



## A REVIEW ON CHALCONES SYNTHESIS AND ITS PHARMACOLOGICAL ACTIVITIES

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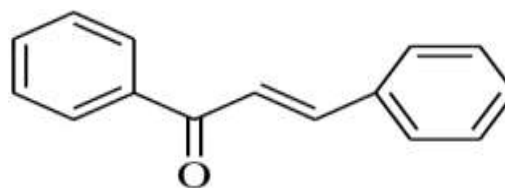
### ABSTRACT

Chalcone is a common simple scaffold found in many naturally occurring compounds. Many chalcone derivatives have also been prepared due to their convenient synthesis. These natural products and synthetic products have been known numerous interesting biological activities with clinical potential against various diseases. In this article we have scope to know or understand many activities of the chalcones. These chalcones briefly helps us to know the several activities like antiviral, antibacterial, antioxidant, anticancer, anti fungal, antimalarial, anti inflammatory, anti leishmanial, anti HIV, antimicrobial, anti tuberculosis, anti anticonvulsant, antihyperglycemic, antifilarial, antidiabetic, anti parasitic, anti angiogenic, MOA inhibition, enzyme inhibitor etc..In the introduction we will know the general activities if chalcones and some chemical properties of chalcones. We will come to know the SAR of chalcones.

### INTRODUCTION

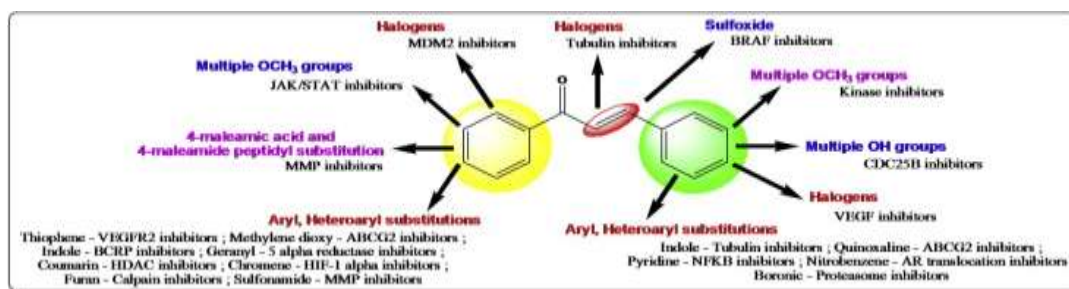
Chalcones are the naturally occurring organic compound  $C_6H_5C(O)CH=CHC_6H_5$ . A variety of biological compounds are known collectively as Chalcones or chalconoids. These are mostly known as bio active substances, fluorescent materials, and chemical intermediates. In the organic chemistry Chalcones have been used as intermediates in heterocyclic compounds synthesis, especially in the synthesis of pyrazoles and aurones.

### CHALCONE CHEMICAL STRUCTURE:



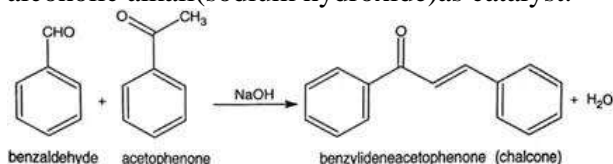
**IUPAC NAME: 1, 3-diphenyl-2-propen-1-one.**

**Structural activity relationship of chalcones:**



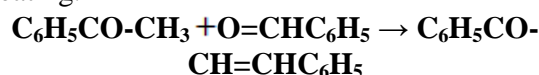
## SCHEMES:

**Claisen Schmidt Condensation:** The most convenient method is the claisen-schmidt condensation of equimolar quantities of aryl methyl ketone (acetophenone) with aryl aldehyde (benzaldehyde) in the presence of alcoholic alkali(sodium hydroxide)as catalyst.

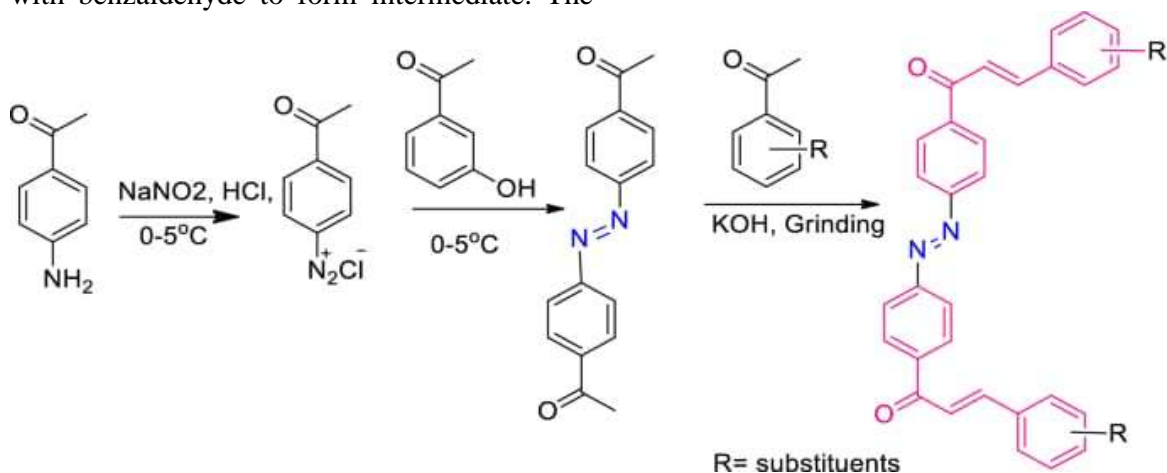


**Aldol condensation:** Acetophenone and benzaldehyde are the starting materials for this reaction. First, acetophenone is treated with a base like KOH which converts it into the more active form, its enolate form. It will then react with benzaldehyde to form intermediate. The

intermediate will then lose water molecule by heating.



**Synthesis of chalcones using grinding method:** In this method, various chalcones were prepared by grinding the mixture of appropriate methyl ketones, aldehydes and sodium hydroxide using pestle in an open mortar. Radhakrishnan et al. Reported a facile solvent free synthesis of Azachalcones through grinding the reactants in another attempt; Arslan et al. were prepared a new series of bis chalcones through diazotization and diazocoupling by applying grinding method with good yields.



## ANTI TUMERGENIC CHALCONES<sup>1</sup>

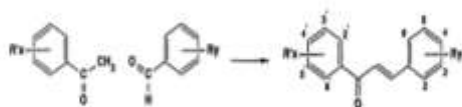
On the basis of our recent findings that licochalcone A isolated from Xin-jiang licorice showed anti-inflammatory and anti-tumorigenic activities, we synthesized more than 40 chalcone derivatives to examine their anti-tumorigenic activities. In vitro inhibitory activity against phosphorylation of

phospholipids promoted by tetradecanoylphorbol-13-acetate (TPA) in HeLa cells was adopted as a screening test for anti-tumor-promoting effect. In vivo experimental mouse skin tumors initiated by dimethylbenz[a]-anthracene (DMBA) and promoted by TPA were used to test the anti-tumour-promoting effect of chalcones. In the

results, 3'- and 4'-methyl-3-hydroxychalcone showed the highest potency in inhibiting tumorigenesis. They also showed a remarkable inhibitory effect on the proliferation of HGC-27 cells derived from human gastric cancer. We discuss the structure-activity relationship, including stereo-chemical photo transformation, of some chalcone derivatives with reference to their ultraviolet (W) and nuclear magnetic resonance (NMR) spectroscopic data.

### CHEMISTRY OF ANTI-TUMORIGENIC CHALCONES:

Since chalcones are a promising group of flavonoids for anti-tumor-promoting activity, we undertook anti-tumorigenic screening tests on a series of synthetic chalcones having simple chemical structures. This series of simple chalcones was synthesized by a classic Claisen-Schmidt condensation of a substituted acetophenone with a benzaldehyde derivative.



### Synthesis of chalcones by Claisen-Schimidt condensation.

### Effects on chalcone derivatives on the enhanced <sup>32</sup>Pi incorporation of HeLa cells induced by TPA:

No	Compound(5µg/ml)	Abbreviation	Inhibition(%)
1	2,4-Dihydroxychalcone	2,4'-C	27.0
2	3,4-Dihydroxychalcone	3,4'-C	35.2
3	4,4'-Trihydroxychalcone	4,4'-C	18.3
4	3,4,4'-Trihydroxychalcone	3,4,4'-C	24.8
5	2,4'-Dimethoxychalcone	2,4'-(MeO) <sub>2</sub> -C	24.2
6	3, 4, 4' - Trimethoxychalcone	3, 4,4' - (MeO) <sub>3</sub> - C	18.0
7	Carboxymethyl licochalcone A methyl ester		0.0
8	2-Methoxy-4'-hydroxychalcone	2-MeO-4'-C	12.1
9	3-Methoxy-4'-hydroxychalcone	3-MeO-4'-C	19.1
10	4-Methoxy-4'-hydroxychalcone	4-MeO-4'-C	35.6
11	4'-Methoxy-3,4-dihydroxychalcone	4'-MeO-3,4-C	34.3
12	4'-Methyl-3,4-dihydroxychalcone	4-Me-3,4-C	44.0
13	2-Methoxy-3-hydroxychalcone	2-MeO-3-C	79.8
14	3-Methyl-3-hydroxychalcone	3-Me-3-C	100.0
15	4'-Methyl-3 hydroxychalcone	4-Me-3-C	97.6
16	4-Methyl-4-methoxychalcone	4-Me-4-MeO-C	74.7

Anti-tumor-promoting activities of synthesized chalcones were initially assayed in vitro by their inhibitory activities against phosphorylation promoted by TPA in HeLa cells at a concentration of 5 µg/ml. The most potent inhibitory activity was shown by 3'-methyl-3-hydroxychalcone (3'-Me-3-C) and 4'-methyl-3-hydroxychalcone (4'-Me-3-C): 100% and 97.6%, respectively. The chalcones 2'-methoxy-3-chalcone, 2',4,4'-trihydroxy chalcone (isoliquiritigenin), 4'-methyl-4-methoxy-chalcone and 2',4-dihydroxy chalcone gave the second highest inhibitory potencies: 79.8%, 76.8%, 74.7% and 73.2%, respectively. Inhibitory activities of nonsubstituted chalcone and licochalcone A were 49.3% and 50.5%, respectively in the table.

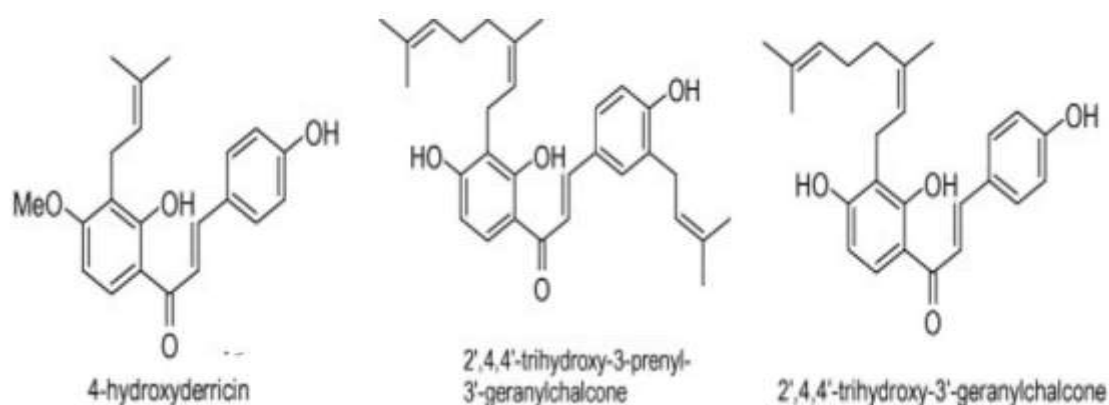
Effects on chalcone derivatives on the enhanced <sup>32</sup>Pi incorporation of HeLa cells induced by TPA:

17	Carboxymethyl licochalcone A		19.7
18	Chalcone	C	49.3
19	2-Hydroxychalcone	2'-C	49.3
20	2,4-Dihydroxychalcone	2,4'-C	73.2
21	2,4,4-Trihydroxychalcone (Isoliquiritigenin)	2,4',4-C	76.8
22	2'-Methoxy-4,4-dihydroxychalcone (Echinatin)	2-MeO-4,4'-C	64.1
23	4'-Chloro-4-hydroxychalcone	4'-Cl-4-C	51.4
24	4'-tert-Butyl-4-hydroxychalcone	4-t-Bu-4-C	64.8
25	2-Methyl-4'-hydroxychalcone	2-Me-4'-C	40.8
26	4-Methyl-4'-hydroxychalcone	4-Me-4'-C	67.6
27	4-Hydroxychalcone	4-C	36.2
28	4-Isopropyl-4'-hydroxychalcone	4-Iso-Pr-4'-C	32.1
29	3'-Methoxy-3-hydroxychalcone	3'-MeO-3-C	37.8
30	4'-Methyl-3-methoxychalcone	4'-Me-3-MeO-C	23.9
31	2-Carboxy-4'-hydroxychalcone	2-COOH-4'-C	27.4
32	4-Carboxy-4'-hydroxychalcone	4-COOH-4'-C	23.4
33	3-Methyl-4'-hydroxychalcone	3-Me-4'-C	24.9
34	3-Hydroxychalcone	3-C	29.9
35	3,3'-Dihydroxychalcone	3,3'-C	29.8
36	4'-tert-Butyl-3-hydroxychalcone	4'-t-Bu-3-C	43.3
37	4'-Methyl-2-hydroxychalcone	4'-Me-2-C	37.54
38	4-Methyl-4-hydroxychalcone	4-Me-4-C	19.6
39	3-Methyl-3'-hydroxychalcone	3-Me-3'-C	31.3
40	2',3-Dihydroxychalcone 2,3-C	2',3-C	34.4
41	4'-Methyl-2',3-dihydroxychalcone	4'-Me-2',3-C	33.2
42	5'-Methyl-2',3-dihydroxychalcone	5'-Me-2',3-C	24.1
43	4'-Methoxy-3-hydroxychalcone	4'-MeO-3-C	18.8
44	5'-Methyl-2',3,4-trihydroxychalcone	5'-Me-2',3,4-C	43.2
45	3'-Methyl-2',3,4-trihydroxychalcone	3'-Me-2',3,4'-C	28.9

### STRUCTURAL ACTIVITY RELATIONSHIP OF ANTIBACTERIAL CHALCONES<sup>2</sup>

The antibacterial activity of chalcones was tested against bacterial strains, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Staphylococcus aureus* ATCC 25923. Some of the tested chalcones showed fair to significant activity against Gram-positive bacteria. By comparison of the results

obtained, the antibacterial activity can be related to features such as the presence of a C-4 hydroxyl group, a C-4' oxygenated substituent or a C-3' isoprenoid side chain, while the C-2' hydroxyl group might have importance for the stability of the molecule. The inhibitory effect of chalcones on human pathogenic microorganisms can be correlated with the substitution patterns of the aromatics rings.

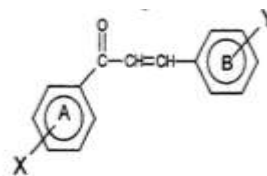


Compounds showed fair to significant activity against gram positive bacteria.

### TRYPANOCIDAL AND LEISHMANICIDAL PROPERTIES OF SUBSTITUTION CONTAINING CHALCONES<sup>3</sup> (Fabinae Lunardi et al.,)

Ten chalcones were synthesized and tested as potential leishmanicidal and trypanocidal agents. All tested compounds caused concentration-dependent inhibition of the in vitro growth of *Leishmania braziliensis* and *Trypanosoma cruzi* with no significant toxic effect towards host macrophages. Our results show that the positions of the substituents seem to be critical for their antiprotozoal activities. The chalcones used in the present study were synthesized in our laboratory by reaction of the appropriate aryl methyl ketone and aryl aldehyde (in a 1:1 ratio) in the presence of sodium hydroxide and ethanol. The products were then added to cooled diluted acetic acid. The synthetic

reaction gave substantial yields (55 to 98%) of all the chalcones and these were characterized by <sup>1</sup>H nuclear magnetic resonance and infrared analyses and by microanalysis. The substitution-containing chalcones were dissolved in 0.5% Tween 80 in phosphate-buffered saline to prepare a working solution with a 0.1 M concentration before being passed through 0.22- $\mu$ m-pore-size Millipore filters. The structures of the chalcones are shown in table:



Chalcone	X	Y
C1	4-H	4-H
C2	4-H	4-Cl
C3	4-Cl	4-H
C4	4-Cl	4-Cl
C5	3,4-Cl <sub>2</sub>	H
C6	3,4-Cl <sub>2</sub>	4-Cl
C7	4-CH <sub>3</sub>	4-Cl
C8	4-Br	4-Cl
C9	4-Br	4-H
C10	3,4-Cl <sub>2</sub>	4-N(CH <sub>3</sub> ) <sub>2</sub>

Synthetic chalcones reported in the present study exhibit marked in vitro leishmanicidal and trypanocidal activities. Nevertheless, the mechanisms by which the substitution-containing chalcones showed leishmanicidal and trypanocidal activities were not addressed in this work. Based on the literature, it can be predicted that chalcones could potentially inhibit the activity of fumarate reductase, succinate dehydrogenase, NADH dehydrogenase, or succinate- and NADH-

cytochrome *c* reductases in the parasite mitochondria. Additional studies are in progress to address this hypothesis. Our results also show that, in vitro, leishmanicidal and trypanocidal concentrations of chalcones showed low cytotoxicity to mouse peritoneal macrophages. Trypanocidal and leishmanicidal activities of substitution-containing chalcones, benzimidazole, and amphotericin B on epimastigote and promastigote forms of *T. cruzi* and *L. braziliensis*, respectively:

Chalcone or control	Trypanocidal activity		Leishmanicidal activity	
		IC <sub>50</sub> (μM)	MI(%)	IC <sub>50</sub> (μM)
C1	24.8 (11.3-54.7)	100	13.7(9.9-18.9)	100
C2	64.5 (45.9-90.5)	100	21.9(20.3-23.7)	100
C3	66.7(47.3-94.1)	94±3	100.5(76.1-132.8)	100
C4	100.3(60.0-167.0)	92±5	98.0(62.6-153.5)	100
C5	82.7(63.3-108.0)	88±7	182.3(179.6-185.0)	100
C6	126.4(73.5-217.4)	93±4	66.7(43.8-54.8)	100
C7	80.8(53.3-122.6)	90±6	45.6(38.1-54.8)	100
C8	65.4(47.6-89.8)	97±3	129.1(93.2-178.8)	100
C9	66.6(44.5-99.8)	100	61.7(57.7-65.9)	100
C10	89.6(71.2-112.8)	90±6	57.4(38.0-86.5)	100
Benznidazole	54.7(42.8-69.8)	100		
Amphotericin B			0.21(0.18-0.24)	100

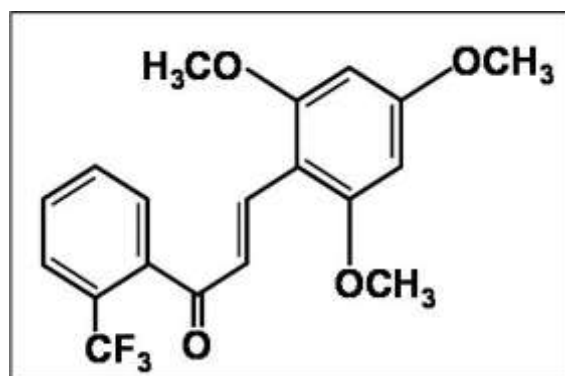
**ANTIBACTERIAL ACTIVITIES:  
CURRENT DEVELOPMENT<sup>4</sup>**

(Man Xu\* et a,)

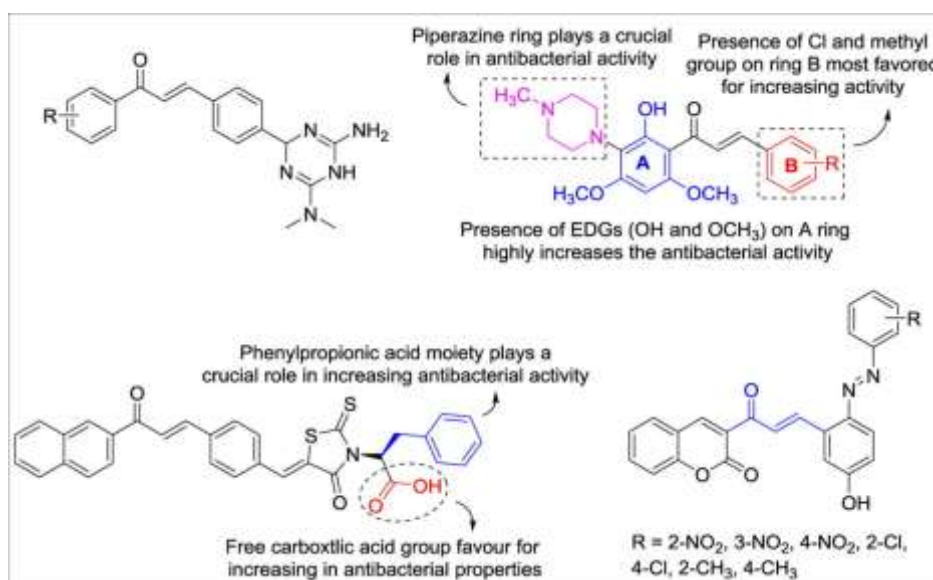
The damage of bacterial and fungal infections has increased in the recent years hugely. Many bacterial strains causing infectious diseases which seem to be controlled are again causing death every year due to absence of suitable drug. Because of this there are many researches for the development or invention of the new drug in the class of many antibiotics. In particular attention has focused on gram positive bacterial organisms. *Staphylococcus aureus* because many stains of this organism are now resistant against clinically useful antibiotics like METHICILLIN and VANCOMYCIN. The occurrence of multi-drug resistant bacteria becomes a severe medical setback in hospital and community

settings. Among these, MSRA (Methicillin-resistance *Staphylococcus aureus*), penicillin resistance *Streptococcus pneumoniae* (PSRA) and Vancomycin resistant enterococci (VRE) are leading concerns.

**Anti-bacterial activity of fluorinated Chalcones:** Fluorine has become an important tool in new drug application, since incorporation of fluorine atom/ fluorinated group into the drugs or drug lead to simultaneous modulation of electronic, lipophilic, steric parameters all of which can critically influence both the pharmacokinetic and pharmacodynamics properties on any drug molecule. Thus, integration of fluorinated chalcone-1, 2, 3 triazole hybrids might exhibit synergistic effect in providing the bio-activity of derivatives.



**GRAPHICAL REPRESENTATION FOR ANTIBACTERIAL ACTIVITY COMPOUNDS:**



In conclusion the development of new antibiotics has been regarded as a potential therapeutic approach and a significant number of diverse structures have been reported to inhibit microbial growth in recent years.

**SYNTHESIS OF NEW CHALCONE DERIVATIVES AS ANTIBACTERIAL AGENTS<sup>5&6</sup>: (Pankit R. Shah\* et al.,)**

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.

**Introduction:** 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



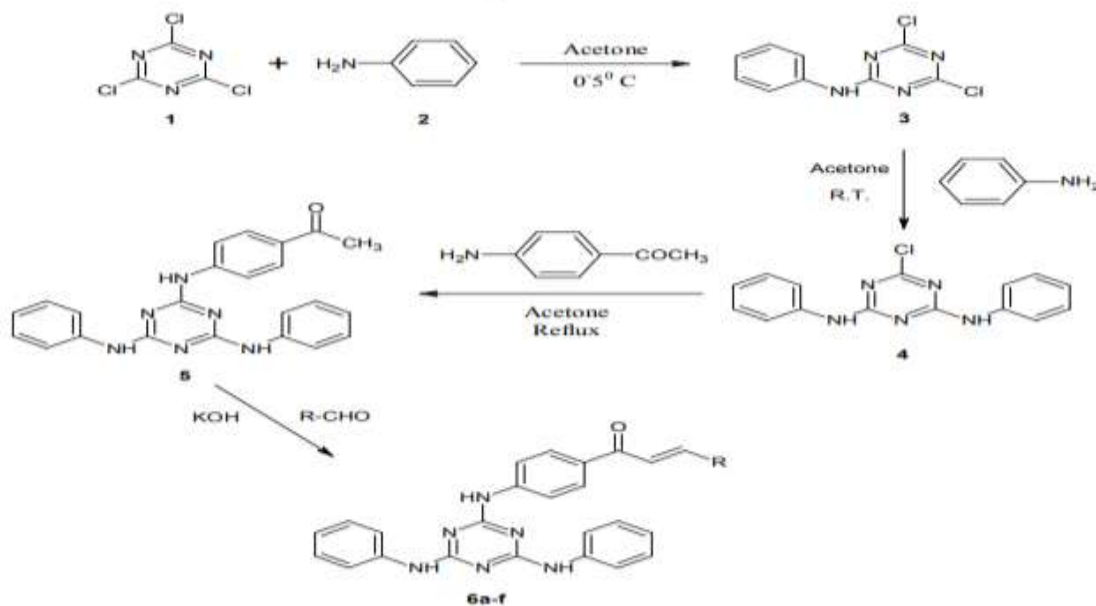
compounds by cup plate method are presented in table-2. All synthesized compounds were screened for their antibacterial activity by using the Cup-plate method. The following bacterial cultures were used for antibacterial studies.

- 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

#### Chemistry of compounds:

Scheme 1: S-triazine containing chalcone:

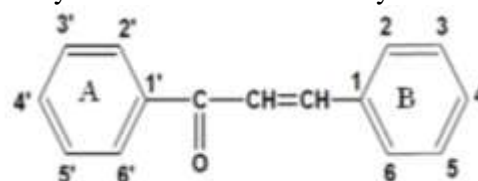


Compound NO.	R
6a	5-methylfurfural
6b	3-nitrobenzaldehyde
6c	2-chlorobenzaldehyde
6d	2-bromobenzaldehyde
6e	3-bromobenzaldehyde
6f	4-bromobenzaldehyde

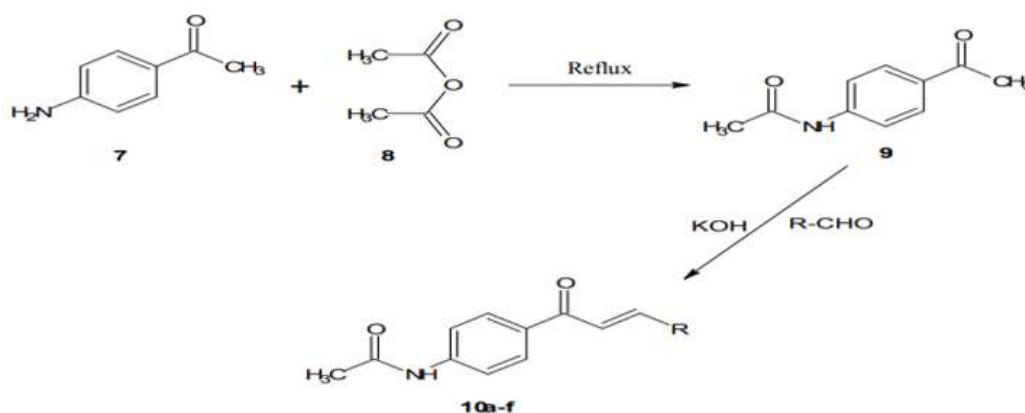
#### Scheme 2: Acetamido containing compound

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 have shown higher and equal activity than Amoxycillin.

In case of Gram negative bacteria, Escherichia coli was inhibited by all synthesized compounds but compound showed excellent activity towards it, even higher than Streptomycin but lower than Amoxycillin.







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

Table 1: Physicochemical and IR data of synthesised compounds

Compound No.	R	M.P(C)	Yield(%)	IR
6a	5-methylfurfural	152	79.65	804.32 (C-N stretch, 8-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, 8-triazine), 1311.59 (C-N stretch), 1350.17 (C-NO <sub>2</sub> stretch), 1600.92 (C=O stretch), 3089.96 (C-H stretch, aromatic), 3283.58 (N-H stretch)
6c	2-chlorobenzaldehyde	160	80.64	754.17 (C-Cl stretch), 804.32 (C-N stretch, 8-triazine), 1338.60 (C-N stretch), 1699.29 (C=O stretch), 3097.68 (C-H stretch, aromatic), 3263.56 (N-H stretch)
6d	2-bromobenzaldehyde	116	83.92	688.59 (C-Br stretch), 806.25 (C-N stretch, 8-triazine), 1338.60 (C-N stretch), 1600.92 (C=C stretch), 1656.85 (C=O stretch), 3091.89 (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, 8-trizine), 1309.67(C-N stretch), 1600.92 (C=C 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, 8-trizine), 804.32 (C-N stretch), 1600.92 (C=C stretch), 3091.89 (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), 1651.07 (C=O stretch, amide), 3043.67 (C-H stretch, aromatic), 3296.85 (N-H stretch)
10b	3-nitrobenzaldehyde	214	89.58	1348.24 (C-NO <sub>2</sub> stretch), 1606.70(C=C stretch), 1651.07 (C=O stretch), 1703.14 (C=O stretch, amide), 3093.82 (C-H stretch, aromatic), 3307.92 (N-H stretch)
10c	2-chlorobenzaldehyde	186	82.34	758.02(C-Cl stretch), 1597.06 (C=C stretch), 1861.07 (C=O stretch), 1676.14 (C=O stretch, amide), 3064.89 (C-H stretch, aromatic), 3307.92(N-H stretch)
10d	2-bromobemnzaldehyde	144	88.49	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), 1658.85 (C=O stretch), 1676.21 (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), 1597.05 (C=C stretch) 1645.28 (C=O stretch), 1672.28 (C=O stretch, amine), 3043.67 (C-H stretch, aromatic), 3236.55(N-H stretch)

*Pseudomonas aeruginosa* and *Klebsiella aerogenes* is not inhibited by standard drug Amoxicillin, but all the synthesized compounds showed inhibition zones which were less than that showed by Streptomycin. Thus compound gave the best activity against both Gram positive and Gram negative bacteria except against *Escherichia coli*. S-Triazine chalcone compounds showed good antibacterial activity than Acetamido chalcone compounds which are comparable with the standard drugs used. From the above

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

#### CONCLUSION:

Chalcone is a  $\alpha, \beta$  - unsaturated ketone. A variety of important biological compounds are known as chalcones or chalconoids. Many chalcones and its derivatives can be synthesized in the laboratory and the chemical structure can be modified, more efficient action against a specific disease pathway can be achieved. This shows a wide spectrum of pharmacological actions. The chalcones and

their derivatives helps us to know about various viral infections and overcome the diseases. Chalcones are not only excellent scaffolds for synthetic manipulations but also possesses multiple biological and medical properties. That is why the attention of scientists has increased towards chalcones in searching for novel and biologically potent derivatives from Chalcones. 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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