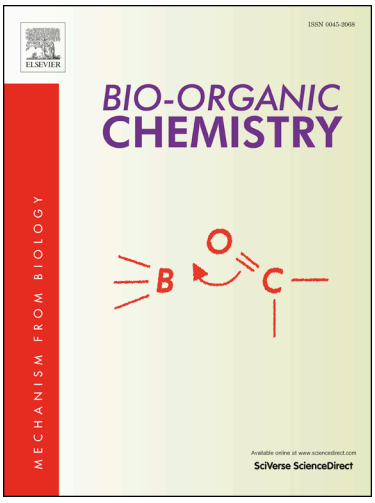

Synthesis and evaluation of novel α-substituted chalcones with potent anti-cancer activities and ability to overcome multidrug resistance

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Synthesis and evaluation of novel α-substituted chalcones with potent anti-cancer activities and ability to overcome multidrug resistance.

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Abstract

A series of forty α-substituted chalcones were synthesized and screened for their antiproliferative activities against HCT116 (colorectal) and HCC1954 (breast) cancer cell lines. Compounds **5a** and **5e** were found to be the most potent compounds with GI_{50} values of 0.63 µM and 0.725 µM in HCC1954 cell line and 0.69 µM and 1.59 µM in HCT116 cell line, respectively. Both compounds induced a G2/M cell cycle arrest and caused apoptotic cell death in HCT116 cells as shown by the induction of PARP cleavage. The compounds also stabilized p53 in a dose-dependent manner in HCT116 cells following 24-hour treatment. Furthermore, both **5a** and **5e** were able to overcome multidrug resistance in two MDR-1 overexpressing multidrug resistant cell lines.

Keywords: α-substituted chalcones; antiproliferative activity; apoptotic activity; cell cycle arrest; multidrug resistance;

1. Introduction

Cancer is a large group of heterogeneous diseases characterized by abnormal division and spread of cells.[1] Chemotherapy, surgery, radiotherapy or their combinations are the current modes of cancer treatment.[2] Among these, systemic chemotherapy is one of the most common and effective treatments for many types of cancer.[3] However, the development of multidrug resistance (MDR) is a major impediment to the success of chemotherapy.[4] It is, therefore, important to design and discover new drugs with anticancer potential and ability to overcome MDR.

Chalcones (α, β-unsaturated aromatic ketones) are medicinally important compounds.[5] Various natural and synthetic chalcones have been shown to display biological properties to act as potential hits for inflammation,[6,7] diabetics,[8] Alzheimer's disease,[9] viral diseases[10] and anti-cancer[11-15] activities. Naturally occurring chalcones such as Isoliquiritigenin and Licochalcone A arrest cells in the S and G2/M phase of the cell cycle.[16] Synthetic chalcones such as compounds (**i–v**) have been shown to overcome Pgp-mediated MDR.[17] Chalcones have gained attention in the recent literature for pharmaceutical[5] and photochemical applications.[18] Recently, a number of chalcone derivatives have been shown to have anticancer potential. **FC77** has been described as a potential agent against MDR

malignancies.[19] Compound **vi,** a thienopyrimidine−chalcone hybrid, showed anticancer activity against a breast cancer cell line MCF-7, with GI_{50} value of 6.52 ± 0.82 μM.[20] Compound **vii** inhibited cell proliferation by arresting the cells at the G_2/M phase in HCCT116 cell line.[21] Similarly benzo[d]imidazo[2,1-b]thiazole-chalcone conjugates (*e.g.*, compound **(viii)**) caused a G_2/M cell cycle arrest in a human breast cancer cell line (MDA MB-231).[22] Compound **(ix)** displayed a GI_{50} value of 2.3 ± 0.3 μM in NCI-H460 cell line and acted through ROS modulation that induced caspase-3 mediated apoptosis.[23] Novel Indolizine-chalcone hybrids **(x)** showed caspase-dependent apoptosis of human Lymphoma U937 cells with GI_{50} of 1.12 μM.[24] Carbazole derivatives containing chalcone analogues (CDCAs), *e.g.*, compound **(xi)**, were found to be apoptotic inducers (GI_{50} = 0.22 μM in human acute leukemia cell line HL-60).[25] **DK-139** was found to induce caspase-mediated apoptosis through unfolded protein response in lung cancer-A549 cell line.[26] Chalcones such as **T37** were reported to activate p53.[27] Similarly, compounds D14 and D15 suppress migration and invasion of osteosarcoma cells through p53 regulation.[28]

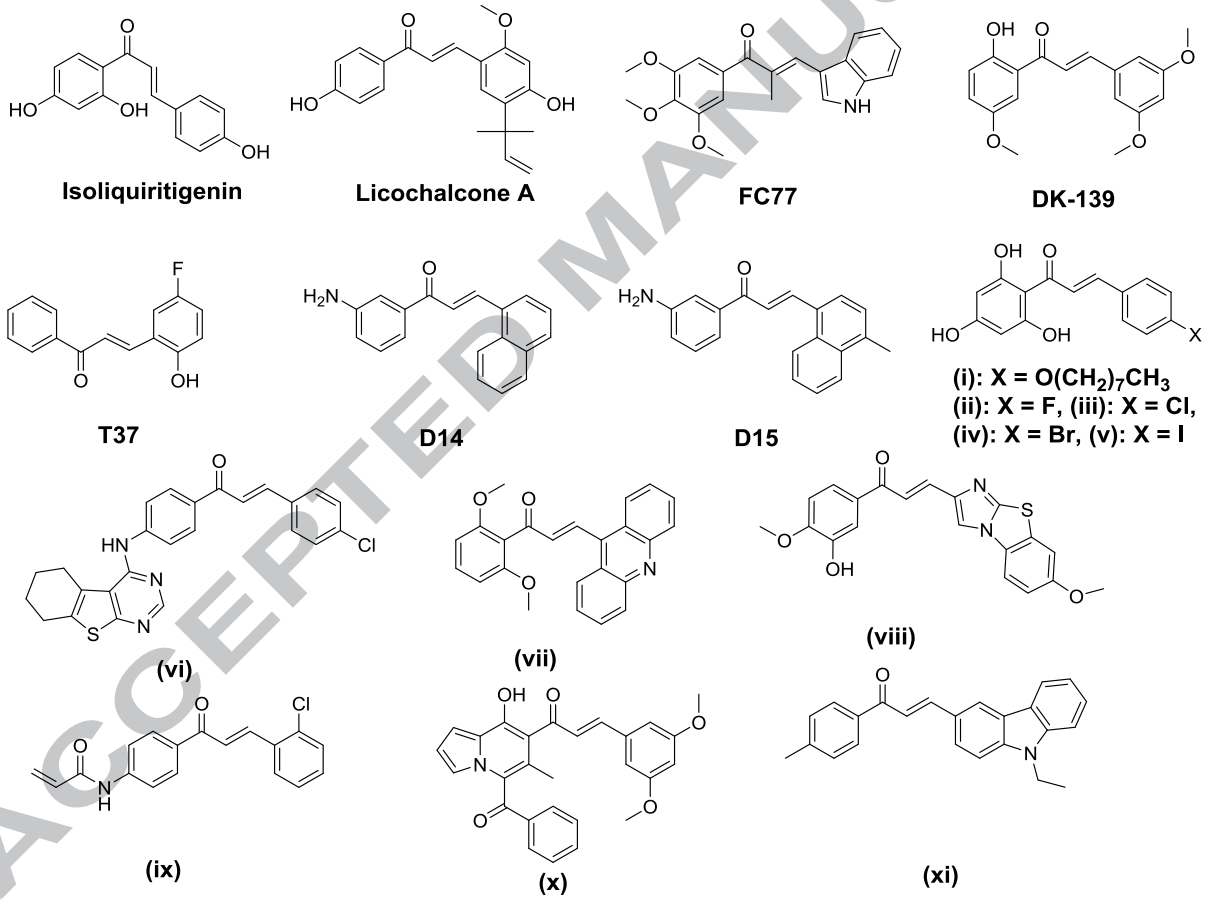


Figure 1 Natural and synthetic chalcones and examples from recent literature (2018)

Despite abundant literature on the chalcones, lesser is known about the activities of the alpha-substituted chalcones. The literature cites only a handful of such compounds, for example, α-Alkyl, α-COOEt, α-COOH, α-CN, α-triazole, α-halo substitutions and their biological profiling have been reported by Duchi,[29] Lawrence,[30] Smith[31] and Yin[32]. We have been interested in secondary metabolites[33-37] as well as in elucidating the bioactivities of small organic molecules.[38-44] Recently, we have reported two chalcone derivatives, **SSE14105** and

SSE14106 that can stabilize p53-tumor suppressor protein in HCT116 cells and inhibit their proliferation.[38] We have also identified the compound **SSE15206**, a pyrazolinethioamide derivative **of SSE14108**, to be a microtubule depolymerizing agent that could overcome MDR.[39]

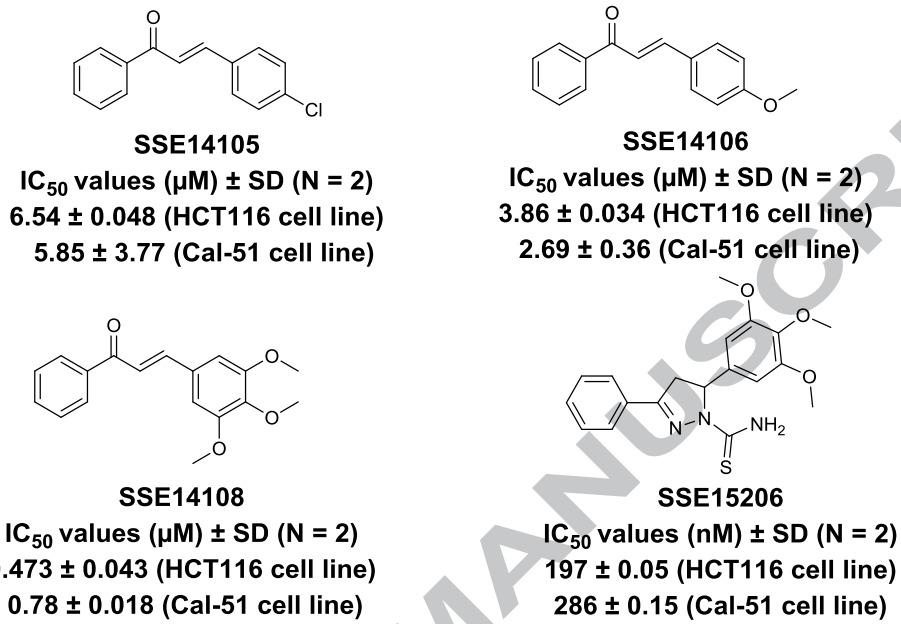


Figure 2 Anti-tumor chalcones from our previous work.

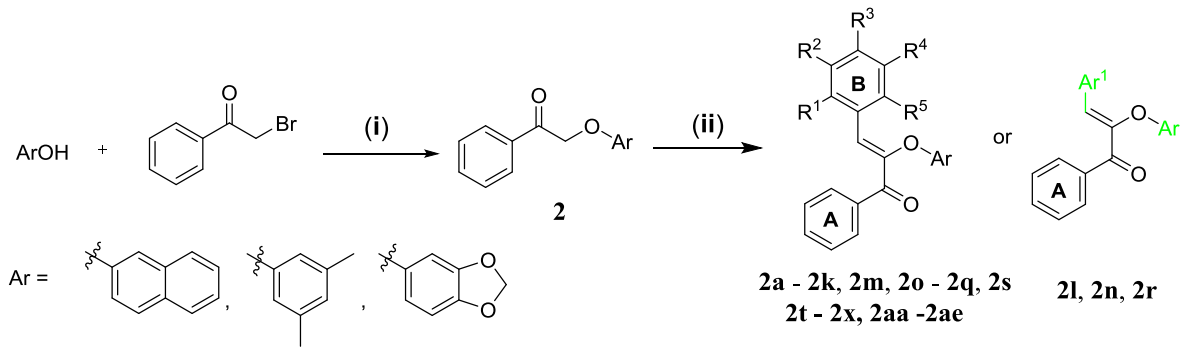
In continuation of our interest in probing the anticancer activities of chalcones, we herein report synthesis and evaluation of anticancer activity of 40 α-substituted chalcones (including 37 novel compounds) that contain α-aryloxy, α-COOEt, α-COOH and α-amide groups. We have determined their antiproliferative activity against HCT116 (colorectal) and HCC1954 (breast) cancer cell lines. Moreover, we have evaluated the most active compounds (**5a** and **5e**) for their ability to induce cell cycle arrest, p53 stabilization, apoptosis and to overcome multidrug resistance. To our knowledge, this is the first report of such molecules overcoming multidrug resistance.

2. Results and Discussion

2.1 Chemistry

2.1.1 Synthesis of α-aryloxy chalcones

We synthesized series of α-2-naphthalen-2-yloxy, α-3,5-dimethyl phenoxy and α-1,3-benzodioxol-5-yloxy substituted chalcones as shown in Scheme 1:

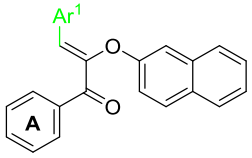


Scheme 1. Synthesis of α-Aryloxy chalcones. Reagents and conditions: (**i**) K_2CO_3, ACN, r.t., 48 hr.; (**ii**) ArCHO, KOH, EtOH, r.t., 24 hr.

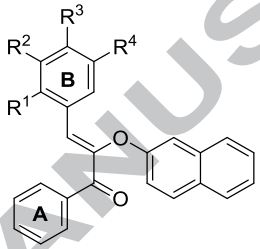
2.1.1.1 Synthesis of α-2-(naphthalen-2-yloxy)-chalcone (2a – 2s)

In order to prepare α-2-(naphthalen-2-yloxy)-chalcone, 2-naphthol was reacted with 2′-bromoacetophenone using Williamson-ether synthesis.[45] The resulting 2-(naphthalen-2-yloxy)-1-phenylethanone (**2**) was then condensed with different aldehydes through Claisen-Schmidt condensation leading to the formation of α-2-(naphthalen-2-yloxy)-chalcone derivatives (**2a - 2s**).

Table 1a: Structure, yields and inhibition of cell proliferation in HCC1954 and HCT116 cell lines.



2l, 2n, 2r



2a - 2k, 2m, 2o - 2q, 2s

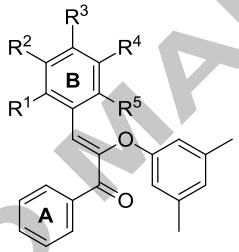
Compound	Ar^1	R^1	R^2	R^3	R^4	Yield (%)	HCC195 GI_{50} (μM) ± SD	HCT116 GI_{50} (μM) ± SD
2a	-	H	H	NO_2	H	85	>100 (N = 2)	>100 (N = 3)
2b	-	H	H	OMe	H	47	>100 (N = 2)	>100 (N = 3)
2c	-	H	H	Cl	H	40	23.54 ± 0.18 (N = 2)	19.35 ± 2.56 (N = 3)
2d	-	Cl	H	H	H	55	64.26 ± 2.89 (N = 2)	43.98 ± 2.71 (N = 3)
2e	-	H	H	Me_2CH	H	74	>100 (N = 2)	>100 (N = 3)
2f	-	OMe	OMe	OMe	H	47	>100 (N = 2)	>100 (N = 3)
2g	-	H	H	Br	H	34	>100 (N = 2)	68.59 ± 22.87 (N = 3)
2h	-	H	H	CF_3	H	18	>100 (N = 2)	67.3 ± 42.23 (N = 3)
2i	-	H	H	F	H	13	61.12 ± 4.31 (N = 2)	45.23 ± 24.67 (N = 3)
2j	-	F	H	H	H	23	>100 (N = 2)	35.37 ± 6.5 (N = 3)
2k	-	F	H	H	F	41	_ (N = 2)	28.61 ± 11.22 (N = 3)
2l	2-thiophenyl	-	-	-	-	78	>100 (N = 2)	>100 (N = 2)
2m	-	H	F	H	H	69	85.23 ± 0.92 (N = 2)	56.07 ± 26.76 (N = 3)
2n	3-pyridyl	-	-	-	-	73	>100 (N = 2)	>100 (N = 2)
2o	-	H	F	F	H	11	>100 (N = 2)	39.61 ± 12.88 (N = 3)

2p	-	H	F	H	F	36	>100 (N = 2)	>100 (N = 2)
2q	-	F	H	F	H	51	>100 (N = 2)	>100 (N = 2)
2r	5-bromothiophenyl	-	-	-	-	29	>100 (N = 2)	>100 (N = 2)
2s	-	H	OMe	H	H	21	>100 (N = 2)	>100 (N = 2)

2.1.1.2 Synthesis of α-(3,5-dimethylphenoxy)-chalcone (2t – 2x)

3,5-dimethylphenol was reacted with 2′-bromoacetophenone to synthesize 3,5-dimethylphenoxy-1-phenylethanone. 3,5-dimethylphenoxy-1-phenylethanone was then condensed with different aldehydes to prepare α-(3,5-dimethylphenoxy)-chalcone derivatives (2t – 2x).

Table 1b: Structure, yields and inhibition of cell proliferation in HCC1954 and HCT116 cell lines.



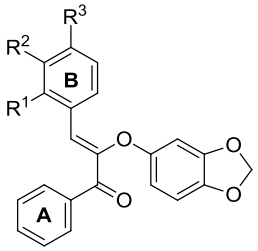
2t - 2x

Compound	R^1	R^2	R^3	R^4	R^5	Yield (%)	HCC195 GI_{50} (µM) ± SD	HCT116 GI_{50} (µM) ± SD
2t	H	NO_2	H	H	H	64	19.19 ± 0.17 (N = 2)	15.93 ± 4.39 (N = 2)
2u	OMe	OMe	OMe	H	H	46	15.9 ± 1.57 (N = 2)	25.66 ± 0.01 (N = 2)
2v	H	OMe	OMe	OMe	H	48	21.66 ± 3.59 (N = 2)	12.72 ± 2.28 (N = 2)
2w	Cl	H	H	H	Cl	45	54.95 ± 4.5 (N = 2)	50.88 ± 1.87 (N = 2)
2x	OMe	H	OMe	OMe	H	44	11.94 ± 1.19 (N = 2)	17.99 ± 0.76 (N = 2)

2.1.1.1 Synthesis of α-(1,3-benzodioxol-5-yloxy)-chalcone (2aa – 2ae)

2-(benzo[d][1,3]dioxol-5-yloxy)-1-phenylethanone was prepared by reacting 2′-bromoacetophenone and sesamol. 2-(benzo[d][1,3]dioxol-5-yloxy)-1-phenylethanone was then conensed with different aldehydes to prepare α-(1,3-benzodioxol-5-yloxy)-chalcone (2aa – 2ae).

Table 1c: Structure, yields and inhibition of cell proliferation in HCC1954 and HCT116 cell lines.

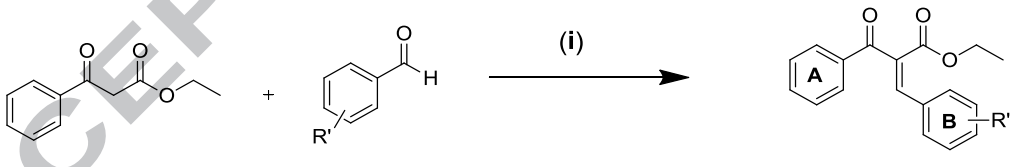


2aa -2ae

Compound	R^1	R^2	R^3	Yield (%)	HCC195 GI_{50} (µM) ± SD	HCT116 GI_{50} (µM) ± SD
2aa	OMe	OMe	OMe	28	46.97 ± 4.43 (N = 2)	57.31 ± 1.43 (N = 2)
2ab	H	H	H	27	41.02 ± 0.98 (N = 2)	35.94 ± 3.39 (N = 2)
2ac	H	H	Br	24	61.36 ± 7.34 (N = 2)	61.51 ± 16.54 (N = 2)
2ad	H	H	NO_2	44	>100 (N = 2)	>100 (N = 2)
2ae	H	H	Cl	13	>100 (N = 2)	>100 (N = 2)

2.1.2 Synthesis of α-COOEt chalcones (3a – 3e)

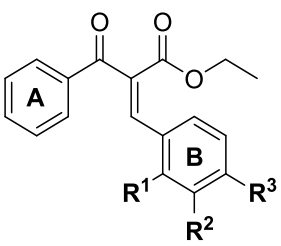
In order to prepare α-COOEt chalcones**,** Knoevenagel condensation was utilized: The ethyl benzoacetate was condensed with different aldehydes using piperidine and acetic acid as a catalyst in ethanol. Upon completion of the reaction, the product was purified by column chromatography to afford pure α-COOEt chalcones.



3a. R' = 4-OMe
3b. R' = 4-Cl
3c. R' = 4-F
3d. R' = 3-OMe
3e. R' = 2-OMe

Scheme 2. Synthetic routes of α-COOEt chalcones (**3a- 3e**). Reagents and conditions: (**i**). Piperidine, EtOH, r.t., 48 hr.

Table 2: Structure, yields and inhibition of cell proliferation in HCC1954 and HCT116 cell lines.

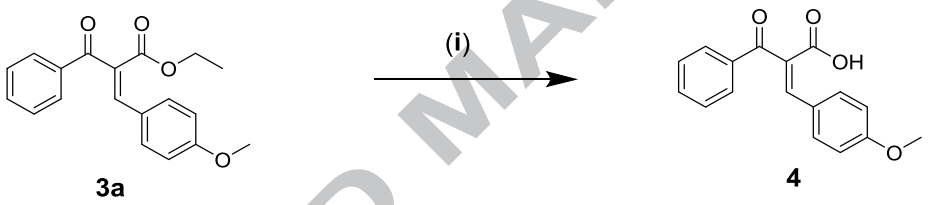


3a - 3e

Compound	R^1	R^2	R^3	Yield (%)	HCC1954 GI_{50} (µM)) ± SD	HCT116 GI_{50} (µM)) ± SD	N
3a	H	H	OMe	51	14.3 ± 2.32	4.04 ± 0.04	2
3b	H	H	Cl	44	6.38 ± 1.86	6.64 ± 0.67	2
3c	H	H	F	39	10.26 ± 1.79	9.69 ± 0.95	2
3d	H	OMe	H	44	8.27 ± 1.69	6.04 ± 1.21	2
3e	OMe	H	H	47	12.38 ± 1.12	9.65 ± 1.62	2

2.1.3 Synthesis of α-COOH chalcone (4)

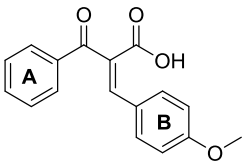
2-benzoyl-3-(4-methoxyphenyl)acrylic acid was prepared through hydrolysis of **3e** using potassium hydroxide in ethanol. The product was portioned into basic aqueous layer, which upon acidification by concentrated HCl yielded the precipitated product.



3a 4

Scheme 3. Synthesis of 2-benzoyl-3-(4-methoxyphenyl)acrylic acid (**4**). Reagents and conditions: (**i**). KOH, EtOH, r.t., 24 hr.

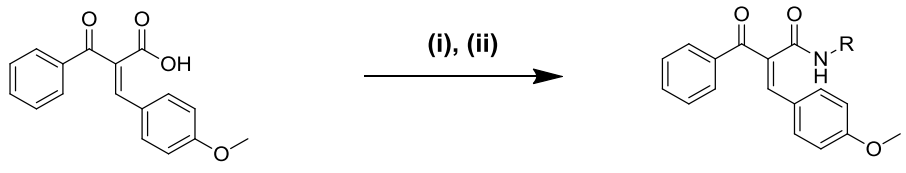
Table 3: Structure, yields and inhibition of cell proliferation in HCC1954 and HCT116 cell lines.



4

Yield (%)	HCC1954 GI_{50} (µM)	HCT116 GI_{50} (µM)	N
70	97.15 ± 1.15	72.7 ± 13.42	2

2.1.4 Synthesis of α-amide chalcones (5a – 5e)

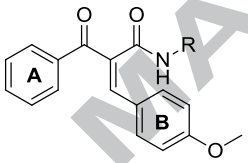


4 **5**

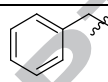
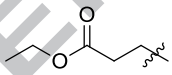
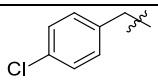
Scheme 4: Synthesis of β-keto amide (**i**) $(COCl)_2$, $SOCl_2$, r.t., 24 hr.; (**ii**) Et_3N, RNH_2, r.t., 6 hr.

In order to prepare α-amide chalcones, compound **4** was converted to the corresponding acid chloride using oxalyl chloride or thionyl chloride. The resulting acid chloride was then reacted with different amines (aliphatic and aromatic) in the presence of trimethylamine in an overnight reaction. The crude product was extracted in ethylacetate layer, given acidic washings and purified using column chromatography to obtain the pure α-amide chalcones (**5a -5e**).

Table 4: Structure, yields and inhibition of cell proliferation in HCC1954 and HCT116 cell lines.



5a - 5e

Compounds	R	Yield (%)	HCC1954 GI_{50} (μM)) ± SD	HCT116 GI_{50} (μM)) ± SD	N
5a		42	0.63 ± 0.06	0.69 ± 0.04	2
5b		21	7.53 ± 1.15	3.83 ± 0.83	2
5c		39	21.88 ± 1.27	13.25 ± 0.28	2
5d		28	6.61 ± 1.91	3.02 ± 0.17	2
5e		35	0.725 ± 0.05	1.59 ± 0.28	2

2.2 Biology

2.2.1 Antiproliferative activities:

All the compounds were evaluated for their antiproliferative activity in colorectal (HCT116) and breast (HCC1954) cancer cell lines. Half-maximal growth inhibition concentrations (GI_{50}) were determined in a 3-day Sulforhodamine (SRB) proliferation assay.

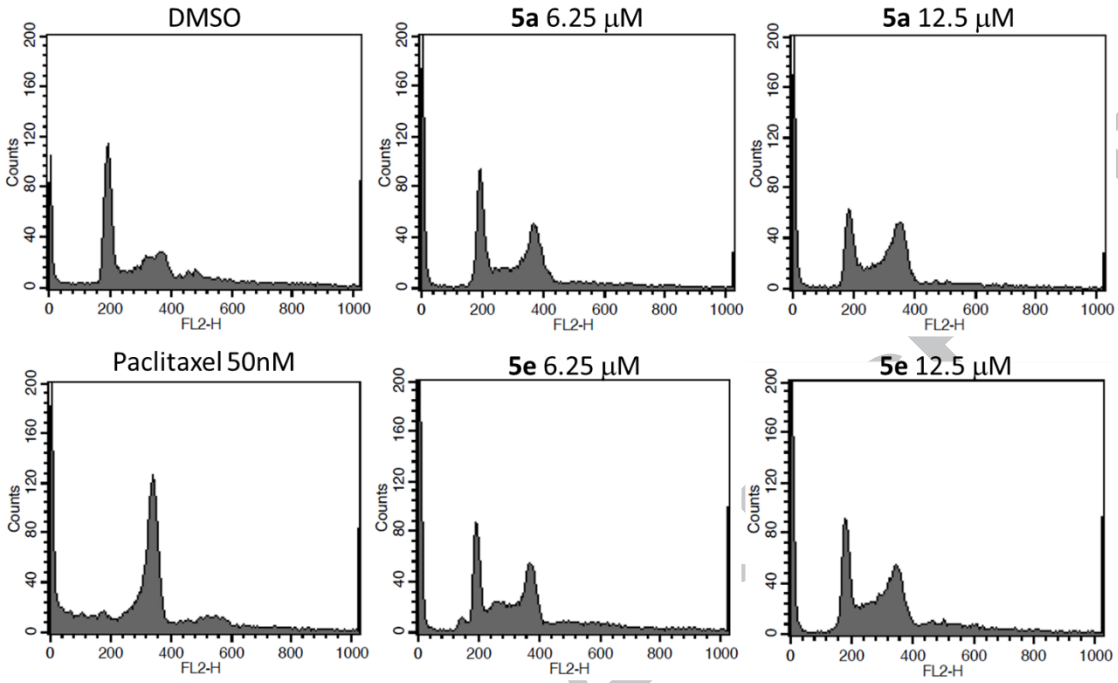
α-2-(naphthalen-2-yloxy)-1,3-diphenylprop-2-en-1-one (**2a - 2s, Table 1a**) were synthesized and evaluated in HCC1954 and HCT116 cell lines. Compound **2c** (R^4 = Cl) showed better activity (GI_{50} values of 19.35 μM and 23.54 μM in HCC1954 and HCT116 cell lines, respectively) than other analogues. Nine compounds out of the 19 α-2-(naphthalen-2-yloxy)-1,3-diphenylprop-2-en-1-one (**2a-2s**) were active with GI_{50} values ranging from 19 – 85 μM in at least one or both of the cell lines. All these nine compounds contain halogen or a trifluoromethyl group on the ring B. Compounds with nitro substitution (**2a**), mono and trimethoxy pattern (**2b**, **2f**, **2s**), alkyl chain (**2e**) difluoro substitution (**2p**, **2q**) and heteroaromatic B ring (**2l**, **2r** and **2n**) were found inactive against HCC1954 and HCT116 cell lines (>100 μM GI_{50}). Five analogues of α-(3,5-dimethylphenoxy)-chalcone (with 4-Cl, 3-NO_2, 2,3,4-trimethoxy, 4-Br) were synthesized and screened against HCC1954 and HCT116 cell line with GI_{50} values ranging from 12 – 55 μM (**2t – 2x, Table 1b)**. Five analogues of α-(1,3-benzodioxol-5-yloxy)-chalcones (**2aa-2ae, Table 1c**) differing in substitution pattern on B ring (4-NO_2, 4-Cl, 2,3,4-trimethoxy, 4-Br and unsubstituted phenyl ring) were synthesized and evaluated for their anticancer activity in both the cell lines. Maximum activity with GI_{50} values of 41.02 μM and 35.94 μM in HCC1594 and HCT116 cells respectively, was observed for compound **2ab** having unsubstituted ring B while the 2,3,4-trimethoxy substitution pattern showed slightly higher GI_{50} values. Descending order of anti-proliferative activity with respect to differentiation of substitution pattern on ring B is as follows: unsubstituted B ring > 2,3,4-trimethoxy > 4-Br > 4-Cl, 3-NO_2.

Among α-COOEt chalcones (**3a-3e, Table 2**), compound **3a** was found to be more active against HCT116 cell line with a GI_{50} value of 4.04 μM (Table 2). α-COOEt chalcones **3a and 3d** with 4-MeO and 3-MeO groups on ring B, respectively, showed better anti-proliferative activity than 2-MeO (**3b**) and 4-halogen substitutions on ring B (**3c and 3e**). Compound **3a** had the best activity and was, therefore, selected as a lead compound and used for the preparation of further derivatives. It was first hydrolysed to yield α-COOH chalcone (**4**) that had GI_{50} value of 97.15 μM and 72.7 μM in HCC1954 and HCT116, respectively. The chalcone (**4**) was then reacted with various amines to prepare α-amide chalcones (compounds **5a – 5e, Table 4**). These compounds showed superior activity than α-COOEt, α-COOH chalcones and α-aryloxy chalcones. Compounds **5a** and **5e** were found to be more active in HCC1954 cell line with GI_{50} values of 0.63 μM and 0.725 μM, respectively. In HCT116 cell line, compounds **5a** and **5e** exhibited GI_{50} values of 0.69 μM and 1.59 μM, respectively. As the compounds **5a** and **5e** displayed the lowest GI_{50} values among the tested compounds, these were chosen for further biological studies.

2.2.2 Compound 5a and 5e cause cell cycle arrest in S and G2/M phases

In order to determine the possible mechanism of action of these compounds, we determined the cell cycle profile using FACS analysis in HCT116 cells following treatment with different concentrations of both compounds for 24 hours. As shown in Figure 4, both compounds **5a** and **5e** induced a G2/M cell cycle arrest at 6.25 μM and 12.5 μM concentrations compared with the DMSO treated controls. Paclitaxel, a positive control completely arrested the cells in the G2/M phase of the cell cycle. An increase in S phase of the cell cycle was also observed following treatment of cells with both the compounds. These compounds are therefore, capable of causing the cell cycle arrest in S and G2/M phase in HCT116 cell line.

A



B

Cell cycle phase	DMSO	5a		5e		Paclitaxel
		6.25µM	12.5µM	6.25µM	12.5µM	50nM
SubG1	10.31	13.42	13.25	23.83	5.38	21.86
G1	46.34	36.86	31.27	31.20	33.94	8.89
S	24.23	23.44	32.17	29.14	30.27	17.06
G2/M	25.28	38.93	34.92	35.71	37.40	54.56

Figure 4: Effect of **5a** and **5e** on cell cycle in HCT116 cells. A. HCT116 cells treated with 6.25µM and 12.5µM concentrations of **5a** and **5e** for 24 hours. Treatment with paclitaxel was used as a control for G2/M cell cycle arrest. Cells were fixed, stained with propidium iodide and analysed through FACS. B. Quantification of cells in different phases of the cell cycle represented as relative percentage in each phase**.**

2.2.3 Compound 5a and 5e induce apoptosis and increase p53 levels in HCT116 cells.

We next determined the ability of compounds **5a** and **5e** to induced apoptosis in HCT116 cells. Cells were treated with three increasing concentrations (1.56, 3.13 and 6.25 µM) of compound **5a** or **5e** for 24 hours and apoptosis was determined through western blotting using antibodies specific for cleaved-PARP, an apoptotic marker. β-actin was used as a loading control. As shown in Figure 4, both compounds induced a robust, dose-dependent increase in cleaved-PARP following 24-hour treatment. The increase in cleaved-PARP was also accompanied by an increase in the expression of the pro-apoptotic p53 protein (Figure 5).

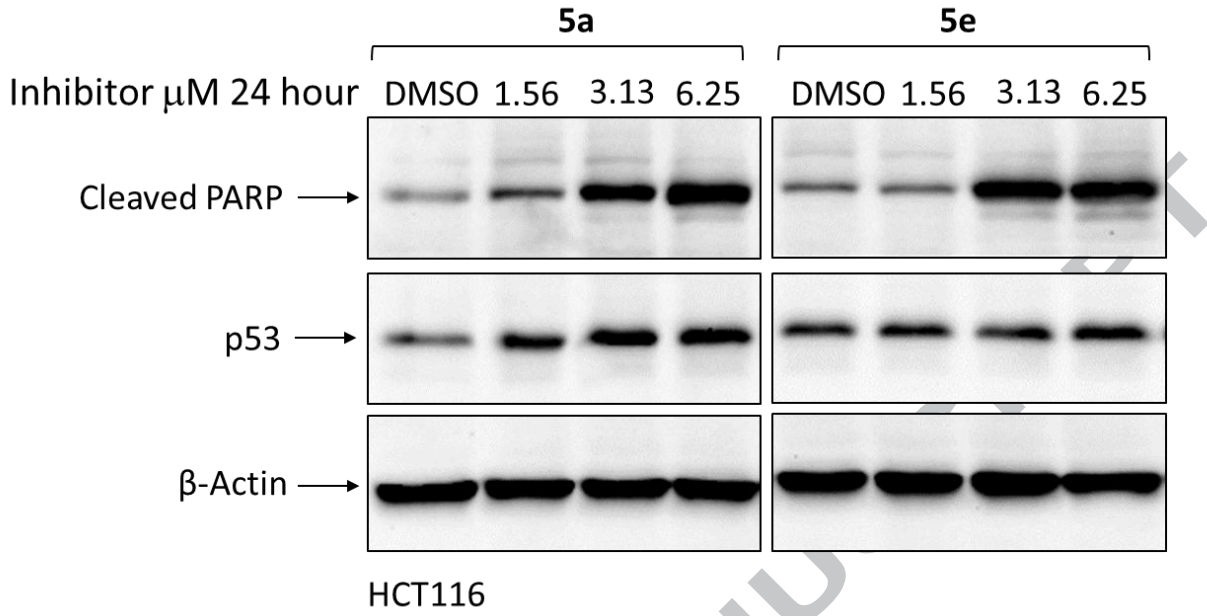


Figure 4: Compounds **5a** and **5e** induce apoptotic cell death in HCT116 cells. Cells treated with three different concentrations of **5a** and **5e** for 24 hours were analysed by western blotting using antibodies specific for Cleaved-PARP, p53 and β-actin.

2.2.4 p53 stabilization by 5a is not through post-translational mechanism:

We have recently shown that chalcone derivatives, **SSE14105** and **SSE14106**, can cause rapid accumulation of p53 in HCT116 cells through a post-translational mechanism.[27] In order to determine whether the increase in p53 levels following treatment with **5a** and **5e** in HCT116 cells is regulated at the transcriptional or post-translational level, we measured p53 levels following treatment with 6.25 µM **5a** in the presence or absence of cycloheximide (CHX; an inhibitor of protein translation) for different time points. Treatment with **5a** did not have any effect on the stability of p53 protein following incubation with CHX at different time points (Figure 5), indicating that **5a** does not regulate p53 protein at the post-translational level. The accumulation of p53 following **5a** treatment, therefore, seems to be regulated through a transcriptional mechanism.

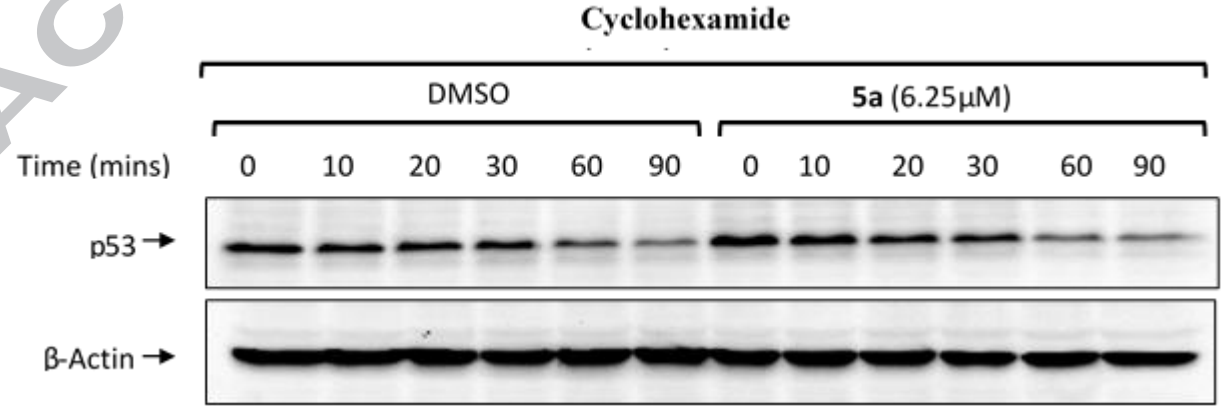


Figure 5: p53 stabilization by compound **5a** is not regulated at the post-translational level. HCT116 cells were treated with DMSO or 6.25 µM **5a** in the presence of CHX and samples

were taken after 10, 20, 30, 60 and 90 minutes of incubation and p53 levels were determined through western blotting.

2.2.5 Compound 5a and 5e overcome multidrug resistance

Compounds **5a** and **5e** were next evaluated for their ability to overcome multidrug resistance in two pairs of parental and MDR1/Pgp expressing cell lines (A2780/A2780-Pac-Res and KB-3-1/KB-V1). As shown in Table 5, both the MDR1 expressing cell lines were highly resistant to paclitaxel when compared to the parental controls (resistance index of 494 and >1000 for A2780-Pac-Res and KB-V1, respectively). Compounds **5a** and **5e** however, were able to overcome the multidrug resistance in both these cell lines with GI_{50} values comparable to parental controls (Resistance index values of 1.15 and 1.28 for A2780-Pac-Res and KB-V1, respectively).

Cell Lines	**GI_{50} value**		
	5a (µM)	**5e (µM)**	**Paclitaxel(nM)**
A2780	2.11±0.01 (2)	2.27±0.05 (2)	0.433
A2780-Pac-Res	2.43±0. 07 (2)	2.91±0.09 (2)	214
Resistance Index	**1.15**	**1.28**	**494**
KB-3-1	3.24±0.02 (2)	4.79±0.05 (2)	0.2085
KB-V1	3.9±0.28 (2)	6.38±0.28 (2)	>2000
Resistance Index	**1.2**	**1.33**	**>1000**

Table 5: GI_{50} values of **5a**, **5e** and paclitaxel in two pairs of parental and MDR cell lines (A2780/A2780-Pac-Res; Human ovarian cancer cell lines and KB-3-1/KB-V1; cervical cancer cell lines)

We next determined whether **5a** compound could directly inhibit the activity of Pgp in an in vitro Pgp-Glo assay. As shown in Figure 6, there was no significant effect of **5a** on the ATPase activity of Pgp. Verapamil, a substrate of Pgp, on the other hand, enhanced its ATPase activity by ~ 3 fold. This confirms that **5a** overcomes multidrug resistance in these cells by not being a substrate of Pgp.

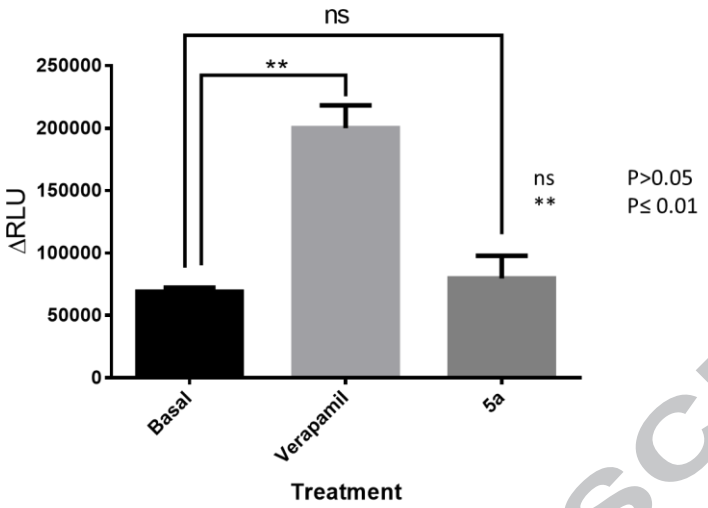


Figure 6: Compound **5a** does not inhibit Pgp ATPase activity *in vitro*. ATPase activity of Pgp was measured using Pgp-Glo assay (Promega) from untreated, 100μM Na_3VO_4, 200μM Verapamil- and 10μM **5a** compound-treated Pgp reactions. Basal, verapamil-treated and **5a**-treated activity of the Pgp ATPase was calculated according to the manufacturer's instructions. ΔRLU= Difference in relative light units.

3. Conclusion

In the current work, we have presented the synthesis of forty chalcone-derived compounds including thirty-seven novel compounds. All the compounds were evaluated for their antiproliferative activities in colorectal (HCT116) and breast (HCC1954) cancer cell lines. Two α-amide chalcones (**5a** and **5e**) showed GI_{50} in the nanomolar range and were identified as the most active compounds. Both these compounds were able to induce G2/M cell cycle arrest and apoptotic cell death in HCT116 cells. Similarly, both the compounds increased p53 levels following 24-hour treatment. Finally, we evaluated these compounds (**5a** and **5e)** for their ability to overcome multidrug resistance in the MDR1 overexpressing multidrug resistant cell lines (A2780-Pac-Res and KB-V1). Both compounds showed that they were capable of overcoming the multidrug resistance without much loss in the activity. We also determined that the **5a** compound does not directly inhibit the ATPase activity of Pgp (MDR1), *in vitro*, and hence overcomes multidrug resistance by being not a Pgp substrate. Compounds **5a** and **5e** therefore could serve as novel hits for further lead optimization studies to discover anticancer compounds with the ability to overcome multidrug resistance.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgement

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4. Experimental

General Method:

Commercial reagents were used without further purification. Reagent grade solvents were distilled before use. Silica gel 60 (230-400 mesh) from Merck was used for column chromatography. Bruker, P Alpha Spectrometer was used for recording IR spectra. Proton and carbon NMR spectra were recorded on Bruker Ascend 600 MHz. Thermo Scientific, 1300 GC-MS), was used to obtain GC-MS spectra. Melting points were taken on STUART SMP3 melting point apparatus.

4.1 General procedure for the synthesis of α-aryloxy chalcones (2a – 2x, 2aa – 2ae)

Preparation of 2- Naphthol, 3,5-dimethylphenol and sesamol ethers (2′, 2′′, 2′′′): Phenol (2-Naphthol, 3,5-dimethylphenol or sesamol) (1 equiv), 2′-bromoacetophenone (1 equiv) were added to a reaction flask followed by addition of acetonitrile (10 mL). K_2CO_3 (2 equiv) was added to the reaction flask and the reaction mixture was stirred at room temperature for 48 hours and the progress of the reaction was monitored using thin layer chromatography.[45] The reaction mixture was then acidified with conc. HCl to bring pH to neutral. The crude product was extracted into ethyl acetate (EtOAc) and purified through column chromatography (using hexanes and ethyl acetate, 9:1). The 2-aryloxy-1-phenylethanones (**2′**, **2′′**, **2′′′**) were obtained in 90 -98% yields.

2-(naphthalen-2-yloxy)-1-phenylethanone (2′): Brown solid (92.7%); m.p. 73-75 °C (Lit: 77 °C)[45]; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 9.7 Hz, 2H), 7.78 (d, *J* = 9.1 Hz, 2H), 7.71 (d, *J* = 9.3 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.44 (t, *J* = 8.1 Hz, 1H), 7.36 (t, *J* = 8.1 Hz, 1H), 7.28 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 5.38 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.5 (C), 156.1 (C), 134.7 (C), 134.4 (C), 134.0 (CH), 129.9 (C), 129.5 (CH), 129.0 (CH), 128.3 (CH), 127.8 (CH), 127.0 (CH), 126.6 (CH), 124.2 (CH), 118.8 (CH), 107.4 (CH), 70.9 (CH_2); MS m/z [M^+] 264.12; FT-IR (ATR): 3050, 1699, 1628, 1597, 1211 cm^{-1}.

2-(3,5-dimethylphenoxy)-1-phenylethanone (2′′): Brown solid (89.6%); m.p. 99.8-103 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.02 (d, *J* = 9.7 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 6.65 (s, 1H), 6.59 (s, 2H), 5.24 (s, 2H), 2.29 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 194.8 (C), 158.2 (C), 139.5 (C), 134.8 (C), 133.9 (CH), 128.9 (CH), 128.3 (CH), 123.6 (CH), 112.6 (CH), 70.8 (CH_2), 21.5 (CH_3); MS m/z [M^+] 240.12; FT-IR (ATR): 2916, 1705, 1593, 1510, 1462, 1417, 1323, 1246, 1211, 1164 cm^{-1}.

2-(benzodioxol-5-yloxy)-1-phenylethanone (2′′′): Brown solid (98.4%); m.p. 102-114 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.97 (d, *J* = 9.8 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 1H), 6.55 (d, *J* = 2.5 Hz, 1H), 6.34 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.88 (s, 2H), 5.19 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 194.7 (C), 153.6 (C), 148.4 (C), 142.4 (C), 134.6 (C), 133.9 (CH), 128.9 (CH), 128.1 (CH), 107.9 (CH), 106.1 (CH), 101.3 (CH_2), 98.7 (CH), 71.8 (CH_2); MS m/z [M^+] 256.07; FT-IR (ATR): 1700, 1494, 1431, 1244, 1179, 1033 cm^{-1}.

Synthesis of α-aryloxy chalcones (2a - 2x, 2aa – 2ae) from ethers: Compounds **2′**, **2′′** and **2′′′** (1 equiv) were condensed with substituted aldehydes (1 equiv) in presence of KOH and ethanol as solvent. The reaction mixture was stirred for 24 hours at room temperature. The crude product was extracted into EtOAc layer and compounds (**2a** – **2x**, **2aa** – **2ae**) were purified through column chromatography (hexanes:ethyl acetate, 8:2).

2-(naphthalen-2-yloxy)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (2a): White solid (84.7%); m.p. 167.7 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.05 (d, *J* = 8.9 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 7.4 Hz, 2H), 7.57 (dd, *J* = 8.6, 3.5 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.23-7.27 (m, 3H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.12 – 7.09 (m, 1H), 7.05 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.88 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.7 (C), 153.5 (C), 151.0 (C), 147.7 (C), 139.5 (C), 136.1, 134.1 (C), 133.4 (C), 130.9 (CH), 130.5 (CH), 130.3 (C), 129.5 (CH), 128.6 (CH), 127.9 (CH), 127.2 (CH), 127.0 (CH), 125.1 (CH), 124.1 (CH), 123.5 (CH), 118.0 (CH), 111.5 (CH); MS m/z [M^+] 395.12; FT-IR (ATR): 3057, 1663, 1625, 1462, 1164 cm^{-1}.

3-(4-methoxyphenyl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2b): Viscous liquid (47.3%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.91 (d, *J* = 6.9 Hz, 2H), 7.77-7.71 (m, 4H), 7.65 (d, *J* = 9.5 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.45-7.37 (m, 3H), 7.33 (t, *J* = 8.1 Hz, 1H), 7.29-7.28 (m, 2H), 7.16 (s, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.2 (C), 161.0 (C), 154.2 (C), 146.6 (C), 137.4 (CH), 134.3 (C), 132.5 (C), 132.5 (C), 130.2 (C), 130.0 (CH), 129.4 (CH), 129.3 (CH), 128.4 (CH), 127.8 (CH), 127.1 (CH), 126.6 (CH), 125.6 (CH), 124.5 (CH), 118.1 (CH), 114.4 (CH), 110.4 (CH), 55.4 (CH_3); m/z [M^+]: 310.06; FT-IR (ATR): 3055, 2837, 1653, 1628, 1596, 1508, 1462, 1246, 1211, 1164, 1027 cm^{-1}.

3-(4-chlorophenyl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2c): Pale Yellow (39.8%); m.p. 101-104 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.78-7.777 (m, 2H), 7.60-7.59 (m, 4H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.30-7.24 (m, 3H), 7.22 – 7.19 (m, 3H), 7.13-7.10 (m, 2H), 6.93 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.0 (C), 153.9 (C), 148.6 (C), 136.8 (C), 135.6 (C), 134.2 (C), 132.9 (CH), 131.7 (CH), 131.5 (C), 130.3 (CH), 130.1 (C), 129.4 (CH), 129.2 (CH), 128.5 (CH), 127.8 (CH), 127.2 (CH), 126.8 (CH), 126.7 CH), 124.8 (CH), 118.0 (CH), 110.8 (CH); MS m/z [M^+] 384.09; FT-IR (ATR): 3057, 1657, 1627, 1597, 1510, 1489, 1463, 1357, 1246, 1212, 1165, 1131 cm^{-1}.

3-(2-chlorophenyl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2d): White solid (55.1%); m.p. 76.81 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.95 (d, *J* = 9.6 Hz, 1H), 7.79 (d, *J* = 6.9 Hz, 2H), 7.56-7.55 (m, 2H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.32 (s, 1H), 7.28-7.23 (m, 4H), 7.17 (t, *J* = 8.2 Hz, 1H), 7.12 (d, J= 2.3 Hz, 1H), 7.10-7.03 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.9 (C), 154.1 (C), 149.1 (C), 136.7 (C), 134.9 (C), 134.2 (C), 133.0 (CH), 131.1 (C), 131.0 (CH), 130.5 (CH), 130.3 (CH), 130.1 (C), 129.9 (CH), 129.6 (CH), 128.5 (CH), 127.8 (CH), 127.2 (CH), 127.1 (CH), 126.8 (CH), 124.8 (CH), 123.5 (CH), 118.2 (CH), 111.0 (CH); MS m/z [M^+] 384.09; FT-IR (ATR): 3057, 1659, 1596, 1509, 1463, 1438, 1243, 1210, 1162, 1124, 1051 cm^{-1}.

3-(4-isopropylphenyl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2e): Viscous liquid (74.2%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.79 (d, *J* = 6.9 Hz, 2H), 7.63-7.61 (m, 4H), 7.53 (d, *J* = 9.6 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.30 – 7.26 (m, 3H), 7.21 (t, *J* = 8.1 Hz, 1H), 7.19 – 7.16 (m, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.04 (s, 1H), 2.77 (hept, *J* = 6.9 Hz, 1H), 1.12 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.2 (C), 154.2 (C), 151.2 (C), 147.6 (C), 137.2 (C), 134.3 (C), 132.6 (CH), 130.8 (CH), 130.5 (C), 130.2 (CH), 130.0 (C), 129.4 (CH), 129.0 (CH), 128.4 (CH), 127.8 (CH), 127.1 (CH), 127.1 (CH), 126.7 (CH), 124.5 (CH), 118.1 (CH), 110.5 (CH), 34.2 (CH), 23.8 (CH_3); MS m/z [M^+] 392.18; FT-IR (ATR): 3054, 2960, 1656, 1597, 1510, 1462, 1316, 1245, 1210, 1164, 1130 cm^{-1}.

2-(naphthalen-2-yloxy)-1-phenyl-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (2f): Yellow solid (47.3%); m.p. 118-119.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.94 – 7.89 (m, 3H), 7.74 (dd, *J* = 9.1, 6.0 Hz, 2H), 7.66 (d, *J* = 9.6 Hz, 1H), 7.55 (s, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.33 (t, *J* = 8.1 Hz, 1H), 7.30- 7.27 (m, 2H), 6.63 (d, *J* = 9.0 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.1 (C), 155.3 (C), 154.3 (C), 153.3 (C), 147.2 (C), 142.1 (C), 137.5 (C), 134.3 (C), 132.5 (CH), 130.1 (CH), 130.0 (C), 129.4 (C), 128.3 (C), 127.8 (CH), 127.1 (CH), 126.6 (CH), 125.8 (CH), 124.4 (CH), 123.3 (CH), 119.8 (C), 118.1 (CH), 110.4 (CH), 107.8 (CH), 61.8 (CH_3), 61.0 (CH_3), 56.1 (CH_3); MS m/z [M^+] 440.16; FT-IR (ATR): 3057, 2937, 1653, 1589, 1494, 1461, 1412, 1298, 1248, 1211, 1165, 1130 cm^{-1}.

3-(4-bromophenyl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2g): Brown solid (34.1%); m.p. 81.3-86 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.13 (d, *J* = 6.3 Hz, 2H), 7.95 (dd, *J* = 8.5, 3.3 Hz, 2H), 7.89-7.86 (m, 3H), 7.74 – 7.70 (m, 3H), 7.64-7.61 (m, 3H), 7.56 (t, *J* = 8.1 Hz, 1H), 7.49-7.49 (m, 2H), 7.45 (dd, *J* = 8.9, 2.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.0 (C), 153.8 (C), 148.7 (C), 136.7 (C), 134.2 (C), 132.9 (CH), 132.2 (CH), 131.9 (CH), 131.9 (C), 130.3 (CH), 130.1 (C), 129.4 (CH), 128.5 (CH), 127.8 (CH), 127.2 (CH), 126.8 (CH), 126.7 (CH), 124.8 (CH), 124.0 (C), 118.0 (CH), 110.9 (CH); MS m/z [M^+] 428.04; FT-IR (ATR): 3055, 1657, 1626, 1596, 1509, 1485, 1462, 1399, 1355, 1309, 1244, 1210, 1163, 1130, 1072, 1009 cm^{-1}.

2-(naphthalen-2-yloxy)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (2h): Viscous liquid (18.1%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.81-7.78 (m, 4H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.29 (m, 3H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.15 (s, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 6.96 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.9 (C), 153.7 (C), 149.8 (C), 136.4 (C), 136.4 (C), 134.1 (C), 133.2 (CH), 130.8 (q, *J* = 32 Hz, C), 130.5 (CH), 130.4 (CH), 130.2 (C), 129.5 (CH), 128.6 (CH), 127.8 (CH), 127.2 (CH), 126.9 (CH), 125.8 (q, *J* = 3 Hz, CH), 125.4 (CH), 124.9 (CH), 124.1 (q, *J* = 252.13 Hz, C), 118.0 (CH), 111.1 (CH); MS m/z [M^+] 418.12; FT-IR (ATR): 3057, 1662, 1598, 1511, 1463, 1320, 1246, 1212, 1165, 1123, 1067, 1016 cm^{-1}.

3-(4-fluorophenyl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2i): Viscous liquid (13.6%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.76 (d, *J* = 7.0 Hz, 2H), 7.65 (dd, *J* = 8.8, 5.6 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.27-7.25 (m, 3H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.13-7.10 (m, 2H), 6.95 (s, 1H), 6.90 (t, *J* = 8.7 Hz, 2H);

^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.1 (C), 163.4 (d, *J* = 252 Hz, C), 153.9 (C), 147.9 (C), 136.9 (C), 134.2 (C), 132.8 (CH), 132.6 (d, *J* = 8 Hz, CH), 130.3 (CH), 130.1 (C), 129.4 (CH), 129.2 (d, *J* = 3Hz, C), 128.5 (CH), 127.8 (CH), 127.2 (CH), 127.1 (CH), 126.8 (CH), 124.7 (CH), 118.0 (CH), 116.1 (CH), 116.0 (d, *J* = 21.7, CH), 110.7 (CH); MS m/z [M^+] 368.12; FT-IR (ATR): 3057, 1656, 1597, 1505, 1463, 1211, 1157, 1010 cm^{-1}.

3-(2-fluorophenyl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2j): Brown solid (23.4%y); m.p. 131.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.04 (t, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 6.7 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.33-7.29 (m, 3H), 7.26-7.19 (m, 3H), 7.16-7.14 (m, 1H), 7.02 – 6.98 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.8 (C), 160.9 (d, *J* = 252 Hz, C), 154.0 (C), 149.2 (C), 136.7 (C), 134.2 (C), 133.0 (CH), 131.4 (d, *J* = 8 Hz, CH), 130.7 (d, *J* = 2 Hz, CH), 130.3 (C), 130.1 (CH), 129.5 (CH), 128.5 (CH), 127.8 (CH), 127.2 (CH), 126.8 (CH), 124.7 (CH), 124.6 (d, *J* = 3 Hz, CH), 121. 1 (d, *J* = 9 Hz, C), 119.0 (d, *J* = 7 Hz, CH), 118.1 (CH), 115.6 (d, *J* = 22 Hz, CH), 111.0 (CH); MS m/z [M^+] 368.12; FT-IR (ATR): 1651, 1625, 1231, 1194, 1116, 1032 cm^{-1}.

3-(2, 5-difluorophenyl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2k): Light brown solid (41.9%); m.p. 127.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.94-7.90 (m, 3H), 7.75 (d, *J* = 9.1 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.45-7.42 (m, 3H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.30-7.25 (m, 3H), 7.11-7.07 (m, 1H), 7.05 – 7.01 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.6 (C), 158.6 (d, *J* = 256 Hz, C), 157.0 (d, *J* = 241 Hz, C), 153.6 (C), 150.2 (C), 136.4 (C), 134.1 (C), 133.2 (CH), 130.4 (CH), 130.3 (C), 129.5 (CH), 128.6 (CH), 127.9 (CH), 127.2 (CH), 126.9 (CH), 124.9 (CH), 122.3 (dd, *J* = 13, 9 Hz, C), 118.1 (CH), 117.7 (dd, *J* = 24, 8 Hz, CH), 117.1 (dd, *J* = 8, 2 Hz, CH), 116.8 (d, *J* = 2 Hz, CH), 116.5 (dd, *J* = 25, 8 Hz, CH), 111.3 (CH); MS m/z [M^+] 386.11; FT-IR (ATR): 3060, 2925, 1663, 1628, 1598, 1510, 1484, 1464, 1357, 1264, 1246, 1212, 1167, 1131 cm^{-1}.

2-(naphthalen-2-yloxy)-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (2l): Light brown solid (41.9%); m.p. 127.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.75 (d, *J* = 8.3 Hz, 2H), 7.58 (t, *J* = 9.1 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.36-7.34 (m, 2H), 7.29-7.22 (m, 5H), 7.18-7.15 (m, 2H), 7.11-7.10 (m, 1H), 6.92 (t, *J* = 9.9 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.0 (C), 153.8 (C), 145.8 (C), 137.2 (C), 135.5 (C), 134.3 (C), 132.7 (CH), 132.4 (CH), 131.2 (CH), 130.1 (C), 130.1 (CH), 129.3 (CH), 128.5 (CH), 127.8 (CH), 127.3 (CH), 127.2 (CH), 126.7 (CH), 124.5 (CH), 123.7 (CH), 118.0 (CH), 110.2 (CH); MS m/z [M^+] 356.09; FT-IR (ATR): 3057, 1651, 1629, 1598, 1510, 1462, 1333, 1267, 1212, 1164 cm^{-1}.

3-(3-fluorophenyl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2m): Viscous liquid (69.0%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.86 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 9.1 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 10.3 Hz, 1H), 7.46 (t, *J* = 8.2 Hz, 2H), 7.37-7.34 (m, 3H), 7.30-7.26 (m, 2H), 7.22 (d, *J* = 2.5 Hz, 1H), 7.20 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.01 – 6.99 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.0 (C), 162.9 (d, *J* = 245 Hz, C), 153.8 (C), 149.1 (C), 136.6 (C), 135.0 (C), 135.0 (C), 134.2 (C), 133.0 (CH), 130.3 (CH), 130.2 (d, *J* = 15 Hz, CH), 129.5 (CH), 128.5 (CH), 127.8 (CH), 127.2 (CH), 126.8 (CH), 126.5 (d, *J* = 2 Hz, CH), 126.2 (d, *J* = 2 Hz, CH), 124.8 (CH), 118.1 (CH), 116.8 (d, *J* = 27 Hz, CH), 116.7

(d, *J* = 21 Hz, CH), 111.0 (CH); MS m/z [M^+] 368.12; FT-IR (ATR): 3057, 1658, 1596, 1509, 1463, 1445, 1355, 1277, 1210 cm^{-1}.

2-(naphthalen-2-yloxy)-1-phenyl-3-(pyridin-3-yl)prop-2-en-1-one (2n): White solid (73.7%); m.p. 78 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.26 (s, 1H), 7.90 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.3 Hz, 2H), 7.06 (d, *J* = 9.2 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.85 (t, *J* = 7.4 Hz, 1H), 6.76-6.73 (m, 3H), 6.68 (t, *J* = 7.7 Hz, 1H), 6.64-6.60 (m, 2H), 6.57 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.38 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.6 (C), 153.6 (C), 151.3 (CH), 150.1 (CH), 150.0 (C), 136.9 (C), 136.4 (CH), 134.1 (C), 133.2 (CH), 130.4 (C), 130.2 (CH), 129.5 (CH), 129.3 (C), 128.6 (CH), 127.8 (CH), 127.2 (CH), 126.9 (CH), 124.9 (CH), 124.0 (CH), 123.5 (CH), 118.0 (CH), 111.0 (CH); MS m/z [M^+] 356.09; FT-IR (ATR): 1660, 1627, 1597, 1510, 1355, 1332, 1246, 1212, 1165, 1132 cm^{-1}.

3-(3,4-difluorophenyl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2o): Viscous liquid (11.9%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.93 (d, *J* = 7.6 Hz, 2H), 7.78-7.75 (m, 3H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.54-7.49 (m, 2H), 7.44-7.42 (m, 3H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.28-7.25 (m, 2H), 7.20-7.15 (m, 1H), 7.02 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.9 (C), 153.7 (C), 151.5 (dd, *J* = 253, 12 Hz, C), 149.8 (dd, *J* = 248, 12 Hz, C), 148.8 (d, *J* = 2 Hz, C), 136.5 (C), 134.1 (C), 133.0 (CH), 130.4 (C), 130.2 (CH), 130.1 (dd, *J* = 6, 4 Hz, C), 129.4 (CH), 128.5 (CH), 127.8 (CH), 127.3 (q, *J* = 3 Hz, CH), 127.2 (CH), 126.9 (CH), 125.3 (CH), 124.9 (CH), 119.0 (d, *J* = 18 Hz, CH), 118.0 (CH), 117.7 (d, *J* = 17 Hz, CH), 111.0 (CH); MS m/z [M^+] 386.11; FT-IR (ATR): 3057, 1660, 1597, 1510, 1264, 1211, 1111, 1083, 1014 cm^{-1}.

3-(3,5-difluorophenyl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2p): Yellow solid (36.5%); m.p. 138.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.91 (d, *J* = 8.2 Hz, 2H), 7.73 (dd, *J* = 8.6, 3.1 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.43-7.39 (m, 3H), 7.37-7.35 (m, 3H), 7.28 (d, *J* = 2.6 Hz, 1H), 7.24 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.95 (s, 1H), 6.80 (t, *J* = 8.7 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.8 (C), 163.1 (dd, *J* = 248, 12 Hz, C), 153.5 (C), 150.0 (C), 136.3 (C), 135.9 (t, *J* = 10 Hz, C), 134.1 (C), 133.2 (CH), 130.4 (CH), 130.2 (C), 129.4 (CH), 128.5 (CH), 127.8 (CH), 127.2 (CH), 126.9 (CH), 124.9 (CH), 124.4 (t, *J* = 2.8 Hz, CH), 118.0 (CH), 113.0 (dd, *J* = 20, 5 Hz, CH), 111.2 (CH), 104.9 (t, *J* = 25 Hz, CH); MS m/z [M^+] 386.39; FT-IR (ATR): 3059, 2927, 1662, 1618, 1587, 1446, 1344, 1262, 1211, 1166, 1119 cm^{-1}.

3-(2,4-difluorophenyl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2q): White solid (51.4%); m.p. 122.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.17 – 8.13 (m, 1H), 7.90 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 9.1 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.40-7.38 (m, 3H), 7.32 (t, *J* = 8.1 Hz, 1H), 7.26 (d, *J* = 3.6 Hz, 2H), 7.22 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.86-6.81 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.7 (C), 163.6 (dd, *J* = 253, 12 Hz, C), 161.3 (dd, *J* = 246, 12 Hz, C), 153.8 (C), 149.0 (C), 136.6 (C), 134.2 (C), 133.0 (CH), 131.8 (dd, *J* = 9, 3 Hz, CH), 130.3 (CH), 130.2 (C), 129.5 (CH), 128.5 (CH), 127.8 (CH), 127.2 (CH), 126.9 (CH), 124.8 (CH), 118.0 (CH), 117.9 (dd, *J* = 6, 1 Hz, CH), 117.5 (dd, *J* = 11, 3 Hz, C), 112.1 (dd, *J* = 21, 3 Hz, CH), 111.0 (CH), 104.1 (t, *J* = 25 Hz, CH); MS m/z [M^+] 386.11; FT-IR (ATR): 3057, 1662, 1596, 1496, 1463, 1429, 1260, 1210, 1163, 1089 cm^{-1}.

3-(5-bromothiophen-2-yl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2r): Black purple solid (29.3%); m.p. 92.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.92 (d, *J* = 8.0 Hz, 2H), 7.76 (m, 2H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.45-7.40 (m, 3H), 7.39 (s, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.32 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.29 (d, *J* = 2.5 Hz, 1H), 7.11 (d, *J* = 4.0 Hz, 1H), 7.04 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 190.5 (C), 153.5 (C), 146.0 (C), 137.2 (C), 136.9 (C), 134.1 (C), 132.8 (CH), 132.2 (CH), 130.2 (C), 130.2 (CH), 130.1 (CH), 129.2 (CH), 128.5 (CH), 127.8 (CH), 127.2 (CH), 126.7 (CH), 124.7 (CH), 122.9 (CH), 119.1 (C), 117.9 (CH), 110.4 (CH); MS m/z [M^+] 386.11; FT-IR (ATR): 3056, 1660, 1597, 1510, 1462, 1417, 1323, 1246, 1211, 1164 cm^{-1}.

3-(3-methoxyphenyl)-2-(naphthalen-2-yloxy)-1-phenylprop-2-en-1-one (2s): Viscous liquid (21.6 %); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.77 (d, *J* = 9.7 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 9.5 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.27-7.23 (m, 4H), 7.21-7.17 (m, 2H), 7.14-7.11 (m, 2H), 7.11 (d, *J* = 2.2 Hz, 1H), 6.96 (s, 1H), 6.76 (dd, *J* = 8.3, 3.6 Hz, 1H), 3.58 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.2 (C), 159.8 (C), 154.1 (C), 148.3 (C), 137.0 (C), 134.3 (C), 134.1 (C), 132.8 (CH), 130.2 (CH), 130.2 (C), 129.8 (CH), 129.5 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.2 (CH), 126.7 (CH), 124.6 (CH), 123.4 (CH), 118.0 (CH), 116.0 (CH),, 115.3 (CH), 110.6 (CH), 55.3 (CH_3)**;** MS m/z [M^+] 380.14; FT-IR (ATR): 3055, 2935, 1655, 1625, 1446, 1353, 1274, 1210, 1160, 1113, 1046 cm^{-1}.

2-(3,5-dimethylphenoxy)-3-(3-nitrophenyl)-1-phenylprop-2-en-1-one (2t): Yellow solid (64.4%); m.p. 135 - 136.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.60 (s, 1H), 8.16 (d, *J* = 11.5 Hz, 1H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 9.7 Hz, 2H), 7.57 – 7.52 (m, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 6.93 (s, 1H), 6.61 (s, 1H), 6.60 (s, 2H), 2.20 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.8 (C), 155.6 (C), 150.5 (C), 148.6 (C), 139.9 (C), 136.4 (C), 135.7 (CH), 134.8 (C), 133.2 (CH), 129.8 (CH), 129.5 (CH), 128.6 (CH), 125.4 (CH), 124.9 (CH), 123.7 (CH), 123.5 (CH), 114.1 (CH), 21.4 (CH_3); MS m/z [M^+] 373.13; FT-IR (ATR): 3062, 2919, 1662, 1592, 1527, 1447, 1346, 1287, 1148, 1032 cm^{-1}.

2-(3,5-dimethylphenoxy)-1-phenyl-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (2u): Pale yellow solid (46.9%); m.p. 107.4 – 113.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.89-7.87 (m, 3H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.39 (s, 1H), 6.66 (d, *J* = 9.0 Hz, 1H), 6.63 (s, 2H), 6.61 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.86 (s, 3H), 2.22 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.1 (C), 156.4 (C), 155.2 (C), 153.1 (C), 147.3 (C), 142.1 (C), 139.6 (C), 137.7 (C), 132.3 (CH), 129.5 (CH), 128.3 (CH), 125.8 (CH), 124.6 (CH), 122.9 (CH), 120.0 (C), 113.7 (CH), 107.8 (CH), 61.8 (CH_3), 61.0 (CH_3), 56.1 (CH_3), 21.4 (CH_3); MS m/z [M^+] 418.18; FT-IR (ATR): 2936, 1654, 1587, 1493, 1459, 1411, 1286, 1146, 1092, 1046 cm^{-1}.

2-(3,5-dimethylphenoxy)-1-phenyl-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (2v): Viscous liquid (48.8%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.89 (d, *J* = 8.5 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.04 (s, 2H), 6.96 (s, 1H), 6.60 (s, 3H), 3.87 (s, 3H), 3.79 (s, 6H), 2.20 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.2 (C), 156.2 (C), 153.2 (C), 147.6 (C), 139.7 (C), 139.6 (C), 137.3 (C), 132.6 (CH), 129.5 (CH), 128.6 (CH), 128.4 (CH) 128.4 (C), 124.7 (CH), 113.4 (CH), 108.0 (CH), 61.0 (CH_3), 56.1 (CH_3), 21.5 (CH_3);

MS m/z [M^+] 418.18; FT-IR (ATR): 1655, 1577, 1503, 1448, 1416, 1290, 1242, 1124, 1002 cm^{-1}.

3-(2,6-dichlorophenyl)-2-(3,5-dimethylphenoxy)-1-phenylprop-2-en-1-one (2w): White solid (45.7%); m.p. 117-118 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.03 (d, *J* = 8.5 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.13 (t, *J* = 8.1 Hz, 1H), 6.79 (s, 1H), 6.56 (s, 2H), 6.52 (s, 1H), 2.15 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.3 (C), 155.9 (C), 151.2 (C), 139.2 (C), 136.6 (C), 135.0 (C), 133.2 (CH), 131.5 (C), 129.8 (CH), 129.5 (CH), 128.5 (CH), 127.8 (CH), 124.9 (CH), 119.8 (CH), 114.7 (CH), 21.3 (CH_3); MS m/z [M^+] 396.07; FT-IR (ATR): 1654, 1579, 1501, 1448, 1417, 1289, 1245, 1122, 1014 cm^{-1}.

2-(3,5-dimethylphenoxy)-1-phenyl-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one (2x): White solid (44.6%); m.p. 128.13 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.89 (d, *J* = 8.2 Hz, 2H), 7.72 (s, 1H), 7.58 (s, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 6.61 (s, 2H), 6.58 (s, 1H), 6.47 (s, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.66 (s, 3H), 2.20 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.1 (C), 156.5 (C), 153.8 (C), 151.7 (C), 145.9 (C), 143.0 (C), 139.5 (C), 137.9 (C), 132.1 (CH), 129.5 (CH), 128.2 (CH), 124.3 (CH), 123.5 (CH), 113.6 (C), 113.2 (CH), 113.1 (CH), 96.4 (CH), 56.6 (CH_3), 56.1 (CH_3), 56.0 (CH_3), 21.4 (CH_3); MS m/z [M^+] 418.18; FT-IR (ATR): 2922, 1664, 1603, 1509, 1464, 1408, 1269, 1207, 1122, 1024 cm^{-1}.

2-(benzo[d][1,3]dioxol-5-yloxy)-1-phenyl-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (2aa): White solid (28.5%); m.p. 145.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.88-7.85 (m, , 3H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.37 (s, 1H), 6.66 (d, *J* = 9.0 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 6.58 (s, 1H), 6.43 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.83 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.9 (C), 155.2 (C), 153.0 (C), 151.4 (C), 148.4 (C), 147.4 (C), 143.1 (C), 142.0 (C), 137.5 (C), 132.4 (CH), 129.3 (CH), 128.2 (CH), 125.6 (CH), 122.6 (CH), 119.7 (C), 108.0 (CH), 107.7 (CH), 107.5 (CH), 101.4 (CH_2), 99.0 (CH), 61.7 (CH_3), 60.9 (CH_3), 56.0 (CH_3).MS m/z [M^+] 434.14; FT-IR (ATR): 3057, 2939, 1653, 1589, 1480, 1412 1244, 1171, 1137, 1092, 1037 cm^{-1}.

2-(benzo[d][1,3]dioxol-5-yloxy)-1,3-diphenylprop-2-en-1-one (2ab): Viscous liquid (27.5%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.90 (d, *J* = 7.0 Hz, 2H), 7.79 (d, *J* = 9.8 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.40 – 7.36 (m, 3H), 6.98 (s, 1H), 6.63-6.61 (m, 2H), 6.46 (dd, *J* = 8.4, 2.6 Hz, 1H), 5.85 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.1 (C), 151.1 (C), 148.5 (C), 148.4 (C) 143.3 (C), 137.0 (C), 132.9 (C), 132.7 (CH), 130.4 (CH), 129.7 (CH), 129.3 (CH), 128.8 (CH), 128.4 (CH), 127.7 (CH), 108.1 (CH), 107.8 (CH), 101.4 (CH_2), 99.3 (CH); MS m/z [M^+] 344.10; FT-IR (ATR): 3056, 2891, 1656, 1479, 1447, 1244, 1177, 1138, 1036 cm^{-1}.

2-(benzo[d][1,3]dioxol-5-yloxy)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one (2ac): Viscous liquid (24.2%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.85 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 6.85 (s, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.53 (d, *J* = 2.5 Hz 1H), 6.38 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.88 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.1 (C), 150.9 (C), 149.1 (C), 148.6 (C),

143.6 (C), 136.9 (C), 133.0 (CH), 132.1 (CH), 131.9 (C), 131.9 (CH), 129.4 (CH), 128.5 (CH), 126.0 (CH), 123.9 (C), 108.2 (CH), 108.1 (CH), 101.6 (CH_2), 99.5 (CH); MS m/z [M^+] 422.02; FT-IR (ATR): 3056, 2921, 2854, 2776, 1659, 1478, 1399, 1245, 1171, 1139, 1073, 1036, 1009 cm^{-1}.

2-(benzo[d][1,3]dioxol-5-yloxy)-3-(3-nitrophenyl)-1-phenylprop-2-en-1-one (2ad): Light brown solid (43.5%); m.p. 95.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.60 (s, 1H), 8.17 (m, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 9.6 Hz, 2H), 7.57-7.53 (m, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 6.88 (s, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 2.5 Hz, 1H), 6.39 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.87 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 191.7 (C), 150.6 (C), 150.6 (C), 148.7 (C), 148.6 (C), 143.9 (C), 136.3 (C), 135.7 (CH), 134.7 (C), 133.3 (CH), 129.8 (CH), 129.4 (CH), 128.6 (CH), 124.8 (CH), 123.8 (CH), 123.1 (CH), 108.3 (CH), 108.2 (CH), 101.7 (CH_2), 99.6 (CH); MS m/z [M^+] 389.09; FT-IR (ATR): 2922, 1666, 1528, 1501, 1348, 1246, 1173, 1091, 1036 cm^{-1}.

2-(benzo[d][1,3]dioxol-5-yloxy)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (2ae): Viscous liquid (12.5%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.86 (d, *J* = 9.7 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 6.88 (s, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 2.5 Hz, 1H), 6.40 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.87 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.0 (C), 151.0 (C), 148.9 (C), 148.6 (C), 143.5 (C), 136.9 (C), 135.5 (C), 132.9 (CH), 131.6 (CH), 131.5 (C), 129.4 (CH), 129.1 (CH), 128.5 (CH), 126.0 (CH), 108.2 (CH), 108.0 (CH) 101.6 (CH_2), 99.4 (CH); MS m/z [M^+] 378.08; FT-IR (ATR): 3055, 2892, 1656, 1479, 1245, 1171, 1138, 1089, 1036 cm^{-1}.

4.1 Procedure for the synthesis of Ethyl 2-benzoyl-3-phenyl acrylate (3a-3e)

Ethyl benzoyl acetate (1 equiv) and the aldehyde (1 equiv) were dissolved in 5 mL ethanol in a 50 mL round bottom flask. Piperidine (0.1 equiv) and acetic acid (0.5 equiv) were added to the reaction flask and the reaction mixture was stirred at room temperature for 48 hours. Crude product was dissolved in ethyl acetate 25 mL, transferred to separating funnel and washed with 5% HCl solution. The compound was further purified through column chromatography (hexanes: ethyl acetate).

Ethyl 2-benzoyl-3-(4-methoxyphenyl)acrylate (3a): White solid (51.1%); m.p. 91.3 °C (Lit: 94 °C)[46]; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.96 (d, *J* = 9.4 Hz, 2H), 7.90 (s, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 2H), 6.74 (d, *J* = 8.9 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 196.3 (C), 165.4 (C), 161.5 (C), 142.4 (CH), 136.4 (C), 133.9 (CH), 132.4 (CH), 129.3 (CH), 128.9 (CH), 128.7 (C), 125.6 (C), 114.4 (CH), 61.4 (CH_2), 55.4 (CH_3), 14.2 (CH_3); m/z [M^+]: 310.06; FT-IR (ATR): 2936, 1713, 1668, 1598, 1510, 1243, 1169 cm^{-1}.

Ethyl 2-benzoyl-3-(4-chlorophenyl)acrylate (3b): Viscous liquid (44.0 %); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.92 (d, *J* = 9.7 Hz, 2H), 7.89 (s, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 195.4 (C), 164.8 (C), 141.1 (CH), 136.5 (C), 136.0 (C), 134.1 (CH), 132.0 (C), 131.3 (CH), 131.0 (C), 129.1 (CH), 128.9

(CH), 61.7 (CH_2), 14.0 (CH_3).; MS m/z [M^+]: 314.07; FT-IR (ATR): 1716, 1670, 1621, 1590, 1490, 1246, 1227, 1192, 1082, 1012 cm^{-1}.

Ethyl 2-benzoyl-3-(4-fluorophenyl)acrylate (3c): Viscous liquid (39.8%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.93 (d, *J* = 8.0 Hz, 2H), 7.90 (s, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.34 (dd, *J* = 8.9, 5.3 Hz, 2H), 6.89 (t, *J* = 8.6 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 195.5 (C), 164.9 (C), 163.7 (d, *J* = 252.6 Hz, C), 141.2 (CH), 136.1 (C), 134.0 (CH), 132.3 (d, *J* = 8.7 Hz, CH), 131.1 (C), 129.2 (CH), 129.1 (C), 128.9 (CH), 116.0 (d, *J* = 21.9 Hz, CH), 61.6 (CH_2), 14.0 (CH_3); m/z [M^+]: 298.10; FT-IR (ATR): 1717, 1670, 1598, 1508, 1224, 1191, 1161, 1085 cm^{-1}.

Ethyl 2-benzoyl-3-(3-methoxyphenyl)acrylate (3d): Viscous liquid (44.0%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.95 (d, *J* = 8.3 Hz, 2H), 7.92 (s, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 6.85 (m, 1H), 6.82 (dd, *J* = 8.3, 3.5 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.60 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 195.7 (C), 165.1 (C), 159.7 (C), 142.6 (CH), 136.3 (C), 134.2 (CH), 134.0 (C), 131.6 (C), 129.9 (CH), 129.2 (CH), 129.0 (CH), 123.1 (CH), 117.0 (CH), 114.6 (CH), 61.7 (CH_2), 55.2 (CH_3), 14.2 (CH_3); m/z [M^+]: 314.07; FT-IR (ATR): 1717, 1671, 1578, 1224, 1190, 1171 cm^{-1}.

Ethyl 2-benzoyl-3-(2-methoxyphenyl)acrylate (3e): Viscous liquid (47.0%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.34 (s, 1H), 7.98 (d, *J* = 9.6 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.77 (t, *J* = 7.6 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 195.3 (C), 165.3 (C), 157.8 (C), 138.5 (CH), 136.6 (C), 133.4 (CH), 131.9 (CH), 131.0 (C), 130.5 (CH), 129.0 (CH), 128.6 (CH), 122.2 (C), 120.5 (CH), 110.8 (CH), 61.3 (CH_2), 55.1 (CH_3), 14.0 (CH_3); m/z [M^+]: 314.07; FT-IR (ATR): 1715, 1670, 1596, 1463, 1258, 1224, 1191, 1115, 1084 cm^{-1}.

4.1 Procedure for synthesis of 2-benzoyl-3-(4-methoxyphenyl)acrylic acid (4)

Compound 3a (1 equiv) was dissolved in 10mL ethanol, 40mL of water was added followed by slow addition of KOH (15 equiv) into the reaction mixture. The mixture was stirred at room temperature for 6 hours. Ethanol was removed using rotary evaporator. The reaction mixture was dissolved into aqueous bicarbonate solution and washed with EtOAc to remove unreacted ester. The acidification of the aqueous layer with HCl led to precipitation of the product which was then filtered, washed with water and dried to obtain product as white solid (70.0%); m.p. 180 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.98 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 196.0 (C), 170.2 (C), 162.0 (C), 144.9 (CH), 136.1 (C), 134.2 (CH), 132.9 (CH), 129.4 (CH), 129.1 (CH), 127.3 (C), 125.3 (C), 114.5 (CH), 55.5 (CH_3); m/z [M^+]: 238.10; FT-IR (ATR): 2500-3500, 1671, 1598, 1512, 1260, 1175 cm^{-1}.

4.1 General procedure for synthesis of α-substituted chalcones (5a - 5e)

Compound **4** (1 equiv) was stirred in $SOCl_2$ (3 equiv) for 24 hours. Toluene was added in the reaction mixture and excess thionyl chloride was removed through distillation using dropping funnel. 5 mL dichloromethane, amine (1.2 equiv) and trimethylamine (4 equiv) were added in reaction mixture and allowed to stir for 3 hours. Organic compound was extracted in ethyl acetate layer and acidic washing was done to remove unreacted to remove triethylamine. Desired product was purified through column chromatography (hexanes: ethyl acetate).

2-Benzoyl-*N*-benzyl-3-(4-methoxyphenyl)acrylamide (5a): White solid (42.7%); m.p. 130.7 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.78 (t, *J* = 6.0 Hz, 1H), 7.89 (d, *J* = 9.6 Hz, 2H), 7.64-7.61 (m, 2H), 7.50 (t, *J* = 9.0 Hz, 2H), 7.31 (d, *J* = 7.1 Hz, 2H), 7.27-7.23 (m, 5H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.36 (d, *J* = 6.0 Hz, 1H), 3.69 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 196.8 (C), 165.1 (C), 160.2 (C), 139.4 (C), 136.1 (CH), 135.7 (C), 134.0 (C), 133.0 (CH), 131.2 (CH), 129.0 (CH), 128.9 (CH), 128.3 (CH), 127.2 (CH), 126.8 (C), 125.8 (CH), 114.3 (CH), 55.2 (CH_3), 42.5 (CH_2); MS m/z [M^+]: 371.21; FT-IR (ATR): 3250, 1661, 1601, 1511, 1248, 1176 cm^{-1}.

Ethyl 2-(2-benzoyl-3-(4-methoxyphenyl)acrylamido)acetate (5b): Viscous liquid (20.5%); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.97 (d, *J* = 9.7 Hz, 2H), 7.92 (s, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz ,2H), 7.32 (d, *J* = 8.9 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 2H), 4.30-4.29 (m, 2H), 3.75 (s, 3H), 3.52 (t, *J* = 4.9 Hz, 2H), 3.32 (q, *J* = 7.0 Hz, 2H), 1.05 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 196.2 (C), 165.4 (C), 161.6 (C), 142.8 (CH), 136.5 (C), 133.9 (CH), 132.5 (CH), 129.4 (CH), 128.9 (CH), 128.4 (C), 125.5 (C), 114.4 (CH), 68.2 (CH_2), 66.7 (CH_2), 64.8 (CH_2), 55.4 (CH_3), 15.2 (CH_3); MS m/z [M^+] 381.10; FT-IR (ATR): 3307, 1729, 1688, 1639, 1395, 1179 cm^{-1}.

2-Benzoyl-*N*-isopropyl-3-(4-methoxyphenyl)acrylamide (5c): White solid (38.9%); m.p. 101.1-102 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.10 (d, *J* = 7.7 Hz, 1H), 7.86 (dd, *J* = 8.4 Hz, 1.6 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.50-7.47 (m, 3H), 7.21 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 3.92 (m, 1H), 3.69 (s, 3H), 1.12 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 196.8 (C), 164.6 (C), 160.1 (C), 136.2 (C), 134.8 (C), 133.8 (CH), 133.6 (CH), 131.0 (CH), 128.9 (CH), 128.8 (CH), 125.9 (C), 114.2 (CH), 55.2 (CH_3), 40.9 (CH), 22.2 (CH_3); MS m/z [M^+] 323.16; FT-IR (ATR): 3316, 1659, 1637, 1600, 1509, 1254, 1128 cm^{-1}.

2-Benzoyl-3-(4-methoxyphenyl)-*N*-propylacrylamide (5d): White solid (28.0%); m.p. 114.7 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 8.18 (t, *J* = 5.7 Hz, 1H), 7.86 (d, *J* = 9.7 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.51 (s, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 3.68 (s, 3H), 3.09 (q, *J* = 6.6 Hz, 2H), 1.46 (h, *J* = 7.3 Hz, 2H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 196.8 (C), 165.0 (C), 160.1 (C), 136.1 (C), 135.1 (CH), 133.9 (CH), 133.4 (C), 131.0 (CH), 128.9 (CH), 128.8 (CH), 125.8 (C), 114.2 (CH), 55.2 (CH_3), 40.8 (CH_2), 22.2 (CH_2), 11.4 (CH_3); MS m/z [M^+] 323.16; FT-IR (ATR): 3325, 1661, 1599, 1504,1255, 1175, 1027 cm^{-1}.

2-Benzoyl-*N*-(4-chlorobenzyl)-3-(4-methoxyphenyl)acrylamide (5e): Viscous liquid (35.0%); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.79 (t, *J* = 6.0 Hz, 1H), 7.89-7.87 (m, 2H), 7.64-7.62 (m, 2H), 7.50 (t, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H),

7.23 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 4.33 (d, *J* = 6.0 Hz, 2H), 3.69 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 196.8 (C), 165.1 (C), 160.3 (C), 138.5 (C), 136.1 (C), 135.9 (C), 134.1 (C), 132.8 (CH), 131.3 (CH), 131.2 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.2 (CH), 125.7 (C), 114.3 (CH), 55.2 (CH_3), 41.9 (CH_2); MS m/z [M^+] 405.11; FT-IR (ATR): 3369, 3054, 1663, 1598, 1551, 1127, 1091 cm^{-1}.

Cell culture and proliferation assays:

Cell lines were grown in their recommended culture media (DMEM or RPMI) supplemented with 10% FBS and 1x antimycotic/antibiotic solution at 37°C in humidified incubators with 5% CO_2. Antiproliferative activities of the compounds against HCC1954 and HCT116 cell lines were determined using a 3-day sulforhodamine B (SRB) proliferation assay as described previously (Safia et al). Cells were plated in 96 well plates and treated the next day with nine 3-fold dilutions of the compounds. Cells were incubated with the compounds for 72 hours at 37°C in humidified incubators with 5% CO_2. At the end of treatment, cells were fixed with 3% ice-cold trichloroacetic acid (TCA) at 4°C for at least 2 hours. Plates were washed with water, air-dried and stained with 0.06% SRB for 30 minutes at room temperature. Stained cells were washed with 0.1% acetic acid, air dried and bound SRB bound to the cells was dissolved in 10mM Tris pH 10.5. O.D. was measured at 490nm on a BioTek microplate reader and GI_{50} values were calculated using GraphPad Prism.

Cell Cycle Analysis:

Cell cycle profile of HCT116 cells treated with compounds **5a** and **5e** was determined through fluorescence-activated cell sorting (FACS) as described previously (Safia et al). Briefly, cells were treated with indicated concentrations for 24 hours, fixed with 85% ethanol and stained with propidium iodide/RNase solution (10μg/ml PI and 0.5% RNase) at 37°C for 30 minutes. Fixed and stained samples were analysed using BD FACSCalibur.

Immunoblotting:

For PARP-cleavage and p53 induction, HCT116 cells were plated in 6-well plates and treated with different concentrations of **5a** and **5e** for 24 hours. Following treatment, cells were lysed with lysis buffer containing 50mM NaCl, 25mM Tris pH 7.5, 1% Triton-X 100 and supplemented with phosphatase and protease inhibitors. The protein concentration of cell lysates was measured using Bradford and equal amounts of proteins were separated on SDS-PAGE. Proteins were transferred onto nitrocellulose membranes and incubated overnight at 4°C with primary antibodies specific for cleaved-PARP, p53 and β actin. Next day, membranes were washed with PBS containing 0.1% Tween 20 (PBST) and incubated for 1 hour with HRP-labelled secondary antibodies. Membranes were washed again with PBST solution, developed using ECL reagent and imaged on BioRad Chemidoc. For p53 stabilization, cells were treated with 6.25mM 5a in the presence and absence of 10μM cycloheximide (CHX). Samples were collected at times indicated and levels of p53 were determined using immunoblotting as described above.

MDR assays:

ATPase activity of Pgp was measured using Pgp-Glo assay (Promega) from untreated, 100μM Na_3VO_4-, 200μM Verapamil- and 10μM **5a** compound-treated Pgp reactions. Basal, verapamil-treated and **5a**-treated activity of the Pgp ATPase was calculated according to the manufacturer's instructions. ΔRLU= Difference in relative light units.

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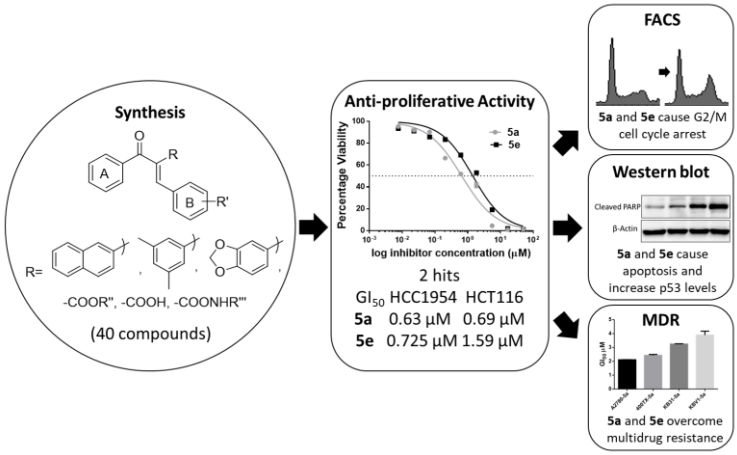
Graphical abstract



Highlights

- A series of forty α-substituted chalcones were synthesized.
- Antiproliferative activity against HCT116 and HCC1954 cancer cell lines identified **5a** and **5e** as hits.
- Both compounds induce a G2/M cell cycle arrest and cause apoptotic cell death.
- Both compounds stabilized p53 in a dose-dependent manner in HCT116.
- Both compounds were able to overcome multidrug resistance in two multidrug resistant cell lines.