IJPSR (2020), Volume 11, Issue 5 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 12 July 2019; received in revised form, 23 November 2019; accepted, 03 April 2020; published 01 May 2020

CHALCONE – PROMISING ENTITY FOR ANTICANCER ACTIVITY: AN OVERVIEW

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Keywords:

Chalcone, Synthesis, Anticancer activity

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ABSTRACT: Chalcones are naturally occurring compounds with a wide range of biological activities along with an anticancer activity through various mechanisms. It is also known as aromatic ketone, which creates a central core for different essential biologically active compounds. The literature on anticancer chalcones shows the use of various prolonged approaches like structural manipulation and replacement of both aryl rings, molecular hybridization by combination with other pharmacological important moieties to enhance anticancer characteristics. Methoxy substitution on both the chalcones A and B aryl rings based on their position in the aryl rings, usually affect anticancer and other activities. Additionally, chalcones affect the anticancer activity proven through the various categories of compounds. Hybrid chalcones developed by chemically linking chalcones to other leading anticancer scaffolds such as benzodiazepines, imidazole, benzothiazole have proved complementary or intrinsic pharmacological behavior. This study summarizes the concerted attempts made in the design and growth of anticancer chalcones reported in the latest literature and also gives an overview of recently released patents.

INTRODUCTION: Drug discovery is conclusively targeting the intention of much natural product chemistry and organic synthesis in laboratories [1]. A significant condition of the drug development process is testing both synthesized, and natural compounds for bioactivities that are associated according to targeted diseases processes [2]. Cancer is a general term to characterize a number of ailments or diseases that are described by the uncontrolled expansion of cells resulting from the interruption or dysfunction of regulatory signaling pathways that are customarily under tight control [3].

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DOI: 10.13040/IJPSR.0975-8232.11(5).2027-41

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(5).2027-41

Cancer can transmit rapidly and infect other tissues and organs, and different cancers are identified to have unique characteristics [4]. Cancer is one of the most dangerous, fast-spreading diseases of the present decade with a high mortality rate even in developed countries [5]. 90-95% of the cancers are caused due to alternative lifestyle and behavioral factors, and only 5-10% is genetically inherited. Various factors lead to cancer include lack of physical activity, tobacco, diet, obesity, infections, ultraviolet radiation, stress, and environmental pollutants [6]. Fifty known carcinogens in tobacco smoke, which include polycyclic aromatic hydrocarbons and nitrosamines. In worldwide, all cancer deaths, one in five, occur due to tobacco [7]. Around 30-35% of cancer deaths are related to diet, obesity, and physical inactivity. High and beyond limit body weight in the United States is related to various cancers, and the same accounts for 14-20% of all cancer deaths.

Physical inactivity is also a major factor in cancer risk due to its effect on body weight and negative effects on the endocrine and immune systems [8]. The high diet also contributes to the induction of cancer. Lesser fruits, whole grains, and vegetables and higher processed or red meats in the diet are other factors that are affected and associate with various cancers [9]. Infectious diseases are contributing nearly 18% of cancer deaths worldwide and it varies area wise such as 25% in Africa and 10% in the developed world. In cancer development, different viruses also play a leading role to such as human papillomavirus causes cervical carcinoma, Epstein–Barr virus causes B-cell lymphoproliferative disease and nasopharyngeal carcinoma, Kaposi's sarcoma herpes virus causes Kaposi's sarcoma and primary effusion lymphomas, hepatitis B and hepatitis C viruses cause hepatocellular carcinoma, and Human T-cell leukemia virus-1causes T-cell leukemia's [10-13].

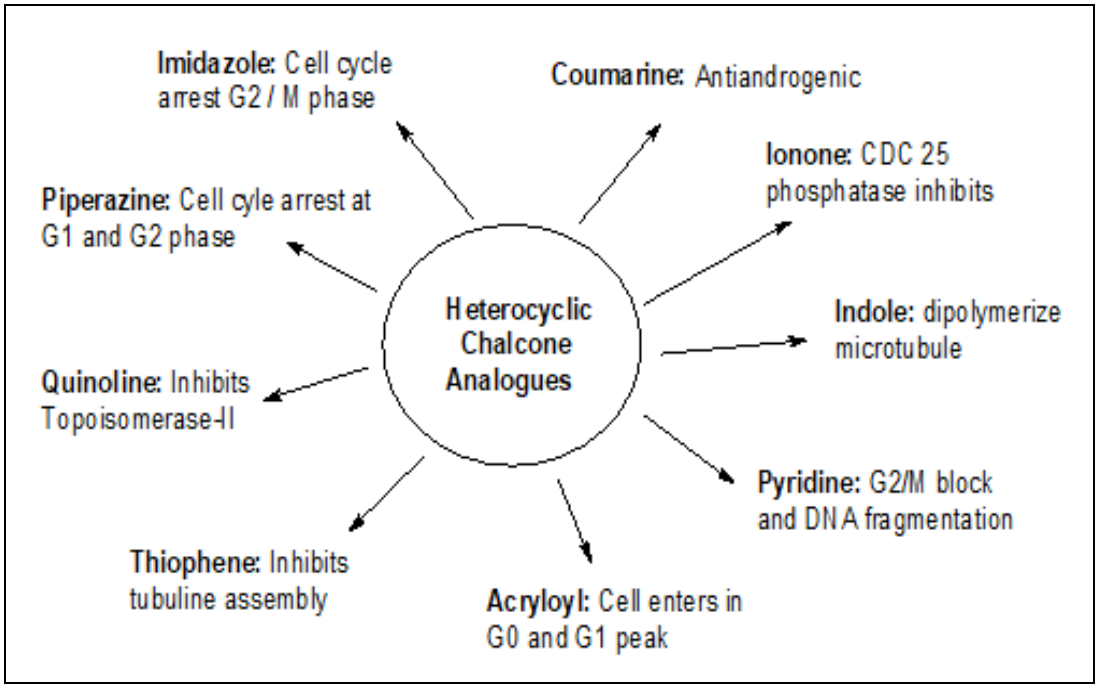


FIG. 1: HETROCYCLIC CHALCONE

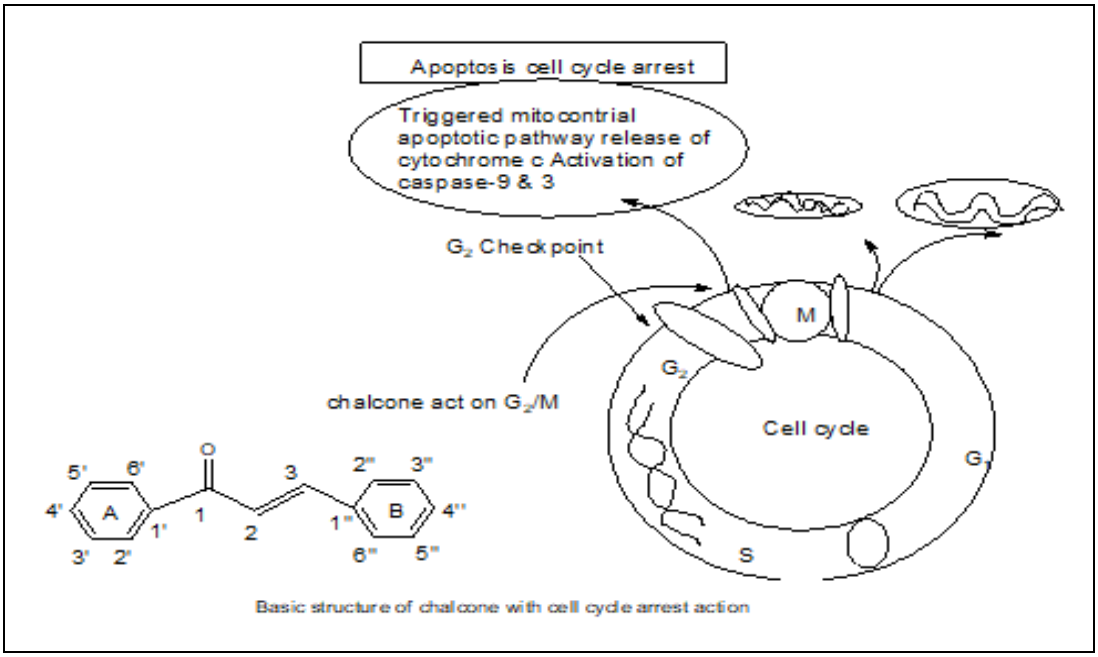


FIG. 2: BASIC STRICTURE OF CHALCONE WITH CELL CYCLE ARREST ACTION

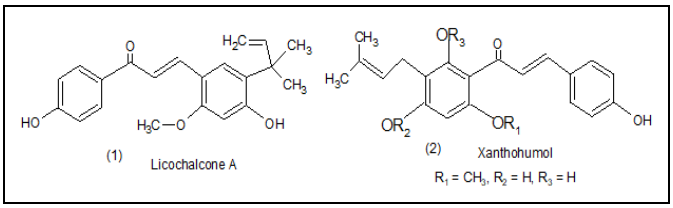
Chalcone is a universal term given to compounds bearing the 1,3-diphenyl-2-propen-1-one frame-work, which is the most important class of flavonoids in the whole plant kingdom [14]. Chalcones are the open-chain starting material for the biosynthesis of flavonoids and isoflavonoids and obtained primarily as polyphenolic compounds in orange color, which is obtained from yellow [15]. As a concern to the structure, they possess open-chain flavonoids containing the two aromatic rings that are connected through three carbons having α, β-unsaturated carbonyl system. Chalcones are generously present in nature, starting from scrubs or ferns to higher plants, and out of them are polyhydroxylated in the aryl rings. In plants, the enzyme chalcone isomerase catalyzes and plays an important role for the conversion of chalcone to corresponding (2S) flavanone in steriospecific reaction. Chalcones and flavanones clarify that they were frequently co-happens as natural products because of close biogenetic and structural relationship between them [16, 17].

Another name for chalcones is "anthochlor pigments", which are beneficial for identifying a group of yellow pigments that turn red in the presence of alkali [18]. Chalcones are recognized as the precursors of flavonoids and isoflavonoids [19] and are secondary metabolites of global plants that show distinct biological activities [20]. Chalcones are famous intermediates for synthesizing and manufacturing numerous heterocyclic compounds [21] like flavones, isoxazoles, pyrazoles, tetrahydro-2-chromens [22-23] *etc*. Chalcones either natural or synthetic are known to display several biological activities [24]. Outstanding initial work in the synthesis of naturally occurring compounds and was the first to provide the term chalcone [25, 26].

The compounds are having of chalcones as a base evaluated for different biological activities such as antimicrobial, [27] anti-inflammatory, [28] anti ulcerative, [29] antimalarial, [30] and anticancer [31, 32] activities. The presence of a reactive α, β- unsaturated keto function in chalcones is found to be important and culpable for their biological activities [33].

Chalcones as Forerunner in Chemical Synthesis: Chalcones are an adventurous precursor for the synthesis of heterocyclic compounds. Chalcones withstand cyclization reactions with various reagents to form diverse classes of heterocyclic compounds extending from five-membered to seven-membered rings containing oxygen, nitrogen, and sulfur heteroatoms [34]. An extremely reactive bielectrophilic ketovinyl chain condenses with a variety of binucleophilic reagents takes place in cyclization reaction to achieve a collection of five-membered heterocyclic derivatives like pyrazolines, phenylpyrazoline and isoxazole [35] six-membered heterocyclic derivatives like aminopyrimidines and cyanopyridines [36] and 1,5-benzodiazepines, 1,5-benzoxazepines, and 1,5-bezothiazepines as concern to seven-membered heterocyclic derivatives [37].

Naturally Occurring Chalcones: Naturally occurring chalcone has been expressed to have collective and numerous biological and pharmacological activities. A study of the recent literature acknowledges series of search for naturally occurring chalcones with adequate anticancer properties and an innovative mechanism of action. Few examples of this class of chalcones are xanthohumol, licochalcones, cardamonin, butein, *etc*. [38]



An oxygenated chalcone Licochalcone A (1) found in the roots of the Chinese liquorice (*Glycyrrhiza uralensis*), has been established to occupy various bioactive properties like anti-parasitic, estrogenic, antimalarial and antitumor activities [39, 40]. LA was also expressed to bring outgrowth control and induction of apoptosis in androgen-independent p53-null PC-3 prostate cancer cells [41-43].

A prenylated chalcone, Xanthohumol (2) isolated and extracted from the hop cones (*Humulus lupulus* L.) is advised to show broad-spectrum anticancer properties against different types of human cancer cells primarily through prevention of the induction and generation of human cancer cell apoptosis [44-46].

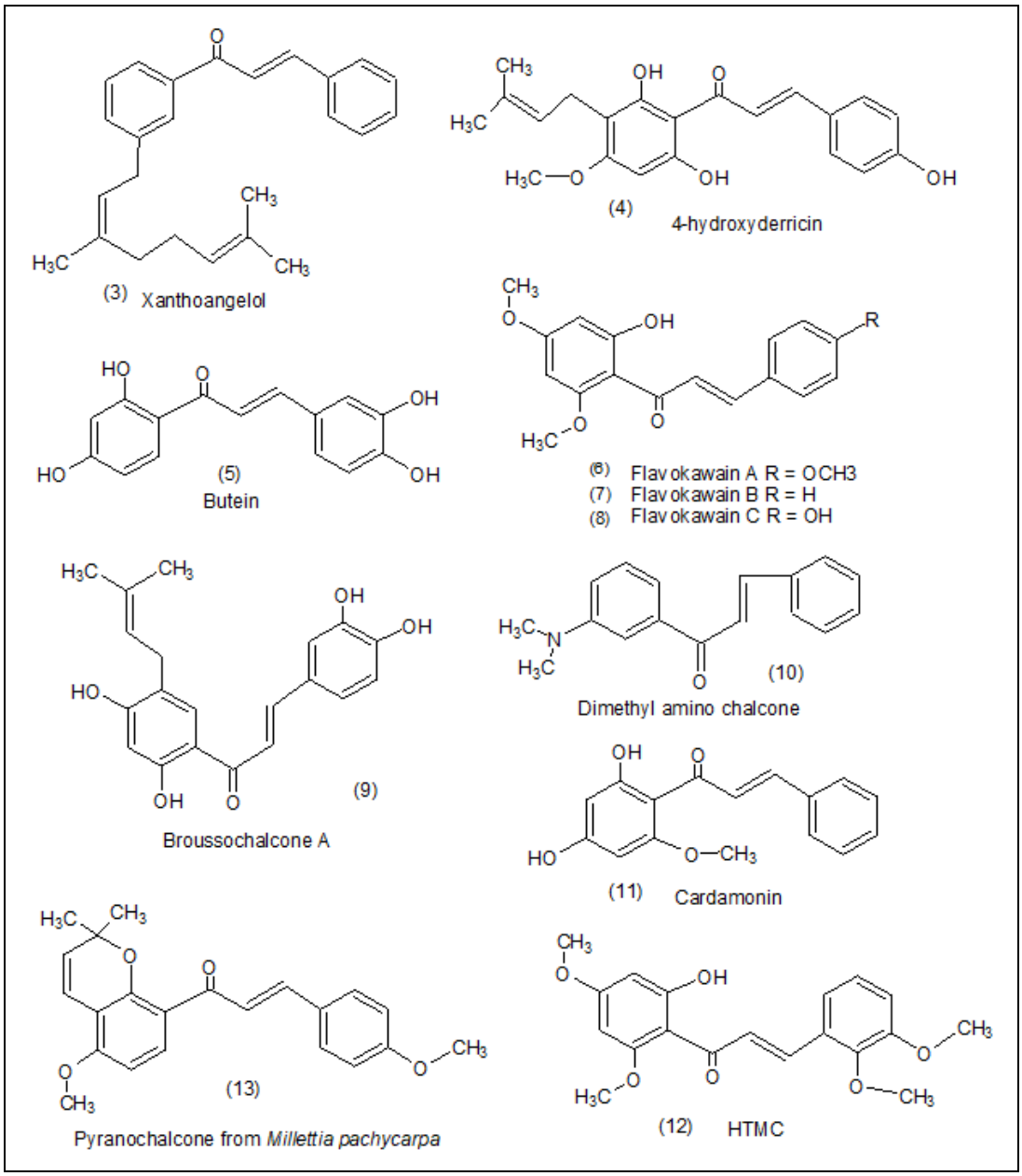
A natural chalcone, Xanthoangelol (3), found in stem exudates of *Angelica keiskei*, lead to apoptotic cell death by activation of caspase-3 in

neuroblastoma and leukemia cells over a mechanism that does not involve Bax/Bcl-2 signal transduction [47].

Another chalcone 4-hydroxyderricin (4), isolated from roots of *Angelica keiskei*, also bring about apoptotic cell death in leukemia cells (HL60) *via* both the death receptor-mediated pathway and the mitochondrial pathway by topoisomerase II inhibition [48].

Stems of *Rhus verniciflua* contains a plant polyphenol like Butein (3, 4, 2', 4'-tetra-hydroxychalone) (5), has been shown to inhibit human colon adenocarcinoma cell proliferation [49, 50].

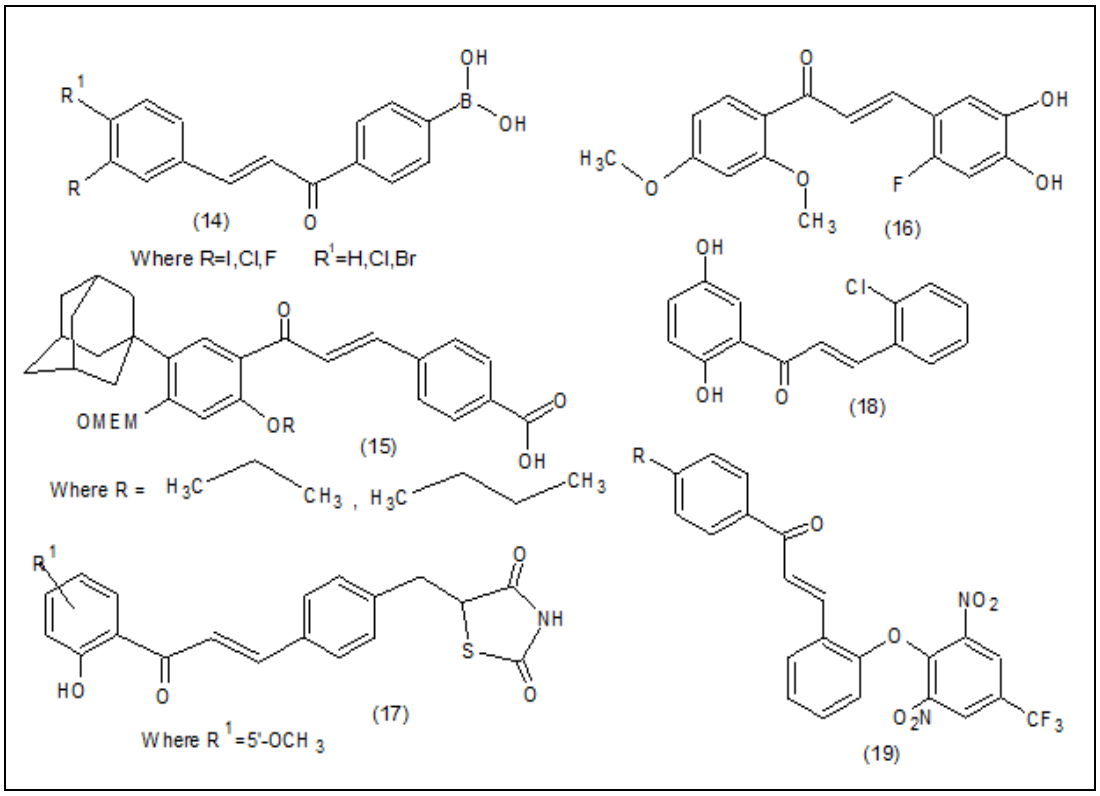
Kava extracts contain Flavokawain A, B, and C (6-8) have been exposed to occupy strong antiproliferative and apoptotic effects in human bladder cancer cells [51, 52].



Broussochalcone A (9), Dimethylamino chalcones (10) and Cardamonin (11) are other natural chalcones that have been expressed to carry anti-inflammatory and anticancer activities [53]. A natural chalcone 2-hydroxy-2, 3, 4,6-tetramethoxychalcone (12) (HTMC), isolated a medicinal plant *Caesalpinia pulcherrima* lead to potent *in-vitro* cytotoxicity selectively against cell lines occurred from human lung cancer. HTMC was found to shown G1 phase cell-cycle arrest in A549 lung

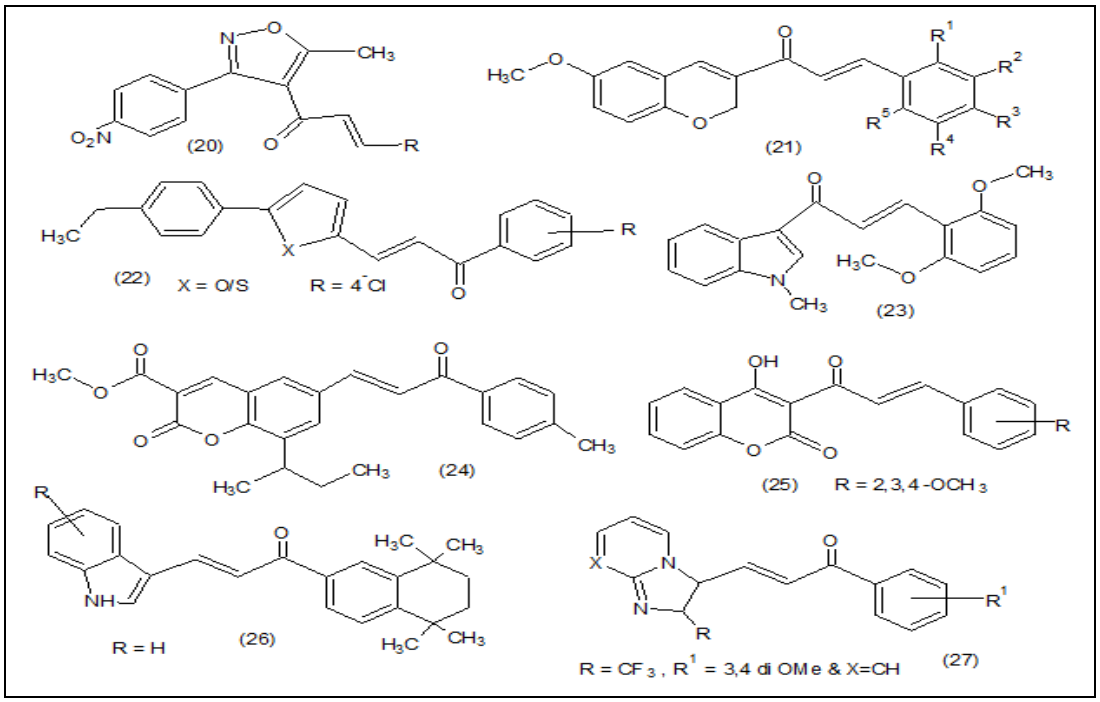
adenocarcinoma cells. Novel pyranochalcone (13) isolated from *Millettia pachycarpa,* which exhibited strong cytotoxic effects against several cancer cell lines [54].

Chalcone Synthesized with Heteroaryl Group:

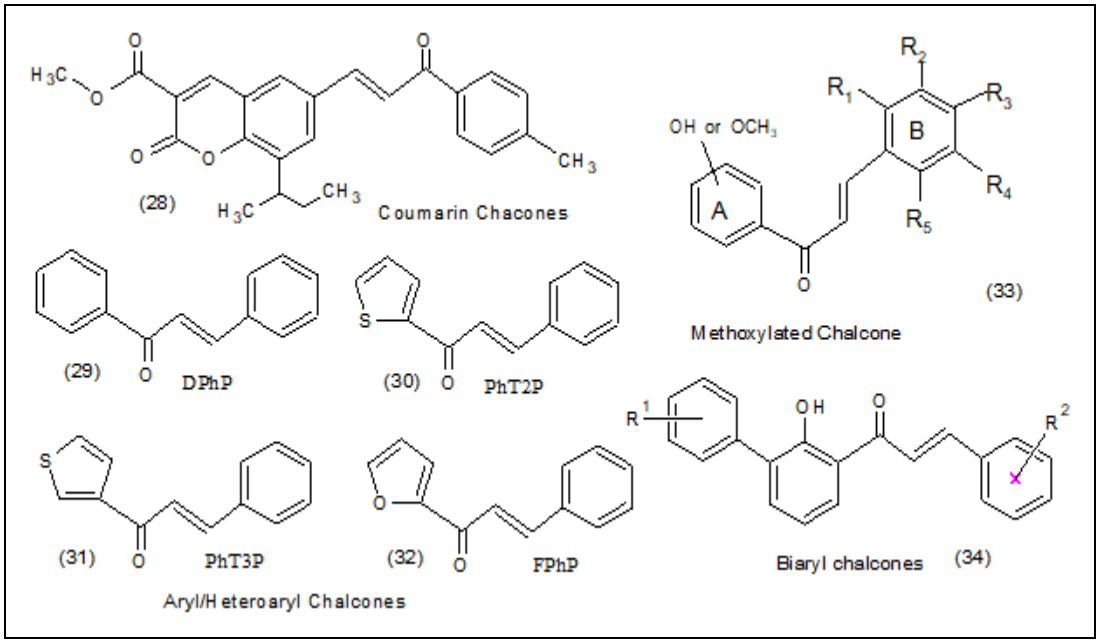


Srinivas K. Kumar *et al.* synthesized series of boronic-chalcone derivatives (14) and evaluated for antitumor activity against human breast cancer cell lines. The results expressed that as compared to other known chalcones boronic chalcones are more toxic to breast cancer cells [55]. Paula Lorenzo *et al.*, have obtained novel chalcones containing adamantyl arotonoids (15) and tested their IKB kinase β (IKKβ) activity, which leads to inhibits cell growth and induces apoptosis in cancer cells [56]. Nakamura Chika *et al*., have synthesized and reported fluorinated chalcones and tested antitumor activity against human cancer cells. Compound (16) was recorded as the most effective compound [57]. Aseries of 2' hydroxy chalcone derivatives containing thiazolodinone (TZD) (17) have been synthesized and tested their peroxisome proliferator-activated receptor-_ (PPAR-_) ligand-binding activities. Among chalconylidene-TZDs derivatives compound 2'-hydroxy-5'-methoxychal-conylidene-TZD exhibited potent peroxisome proliferator-activated receptor- _ (PPAR- _) ligand-binding active [58]. Nam Nguyen-Hai *et al*., have synthesized and reported a series of 2', 5'-dihydroxychalcones and tested for cytotoxicity towards HUVEC. Out of them compounds (18) exhibits the highest activity on HCT116 cells [59]. Hui Zhang *et al*., have been arranged and synthesized, and their biological activities were also tested as potential inhibitors of tubulin. These compounds were evaluated and assayed for growth-inhibitory activity against A549 and MCF-7 cell lines *in-vitro*. Compound (19) expressed the better potent antiproliferative activity against MCF-7 and A549 cell lines with IC_{50} values of 0.03 and 0.95 µg/mL and shown the much more potent tubulin inhibitory activity with IC_{50} of 1.42 µg/mL. Docking simulation was carried out to insert compound into the crystal structure of tubulin at colchicines binding site to calculate the probable binding model. On the basis of preliminary reports, compound with strong inhibitory activity in tumor growth may be a potential anticancer agent [60].

Wan *et al*., have synthesized isoxazol aryl chalcone derivatives (20) as anticancer drugs and leads to inhibiting proliferation of human lung cancer cells [61].



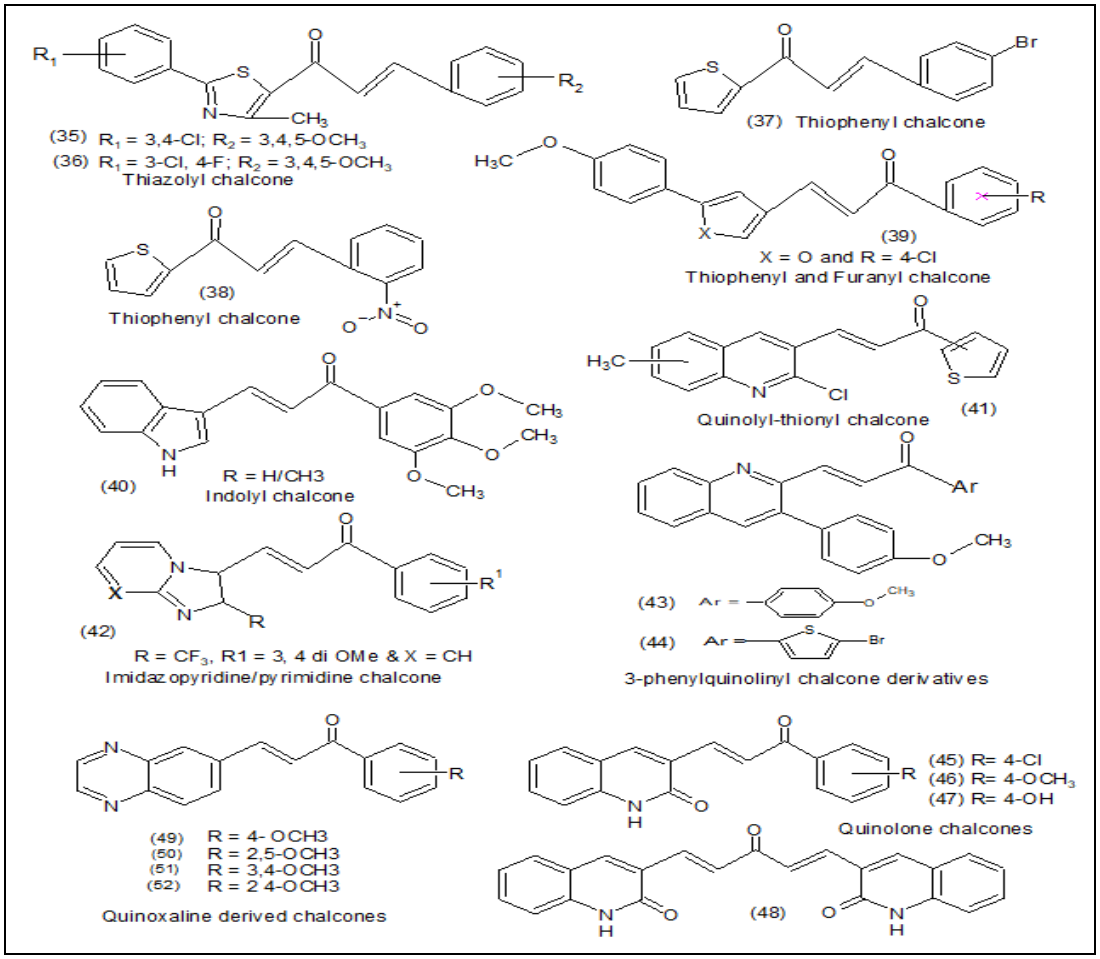
Lim *et al*., have synthesized methoxy chromenyl-chalcone derivative (21) as anticancer agent [62]. Solomon *et al.*, comparative studied the anti-proliferative activity in breast cancer cells. Within aryl thiophenyl chalcones and aryl furanyl chalcones [63] (22) Martel-Frachet *et al.*, entrenched 1- (*N*- methylindolyl)- 3 phenylpropenones especially methoxylated analogues (23) as effective anticancer agents acting on bladder carcinoma cells [64]. Sashidhara *et al*., established, evaluated and reported a series of coumarin-chalcone hybrids (24) showed *in-vitro* cytotoxicity against a panel of four human cancer cell lines and normal fibroblasts (NIH3T3) [65]. Patel *et al*., tested a series of 4-hydroxy coumarinyl chalcones (25) for anti-breast cancer activity with the help of breast cancer cell lines (MDA-MB231, MDAMB468, MCF7) and one non-cancerous breast epithelial cell line (184B5) [66]. Gurkan-Alp *et al.*, evaluated anticancer properties and synthesized novel (*E*)-3-(5-substituted- 1*H*-indol-3-yl)- 1-(5,5,8,8- tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-2-en-1- one derivatives (26), which merge both indole and retinoid components in a chalcone structural framework [67].



Karthikeyan *et al.*, evaluate a novel series of isatin linked chalcones (27) incorporating pharmacophoric elements of isatins and chalcones was expressed for anti-breast cancer activity [68].

Coumarins are a compelling class of compounds enriched with broad-spectrum antitumor activities, hence chalcones operating coumarinyl moiety as a substitute for ring A or B have been expressed in literature for anticancer properties. Sashidhara *et al.*, synthesized and tested a series of coumarin-chalcone hybrids for their *in-vitro* cytotoxicity against a panel of four human cancer cell lines and normal fibroblasts (NIH3T3). Compound (28) led to being the most promising in the series with 30-fold more selectivity towards C33A (cervical carcinoma) cells over normal fibroblast NIH3T3 cells with an IC_{50} value of 3.59 µM.A recent survey shows 1,3-diphenyl propenone (29) to be potent anti-angiogenic as compared to heteroaryl chalcones 3- phenyl-1-thiophen-2-yl-propenone (PhT2P) (30), 3-phenyl-1-thiophen-3-yl-propenone (PhT3P) (31) and 1-furan-2-yl-3-phenyl-propenone (FPhP) (32).

Methoxylated chalcones bind to the tubulin adequately like combretastatin and colchicines (33) [69] thus, it shows predominant anticancer activity against different cancer cell lines. Reviews on these methoxylated chalcones considered that the number and the position of methoxy substituents on the aromatic rings use to be critical for cytotoxicity. The antimitotic effect of chalcones is dependent on the substitutions at the B ring, generally in 2-, 4-, and 6-positions. In dimethoxylated derivatives, the methoxy groups should alternatively be linked to carbons 2 and 6 in the B ring [70]. However, methoxylation at 3, 4, and 5th position of the B ring is preferable in case of the trimethoxylated chalcones, 3,4,5-trimethoxychalcones have been found to exert prominent anticancer activity against five distinct cancer cell lines (ACHN, Panc 1, Calu 1, H460 and HCT116). A novel series of biaryl chalcones (34), which combines a basic chalcone framework with a biphenyl moiety, has also led to show significant NF-kB inhibitory activity and cytotoxicity against a panel of cancer cell lines [71].



A list of novel thiazolyl-chalcones was lead to show potent growth inhibitory activity on four human cancer cell lines (BGC-823, PC-3, NCI-H460 and BEL-7402) [72]. Two compounds (35 and 36) for *in-vivo* antitumor activity was tested in ICR mice addressing sarcoma 180 tumors and the reports shows that the compounds (35) and (36) shows moderate *in-vivo* activity with 22-25% tumor weight inhibition.

Solomon *et al.,* evaluate antiproliferative activity with a comparison between aryl thiophenyl chalcones and aryl furanyl chalcones in breast cancer cells [73]. Their reports determined that the thiophene chalcones definitely inhibit the proliferation of MDA-MB231 and the furan chalcones expressed potent antiproliferative activity on MDA-MB468 breast cancer cells. Compound (39) ((*E*)-1-(4-chlorophenyl)-3-(5-(4-methoxyphenyl) furan-2-yl)prop-2-en-1-one) was assured to be have most potent antiproliferative activity.

A recent record by de Vasconcelos *et al.,* designed the cytotoxic and apoptotic effects of six chalcone derivatives containing a thiophene ring on human colon adenocarcinoma cells [74].

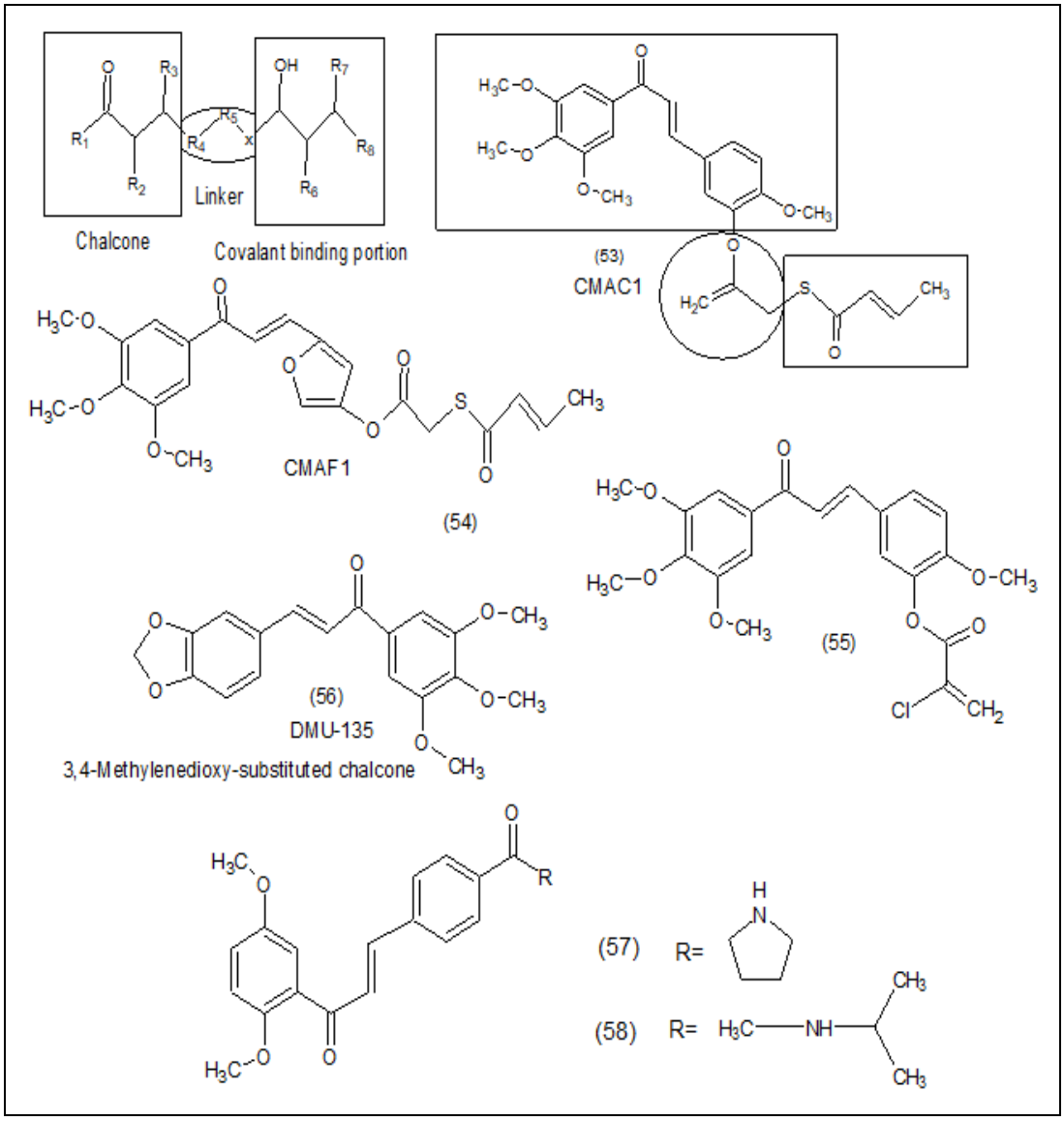
Chalcones, 3-(4-bromophenyl)-1-(thiophen-2- yl) prop-2-en-1-one (37) and 3-(2-nitrophenyl)-1-(thiophen-2- yl) prop-2-en-1-one (38) exerted greater cytotoxicity as compared to other chalcones in cell morphology, live/dead and MTT assays. Also, compound (37) was also lead to exhibit apoptosis in flow cytometry annexin V assay. 3,4,5-trimethoxy substitution on Indolyl chalcones in phenyl ring A (40) were informed to show significant cytotoxic activity against pancreatic cancer cell lines [75]. Rizvi *et al.,* invented a series of quinolyl-thienyl chalcones (41) as potential VEGFR-2 kinase inhibitors on the basis of structure-based virtual screening protocols [76]. One of the analyzed quinolyl-thienyl chalcones expressed *in-vitro* VEGFR-2 kinase inhibitory activity and inhibition of HUVEC proliferation at nanomolar concentrations. 3-Phenylquinolinyl chalcone derivatives with potent antiproliferative activity evaluated on a panel of six cancer cell lines were recorded by Tseng *et al.* [77] A new series of isatin connected with the chalcones incorporating pharmacophoric elements of isatins and chalcones were described for anti-breast cancer activity by Karthikeyan *et al.* [78] Chalcones with imidazo[2,1-*b*] pyridine/pyrimidines as ring B have been expressed to possess promising anticancer activity against NCI panel of cancer cells. More specifically, compound (42), which is having a trifluoromethyl substituent in ring B and a 3,4,5-trimethoxy substitution in ring A shown good antiproliferative potency at submicromolar concentrations against colon, breast, leukemia, lung, melanoma and ovarian cancer cells.

Two compounds in the series; (*E*)-3-(3-(4-methoxyphenyl)quinolin-2-yl)-1-phenylprop-2-en-1-one (43) and (*E*)-1-(5-bromothiophen-2-yl)-3-(3-(4-methoxyphenyl) quinolin-2-yl)prop-2-en-1-one (44) were lead to expressed most potent anticancer activities [79]. Abonia *et al*., recently synthesized and designed a series of new quinoline- 2-one based chalcones and their anticancer activity against NCI panel of 60 different human tumor cell lines [80]. Out of nine synthesized derivatives, four screened for anticancer activity (45-48) exerted the good antiproliferative potency. A novel series of quinoxaline derived chalcones expressed as structurally analogous to selective PI3Kg inhibitor AS605240 was recorded by Mielcke and co-workers against potent inhibitory activity on glioma cell lines from human and rat origin (U-138 MG and C6, respectively) [81]. The reports of their study concluded that four chalcones (49-52), which contain methoxy groups at A-ring, show better potency against glioma cells. Flow cytometry review shows that the compound (50) produces apoptosis in C6 cells by affecting G1 phase arrest.

Patented Chalcones with Active Moieties: As noticeable from the recently reviewed literature, chalcones, and its derivatives have been broadly designed and studied for cytotoxic as well as antiproliferative activity against many types of cancer. This active growth of interest in the anticancer potential of chalcones has been adopted into many patents; in this current article study of chalcones patented for anticancer activity through various mechanisms.

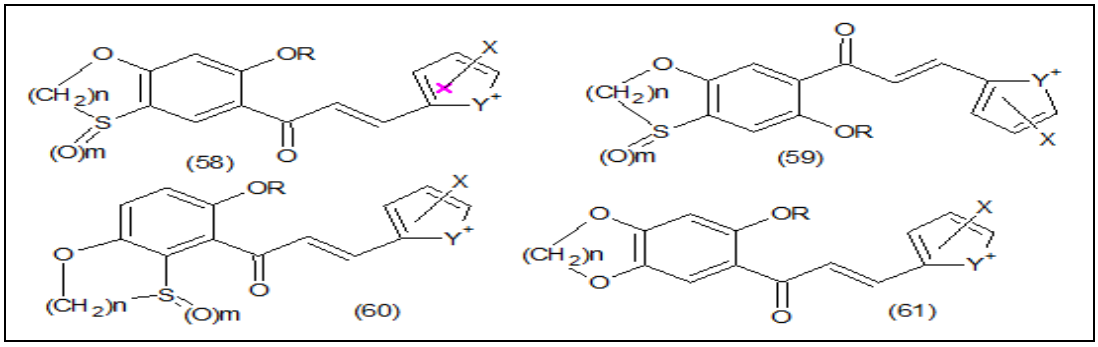
Rose *et al*., patented few modified chalcones (CHAL), including a covalent bonding portion (COV) and an alternative linker portion (LIN) as antimitotic agents [82]. They presupposed that

incorporating of a covalent bonding portion in the chalcone moities either directly or with the help of a linker will increases its tubulin binding affinity and also avoiding multidrug resistance (MDR) correlated with traditional antimitotic chalcones. Thirty seven chalcones synthesized and designed on the basis of introductory explanation were tested for growth inhibitory activity against NCI 60 cell line panel. After all, the growth inhibitory activity was only admitted for three altered and modified chalcones (CMAC-1 (53), CMAF-1 (54), 3-[3-(2-chloroacryloyloxy)- 4- ethoxyphenyl]- 1- (3, 4, 5-trimethoxyphenyl) propenone (55)). Out of these, the chalcone CMAC-1 was lead to expressed and showed potent growth inhibitory activity across the collective cancer cell lines



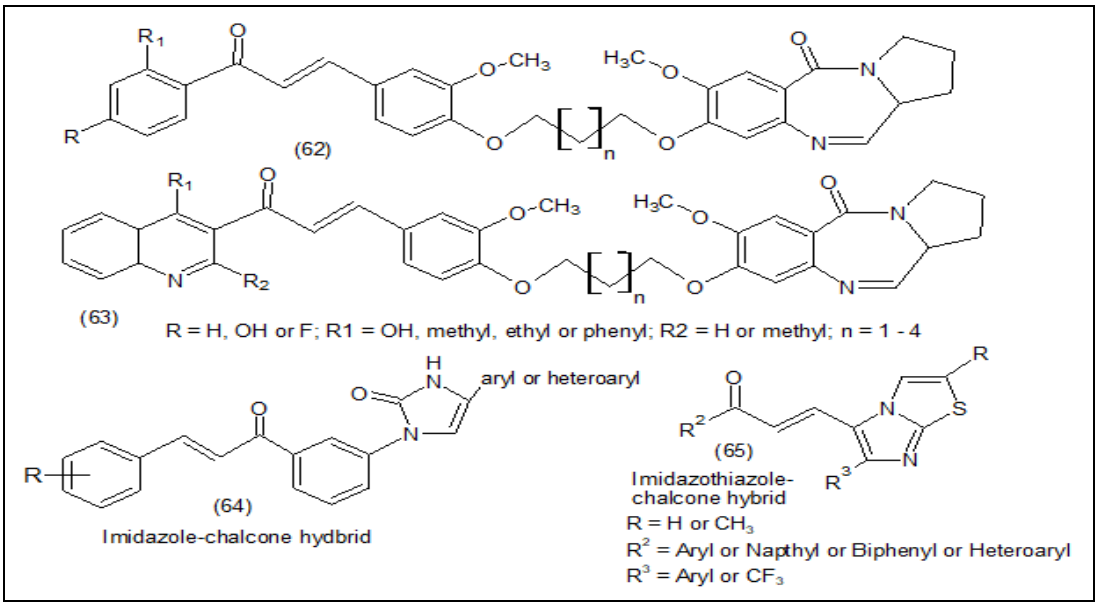
Butler *et al*., patented and disclosed a series of 3,4-methylenedioxy-substituted chalcones as potent antiproliferative agents [83]. The 3,4- methylene-dioxy-substituted chalcones were challenged to selectively obstruct the proliferation of tumor cells indicating cytochrome P450 1B1 (CYP1B1) enzyme with a comparatively lesser effect on normal cells which do not show CYP1B1. These chalcones were evaluated for cell growth inhibition in a MTT assay against TCDD (Dioxin) induced MCF-7 cells (expresses CYP1B1) and non-induced MCF-7 cells. Cytotoxicity of compounds in non-induced MCF-7 cells corresponds to the cytotoxicity of compounds against normal cells and the cytotoxicity of compounds against TCDD-induced MCF-7 cells corresponds to the cytotoxicity of compounds against real tumors that show CYP1B1. The report of this assay expressed that compound DMU-135 (56) is 65-fold more toxic to tumor cells than to normal cells.

In a US patent, Lin *et al*., reported on NTUB1 and PC3 cell line some 2',5'-dimethoxychalcone derivatives with microtubule targeted anticancer activity (tubuline polymerizing agent). The patent reported 2 ', 5'- dimethoxychalcone derivatives displayed by introduce a 2',5'-dimethoxy substitution in aryl ring A and 4-carboxyl groupor its derivatives in aryl ring B. Amongst the compounds developed and assessed for cytotoxicity, pyrrolidine ((57); IC_{50} = 1.26 and 0.53 µM) and N, Nisopropyl ((58); IC_{50} = 1.97 and 1.58 µM) substitution on R had important anticancer activity as compound reference cisplatin (IC_{50}s 3.27 and 4.56 µM) against NTUBI and PC3 cell lines. Flow cytometric analysis of the effects of these two compounds on the progression of the cell cycle showed that these molecules led to phase G1 arrest accompanied with n rise in apoptotic cell death in NTUB1 cells and phase S / G1 arrests followed by an increase in apoptotic cells in PC3 cell lines respectively. In fact immune fluorescent microscopic studies disclosed that compound (57) (4-tetrahydro pyrrolyl carbamoyl-2',5'- dimethoxy-chalcone) caused the development of microtubule bundles in NTUB1 cells and mimicked paclitaxel impact [84].

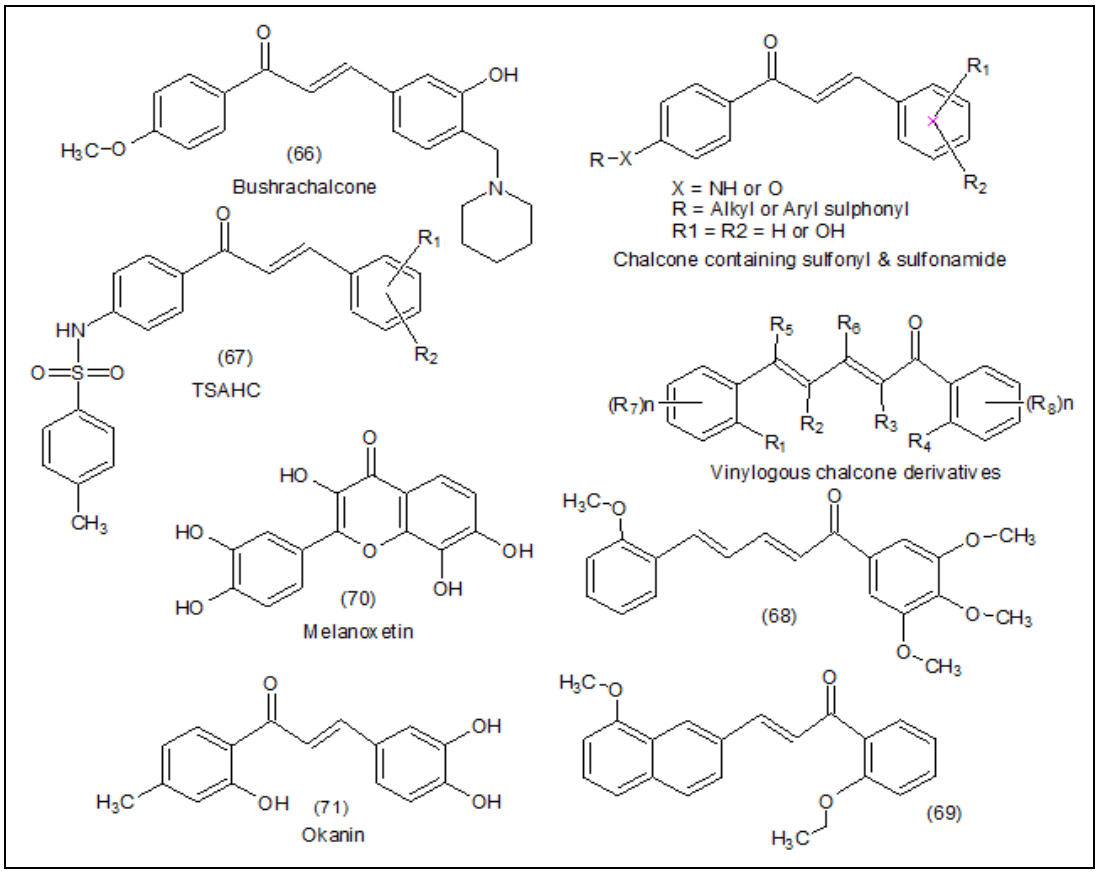


Konieczny and his colleagues patented a sequence of novel general structures of chalcone derivatives (58) to (61) as cytotoxic agents that are helpful for the therapy of neoplastic diseases [85]. In an MTT assay against A549, HCT-116 and HeLa cancer cell lines more than 178 chalcone derivatives were formulated and evaluated for *in-vitro* cytotoxic activity, and the result indicated that several compounds were cytototoxic to the cancer cell lines analyzed at submicromolar to nanomolar concentration. These compounds have been shown to exert *in-vivo* anticancer activity in mice with cancer line HCT116-luc2 in relation to *in-vitro* cytotoxicity.

Kamal *et al*., of the Council of Scientific and Industrial Research patented as prospective anticancer agents a set of chalcones linked to pyrrolo[2,1-c][1,4]benzodiazepine hybrids [86].



The hybrid compounds were obtained synthetically either by connecting substituted chalcone or quinolinyl chalcone with pyrrolo[2,1-c][1,4] benzodiazepines through the carbon chain linker. They have been screened toward human tumor cells obtained from cancer, ovarian, CNS, prostate. The resulting information *in-vitro* suggested that 7-methoxy-8-{n-[4-1-(2 or 4-substituted phenyl)- 3-(4-hydroxy-3-methoxyphenyl)-2-propen-1-one]alkyl}-oxy}-(11aS)-1,2,3, 11a-5H-pyrrolo[2,1-c] [1,4] benzodiazepine-5-ones (62) exhibited selective and powerful growth inhibition against multiple cell lines of cancer compared to 7-methoxy-8-{n[4-1-(3-methoxyphenyl)-1-(2,4-alkyl-3- quinolyl)-2-propen-1-one]alkyl}-oxy}-(11aS)- 1, 2,3,11a-5H-pyrralo[2,1c][1,4]ben-zodiazepin-5-one (63).



A series of patents by the same group synthesized and evaluated imidazolone-chalcone derivatives, (64) with auspicious anticancer activity. In this patent design and establish innovative hybrid chalcones with promising anticancer activity by including chalcones and imidazolines (pharmaco-phores) which are common for antimitotic and anticancer activities. Some compounds from recorded imidazolone-chalcones shows significant cytotoxic activity against fifty three human cancer cell lines in a sulforhodamine B (SRB) assay [86].

One more patent from the same group performed a series of imidazothiazole-chalcone hybrids (65) as potential anticancer agents. These synthesized novel chalcones hybrids expressed by the structure given.

Inducing a well-substituted phenyl/napthyl/ biphenyl or heteroaryl as ring "A" and substituted imidazothiazole as ring "B" in the chalcone scaffold. The imidazothiazole-chalcone hybrids were evaluated against sixty human tumor cell lines derived from nine cancer types (leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer) in an SRB assay as per NCI protocol. Five among the 180 compounds recorded in the patent exerted a wide spectrum of activity against sixty cell lines in nine cell panels, with GI_{50} value of < 9 µ M87 the synthesis and use of "B" aminoalkyl replaced chalcones (bushrachalcones) as an anticancer and antimalarial agents was patented [88].

The bushra chalcones were assessed for *Plasmodium falsiparum* parasite chloroquine sensitive activity and the findings revealed that some compounds had excellent antimalarial activity (IC_{50} < 3 μM) against the parasite. In MTT assay, the compounds cytotoxic activity was screened against TK, UACC-62 and MCF-7 cell lines. Busrachalcone (66) with piperidin-1-yl-methyl substitution at the phenyl ring B para position was discovered and become a most powerful with IC_{50} values against said cell lines.

Induce adiponectin manufacturing and helpful for the therapy of circulatory illness, diabetes and cancer has been shown to be a composition containing extracts of *Angelica keiskei* consisting of chalcone and isoflavones [89].

Researchers at the National University of Gyeonsang and the National University Seoul have created a technique for screening anticancer compounds based on multiple biochemical occurrence caused by TM4SF5 expression [90]. They revealed screening for the anticancer impact on TM4SF5-expressing cells of a sequence of chalcone comprising a sulfonyl (SO_3-) or sulfonamide (SO_2NH-_ group. it has been shown these chalcones represents antagosnistic activity and ability for tumorigenesis mediated by TM4SF5. A separate chalcone derivative TSAHC (67) inhibited the activity of matrix metalloprotiens (MMPs) and probably also showed antagonistic activity by targeting the extracellular region of TM4SF5. *In-vivo* research shown that TSAHC reduces 88% tumor size without any poisonous impacts.

A novel class of vinylogous chalcone derivatives has been indicated for cancer treatment especially malignant tumor hematological disorders. Researchers from the Medizinische Universitat Wien identified a novel lead compound (68) with encouraging potential for anticancer in their attempts to improve the anticancer potential of chalcones by current structural alteration with vitro test to assesses their cytotoxic potential in various cancer and non-cancer lines [91]. The optimization of lead compound (68) through comprehensive SAR research led to extremely cytotoxic compound (69). Both these compounds screened against cancer cell lines like HUVEC, colon cancer and melanoma for antiproliferative activity. Lead Compound (68) was discovered to inhibit the development of all cell lines at nanomolar concentration where compound (69) shows deep inhibitory growth (<50nM) against SW80 and 518A2 cells. Studies of cell viability using both these compounds on cancer cell lines representing that compound (69) showed stronger cytotoxicity. In addition these synthesized compounds also assesses using the cell Titer-Blue cell Viability Assay for their cytitoxic potential against main acute lymphocytic cancer (CLL) bacteria and co-culture model of CLL neurons and stromal cells. The findings shows that compound (68) and (69) given greater cytotoxicity against both CLL models than control medicines fludarabine and cyclophosphamide.

Chang and colleagues outlined the synthesis and growth of fresh diamino-chalcone fluorescence dye with prospective implementation as an embryonic stem cell sample for cell imaging assessment for different disorders [92].

National Taiwan University researchers outlined a structure to inhibit xanthine oxidase that includes an efficient quantity of Acacia species extracts [93].

Ethanolic extracts from different compounds of Acacia confuse have been isolated with ethyl acetate, n-butyl alcohol, and water in a liquid-liquid mixture to produce ethyl acetate fraction, n-butyl alcohol fraction and water fraction. Each sample was further assessed for the inhibitory activity of xanthine oxidase and findings shown that the fraction of ethyl acetate had stronger inhibitory activity of xanthine oxidase. Eight main compounds mostly flavanoids (3, 7, 8, 3', 4'-penta-hydroxyflavone (Melanoxetin), 7, 8, 3', 4'-tetrahy-droxyflavone, 7, 8, 3', 4'-tetrahydroxy- 3-methoxy-flavone (Transilitin), 3, 7, 8, 3'-tetrahydroxy-4'-methoxyflavone, 7, 8, 3'-trihydroxy-3, 4'-dime-thoxyflavone, 7, 3', 4'- trihydroxyflavone, 7, 3', 4'-trihydroxy-3-methoxyflavone and a chalcone (3, 4, 2', 3', 4'-pentahydroxy trans-chalcone (Okanin)) were separated from the ethyl acetate extract and among them, melanoxetin (70) and okanin (71) displayed powerful inhibitory activity on xanthine oxidase greater than standard drug allopurinol.

CONCLUSION: The present study achieves that the chalcones show a wide spectrum of activity

against many kinds of cancer, even after three decades of wide-ranging studies remains an exciting scaffold for anticancer drug discovery. The anticancer characteristics of chalcones are primarily affected by the substitutions and their patterns of two aryl rings of chalcone molecule.

The literature on anticancer chalcones emphasizes the use of the three-pronged approaches like structural manipulations of both aryl rings, replacement of aryl rings with heteroaryl scaffolds, molecular hybridization by combination with other pharmacological important scaffolds to enhances anticancer characteristics. Methoxy combinations on both phenyl rings *i.e.* A and B and their attachment pattern principally cause the anticancer activity exerted by simple chalcones. Heteroaryl molecules, particularly indole, thiazoleor quinoline as a ring A or B, seem to increase cytotoxic activity of chalcones against various cancer cells.

In addition, chalcones have been shown to exercise cytotoxic activity against many cancer cells through various mechanisms, including angiogenesis inhibition, cell cycle disruption, apoptosis induction, cell cycle regulatory kinase inhibition.

All the studies submitted in this review show chalcone as an advanced scaffold for cancer-focused drug discovery attempts. The review work and patents published in the literature on anticancer chalcone based only on educational and industrial field. It seems expected that novel anticancer chalcones wit required potency, specificity, and in vivo efficacy will eventually arise in the coming years for clinical, medical, and surgical use.

ACKNOWLEDGEMENT: The author would like to express my gratitude to the Principal, B. R. Nahata College of Pharmacy, Mandsaur, Mandsaur University, Mandsaur (MUM), Madhya Pradesh and Shivaji University, Kolhapur (SUK) for support to conduct this study.

CONFLICTS OF INTEREST: The author declared that there is no conflict of interest.

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How to cite this article:
Alman AA, Daniel K and Killedar SG: Chalcone – promising entity for anticancer activity: an overview. Int J Pharm Sci & Res 2020; 11(5): 2027-41. doi: 10.13040/IJPSR.0975-8232.11(5).2027-41.