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RESEARCH ARTICLE

CHALCONES AS SYTHONS FOR HETEROCYCLIC COMPOUNDS- A REVIEW

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ABSTRACT

Chalcones are α, β-unsaturated ketones derived from acetate and Shikimic acid pathways, used in the biosynthesis of flavonoids and isoflavonoids. 1,3-diphenyl-2-propen-1-one is the simplest member of the chalcone series, with the molecular formula $C_{15}H_{12}O$, molar mass of 208.26g/mol, and a melting point of 55-57°C. Chalcones are synthesized by Aldol Condensation reaction using Claisen-Schmidt method which involves reacting equal molar ratios of benzaldehyde and acetophenone in an alcoholic base or their substituted derivatives. The presence of α, β unsaturated ketone makes chalcone a versatile molecule for the synthesis of heterocyclic compounds through reaction with a bi-nucleophile such as hydrazine, urea, guanidine or o-phenylenediamine, to afford five, six or seven membered heterocyclic compounds such as pyrazoles, pyrimidones, pyrimidines, 1,5-benzodiazepines, and1,5-benzothiazepines. Heterocyclic nuclei are present as core structural components in an array of drug categories, such as anti-inflammatory, antihypertensive, antiepileptic, antidepressant and antimicrobial agents. Many chalcones could be used as lifesaving agents because of their immense pharmacological activities, such as antibacterial, antimalarial, antioxidant, anti-HIV and antitumor activities. Thus, they continue to enjoy lots of attention from researchers in the field of drug discovery.

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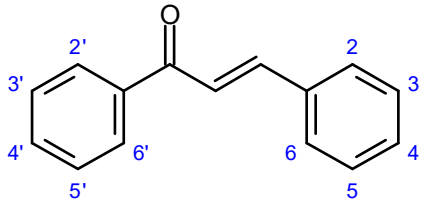
INTRODUCTION

Chalcone is an aromatic ketone, an enone that forms the central core for a variety of important biological compounds which are known collectively as chalcones or chalconoids. Chalcone is a biosynthetic product of the acetate and Shikimic acid pathways. Chalcones belong to the flavonoid family but are not strictly flavonoid though they are biosynthetically related, and are useful precursors for flavonoids and isoflavonoid which are very much abundant in many plants including edible plants such as pears, strawberries, bearberries, certain wheat products and tomatoes [1-3] as shown in Scheme. 1.0).



Scheme 1.0 Chemical Structure of Chalcone

The term chalcone was first coined by Kostanecki who did the pioneering work in the synthesis of natural colouring compounds. Chalcones bear a synthon; hence a variety of novel heterocyclic compounds could be synthesized from it. The IUPAC name of the parent member is 1,3-diphenyl-2-propen-1-one. Common names include benzylideneacetophenone and phenylstyrylketone.

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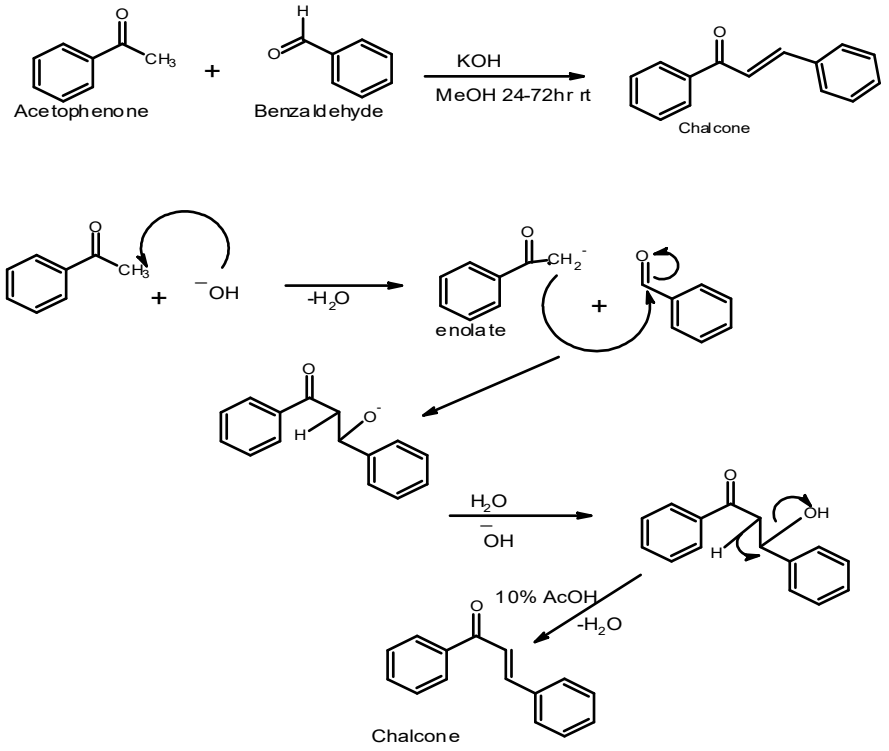
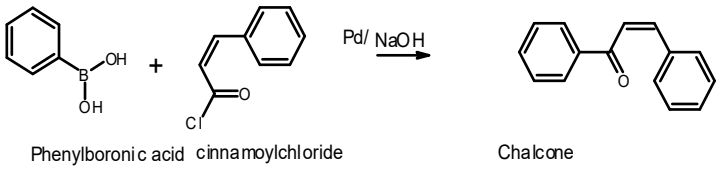
It has a molecular formula $C_{15}H_{12}O$, molar mass 208.26g/mol and melting point 55-57°C. Chalcones are α, β-unsaturated ketone containing the reactive keto-ethylenic group. These are coloured compounds because of the presence of a chromophore [4].

Synthesis of Chalcones: Chalcones can be prepared by aldol condensation reaction between equal molar ratio of benzaldehyde and acetophenone or their substituted derivatives in methanol and potassium hydroxide as a catalyst, commonly referred to as Claisen Schmidt condensation reaction [5] as shown in Scheme 2.



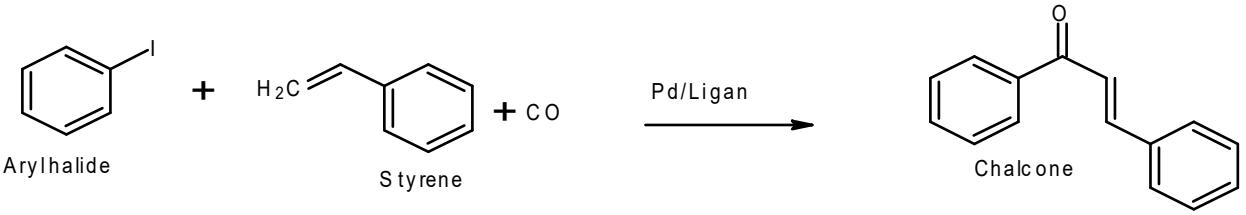
Scheme 2.0: Synthesis of Chalcone and reaction mechanism

Claisen Schmidt Condensation is a reaction between an aldehyde or ketone and a carbonyl compound lacking α-hydrogen, leading to the formation of an α, β-unsaturated ketone. The first part of the reaction is an aldol reaction; the second part is dehydration reaction leading to elimination of a molecule of water. Aldol addition product can be dehydrated via two mechanisms; a strong base like potassium t-butoxide, potassium hydroxide in an enolate or acid catalyzed enol mechanism. There are other synthetic methods that could be used in the synthesis of chalcones such as Suzuki coupling using cinnamoyl chloride, phenylboronic acid as reagent and palladium as a catalyst [6] (Scheme 3).



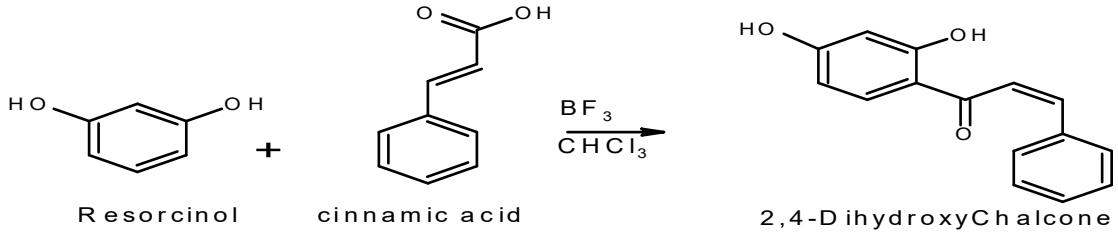
Scheme 3.0: Synthesis of Chalcone using Cinnamoyl chloride and Phenylboronic acid

Heck Coupling reaction using Palladium as catalyst is another protocol to synthesize chalcones, by reaction of arylhalide and styrene in the presence of carbon monoxide [7] (as illustrated in Scheme. 4)



Scheme 4.0: Synthesis of Chalcone using Arylhalide and Styrene.

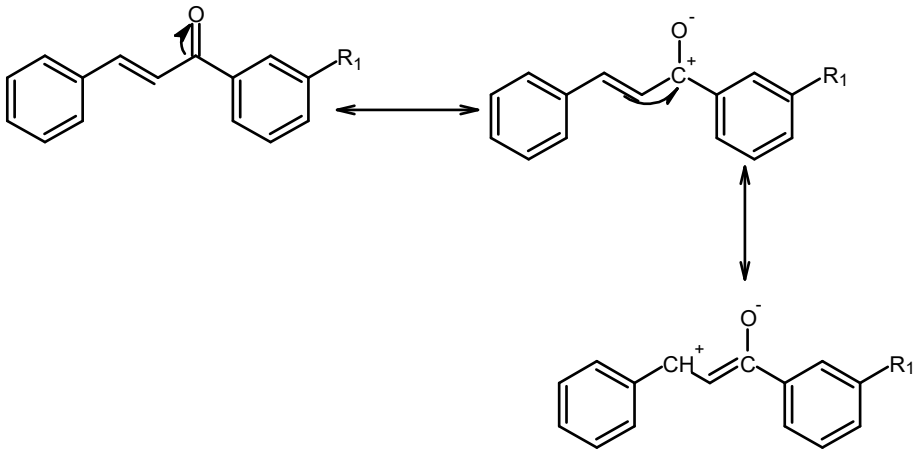
Kumar *et al*., [8] used condensed resorcinol with cinnamic acid in chloroform in the presence of boron triflouride yielding 2,4-dihydroxychalcone (Scheme. 5).



Scheme 5: Synthesis of dihydroxychalcone from Resorcinol and Cinnamic acid.

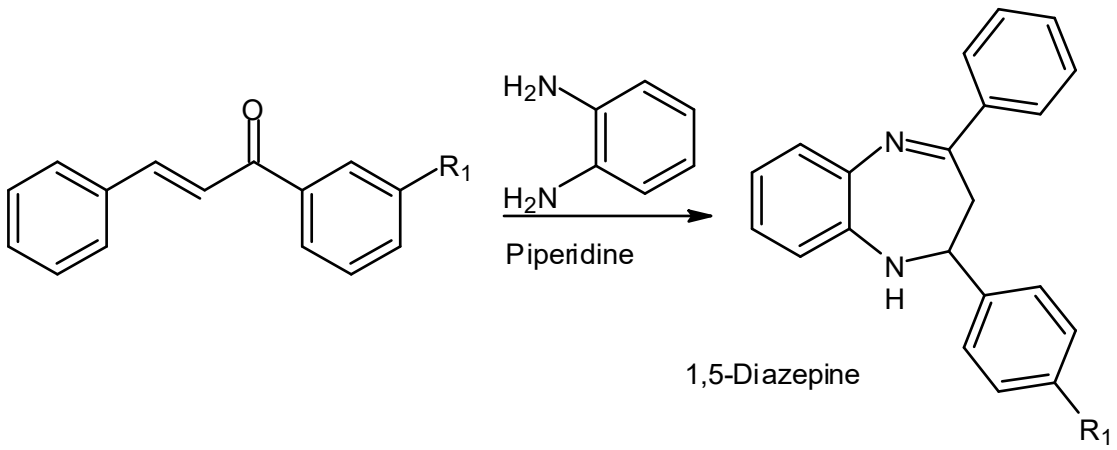
Jayapal and Sreedhar [9] synthesized chalcones using thionylchloride in ethanol as catalyst.

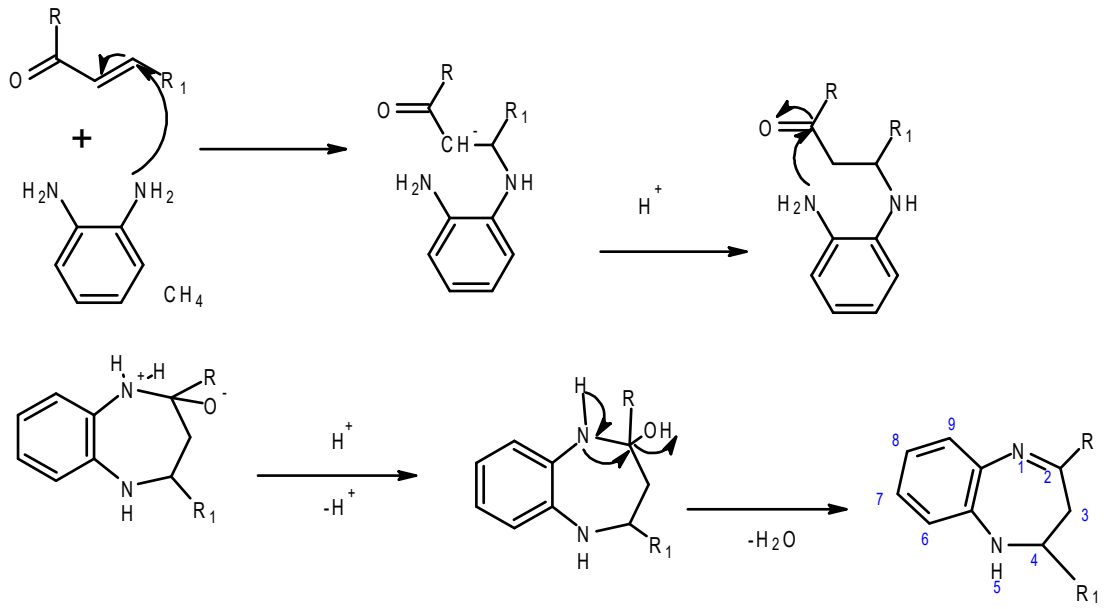
Chalcones as Useful Intermediates for the Synthesis of Heterocyclic Compounds: Chalcones are versatile precursors for the synthesis of heterocyclic compounds. The enone moiety is important for the structural transformation of Chalcones [10]. Chalcones can react with a nucleophile via Micheal addition. In cyclocondensation reaction, it can act as a bi-electrophile which reacts with a bi-nucleophile and this is an attractive route for the synthesis of heterocyclic compounds [11,12]. A carbonyl compound can undergo a carbonyl addition reaction which would lead to the formation of hemiacetals, hemiketals, schiff bases; in all of these a nucleophile directly attacks a carbonyl carbon. However, if the electrophilic carbonyl carbon is β-unsaturated, that is, it has a double bond at α, β - carbon position conjugated to the carbonyl group, a different reaction pathway is possible. A resonance structure can be drawn in which the β-carbon has a positive charge meaning that it has the potential to be an electrophilic target, as illustrated in Scheme.6.



Scheme 6: Resonance Structure of Chalcone.

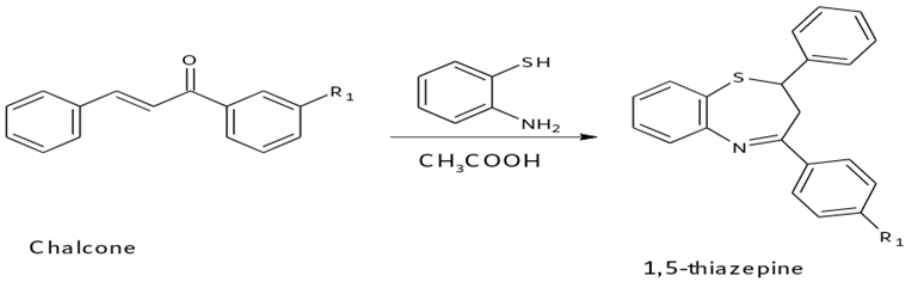
Synthesis of Seven Membered Ring Heterocyclic Compounds: The classical method to synthesize seven membered heterocyclic compounds is ring enlargement using Beckmann rearrangement reaction. However, due to its bi-electrophilic character, chalcones give an alternative route to build seven membered ring through reaction with a bi-nucleophile to form derivatives of azepines, oxepines and thiazepines, using chalcone derivatives as intermediate, and o-phenylenediamine in the presence of piperidine as a catalyst gives 2,4-disubstituted 1,5-benzodiazepines. This route has been used to synthesize benzodiazepines (Scheme. 7) [10, 13]





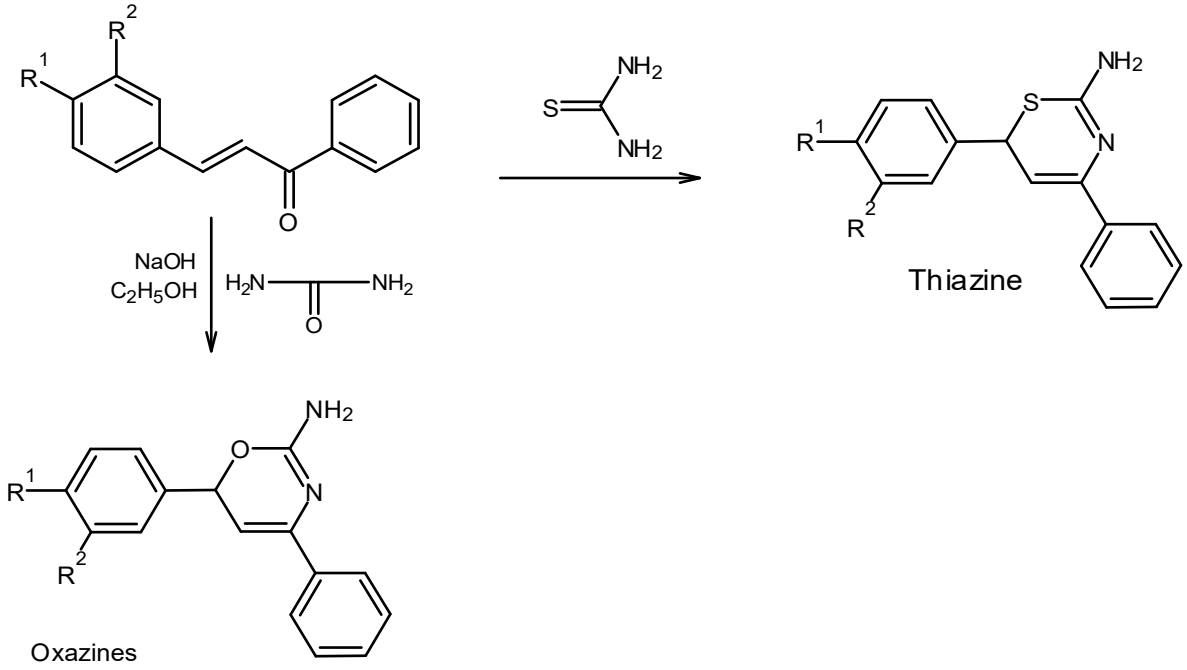
Scheme 7. Synthesis of Benzodiazepine from Chalcone and O-Phenylenediamine and reaction mechanism

Applying this synthetic route, benzothiazepine derivatives are obtained by the reaction of chalcones or its analogs with 2-aminothiophenol as shown in Scheme 8.



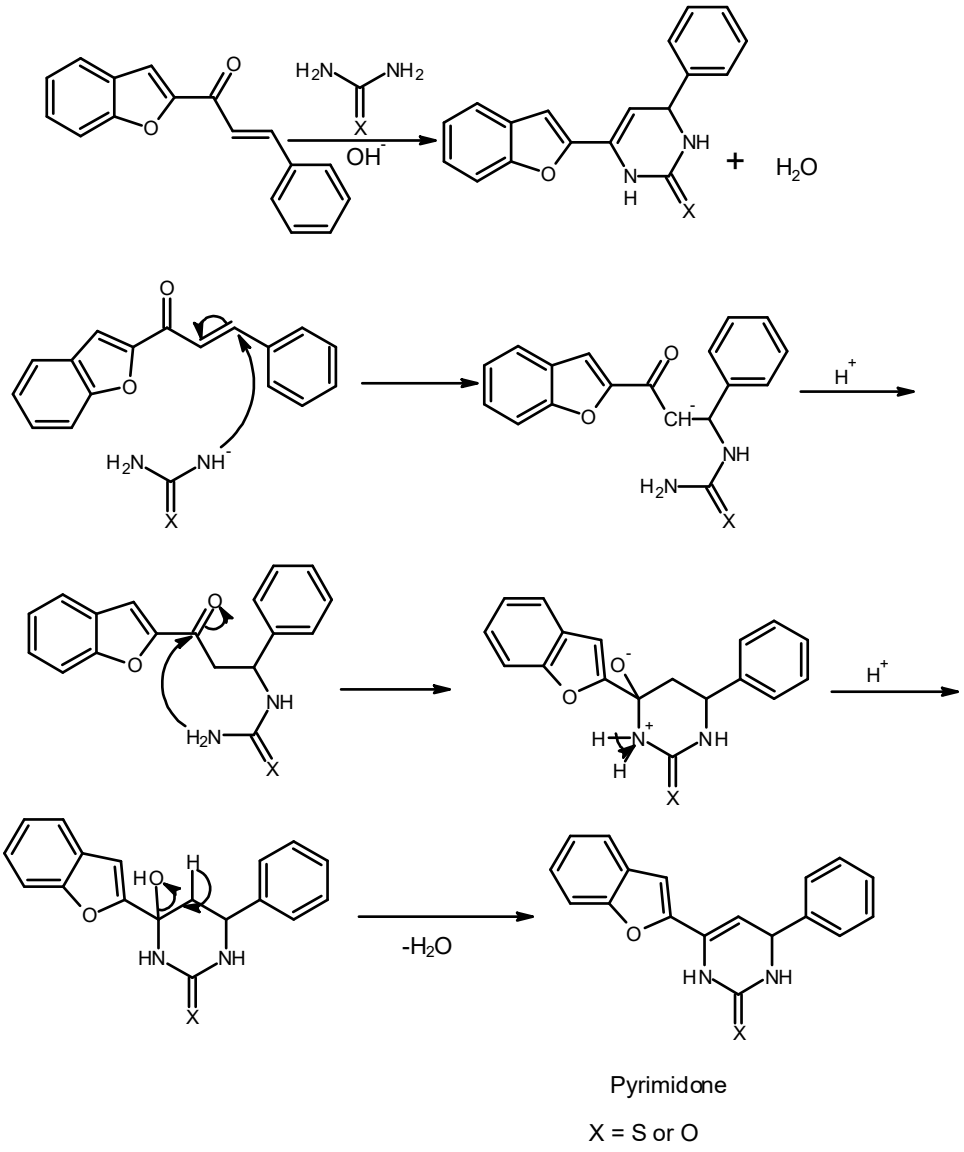
Scheme 8. Synthesis of 1, 5-Benzothiazepine using Chalcone and Aminothiophenol

Synthesis of Six-membered ring heterocycles: The most common method of preparing pyrimidine is by reaction between 1,1,3,3- tetraethoxypropane and formamide. However, chalcones react with urea, thiourea and hydroxylamine derivatives depending on the reaction condition to afford pyrimidone, pyrimidol, oxazines and thiazines [14,15].(Finar, 1975; as shown in Scheme 9.0.



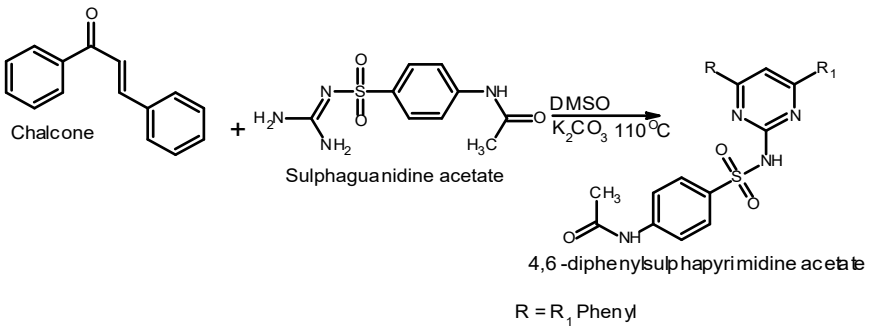
Scheme 9: Synthesis of oxazines and thiazines using chalcones and urea analogue

Synthesis of Pyrimidone: Chalcones react with urea and thiourea in the presence of base to give pyrimidine-2-one and pyrimidine-2-thione (scheme. 10) [16-18].



Scheme. 10: Synthesis of Pyrimidone, Pyrimidine-2-thione derivatives and reaction mechanism.

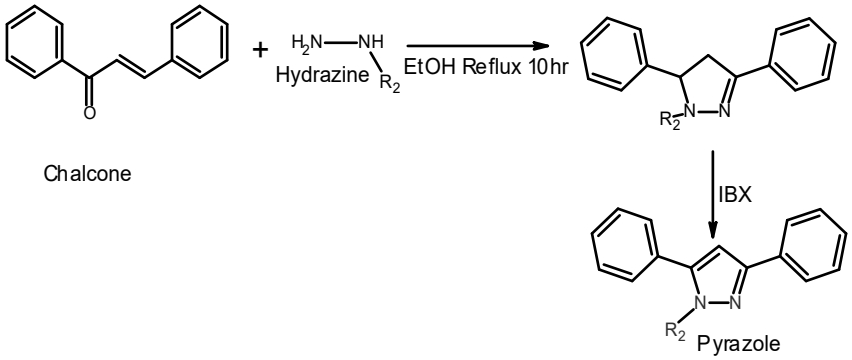
Synthesis of Sulphapyrimidine: Cyclocondensation of sulphaguanidine acetate with chalcones in dimethylsulphoxide at 110^{o}C gives 4,6-diphenylsulphapyrimidine acetates [10,19], as shown in Scheme 11.



Scheme 11: Synthesis of Diphenylsulphapyrimidine using Chalcone and Sulphapyrimidine acetate

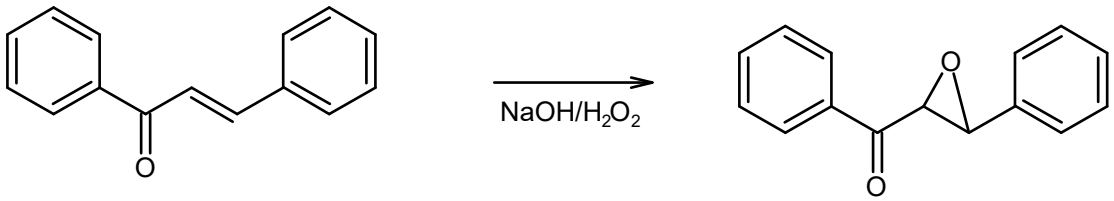
Synthesis of five membered Heterocyclic Compounds: There are conventional methods for the synthesis of five membered ring heterocycles such as pyrazole, isoxazole, oxazole and imidazole rings. One of such convenient protocols to prepare pyrazoles and isoxazoles is by condensation of 1,1,3,3-tetraethoxypropane with hydrazine dihydrochloride and hydroxylamine hydrochloride, which affords pyrazoles and isoxazoles respectively. Chalcones utilize an alternative route to synthesize pyrazole and isoxazole derivatives [13,14,20,21].

Synthesis of Pyrazole: Condensation of chalcones with hydrazine hydrate in absolute ethanol under reflux gives pyrazoline, and when treated with iodoxybenzoic acid gives pyrazole [20-23] as shown in Scheme. 12.



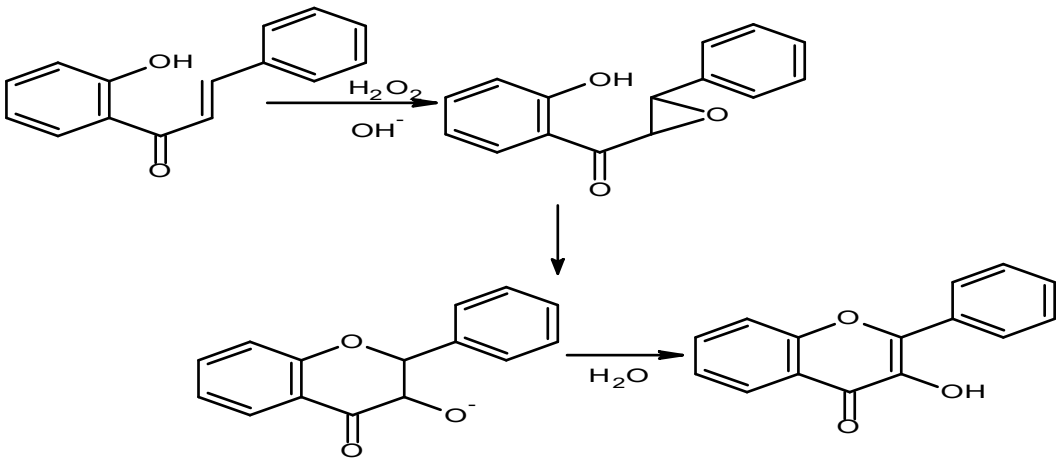
Scheme 12: Synthesis of Pyrazoles using Chalcones and Hydrazine

Reaction of Chalcones with Oxidizing Agents: Since chalcone is an unsaturated α, β ketone, the olefinic double bond can be oxidized with various oxidizing agents. Epoxidation of chalcones with hydrogen peroxide in alkaline medium has been achieved, and is used in the preparation of heterocyclic epoxy chalcones (Scheme. 13).



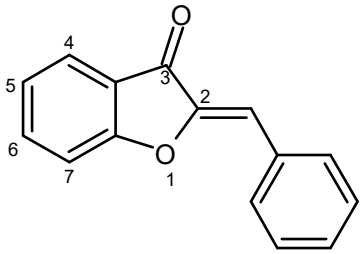
Scheme 13: Synthesis of Epoxy chalcones

This synthetic route, known as the Algar-Flynn Oyamada reaction (Scheme. 14), is useful for the synthesis of 3-hydroxyflavonone, and then into flavonol [14,24].



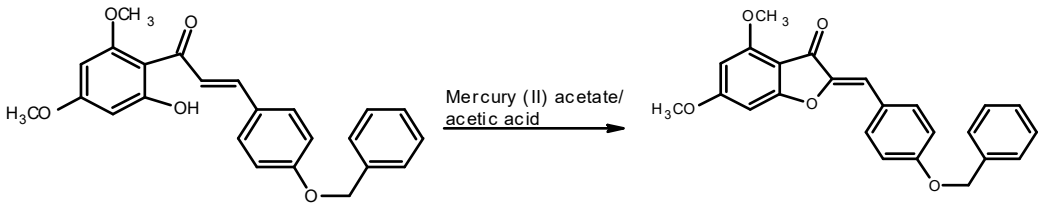
Scheme 14: Synthesis of 3-Hydroxyflavone and Flavonol.

Synthesis of Aurones from Chalcones: An aurone is a type of flavonoid containing a benzylidene unit linked to benzofuran at position 2 (Scheme. 15). The presence of aurones imparts a typical bright yellow colour to some popular ornamental flowers, such as cosmos and snapdragon [25-27].



Scheme 15: Chemical structure of Aurone

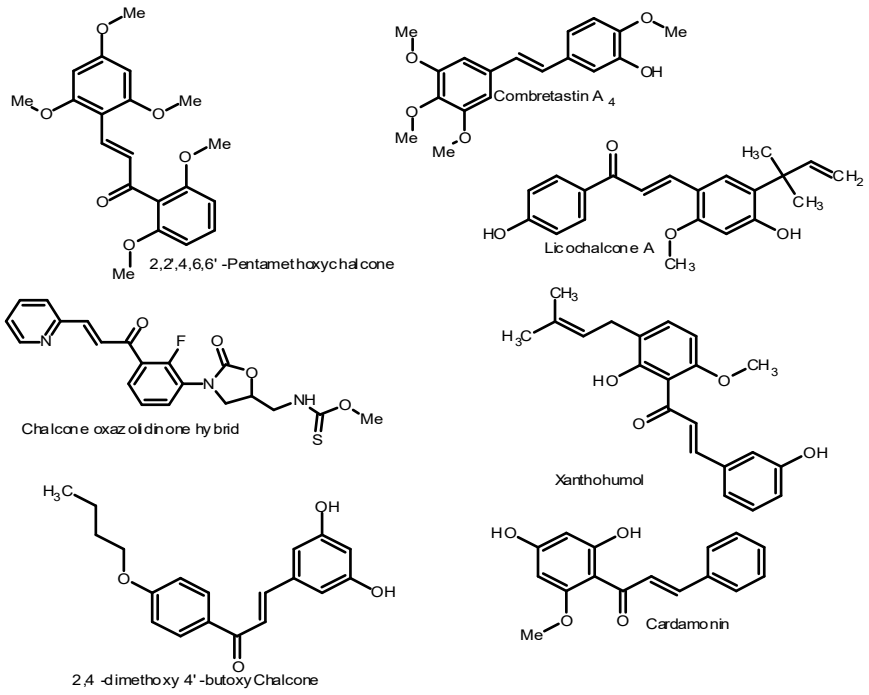
A major route for the synthesis of aurones involves the oxidative cyclization of 2'- hydroxyl chalcones. This can be achieved by using mercury (II) acetate in pyridine or acetic acid. Scheme16 shows the oxidative cyclization of a 2'- hydroxychalcone to its corresponding aurone [25-27].



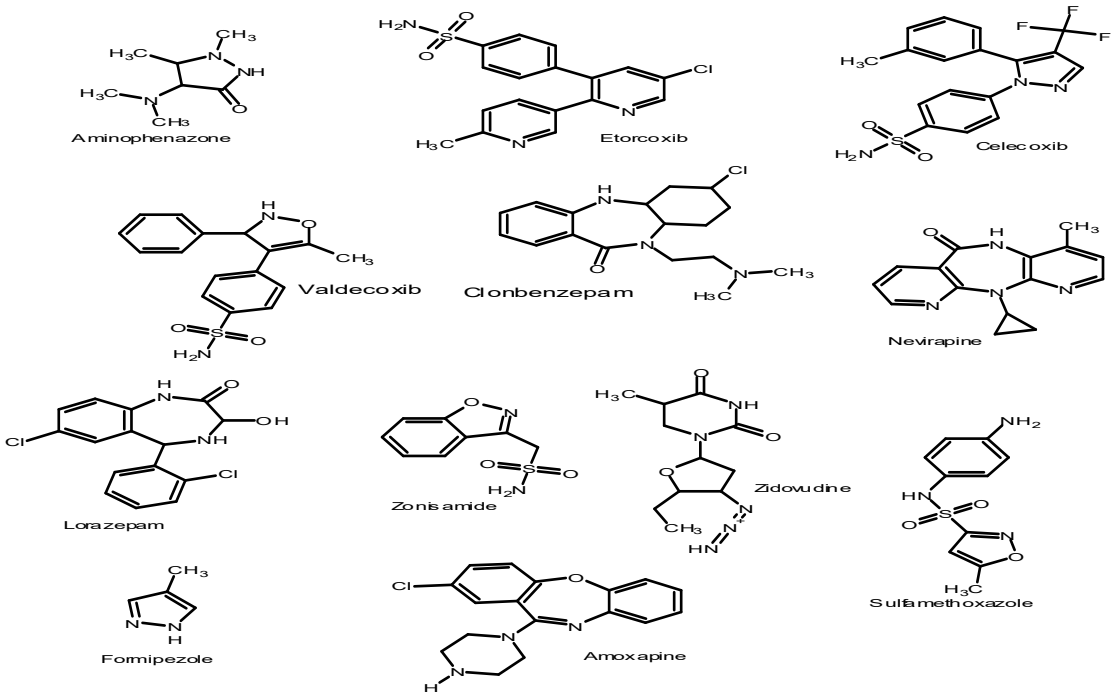
(2E)-1-(2-hydroxy-4,6-dimethoxyphenyl)-3-[(4-benxyloxy)phenyl]prop-2-ene-1-one

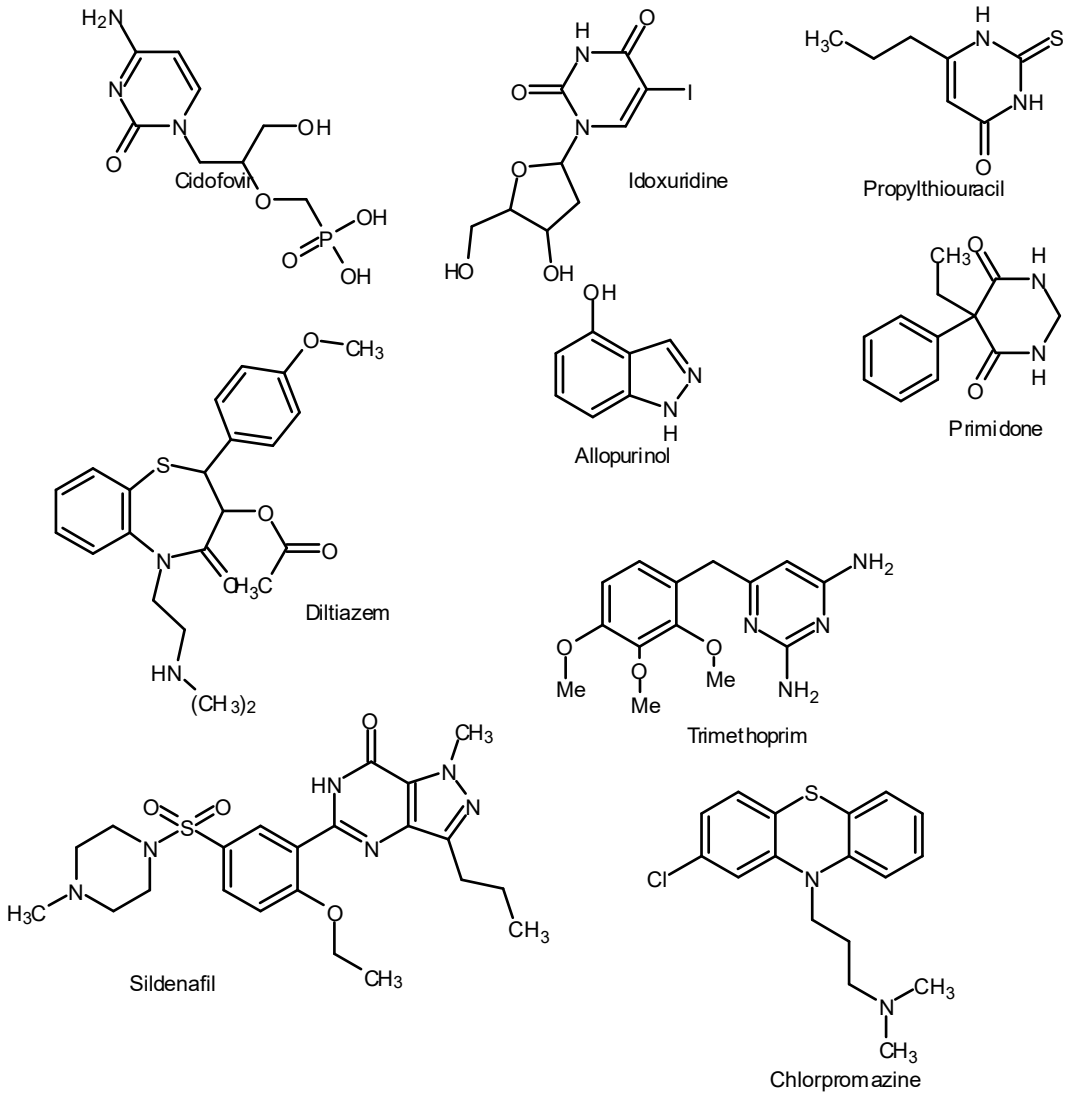
(2Z)-2-[4-(benzyloxy)benzylidene]-4,6-dimethoxy-1-benzofuran-3(2*H*)-one

Scheme 16: Synthesis of Aurone from 2'-hydroxychalcone



Scheme 17: Chemical Structures of Chalcones with biological activities





Scheme 18: Chemical Structures of medicinal agents with heterocyclic core

DISCUSSION

Chalcones are an interesting target class of compounds which have been extensively investigated due to their broad-spectrum biological activities, such as anti-inflammatory, antitumor, antioxidant and antibacterial activities [8, 28-30] as shown in Scheme. 17. Oxygenated chalcones such as 2,4-dimethoxy-4'-butoxychalcone exhibited potent activity against human malaria parasite *Plasmodium falciparum,* and xanthohumol is characterized as a broad-spectrum cancer chemopreventive agent in vitro [1,10]. Cardamonin, is a 2'4'-dihydroxy-6'- methoxychalcone isolated from a zingiberus plants species such as *Alpinia katsumadai* and *Alpinia conchigera* which possesses antimutagenic, vasorelaxant and anti-inflammatory properties [1]. Chalcone oxazolidinone hybrid and lichochalcone showed potent antibacterial property [27] and 2,2',4,6,6'-Pentamethoxychalcone is a structural analogue of combretastin A_4 which has high anticancer and low toxicity in animals [10, 32-38, 39] as shown in Scheme. 17. Heterocycles form the largest classical division in organic chemistry and are of immense importance biologically and industrially. One striking structural feature common to heterocycles which continue to be exploited to greater advantage by drug industries lies in their ability to manifest substituents around a core scaffold in defined three dimensional representations [33 - 34]. Heterocyclic nuclei are present as core structural components in an array of drug categories such as antimicrobial, anti-inflammatory, antiepileptic, anxiolytic, antipsychotic, antimalarial, analgesic, antihypertensive, antioxidant, antidiabetic and aphrodisiac agents. Some examples are shown in Scheme.18 [34-37]. Heterocycles play an important role in biochemical process because the side groups are the most typical and essential constituents of living cells. DNA and RNA are based on aromatic heterocycles [34].

Conclusion

Chalcones are versatile molecules for the synthesis of an array of heterocyclic compounds. Heterocycles display intrinsic reactivity which enables rich, versatile and productive transformations to occur. Taking into cognizance the ubiquitous presence of heterocycles in natural products and drugs, the development of new, fast and efficient preparative protocols for these structures remains an urgent task in medicinal chemistry. Chalcone-based heterocycles are numerous, many of which have been shown to be lifesaving medicinal agents. Due to the intrinsic pharmacological properties displayed by this important class of compounds, it is known to enjoy wide range of research-oriented use, geared towards the discovery of many more pharmaceutical and medicinal products.

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