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Review Article

Chalcones: Promising therapeutic agents targeting key players and signaling pathways regulating the hallmarks of cancer

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ABSTRACT

The need for innovative anticancer treatments with high effectiveness and low toxicity is urgent due to the development of malignancies that are resistant to chemotherapeutic agents and the poor specificity of existing anticancer treatments. Chalcones are 1,3-diaryl-2-propen-1-ones, which are the precursors for flavonoids and isoflavonoids. Chalcones are readily available from a wide range of natural resources and consist of very basic chemical scaffolds. Because the ease with which the synthesis it allows for the production of several chalcone derivatives. Various *in-vitro* and *in-vivo* studies indicate that naturally occurring and synthetic chalcone derivatives exhibit promising biological activities against cancer hallmarks such as proliferation, angiogenesis, invasion, metastasis, inflammation, stemness, and regulation of cancer epigenetics. According to their structure and functional groups, chalcones derivatives and their hybrid compounds exert a broad range of biological activities through targeting key elements and signaling molecules relevant to cancer progression. This review will provide valuable insights into the latest updates of chalcone groups as anticancer agents and extensively discuss their underlying molecular mechanisms of action.

1. Introduction

Cancer is a devastating disease that affects individuals globally, and it's the second leading cause of death worldwide [1]. 19.3 million new cancer cases were detected in 2020, while 10 million people died from cancer [2]. Cancer is a complex disease whereby a group of cells abnormally grows *via* uncontrolled signals. Normal cells are regulated by signals that control cell division, differentiation, or cell death. In contrast, cancer cells can govern these signals, leading to a loss of control [3]. During the development of a neoplastic clone, cells accumulate a series of genetic or epigenetic modifications, altering gene expression and resulting in altered phenotypes [4]. Cancer acquires six biological capabilities gained during multistage tumor development and is considered the main cancer hallmarks. Prolonged proliferation signals, evasion of growth suppressors, resistance to cell death, immortal replication, induction of angiogenesis, activation of invasion and metastasis, and evasion of cell death are all hallmarks of cancer. These hallmarks are the basis for the complexity of the neoplastic disease. A summary of the main hallmarks of cancer is shown in Fig. 1 [5].

Chemotherapy is a crucial conventional treatment for cancer patients and has been used for several decades to improve patient outcomes [6]. Despite the chemotherapeutic medications' enhanced efficacy, their long-term administration is hindered by both the tumor drug resistance developed to many treatments and undesirable side effects [7,8]. So, the major challenge is developing effective anti-cancer drugs with no/or low toxicity and minimum acute and long-term side effects on normal tissues. In this context, chalcones appear as promising anticancer drugs.

1.1. Chalcones

The chalcones scaffolds are flavonoid and isoflavonoid precursors [9]. There are nine different categories of flavonoids. These categories are as follows: flavonols, flavones, flavanones, flavan-3-ols, anthocyanidins, isoflavones, aurones, and chalcones [9,10]. They may be found

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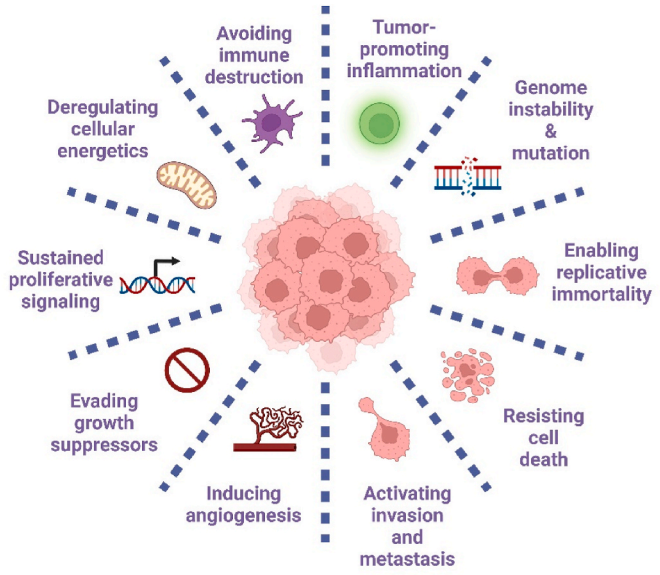


Fig. 1. Summary of main cancer hallmarks (modified from Hanahan & Weinberg, 2011).

Fig. 2. Basic chemical structure of chalcones.

in a broad variety of natural items, including citrus fruits, and vegetables [10,11]. Chalcones, either found in nature or as synthetic analogs [11–21] exhibit various anti-cancer, anti-inflammation, and anti-mutagenic activities [14,15]. They have the potential to target critical molecular elements involved in the initiation and progression of cancer [12]. Synthetic chalcone derivatives exert its biological activities *via* their different functional groups. Benzylideneacetophenone or 1, 3-diphenyl-2-propene-1-one comprises two aromatic rings linked to one another by an α,β-unsaturated carbonyl bridge containing three carbons.

1.1.1. Chemistry of chalcones

Chalcones occur as two isomers, the trans (E, 1) or cis (Z, 2) (Fig. 2). The E isomer is the predominant structure among chalcones because, from a thermodynamic perspective, it is the more stable of the two isomers [22,23]. Due to the numbers of replaceable hydrogens, it opens the way for the synthesis of many chalcone derivatives with different functional groups which results in various biological activities. As a result, chalcones have become attractive area of research cancer treatment [24].

1.1.2. Synthetic chalcones

Extensive research has been devoted to synthesize new chalcones that exert anti-cancer activities similar to naturally occurring chalcones. The difference between natural and synthetic reactions is illustrated in Fig. 3. Chalcones have basic chemistry that allows the fast synthesis of various substitutions. Several methods and schemes for synthesizing chalcone derivatives are currently available. The most common method is the Claisen-Schmidt Condensation and Aldol condensation [25]. Other schemes are also available such as Carbonylative Heck Coupling Reaction [26], Coupling Reaction Chalcones [27], Sonogashira Isomerization Coupling [28], Continuous-Flow Deuteraction Reaction [29], Suzuki–Miyaura Coupling Reaction [30], and Solid Acid Catalyst Mediated Reaction [31].

1.2. Biological activities of chalcones

Chalcones are considered Michael acceptors. Biologically, to acquire the Michael adduct, the Michael acceptor may quickly form covalent bonds with cysteine sulfhydryl or other thiols (Fig. 4). In addition, Michael adducts can be formed with Lysine, Histidine, Arginine, Serine, and N-terminal residues of proteins [33–37], through which they exhibit their biological activities [38–40].

The most frequently studied chalcones with anticancer effects are diphenyl-2-propen-1, the simplest chalcone structure. Structural manipulations are predominant on both ring A and ring B [41]. Chalcone derivatives anti-cancer properties are significantly influenced by changing the functional groups on the rings of chalcones, and the biological activities of chalcones are summarized in Fig. 5

1.2.1. Antiproliferative activities of chalcones

Normal tissues carefully regulate the secretion of growth-promoting signals to retain normal cell numbers. When these signals are dysregulated, cells loss their control of their growth and tumor will be formed [5]. Cancer cells are able to maintain proliferative signals too. Their self-produced growth factors may cause them to react by expressing homologous receptors, which stimulate autocrine proliferative processes. Alternatively, normal cells in the stroma that support the tumor may be stimulated by signals from cancer cells and reciprocally respond by secreting numerous growth factors to support cancer cell survival [5, 42,43]. Chalcones can inhibit cancer cell growth through different mechanisms, which will be discussed in the following section.

1.2.1.1. Chalcones as inhibitors of microtubule formation. Microtubules, a fundamental structural component of eukaryotic cells, are associated with various cellular functions, including maintaining the cell's shape and division, cell signaling, cell motility, and the transport of intracellular vesicles [44]. Microtubules are composed of alpha and beta dimeric protein subunits. Small-molecule inhibitors may disrupt the tubulin polymerization and depolymerization, resulting in cell cycle arrest and subsequent cell death. Therefore, microtubules emerge as an appealing pharmacological target in cancer [45–47]. Both natural and synthetic chalcones showed a very interesting anticancer activity *via* inhibiting microtubule formation. Structure-activity relationships of 1, 3-diarylprop-2-en-1-ones bearing both the A- and B-ring substitution revealed that replacing electrostatic, steric, and donor groups in compounds acting as inhibitors of microtubule polymerization alters their biological activity. Molecular docking of chalcone compounds showed their ability to bind to the tubulin protein's active site [48]. The amino-substituent millepachine derivative (A-ring: 5-methoxy-2, 2-dimethyl-2*H*-chromen-8-yl/B-ring: 3-amino-4-methoxyphenyl) demonstrated remarkable anticancer efficacy against a panel multidrug-resistant cancer cells by binding to the colchicine binding domain and resulting in the inhibition of tubulin polymerization [49]. A new o-aryl chalcone (A-ring: 3′-fluoro-[1,1′-biphenyl]-2-yl/B-ring: 3-hydroxy-4-methoxyphenyl) displayed potent cytotoxicity in low nanomolar concentration against multidrug-resistant cell lines namely, human ovarian paclitaxel-resistant cells, ileocecum vincristine-resistant cells, and breast doxorubicin-resistant cells [50]. In addition, complexes of chalcone such as Pt showed a high affinity to tubulin's colchicine site against CDDP-resistant cells [51]. Benzo [*d*]imidazo [2,1-*b*]thiazole conjugates with chalcone (A-ring: 2,3,4,5-substututed benzene/B-ring: 7-R-benzo [*d*]imidazo [2,1-*b*]thiazol-2-yl) efficiently blocked microtubule assembly in MDA MB-231 cancer cells [52]. Indolyl-chalcones ((*E*)-2-((1*H*-indol-3-yl)methylene)-3,4-dihydronaphthalen-1(2*H*)-one) caused destabilization of the microtubules, cell death, and inhibited proliferation in prostate and lung cancer cells, which was dependent on

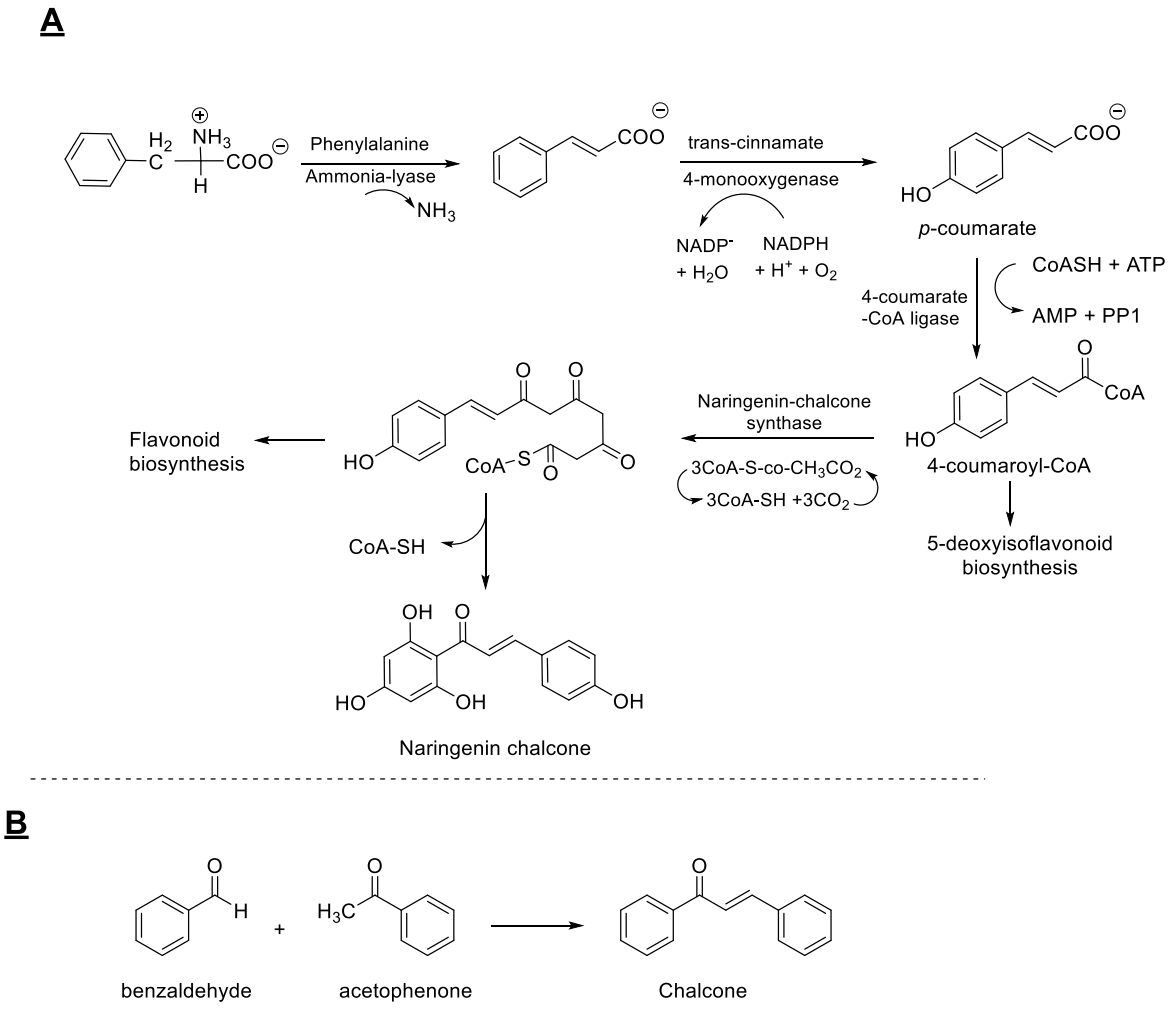


Fig. 3. A schematic diagram shows the difference between natural (A) and synthetic methods (B), showing the simple synthetic reaction compared to the natural process [32].

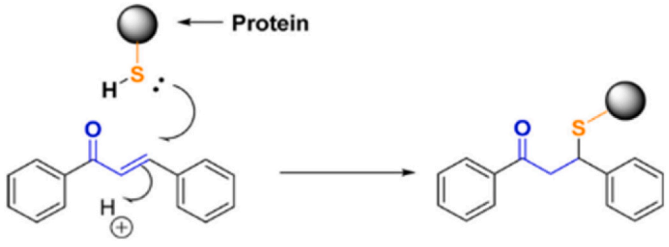


Fig. 4. Schematic illustration of Michael Addition reaction of chalcone with cysteine forming a covalent interaction.

expression of stathmin (STMN1) (which is known to regulate the microtubule filament system by destabilizing microtubules) [53]. (*E*)-2-(2′,4′-Dimethoxybenzylidene)-1-tetralone disrupted microtubule architecture and tubulin downregulation in HCT116 colorectal cancer cells [54]. Various chalcones derivatives act as inhibitors of microtubule formation are depicted in Table 1.

Surprisingly, on the other hand, hybrid chalcones stabilized tubulin polymers in both live cells and cell lysates, in contrast to the microtubule targeting drugs, which have the ability to inhibit tubulin polymerization. This was achieved by combining combretastatins chalcones and (Z)-5-chloro-3-(2-oxo2 (3,4,5trimethoxyphenyl) ethylidene) (Fig. 6.1) [81]. In addition, the action of cyano bis(indolyl) chalcones acts as a

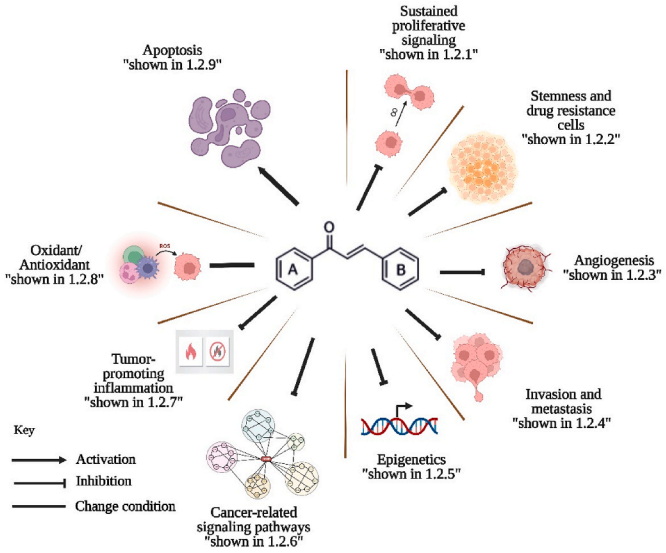
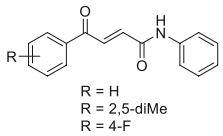
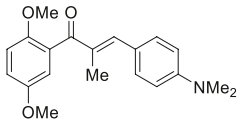
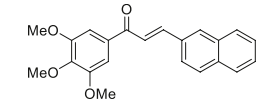
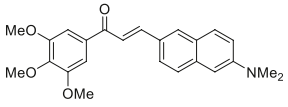
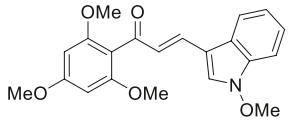
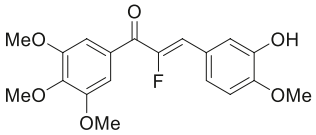
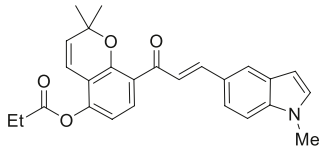
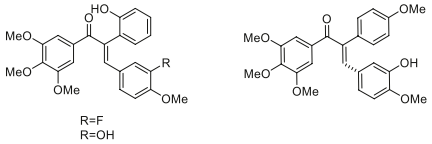
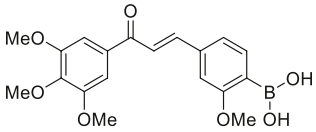
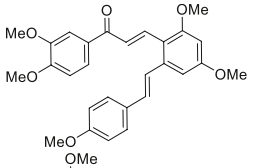
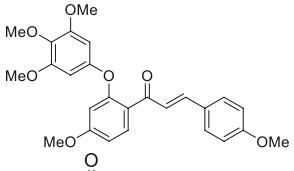
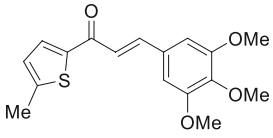


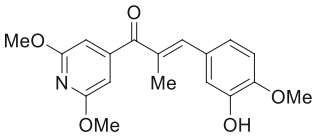
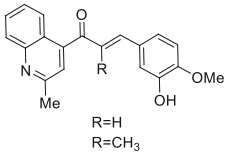
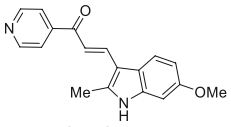
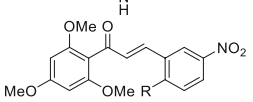
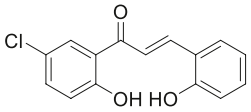
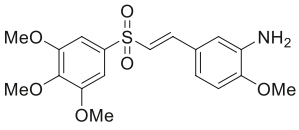
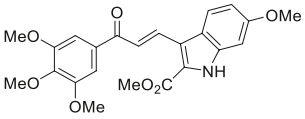
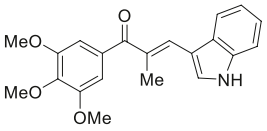
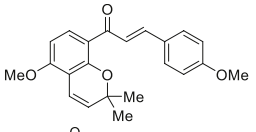
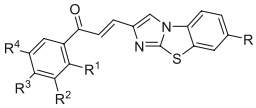
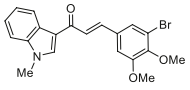
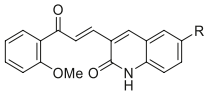
Fig. 5. Summary of the biological activities of chalcone derivatives.

Table 1
Summary of the antimicrotubule activity of chalcones.

A-Ring/B-Ring	Structure	Cancer model	Biological activity	References
Aryl/phenylamino (Amide chalcone attached to B-ring)	 R = H R = 2,5-diMe R = 4-F	Hela, K562, and FemX	Inhibitors of tubulin polymerization	[55]
2,5-dimethoxyphenyl/4-(dimethylamino)phenyl		Porcine brain tubulin	Inhibits the assembly of microtubules	[56]
3,4,5-trimethoxyphenyl/naphthalen-2-yl (or 6-(dimethylamino) naphthalen-2-yl)	 	Leukemia cancer cells, cervical cancer cells , and breast cancer cells	Destabilization of microtubules	[57]
2,4,6-trimethoxyphenyl/1-methoxy-1*H*-indol-3-yl		Brain tumors	Tubulin polymerization inhibition and, M phase cell cycle arrest	[58]
3,4,5-trimethoxyphenyl/3-hydroxy-4-methoxyphenyl (Also, it has α-fluorenone)		K562 cell line	Tubulin polymerization inhibitor	[59]
2,2-dimethyl-5-(propionyloxy)-2*H*-chromene-8-yl/1-methyl-1*H*-indole-5-yl		SKOV3, HepG2, PC-3, A549, K562, SMMC-7221, HCT116, and MCF-7), (HCT-8/V), (HCT-8/T)	Tubulin polymerization inhibition and, M phase cell cycle arrest	[60]
3,4,5-trimethoxyphenyl/2-fluoro (hydroxy)-4-methoxyphenyl (Comberstatin-like)	 R=F R=OH	P388, L1210, A549, and A2780	β-tubulin inhibition colchicine binding site G2/M phase	[61]
3,4,5-trimethoxyphenyl/(2-methoxybenzene)boronic acid (Boronic acid chalcone analogs of comberstatin		NCI Cancer Cell	Polymerization inhibitor	[62]
3,4-dimethoxyphenyl/(*E*)-1,3-dimethoxy-5-(4-methoxystyryl) phenyl (Resveratrol)		HepG2, B16–F10, and A549 cell lines	Tubulin polymerization inhibitory	[63]
1,2,3-trimethoxy-5-(3-methoxyphenoxy)phenyl/4-methoxyphenyl (Chalcone containing diaryl ether)		Molecular docking research	Tubulin's colchicine binding	[64]
5-methylthiophen-2-yl/3,4,5-trimethoxyphenyl		Chemosensitivity to low paclitaxel doses in NCI–H460 cells	Antimitotic behavior	[65]
2,6-dimethoxypyridin-4-yl/3-hydroxy-4-methoxyphenyl		K562 and MDA-MB-231	Microtubule polymerization inhibitory colchicine binding site	[66]

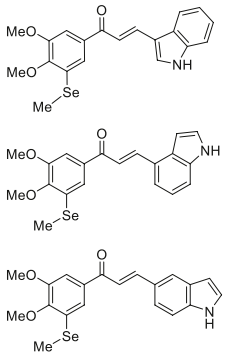
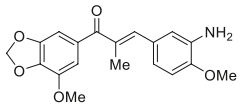
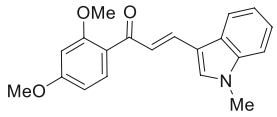
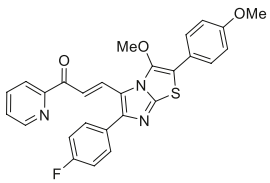
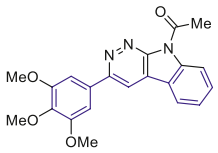
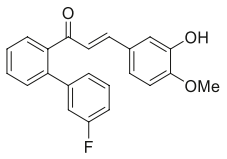
(*continued on next page*)

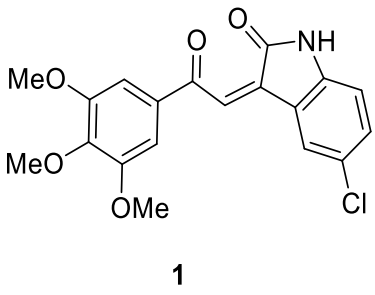
Table 1 (*continued*)

A-Ring/B-Ring	Structure	Cancer model	Biological activity	References
2-methylquinolin-4-yl/3-hydroxy-4-methoxyphenyl	  R=H R=CH_3	K562 cancer cells	Tubulin's colchicine site inhibition	[67]
pyridin-4-yl/6-methoxy-2-methyl-1*H*-indol-3-yl		U251 glioblastoma U251 cells *in vitro* and xenograft model	Cross blood-brain barrier tubulin's colchicine site causing mitotic arrest	[68]
2,4,6-trimethoxyphenyl/2-methoxy (chloro)-5-nitrophenyl (Plant-based chalcones)	 R=H R=OMe R=Cl	Breast cancer triple-negative cell line	Interfering with microtubule structure and causing G1 phase arrest	[69]
5-chloro-2-hydroxyphenyl/2-hydroxyphenyl (5'-Chloro-2,2'-dihydroxychalcone)		PC-3 cells (androgen-independent and taxane-resistant prostate cancer)	Disruption of microtubule	[70]
sulfonyl-3,4,5-trimethoxyphenyl/3-amino-4-methyxyphenyl (Vinyl sulfone or sulfoxide moieties)		H22 allograft liver cancer mouse model	G2/M phase arrest, cell death, and microtubule disruption	[71]
3,4,5-trimethoxyphenyl/6-methoxy-2-(methoxycarbonyl)-1*H*-indole-3-yl		HT29, HeLa, and MCF-7	Tubulin polymerization inhibition	[72]
3,4,5-trimethoxyphenyl/1*H*-indol-3-yl (*α*-methyl-substituted indole-chalcone)		NCI-60 cell lines	Hindering microtubule dynamics	[51]
5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)/4-methoxyphenyl (Millepachine, a natural chalcone)		G2/M cell cycle arrest	Interact with *β*-tubulin directly and irreversibly colchicine	[73]
2,3,4,5-substututed benzene/7-R-benzo [*d*]imidazo [2,1-*b*]thiazol-2-yl	 R = H, Me, OMe, OEt, F R^1 = H, Br R^2 = H, OMe, OH R^3 = R^4 = H, OMe	A549 cell	Antimicrotubule polymerization	[74]
1-methyl-1*H*-indol-3-yl/3-bromo-4,5-dimethoxyphenyl (Indole-based chalcone)		A549 cell	Antimicrotubule polymerization	[74]
2-methoxyphenyl/6-alkyl-2-oxo-1,2-dihydroquinoline-3-yl	 R = H R = OMe	Multidrug-resistant cancer cells	Colchicine-binding site inhibitor, Strong inhibition of microtubule activity	[75]
3,4-dimethoxy-5-(methylselanyl) phenyl/1*H*-indol-(3, 4, or 5)-yl (Selenium-containing indole chalcone)		A549, HepG2, HeLa, HCT116, MDA-MB-231, and RKO cells.	Inhibiting tubulin polymerization	[76]

(*continued on next page*)

Table 1 (*continued*)

A-Ring/B-Ring	Structure	Cancer model	Biological activity	References
				
7-methoxybenzo[*d*][1,3]dioxol-5-yl/ 3-amino-4-methoxyphenyl		MDA-MB-231	Colchicine site of tubulin	[77]
2,4-dimethoxyphenyl/1-methyl-1*H*-indol-3-yl		Bladder cancer cells	T¦ubulin polymerization inhibition at colchicine binding site	[78]
pyridin-2-yl/6-(4-fluorophenyl)-3-methoxy-2-(4-methoxyphenyl) imidazo [2,1-*b*]thiazol-5-yl		A549 cells	Suppressed microtubule assembly	[79]
1-(3-(3,4,5-trimethoxyphenyl)-9*H*-pyridazino [3,4-*b*]indol-9-yl)ethan-1-one		Acute monocytic leukemia THP-1	Tubulin polymerization inhibitor in colchicine binding site	[80]
azacarboline- chalcone hybrids as constrained chalcone analogues				
3′-fluoro-[1,1′-biphenyl]-2-yl/3-hydroxy-4-methoxyphenyl (Ortho-aryl chalcone)		A549 cancer cells A549 tumor xenograft	G2/M cell cycle arrest and tubulin inhibition in colchicine binding site	[50]



1

Fig. 6. Chemical structure of chalcone hybrid induced stabilization of tubulin polymers.

stabilizer of tubulin polymerization [82].

1.2.1.2. Chalcones as inhibitors of topoisomerase expression or activity. Topoisomerase II is an enzyme that can cut both DNA strands and reseal them [83]. The inhibition of topoisomerase results in a double-strand break inside the DNA, which causes G2 phase cell cycle arrest. Inhibition may occur through interfering with the enzyme's activity or by stabilizing the topoisomerase-DNA complex. Eventually, this results in double-strand breaks of DNA [10,84]. Novel N-4-piperazinyl-ciprofloxacin-chalcone hybrids showed anticancer activity *via* inhibition of topoisomerase I and II activity compared to the conventional etoposide chemotherapy [10]. Also, urea-linked ciprofloxacin (CP)-chalcone (Fig. 7.2 and 3) showed similar inhibitory activity compared to topotecan and camptothecin [85]. Using quantitative structure-activity relationships (QSAR) techniques, carbazole chalcone analogs showed an inhibitory impact on topo II. The most important factor that influences the activity of the compounds under consideration is the octanol-water partition coefficient, highlighting the significance of flexibility as a crucial molecular characteristic to enhance cell membrane crossing and improve the activity of these compounds against topoisomerase II [86]. As non-interactive Topo II catalytic inhibitors, benzimidazole-chalcone hybrids have an excellent inhibitory effect confirmed by DNA relaxation assay and anti-proliferative impact in four tumor cell lines. According to the docking studies and structure-activity relationship, the chalcone motif [(A-ring: 2-fluorobenzyl-1H-benzo [*d*] imidazole-2-yl; B-ring: 4-bromophenyl) and (A-ring: 4-Methylbenzyl)-1H-benzo [*d*]imidazole-2-yl; B-ring: 3,4,5-trimethoxyphenyl)] may contribute to the inhibitory and anti-proliferative effect of Topo

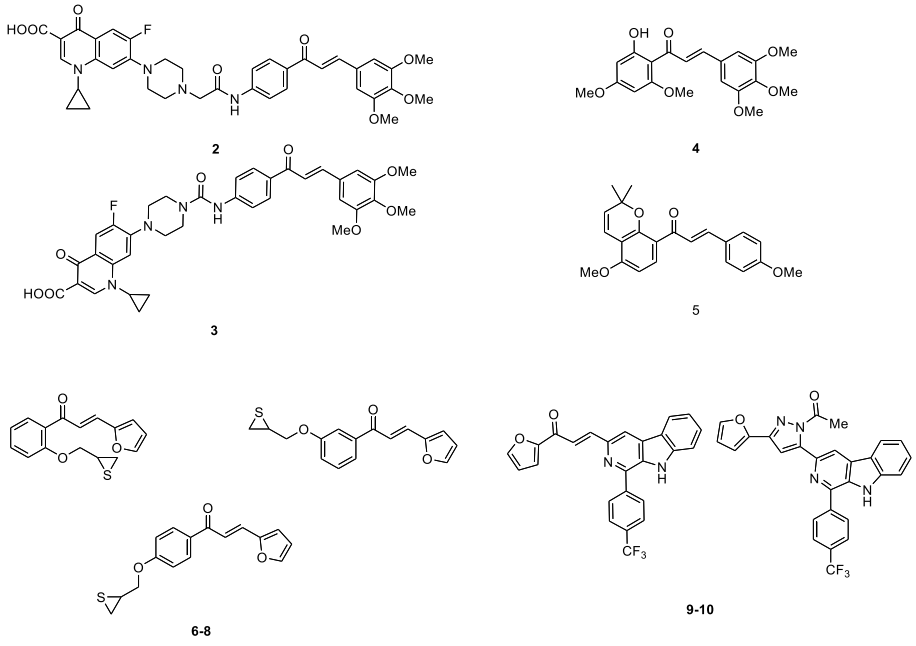


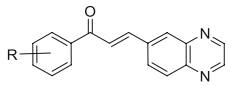
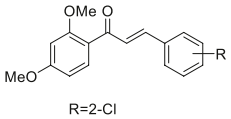
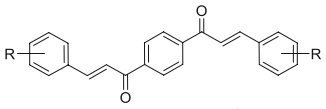
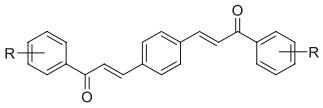
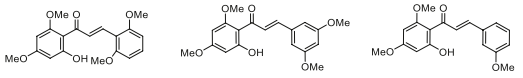
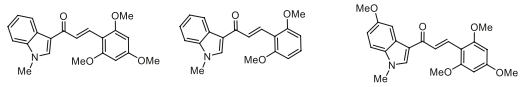
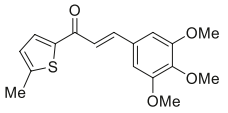
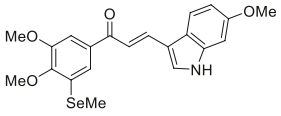
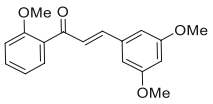
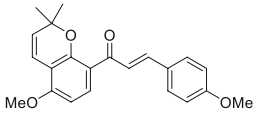
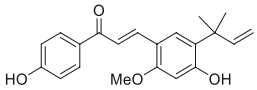
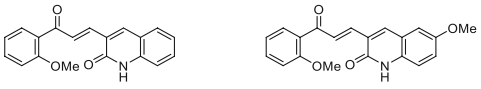
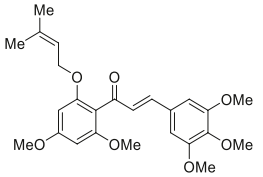
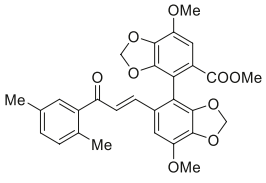
Fig. 7. Chemical structures of chalcones exhibit anti-topoisomerase activity.

II [87]. The chalcone 2,4-dimethoxy and 6-hydroxy groups on ring A; 3, 4,5-trimethoxy on ring B (Fig. 7.4) demonstrated a potent cytotoxicity activity on the HT-1376, HeLa, and MCF-7 cell lines, with inhibitory action to hTopoII-ATPase compared to salvicine. Utilizing molecular dynamics of ligand-protein interaction showed that the compounds had strong interactions with the ATP-binding pocket domain [88]. Millepachine (MIL) (Fig. 7.5) a bioactive natural chalcone induced a cell cycle arrest and resulted in a proliferation of cisplatin-resistant A2780CP cells by suppressing topoisomerase II protein activity [89]. Another study on MIL showed that MIL has an anti-tumor effect by suppressing topoisomerase II activity by attaching to the Topoisomerase II-cleaved DNA complex and stabilizing it, causing DNA damage in tumor cells [90]. Chalcone analog-containing carbazole derivatives CDCAs inhibited Topo II activity in HL-60 cells. The link between structure and activity showed that the halogen group in the phenyl ring is crucial to enhanced activity. In addition, mechanistic studies have shown that CDCAs are non-intercalative Topo II catalytic inhibitors [91]. 2, 2′-Bipyridine and a chalcone-based homodinuclear (Cu–Cu, Zn–Zn) nitrato bridging complexes demonstrated two distinct kinds of interactions by preferentially attaching to the major groove of DNA and employing either an oxidative mechanism or a hydrolytic process to adhere to the minor groove of DNA. In HeLa cell lines, complexes blocked topoisomerase I relaxation activity. The complexes' groove binding and topoisomerase I binding are supported by molecular docking experiments [92]. Another study revealed that the function of topoisomerase II was inhibited more strongly by heteroaromatic ring-incorporated chalcone derivatives (Figs. 7.6–8) than by etoposide with almost the same degree [93]. According to docking studies of chalcone-triazole compounds with topoisomerase II, the LibDock score demonstrated strong topo-II inhibitory activity by triazole chalcone [94]. DNA topoisomerase I activity was significantly decreased by carboline hybrids with phenyl substitution and chalcone/(N-acetyl) pyrazole moiety groups at positions C1 and C3 (Figs. 7.9 and 10) while maintaining DNA in the supercoiled form [95].

1.2.2. Chalcones regulates cancer stemness via targeting multi-drug resistance

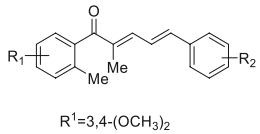
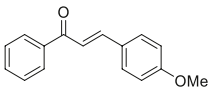
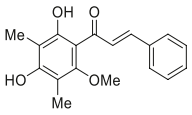
Cancer stem cells are capable of inducing cancer recurrence and drug resistance. They can self-renew and differentiate into a variety of cancer cell populations [96]. Several solid tumors, including retinoblastoma, neuroblastoma, breast cancer, lung cancer, and glioblastoma, have side populations of cancer stem-like cells with upregulated levels of transporter proteins such as MDR1, ABCG2, and ABCB1 that can expel cytotoxic agents outside cancer stem cells [96–99]. The transporter family of ATP-binding cassettes (ABC) includes membrane proteins involved in the exchange through extracellular and intracellular membranes of a wide range of substrates, including drugs. P-glycoprotein (ABCB1, MDR1), breast cancer resistance protein (BCRP, ABCG2, MXR, ABCP), and multidrug resistance-associated protein 1 (MRP1, ABCC1) are thought to be responsible for the vast majority of cases of multidrug resistance [100,101]. Synthetic quinoxaline chalcones showed potent inhibitory activity against ABCG2 in breast cancer resistance to protein-mediated mitoxantrone efflux. Moreover, the best inhibitory activity was achieved by compounds containing a minimum of two methoxy groups [102]. Symmetric bis-chalcones synthesized by Winter et al. showed a high ability to suppress the efflux of mitoxantrone from HEK293 cells transfected by ABCG2. The inhibitory activity and selectivity of chalcone compounds against multiple drug-selected cancer cells with several methoxy groups showed high activity against ABCG2 and MRP1 [103]. BCRP is an efflux transporter protein with a wide range of specificity for recognizing molecules that contain a positive or negative charge, organic anions, and conjugated sulfates. The BCRP protein can be found in stem cells or breast cancer stem cells and helps in drug exclusion, thus acting as adefense mechanism against drugs, including chemotherapies and toxins [104,105]. Juvale et al. synthesized several chalcone derivatives acting as possible inhibitors for BCRP. Substituting chalcones with dimethoxy groups on ring A at positions 2 and 4 and B at positions 3,4 is important for their potent activity [106].)E)-3-(acridin-9-yl)-1-(2,6-dimethoxyphenyl)prop- 2-en-1-one exhibited antiproliferative with inhibitory activity against ABCB1 in addition to its synergistic effect with doxorubicin against T-cell lymphoma multidrug-resistant and PAR, MDR, Colo 205 and Colo 320 colon adenocarcinoma cells [107]. ISL is extracted from *licorice plant*. ISL enhanced chemotherapy sensitivity by lowering the expression of ABCG2. The combination of ISL and Cisplatin exhibited a synergistic effect that dramatically reduced the ability of cancer stem cells from oral squamous cell carcinomas-to invade and colonize [108]. Several other chalcones with multidrug resistance inhibitors are summarized in Table 2.

Table 2
Summary of the chalcones compound as multidrug resistance inhibitors.

A-Ring/B-Ring	Structure	Cancer model	Biological activity	References
Aryl/quinoxalin-6-yl)		MDA-MB-231 (BCRP/ABCG2) breast cancer resistance protein	Antiproliferation activity	[109]
2,4-dimethoxyphenyl/2, 3, or 4-chlorophenyl	 R=2-Cl R=3-Cl R=4-Cl			
(2*E*,2′*E*)-1,1'-(1,4-phenylene) bis (3-phenylprop-2-en-1-one)				
(2*E*,2′*E*)-3,3'-(1,4-phenylene) bis (1-phenylprop-2-en-1-one)				
2-hydroxy-4,6-dimethoxyphenyl/2,6 (or 3,5)-dimethoxyphenyl		HEK293-*ABCG2*	Inhibitory effect on Mitoxantrone transport	[110]
1-methyl-1*H*-indol-3-yl/(di or tri)methoxyphenyl				
5-methylthiophen-2-yl/3,4,5-trimethoxyphenyl		NCI–H460 cells	Improving tumor cell chemosensitivity to low paclitaxel doses antimitotic behavior	[65]
3,4-dimethoxy-5-(methylselanyl)phenyl/6-methoxy-1*H*-indol-3-yl		ADR/MCF-7 (adriamycin-resistant, VCR/HCT-8 (vincristine-resistant), TAX/A2780 (adriamycin-resistant)	TrxR inhibition causing aberrant ROS generation	[111]
2-methoxyphenyl/3,5-dimethoxyphenyl		Cisplatin sensitive A2780 and cisplatin-resistant A2780/CisR ovarian cell line	ROS-mediated activate unfolded protein response (UPR)	[112]
5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl/4-methoxyphenyl (Millepachine)		Cisplatin-resistant A2780/CP cells cisplatin-resistant A2780/CP xenograft model	G2/M arrest inhibition topoisomerase II protein activity	[112]
4-hydroxyphenyl/4-hydroxy-2-methoxy-5-(2-methylbut-3-en-2-yl)phenyl (Licochalcone A)		MCF-7 and BT-20	Inhibits MDR-1 protein expression	[113]
2-methoxyphenyl/2-oxo-1,2-dihydropyridine-3-yl		Overexpressing KB-C-2 MDR1- cells and MRP1-overexpressing HEK293 cells	Antiproliferative	[75]
2-methoxyphenyl/2-oxo-1,2-dihydroquinoline-3-yl				
2,4-dimethoxy-6-((3-methylbut-2-en-1-yl)oxy) phenyl/3,4,5-trimethoxyphenyl		MCF-7 and NCI–H460 cells	Increase the sensitivity of tumor cells to Paclitaxel	[114]
2,5-dimethylphenyl/7,7′-dimethoxy-5'-(methoxycarbonyl)-[4,4′-bibenzo[*d*][1,3]dioxole]-5-yl (Bifendate-chalcone hybrids)		HEK293/BCRP cells	Decrease BCRP function as a drug efflux inhibitor for both P-gp and BCRP	[115]

(*continued on next page*)

Table 2 (*continued*)

A-Ring/B-Ring	Structure	Cancer model	Biological activity	References
o-tolyl/styryl	 R^1=3,4-$(OCH_3)_2$ R^2=4-$N(CH_3)_2$	2D and 3D QSAR studies	P-gp inhibitory	[116]
Methoxy chalcone		A549 lung cancer cells	Improved tumor cell sensitivity to the therapeutic action of cisplatin	[117]
(*E*)-1-(2,4-dihydroxy-6-methoxy-3,5-dimethylphenyl)-3-phenylprop-2-en-1-one		BEL-7402/5-FU cells	Inhibited MRP1 and GST-mRNA expression and MRP1 protein production	[118]

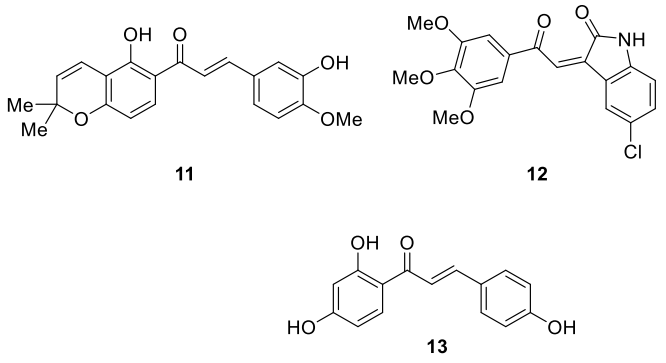


Fig. 8. Chemical structures of chalcones as hypoxia-inducible factor inhibitors.

1.2.3. Chalcones have antiangiogenic activity

Angiogenesis is a characteristic of cancer and is required to ensure that adequate nutrients are delivered to the tumor so that it can continue to develop and metastasize to other locations [119]. Several pro-angiogenic factors can affect the tumor vascularization process such as angiogenin, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and transforming growth factor beta (TGF-b) [120]. Recent investigations have also shown clear evidence of a link between high hypoxia-inducible factor-1 (HIF-1) levels and metastasis, angiogenesis, bad patient prognosis, and tumor drug resistance [121].

1.2.3.1. Chalcone as a hypoxia-inducible factor inhibitor. Hypoxia (low oxygen levels) is a frequent feature in many forms of solid tumors. Hypoxic tumor cells can activate various pathways including survival as a response to hypoxic conditions, allowing them to carry out their critical biological functions differently than normal cells [122]. Recent cellular and molecular studies in cancer biology have identified the HIF-1 pathway as a critical target for newly synthesized cancer therapeutic agents [121]. Chalcone compound with 2,2-dimethylbenzopyran (Fig. 8.11), besides its inhibitory effect on VEGF, downregulated HIF-1 under hypoxic conditions [123]. HepG2 cells treated with 3′,4′,5′-trimethoxy-5-chloro-isatinylchalcone (Fig. 8.12) had dramatically lowered HIF-1 levels compared with control cells [81]. ISL (Fig. 8.13) decreased the stability of HIF-1 in mouse melanoma B16F10 cells under hypoxia [124].

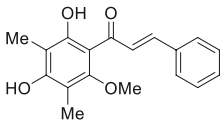
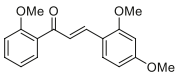
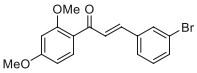
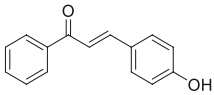
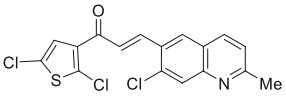
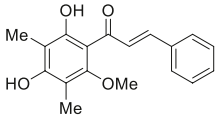
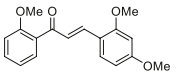
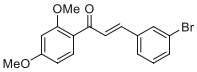
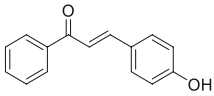
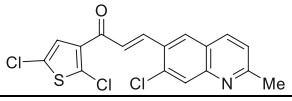
1.2.3.2. Chalcones as inhibitors of key angiogenic factors. Angiogenesis inhibition by suppressing pro-angiogenic factors stops tumor growth and metastasis [125,126]. VEGF expression is known to be high during embryogenesis and is thought to have a crucial role in vasculogenesis [127]. Upregulation of VEGF contributes to accelerated tumor development and metastasis in certain solid tumors, which may be attributed to an increased supply of nutritional replenishment to metabolic cells [128,129]. Various approaches were used to target angiogenesis, such as nanoparticle composition [119], or chemotherapies, such as chalcones, to target key angiogenic players [130]. *In-vitro* and *in-vivo* studies showed angiogenesis inhibitory function of 2-methoxy-chalcone hydroxy-4 in both the chorioallantoic membrane model and the mouse Matrigel plug assay stimulated with basic fibroblast growth factor (bFGF) [131]. In a chorioallantoic membrane model, nitrogen chalcone-based drugs suppressed angiogenesis and reduced the invasion ability of SKBR3 and ZR75 cancer cells [132]. A chalcone based on 2-methoxyestradiol, was shown to exhibit substantial antiangiogenic action and inhibit tumor development in mice xenografted with MCF-7 breast cancer cells with no noticeable adverse effects [133]. Xantohumol is a hops-derived prenylated chalcone from *Humulus lupulus* L. In pancreatic cancer cell lines, xanthohumol dramatically reduced the expression of VEGF and interleukin-8 (IL-8) at both the mRNA expression and protein [134]. At a concentration of 10 mM, xanthohumol compounds reduced the proliferation, adhesion, migration, invasion, and capacity to form capillary-like structures of human umbilical vein endothelial cells (HUVECs) [135]. At very low and non-toxic levels, the chalcone flavokawain B (FKB), which was isolated from *kava-kava* root extracts, prevents the migration of human brain endothelial cells and the development of small vessels in human brain tissue. Furthermore, FKB inhibits angiogenesis in zebrafish in a dose-dependent manner in the development of sub-intestinal veins [136]. Angiogenesis was also reduced by chalcone derivatives containing a pyrazole ring in a variety of human cell lines, including (MCF-7, HCT-116, and HEPG2 cell lines [18]. ISL, a dietary component, suppresses breast cancer neo-angiogenesis by inhibiting the VEGF/VEGFR-2 signaling pathway [137]. Other chalcones derivatives inhibiting the angiogenesis process are summarized in Table 3.

However, one should take into consideration that other forms of chalcones such as the sulfonamide-chalcone hybrid induced angiogenesis and upregulated VEGF *in-vivo* using the chorioallantoic membrane (CAM) model [142].

1.2.4. Chalcones as cancer metastasis inhibitors

The invasion-metastasis cascade describes the last stages of a multistep cellular biological process that includes the spread of cancer cells to distant organ locations and their following adaption to new tissue microenvironments [143]. From the initial stages of cancer prognosis until the formation of a metastatic niche in a secondary organ, matrix metalloproteinases (MMPs) play a major role. Their function in cancer development is linked to their roles in ECM degradation, adhesion, and cytoskeletal protein regulation [143,144]. Cathepsins have been linked to tumor metastasis and are significantly expressed in a variety of human malignancies. Each lysosomal proteinase or

Table 3
Summary of chalcones as an inhibitor of angiogenesis.

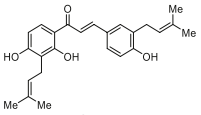
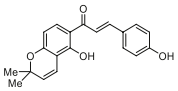
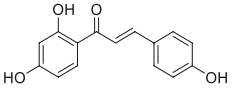
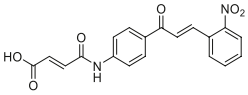
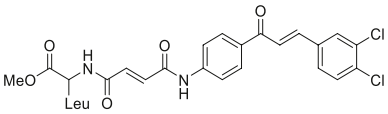
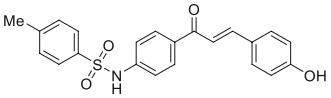
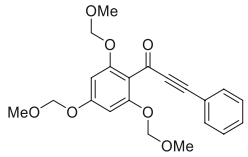
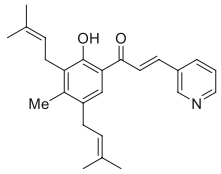
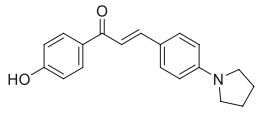
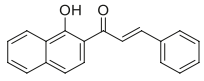
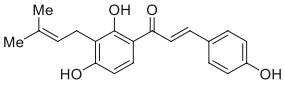
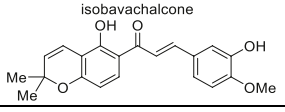
A-Ring/B-Ring	Structure	Cancer or angiogenesis model	Biological activity	References
2,4-dihydroxy-6-methoxy-3,5-dimethylphenyl)/phenyl		Human hepatocarcinoma (Bel7402) and GLC-82 lung xenografts	Reversibly inhibited the phosphorylation of KDR tyrosine kinase (VEGF)	[138]
2-methoxyphenyl/2,4-dimethoxyphenyl		HMEC-1 (human microvascular endothelial cells)	Anti-endothelial effects	[139]
2,4-dimethoxyphenyl/3-bromophenyl		HMEC-1 (human microvascular endothelial cells)	Anti-endothelial effects	[139]
4-hydroxy chalcone		HeLa, MCF-7, A549 cancer cell lines	Modulating phosphorylation caused by both VEGF and FGF	[140]
2,5-dichlorothiophen-3-yl/7-chloro-2-methylquinolin-6-yl		HUVEC	VEGFR-2 kinase inhibitory activity	[141]
2,4-dihydroxy-6-methoxy-3,5-dimethylphenyl)/phenyl		Human hepatocarcinoma (Bel7402) and GLC-82 lung xenografts	Reversibly inhibited the phosphorylation of KDR tyrosine kinase (VEGF)	[138]
2-methoxyphenyl/2,4-dimethoxyphenyl		HMEC-1 (human microvascular endothelial cells)	Anti-endothelial effects	[139]
2,4-dimethoxyphenyl/3-bromophenyl		HMEC-1 (human microvascular endothelial cells)	Anti-endothelial effects	[139]
4-hydroxy chalcone		HeLa, MCF-7, A549 cancer cell lines	Modulating phosphorylation caused by both VEGF and FGF	[140]
2,5-dichlorothiophen-3-yl/7-chloro-2-methylquinolin-6-yl		HUVEC	VEGFR-2 kinase inhibitory activity	[141]

endopeptidase in this category has a distinct function, contributing to several tumorigenic processes such as proliferation, angiogenesis, metastasis, and invasion [145,146]. Cathepsins are members of a wide range of enzyme subtypes, such as cysteine, serine, and aspartic proteases [145].

1.2.4.1. Chalcones as MMP2/9 inhibitors. Matrix metalloproteinases (MMPs) are enzymes that can degrade several extracellular matrix molecules. It is known that MMP-9 degrades basement membrane collagens and remodels the extracellular matrix to enable proliferation and migration [147]. By releasing matrix-bound VEGF, MMP-9 activates an angiogenic transition for tumor development and initiates angiogenesis [148]. MMP enzymes are extensively involved in natural, pathological, biochemical, and biological mechanisms such as embryogenesis, normal tissue remodeling, wound healing, angiogenesis, atheroma, inflammation, tissue ulceration, and cancer [149]. Thus, inhibition of MMPs is crucial in halting cancer progression. Several chalcones appeared to have interesting anticancer activity *via* inhibiting MMPs activity. The expression of MMP-9 in mammary breast cancer in rats was downregulated by (*E*)-1-(4′-aminophenyl)-3-phenylprop-2-en-1-one [150]. (*E*)-1-(2-hydroxy-4-methoxy-3,5-diprenyl) phenyl-3-(3-pyridinyl)-propene-1-one, a 3′,5′-diprenylated chalcone reduced the expression of MMP-1in PC3 cells [151]. Hybrids of chalcone and dithiocarbamate (*E*)-2-oxo-2-((4-(3-(3,4,5 trimethoxyphenyl)acryloyl)phenyl)amino) ethyl-4-(2-hydroxyethyl) piperazine-1-carbodithioate showed anticancer activity against cancer cell lines MGC803, MCF7, and PC3 by suppressing MMP2- and MMP-9-dependent epithelial-mesenchymal transition (EMT) process [152]. The chalcone derivative of benzylideneacetophenone decreased the metastasis capability of AGS cells by downregulating MMP-2 and MMP-9, which was accompanied by a significant reduction in cell invasion and migration [153]. Hydroxychalcone and xanthohumol have inhibitory activity on MDA-MB-231 cells proliferation, MMP-9 expression, and invasion behavior of [154]. Several other chalcones acting as MMP inhibitors are summarized in Table 4.

1.2.4.2. Chalcones as cathepsins inhibitors. Proteases, particularly lysosomal cathepsins, are engaged in various events that contribute to cancer development, from the genesis of the disease through invasion and metastatic dissemination. Only recently, cathepsin K (Cat K), a cysteine protease initially identified as a collagenolytic protease generated by osteoclasts, was overexpressed in several malignancies, including breast, lung, and prostate cancers [164]. Some chalcones exhibited inhibitory activity against cathepsins. For example, (*E*)-3-(3,4-dimethoxyphenyl)-1-phenylprop-2-en-1-one, (*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one, (*E*)-3-(4-methoxyphenyl)-1- phenylprop-2-en-1-one and (*E*)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one chalcones (Fig. 9.14) inhibited Cathepsin-K activity associated with potent cell growth retardation inMDA-MB-435, HCT-8, and SF-295 cells, [165]. Raghav and Singh conducted drug screening on certain low molecular weight substituted chalcones (Fig. 9.15) and reported that chalcone-containing hydrazones effectively inhibited cathepsin B, while chlorosubstituted chalcones exerted an inhibition effect on cathepsin H [166]. Natural cyclohexenyl chalcone, namely the panduratin (Fig. 9.16) and

Table 4
Summary of chalcone as inhibitors of matrix-metalloproteases family.

A-Ring/B-Ring	Structure	Cancer model	Biological activity	References
2,4-dihydroxy-3-(3-methylbut-2-en-1-yl)phenyl/4-hydroxy-3-(3-methylbut-2-en-1-yl)phenyl (Turbinatocoumarin)		Brain tumor	Inhibitory activity for 80% MMP-2 secretion Compared to coumarins	[155]
5-hydroxy-2,2-dimethyl-2*H*-chromen-6-yl/4-hydroxyphenyl				
2,4-dihydroxyphenyl/4-hydroxyphenyl (Isoliquiretigenin)		MDA-MB-231 cells	MMP-2 and MMP-9 inhibition	[156]
4-(3-carboxyacrylamido)phenyl/2-nitrophenyl		Human prostate cancer cell	MMP-9 inhibition	[157]
4-((*E*)-4-((2-methoxy-1-(((*S*)-4-methyl-1-oxopentan-2-yl)amino)-2-oxoethyl)amino)-4-oxobut-2-enamido)/3,4-dichlorophenyl				
4-((4-methylphenyl)sulfonamido)benzene/4-hydroxyphenyl (Garcinol polyisoprenylated benzophenone)		PaCa cells	Downregulating MMP-9	[158]
3-phenyl-1-(2,4,6-tris(methoxymethoxy)phenyl) prop-2-yn-1-one		Colorectal cancer cells (HT-29 and SW620)	MMP-7 expression	[159]
2-hydroxy-4-methyl-3,5-bis(3-methylbut-2-en-1-yl)phenyl/pyridin-3-yl		Prostate Cancer Cells	Reduced the expression of MMP-1	[151]
4-hydroxyphenyl/4-(pyrrolidin-1-yl)phenyl		A549 cells	Inhibition MMP-2 and MMP-9	[160]
1-hydroxynaphthalen-2-yl/phenyl		MDA-MB-231 breast cancer cells	Downregulating NF-κB -mediated MMP-9 activation	[161]
2,4-dihydroxy-3-(3-methylbut-2-en-1-yl)phenyl/4-hydroxyphenyl		Tongue squamous cell carcinoma cells Tca8113	Downregulating MMP-2 and MMP-9 protein expression	[162]
5-hydroxy-2,2-dimethyl-2*H*-chromen-6-yl/3-hydroxy-4-methoxyphenyl		Hep3B xenograft models	Decreased MMP-2 expression	[163]

nicolaioidesin C (Fig. 9.17), inhibited cathepsins as confirmed by protease profiling assay [167].

1.2.5. Chalcones are regulators of epigenetic machinery via inhibition of histone deacetylases (HDACs)

The acetylation of histones is a necessary step that must be completed before the transcription process can begin. This process occurs pre-transcriptionally on the lysine residue NH3 group that is incorporated in the N-terminal tails in the central region, and it helps to create chromatin that is less compact and more transcriptionally active [168]. However, HDACs detach the acetyl group, thus halting the mechanism of transcription [169,170]. HDAC inhibitors are new groups of anti-cancer treatments which are crucial in the control of epigenetic or non-epigenetic processes, affecting cancer cells and causing apoptosis and arresting the cell cycle [171]. Chalcone compounds showed potent HDAC inhibitory activity as reported in several studies. Coumarin-based chalcones had a potent inhibitory activity against histone deacetylase in myeloid leukemia K-562 nuclear extracts and histiocytic lymphoma U-937 cell lines [172]. Orlikova et al. studied different natural chalcones and assessed their inhibitory function on HDACs, where four chalcones strongly inhibited HDACs, namely ISL, butein, homobutein, and marein. The substitution of C-2, C-4, C-30, and C-40 hydroxy groups is important for successfully inhibiting HDACs [173]. Hybrids based on alpha-phthalimido-substituted chalcones with trimethoxy groups (Fig. 10.18) demonstrated the most potent anticancer activity, with the most potent inhibitory activity of β-tubulin polymerase and HDAC- 1

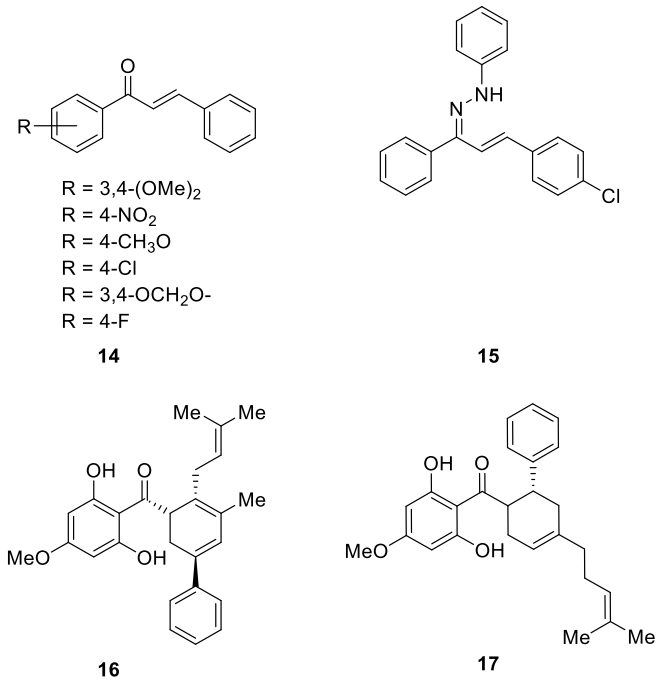


Fig. 9. Chemical structures of chalcones exhibiting Cathepsin-K inhibitory activity.

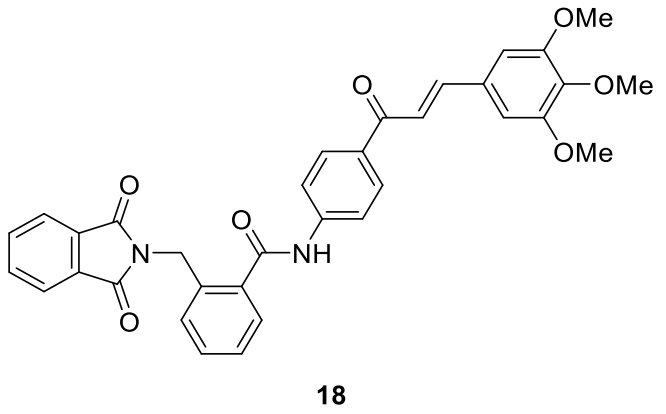


Fig. 10. Chemical structure of alpha-phthalimido-substituted chalcones as HDAC1 inhibitor.

and - 2 [174].

1.2.6. Chalcones as inhibitors of key signaling pathways implicated in cancer hallmarks

1.2.6.1. Chalcone as inhibitors of JAK/STAT pathway. The signaling cascade of JAK/STAT mediates several relevant cellular activities such as the proliferation of cells, programmed cell death, and immune system responses. Pathway activation mediates several malignancies with neoplastic transformation and irregular replication [175]. Increased STAT-3 phosphorylation contributes to breast cancer progression. In addition, the mitochondrial expression of STAT3 (mitoStat3) tends to affect cell growth and proliferation [176]. Pinz et al. reported that the signaling pathway of JAK/STAT could be inhibited by a-Bromo-2,30,4, 40-Tetramethoxychalcone (Fig. 11.19) that targets the JAK/STAT pathway, inhibiting phosphorylation of both JAK2 and STAT5 in Ba/F3 (a pro-B murine cell line dependent on interleukin-3 (IL-3) for growth) [177]. Aromatic alkyl-amino analogs of thiazole-based chalcones (Figs. 11.20–22) demonstrated a dual inhibitor of JAK2 and EGFR against HEL and A431 cell lines [178]. Inhibition of IL-2-induced Jak/STAT by Xanthohumol (XN) (Fig. 11.23), a prenylated chalcone, has been shown to inhibit the proliferation of mouse lymphoma cells [179].

1.2.6.2. Chalcone as inhibitors of wnt/β-catenin signaling pathway. The Wnt/β-catenin signaling pathway is dysregulated in cancer stem cells. This abnormal signaling pathway promotes cancer stem cell renewal, cell proliferation, and differentiation, all of which play critical roles in carcinogenesis and therapeutic response [180,181]. Multiple research findings have shown the therapeutic potential of drugs that interfere with cancer cells' Wnt/β-catenin pathway [182]. In an animal model of an adenomatous polyposis coli multiple intestinal neoplasia, treatment with the chalcone derivative 4′-hydroxychalcone (Fig. 12.24) reduced the protein levels of β-catenin [183]. Through blocking MAPK and Wnt/β-catenin pathways, 4′-*O*-Methyl brousso chalcone B decreased acute myeloid leukemia (AML) cell proliferation and migration [184]. Also, *trans*-chalcone (TC) (Fig. 12.25) inhibited Wnt/β-catenin and lowered HuH7.5 cell line metastatic capability [185]. KYSE-4 esophageal cancer cells' proliferation, migration, and invasion were inhibited by dithiocarbamate scaffolds-based chalcone derivative in a concentration-dependent manner. This chalcone blocked the Wnt/β-catenin pathway and regulated migration-related markers (E-cadherin, N-cadherin, and Slug). In a dose- and time-dependent treatment, it also inhibited the expression of proline-rich protein 11 (PRR11) [186] –a key gene that is linked to poor ER hormonal therapy In addition, PRR11 promotes an ER-independent proliferation [187]. Lonchocarpin (Fig. 12.26) isolated from *Lonchocarpus sericeus* was able to suppress cell migration and proliferation in HCT116, SW480, and DLD-1 colorectal cancer cell lines, while no impact on the non-tumoral intestinal cell line IEC-6 was observed. In the colorectal cancer AOM/DSS mice model, lonchocarpin decreased tumor growth by inhibiting Wnt/β-Catenin Signaling [188]. Broussochalcone A (BCA), a prenylated chalcone from *Broussonetia papyrifera.* BCA increased intracellular β-catenin turnover and its phosphorylation at Ser33/37/Thr41 in colon and liver cancer cells, indicating ubiquitin-dependent proteasomal destruction *Via* suppressing the Wnt/β-catenin signaling pathway [184]. The active chalcone cardamonin (Fig. 12.27), significantly increased the chemosensitivity of 5-FU in GC cells. In BGC-823/5-FU human gastric cancer cell line cells, combining cardamonin with 5-FU resulted in reduced β-catenin and TCF4 expression levels [189]. In addition, in triple-negative breast cancer BT-549 cells, cardamonin lowers β-catenin stability and nuclear translocation and downregulation of β-catenin target genes. By blocking the phosphorylation of GSK3 by Akt, cardamonin restores the activity of glycogen synthase kinase-3 (GSK3), which is essential for β-catenin degradation through the proteasome-mediated pathway [190]. 3′,4′,5′-Trimethoxy-5--chloro-isatinylchalcone, a new hybrid molecule (Fig. 12.12), blocked the Wnt/β-catenin pathway in HepG2 cells by downregulating β-catenin, c-Myc, cyclin D1, and E2F1 [81]. Both chalcones, derricin (Fig. 12.28) and derricidin, (Fig. 12.29), showed an ability to influence β-catenin cell distribution and suppress Wnt signaling activity in HCT116 cells [191].

1.2.6.3. Chalcone as inhibitors of the NF-κB pathway. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) family consists of five transcription factors that bind to consensus DNA sequences at promoter regions of their responsive genes to regulate a broad spectrum of cellular activities. Because of the inflammatory microenvironment and numerous oncogenic alterations, many human malignancies have constitutive NF-κB activation [10,192,193]. In normal cells, NF-κB is stabilized by the inhibitory kappa B (IkB) proteins which upon phosphorylation degrades and make the NF-κB free to translocate to the nucleus and activate target genes [194]. Chalcones inhibit the NF-κB

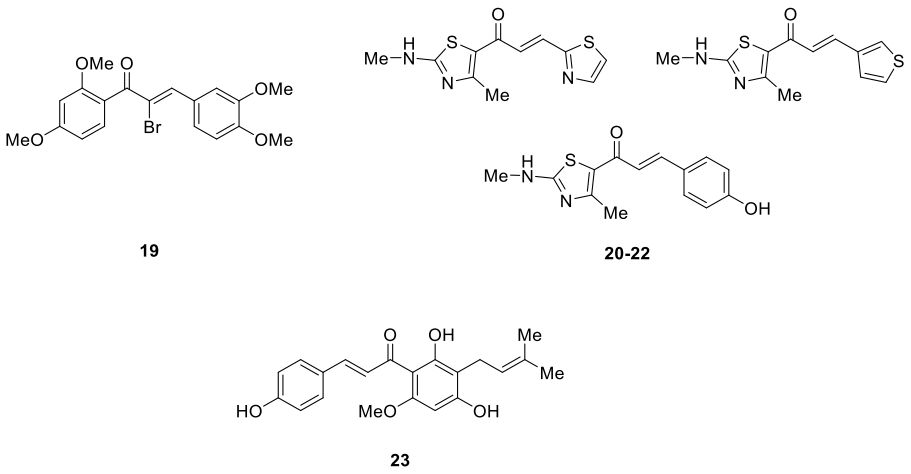


Fig. 11. Chemical structures of chalcone that inhibit the JAK/STAT pathway.

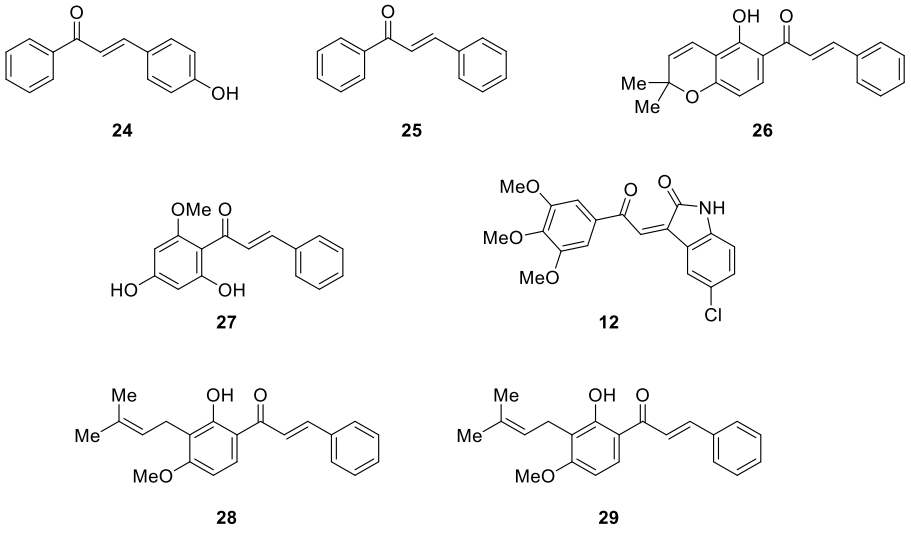
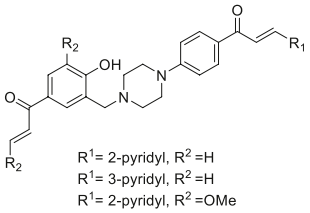
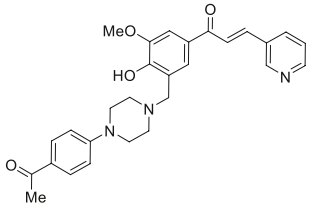
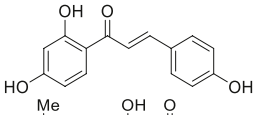
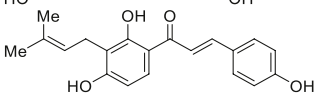
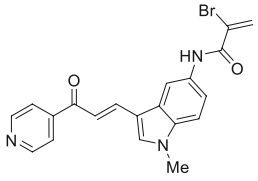
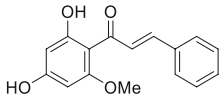
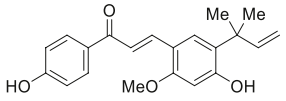
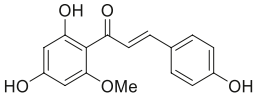
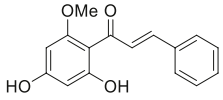
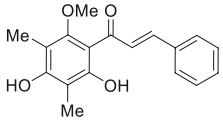
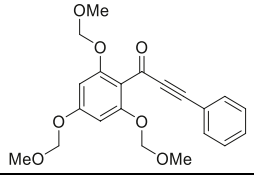


Fig. 12. Chemical structures of chalcone that inhibit the WNT/β-catenin pathway.

pathway through covalent interaction with the IKK protein, (The IκB kinase enzyme complex is part of the upstream NF-κB signal transduction cascade) *via* the α,β-unsaturated ketone in the chalcone scaffold [195]. By blocking the NF–B signaling pathway, dihydrot riazine-chalcone derivatives reduce MDA-MB-231 cancer cell migration and inflammation [196]. In pancreatic cancer, xantohumol isolated from hops *Humulus lupulus* L., reduced angiogenesis *via* inhibiting NF-κB activity [134]. Methoxylation at 3, 4, and 5 for trimethoxylated chalcones in the B ring is preferred. Moreover, Srinivasan et al. documented that ((*E*)-1-(3,4,5-trimethoxyphenyl)-2-en-1-one) chalcone inhibits IKK-mediated NF-κB activation in lung cancer cells (A549) and interleukin-1 kinase-receptor 4 (IRAK4) [39]. 3-Hydroxy-4,3′,4′,5 tetramethoxychalcones showed potent *in vitro* and *in vivo* anti-cancer activity *via* inhibition of NF-κB by 46% at a concentration of 10 μM through reaction with cysteines of ikkb and [39]. Another study on the same compound showed a potent effect on multiple cell lines through a JNK autophagy pathway that triggers c-IAP [197]. Several promising chalcones acting as NF-κB pathway inhibitors are depicted in Table 5.

1.2.6.4. Chalcones as inhibitor of human epidermal growth factor receptors. The human epidermal growth factor receptors (HER), also called ErbB receptors, are receptor tyrosine kinases (RTKs) playing important roles under physiology and pathological conditions. The ErbB family of receptors includes the epidermal growth factor receptor (EGFR), ErbB2 (HER-2), ErbB3 (HER-3), and ErbB4 (HER-4). These are common RTKs with a domain of extracellular ligand binding, a single domain of membrane-spanning, and a domain containing cytoplasmic tyrosine kinase [209,210]. In certain epithelial tumors, EGFR and ErbB2 are mutated, and clinical findings indicate that they play a role in the development and progression of cancer. An immense effort has been made to develop selective therapeutics based on the importance of ErbB receptors in human cancer [211]. Chalcone shows an interesting activity as an inhibitor of the RTKs family. The chalcone Isliquiritigenin caused downregulation of mRNA levels of *ErbB3* in a dose-dependent manner and induced apoptosis in DU145 human prostate cancer cells besides the MLL rat prostate cancer cell line [212]. Li et al. isolated 2,4-dihydroxy-6-methoxy-3,5-dimethylchalcone (Fig. 13.30) from dry flower *Cleistocaly xoperculatus* and tested its activity on MDA-MB-453 cells. They found inhibition of ErbB2 tyrosine phosphorylation without affecting the ErbB2 receptor expression [213]. A series of chromene chalcones (Fig. 13.31) showed inhibition of aurora kinases by binding assay in the HCT116 colorectal cancer cell line [214]. Quinoline chalcone hybrids containing triazole moiety, similar to the reference drug erlotinib, showed remarkable antiproliferative activity by binding to the active site of EGFR and BRAFv600 kinases [215]. Xanthine/chalcone combinations (Fig. 13.32) demonstrated a potent inhibitory activity against

Table 5
Summary of chalcones affecting the NF-KB pathway.

A-Ring/B-Ring	Structure	Cancer model	Biological activity	references
1-benzyl-4-phenylpiperazine/pyridine-(2 or 3)-yl (Bichalcone)		KB, A-549, HCT-8 and DU145	Blocked the NF-κB nuclear translocation	[198]
4-acetylphenyl)piperazin-1-yl)methyl)-4-hydroxy-5-methoxyphenyl/pyridin-3-yl				
2,4-dihydroxyphenyl/4-hydroxyphenyl (Butein)		H1299, KBM-5, and Jurkat cells	NF-κB inhibition phosphorylation and degradation of IκBa	[199]
2,4-dihydroxy-3-(3-methylbut-2-en-1-yl) phenyl/4-hydroxyphenyl (Isobavachalcone)		RAW264.7 cells	NF-κB and IRF3 inhibition	[200]
pyridin-4-yl/5-(2-bromoacrylamido)-1-methyl-1*H*-indole-3-yl		SK-MEL-1 human melanoma cell lines	Downregulation of p21Cip1/WAF1 and suppressed the NF-κB pathway	[201]
2,4-dihydroxy-6-methoxyphenyl/phenyl (Cardamonin)		SKOV3-Taxol cells	P-gp efflux pump inhibition downregulated MDR1 mRNA	[202]
4-hydroxyphenyl/4-hydroxy-2-methoxy-5-(2-methylbut-3-en-2-yl)phenyl (Licochalcone A)		Colon cancer cells	Targeting PD-L1 *via* the NF-κB inhibition and Ras/Raf/MEK signaling pathways	[203]
		Gastric cancer	inhibited various signaling pathways, including Akt, ERK, and NF-κB	[204]
2,4-dihydroxy-6-methoxyphenyl/4-hydroxyphenyl (Helichrysetin)		HeLa and T98G cells	TAK1/IKK/NFB and TAK1/EGFR signaling pathways	[205]
2,4-dihydroxy-6-methoxyphenyl/phenyl (Cardamonin)		Ovarian cancer cells HepG2 cells	Selective inhibition of the NF-κB and mTOR pathways	[206, 207]
2,4-dihydroxy-6-methoxy-3,5-dimethylphenyl/phenyl		Multi-drug resistant BEL-7402/5-FU cells	Suppressing the PI3K/AKT signaling axis	[208]
3-phenyl-1-(2,4,6-tris(methoxymethoxy) phenyl)prop-2-yn-1-one		CRC cells (HT-29 and SW620)	Suppression of NF-κB	[159]

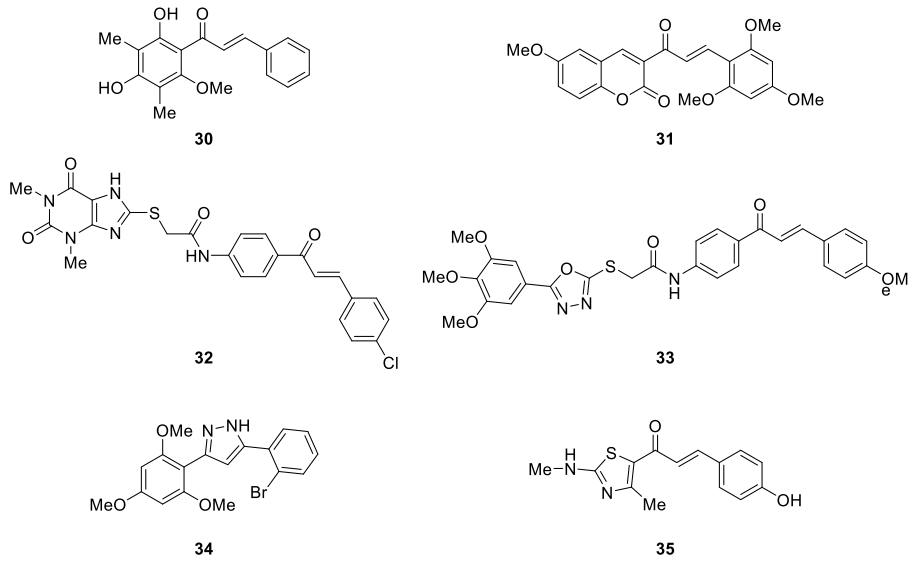


Fig. 13. Chemical structures of chalcones that inhibit receptor tyrosine kinase.

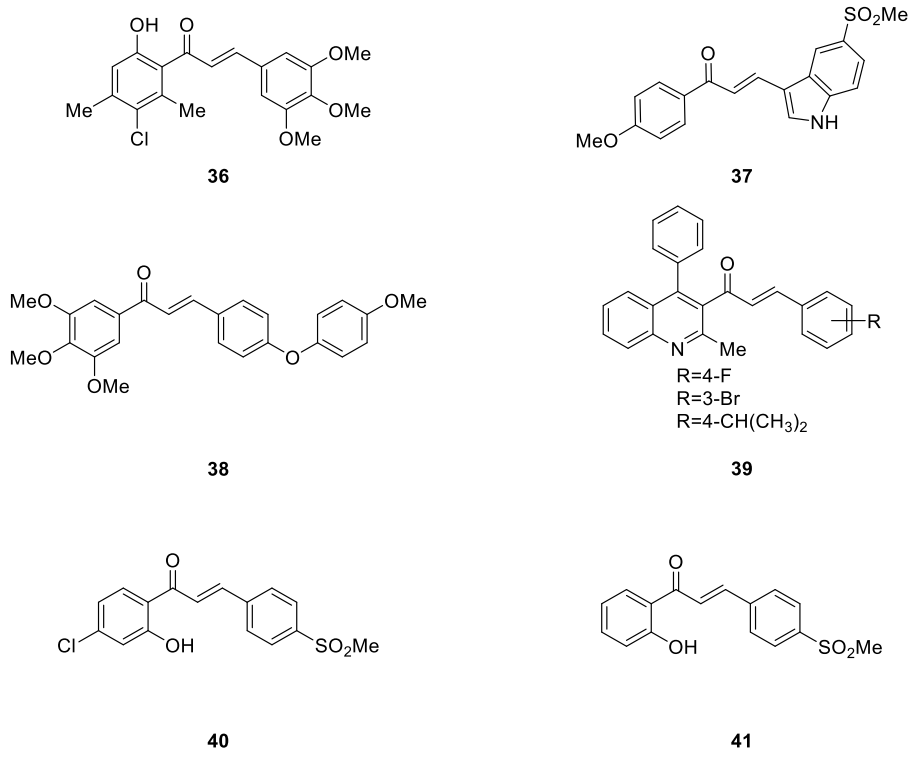


Fig. 14. Chemical structure of chalcones as cyclooxygenase inhibitors.

EGFR in comparison to the reference drug staurosporine [216]. 1,3,4-oxadiazole/chalcone hybrids (Fig. 13.33) have been assessed as EGFR inhibitors and displayed the highest cytotoxic effect against K-562, Jurkat, and KG-1a leukemia cell lines. A 2-Bromo-substituted pyrazole derivative (Fig. 13.34) showed docking scores of −5.912 and −6.949 kcal/mol, toward EGFR and VEGFR2, in PC3 and DU145 cells, respectively, using GLIDE standard precision-based docking simulations [217]. Sulfonamide 1-benzenesulfonyl-3-(4-bromobenzylidene)-2-(2-chlorophenyl)-2,3-dihydro1*H*-quinolin-4-one (Fig. 13.35) revealed seven μ-alkyl binding with the ligand-binding domain of EGFR [218]. Aromatic alkyl-amino analog of thiazole-based exhibited inhibitory activity against both JAK2 and EGFR and could bind with Met769 at the hinge region, Lys721 near a glycine loop, and Asp831 by hydrogen bond in the EGFR activation loop, according to molecular docking study [178].

Docking simulation studies for the chalcone tetrahydro [1,2,4]triazolo [3,4-*a*]isoquinolin-3-yl)-3-arylprop-2-en-1-one revealed their potent inhibitory activity against EGFR pathways [16]. Molecular docking experiments indicated that the CDK2 and EGFR TK domains had a high binding affinity for the thiadiazolyl isoquinoline chalcone, which exhibited potent *in-vitro* cytotoxicity against A549, MCF7, HCT116, and HELA cancer cells [13].

Fig. 15. Chalcone compounds act as antioxidants.

1.2.7. Chalcones have anti-inflammatory actions via cyclooxygenase inhibition

A crucial enzyme in the metabolism of fatty acids, cyclooxygenase-2 (COX-2), is increased during both inflammation and cancer. At the location of inflammation, pro-inflammatory cytokines trigger COX-2, and increased COX-2-induced prostaglandin production enhances cancer cell proliferation, encourages angiogenesis, inhibits apoptosis, and promotes metastatic potential [219,220]. Suppression of COX action can alleviate symptoms of inflammation. Thus, numerous attempts have been made to produce new and more effective anti-inflammatory drugs by inhibiting the action of COX. For example, the most potent anti-inflammatory chalcone derivative is 5′-chloro-2′-hydroxy-4′6′-dimethyl-3, 4, 5-trimethoxychalcone which suppressed COX-1 and COX-2 [221] (Fig. 14.36). The Indole-based chalcone 3-(5-Bromo-1H-indol-3-yl)-1-(4-cyanophenyl) prop-2-en-1-one showed potent inhibitory activity for COX-1 and COX-2 (Fig. 14.37) [222]. Methoxylated phenyl-based chalcone (Fig. 14.38) was a potent inhibitor of COX-2 and nitric oxide reduction [223]. 2-Methyl-4-phenylquinoline-chalcone analogs (Fig. 14.39), similar to the reference compound celecoxib, showed a cyclooxygenase-2 inhibitory activity [224]. Chalcones possessing a SO2CH3 (Figs. 14.40 and 41) displayed a moderate-to-strong COX-2 inhibitory activity relative to celecoxib, ibuprofen and nimesulide. Molecular docking unveiled that the most efficient compounds relevant for COX-2 selectivity can bind with amino acids, such as Arg499 and Phe504, [225]. Prostaglandin E 2 (PGE2), the main metabolic product of COX-2, is produced in higher quantities as a result of deregulated COX-2 expression, and its pleiotropic effects appear to impact the majority of the hallmarks of cancer [226]. In the HepG2 cell line, chalcone-epoxide, similar to celecoxib, exhibited its anticancer activity *via* COX-dependent pathways and the PGE2 pathway [227]. In lipopolysaccharides (LPS)-stimulated murine macrophage-like RAW 264.7 cells, dihydrotriazine chalcone inhibited the inflammatory mediators such as COX-2 [196]. Integrating the ferrocenyl moiety into a chalcone-based COX-2 inhibitor scaffold increased the selectivity and inhibitory activity of Cox-2in the MCF-7 breast cancer cell line [228]. Retinoic acid chalcone (RAC) suppressed COX-2, PGE2, and PGE2 receptor (EP1 and EP4) overexpression in colon cancer cell lines. Also, treatment with RAC-supplemented food inhibited COX-2, PGE2, and PGE2 receptors (EP1, EP3, and EP4) in tumors of xenografted mice models [229]. Several pro-inflammatory mediators such as NO, iNOS, NF-KB, ICAM, and COX-2 have decreased upon flavokawain A chalcone treatment in 4T1 breast cancer tumor-bearing mice [230]. In PC-3 prostate cancer cells, DU145, (2′-hydroxy-4-methylsulfonylchalcone), and (4′-chloro-2′-hydroxy-4-methylsulfonylchalcone) displayed significant antiproliferative and pro-apoptotic actions *via* modulating the Akt/NF–B/COX-2 signal transduction pathways [231].

1.2.8. Chalcone as antioxidant\oxidant regulators

Oxidative stress regulation is important in developing tumors and in response to anticancer therapies [232]. Numerous signaling pathways associated with cancer may also control the metabolism of reactive oxygen species (ROS) *via* direct or indirect processes. High ROS levels can cause damage to cells, and the redox state of cancer cells typically varies from that of normal cells. ROS levels are elevated in cancer cells as a result of abnormal metabolic and signaling processes [232]. An increase in the antioxidant capacity can lead to a possible barrier to tumorigenesis resulting from the high ROS levels. ROS, on the other hand, may potentially promote the growth of tumors by inducing DNA mutations and pro-oncogenic signaling pathways [233]. Oxidative stress is caused by an imbalance in the generation and clearance of ROS. Increased ROS levels in cancer cells cause changes in multiple signaling pathways that affect cellular metabolism. Increased antioxidant defense mechanisms in cancer cells aid in the fight against ROS [234,235]. Cancer cells' response to redox deregulation is caused by fast growth [236]. Because high levels of ROS are harmful to cells, oxidative stress may slow tumor development. This stresses cancer cells, causing them to react by producing powerful antioxidant systems. On the other hand, cancer cells have higher ROS levels than normal cells despite having a superior antioxidant system [237]. Because cancer cells are more vulnerable to drugs that cause higher ROS levels than normal cells, this trait presents an exciting therapeutic option [233].

1.2.8.1. Chalcones as antioxidants. The antioxidant efficacy of chalcone derivative, (*E*)-1-(4-bromophenyl)-3-(2,3,4-trimethoxyphenyl) prop-2-en-one (Fig. 15.42), has been evaluated by three different techniques, namely, 1,1-diphenyl-2-picrylicryl hydrazyl (DPPH), photobleaching fluorescence recovery (FRAP), and metal chelating to measure the ability of compound for radicals scavenging, restore redox potential and suppressing metabolic activity. The chalcone was able to chelate metal by 72.23%. These results show the high chalcones' capacity to deactivate transition metals and prevent this reaction from triggering lipid peroxidation and oxidative stress [238]. The chelating features of the

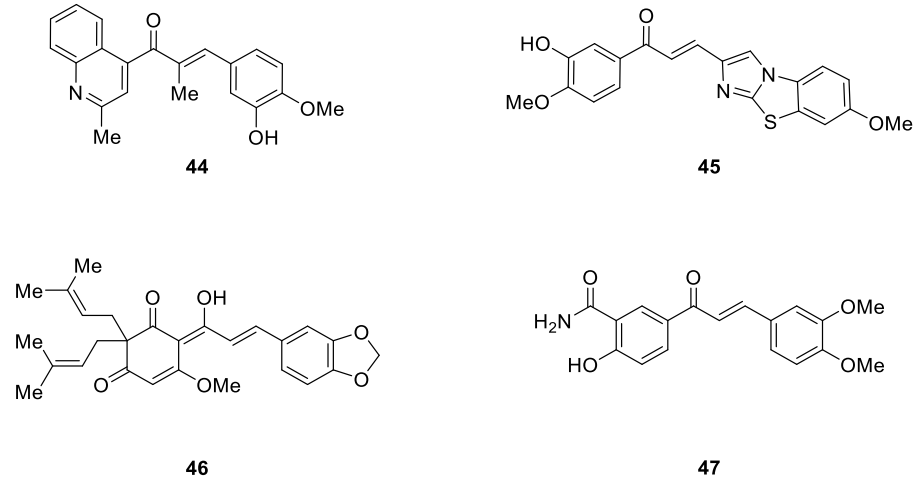


Fig. 16. Chemical structure of chalcones as oxidant inducer.

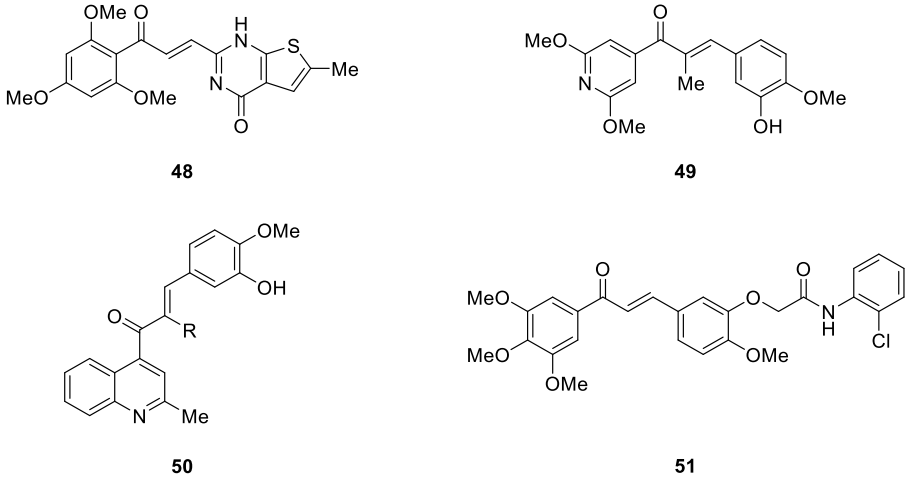


Fig. 17. Chemical structures of chalcones inducing apoptosis *via* the mitochondrial pathway.

compound may be due to carbonyl (C═O) and methoxy (–O–) moieties, as Gülçin et al., pointed out [239]. Flavokawain A chalcone (Fig. 15.43) extracted from the *kava* plant significantly reduced the proinflammatory cytokines and induced the secretion of IL-10 *in-vitro*, which is known to be an anti-inflammatory cytokine. *Ex-vivo* results indicated similar activity to the *in-vitro* results and confirmed that flavokawain is a potent antioxidant and anti-inflammatory agent [240].

1.2.8.2. Chalcones as inducers for oxidative stress. K562 cells exposed to a quinoline-chalcone derivative (Fig. 16.44) produced ROS that eventually resulted in apoptosis induction [67]. Assessed by 2′, 7′-dichlorofluorescin diacetate (DCFDA) and annexin V-FITC/PI assays, treatment with benzo [*d*]imidazo [2,1-*b*]thiazole-chalcone-conjugates (Fig. 16.45) caused ROS-induced apoptosis in breast cancer MDA-MB-231 cells [52]. Derrischalcone (DC) (Fig. 16.46) is a new chalcone isolated from the fruit of the *Derris indica* plant. Due to ROS production and oxidative stress, DC promoted cytotoxicity and apoptosis against CCA KKU-M156 and KKU-100 cells [241]. (*E*)-1,3-diphenyl-2-propene-1-one (Fig. 16.47 showed antitumor activity against four human cancer cell lines (A549, HeLa, HepG2, and HL-60) *via* robust ROS production inducing apoptosis. In addition, the mitochondrial membrane potential (MMP) of HepG2 cells was slightly reduced [242]. Flavokawain B extracted from *Alpinia pricei* rhizomes induced ROS formation, which eventually caused apoptosis and autophagy in lung adenocarcinoma cells [243].

1.2.9. Chalcones and apoptosis

1.2.9.1. Chalcones as apoptosis inducers via mitochondrial death pathway. "Apoptosis" or "programmed cell death" has a crucial role in patho (physio)logical processes. Apoptosis is either initiated with mitochondria (intrinsic), or, or mediated by death receptor (extrinsic), pathways. Intrinsic apoptosis involves cytochrome *c* release into the cytosol, where it interacts with the apoptotic protease activating factor-1 (Apaf-1) and activates procaspases-9 and -3 [244–246]. Chalcone analogs containing a thieno [2,3-*d*] pyrimidin-2-yl group (Fig. 17.48) exhibited cytotoxic activity against human lung cancer A549 and colorectal HCT-116 cells. Further, immunoblotting revealed poly-ADP-ribose polymerase (PARP-1) and caspases-3, -7, and -9 cleavages, indicating the mitochondrial death pathway-mediated apoptosis induction [247]. Two series of chalcone analogs were synthesized and then evaluated for their cytotoxic activity in HCT-116 and MCF-7 cell lines based on the replacement of the chalcone B-ring or A-ring with a 4-oxoquinazolin-2-yl group. This new chalcone analog has a cytotoxic effect mediated by inducing apoptosis *via* the mitochondrial death pathway [248]. Pyridine-chalcone derivatives (Fig. 17.49) [66] and the

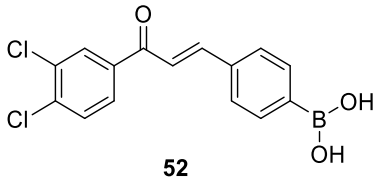


Fig. 18. Chemical structure of chalcone boronicechalcone as MDM2 antagonist.

quinoline-chalcone derivative (Fig. 17.50) [67] induced apoptosis associated with depolarization of the mitochondrial membrane potential in K562 cancer cells. This chalcone derivative also reduced the tumor volume of the H22 liver cancer allograft mouse model. Chlorosubstituted chalcone derivative (Fig. 17.51) with three methoxy groups were discovered to induce apoptosis in NCI–H460 cells through a decrease in mitochondrial membrane potential, the release of cytochrome *c*, and the down-regulation of Bcl-2 and the up-regulation of Bax, as well as the activation of caspase-9 and caspase-3 [249]. (*E*)-2-(2′, 4′-Dimethoxybenzylidene)-1-tetralone chalcone boosted caspase-3,-7 activity in HCT116 cells and caused PARP cleavage. These effects were associated with reductions in *BCL-xL* expression and an increase in the overall ratio of *Bax/BCL-xL* mRNA levels [54]. *Trans*-chalcone treatment induced damage to the mitochondrial membrane and increased the p53 protein level and decreased β-catenin [185] in the human HuH7.5 cell line.

1.2.9.2. Chalcones as inhibitors for p53 degradation. Tumor protein p53 is a protein referred to as tumor suppressor p53. It controls the cell cycle and acts as a suppressor of tumors, thereby preventing cancer. In anticancer activity, p53 plays a significant role and mediates DNA repair, apoptosis, angiogenesis inhibition, genomic stabilization, and activation of key genes. Various compounds, such as MDM2 and Sirtuin-1, control the degradation of p53. So, inhibition of p53 protein degradation is an effective anticancer therapy technique [250,251]. Kumar et al. have identified a new boronicechalcone (Fig. 18.52) as a possible MDM2 antagonist against cancer cell lines with antitumor activity. The mechanism was demonstrated by basic interaction inhibition of p53-MDM2 [252].

1.2.9.3. Chalcone and DNA damage. DNA damage may change nucleotide sequences and produce defective proteins that impair normal cellular functioning. Sources of DNA damage may be endogenous or

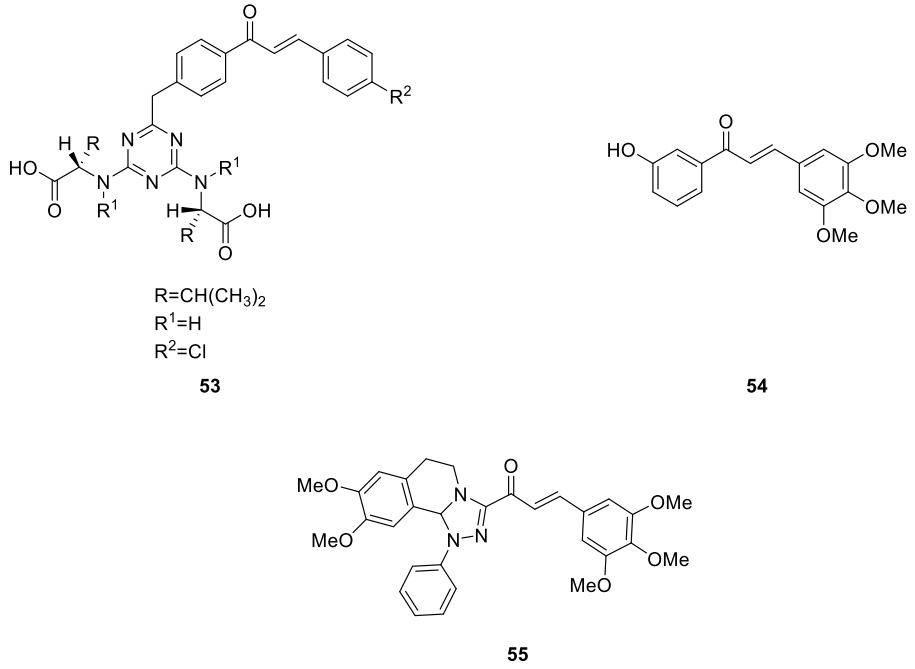


Fig. 19. Chemical structure of chalcones inducing DNA damage.

exogenous, including ROS or ionizing radiation. P53 becomes active in response to DNA damage, and its expression level increases [253]. Target genes stimulated by p53 lead to the repair of DNA damage. P53 promotes pro-apoptotic genes like Bax when DNA damage is substantial, which results in programmed cell death [254]. Chalcones are thought to interact with DNA by stacking aromatic rings and forming van der Waal interactions, which join DNA strands [255,256]. Several 1,3,5-triazines chalcone derivatives (Fig. 19.53) were synthesized and used as co-treatment with cisplatin to increase its efficacy against lung adenocarcinoma and finally caused DNA double-strand breaks. Molecular docking studies revealed compounds that displayed a binding with DNA dodecamer with many hydrogen bonds and π –H interactions [255]. Several synthesized chalcone derivatives containing the methoxy group were tested against a panel of canine lymphoma and leukemia cell lines. The derivatives demonstrated a selective antiproliferative against cell lines. The most potent compounds 2′-hydroxy-2″,5″-dimethoxy chalcone and 2′-hydroxy-4′,6′ dimethoxy chalcone triggered DNA damage in cell lines, even the ones resistant to apoptosis [257]. A study on melanoma *in-vitro* and *in-vivo* revealed that ((*E*)-1-(3-hydroxyphenyl)-3-(3,4,5-trimethoxyphe-nyl)prop-2-en-1-one chalcone derivative (Fig. 19.54) induced apoptosis and caused DNA damage by increasing the ROS level even in BRAFi-resistant melanoma cells [258]. In addition, recently we have shown that isoquinoline chalcone derivative (Fig. 19.55) caused DNA damage leading to activation of apoptotic genes, such as p53 and Bax and ultimately reduction of the tumor volume in mice model of Ehrlich solid carcinoma. Interestingly, this chalcone derivative had no toxic effects on vital organs [259].

2-Hydroxy-3′,5,5′-trimethoxychalcone activated ROS-mediated DNA damage and caspase-2 cascade activation in the human lung cancer A549 cells [260]. Benzylidenetetralones chalcones caused DNA damage-related H2AX histone alterations in HCT116 colorectal cancer cells [54]. Chalcone-dithiocarbamate hybrids were evaluated against selected cancer cell lines (MGC803, MCF7, and PC3) for its anti-proliferative action. Among these analogs, the best inhibitory action was observed in PC3 cells treated with (*E*)-2-oxo-2-((4-(3-(3,4,5-trimethoxyphenyl) acryloyl) phenyl) amino) ethyl-4-(2-hydroxyethyl) piperazine-1-carbodithioate, where it caused DNA damage and impaired colony formation [152]. In comparison to doxorubicin, pyrazolyl–chalcones induced DNA damage against four human cancer cell lines, namely A549, MCF7, and HePG2 vs normal skin fibroblast BJ1 [19]. Novel 3-(furan-2-yl)pyrazolyl and 3-(thiophen-2-yl)pyrazolyl hybrid chalcones induced DNA fragmentation revealed by agarose gel electrophoresis in lung cancer cells [12]. Bis(furan-based chalcone) derivatives coupled to aliphatic linkers with furan units at the A- or B-rings demonstrated considerable anticancer efficacy against lung and skin cancer cell lines *via* induction of DNA damage evidenced by the comet test. The biological activity was increased by the presence of the furan ring linking to the carbonyl group (ring A). On the other hand, molecules with the furan ring linked to the α,-unsaturated -bond side have lower anticancer action (ring B) [20].

1.2.10. Chalcones and autophagy

Autophagy functions either as a tumor suppressor or cancer cell survival protector. It preserves intracellular homeostasis and is linked to

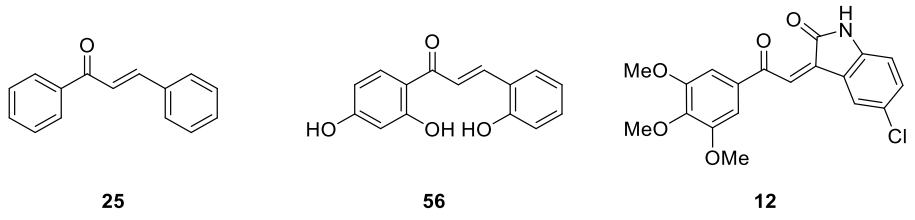


Fig. 20. Chemical structures of chalcone derivatives as autophagy inducers.

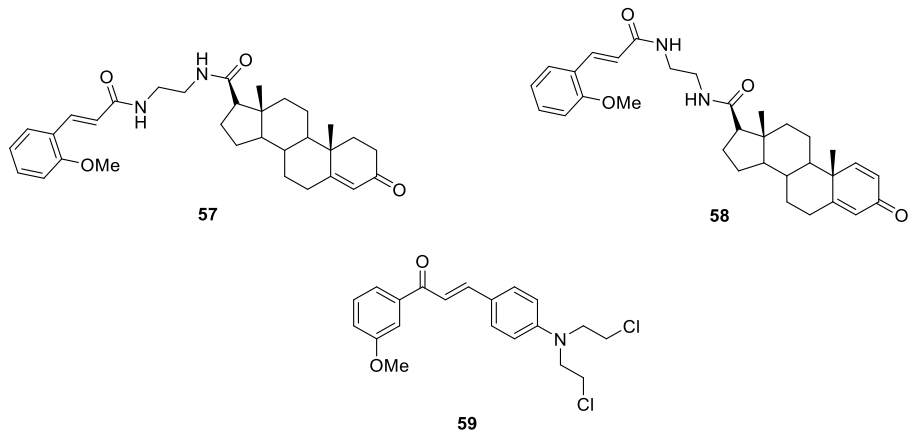


Fig. 21. Chemical structures of chalcone derivatives as antiproliferative agents against triple-negative breast cancer.

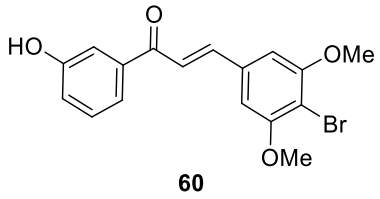


Fig. 22. Chemical structure of chalcone derivative as a Fyn kinase inhibitor.

several diseases including cancer [261,262]. Microtubule-associated light chain 3 (LC3) is the primary protein implicated in the autophagy pathway, specifically in autophagosome synthesis (which is used as a marker for autophagosomes) [263]. A study on human melanoma cells and a xenograft nude mouse showed that chalcone flavokawain B is associated with ROS-mediated autophagy [244]. The direct *in-vitro* action of *trans*-chalcone (Fig. 20.25) on the human HCC HuH7.5 cell line causes cell death mediated by autophagy [185]. A study on phytochemical compounds showed that 2,2′,4′-trihydroxy chalcone (Fig. 20.56) improved the autophagy flux in the HeLa cancer cell line without relying on the mTOR signaling pathway [264]. Flavokawain B-induced autophagy was associated with increased sequestosome 1 (SQSTM1/p62), reduced protein kinase B (AKT)/mTOR expressions, and dysregulated Beclin-1/Bcl-2 levels as a result of increased microtubule-associated (LC3-II) accumulation [244]. The caspase-3-dependent apoptotic pathway was triggered by 3′,4′,5′-trimethoxy-5-chloro-isatinylchalcone (Fig. 20.12) treatment, but it also induced extensive autophagy, as indicated by fast and dramatic alterations in LC3 and p62 [81].

In addition to upregulating the autophagic markers ATG5 and LC3B, fluorinated Tetrahydro-[1,2,4 Triazolo [3,4-*a*] isoquinolin chalcones increased the mRNA expression levels of apoptotic genes in breast cancer cell lines [14].

1.2.11. Chalcone and triple-negative breast cancer

Triple-negative breast cancer (TNBC), the most aggressive form among all breast cancer subtypes, is distinguished from other breast cancer variants by the absence of expression of the human epidermal growth factor receptor 2 (HER-2), estrogen receptor (ER), and progesterone receptor [265]. Consequently, target treatment for TNBC patients is not an amenable choice, such as endocrine therapy, thus chemotherapy is the sole strategy for TNBC patients [266,267].. Chalcone appeared to be an interesting scaffold for developing chemotherapeutics against TNBC. A sequence of novel derivatives of steroidal-chalcone (Figs. 21.57 and 58) was designed and synthesized. Cytotoxic activity against TNBC MDA-MB-231 cells with IC50 values of 0.42 μM was 23-fold higher than 5-flourouracil. Further studies of the mechanism showed that compounds cause cell apoptosis by controlling Bcl-2/Bax proteins and triggering the signaling cascade for caspase-3. Furthermore, the chalcone upregulated the cellular ROS levels inducing the apoptosis of MDA-MB-231 cells [268]. Fourteen new chalcone analogs contain nitrogen mustard (Bis-(2-chloroethyl) amine) or alicyclic amine (pyrrolidine, morpholine, and piperidine) substituents. Among them, the most potent compound ((E)-3-(4-(Bis(2-chloroethyl) amino) phenyl)-1-(3-methoxyphenyl) prop-2-en-1-one) (Fig. 21.59) exhibited antiproliferative activity against TNBC cells. In an orthotopic xenograft model of TNBC MAD-MB-231 cells, compound 59 retarded the tumor growth [269].

1.2.12. Chalcone as fyn inhibitors

Fyn is a kinase of the SRC family, which contains 11 members. Fyn is a proto-oncogene with several biological activities such as cell proliferation, survival, adhesion, and platelet activation [270]. Fyn knockdown repressed the invasion and migration of cancer cells through controlling the AMPK/mTOR signaling pathway [271]. A study was conducted to screen 111,000 compounds, 83 of them emerge as potential inhibitors of Fyn, ((E)-3-(4-Bromo-3,5-dimethoxyphenyl)-1-(3-hydroxyphenyl) prop-2-en-1-one (Fig. 22.60) was directly linked with Fyn and inhibited its kinase activity and resulted in inhibition of melanoma growth *in-vitro* and *in-vivo* by causing cell cycle arrest and apoptosis [272].

2. Conclusion

Chalcones (1,3-diaryl-2-propen-1-ones) are typical simple chemical scaffolds found in many naturally occurring compounds. They are precursors of flavonoids and isoflavonoids. Many chalcone derivatives can be formulated owing to their simple chemical synthesis. Chalcones demonstrate a wide range of biological activities and dichotomous functions in regulating hallmarks of cancer and their associated signaling pathways (i.e., inhibitors for proliferation, angiogenesis, invasion, metastasis, inflammation, stemness, and cancer epigenetics).

Given that several chalcone-based compounds have promising results in preclinical models and have been approved for medical usage to treat numerous disorders, such as the choleretic metochalcone and the sofalcone antiseptic mucoprotective ulcer, this strongly advocates the evaluation of chalcone derivatives in clinical trials as anticancer therapeutics. However, further extensive investigations are needed to fully examine their potential adverse effects before their exploitability in a translational or clinical setting.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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