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Research Article

A Report On Chalcone Derivatives: Anticancer Effect In Drug Developments

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Abstract
Chalcones and their derivatives are emerging as a class of drugs with promising potential for use in oncology, particularly in the field of oncology. Chalcones consist of a linear α- and variable α, β-unsaturated carbonyl backbone and exhibit diverse biological activities, including anti-inflammatory, antimicrobial, antioxidant, and anticancer properties. Their structural modifications allow for targeted modifications that enhance the leading and receptor efficacy. This review focuses on recent advances in the synthesis, structural modification, and anticancer properties of chalcones. Their mechanisms of action are well understood and include induction of apoptosis, cell cycle arrest, inhibition of angiogenesis, and regulation of key signaling pathways such as NF-κB, PI3K/Akt, and MAPK. In addition, examples of chalcone hybrids and their efficacy against various cancer cell lines are presented, demonstrating the importance of structural modifications in enhancing cytotoxicity and selectivity. Chalcones are also being investigated as potentially safe and effective alternatives to current chemotherapeutic drugs, with interesting applications in overcoming drug resistance. This review aims to provide insight into the design and development of chalcones for cancer treatment and to lay the foundation for future advances in medicinal chemistry.

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Introduction

Chalcones and their derivatives have emerged as promising anticancer drug candidates due to their remarkable pharmacological properties [1,78]. The chalcone system is a stable and adaptable chemical structure that is the basis of many biologically active compounds [2]. These compounds possess a variety of therapeutic properties, including anti-inflammatory [3,4], antimicrobial [5,6], antioxidant [7], and anticancer effects [8,9,79,80]. The chalcone backbone can be easily structurally altered to increase its functionality, allowing the creation of materials for specific biological purposes. The reactivity of chalcones makes them of great importance for the development of drugs and the pharmaceutical industry [10].

Chalcone, also known as 1,3-diphenyl-2-propen-1-one, is a synthetic compound with an α,β-bonded carbon structure [11]. Its basic structure consists of two aromatic rings (A and B) connected by a three-carbon α,β-unsaturated carbonyl segment (-CO-CH=CH-). This unique structure has important biological functions because the integrated system facilitates its interaction with various biomolecular targets. The aromatic rings can be substituted with various functional groups, resulting in a variety of compounds with improved or selective biological activities. The simplicity and

flexibility of the chalcone system make it an attractive platform for drug development.

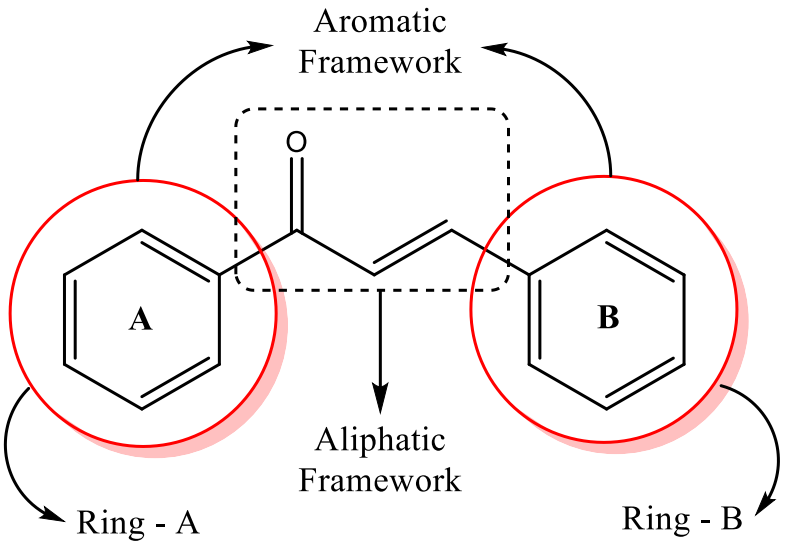
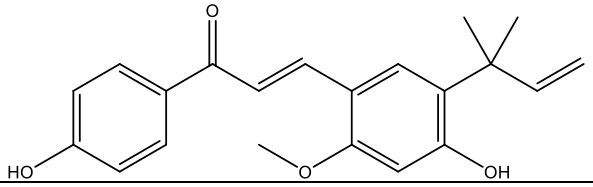
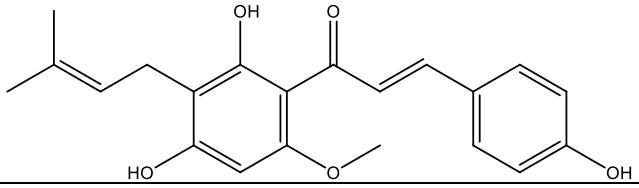
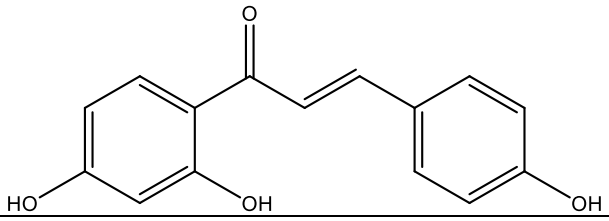


Figure-1: General Structure of Chalcone

Chalcone and its derivatives are highly effective anticancer drugs, affecting multiple pathways involved in tumor growth and metastasis [12]. The mechanisms of action include induction of apoptosis, inhibition of angiogenesis, interruption of cell cycle progression, and modulation of signaling pathways such as NF-κB, PI3K/Akt, and MAPK. In addition, chalcones can disrupt the activity of cancer-promoting enzymes such as topoisomerase and matrix metalloproteinases [13]. Some chalcone products have shown cytotoxicity against cancer cells while sparing normal cells, demonstrating their potential as a safe alternative to current anticancer agents [14]. The ability to overcome drug resistance increases medical prospects in oncology. In addition to their anticancer properties, chalcones exhibit a variety of biological activities. They are known for their anti-inflammatory effects through the inhibition of pro-inflammatory mediators such as cyclooxygenase (COX) and lipoxygenase (LOX) [15]. Chalcones exhibit potent antimicrobial activity against bacteria, fungi, and viruses and are therefore useful in combating infectious diseases [16]. Through their antioxidant properties known as free radical scavenging, they help prevent diseases associated with oxidative stress. In addition, chalcones exhibit antidiabetic, antihypertensive, and neuroprotective effects, expanding their therapeutic potential in many areas of medicine [17]. This broad range of biological activities highlights the diversity and importance of chalcones in drug discovery and development.

Table-1: Some Pre-Occurring Chalcone-based Derivatives as Anti-Cancer agents

S. No.	Drug's Name	Drug's Structure	Reference
1.	Licochalcone A		[18]
2.	Xanthohumol		[19]
3.	Isoliquiritigenin		[20]

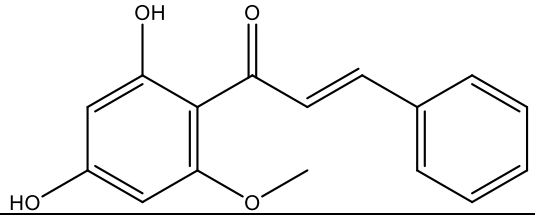
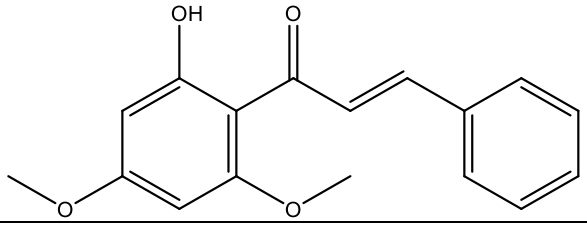
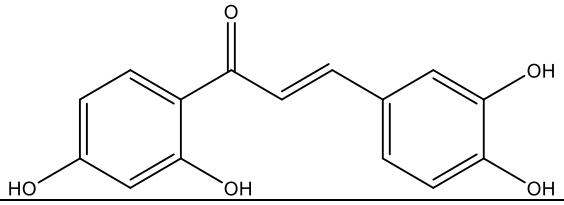
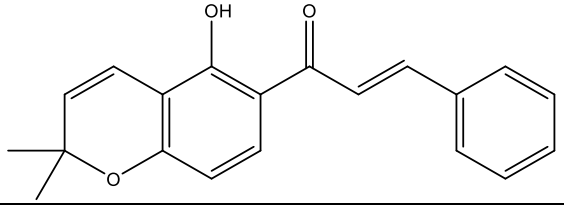
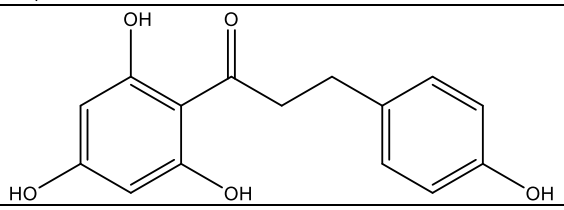
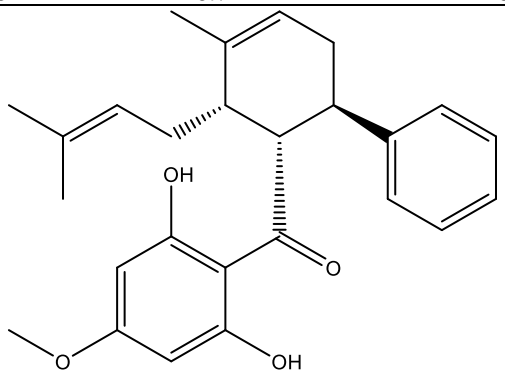
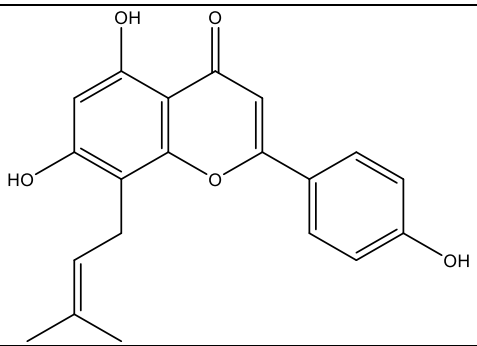
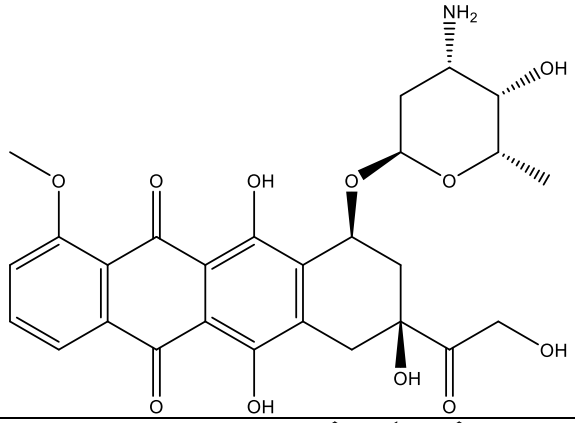
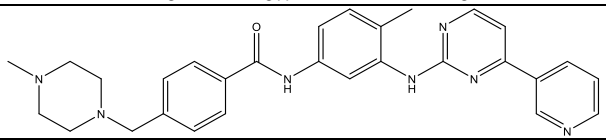
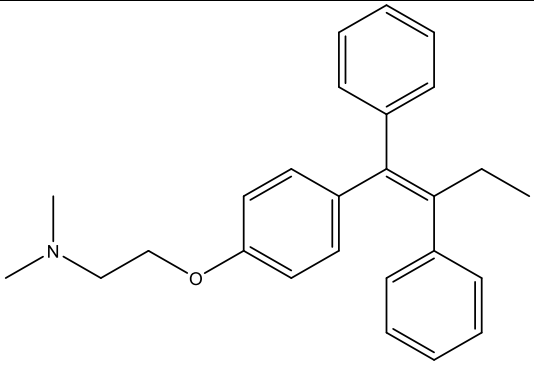
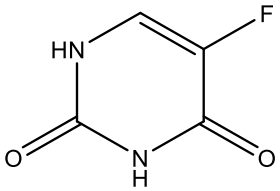
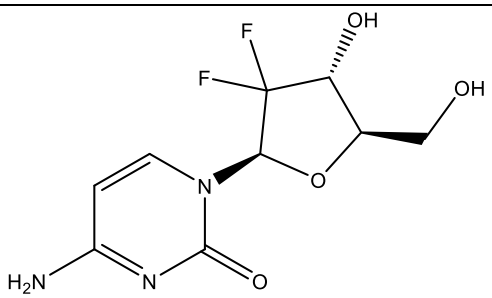
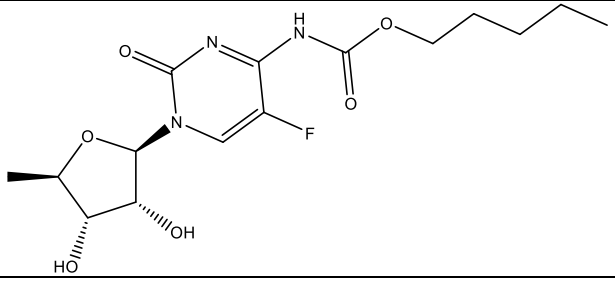
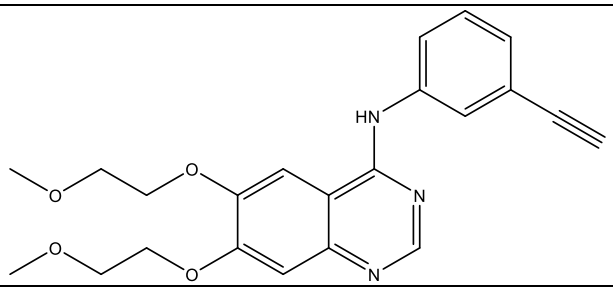
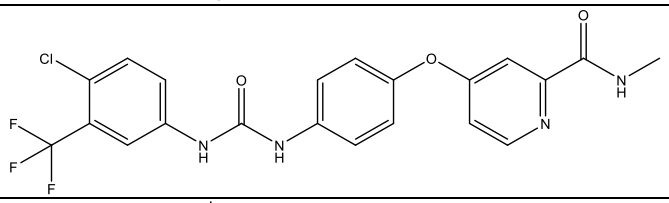
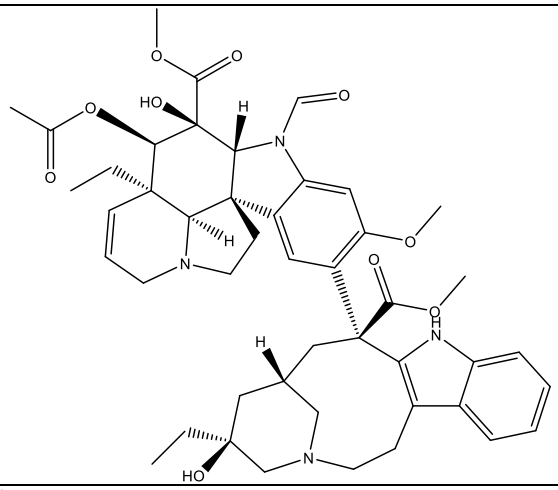
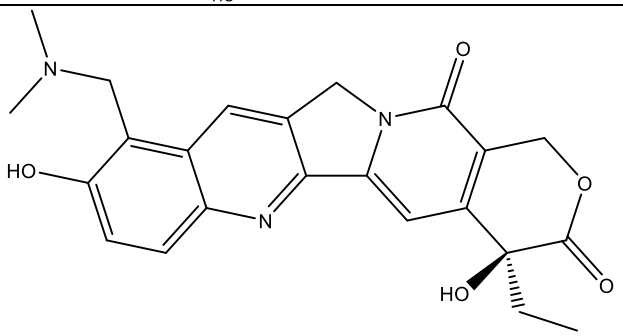
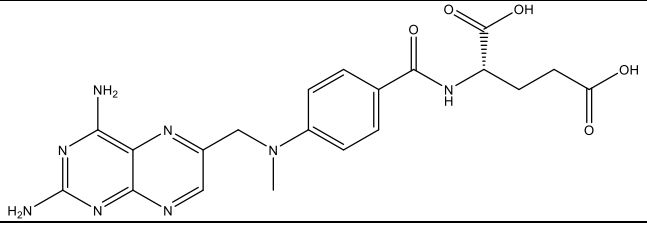
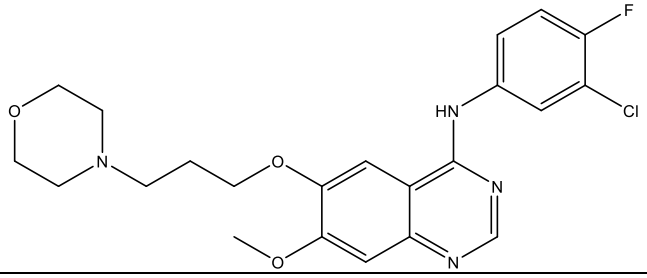
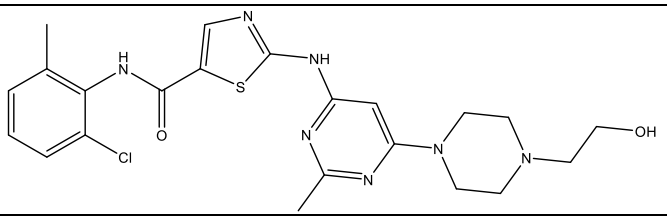
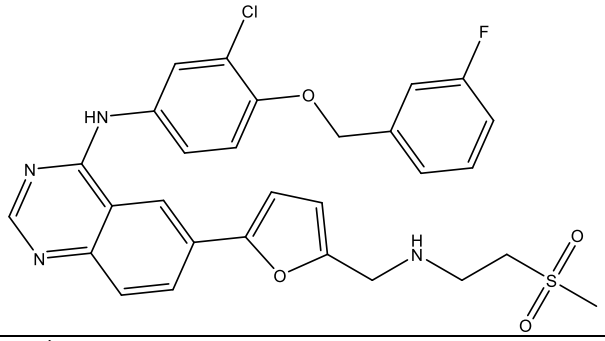
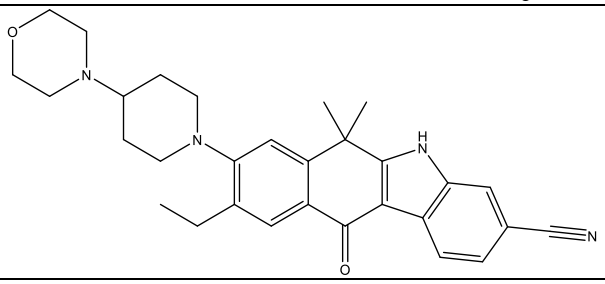
4.	Cardamonin		[21]
5.	Flavokawain B		[22]
6.	Butein		[23]
7.	Lonchocarpin		[24]
8.	Phloretin		[25]
9.	Panduratin A		[26]
10.	Licoflavone C		[27]

Table-2: Some other Marketed Drugs which serve for Anti-Cancer Activity

S. No.	Drug's Name	Drug's Structure	Reference
1.	Doxorubicin		[28]
2.	Imatinib		[29]
3.	Tamoxifen		[30]
4.	5-Fluorouracil (5-FU)		[31]
5.	Gemcitabine		[32]
6.	Capecitabine		[33]

7.	Erlotinib		[34]
8.	Sorafenib		[35]
9.	Vincristine		[36]
10.	Topotecan		[37]
11.	Methotrexate		[38]
12.	Gefitinib		[39]

13.	Dasatinib		[40]
14.	Lapatinib		[41]
15.	Alectinib		[42]

Chalcone Hybrids as Anti-Cancer Agents

In 2018, Dong et al. reported that the synthesized derivative 1 can inhibit migration of cancer and invasion. At concentrations of 5-FU of 30, 50, and 100 μmol/L, they induced apoptosis in human liver cancer and lung cancer cells. In a mouse xenograft tumor model, the compound significantly reduced tumor growth. As a positive control, chalcone (1) showed anticancer efficacy similar to 5-fluorouracil (5-FU), but was harmless to non-cancerous cells [43].

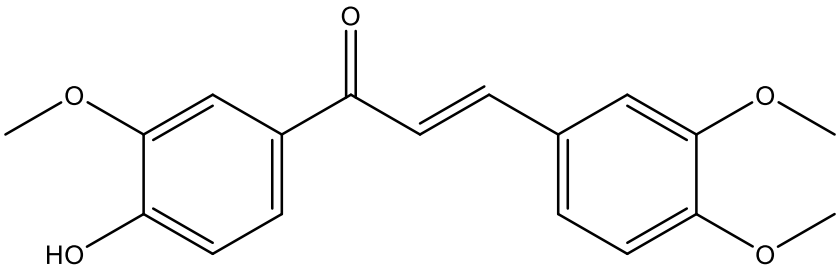


Figure-2: Structure of Chalcone derivative synthesized by Dong et al

In 2018, Wang et al. synthesized chalcone derivatives (2a-o and 3a-i) containing benzamide or benzenesulfonamide groups and evaluated their anticancer activities against HCT116, MCF7 and 143B cells. Compound (3e) exhibited high potential as antitumor agent with an IC_{50} value of 0.790±0.077, 0.596±0.165 & 0.887±0.130 μM for 143B, HCT116 and MCF-7 cells respectively. The study showed that the compounds which contain a monomethyl group or a halogen (monohalogen) group at the 3rd position of the benzene ring exhibited highest potential than those which contain a tri-fluoromethyl group or a mono methoxy group [44].

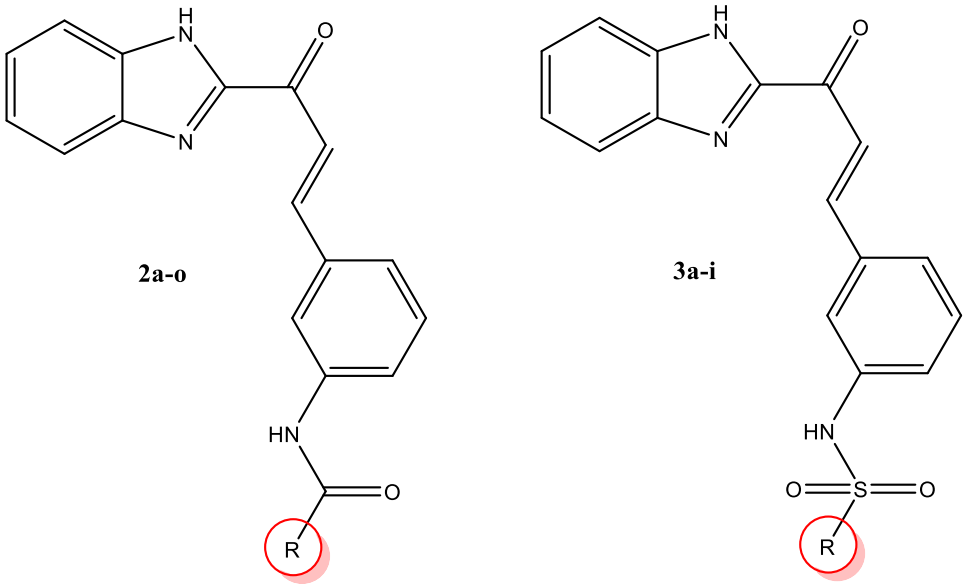


Figure-3: Structure of Chalcone derivative synthesized by Wang et al

Table-2: Structural Modifications of Compound 2

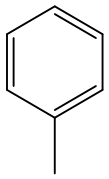
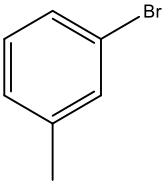
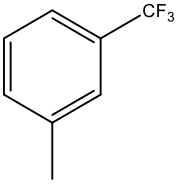
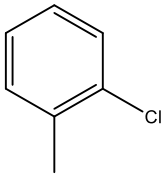
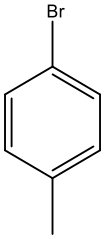
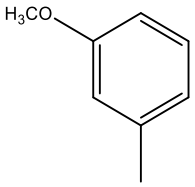
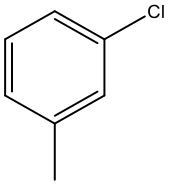
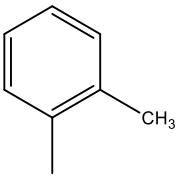
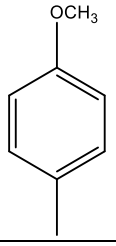
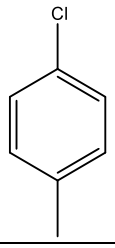
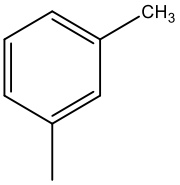
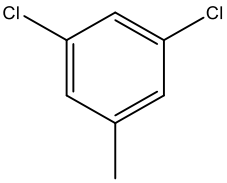
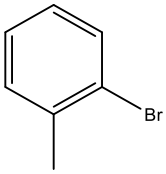
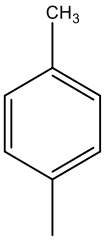
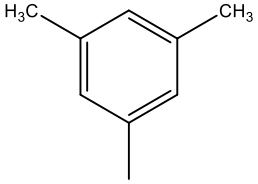
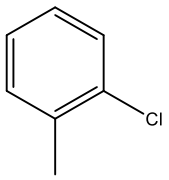
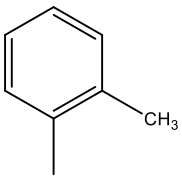
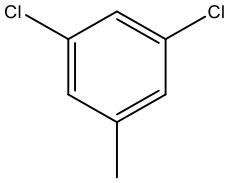
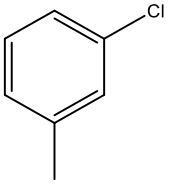
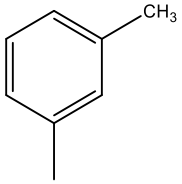
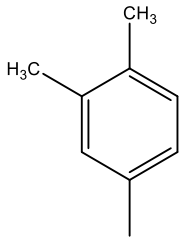
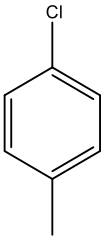
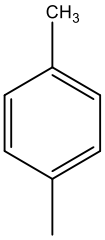
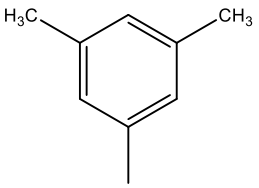
Compound Name	R	Compound Name	R	Compound Name	R
2a		2f		2k	
2b		2g		2l	
2c		2h		2m	
2d		2i		2n	
2e		2j		2o	

Table-3: Structural Modifications of Compound 3

Compound Name	R	Compound Name	R	Compound Name	R
3a		3d		3g	
3b		3e		3h	
3c		3f		3i	

In 2018, Susanti et al. used annealing as a green chemistry method to synthesize three chalcone derivatives: 4a-c. The antioxidant and cytotoxic effects of chalcones (4a–c) on HeLa cervical cancer cells were tested. The IC_{50} value of these synthetic chalcones against HeLa cell line was 31.75, 36.65 and 49.04 µg/mL. 4a showed significant cytotoxicity (IC_{50}: 31.75 µg/mL), while 4c showed a significant cytotoxicity (IC_{50}: 31.74µg/mL). The effect was minimal for 4b (IC_{50}: 49.04 µg/mL). Study shows turmeric produces chalcones with anti-cancer properties [45].

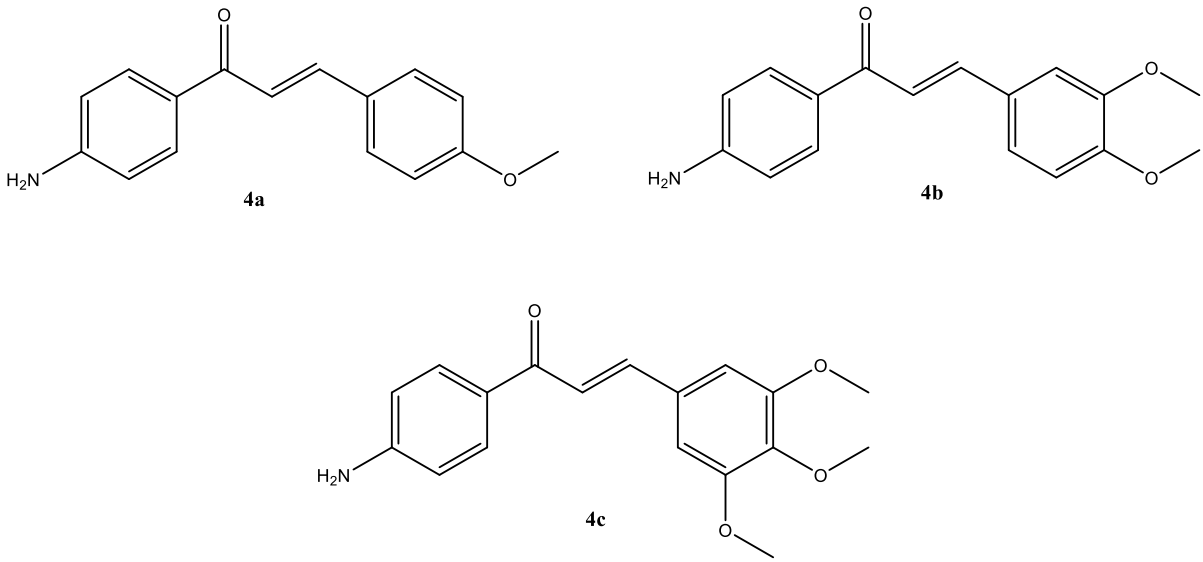
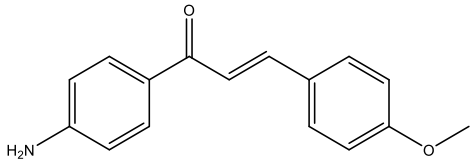
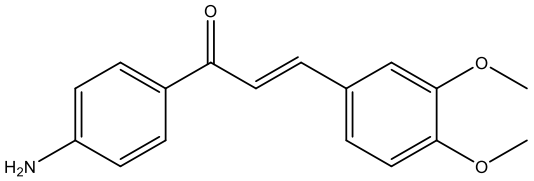
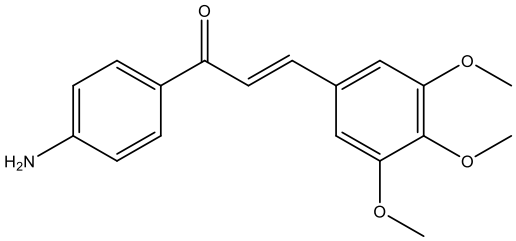
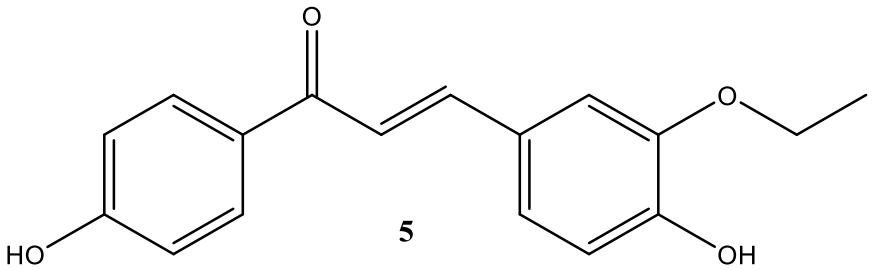


Figure-3: Structure of Chalcone derivative synthesized by Susanti et al

Table-4: IC_{50} values of the compounds 4a-c

Compound's Structure	Compound's Name	IC_{50} Value (µg/mL)
	4a	31.75
	4b	36.65
	4c	49.04

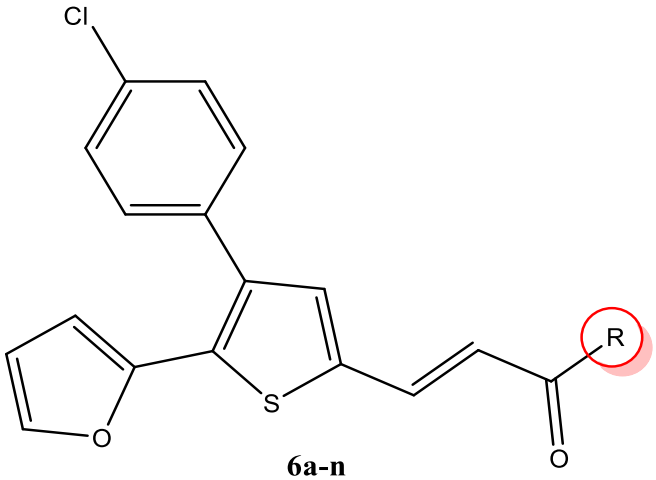
In 2018, Devi et al., discovered that the synthesized derivative 5 was found to have chemo-preventive and anticancer effects. The anticancer activity of the monomer and co-polyester was analysed in the MCF7 cell line and the observed results showed an IC_{50} value of 2.754 µM. [46].



5

Figure-4: Structure of Chalcone derivative synthesized by Devi et al

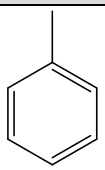
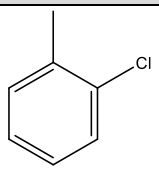
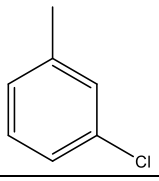
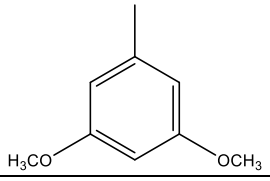
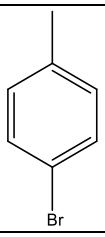
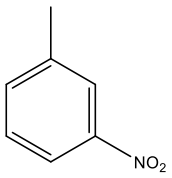
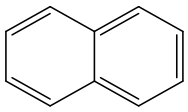
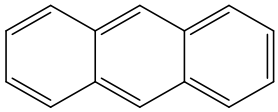
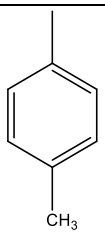
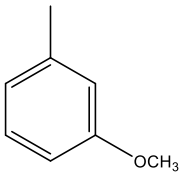
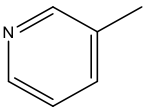
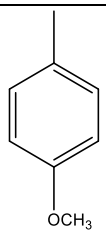
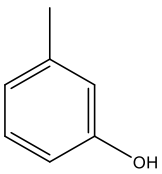
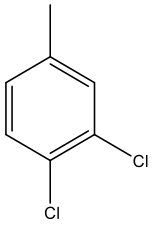
In 2018, Dudukuri et al. created new thiophene-linked chalcone compounds (6a-n). The synthesized derivatives were tested in order to find their potential to inhibit proliferation of human breast-cancer (MCF7 & MDA-MB-453), prostate-cancer (PC-3), and lung-cancer (A549) cell lines. The test substance exhibited significant anti-cancer activity in both cancer cell lines tested. Thiophene-chalcone derivative 6e showed the highest IC_{50} value (6.3±0.9µM), and the lowest GI_{50} value in A549 cells was 1.9±0.3µM. This method for preparing anticancer agents is simple and applicable to a variety of matrices, paving the way for future research [47].



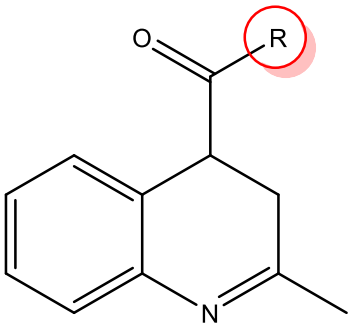
6a-n

Figure-5: Structure of Chalcone derivative synthesized by Dudukuri et al

Table-5: Structural modifications of synthesized derivative 6

Compound Name	R	Compound Name	R
6a		6h	
6b		6i	
6c		6j	
6d		6k	
6e		6l	
6f		6m	
6g		6n	

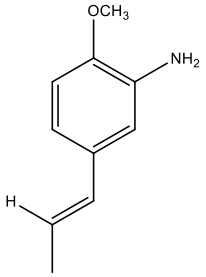
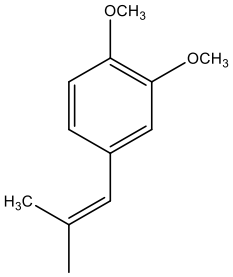
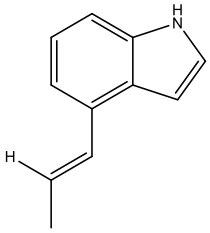
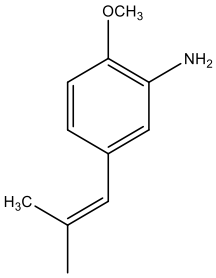
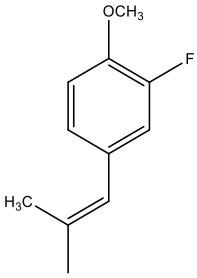
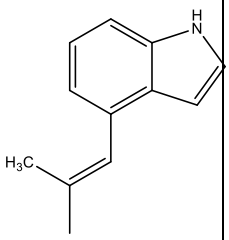
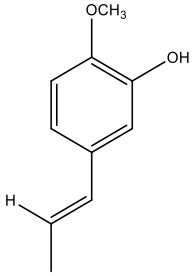
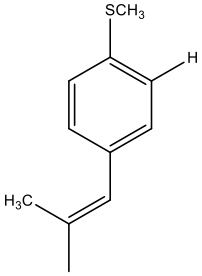
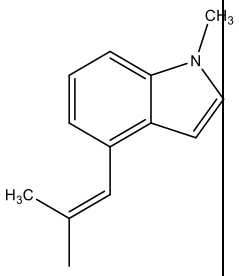
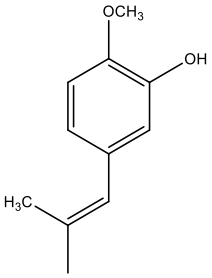
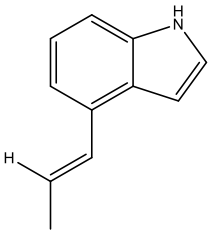
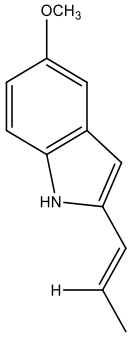
In 2019, Li et al. discovered novel quinolone chalcone derivatives (7a-o) and analysed their respective antibacterial activity. This study showed that the activity of the synthesized derivatives by using IC_{50} values which range from 0.0089 to 0.0159 μM. The LD_{50} value of the drug was found to be 665.62 mg/kg and was effective. In K562 cells, compound 7d (IC_{50}: 0.009 ± 0.001 μM) interacted with the colchicine site on tubulin and further cause the cell cycle arrest at the G2/M phase. It also causes reactive oxidative stress, mitochondrial depolarization and apoptosis. The outcomes of this study provide new perspectives on the use of chalcone derivatives as cancer treatment options [48].

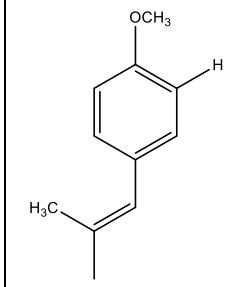
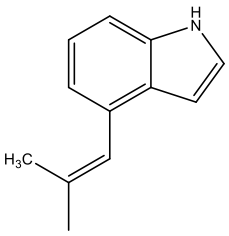
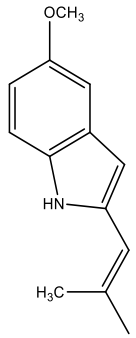


7a-o

Figure-6: Structure of Chalcone derivative synthesized by Li et al

Table-6: Structural modifications and IC_{50} values of synthesized derivative 7

Compound Name with IC_{50} (µM)	R	Compound Name with IC_{50} (µM)	R	Compound Name with IC_{50} (µM)	R
7a (0.850±0.032)		7f (1.055±0.040)		7k (>1)	
7b (0.011±0.001)		7g (0.069±0.007)		7l (0.346±0.015)	
7c (0.127±0.07)		7h (0.563±0.021)		7m (0.074±0.009)	
7d (0.009±0.001)		7i (>1)		7n (>1)	

7e (0.108±0.009)		7j (>1)		7o (>1)	

In 2019, Zhao et al., crafted chalcone backboned derivatives (8a-k). The designed derivatives showed significant 50% inhibition of the growth of the cancer cell line MGC803 (IC_{50} value 0.84 ± 0.10 µM), outperforming the positive controls (5-Fu & PCA-15) [49].

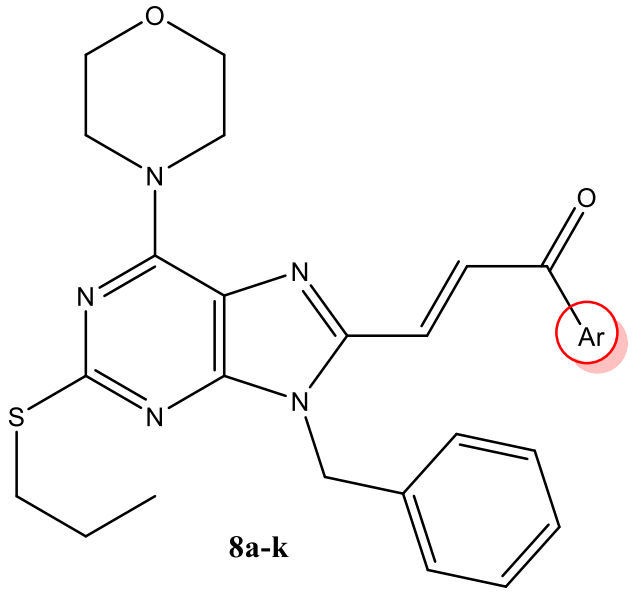
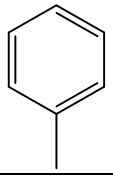
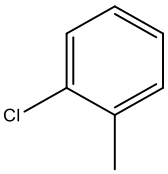
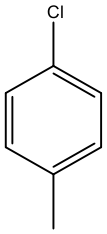
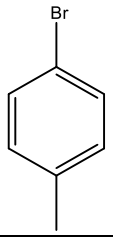
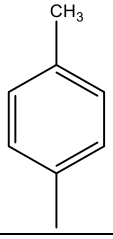
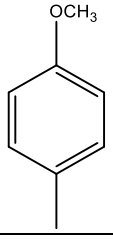
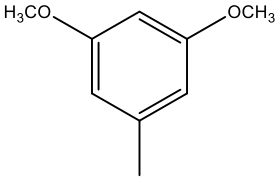
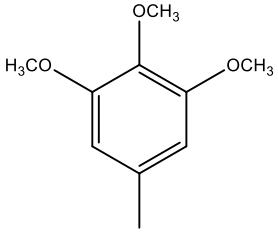
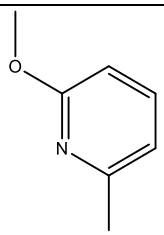
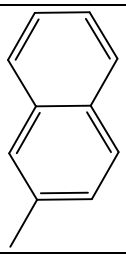
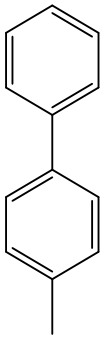


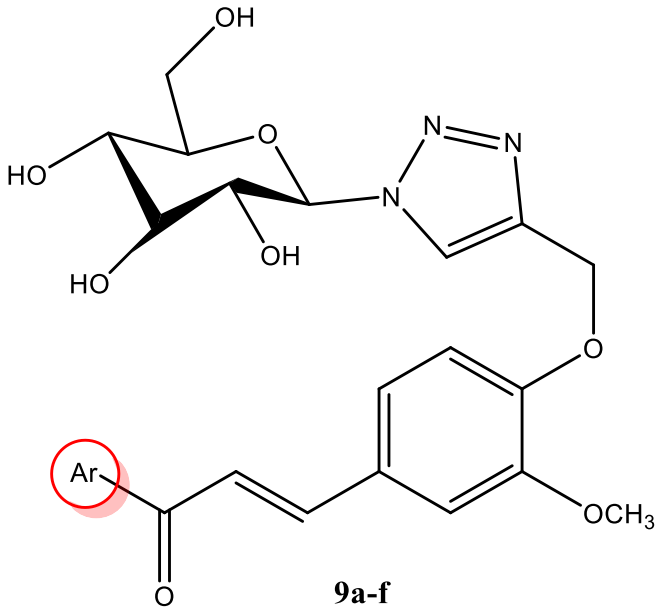
Figure-7: Structure of Chalcone derivative synthesized by Zhao et al

Table-7: Structural modifications and IC_{50} values of synthesized derivative 8

Compound's Name	Ar	IC_{50} Value (µM)
8a		4.74±0.67 & 14.89±1.17
8b		2.41±0.38 & 9.19±0.96
8c		8.32±0.92 & 17.13±1.23
8d		3.41±0.53 & 10.70±1.03
8e		1.55±0.19 & 4.90±0.69
8f		3.10±0.49 & 7.63±0.88
8g		4.91±0.69 & 9.74±0.99
8h		6.52±0.81 & >32

8i		8.62±0.93 & >32
8j		7.75±0.89 & 28.06±1.45
8k		>32 & >32

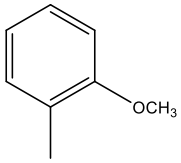
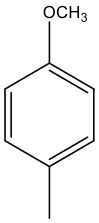
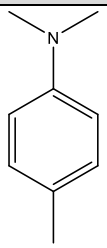
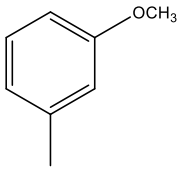
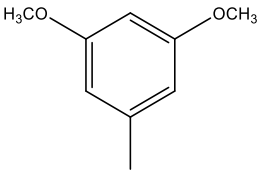
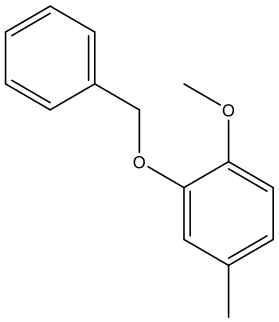
In 2019, Manna et al. used the 1,3-cycloaddition process of D-glucosyl azides with the chalcone derivatives concluding by de-O-acetylation to produce a series of derivatives (9a–f). Three compounds 9c, 9e, and 9f, were the most potent in MDA-MB-468 cells line, with LD_{50} values of 39±1.86, 28±1.91, and 64±3.82 µM, respectively compared to normal cells and breast-cancer cell line as shown by the MTT assay. In MCF-7 cells, compounds 9c, 9e, and 9f showed similar potency by exhibiting the LD_{50} values of 53±1.12, 31±2.31, and 84±3.39 µM, respectively [50].



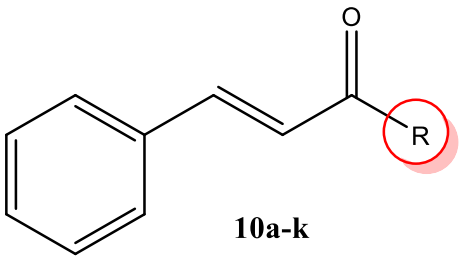
9a-f

Figure-8: Structure of Chalcone derivative synthesized by Manna et al

Table-8: Structural modifications of synthesized derivative 9

Compound Name	R	Compound Name	R	Compound Name	R
9a		9c		9e	
9b		9d		9f	

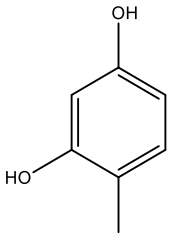
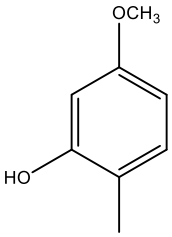
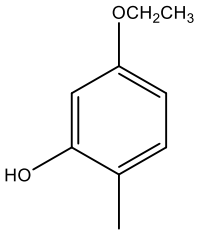
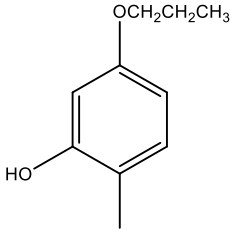
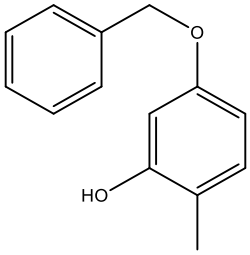
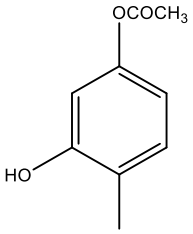
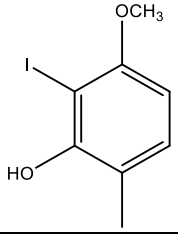
In 2019, Marquina et al. conducted a comparative study, synthesized 4'-alkoxy substituted chalcone (10a-k) and screened their biological activities. The inhibitory effects of these compounds were evaluated in the following cell lines PC-3, MCF7, HF-6 & CaSki. Derivatives 10a-d & 10f showed selectivity for PC-3 with IC_{50} values of 8.08±0.031 and 13.75 ±0.34 µM. In addition, chalcone 10a-c had no effect on normal BJ fibroblasts. The most potent and selected compounds were screened to test their antitumor effects in PC-3 cells. [51].

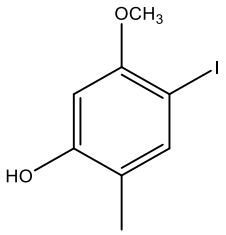
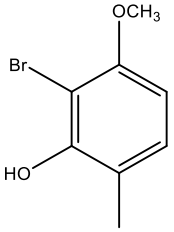
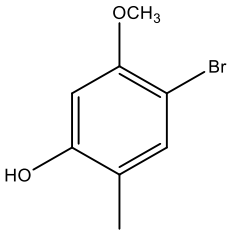
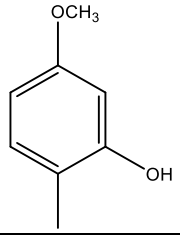


10a-k

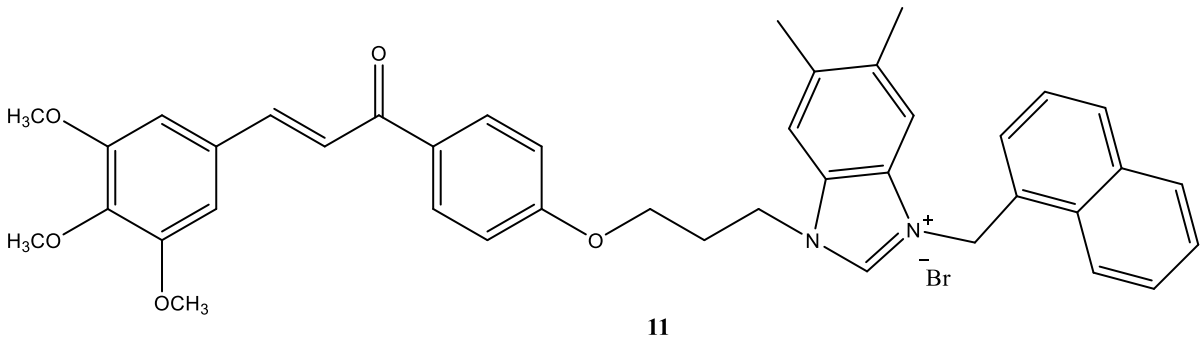
Figure-9: Structure of Chalcone derivative synthesized by Marquina et al

Table-9: Structural modifications of synthesized derivative 10

Compound's Name	R
10a	
10b	
10c	
10d	
10e	
10f	
10g	

10h	
10i	
10j	
10k	

In 2019, Yang et al. evaluated the tri-methoxyphenyl derivative of benzimidazolium chalcone for in-vitro cytotoxicity against the following cell lines: HL-60, SMMC-7721, A-549, MCF-7, and SW480. The IC_{50} values obtained were 0.83, 6.35, 7.97, 1.57 and 2.92 μM. Compound (11) showed potent activity against HL-60, MCF7 & SW-480 cell lines with IC_{50} values of 8.01, 11. 11 and 5.80. Compound (11) was found to induce G1 cell cycle arrest and apoptosis in SMMC-7721 cells [52].



11

Figure-10: Structure of Chalcone derivative synthesized by Yang et al

In 2019, Malhotra et al., crafted chalcone-backboned derivatives (12a-d) containing 4-aryloxyquinazolines. In this study, compound (12b) showed significant antileukemic activity, reducing cancer cell growth by an average of 70%. This substance showed a 75% reduction in cancer cell lines of colon and a 42.57% reduction in mortality in the HCT-116 cell line [53].

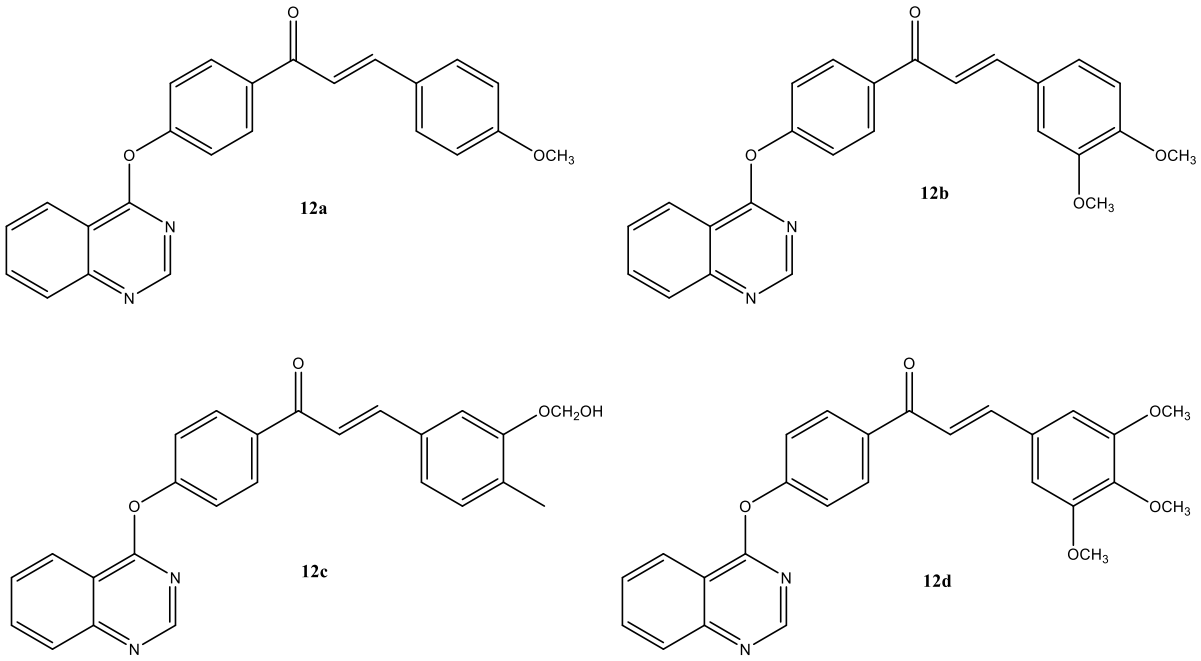
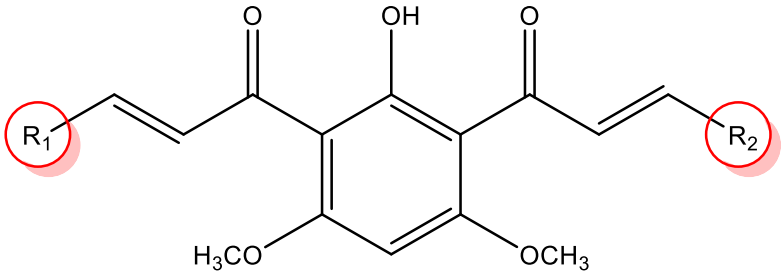


Figure-11: Structure of Chalcone derivative synthesized by Malhotra et al

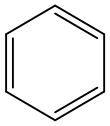
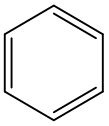
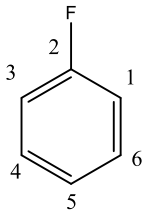
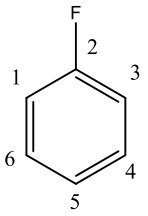
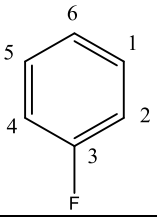
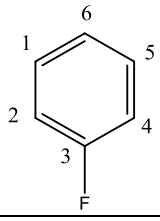
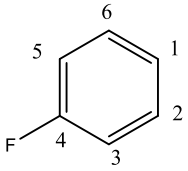
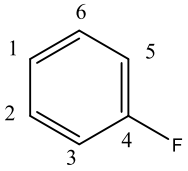
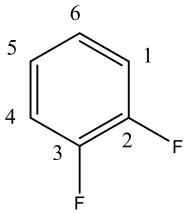
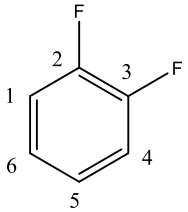
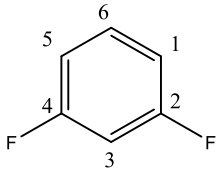
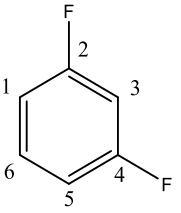
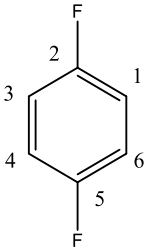
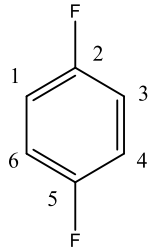
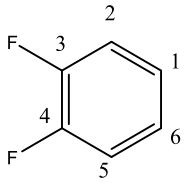
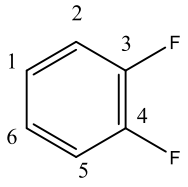
In 2019, Burmaoglu et al., manufactured chalcone based derivatives (13a-h) by Claisen-Schmidt coupling reaction. The derivatives were tested in-vitro for their ability to inhibit the xanthine oxidase activity and cell proliferation in human (MCF7) and breast cancer cells (Caco-2). Compounds 13g and 13h showed inhibitory effects on in-vitro growth in both cell lines, with IC_{50} values of 1.91 and 6.82 µM, respectively. The MTT assay was used to assess cytotoxicity in MCF7 & Caco-2 cell lines. The compound (13 g) exhibited the highest potential for antitumor activity against MCF7 cells with an IC_{50} value of 1.91 µM. Derivatives 13a and 13b were more toxic to the cell line compared to compounds 13b-13g. Compound 13g showed the lowest toxicity in the MCF7 cell line with an IC_{50} value of 103.70µM. This study suggests that a compound (13 g), which inhibits XO and cell proliferation, may be an anticancer agent [54].



13a-h

Figure-12: Structure of Chalcone derivative synthesized by Burmaoglu et al

Table-10: Structural modifications of synthesized derivative 13

Compound's Name	R_1	R_2
13a		
13b		
13c		
13d		
13e		
13f		
13g		
13h		

In 2019, Mahammadali Khanusiya and Zakirhusen Gadhawala produced chalcone derivatives (14a-r). These hybrid drugs were produced as multiple target drugs for cancer testing by incorporating a flexible sulfonamide framework. Chalcones are efficiently synthesized via the Claisen-Schmidt synthesis technique. The produced compounds have been tested for their anticancer activity against other cancer cell lines like HT-3, HCT-15, NCIH-522, DU-145 and MCF7 [55].

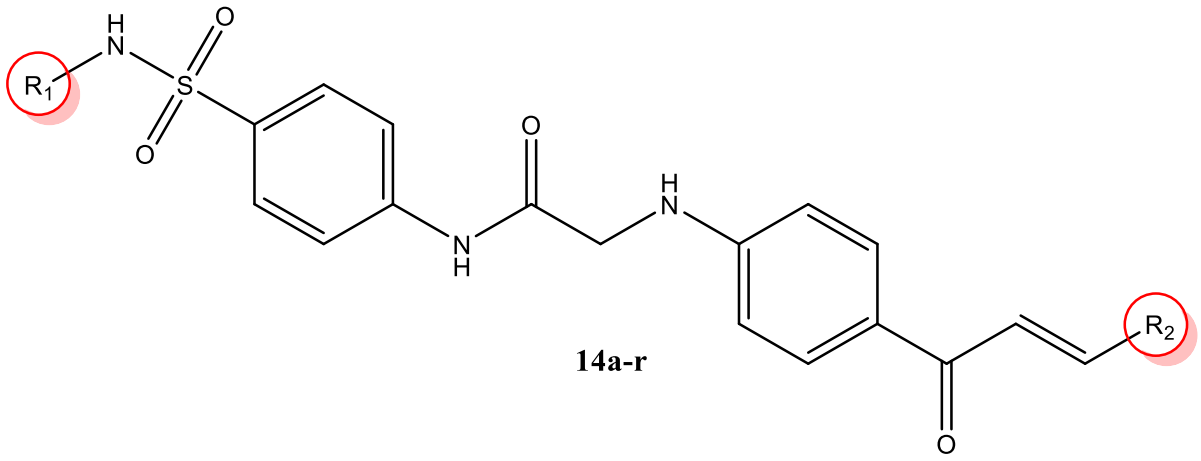
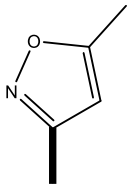
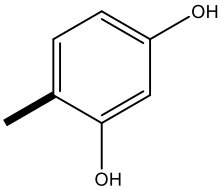
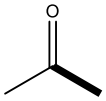
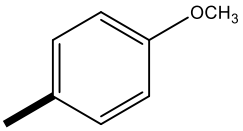
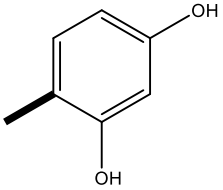
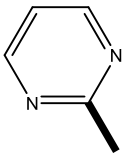
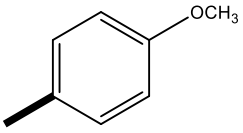
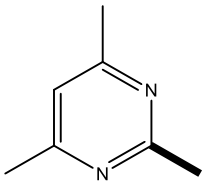
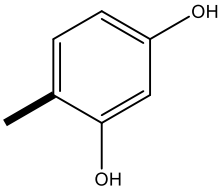
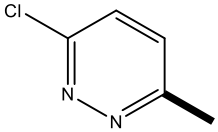
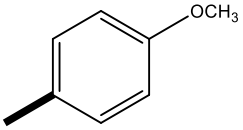
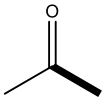
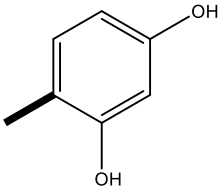
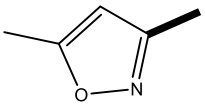
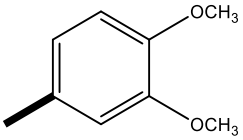
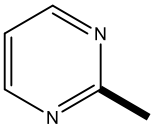
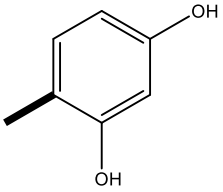
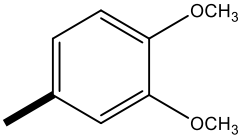
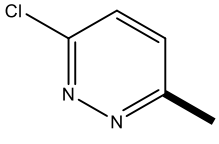
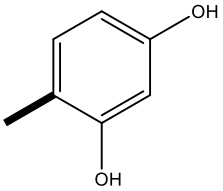
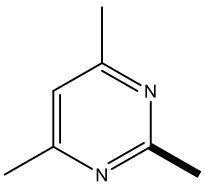
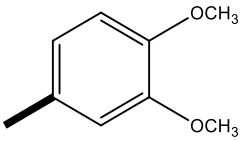
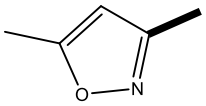
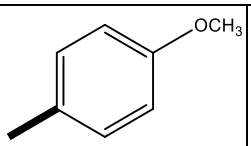
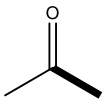
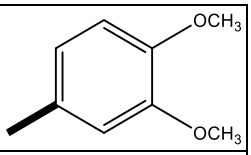
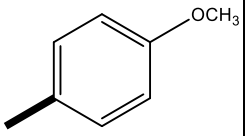
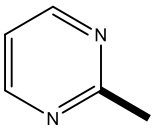
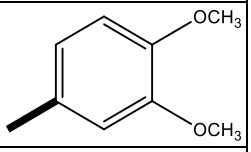
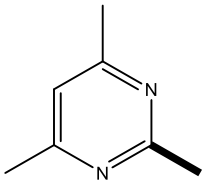
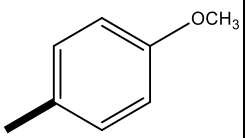
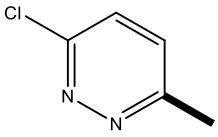
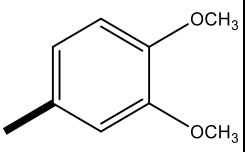


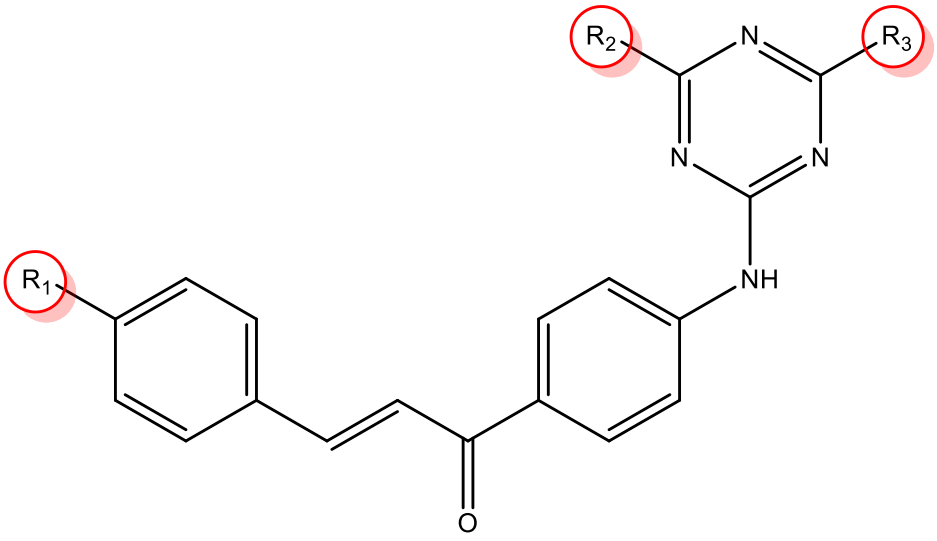
Figure-13: Structure of Chalcone derivative synthesized by Mahammadali Khanusiya and Zakirhusen Gadhawala

Table-11: Structural modifications of synthesized derivative 14

Compound Name	R_1	R_2	Compound Name	R_1	R_2
14a			14j		
14b	H		14k		
14c			14l		
14d			14m		
14e			14n	H	
14f			14o		

14g			14p		
14h	H		14q		
14i			14r		

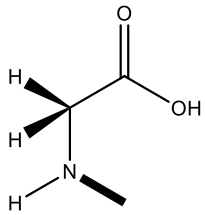
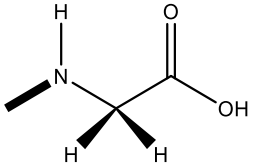
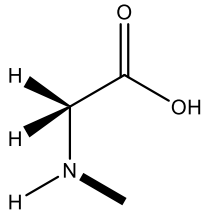
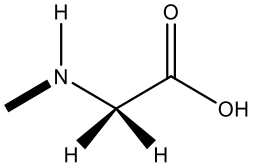
In 2020, Marwa et al., designed and synthesized chalcone-backboned derivatives (15a-h). MTT assay showed that the two compounds (15d and 15e) pose reduction in the viability of A-549 breast-cancer cells with IC_{50} value of 24.51 & 17.10 µM, respectively, which were comparable to cisplatin (IC_{50} = 21.51 µM) [56].

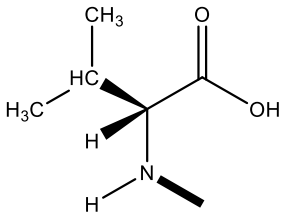
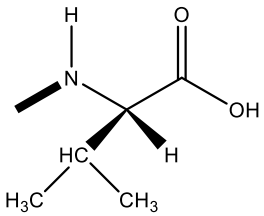
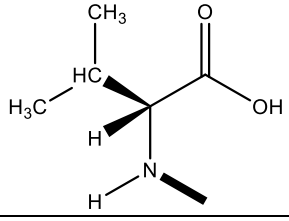
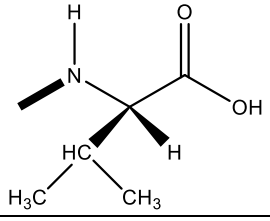
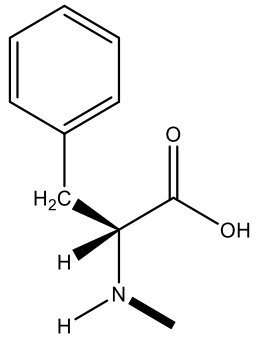
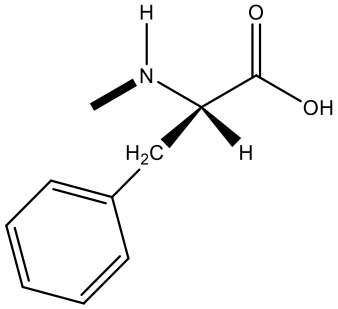
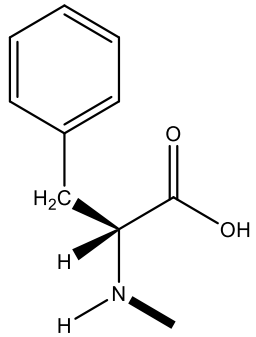
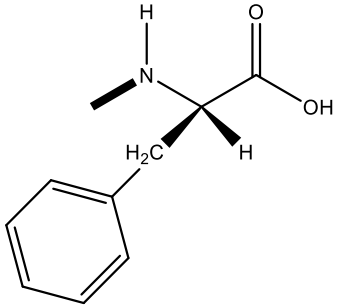
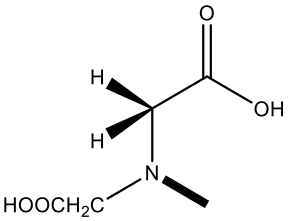
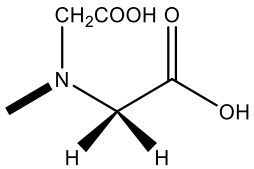
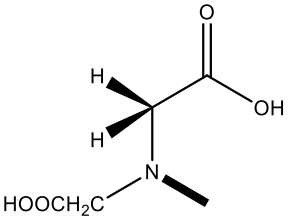
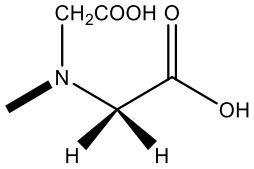


15a-h

Figure-14: Structure of Chalcone derivative synthesized by Marwa et al

Table-12: Structural modifications of synthesized derivative 15

Compound Name	R_1	R_2	R_3
15a	H		
15b	Cl		

15c	H		
15d	Cl		
15e	H		
15f	Cl		
15g	H		
15h	Cl		

In 2020, Suma et al., synthesized a plenty of chalcone-based derivatives (16a-j). The compound was tested for its antitumor activity against the following cell lines: A549, MCF7, MDA MB-231 and DU-145. Derivative (16b) was a positive control (IC_{50}: MCF7 = 0.18±0.093 µM, A549 = 0.66±0.070 µM, DU-145 = 1.03±0.44 µM, MDA MB231 = 0.065±0.0081 µM) [57].

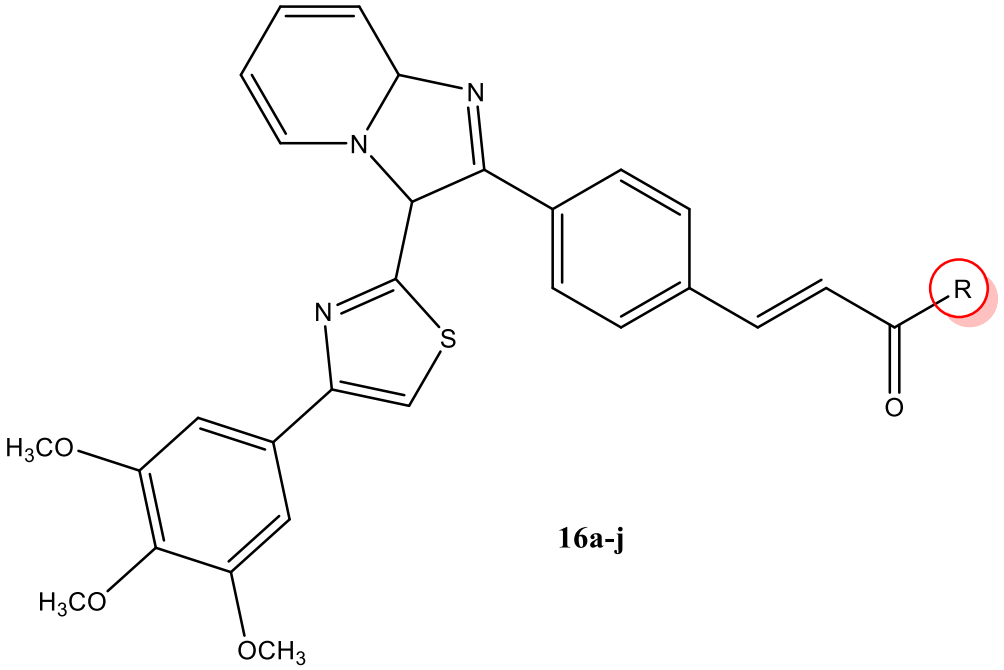
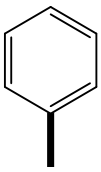
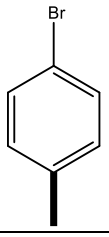
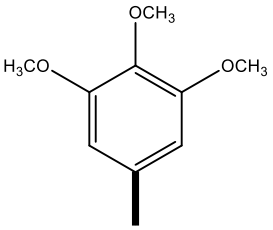
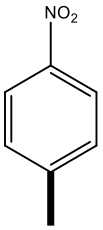
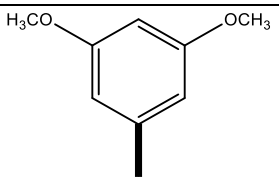
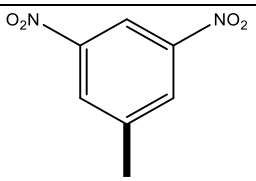
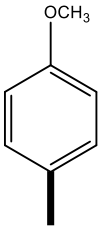
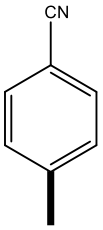
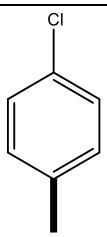
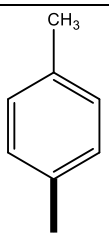


Figure-15: Structure of Chalcone derivative synthesized by Suma et al

Table-13: Structural modifications of synthesized derivative 16

Compound Name	R	Compound Name	R
16a		16f	
16b		16g	
16c		16h	
16d		16i	
16e		16j	

In 2020, Li et al. clearly showed the efficacy of the chalcone derivatives (17). This compound inhibited melanoma cell growth by cytotoxicity and colony formation in the LJ-1-59 cell line, (IC_{50} = 1.172µM & 1.368µM (intermediate)). The study also used RNA sequencing to identify gene pathways that showed enhanced differentiation. Western blotting & Q-RT-PCR were used in order to assess the effect of lj-1-59 on the growth of melanoma. The results demonstrated that this expression promoted apoptosis, caused cells to arrest in G2/M phase & reduced growth of tumor in both in-vitro & in-vivo. RNA-Seq analysis showed that lj-1-59 modulates multiple pathways like P53, DNA replication, apoptosis & cell cycle [58].

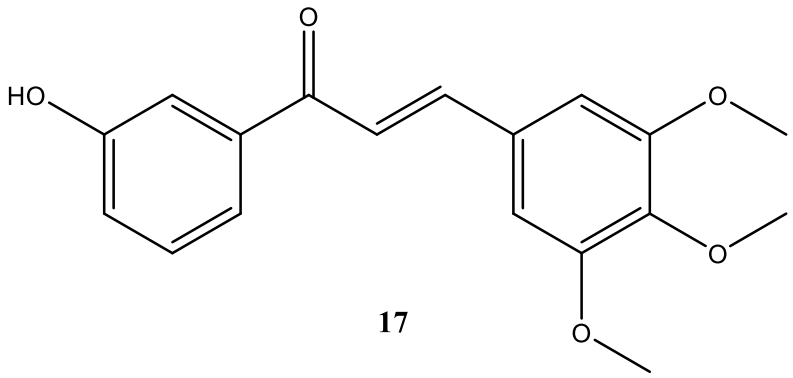


Figure-16: Structure of Chalcone derivative synthesized by Li et al

In 2020, Djemoui et al. Triazole-benzimidazole-chalcone hybrids (18a-h) were synthesized by combining benzimidazole-substituted alkynes, chalcone moieties, & azide hybrids. The benzimidazole based chalcone group was primarily synthesized, then the nitrogen was alkylated to generate the primary alkyne. Triazole-benzimidazole-chalcone hybrids (18a, 18d, 18e and 18h) showed inhibitory effects on the breast-cancer cell line T47-D (IC_{50} = 36.7±4.61, 6.23±1.02, 38.8±2.57 & >100µM), MDA-MB-231 (IC_{50} = 51.2±5.16, 5.89±1.34, 58.4±0.17 & >100µM), & prostate-cancer cell line PC3 (IC_{50} = 87.6µM) [59].

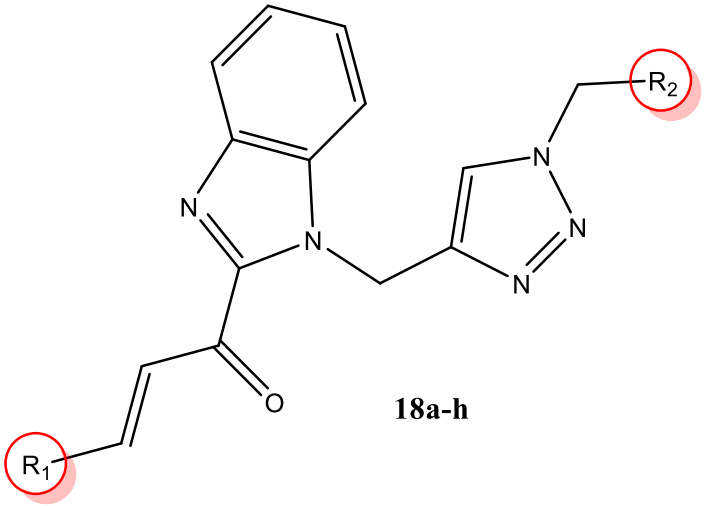
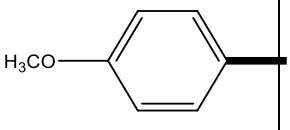
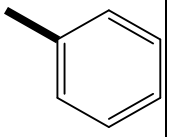
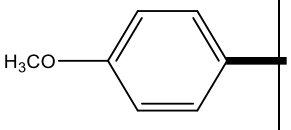
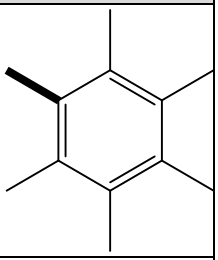
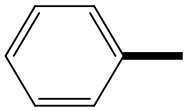
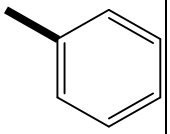
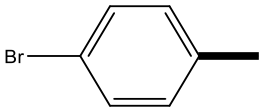
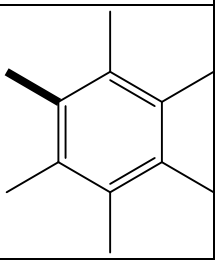
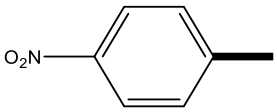
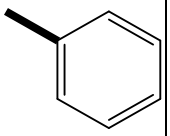
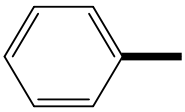
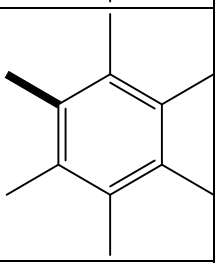
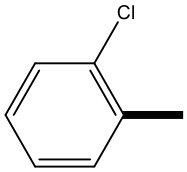
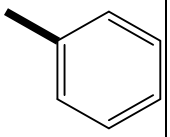
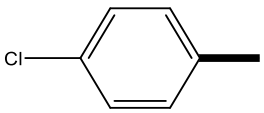
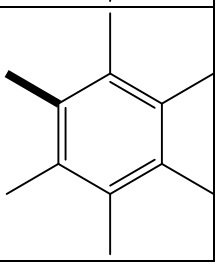
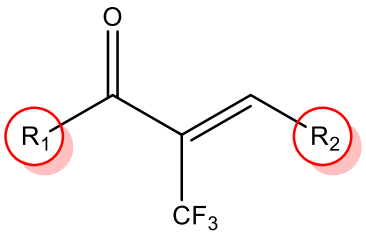


Figure-17: Structure of Chalcone derivative synthesized by Djemoui et al

Table-14: Structural modifications of synthesized derivative 18

Compound Name	R_1	R_2	Compound Name	R_1	R_2
18a			18e		
18b			18f		
18c			18g		
18d			18h		

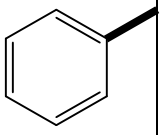
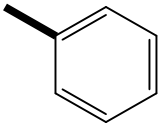
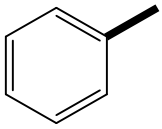
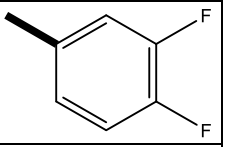
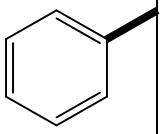
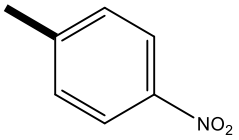
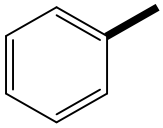
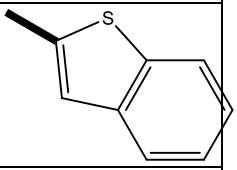
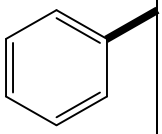
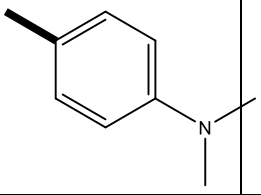
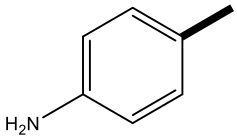
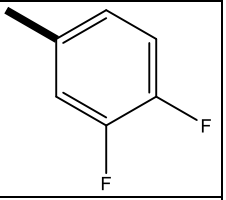
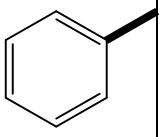
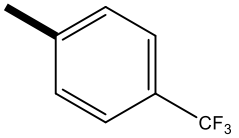
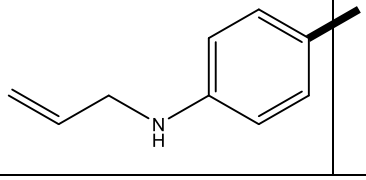
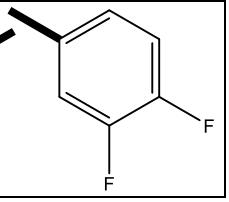
In 2021, Saito et al., analysed the effects of α-trifluoromethyl chalcones (19a-h) on human cancer cell lines like A549, MCF7, MDA-MB-231, KB-VIN, KB, PC-3 & DU145 and prostate cancer cells independently. Chalcone 19e showed the strongest anticancer activity (IC_{50}: 0.33±0.03, 0.46±0.01, 0.60±0.01, 0.58±0.02, 0.67±0.35,0.19±0.04 and 0.15±0.02 µM) against A-549, MDA-MB-231, MCF7, KB, KB-VIN, DU145 & PC-3 cells, resulting in the 50% decrease in the cell proliferation. It was administered at a dose of 3.0 mg/kg orally and intraperitoneally. Chalcone 19e was shown to promote cell proliferation in G1 and G2/M phases without inhibiting polymerization of micro-tubule. The use of derivative 19e as the probe led to the discovery of proteins associated with cancer cell proliferation [60].



19a-h

Figure-18: Structure of Chalcone derivative synthesized by Saito et al

Table-15: Structural modifications of synthesized derivative 19

Compound Name	R_1	R_2	Compound Name	R_1	R_2
19a			19e		
19b			19f		
19c			19g		
19d			19h		

In 2021, Fathi et al., synthesized multiple chalcone hybrids (20a-c & 21a-c), integrated with aliphatic (non-cyclic) groups & assessed for their anti-cancer activities. Created compounds were examined in-vitro against multiple cell lines like HCT-116, A-549, PC-3, HePG2, A-431, & BJ1. Derivatives 21a & 21c showed the most favorable outcomes (IC_{50} = 24.91 & 13.71 µg/ml for A549 & 26.10 & 14.41 µg/ml for A-431. The analysis indicated a notable reduction in gene expression of hBD-2 & hBD-3 when compared to the cell lines of negative control. These recently created compounds have the potential for advancement as anticancer pharmaceuticals [61].

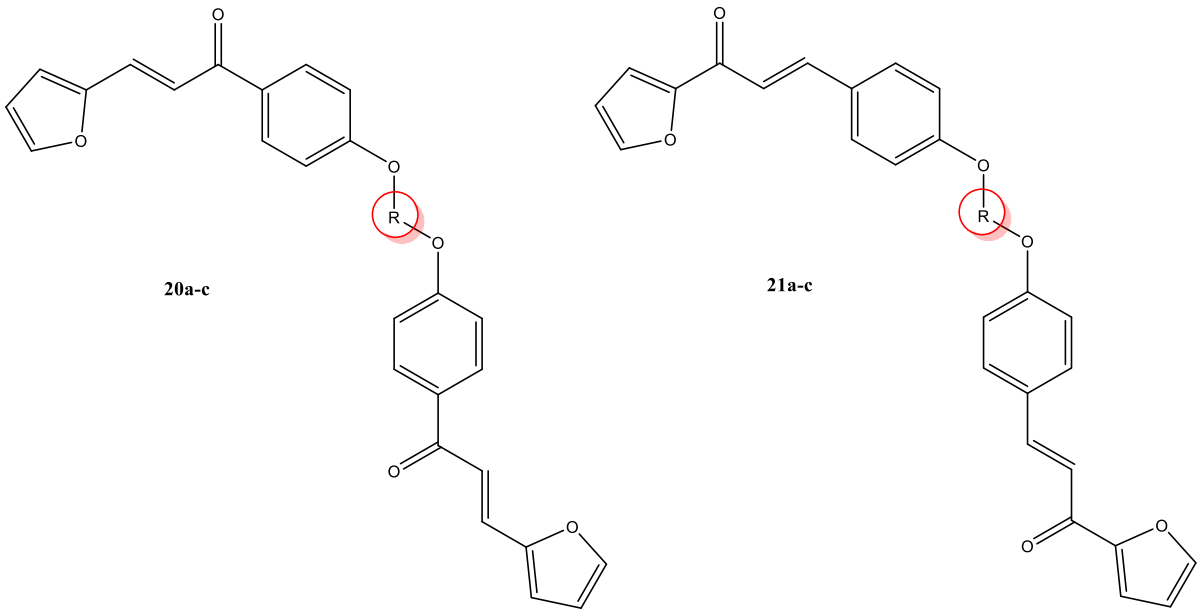


Figure-19: Structure of Chalcone derivative synthesized by Fathi et al

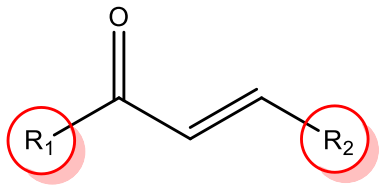
Table-16: Structural modifications of synthesized derivative 21

Compound Name	R	Compound Name	R
20a	C_2H_4	21a	C_2H_4
20b	C_3H_6	21b	C_3H_6
20c	C_4H_8	21c	C_4H_8

Table-17: IC_{50} values of the synthesized derivative 21

Compound Name	IC_{50} values (µg/ml)					
	A549	HCT116	HePG2	PC3	A431	BJ1
20a	38.7	-	-	38.4	29.3	-
20b	-	-	-	77.7	-	-
20c	18	71	-	38.6	-	-
21a	24.9	-	-	29.4	26.1	38.3
21b	44.7	-	-	60.3	-	-
21c	13.7	35	-	35.2	14.4	41.4

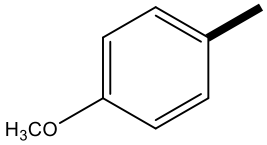
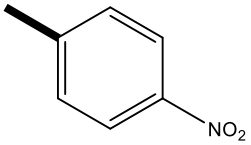
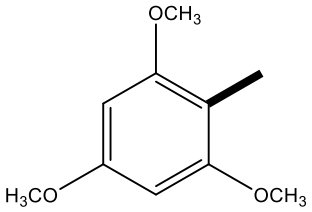
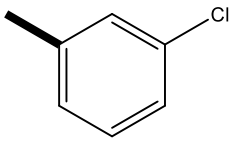
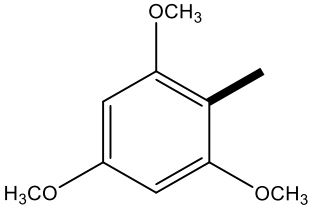
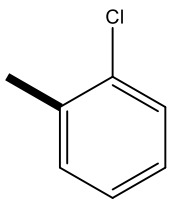
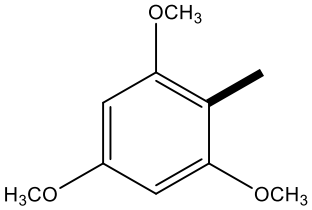
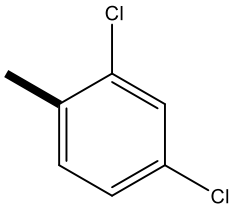
In 2021, Abosalim et al created 20 derivatives of chalcones (22a-t) and analysed their anti-cancer effectiveness on multiple cell lines. Derivatives 22b, 22d, 22h, 22j, and 22l demonstrated significant anticancer effects against MCF-7 & HepG2 cell lines. Derivative 22j was found to be have the most potential for inhibitor of tubulin, exhibiting low toxicity toward normal cell lines (GI_{50}: 5.43±0.170 µM for MCF-7 & 1.80±0.51 µM for HepG2). The IC_{50} for inhibition of tubulin was measured at 4.51±0.12 µM. It induced apoptosis & caused cell-cycle arrest at the phase G2/M. Molecular-Docking studies revealed the optimal binding configuration among the derivatives [62].

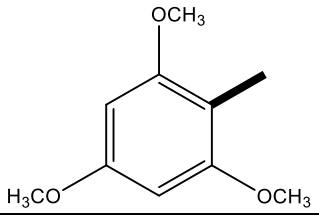
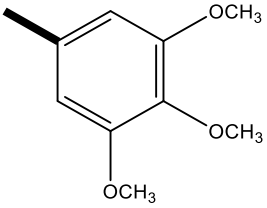
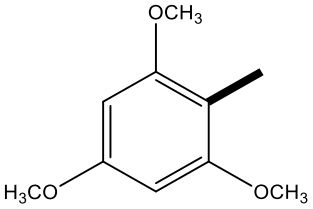
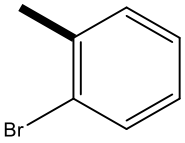
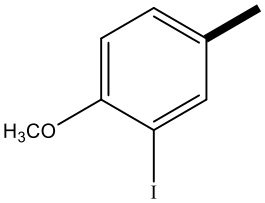
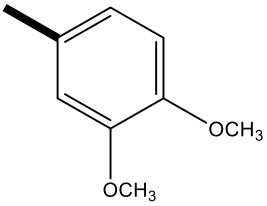
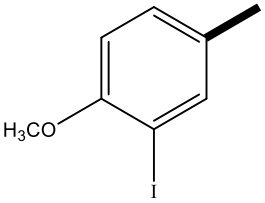
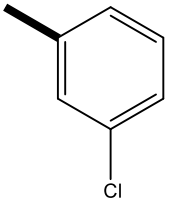
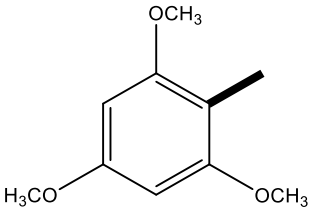
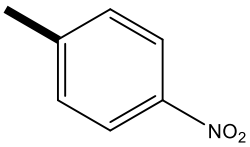
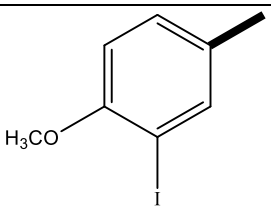
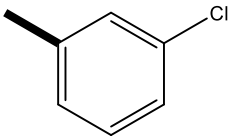
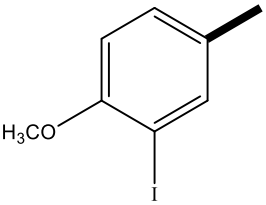
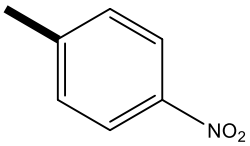
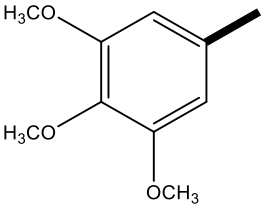
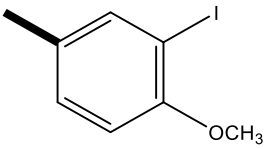
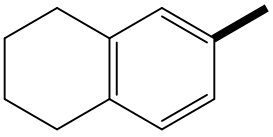
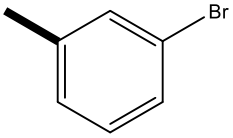


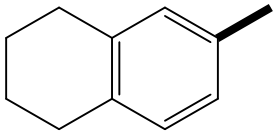
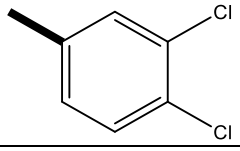
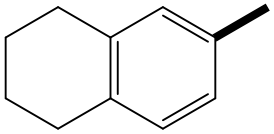
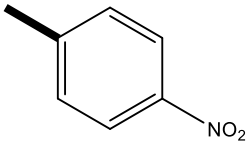
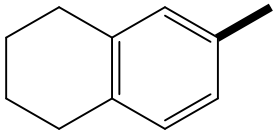
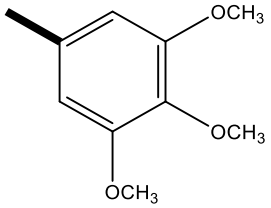
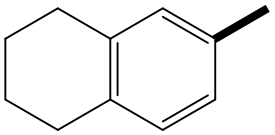
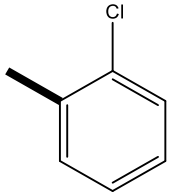
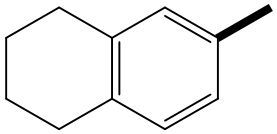
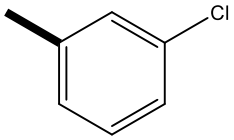
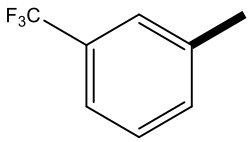
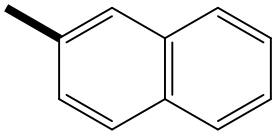
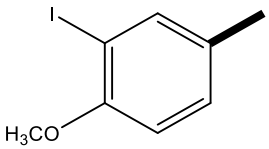
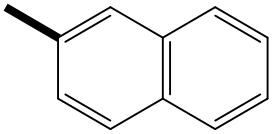
22a-t

Figure-20: Structure of Chalcone derivative synthesized by Abosalim et al

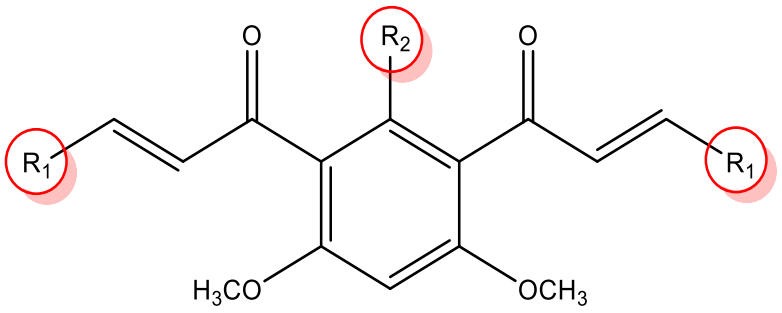
Table-18: Structural modifications and IC_{50} values of synthesized derivative 22

Compound Name	R_1	R_2	GI_{50} Values (µM)	
			MCF7	HepG2
22a			7.33	52.21
22b			6.12	12.72
22c			40.92	20.72
22d			22.21	3.37

22e			62.94	13.48
22f			31.56	6.09
22g			43.74	43.33
22h			5.09	54.67
22i			5.43	1.8
22j			18.34	14.73
22k			10.82	54.09
22l			9.95	26.38
22m			>100	63..24

22n			7.42	>100
22o			16.41	14.2
22p			6.092	63.53
22q			37.62	9.83
22r			7.55	7.33
22s			21.43	42.28
22t			16.89	13.19

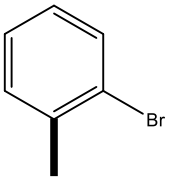
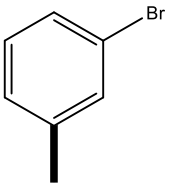
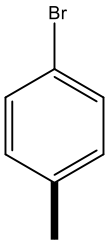
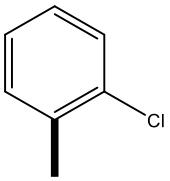
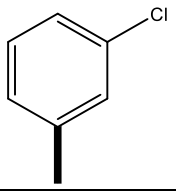
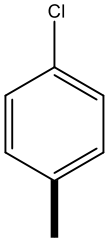
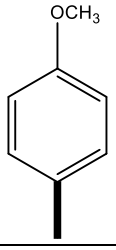
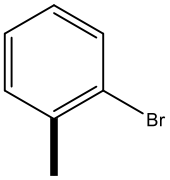
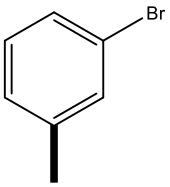
In 2021, Burmaoglu et al. discovered new bischalcone derivatives (23a-o) that are intriguing pharmacophores for anticancer properties. Compounds 23h, 23i, and 23j showed the highest anti-proliferative activity for A549 cancer cell line (presenting mean IC_{50} = 4.18±1.74, 4.52±1.22 & 5.04±0.32 µM, respectively. Derivative (23k) showed promising anti-proliferative effects against Caco-2 cell line (IC_{50} = 3.69±0.62 µM). Compounds 23j and 23k induced cell cycle arrest during the S-phase & G0/G1 phase, respectively. Compound (23k) displayed the greatest apoptosis/necrosis ratio when compared to other examined derivatives and the benchmark. The anti-cancer effects of the derivative were confirmed by molecular-docking on EGFR & HER2. These findings indicate that chalcone hybrids may represent significant therapeutic option for lung-cancer [63].

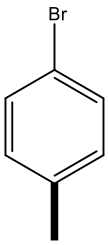
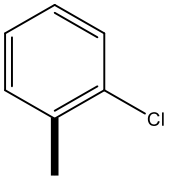
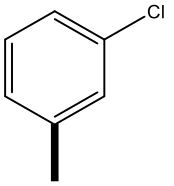
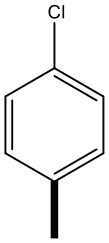
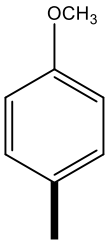
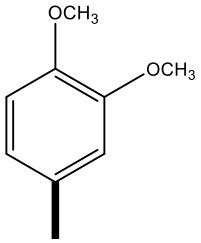


23a-o

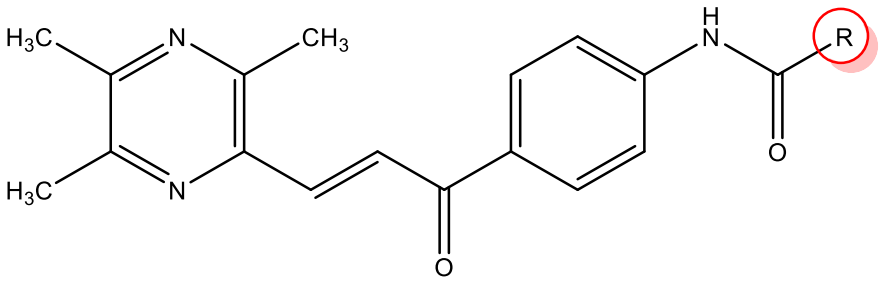
Figure-21: Structure of Chalcone derivative synthesized by Burmaoglu et al

Table-19: Structural modifications and IC_{50} value of synthesized derivative 23

Compound Name	R_1	R_2	IC_{50} (µM) for A-549
23a		OH	11.25±2.10
23b		OH	11.73±1.95
23c		OH	17.94±1.68
23d		OH	11.90±0.16
23e		OH	21.89±2.49
23f		OH	10.02±0.76
23g		OH	5.72±0.38
23h		OCH_3	4.18±1.75
23i		OCH_3	4.52±1.23

23j		OCH_3	5.04±0.31
23k		OCH_3	8.56±0.98
23l		OCH_3	11.68±0.42
23m		OCH_3	11.25±0.98
23n		OCH_3	4.95±1.63
23o		OCH_3	5.44±1.01

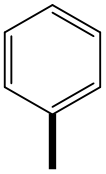
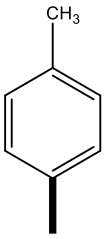
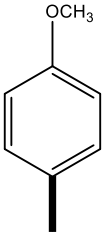
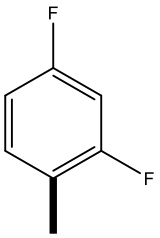
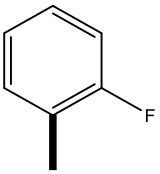
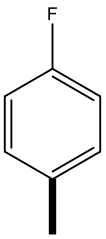
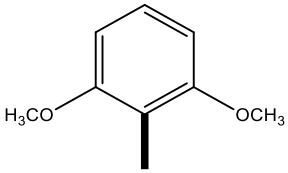
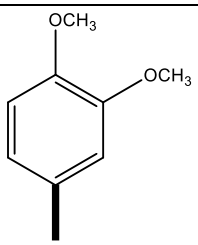
In 2021, Luo et al. created and assessed novel ligustrazine-chalcone hybrids (24a-j) for their anti-cancer properties in both in-vitro & in-vivo. The derivatives demonstrated notable in-vitro cytotoxicity (50%) for the MCF7, MDA-MB-231, A-549 & HepG2 cell lines. Derivatives 24c & 24f exhibited enhanced anti-proliferation properties against MDA-MB-231 (IC_{50}: 1.60±0.20 µM; 1.67±1.24 µM) & MCF7 (IC_{50}: 1.41±0.22 µM; 1.54±0.31 µM) [64].

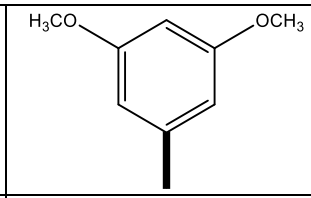
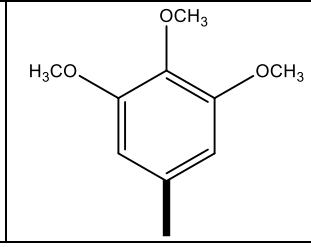


24a-j

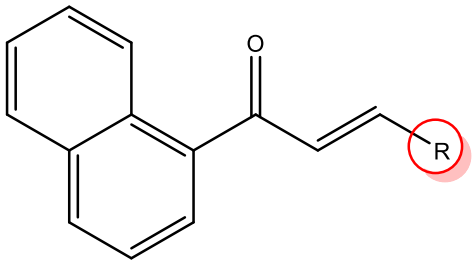
Figure-22: Structure of Chalcone derivative synthesized by Luo et al

Table-20: Structural modifications and IC_{50} values of synthesized derivative 24

Compound Name	R	IC_{50} Values (μM)			
		MDA-MB 231	MCF7	A-549	HepG2
24a		1.84±0.11	0.99±0.33	7.27±1.70	1.31±0.21
24b		1.78±0.14	1.18±0.13	9.99±1.70	5.45±2.15
24c		1.60±0.21	1.41±0.23	4.15±0.37	1.19±0.33
24d		1.77±0.13	1.61±0.35	2.45±0.15	2.99±0.53
24e		1.98±0.39	1.27±0.68	7.39±0.29	2.04±0.21
24f		1.67±1.25	1.54±0.30	4.48±0.31	2.25±0.46
24g		3.85±0.78	2.47±0.21	8.47±0.53	3.38±0.37
24h		3.36±0.52	1.66±0.42	5.06±0.12	2.56±0.16

24i		11.55±0.75	6.27±0.28	10.18±1.46	11.00±0.39
24j		4.74±0.64	2.76±0.66	7.35±0.27	4.86±0.85

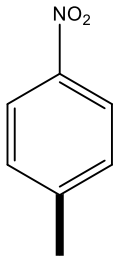
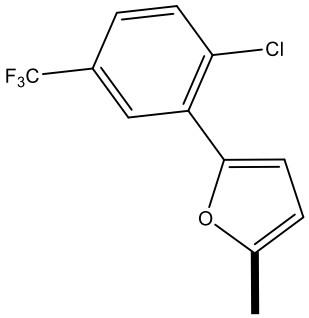
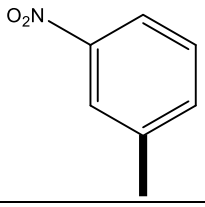
In 2021, Jacques et al. discovered that a range of chalcones generated from 1-naphthylacetophenone (25a-k) can significantly reduce the proliferation of leukemic cells. The investigation explored the cytotoxic properties of derivatives (25e, 25g, and 25h) on acute leukemia cell lines like K-562 & Jurkat. Expression levels of Caspase-3 were measured at 85. 88 ± 6. 77%, 7. 41 ± 1. 59%, and 8. 07 ± 1. 93% in K562, and 58. 68 ± 5. 66%, 84. 19 ± 1. 99%, and 34. 17 ± 6. 50%, respectively [65].

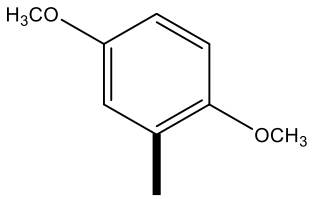
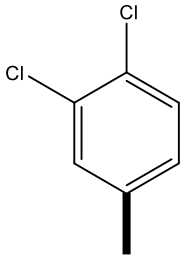
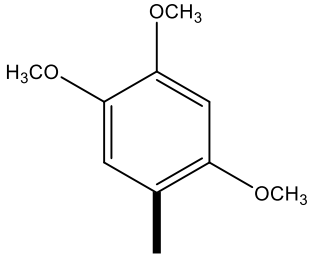
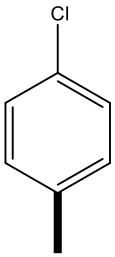
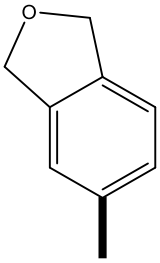
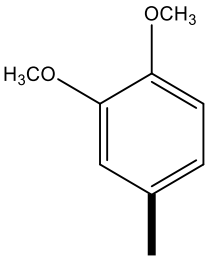
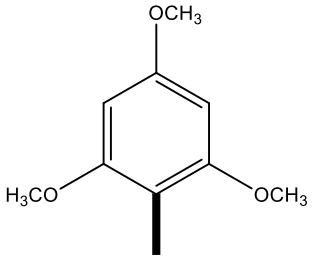


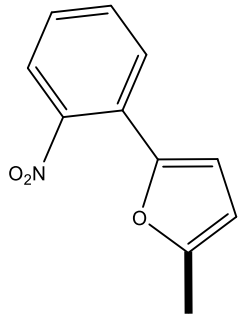
25a-k

Figure-23: Structure of Chalcone derivative synthesized by Jacques et al

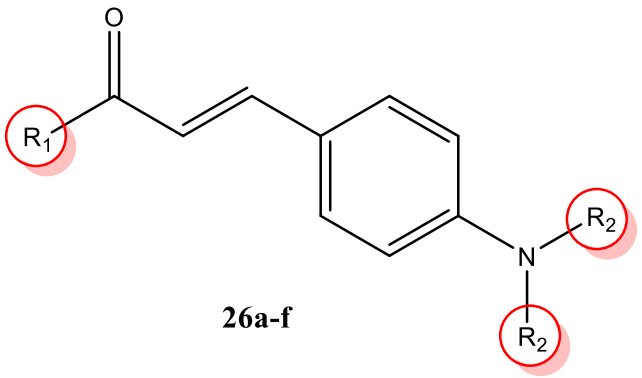
Table-21: Structural modifications of synthesized derivative 25

Compound Name	R
25a	
25b	
25c	

25d	
25e	
25f	
25g	
25h	
25i	
25j	

25k	

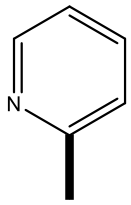
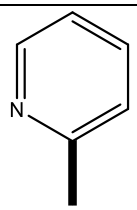
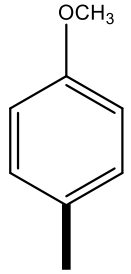
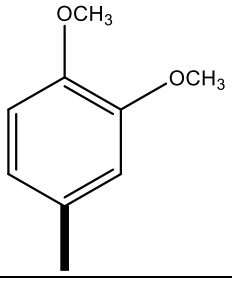
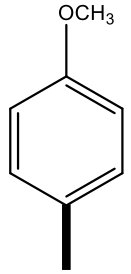
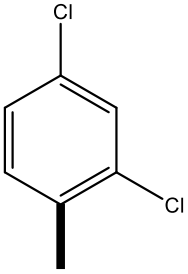
In 2021, Len et al. developed chalcone analogs (26a-f) featuring di-alkylamino pharmacophores & examined their potential for the cervical-cancer cell line (OV2008). Derivative 26f exhibited greatest in-vitro potency (IC_{50} = 7.81 µM) & induce cytotoxicity in OV2008 cell lines, without affecting other cell lines significantly (DU-145, HEK293, MDAMB-231, LOVO & A-549). The treatment of OV2008 led to cell-cycle arrest at G2 phase, heightened reactive oxygen species production & disrupt mitochondrial membrane. It also results in activation of caspase-9, caspase-3 & caspase-7, contributing to cell-death in OV2008. The results suggest that it is a significant therapeutic agent against cervical-cancer, showing a inhibition rate of about 70% [66].



26a-f

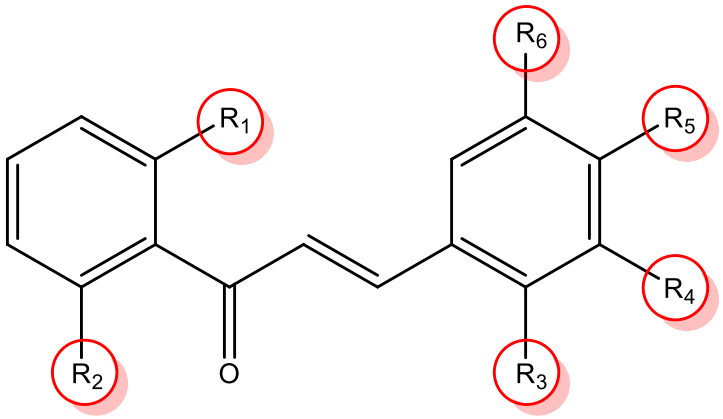
Figure-24: Structure of Chalcone derivative synthesized by Len et al

Table-22: Structural modifications and IC_{50} values of synthesized derivative 26

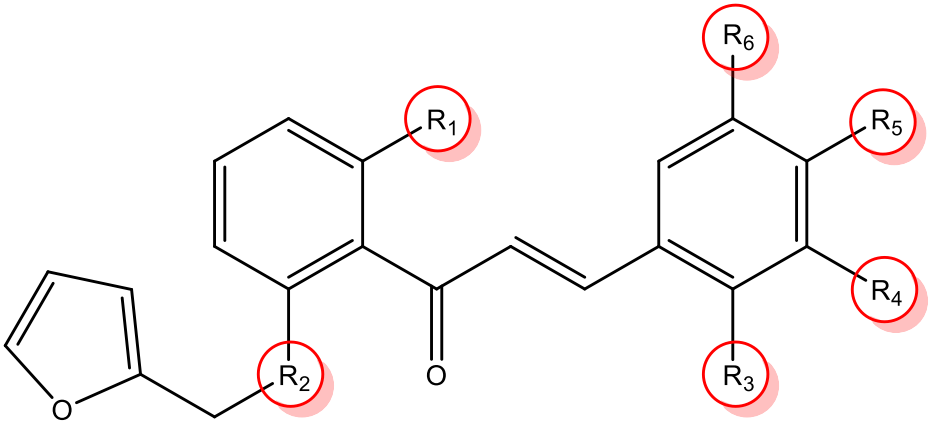
Compound Name	R_1	R_2	IC_{50} Values (µM)					
			HEK293	LOVO	DU145	MB-231	A549	OV2008
26a		CH_3	>100	>100	>100	>100	>100	>100
26b		C_2H_5	>100	>100	>100	>100	>100	>100
26c		CH_3	>100	>100	>100	>100	>100	>100
26d		CH_3	68.5±2.1	45±22.6	22.5±4.9	26.2±23.9	66.3±4.6	13.8±7
26e		C_2H_5	>100	>100	>100	>100	>100	>100
26f		CH_3	70±42.4	65±49.5	96.9±4.4	91.9±11.5	84.9±21.4	7.8±0.0

In 2022, Rosario et al created 12 2-furoyloxy chalcone derivatives (27a-f & 28a-f) and assessed the antiproliferative effectiveness on tumor cell lines. The most significant notable cytotoxicity was noted when a furoyl is substituted to the 2-hydroxy or 2-amino group of A-ring of the framework of chalcone utilizing ester or an amide. Inhibitory concentrations (IC_{50}) against human leukemia cells were found to be 0. 2 ± 0. 1 µM and 1. 3 ± 0. 1 µM. Nevertheless, the chalcones exhibited lower cytotoxicity towards peripheral-blood-mononuclear-cells. The chalcone FMC induced cell cycle arrest at the G2-M phase, heightened the proportion of sub G1 & Annexin-V positive cell, released mitochondrial cytochrome-c, triggered caspase activation. Furthermore, it diminished polymerization of tubulin in-vitro in the concentration dependent manner. The pan caspase inhibitor z-VAD-fmk mitigated the cell-death induced by the FMC, which was directly

dependent on the production of reactive oxygen species. FMC possess the property to be an effective anti-leukemia method [67].



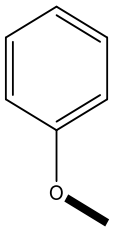
27a-f



28a-f

Figure-25: Structure of Chalcone derivative synthesized by Rosario et al

Table-23: Structural modifications of synthesized derivative 27

Compound Name	R_1	R_2	R_3	R_4	R_5	R_6
27a	H	OH	H	H	OCH_3	H
27b	H	NH_2	H	H	OCH_3	H
27c	H	OH	H	OCH_3	OCH_3	OCH_3
27d		OH	H	OCH_3	OCH_3	OCH_3
27e	H	NH_2	H	CH_3	OCH_3	OCH_3
27f	H	OH	OCH_3	OCH_3	OCH_3	H
28a	H	O	H	H	OCH_3	H
28b	H	NH	H	H	OCH_3	H
28c	H	O	H	OCH_3	OCH_3	OCH_3

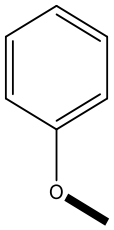
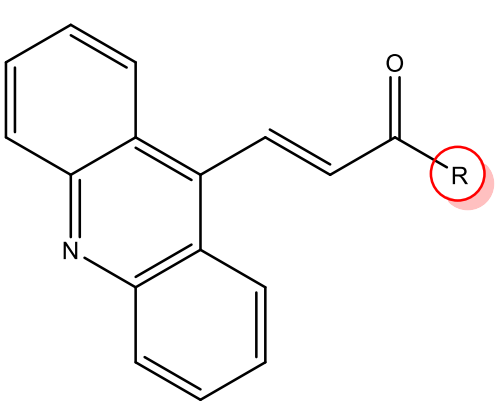
28d		O	H	OCH_3	OCH_3	OCH_3
28e	H	NH	H	OCH_3	OCH_3	OCH_3
28f	H	O	OCH_3	CH_3	OCH_3	H

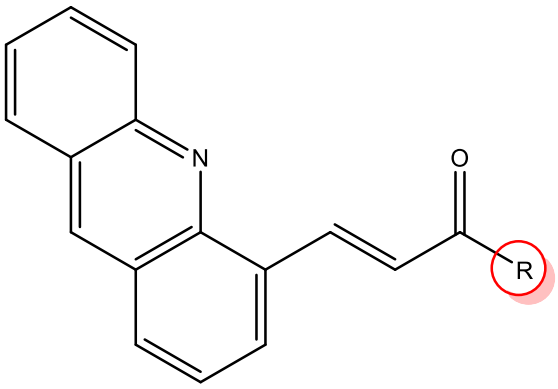
Table-24: IC_{50} values of the synthesized derivative 27

Compound Name	IC_{50} values (µM)				
	HL-60	MEL-HO	U-937	MOLT-3	SK-MEL-1
27a	35.2±7.5	26.8±2.1	44.9±4.4	23.5±9.9	40.7±10.2
27b	12.4±2.2	34.2±7.9	10.9±2.4	7.4±1.1	28.2±4.8
27c	46.6±9.8	71.1±19.2	38.7±8.5	12.6±5.8	>100
27d	5.8±2.2	11.9±3.4	4.1±1.6	3.6±0.8	19.3±2.4
27e	6.3±0.9	11.6±2.2	5.9±1.5	6.4±3.0	31.2±3.1
27f	>100	>100	>100	>100	>100
28a	0.3±0.1	2.0±0.1	0.2±0.1	0.6±0.1	12.5±1.5
28b	0.5±0.2	11.8±3.8	0.9±0.2	1.3±0.1	1.2±0.6
28c	23.1±7.5	28.2±2.7	21.7±12.3	11.8±6.7	30.3±7.9
28d	3.6±1.3	6.2±1.6	5.0±1.6	2.8±0.5	17.8±0.4
28e	26.1±4.9	>100	4.2±1.5	23.1±8.6	>100
28f	7.8±1.8	>100	7.1±0.6	5.8±1.2	>100

In 2022, Vilkova et al. created new acridinechalcone hybrids (29a-g & 30a-f) & tested their anti-cancer activity. Derivative 30b demonstrated sensitivity of estrogen & exhibited the significant cytotoxic effect for triple-negative breast-cancer cell lines (MDA-MB-231 & MCF7 with IC_{50} = 8.4±0.04 & 7.7±0.11 µM, respectively). Flow cytometry examination showed that compound (30e) induced G2/M cell-cycle arrest & elevate number of cells with sub G0/G1 content therefore indicating apoptosis. The strong binding affinity of the compound for bovine serum albumin indicates rapid transit through the bloodstream. The compound (30e) appears promising for further advancement as an anticancer medication targeting breast cancer [68].



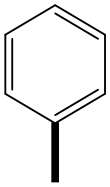
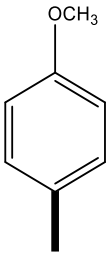
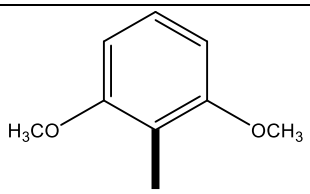
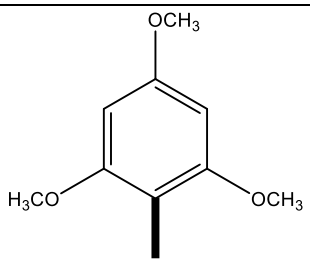
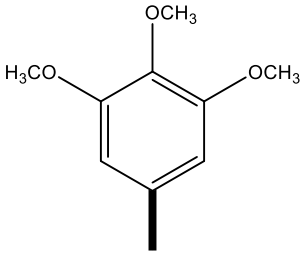
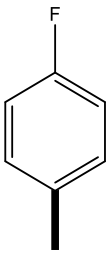
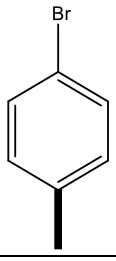
29a-g

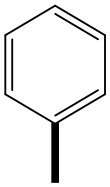
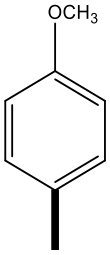
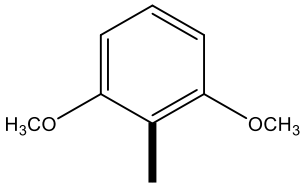
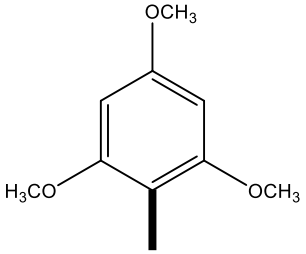
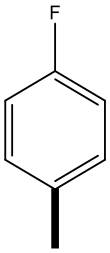
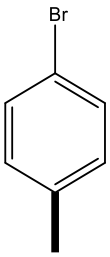


30a-f

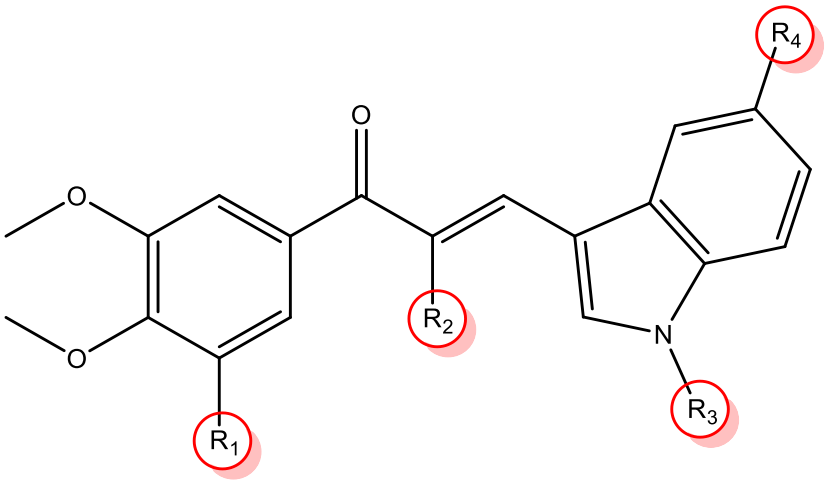
Figure-36: Structure of Chalcone derivative synthesized by Vilkova et al

Table-25: Structural modifications and IC_{50} values of synthesized derivative 29

Compound Name	R	IC_{50} values (µM)				
		HeLa	A-549	MDA-MB-231	HCT116	MCF-7
29a		>100	>100	>100	>100	>100
29b		>100	>100	>100	>100	>100
29c		24.43±3.7	10.67±4.23	10.88±1.9	4.13±0.35	16.38±6.2
29d		79.22±6.86	>100	78.55±12.33	>100	83.21±10.33
29e		>100	>100	92.18±16.64	>100	90.56±11.84
29f		84.25±16.56	82.44±19.56	65.55±17.64	>100	59.52±14.53
29g		-	-	-	-	-

30a		32.0±1.23	>100	33.1±2.34	6.23±0.88	33.5±3.35
30b		22.64±3.67	35.56±3.283	>100	5.28±1.01	29.45±2.58
30c		70.55±7.23	>100	>100	35.88±0.87	>100
30d		-	-	-	-	-
30e		30.7±0.11	35.26±6.45	8.4±0.05	36.0±0.2	7.7±0.1
30f		36.21±2.36	>100	83.0±11.98	29.34±2.56	50.34±6.18

In 2022, Yan et al. observed that acquired resistance diminishes the efficacy of Microtubule Targeted Agent (MTA), which have been commonly used as anticancer medications in clinical settings. Thioredoxin Reductases (TrxR) have been observed as the significant target due to their overexpression property in tumor(s), which is associated by the heightened risk of cancer recurrence & resistance of drug. Multi-Target-Directed-Ligands provides another method for combined therapies, employing one molecule to pose activity on various targets. The authors altered MTA compounds to maintain their ability to inhibit tubulin polymerization while also integrating TrxR inhibitory action through selenium-containing structures, informed by previously established structure-activity relationships. Synthesised hybrids (31a-p) demonstrated enhanced antiproliferative activity for several cancer cell lines. Derivative 31o is being investigated as significant medicinal agent for treatment of cancer in the MHCC-97H (IC_{50} = 0.006±0.001 μM [69].



31a-p

Figure-27: Structure of Chalcone derivative synthesized by Yan et al

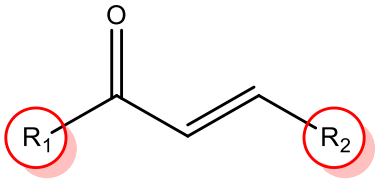
Table-26: Structural modifications of synthesized derivative 31

Compound Name	R_1	R_2	R_3	R_4
31a	NO_2	H	H	H
31b	NO_2	H	CH_3	H
31c	NO_2	H	H	OCH_3
31d	NO_2	H	CH_3	OCH_3
31e	NH_2	H	H	H
31f	NH_2	H	CH_3	H
31g	NH_2	H	H	OCH_3
31h	NH_2	H	CH_3	OCH_3
31i	SCH_3	H	H	H
31j	SCH_3	H	CH_3	H
31k	SCH_3	H	H	OCH_3
31l	SCH_3	H	CH_3	OCH_3
31m	$SeCH_3$	H	H	H
31n	$SeCH_3$	H	CH_3	H
31o	$SeCH_3$	H	H	OCH_3
31p	$SeCH_3$	H	CH_3	OCH_3

Table-27: IC_{50} values of the synthesized derivative 31

Compound Name	IC_{50} values (μM)					
	HeLa	A2780	MHCC-97H	A-549	HCT-8	MCF7
31a	1.35±0.16	1.28±0.08	0.83±0.08	1.51±0.23	1.39±0.21	1.29±0.670
31b	1.96±0.17	1.89±0.11	0.85±0.06	1.06±0.11	1.66±0.32	1.77±0.151
31c	0.850±0.022	0.742±0.024	0.289±0.017	0.331±0.025	0.982±0.032	0.662±0.022
31d	0.951±0.033	0.952±0.014	0.562±0.022	1.02±0.17	0.753±0.041	1.52±0.350
31e	0.529±0.015	0.351±0.014	0.263±0.016	0.342±0.012	0.577±0.021	0.595±0.034
31f	0.668±0.023	0.441±0.028	0.289±0.368	0.498±0.018	0.605±0.022	0.631±0.017
31g	0.155±0.023	0.204±0.017	0.186±0.017	0.193±0.025	0.368±0.018	0.249±0.015
31h	0.356±0.015	0.153±0.024	0.198±0.022	0.106±0.032	0.455±0.015	0.505±0.008
31i	0.159±0.015	0.169±0.012	0.131±0.006	0.152±0.012	0.167±0.014	0.186±0.023
31j	0.105±0.027	0.193±0.012	0.150±0.012	0.188±0.011	0.210±0.016	0.102±0.010
31k	0.131±0.007	0.139±0.004	0.112±0.006	0.115±0.003	0.138±0.003	0.101±0.017
31l	0.167±0.018	0.145±0.018	0.122±0.005	0.156±0.012	0.157±0.008	0.166±0.004
31m	0.034±0.005	0.025±0.008	0.018±0.003	0.012±0.007	0.032±0.003	0.059±0.010
31n	0.063±0.014	0.035±0.004	0.026±0.004	0.018±0.013	0.048±0.005	0.077±0.012
31o	0.021±0.004	0.018±0.004	0.006±0.001	0.008±0.003	0.029±0.012	0.035±0.002
31p	0.032±0.015	0.026±0.010	0.015±0.005	0.015±0.002	0.025±0.001	0.044±0.005

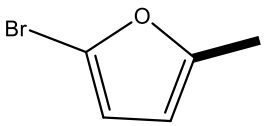
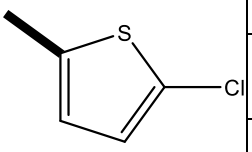
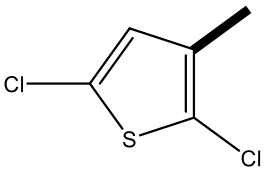
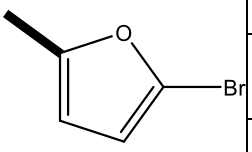
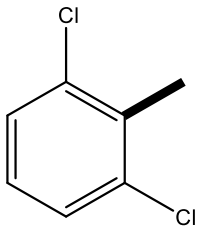
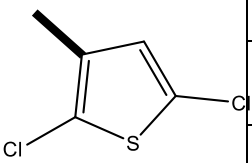
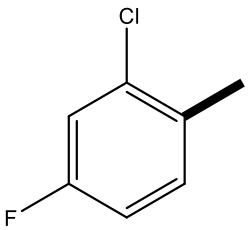
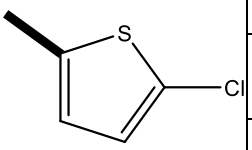
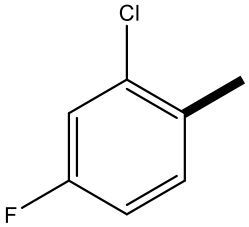
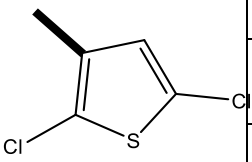
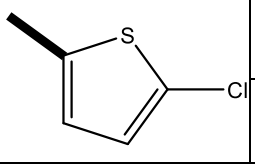
In 2022, Alidmat et al., analysed the cytotoxic properties of new synthesized derivatives (32a-k) on MCF7 & MD-MB-231 and also on normal breast cells. Compounds 32e and 32h exhibited notable cytotoxicity against MCF7 (7.79±0.80 μM & 7.24±2.11 μM, respectively) & MDA-MB-231 (5.27±0.97 μM & 21.58±1.51 μM, respectively) [70].

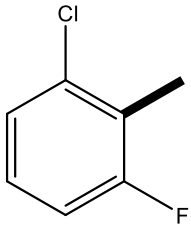
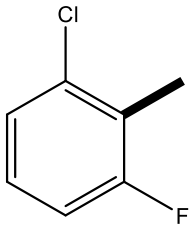
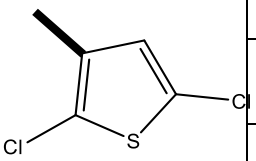
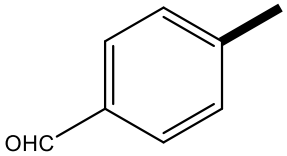
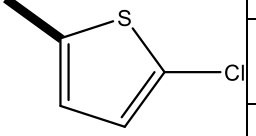
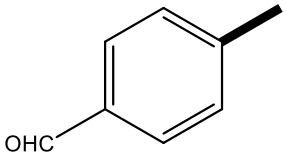
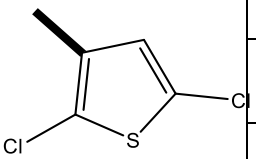
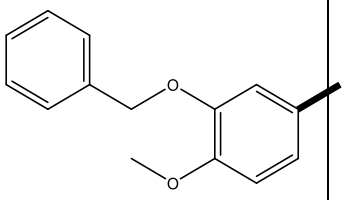
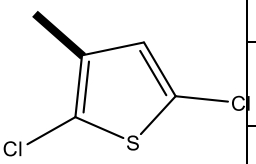
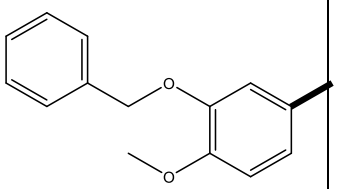
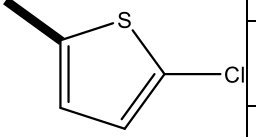


32a-k

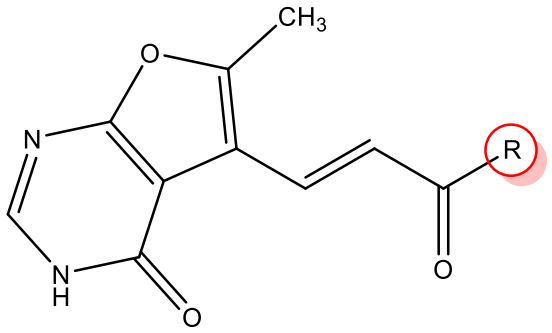
Figure-28: Structure of Chalcone derivative synthesized by Alidmat et al

Table-28: Structural modifications with IC_{50} values of synthesized derivative 32

Compound Name	R_1	R_2	Duration (Day)	IC_{50} values (µM)		
				MDA-MB-231	MCF-7	MCF-10A
32a			1	58.89±1.36	100±0.01	100±0.01
			2	59.12±1.41	38.1±2.97	100±0.01
			3	60.03±0.40	39.57±2.87	100±0.01
32b			1	50.70±0.58	47.19±2.75	100±0.01
			2	57.32±0.38	50.91±1.36	100±0.01
			3	62.15±1.64	64.6±2.61	100±0.01
32c			1	33.66±1.94	83.24±3.83	79.0±6.35
			2	40.44±1.08	20.27±0.54	44.69±1.80
			3	42.33±0.56	21.24±1.11	44.0±1.16
32d			1	66.12±3.04	100±0.01	100±0.01
			2	44.68±1.03	26.36±2.15	100±0.01
			3	43.87±5.49	27.90±1.47	100±0.01
32e			1	6.15±1.24	34.55±3.85	44.03±7.32
			2	6.26±0.08	7.24±0.33	36.07±2.08
			3	5.27±0.98	7.79±0.81	30.7±1.77
32f			1	42.68±1.68	60.35±0.16	74.81±4.87
			2	43.34±1.52	59.35±1.57	71.36±1.88

			3	50.69±5.22	54.21±3.77	65.58±1.76
32g			1	34.87±8.67	61.25±3.21	100±0.01
			2	35.72±4.96	53.71±1.24	100±0.01
			3	42.95±5.97	54.59±3.14	100±0.01
32h			1	18.22±1.13	8.16±0.87	87.16±4.01
			2	21.89±1.01	7.14±0.19	100±0.01
			3	21.58±1.50	7.24±2.10	100±0.01
32i			1	100±0.01	100±0.01	100±0.01
			2	100±0.01	100±0.01	100±0.01
			3	100±0.01	100±0.01	100±0.01
32j			1	100±0.01	100±0.01	100±0.01
			2	100±0.01	100±0.01	100±0.01
			3	100±0.01	100±0.01	100±0.01
32k			1	100±0.01	100±0.01	100±0.01
			2	100±0.01	100±0.01	100±0.01
			3	100±0.01	100±0.01	100±0.01

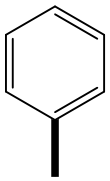
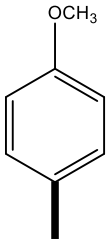
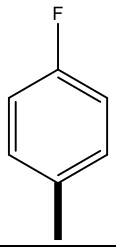
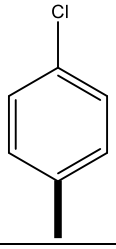
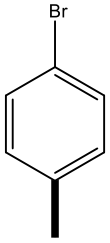
In 2022, Mansour et al., discovered various chalcone-backboned hybrids (33a-k) exhibiting significant anti-cancer characteristics. Two halogen-substituted chalcones, 33d and 33e, exhibited notable antiproliferative effects for the NCI-59 cell line, as compared to other synthesized hybrids. The hybrids (33d & 33e) possess average GI_{50} values = 2.40 & 1.22 µM, respectively. Both hybrids exhibited potential cytotoxicity for the drug resistant MCF7, with IC_{50} = 1.20±0.20 and 1.90±0.31 µM, surpassing doxorubicin at 3. 30 ± 0. 18 µM. Compound (33e) showed similar efficacy to doxorubicin in vivo and merits further exploration [71].

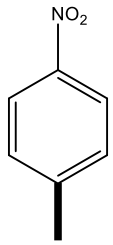
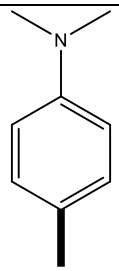
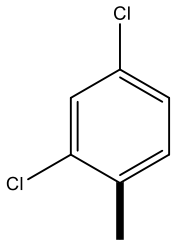
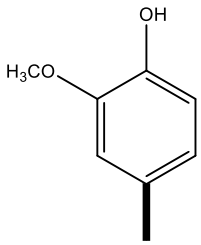
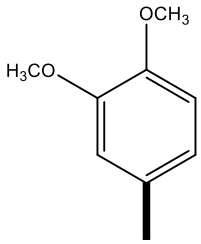
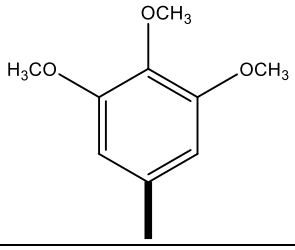


33a-k

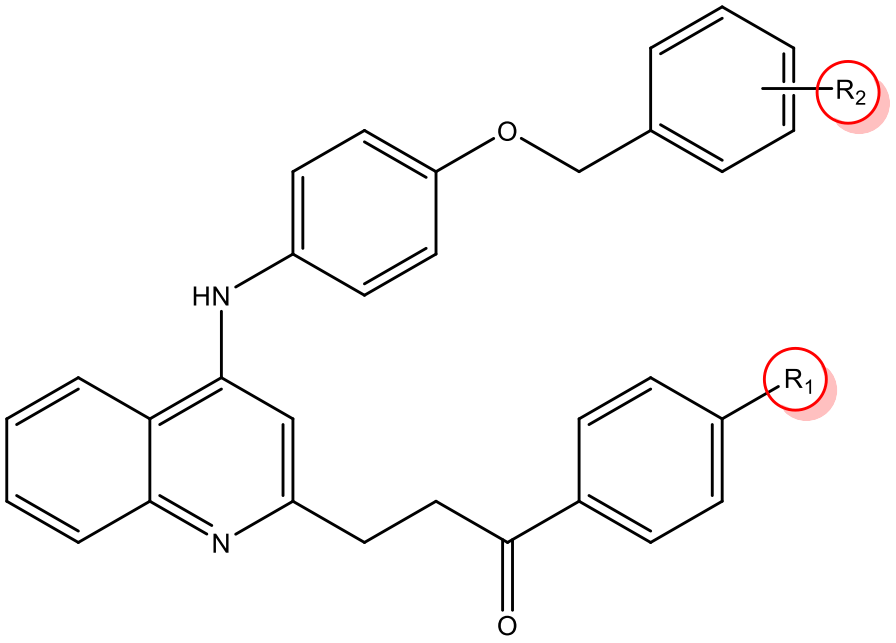
Figure-29: Structure of Chalcone derivative synthesized by Mansour et al

Table-29: Structural modifications of synthesized derivative 33

Compound Name	R
33a	
33b	
33c	
33d	
33e	

33f	
33g	
33h	
33i	
33j	
33k	

In 2023, Yang et al. investigated the antiproliferative effects of 4-anilinoquinolinyl chalcone derivatives (34a-p) on the Huh-7 & MDA-MB-231, MRC5 (normal lung cells). MRC5 (lung cells) demonstrated minimal cyto-toxicity. Derivative 34a exhibited greatest cyto-toxicity for breast cancer & the least in normal-cells (IC_{50}: 1. 47 ± 0. 07, 0. 11 ± 0. 07, and >20 μM, respectively). Compound 34p triggers ROS-dependent caspase 3/7 & decreases ATP levels in MDA-MB-231 [72].



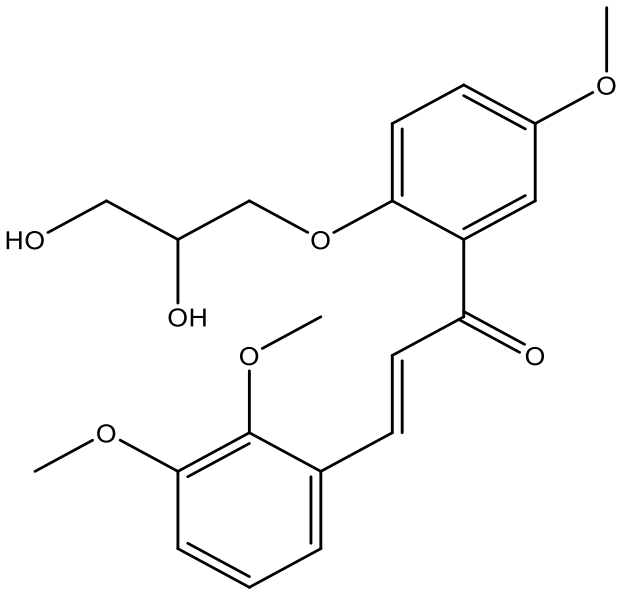
34a-p

Figure-30: Structure of Chalcone derivative synthesized by Yang et al

Table-30: Structural modifications of synthesized derivative 34

Compound Name	R_1	R_2	Compound Name	R_1	R_2
34a	OCH_3	H	34i	F	H
34b	OCH_3	2-Cl	34j	F	2-Cl
34c	OCH_3	2-F	34k	F	2-F
34d	OCH_3	3-Cl	34l	F	3-Cl
34e	OCH_3	3-F	34m	F	3-F
34f	OCH_3	3- OCH_3	34n	F	3- OCH_3
34g	OCH_3	4-Cl	34o	F	4-Cl
34h	OCH_3	4-F	34p	F	4-F

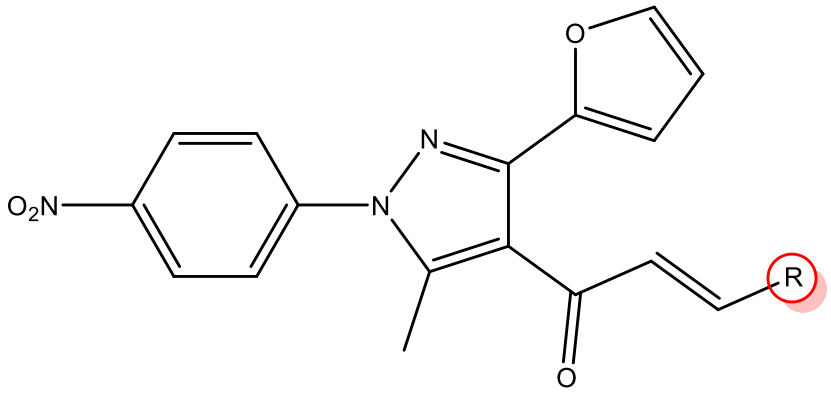
In 2023, Baek et al. created a chalcone derivative (35) that incorporates a hydroxyl group and investigated its potential as a cancer therapy by triggering apoptosis in BXPC-3 cancer cells (IC_{50} = 32. 1 μM) [82].



35

Figure-31: Structure of Chalcone derivative synthesized by Baek et al

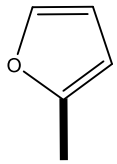
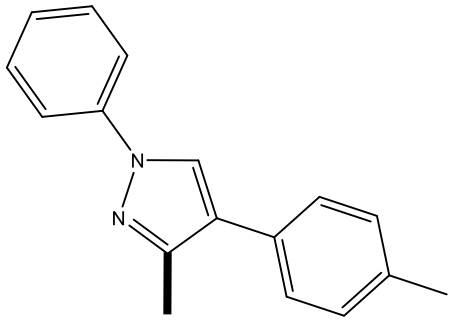
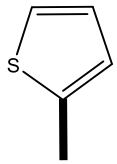
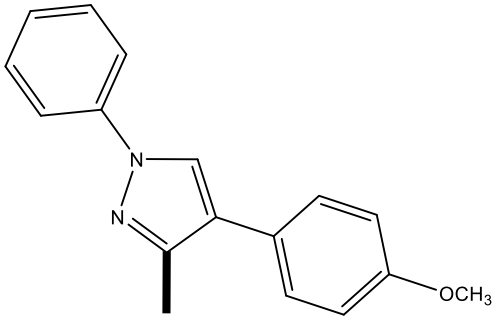
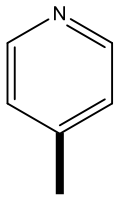
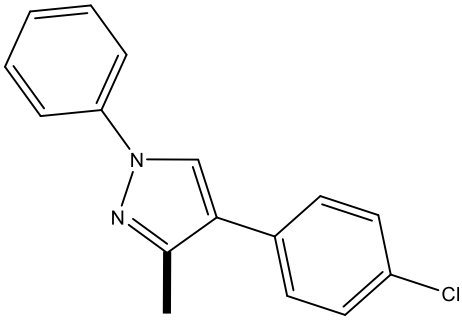
In 2023, Mohamed et al. identified novel chalcone hybrids (36a-h) that exhibit promising potential for lung-cancer treatment. Authenticity of this were verified through spectral methods. The anti-cancer properties of chalcone compounds 36a-h were assessed by MTT assay on A-549 & Wi38, yielding IC_{50} values of 42.701, 20.050, 13.860, 76.521, 217.010, 237.840, 251.491, and 211.301 µg/ml correspondingly, alongside IC_{50} = 68.0, 108.410, 18.20, 261.321, 295.590, 296.241, 379.220, & 224.360. Molecular docking on 36b and 36c, demonstrated remarkable potency. Furthermore, advanced molecular technique was employed in order to examine the effect & activity of these 36b & 36c on A-549 apoptosis. These findings hold considerable promise for enhancing lung cancer treatment [73].

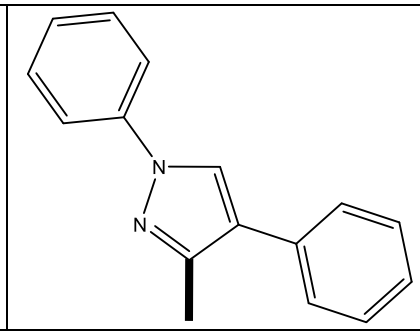
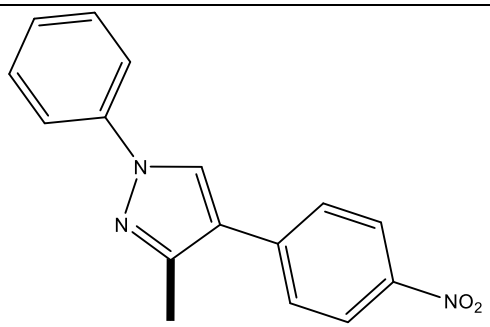


36a-h

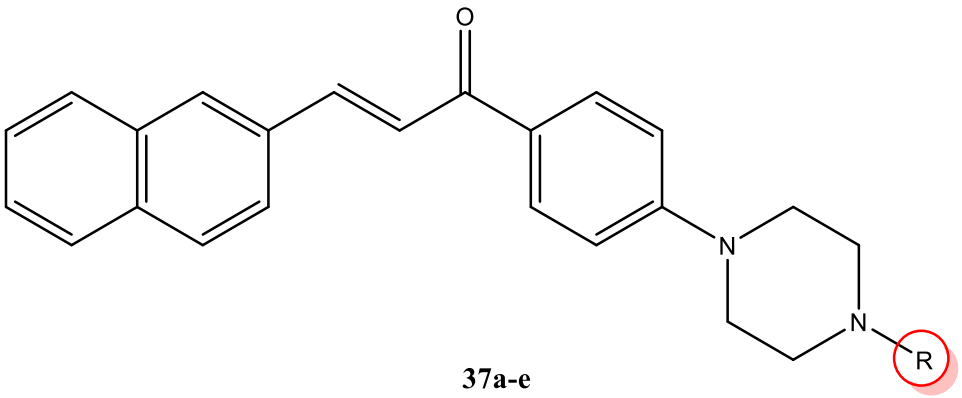
Figure-32: Structure of Chalcone derivative synthesized by Mohamed et al

Table-31: Structural modifications of synthesized derivative 36

Compound Name	R	Compound Name	R
36a		36e	
36b		36f	
36c		36g	

36d		36h	

In 2023, Osmaniye et al. discovered novel naphthalenechalcone derivatives (37a-e) that show anticancer effects. Compound 37e exhibited promising activity for the A-549, presenting IC_{50} = 7.834±0.597µM [74].



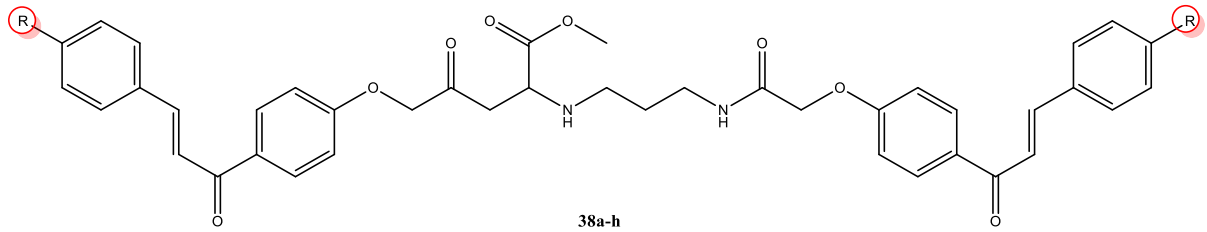
37a-e

Figure-33: Structure of Chalcone derivative synthesized by Osmaniye et al

Table-32: Structural modifications of synthesized derivative 37

Compound Name	R
37a	CH_3
37b	C_2H_5
37c	$CH(CH_3)_2$
37d	$CH_2 = CH_2 – CH_3$
37e	-O-CH_2-CH_3

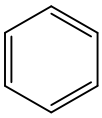
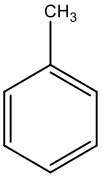
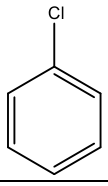
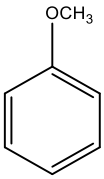
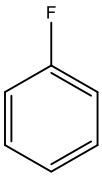
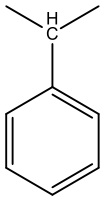
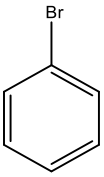
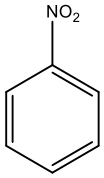
In 2023, Li et al., illustrated the anticancer properties of synthesized chalcone derivatives (38a-h). CCK-8 assay was employed to evaluate novel synthesized derivatives for gastric-cancer, which included TMK-1, MHCC-97H, HCT-116, and various hybrids (except 38d and 38f). Cell lines like MKN-45, AGS, IM95 & GES1, were tested for the derivatives. The findings indicated that the hybrid 38a exhibited the most potential on TMK1 & AGS (IC_{50} = 22.13µM & 22.28µM, respectively), comparable to standard drug 5-FU [75].



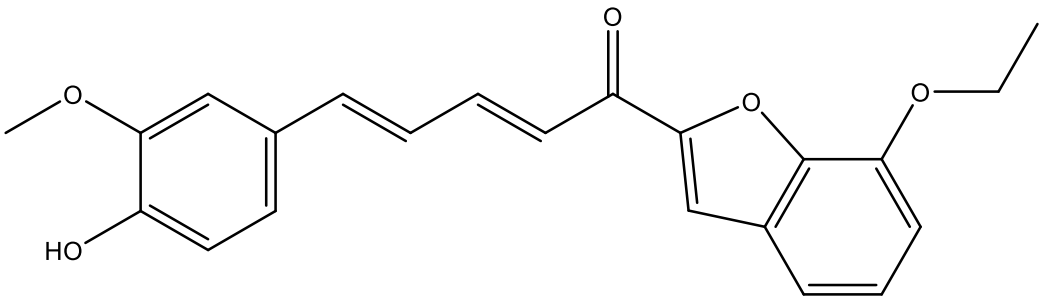
38a-h

Figure-34: Structure of Chalcone derivative synthesized by Li et al

Table-33: Structural modifications of synthesized derivative 38

Compound Name	R	Compound Name	R
38a		38e	
38b		38f	
38c		38g	
38d		38h	

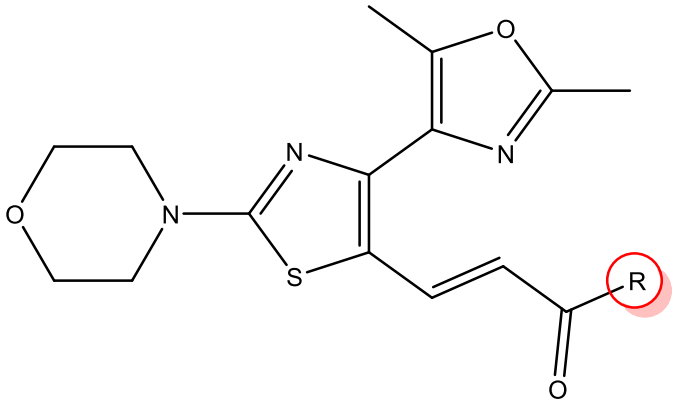
In 2023, Erturk et al. synthesized chalcone derivative compounds using the Claisen-Schmidt reaction to produce chalcone derivative (39) from the curcumin structure in human lung (A549, H1299) and colon cancer (HCT116, HT29) cells. The impact of the Chalcone compound on cell viability was evaluated via the SRB test. Moreover, combination experiments with 5-FU, a chemotherapeutic agent, were performed. The mode of cell death was evaluated through fluorescent imaging utilizing Hoechst 33342, Annexin-V-FITC, and Propidium iodide (PI) triple staining. The IC_{50} values for the Chalcone compound were 2. 85, 1. 46, 0. 59, and 0. 35 μM for A549, H1299, HCT116, and HT29, respectively. Fluorescent imaging exhibited pycnotic nuclei and chromatin condensation in the cells, along with positive Annexin-V-FITC staining (green). The findings indicated that the newly synthesized Chalcone derivative compound possesses a notable cytotoxic effect on cancer cells and promotes apoptosis [76].



39

Figure-35: Structure of Chalcone derivative synthesized by Erturk et al

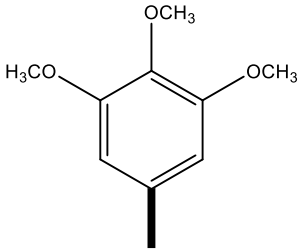
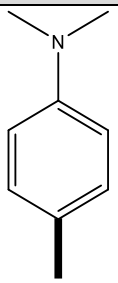
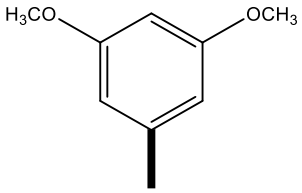
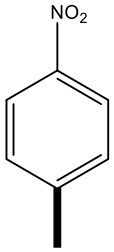
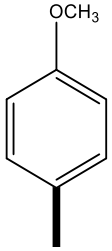
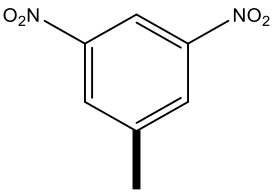
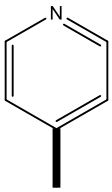
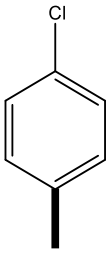
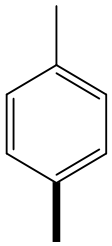
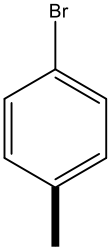
In 2023, Rachala et al. presented a library of chalcone-based hybrids (40a-j). The in-vitro anti-cancer properties of newly identified derivatives were analysed different cancer cell lines by the MTT assay. The cancer cell lines include A-549, PC-3, MCF7 & DU-145. Most compounds analyzed exhibited excellent to moderate activity, including etoposide. Compounds 40a-f exhibited the highest activity among all tested compounds. A significant part of this research has focused on 40d, which displayed outstanding anti-cancer characteristics (IC50: 1. 02 ± 0. 026; 0. 01 ± 0. 0062; 0. 05 ± 0. 0043; 1. 10 ± 0. 93 μM) [78].



40a-j

Figure-36: Structure of Chalcone derivative synthesized by Rachala et al

Table-34: Structural modifications of synthesized derivative 40

Compound Name	R	Compound Name	R
40a		40f	
40b		40g	
40c		40h	
40d		40i	
40e		40j	

Conclusion

Heterocyclic chalcone derivatives are a diverse and versatile class of chemical substances that hold great promise in cancer therapy. Their simple and flexible structure allows for significant modifications to improve biological activity and specificity against cancer types. These compounds have multiple effects, including induction of apoptosis, inhibition of angiogenesis, disruption of the cell cycle, and modulation of key signaling pathways. The reviewed literature demonstrates the potential of chalcone derivatives to overcome drug resistance while maintaining cancer cell selectivity, making them attractive candidates for next generation cancer therapeutic approaches. The development of chalcone hybrids and structural modifications has increased their therapeutic potential and created new avenues for drug design. Although many compounds have shown potent anticancer activities in in vitro and in vivo studies, further studies are needed to translate these results into practical applications. Future studies should focus on enhancing pharmacokinetic properties, minimizing off-target effects, and exploring synergies with existing drugs. By addressing these issues, chalcone derivatives could revolutionize cancer treatment, offering safer and more effective alternatives to traditional chemotherapy.

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Authors Contributions

SNA: Manuscript writing
MAK: Drawing Schemes and Data Collection
ARK: Supervision and drafting the manuscript
FH: Supervision and proof-reading

Competing Interest

The authors declare no competing interests.

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