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Review Article

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Chalcones as Next-generation Antimicrobial Agents: Deep Insights into Anti-infective Perspectives and Novel Synthesis Routes

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ABSTRACT

Chalcones, containing an α,β-unsaturated ketone fragment, are an important pharmacologically active agents because of their diverse mechanisms. The antibacterial activity of natural and manufactured chalcones has recently undergone some changes, and this study gives an update on those changes. Understanding the mechanisms of action of various processes, compounds, or drugs is essential for advancing scientific knowledge and facilitating the design and synthesis of new treatments and interventions. When researchers comprehensively summarize the mechanisms of action, it can offer critical insights and guidance for future studies and developments. This all-encompassing and evaluative analysis will offer valuable insights to medicinal chemists aiming to enhance the creation of potential antibacterial agents.

Keywords: Chalcone, Antimicrobial, Antiinfective, Synthesis, Pharmacology, Natural

INTRODUCTION

Natural products have historically been the primary source of medicines for the treatment of human disease. Detailed analysis of the new drugs approved by the U.S. Food and Drug Administration (FDA) between 1981 and 2021 revealed that more than half of the clinical drugs were derived from natural products or their synthetic derivatives. For example, approximate 200 of microbial-sources natural antibiotics were directly used as drugs. Natural selection has shaped these chemicals through millions of years of evolution to interact with biological targets with great selectivity and efficiency while avoiding resistance. Moreover, they intrinsically possess the physiochemical properties necessary for penetrating bacterial cells, unlike many pure synthetic molecules [1].

CHALCONES

Natural products have been reported to exhibit promising anti-infective activity. They have been the mainstay of various biological activities, of them flavonoids frameworks remained the principle candidate. Flavonols, flavones, flavanones, flavanols, isoflavones, anthocyanidins, proanthocyanidins, aurones and chalcones are classes well associated with their impressive antiinfective activities. Chalcones or 1,3-diphenyl-2*E*-propene-1-one are one of the most important classes of natural products across the plant kingdom containing benzylideneacetophenone scaffold where the two aromatic nuclei are joined by a three carbon α, β unsaturated carbonyl bridge. Basically, chalcones are open chain intermediate in aurones synthesis of flavones that exists in many conjugated forms in nature as the precursors of flavonoids and isoflavonoids. Kostanecki and Tambor were the first to synthesize a series of natural chromophoric products comprising of α, β unsaturated carbonyl bridge and termed them "chalcone" [2].

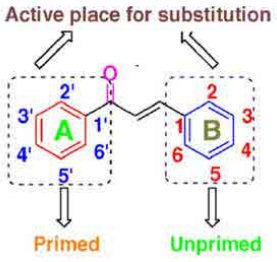

Figure 1: Structure of Chalcone.

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Chalcones have a fairly straightforward chemistry that makes it possible to make many different replacements with convenience, and they offer a wide range of therapeutic prospects, including anti-arrhythmic, anti-platelet, anti-hypertensive, antineoplastic, anti-angiogenic, anti-diabetic, anti-inflammatory, anti-gout, anti-retroviral, anti-oxidant, anti-obesity, anti-histaminic, anti-tubercular, anti-filarial, hypolipidemic, anti-malarial, anti-protozoal, anti-invasive, anti-fungal, anti-ulcer, anti-bacterial, immunosuppressant, hypnotic, anti-steroidal, anti-spasmodic, anti-nociceptive, anxiolytic, osteogenic, etc [3].

The credit for being prospective anti-infective candidates that block numerous parasite, malarial, bacterial, viral, and fungal targets goes to a number of natural and (semi) synthetic chalcones like trypanopain-Tb, trans-sialidase, cruzain-1/2, fumarate reductase, falcipain-1/2, glyceraldehyde-3-phosphate dehydrogenase, topoisomerase-II, plasmepsin-II, β-hematin, protein kinases (Pfmrk and PfPK5), sorbitol-induced hemolysis, lactate dehydrogenase, H1N1, HIV (Integrase/Protease), DEN-1 NS3, FtsZ, FAS-II, protein tyrosine phosphatase A/B (Ptp-A/B), NorA efflux pump, DNA gyrase, fatty acid synthase, lactate/isocitrate dehydrogenase, β-(1,3)-glucan synthase, and chitin synthase [4].

More importantly, several chalcone compounds have been approved for market and clinical use for various health conditions [e.g., as metochalcone-choleretic/diuretics **(1)**; sofalcone-based anti-ulcer/mucoprotectives **(2)**; and hesperidin methylchalcone-vascular protectives **(3)**], exemplifying the clinical potential of chalcones (**Figure 2**) [5].

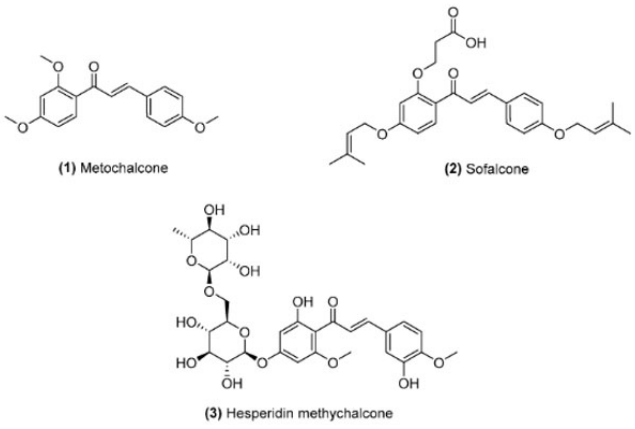


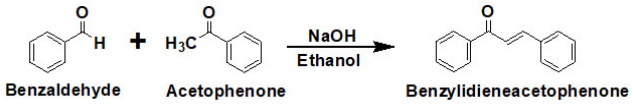
Figure 2: Chalcones in clinical trials.

SYNTHESIS OF CHALCONE SCAFFOLD

The synthesis of chalcones can be accomplished using a number of techniques. The condensation of both cyclic structures to produce benzylideneacetophenone scaffold is the key step in each of these processes. A few naming reactions that are frequently utilised to create chalcones have been listed [6-8].

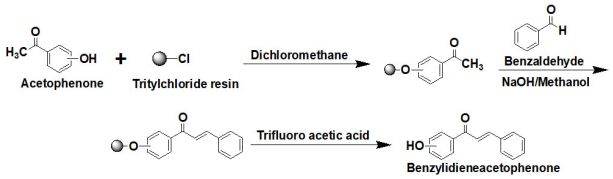
Claisen-Schmidt Condensation

The equimolar condensation of acetophenone and benzaldehyde in the presence of an alcoholic alkaline solution is the most practical process for the synthesis of chalcones. The Cannizaro reaction is frequently started by the use of benzaldehyde and is reduced by using benzylidene-diacetate. Alkaline solution mediates the condensations of both cyclic structures, although other reagents like ethylacetate, HCl gas, $AlCl_3$, etc. are also employed.



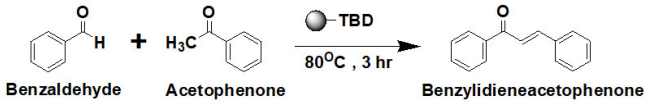
Solid phase Claisen-Schmidt reaction

Solid phase syntheses of chalcones are performed by employing 2-chlorotrytilchloride as supporting resin. The hydroxy-acetophenone derivatives are bounded to the resin primarily and then treated with benzaldehydes derivatives using NaOH in methanol as catalyst. The formed hydroxy-chalcones are released by addition of trifluoro acetic acid.



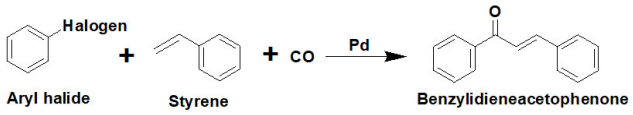
Solvent free Claisen-Schmidt reaction

Chalcones are synthesized by equimolar condensation of benzaldehyde and acetophenone in presence of catalyst 1,5,7-trisazabicyclo[4,4,0]decen (TBD) for 3 hr at 100°C.



Carbonylative Heck coupling reaction

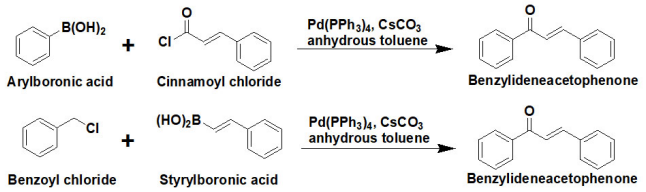
Chalcone are synthesized by reaction between aryl halide and styrene in the presence of carbon monoxide using Pd as catalyst.



Suzuki – Miyaura coupling

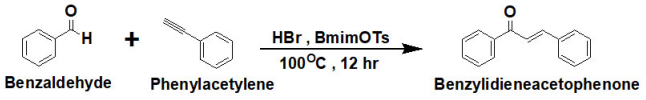
This is a Palladium catalyzed cross-coupling reaction of organoboranes with organic halide in presence of base. There

are two methods for creating chalcones: either combining arylboronic acids with cinnamoyl chloride employing $Pd(PPh_3)_4$, $CsCO_3$ and anhydrous toluene to yield 41-51% or coupling of styrylboronic acid with benzoyl chloride employing $Pd(PPh_3)_4$, $CsCO_3$ and anhydrous toluene to yield 68-93%.



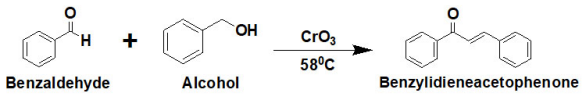
Halogen mediated synthesis

Chalcones are synthesized by a coupling reaction between equimolar concentration of phenylacetylene and benzaldehyde in presence of HBr and BmimOTs for 12 hr at 100°C.



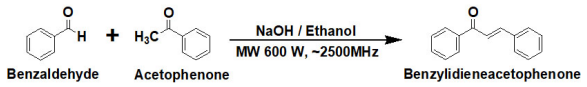
One-Pot synthesis of chalcones

The reactants of a one-pot chemical reaction are exposed to subsequent chemical reactions in a single reactor, which is a novel technique. This approach has a number of benefits, including an improvement in reaction efficiency, the avoidance of time-consuming intermediate chemical compound purification processes, and a general time and resource savings. In one pot condensations, primary alcohol and matching ketone are combined in the presence of the oxidising agent CrO_3 to create chalcones. This process is described in patent CN102786371. By producing the aldehyde, which then interacts with the ketone to form the required chalcone, CrO_3 plays a crucial part in this process.



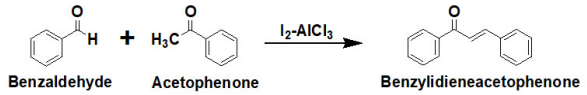
General microwave assisted synthesis

An equimolar mixture of methyl ketone and aromatic aldehydes dissolved in minimum amount of rectified spirit and NaOH (40%) were placed in a conical flask. The conical flask was covered with a funnel and then the flask was taken in a domestic microwave oven irradiating under 160-320 watt microwave irradiation for 60-120 sec. The reaction mixture was cooled and the obtained solid was recrystallized from ethyl acetate and *n*-hexane solvent mixture.



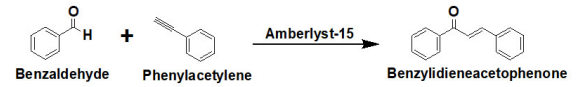
Solvent free microwave assisted synthesis

A reaction between an equimolar quantity of acetophenone and benzaldehyde without a protecting group produces chalcones. As a catalyst, microwave radiation is used to neutral alumina (Al_2O_3) that has been impregnated with molecular iodine (I_2). The molecular iodine functions as a Lewis acid and makes the aryl ketone easier to enolate while also preparing the benzaldehyde carbonyl group for nucleophilic assault. In order to increase the effective catalytic surface area, neutral alumina powder is used.



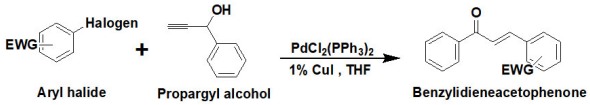
Acid catalyst mediated synthesis

The chalcones are created by combining an equimolar amount of phenyl acetylene and benzaldehyde with amberlyst-15, a solid acid catalyst, in 1,2-dichloroethane medium. The reaction is then microwave-irradiated for 18 to 25 minutes to produce the chalcones.



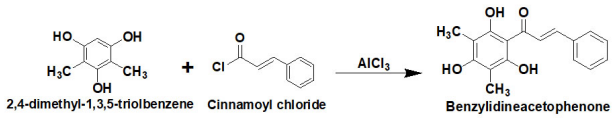
Sonogashira isomerization coupling

By using $PdCl_2(PPh_3)_2$ as a catalyst and microwave irradiation for 8–25 minutes, chalcones are created by reacting an equimolar concentration of an aryl-halide attached to an electron withdrawing group with propargyl alcohol.



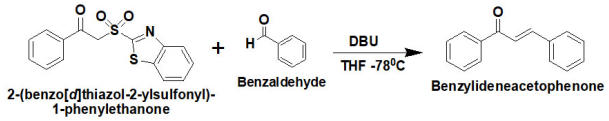
Friedel-Crafts Reaction

Chalcones are also synthesized direct by Friedel-Crafts acylation of a phenol. In this method of synthesis, the phenol is built up into A-ring and the acylating agent provides both B-ring carbons and the three-carbon bridge. 2,4,6-trihydroxy-3,5-dimethylchalcone was fabricated by Friedel-Crafts acylation of 2,4-dimethyl-1,3,5-triolbenzene with cinnamoyl chloride.



Julia-Kocienski Olefination

Julia-Kocienski Olefination involves reaction between 2-(benzo[d]thiazol-2-ylsulfonyl)-1-phenylethanone and benzaldehyde at -78°C where (*E*)-chalcone product is the major diastereomer formed. However, at -78°C the reaction yield gets decreased significantly. The carbonyl group in the -position of the generated anion in this reaction might destabilise it. However, at lower temperatures, the sulfonyl anion inhibits its reactivity and renders relatively good stability.



CHALCONES AS ANTI-MICROBIAL AGENTS

Dithiocarbamate chalcone-based compounds were created by Ayman et al. (2019) and showed promising activity with a MIC of 8 µg/mL [9].

A group of new chalcone analogues with a potential MIC of 1.56 µg/mL against *Bacillus anthracis* were synthesised by Zhang et al. (2018) [10].

Yadav et al. (2018) created a number of fluorinated chalcone-triazole hybrids, one of which had a peak MIC of 3.2 µM and had strong antibacterial activity [11].

The dihydrotriazine-based chalcones that Zhang et al. (2018) created shown promising antibacterial activity with the MIC of 4 µg/mL [12].

The hybrid chalcone comprising pyrazole and thiophene was described by Khan et al. (2017) and showed promising antibacterial activity [13].

Quinoxalinyl chalcones were created by Desai et al. (2017) and demonstrated promising antibacterial activity with a peak MIC of 3.12 µg/mL [14].

Some hybrid chalcones connected to pyrroles have been shown to have antibacterial action by Joshi et al. (2016) [15].

A few halogenated pyrazine-based chalcones were created by Kucerova-Chlupacova et al. (2016) and demonstrated excellent efficacy against *M. tuberculosis* H37Rv with a MIC of 3.13 µg/mL [16].

Some 1,2,3-triazole linked chalcones with potential activity and a MIC of 6.25 µg/mL were synthesised by Kant et al. (2016) [17].

The MRSA ST1745, MRSA ST2071, MRSA ST2438, MRSA B10732, MRSA P8029, MRSA ST5457, MRSA ST10342, MRSA B10760, MRSA ST3151, and MRSA P6642 were only a few of the MRSAs that Gaur et al. (2015) synthesised and tested for action against [18].

According to Feng et al. (2014), certain modified chalcones shown effective antibacterial properties against MRSA with MICs as low as 0.39 µg/mL. According to investigations on their mode of action, they may be able to block DNA topoisomerase-IV and have an impact on macromolecular biosynthesis [19].

A group of chalcones based on quinoline that Abdullah et al. (2014) reported on had modest antibacterial activity and were directed towards DNA gyrase [20].

Shelke et al. (2012) created a number of pyrazole-containing chalcone derivatives, including substances that showed promising antibacterial action, particularly against *M. tuberculosis* H37Rv with a MIC of 6.25 µg/mL [21].

A series of chalcones with promising antibacterial action against MSSA and MRSA with a peak MIC of 32 µg/mL were synthesised by Tran et al. (2012) [22].

Compounds' antibacterial activity against MSSA and a number of MRSAs was assessed by Osório et al. (2012) [23].

A number of chalcone derivatives were created by Jin et al. (2012). One of these compounds, the C-5 substituted rhodanine fragment generated from L-phenylalanine, had remarkable action against quinolone-resistant *S. aureus* (QRSA) with a peak MIC of 2 µg/mL [24].

Analogues of certain heterocyclic chalcones were reported by Tran et al. in 2012. Among these, a substance with a MIC value of 64 µg/mL against MRSA ATCC 44330 shown potential antibacterial action [25].

Sharma et al. (2012) created a number of chalcones generated from β-ionones, including substances that had high antibacterial activity with a peak MIC of 0.78 µg/mL. They continued to be active against the Gram-negative bacteria *P. aeruginosa* and *E. coli*, which is interesting [26].

A series of thiazole-based chalcones with modest activity were created by Liaras et al. (2011). Contrary to popular belief, compounds demonstrated three times greater MIC against *Micrococcus flavus* than Ampicillin. They further created a few novel substituted compounds to increase the antibacterial activity [27].

The 2,4-thiazolidinedione and benzoic acid-containing compounds Liu et al. (2011) created showed strong antibacterial activity with MICs ranging from 0.5 µg/mL to 4 µg/mL, outperforming the common antibiotic norfloxacin [28].

A series of β-chloro vinyl chalcones were synthesised by Bandgar et al. (2010), and the chemical showed average antibacterial activity [29].

By creating chalcones and testing their antibacterial activity against *S. aureus* and *E. coli*, Batovska et al. (2009) found that these compounds were ineffective against *E. coli* and that various substitutions on the A or B ring would result in variable antibacterial activity [30].

CONCLUSION

The most current antibacterial activity of natural and synthesised chalcones has been discussed in this study. It is obvious that chalcone-based molecules have a lot of promise for use in medicinal chemistry. The chalcone skeletons were accessible. Additionally, other bioactive moieties may be included into A or B rings as well as the,-unsaturated ketone fragments. Indeed, the successful development and commercialization of a few chalcone-based medications, such as metochalcone, sofalcone, and ilepcimide, attests to the medication's promise. Chalcone research and development as an antibacterial medication is, and undoubtedly will continue to be, one of the most crucial areas of medical chemistry. This is due to its potential antibacterial properties.

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