-N stretch, s-triazine), 1311.59 (C-N stretch), 1598.99 (C=C stretch), 1697.36 (C=O stretch), 3097.68 (C-H stretch, aromatic), 3263.56 (N-H stretch)
10a	5-methylfurfural	162	93.89	1600.92 (C=C stretch), 1647.21 (C=O stretch), 1683.86 (C=O stretch, amide), 3043.67 (C-H stretch, aromatic), 3296.35 (N-H stretch)
10b	3-nitrobenzaldehyde	214	89.59	1348.24 (C-NO_2 stretch), 1606.70 (C=C stretch), 1651.07 (C=O stretch), 1703.14 (C=O stretch, amide), 3093.82 (C-H stretch, aromatic), 3336.85 (N-H stretch)
10c	2-chlorobenzaldehyde	186	82.34	758.02 (C-Cl stretch), 1597.06 (C=C stretch), 1651.07 (C=O stretch), 1676.14 (C=O stretch, amide), 3064.89 (C-H stretch, aromatic), 3307.92 (N-H stretch)
10d	2-bromobenzaldehyde	144	86.49	592.15 (C-Br stretch), 1597.06 (C=C stretch), 1654.92 (C=O stretch), 1676.14 (C=O stretch, amide), 3064.89 (C-H stretch, aromatic), 3311.78 (N-H stretch)
10e	3-bromobenzaldehyde	154	88.92	590.22 (C-Br stretch), 1598.99 (C=C stretch), 1656.85 (C=O stretch), 1674.21 (C=O stretch, amide), 3018.60 (C-H stretch, aromatic), 3309.85 (N-H stretch)
10f	2-methoxybenzaldehyde	124	82.74	1105.21 (C-O-C stretch), 1597.06 (C=C stretch), 1645.28 (C=O stretch), 1672.28 (C=O stretch, amide), 3043.67 (C-H stretch, aromatic), 3236.55 (N-H stretch)

3.2 Antibacterial activity

All the synthesized compounds were screened for their antibacterial activity by using the Cup plate method, against selected Gram-positive and Gram-negative bacteria. Dimethyl sulfoxide (DMSO) was used as a solvent while Amoxycillin and Streptomycin were used as the standard drugs. The results of antibacterial activity of all the synthesized compounds by cup plate method are presented in table-2.
All synthesized compounds were screened for their antibacterial activity by using the Cup-plate method. The following bacterial cultures were used for antibacterial studies.

1) *Bacillus subtilis*
2) *Staphylococcus aureus*
3) *Escherichia coli*
4) *Pseudomonas aeruginosa*
5) *Klebsiella aerogenes*

All the synthesized compounds were screened for antibacterial activity at the concentration of 100µg/ml. Dimethyl sulfoxide (DMSO) was used as a solvent while Amoxycillin and Streptomycin were used as the standard drugs.
The antibacterial studies showed that, almost all the synthesized compounds were active against both Gram positive and Gram negative bacteria. Following observation were made from the results of antibacterial activity.
In the case of Gram positive bacteria, except compound **10c** and **10e,** all other compounds were found to be effective against Bacillus subtilis, and showed activity which was lower than Streptomycin but compound **6a** and **6b** have shown higher and equal activity than Amoxycillin. All the synthesized compounds except **10a**, **10b** and **10f** inhibited *Staphylococcus aureus* with

lower activity than Streptomycin and with higher activity than Amoxycillin, as this bacterium was not inhibited by Amoxycillin.

Table-2: Results of antibacterial activity of all the synthesized compounds

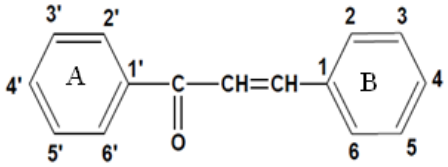
Compound No.	Mean zone of inhibition (mm)				
	Gram positive bacteria		Gram negative bacteria		
	B.s	S.a	E.c	P.a	K.a
6a	12	09	18	05	10
6b	11	08	08	05	06
6c	10	03	07	04	09
6d	10	05	06	04	07
6e	08	04	09	04	02
6f	07	06	08	04	07
10a	02	-	02	05	01
10b	01	-	04	05	01
10c	-	04	01	05	04
10d	01	04	02	08	02
10e	-	04	02	06	01
10f	03	-	01	07	01
Amoxycillin	11	-	20	-	-
Streptomycin	21	14	16	23	20

In the following table, Mean zone of inhibition is expressed in mm at concentration level of 100µg/ml of test Compounds and standard drugs;- No inhibition; B.s- Bacillus subtilis, S.a- Staphylococcus aureus, E.c- Escherichia coli, P.a- Pseudomonas aeruginosa, K.a- Klebsiella aerogenes.

In case of Gram negative bacteria, *Escherichia coli* was inhibited by all synthesized compounds but compound **6a** showed excellent activity towards it, even higher than Streptomycin but lower than Amoxycillin. *Pseudomonas aeruginosa* and *Klebsiella aerogenes* is not inhibited by standard drug Amoxycillin, but all the synthesized compounds showed inhibition zones which were less than that showed by Streptomycin.

Thus compound **6a** gave the best activity against both Gram positive and Gram negative bacteria except against *Escherichia coli*. S-Triazine chalcone compounds (**6a-f**) showed good antibacterial activity than Acetamido chalcone compounds (**10a-f**) which are comparable with the standard drugs used.

From the above discussion, following SAR points can be predicted for synthesized compounds.



- ✓ Substitution on both the aryl rings (A and B) of chalcone produced significant antibacterial activity which can be investigated further for better antibacterial agent.
- ✓ Bulkier group on the 4th position of ring A is necessary for good antibacterial activity. E.g. compounds containing s-triazine ring (**6a-f**) showed good antibacterial activity than compounds containing acetamido group (**10a-f**).
- ✓ Substitution of ring B with heterocyclic ring. E.g. compound **6a** containing furan ring have shown to have excellent activity.
- ✓ Electron withdrawing group on ring B such as nitro group, halogens, etc., may increase activity. As compound **6b**, **6c**, **6d**, **6f** have shown comparable antibacterial activity.

4. CONCLUSION

Almost all the synthesized compounds were found to be active against both Gram positive and Gram negative bacteria. Compound **6a** was found to show best activity while other synthesized compounds have also shown comparable activity when compared with standard used. Based on the activity obtained, some conclusion has been made upon the type of substituent's that can be incorporated in order to increase the activity, which can be further investigated.

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