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CHALCONES: AN INSIGHT INTO THEIR ANTICANCER POTENTIAL AND ACTION MECHANISM

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Abstract
Chalcones (1,3- diphenyl-2-propen-1-ones) are the well-known precursors of flavonoids and isoflavonoids, showing a broad spectrum of biological activities embracing anticancer activity. Several chalcones and their heterocyclic analogues act as an efficient anticancer agents through different mechanisms of action, including inhibition of tyrosine kinase activity, angiogenesis, cell proliferation, stimulation of apoptosis, and cell cycle disruption in different carcinoma cells. The goal of this review is to give clear and comprehensive insights relating the anticancer properties of chalcones, their heterocycles, and their likely mode of action. The papers provide an update on the several anticarcinogenic mechanisms of action of chalcones and the necessity of creating new anticancer medications with high levels of selectivity, efficiency, and in-vitro work efficiency.

Keywords: Cancer, Chalcones, Anticarcinogenic, Angiogenesis.

1 Introduction:

Cancer, a condition caused by genetic, immune, oxidation, and inflammatory mechanisms is one of the major causes of human morbidity, mortality, and premature death worldwide. It results from bizarre and complex variations occurring at multi-cellular and molecular levels[i]. According to estimates from the World Health Organization (WHO) in 2019, cancer is among the top two disease-related reasons for the deaths of people under 70 years in 112 of 183 countries. It holds third or fourth in the other 23 countries[ii]. Despite several efforts to decrease the cancer incidence rate in the United States, the patient count is increasing enormously[iii]. Although significant progress has been made in cancer treatment, searching for new promising molecules is challenging due to the elevated number of new cases every year. After analysing previous cancer estimates, it is predicted that by 2030, the incidence rate of cancer will be

almost 26 million people, and the mortality rate will be 17 million deaths per year[iv]. Cancer treatment has become a vital and exciting curative task in pharmaceutical chemistry. There are three major strategies for cancer treatment, especially at primary, advanced, and metastatic stages: surgery, radiation therapy, and chemotherapy. Out of these, chemotherapy has the most promising effects for cancer treatment. However, the absence of selectivity and improvement of drug endurance reduces the effectiveness of cancer chemotherapy[v]. This conflict with chemotherapy is due to the patient's discrete dissimilarities like gender, age, *etc*., and genetic variations in the cancer cells. The most predominant cause of drug conflict is the altered expression of one or more energy-dependent transporters, insensitivity to drug-induced apoptosis, and induction of drug-detoxifying effects[vi]. Chemotherapy is one of the common treatments for frequent tumors using established anticancer drugs, which may lead to crucial side effects like nausea, vomiting, hair loss, anaemia, fatigue, appetite changes, and pain. So, during the treatment, patients suffer a lot[vii-viii]. The side effects are primarily related to high dosage, non-specific allocation of chronic toxicity to normal tissues, insufficient drug concentrations at carcinoma tissues, and improving multidrug conflict[ix]. To eliminate such adverse effects of chemotherapy, researchers have acquired the targeted therapies that can suppress the growth of cancer cells and keep the normal cells intact by intruding with the selected moieties and routes, which are the possible causes of carcinogenesis. Chemotherapy is less likely to be effective in treating different types of cancers. Several drugs having antiproliferative activity are taken into clinical use, such as cisplatin, paclitaxel, carboplatin, oxaliplatin, *etc*[x]. (Figure 1) Paclitaxel (I) was one of the clinically accepted antineoplastic drugs for the treatment of different cancers like breast cancer, lung cancer, ovarian cancer *etc*., which was derived from the bark of the western Yew tree, *Taxus brevifolia.* It induces microtubule conclave for showing anticancer activity. Despite having effective anticancer properties, the drug paclitaxel has many toxic side effects on patients' central nervous systems, making it illegal to use it alone or in combination with other neurotoxic medications like cis-platin (II) [xi].

Furthermore, paclitaxel shows peripheral neurotoxicity and can induce diabetes mellitus in some patients[xii].Cyclosporine A (III) is an immunosuppressant for treating cancer patients' organ and bone marrow transplants[xiii-xiv]. Herman, a scientist, proved that the person consuming Cyclosporin A has a lesser DNA repair effect than azathioprine (IV) or prednisolone for the treatments after undergoing a kidney transplant and performing DNA damage using UV radiations*xv*. Another group of scientists demonstrated that cyclosporine-A can prohibit the gene coding for DNA polymerase β, which acts as a DNA repair enzyme[xvi].Cyclosporine A can perform apoptosis of T-cells[xvii]. The consequence of the binding action of cyclosporine A with cyclophilin D is that it can prohibit apoptosis by stopping the opening of the permeability pore of the inner membrane of mitochondria[xviii]. These biochemical reactions of cyclosporin A supposedly work in combination, which induces cancer growth. A cytotoxic drug like doxorubicin (V) causes damage to the DNA, and later, the cell cycle advancement becomes detrimental to the cells[xix]. Oxaliplatin (VI) is another crucial patinated drug with collateral and analgesic properties against metastatic rectal carcinoma. It is demonstrated that the risk of stage III colorectal cancer recurrence treated *via* surgical elimination is 50 to 80%[xx-xxi]. Hence, collateral chemotherapeutic treatments like oxaliplatin in combination with other chemotherapeutic drugs are suggested[xxii-xxiv] because of the ability of oxaliplatin to hinder the DNA replication and transcription primarily *via* cross-linking of metal atoms with DNA strands. Despite this, oxaliplatin is less efficient against tumor cells as most of the cells develop resistance against these chemotherapeutic drugs. Also, it has several adverse effects on the central nervous system with increased dosage throughout the treatments, suggesting the restricted clinical use of oxaliplatin[xxv-xxviii].

Another analogue of cisplatin, called carboplatin (VII), has a similar mode of action and perceives higher efficiency against metastatic ovarian cancer[xxix-xxx]. The resistance to the intracellular response is the primary reason for the clinical exclusion of carboplatin. Like other chemotherapeutic drugs, carboplatin also shows cytotoxic effects such as nausea, vomiting, anemia, hypersensitivity, genitourinary disorders, *etc*[xxxi]. Higher dosages of carboplatin show damaging action on the patient's bone marrow.[xxxii]. These chemotherapeutic agents seem to be moderately efficient and have several side effects. Therefore, in the present situation, the invention of novel anticancer drugs for cancer treatment has become a center of attraction for many researchers. Approximately 74% of anticancer drugs are derived from natural source, semi-synthetic compounds, or their molecular models[xxxiii]. Chalcones are acknowledged among the presently known drug candidates because of their varying pharmacological properties. Natural substances are proven as worthy resources for the development of a drug. In this regard, Phytochemicals- chalcones (1,3-diphenyl-2-propen-1-one) (Figure 2) are structurally simple, inexpensive, readily available, and relatively nontoxic organic compounds[xxxiv]. The term 'Chalcone' was given by Scientists Kostanecki and Tambor.[xxxv] Chalcones are also known as phenyl styryl ketone and exist in both *cis* and *trans* forms[xxxvi], out of which the *trans* form is thermodynamically more stable[xxxvii]. Chalcones have two aromatic rings joined by three carbons, conjugating α and β-unsaturated carbonyl systems. This conjugated α, β-unsaturated carbonyl system in chalcones is responsible for their biological activity[xxxviii]. Chalcones are synthesized in higher plants and are the precursors of diverse groups of flavonoids and isoflavonoids, simple chemical scaffolds abundant in plant products, including vegetables, spices, fruits, and teas. Due to cyclization's ease of forming heterocycles, they are easily accessible by synthetic methods[xxxix]. Many chalcone derivatives were also prepared due to their convenient synthesis. The scientist Toru and co-workers noted the promising anticancer activity of chalcones for the first time[xl]. Heterocyclic chalcones have gained the interest of scientists to their diverse, remarkable, and broad spectra of biological activities against various diseases including antidiabetic,xli cancer chemopreventive[xlii], antileishmanial[xliii],anticancer[xliv],anti-inflammatory[xlv], antioxidant[xlvi], antimicrobial[xlvii], anti-tubercular[xlviii], anti-HIV[xlix], antimalarial[l], and anti-allergic[li] behaviours, etc. More importantly, several chalcone compounds have been approved for market and clinical use for various health conditions, e.g., as metochalcone-choleretic / diuretics[lii], sofalcone-based anti-ulcer / mucoprotectives[liii] and hesperidin methylchalcone-vascular protectives[liv], supporting the clinical potential of chalcones[lv] The chalcone family has demonstrated potential *in-vitro* and *in-vivo* activity against cancers *via* multiple mechanisms. A wide range of data on molecular mechanisms of action has been documented, including induction of apoptosis, autophagy, immunomodulatory and inflammatory mediators, cell cycle changes, and modulation of several signalling pathways associated with cell survival or death. In addition, the blockade of several steps of angiogenesis and proteasome inhibition has also been documented[lvi]. The antitumor activities of heterocyclic chalcones are especially remarkable, and the growing number of publications dealing with this topic warrants an up-to-date compilation. Prepared chalcones have emerged over the last years with promising antitumor activities. Among them, there are a considerable number of tubulin polymerization inhibitors. But there are also new chalcones targeting special enzymes such as histone deacetylases or with DNA-binding properties[lvii].

Chalcones are becoming the era of attraction for researchers in the pharmaceutical sector due to their exceptional characteristics, broad range of biological activities, and excellent medicinal efficiency against various diseases (Figure 3), especially cancer. It represents a promising strategy to develop chalcones as novel anticancer agents. In addition, combining chalcones and other therapies is expected to be an effective way to improve anticancer therapeutic efficacy.

However, despite the encouraging results for their response to cancers observed in clinical studies, a complete description of toxicity is required for their clinical use as safe drugs for treating cancer. The presence of a variety of physicochemical and pharmacological activity, as well as an exceptional involvement in life nourishment processes, has captivated biologists and chemists. However, few such data explain the efficient in-depth source of the cytotoxic or antiproliferative activity shown by the chalcones[lviii]. Several collections of heterocycles with significant synthetic derivatives prepared from chalcones propose improved medicinal characteristics, and structural changes have proven to be efficient chemotherapeutic and pharmacotherapeutic agents. The chalcone derivatives play a vital role in the skeleton of pharmacological outlines, making this framework a supreme nominee to develop more efficient and safer drugs, especially for cancer. The available cancer treatments have many limitations and side effects. Hence, innovating more efficient and selective anticancer drugs with fewer side effects is a challenge in improvising chemotherapeutics agents for the forthcoming generations.

2 Mechanism of action of chalcones:

Several biological demonstrations proved the application of infinite pathways through which chalcones show their anticancer activity. Chalcones aim for several pathways in cancer treatment, namely apoptosis inducer, heat shock protein 90 (HSP90) inhibitor, Telomerase inhibitor, Antimitotic inhibitor, carbonase anhydrase inhibitor, multidrug resistance inhibitor, hormone inhibitor, angiogenesis inhibitor, monocarboxylate transporter inhibitor, aromatase inhibitor, inhibition of protein deacetylation, inhibition of p53 degradation, inhibition of cell cycle proliferation, etc.

2.1 Apoptosis inducer:

A well-organized series of incidents that causes programmed cell death is known as apoptosis. This phenomenon can decrease the cell volume and nuclear size *via* contraction and slicing of chromatins and reduces the adhesion, thus producing small apoptotic bodies that induce phagocytosis. The apoptosis process is subcategorized as intrinsic or extrinsic trials[lix]. Apoptosis at a cellular level is controlled by the Bcl-2 protein family, which consists of pro-apoptotic (Bcl-xl) and antiapoptotic protein (Bid, Bad, Bax, and Bak) families. Moreover, one of the proteolytic enzymes, caspases, is the crucial executor of apoptosis[lix].

i **Extrinsic trial (Route for death receptors):**

Once the tumor necrotic factor functioning as a cell surface receptor is promoted for death, the receptor trimerization occurs afterward through the recruitment adaptor proteins (TADD and FADD) and caspases (initiator and effector). The cell death occurs after stimulation of effector caspases (caspases-3, 6, 7) by initiator caspases (caspases-2, 8, 9, 10)[lix].

ii **Intrinsic trail (negotiated by mitochondria):**

This trail is chiefly controlled by Bcl-2 family associates, *i.e.,* Bax, Bak, stimulated Bax, and Bak connect to the outer membrane of mitochondria, making this membrane porous and liberating cytochrome C in the intermembrane space. The cytochrome C plays a vital role in apoptosome formation *via* the binding action of apaf-1 and initiator caspase 9. After this, the initiator caspase activates lower effector caspases, leading to apoptosis. Stimulation of apoptosis is assumed to be a critical trail for the action of chemotherapeutic mediators involving chalcones[lix]. It was observed that an increase in the antiapoptotic marker, *i.e.,* Bcl-2 levels, since an increase in the Bcl-2 level, would further form a heterodimer. Therefore, the rise in the Bcl-2 level can be considered to decrease the apoptosis rate. In contrast, an increase in the Bax level shows a considerable increase in the rate of apoptosis because of the formation of the homodimer, which will further increase the permeability of the outer layer of the mitochondrial membrane and release cytochrome C in the mitochondrial cytoplasmic fluid

where caspase-9 is stimulated and leads further to the activation of caspase-3 which finally promoted apoptosis[lx].

Based on these considerations, a group of scientists, Heba *et al*., also discovered a drug {1} that can continuously stimulate apoptosis in RPMI-8226 cancer cells by impacting the demonstrations of apoptotic and antiapoptotic markers. Also, these compounds can decrease the Bcl-2 levels by acting as an antiapoptotic marker, ultimately increasing the Bax/Bcl-2 ratio. This suggests that compound {1} will considerably stimulate apoptosis *via* intrinsic trials to a greater extent[lxi]. Also, upon further investigations, it was demonstrated that the compound {1} induces the accumulation of reactive oxygen species (ROS) in RPMI-8622 cells to the slightly greater extent of 86.22 Pg/mL than the reference used gefitinib (80.29 Pg/ml). It also showed three times higher ROS accumulation than the control cells. These results predict that ROS accumulation is the chief reason behind the apoptosis stimulation due to compound {1}.

Hesham et al. synthesized a novel series of xanthine and chalcone-based hybrids showing anticancer activity. Their study demonstrated that the compound {2} showed exceptional anticancer activity with IC_{50} of 0.3 μM on the targeted enzyme compared to staurosporine with an IC_{50} value of 0.4 μM, which was used as a reference drug. Further, it was confirmed that this compound has an efficient apoptotic effect because of the remarkable elevation in Bax level up to 29 times and decreased regulation in Bcl-2 to 0.28 times, compared to the standard used[lxii]. Mitochondria are vital cell organelles because they are the key regulators for programmed cell death, *i.e.*, apoptosis. It is often observed that the inner membrane of mitochondria is linked with the early stages of apoptosis[lxiii]. Compared to untreated cells, it was found that the cells treated with chalcone derivative {3} cause a considerable decrease in the potential of mitochondria's inner membrane, stimulating apoptosis in breast, prostate, and lung cancer cell lines *via* the intrinsic pathway. This group of scientists experimentally proved that treating lung, breast, and pancreatic cancer lines with 20 μM of compound {3} for 48 h stimulates apoptosis to a remarkably higher percentage than the control. Further investigations predicted that this compound has an IC_{50} value of 9, 2, 10 for A549, MCF-7, and PC-3 cancer cell lines, respectively, which suggests promising anticancer activity possessed by this compound[lxiv].

Another study revealed that the compounds {4-5} display high antitumor activity against various cancer cell lines, namely, breast cancer (MCF-7) and human liver carcinoma (HepG-2) with IC_{50} values of 2.47, 3.02 μM, respectively, as compared to the standard used, Imatinib having an IC_{50} value of 6.06, 5.50, and moderate activity against colon cancer cell lines (HCT-112). In addition, these compounds exhibited increased apoptotic protein (BAX) and decreased antiapoptotic (Bcl-2) protein. This suggests that the compounds {4-5} stimulate apoptosis with BAX protein values of 328.58 and 365.41 pg/mL, respectively 6.95 and 7.73 times that of control with BAX protein value of 47.32 pg/mL. Another reason for the high apoptotic induction by compounds {4-5} is the furo [2,3-b] indole and carboxamide moiety present in it. These derivatives have Caspase-3 stimulator properties, having 328.58 and 365.41 pg/mL concentrations, which further induces apoptosis. But compound {5} can pass through the blood-brain barrier, resulting in cerebrospinal side effects[lxv].

2.2 Inhibition of heat shock protein 90 (HSP90):

HSP90 are molecular chaperones that can stabilize and support conformational folding when they act with other proteins and prevent the abnormal folding and destruction of proteins.[lxvi] The cells undergoing damaged or stressed cells have a higher level of these HSPs. Due to the stressed environment or damaging cells, the HSP90 level increases and causes a reduction in nutrition, oxygen deficiency, and uncontrolled growth. As a result, the oncogenic proteins get stabilized, and the conversion and multiplication of the normal cells into cancerous cells take place. Also, the HSP90 proteins can inhibit the natural apoptosis or prevent the natural

apoptosis or signals from tumor suppressor genes to stop cell multiplication[lxvii]. HSP90 has an additional role in suppressing the mutations in the fatal genes in cancer cells. HSP90 buffering of mutations may have the capability to inhibit apoptosis by preventing catastrophic phenotypes[lxviii]. This characteristic behaviour of HSP90 suggests that these are vital links between genotypes and phenotypes. Scientists designed and synthesized a series of chalcone-templated HSP90 inhibitors and considered them against gefitinib-resistant non-small cell lung cancer cells (H1975). Out of these synthesized compounds, compound {6} efficiently prohibits the proliferation of H1975 cell lines. This is due to the remarkable property of compound {6} to deuterate the consumer proteins of HSP90, namely, EGFR, Met, Her2, and Akt. Also, the dose-dependent stimulation of HSP70's demonstration level strongly suggests that the compound {6} focuses on the HSP90 molecular chaperone system[lxix].

Another group of scientists has designed a novel analogue of chalcone, HYQ97 {7}, which showed promising anticancer activity. Upon demonstrating the interaction between the chalcone hybrid and the HSP90 protein through molecular docking, it was observed that this chalcone analogue could easily fit into the active site of HSP90. There is a bond formation between HYQ97 {7} and the residues of Gly135. Later, they performed immune precipitation to detect whether the HYQ97 {7} would obstruct the HSP90. This chalcone hybrid can inhibit the HSP90 from binding to its antibody in a dose-dependent manner. Also, the hybrid can reduce the manifestation levels of consumer proteins containing AKT, NF-kB, and HER-2 in a dose-dependent manner. It was demonstrated that HYQ97 (500nM) could efficiently inhibit HSP90 *via* direct binding. This shows that the novel chalcone hybrid HYQ97 can efficiently prohibit the proliferation of lung cancer (A549) cell lines by inhibiting HSP90 and degrading its consumer proteins[lxx].

Another study has synthesized a chalcone-based scaffold {8}, and it was analyzed for HSP90 inhibitory action using a strategy associated with the linkage of fragments [lxxi]. The results were quite depressing. After all, despite compound {8} anticancer efficiency, there were various difficulties in its medical practice, such as a non-specific binding issue and its susceptibility when tackled by endogenic cellular nucleophiles like cysteine, lysine, and histidine. Also, its anticancer efficiency was not strong enough and may require more structural improvisation. So, for now, the amide group replaced the enone moiety in the compound {8}[lxxii].

2.3 Inhibition of protein kinase:

Enzymes that can transmit phosphate groups to the targeted proteins are kinases. Activation of kinases results in various cancer-inducing phenomena like cellular proliferation, apoptosis inhibition, angiogenesis stimulation, and inducing the formation of metastatic tumors. Also, activating kinases due to the somatic mutation is the elementary step for tumorigenesis[lxxiii] These are subcategorized based on their function and the amino acid they are attached to.

i. Serine/threonine protein kinases:

Serine threonine-specific protein kinases are collectively known as Akt/PKB kinases. Chalcones are vital scaffolds that have remarkable anticancer properties. One is quercetin, which has exceptional inhibitory activity on serine/threonine kinases. This inhibition of serine/threonine kinases is carried out *via* quercetin obstruction in the Akt/PKB pathway, which prevents proliferation and apoptosis stimulation[lxxiv]. Also, quercetin can inhibit the CK2 protein kinases, the secured serine/threonine protein kinases that can control cell cycle, proliferation, apoptosis, transfer of proteins, etc. CK2 protein kinases can stimulate the Akt/PKB *via* hyperphosphorylation, as a result of which the PI3K and CK2, *viz.*, two self-regulating kinases, act together on Akt/PKB, which further stimulates proliferation and can be inhibited by quercetin[lxxv].

Cyclin-dependent kinases (CDK) are the major subdivision of serine/threonine protein kinases, which function *via* dominating cell cyclin-dependent proteins[lxxvi]. Time-bound synthesis and degradation of positive regulatory cyclins, negative regulators, and CDK inhibitors are the significant functions performed by the kinases[lxxvii]. Down-regulation of these functions induces tumorigenesis and introduces various kinds of cancers. Dysregulation of these factors is essential in tumorigenesis and the progression of multiple cancers. The improvisation and development of particular inhibitors target the cyclin-dependent kinases. This is one of the most uplifting strategies for developing anticancer drugs. Controlling the cell cycle through phosphorylation of CDK1 and phosphorylation-based initiation of transcription are the two significant features of CDK7 protein kinase. Thus, upon inhibition of CDK7, both processes will be terminated, leading to an efficient and precise anticancer response. This shows that the inhibition of CDK7 is a significant phenomenon altering the anticancer behaviour of various scaffolds[lxxviii].

Another class of serine-threonine protein kinases that have reacting properties intensify towards various extracellular stimuli and give suitable biological responses like uncontrolled cell progressions, apoptosis, differentiation, development, endurance, cellular multiplication, *etc*.[lxxix] These mitogen-activated protein kinase (MAPK) are classified into conventional and non-conventional MAPK. The classical MAPK pathways consist of extracellular signal-regulated kinase (ERK) 1/2, p38s, JNKs, and ERK5, while the nonclassical MAPK pathways consist of ERK3/4, ERK7/8, and nemo-like kinase (NLK).

The ERK1/2 is considered one of the most significant MAPK signaling pathways. These ERK1/2 MAPK signalling pathways are stimulated by the MEK 1/2, which sends signals from various upstream kinases. The RAS-activated RAF further phosphorylates MEK 1/2; this MEK 1/2 is later utilized for the phosphorylation of ERK1/2. These phosphorylated ERK 1/2 then ze apoptotic controllers can inhibit the cell progression by stimulating positive cell cycle regulators. In healthy cells, these kinases require constant stimulation for significant transformation of the G1 phase to the S phase[lxxx]. p38 is another conventional MAPK that responds to stress stimuli[lxxxi]. Mitogen-activated protein kinase kinase (MKK)-3 and MKK-6 activate this p38. MKK-3 carries out further phosphorylation of α, β, γ homologs. The activity of p38 can be elevated by duplication of MKK6/6b[lxxxii]. The most vital function of p38 MAPK is that it inversely operates the cell proliferation at G1/S and G2/M phases *via* stimulation of p53 and inactivating CDC-2 by the stabilized p21, respectively. Generally, the inhibition of p38 MAPK is related to the stimulation of apoptosis. Still, it also induces cell survival in cells that have undergone DNA damage due to the action of different chemotherapeutic drugs[lxxxiii]. As a result, the inhibition of p38 MAPK is a key strategy for treating various cancers. The last conventional mitogen-activated protein kinase is ERK-5, also known as big mitogen-activated protein kinase 1(BMK-1). It is larger (almost double) as compared to other MAPKs. Various mitogens, like a serum, can stimulate endothelial growth factor, brain-derived neurotrophic factor, nerve growth factor, vascular endothelial growth factor, etc., as well as several stress stimuli. Like oxidative stress and hyperosmolarity[lxxxiv]. The various necessary phenomena, like embryonic development, vascular development, and cell survival, efficiently utilize ERK-5 for their progress. The inhibition of vascular stabilization and angiogenic remodeling due to the lteration in the level of VEGF are the major drawbacks caused by the deficiency of ERK5[lxxxv]. The CCL39 cells and spread of stimulated ERK-5 and MEK-5 stimulate the ERK-5 cascade, which later promotes G1/S transformation. Cyclin-D-1[lxxxvi]. Various carcinogenic characteristic behaviours like consistent growth of ErbB-2 in breast cancer and resistance to chemotherapeutic treatments are mainly caused by the malfunctioning in the ERK-5 pathway[lxxxvii]. There is another stress-stimulated mitogen-activated protein kinase named JNK, whose activation results from

different stress stimuli like heat shock, UV radiations, and DNA damaging agents (chemotherapy, radiation therapy, etc., for the case of cancer patients). The JNK protein inhibitor D-JNKI-1 can lower cell proliferation in melanoma cancer. Also, these inhibitors play a crucial role in reducing the tumor size caused by carcinogen injection[lxxxviii]. Furthermore, JNK has a unique feature of not only increasing the activities of pro-apoptotic proteins like BAX and BAK but also prohibiting the antiapoptotic proteins like Bcl-2, suggesting that the JNK are involved in mitochondria-mediated apoptosis[lxxxix].

There are three non-conventional activated protein kinases: ERK 3/4, ERK-7, and NLK. ERK 3/4 is responsible for various biological processes like cellular proliferation, cell cycle progression, differentiation, embryogenesis, etc. Instead of having phosphoacceptor Tyr residue, the ERK 3/4 have Ser-Glu-Gly scaffolds; they belong to a non-conventional module. Furthermore, the C and N-terminals have different significant roles in subcellular targeting[xc] and degradation of ERK-3 by ubiquitin-proteasome pathway, respectively[xci].

The C-terminal present in another non-conventional MAPK, *i.e.*, ERK-7, is responsible for its autoactivation[xcii], while N-terminal promotes its degradation via the Ubiquitin-proteasome pathway[xciii]. The ERK-7 induces cellular proliferation and responses to estrogenxciv and glucocorticoids. Also, the ERK7 can suppress kinase-independent DNA synthesis[xcv].

NLK (Nemo-like kinases) is another non-conventional mitogen-activated protein kinase stimulated by Wnt trail stimuli. Wnt1 and Wnt5a. The IL-6 granulocyte, colony-promoting factor (G-CSF), and conversion of growth factor β (TGF-β) results in the stimulation of NLK [xcvi]. The NLK controls the β-catenin pathway as a stimulus to the Wnt pathway[xcvii].

ii. Tyrosine kinase inhibitors:

Receptor tyrosine kinases:

A group of scientists, Federica et al., experimented to determine the drugs vulnerable to inhibition *via* analysing the deregulation of receptor tyrosine kinases, namely, EGFR, PDGFRA, and PDGFRB, along with their downstream effectors. Here the effect of some kinase inhibitors on the proliferation of diffuse malignant peritoneal mesothelioma (DMPM) was investigated. This analysis used NIH3T3, Cal27, and 2N5A cell lines as positive controllers for the expression/phosphorylation of PDGFRA, EGFR, and PDGFRB receptor tyrosine kinases, respectively. On performing the biochemical analysis on 20 DMPMs for determining the RTK expression/activation, they found that the maximum cases displayed EGFR and PDGFRB expression nearly 90% and 75%, respectively. Almost 17 of the cases showed PDGFRA expression, and a low level of receptor activation was seen in about 45%.

Further, the immunohistochemical analysis demonstrated that, out of 16 cases, 14 displayed EGFR activation within the high to moderate levels range. The immune reactivity of PDGRFB levels was also found in 80% of cases. The determination of cytoplasmic receptor expression *via* immune staining proved that almost 18 cases displayed cytoplasmic receptor expression, while only 2 cases were slightly positive. The determination of the activity of phosphorylated receptor tyrosine kinases *via* phospho-proteome profiler kit and immune-reprecipitation by western blot suggested that all the tumors have nearly the same activation profile segregated in high level to a lower level, as high levels of activation for EGFR, high/moderate levels of activation for PDGFRB and negligible activation for PDGFRA.

The molecular pathology findings confirmed that the activation of EGFR and PDGFRB receptor tyrosine kinases is the main reason behind the activation of downstream RTK signalling in the DMPM cell lines. This signified that RTK and mTOR inhibitors could be utilized individually or combined for cancer treatment. To determine whether this assumption is right or wrong, this group of scientists further evaluated the antiproliferative activities of gefitinib (EGFR inhibitor), RAD001 (mTOR inhibitor), and sorafenib (multi-kinase inhibitor against PDGFRB, VEGFR-2, VEGFR-3, the serine-threonine kinase Raf) against the STO

human peritoneal mesothelioma cell line. The results obtained for the RTK activation profile revealed that even in the absence of any receptor mutation, EGFR gets expressed and activated. However, both PDGRFB and PDGFRA were unexpressed and dormant. However, ERK1/2, AKT, mTOR, S6, and 4EBP1 showed significant expression and phosphorylation. Due to drug resistance for gefitinib by STO cells (from DMPM cell lines), a mutational investigation of downstream RTK effectors was carried out, which proved the presence of KRAS mutation and absence of BRAF, PI3KCA, and PTEN mutations. The consistency in the phosphorylation of mTOR and its effectors is due to the fact of activated EGFR and PDGFRB RTKs, as a result of which KRAS/BRAF mutations and PI3KCA mutation/amplification are absent and the inactivation of PTEN.

Besides, the antiproliferative activity of gefitinib showed activity with an IC50 value of 40.1 ± 1.3 μM at a comparatively higher drug dosage. Also, the RAD001 was adequately active when used individually, but when combined with the sorafenib, the STO cells were susceptible with an IC50 value of 0.55± 0.07μM. Further, the dose-dependent exposure to this combination displayed higher antiproliferative activity with increasing concentration of this combination [xcviii].

Non-receptor tyrosine kinases:

In the past few years, Linlang and co-workers intend to determine whether Epithelial and endothelial tyrosine kinase (Etk) plays a role in the drug resistance of small cell lung cancer (SCLC) and its relation with antiapoptotic proteins like Bcl-2, Bcl-XL, and p53. Etk belongs to the Tec family of non-receptor tyrosine kinases, also known as bone marrow C kinase (Bmx). Both the epithelial and hematopoietic cells can express the Etk. It can act as both pro-apoptotic and antiapoptotic proteins. Further, they performed a western blot and flow cytometric analysis to investigate the expression caused by Etk on the protein level of the drug-resistant H69AR cells concerning H69 cell lines. The results demonstrated the overexpression of the antiapoptotic proteins in the H69AR cell lines, which may be one of the reasons behind the chemoresistance of H69AR cell lines. To determine the exact reason, further analysis was done, which explained precisely that the level of Bcl-XL gets elevated in H69AR cell lines than the H69 cells while the Bcl-2 and p53 proteins were slightly increased in the H69 cells than the H69AR cell lines.

Further, to determine the inhibitory action of Etk-siRNA on Etk mRNA and protein expression, they induced the Etk siRNA into H69AR cell lines along with Lipofectamine 2000; the result was quite shocking. There was a significant decrease of 72% in the Etk levels due to its pre-treatment with siRNA for 48 hours. Later on, the effect of Etk mRNA on the cell sensitivity against the chemotherapeutic agents was analysed *via* cell *via*bility assay. The result concluded that the Etk-siRNA treated H69AR cells have almost 2.64-9.36 times higher IC50 values than the control. This confirms that to suppress the resistance to chemotherapeutic drugs by small cell lung cancer (SCLC) cells, the level of Etk should be decreased. This strategy of reducing the Etk level should be applied to overcome chemotherapeutic drug resistance shortly[xcix].

3 Analogues of Chalcones As Potent Anticancer Agents:

3.1 Chalcones Derivatives Against Breast Cancer:

Breast cancer is one of the significant causes of death in women. According to the World Health Organization (WHO) global estimates, female breast cancer is the most commonly diagnosed cancer (11.7% of total cases). In comparison, the mortality rate for breast cancer is 6.6% of total cases.[c] Breast cancer is further classified into four categories based on their characteristic behaviour: Luminal A, Luminal B HER-2 positive, Luminal b HER-2 negative, HER-2 and triple-negative tumors[ci].

Trans- chalcone (TChal) {9} is a thermodynamically more stable isomer of chalcones. It shows highly antitumorigenic behavior *via* different action modes: angiogenesis inhibition, apoptosis

induction, cell cycle arrest, topoisomerase 2α, etc[cii] Heme oxygenase-1 (HO-1), *i.e.,* heat shock protein 32,[ciii] is a phase II enzyme that responds to cellular injury, oxidative stress, and various diseases. The cancer treatment using trans chalcones had remarkably increased the level of HO-1, resulting in various cancer-inducing phenomena like induction of angiogenesis, metastasis, and inducing cancer cell growth. It also generates resistance to chemo and radiation therapy[civ]. However, studies by other scientists concluded that HO-1 is one of the significant proteins that reduce tumorigenesis in various cancers[cv]. It mainly shows an antitumorigenic response against breast cancer cell lines[cvi]. Based on this, it can be concluded that the HO-1 shows both anticarcinogenic and malignant activity, depending upon the nature of tumor cells. Considering these considerations, another group of scientists discovered a most efficient technique for treating triple-negative tumor cells, *i.e.,* BT-20 cell line using TChal successfully induces the manifestations of HO-1 protein in a dose-dependent manner. When these tumor cells are treated with siRNA, focusing on HO-1 mRNA makes these cell lines less sensitive toward TChal, implying that the TChal-stimulated antiproliferative activity is due to specific HO-1 illustration. A significant decrease in the tumor size of BT-20 was observed in the xenograft vivo models because of the usage of 30 μM of TChal for 24 h[cvii].

Another group of scientists synthesized 14 nitrogen-based chalcones *via*. Claisen-Schmidt condensation exhibiting anticarcinogenic properties. Of these 14 chalcone analogues, only one analogue showed efficient anticancer activity against triple-negative breast cancer. This compound {10} appreciably inhibited cell aggression and prevented MDA-MB-231 and MCF-7 BC cancer cell migration. The anticarcinogenic behaviour of compound {10} affirmed that this compound {10} promotes apoptosis by increasing the pro-apoptotic protein levels and reducing the antiapoptotic protein levels. The compound {10} attacks the triple-negative breast cancer cells *via* a different mechanism of action, namely, cell cycle arrest at the G2/M phase and stimulation of a reversal of epithelial-mesenchymal transition (EMT) by increasing the level of E-cadherin and Pancadherin *viz.,* epithelial markers and decreasing the level of focal adhesion kinases. The compound {10} effectively restricts tumor growth by dominating cellular proliferation, which inhibits tumor development. It acts as a promising cancer agent with an IC50 value of 8.00 ± 0.07 μM against MDA-MB- 231, 6.43±0.18 μM against MCF-7[cviii].

Recently, another group of scientists demonstrated a novel chalcone with a promising anticancer effect. According to them, this hybrid {11} was susceptible to triple-negative breast cancer cells, *i.e.,* MDA-MB-231, and exhibited potent antiproliferative activities with an IC50 value of 0.42 μM. This compound promotes cell cycle arrest in the MDA-MB-231 at the S phase in a concentration-dependent manner. Compound {11} at 10 μM concentration significantly induces apoptosis in MDA-MB-231 cell lines up to 58.50 %. It remarkably induces apoptosis *via* a decrease in the level of BCl-2 and an increase in the BAX level. The caspase pathway plays a pivotal role in this case of compound {11} anticancer behaviour in MDA-MB-231 cell lines. It considerably increases cleaved caspase-3 and PARP levels in triple-negative breast cancer, *i.e.,* MDA-MB-A231 cells[cix].

3.2 Chalcones Derivatives Against Colorectal Cancer

Zuzana et al. demonstrated a series of novel indole-chalcone analogues with novel indole-chalcone analogues that have efficient activity against human colorectal cancer. In the primarily analysed series, compound {12b} having three methoxy groups at 2,4,6 positions proven to have efficient activity against HCT116 with IC50 value < 7 μM. Another 3,5-dimethoxy and 3,4,5-trimethoxy analogues of chalcone {12a and c} exhibited remarkable specificity against HCT116 cells. 2-fluorophenyl derivative{12d} showed a remarkable cytotoxic effect against Caco-2 cell lines with an IC50 value of 8.5 μM but showed significant toxicity against non-cancerous cell lines 3T3. In contrast, other derivatives {12e} displayed a

promising anticancer activity against HCT116 with IC50< 8μM but showed very low toxicity against fibroblast cell lines of mice[cx].

Another group of researchers synthesized a series of new chalcone-polyamine derivatives in which the chalcone core is fused with the polyamine moiety, forming an amine linkage. All the compounds had remarkable antiproliferative activity against human colorectal carcinoma cell lines, i.e., HT-29 and HCT-116. Amongst these series of chalcone-polyamine moieties, compound {13} showed 2 to 3 times more efficient activity than the other derivatives against HT-29 and HCT-116 cell lines to a greater extent with IC50 values of 10.76 and 8.13μM respectively. Further investigations based on cell cycle distribution revealed that this compound could efficiently hinder the cell progression at the G1 phase and consequently decrease at the S phase, which finally results in the inhibition of proliferation of human colon cancer (HT-29 and HCT116) cell lines. Performing the comparative analysis of cell cycle arrest between control cells and HT-29 and HCT-116 cell lines revealed that the cell cycle arrest at the G1 phase was 64.89% and 67.02%, which is relatively higher for the tested compounds than the reference used (47.25% and 51.71%) respectively. Depending upon the type of cancer, the compound {13} induces different kinds of cell cycle progress along with cell cycle arrest at the G1 phase for HT-29 and HCT-116 carcinoma cell lines. This compound can inhibit several protein kinases, several protein kinases, cyclin D1, CDK4, CDK6, cyclin E2, and CDK2, etc., in the HT-29. When compound {13} tested on the HT-29 and HCT-116 for 48 h, the result obtained revealed that the percentage of apoptosis induced in the cells related to the percentage of early (annexin-Vþ/PI) and late apoptotic (annexin-Vþ/PIþ) stage combined showed a drastic increase to 42.73% and 44.52% that of control (12.89% and 12.43%) in case of HT-29 and HCT-116 carcinoma cell lines respectively. This suggests that the compound {13} can efficiently promote apoptosis at early stages in the HT-29 and HCT-116. The compound {13} having chalcone-spermidine moiety could be considered one of the most promising anticancer pharmacophores with a noticeable *in-vitro* efficiency for inhibiting proliferation[cxi].

Another group of scientists synthesized a novel chalcone-quinazolinone-based analogue {14}, which showed promising activity against the human colon cancer line (HCT-116) with a significant decrease in the IC50 values with increasing time intervals. Also, the HCT-116 cancer cells were susceptible towards {14}. Hence, {14} inhibits the cell proliferation in HCT-116 in a concentration-dependent manner compared to the control cells. The percentage of G0 phase apoptosis induced was increased to 23% after treatment of HCT-116 cells with 40 μM of {14}. Further investigations proved that the {14} blocks the S and G2/M phase of the HCT-116 cell line. It induces apoptosis *via* an intrinsic pathway in which a considerable decrease in the level of antiapoptotic protein and an increase in the level of pro-apoptotic protein is seen. This suggests that a lowered Bcl-2/ BAX ratio and activated caspase-9 induce an intrinsic type of apoptosis. The tumor suppression assay predicted that the 5-fluorouracil shows higher tumor inhibition I compared to {14} but causes many side effects in the existing chemotherapeutic treatments. Besides, the {14} was observed to be more specific against targeted cells than 5-fluorouracil. It is also seen that the {14} inhibits the PI3K/Akt/ mTOR pathways, which are more often altered in most cancers.{14} exhibit high antitumor activity against the tumor caused in the Peritoneal cavity due to the presence of excess fluid than the solid tumors. It also inhibits the proliferation of EAC, EAT, and Sarcoma-189 tumors with no future toxic effects. So, it is necessary to develop quinazolinone- chalcone-based drugs to treat cancer[cxii].

4 Conclusion:

Chalcones continue to be one of the most intriguing drug prospects for the synthesis and development of anticancer therapies due to their widespread use as an effective scaffold in

numerous anticancer medications. The primary reason behind the anticancer activity of chalcones and their derivatives is the presence of different substituents on the two aryl rings and their substitution patterns. Chalcones can efficiently induce cytotoxic effects in several cancer cell lines *via* various modes of action, including stimulation of cell cycle arrest, apoptosis, inhibition of tyrosine kinase activity, angiogenesis, protein kinases, cell proliferation, *etc*. The studies mentioned in the present review suggest that chalcones are one of the supreme candidates for developing novel anticancer drugs with high potency, selectivity, and *in-vitro* work efficiency.

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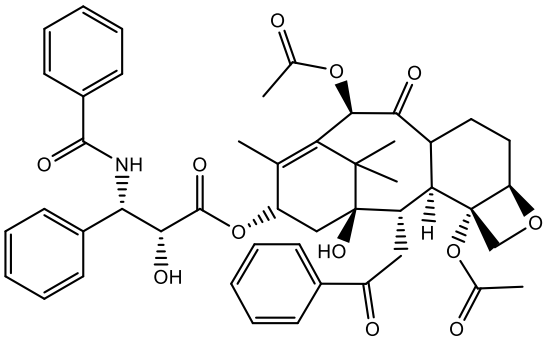
Figure legends

Figure 1 Some of the clinically accepted drugs for the treatment of cancer.

Figure 2 General structure of chalcone.

Figure 3 Sources of chalcones and their biological activities.

Figure 1



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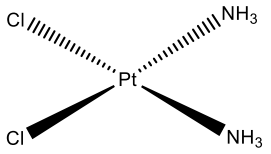

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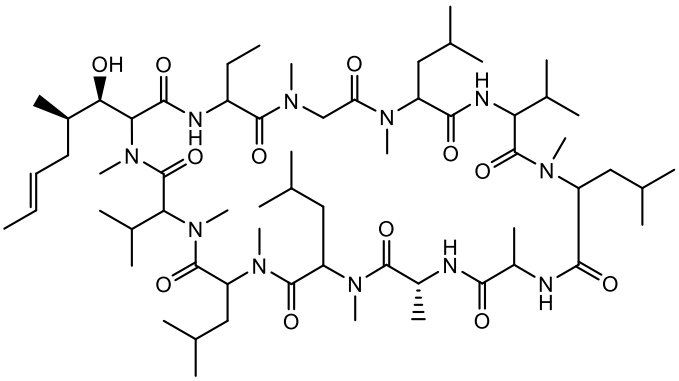

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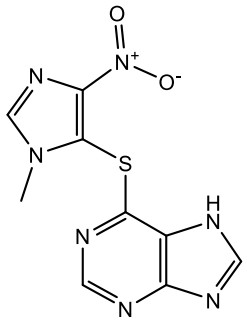

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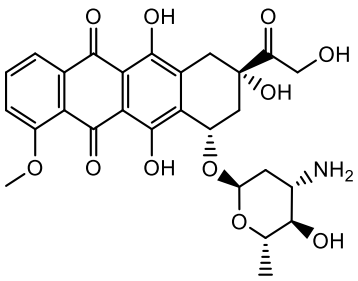
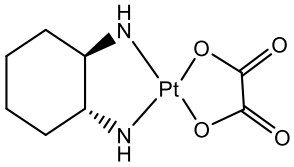
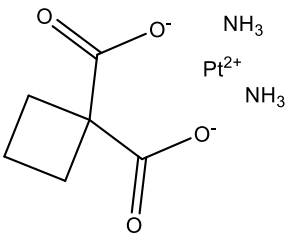


Doxorubicin (V)



Oxaliplatin(VI)



Carboplatin (VII)

Figure 2

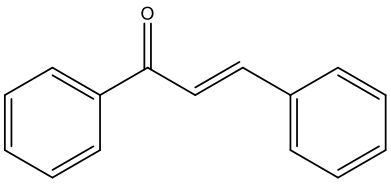
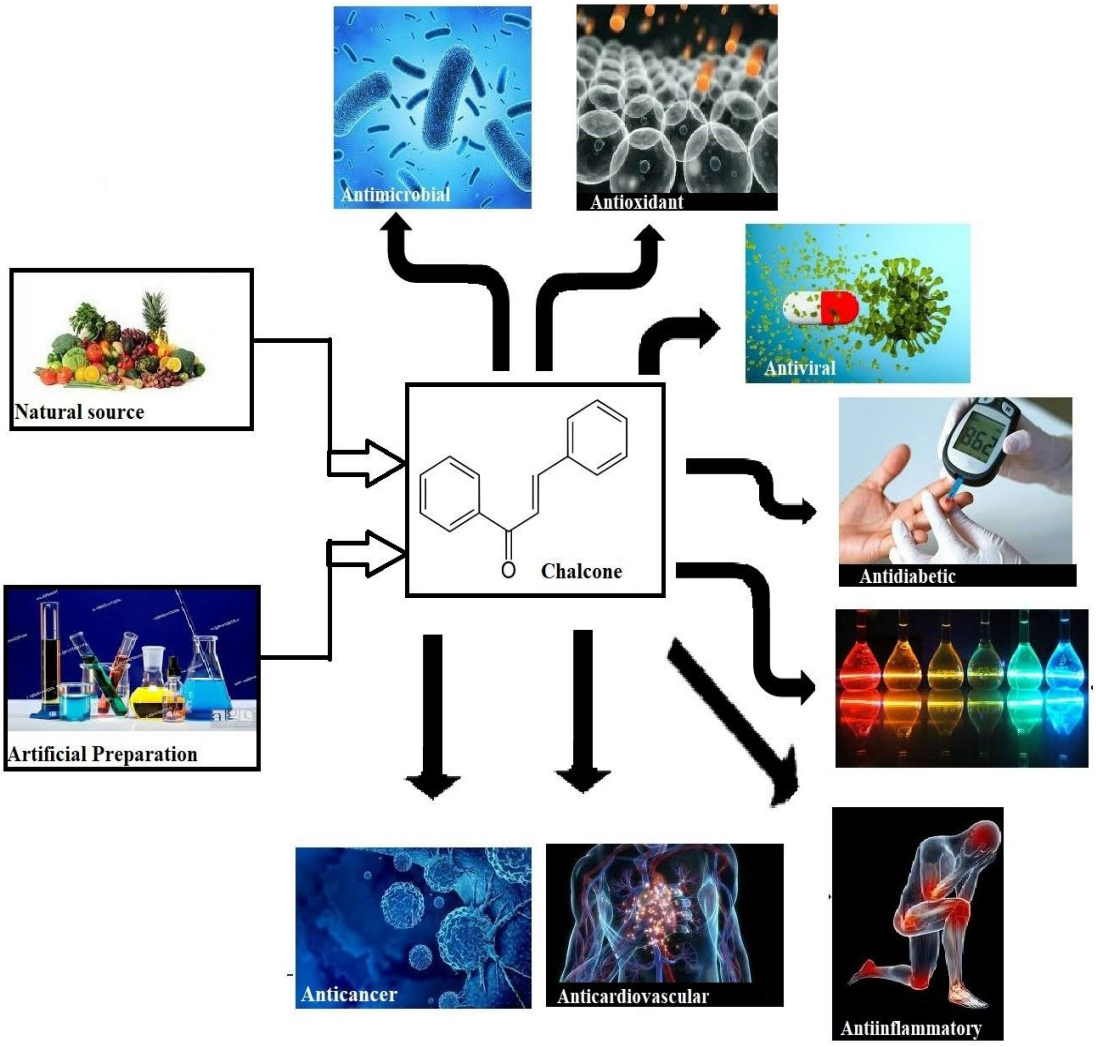
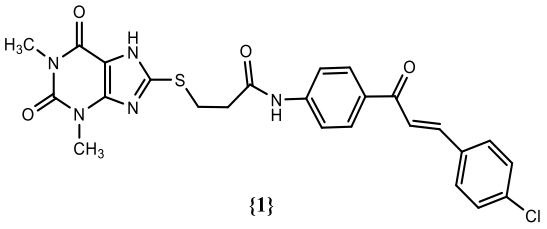


Figure 3


Antimicrobial
Antioxidant
Antiviral
Natural source
Chalcone
Antidiabetic
Artificial Preparation
Anticancer
Anticardiovascular
Antiinflammatory



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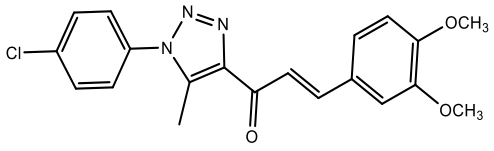

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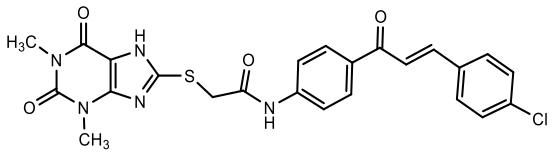

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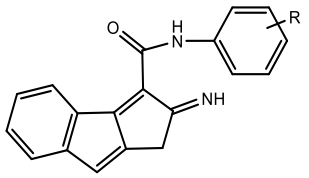
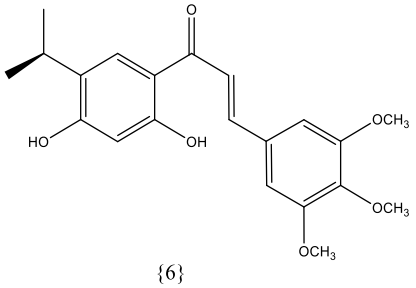


{4} R : 2,4 -OCH3
{5} R : 4F

Chalcone based pharmacophores which have ability to induce apoptosis



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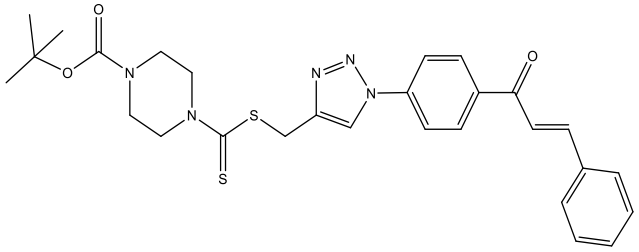

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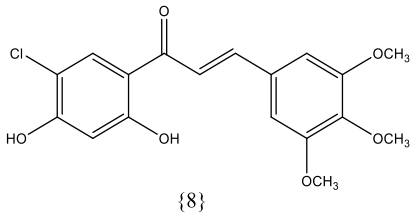

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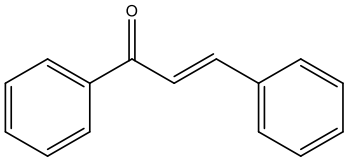
Chalcone based pharmacophores which have ability to inhibit HSP90



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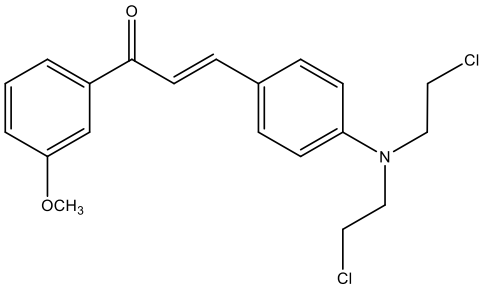

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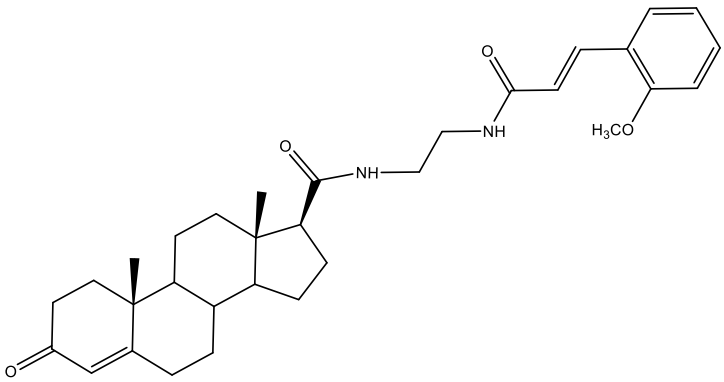
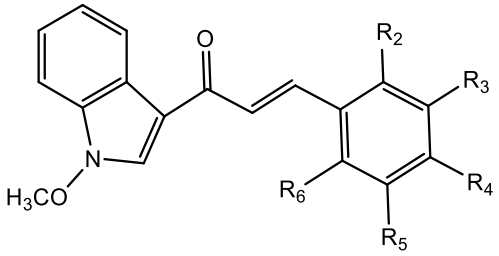


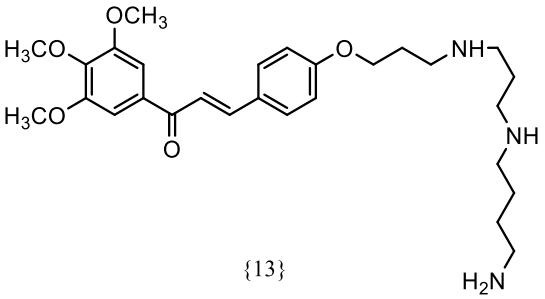
{11}

Analogues of chalcones showing efficient anticancer activity against breast cancer



12a : R_2, R_6 = OCH_3; R_3, R_4, R_5 = H
12b : R_2, R_4, R_6 = OCH_3; R_3, R_5 = H
12c : R_3, R_4, R_5 = OCH_3; R_2,R_6 =H
12d : R_2 =F ; R_3, R_4, R_5, R_6 =H
12e : R_4 = F ; R_2,R_3,R_5,R_6=H

{12 a, b, c,d,e}



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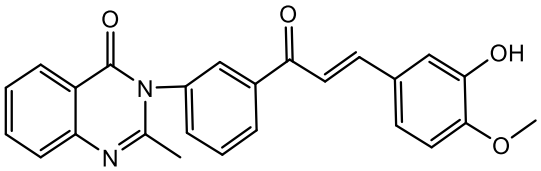

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Analogues of chalcones showing efficient anticancer activity against human colorectal cancer

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