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An Overview of Synthesis and Applications of Chalcone Derivatives

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Abstract

Chalcone and its derivatives have attracted great attention because of a wide range of biological activities such as, antimicrobial, anticancer, antioxidant, anti-anthelmintic, anti-amoebicidal, antiulcer, antiviral, insecticidal and immunosuppressive. The presence of functional groups and conjugation within the structure make it a good candidate for these applications. This review highlighted the synthesis of chalcone derivatives which were described by researchers and studied their biological activity.

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1. Introduction

Chalcones are flavonoid-derived secondary metabolites that occur in edible and medicinal plants. Two aryl moieties linked by an unsaturated carbonyl group form the chalcones 1, 3-diphenyl-2-propen-ones. The existence of a keto-ethylenic group (CO-CH=CH-) chromophore group generated a colored molecule.[1].Figure 1.

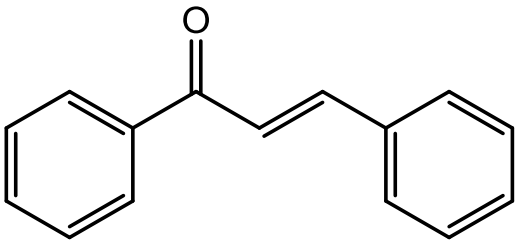

Figure 1. Structure of chalcone.

Chalcones are naturally occurring compounds that can be found in fruits herbs, spices, teas, and metals containing soy. Because of its beneficial properties, like the presence of a double bond of an,-unsaturated ketone and two aromatic rings. Furthermore, these compounds can be naturally occurring such as insect hormones, plant, allelochemicals, and pheromones [2]. Chalcones are utilized as basic intermediate structures in a variety of biosynthetic pathways that lead to the production of aurones, iso-flavonoids, and flavonoids [3]. In 20th century the majority of inquiry in medicinal chemistry has concentrated on both natural and manufactured chalcones due to their special pharmaceutical action such antibacterial,[4] anti-inflammatory,[5] analgesic,[6] antiulcer,[7] antioxidant,[8] antimalarial,[9] anticancer[10] antiviral,[11] aldose reductase inhibition,[12] estrogenic,[13] Acetylcholinesterase inhibition,[14] and non-purine xanthin oxidase Inhibitors,[15]. Chalcones are highly sought-after compounds due to their simple structure, simplicity of synthesis, and intriguing biological implications. Chalcones are very appealing compounds because of their interesting biological applications, easy synthesis, and simple structure. The compound synonyms benzyl acetophenone and benzylideneacetophenone are further names for chalcone. They are produced by some plant species, including Humulus Scutellaria, Angelica and Glycyrrhiza These compounds are considered important in the synthesis of heterocyclic compounds, including pyrimidines, isoxazoles, cyanopyridines, and pyrazolines, as well as precursors to the biosynthesis of iso flavonoids. and flavonoids [16]. The Chalcone of unsaturated ketone consists of rings A and ring B with various substituents. [17]. The rings are connected by an unsaturated carbonyl group called (keto ethylene group -CO-CH=CH-).

Chalcone has conjugated double bonds in both benzene rings and a completely delocalized electronic system. Chalcone is also used in the synthesis of medicines [18]. When exposed to strong sulfuric acid, all chalcones turn pink (positive Wilson test). The presence of phenolic hydroxyl groups gives it a purple color in ferric chloride alcohol solution [19]. Heating in dimethyl sulfoxide (DMSO) with trace amounts of iodine for 2 hours generates flavones from chalcone. When chalcone was oxidized with H_2O_2 in CH_3OH/NaOH soln., these flavonols exhibited a yellowish-green fluorescence in CH_2CH_2OH/H_2SO_4 solution [20]. In this review, we discuss the synthesis and chemistry of chalcone derivatives and their applications. Chalcone belongs to the most important class of plant secondary metabolites. It is used in the plant's defense mechanism to combat reactive oxygen species, ensuring that the plant survives and avoids molecular damage from microorganisms, insects and animals [21].

1. Synthesis of chalcones

In general, chalcones are synthesized by different methods, the most important techniques are mentioned as follows:

i. Claisen-Schmidt Reaction

The most convenient approach to synthesizing chalcone is the Claisen-Schmidt condensation of equivalent molar amounts of substituted acetophenones and substituted aldehydes in alcoholic alkaline solution (Figure 2). The alkali concentrations used in Claisen-Schmidt reactions are typically (10-60) %. The reaction takes approximately 14 h at 50 °C and 1 week at 25 °C (Cannizzaro reaction), resulting in lower product yields. Benzylidene diacetate should be used instead of aldehyde to prevent th disproportionation of aldehyde in the previous step [22].

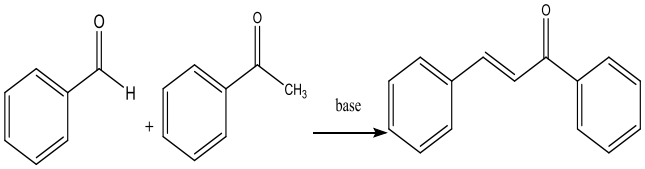

Figure 2. Reaction of benzaldehyde with acetophenone

ii. Suzuki Reaction

Suzuki can make chalcone synthesized by reacting phenyl boronic acid with cinnamyl chloride or benzoyl chloride and phenyl vinyl boronic acid (Figure 3) [23].

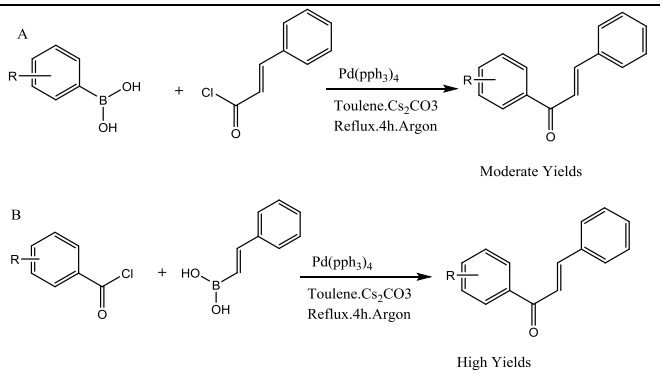

Figure 3. A. Reaction of phenyl boronic acid with cinnamyl chloride (moderate yield), B. Reaction of phenyl vinyl boronic acid with benzoyl chloride (high yield)

iii. Fridel-Graft Reaction

A connection is formed between the Lewis acid and the chlorine atom of the acid chloride. (Figure 4). The C-Cl bond of the complex is broken and an acylium ion is formed. The acylium ion is resonance stabilized and has a positive charge on the carbon. This acylium ion interacts with the arene as an electrophile to form (aryl ketone). Chalcone can be produced by reacting with aluminum chloride $AlCl_3$. [24].

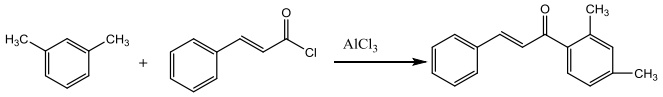

Figure 4. Complex between Lewis acid and acid chloride.

2. Applications of Chalcone

Recently chalcone derivatives have attracted great attention. Different researches have been done on chalcone and development on it to find new therapeutic agents. New methods of producing chalcone derivatives with varied medicinal and biological effects have been investigated. [25].

i. Antimicrobial activity

The antibacterial activity of chalcone has become more known and more familiar the in biomedical field. Researchers have done different research in this field, especially on antimicrobial agents. The existence of keto groups in chalcone undergoes nucleophilic addition with groups such as thiol groups of essential proteins and thus contributes to their antibacterial activity. However, its antibacterial activity may vary depending on the species and the aromatic ring substituent's type location. [26]. 3-[1-oxo-3-(2, 4, 5-trimethoxyphenyl)-2-propenyl] synthesized-2H-1-benzopyran-2-one (Figure 5) and evaluated it at doses of µg/ml in

Bacillus subtilis, B. 1000 pumilus, and *E. coli*. This study demonstrated the significance of electron-donating groups for increasing activity, like (OH) and ($ROCH_3$) groups. Chalcone's antifungal action is significantly enhanced by halogen substituents like bromine and chlorine.

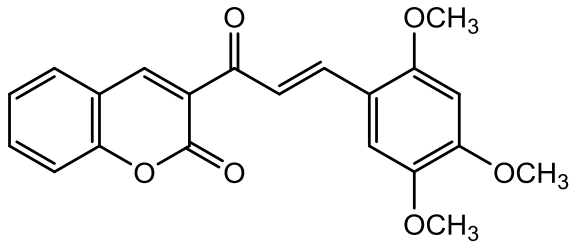

Figure 5. 3-[1-oxo-3-(2, 4, 5-trimethoxyphenyl)-2-propenyl].

Nielsen *et al.*[27] describe the exchange of the hydroxychalcone's vital 4′-hydroxy group by bio isosteres of different acidities, producing molecules that are more soluble and powerful. Hydroxyl groups can be substituted, particularly carboxyl groups, to create strong, highly water-soluble compounds. A soluble and powerful carboxy chalcone with dibromo or trifluoromethyl replacements on the ring B was produced by additional optimization and (SAR) analysis (Figure 6). He tested these compounds against the Gram-positive bacterium *Staphylococcus aureus* and found that their MIC values were 2 µM and 40 µM, respectively. It was discovered that a carboxy group on the ring A raised the necessary water solubility, while dibromo or trifluoromethyl substitution on the ring B improved lipophilicity.

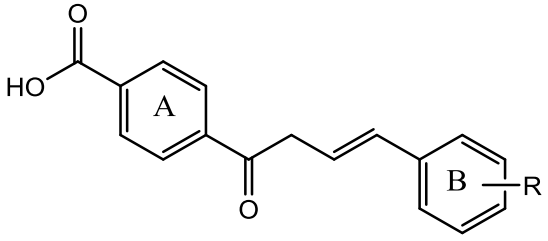

Figure 6. 4′-hydroxy group with bio isosteres.

Karthikeyan *et al.* synthesized antibacterial 3-aryl-1-(2,4-dichloro-5-fluorophenyl)-2-propen-1-ones [28] (Figure 7). This is consistent with the observation that halogens have a good lipophilicity. Character is required for antibacterial action.

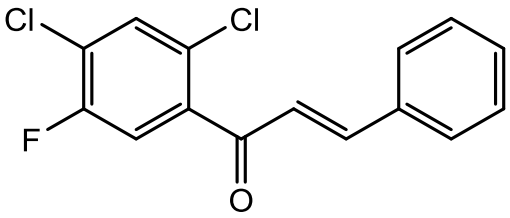

Figure 7. 3-aryl-1-(2, 4-dichloro-5-fluorophenyl)-2-propen-1-ones.

ii. Anticancer activity

Certain chalcones natural and synthetic, have been shown to have antioxidant properties and to be effective against tumor cells by preventing the generation of superoxide and peroxidation of lipids [29]. Millepachine (Figure 8(a)) is obtained from Millet-tia pachycarpa and is reported to be anticancer chalcone. Glycyrrhiza inflata is the source of Licochalcone A (Figure 8 (b)), a further anticancer chalcone that is shown cytotoxic to B16 melanoma and L1210 leukemia cells [30]. A novel class of chalcone shown in (Figure 8(c)) that prolongs mice's survival has been suggested as an antimitotic agent. administered a leukemia vaccine (L1210) at dosages ranging from 2.65 to 5,000 mg/kg. Another naturally occurring chalcone is butein (shown in Figure 8 (d)), which can reduce the number of human malignancies, such as osteosarcoma, colon carcinoma, breast cancer, and In vitro hepatic stellate cells [31].

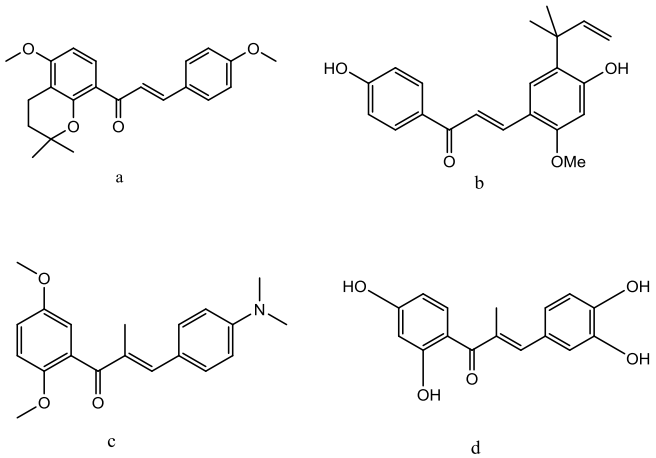

Figure 8. (a- Millepachine, b- Licochalcone A, c- Novel class of chalcone, d-Butein).

iii. Anti- HIV

A small number of well-known chalcones synthetic and natural are effective against HIV virus. Xanthohumol, a naturally occurring chalcone that was isolated from Hops Humulus, has anti-HIV characteristics [32]. Discovered a distinct ß-hydroxy

chalcone (Figure 9(a)) with strong anti-HIV properties that comes from the genus Desmos [33]. A different chalcone (Figure 9(b)) that was extracted from Maclura tinctoria (Moraceae) leaves showed inhibitory efficacy against AIDS-related infections Candida albicans and Cryptococcus neoformans. A synthetic chalcone (Figure 9(c)) with negligible anti-HIV efficacy was granted an HIV patent [21].

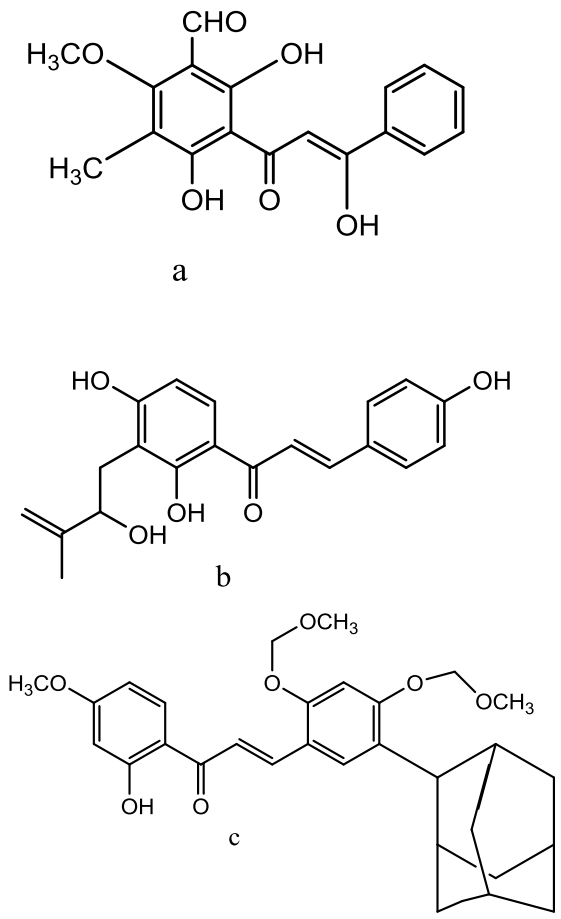

Figure 9. (a-Xanthohumol, b-Moraceae and c-Chalcone)

iv. Anti-Diabetic activity

Chalcones are significant medicines for the treatment of diabetes mellitus because they are effective inhibitors of aldose reductase, α-glucosidase, protein tyrosine phosphatase 1B (PTP1B), peroxisome proliferator-activated receptors-γ (PPAR), and dipeptidyl peptidase-4 (DPP4). Glycyrrhiza inflata yielded isoliquiritigenin (Figure 1(a)), echinatin (Figure 1(b)), licochalcone A (9), lichochalcone C (Figure 1(c)) and lichochalcone E (Figure 1(d)) [34]. Its synthetic derivatives, known as PTP1B, are reported to be essential in the treatment of type II diabetes and obesity because they function as a negative regulator of the insulin and leptin signaling pathway. Abyssinone-VI-4-O-methyl ether (Figure 11(e)) [35], a new chalcone, was extracted from the root bark of Erythrina mildbraedii and had strong anti-diabetic properties. PTP1B inhibition revealed novel sulfonamide chalcones (Figure11 (f-m)) as a potent α-glucosidase enzyme inhibitor [36].

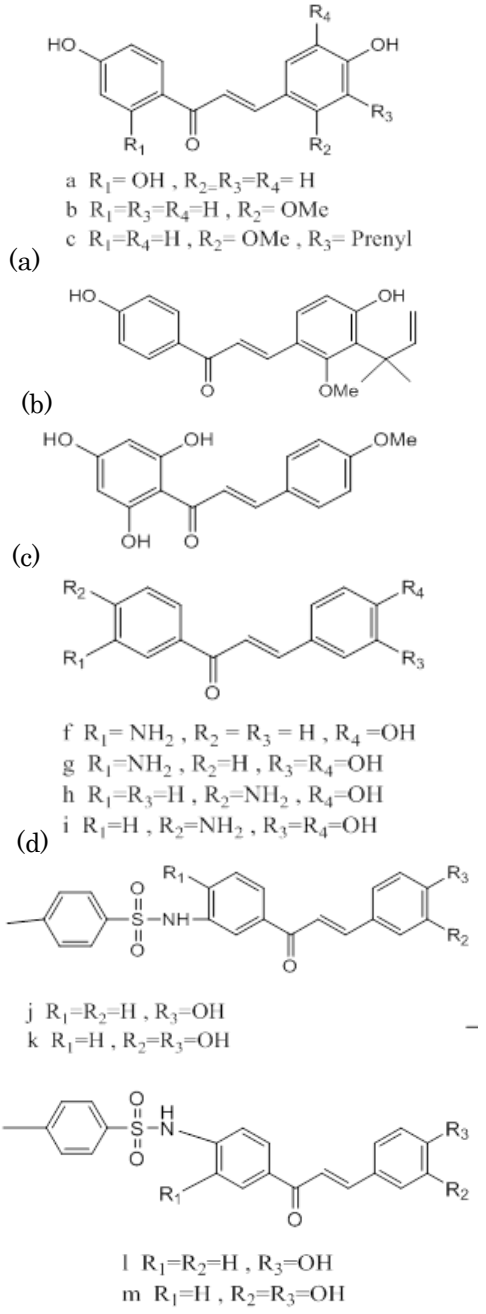

Figure 10. (a-Iso-liquiritigenin, b- Echinatin, c-Lichochalcone C, d-Lichochalcone E, e-Abys-sinone-VI-4-O-methyl ether and f- m-Sulfonamide chalcones).

v. Anti-inflammatory activity

A well-known organic compound called naringenin-chalcone (Figure 11(a)) has anti-inflammatory properties by preventing the generation of cytokines, which are agents that promote inflammation [37]. Another significant natural chalcone that has strong anti-inflammatory properties is iso liquiritigenin (Figure 11(b)) from Nepalese propolis [38] and butein (Figure 11(c)) from Rhus vernicifua. These compounds prevent LPS-induced COX-2 and iNOS production [39]. Revealed a decreased chalcone (Figure 11(d)), which was identified as an anti-inflammatory agent by preventing the generation of NO in mice microphage-like cell lines that were triggered by LPS and INF-γ. Another synthetic heterochalcone (Figure 11(e)), which is utilized to treat anti-inflammatory conditions, has been described as a strong cytokine inhibitor [40].

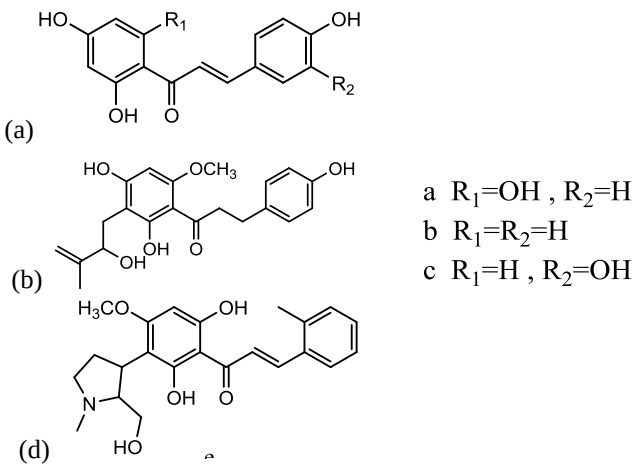

Figure 11. (a-Naringenin- chalcone, b-Iso liquiritigenin, c- Butein, d-Reduced chalcone and e-Heterochalcone).

vi. Anti-leishmanial activity

Licochalcone A (Figure 8(b)), was utilized as antiparasitic, to treat a variety of symptoms related to abdominal spasms. After being separated from the roots of licorice (Glycyrrhiza eurycarpa, Leguminosae) [41]. kanzonol C (Figure 12(a)) exhibited potent antileishmanial activity. Another significant chalcone identified from Crotolaria rosmosissima is crotaramosmin (Figure 12(b)) which shows strong antileishmanial activity [42]. The antileishmanial activity of a dihydrochalcone (Figure 12(c)) was negligible. created a novel family of dihydro pyrimidine derivatives, and the compound (Figure 12(d)) showed antileishmanial activity against promastigotes of Leishmania major and L. donovani, respectively [43].

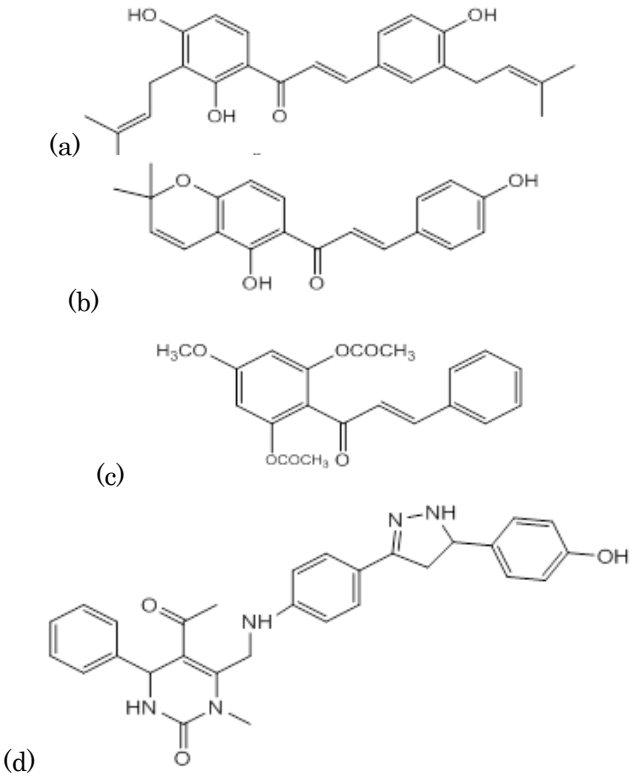

Figure 12. (a-Kanzonol C, b- Crotaramosmin, c-Dihydro-chalcone and d-Dihydro Pyrimidine derivates).

vii. Antioxidant activity

Free radicals that are produced by the human body during metabolism may be able to damage biomolecules including DNA, proteins, and lipids, leading to several diseases linked to oxidative damage, including cancer and non-inflammatory tumors, digestive ulcers, rheumatoid arthritis and aging [44]. Northeastern China's traditional medicine uses a penta-oxygenated chalcone (Figure 13(a)) that was isolated from Glycyrrhiza uralensis (Leguminosae) and has strong DPPH radical activity. One other chalcone is cedrelipronone (Figure 13(b)) [45]. From Cedrelopsis grevei fruit and seed extracts (Ptaeroxylaceae) shown potent superoxide scavenging capabilities. Isolated from the bark of Maclura tinctoria (Moraceae), prenylated chalcone glycoside (Figure 13(c)) showed radical scavenging efficacy in various antioxidant principles [46]. produced an allylated chalcones (Figure 13(d-f)) that, by suppressing free radicals, demonstrated better antioxidant activity than non-allylated chalcones [47].

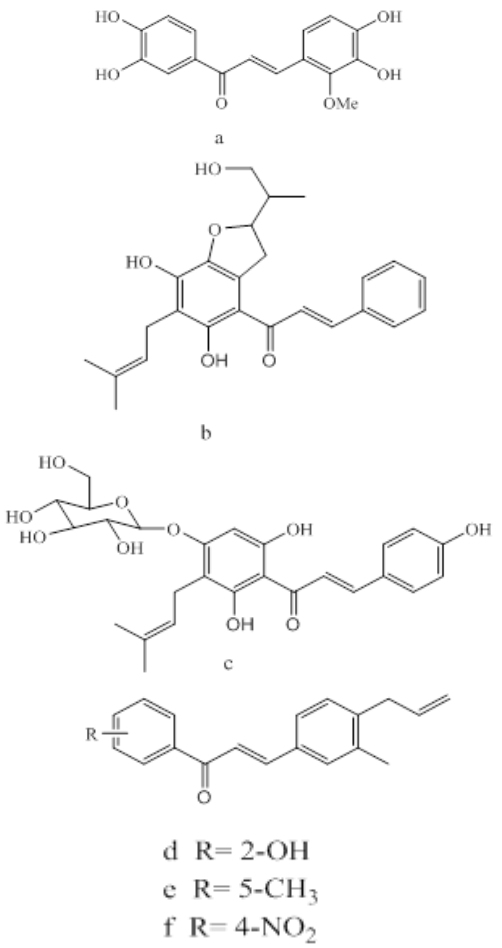

Figure 13. (a) Penta-oxygenated chalcone, (b) Cedredipronone, (c) Prenylated chalcone glycoside, (d-f) Allylated chalcones.

viii. Anti-tuberculosis activity

Promising antituberculosis action was demonstrated by nardoaristolone A (Figure 14(a)), a new terpenoid chalcone with a unique structure that was isolated from Nardostachys chinansis. There have been reports of the antitubercular properties of fluorine-substituted synthetic chalcone (Figure 14(b)) against the Mycobacterium TB strain [21].

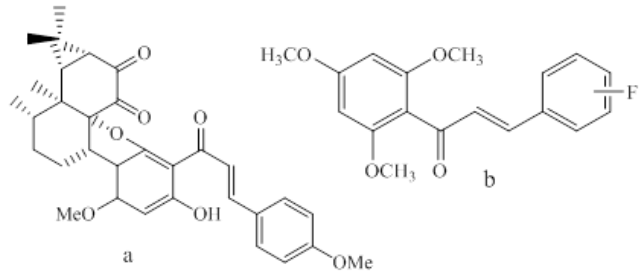

Figure 14. (a) Nardoaristolone A (b) Fluorine-substituted synthetic chalcone.

ix. Anti-viral activity

Citrus fruits contain a compound called naringenin-chalcone (Figure 11(a)), which has been shown to have antiviral qualities [48]. Myrigalone G (Figure 15(a)) is a naturally occurring chalcone that has been isolated from Leptospermum recurvum (Myrtaceae) and has demonstrated antiviral action against the herpes simplex virus. The two antiviral chalones that were isolated from Iryantheria megistophulla [49], iryantherin K and L (Figure 15 (b, c)) demonstrated substantial inhibition against the potato virus and mild inhibition against acetylcholinesterase. It is extremely uncommon for compounds (Figure 15 (a, c)) to arise in nature as C-benzylated conjugate diastereoisomers of dihydrochalcone-lignan [50].

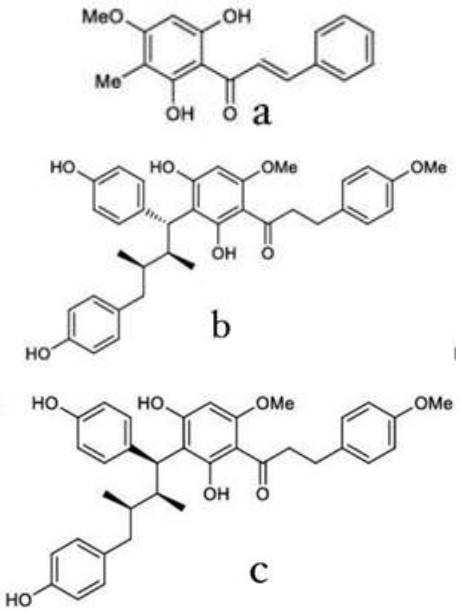

Figure 15. (a) Myrigalone G, (b) Iryantherin K, (c) Iryantherin L.

x. Neuroprotective activity

Alzheimer's disease is the most common metabolic problem affecting people globally and is a neurodegenerative disorder caused by the aggregation of beta-amyloid peptides. Currently, neurodegenerative disorders are treated with memantine inhibitors, such acetylcholinesterase inhibitors and butyrylcholinesterase inhibitors (AChE, BuChE). Synthetic scaffold thienylchalcone (Figure 16 (a)) functions as a strong transglutaminase inhibitor and shows promise in the management or prophylaxis of Alzheimer's disease [51]. Additionally, certain nitro-substituted chalcones can suppress the activity of the catechol-O-methyltransferase enzyme and are helpful in the

treatment of neurological conditions such as Parkinson's symptoms [52]. Synthetic chalcones, as reported in functions (Figure 16(b,c)), showed strong inhibition against cathepsin B and ε-calpain, suggesting potential benefits for treating Alzheimer's-related conditions [53]. A coumarin-chalcone hybrid (Figure 16 (d)) has been identified as a strong AChE inhibitor in an additional attempt, and it may be helpful in the treatment of neurodegenerative disease [54].

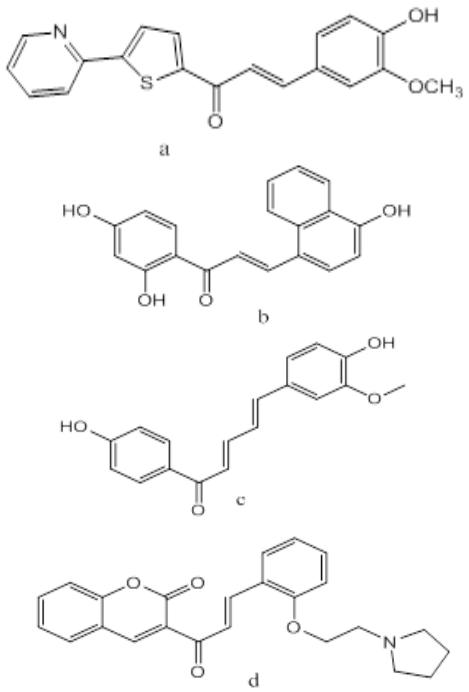

Figure 16. (a- Thienyl chalcone, b and c – Strong inhibition chalcones, d- Coumarin chalcone hybrid).

ix. Antiulcer activity

Kanzonol C (Figure 12 (a)) is a substance that has both synthetic and natural sources. Strong antiulcer action is demonstrated by chalcone, a synthetic derivative [55]. Prenylated chalcones like sophoradin (Figure 17 (a)) are found in nature, and their derivatives have been shown to have antiulcer properties [56]. The most potent antiulcer efficacy was demonstrated by synthetic compounds of sophoradin as shown in (Figure 17 (b, c and d)).

4- Complexation of chalcone with metal ion

It has been possible to create complexes of Co (II), Ni (II), Cu (II), Zn (II), and Cd (II) with substituted chalcones .and structurally studied [57]. In general, Schiff derivatives of chalcones are chosen for complexation with metal ions to improve its biological activities.

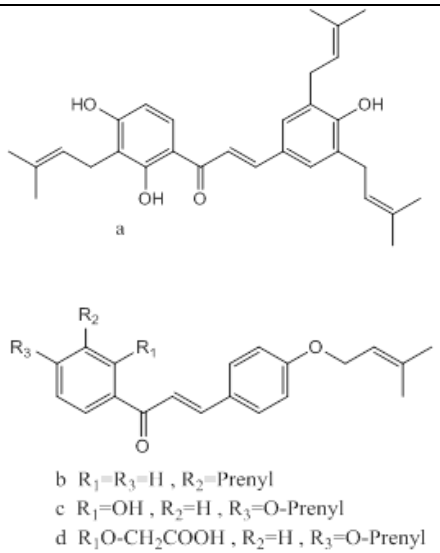

Figure 17. (a-Sophoradin, (b, c and d)-Synthetic analogues of sophoradin).

5. Conclusions

In conclusion, this study focuses on new compounds that have been reported to have both synthetic and natural origins and show great potential for use. This thorough overview also covers the biosynthesis of chalcones, their structural relevance as fluorescent materials, several synthetic methods for preparing them, medicinal uses, and studies on the structure–activity link. The fact that the chalcones have α, ß-unsaturated carbonyl system and a favored template that readily permits structural modifications is an intriguing observation. Because of this, scientists are very interested in modifying the skeleton of chalcones to create new and innovative materials with a variety of uses. Chalcone, then, is a novel scaffold that is crucial to the process of developing new drugs.

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