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RESEARCH ARTICLE

Heteroaryl Chalcones: A Review with Special Focus on Heterocyclic Aryl Ring and their Pharmacological Activities

Siraj B. Shaikh*, Sadiqua Mujahid, Nazia Tambat, Khudeja Salgar, Rajendra V. Nimbale

Department of Chemistry, Abeda Inamdar Senoir College, Pune-01, Maharashtra, India.

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ABSTRACT

Chalcones have characteristic 1, 3-diaryl-2-propen-1-one backbone skeleton. Changes in their aryl ring have offered a high degree of diversity that has proven useful for the development of new medicinal agents with improved potency and lesser toxicity. This review article covers most of hetero-aryl chalcone and their derivatives that had shown broad spectrum of biological activity and also highlights the important pharmacological activities by variation of heteroaryl ring in chalcones skeleton containing five membered, six membered and fused heteroaryl ring with nitrogen, oxygen or sulphar as hetero atom.

KEYWORDS

Heteroaryl Chalcones, Furanochalcone, Indolylchalcone, Heterocyclic Moiety

INTRODUCTION

Chalcones are 1, 3-diaryl-2-propen-1-ones in which two aromatic rings are joined by a three carbon bridge having a keto carbonyl moiety and α, β unsaturation. Chalcones are synthesized by Claisen-Schmidt condensation of aromatic aldehyde and aromatic acetophenone as ketone either catalyzed by base or acid. They are intermediates for synthesizing various heterocyclic compounds. Cyclization of chalcones leads to pyrimidines, pyrazline, thiazines has been a developing field of heterocyclic chemistry for the past several years. Chalcone derivatives have attracted increasing attention due to their numerous pharmacological activities. The presence of a reactive & unsaturated keto moiety as well as aryl conjugation in chalcones is found to be responsible for their biological activity.

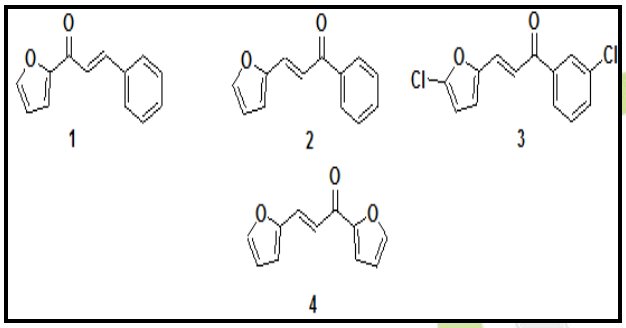
***Address for Correspondence:**
Siraj B. Shaikh
Department of Chemistry, Abeda Inamdar Senior College,
Azam Campus, Camp,
Pune-01, Maharashtra, India.
E-Mail Id: sirajshaikh174@gmail.com

The chalcones with the backbone of 1, 3-diaryl-2-propen-1-ones have been reported to possess various biological activities such as Antioxidant, anticancer, Antitubercular, antimicrobial, anti-inflammatory, analgesic, antiplatel, antiulcerative, antimalarial, antiviral, antileishmanial, antihyperglycemic, antiproliferative activities.[1-7]

In the ongoing search of literature, it was observed that the reviews gives only idea about synthesis, biological activities, cyclization reaction of chalcones and heterocyclic derivatives, cytotoxic and chemoprotective properties and potential pharmacological activities etc.[8-20] Hence we aimed to summarize some hetero-aryl chalcones containing heterocyclic aromatic ring such as furan, pyrrole, thiophene, pyridine, indole, azoles as a one of the part of aryl ring in chalcone moiety and their pharmacological activities. This review highlights some synthesized chalcones containing the hetroaryl rings as a moiety and their biological activities.

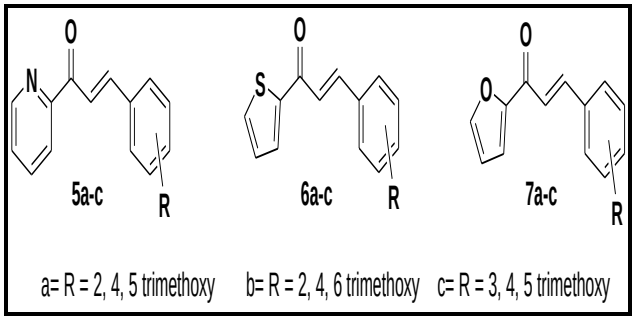
Chalcones with Five Membered Heteroaryl Rings

Sarel J. *et al.* derived a series to predict the structure activity relationships for the MAO-B inhibitory activity of Furanochalcones **(1-3)** that showed variation with respected to the positions of the furan and phenyl rings interchanging and with different substituent. The most active chalcones **(3)** 2E-3-(5-chlorofuran-2-yl)-1-(3-chlorophenyl) prop-2-en-1-one, exhibited an IC_{50} value of 0.174 lM for the inhibition of MAO-B and 28.6 lM for the inhibition of MAO-A. These furan substituted derivatives acted as reversible inhibitors, while kinetic analysis revealed a competitive mode of binding for them.[21]

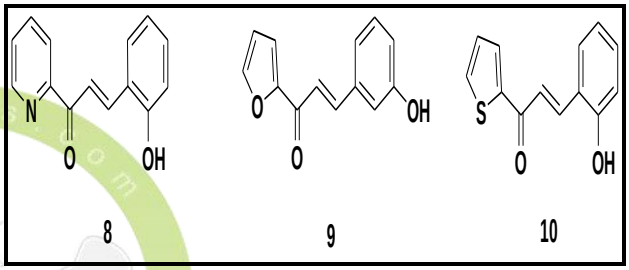


Ruhoglu *et al.* synthesized chalcones **(4)** in corporting oxygen in either part of five member's aromatic ring in the form of furan ring as heteroaryl ring. This an intermediate compound for antidepressant and anticonvulsant activities of some 1, 3, 5-trisubstituted pyrazolines.[22]

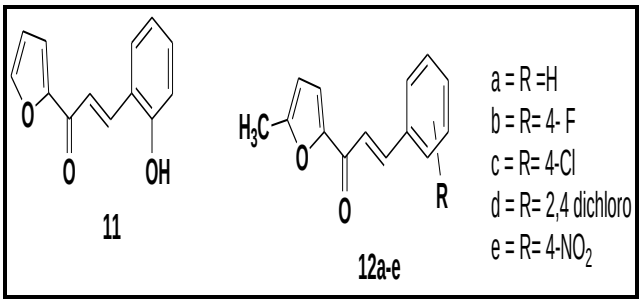
Crystal structure of chalcones **(5-7a-c)** containing pyridine, furan and thiophene ring as heteroaryl ring had been reported bt T. Suwungwong *et al.* and studied their fluorescent properties.[23]



A series of simple heteroaryl chalcone analogues have been synthesized by Thanh-Dao Tran *et al.* and evaluated for their antibacterial activity. They had proved that the synthesized heterocyclic chalcone analogues have some anti- *Staphyloccus aureus* effects and the furan-2-yl moiety is more active than either the thiophene-2-yl or pyridine-2-yl one in anti-*Staphylococcus aureus* activity. Chalcones **(8-10)** exhibited potent inhibitory activity against methicillin-resistant *Staphylococus aureus* in combination with vancomycin and oxacillin. The structure and activity relationships have been evolved and confirmed that these chalcones **(8-10)** had potential candidates for future drug discovery and development.[24]

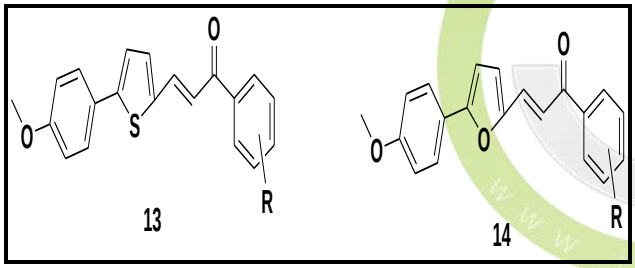


Same series of above furanochalcones **(9)** and their hydroxyl derivatives have been synthesized and subjected to the mosquito larvicidal study (larvae of *Culex quinquefasciatus*), SAR and QSAR by Begum *et al.* The favorable chemical structures of chalcone **(11)** had been found to have a hydroxyl substituent in ring B at 2'-position which may be hydrogen bonded with the electron pair on α,β-unsaturated ketone moiety The investigation had clearly shown that certain chalcone analogues had potent mosquito larvicidal activity. Most of the hydroxyl chalcones showed toxicity against the third instar larvae of *C. quinquefasciatus.*[25]

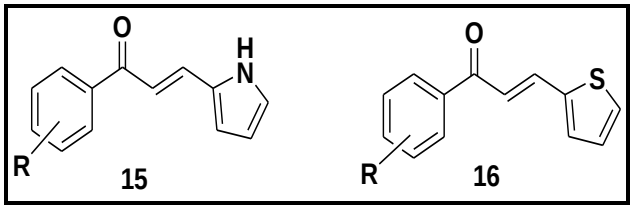


Ahmed *et al.* tested Cytotoxicity against tumor cell lines of the furanochalcone **(12a-e)** by the BSLT bioassay method. All these furanochalcone compounds had been found to possess cytotoxic activity. Among them, compounds **12a, 12c** showed dose dependent cytotoxic activity at concentrations of **(12a)** 24.27µg/ml, **(12c)** 37.05µg/ml, respectively as compared to Podophyllotoxin standard drug for BSLT assay method.[26]

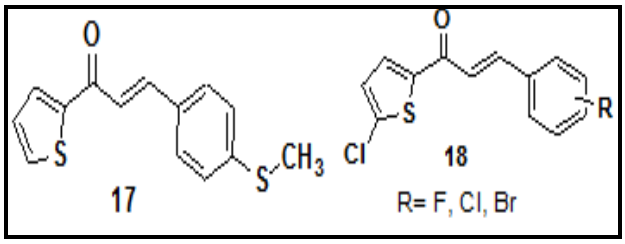
A new series of heteroaryl chalcones **(13 & 14)** were designed, synthesized by Soloman *et al.* to develop effective anticancer therapeutics and examined for their antiproliferative effects on two breast cancer cell lines and one matching non-cancer breast cell line. The structure-activity relationship (SAR) analysis recommended that the compounds derived from thiophene chalcones exhibited generally better antiproliferative activity than those derived from bioisoteric replacement of furan chalcones on MDA-MB231 breast cancer cells.[27]



A series of conjugates of α, β-unsaturated ketone diaryl-propenones, chalcones **(15 & 16)** as an intermediate for the tricyclic planar pyrroloquinoline nucleus have been synthesized by Via L. *et al.* and evaluated for their anticancer properties. The aim of this synthesis was to target DNA by butenone and chalcones, and determine the occurrence of interactions with the macromolecule or related functional enzymes. The unconjugated chalcones and butenone had a lower or no effect at the tested concentration.[28]

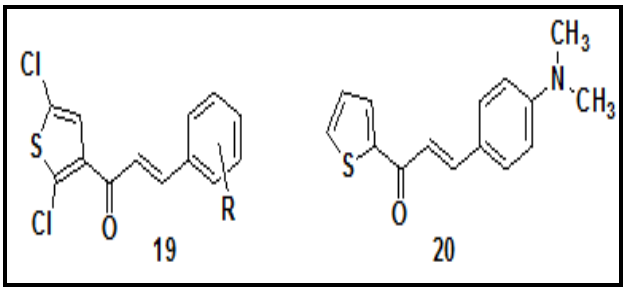


Bag *et al.* synthesized a series of chalcones containing sulfur either as part of a hetero-aromatic thiophene ring and tested for their *in vitro* activity against fluconazole-sensitive and fluconazole-resistant strain. Chalcone **(17)** 3-(4-(methylthio) phenyl)-1-(thiophen-2-yl) prop-2-en-1-one' exhibited the highest activity.[29]



Halogen-substituted chalcones **(18)** bearing the 5-chlorothiophene moiety were synthesized by Kumar *et al.* and *in vitro* antimicrobial and reducing power ability of these chalcones were evaluated. Chalcones produced a varied range of inhibition results against the tested microbial strains, which is due to the presence of electron negative halogen(s) substituents at different positions on the phenyl ring. These prepared halogenated chalcones displayed about 40% less reducing ability for ferric and cupric ions when compared to the standards.[30]

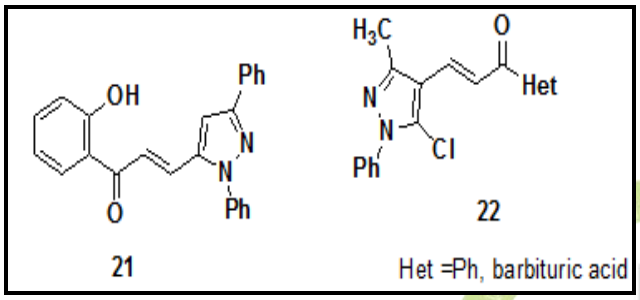
A series of di-chloro substituted thiophene chalcones **(19)** prepared by Tomar V *et al.* from 3-acetyl-2, 5-dichlorothiophene reacting with different substituted aromatic aldehyde and had been evaluated for antimicrobial activity, the prepared chalcone derivatives are potentially active against Gram-positive bacteria; *Staphylococcus aureus* and *Escherichia coli*.[31]



Gaber, M., *et al.* investigated the absorption and fluorescence characteristics of chalcones in different solvents. '3-(4′-dimethylaminophenyl)-1-(2-thienyl) prop-2-en-1-one' chalcone **(20)** was one the chalcone compound investigated in

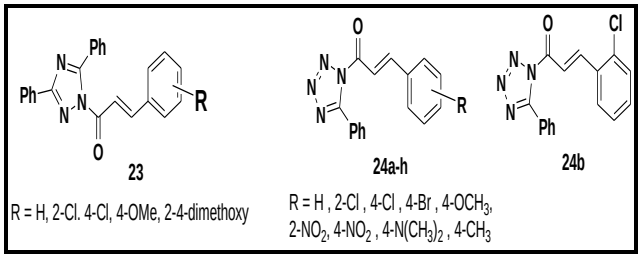
different solvents for a model of solvatochromic fluorophore.[32]

Synthesis of 2, 3-dimethoxy-3-hydroxy-2-(1-phenyl- 3-aryl-4-pyrazolyl) chromanones via formation of pyrazolinochalcone **(21)** were reported by Prakash *et al.*., the synthesized chalcones and chromones were tested for their antibacterial activity against Gram-positive bacteria namely, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Bacillus pumilus* and two Gram-negative bacteria namely, *Salmonella typhi* and *Pseudomonas aeruginosa shows good activity*.[33, 34]



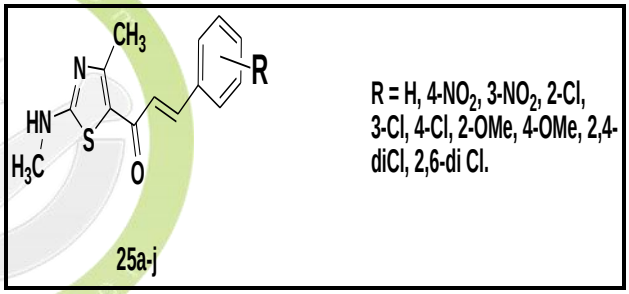
A series of new pyrazolyl chalcones **(22)** under thermal solvent-free condition was synthesized by Siddiqui *et al.* The investigation of antimicrobial screening by disk diffusion assay of synthesized chalcone showed good antibacterial and antifungal activities against Gram-positive, Gram-negative strains of bacteria as well as fungal strains.[35]

Anticancer activity of synthesized Chalcones 1-(3, 5-diphenyl-1H-1, 2, 4-triazol-1-yl)-3-substituted aryl) prop-2-en-1-one **(23)** had been reported by Khanage *et al.* The synthesized chalcones showed a broad spectrum of growth inhibitory activity against human tumor cells, as well as some distinctive pattern of selectivity toward CNS Cancer (SNB-75), Renal Cancer (UO-31), Non-Small Cell Lung Cancer (NCI-H522) and Leukemia (SR).[36]

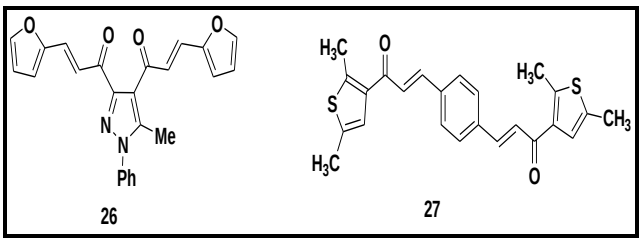


Synthesis of 5-phenyl tetrazole chalcones **(24)** were reported by Bhaskar *et al.* The synthesized chalcones were screened and evaluated for their anticancer activity for testing against a panel of approximately 60 different human tumor cell lines derived from nine neoplastic cancer types. The most efficient anticancer compound **(24b)** was found to be active with selective influence on ovarian cancer cell lines.[37-38]

A new class of structurally novel derivatives, which incorporated two known bioactive structures a thiazole and chalcone **(25),** was synthesized by Liaras *et al.* for evolution of antimicrobial properties and antifungal properties. The investigation of antibacterial activity showed that almost all the chalcones **(25a-j)** exhibited greater activity than reference drugs and thus could be promising novel drug candidates.[39]



Farag M. A. *et al.* synthesized heterocyclic furano bis-chalcone **(26)** by reaction of 1, 1'-(5-methyl-1-phenyl-1*H* pyrazole- 3,4-diyl) diethanone with furfural as an aldehyde and screened these chalcones for their antibacterial against a Gram negative bacterium (*Escherichia coli* anaerobic), a Gram positive bacterium (*Staphylococcus aureus*) and for antifungal activity against *Candida albicans* and *Aspergillus flavus* by diffusion technique. It shows good activity against *Escherichia coli anaerobic* only.[40]



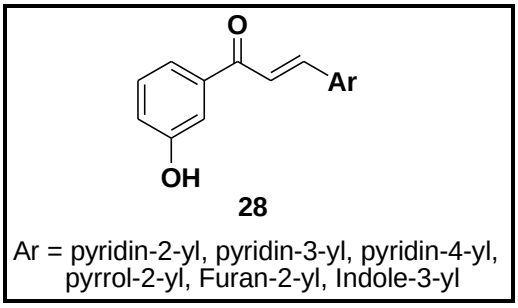
Abdullah M. Asiri *et al.* prepared thiophene bis-chalcone **(27)** as intermediate compound by the reaction of terephthalaldehyde with 3-acetyl-2, 5-dimethylthiophene. The anti-bacterial activity was examined using bacterial cultures and the results showed good antibacterial activity against *S. aureus, S. pyogenes, S. typhimurium* and *E. coli*.[41]

A solvent-free protocol for the green synthesis of heterocyclic chalcones bearing five membered and six membered heteroaryl ring was developed by Sanal Dev *et al..*, These chalcones were prepared by grinding equimolar quantities of (hetero) aryl methyl ketone with (hetero) arylaldehyde in presence of sodium hydroxide in solvent free condition.[42]

Chalcones with Six Membered Heteroaryl Rings

T. Maruthavanan *et al.* reported the synthesis and substituent effect of some novel pyridine based chalcones and also it revealed that all the synthesized chalcones compounds were in good correlation with Hammet, Brown –Okamoto, Swain and Lupton's constants.[43]

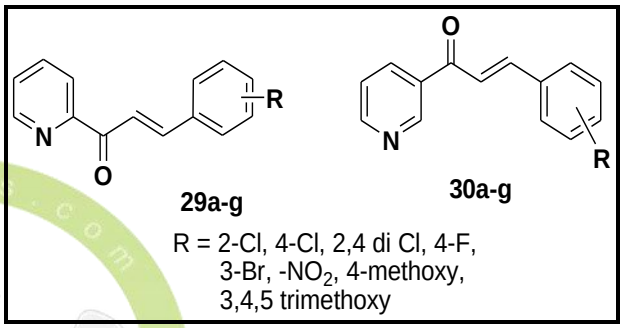
Farzana Ansari *et al.* synthesized a library of aryl- and heteroaryl chalcones **(28)** by reaction of 3-hydroxyacetophenone with different substituted aryl- and heteroaryl aldehydes by Microwave assisted synthesis. The synthesized chalcones are significantly active against Bordetella bronchiseptica (ATCC 4617), gram negative respiratory pathogen that infects wide range of animals and human using cefixime as standard antibiotic as control.[44]



28

Ar = pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrrol-2-yl, Furan-2-yl, Indole-3-yl

Rajendra Prasad *et al.* synthesized new chalcones **(29)** by condensing 2-acetyl pyridine with aldehyde derivatives according to Claisen-Schmidt condensation. The antimicrobial activity of these chalcones was evaluated by the cup plate method. The screening results revealed that the all these chalcones showed significant antimicrobial activity against *B. pumilis, B. substilis, E.coli. and P. Vulgari* at a conc. of 1000 µg/mL (0.1 mL dose level) and are comparable to that of standard drug Benzyl Penicillin. 2,4-dichloro, 4-chloro, 4-methoxy and 3-Bromo substituted chalcones showed moderate to considerable antifungal activity against *spergillus niger, Rhizopus oryzae* and *Candida albicans* at a conc. of 1000 µg/mL (0.1 mL dose level) and are comparable to that of standard drug Fluconazole.[45]



29a-g **30a-g**

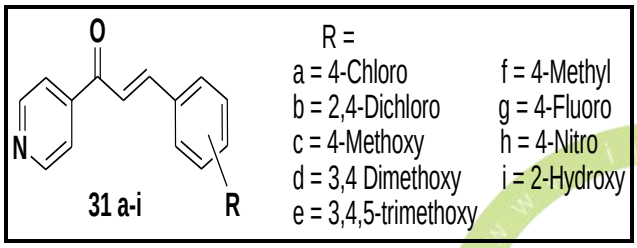
R = 2-Cl, 4-Cl, 2,4 di Cl, 4-F, 3-Br, -NO_2, 4-methoxy, 3,4,5 trimethoxy

Similar work was repeated by M.V. Jyothi *et al.* for third position in pyridine ring. They synthesize same chalcones **(30a-g)** from 3-acetylpyridine by reaction with either aromatic or heteroaromatic aldehyde using Claisen-Schmidt condensation. These chalcones were evaluated for antifungal and antimicrobial activities by cup plate method. The screening results of antimicrobial activities showed that all chalcone posses significant antibacterial activity. Whereas 3,4,5-trimethoxy group showed moderate to considerable antibacterial activity at a conc. of 1000 µg/mL (0.1 mL) dose level.[46]

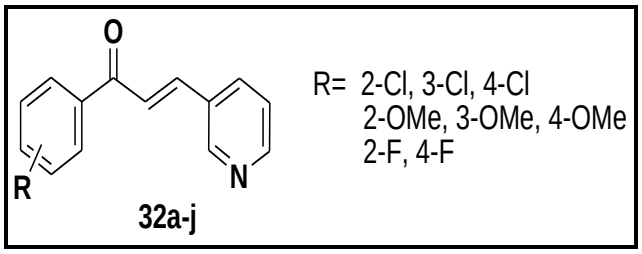
Same series of chalcones **(30)** were prepared by Sudhakar Patil *et al.* as an intermediate for cyclization reaction. The synthesized chalcones were further converted into respective Pyrimidines, Isoxazoles and Pyrazoles by treatment with Urea or Thiourea, Hydroxylamine hydrochloride and Hydrazine hydrates.[47]

A series of chalcones **(31)** of 4-acetyl pyridines and substituted aryl aldehydes have been

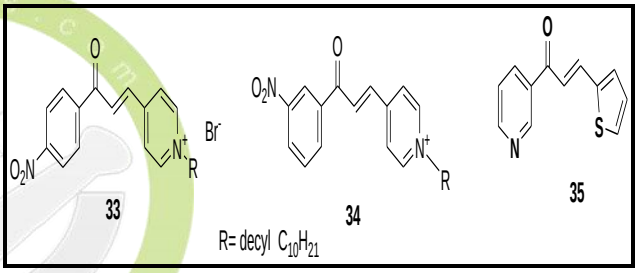
synthesized by Alam, Shadab *et al.* and evaluated for antitubercular, antioxidant and anti-inflammatory activity. The new chalcones have been evaluated for antitubercular activity against *Mycobacterium tuberculosis* H37 Rv using MABA method. *In vitro* anti-inflammatory activity has been performed by using bovine serum albumin assay method with diclofenac as standard and antioxidant activity by DPPH method. The chalcone **31a** and **31f** exhibited good antitubercular activity. The chalcone **31a, 31b and 31i** showed maximum anti-inflammatory activity. The chalcones **31c, 31d and 31f** exhibited maximum oxygen scavenger activity.[48]



Mahdi Mojarrab *et al.* prepared a series of pyridine based chalcones **(30a-j)** and their antioxidant properties were assessed by four antioxidant procedures. Chalcones bearing 3-mehoxy substituent (16.53 ± 1.21 µg/mL), 2-hydroxy (58.85 ± 1.10 µg/mL) and 2-fluoro substituent (58.73 ± 12.94 µg/mL) showed higher antioxidant activity (EC50 ± SD) in comparison with quercetin (87.24 ± 3.93 µg/mL) as reference agent in ferrous ion chelating method.[49]



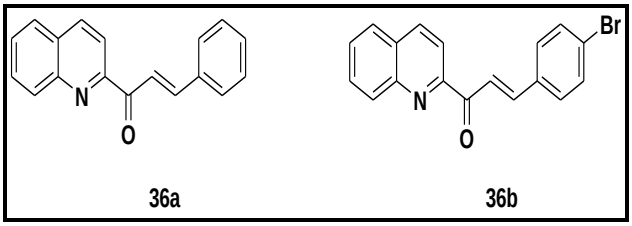
Yayli *et al.* synthesized *N*-alkyl derivatives and photochemical dimers of 3 *o*-, *m*-, and *p*-nitro substituted 4-azachalcones. The synthesized chalcones monomers were tested for antimicrobial, antioxidant activities. The chalcones showed good antimicrobial activity against *E. coli, K. pneumoniae, Yersinia pseudotuberculosis, P. aeruginosa, Enterococcus faecalis, S. aureus, Bacillus cereus*, and *Candida tropicalis*. The chalcones '1-decyl-4-(3-(4-nitrophenyl)-3-oxoprop-1-enyl) pyridinium bromide' **(33)** and '1-decyl-4-(3-(3-nitrophenyl)-3-oxoprop-1-enyl) pyridinium bromide' **(34)** exhibited broad range of antimicrobial activity. The synthesized chalcones were also tested for their antioxidant activity based on their ability to scavenge the stable radical DPPH (2, 2-diphenyl-1-picrylhydrazine). The monomers showed high anti-oxidant activity, while the dimerization products were less active. The monomeric compounds exhibited higher radical scavenging potential in general, with low IC_{50} values. The chalcones **(33)** '1-decyl- 4-(3-(4-nitrophenyl)-3-oxoprop-1-enyl)pyridinium bromide' was found to have similar or even higher activity when compared to the standard anti-oxidants Trolox and vitamin C, respectively.[50-51]



The chalcone containing both five as well as six membered heteroaryl ring was synthesized by Jyothi M.V. *et al.* along with chalcones **(35)**. This chalcone shows moderate anti-inflammatory activity.[52]

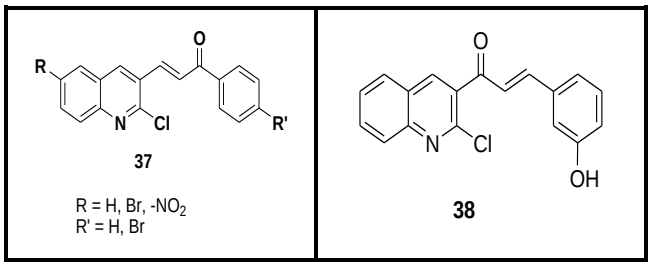
Chalcones with Benzo-Fused Hetero-Aryl Rings

Due to the diverse biological activity of indolizidine alkaloids, M. J. Albaladejo *et al.* Synthesized the Heterocyclic Chalcones **(36)** Catalyzed by Supported Copper Nanoparticles.[53]



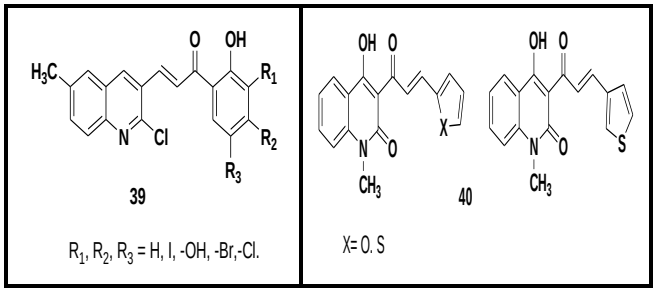
A series of various heteroaryl chalcones **(37)** for quinoline based pyrazolines were synthesized by Banewar V *et al.* by condensing

formylquinolines with diverse ketones. The entire newly synthesized chalcones were screened for *in vitro* biological evaluation. These active compounds exhibited broad spectrum of various biological activities. Most of the compounds showed potent activity.[54]



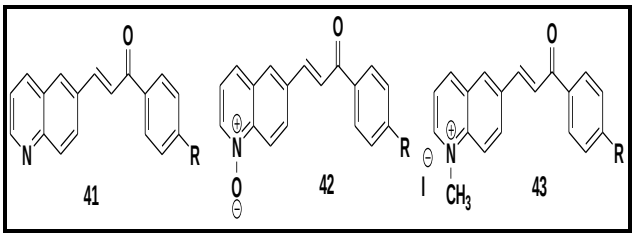
Quinoline based chalcones synthesized by Cheng *et al.* on the basis of their structure activity relationship (SAR) and computer modeling data to accelerate the development of relatively inexpensive antimalarials that are effective against chloroquine-resistant strains of *P. falciparum*. They reported that the chalcone **(38)** '1-(2-chloroquinolin-3-yl)-3-(3-hydroxyphenyl) prop-2-en-1-one' posses the highest activity.[55]

Mokle S.S *et al.* synthesized quinoline based chalcones **(39)** for antimicrobial activity. All synthesized chalcones possessed good antimicrobial activity against *Xanthomanas citri, Ervinia carotovara, Escherichia coli* and *Bacillus subtilis.*[56]

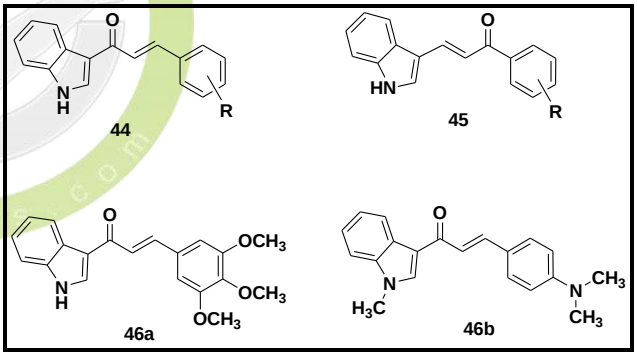


A series of N- alkyl Quinoline based chalcones **(40)** have been synthesized by Azad M. *et al.* the prepared chalcones had been screened for antimicrobial activity. All the prepared chalcone had showed significant activities.[57]

Tavares *et al*. synthesized a series of new 6-quinolinyl and Quinolinyl N-oxide Chalcones **(41-43)**. All chalcones were tested by minimal inhibitory concentration (MIC) against three species of *Candida*, *Cryptococcus gattii* and *Paracoccidioides brasiliensis*. The effect of these compounds was also tested on the survival and growth of the human cancer cell lines UACC-62 (melanoma), MCF-7 (breast), TK-10 (renal) and leukemic cells, Jurkat and HL60 and showed the best activity.[58]

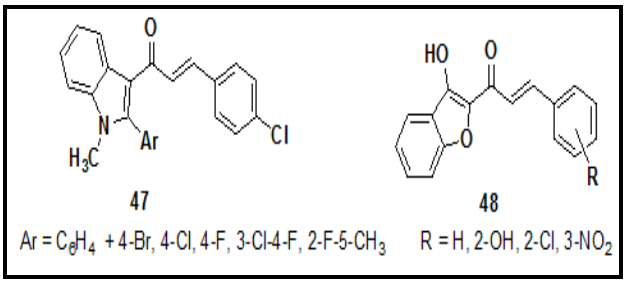


A series of indolyl chalcones **(44-45)** were synthesized and evaluated in vitro for their anticancer activity against three human cancer cell lines by Kumar *et al*. the synthesized indolyl chalcone showed significant cytotoxicity, particularly indolyl chalcones **46a and 46b** were identified as the most potent and selective anticancer agents with IC_{50} values 0.03 and 0.09 μM, against PaCa-2 cell line, respectively.[59]



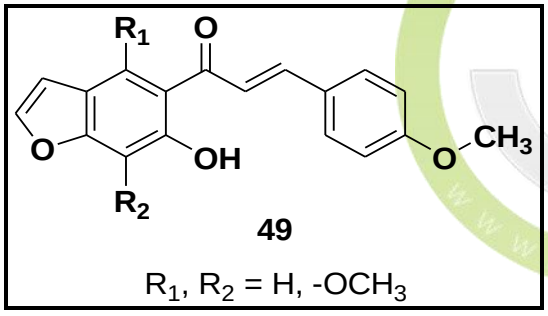
Bhatia *et al.* synthesized a some mini libraries of heteroaryl chalcones which were screened for antibacterial activity. The mini-library includes chalcones **(45)** with phenyl ring as 4-OCH_3, 4-Cl, 4-CH_3, 4-NO_2, and 4-$N(CH_3)_2$, which were found to be most active in the synthesized mini libraries.[60]

Pathak *et al.* synthesized indolylchalcone **(47)** for cyclization to afford 4, 5-dihydro-3-(2-arylindol-3-yl)-5- (4-chlorophenyl)-N-phenylpyrazoles. Antibacterial and antifungal activities of all synthesized chalcones compounds had been evaluated and some of them show promising results against *E. coli, S. aureus, C. albicans* and *A. niger*.[61]

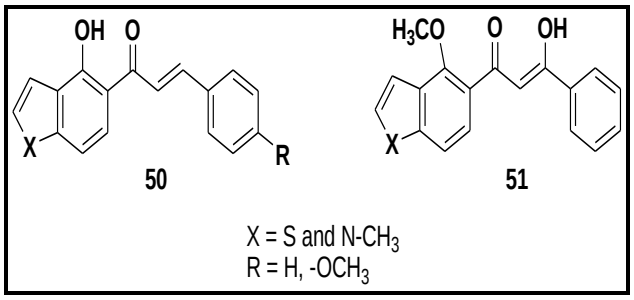


A group of chalcones and their derivatives bearing 3-hydroxyl benzofuran moiety **(48)** have been synthesized by Swamy *et al.* and analyzed for their antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli* and antifungal activity against *Candida albicans* and *Asperagillus flavus* according to cup plate method. Most of the chalcones are very weakly active and few are moderately active. Chalcone with 2-Cl and 3-NO_2 possessed very good activity against fungi *Aspergillus flavus.*[62-63]

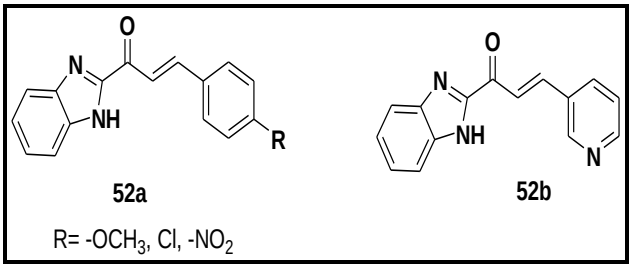
C. Julia *et al.* synthesized chalcones **(49)** which were screened for bioactivity against the voltage-gated potassium channel Kv1.3.[64]



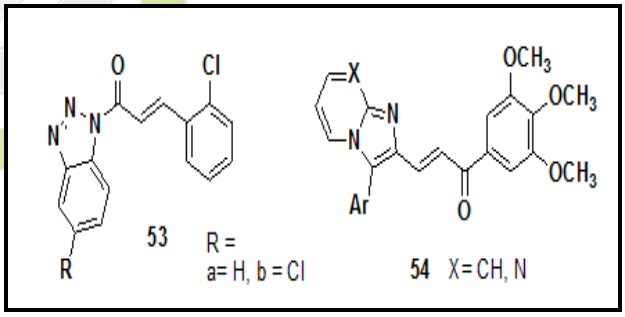
Nitrogen and sulfur heterocyclic mimics of furanochalcone **(50-51)** were synthesized and screened for antibacterial activity by Yadav *et al.* synthesized indolyl and thiophenyl chalcones have been screened for antifungal and antibacterial activities. All the test chalcones exhibited antifungal and antibacterial activity.[65]



Hassanien, Abu *et al.* synthesized the chalcones **(52)** from reaction of 2-acetylbenzoimidazole with some arylaldehydes which an intermediate for 1,5-pentanediones and pyridines.[66]



New heteroaryl chalcones **(53)** having a benzotriazole moiety were synthesized by both conventional and microwave irradiation methods by S. S. Vaidya *et al.* In vivo acute toxicity studies and analgesic, anti-inflammatory and antimalarial activities of these chalcones were evaluated. benzotriazole moiety at position 1 (chalcone **53a**) of 1, 3-diaryl-2-propen- 1-ones (chalcones), showed greater analgesic activity than the standard drug, aspirin whereas 5′-chlorobenzotriazole moiety at 1 position (chalcone **53b**) of 1, 3-diaryl-2-propen-1-ones, showed slightly lower analgesic activity as compared to aspirin.[67]



A new series of imidazo [2,1-*b*]pyridine/pyrimidine chalcone **(54)** derivatives were synthesized and evaluated for their anticancer activity by Ahmed Kamal *et al.* These chalcone derivatives showed promising activity with GI_{50} values ranging from 0.28 to 30.0 μM.[68]

CONCLUSION

In this review, we focused on heterocyclic ring chalcones which are synthesized by various researchers and their activities. It can be concluded that changes in aryl rings in chalcone to one that contain heteroaryl ring have

displayed high degree of diversity that has proven to result in a broad spectrum of high biological activities. The vital information given in this article can be utilized further by researchers in the design and development of novel and potent Chalcones in the biological activities which are mentioned in this article.

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