

University of Tikrit
Collage of science
Department of Chemistry



A scientific essay:-

Review on Chalcone

Papered by PhD student

Mohammed.K. Mukhlif

INTRODUCTION

Chalcone compounds are unsaturated ketone involving the reactive keto-ethylenic group ($\text{CO}-\text{CH}=\text{CH}-$) which gave colored compounds due to the presence ($\text{CO}-\text{CH}=\text{CH}$) the chromophore group:

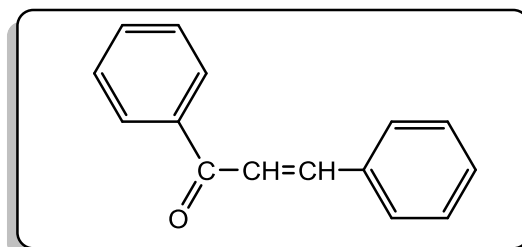


Fig. 1. Formula of Chalcone.

Kostanecki and Tambor named “Chalcones” which have other names like (benzalacetophenone or benzylidene acetophenone). Chalcones are starting material to synthesize many cyclic derivatives ⁽¹⁾ like pyrazolines isoxazoles. Chalcone compounds have conjugated double bonds with absolute delocalization with two aromatic rings ⁽²⁾ that possess an (p-electron system). Chalcones are naturally abundant in medical plants which including vegetables, fruits and natural foods.⁽¹⁾

Preparation of Chalcone Compounds⁽¹⁾:

1. Claisen-Schmidt Reaction

This method for the preparation of chalcones is the classical Claisen-Schmidt summarized by condensation of ketone with aldehyde in the presence of aqueous alkaline bases or in the presence of alcoholic alkali:

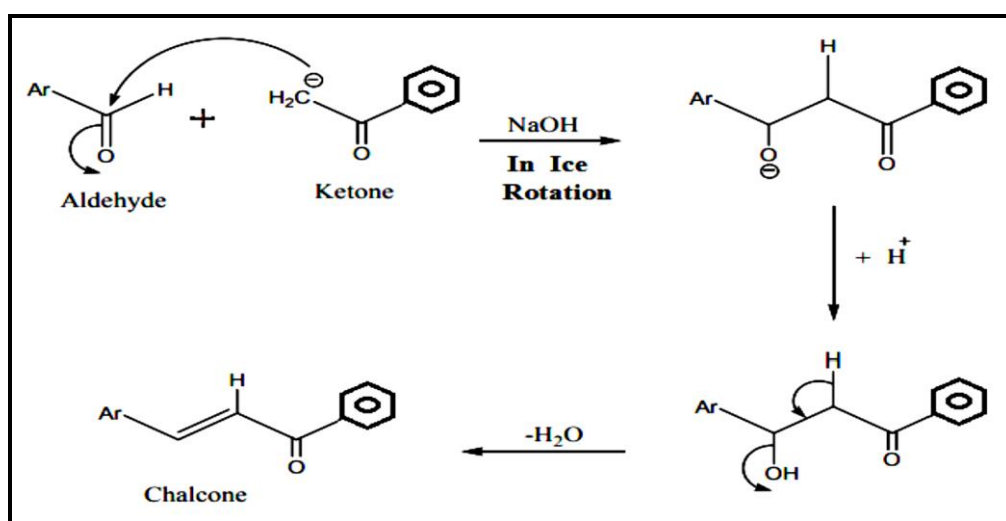


Fig. 2. Mechanism of Chalcone synthesis.

Synthesis of chalcones by an aqueous solution of an appropriate concentration of (30, 40, 50 or 70) %. Hydrochloric acid or Alkali as condensing agent:

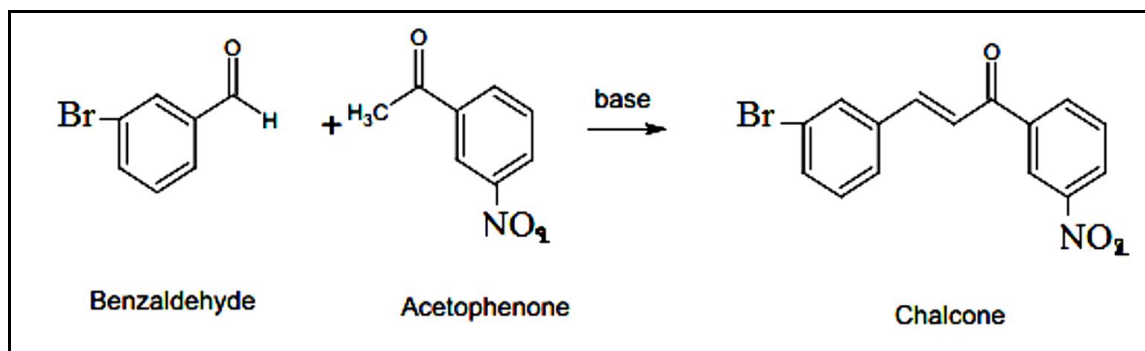


Fig. 3. Formula of Chalcone.

2. By Suzuki Reaction⁽²⁾ :

Chalcones can be prepared by Suzuki through a reaction between phenyl boronic acid and cinnamyl chloride or benzoyl chloride and phenyl vinyl boronic acid.

3. Reaction of ketones and aromatic aldehyde (Aldole Reaction)⁽³⁾

prepared chalcones in basic medium by reaction of ketones with aromatic aldehyde in ethanol:

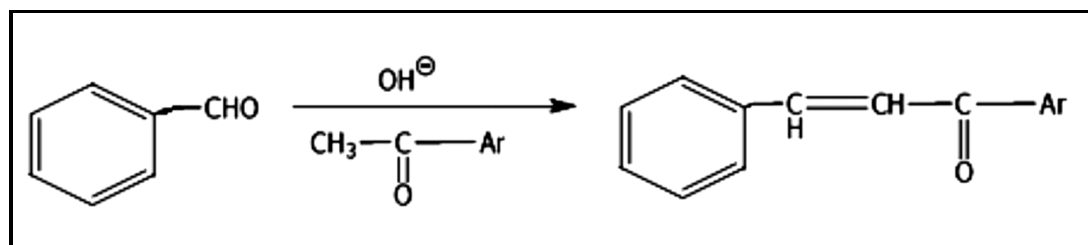


Fig. 4. Preparation of Aldole –Chalcone.

4. New Method⁽⁴⁾

Prepared chalcone by reaction through condensation between aldehyde and ketone with pyridine or piperidine as catalyst , which gave high product:

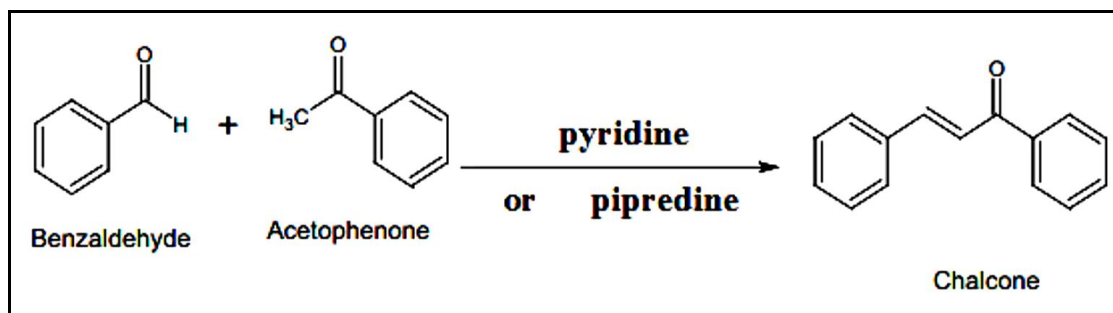


Fig. 5. Synthesis of High Product of Chalcone

5. By Fridel –Graft Reaction⁽¹⁾ :

By reaction with aluminium chloride AlCl_3 :

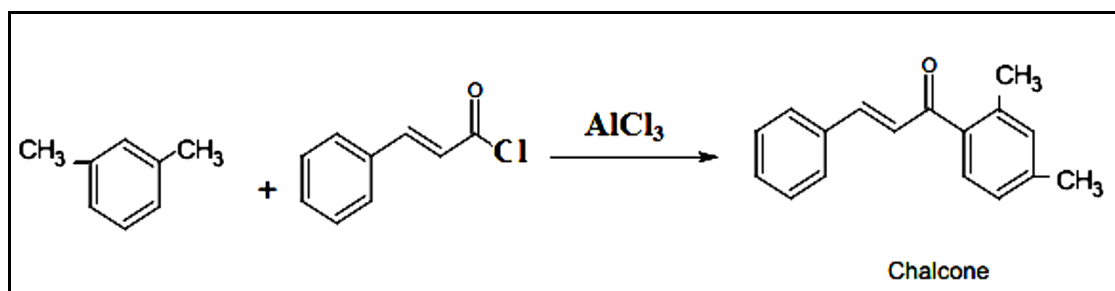


Fig. 6. Synthesis of High Product of Chalcone.

Reactions of Chalcone⁽⁵⁾ :

Chalcone compounds can be used to preparation types of heterocyclic rings via ring closure reactions.

1. Cyclization of Chalcone with di nucleophile

By cyclization of chalcone with diamine compounds:

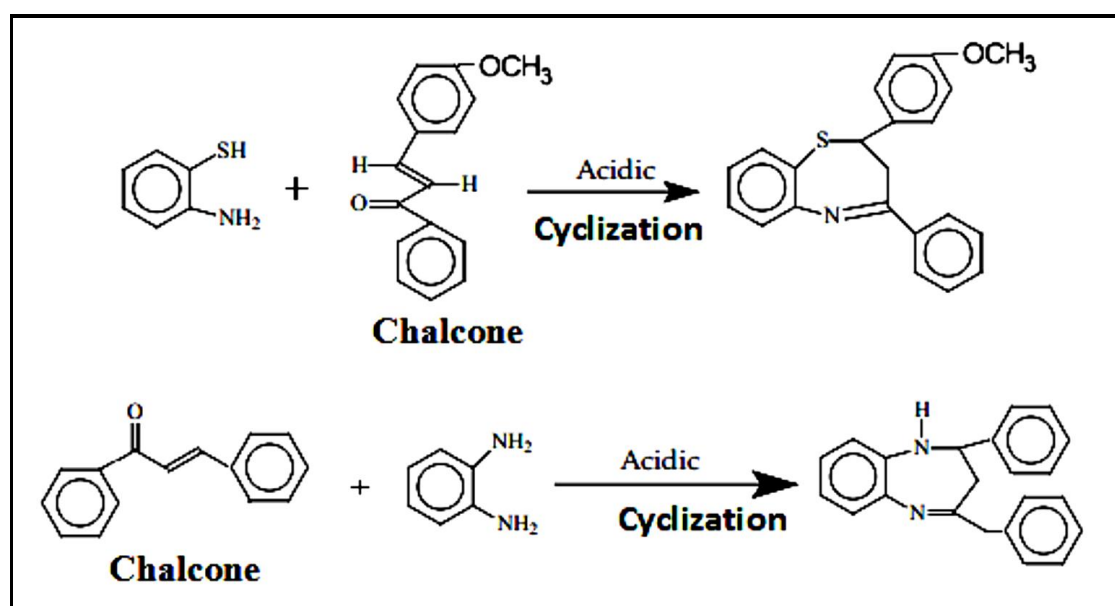


Fig. 7. Synthesis of Seven Membered Ring From Chalcone.

2. Cyclization of Chalcone with di amine compounds⁽⁶⁾

Cyclic compounds were prepared via cyclization reaction to give pyrimidine derivatives :

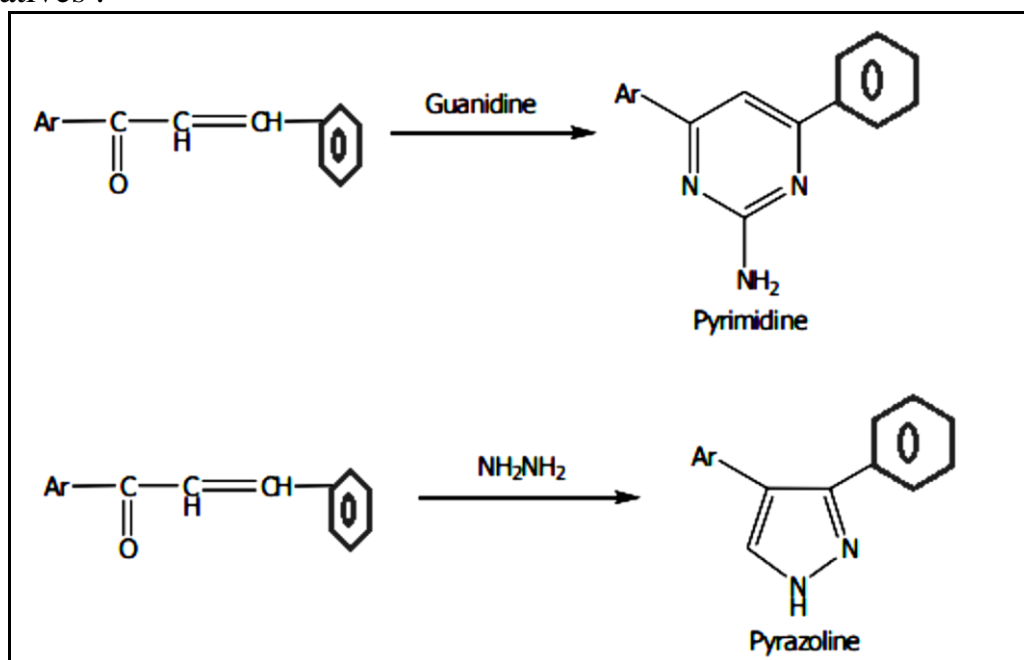


Fig. 8. Synthesis of Five Membered Ring.

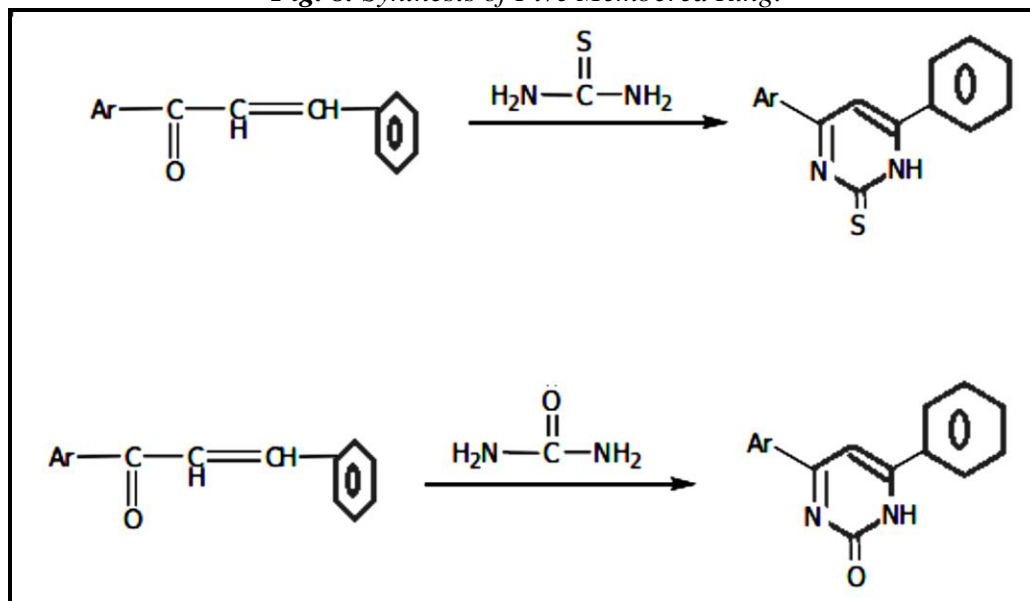


Fig. 9. Synthesis of Six Membered Ring.

Medical Applications of Chalcone⁽⁷⁾

Chalcones and their derivatives have been great interest through recent years. Many research studies have been published, and chalcones continue to yield new drug investigations. Researchers have explored new procedures for the formation of chalcone derivatives, which have abstracted an array of medicinal and biological effects. These chalcone derivatives have appeared important antiviral effect:

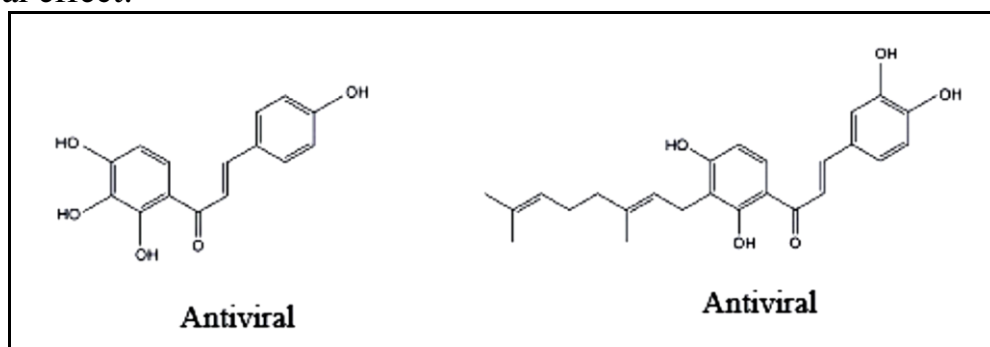


Fig. 10. Synthesis of Antiviral Compounds.

While other chalcone derivatives showed greater antibacterial activity, Several chalcone derivatives screened as antioxidant:

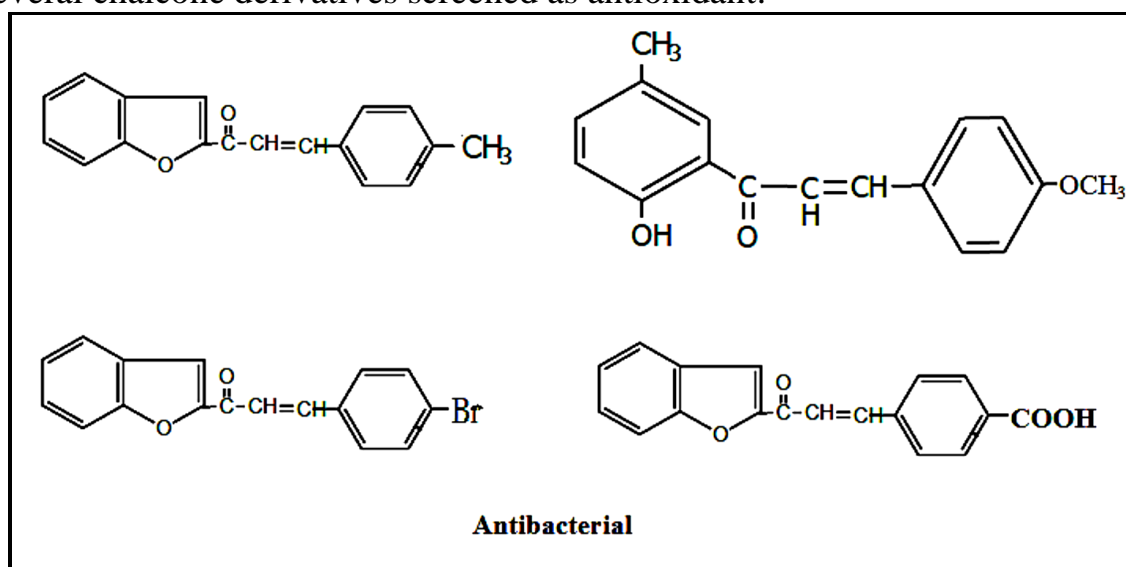


Fig. 11. Synthesis of Antibacterial Compounds.

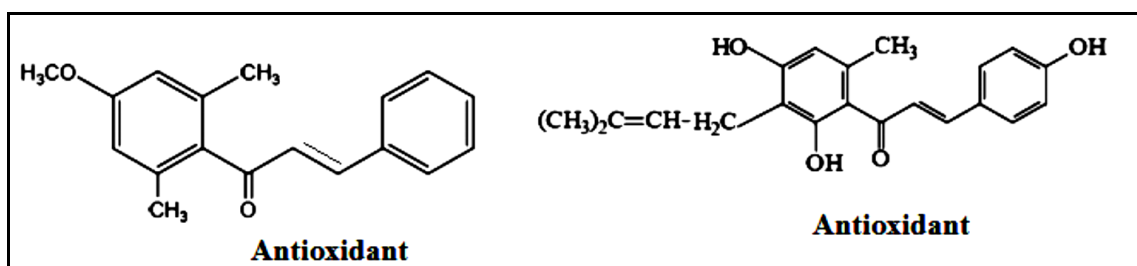


Fig. 12. Synthesis of Antioxidant Compounds.

Antitubercular activity⁽⁸⁾

But some of chalcone derivatives tested them for anti-inflammatory, analgesic and Antitubercular activities:

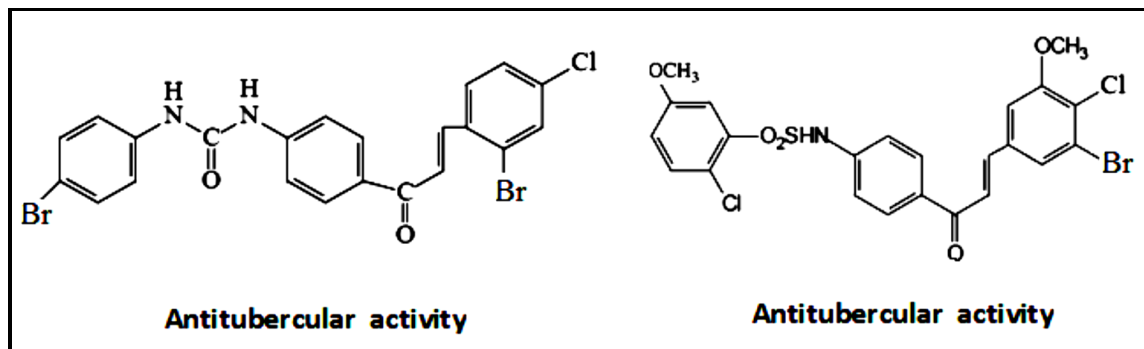


Fig. 13. Synthesis of Antitubercular Compounds.

Anticancer activity⁽⁹⁾

Chalcone derivatives have been studied as anticancer which showed good results in studies as a drugs:

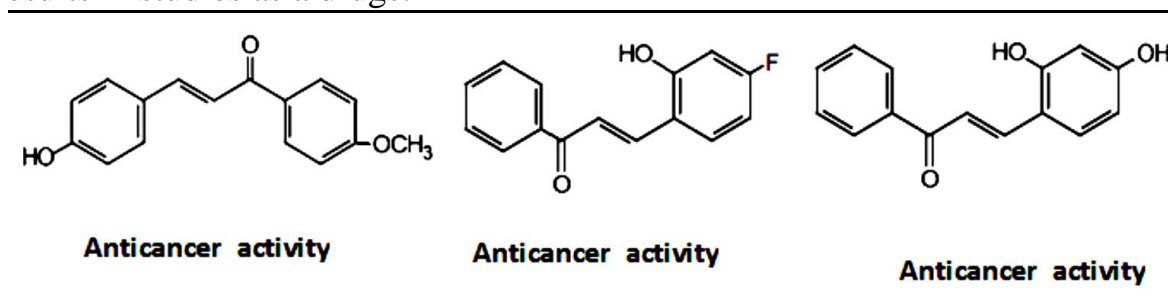


Fig. 14. Synthesis of Anticancer Compounds.

Anti-HIV activity⁽¹⁰⁾

Chalcone derivatives have been screened as anti- HIV which indicated to good results in studies as a drugs:

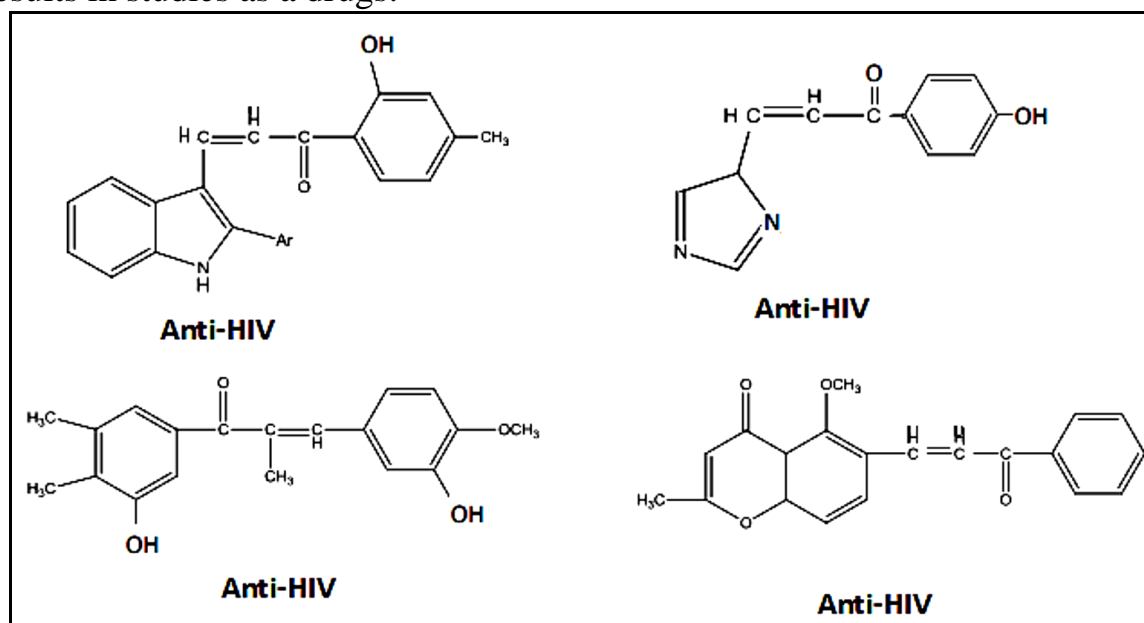


Fig. 15. Synthesis of Anti-Hiv Compounds.

Several chalcone derivatives appeared a broad spectrum of pharmaceutical and biological effectiveness like antimicrobial, antifungal, antimalarial, antiviral, anti-inflammatory, antileishmanial anti-tumor and anticancer properties . The alpha , beta -unsaturated carbonyl system in chalcones makes them biologically active:

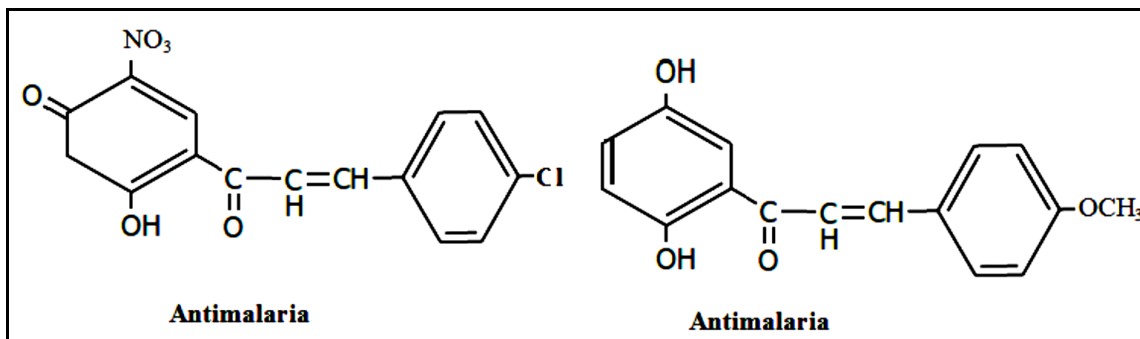


Fig. 16. Synthesis of Antimalaria Compounds.

Other researchers prepared bis-(chalcone group):

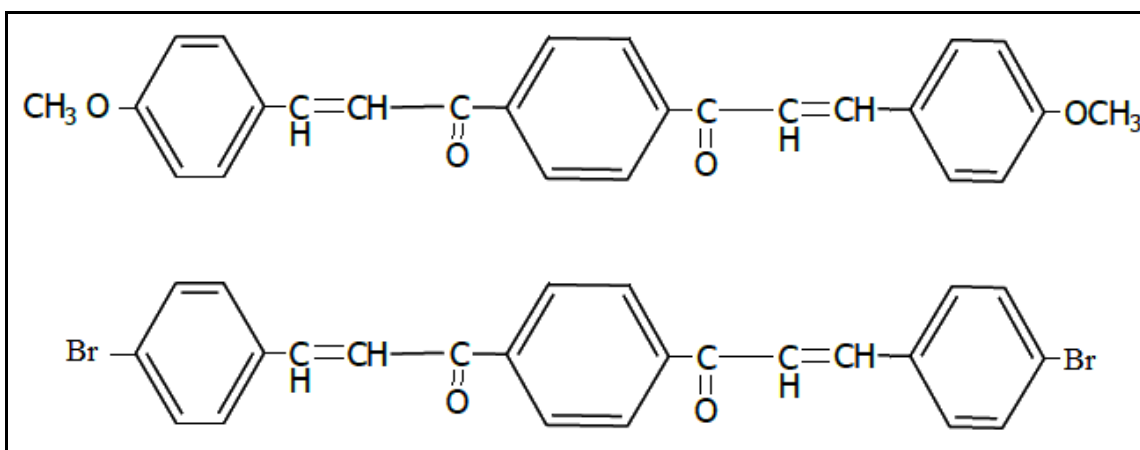


Fig. 17. Synthesis of Bis-Chalcone Groups.

Some of them screened as antifungal compound due to (chalcone group with heterocycle) in same compound:

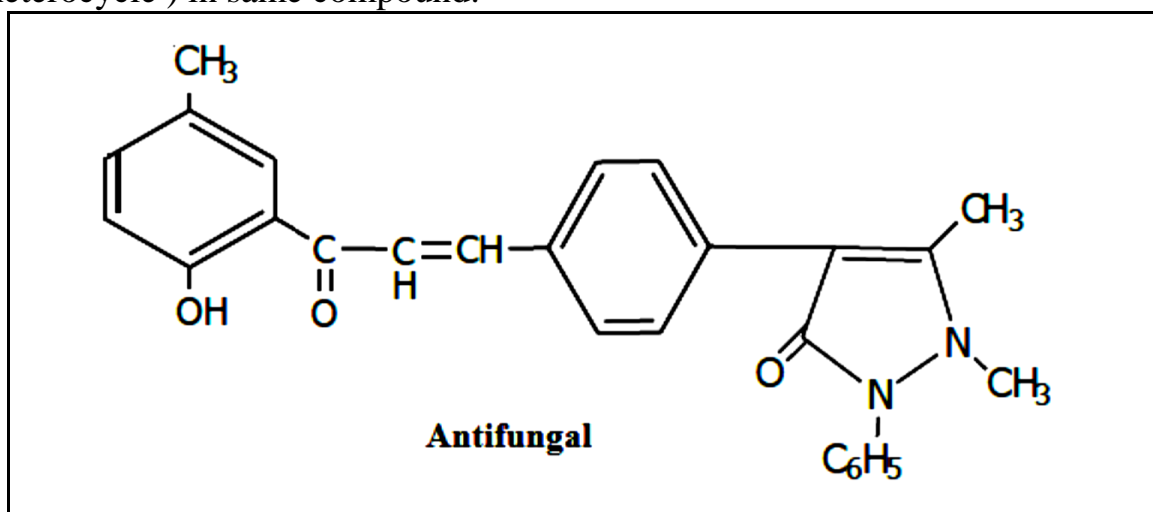
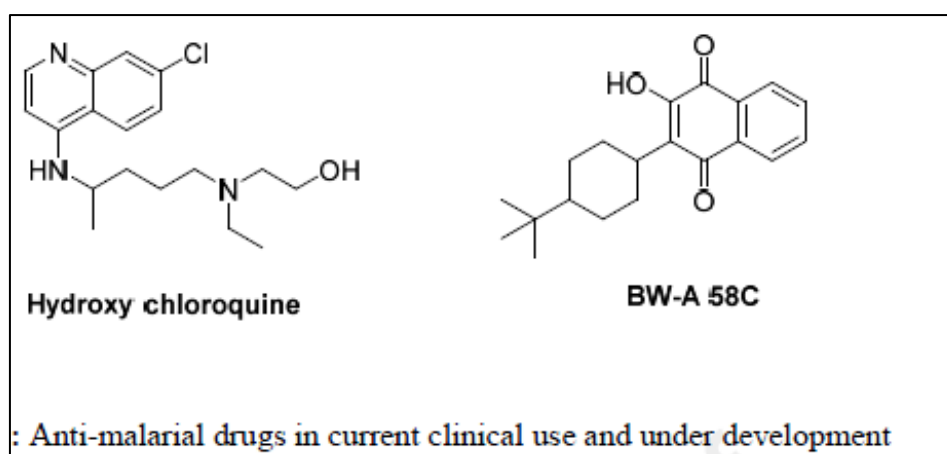


Fig. 18. Synthesis of Antifungal Compounds.

Chalcone derivatives have a great applications in chemical fields like coordination chemistry as a ligands , medical chemistry as antibacterial , anticancer , antifungal , in analytical chemistry as a reagents, and other uses.

Chalcone hybrids and their antimalarial activity:

Malaria ruins a genuine all inclusive wellbeing danger and tremendous financial difficulty to infection endemic countries. Although expanded consideration and new affirmation to the suppression of malaria, which has been caused for over a million of deaths consistently, and drug protection from each new chemotherapeutic methodology has grown, particularly in *Plasmodium falciparum*, the parasite causing practically all malaria-related deaths ⁽¹¹⁾. It is the most common and deadliest disease that occurred in 2015 with 429,000 deaths from 212 million medical cases, particularly pregnant women's and children's, according to 2016 data of World Health Organization (WHO)⁽¹²⁾. Human Malaria, a critical scrounging syndrome transmitted by mosquitoes, is four types such as, *Plasmodium ovale*, *P. vivax*, *P. falciparum*, and *P. malariae*. Among them the first two are widespread and *Plasmodium falciparum* is more fatal species, mainly found in Africa ⁽¹¹⁾, accumulated in organ failures and brain capillaries foremost to coma then finally becomes death. There is an upward proof that the fatality of *Plasmodium vivax* has been miscalculated⁽¹³⁾. An established first-line antimalarial drugs for example, amodiaquine ,chloroquine and quinine:



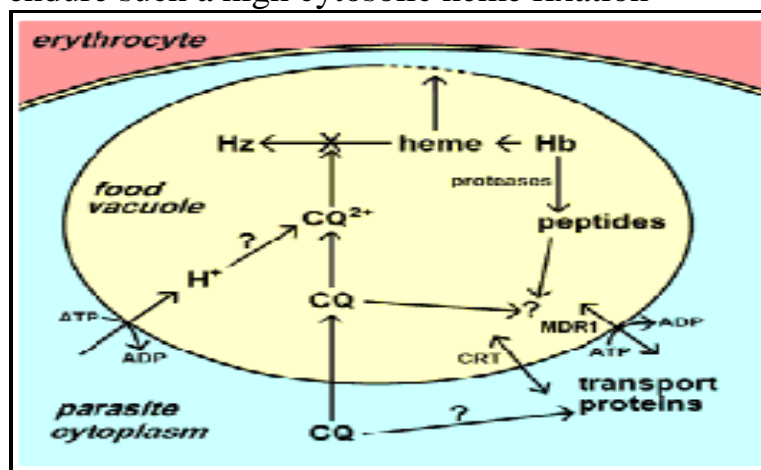
are regarded as a foundation for the chemotherapy of antimalarial for long time, which have vanished their efficiency and utility as antimalarial drug has also been restricted because of the rising *Plasmodium falciparum* drug resistance⁽¹¹⁾.. Malarial chemotherapy mainly involves the slaughter of asexual parasite and provides helpful therapy to improve its resistant system. Before the 2nd World War, chloroquine, quinine, pamaquine and also mepacrine were discovered. Then after, in 1940s proguanil, primaquine (7, PQ), in 1950s.

Chalcones are α, β -unsaturated carbonyl groups and vital flavonoid compounds derived from synthetic and nature products belongs to the family of flavonoid which remain an attraction among medicinal and synthetic chemistry scholars in 21st century because of their simple synthetic chemistry and a huge amount of replaceable hydrogen atoms to furnish a diverse structural compounds. Because of their simple synthetic procedure and plenty of in plants, these compounds have gained significant attention in the use of possible therapeutics ⁽¹¹⁾. Till date, a huge number of chalcones have been furnished, which contain numerous functional groups with a broad range of clinical and pharmaceutical applications such as antimicrobial⁽¹⁴⁻¹⁵⁾, antibacterial ⁽¹⁶⁾, anti-Alzheimer's⁽¹⁷⁻¹⁸⁾, antimalarial ⁽¹⁹⁾, anticancer⁽²⁰⁻²¹⁾, anti-inflammatory, antiprotozoal, anti-HIV⁽¹⁰⁾, antioxidant, antiulcer⁽²²⁾, α -glucosidase inhibitory activity, tyrosinase inhibitor and estrogenic activities and so on⁽¹¹⁾. Right now, we spread ongoing advancement in the utilization of chalcones as privileged scaffolds in the area of medicinal chemistry, and significant developments in malarial drug discovery since 2005.

Mechanism action of antimalarial activity^(11,23-24):

Small organic molecules such as nutrients and drugs enter cells by crossing the surface membrane, which is made of phospholipids, cholesterol and other bio organics arranged in a bilayer. Biological membranes are embedded with proteins that may function as receptors and solute transporters. Thus, biologically active molecules like nutrients and drugs may cross the film either by dissemination through the lipid bilayer divide or by utilization of a bearer or transporter protein. Antimalarials dominantly act by parts that hope to curb a few periods of the parasite's life cycle. The treatment plans to catch up on the parasite in two unmistakable habits. One of them is to encroach upon the schizogonic blood sort out obligated for the signs of the contamination, that is, to butcher the parasite during the formative cycle. The other is to use sedates that hinder the progression of gametocytes, in other words, to crush the parasite in the tissue example of the species *P. vivax* and *P. ovale*, meddling with the transmission of the parasite and avoiding falls away from the faith. A few drugs are open for achieving these destinations, Small organic molecules such as nutrients and drugs enter cells by crossing the surface membrane, which is made of phospholipids, cholesterol and other bio-organics arranged in a bilayer. Biological membranes are embedded with proteins that may function as receptors and solute transporters. Thus, biologically active molecules like nutrients and drugs may cross the film either by dissemination through the lipid bilayer divide or by utilization of a bearer or transporter protein. Antimalarials dominantly act by parts that hope to curb a few periods of the parasite's life cycle. The treatment plans to catch up on the parasite in two unmistakable habits. One of them is to encroach upon the schizogonic blood sort out obligated for the signs of the contamination, that is, to butcher the parasite during the

formative cycle. The other is to use sedates that hinder the progression of gametocytes, in other words, to crush the parasite in the tissue example of the species *P. vivax* and *P. ovale*, meddling with the transmission of the parasite and avoiding falls away from the faith. A few drugs are open for achieving these destinations, where each showing in light of a specific objective to curb the improvement of the parasite in the host. For example, chloroquine shows antimalarial property with various component of activity and which can be clarify by five diverse system of activity. Intestinal sickness parasites blend a huge assortment of proteins at various stages throughout their life cycle. The organic chemistry included is like that of other eukaryotic cells, As chloroquine treatment doesn't repress protein union in *P. berghei*, *P. lophurae* or *P. falciparum* trophozoites, it has been generally acknowledged that blocking protein blend doesn't identify with the antimalarial activity of this medication. In any case, it has as of late been accounted for that high chloroquine focuses diminish protein amalgamation in *P. falciparum* trophozoites around half and that ribosomes arranged from also treated cells are inadequate in blending proteins *in vitro*. It isn't known whether this outcome holds at fixations underneath 100 nM outside chloroquine. Surolia and Padmanaban, also found that cell free protein combination in trophozoite removes was invigorated by the expansion of heme. They suggested that as chloroquine ties heme with high liking and parasite protein amalgamation is animated by heme, at that point chloroquine could decrease protein union in the parasite by restricting heme. An issue with this component is that there is no proof that intestinal sickness protein combination in situ is heme subordinate. Additionally, the ideal heme fixation for animating protein amalgamation is adequate to cause lysis of confined *P. falciparum* trophozoites. It is accordingly improbable that the parasite could endure such a high cytosolic heme fixation



Chloroquine amasses in the food vacuole of the parasite. This gathering may include particle catching after protonation, explicit vehicle, as well as official to a receptor (model heme). The significant activity of chloroquine is to hinder the arrangement of hemozoin (Hz) from the heme discharged by the processing of hemoglobin (Hb).

REFERENCES

- 1- Aseel. M. Jawad, Mostafa N. Mohamed Salih, et al . Review on Chalcone (Preparation ,Reactions, Medical and Bio Applications). ***International Journal of Chemical Synthesis and Chemical Reactions.***; 5(1): 16–27p. **2019.**
- 2- Nagham Mahmood Aljamali .,"***The Various Preparation Methods in Synthetic Chemistry***" ., **1 Edt. ,Evincepub Publishing house, , ISBN :978-93-88277-82-2 , 2019 .**
- 3- Nagham Mahmood Aljamali .,"***Reactions and Mechanisms***".,**1 Edt., IJMRA Publication ,,, ISBN : 978-93-87176-25-6 , 2018**
- 4- Nagham Mahmood Aljamali , Intisar O Alfatlawi , "Synthesis of Sulfur Heterocyclic Compounds and Study of Expected Biological Activity" , ***Research J. Pharm. and Tech.***, 8(9),1225-1242 .,DOI: 10.5958/0974-360X.2015.00224.3 ,**2015.**
- 5- Mahapatra, Debarshi Kar; Bharti, Sanjay Kumar; Asati, Vivek "Chalcone Derivatives: Anti-inflammatory Potential and Molecular Targets Perspectives ". ***Current Topics in Medicinal Chemistry.*** 17 (28): 3146–3169. **2017.**
- 6- Santos, Mariana B.; Pinhanelli, Vitor C.; Garcia, Mayara A.R.; Silva, Gabriel; Baek, Seung J.; França, Suzelei C.; Fachin, Ana L.; Marins, Mozart; Regasini, Luis O. "Antiproliferative and pro-apoptotic activities of 2'- and 4'-aminochalcones against tumor canine cells". ***European Journal of Medicinal Chemistry.*** 138: 884–889. **2017.**
- 7- Mieaad Mohamd , Nagham Mahmood Aljamali , Wassan Ala Shubber , Sabreen Ali Abdalrahman .," New Azomethine- Azo Heterocyclic Ligands Via Cyclization of Ester " ., ***Research J. Pharm. and Tech.*** 11, 6 , **2018 .**
- 8- Nagham Mahmood Aljamali .,"Synthesis and Chemical Identification of Macro Compounds of (Thiazol and Imidazol)".,***Research J. Pharm. and Tech.***, 8,1, 78-84., DOI : 10.5958/0974-360X.2015.00016.5 , **2015.**
- 9- P. Page, F. Gaggini and B. Laleu, "***Pyrazoline Dione Derivatives as NADPH Oxidase Inhibitors*** ", ***US Patent, 0172352 A1, 2012.***
- 10- A. V. Leovezijn, W. I. Iwema and A. Stoit, "***Arylsulfonyl Pyrazoline Carboxamide Derivatives as 5-HT6 Antagonists***", ***US Patent, 0011775A1, 2014.***
- 11- H.-L. Qin, Z.-W. Zhang, R. Lekkala, H. Alsulami, K.P. Rakesh, Chalcone hybrids as privileged scaffolds in antimalarial drug discovery: ***European***

Journal of Medicinal Chemistry doi:<https://doi.org/10.1016/j.ejmech.2020.112215>. 2020.

- 12- World Malaria Report, World Health Organization, 2016.
- 13- K.E. Battle, P.W. Gething, I.R.F. Elyazar, C.L. Moyes, M.E. Sinka, R.E. Howes, C.A. Guerra, R.N. Price, J.K. Baird, S.I. Hay, *in: R.P.S.I. Hay, J.K. Baird (Eds.), Advances in Parasitology, vol. 80, Academic Press, 1-111, 2012.*
- 14- P.S. Bhale, S.B. Dongare, U.B. Chanshetti, Synthesis and antimicrobial screening of chalcones containing imidazo[1,2-a] pyridine nucleus, *Res. J Chem. Sci.* 3 38-42, **2013**.
- 15- S.A. Khan, A.M. Asiri, Green synthesis, characterization and biological evaluation of novel chalcones as antibacterial agents, *Ara. J. Chem.* 10 S2890-S2895, **2017**.
- 16- Man Xu, Piye Wu, Fan Shen, Jiayou Ji, K.P. Rakesh, Chalcone derivatives and their antibacterial activities: Current development, *Bioorg. Chem.* 91, 103113. **2019**.
- 17- X. Zhang, K.P. Rakesh, S.N.A. Bukhari, M. Balakrishna, H.M. Manukumar, H.L. Qin, Multi-targetable chalcone analogs to treat deadly Alzheimer's disease Current view and upcoming advice, *Bioorg. Chem.* 80, 86-93. **2018**.
- 18- C. Zhao, K.P. Rakesh, L. Ravindar, W.Y. Fang, H.L. Qin, Pharmaceutical and medicinal significance of sulfur (SVI)-Containing motifs for drug discovery: A critical review, *Eur. J. Med. Chem.* 162, 679-734. 3009744916, **2019**.
- 19- B. Insuasty, J. Ramírez, D. Becerra, C. Echeverry, J. Quiroga, R. Abonia, S. M. Robledo, I.D. Velez, Y. Upegui, J.A. Munoz, V. Ospina, M. Nogueras, J. Cobo, An efficient synthesis of new caffeine-based chalcones, pyrazolines and pyrazolo[3,4-b][1,4]diazepines as potential antimalarial, antitrypanosomal and antileishmanial agents, *Eur. J. Med. Chem.* 93, 401-413. **2015**
- 20- B. Moku, L. Ravindar, K.P. Rakesh, H.L. Qin, The significance of N-methylpicolinamides in the development of anticancer therapeutics: synthesis and structure-activity relationship (SAR) studies, *Bioorg. Chem.* 86, 513-537. **2019**.

- 21- W.Y. Fang, L. Ravindar, K.P. Rakesh, H.M. Manukumar, C.S. Shantharam, Njud S. Alharbi, H.L. Qin, Synthetic approaches and pharmaceutical applications of chloro-containing molecules for drug discovery: A critical review, *Eur. J. Med. Chem.* 173, 117-153, **2019**.
- 22- K.V. Sashidhara, S.R. Avula, V. Mishra, G.R. Palnati, L.R. Singh, N. Singh, Y. S. Chhonker, P. Swami, R.S. Bhatta, G. Palit, Identification of quinolinechalcone hybrids as potential antiulcer agents, *Eur. J. Med. Chem.* 89, 638-653, **2015**.
- 23- K. Basore, Y. Cheng, A.K. Kushwaha, S.T. Nguyen, S.A. Desai, How do antimalarial drugs reach their intracellular targets? *Front. Pharmacol.* (6) 91. **2015**
- 24- C.S.L. Pinheiro, L.M. Feitosa, F.F. Dasilveira, N. Boechat, Current antimalarial therapies and advances in the development of semi-synthetic artemisinin derivatives, *An. Acad. Bras. Cienc.* 90 , 1251-1271. **2018**.