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Exploring the Pharmacological Significance of Chalcone Derivatives: A Review

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ABSTRACT

One of the world's most deadly diseases, cancer has a wide range of possible origins. For scientists and researchers, it can be difficult to identify new treatments or substitute medications as a means of battling cancer. Chalcones are phenolic chemicals that belong within the flavonoid category. They include one of the major categories of naturally occurring bioactive substances. Numerous chalcone derivatives have been created due to their potential anti-inflammatory, anti-cancer, antimicrobial, antioxidant, and antiparasitic, antidiabetic, antimalarial activities Some chalcones exist naturally as well as their distinctive chemical structural features. In reality, it is straightforward to manufacture the structural characteristics of chalcones from simple aromatic compounds, and it is convenient to execute structural alterations to produce functionalized chalcone derivatives. It has been found that many of these synthetic analogs have bioactivities that are comparable to those of their natural equivalents, but frequently with increased potency and lower toxicity. The purpose of this review article is to show how the creation of derivatives of chalcone using bioinspired principles can create a new chemical field that can be studied in the development of novel therapeutics. However, the attention continues to be on critically evaluating synthesized derivatives of chalcones for their bioactivities, relating to their interactions at the biomolecular level where applicable, and describing their potential mechanisms of action.

INTRODUCTION

Cancer is a collection of disorders characterized by abnormal cell proliferation and the ability to infiltrate or spread to other regions of the body. This differs from benign tumors, which do not spread(1). A lump, irregular bleeding, a persistent cough, unexplained weight loss, and a change in bowel habits are all potential signs and symptoms. While these symptoms may signal cancer, they could be caused by something else. Humans are affected by about 100 different types of cancer. Infections such as Helicobacter pylori(2), hepatitis B, hepatitis C, human papillomavirus infection, Epstein-Barr virus, and human immunodeficiency virus cause 15% of malignancies in underdeveloped countries (HIV). These variables influence a cell's genes, at least in part. Many genetic alterations are usually needed before cancer starts. Inherited genetic abnormalities are responsible for 5-10% of malignancies. Certain indications and symptoms, as well as screening tests, can detect cancer. It is then often studied further through medical imaging and confirmed through biopsy(3).

Lung cancer, prostate cancer(4), colorectal cancer, and stomach cancer are the most prevalent cancers in men. The most prevalent forms in females are cervical, colorectal, lung, and breast cancer(5), and ovarian cancer (PCOD)(6). In the annual total of new cancer cases, skin cancers other than melanoma would make up about 40% of the total. Except in Africa, where non-Hodgkin lymphoma is more prevalent, acute lymphoblastic leukemia and brain tumors are the most frequent cancers in children(7).

A cancer diagnosis in a child under the age of 15 occurred roughly 165,000 times in 2012. Age considerably raises one's cancer risk, and industrialized nations have higher rates of numerous malignancies. In most industrialized nations, cancer is a significant public health issue; yet, due to early detection and advancements in medical treatment, patient survival rates have improved considerably throughout the last three decades (8). The treatment with anticancer medications is beneficial for a significant number of cancer patients who get chemotherapy or chemoradiotherapy. Anticancer medications, however, have several toxic side effects with a variety of symptoms, including nausea, vomiting, anorexia, diarrhea, oral mucositis, and numbness, which are all caused by their toxic effects on normal cells and tissues. These adverse reactions frequently lower patients' quality of life (QOL) and can make it difficult to continue chemotherapy or chemoradiotherapy(9).

Most common types of cancer

- Breast Cancer
- Cervical Cancer
- Bladder Cancer
- Colon Cancer
- Colorectal Cancer
- Kidney Cancer
- Lung cancer-Non-Small Cancer
- Lymphoma-Non-Hodgkin
- Melanoma
- Oral and Or pharyngeal Cancer(10)

TYPES OF CANCER TREATMENT

With the advancement of civilization, medicinal herbs have long been used conventionally to address a range of diseases. There is a promise for the discovery of new medicines in both plants and animals(11). Medicinal herbs are employed to treat a range of infections and have contributed as a foundation for the development of new medicinal medicines. The ancient applications of medicinal herbs are still used by 80% of the world(12).

Cancer is typically treated with surgery, ionizing radiation, chemotherapy, photodynamic therapy (PDT), or a combination of these methods(13). It is well-recognized that the most challenging obstacle to overcome in the treatment of the disease is metastasis(14). Many of the traditional medicines currently in use are made of plants, minerals, and organic material, and many of them have been researched for their pharmacological effects in line with contemporary medicine. Examples of medications based on plant bioactive principles include paclitaxel from the Pacific yew (Taxus brevifolia), capsaicin from chili peppers (Capsicum species), galantamine from the Caucasian snowdrop (Galanthus caucasicus), vinblastine, and vincristine, their semi-synthetic derivatives from the Madagascar periwinkle (Catharanthus

roseus)(15). Nearly 21,000 plants used for medical reasons worldwide are listed byWorld Health Organization (WHO). It is unnecessary to stress the fact that different traditional medical practices used in China (TCM), Indonesia (Jamu), India (Siddha and Ayurveda), and Africa (sangoma, n′anga, and inyanga) have successfully treated a variety of illnesses, including jaundice, diabetes, dysentery, tumors, vaginitis, kidney stones, diuretics dyspepsia, and hepatotoxicity, hepatitis B(16).

Chemotherapy

Chemotherapy, which uses pharmacological substances to kill cancer cells, is currently among the most widely used cancer treatment modalities. Chemotherapy is intended to stop the spread of cancer cells, protect against metastases, and then remove the tumor (17)(18). Charles Heidelberger's discovery of 5-fluorouracil in 1957 marked the beginning of the history of chemotherapeutic drugs. The results of the pharmacological studies indicated that this substance might be utilized to successfully treat several malignant cancers(5). The anticancer effect of 5-fluorouracil is time-dependent, and it must be kept constant in blood concentration. A combination medication including ftorafur (tetrahydro furanyl-5-fluorouracil, tegafur, FT) and uracil were designed to provide a larger drug concentration in blood and tumor tissues for a longer time. Though its cardiotoxicity restricted its use, 5-fluorouracil was still used(19).

Biomarker Testing for Cancer Treatment

Testing for biomarkers is a means to find proteins, genes, and other elements (also known as tumor markers or biomarkers) that can reveal cancer information(20). You and your doctor can choose a cancer treatment with the aid of biomarker testing(21).

Hormone Therapy

Breast and prostate cancers that depend on hormones for growth can be controlled or slowed down by hormone therapy(22). Menopausal hormone therapy (MHT), commonly known as hormone replacement therapy (HRT), involves replacing progesterone (or compounds exerting progestogenic effects) and oestrogen (or compounds exerting estrogenic effects) when the production of cyclic ovarian hormones has ceased(23).

Hyperthermia

An approach to treating cancer that causes little to no harm to healthy tissue is called hyperthermia, which involves heating body tissue to as much as 113 °F(24). Learn more about the various malignancies and precancers that hyperthermia is used to treat, how it is administered, and its advantages and disadvantages of it(25).

Immunotherapy

The immune system assisted in fighting cancer via immunotherapy, a sort of cancer treatment(26). Human immune cells that can trigger an immune response are added to Cancer-on-Chip models, which include human cancer cells that exhibit the target antigen and carefully designed TME pertinent to a particular type of human tumor, to provide them immunocompetence(27).

Photodynamic Therapy

A medication that is triggered by light is used in photodynamic treatment to eliminate malignant cells and other aberrant cells(20). A cancer treatment called photodynamic therapy (PDT) employs light, a photosensitizer (PS) molecule, and oxygen to eradicate tumors (28). With the use of PS that can absorb NIR and produce singlet oxygen at deeper tissue depths, PDT cancer treatments may advance. To begin the anti-cancer effect of photodynamic action, a PS employed in PDT must absorb visible light(29).

Radiation Therapy

High doses of radiation are used in radiation therapy, a specific cancer treatment, to eliminate malignant cells and shrink tumors (30). The common integration of 4D-CT and PET imaging, or positron emission tomography in treatment planning, precise dosage calculation algorithms, and better imaging for therapy verification on the treatment machine are a few examples(31).

Stem Cell Transplant

People who have had their stem cells destroyed by aggressive chemotherapy or radiation therapy can have their stem cells restored by stem cell transplantation(32). Haematopoietic

system transplantation became conceivable after it was discovered that the bone marrow is a source of hematopoietic stem cells (HSCs)(33).

Surgery

Surgery is a process in which a surgeon removes cancer from your body to treat cancer. For cancer patients, surgery is an essential step that increases their likelihood of recovery(34). Surgery causes an increase in the release of cancer cells into the bloodstream, suppresses antitumor immunity, upregulates adhesion molecules in target organs, attracts immune cells that can engulf tumor cells(35), and causes changes in the target tissue and the cancer cells themselves to enhance migration and invasion to establish at the target site(36).

Targeted Therapy

The modifications in cancer cells that enable them to proliferate, divide, and spread are the focus of a type of treatment called targeted therapy(37). Targeted medicines work by obstructing vital metabolic processes or mutant proteins that are necessary for the growth and survival of tumor cells. In molecularly defined patient subsets, these medications can halt tumor growth and cause startling regressions(38).

CHALCONE

Chalcones are flavonoid-type phenolic phytochemicals that are biosynthesized through the shikimate pathway and are sometimes referred to as "open-chain flavonoids". Chalcones are regarded as flavonoids' biosynthetic precursors. Chemically speaking, chalcones are typical, -unsaturated ketones made up of two aromatic rings (rings A and B) connected by a three-carbon alkenone unit. However, these can also include saturated ketones, sometimes referred to as dihydrochalcones, in which a three-carbon alkenone unit is present in place of the three-carbon alkenone unit(39). The naturally occurring chalcones typically exhibit substitutions of prenyl and geranyl on the aromatic rings. (40). Additionally, one or more phenolic hydroxyl functionalities are almost always present. Some thousands of chalcones are found naturally, and many of these chalcones have been shown to interact with different biomolecules and have cytoprotective and modulatory properties, making them potential candidates for therapeutic interventions with a variety of human illnesses (6).

Chemistry of chalcone

The chemical formula for chalcone is $C_{15}H_{12}O$. It belongs to the class of organic compounds. It is a yellow, crystalline substance that is frequently utilized in the creation of numerous drugs and chemical compounds(41). A variety of processes and characteristics are involved in the chemistry of chalcone, including:

Chalcone is produced through the Claisen-Schmidt condensation of an aromatic aldehyde and a ketone. An aldol reaction on an intermediate known as an enone created during this reaction yields the final chalcone product. Chalcone can be isomerized into both the keto and enol forms since it is a keto-enol tautomer. The enol form of chalcone, which is more reactive in several chemical processes, can be created by isomerization when the environment is acidic. Chalcone is subject to electrophilic addition reactions due to the double bond that connects the carbonyl and aromatic rings. Chalcone, for instance, can create a range of organic compounds through a Michael addition reaction with nucleophiles such as amines, thiols, and carbanions. Chalcone has been discovered to have antioxidant qualities since it contains phenolic groups in its structure. This makes it valuable in a variety of applications, including pharmaceuticals, cosmetics, and food production. Chalcones are a class of compounds that are also covered by many patents for their cytotoxic, antioxidant, antimitotic, anticancer, and anti-inflammatory characteristics. The IUPAC's name of chalcone is 1,3-diphenyl-1-proper-1-one. The molar weight of the chalcone is 202.25g/mol(42).

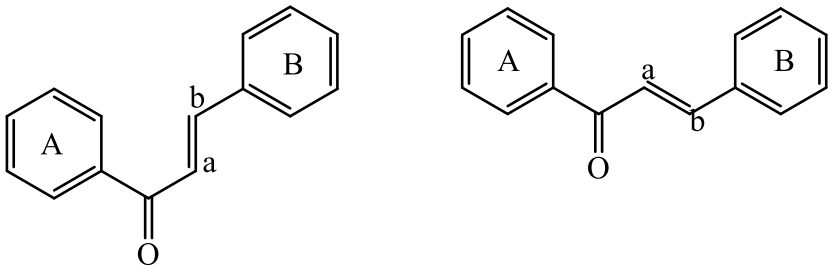


Figure 1: Structure of chalcone

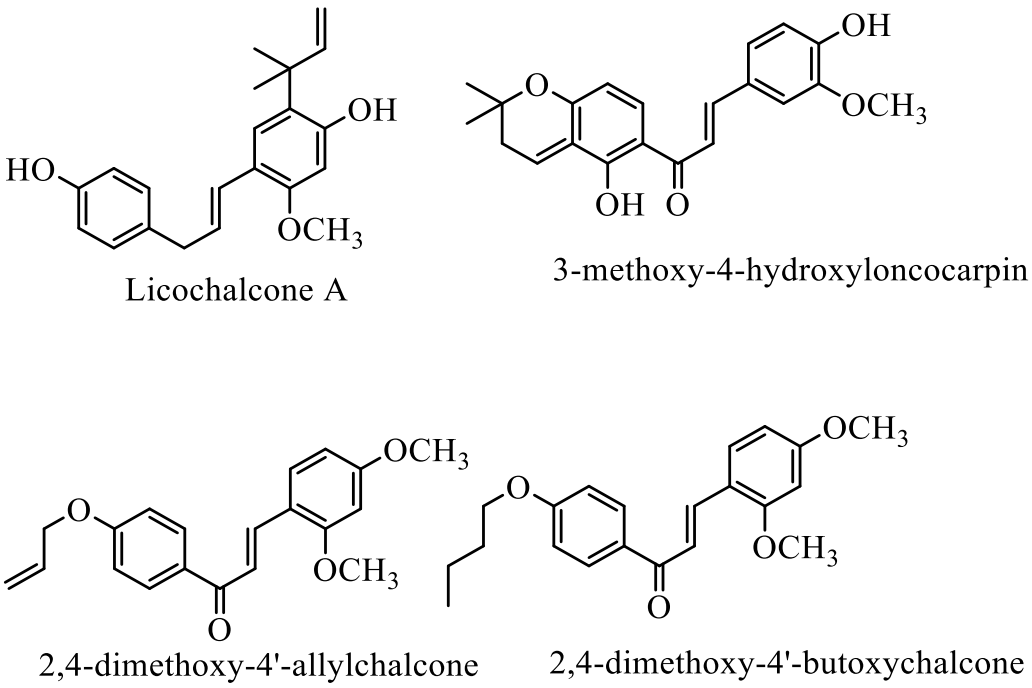


Figure no 2: Naturally occurring chalcone derivatives(43)

METHODS OF PREPARATION OF CHALCONE

Several traditional medical approaches, including homeopathy and Chinese medicine, have made successful use of chalcone and its derivatives. They are usually made via the Claisen-Schmidt condensation, a more modern development referred to as the aldol condensation, and the homogeneous reaction of benzaldehydes with active methylene ketones(44). Nevertheless, new techniques for creating chalcones provide multiple advantages depending on the kind of catalyst, solvent, base, and reaction parameters(45).

Claisen-Schmidt Condensation

To obtain the desired, α, β-unsaturated ketone, the Claisen-Schmidt condensation process combines a ketone with an aldehyde that has the carbonyl group absent hydrogen atoms in the α-position. Because acetophenone and benzaldehyde are present in equimolar amounts, this is one of the procedures used to create chalcone in a lab. Acetophenone and benzaldehyde are combined to form Claisen Schmidt condensation, which is catalyzed by aqueous-alcoholic alkali at concentrations of 10 to 60% (46). The reaction can occur for 12 to 15 hours at 50 degrees Celsius or for a week at room temperature (20 to 25 °C)(46).

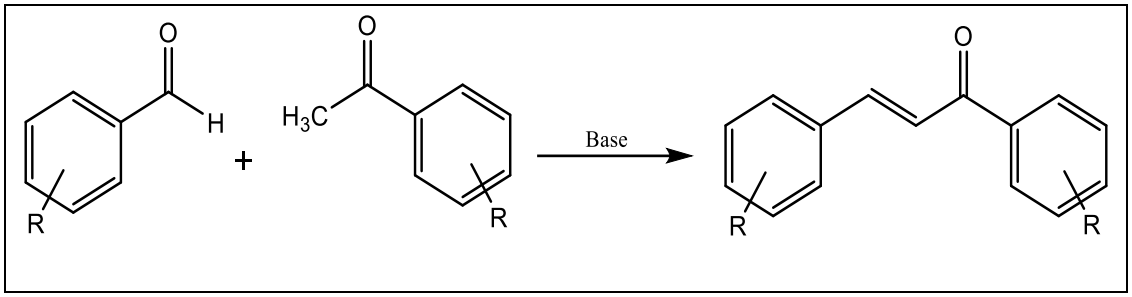


Figure 3: Claisen-Schmidt Condensation

Aldol Condensation

Besides Claisen-Schmidt condensation, another synthetic technique that is often employed is aldol condensation. The solid-state process, also referred to as the aldol condensation reaction substitutes benzylidene-diacetate for aldehydes and employs heat (200–350 °C) and a base such as potassium hydroxide as a catalyst for the reaction between the two substances. Distillation must be carried out at a constant temperature, it employs calcium, barium, or strontium hydroxides or carbonates as catalysts in a liquid combination comprising water with a low boiling point. The reaction time, expense, and contaminants in the finished products are all decreased when a ketone and an aldehyde are combined. Acetophenone and 1-phenyl-3-aryl-4-formyl pyrazole are the starting materials, while tetrabutylammonium bromide acts as the catalyst when microwave radiation and an inorganic alkaline solution are present. (47).

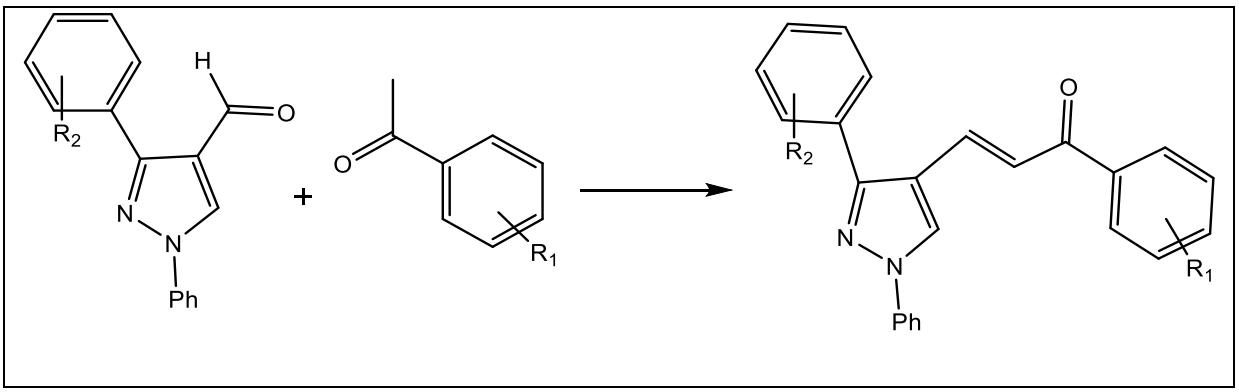


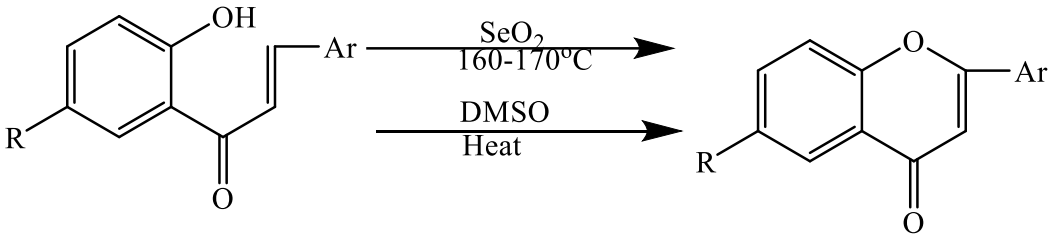
Figure no 4: Chalcone-containing heterocyclic ring utilizing a phase-transfer catalyst

CHEMICAL REACTIONS OF CHALCONES

Oxidation of chalcones

Algar-Flynn oxidation of chalcones

While acetaminochalcones react with selenium dioxide to produce 6-acetaminoflavones, acetaminochalcones react with alkaline hydrogen peroxide to produce 6-acetaminoflavonols through an Algar-Flynn oxidation process. To produce flavones, I2 and DMSO can also be utilized as oxidation agents. 2'-hydroxy chalcones and glacial acetic acid are refluxed to create flavanone derivatives.



Ar:C_6H_5, p-$C_6H_4OCH_3$,3,4-C_6H_3 (CH_2O_2), m-C_6H_4OH R:CH_3CONH, H

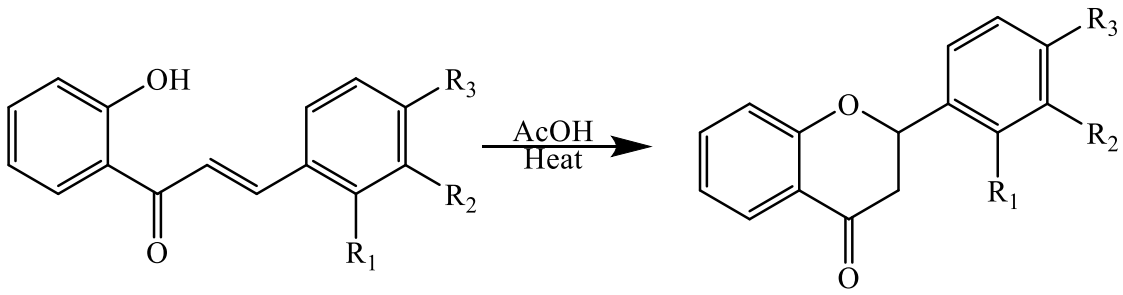


Figure 5: Algar-Flynn oxidation of chalcones

Epoxidation of chalcones

Natural ethylenic groups are present in 1-butyl-3-methyl imidazolium tetrafluoroborate ([bmim] BF4) compounds such as chromone, chalcone, and isoflavone are epoxidized with hydrogen peroxide relatively quickly, and with a high yield.

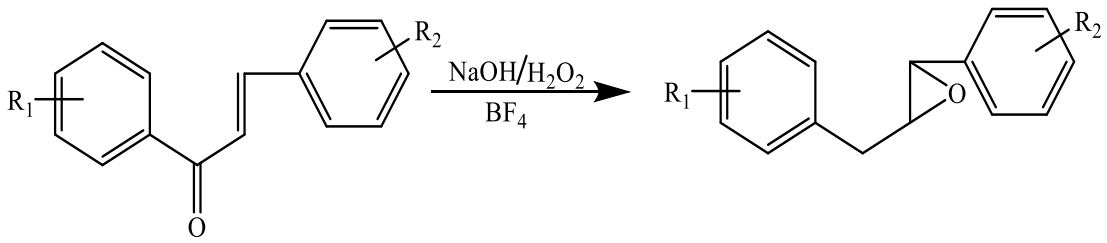


Figure 6: Epoxidation of chalcones

Substitution reaction of chalcones

S-Alkylation reaction

When (E)-4- Mercaptochalcones and dibromo alkanes react at room temperature with N, N-Dimethyl formamide, and triethylamine (TEA), S-Alkylation results(48).

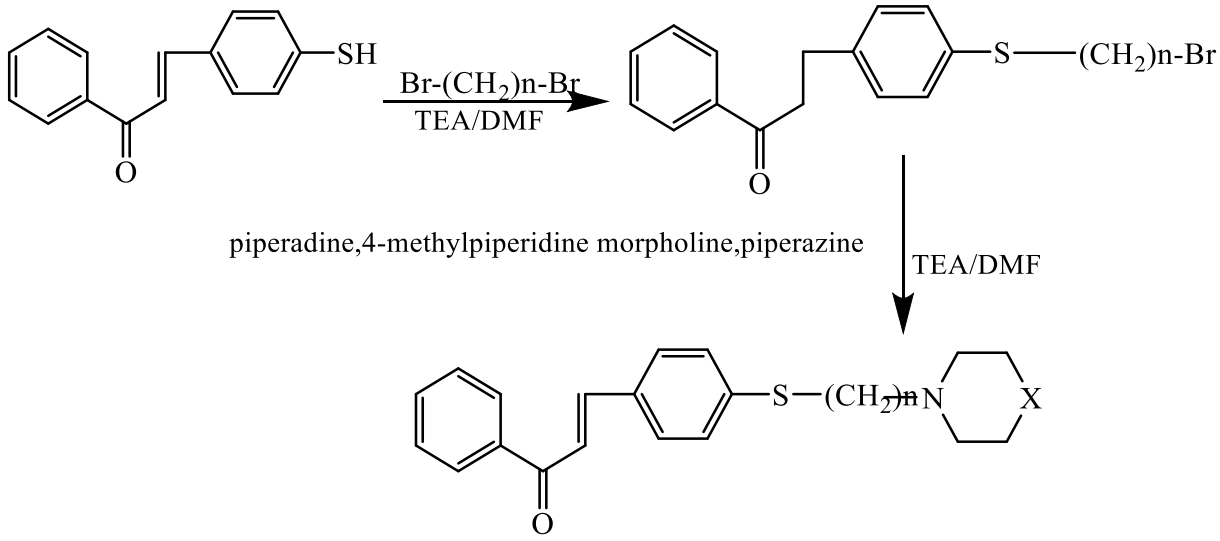


Figure 7: Substitution reaction of chalcones

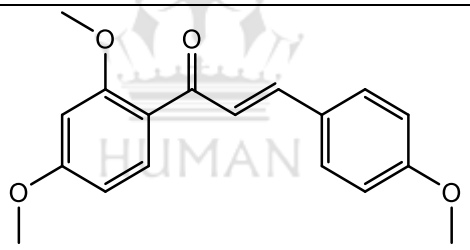
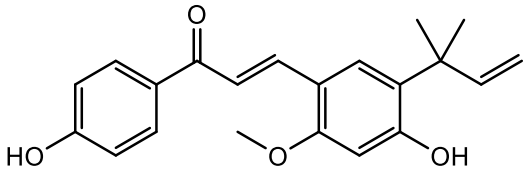
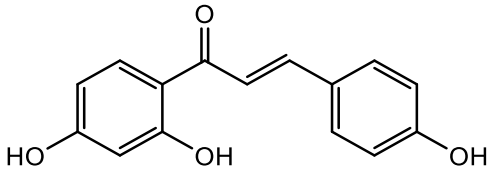
Chalcone as Anticancer agent

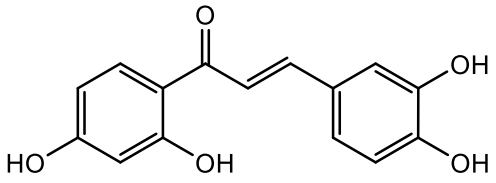
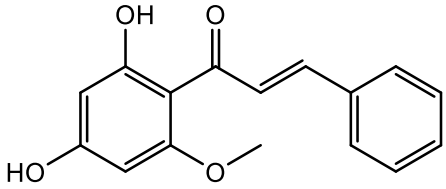
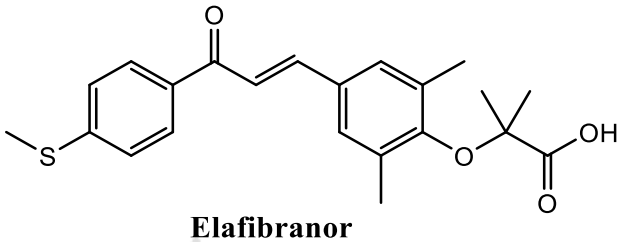
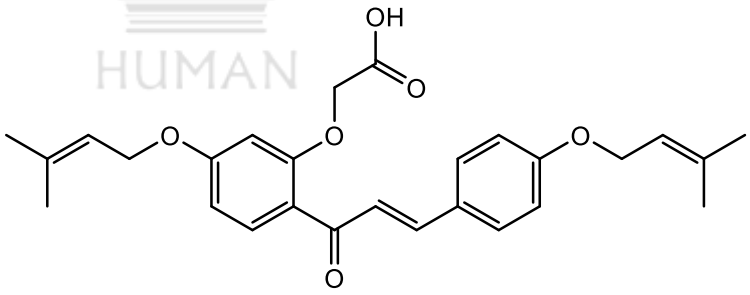
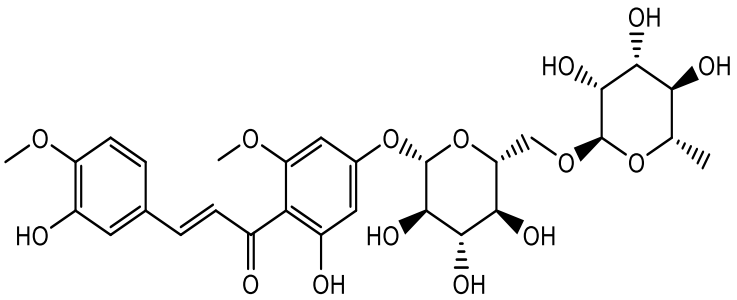
Chalcone derivatives are a class of chemicals that are derivations of the straightforward flavonoid chalcone, which has been investigated as a possible anticancer drug. Several chalcone derivatives have been created, and their capacity to prevent the proliferation of cancer cells has been tested. Several derivatives have shown encouraging outcomes, and some of them even have more efficacy than the original substance(49). The inhibition of

several molecular pathways is thought to be part of the chalcone derivatives' mode of action, albeit this is not fully understood. It has been discovered that some derivatives can both stop tumor cell growth and trigger apoptosis(50). Moreover, several products have been demonstrated to prevent angiogenesis, a critical component in the development and spread of tumors. Various compounds have been shown to have antioxidant and anti-inflammatory properties, which may help explain why they are anti-cancer(51). The effectiveness of chalcone derivatives against different forms of cancer has been assessed in several studies, both in vitro and in vivo. The bulk of these investigations has shown strong anticancer action, with several drugs showing dose-dependent reduction of cell growth and activation of apoptosis(52). Moreover, it has been discovered that certain chalcone derivatives are more effective than some conventional chemotherapeutic drugs. Many derivatives have also been investigated in preclinical and clinical studies with encouraging results(53).

Marketed Products of Chalcone-Based Moiety

Table no 1: Marketed Products of Chalcone-Based Moiety

Metochalconewas isolated from *Pterocarpusmarsuoium*h eartwood. Uses: It is employed as a diuretic and choleretic**.**	 **Metochalcone**
Licochalcone-A Stopping the advancement of the cell cycle and triggering apoptosis can stop the growth of stomach cancer cells.	 **Licochalcone A**
Isoliquiritigenin is a chalcone that has been shown to have intriguing biological qualities, such as antioxidant, anti-inflammatory, antiviral, and antidiabetic.	 **Isoliquiritigenin**

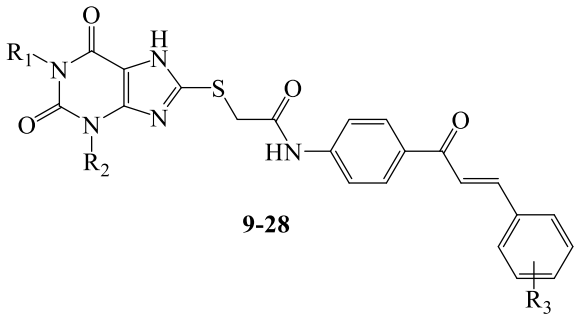
Buteinis a member of the class Chalconoids. It has actions that inhibit aldose reductase, advanced glycation end products, and antioxidants.	 **Butein**
Cardamoninisa functional chalconoid. It is applied to stomach cancer.	 **Cardamonin**
Elafibranor is a peroxisome proliferator-activated receptor (PPAR) agonist for both the PPAR alpha and PPAR delta. Elafibranor reduces inflammation while enhancing insulin sensitivity, glucose balance, and lipid metabolism.	 **Elafibranor**
Sofalconeis applied to the treatment of intestinal and stomach ulcers. The treatment of stomach mucosal lesions is another application for it.	 **Sofalcone**
Hesperidin methyl chalcone is a flavonoid utilized to treat chronic venous disease because of its anti-inflammatory, analgesic, and antioxidant properties.	 **Hesperidin methylchalcone**

PHARMACOLOGICAL ACTIVITIES OF CHALCONE

According to multiple literature evaluations, chalcone derivatives have a variety of pharmacological actions. These pharmacological activities are shown as follows.

Anticancer activity

Hesham A. Abou-Zied et al; synthesized 9-28 new xanthine/chalcone hybrids with anticancer properties. Using the MTT assay all final hybrids 9–28 were tested for their ability to inhibit the proliferation of four cancer cell lines: human pancreatic cancer cell line (Panc-1), breast cancer cell line (MCF-7), colon cancer cell line (HT-29), and epithelial cancer cell line (A–549). In comparison to doxorubicin, which served as a reference, compounds 10, 11, 13, 14, 16, 20, and 23 exhibited potent inhibition of cancer cell proliferation. Compound 11 was more effective than the staurosporine as reference (IC50 = 0.3 M) at inhibiting the target enzyme(54).

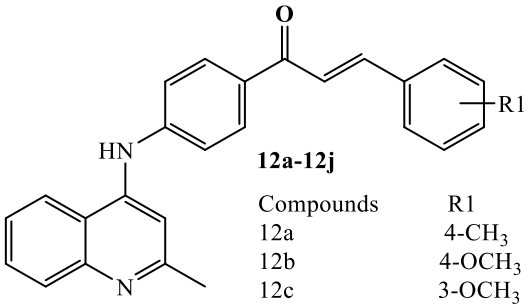


9-28

Figure: 8

Comp	R_1	R_2	R_3	Comp	R_1	R_2	R_3
9	Methyl	Methyl	H	19	Methyl	H	H
10	Methyl	Methyl	2-Cl	20	Methyl	H	2-Cl
11	Methyl	Methyl	4-Cl	21	Methyl	H	4-Cl
12	Methyl	Methyl	4-Br	22	Methyl	H	4-Br
13	Methyl	Methyl	4-OCH_3	23	Methyl	H	4-OCH_3
14	Methyl	Methyl	3,4-di-OCH_3	24	Methyl	H	3,4-di-OCH_3
15	Methyl	Methyl	3,4,5-tri-OCH_3	25	Methyl	H	3,4,5-tri-OCH_3
16	Methyl	Methyl	3-NO_2	26	Methyl	H	3-NO_2
17	Methyl	Methyl	4-CH_3	27	Methyl	H	4-CH_3
18	Methyl	Methyl	2,4-di-CH_3	28	Methyl	H	2,4-di-CH_3

Yong-Feng Guan et al; designed and synthesized the quinoline-chalcone derivatives and evaluate their antiproliferative activity against MGC-803, HCT-116, and MCF-7 cells. When compared to 5-FU (IC50 values = 6.22, 10.4, and 11.1 M, respectively), compound 12e demonstrated the highest inhibitory activity against MGC-803, HCT-116, and MCF-7 cells. Apoptosis-related proteins (Caspase3/9 and cleaved-PARP) are significantly increased in MGC-803 cells by compound 12e, which also can stop MGC-803 cells at the G2/M phase(55).

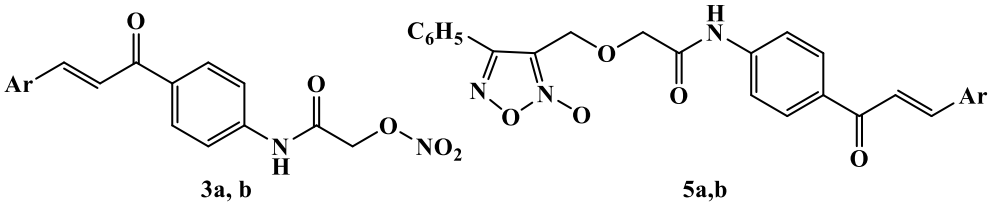


12a-12j

Compounds	R1
12a	4-CH_3
12b	4-OCH_3
12c	3-OCH_3
12d	3,4-diOCH_3
12e	3,4,5-triOCH_3
12f	H
12g	4-Cl
12h	4-Br
12i	3-Cl
12j	3-Br

Figure: 9

Mai A.E. Mourad et al; synthesized by fusing amino chalcones with various NO-donating moieties, such as nitrate esters, oximes, and furoxans, a group of nitric oxide (NO) donating chalcone derivatives was produced. Various cancer cell lines were tested, including leukemia, lung, renal, breast, colon, melanoma, ovarian, and skin cancer cell lines. Compounds 3a and 3b show excellent cytotoxic action against these cancer cell lines. Nitrate ester 3a had the strongest inhibitory activity. Comparatively, compound 3a only showed a moderate selectivity towards the subpanel for colon cancer, with a selectivity ratio of 5.87 at the TGI level(56).

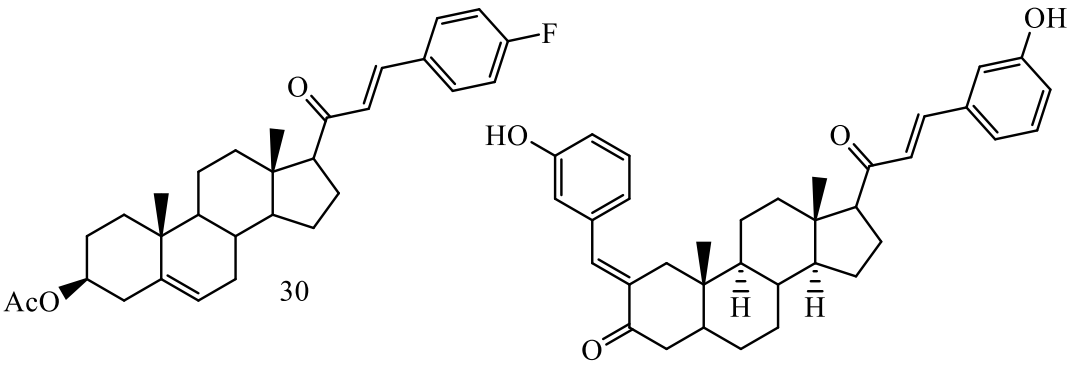


3a, 5a: Ar=(4-Cl-C_6H_4); 3b,5b: Ar=(3',4'-OCH_2O-C_6H_4)

Figure: 10

Antibacterial activity

In 2013, Kakati and colleagues created a novel series of steroidal chalcones and tested them against B. subtilis and E. coli for their ability to fight bacteria. Against the studied bacterial strains, some of the compounds exhibit great inhibitory action. The most promising compound was determined to be compound 30 which exhibited both bactericidal and fungicidal activity against E. coli with MIC values of 150 g/mL. The presence of the, -unsaturated carbonyl moiety in the produced compounds was discovered to be crucial for activity, and epoxidation of the double bond results in a loss in antibacterial activities. Abood and Ibraheem were created through the synthesis of progesterone-based chalcone hybrids, and their in vitro antibacterial properties were evaluated. Some of the examined compounds had strong antibacterial activity against the antibacterial standard medication, ampicillin. In comparison to the conventional antibiotic Ampicillin, compound 31 showed outstanding antibacterial activity against S. pneumonia and S. aureus(57).

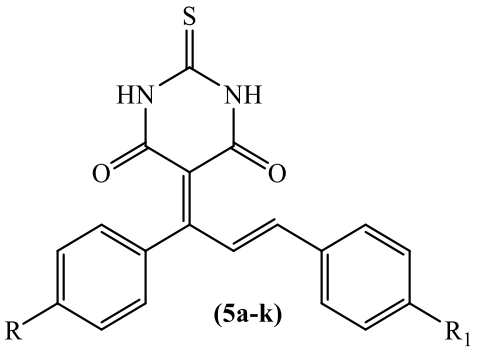


Zol=26mm against E. coli

Zol=30mm against S. pneumonia
Zol=24mm against S. aureus

Figure: 11

Talavara Venkatesh et.al synthesized a new series of 5- [1,3-bis (4- substituted phenyl) prop-2-en-1-ylidene] - 2-thioxodihydropyrimidine the -4,6(1H, 5H)-diones (5a-k). By using ethanol as a catalyst and acetic acid as a condensation catalyst in the Knoevenagel condensation of various chalcones (3a-k) with thiobarbituric acid, the target compounds were synthesized. It was discovered that the compounds 5a, 5e, and 5k, which have Cl substituents on the para position of the phenyl ring, have good antibacterial activity against Staphylococcus aureus and Bacillus subtilis with MIC values of 27.72-37.42 g/mL. Compounds 5i and 5j exhibited excellent activity against Pseudomonas aeruginosa with MIC values of 28.11 g/mL and 29.86 g/mL, respectively; compound 5c is inactive against Staphylococcus aureus, while the remaining compounds showed great action against all tested pathogens(58).



(5a-k)

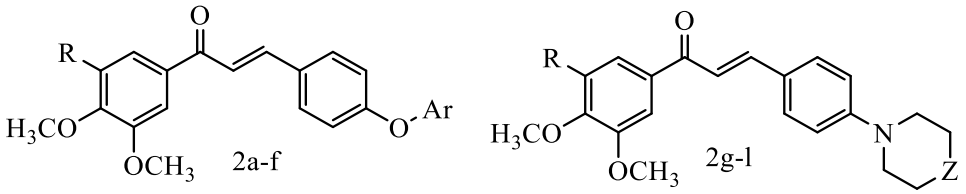
HUMAN

Figure: 12

Comp	R	R_1	Comp	R	R_1
5a	H	Cl	5h	OCH_3	H
5b	H	CH_3	5i	NO_2	OCH_3
5c	H	OCH_3	5j	NO_2	$N(CH_3)_2$
5d	H	$N(CH_3)_2$	5k	Cl	Cl
5e	OCH_3	Cl			
5f	OCH_3	CH_3			
5g	OCH_3	OH			

Anti-inflammatory activity

In 2021 Soha H. Emam synthesized two series of chalcone derivatives that were prepared as anti-inflammatory agents. Methoxylated phenyl-based chalcones 2a-l and coumarin-based chalcones 3a-f were synthesized and compared for their inhibition of COX-2 enzyme and nitric oxide production suppression. Compound 2f exhibited the greatest anti-inflammatory effect by inhibiting NO (IC50 = 11.2 M) among the 18 synthesized chalcone derivatives. By lowering the expression of NF-B in LPS-stimulated macrophages, the tested chemical 2f showed inhibition of iNOS and COX-2(59).

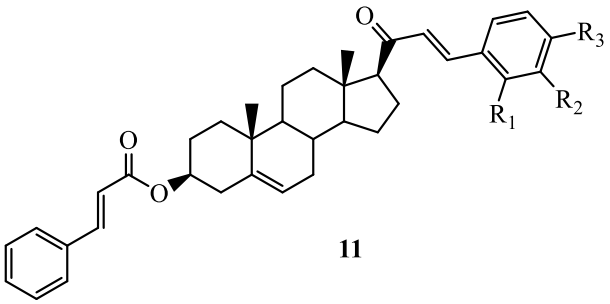


2a: R=H; Ar=$_4$-Clc$_6$h$_4$-
2b: R=H; Ar=$_4$-BrC$_6$H$_4$-
2c: R=H; Ar=$_4$-OCH$_3$C$_6$H$_4$-
2d: R=OCH$_3$; Ar=$_4$-ClC$_6$H$_4$-
2e: R=OCH$_3$; Ar=$_4$-BrC$_6$H$_4$-
2f: R=OCH$_3$; Ar=$_4$-OCH$_3$C$_6$H$_4$-

2g: R=H; Z=CH$_2$
2h: R=H; Z=O
2i: R=H; Z=NCH$_3$
2j: R=OCH$_3$; Z=CH$_2$
2k: R=OCH$_3$; Z=O
2l: R=OCH$_3$; Z=NCH$_3$

Figure: 13

In 2021 Xiaorui Cai synthesized new steroidal chalcones containing 3-pregnenolone esters of derivatives of cinnamic acid using pregnenolone as the starting material. The substance 3-3-phenyl acrylate-pregn-5-en17-yl-3′ was examined (p-fluoro) The powerful inhibition of inflammatory enzymes was shown by -phenylprop-2′ -en-1′ -(11e). In identifying the preferences for the target sites, compound 11e possessing chalcone analogs (1, 3-diphenyl-2-proper-1-one) and styryl ketone (trans-4-phenyl-3-button-2-one) pharmacophores in the side chain is crucial. The addition of aryl groups with potent electron-withdrawing substituents, such as fluorine, may be the cause of compound 11e's potent inhibitory activity. Against RAW 264.7 cells, the powerful NO inhibitor 11e was tested for its ability to reduce inflammation. In LPS-induced RAW 264.7 cells, compound 11e had the strongest anti-NO generation action, with an IC50 value of 1.46 M(60).



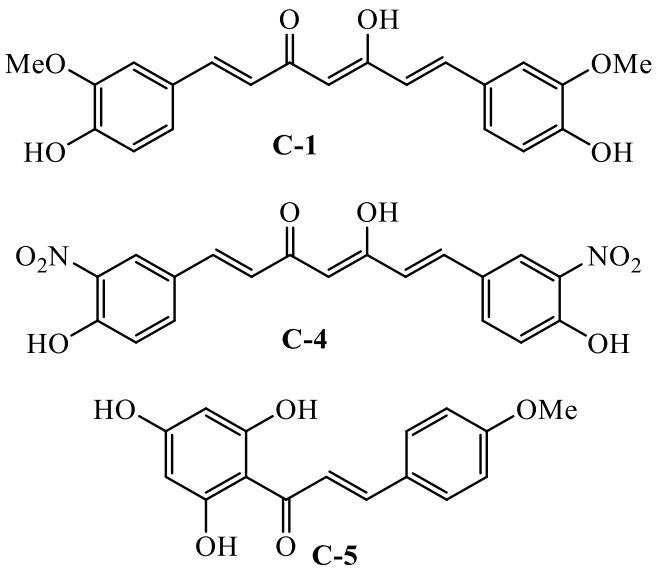
11

11a: R_1=H, R_2=H, R_3=OCH_2Ph
11b: R_1=H, R_2=H, R_3=OCH_3
11c: R_1=H, R_2=H, R_3=Br
11d: R_1=H, R_2=H, R_3=Cl
11e: R_1=H, R_2=H, R_3=F
11f: R_1=H, R_2=H, R_3=CH_3
11g: R_1=H, R_2=OCH_3, R_3=OCH_3
11h: R_1=H, R_2=H, R_3=SCH_3
11i: R_1=F, R_2=H, R_3=H

Figure: 14

Antioxidant activity

Two complementary assays, DPPH and b-carotene/linoleic acid were used to assess the antioxidant activities of the synthetic compound (C1) -(C8), which consisted of 7 curcuminoids and a chalcone. The highly effective antioxidant properties of Compounds (C1) and (C4) with (4-OH) phenolic groups were discovered to have greater concentrations than BHT, indicating that synthetic curcuminoids are more potent antioxidants than typical antioxidants like BHT. Only the water-soluble 2, 4,6-trihydroxyphenolic chalcone (C5) demonstrated an 85.2% suppression of conjugated dienes production using the b-carotene-linoleic acid assay, demonstrating its powerful antioxidant action(61).



C-1

C-4

C-5

Figure: 15

Antimalarial activity

There are various naturally occurring chalcone-based antimalarial agents but mostly licochalcone is used to cure malaria in ancient medicine because it had a bitter taste, just like quinine and other antimalarial medications. Recent research gives its anti-plasmodial action an experimental foundation.

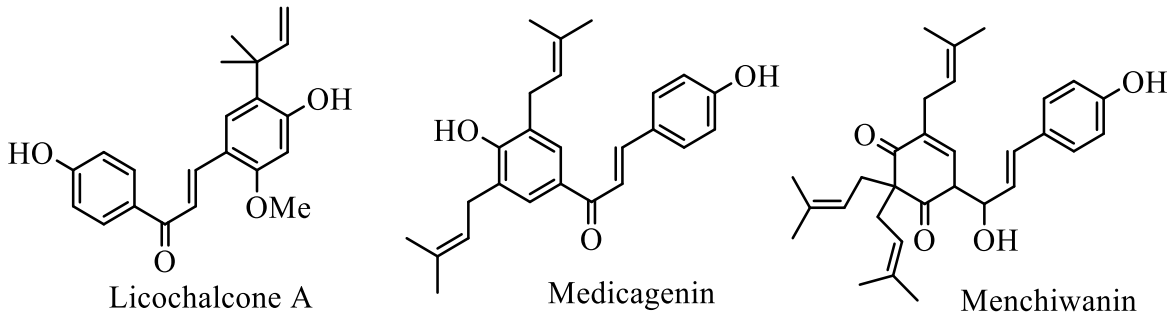
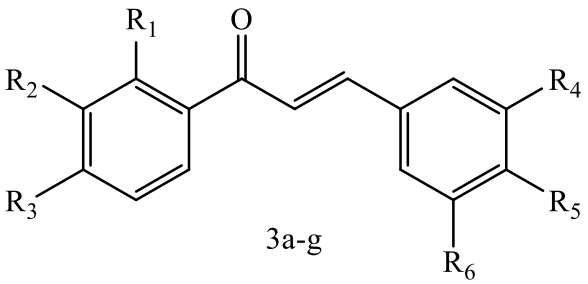


Figure 16: Naturally occurring chalcone-based antimalarial drugs(62)

The Claisen-Schmidt technique was used to synthesise the chalcone derivatives, with NaOH 60% base serving as the catalyst. The chloroquine-sensitive Pf3D7 strain was subjected to an in vitro antimalarial activity assay using the Rieckmann method. The most effective antimalarial activity was displayed by 3b, exhibiting a methoxy group, three hydroxy groups, and an IC50 of 0.59 mM. Compound 3b shows excellent antimalarial activity with IC 50 less than 1mM, compounds 3a and 3d-g exhibit good antimalarial activity, and compound c shows moderate activity(63).

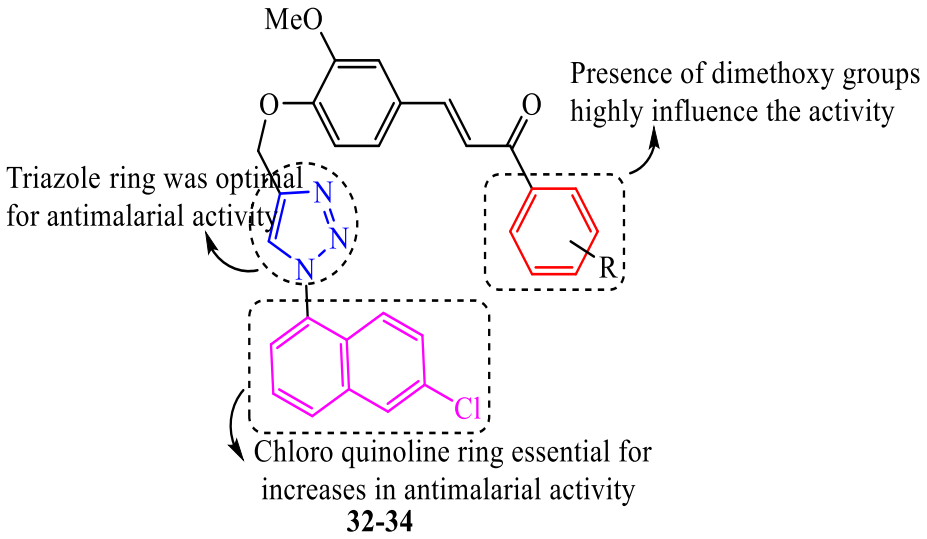


3a-g

3a R_1=OH; R_2=R_4=R_6=H; R_3=OCH_3;R_5=Diethylamine
3b R_1=OH; R_2=R_6=H; R_3=OCH_3; R_4=R_5=OH
3C R_1=R_2=R_4=H; R_3=Cl; R_5=OH; R_6=OCH_3
3d R_1=R_2=R_4=H; R_3=Cl; R_5=O-Alkyl; R_6=OCH_3
3e R_1=R_2=R_4=H; R_3=Cl; R_5 =R_6=OCH_3
3f R_1=R_6=H; R_2=R_3=R_4=R_5=OCH_3
3g R_1=H; R_2=R_3=R_4=R_5=OCH_3; R_6=Cl

Figure: 17

Guantai et al.developed and tested a novel class of chalcones and dienone-contain aminoquinoline-based triazoles (32e34) for their in vitro anti-malarial activity. The three D10, Dd2, and W2 strains of P. falciparum that were examined exhibited high activity against all of the manufactured antimalarial drugs. In particular, compound 33 was found to have the strongest effects on the Plasmodium falciparum strains D10, Dd2, and W2 (IC50: 0.04 mM, 0.07 mM, and 0.08 mM, respectively) (IC50: 0.09 mM). According to the SAR, triazole rings have a significant role in boosting antimalarial action, and chloroquinoline rings are essential for enhancing antimalarial activity(64).

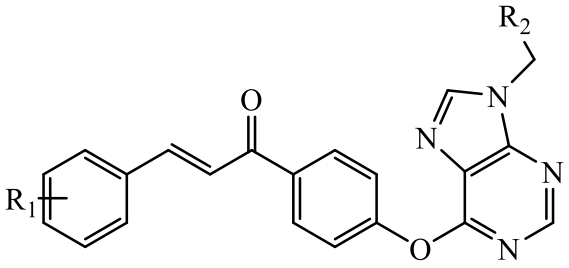


32-34

Figure: 18

Antiviral activity

The antiviral properties of new chalcone derivatives with purine moiety against tobacco mosaic virus (TMV) and cucumber mosaic virus (CMV) were designed and produced (TMV). In comparison to Dufulin (50.6%) and Ribavirin (40.8%), compounds 3k, 3o, 3p, 3s, 3w, and 3x showed good curative activity against CMV with values of 52.3%, 58.3%, 51.3%, 52.5%, and 53.3%, respectively. Similarly, the inhibitory effects of compounds 3e, 3k, 3n, 3o, and 3t were 51.9%, 49.0%, 50.5%, 52.4%, and 48.5%, respectively, and were comparable to those of tubulin (51.5%) and ribavirin (50.5%). Compounds 3d, 3f, 3p, 3u, 3x, and 3y showed good anti-TMV curative effects, with respective inhibitory activity ratios of 50.8%, 50.3%, 52.0%, 48.5%, 49.3%, and 49.4%, which were comparable to Dufulin's (49.3%) and better than Ribavirin's (38.3%)(65).



3a-3z

3a: R_1=H, R_2=H
3b: R_1=$_2$-F, R_2=H
3c: R_1=$_4$-Cl, R_2=H
3d: R_1=$_2$-Br, R_2=H
3e: R_1=$_4$-CH_3, R_2=CH_3
3f: R_1=$_2$-OCH_3, R_2=CH_3
3g: R_1=H, R_2=CH_3
3h: R_1=$_2$-F, R_2=CH_3
3i: R_1=$_4$-Cl, R_2=CH_3
3j: R_1=$_4$-NO_2, R_2=CH_3

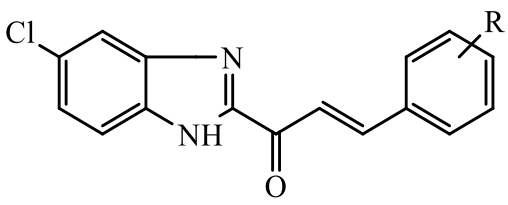
3k: R_1=$_4$-CH_3, R_2= Ph
3l: R_1=$_2$-OCH_3, R_2=Ph
3m: R_1=H, R_2=Ph
3n: R_1=$_2$-F, R_2=Ph
3o: R_1=$_4$-Cl, R_2=Ph
3p: R_1=$_4$-NO_2, R_2=Ph
3q: R_1=$_2$-Br, R_2=Ph
3r: R_1=$_4$-F, R_2=Ph

3s: R_1=$_2$,4-diOCH_3, R_2=Ph
3t: R_1=$_4$-CH_3, R_2=$_2$-Cl-Py
3u: R_1=$_2$-OCH_3, R_2=$_2$-Cl-Py
3v: R_1=H, R_2=$_2$-Cl-Py
3w: R_1=$_2$-F, R_2=$_2$-Cl-Py
3x: R_1=$_4$-Cl, R_2=$_2$-Cl-Py
3y: R_1=$_4$-NO_2, R_2=$_2$-Cl-Py
3z: R_1=$_2$,4-diCl, R_2=$_2$-Cl-Py

Figure: 19

Antileishmanial activity

D. U. J-P. N'Guessan et al; synthesized 2-arylpropenone-benzimidazole hybrids and evaluate their antiprotozoal activity. The 5-chlorobenzimidazole chalcone hybrids produced generally very effective compounds against L. donovani (IC50 25 mM). In the context of their excellent efficacy against Leishmania parasites when compared to the reference medication pentamidine, hybrids 4c, 4b, and 4a, with corresponding IC50 values of 0.47, 0.5, and 0.53 M, are viable candidates for antileishmanial drug development. The 4'-chloro derivative 4f exhibited a lesser activity (IC50 = 24.59 M) than the 2'-chloro derivative 4c (IC50 = 0.47 M). Furthermore, adding two chlorine atoms to the phenyl ring (4g) didn't significantly increase activity. The chlorine derivatives in the series can be divided into the following categories based on their activity. IC50 values for 2-Chloro, 2.4-Dichloro, and 4-Chloro are 0.47, 1.79, and 24.59 M(66).



Comp.	R
4a	H
4b	3-OH
4c	2-Cl
4d	3-NO_2
4e	4-CH_3
4f	4-Cl
4g	2,4-diCl

Figure: 20

Antidiabetic activity

Amino chalcones (numbers 3a–j) were produced synthetically, and hydroxy chalcones (numbers 3g–j) were extracted from natural sources such as Andrographis macrobotrys, Sophora interrupts, and Clerodendrumphlomidis. To evaluate the antidiabetic effect of chalcones, in vivo tests were conducted on Wistar male albino rats that had been given alloxan to induce diabetes. When diabetic rats are compared to control rats, compounds 3c, 3a, and 3h exhibit significantly greater antidiabetic activity and lower blood glucose levels. Furthermore, docking studies with the enzyme's aldose reductase, dipeptidyl peptidase, PPAR, and glucosidase were observed, achieving that the compounds 3c, 3i, 3a, and 3d have an excellent binding affinity (kcal/mol) with aldose reductase. In addition, the chalcones 3c, 3b, 3d, 3e, and 3i were also shown inhibition with DPP-IV, PPAR-α, and α-glucosidase(67).

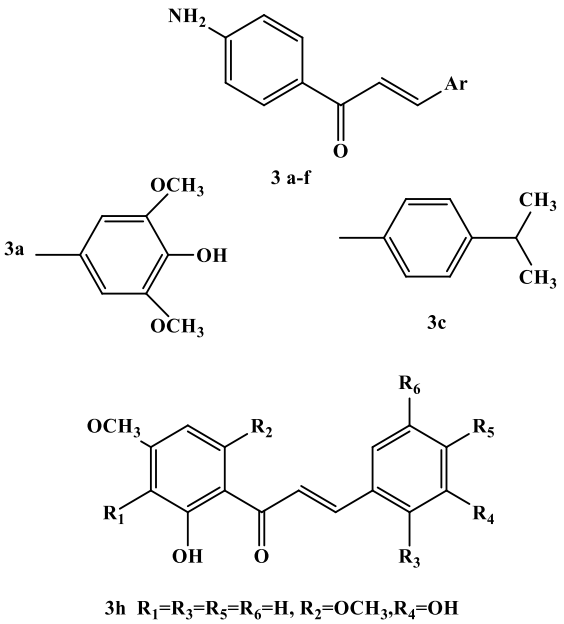
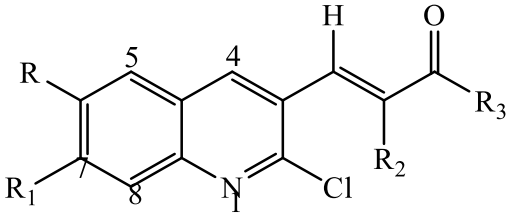
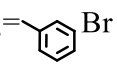


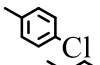
Figure:21

Antiamoebic activity

The HM1: IMSS strain of E. histolytica was used in preliminary experiments to ascertain all of the compounds' in vitro antiamoebic activity. A 50% inhibitory concentration (IC50) of 1.46 mM for the most popular antiamoebic drug, metronidazole, was used to compare the antiamoebic effect to it. In contrast, compounds (4, 5, 7, and 9) with a methyl group as a substituent at C6 and C7 of the chloroquinoline ring (except for compounds 6, 8, and 10) showed an IC50 value in the range of 0.05e7.53 mM. SAR revealed that compounds (4e10) contained chloro and bromo groups as substituents at the C-3 and C-4 positions of the phenyl ring. Except for compound (13), compounds (11–15), all contain a methyl group at the a–b unsaturated carbonyl position and have the same substitution of chloro and bromo groups at C-3 and C-4 of the phenyl and a methyl group at C-6 and C-7 of the chloroquinoline ring. These compounds have an IC50 value in the range of 0.06–7.03 mM. Among these 15, (5, 10, 11) were discovered to be more effective against.E. histolytica than metronidazole (IC50 14 1.46 mM(68).



5. R=H, R_1=CH_3, R_2=H, R_3=  Br

10. R=H, R_1=H, R_2=H, R_3=  Cl

11. R=H, R_1=CH_3, R_2=CH_3, R_3=  Br

Figure: 22

CONCLUSION

Several chalcones and their derivatives have been identified from natural sources throughout the years, and many of them have undergone screening for possible bioactivities, primarily for their ability to fight cancer, inflammation, bacteria, viruses, and parasites. An extensive collection of bioactive synthetic chalcone derivatives, some of which have enhanced bioactivities and/or reduced toxicities compared to relevant natural chalcones, has been created as a result of the total or partial synthesis of chalcone analogs as well as minor

structural modifications of natural chalcones. This review article has shown that the process of creating chalcone derivatives with a bioinspired approach may provide a new chemical area that can be explored for the development of novel drugs.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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None

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