Synthesis and Medicinal Significance of Chalcones- A Review

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ABSTRACT :

Chalcone is an aromatic ketone that forms a central core for a variety of important biological compounds, which are collectively known as chalcones. They possess different activities like antibacterial, antifungal, anti-inflammatory and anti tumor etc depending on the substitution made on them.

Chalcones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α, β-unsaturated carbonyl system.These are abundant in edible plants and are considered to be precursors of flavonoids and isoflavonoids. Chalcones possess conjugated double bonds and a completely delocalized Π-electron system on both benzene rings. Molecules possessing such system have relatively low redox potentials and have a greater probability of undergoing electron transfer reactions. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial, anti-inflammatory, analgesic, anti platelet, anti ulcerative, anti malarial, anticancer, antiviral, anti leishmanial, antioxidant, anti tubercular, anti hyperglycemic, immunomodulatory, inhibition of chemical mediators release, inhibition of leukotriene B4, inhibition of tyrosinase and inhibition of aldose reductase activities. The presence of a reactive alpha, beta -unsatutated keto function in chalcones is found to be responsible for their antimicrobial activity. In this paper through reviewing different biological significance of chalcones and their derivatives have been reported along with their chemistry and of synthesis.

Synthetically or chemically chalcones are synthesized by two reactions:

a) Aldol condensation and

b) Claisen Schmidt condensation.

But here is a focus on chalcones synthesized by Claisen Schmidt condensation which involves the condensation between an aromatic aldehyde or ketone with an aliphatic ketone or aldehyde catalysed by the presence of dilute alkali or acid to form alpha beta unsaturated compound.

Keywords: Chalcone, Synthesis, Aldol condensation, Claisen Schmidt condensation, Biological activity.

INTRODUCTION:

The term "chalcone" is a generic term used to describe compounds with the 1,3-diphenylprop-2-en-1-one framework (Figure 1). Chalcones are naturally occurring compounds found in various plant species like *Angelica, Glycyrrhiza, Humulus* and *Scutellaria*, which are widely used as traditional folk remedies. Chalcones are intermediates in the biosynthesis of flavonoids, which are substances widespread in plants and with an array of biological activities. These are abundant in edible plants and are considered to be precursors of flavonoids and isoflavonoids. Chalcones are also intermediates in the Auwers synthesis of flavones. Chalcone (and related compounds "chalconoids") is an aromatic ketone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones. They show antibacterial, antimicrobial, antifungal, antitumor and anti-inflammatory properties. Methyl hydroxychalcone found in cinnamon, was thought to be insulin mimetic, improving insulin response of diabetics. It has since been determined that a flavonoid is responsible for the insulin-like biological activity[1,2].

Chemically these are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α,β-unsaturated carbonyl system. It could be considered that their true importance is extended in two branches. The biological activity associated with them, including anti-inflammatory, antimitotic, anti-leishmanial, anti-invasive, anti-tuberculosis, anti-fungal, anti-malarial, anti-tumor, and anti-oxidant properties; as well as their recognized synthetic utility in the preparation of pharmacologically-interesting heterocyclic systems like pyrazolines, which have also been largely studied owing to their pharmacological activities, which includes anti-tumor anti-inflammatory, anti-parasitary, anti-depressive, anticonvulsant, antimicrobial, antinociceptives and nitric oxide synthase inhibitors, associated with diseases such as Alzheimer, Huntington, and inflammatory arthritis[3].

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Conflict of interest: Authors reported none

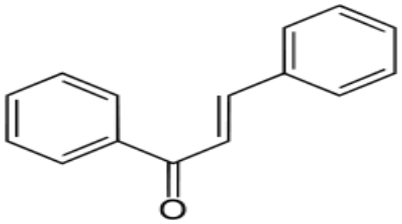


Fig 1: Chalcone

Natural chalcone from Ashitaba angel of herb[4,5,6]:

Herb Name: Angelica Keiskei Koidzmi, **Common Name**: Ashitaba (Indonesia), **Source**: Jawa Timur & Nusa Tenggara Barat, Indonesia.

Ashitaba (Angelica Keiskei Koidzmi) discovered in Japan on Hachi Jo Island (Longevity Island), is an Asian Herb belonging to the same genus as Angelica Sinensis (Chinese Angelica or Dong Quai) "Angelica" comes from the Latin name for angel and was given to this herb because of its godly effects, namely its extra ordinary ability to slow the aging process, for which ashitaba is now attracting more and more attention from the scientific community. This herb has been used in Traditional Chinese Medicine for 2,000 years to replenish energy by supplying the blood with vital nutrients and promoting circulation. The oldest written record of the medicinal value of ashitaba appears in a Chinese book first published in the Ming Dynasty written by Dr. Lee (1518-1593). Ashitaba is a species of the celery family. Its stems have a thick yellow juice containing chalcones which is unique to this strain of angelica (Angelica Keiskei Koidzmi).

Chalcone are rarely found anywhere in the natural world but are the key factor in ashitaba (Angelica Keiskei Koidzmi). Research has shown that the unique properties of ashitaba are at least partly due to these remarkable compounds. The chalcones that are in ashitaba are known as Xanthoangelol, Xanthoangelol-E and 4-Hydrooxyderricin and were discovered by Dr. Kimie Baba (MD, Osaka University of Pharmacy). These organic compounds are flavonoids and they give the plant its characteristic yellow sap. This differentiates ashitaba from all other strains of angelica. The antioxidant activity of flavonoids is due to their molecular structure, and these structural characteristics of certain flavonoids found in ashitaba confersurprisingly potent antioxidant activity exceeding that of red wine, green tea, or soy. The Ashitaba stem contains the thick, sticky-yellow juice, which is not found in other celery plants. This yellow pigment element in Ashitaba is neither flower pigment norcarotene, but rather two kinds of CHALCONE conductors, named "Xanthoangelol" and "4-Hydroxyderricin". While the Ashitaba produced on Hachi Jo Island is rich in these two conductors, almost little or no such substances are found in other Ashitaba plants produced outside of the island.

Fig 2: Ashitaba angel of herb

SYNTHESIS OF CHALCONES[7,8,9,10]:

Chalcones can be prepared by any two condensation reactions namely:

1. Claisen Schmidt condensation
2. Aldol condensation

Both of this reaction results in the condensation of aromatic aldehyde or ketone with an aliphatic ketone or aldehyde to give a condensed product known as chalcone.

1. Claisen Schmidt condensation-

Claisen Schmidt condensation involve condensation of aldehyde and ketone catalysed by an acid or a base followed by dehydration to yield chalcone as follows:

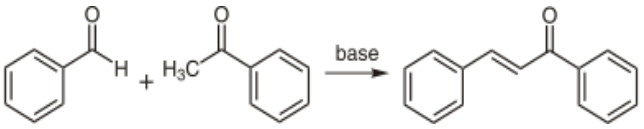
$C_6H_5CO\text{-}CH\ H_2 + O{=}CHC_6H_5 \rightarrow C_6H_5CO\text{-}CH{=}CHC_6H_5$

Acetophenone Benzaldehyde Benzalacetophenone

Fig 3: Claisen Schmidt condensation reaction

2. Aldol condensation reaction method:

The starting material for this reaction is acetophenone and benzaldehyde. First acetophenone is treated with a base like KOH which convert it into more active form, its enolate form. It will then react with benzaldehyde to form intermediate. The intermediate will then lose water molecule by heat to form chalcone.



Benzaldehyde Acetophenone Chalcone

Fig 4: Aldol condensation reaction

MEDICINAL SIGNIFICANCE OF CHALCONES:

As said earlier that chalcones are the precursor of flavanoid synthesis and known to possess a wide range of activities like Antiviral, Anti inflammatory, Antimicrobial, Antibacterial, Analgesics, Antileishmanial, Antiplatelet, Anticancer, antioxidant and some of these are explained as follows:

1. **Antiviral Activity of Substituted Chalcones and their respective Cu(ii), Ni(ii) and Zn(ii) Complexes[11,12]:**

Complexes of Cu(II), Ni(II) and Zn(II) with of 3-(phenyl)-1-(2'- hydroxynaphthyl) – 2 – propen – 1 – one (PHPO) , 3 - (4-chlorophenyl) - 1- (2'- hydroxynaphthyl)–2–propen – 1 –one (CPHPO), 3 - (4 -methoxyphenyl) -1-(2'- hydroxynapthyl)-2-propen-1-one(MPHPO),3 - (3,4-dimethoxyphenyl) –1-(2'- hydroxynaphthyl) – 2 - propen – 1 – one (DMPHPO) have been found to be having antiviral action.

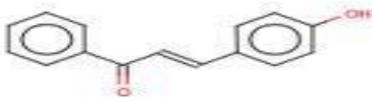


Fig 5: o-hydroxychalcone

2. **Anti-Inflammatory Activity of Chalcones and Related Mannich bases[13,14,15]:**

Published results have revealed that conversion of various acyclic conjugated styryl ketones e.g. chalcones, into the corresponding Mannich bases was often accompanied by increased bioactivity both *in vitro* and *in vivo*[20] Won *et al.*,[21,22] synthesized (*E*)-1(2hydroxyphenyl)-3(thiophen-

2-yl)prop-2-en-1-one, a chalcone derivative (Fig. **6**) which was tested *in vitro* for its inhibitory activity on chemical mediators released from mast cells, neutrophils, macrophages and microglial cells with satisfactory results.

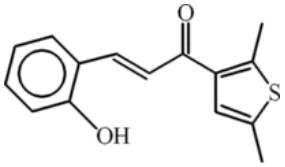


Fig 6: 1-(2-Hydroxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one.

3. Study of the Anti-inflammatory and analgesic effects of novel rigid benzofuran-3, 4- dihydroxy chalcone[16,17,18]:

It is reported that dihydroxy chalcones have analgesic and anti-inflammatory effects. Study of the structure activity relationship (SAR) shows that benzofuran-3-one derivatives may be more effective in this respect.

In this study, (Z)-2-(3,4-dihydroxybenzylidene)-5-methoxybenzofuran-3(2*H*)-one (compound **5**) synthesized and its analgesic and anti-inflammatory effects were evaluated by formalin, carrageenan and hot- Plate methods in mice.

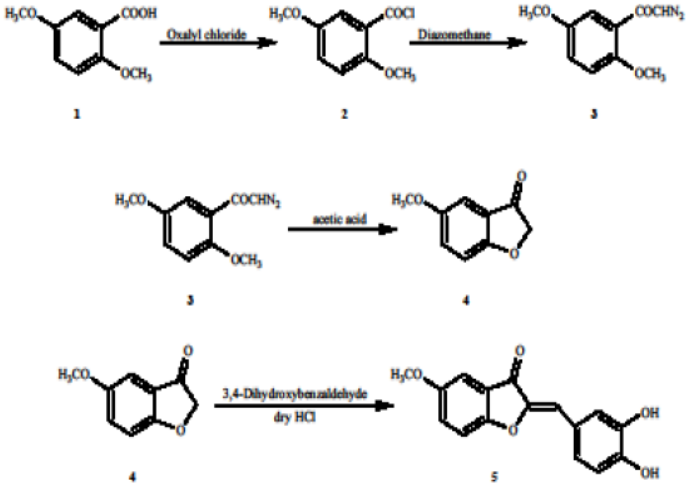


Fig 7: Synthesis of (Z)-2-(3,4-dihydroxybenzylidene)-5-methoxybenzofuran-3(2*H*)-one-(compound 5)

4.Antimicrobial Activity of Some Novel Chalcones of 2-Hydroxy -1-Acetonapthone and 3-Acetyl Coumarin[19,20,21]:

Chalcones either natural or synthetic are known to exhibit various biological activities. They have been reported to possess antioxidant[27-30], antimalarial[31], antileishmanial[32], antiinflammatory[33], antitumor[34] and antibacterial activity[35].The presence of a reactive alpha, beta unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity, which may be altered depending on the type and position of substituent on the aromatic rings. In the present communication we report the reaction of 2-hydroxy-1- acetonaphthone as well as 3-acetyl coumarin with different aromatic and heterocyclic aldehydes to form Chalcones.

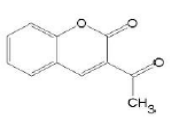


Fig 8: 3-acetyl coumarin

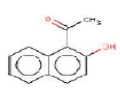


Fig 9: 2-hydroxy aceto naphthone

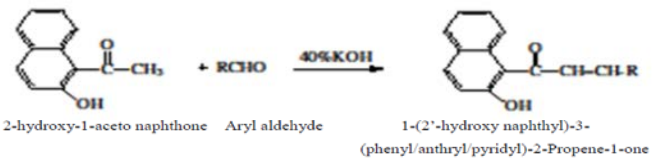


Fig 10: Reaction of 2-hydroxy-1-aceto naphthone with aryl aldehyde

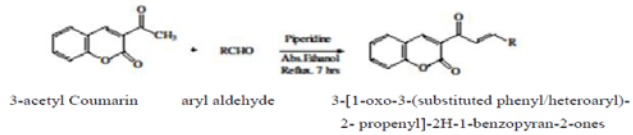


Fig 11: Reaction of 3-acetyl coumarin with aryl aldehyde

5. Antimicrobial Activity of Some Chalcone Derivatives[22,23]:

In an effort to develop antimicrobial agents, a series of chalcones prepared by Claisen-Schmidt condensation of appropriate acetophenones with appropriate aromatic aldehydes in the presence of aqueous solution of potassium hydroxide and ethanol at room temperature were found to be having antibacterial and antifungal activities.

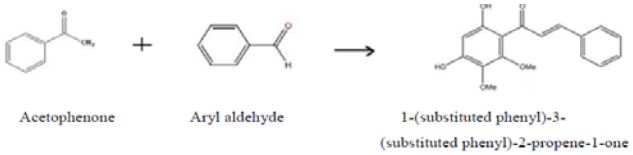


Fig 12: Reaction of Acetophenone with Aryl aldehyde

6. Some new Chalcones and Flavanones having 2-chloro-8-methoxyquinolinyl moiety[24,25,26]:

Chalcones, analogs of 1,3-diarylprop-2-en-1- one, form a wide class of compounds containing two aromatic rings bound with vinyl ketone fragment. They are useful in synthesis of various heterocyclic compounds.

Chalcones present great interest as compounds exhibiting antimalarial, antibactrial, antifibrogenic, anticancer, antitrichomonal, antiinflammatory, antileishmanial, cytotoxic and antitrypanosoma cruzi activities. While the flavonoid compounds are a group of natural products found in fruits, vegetables, nuts, seeds and flowers as well as in teas and are important constituent of human diet. They have been demonstrated to possess antioxidant, antihypertensive, antiallergic, antinocicepative, trypsin inhibitors, plant growth regulator, antibacterial and antifungal activities.

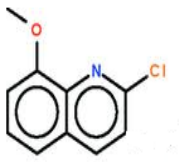


Fig 13: 2-chloro-8-methoxyquinolinyl moiety

7. Novel quinolinyl chalcones as antibacterial agents[27,28,29]:

Biological activity of some quinolinyl chalcones and pyrimidines chalcones are a class of privileged structures that have a wide range of biological properties. Chalcones are also reported as anticancer agents, and antimalarial agents. Quinoline-based fused heterocyclic systems are found as potential anticancer agents and have antimalarial activities. Pyrimidine derivatives form a component in a number of useful drugs and are associated with many biological pharmaceutical and therapeutical activities. Condensed pyrimidine derivatives have been reported as analgesics, antiviral

and as anti-inflammatory agents, antibacterial and anti-tubaculustic agent, diaryl pyrimidine (DAPY'S) appears to be the more effective against wild type and various mutant strains of HIV-1.

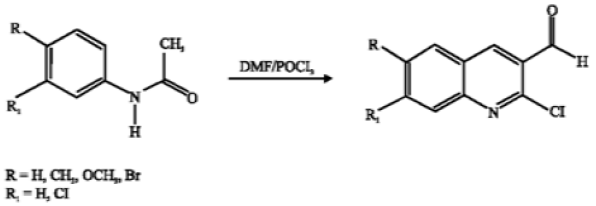


Fig. 14: Synthesis of quinoline carbaldehydes

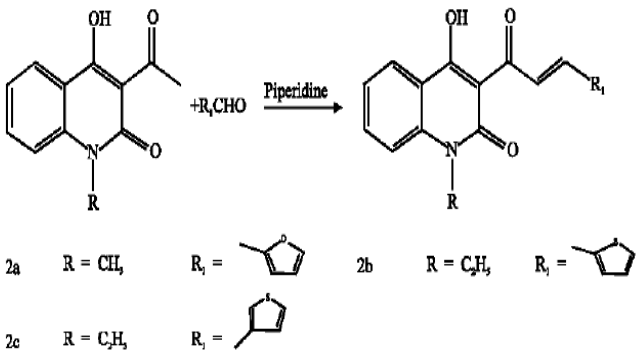


Fig 15 : Synthesis of Novel Quinolinyl Chalcone derivatives

8. Chalcone with antihepatotoxic activity[4,30,31]:

Some of the compounds namely 2-hydroxy- 4-methoxy-3',4'-(2"- hydroxy methyl-1", 4" - dioxano) chalcone and 2-hydroxy- 4, 6 - dimethoxy-3',4'-(2"- hydroxy methyl-1", 4"- dioxano) chalcone showed a potent antihepatotoxic activity, whereas other compounds exhibited moderate activity with respect to standard drug silybon-70.

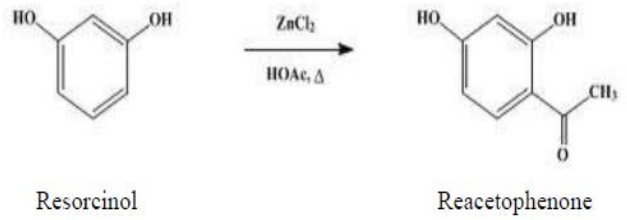


Fig 16: Reacetophenone synthesis

9. Chalcone with hypoglycemic activity[3, 32,33]:

The aryloxypropanolamines were first described as β3-AR agonists. Chalcones with proper substitution have recently been isolated from *Broussonetia papyrifera* known to selectively inhibit enzymes like protein tyrosine phosphatase 1B (PTP1B) and aldose reductase. Their antioxidant property attracted to explore hybrid structures as antihyperglycemic agents, because oxidative stress also plays an important role in diabetic patients leading to vascular complications. 3, 4-Dimethoxy compound displayed significant antihyperglycemic effect. Mono methoxy series showed bloodglucose lowering activity. Compounds vicinally deoxygenated as dimethoxy and methylenedioxy substitution showed the best antihyperglycemic activity when compared to the corresponding monomethoxy compounds.

Compounds containing propanolamine chain at *para* position showed significant activity as compared to *meta* and *ortho* substituted compounds.

10. Chalcone with Antioxidants activity[1,34,35]:

Antioxidants are the agents, which can inhibit or delay the oxidation of an oxidisable substrate in a chain reaction. Chalcones belongs to the largest class of plant secondary metabolites. Which, in many cases, serve in plant defense mechanisms to counteract reactive oxygen species (ROS) in order to survive and prevent molecular damage and damage by microorganisms, insects, and herbivores. They are known to possess antioxidant character at various extents. The antioxidant activity of natural compounds like chalconoids is related to a number of different mechanisms such as free radical scavenging, hydrogen donation singlet oxygen quenching, metal ion chelation and acting as a substrate for free radicals such as superoxide and hydroxide.

Compound code	2'-hydroxychalcones Series
A	1-[2'-hydroxyphenyl]-3-phenyl-2-propen-1-one
B	1-[2'-hydroxyphenyl]-3-[4'-methoxyphenyl]-2-propen-1-one
C	1-[2'-hydroxyphenyl]-3-[4-chlorophenyl]-2-propen-1-one
D	1-[2'-hydroxyphenyl]-3-[2-chlorophenyl]-2-propen-1-one
E	1-[2'-hydroxyphenyl]-3-[2-bromophenyl]-2-propen-1-one
F	1-[2'-hydroxyphenyl]-3-[3, 4, 5-trimethoxyphenyl]-2-propen-1-one

Fig 17: 2-Hydroxy chalcone series

Compound code	3-hydroxyflavones Series
1	1-[2'-Hydroxyphenyl]-3-[2-Carboxyphenyl]-2-propen one
2	3-Hydroxy-4'-Methoxyflavone
3	3-Hydroxy-4'-Chloroflavone
4	3-Hydroxy-3', 4', 5'-Trimethoxyflavone
5	3-Hydroxy-2'-chloroflavone

Fig 18: 3-hydroxyflavones series

11. Chalcone with potent antiplatelet activity[36]:

In an effort to continually develop potent antiplatelet agents with vasorelaxing and antiinflammatory actions, a novel series of antiinflammatory chalcones was continually screened to evaluate their antiplatelet and vasorelaxing effects. Their structure–activity relationships and mode of action were discussed and characterized. A novel series of antiinflammatory chalcones was studied on antiplatelet effect in rabbit washed platelets and human platelet-rich plasma (PRP) and vasorelaxing effect in rat thoracic aorta. Arachidonic acid-induced platelet aggregation was potently inhibited by almost all the chalcone derivatives and also had a potent inhibitory effect on cyclooxygenase.

The selective chalcones tested in human PRP significantly inhibited secondary aggregation induced by adrenaline. In rat thoracic aorta, most of chalcones at high concentration significantly depressed the contractions induced by Ca^{2+} (1.9 mM) in high K^+ (80 mM) medium and the phasic and tonic contractions caused by norepinephrine (3 μM). In the rat thoracic aorta, the phenylephrine- and high K^+-induced $^{45}Ca^{2+}$ influx were both inhibited by a selective chalcone derivative.

These results indicate that the antiplatelet actions of chalcones are mainly mediated through the suppression of cyclooxygenase activity and reduced thromboxane formation and their inhibitory effects on the contractile response caused by high K^+ and norepinephrine in rat thoracic aorta are mainly due to inhibition of Ca^{2+} influx through both voltage-dependent and receptor-operated Ca^{2+} channels.

12. The antileishmanial activity of novel oxygenated chalcones[37]:

Licochalcone A, an oxygenated chalcone, has antileishmanial and antimalarial activities, and alters the ultrastructure and function of the mitochondria of *Leishmania* spp. parasites. The study investigates the antileishmanial activity and the mechanism of action of a group of new oxygenated chalcones. The tested oxygenated chalcones inhibited the in-vitro growth of *Leishmania major* promastigotes and *Leishmania donovani* amastigotes. Treatment of hamsters infected with *L.donovani* with intraperitoneal administration of two oxygenated chalcones resulted in a significant reduction of parasite load in the liver and the spleen compared with untreated control animals. The oxygenated chalcones also inhibited the respiration of the parasite and the activity of mitochondrial dehydrogenases. Electron microscopic studies illustrated that they altered the ultrastructure of the mitochondria of *L. major* promastigote. The data clearly indicate that this group of oxygenated chalcones has a strong antileishmanial activity and might be developed into a new antileishmanial drug. The antileishmanial activity of oxygenated chalcones might be the result of interference with function of the parasite mitochondria.

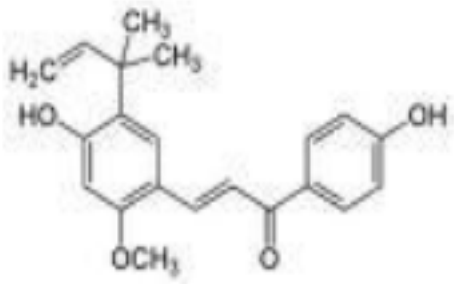


Fig 19: Licochalcone-A

13. Chalcone with Immunosuppressive activity[38,39]:

The immunosuppressive activity of licochalcone A was noted during investigations of its antileishmanial activity, when low concentrations of licochalcone A were found to inhibit proliferation of phytohemmagglutinin A-stimulated lymphocytes. It was subsequently shown that the structural requirements for antileishmanial and lymphocyte-suppressing activities were different and it would be possible to design chalcones with selective activity.

The immune suppressing potential of chalcones is not altogether an undesirable feature. Immunosuppression reduces graft- related symptoms and is beneficial for certain autoimmune diseases. Licochalcone A and some synthetic analogues have been reported to inhibit generalized lymphocyte proliferation that was not restricted to any particular T lymphocyte subset. The same study reported the chalcones to cause down regulation of pro- and anti-inflammatory cytokine production from monocytes as well as to interfere with the production but not release of tumor necrosis factor – α (TNF-α). The substitution pattern on the chalcone skeleton is important to this end but no details were revealed in the report.

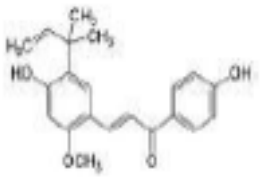


Fig 20: Licochalcone-A

14. A Boronic-Chalcone Derivative Exhibits Potent Anticancer Activity[40]:

Chalcones and their derivatives have been shown to have potent anticancer activity. However, the exact mechanisms of cytotoxic activity remain to be established. In this study a series of boronic chalcones were evaluated for anticancer activity and mechanisms of action. Among them 3,5-bis-(4-boronic acid-benzylidene)-1-methyl-piperidin-4-one (AM114) exhibited most potent growth inhibitory activity with IC_{50} values of 1.5 and 0.6 μM in 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay and colony formation assay, respectively. The cytotoxic activity of AM114 was shown to be associated with the accumulation of p53 and p21 proteins and induction of apoptosis. Mechanistic studies showed that AM114 treatment inhibited the chymotrypsin-like activity of the 20S proteasome in vitro, leading to a significant accumulation of ubiquitinated p53 and other cellular proteins in whole cells.

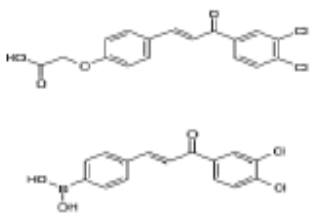


Fig 21 : Structure of boronic chalcone

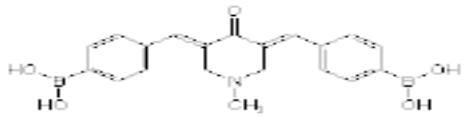
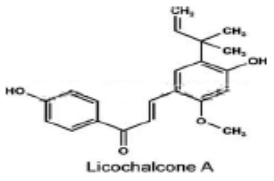


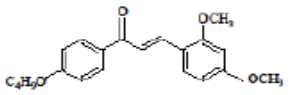
Fig 22 : Structure of 3,5-bis-(4-boronic acid-benzylidene)-1-methyl-piperidin-4-one (AM114)

15. Antimalarial chalcones[41]:

Gan Cao as a plant is a perennial herb used in traditional Chinese medicine as a sweetening agent and as a tonic to improve the immune response of the body. The isolate from the Gan Cao root (licochalcone A) was found to inhibit the *in vitro* growth of chloroquine resistant and chloroquine sensitive *P. falciparum* and protected mice from lethal infections of *P. yoelii*. 68 However, it was also observed to inhibit phytohemmagglutinin A-induced proliferation of human lymphocytes in vitro, which are indicative of immunosuppressive effects. This led to the synthesis of other oxygenated chalcones, of which 2,4-dimethoxy-4'-butoxychalcone was found to be outstanding. This compound is comparable to licochalcone A in terms of antimalarial activity but is significantly less toxic than licochalcone A against human leukocytes.

Fig 23 : Gan cao plant





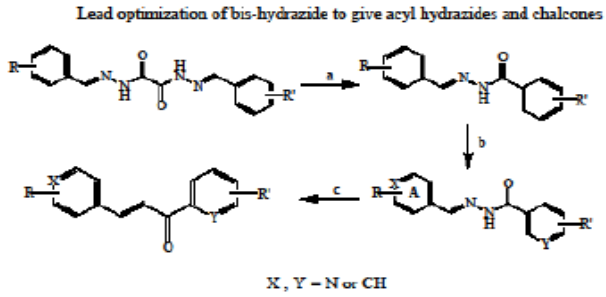


Fig 24 : Structures of chalcone with antimalarial action

16. Biological evaluation of some heterocyclic derivatives of Chalcones[42]:

Some novel heterocyclic derivatives such as Thazines, Oxazines, Isoxazoles and Pyrazoles of chalcone were characterized for their Anti inflammatory, Anti Bacterial and Anti fungal activities.

Chalcones are prepared by condensing Aryl ketones with aromatic aldehydes in presence of suitable condensing agents. They undergo a variety of chemical reactions and are found useful in synthesis of variety of heterocyclic compounds. Chalcones have been used as intermediate for the preparations of compounds having therapeutic value. Literature review reveals that chalcone derivatives exhibit diverse pharmacological activities such as potential cytotoxic agents, antimicrobial agents, antiviral, antiinflammatory, anesthetics, mydriatics etc. Based on the above observation it is worthwhile to prepare newer compounds for their antimicrobial and antiinflammatory activities.

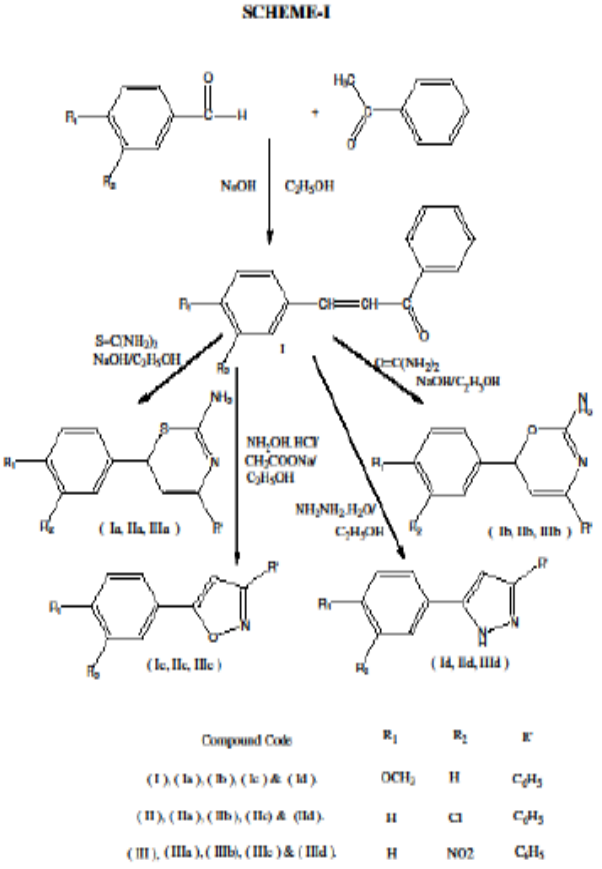


Fig 25 : Chalcone with various substituents

CONCLUSION:

There is a continuous methodology for the synthesis of variety of chalcone derivatives with increase in the number of diseases. Since the chalcone back bone is found be very effective and potent against a list of diseases. They place a wide range of medicinal activity in today's life. They are the precursors in flavanoid synthesis found in every edible plant but difficult to isolate. Initially they were found in natural source like ashitaba herb also know as angel of herb because of wide range of biological significance like purifies blood, strengthens immune system, monitors cholesterol level, regulates blood pressure, suppresses acid secretion, prevents thrombus, suppresses cytophy, antibacterial, prevents cancer, and promotes metabolism etc. and from that it is thought to synthesize chalcone meant for a specific disease. Chalcone are rarely found anywhere in the natural world but are the key factor in ashitaba. This has created the need for synthesizing chalcones synthetically i.e from aromatic aldehyde and aliphatic ketone by claisen Schmidt condensation. The various activities of chalcone includes antimicrobial, anti-inflammatory, analgesic, antiplatelet, antiulcerative, antimalarial, anticancer, antiviral, antileishmanial, antioxidant, antitubercular, antihyperglycemic, immunomodulatory, inhibition of chemical mediators release, inhibition of leukotriene B4, inhibition of tyrosinase and inhibition of aldose reductase activities.

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