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Chalcones As Versatile Scaffolds in Cancer Therapy: Integrating Synthesis with Multi-Target Anticancer Mechanisms

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Abstract

On global scale cancer continues to be one of the leading causes of mortality and creating successful treatments for it is quite challenging. Finding appropriate pharmaceuticals for cancer treatment is the focus of continuing research. Chalcones are one of these substances that has garnered plenty of interest because of their eccentric and diverse pharmacological properties. They are pharmacologically active substances and can be synthesized naturally and synthetically. Chalcones, specifically 1, 3-diaryl-2-propen-1-one, represent a category with extensive anticancer efficacy in opposition to a range of cancerous cell lines. This review discusses recent developments in the study of chalcones that have anticancer property, conventional and green synthesis of chalcones and also examine various targets involved in cancer and their corresponding mechanisms. The outstanding results of these chalcone-based structures make them front-runners in the search for new anticancer therapy options, providing insightful information to scientists working on the synthesis of innovative therapeutic medicines.

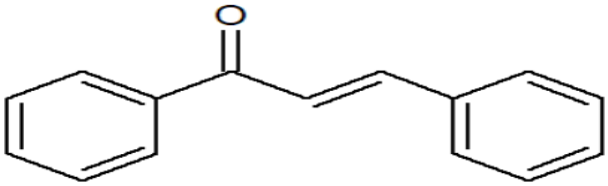
Keywords: Anticancer, chalcones, synthesis, Tubulin inhibition, Topoisomerases, Histone deacetylase inhibitors, Nuclear Factor Kappa B pathway, P-glycoprotein inhibition, apoptosis induction

Introduction

Cancer continues to be one of the main reasons of death worldwide. It affects every living thing. There are 200 types of cancer and global cancer burden is adding day by day. According to WHO statistics, globally lung cancer is the most common type of cancer followed by female breast cancer, colorectal cancer, prostate cancer and stomach cancer. In 2025, more than 35 million more instances of cancer are expected, a 77% increase from the estimated 20 million cases in2022[1,2]. Genetic and epigenetic alterations occurring in specific cells which leads to cancer, certain types may disseminate and infiltrate other tissues[3]. It is distinguished by the unbridled, aberrant cell division and growth. Even though various anticancer drugs are there to treat and prevent

cancer but one of the major issues are the emergence of medication resistance and harmful side effects. Therefore, in order to avoid these challenges in cancer treatment it is necessary to identify new molecules with reduced side effect and overcome drug resistance [2]. Cancer can be treated by various methods like chemotherapy, radiation therapy, surgery and widely used method is chemotherapy [4].

Chalcones are important natural compounds belongs to flavonoid family. Chemistry of chalcones is most sought-after and concentrated field of study among the scientific circles. Chalcones are privileged scaffolds in chemistry for drug discovery. Chalcones were discovered to be a crucial precursor for the flavonoid production [5]. They are secondary metabolites of plants [6]. The word "chalcone" is arisen from the Greek word "chalcos", meaning "bronze", which results from the colours of majority of natural chalcones [7]. They are also known as 1,3-diaryl-2-propen-1-one, a α, β-unsaturated carbonyl bridge with three carbon atoms connects two aromatic rings. It exists as in two isomers, cis and trans. They are present either natural or as synthetic analogues [8]. Chalcones have documented a spectrum of biological functions including anticancer, antioxidant, antidiabetic, antimicrobial, anti-malarial, anti-inflammatory [9-13], anti-Alzheimer's [14], anti-Parkinson's [15]. Many chalcone based marketed drugs are available nowadays for various activities.so synthesis of various chalcone derivatives possessing anticancer activity is an important step in drug discovery. Common method used for production of chalcone is Claisen - Schmidt condensation [16].



General structure of chalcone

Chalcones contains a variety of functional groups (halogens, aryls, hydroxyls, carboxyl's, phenyl, etc.) that exhibit a broad spectrum of biological activities [17], which facilitate their binding with numerous molecular targets and interactions with other substances. Consequently, chalcones serve as valuable frameworks for the creation of innovative anticancer drugs. The incorporation of any electron-withdrawing group, such as chloro, bromo, or nitro, or the substitution of a phenyl ring in chalcone with any heteroaromatic ring, may boost the potency and biological activity of chalcone. Thiazole, imidazole, Pyrrole, pyrazole, oxazole, isoxazole, pyrazoline, pyridine, indole, benzothiazole, benzimidazole, and quinoline structures are examples of chalcones having an N-heterocyclic moiety that are important in medicine [18].

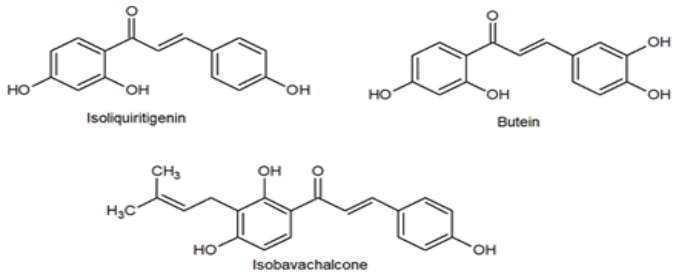
Classification of chalcones:

1. Natural chalcones: they are found in plants
2. Hybrid chalcones: here 1,3-diaryl-prop-2-en-1-one part associated with different chemical structure [19].
3. Bis-chalcones: it has a single structure with two chalcone moieties [20].
4. Heteroaryl or Heterocyclic chalcones: here either one or both aromatic rings of chalcone are replaced by heterocyclic moieties.

General synthetic methods of chalcones

- **Biosynthesis**

Chalcones can be synthesized naturally and synthetically. In plants natural chalcones are synthesized by the influence of an enzyme Chalcone Synthase (CHS), is a polyketide synthase of type III [21]. The enzymes in the CHS family relate with the creation of various secondary metabolites such as flavonoids, stilbenes and aurones [22]. some important naturally occurring anticancer chalcones are isoliquiritigenin, butein and isobavachalcone which are isolated from natural sources.



Structure of naturally derived chalcone

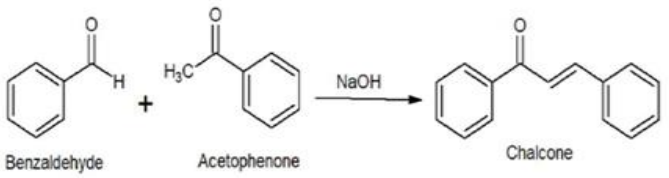
Isoliquiritigenin have therapeutic potential against various cancers such as breast cancer, lung cancer, colon cancer, ovarian cancer, gastrointestinal cancer, leukaemia[23].

Butein have reported anticarcinogenic effects in non-small cell lung cancer [24]. Isobavachalcone have been reported to disrupt cell the AKT/glycogen synthase kinase 3β (GSK3β)/β-catenin route in colorectal cancer cells, thereby blocking cell growth and inducing death [25]. It also has activity against breast cancer [26].

- **Chemical synthesis**

Chalcones are mostly synthesized by condensation reaction through acid or base catalysis. One type of easily produced α, β-unsaturated ketone is chalcone, however an increasing quantity of novel techniques are available because of their fascinating biological functions and the discovery of alternative catalysts or reaction conditions.

a) Conventional Synthesis: A standard method for creating chalcones is Claisen -Schmidt condensation [16]. By reacting aromatic ketones with aromatic aldehydes in the company of strong base catalysts such as KOH, NaOH, Ba (OH)2, or LiOH.2H2O, within polar solvents like ethanol, chalcones can be produced in the lab using the Claisen-Schmidt reaction. Alternative catalysts for this response include sodium phosphate and aluminium-magnesium hydroxide hydrate [27].

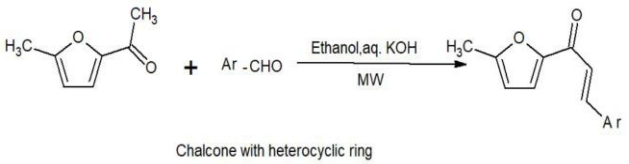


Claisen-Schmidt reaction

Additional synthetic methods employed include one-pot synthesis, solid acid catalyst-mediated reaction, carbonylative Heck coupling reaction, continuous-flow deuteraction reaction, coupling reaction, Sonogashira isomerization coupling reaction and Suzuki-Miyaura coupling reaction [28,29].

b) Green synthetic methods: Conventional chemical synthesis often involves high energy consumption, toxic reagents and time consuming whereas green chemical synthesis focuses on eco-friendly methods that reduce toxicity, energy usage and waste.

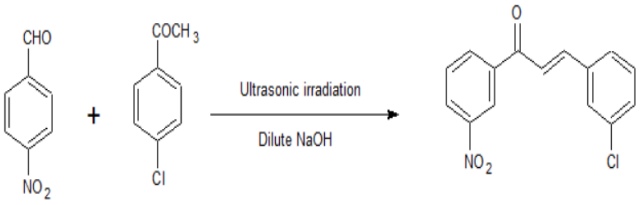
1. **Synthesis of chalcones by microwave assistance method:** A well-liked technique for organic synthesis using a green chemistry approach is microwave assistance. A new chalcone was produced from 2-acetyl heterocyclic analogous and the corresponding aldehyde in an aqueous potassium hydroxide solution via microwave irradiation for around two to six minutes at 180 watts. Additionally, this chalcone was made traditionally at ambient temperature, with the reaction completing in 24 hours[30].



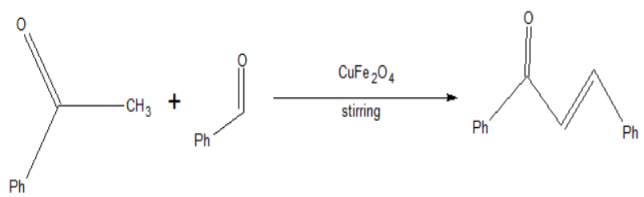
Chalcone with heterocyclic ring

2. **Synthesis of chalcones by ultrasound irradiation:** Ultrasound waves are commonly utilized in many

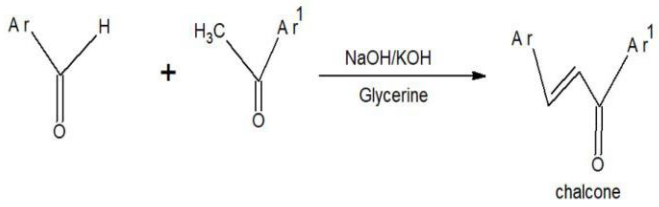
applications within organic synthesis reactions. These waves enhance the reaction rate by lowering energy required for activation. These waves are vital to synthetic organic chemistry as it lowers temperature and duration of reaction. Initially, diluted sodium hydroxide solution was combined with the necessary quantity of aromatic ketone and aromatic aldehyde. After that, this solution was kept at room temperature under ultrasonic radiation in the water bath of an ultrasonic cleaner. This procedure was carried out into 1-2hours.After this hour yellowish product will form. The product is now recrystallized [27].



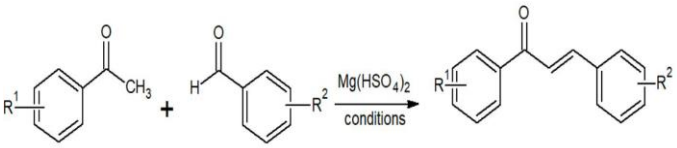
3. **Synthesis of chalcones by Nano catalyst:** Nano catalyst is defined as materials that are at least one-sided nanoscale in size. Catalytic activity is enhanced at the nanoscale. Use of nano catalyst is a new method in modern synthetic compounds. Acetophenone and benzaldehyde were combined in an equimolar quantity. The nano catalysts MCM-41-SO3H, CuNPs/C, and copper ferrite (CuFe2O4) were then added to this solution mixture. After that, keep stirring this mixture until a yellow precipitate forms. The rudimentary chalcone was so made. The crude chalcone was then refined using either recrystallization or collum chromatography [31].



4. **Synthesis of chalcone by using solvent glycerine:** Glycerine is currently frequently utilized as a solvent for the synthesis of chalcones since it is less polar than water. Because this solvent increases the product's yield value. The necessary quantity of acetophenone and benzaldehyde derivatives was combined. The diluted sodium hydroxide/potassium hydroxide solution was then added to this mixture of solutions. Finally, glycerine was added to this chemical mixture as a solvent. After that, mixture of reaction was agitated at room temperature one-two hours. The yellow precipitate collapsed beneath the reaction medium. After neutralizing the reaction media with the HCl solution, it was filtered. As a result, an ethanolic solution was used to produce and recrystallize the yellowish crude chalcone [32].



5. **Solvent-free synthesis of chalcones:** chalcone derivatives synthesis without use of solvent has attracted considerable attention due to its environmental and operational advantages. An effective solvent-free technique for the synthesis of chalcone was described by Ervis saraci and team (2023) using Mg (HSO4)2 as a catalyst. They used Claisen -Schmidt reaction by combining 4-methylthio acetophenone and aldehyde both as solids and Mg (HSO4)2 (200 mol%) under mechanical stirring at 200 rpm at 50 °C for 30 minutes and finally yielded corresponding chalcone [33].



Anticancer activity of chalcones

Chalcones potential anticancer properties have drawn a lot of interest in medicinal chemistry. Chalcones have numerous biological uses because of their pliable shape, which enables them to attach to a broad range of enzymes and receptors [34]. The anticarcinogenic activity of chalcones is mainly associated with their ability to modulate multiple molecular targets involved in cancer progression. The advantage of hybrid compounds is that they show improved selectivity and activity while avoiding drug resistance [35-37]. Therefore, integrating the chalcone moiety with other pharmacological compounds that have anticancer properties is an effective way to develop new medicines [38].

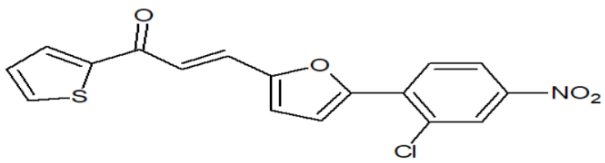
- **mechanism of chalcone against cancer**

Chalcone derivatives exhibit significant actions both in vivo and in vitro in vulnerable and treatment-resistant malignancies by taking action against a range of targets, including aromatase, topoisomerase, tubulin, HDAC, breast cancer resistant protein (BCRP), NF-KB pathway inhibition, and epidermal growth factor receptor (EGFR) and P-glycoprotein inhibition [39,40].

Tubulin inhibition

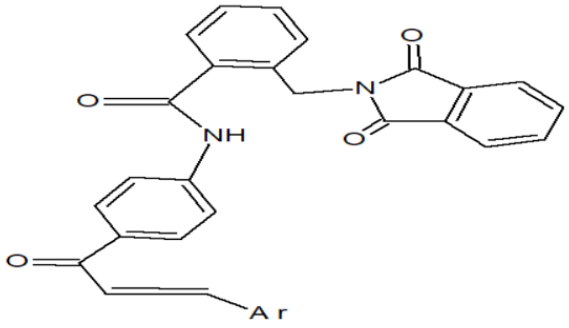
A crucial method of the antiproliferative activity of chalcones is the inhibition of tubulin and the disruption of microtubule assembly, which are vital for preserving cellular form and function during mitosis and cell reproduction [41]. Many chalcone derivatives inhibit the polymerization of Tubulin, which is essential for microtubule formation during cell division. Inhibition of tubulin disrupts mitotic spindle development, leading to G2/M phase cell cycle arrest and apoptosis in cancer cells [42]. The investigation of microtubule proteins has revealed four action targets, categorized into two classes: microtubule-stabilizing binders, which include taxanes and laurimalide binding sites; and microtubule-destabilizing binders, which encompass vinca alkaloids and colchicine binding sites. Both can stop the growth of tumour cells during the cell division phase. The former can encourage the polymerization of microtubule proteins, while the latter prevents the polymerization of tubulin [43].

Ahmed Mutanabbi Abdula *et al.* reported the synthesis and biological evaluation of novel furan–thiophene-based Chalcones as possible anticancer agents. The compounds were produced using the Claisen–Schmidt Condensation between heteroaromatic aldehydes and substituted acetophenones. The antibacterial and anticancer characteristics of generated compounds were evaluated, and in silico molecular docking studies suggested strong binding interactions with the anticancer target Tubulin. The action mechanism of these novel manufactured compounds (AM1–AM4) as possible anticancer drugs was examined in silico against the tubulin colchicine binding site (PDB: 4O2B). MCF-10A the highly popular cell line used as a model for normal human breast cells, exhibits no toxicity to any of the produced compounds. The composite AM4 displayed the strongest activity. The presence of heterocyclic moieties such as Furan and Thiophene in the chalcone framework was reported to enhance the interaction with tubulin, proving their potential as effective tubulin inhibitors for anticancer drug development [44].



Compound AM4

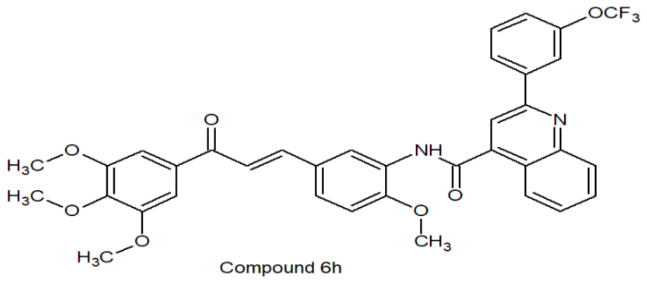
Ahmed A. E. Mourad *et al.* created and synthesized a number of α-phthalimido-substituted Chalcones as dual inhibitors targeting both Histone Deacetylase and Tubulin. The synthesized chalcone hybrids were described by utilizing spectroscopic techniques and evaluated for anticancer activity against human cancer cell lines such as MCF-7 and HepG2. Biological studies demonstrated that several derivatives exhibited significant cytotoxic activity and effectively inhibited β-tubulin polymerization, leading to disruption of microtubule formation and induction of apoptosis in cancer cells. Molecular docking analysis further supported the strong interaction of these chalcone derivatives with the tubulin binding site, suggesting that α-phthalimido-chalcone hybrids could be effective dual-target anticancer agents.7j hybrid had strongest β-tubulin polymerization inhibitory activity [45].



A r = 3,4,5 - Trimethoxyphenyl

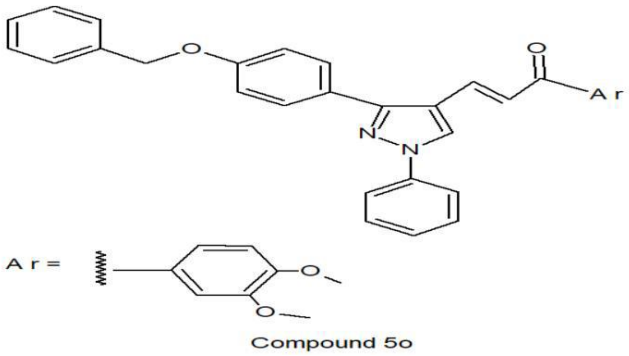
Compound 7j

Tong yan *et al.* designed and synthesized a series of new quinoline based chalcones as dual inhibitors targeting tubulin polymerization and P-glycoprotein. The synthesized 23 derivatives analysed for anticancer activity against cervical cancer cell lines such as cisplatin-sensitive HeLa cells and cisplatin-resistant HeLa cells. Among the tested compounds 6h showed tubulin polymerization inhibition and induced G2/M arrest and apoptosis in both cell lines. The stable binding of 6h to the tubulin CBS and the p-glycoprotein hydrophobic lumen was confirmed by structural insights obtained from molecular docking and dynamic simulations [46].



Compound 6h

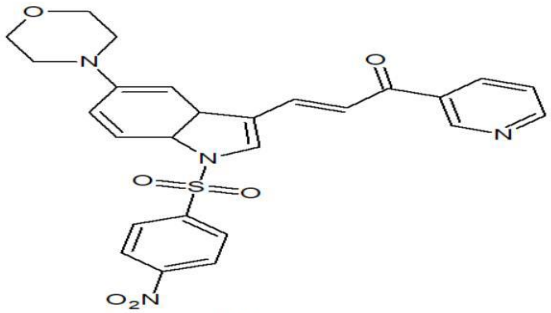
Md. Jahangir Alam *et al.* created and synthesized a number of pyrazole-Chalcone hybrid conjugates as possible anticancer drugs targeting Tubulin polymerization. The produced substances invitro cytotoxic activity against a number of cancer cell lines including (breast) MCF-7, (cervical)SiHa, and (prostrate)PC-3 was assessed. Among the tested derivatives, compound 5o exhibited significant anticancer activity and effectively inhibited tubulin polymerization by interacting with the colchicine-binding site of tubulin. The tight binding relationship between these chalcone conjugates and the tubulin protein was further confirmed by molecular docking experiments, suggesting their potential as promising tubulin-targeting anticancer agents [47].



Compound 5o

M. Zheng *et al.* developed a sequence of 55 novel indole-based chalcone analogous aimed at inhibiting Tubulin and HK2, and evaluated their cytotoxic action on different cancer cell lines. The findings concluded that the compound 20 exhibited notable dual-target inhibitory efficacy against MD-MBA-231 cell lines with IC50

values of 0.76 μM and Hexokinase 2 inhibitory activity with IC50 values of 1.56 ± 0.23 μM [48].



Compound 20

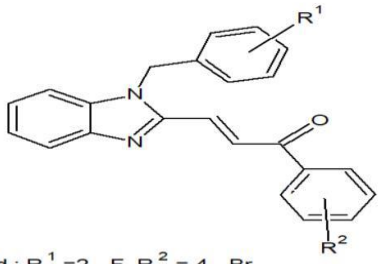
Topoisomerases

Topoisomerases are one of the major targets in cancer treatment. They are enzymes that regulate DNA topology. Topoisomerases take part in several remarkable biological processes in the cells such as DNA replication, transcription and recombination or chromosome condensation [49]. The activity of these enzymes is by binding covalently to the DNA phosphorous group, dividing the DNA strand or strands and at last reunite them. Based on their mechanism of action topoisomerases are of two types: Topoisomerases I (Topo I) and Topoisomerases II (Topo II). The administration of cytostatic drugs, which impede enzyme function results in the permanent disruption of DNA strands (through a stable DNA-topoisomerase complex), ultimately leading to cellular demise. Elevated topoisomerase activity noted in numerous malignancies leads to the targeted efficacy of topoisomerase inhibitor medicines [50].

Table 1: Types and subdivision of Topoisomerase

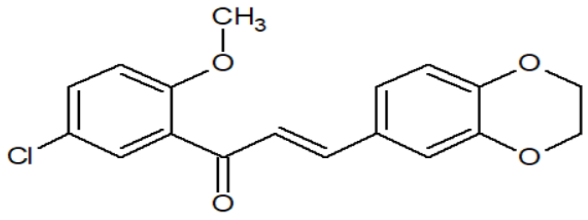
Types of Topoisomerases	subdivision	Subunit Structure
Topoisomerases I	IA	Monomer
	IB	Monomer
	IC	Monomer
Topoisomerases II	IIA	Heterodimer
	IIB	Heterotetramer

Zhou W and team designed and produced a unique class of benzimidazole derivatives in conjunction with chalcone fragment as prospective Topo II-targeting anticancer drugs. These benzimidazole chalcone hybrids demonstrated an antiproliferative effect in four tumour cell lines such as LNCaP (human prostate cancer cell line), HepG2(human hepatoma cell line), A549(human lung cancer cell line), MG63(human osteosarcoma cell line) shows a strong inhibitory impact in the assay for Topo II – induced DNA relaxation. According to mechanistic investigation these hybrids acts as non-intercalative Topo II catalytic inhibitors.4d and 4n showed a variety of anti-tumour activities such as promoting cell death, preventing cell migration and colony formation [51].



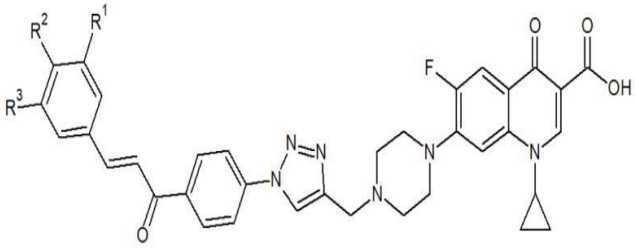
4d : R^1 =2 - F ,R^2 = 4 - Br
4n : R^1 = 4 - CH_3 ,R^2 = 3 - OCH_3,4 - OCH_3,5 - OCH_3

Chen X *et al.*2023 reported that they have discovered a class of new chalcone derivatives that suppressed Wnt signalling and colorectal cancer cell proliferation after screening more than 300 semisynthetic and natural chemicals by utilizing a Wnt reporter assay. CX258 is selected from the family for invitro and in vivo study to delve the molecular mechanism. In colorectal cancer cell they discovered that compound CX258 dramatically reduced nuclear translocation and β-catenin expression, resulting in G2/M phase cell cycle halt. Furthermore, in colorectal cancer cells, CX258 decreased DNA Topoisomerase II alpha (TOP2A) expression [52].



Compound 258

Mohammed HH and coworkers synthesized a number of novel 1,2,3-Triazole linked-ciprofloxacin chalcones. All the 4a-j hybrids are tested for antiproliferative activity. The in-vitro cytotoxic effect of these compounds were evaluated using 59 cancer cell lines (breast, colon, overian ,melanoma ,leukaemia ,renal, CNS, prostate, lung cancer cell lines).4a,4b,4i,4e and 4j hybrids produced notable anti-proliferative effect in leukaemia(RPMI-8226) and colon (HCT116) cancer cells with growth percent of 7.87, -14.59, -24.56, -24.42, -15.84, -9.74, -53.36,-10.26, -31.29, and -39.51% respectively. These 4a-j hybrids were checked for whether they can obstruct the catalytic activity of Topoisomerases I, Topoisomerase II and inhibit tubulin polymerization. The DNA relaxation assay was used to measure the Topo I activity.4a, 4e, 4b, 4i and 4j exhibited Topo I catalytic activity inhibition. Topo II alpha inhibitory activity was evaluated using human topoisomerase II assay kit and 4a had best inhibitory action on both Topo I and Topo II enzymes [53].



4a - j

4a : $R^1=R^2=R^3=H$

4b : $R^1 = Cl ; R^2 = R^3 = H$

4e : $R^1 = R^3 = H ; R^2 = F$

4i : $R^1 = R^2 = OMe ; R^3 = H$

4j : $R^1 = R^2 = R^3 = OMe$

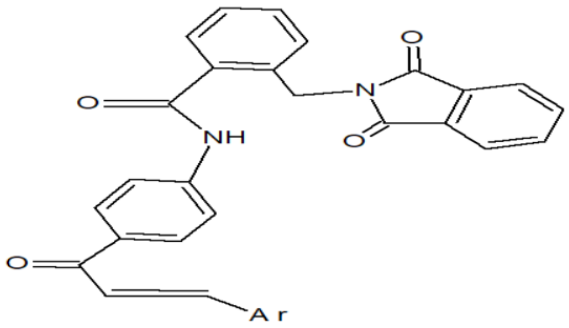
Histone deacetylase inhibitors (HDACi)

Enzymes called Histone deacetylases (HDACs) are essential for the epigenetic control of gene expression through chromatin remodelling. These enzymes eliminate acetyl group from histones [54]. There are 18 HDACs are recognized and they are break down into four classes. HDAC1,2,3 and 8 are included in Class I HDACs. HDAC 4,5,6,7,9 and 10 are under Class II HDACs. SIRT1-7 belongs to Class III HDACs and HDAC11 included in Class IV [55]. One potential treatment strategy for undoing epigenetic changes in a number of diseases is the inhibition of HDACs. Many kinds of HDAC inhibitors were resulted to show strong and specific anticancer effects in preclinical studies [56]. According to the research studies HDAC inhibitors stop the growth of a number of transformed cells in vitro such as lymphoma, myeloma, leukaemia and non-small cell lung cancer. They also stop the spread of solid tumours and haematological malignancies such as lung cancer [57]. The HDAC inhibitors are classified mainly into 4; it is given below [56].

1. Short-chain fatty acid: Butyrate, Valproic acid
2. Hydroxamate: Trichostatin A, Suberoylanilide hydroxamic acid, PXD101, Oxamflatin, LAQ824, LBH589, Pyroxamide, Tubacin, SK-7041
3. Benzamide: MS-275
4. Cyclic tetrapeptide: Depsipeptide, Trapoxin A, Apicidin

Ahmed A. E. Mourad and coworkers synthesized a series of α-phthalimido substituted chalcone hybrids for developing novel anticancer HDAC and Tubulin dual inhibitors. The synthesis of the targeted compound 7a-j is by Claisen -Schmidt Condensation. Three compounds 7c, 7g and 7j were tested for the in-vitro HDAC inhibitory activity. Using entinostat as a reference drug the IC50 values for the chosen derivatives were calculated against

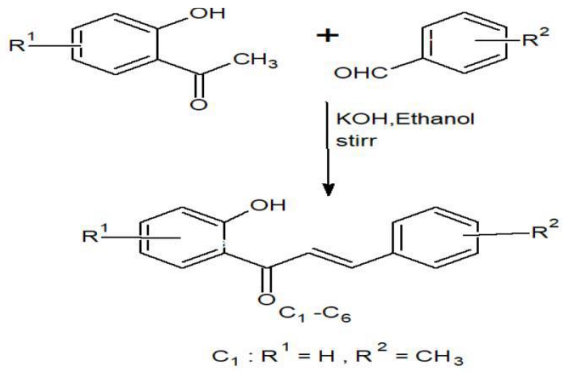
HDAC1 and 2 isoforms. The results revealed that the 7j hybrid given highest HDAC1 HDAC2 inhibitory activity [45].



A r = 3,4,5 - Trimethoxyphenyl

Compound 7j

Recently, Mansour MA and colleagues designed and synthesized a series of novel quinazoline-chalcone hybrids as HDAC and EGFR dual inhibitors in many cancer cell lines. Compound 5e, a powerful derivative with a 3,4,5-trimethoxyphenyl chalcone component, showed the best growth inhibition value against the panel of NCI 60 human cancer cell lines among the produced compounds. To confirm its selectivity, this substance was evaluated against a panel of tyrosine kinase enzymes. It specifically suppressed HDAC8, EGFR and HDAC6 according to the results. Insilico analysis was used to examine the binding interaction of the most active chemicals inside the zinc-containing binding domain of HDAC8 and HDAC6[58]. Pande AN and coworkers reported synthesis of six 2′-hydroxy chalcones (C1-C6) and evaluated their in-vitro cytotoxicity on human colon carcinoma (HCT116) and African Green monkey kidney epithelial cells. Additionally, they screened HDAC enzyme inhibition experiments. They synthesized compounds through Claisen-Schmidt condensation. The scheme is given below. The impact of test substances on the epigenetic machinery of HCT116 cells was assessed using the whole cell HDAC enzyme inhibition assay. The results showed the compound C1 as most potent with HDAC inhibition and obtained an IC50 value of 105 ± 10 μM [59].



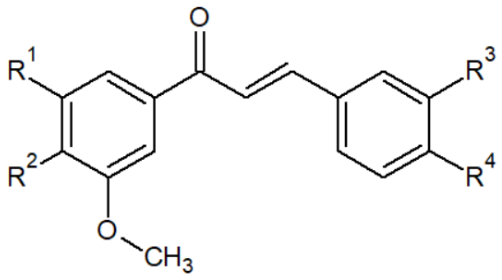
$C_1 : R^1 = H , R^2 = CH_3$

NF- k B Pathway inhibition

Nuclear Factor Kappa B (NF- KB) pathway is a prominent pathway in inflammatory and immune responses, any hindrance to the route leads to several consequences including cardiovascular diseases, cancer, neurological disorders and inflammatory diseases. Numerous target genes that support cell cycle progression, control cell apoptosis and encourage cell adhesion, angiogenesis and metastasis are expressed when NF-kB is present [60]. Recent research studies showing that chalcones can impede the lkB degradation or interfere with NF-kB's ability to bind DNA, hence blocking the NF-kB pathway. In hematologic malignancies NF-kB pathway inhibitors have demonstrated the best clinical success [61,62,63].

It has been observed that the natural chalcone lichochalcone A decrease the growth of colon cancer cells. Additional Western blot and Rt-PCR studies have showed that LiA suppresses p65 phosphorylation, which in turn negatively controls NF-KB signaling. It is necessary to emphasize that p65 phosphorylation is essential for NF-KB transcriptional activation[64].Recently a study was conducted by Papierska and coworkers ,they synthesized new Thio derivative chalcones and investigated their impact on NF-KB,STAT3,EGFR and NrF2 signalling pathway in colorectal cancer cells.DLD-1 and HCT116 colorectal cancer cell lines are used for

the study .In both studied cell lines, chalcone 4 inhibited NF-KB activation, both subunits translocation into the nucleus fraction-KB's binding to DNA and mRNA[65].

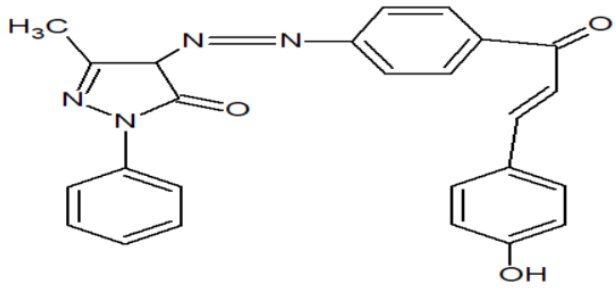


chalcone 4 : R^1 = Br ,R^2 = OMe ,R^3 = SMe , R^4 = H

Another study was conducted in 2024, where they investigated about anti-breast cancer activity of 2'-Hydroxychalcone against two breast cancer cell lines MCF-7 and CMT-1211.They have conducted both in-vitro and in-vivo studies. Mechanistic analysis showed that 2'-Hydroxychalcone therapy markedly suppressed the NF-KB pathway along with excessive intracellular reactive oxygen species accumulation, endoplasmic reticulum stress induction and JNK/MAPK activation. Also, in breast cancer cells these chalcone increases autophagic levels and triggers apoptosis, which may be related to the suppression of pro-survival NF-KB signaling [66].

PI3K/Akt signaling pathway inhibition

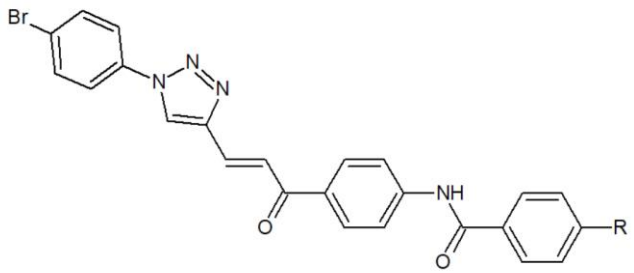
Cell proliferation and survival, differentiation, migration and metabolism all depend on phosphatidylinositol 3 kinase (PI3K) and its downstream target, Protein kinase B or Akt [67]. So PI3K/Akt signaling pathway is crucial for cell division. PI3K is a family of heterodimeric lipid kinases. Akt belongs to the protein kinase AGC subfamily and is a serine protein kinase [68]. When a PI3K-phosphorylated phosphoinositide (PI) known as PIP3 binds to the homology Akt domain, it translocates to the plasma membrane and is phosphorylated by PDK1and PDK2 at two phosphorylation sites, Ser473 and Thr308 which activates Akt in tumour cells. Direct PI3K/Akt degradation leads to inhibition of Akt activation and causes apoptosis [69]. Inhibition of PI3K/Akt pathway has leaded to anticancer activity in many studies, so there are different PI3K/Akt inhibitors. PI3K inhibitors are divided into three such as pan-PI3K, isoform selective and dual inhibitors. While Akt inhibitors are of two types Allosteric inhibitors and ATP-competitive inhibitors [68]. Various chalcone derivatives were studied for anticancer activity through inhibition of PI3K/Akt signaling pathway. A study was conducted by Noser AA *et al.* They synthesized novel pyrazolinone chalcones and its anticancer activity was investigated via inhibition of PI3K/Akt/ERK1/2 signaling pathway. By condensing azo Pyrazolinone derivatives with different aromatic aldehydes, pyrazolinone chalcone derivatives have been created. By focusing on the PI3K/Akt signaling pathway, all compounds were evaluated Insilico for their capacity to prevent cancer growth and metastasis. The outcome showed that compound 6b have potent blocking action on A549, MDA-231, Caco, MCF-7 and PCL cancer cell lines. Insilico study was conducted with this compound 6b and invitro studies supported this compound cause cell death and apoptosis by promoting ROS generation-mediated inhibition of PI3K/Akt [69].



Compound 6b

Abbas SH et al. reported production of new quinoline chalcone hybrids and their anticancer efficacy was evaluated by cytotoxicity and PI3K inhibitory activity. The hybrids were synthesized through Claisen-Schmidt

condensation. Compounds 9i and 9j showed potent activity. Mechanistically these two derivatives caused apoptosis and G2/M cell cycle arrest in A549 and K562 cancer cell lines. Compound 9i demonstrated the strongest efficacy against PI3K-γ isoform. In-vitro Western blotting analysis demonstrated that 9i and 9j obstructed phosphorylation of PI3K, Akt, Mtor [70]. Another study was conducted for the development of novel 1, 2, 3-triazole chalcone derivatives as possible agents against Osteosarcoma. The luminescent kinase test was employed to evaluate the compounds P13K inhibitory activity, and the MTT test was used to assess the anticancer activity of compounds 4e, 4f and 4g against human OS cell lines (MG-63), liver cancer cell lines, cervical cancer cell lines and lung cancer cell lines. Compound 4e demonstrated potent P13K inhibitory profile [71].

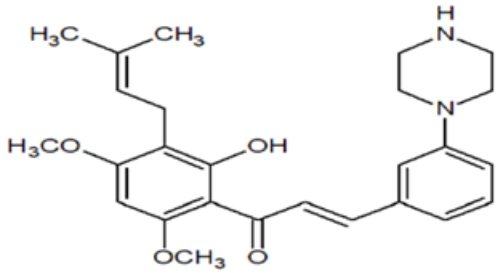


compound 4e : R = F

P-glycoprotein inhibition

The most researched and well characterized ABC (ATP-binding cassettes) transporter linked to chemotherapy resistance in cancer is p-glycoprotein (P-gp)[72]. Permeability glycoprotein (P-gp) was the first ABC transporter to be identified. P-gp is mostly located in the apical membranes of epithelial cells in the body including GI system, ovaries, liver, placenta, adrenal and pituitary glands, kidney, choroid plexus and brain capillaries [73]. The ABCB1 gene encodes p-gp, it is a transmembrane protein that belongs to ABC transporter superfamily. It acts as an efflux pump for various anti-cancer drugs. Overexpression of P-gp is a critical mechanism of multidrug resistance in many cancers [74]. P-gp inhibitors are compounds intended to address MDR in oncology by obstructing the efflux pump that expels chemotherapeutic medicines from neoplastic cells. They are classified into three; first generation inhibitors (eg. verapamil), second generation inhibitors (eg. Dexverapamil) and third generation inhibitors (eg. tariquidar) [75,76].

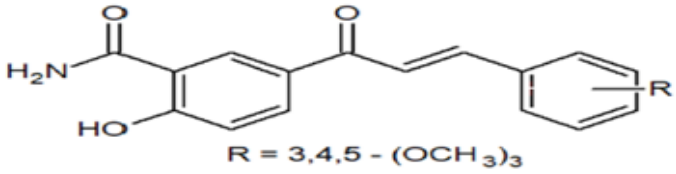
A study was reported by Minh-Tri Le and team in 2021, they screened chemo library of 95 in-house chalcone derivatives using the structure of targets P-gp and NorA and two compounds F88 and F90 as prospective influencers of both transporters. Their efficiency was confirmed by invitro experiments [77]. Another study was conducted by Ting Wang and coworkers synthesized novel chalcone derivative C49 which has ability to reverse Doxorubicin resistance in MCF-7/DOX cells by inhibiting P-glycoprotein. They confirmed the activity of C49 by In-vitro and in-vivo experiments. Western blot analysis was employed to assess the alterations I protein expression in MCF-7/DOX cells before and after drug intervention. The role of C49 on breast cancer was confirmed in-vivo by constructing a breast cancer Xenograft on nude mouse. They find out that C49 may impair the functionality of P-glycoprotein in expelling DOX from cells by downregulating p-gp expression, hence elevating intracellular DOX level [78].



Compound C49

Apoptosis Induction

Apoptosis is a well-planned and coordinated cellular process where cells destroy themselves to maintain normal tissue balance and remove unwanted or damaged cells. Apoptosis induction in cancer seeks to eradicate malignant cells [79]. Certain regulatory proteins like BCL-2, BAX, Tubulin, Caspase-3, Caspase-9, and other kinases may be inhibited or activated to induce apoptosis. Several studies showed chalcone derivatives can act as apoptosis inducers [80]. Othman EM and coworkers conducted a study about novel synthetic1,2,3 Triazole chalcones conjugates treated with leukemia cancer cells and evaluation of their cell cycle analysis, PARP-1 inhibition and apoptosis induction. By combining the 1,2,3-triazole and chalcone favoured fragments into a single scaffold a series of new compounds were created. A panel of sixty cancer cell lines has been used to test each of the compounds for cytotoxicity. The finding of those investigations demonstrated 11e has the capacity to halt the cell cycle at the s phase and cause apoptosis by upregulating BAX, Caspase-3 and Caspase-9 [81]. Another study was reported by synthesizing 14 chalcone derivatives and analysed their antitumor activity against four human cancer cell lines such as HeLa, A549, HL-60, HepG2.Out of all compounds inhibitory activity against HepG2 cells was better for compound a14.This work investigated the inhibitory mechanism of a14 towards HepG2 using apoptosis, Cyle arrest, measurement of mitochondrial membrane potential and evaluation of reactive oxygen species (ROS) level. Western blot experiment is used for apoptosis induction analysis [82].



Compound a14

Conclusion

Chalcones are reported to exhibit various biological activities. Chalcones represent a prominent class of both naturally occurring and synthetic compounds that have significant attention for their potential anticancer activity. Generally used synthetic method for chalcone is Claisen - Schmidt condensation. Cancer is still one of the major mortality rates increasing disease in world and development of novel drugs for cancer is an important task in world. Several research studies are reported about anticancer activity of chalcone derivatives. This review covers latest studies about synthesis of chalcones, anticancer activity of chalcones against various breast, lung, colorectal, cervical, prostate cancer cell lines. Also explain about chalcone derivatives mechanism against various targets. This review aims to motivate researchers and students to design and produce a wide range of powerful chemicals with the potential to greatly impact cancer treatment by providing a thorough grasp of the chalcone framework.

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