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Exploring The Recent Advances In Anti-Cancer Potency Of Chalcone Containing Hybrids

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Abstract
Chalcones due to their easy and simple synthesis route and broad spectrum of biological activities, emerged as the outstanding candidate for medicinal and pharmaceutical chemistry. In addition to numerous other biological activities, anticancer activity of the chalcone-based compounds has been in particular focused, and is being predominantly mediated through apoptosis induction, cell cycle arrest, angiogenesis & metastasis inhibition as well as by modulating key signalling pathways which include NF-κB, PI3K/Akt/mTOR, MAPK and STAT3. An outstanding chalcone-based hybrid development has been witnessed in the past decade, explicitly aimed at different human cancer cell lines for potency and selectivity. The bioactivities were remarkably increased when introducing heterocycles, halogen substituents and fusing to other drug-like moieties into the chalcone scaffold. This not only results in enhanced cytotoxicity against cancer cells, but also lower toxicity on benign cell and opens many new drug candidates. There are already a number of chalcone derivatives such as sofalcone and metochalcone, which have been administered clinically for several years. This review provides a detailed account of the developments, from inception to date, in the synthesis and mechanistic study as well as in-vitro assays of chalcone-based hybrids specifically for their potential role as anticancer agents.
Keywords: *Chalcones; apoptosis; angiogenesis; metastasis inhibition; cytotoxicity; drug development; anticancer agents.*

1. INTRODUCTION

The growth and spread of malignant tumors, which are defined as neoplasm which have an unrestricted cell multiplication that outpaces normal angiogenesis, cell-cell and cell-matrix interactions, as well as programmed cell death and apoptosis, is regarded as one of the most dreadful aspects of oncology and health care globally [1]. Irrespective of the recent advancements in chemotherapy, radiology and surgery, cancer remains an unprecedented problem worldwide. Due to this the modern upcoming research primarily focuses on developing a drug which possess less toxicity, minimal or no side effects and targeted delivery. Some of the naturally derived drugs which possess anti-cancer potential are paclitaxel [2], vincristine [3] and camptothecin [4]. Due to the simple structure and potential pharmacological spectrum and previously reported work, chalcone gains attention in the recent research, especially in the field of oncological drug development [5-7].

Chalcones are the α,β-unsaturated carbonyl compounds in which two aromatic rings are present (commonly represented as Ring A and Ring B). These rings are connected via a 3-carbon aliphatic framework containing a carbonyl and a akene group which also provides conjugation for stability [8]. Due to this, chalcones undergo Michael addition which leads to formation of covalent bonds with nucleophilic sites of proteins, enzymes and DNA [9]. As one of the main factors that lead to the anticancer props of chalcones, they indicate a vast number of other biological activities like antioxidant [10], [11], anti-inflammatory [12], [13], [14], antimicrobial [15], [16], antiviral [17], [18], anti-obesity [19], antidiabetic [20] and neuroprotection [21], [22].

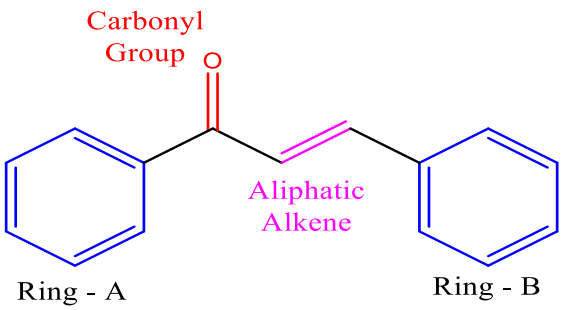

Figure-1: General Structure of Chalcone

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Medium lipophilicity for chalcones from the viewpoint of their physicochemical properties basically gives them the ability to penetrate the cell membrane with ease and to bind with the intracellular targets [23]. These are compounds that are somewhat soluble in organic solvents, but their water solubility is limited. Some of the structural changes that are performed by the insertion of hydroxyl, methoxy, halogen and amino groups in the aromatic rings may provide additional improvements in terms of solubility, stability and bioavailability. [24]. Besides changing the physical properties of the compound, the role of the substituents in the electronic and steric aspects of the molecule to reveal the chemical reactivity and pharmacological potency of the molecule is also crucial.

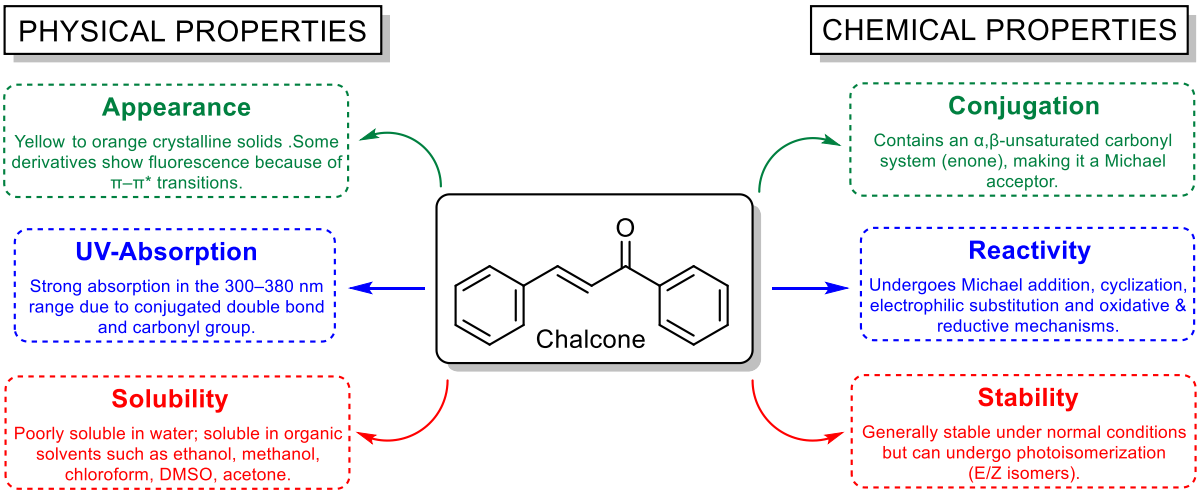


Figure-2: Some physical and chemical properties of chalcones

Chalcones exhibit a broad-spectrum of medicinal properties whereby their anticancer potential is the most remarkable. Their antioxidative feature is mainly due to their activity of neutralizing radicals and inhibiting lipid peroxidation [25]. The anti-inflammatory property comes from their capability of blocking the enzymes cyclooxygenase and lipoxygenase and thus the secretion of inflammatory mediators is lowered [26]. The antimicrobial and antiviral properties of them are the consequence of the disruption of the membranes of microorganisms, the inhibition of enzymes and the interference with replication pathways [27]. Presently, the multiple-targeting nature of this single compound is considered as a brilliant asset in the field of cancer especially in drug-resistance area. Chalcones have been reported as quite safe, since the major part of the naturally occurring chalcones were found to be of low toxicity toward the normal cells but on the other hand, they exhibited a high cytotoxic activity against the cancer cells.

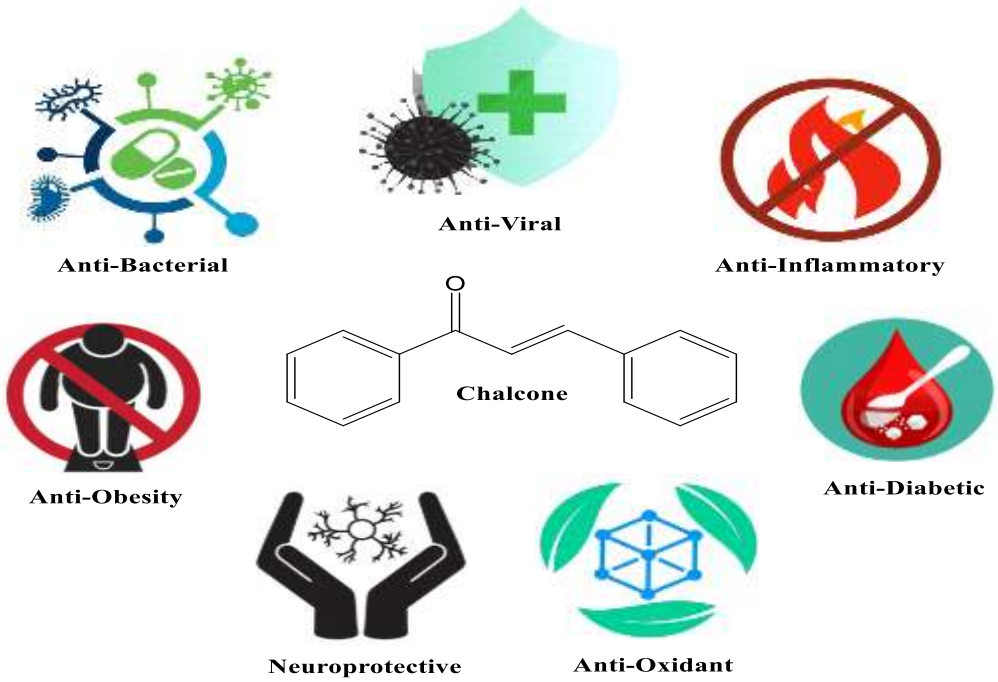


Figure-3: Some Biological Activities shown by Chalcones

The activity of chalcones in cancer has been linked to their different mechanism of actions as they are capable of initiating apoptosis [28] by activating caspase-3 and -9, overexpressing the apoptotic protein Bax and decreasing the levels of anti-apoptotic proteins Bcl-2 and Survivin. The majority of chalcones can empower the process of the cell cycle halt either at G0/G1 or at the G2/M phase via modulation of cyclins and cyclin-dependent kinases [29]. The α,β-unsaturated carbonyl group present in their structure is a Michael acceptor, which interacts with the nucleophilic sites of proteins, leading to the inhibition of main signalling pathways such as NF-κB, PI3K/Akt/mTOR, MAPK and STAT3 [30]. The inhibition of chalcones on angiogenesis is caused by the upregulation of vascular endothelial growth factor (VEGF) while their suppressive impact on metastasis is through the reduction of the activity of matrix metalloproteinases (MMP-2 and MMP-9) [31]. One of the additional features is that they can generate reactive oxygen species in cancer cells that result in oxidative stress, mitochondrial dysfunction, DNA damage, and finally apoptosis. In several experiments chalcones have demonstrated selectivity by influencing cancer cells to a greater extent than healthy ones and therefore they are regarded as having a high potential for being used as anticancer agents.

Some derivatives of chalcone have crossed the threshold of clinical applications and drug development. Phenotypic chalcones including butein, xantholum, licochalcone A and isoliquiritigenin have been recognized to display potent anticancer and chemo-preventive effects through their *in-vitro* studies [32]. Metochalcone, a synthetic chalcone, has been introduced as a choleretic agent. Sofalcone has been commercialized is a medicine for gastric ulcers and is also reported to have preventive effects on gastric cancer [33]. These examples demonstrate that chalcone-based scaffolds can become the sources of safe and effective anticancer drugs.

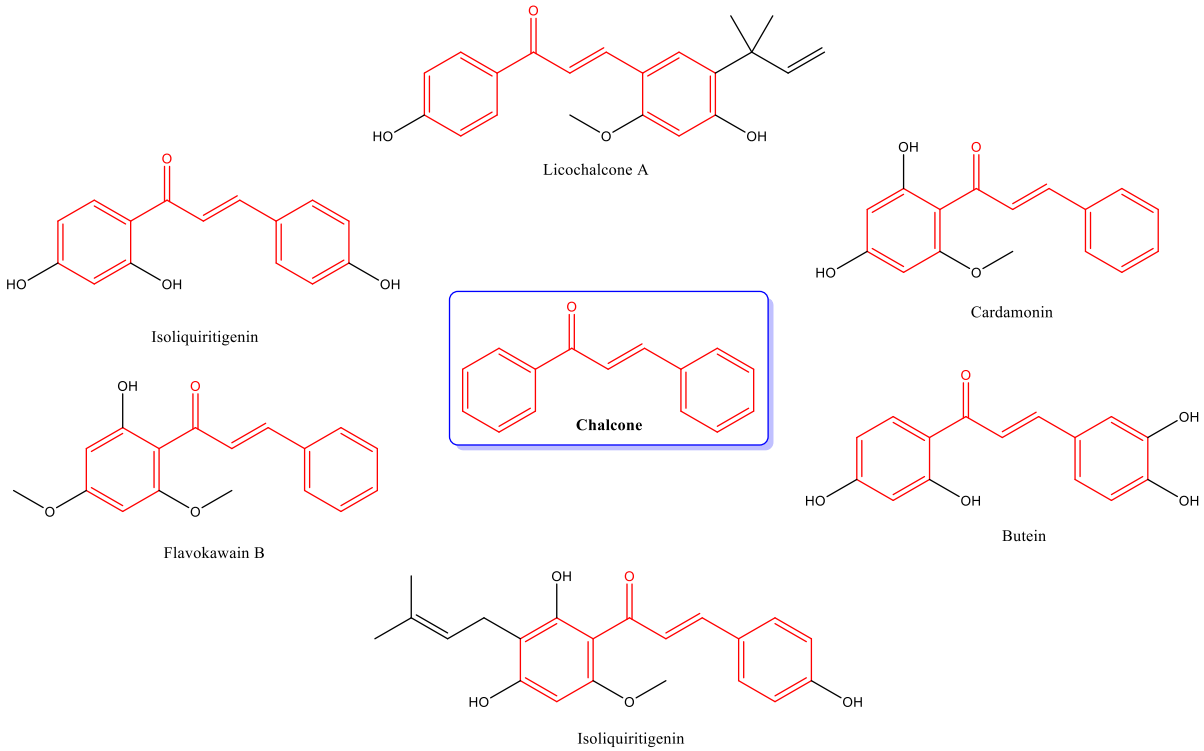
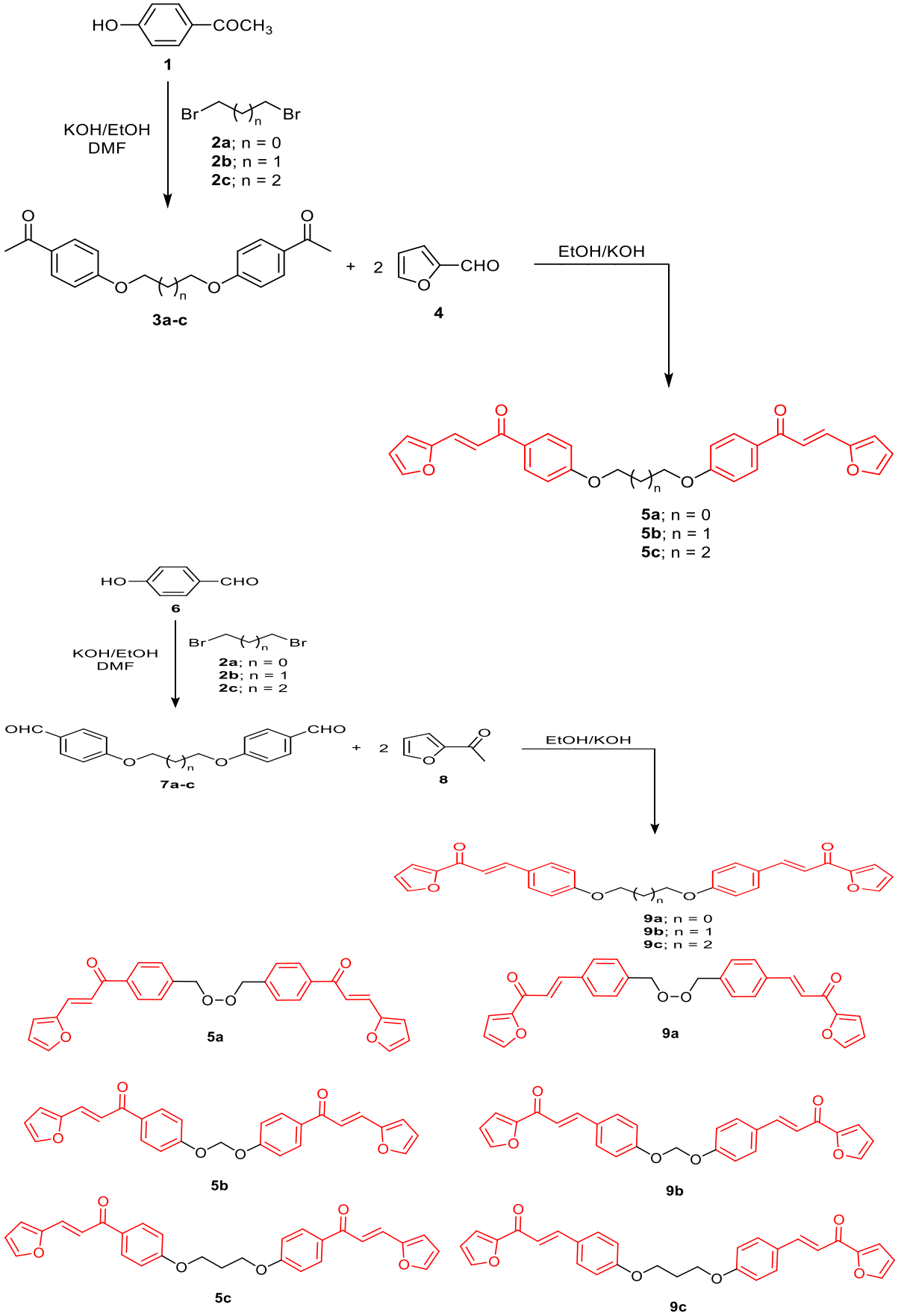


Figure-4: Some FDA approved drugs containing chalcone moiety

2. Anti-Cancer Evaluations

In 2021, Fathi et al., fabricated two series of new hybrids 5a-c & 9a-c by the Knoevenagel condensation reaction and tested them against the following cell lines: A-549, HCT116, HePG2, PC3, A431 and BJ1 at a concentration of 100μg/ml. All the compounds exhibited 100% anti-cancer potential on A-549 cells, while 9c showed moderate potency, which is greater than 50% against HCT116 cells. However, all the compounds exhibited 67-100% mortality against PC3 cells, while 9a-c compounds showed 100% activeness against A431 cells. On the other hand, compounds 9a and 9c had the highest potency against A549 and A431 cells with IC_{50} values of 24.9μg/ml (9a against A549) and 13.7μg/ml (9c against A549) and 26.1μg/ml (9a against A431) and 14.4μg/ml (9c against A431). Moreover, the selectivity index of compound 9c was higher than that of 9a; therefore, it is more active on PC3 cells with an IC_{50} ranging between 35.2μg/ml and 77.7μg/ml. Compound 9c outperformed other derivatives as the most potent

compound against PC3 cells but was less active than that against the A549 cells. These findings demonstrate that compounds 9a and 9c specifically target the A549 and A431 cell lines [34].



Scheme-1: Synthesis of chalcone derivatives 5a-c & 9a-c

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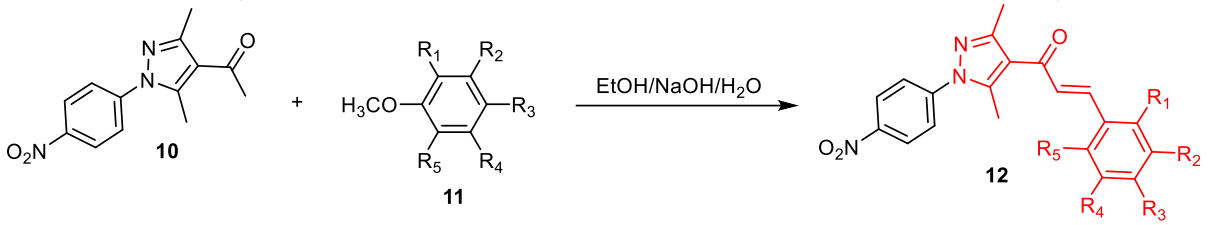
Table-1: Mortality percentage and IC_{50} (µg/ml) determination of chalcone derivatives 5a-c & 9a-c

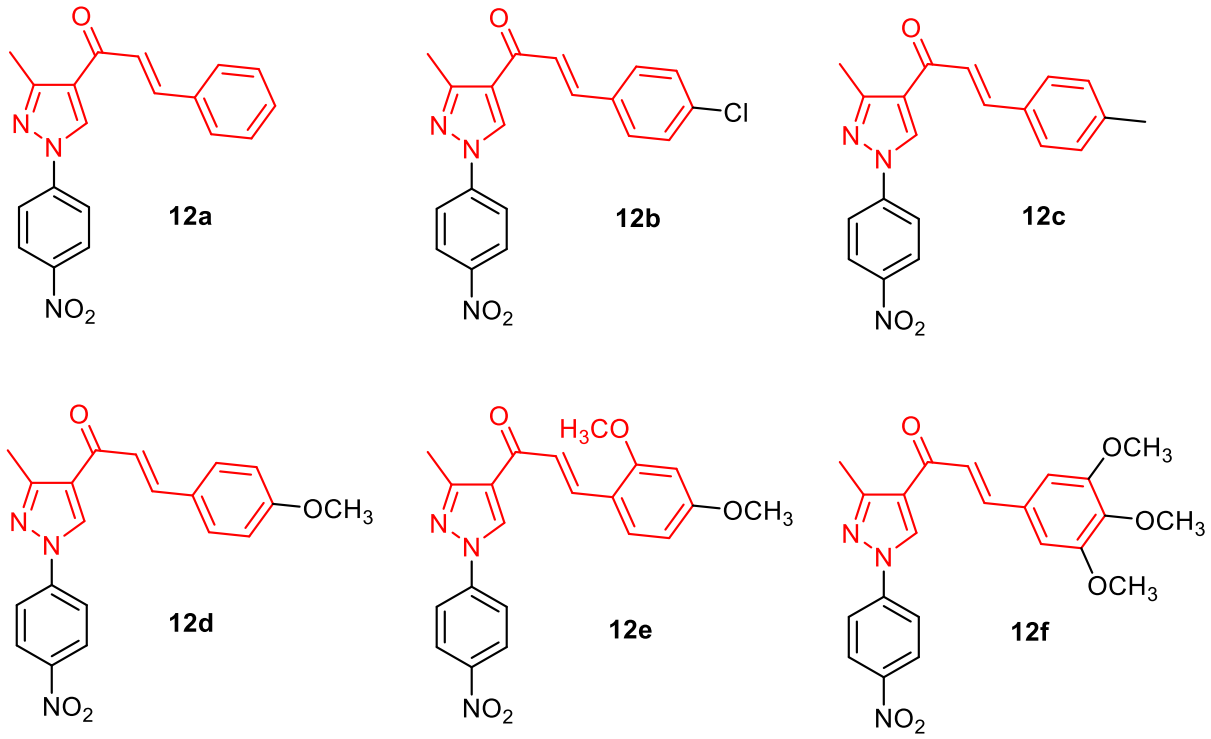
Compound	A549		HePG2		HCT116		PC3		A431		BJ1	
	M%	IC_{50}	M%	IC_{50}	M%	IC_{50}	M%	IC_{50}	M%	IC_{50}	M%	IC_{50}
5a	100	38.7	23.3	ND	ND	ND	100	38.4	100	29.3	38.2	ND
5b	100	ND	37.5	ND	13.6	ND	88.3	77.7	100	ND	-	ND
5c	100	18.0	27.2	ND	91.3	71.0	96.4	38.6	100	ND	20.5	ND
9a	100	24.9	23.3	ND	ND	ND	100	29.4	100	26.1	38.2	38.3
9b	100	44.7	37.5	ND	13.6	ND	88.3	60.3	100	ND	-	ND
9c	100	13.7	27.2	ND	91.3	35.0	96.4	35.2	100	14.4	20.5	41.4

M% = Mortality Percentage

In 2022, Kamel et al., synthesized a novel series of six pyrazolyl-chalcone derivatives (12a-f) via Claisen-Schmidth condensation reaction. The synthesized compounds were analysed for their anti-cancer potential by in-vitro evaluations against A549, MCF-7, HePG2 and BJ1 cell lines at a concentration of 100µg/cm^3. It was observed that compound 12c exhibited 100% mortality rate against A549 cells and an IC_{50} vale of 44.30µg/cm^3 while 84.2% mortality rate for HePG2 cells (IC_{50} value of 57.90µg/cm^3) [35].



	R_1	R_2	R_3	R_4	R_5
12a	H	H	H	H	H
12b	H	H	Cl	H	H
12c	H	H	CH_3	H	H
12d	H	H	OCH_3	H	H
12e	OCH_3	H	OCH_3	H	H
12f	H	OCH_3	OCH_3	OCH_3	H



Scheme-2: Synthesis of chalcone derivatives 12a-f

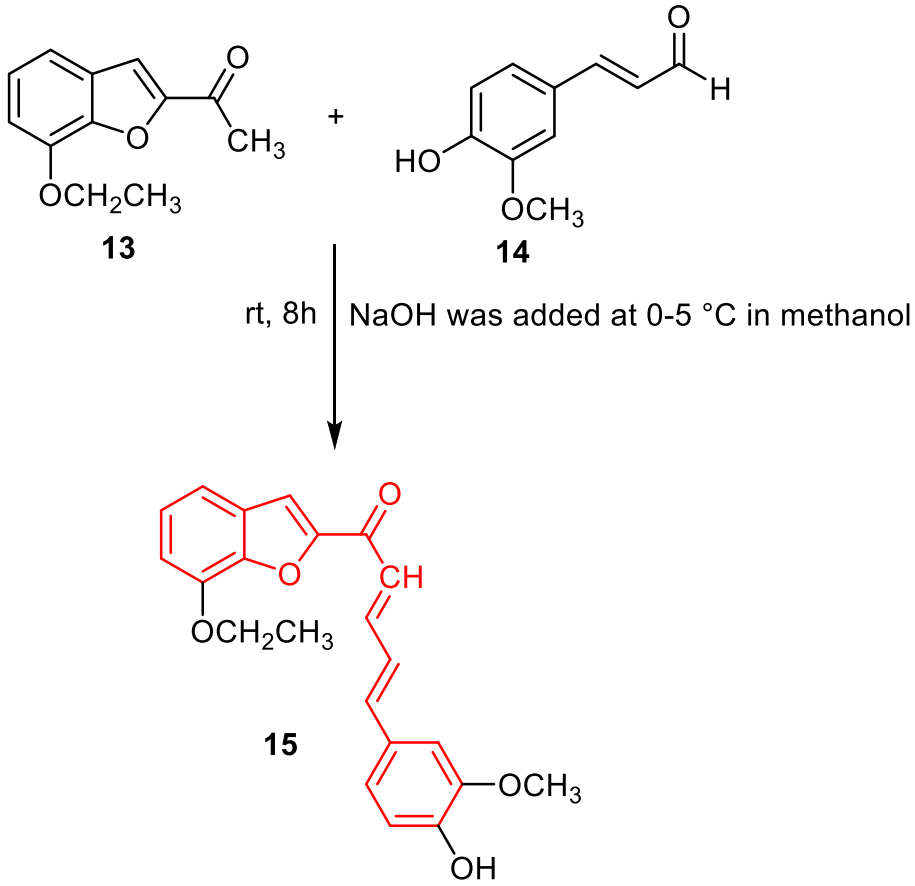
Table-2: IC_{50} (µg/cm^{-3}) calculations of the synthesized derivatives 12a-f

Compound	A549	MCF7	HePG2	BJ1

	M%	IC_{50}	M%	IC_{50}	M%	IC_{50}	M%	IC_{50}
12a	23.1	ND	1.7	ND	27.3	ND	-	ND
12b	21.4	ND	4.2	ND	4.6	ND	-	ND
12c	100	44.3	15.2	ND	84.2	57.9	32.3	62.2
12d	37.5	ND	12.4	ND	11.3	ND	-	ND
12e	23.5	ND	3.4	ND	29.5	ND	-	ND
12f	12.5	ND	2.2	ND	30.2	ND	-	ND

ND = Not Detected; M% = Mortality Percentage

In 2023, Erturk et al., created a novel curcumin-based chalcone compound (15) via Claisen-Schmidth condensation reaction. The synthesized compound was tested for its anti-cancer activity against multiple cells lines including A549, H1299 (Lung cancer), HCT116 and HT29 (Colon cancer). Cell viability of compound 15 was determined by SRB test and the mechanism of cell apoptosis was studied via fluorescent imaging by Annexin-V-FITC, Hoechst 33342 and Propidium Iodide (PI) triple staining. The IC50 values of the tested compound against multiple cell lines are as follows: 2.85µM (A549), 1.46µM (H1299), 0.59µM (HCt116) and 0.35µM (HT29). These findings resulted that the compound possess significant cytotoxicity on cancer cells resulting in cell apoptosis [36].



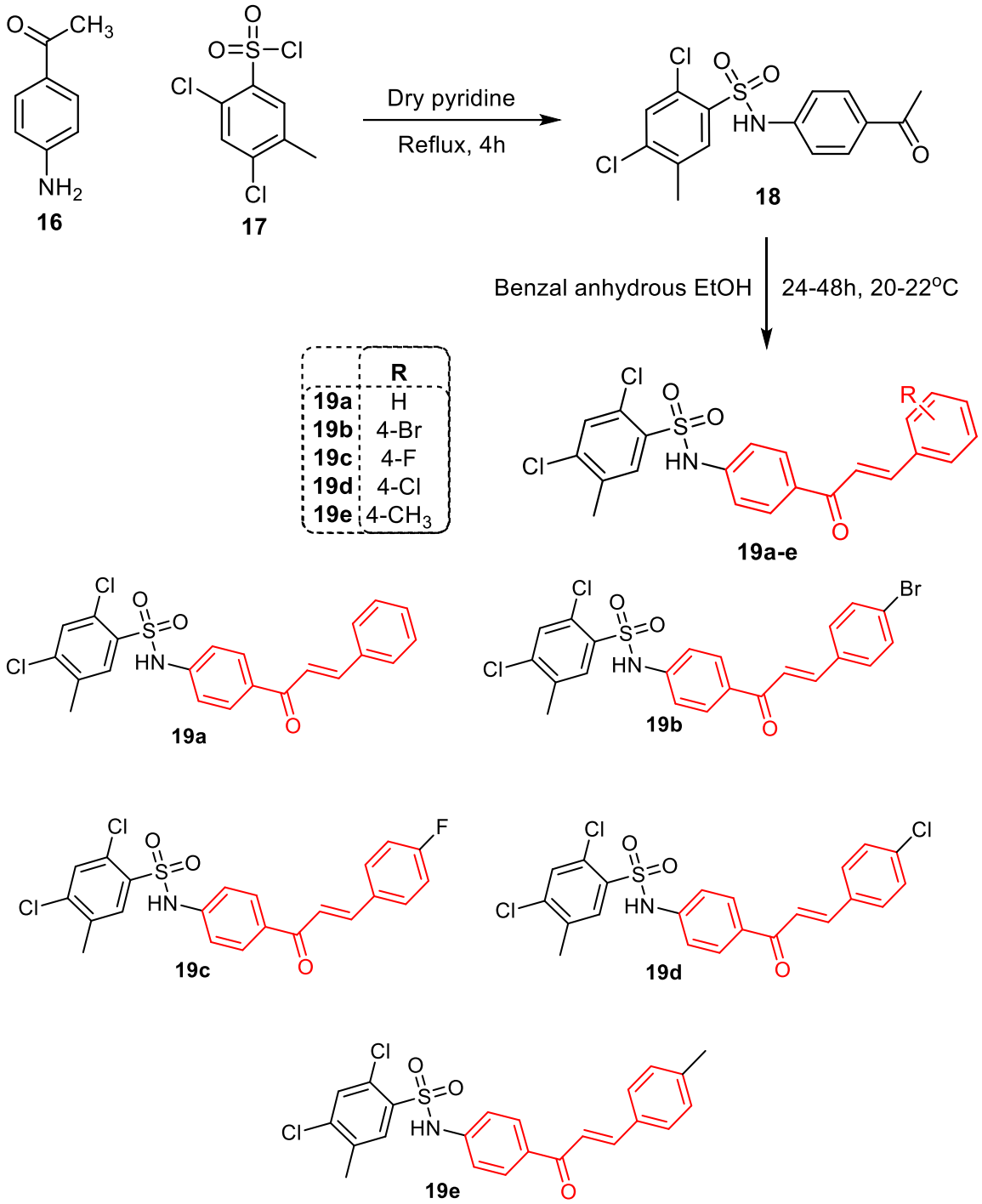
Scheme-3: Synthesis of chalcone derivative 15

Table-3: IC_{50} (µM) calculations of the synthesized derivatives 15

Compound	Cell Line	IC_{50} (µM)
15	A549	2.85
	H1299	1.46
	HCT116	0.59
	HT29	0.35

In 2023, Bułakowska et al., created a novel series of chalcone hybrids 19a-e via Claisen–Schmidt Condensation reaction. The synthesized compounds showed high potential for anti-cancer activity when tested against HeLa, HL-60 and AGS. Compounds 19b and 19d exhibited highest activity with IC_{50} values

of <1.000 and 1.570µg/mL for AGS and HL-60 cells respectively. For the HeLa cell line, these values were 5.670 ± 0.350 (19b) and 6.340 ± 0.040µg/mL (19d). However, compounds containing hydrogen, fluorine and methyl substituents in "R" are comparatively weaker (compounds 19a, 19c and 19e). No significant activity was observed by synthesized derivatives on the non-cancerous cell line (i.e. human neonatal fibroblasts) with IC_{50} values ranging from 25.59 to 32.15µg/mL [37].



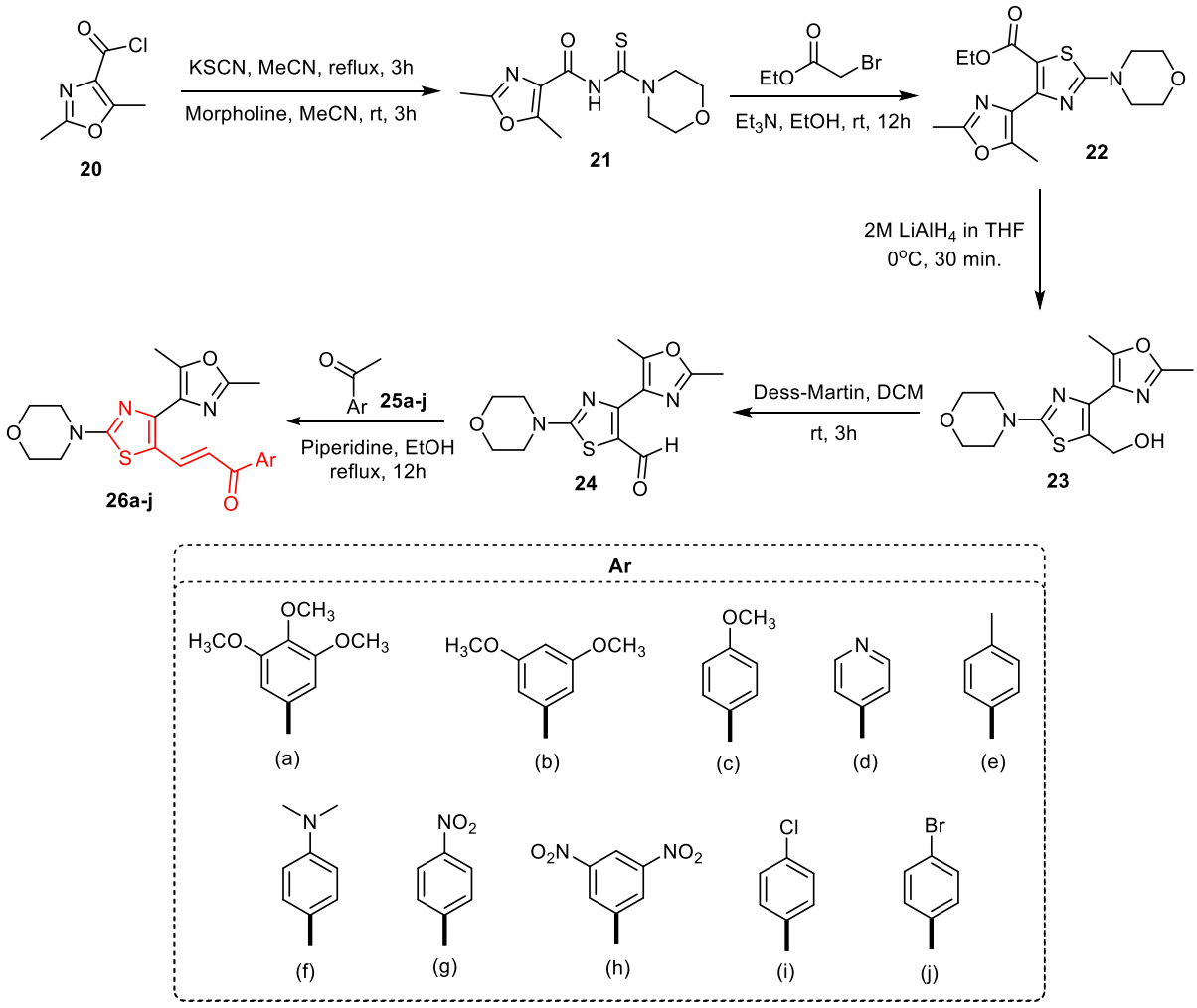
Scheme-4: Synthesis of chalcone derivative 19a-e

Table-4: IC_{50} values (µg/mL) for the synthesized derivatives 19a-e

Compound	AGS	HeLa	HL-60	Fibroblasts
19a	1.23 ± 0.23	9.63 ± 0.06	2.37 ± 0.23	32.15 ± 2.91
19b	0.89 ± 0.04	5.67 ± 0.35	0.93 ± 0.09	25.59 ± 1.04
19c	4.49 ± 0.44	8.65 ± 0.52	1.69 ± 0.20	27.00 ± 2.29
19d	1.57 ± 0.20	6.34 ± 0.04	1.46 ± 0.20	29.95 ± 3.27

19e	3.60 ± 0.33	7.96 ± 0.37	2.90 ± 0.17	27.79 ± 2.82

In 2023, Rachala et al. synthesized a novel series of chalcone derivatives (26a-j). The *in-vitro* anti-cancer evaluation was determined with the MTT assay against multiple cancer cells including A-549, PC-3, MCF-7 and DU-145. Compounds 26a-f showed maximum activity among other compounds. Compound 26d emerged with the excellent anti-cancer potency with IC_{50} values of 1.02 ± 0.026 (A-549), 0.01 ± 0.0062 (PC-3), 0.05 ± 0.0043 (MCF-7) and 1.10 ± 0.93µM (DU-145) [38].



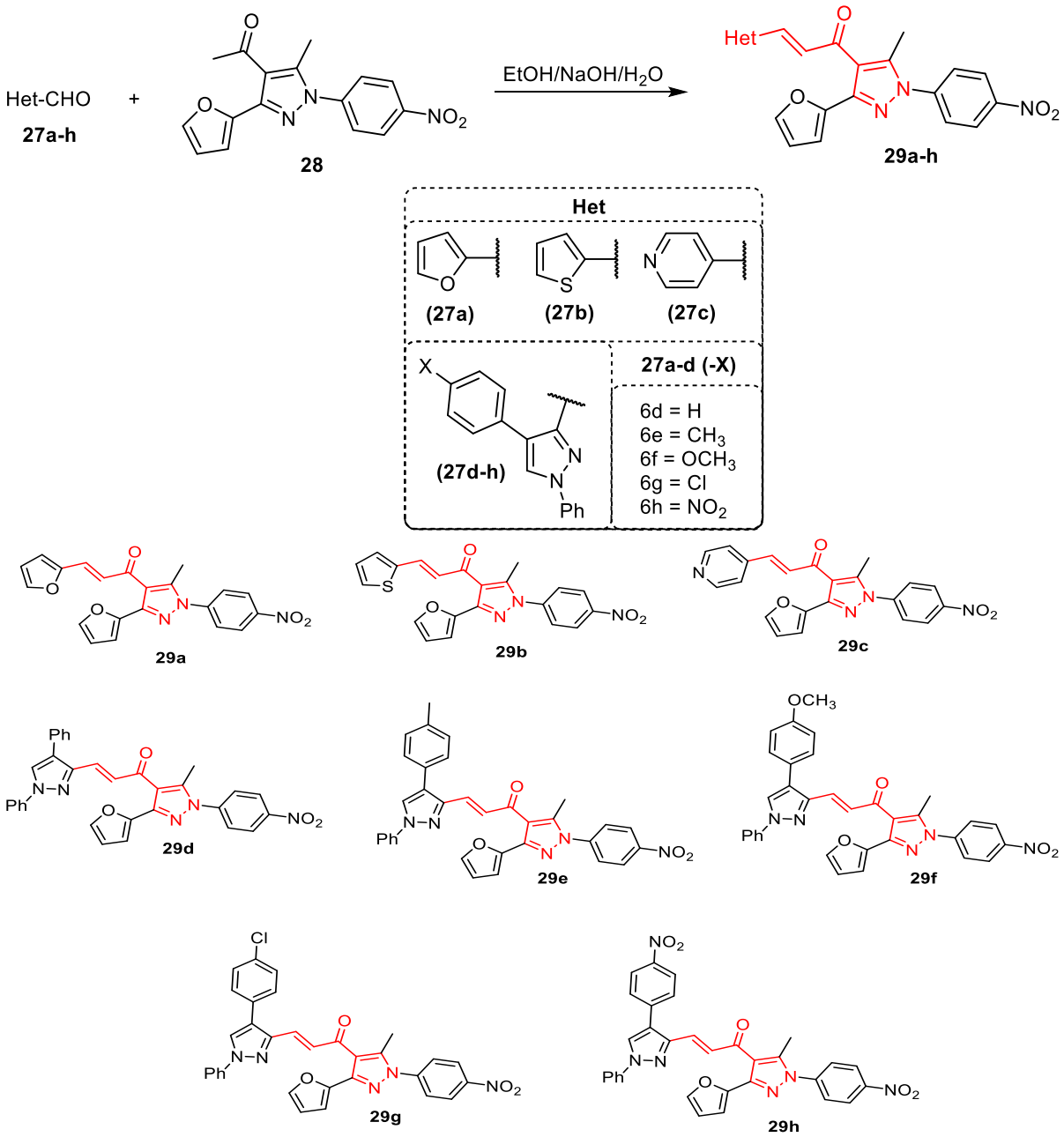
Scheme-5: Synthesis of chalcone derivative 26a-j

Table-5: IC_{50} values (µM) for the synthesized derivatives 26a-j

Compound	PC3	A549	MCF-7	DU-145
26a	0.18 ± 0.096	0.10 ± 0.064	0.13 ± 0.057	0.19 ± 0.063
26b	1.45 ± 0.69	1.36 ± 0.71	1.29 ± 0.83	1.22 ± 0.67
26c	1.97 ± 0.45	1.77 ± 0.54	1.48 ± 0.66	1.39 ± 0.32
26d	1.02 ± 0.026	0.01 ± 0.0062	0.05 ± 0.0043	1.10 ± 0.93
26e	2.16 ± 1.46	2.76 ± 1.75	2.11 ± 1.32	2.17 ± 1.66
26f	2.61 ± 1.49	2.34 ± 1.43	2.46 ± 1.60	2.84 ± 1.74
26g	ND	3.48 ± 2.61	ND	4.21 ± 2.36
26h	4.87 ± 2.95	6.32 ± 3.44	7.22 ± 5.34	ND
26i	ND	7.13 ± 5.32	3.97 ± 2.18	4.15 ± 2.65
26j	ND	ND	ND	9.64 ± 6.46

In 2023, Mohamed et al. created new chalcone derivatives (29a-h) emphasizing on lung-cancer treatment. The *in-vitro* anti-cancer evaluations were determined in an MTT assay on A-549 and Wi38 cells. IC_{50} values obtained for A-549 cells were observed as 42.701 (29a), 20.050 (29b), 13.860 (29c), 76.521 (29d), 217.010

(29e), 237.840 (29f), 251.491 (29g) and 211.301 µg/ml (29h) while for Wi38 cells as 68.0 (29a), 108.410 (29b), 18.20 (29c), 261.321 (29d), 295.590 (29e), 296.241 (29f), 379.220 (29g) and 224.360 µg/ml (29h). Molecular docking analysis on the 29b and 29c exhibited effective potential of these derivatives while more advanced molecular studies were done in order to determine the effects & activity of these compounds on A-549 cell apoptosis [39].



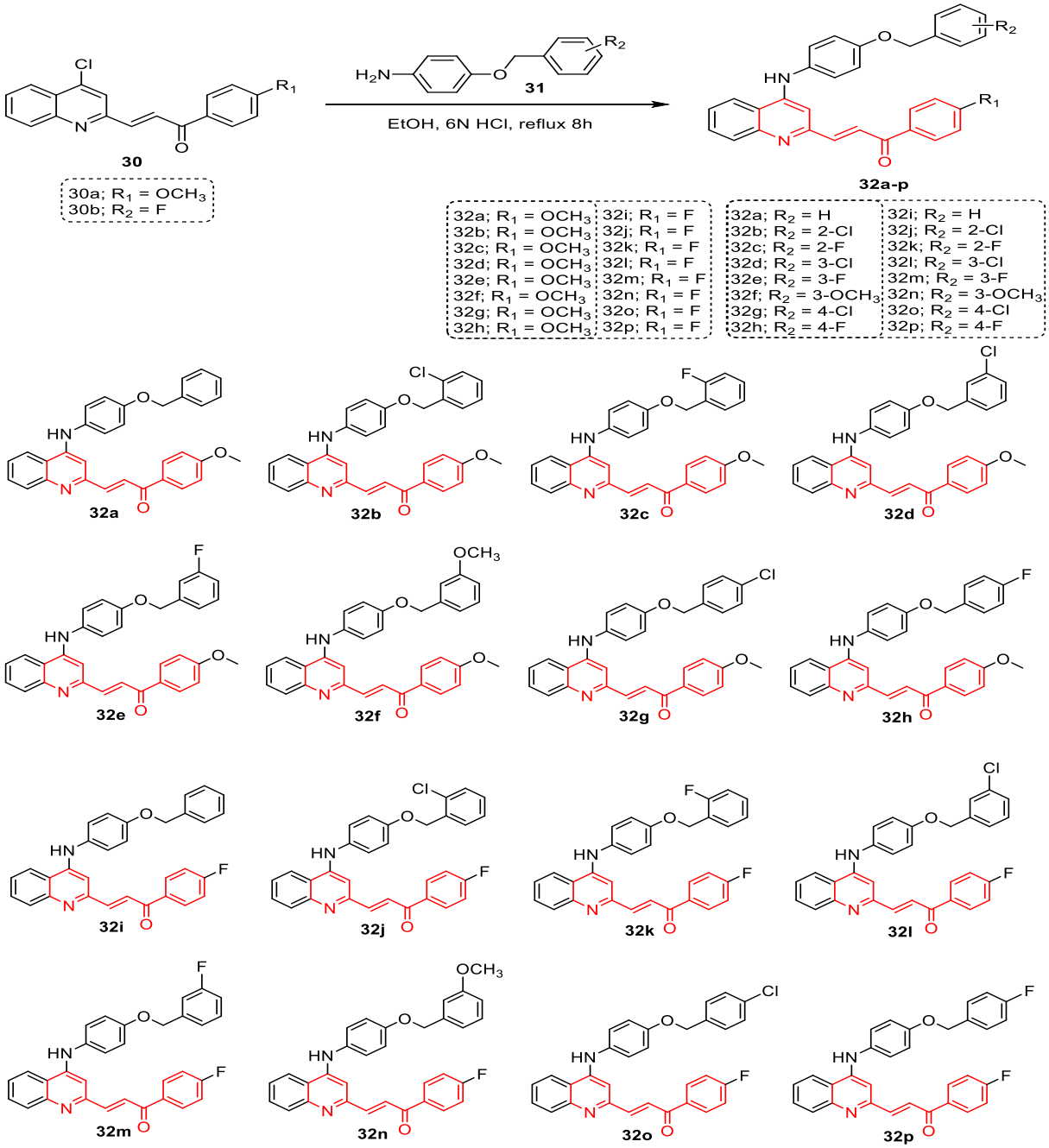
Scheme-6: Synthesis of chalcone derivative 29a-h

Table-6: IC_{50} values (µg/ml) for the synthesized derivatives 29a-h

Compound	Cell Line	IC_{50} (µg/ml)
29a	A-549	42.70
	Wi38	68
29b	A-549	20.05
	Wi38	108.41
29c	A-549	13.86
	Wi38	18.2
29d	A-549	76.52
	Wi38	261.32

29e	**A-549**	217.01
	Wi38	295.24
29f	**A-549**	237.84
	Wi38	296.24
29g	**A-549**	251.49
	Wi38	379.22
29h	**A-549**	211.30
	Wi38	224.36

In 2023, Yang et al. synthesized novel 4-anilinoquinolinyl chalcone hybrids (32a-p) and explored their antiproliferative activity against the Huh-7 & MDA-MB-231 (breast cancer) and MRC5 (normal lung cells) cells in which MRC5 cells exhibited lowest cytotoxicity. Compound 32a exhibited highest cytotoxicity against breast cancer and lowest cytotoxicity against normal-cells with IC_{50} values as 1.47 ± 0.07 (Huh-7), 0.11 ± 0.07 (MDA-MB-231) and >20 µM (MRC5). Compound 32p triggered ROS-dependent caspase 3/7 and inhibited ATP levels in MDA-MB-231 [40].



Scheme-7: Synthesis of chalcone derivative 32a-p

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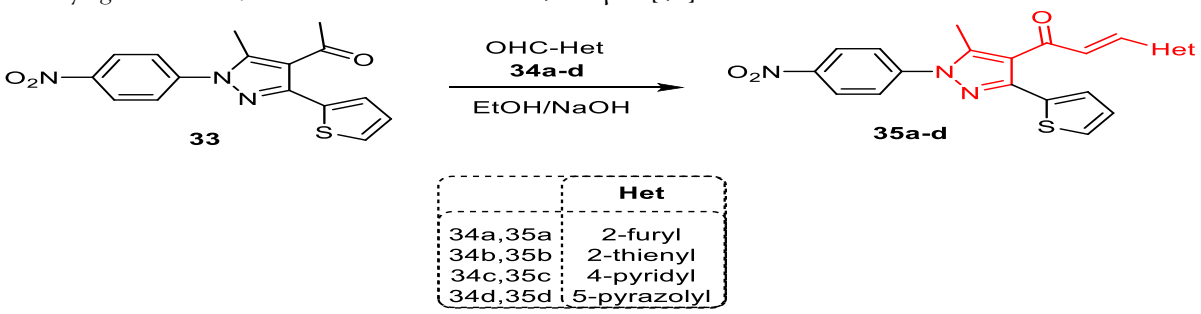
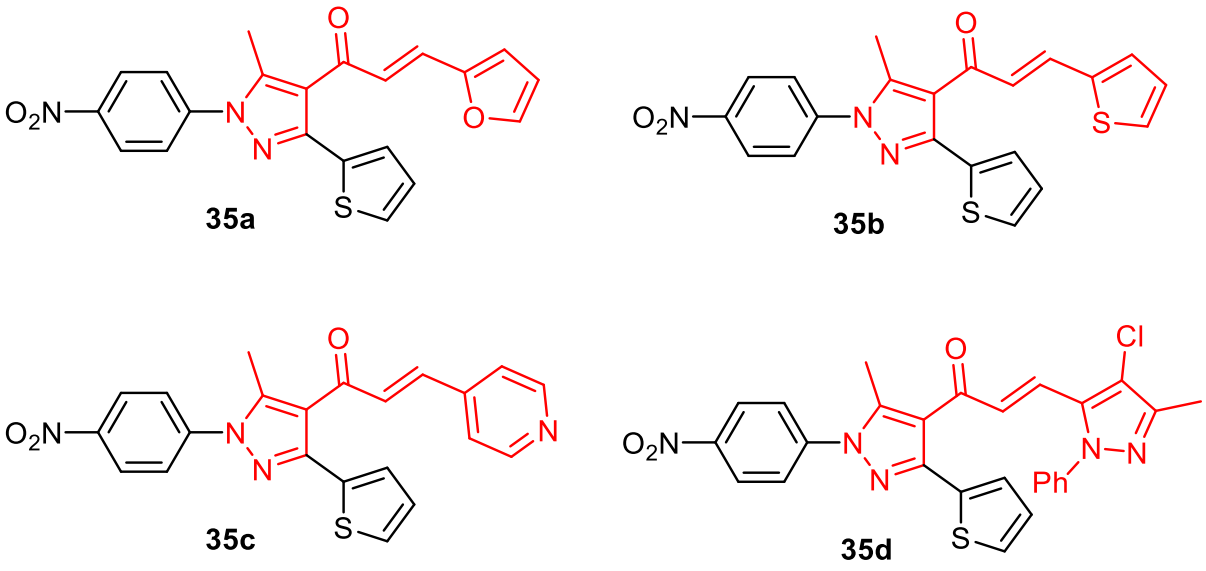
Table-7: IC_{50} values (µM) for the synthesized derivatives 32a-p

Compound	Huh-7	MDA-MB-231	MRC-5
32a	1.47 ± 0.07	0.11 ± 0.07	>20
32b	1.83 ± 0.22	1.59 ± 0.15	>20
32c	0.81 ± 0.06	1.04 ± 0.04	>20
32d	0.69 ± 0.04	0.18 ± 0.06	>20
32e	1.45 ± 0.28	0.54 ± 0.11	>20
32f	1.41 ± 0.04	1.94 ± 0.52	>20
32g	1.31 ± 0.56	1.71 ± 0.35	>20
32h	1.37 ± 0.28	1.69 ± 0.21	>20
32i	1.24 ± 0.09	1.65 ± 0.77	>20
32j	1.24 ± 0.30	1.53 ± 0.21	>20
32k	1.25 ± 0.07	1.42 ± 0.70	>20
32l	1.28 ± 0.21	1.76 ± 0.13	>20
32m	1.27 ± 0.06	1.82 ± 0.28	>20
32n	1.34 ± 0.35	2.03 ± 0.14	>20
32o	1.30 ± 0.14	1.50 ± 0.77	>20
32p	1.29 ± 0.28	1.68 ± 0.21	>20

In 2024, Yasser et al., designed two series of novel pyrazolyl-chalcone derivatives (35a-d and 37a-f) by reacting 4-acetyl-5-thiophene-pyrazole with heteroaryl aldehydes via Claisen-Schmidt condensation. The synthesized compounds were tested for their anti-cancer potential against multiple cell lines including MCF-7, PC3, PACA2 and BJ1. Among the synthesized compounds, 37e emerged with the highest potential against PACA2 cells with n IC50 value of 27.60µM, however compound 35d showed maximum activity against MCf-7 cells with IC50 value of 42.60µM [41].



	Het
34a,35a	2-furyl
34b,35b	2-thienyl
34c,35c	4-pyridyl
34d,35d	5-pyrazolyl



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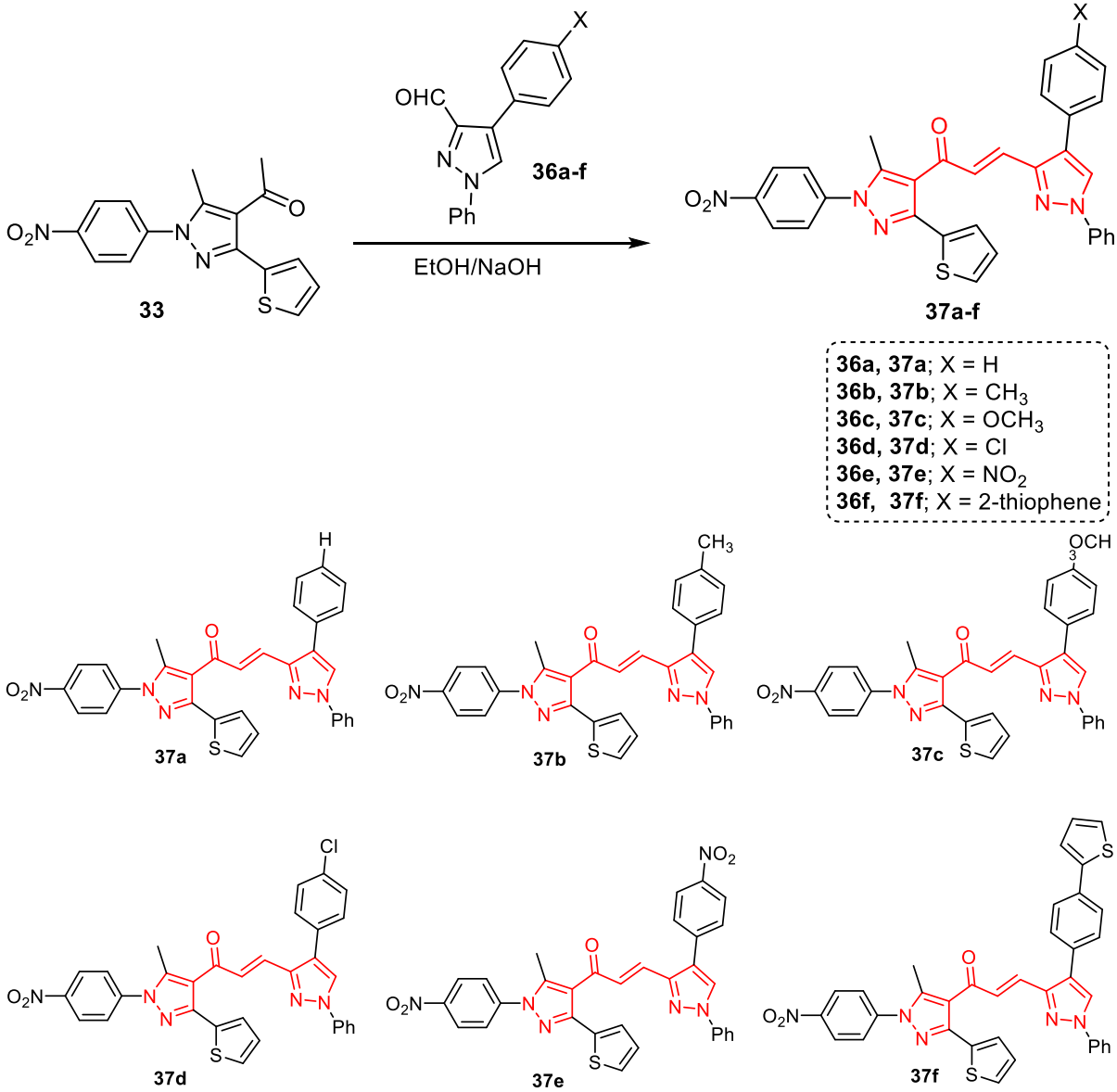


Scheme-8: Synthesis of chalcone derivative 35a-d & 37a-f

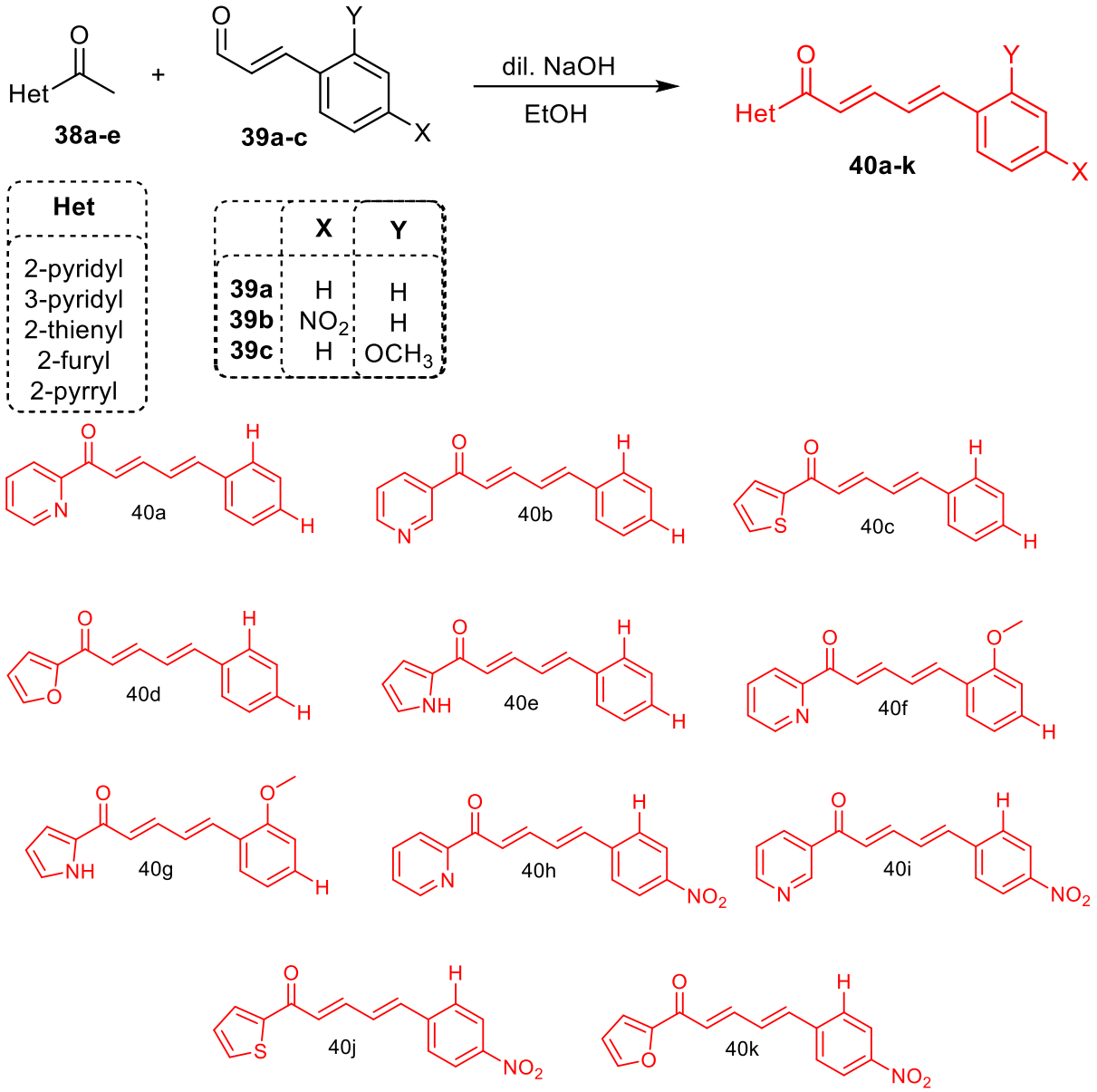
Table-8: IC_{50} values (µM) for the synthesized derivatives 35a-d & 37a-f

Compd	MCF7		PACA2		PC3		BJ1	
	M%	IC_{50}	M%	IC_{50}	M%	IC_{50}	M%	IC_{50}
35a	63.5±0.11	72.3±0.34	17.3±0.13	-	3.8±0.65	-	11.2±0.48	-
35b	45.3±0.98	-	32.5 ± 0.74	-	4.2±0.73	-	-	-
35c	100%*	-	100%*	-	100%*	-	52.3±0.76	86.2±0.22
35d	71.2±0.14	42.6±0.71	80.3±019	51.9±0.29	70.6±0.97	66.9±0.98	12.3±0.23	-
37a	42.3±0.21	-	50.3±0.42	-	4.5±0.26	-	-	-
37b	44.5±0.74	-	39.5±0.91	-	27.2±0.31	-	-	-
37c	25.2±0.41	-	19.8±0.68	-	2.9±0.57	-	-	-
37d	44.2±0.33	-	54.5±0.84	-	3.5±0.92	-	-	-
37e	14.2±0.37	59.3±0.85	100	27.6±0.33	5.3±0.94	-	5.6±0.55	-
37f	80.4±0.25		16.5±0.35		4.5±0.23		-	-

* = up to 6.25 µg ml^{-1}

In 2024, El-Atawy et al., synthesized a novel series of cinnamaldehyde chalcone derivatives (40a-k) through Claisen-Schmidth condensation reaction. The newly synthesized derivatives were tested for their anti-cancer activities against Caco-2 (Colon Cancer) cancer cells. The cytotoxicity assessments were carried out, and it was found that by increasing the doses from 50µM to 1000µM for 24 hours incubation time,

a decrease in the percentage of cell viability was observed for compounds against Caco-2 cancer cells. The results of cytotoxicity clarify the capability of 40e to restrain Caco-2 proliferation over other synthesized derivatives with the smallest IC_{50} value of 32.19 ± 3.92µM [42].

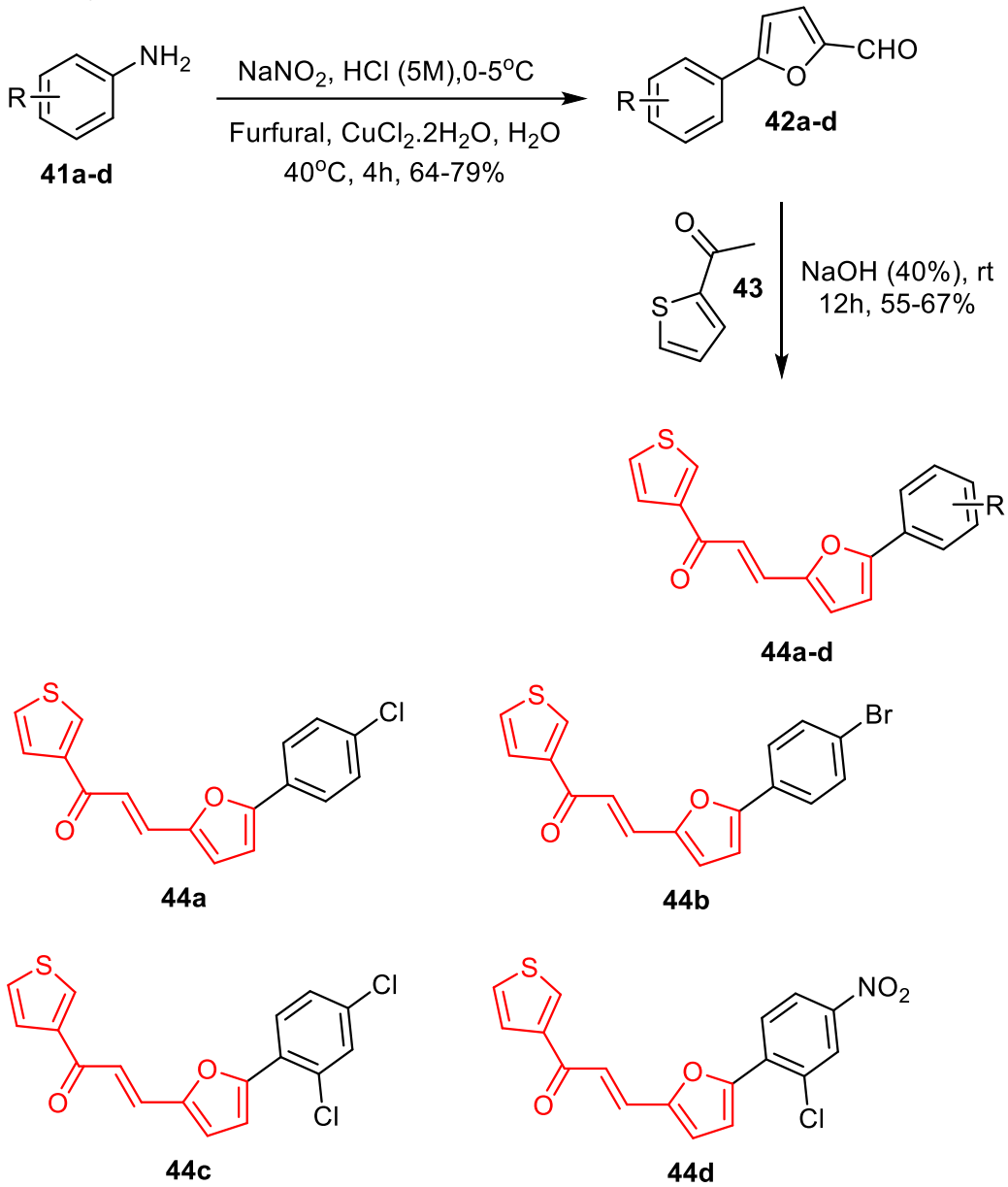


Scheme-9: Synthesis of chalcone derivative 40a-k

Table-9: IC_{50} values (µM) for the synthesized derivatives 40a-k

Compound	Caco-2 cells
40a	725.57 ± 3.69
40b	1624.2 ± 4.69
40c	1213.51 ± 4.98
40d	1209.91 ± 4.22
40e	32.19 ± 3.92
40f	172.74 ± 3.84
40g	336.17 ± 4.96
40h	548.58 ± 3.76
40i	206.64 ± 2.31
40j	149.37 ± 2.55
40k	130.38 ± 3.28

In 2024, Abdula et al., synthesized novel chalcone derivatives (44a-d) via Claisen-Schmidt condensation reaction. The chalcone derivatives were subjected for the anti-cancer cancer evaluations against breast-cancer cells including MCF-7 (cancerous) and MCF-10A (non-cancerous). The IC_{50} values were determined by examining the relationship between the concentrations of synthesized compounds and their cytotoxic effect on the MCF-7 cells were 27.456 (44a), 25.870 (44b), 22.870 (44c) and 19.354µg/mL (44d). Compound 44d poses significant inhibitions on cell proliferation of MCF-7 as compared to other tested compounds 44a-c, however there was no toxicity from any of the tested compounds against MCF-10A. The results of the biological evaluations illustrates that compound 44d possess lowest IC_{50} value of 19.354 µg/mL [43].



Scheme-10: Synthesis of chalcone derivative 44a-d

In 2025, Malik et al., created a novel series of α-cyano-bis(indolyl) chalcones (47a–r) and evaluated their anti-cancer potential against prostate cancer, breast cancer and epithelial cancer cells. The compound 47a (3.9 mM), 47c (7.5 mM), 47i (2.2 mM) and 47o (5.9 mM) showed significant cytotoxicity against C4-2 cells, while compound 47c (1.23 mM), 47h (5.23 mM) and 47l (2.5 mM) showed selective cytotoxicity against 22Rv1 cells. Compound 47j showed excellent activity against C4-2 prostate cancer cells with IC_{50} value of 0.9mM. Compound 47j increases the endogenous levels of Reactive Oxygen Species thereby inducing mitochondrial dysregulation, resulting in apoptosis [44].

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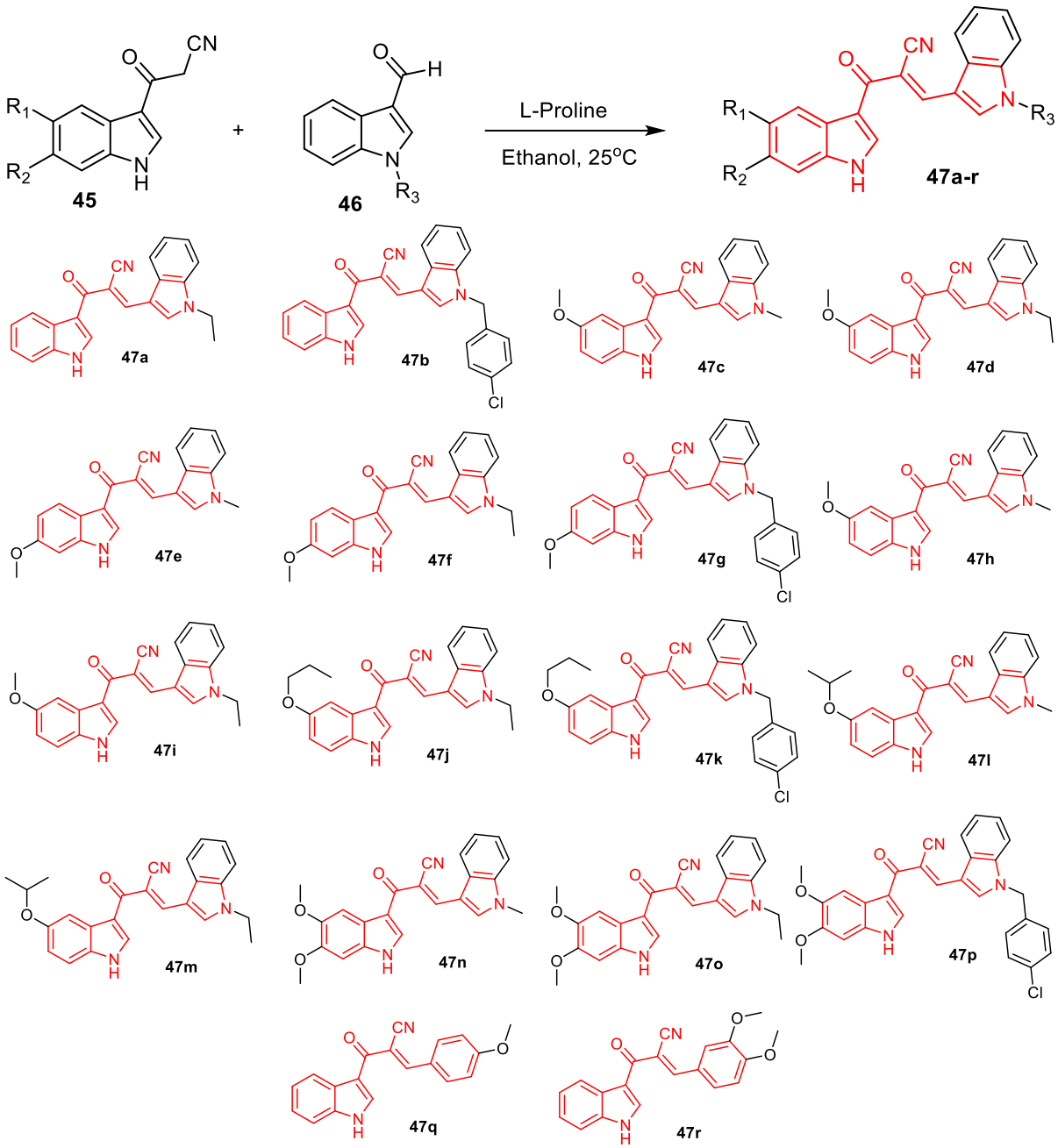


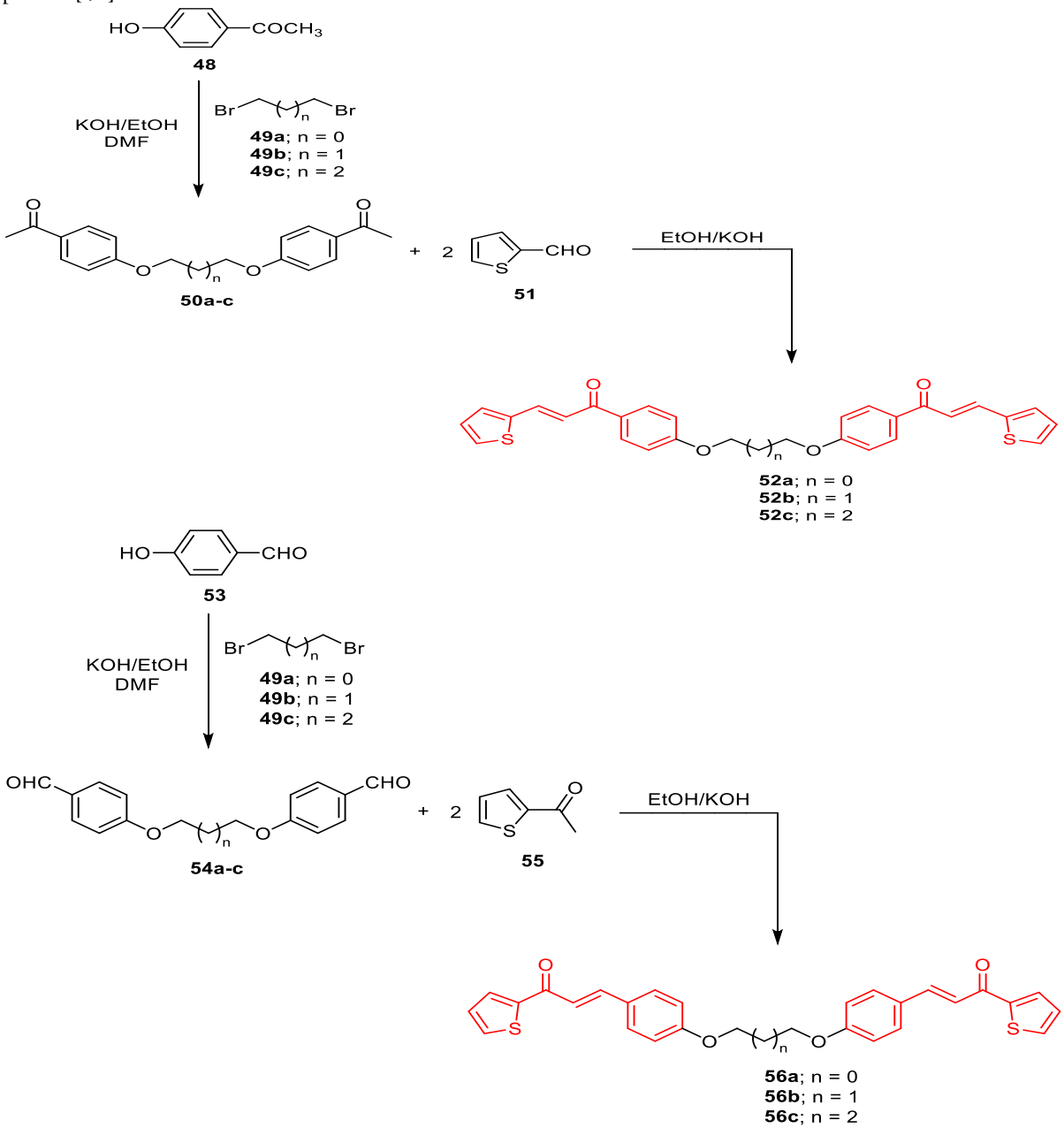
Scheme-11: Synthesis of chalcone derivative 47a-r

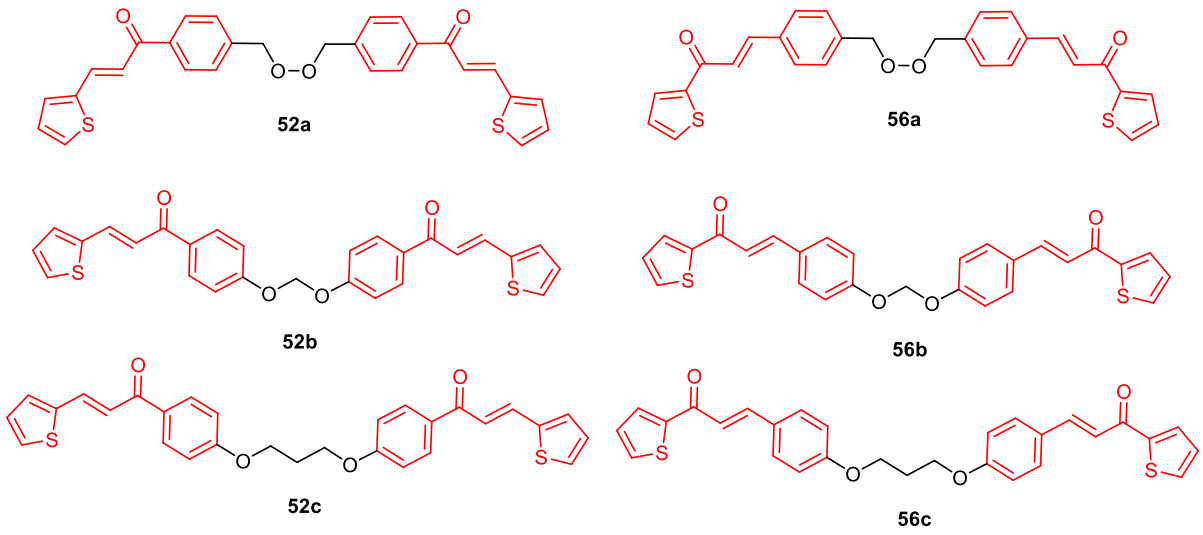
Table-10: IC_{50} values (µM) for the synthesized derivatives 47a-r

Compound	MCF7	PC3	C4-2	22Rv1	MIAPACA	HEK293
47a	10.2	13	3.9	>40	>40	>40
47b	6.9	10.6	13.5	21.5	4.9	40
47c	25.3	15.45	7.5	1.23	4.5	>40
47d	10.9	>40	8	25	15.5	39.2
47e	12.47	7.61	15.7	28	>40	>40
47f	37	24	12.5	>40	>40	40
47g	10.5	14.3	13.3	34	7.9	>40
47h	16.75	27.3	10	5.23	1.35	40
47i	7.38	2.63	2.2	8.9	5.8	>40
47j	1.2	5.6	0.98	2.9	5.3	>40
47k	18.6	16.1	13.8	28	28.9	39.8
47l	7.95	4.6	26.4	2.5	37.6	37.9

47m	2.98	11.7	17.6	16.4	1.6	>40
47n	5.61	7.1	1.02	20.5	15.6	>40
47o	31.5	19	5.9	26	12.95	>40
47p	>40	>40	31	>40	>40	>40
47q	25	37	>40	28	15.4	>40
47r	>40	25	>40	34	37	31

In 2025, Fati et al., created two novel series of bis-chalcone derivatives (52a-c and 56a-c) which contain thiophene moiety in their chemical structures through a Claisen-Schmidt condensation reaction. Compounds 52a, 52b, 56a and 56b showed significant cytotoxicity against breast cancer cells with IC_{50} values of 7.87 ± 2.54 (52a) and 4.05 ± 0.96 µM (52b), colon cancer cells (IC_{50} = 18.10 ± 2.51 (52a) and 17.14 ± 0.66 µM (56a) and lung cancer cells (IC_{50} = 41.99 ± 7.64 (52a) and 92.42 ± 30.91 µM (56b). These compounds upregulated the proapoptotic genes and caspase-3 and caspase-9 protein however downregulated the anti-apoptotic and matrix metalloproteinase-2 (MMP-2) gene expression. Furthermore, these compounds significantly promoted early and late apoptosis and necrosis and caused subG1 cell cycle arrest accompanied by a concurrent decrease in cell fraction percentages in the G0/G1, S and G2/M phases [45].





Scheme-12: Synthesis of chalcone derivative 52a-c & 56a-c

Table-11: IC_{50} values (µM) for the synthesized derivatives 52a-c & 56a-c

Compound	A549	HCT116	MCF7	CCD-16Lu
52a	41.99 ± 7.64	18.10 ± 2.51	7.87 ± 2.54	52 ± 0.70
52b	114.96 ± 18.86	30.73 ± 2.58	4.05 ± 0.96	ND
52c	ND	356.00 ± 30.71	ND	NA
56a	272.55 ± 49.45	17.14 ± 0.66	11.47 ± 1.25	ND
56b	92.42 ± 30.91	120.30 ± 12.90	30.08 ± 4.04	34.5 ± 1.4
56c	232.40 ± 73.59	277.75 ± 53.35	134.13 ± 17.48	NA

ND = Non-Detectable; NA = Not Applicable

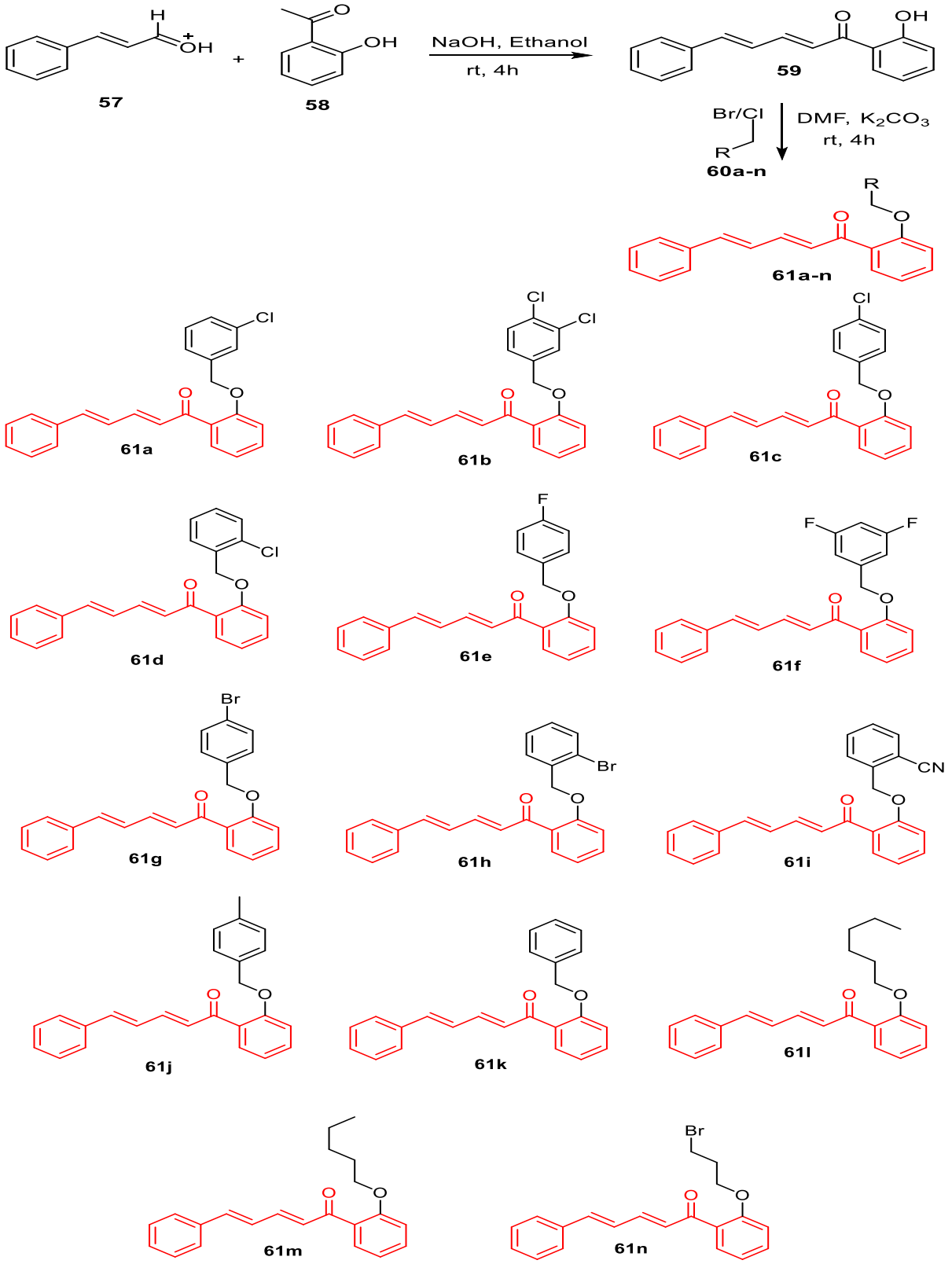
In 2025, Kumar et al., created novel series of cinnamaldehyde based chalcones derivatives (61a-n). The brominated ethyl chalcone derivative 61n showed highest cytotoxicity toward DU145 (IC_{50} of 8.719 ± 1.8 mM), SKBR-3 (IC_{50} of 7.689 ± 2.8 mM) and HePG2 (IC_{50} of 9.380 ± 1.6 mM) as compared to other compounds but still showed decreased toxicity relative to doxorubicin (IC_{50} of 0.45 ± 0.52 (DU145), 0.7 ± 0.56 (SKBR-3) and 2.5 ± 1.42mM (HePG2). The para-methyl benzyl chalcone derivative 61j also exhibited high cytotoxicity against SKBR3 (IC_{50} of 7.871 ± 2.1mM). The 2,3-dichloro benzyl chalcone de`rivative 61b exhibited one of the highest cytotoxicity against HePG2 cells with IC_{50} value of 9.190 ± 0.6mM. Both of these compounds displayed equal to or approximately equal to the cytotoxicity of doxorubicin (IC_{50} of 0.7 ± 0.56 (SKBR3) and 2.5 ± 1.42 (HePG2)). The 4-bromo benzyl chalcone derivative 61g exhibited moderate toxicity against DU145 and SKBR3 cells with IC_{50} values of 16.914 ± 2.3mM and 15.711 ± 2.8mM, respectively, but still less than doxorubicin (IC_{50} of 0.45 ± 0.52 (SKBR3) and 0.7 ± 0.56 (HePG2). It was observed that by modifications of electron withdrawing groups or lipophilic chains at the benzyl position (61n, 61j and 61b) showed enhanced toxicity as compared to non-modified cinnamaldehyde [46].

Scheme-13: Synthesis of chalcone derivative 61a-n

Table-12: IC_{50} values (µM) for the synthesized derivatives 61a-n

Compound	HEK-293	DU145	SKBR-3	HEPG2
61a	30.092 ± 8.3	45.217 ± 2.1	20.839 ± 1.7	40.322 ± 2.9
61b	20.391 ± 1.6	17.861 ± 3.4	22.421 ± 2.4	9.190 ± 0.6
61c	22.321 ± 1.2	47.064 ± 4.5	30.745 ± 2.0	40.170 ± 0.2
61d	202.78 ± 5.3	46.055 ± 1.1	75.883 ± 4.8	41.449 ± 3.9
61e	49.837 ± 2.8	278.60 ± 1.7	56.126 ± 1.8	282.42 ± 5.7
61f	36.978 ± 0.9	47.073 ± 0.5	16.898 ± 2.3	30.825 ± 2.5
61g	27.588 ± 4.2	16.914 ± 2.3	15.711 ± 2.8	25.825 ± 1.6
61h	23.387 ± 4.7	28.630 ± 2.2	243.79 ± 4.7	44.965 ± 3.3

61i	48.182 ± 5.0	68.374 ± 2.8	75.293 ± 2.1	42.012 ± 2.1
61j	23.570 ± 1.4	21.260 ± 5.6	7.871 ± 2.1	25.678 ± 1.5
61k	109.383 ± 0.7	55.586 ± 3.7	80.336 ± 8.7	46.573 ± 1.4
61l	97.976 ± 10.1	29.036 ± 2.1	23.466 ± 4.1	46.681 ± 2.2
61m	104.184 ± 7.3	126.83 ± 0.2	125.34 ± 6.0	33.159 ± 0.7
61n	18.461 ± 1.1	8.719 ± 1.8	7.689 ± 2.8	9.380 ± 1.6



CONCLUSION

One of the most trending areas in the discovery of new anticancer drugs is the synthesis of chalcone-based hybrids that shows potential. Due to the structural simplicity and chemical versatility of chalcones, modulations would increase the bioactivity, selectivity and pharmacokinetic profiles of these compounds to a larger extent. Various researches have been identifying chalcone derivatives as a successful way to kill cancer cells of different origins. Moreover, they do not only kill cancer cells but they do so by different mechanisms, among them being apoptosis induction, reactive oxygen species generation, angiogenesis inhibition and the metastatic pathways blockade. The anticancer activity of several chalcone hybrids was often accompanied by very low toxicity toward the normal cells making these compounds the right candidate drugs for therapies with fewer side effects. One of the clinical examples of success among the derivatives is sofalcone that actually proves the importance of this study. Preclinical evaluation and *in-silico*, *in-vitro* & *in-vivo* studies combined promote the facilitation of the chalcone-based anticancer drug development. Chalcone hybrids have a significant opportunity to raise the diversity of targeted and effective anticancer treatments that would be very helpful in cancer management.

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Conflict of interest: The authors declare no competing interests.

Author contributions: Atif Husain (Synthesis and writing the original manuscript), Abdul Rahman Khan (Supervision, proof reading), Mohd Arsh Khan (Writing-original draft preparation, Data Curation, Visualization), Malik Nasibullah (Supervision and writing manuscript).

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