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Research paper

Synthesis and antiproliferative activity of α-branched α,β-unsaturated ketones in human hematological and solid cancer cell lines

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ABSTRACT

A series of α-branched α,β-unsaturated ketones were prepared *via* boron trifluoride etherate mediated reaction between arylalkynes and carboxaldehydes. The evaluation of the antiproliferative activity over hematological (NB4) and solid cancer (A549, MCF-7) cell lines provided a structure-activity relationship. 5-Parameter QSAR equations were built which were able to explain 80%–92% of the variance in activity. The resulting selective lead compound showed IC_{50} value 0.6 μM against the hematological cell line and did not cause apoptosis, but blocked cell cycle in G0/G1. Moreover, it was demonstrated that this compound enhances and accelerates retinoic acid induced granulocytic differentiation.

1. Introduction

Various natural and synthetic α,β-unsaturated ketones are known to exhibit antitumor activities [1]. The conjugated ketone functional group has been hypothesized to work in cancer chemotherapy *via* thiol alkylation without interaction with amino or hydroxy groups of cellular constituents, and therefore, enones could have remarkable advantages over classical alkylators since these compounds probably could not cause genotoxic effects associated with a number of anticancer drugs [2]. Moreover, the antitumor activity of the enone framework containing materials is linked with various effects including inhibition on NF-KB [3] or mitochondrial mediated [4] pathways, stimulation of death receptors (DRS) of the tumor necrosis factor (TFN) [5], inhibition of cyclin-depended kinases [6] or DNA topoisomerase II [7] and so forth. Thus, the synthesis of new α,β-unsaturated ketones is currently of high priority.

Chemically, α,β-unsaturated ketones can be prepared by different methods, including classical aldol-type condensations or Wittig reactions or some more modern synthetic approaches [8]. Recently, we developed and described a unique reaction between propargylic esters and aldehydes leading to a variety of α-branched α,β-unsaturated ketones in one atom-economic step [9a]. We also showed that the outcome of this process strongly depends on the structure of the starting materials; mechanism of this transformation proved by isotopic labeling studies and quantum chemical calculations [9b]. Moreover, we recently reported on the synthesis and the preliminary investigation for the antiproliferative activity of α-branched α,β-unsaturated ketones, which showed remarkable biological activity towards human solid cancer cell lines [10]. Therefore, our one-step synthetic approach gives a diverse range of enone functionality containing bioactive materials. As a continuation of our study, herein we report the synthesis of novel α-branched α,β-unsaturated ketones that have antiproliferative activity against human hematological (NB4, leukemia) and solid (A549, lung and MCF-7, breast) cancer cell lines.

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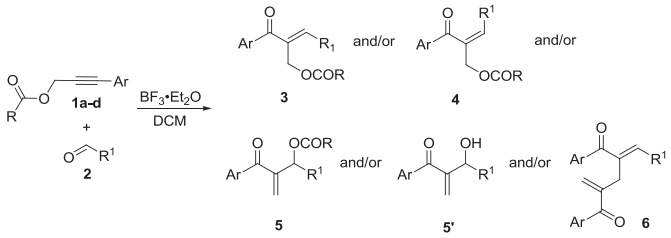
2. Chemistry

The target compounds were synthesized from aryl alkynes **1** and aldehydes **2** under our previously determined reaction conditions [9]. Mixtures of starting materials in dichloromethane were treated with 1 equivalent of boron trifluoride diethyletherate at room temperature (Schemes 1 and 2). The outcome of this reaction strongly depends on the structures of the starting materials. Thus, reactions between propargylic esters **1a-d** and various aldehydes in principle can lead to the formation of *E*-(**3**) or *Z*-chalcones (**4**), Morita-Baylis-Hillman adducts (**5** and **5'**) or 2:1 adducts (**6**) or mixtures of these compounds (Scheme 1). Structures and yields of the isolated products are shown in Table 1.

In contrast to the propargylic esters, reactions of 4-(4-methoxyphenyl)but-3-ynyl acetate **1e**, 5-(4-methoxyphenyl)pent-4-yn-2-yl acetate **1f**, alkynes **1g**,**h** or *N*-(3-(4-methoxyphenyl)prop-2-ynyl)-*N*-methylbenzamide **1i** with various aldehydes resulted in the exclusive formation of *E*-enones (**3**) in low or good yields (Scheme 2, Table 2).

To further functionalize the α-substituent in the synthesized enones, some of the isolated Morita-Baylis-Hilman adducts **5** were transformed into the corresponding amino functionalized α-substituted α,β -unsaturated ketones **7** by reacting with amines [11], as presented in Scheme 3. All the reactions performed proceeded smoothly, and the products were isolated in moderate to good yields. Unfortunately, most of compounds **7** were decomposed over time, and therefore were not stable enough to be tested (Table 3, entries 2, 4, 5, 7).



Scheme 1. Reaction between propargylic esters **1a-d** and aldehydes **2**.

Scheme 2. Reaction between alkynes **1e-i** and aldehydes **2**.

3. Antiproliferative activity and SAR's of synthesized compounds

All synthesized compounds were tested in vitro for their antiproliferative activity using three different human cancer cell lines: NB4 acute promyelocytic leukemia cells, A549 lung cancer cell line and MCF-7 breast cancer cells. After 48 h treatment, the effect of compounds was evaluated using XTT assay according to the manufacturer's instructions as described in Experimental section.

For a better evaluation of structure-activity relationship, the compounds were divided into three main groups: the first group containing α-substituted chalcones **3**, **4** and **7**, the second group representing 2:1 adducts **6,** and the third group including Morita-Baylis-Hillman's adducts **5** and **5'** (Fig. 1). IC_{50} values of all these compounds are listed in Tables 4–6, respectively.

The data presented in Tables 4–6 revealed that the A549 cancer cell line was the most resistant, and therefore almost all compounds showed weak or moderate antiproliferative activities against this cell line. In contrast, the NB4 hematological cell line was extremely sensitive to the majority of the tested compounds.

The analysis of the IC50 values allowed us to establish several SARs. Among compounds of the Group 1 (Table 4), *E*-chalcone analogues of the subset **3ax-3dx** exhibited notable antiproliferative

Table 1
Data on the reactions between propargylic esters **1a-d** and aldehydes **2**.

Entry	Alkyne 1	Ar	R	Aldehyde 2	R^1	Products (yields, %)
1	**1a**	Ph	Me	**2a**	2-FC_6H_4	**3aa** (51), **4aa** (26)
2				**2b**	2,4-$Cl_2C_6H_3$	**3 ab** (46), **4 ab** (23)
3				**2c**	4-MeC_6H_4	**6ac** (22)
4				**2d**	4-$BzOC_6H_4$	**6ad** (14)
5	**1b**	4-$MeOC_6H_4$	Me	**2a**	2-FC_6H_4	**3ba** (34), **5ba** (31)
6				**2b**	2,4-$Cl_2C_6H_3$	**5bb** (75)
7				**2d**	4-$BzOC_6H_4$	**3bd:4bd**[a] (12), **6bd** (12)
8				**2e**	$CHEt_2$	**3be** (22), **5be** (36)
9				**2f**	*c*Hex	**3bf** (37), **5bf** (29)
10				**2g**	Ph	**3bg:4bg**[a] (53), **6bg** (17)
11				**2h**	4-$O_2NC_6H_4$	**5bh** (63)
12				**2i**	C_6F_5	**5bi** (60)
13	**1c**	2,4-$(MeO)_2C_6H_3$	Me	**2h**	4-$O_2NC_6H_4$	**5ch** (21)
14				**2j**	2-$O_2NC_6H_4$	**5cj** (32)
15	**1d**	4-$MeOC_6H_4$	Ph	**2a**	2-FC_6H_4	**5da** (42), **5'da** (9)
16				**2b**	2,4-$Cl_2C_6H_3$	**5 db** (56), **5'db** (32)
17				**2c**	4-MeC_6H_4	**3dc:4dc**[a] (16), **6dc** (26)
18				**2e**	$CHEt_2$	**3de** (4), **5de** (37)
19				**2f**	*c*Hex	**3df** (8), **5df** (55)
20				**2h**	4-$O_2NC_6H_4$	**5dh** (43), **5'dh** (27)
21				**2i**	C_6F_5	**5di** (28), **5'di** (38)
22				**2j**	2-$O_2NC_6H_4$	**5dj** (22), **5'dj**[b] (47)
23				**2k**	Me	**3dk** (22), **5dk** (23)
24				**2l**	2-ClC_6H_4	**3 dl** (33), **4 dl** (20), **5 dl** (46), **5'dl** (13)
25				**2m**	2,4- $(NO_2)_2C_6H_3$	**5 dm** (31), **5'dm** (59)

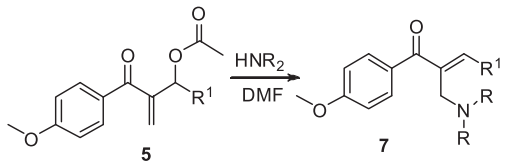
[a] Mixtures of products **3** and **4** were isolated due to same Rf's.
[b] Compound **5'dj** contained impurity of **5dj** due to very similar Rf's.

Table 2
Data on the reactions between propargylic esters **1e-i** and aldehydes **2**.

Entry	Alkyne 1	Ar	R	Aldehyde 2	R^1	Product (yield, %)
1	**1e**	4-$MeOC_6H_4$	CH_2OAc	**2a**	2-FC_6H_4	**3ea** (50)
2				**2b**	2,4-$Cl_2C_6H_3$	**3eb** (61)
3				**2e**	$CHEt_2$	**3ee** (21)
4				**2f**	*c*Hex	**3ef** (40)
5				**2h**	4-$O_2NC_6H_4$	**3eh** (53)
6				**2i**	C_6F_5	**3ei** (21)
7				**2l**	2-ClC_6H_4	**3el** (55)
8				**2n**	4-ClC_6H_4	**3en** (25)
9	**1f**	4-$MeOC_6H_4$	CHMeOAc	**2b**	2,4-$Cl_2C_6H_3$	**3 fb** (70)
10				**2f**	*c*Hex	**3ff** (30)
11				**2i**	C_6F_5	**3fi** (8)
12				**2n**	4-ClC_6H_4	**3fn** (21)
13	**1g**	4-$MeOC_6H_4$	$CHMe_2$	**2b**	2,4-$Cl_2C_6H_3$	**3gb** (70)
14				**2h**	4-$O_2NC_6H_4$	**3gh** (76)
15				**2n**	4-ClC_6H_4	**3gn** (46)
16				**2o**	4-$F_3CC_6H_3$	**3go** (71)
17	**1h**	4-$MeOC_6H_4$	*c*Hex	**2b**	2,4-$Cl_2C_6H_3$	**3 hb** (50)
18				**2o**	4-$F_3CC_6H_3$	**3ho** (54)
19	**1i**	4-$MeOC_6H_4$	NMeBz	**2b**	2,4-$Cl_2C_6H_3$	**3ib** (51)
20				**2f**	*c*Hex	**3if** (49)

activities. Moreover, *E*-enones showed better activities than their corresponding *Z*-isomers against the NB4 and MCF-7 cell lines, as shown in the comparisons of **3aa**, **3 ab** and **3 dl** *vs* **4aa**, **4 ab** and **4 dl**, respectively (Table 4, entries 1, 2, 4–7). This result was consistent with our previous observation [10]. However, the *E*-chalcones **3aa** and **3 ab** (Table 4, entries 1,4) were less potent than the respective *Z*-isomers **4aa** and **4 ab** (Table 4, entries 2, 5) towards the A549 cell line. Also, *E*-enones bearing alkyl substituent in β-position did not show any significant activity against the A549 cell line, while displayed moderate antiproliferative activities against the other cell lines (Table 4, entries 8–10). Incorporation of benzoyloxy functionality at the α-substituent (compound **3df**, entry 12) seems to favor antiproliferative activity towards all cancer cell lines, as exemplified by comparing **3df** to its counterpart **3bf** (Table 4, entry 11). Elongation of the α-substituent by one CH_2 group, as in **3ea-3ei** (Table 4, entries 13–20) led to a substantial loss of activity for all cell lines. Introduction of the $CH_2CH(CH_3)OAc$ moiety at the α-position of the α,β-unsaturated ketone framework or replacement of the ester group in the α-substituent by the *N*-methylbenzamide functionality gave compounds with modest to negligible activities (Table 4, entries 21–26).

Interestingly, *E*-chalcones **3** bearing a branched aliphatic substituent (isobutyl or cyclohexylmethyl groups) at the α-position displayed a selective activity towards the leukemia cancer cells line (Table 4, entries 27–32), with **3gh** (entry 28) being active at submicromolar concentration. However, the presence of the more bulky cyclohexylmethyl substituent caused a decrease in potency against the above cancer cells, as exemplified by comparing **3gb** (entry 27) *vs* **3 hb** (entry 31) and **3go** (entry 30) *vs* **3ho** (entry 32). Moreover, benzene ring C4-methoxy substitution adjacent to the carbonyl function in combination with C4-substitution on the β-phenyl moiety with nitro, chloro and trifluoromethyl groups led to a very effective growth inhibition of the leukemia cancer cells, as evidenced by compounds **3gh**, **3gn** and **3go**.



Scheme 3. Nucleophilic modification of compounds **5**.

Incorporation of a tertiary amino functionality in α-position along with a combination of electron-donating (methoxy) and electron withdrawing (nitro) groups on the aromatic rings of the chalcone scaffold, as in **7a** and **7c** (Table 4, entries 33, 34), gave an effective growth inhibition of both leukemic (NB4) and breast (MCF-7) cancer cell lines. Compound **7f** (entry 35) bearing dichlorophenyl portion in β-position was less active against the MCF-7 cell line, but retained satisfactory activity and selectivity towards the leukemic cell line (NB4).

Group 2 of the tested compounds includes a small number of 2:1 adducts (Table 5), which exhibited satisfactory micromolar growth inhibitory activity against the leukemic cancer cells (NB4), the most active and selective being the bis(methoxy) substituted analogue **6bd** (Table 5, entry 5). However, its unsubstituted counterpart **6ad** was less selective and showed weak activities towards the A549 and MCF-7 solid cancer cells (Table 5, entry 4). Noticeably, enhanced anti-A549 and MCF-7 activities were observed in the cases of compounds **6ac**, **6dc** and **6bg** (Table 5, entries 1–3), indicating that absence of the benzoate functionality had a favorable effect on the antiproliferative activity over the A549 and MCF-7 cell lines.

The third group of the tested compounds represents the class of Morita-Baylis-Hilman adducts **5** and **5'** (Table 6), which were found to be the most potent over all cancer cell lines, although their majority showed low to moderate growth inhibitory activities against the A549 cell line. It is evident from Table 6 that the presence of the *ortho*-halogenaryl portion in the α-substituent was responsible for enhanced anti-NB4 activity (entries 6, 8–11). Furthermore, the acylated derivatives (entries 6, 11, 16) were more potent than their respective benzoylated counterparts (entries 7, 12, 18). Dimethoxyphenyl moiety present in compounds **5cj** and

Table 3
Data on the reactions between compounds **5** and secondary amines.

Entry	Comp. 5	R^1	Amine	Product	Yield, %
1	**5bh**	4-$O_2NC_6H_4$	diethylamine	**7a**	48
2			piperidine	**7b**	80[a]
3			morpholine	**7c**	77
4			aniline	**7d**	99[a]
5	**5bb**	2,4-$Cl_2C_6H_3$	diethylamine	**7e**	84[a]
6			morpholine	**7f**	53
7			aniline	**7g**	70[a]

[a] Unstable product over time at room temperature.

Table 4
In vitro antiproliferative activity of compounds **3**, **4** and **7** against human cancer cell lines (IC_{50} in μM).

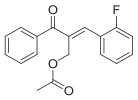
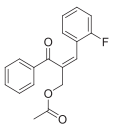
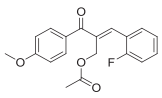
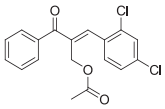
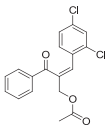
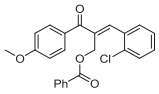
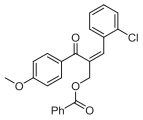
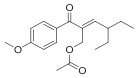
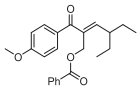
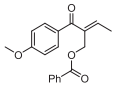
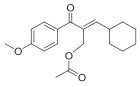
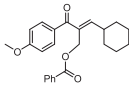
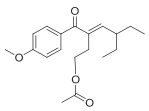
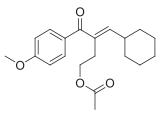
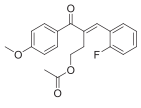
Entry	Compound	Structure	IC 50% (μM)		
			NB4	A549	MCF-7
1	**3aa**		5.8 (±1.2)	68.7 (±0.04)	14.6 (±2.16)
2	**4aa**		8.3 (±0.55)	20.3 (±0.15)	39.8 (±0.67)
3	**3ba**		8.2 (±1.24)	22.5 (±0.17)	30 (±0.27)
4	**3 ab**		6.6 (±0.84)	97 (±0.13)	8.7 (±1.01)
5	**4 ab**		12.6 (±0.72)	74.5 (±0.13)	31.7 (±0.68)
6	**3 dl**		7 (±0.76)	20.1 (±1.01)	9 (±0.05)
7	**4 dl**		18 (±0.69)	52 (±0.15)	36 (±0.93)
8	**3be**		9.5 (±0.22)	>100	13.7 (±0.94)
9	**3de**		26.8 (±0.06)	>100	28 (±0.35)
10	**3dk**		16.2 (±1. 18)	>100	29.8 (±0.29)
11	**3bf**		23.3 (±0.29)	90 (±0.22)	24 (±0.30)
12	**3df**		10.2 (±1.09)	36 (±0.19)	13.7 (±0.75)
13	**3ee**		91.1 (±0.09)	>100	>100
14	**3ef**		>100	>100	>100
15	**3ea**		>100	>100	>100

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Table 4 (*continued*)

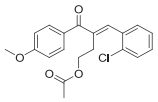
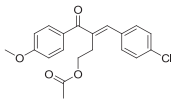
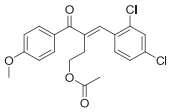
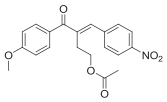
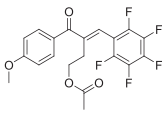
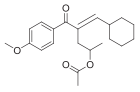
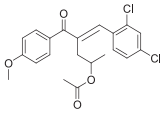
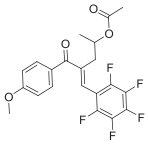
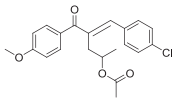
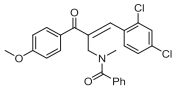
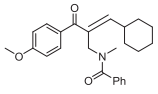
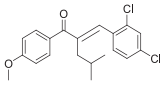
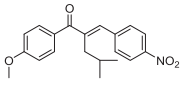
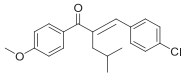
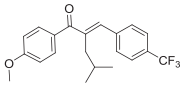
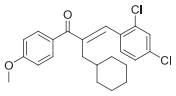
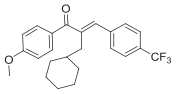
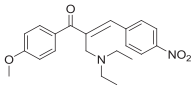
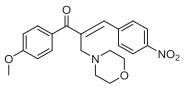
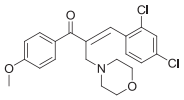
Entry	Compound	Structure	IC 50% (μM)		
			NB4	A549	MCF-7
16	**3el**		51.6 (±0.06)	>100	>100
17	**3en**		36.3 (±0.28)	86 (±0.09)	>100
18	**3eb**		34.8 (±0.19)	69.2 (±0.04)	83.4 (±0.03)
19	**3eh**		>100	>100	>100
20	**3ei**		28.5 (±0.20)	58.1 (±0.08)	>100
21	**3ff**		33.4 (±0.17)	98 (±0.09)	>100
22	**3 fb**		36.8 (±0.09)	40.3 (±0.10)	>100
23	**3fi**		49 (±0.10)	91.7 (±0.11)	>100
24	**3fn**		62 (±0.17)	73.2 (±0.13)	>100
25	**3ib**		24 (±0.38)	32.4 (±0.22)	>100
26	**3if**		39.7 (±0.22)	69.7 (±0.01)	32.7 (±0.18)
27	**3gb**		14.6 (±0.05)	80.3 (±0.27)	>100
28	**3gh**		0.6 (±0.02)	>100	>100
29	**3gn**		12.1 (±0.07)	>100	>100
30	**3go**		12.6 (±0.01)	>100	>100

Table 4 (*continued*)

Entry	Compound	Structure	IC 50% (μM)		
			NB4	A549	MCF-7
31	**3 hb**		48.9 (±0.21)	>100	>100
32	**3ho**		18.2 (±0.06)	>100	>100
33	**7a**		1.2 (±0.99)	22 (±0.18)	4.3 (±1.06)
34	**7c**		5.6 (±1.01)	70.1 (±0.06)	7 (±0.88)
35	**7f**		8.5 (±0.32)	>100	42.3 (±0.59)

5ch had a negative effect on their antiproliferative activity towards the A549 and MCF-7 cancer cell lines (Table 6, eg entry 16 *vs* entry 17). Changing the aromatic component in the α-substituent for an aliphatic residue did not inhibit the cell growth to a considerable extent (Table 6, entries 1–5). Compounds with electron deficient aryl moieties at the α-substituent along with acetyloxy or hydroxyl functionalities gave improved growth inhibitory activity against the MCF-7 cell line (Table 6, entries 11, 13, 16, 21), while the benzoyloxy functionalized analogues displayed significantly lower antiproliferative activity over the same cell line, (Table 6, entries 12,18, 20, 22).

In summary, the following structural features of unsaturated ketones were found to improve the antiproliferative activity and selectivity (Fig. 2): (a) the aryl group in the β-position of the enone fragment is always a better option compared to an aliphatic chain or the cyclohexyl ring; (b) the presence of the methylene linker between the α-position and the acetoxy, benzoyloxy, dialkylamino, or branched alkyl groups is important for the notable

Table 5
In vitro antiproliferative activity of compounds **6** against human cancer cell lines (IC_{50} in μM).

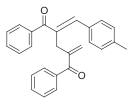
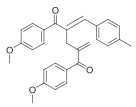
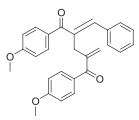
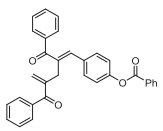
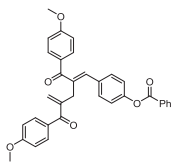
Entry	Compound	Structure	IC 50% (μM)		
			NB4	A549	MCF-7
1	**6ac**		7.6 (±1.04)	20.9 (±0.04)	15.9 (±1.11)
2	**6dc**		11.4 (±1.07)	43.8 (±0.57)	26.9 (±0.43)
3	**6bg**		7.4 (±0.74)	22.9 (±0.47)	27.1 (±0.65)
4	**6ad**		8 (±0.79)	44.4 (±0.06)	61.6 (±0.17)
5	**6bd**		6.7 (±0.25)	>100	>100

Table 6
In vitro antiproliferative activity of compounds **5** and **5'** against human cancer cell lines (IC_{50} in μM).

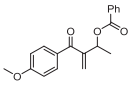
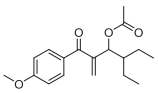
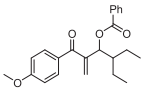
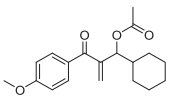
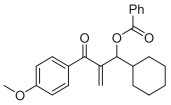
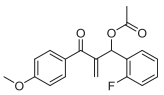
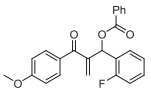
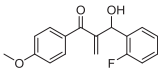
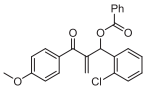
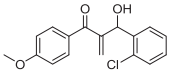
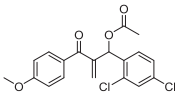
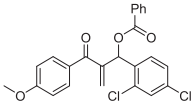
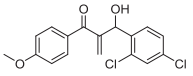
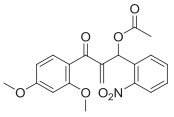
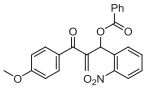
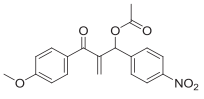
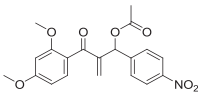
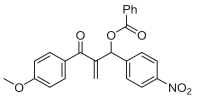
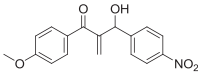
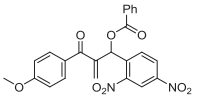
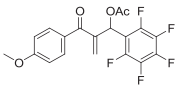
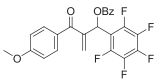
Entry	Compound	Structure	IC 50% (μM)		
			NB4	A549	MCF-7
1	**5dk**		15.7 (±0.34)	>100	14.5 (±0.63)
2	**5be**		11.8 (±0.31)	32.9 (±0.33)	38.9 (±0.19)
3	**5de**		13 (±0.56)	35.2 (±0.25)	17.9 (±0.56)
4	**5bf**		10.5 (±0.57)	>100	14 (±1.73)
5	**5df**		10 (±1.07)	62.1 (±0.02)	34.3 (±0.01)
6	**5ba**		9.5 (±1.43)	67.3 (±0.07)	18 (±0.54)
7	**5da**		14.3 (±0.47)	73.7 (±0.12)	34.2 (±0.18)
8	**5'da**		6.9 (±0.78)	15.7 (±0.08)	30.9 (±0.04)
9	**5 dl**		8.5 (±0.85)	30.5 (±0.14)	36 (±0.94)
10	**5'dl**		8.1 (±0.80)	28.5 (±0.11)	29.6 (±1.20)
11	**5bb**		5.4 (±1.01)	17.6 (±0.01)	8.3 (±0.78)
12	**5 db**		9.7 (±0.28)	79.2 (±0.09)	26.8 (±0.27)
13	**5'db**		26.1 (±0.33)	70 (±0.07)	9 (±0.07)
14	**5cj**		8.8 (±2.23)	>100	70.1 (±0.36)
15	**5dj**		12.7 (±0.42)	45.5 (±0.14)	11.8 (±0.48)
16	**5bh**		10.3 (±1.19)	21.3 (±0.27)	6.1 (±0.86)

Table 6 (*continued*)

Entry	Compound	Structure	IC 50% (μM)		
			NB4	A549	MCF-7
17	**5ch**		5 (±1.53)	43.5 (±0.04)	10.4 (±0.79)
18	**5dh**		13.2 (±0.83)	66.6 (±0.16)	56.1 (±2.03)
19	**5'dh**		5.4 (±0.76)	23.8 (±0.14)	11 (±0.73)
20	**5 dm**		10 (±1.07)	13 (±0.41)	>100
21	**5bi**		12.6 (±1.12)	14.8 (±1.19)	6.7 (±0.79)
22	**5di**		12.9 (±0.74)	32.1 (±0.32)	45.3 (±0.17)

antiproliferative activities of compounds **3** and **7**; (c) Morita-Baylis-Hillman adducts **5** are generally more active towards all the tested cancer cell lines, but they are less selective; (d) compounds **5** and **5'** bearing hydroxyl or acetyloxy groups show improved activity towards all the tested cancer cells lines; (e) the presence of *ortho*-halogenaryl group could be associated with improved activities towards NB4 cells; (f) α,β-unsaturated ketones motifs containing electron deficient aryl groups are exhibit better activities towards MCF-7 cells.

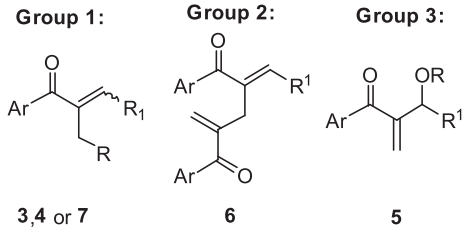


Fig. 1. The three main structural groups of the tested compounds.

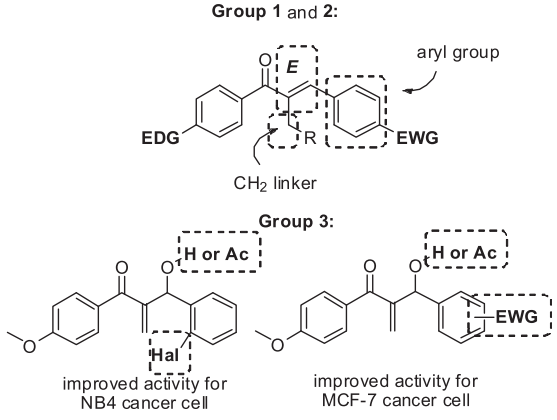


Fig. 2. A summary of the main structural features of the active compounds.

It should be noted, that we did not evaluate the cytotoxicity of synthesized compounds on normal cells, so at this stage of the investigation we can only speculate about possible selective toxicity. In principle, both cancer cells and healthy cells are sensitive to cytotoxic agents, only effective drug concentrations can vary. Our results showed that there are some selective compounds for different cancer cells (e.g. compounds **3gh**, **3gn**, **3go**, **3ho**, **6bd** exhibited satisfactory growth inhibitory activity against the leukemic cancer cells NB4 but were inactive towards solid human cancer cells); so we can presume that some of the active compounds could exert quit different antiproliferative activities towards cancer and healthy cells.

4. QSAR studies

The Quantitative Structure-Activity Relationships (QSAR) for the tested compounds were further explored using computational methods.

4.1. Data set

A total data set of 62 molecules was divided into two sets classified based on presence of the terminal alkene group: Set 1 accommodated compounds **3**, **4** and **7** (35 molecules), and Set 2 included compounds **5**, **5′** and **6** (27 molecules). The IC_{50} activities of compounds were converted to $pIC_{50} = -\log(IC_{50})$ for the sake of convenience. For computational purposes, compounds with $IC_{50} > 100$ μM ('inactives') were assumed to have $pIC_{50} = 4$.

4.2. Molecular modeling

Compound structures were sketched and afterwards optimized in 3-D using Avogadro v.1.1.1 [12]. Activity data for some chiral molecules present in the Set 1 were for the racemic mixtures, with undetermined enantiomer activities. For these molecules, the same

chirality was used to prevent introduction of noise. The generated molecular structure files were merged into a single sdf molecular format file with Open Babel v.2.3.1 [13]. The combined sdf file was used as an input to E-DRAGON program [14]. E-DRAGON calculates numerous descriptor families such as (a) 2D-descriptors: topological indices, walk and path counts, connectivity indices, information indices, 2D-autocorrelations, Burden eigenvalues, Galvez topological charge indices; and (b) 3D-descriptors: aromaticity indices, Randic molecular profiles, geometrical indices, radial distribution functions, 3D-MoRSE descriptors, WHIM (Weighted Holistic Invariant Molecular) descriptors, GETAWAY (Geometry, Topology and Atoms-Weighted Assembly) descriptors, and charge indices [15]. The resulting pool consisted of 1666 structural descriptors. Linear regression QSAR models where developed within R software environment using leaps package. Leaps warned about issues arising from the linear dependence of the descriptors, and such QSAR models were rejected. The final QSAR equations were built using 5 descriptors according to the generally accepted rule that at least 5 molecules should be present for each selected descriptor [16].

4.3. QSAR results

Using the activity data against the NB4, A549 and MCF-7 targets, several QSAR models were developed for the compound sets 1 and 2. The best models are presented below.

$$pIC_{50}(NB4;Set1) = 5.111\cdot MATS1m - 1.83\cdot MATS5p - 2.47\cdot HOMA + 14.1\cdot E2u - 10.4\cdot E2e + 4.27 \quad (1)$$

$$R^2 = 0.86,\ R^2_{ADJ} = 0.83,\ Q^2 = 0.75,\ F(5,29) = 35.1,\ p < 10^{-5}$$

$$pIC_{50}(A549;Set1) = 0.968\cdot ATS6e + 1.55\cdot MATS8m + 0.370\cdot Mor05v - 0.484\cdot Mor11p + 0.765\cdot Mor20p + 1.59 \quad (2)$$

$$R^2 = 0.81,\ R^2_{ADJ} = 0.78,\ Q^2 = 0.75,\ F(5,29) = 25.3,\ p < 10^{-5}$$

$$pIC_{50}(MCF-7;\ Set\ 1) = 0.0457\cdot RDF050u - 0.119\cdot RDF035p - 0.620\cdot Mor20m - 3.20\cdot H7u - 9.44\cdot HATS2u + 8.73 \quad (3)$$

$$R^2 = 0.92,\ R^2_{ADJ} = 0.90,\ Q^2 = 0.88,\ F(5,29) = 64.8,\ p < 10^{-5}$$

$$pIC_{50}(NB4;\ Set\ 2) = -5.17\cdot MATS2m + 5.25\cdot MATS2e - 3.90\cdot E3u + 8.17\cdot G2s - 1.29\cdot R4v + 5.69 \quad (4)$$

$$R^2 = 0.86,\ R^2_{ADJ} = 0.82,\ Q^2 = 0.77,\ F(5,21) = 24.8,\ p < 10^{-5}$$

$$pIC_{50}(A549;Set\ 2) = -25.0\cdot X3Av + 1.34\cdot Mor16u + 7.19\cdot G3u8.85\cdot G3p - 0.140\cdot Htv + 7.97 \quad (5)$$

$$R^2 = 0.80,\ R^2_{ADJ} = 0.75,\ Q^2 = 0.67,\ F(5,21) = 16.4,\ p < 10^{-5}$$

$$pIC_{50}(MCF-7;Set\ 2) = 0.0149\cdot CSI - 0.109\cdot UNIP - 0.0475\cdot MPC10 + 0.815\cdot X2 - 0.909\cdot GATS1v + 1.11 \quad (6)$$

$$R^2 = 0.89,\ R^2_{ADJ} = 0.87,\ Q^2 = 0.83,\ F(5,21) = 34.7,\ p < 10^{-5}$$

The models are described by several statistical parameters which are provided below each equation. The acceptance of the model was based on the correlation coefficients R^2, the adjusted correlation coefficients R^2_{ADJ}, and the F-test (F) values. The performance of the models was validated using the Leave One Out (LOO) method with the variance Q^2. The molecular descriptors appearing in the Equations (1)–(6) are listed in the Supporting Information. Plots of the experimentally determined versus predicted pIC_{50} values are presented in Fig. 3. A straight line represents an ideal agreement between the observed and calculated values. Interestingly, the correlation coefficients R^2 are similar for the same cell line, regardless of the compound set, even though the QSAR equations are different. For the A549 cell line measured pIC_{50} data

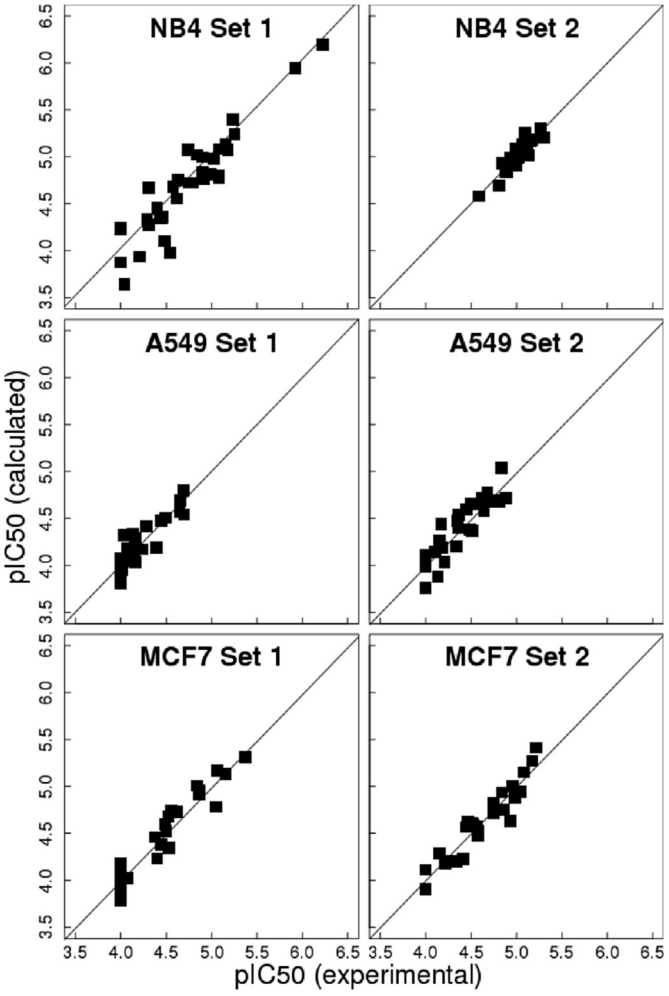


Fig. 3. Plot of experimentally determined versus predicted pIC_{50} values. Straight line represents agreement between experimental and calculated values. The scaling of *x*- and *y*-axes is the same for all subplots for a better comparison.

ranges are only 0.7 and 0.9 log units for Sets 1 and 2, respectively, and this partly explains a lower QSAR model quality for A549 compared to others. It is interesting to investigate how well the models are able to classify compounds as 'actives' and 'inactives'. For the numerous points in Fig. 3 corresponding to 'inactives' with the experimental IC_{50} > 100 μM (pIC_{50} = 4), QSAR models predict pIC_{50} in the range from 3.76 to 4.25, i.e. the "true negatives" are reasonably well predicted by the QSAR equations. There are only two "false negatives" **3ei** and **3fn** (Set 1, NB4 cell line) with the predicted pIC_{50} lower than 4.0 and the experimental activity pIC_{50}>=4.2, a relatively small error. Thus, we show that the QSAR models are able to distinguish between the active and inactive compounds, and they can be useful for designing molecules with improved antiproliferative properties.

5. Effect on cell cycle distribution and induction of apoptosis

Cytotoxic compounds are known to be capable of altering cell cycle progression [17]. Via various molecular effects, cytotoxic agents have an impact on a cell cycle arrest at G0/G1, S or G2/M phases. These effects may also be followed by a programmed cell death (apoptosis) [18].

In order to determine if cell growth inhibition was mediated by the cell cycle arrest, a flow cytometrical cell cycle analysis was performed. For this study, we selected the most efficacious and selective compounds for each cell line: **3aa**, **3gh**, **5bb**, **5ch**, **5'dh**, **6bd**, **7a** for the NB4 cells; **3 dl**, **5bb**, **5bi**, **5 dm**, **5'da** for the A549 cells, and **3 dl**, **3 ab**, **5bb**, **5bi**, **5'dh**,**7a** for the MCF-7 cells.

Cell cycle phase distributions were examined in the NB4, A549 and MCF-7 cells after a 48 h treatment with the selected compounds. The cells were exposed to the compounds using the average effective concentrations depending on IC_{50} values for each cell line. Control cells were incubated with an appropriate amount of solvent (DMSO).

Cell cycle distribution data indicated high sub-G1 peaks and cell death after treating the NB4 cells using 10 μM concentration of compounds. For this reason, it was difficult to evaluate the specific cell cycle arrest phases. Therefore the experiment was conducted using a lower concentration of the compounds (5 μM). Fig. 4a shows that the chosen compounds arrested the NB4 cells in the S (**3aa**, **5bb**, **5ch**, **7a**), G0/G1 (**3gh**), or G2/M cell cycle phase (**5'dh** and **6bd**).

A treatment of the A549 cells using 20 μM concentration of the compounds did not have a marked effect on the cell cycle phase distribution (Fig. 4b). Only a slight increase in the G2/M phase accumulation was observed after the treatment with **3 dl**, **5bb**, **5bi** and **5 dm**. Using a larger 30 μM concentration had a more noticeable impact on the cell cycle phase distribution. The compounds **3 dl**, **5bb**, **5bi** only slightly arrested cells in the G2/M and S phases at 20 μM concentration, but had a pronounced potency to force cells accumulate in the S phase at 30 μM.

Similar to the other cell lines, MCF-7 cell cycle was also arrested in the S and G2/M phases after a treatment with 10 μM concentration of the agent (Fig. 4c). The accumulation in the S and the G2/M phases was the most evident for the compounds **3 ab** and **7a**.

Annexin V binding assay was performed for the elucidation of apoptosis as described in the Experimental section. The apoptotic effect was studied using the following concentrations of the selected compounds: 5 μM for the NB4 cell line (Fig. 5a), 20 μM and 30 μM for the A549 cell line (Fig. 5b), and 10 μM for the MCF-7 cell line (Fig. 5c). The percentage of the apoptotic cancer cells was measured after 24 and 48 h of treatment.

Notably, **3gh** did not induce apoptosis of the leukemia NB4 cells, even though it was the most active in arresting NB4 cell cycle in the G0/G1 cycle phase.

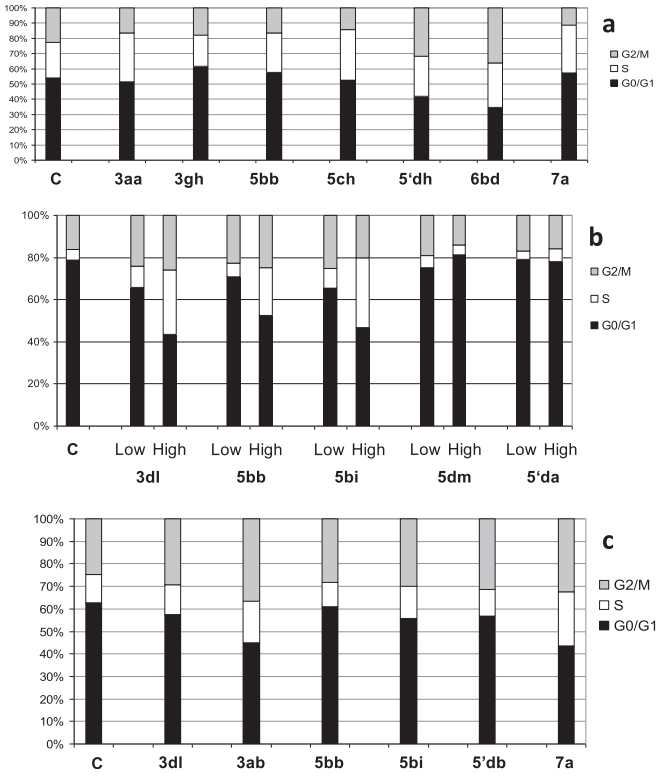


Fig. 4. Cell cycle phase distribution in NB4 (a), A549 (b) and MCF-7 (c) cells after 48 h treatment with selected compounds. Values are mean of two independent experiments (n = 2). SDs (not indicated) were less than 10%. The compound concentrations in (a) and (c) are 10 μM; in (b), "High" and "low" in (b) refer to 30 and 20 μM concentration, respectively.

Previously, it has been demonstrated that the NB4 cell cycle arrest in the G0/G1 phase may be accompanied by a granulocytic differentiation [19]. Therefore, the effect of the compound **3gh** on the acute promyelocytic leukemia (APL) NB4 cell granulocytic differentiation induced by all-trans retinoic acid (RA) was also evaluated (results presented in Section 6). In contrast to **3gh**, other tested compounds displayed an obvious pro-apoptotic effect on the NB4 cells. The most potent apoptosis inducing agents at early time points were **3aa**, **5bb**, **5ch** (24 h treatment using 5 μM concentration caused death of >50% of the cell population). This effect is comparable to the effect of other drugs already used for leukemia therapy. Recently we demonstrated that a treatment of the NB4 cells with histone deacetylase inhibitor Belinostat caused around 20% of the cell population to undergo apoptosis [19c]. Additionally, it has been reported that after a treatment with chemotherapeutic drugs As_2O_3 and Doxorubicin nearly 27% and 80% of the NB4 cells were dead, respectively [20].

The most prominent apoptotic effect in the A549 cells was detected upon treatment with agents **3 dl**, **5bb** and **5bi** using low and high concentrations (Fig. 5b). Compound **7a** (Fig. 5c) had the most pronounced effect on apoptosis induction as well as the strongest effect on the MCF-7 cell cycle arrest in the G2/M and S phases. This tendency of the strong apoptotic effect of compounds arresting the cell cycle in S phase was evident in the NB4 and A549 cell lines as well.

There is some evidence that G2/M arrest may enhance apoptotic cancer cell death [21]. Therefore, combination therapies with drugs, capable of arresting cells in the G2/M or S cell cycle phase may suggest more potent therapy strategies.

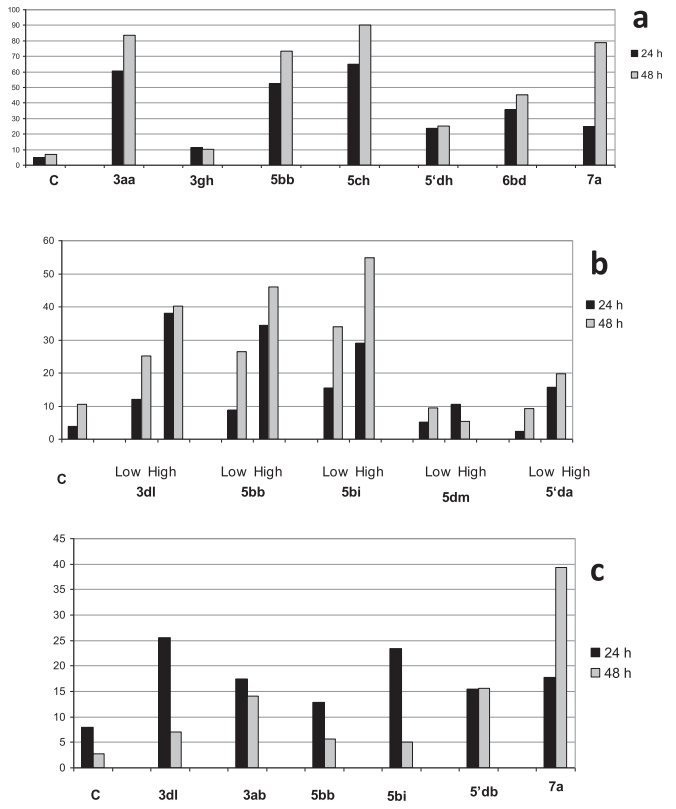


Fig. 5. Percent of apoptotic NB4 (a), A549 (b) and MCF-7 (c) cells after 24 h and 48 h treatment with selected compounds. Values are mean of two independent experiments (n = 2). SDs (not indicated) were less than 10%.

6. The effect of compound 3gh on the promyelocytic leukemia cell line NB4 proliferation and the granulocytic differentiation

The effect of the compound **3gh** on leukemia cell granulocytic differentiation in the APL cell line NB4 is shown in Fig. 6. 1 μM concentration of **3gh** was chosen due to its low IC_{50} value (0.6 ± 0.02 μM) against the NB4 cell line (Table 4), and also considering the fact that **3gh** effectively arrests the NB4 cell growth in the G0/G1 cell cycle phase (Fig. 4a). To determine the impact on the leukemia cell differentiation, the NB4 cells were treated with 1 μM **3gh** alone and combined with RA (1 μM **3gh** + 1 μM RA).

RA is a known granulocytic differentiation inducer and is used to treat acute promyelocytic leukemia together with other anti-cancer drugs. It was shown that a treatment of APL leukemic cells with RA causes them to differentiate into mature granulocytes [22]. The differentiation therapy is less aggressive treatment compared to other treatment strategies, such as chemotherapy. However, resistance to the RA cytodifferentiation effects is frequently acquired [23]; therefore, RA treatment in combination with other drugs that are capable to resensitize RA-resistant APL cells or drugs that may strengthen RA's pro-differentiation effect might be beneficial.

Fig. 6 shows that 1 μM of **3gh** partly inhibits the NB4 cell proliferation. However, this effect is less pronounced compared to the treatment using either RA alone or RA combined with **3gh**. The highest drop in the cell viability was detected upon 96 h treatment with **3gh** as a single agent. The effect of the used compounds on the cell cycle distribution was also evaluated (data not shown). 1 μM **3gh** as a single agent had only a negligible impact on the cell cycle arrest in the G0/G1 phase. However, RA alone or the RA + **3gh** combination effectively arrested the NB4 cell cycle in G0/G1 phase after 24 h treatment (the resulting accumulation in the G0/G1 cell cycle phase was 17.3% and 18.2%, respectively).

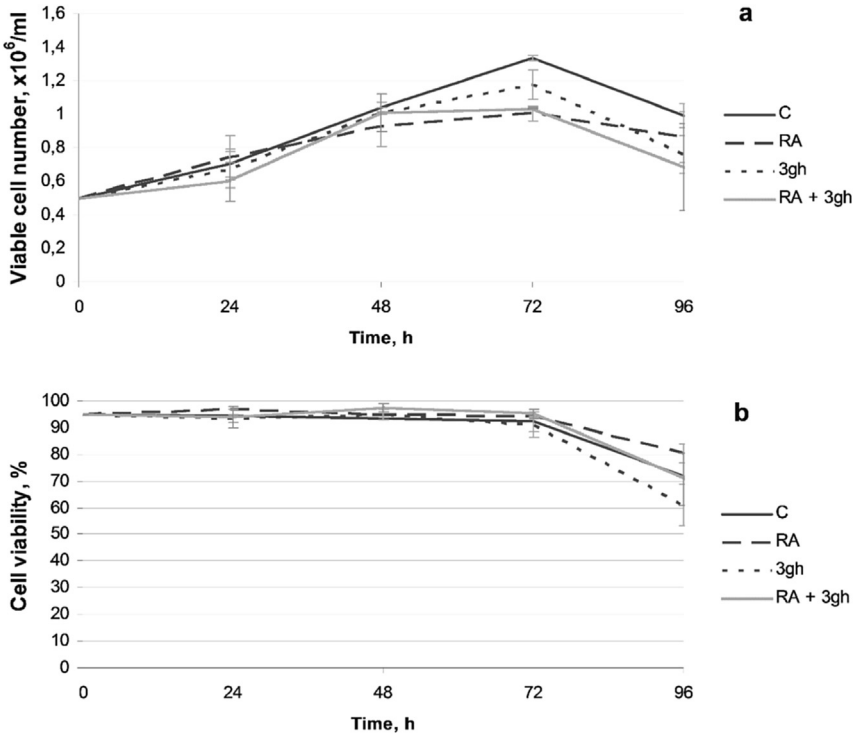


Fig. 6. Cell growth (a) and cell viability (b) of the control NB4 cells and the NB4 cells treated with 1 μM **3gh**, 1 μM RA and with 1 μM **3gh** + 1 μM RA. At each of the indicated time points, aliquots of the cultures were subjected to 0.2% trypan blue staining. Results are shown as mean ± SD (n = 3).

NBT and CD11b tests (see Experimental section) revealed that **3gh** alone was not sufficient to induce the NB4 cell differentiation into mature granulocytes (Fig. 7). However, **3gh** in combination with RA enhanced and accelerated the RA induced granulocytic differentiation up to 8% in comparison with RA alone (Fig. 7). It should be emphasized that it is a common practice in leukemia differentiation therapy to use drugs that are incapable of inducing differentiation alone. However, when used in combination with RA they effectively promote and accelerate the APL granulocytic differentiation. Previously our group demonstrated that histone deacetylase inhibitor Belinostat did not induce the APL granulocytic differentiation when used as a single agent, but it enhanced the NB4 cell differentiation to the mature granulocytes by 13% in combination with RA [19c]. The same activity pattern was also shown for histone methyltransferase 2 inhibitor Bix-01294, which promoted granulocytic differentiation by 10% [18b].

7. Conclusions

A series of α,β-unsaturated ketones with various α- and β-substituents were synthesized, and their in vitro antiproliferative activities and selectivities against human hematological and solid cancer cell lines were examined. (*E*)-1-(4-Methoxyphenyl)-4-methyl-2-(4-nitrobenzylidene)pentan-1-one **3gh** was found to be the most potent and selective agent towards the NB4 hematological cell line; it was shown that this compound did not induce apoptosis but blocked cell cycle in the G0/G1 phase. It was also demonstrated that the anti-NB4 activity of **3gh** may be associated with a promotion of leukemia cells to differentiation. Compounds **3 ab**, **3 dl, 7a** and **7c** exhibited marked growth inhibition of the NB4 and MCF-7 cancer cells with a marked apoptotic effect.

Using QSAR computational techniques, we have successfully developed and validated models that provide foundation for the design of new molecules with improved cancer cell growth inhibitory activities.

Our results revealed a set of compounds-promising candidates for further biological evaluations.

8. Experimental

8.1. Biology

8.1.1. Cell lines, culture and plating

Human acute promyelocytic leukemia cells NB4, lung cancer cell line A549 and breast cancer cells MCF-7 were used in this study. NB4 cells were maintained in RPMI 1640 + GlutaMAX medium supplemented with 10% fetal bovine serum, 100 U/ml penicillin and 100 mg/ml streptomycin (Gibco, Grand Island, NY, USA) in a humidified incubator at 37 °C with 5% CO_2. A549 and MCF-7 cells were cultivated at the same conditions in DMEM + GlutaMAX medium (Gibco, Grand Island, NY, USA) with indicated supplements. For chemosensitivity testing, exponentially growing cells were seeded to 96 well plates at a density of $1.5 \cdot 10^4$ (NB4) and $1.0\ 10^4$ (A549 and MCF-7) cells per well. For cell cycle and apoptosis analysis cells were seeded in 6 well plates at a density of $1 \cdot 10^6$ (NB4) and $0.45 \cdot 10^6$ (A549 and MCF-7) cells per well. For evaluation of **3gh** effect on cell proliferation and viability, logarithmically growing NB4 cells were seeded at a density of 0.5×10^6 cells/ml in 5 ml of RPMI medium.

8.1.2. Chemosensitivity testing

Compounds were dissolved in DMSO at 200 times the final maximum concentration used in the test. For negative control, cells were treated with an equivalent concentration of DMSO (0.5% v/v). Each agent was tested in triplicate at different concentrations in the range of 0.1–100 μM. For adherent cells (A549 and MCF-7) drug treatment was started 24 h after plating, whereas NB4 cells were treated shortly after plating. Cells were incubated with drugs for 48 h, then XTT reagent (Sigma, St. Louis, USA) was added to the medium (20% of the culture medium volume) and cells were further incubated for 2 h. The absorbance of each well was measured at 450 nm and 690 nm (for background evaluation) using Infinite M200 PRO (Tecan, Mannedorf, Switzerland). Measurements were corrected for background by subtracting 690 nm value from the 450 nm value. Data was expressed as GI_{50} values with SE.

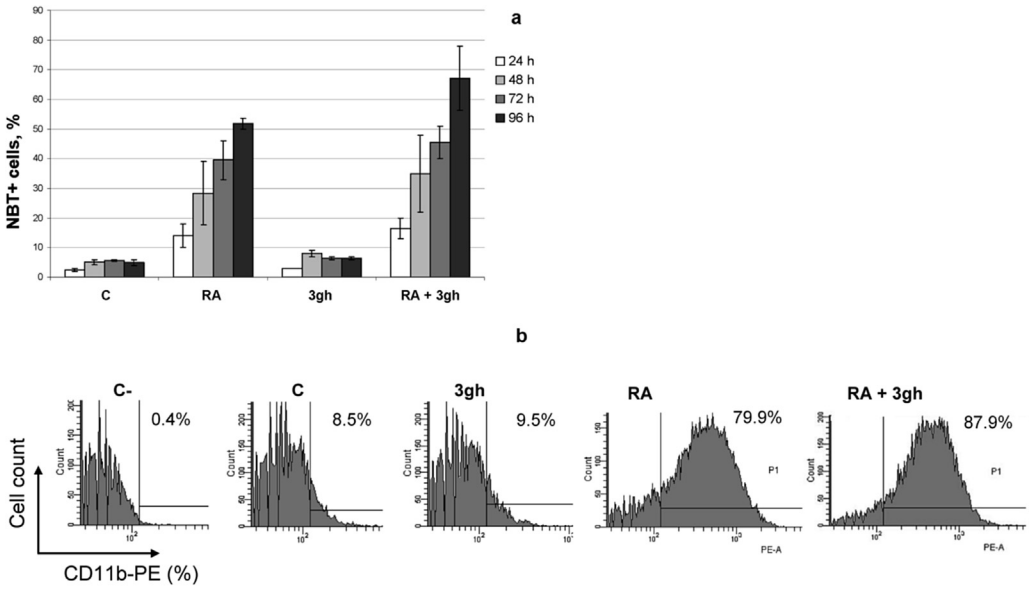


Fig. 7. Effects of **3gh**, RA and their combined treatment on NB4 cell granulocytic differentiation. Control and NB4 cells treated with 1 μM **3gh**, 1 μM RA and with 1 μM **3gh** + 1 μM RA were subjected to granulocytic differentiation analysis, using NBT test (at 24–96 h time points; a) and CD11b assay (at 48 h; b). NBT test results are given as mean (±SD, n = 3), whereas CD11b assay results are representative of two independent experiments.

8.1.3. NB4 cell proliferation, viability and differentiation assays

NB4 cells were exposed to 1 μM RA (Sigma, St. Louis, USA), 1 μM 3gh alone or in combination with 1 μM RA for 24, 48, 72 and 96 h. Cell proliferation was evaluated using the trypan blue exclusion test. Viable and dead (blue colored) cell count was determined using a hematocytometer. The degree of granulocytic NB4 cell differentiation was evaluated by cells' ability to reduce soluble nitro blue tetrazolium (NBT) to insoluble blue-black formazan after stimulation with phorbolmyristate acetate (PMA). NBT stained cells were counted in 5 consecutive non-overlapping microscopic fields at a magnification of 400. The average percent of NBT positive cells per high power field was calculated. Three independent experiments were performed and their results were averaged.

8.1.4. Flow cytometric analysis of the cell cycle distribution, apoptosis and CD11b surface biomarker

Cell cycle distribution and assessment of apoptosis and CD11b surface marker of treated cells was analysed as described by Savickiene et al. (2014) [19c].

8.2. Chemistry

8.2.1. General information

IR spectra were run in KBr discs on a Perkin–Elmer FT spectrophotometer Spectrum BX II. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Unity INOVA spectrometer (300 MHz) or Brucker (400 MHz) in chloroform-d, using residual solvent signal as internal standard. HRMS spectra were obtained on a mass spectrometer Dual-ESI Q-TOF 6520 (Agilent Technologies). All reactions and the purity of the synthesized compounds were monitored by TLC using Silica gel 60 F_{254} aluminium plates (Merck). Visualization was accomplished by UV light. Final purification of synthesized compounds was performed on Flash Chromatography system CombiFlash (Teledyne Isco), using hexane – ethyl acetate mixtures.

Starting alkyne **1a** was prepared according to literature procedure [24] and alkynes **1b-i** were prepared *via* Sonogashira coupling reaction as described in our previously published protocol [9b].

*8.2.2. General method for the preparation of compounds **3**–**6***

To a stirred solution of alkyne **1** (0.5 mmol) and aldehyde **2** (0.5 mmol) in dry dichloromethane (3 mL), boron trifluoride diethyl etherate (0.071 g, 0.065 mL, 0.5 mmol) was added. Stirring was continued at room temperature till the reaction was completed (monitored by TLC). The mixture was then quenched with sodium bicarbonate solution, and the organic layer was separated, washed with water (2*20 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by Flash Column chromatography eluting with hexane–ethyl acetate mixtures.

*8.2.3. General method for the preparation of compounds **7***

A solution of the MBH adduct **5bb** or 5**bh** (0.14 mmol) and appropriate amine (0.168 mmol) in dimethylformamide (2 mL) was stirred at room temperature till the reaction was completed (monitored by TLC). The mixture was then quenched with ethyl acetate (10 mL), and the organic solution was washed with water (2 x 20 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by Flash Column chromatography eluting with hexane–ethyl acetate mixtures.

*8.2.4. Spectral and physical data of compounds **3**–**7***

Compounds **3 ab**, **4 ab**, **6ac**, **5bb**, **5bh**, **5bi**, **5ch**, **5cj**, **5 db**, **5dh**, **5di**, **5 dl** and **5 dm** [9a] and compounds **3aa**, **3eb**, **4aa** and **5'dh** [9b] have been described in our previous publications. The NMR data of the unstable compounds **7b**, **7d**, **7e** and **7g** are presented in supporting information.

*8.2.4.1. (E)-3-(2-Fluorophenyl)-2-(4-methoxybenzoyl)allyl acetate (**3ba**).* Yellowish oil. Yield 34%. IR (KBr): ν_{max} = 1737, 1650 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.98 (3H, s, $OCOCH_3$), 3.87 (3H, s, OCH_3), 5.07 (2H, s, CH_2OCOMe), 6.97 (2H, d, 6.18 $^{3}J_{H,H}$ = 9.2 Hz, ArH), 7.07–7.12 (1H, m, ArH), 7.19 (1H, td, $^{3}J_{H,H}$ = 7.6 Hz, $^{4}J_{H,H}$ = 0.8 Hz, ArH), 7.27 (1H, s, =CH), 7.33–7.43 (2H, m, ArH), 7.89 (2H, d, $^{3}J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.67, 55.43, 60.46, 113.69, 115.68 (d, $^{2}J_{C,F}$ = 21.4 Hz), 122.32 (d, $^{2}J_{C,F}$ = 14.0 Hz), 124.21 (d, $^{3}J_{C,F}$ = 3.7 Hz), 129.76, 130.20 (d, $^{3}J_{C,F}$ = 2.4 Hz), 131.02 (d, $^{4}J_{C,F}$ = 8.4 Hz), 132.15, 134.62 (d, $^{3}J_{C,F}$ = 3.6 Hz), 137.26, 160.20 (d, $^{1}J_{C,F}$ = 248.3 Hz), 163.42, 170.57, 195.06 ppm. HRMS (ES): M + Na^+, found 351.1007. $C_{19}H_{17}FNaO_4$ requires 351.1003.

*8.2.4.2. (E)-4-Ethyl-2-(4-methoxybenzoyl)hex-2-en-1-yl acetate (**3be**).* Yellowish oil. Yield 22%. IR (KBr): ν_{max} = 1737, 1647 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (6H, t, $^{3}J_{H,H}$ = 7.6 Hz,$CH(CH_2\underline{CH_3})_2$), 1.21–1.32 (2H, m, $\underline{CH_2}CH_3$), 1.48–1.59 (2H, m, $\underline{CH_2}CH_3$), 2.00 (3H, s, $OCOCH_3$), 2.38–2.48 (1H, m, $\underline{CH}(CH_2CH_3)_2$), 3.85 (3H, s, OCH_3), 4.97 (2H, s, CH_2OCOMe), 6.07 (1H, d, $^{3}J_{H,H}$ = 10.8 Hz, =CH), 6.93 (2H, d, $^{3}J_{H,H}$ = 8.8 Hz, ArH) 7.73 (2H, d, $^{3}J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.92, 20.85, 27.66, 42.63, 55.40, 59.32, 113.45, 130.35, 131.81, 135.53, 152.29, 162.92, 170.85, 195.69 ppm. HRMS (ES): M + Na^+, found 327.1571. $C_{18}H_{24}NaO_4$ requires 327.1567.

*8.2.4.3. (E)-3-Cyclohexyl-2-(4-methoxybenzoyl)allyl acetate (**3bf**).* Colorless oil. Yield 37%. IR (KBr): ν_{max} = 1738, 1650 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.07–1.19 (3H, m, *c*Hex), 1.27–1.38 (2H, m, *c*Hex), 1.65–1.74 (5H, m, *c*Hex), 1.99 (3H, s, $OCOCH_3$), 2.49–2.59 (1H, m, *c*Hex), 3.84 (3H, s, OCH_3), 4.97 (2H, s, CH_2OCOMe), 6.18 (1H, d, $^{3}J_{H,H}$ = 10.0 Hz, =CH), 6.90 (2H, d, $^{3}J_{H,H}$ = 8.8 Hz, ArH), 7.70 (2H, d, $^{3}J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.80, 25.20, 25.59, 32.24, 38.05, 55.34, 59.24, 113.40, 130.30, 131.86, 133.00, 152.61, 162.91, 170.82, 195.73 ppm. HRMS (ES): M + Na^+, found 339.1576. $C_{19}H_{24}NaO_4$ requires 339.1567.

*8.2.4.4. (E)-4-Ethyl-2-(4-methoxybenzoyl)hex-2-en-1-yl benzoate (**3de**).* Yellowish oil. Yield 4%. IR (KBr): ν_{max} = 1717, 1647 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (6H, t, $^{3}J_{H,H}$ = 7.6 Hz,$CH(CH_2\underline{CH_3})_2$), 1.26–1.34 (2H, m, $\underline{CH_2}CH_3$), 1.52–1.58 (2H, m, $\underline{CH_2}CH_3$), 2.50–2.59 (1H, m, $\underline{CH}(CH_2CH_3)_2$), 3.87 (3H, s, OCH_3), 5.24 (2H, s, CH_2OCOMe), 6.13 (1H, d, $^{3}J_{H,H}$ = 10.4 Hz, =CH), 6.94 (2H, d, $^{3}J_{H,H}$ = 8.8 Hz, ArH), 7.38 (2H, t, $^{3}J_{H,H}$ = 7.2 Hz, ArH), 7.52 (1H, t, $^{3}J_{H,H}$ = 7.2 Hz, ArH), 7.78 (2H, d, $^{3}J_{H,H}$ = 8.8 Hz, ArH), 7.96–7.98 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.99, 27.72, 42.71, 55.45, 59.86, 113.54, 128.28, 129.61, 130.07, 130.50, 131.87, 132.87, 135.64, 152.27, 162.98, 166.34, 195.80 ppm. HRMS (ES): M + Na^+, found 389.1730. $C_{23}H_{26}NaO_4$ requires 389.1723.

*8.2.4.5. (E)-3-Cyclohexyl-2-(4-methoxybenzoyl)allyl benzoate (**3df**).* Yellowish oil. Yield 8%. IR (KBr): ν_{max} = 1717, 1646 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14–1.20 (3H, m, *c*Hex), 1.29–1.35 (2H, m, *c*Hex), 1.66–1.75 (5H, m, *c*Hex), 2.61–2.71 (1H, m, *c*Hex), 3.86 (3H, s, OCH_3), 5.24 (2H, s, CH_2OCOPh), 6.24 (1H, d, $^{3}J_{H,H}$ = 10.0 Hz, =CH), 6.93 (2H, d, $^{3}J_{H,H}$ = 7.6 Hz, ArH), 7.39 (2H, t, $^{3}J_{H,H}$ = 8.8 Hz, ArH), 7.52 (1H, t, $^{3}J_{H,H}$ = 7.6 Hz, ArH), 7.76 (2H, d, $^{3}J_{H,H}$ = 8.8 Hz, ArH), 7.97 (2H, d, $^{3}J_{H,H}$ = 7.6 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.25, 25.64, 32.35, 38.20, 55.43, 59.82, 113.49, 128.28, 129.58, 130.05, 130.43, 131.96, 132.89, 133.12, 152.71, 162.97, 166.40, 195.93 ppm. HRMS (ES): M + Na^+, found 401.1730. $C_{24}H_{26}NaO_4$ requires 401.1723.

*8.2.4.6. (E)-2-Benzoylbut-2-en-1-yl benzoate (**3dk**).* Colorless oil. Yield 22%. IR (KBr): ν_{max} = 1715, 1644 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.05 (3H, d, $^3J_{H,H}$ = 7.2 Hz, CH_3), 3.85 (3H, s, OCH_3), 5.26 (2H, s, CH_2OCOPh), 6.54 (1H, q, $^3J_{H,H}$ = 7.2 Hz, =CH), 6.92 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.39 (2H, t, $^3J_{H,H}$ = 7.6 Hz, ArH), 7.52 (1H, t, $^3J_{H,H}$ = 7.6 Hz, ArH), 7.75 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.97–7.99 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.63, 55.43, 59.28, 113.49, 129.62, 129.98, 130.35, 131.86, 132.92, 136.56, 142.72, 162.95, 166.43, 195.59 ppm. HRMS (ES): M + Na^+, found 333.1100. $C_{19}H_{18}NaO_4$ requires 333.1097.

*8.2.4.7. (E)-3-(2-Chlorophenyl)-2-(4-methoxybenzoyl)allyl benzoate (**3 dl**).* Colorless solid m. p. = 94–96 °C. Yield 33%. IR (KBr): ν_{max} = 1715, 1651 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.88 (3H, s, OCH_3), 5.29 (2H, d, $^4J_{H,H}$ = 0.8 Hz, CH_2OCOPh), 6.99 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.29–7.32 (2H, m, ArH), 7.33–7.38 (3H, m, ArH, =CH), 7.42–7.46 (2H, m, ArH), 7.50 (1H, t, $^3J_{H,H}$ = 7.6 Hz, ArH), 7.88–7.90 (2H, m, ArH), 8.01 (2H, d, $^3J_{H,H}$ = 9.2 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.46, 60.78, 113.76, 126.90, 128.24, 129.56, 129.65, 129.73, 129.76, 130.18, 130.21, 132.28, 132.92, 133.11, 133.94, 136.94, 138.68, 163.53, 166.03, 195.14 ppm. HRMS (ES): M + Na^+, found 429.0859. $C_{24}H_{19}ClNaO_4$ requires 429.0864.

*8.2.4.8. (E)-4-(2-Fluorophenyl)-3-(4-methoxybenzoyl)but-3-enyl acetate (**3ea**).* Bright yellow oil. Yield 50%. IR (KBr): ν_{max} = 1650, 1738(C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.92 (3H, s, $OCOCH_3$), 3.01 (2H, t, $^3J_{H,H}$ = 6.6 Hz, $=CCH_2$), 3.87 (3H, s, OCH_3), 4.25 (2H, t, $^3J_{H,H}$ = 6.6 Hz, CH_2OCOMe), 6.94–7.00 (2H, m, ArH), 7.07–7.24 (3H, m, =CH, ArH), 7.30–7.38 (1H, m, ArH), 7.43–7.51 (1H, m, ArH), 7.86–7.91 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ20.62, 27.82, 55.34, 62.43, 113.49, 115.59 (d, $^2J_{C,F}$ = 21.7 Hz), 123.12 (d, $^2J_{C,F}$ = 14.3 Hz), 124.03 (d, $^3J_{C,F}$ = 3.6 Hz), 129.87 (d, $^3J_{C,F}$ = 2.8 Hz), 129.99, 130.23 (d, $^4J_{C,F}$ = 8.3 Hz), 132.08, 133.40 (d, $^3J_{C,F}$ = 3.2 Hz), 139.59, 159.97 (d, $^1J_{C,F}$ = 247.1 Hz), 163.13, 170.65, 196.65 ppm. HRMS (ESI^+): M + Na^+, found 365.1160. $C_{20}H_{19}FNaO_4$ requires 365.1166.

*8.2.4.9. (E)-5-Ethyl-3-(4-methoxybenzoyl)hept-3-enyl acetate (**3ee**).* Bright yellow oil. Yield 21%. IR (KBr): ν_{max} = 1639, 1736 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.92 (6H, t, $^3J_{H,H}$ = 7.5 Hz, $CH(CH_2\underline{CH_3})_2$), 1.22–1.35 (2H, m, $CH(\underline{CH_2}CH_3)_2$), 1.48–1.61 (2H, m, $CH(\underline{CH_2}CH_3)_2$), 1.98 (3H, s, $OCOCH_3$), 2.40 (1H, m, $\underline{CH}(CH_2CH_3)_2$), 2.86 (2H, t, $^3J_{H,H}$ = 6.9 Hz, $=CCH_2$), 3.87 (3H, s, OCH_3), 4.18 (2H, t, $^3J_{H,H}$ = 6.9 Hz, CH_2OCOMe), 5.97 (1H, d, $^3J_{H,H}$ = 10.4 Hz, =CH), 6.91–6.97 (2H, m, ArH), 7.66–7.74 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ:12.02, 20.93, 26.99, 27.73, 42.45, 55.43, 63.26, 113.40, 130.92, 131.78, 136.90, 150.33, 162.71, 170.97, 197.32 ppm. HRMS (ESI^+): M + Na^+, found 341.1723. $C_{19}H_{26}NaO_4$ requires 341.1723.

*8.2.4.10. (E)-4-Cyclohexyl-3-(4-methoxybenzoyl)but-3-enyl acetate (**3ef**).* Bright yellow oil. Yield 40%. IR (KBr): ν_{max} = 1640, 1736 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.07–1.79 (11H, m, *c*Hex) 1.98 (3H, s, $OCOCH_3$), 2.83 (2H, t, $^3J_{H,H}$ = 6.7 Hz, $=CCH_2$), 3.85 (3H, s, OCH_3), 4.17 (2H, t, $^3J_{H,H}$ = 6.7 Hz, CH_2OCOMe), 6.09 (1H, d, $^3J_{H,H}$ = 10.0 Hz, =CH), 6.89–6.93 (2H, m, ArH), 7.65–7.69 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.87, 25.42, 25.74, 26.82, 32.40, 38.12, 55.38, 63.46, 113.34, 130.90, 131.83, 134.33, 151.08, 162.68, 170.89, 197.45 ppm. HRMS (ESI^+): M + Na^+, found 353.1723. $C_{20}H_{26}NaO_4$ requires 353.1718.

*8.2.4.11. (E)-3-(4-Methoxybenzoyl)-4-(4-nitrophenyl)but-3-enyl acetate (**3eh**).* Brownish solid; m.p. = 121–122 °C. Yield 53%. IR (KBr): ν_{max} = 1636, 1734 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.94 (3H, s, $OCOCH_3$), 3.05 (2H, t, $^3J_{H,H}$ = 6.6 Hz, $=CCH_2$), 3.88 (3H, s, OCH_3), 4.26 (2H, t, $^3J_{H,H}$ = 6.6 Hz, CH_2OCOMe), 6.94–7.00 (2H, m, ArH), 7.12 (1H, s, =CH), 7.56–7.62 (2H, m, ArH), 7.81–7.87 (2H, m, ArH), 8.22–8.28 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.76, 27.94, 55.53, 62.39, 113.78, 123.84, 129.69, 129.76, 132.16, 137.54, 140.88, 141.84, 147.35, 163.49, 170.68, 196.39 ppm. HRMS (ESI^+): M + Na^+, found 392.1105. $C_{20}H_{19}NNaO_6$ requires 392.1107.

*8.2.4.12. (E)-3-(4-Methoxybenzoyl)-4-(2,3,4,5,6-pentafluorophenyl) but-3-enyl acetate (**3ei**).* Yellowish oil. Yield 21%. IR (KBr): ν_{max} = 1654, 1741 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.89 (3H, s, $OCOCH_3$), 2.80 (2H, m, $=CCH_2$), 3.91 (3H, s, OCH_3), 4.17 (2H, t, $^3J_{H,H}$ = 6.4 Hz, CH_2OCOMe), 6.62 (1H, m, =CH), 6.97–7.04 (2H, m, ArH), 7.89–7.95 (2H, m, Ar–H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.53, 29.50, 55.51, 61.74, 110.14 (m), 113.82, 122.05, 129.15, 132.26, 136.45 (m), 138.97 (m), 139.74 (m), 142.34 (m), 144.85 (m), 145.59, 163.77, 170.56, 195.08 ppm. HRMS (ESI^+): M + Na^+, found 437.0783. $C_{20}H_{15}F_5NaO_4$ requires 437.0790.

*8.2.4.13. (E)-4-(2-Chlorophenyl)-3-(4-methoxybenzoyl)but-3-enyl acetate (**3el**).* Yellow oil. Yield 55%. IR (KBr): ν_{max} = 1645, 1739 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.92 (3H, s, $OCOCH_3$), 2.96 (2H, t, $^3J_{H,H}$ = 6.5 Hz, $=CCH_2$), 3.89 (3H, s, OCH_3), 4.19 (2H, t, $^3J_{H,H}$ = 6.5 Hz, CH_2OCOMe), 6.96–7.01 (2H, m, ArH), 7.19 (1H, s, =CH), 7.28–7.35 (2H, m, ArH), 7.40–7.47 (2H, m, ArH), 7.93–7.99 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.80, 27.53, 55.50, 62.55, 113.65, 126.80, 129.61, 130.01, 130.06, 132.30, 132.56, 133.82, 134.17, 137.77, 139.17, 163.35, 170.76, 196.84 ppm. HRMS (ESI^+): M + Na^+, found 381.0864. $C_{20}H_{19}ClNaO_4$ requires 381.0868.

*8.2.4.14. (E)-4-(4-Chlorophenyl)-3-(4-methoxybenzoyl)but-3-enyl acetate (**3en**).* Yellow solid; m.p. = 64–65 °C. Yield 25%. IR (KBr): ν_{max} = 1643, 1739 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.97 (3H, s, $OCOCH_3$), 3.08 (2H, t, $^3J_{H,H}$ = 6.7 Hz, $=CCH_2$), 3.90 (3H, s, OCH_3), 4.29 (2H, t, $^3J_{H,H}$ = 6.7 Hz, CH_2OCOMe), 6.95–7.01 (2H, m, ArH), 7.11 (1H, s, =CH), 7.36–7.43 (4H, m, ArH), 7.81–7.85 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.83, 27.66, 55.50, 62.66, 113.64, 128.90, 130.33, 130.35, 132.09, 133.67, 134.58, 138.24, 139.90, 163.16, 170.84, 197.08 ppm. HRMS (ESI^+): M + Na^+, found 381.0864. $C_{20}H_{19}ClNaO_4$ requires 381.0864.

*8.2.4.15. (E)-5-(2,4-Dichlorophenyl)-4-(4-methoxybenzoyl)pent-4-en-2-yl acetate (**3 fb**).* Yellowish oil. Yield 70%. IR (KBr): ν_{max} = 1650, 1738 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.18 (3H, d, $^3J_{H,H}$ = 6.2 Hz, $CH_2CH\underline{CH_3}$), 1.80 (3H, s, $OCOCH_3$), 2.88 (2H, d, $^3J_{H,H}$ = 6.5 Hz, $=CCH_2$), 3.87 (3H, s, OCH_3), 5.02 (1H, tq, $^3J_{H,H}$ = 6.5 Hz, $^3J_{H,H}$ = 6.2 Hz, $CH_2\underline{CH}CH_3$), 6.94–6.99 (2H, m, ArH), 7.04 (1H, s, =CH), 7.31 (1H, dd, $^3J_{H,H}$ = 8.31 Hz, $^4J_{H,H}$ = 1.96 Hz, ArH), 7.38 (1H, d, $^3J_{H,H}$ = 8.31 Hz, ArH), 7.45 (1H, d, $^4J_{H,H}$ = 2.08 Hz, ArH), 7.90–7.95 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.26, 21.04, 34.12, 55.47, 69.64, 113.69, 127.18, 129.49, 129.54, 130.83, 132.28, 132.87, 134.62, 134.66, 135.67, 140.02, 163.40, 170.14, 196.25 ppm. HRMS (ESI^+): M + Na^+, found 429.0631. $C_{21}H_{20}Cl_2NaO_4$ requires 429.0632.

*8.2.4.16. (E)-5-Cyclohexyl-4-(4-methoxybenzoyl)pent-4-en-2-yl acetate (**3ff**).* Yellowish oil. Yield 30%. IR (KBr): ν_{max} = 1644, 1736 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.06–1.81 (10H, m, *c*Hex), 1.26 (3H, d, $^3J_{H,H}$ = 6.2 Hz, $CH_2CH\underline{CH_3}$), 1.88 (3H, s, $OCOCH_3$) 2.45–2.57 (1H, m, $=CH\underline{CH}$), 2.81 (2H, d, $^3J_{H,H}$ = 6.2 Hz, $=CCH_2$), 3.87 (3H, s, OCH_3), 5.03 (1H, sext, $^3J_{H,H}$ = 6.2 Hz, $CH_2\underline{CH}CH_3$) 6.04 (1H, d, $^3J_{H,H}$ = 10.0 Hz, =CH) 6.90–6.95 (2H, m, ArH), 7.67–7.73 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.20, 21.23, 25.43, 25.48, 25.78, 32.27, 32.39, 33.21, 38.14, 55.41, 70.56, 113.37, 130.71, 131.94, 134.53, 150.30, 162.70, 170.49, 197.37 ppm. HRMS (ESI^+): M + Na^+, found 367.1880. $C_{21}H_{28}NaO_4$ requires 367.1882.

*8.2.4.17. (E)-4-(4-Methoxybenzoyl)-5-(2,3,4,5,6-pentafluorophenyl) pent-4-en-2-yl acetate (**3fi**).* Greenish oil. Yield 8%. IR (KBr): ν_{max} = 1651, 1738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.20 (3H, d, *J* = 6.4 Hz, $CH_2CH\underline{CH_3}$), 1.77 (3H, s, $OCOCH_3$), 2.72 (1H, dd, $^2J_{H,H}$ = 14.1 Hz, $^3J_{H,H}$ = 8.4 Hz, $=C\underline{CH_2}$), 2.76 (1H, dd, $^2J_{H,H}$ = 14.1 Hz, $^3J_{H,H}$ = 4.4 Hz, $=C\underline{CH_2}$), 3.90 (3H, s, OCH_3), 5.01 (1H, dqd, $^3J_{H,H}$ = 8.4 Hz, $^3J_{H,H}$ = 6.4 Hz, $^3J_{H,H}$ = 4.4 Hz, $CH_2\underline{CH}CH_3$), 6.59 (1H, s, =CH), 6.96–7.02 (2H, m, ArH), 7.88–7.93 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.23, 20.77, 36.18, 55.48, 69.09, 110.28 (m), 113.83, 121.61, 128.89, 132.24, 136.46 (m), 138.99 (m), 139.71 (m), 142.32 (m), 144.83 (m), 145.74, 163.72, 170.09, 194.92 ppm. HRMS (ESI^+): M + Na^+, found 451.0939. $C_{21}H_{17}F_5NaO_4$ requires 451.0944.

*8.2.4.18. (E)-5-(4-Chlorophenyl)-4-(4-methoxybenzoyl)pent-4-en-2-yl acetate (**3fn**).* Yellowish oil. Yield 21%. IR (KBr): ν_{max} = 1644, 1736 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.31 (3H, d, $^3J_{H,H}$ = 6.2 Hz, $CH_2CH\underline{CH_3}$), 1.85 (3H, s, $OCOCH_3$), 2.99 (1H, dd, $^2J_{H,H}$ = 13.9 Hz, $^3J_{H,H}$ = 5.0 Hz, $=C\underline{CH_2}$), 3.04 (1H, dd, $^2J_{H,H}$ = 13.9 Hz, $^3J_{H,H}$ = 8.7 Hz, $=C\underline{CH_2}$), 3.90 (3H, s, OCH_3), 5.18 (1H, dqd, $^3J_{H,H}$ = 8.7 Hz, $^3J_{H,H}$ = 6.2 Hz, $^3J_{H,H}$ = 5.0 Hz, $CH_2C\underline{H}CH_3$), 6.95–6.99 (2H, m, ArH), 7.05 (1H, s, =CH), 7.39–7.41 (4H, m, ArH), 7.81–7.85 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.58, 21.12, 34.42, 55.50, 70.14, 113.63, 128.85, 130.07, 130.36, 132.16, 133.80, 134.45, 138.74, 139.18, 163.15, 170.36, 196.98 ppm. HRMS (ESI^+): M + Na^+, found 395.1021. $C_{21}H_{21}ClNaO_4$ requires 395.1024.

*8.2.4.19. (E)-2-(2,4-Dichlorobenzylidene)-1-(4-methoxyphenyl)-4-methylpentan-1-one (**3gb**).* Yellow oil. Yield 70%. IR (KBr): ν_{max} = 1650 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.82 (6H, d, $^3J_{H,H}$ = 6.8 Hz, $CH(CH_3)_2$), 1.72 (1H, sept, $^3J_{H,H}$ = 6.8 Hz, $CH(CH_3)_2$), 2.49 (2H, dd, $^3J_{H,H}$ = 6.8 Hz, $^4J_{H,H}$ = 0.4 Hz, CH_2), 3.86 (3H, s, OCH_3), 6.95–6.98 (3H, m, ArH, =CH), 7.26–7.27 (2H, m, ArH), 7.42–7.43 (1H, m, ArH), 7.99 (2H, d, $^3J_{H,H}$ = 9.2 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.55, 27.40, 36.69, 55.35, 113.58, 126.88, 129.26, 129.82, 130.89, 132.21, 133.36, 134.14, 134.18, 134.51, 143.53, 163.26, 196.93 ppm. HRMS (ES): M + Na^+, found 385.0727. $C_{20}H_{20}Cl_2NaO_2$ requires 385.0733.

*8.2.4.20. (E)-2-(4-Nitrobenzylidene)-1-(4-methoxyphenyl)-4-methylpentan-1-one (**3gh**).* Yellow oil. Yield 76%. IR (KBr): ν_{max} = 1646 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.89 (6H, d, $^3J_{H,H}$ = 6.8 Hz, $CH(CH_3)_2$), 1.82 (1H, sept, $^3J_{H,H}$ = 6.8 Hz, $CH(CH_3)_2$), 2.60 (2H, d, $^3J_{H,H}$ = 7.2 Hz, CH_2), 3.85 (3H, s, OCH_3), 6.95 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 6.99 (1H, s, =CH), 7.49 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.88 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 8.21 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.66, 27.98, 37.02, 55.35, 113.62, 123.55, 129.56, 129.60, 132.04, 135.11, 142.55, 145.06, 146.89, 163.28, 196.89 ppm. HRMS (ES): M + Na^+, found 362.1357. $C_{20}H_{21}NNaO_4$ requires 362.1363.

*8.2.4.21. (E)-2-(4-Chlorobenzylidene)-1-(4-methoxyphenyl)-4-methylpentan-1-one (**3gn**).* Yellow oil. Yield 46%. IR (KBr): ν_{max} = 1644 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.92 (6H, d, $^3J_{H,H}$ = 6.8 Hz, $CH(CH_3)_2$), 1.86 (1H, sept, $^3J_{H,H}$ = 6.8 Hz, $CH(CH_3)_2$), 2.63 (2H, d, $^3J_{H,H}$ = 7.2 Hz, CH_2), 3.87 (3H, s, OCH_3), 6.94–6.97 (3H, m, ArH, =CH), 7.29 (2H, d, $^3J_{H,H}$ = 8.4 Hz, ArH), 7.35 (2H, d, $^3J_{H,H}$ = 8.4 Hz, ArH), 7.87 (2H, d, $^3J_{H,H}$ = 9.2 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.76, 28.10, 36.72, 55.39, 113.54, 128.61, 130.28, 130.31, 132.08, 133.85, 134.32, 137.38, 142.60, 163.04, 197.66 ppm. HRMS (ES): M + Na^+, found 351.1117. $C_{20}H_{21}ClNaO_2$ requires 351.1122.

*8.2.4.22. (E)-2-(4-Trifluoromethylbenzylidene)-1-(4-methoxyphenyl)-4-methylpentan-1-one (**3go**).* Yellow oil. Yield 71%. IR (KBr): ν_{max} = 1647 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.92 (6H, d, $^3J_{H,H}$ = 6.4 Hz, $CH(CH_3)_2$), 1.86 (1H, sept, $^3J_{H,H}$ = 6.8 Hz, $CH(CH_3)_2$), 2.63 (2H, d, $^3J_{H,H}$ = 6.8 Hz, CH_2), 3.87 (3H, s, OCH_3), 6.97 (2H, d, $^3J_{H,H}$ = 9.2 Hz, ArH), 7.01 (1H, br. s, =CH), 7.47 (2H, d, $^3J_{H,H}$ = 8.4 Hz, ArH), 7.64 (2H, d, $^3J_{H,H}$ = 8.4 Hz, ArH), 7.91 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.73, 28.08, 36.90, 55.38, 113.63, 123.99 (q, $^1J_{C\text{-}F}$ = 270.5 Hz), 125.31 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 129.18, 129.73 (q, $^2J_{C\text{-}F}$ = 32.4 Hz), 130.02, 132.13, 136.52, 139.58, 143.92, 163.24, 197.40 ppm. HRMS (ES): M + Na^+, found 385.1390. $C_{21}H_{21}F_3NaO_2$ requires 385.1386.

*8.2.4.23. (E)-2-(Cyclohexylmethyl)-3-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**3 hb**).* Yellow oil. Yield 50%. IR (KBr): ν_{max} = 1651 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.75–0.84 (2H, m, *c*Hex), 1.01–1.16 (3H, m, *c*Hex), 1.35–1.44 (1H, m, *c*Hex), 1.53–1.66 (5H, m, *c*Hex), 2.49 (2H, d, $^3J_{H,H}$ = 6.8 Hz, CH_2*c*Hex), 3.87 (3H, s, OCH_3), 6.96–6.98 (3H, m, ArH, =CH), 7.27–7.28 (2H, m, ArH), 7.44 (1H, d, $^4J_{H,H}$ = 1.2 Hz, ArH), 7.99 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.05, 26.19, 33.30, 35.41, 36.80, 55.41, 113.62, 126.91, 129.30, 129.93, 130.95, 132.25, 133.43, 134.16, 134.39, 134.55, 143.30, 163.28, 197.06 ppm. HRMS (ES): M + Na^+, found 425.1041. $C_{24}H_{25}Cl_2NaO_2$ requires 425.1046.

*8.2.4.24. (E)-2-(Cyclohexylmethyl)-3-(4-trifluoromethylphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**3ho**).* Bright yellow oil. Yield 54%. IR (KBr): ν_{max} = 1646 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.89–0.98 (2H, m, *c*Hex), 1.10–1.22 (3H, m, *c*Hex), 1.49–1.73 (6H, m, *c*Hex), 2.63 (2H, d, $^3J_{H,H}$ = 6.8 Hz, CH_2*c*Hex), 3.88 (3H, s, OCH_3), 6.97 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.01 (1H, s, =CH), 7.46 (2H, d, $^3J_{H,H}$ = 8.0 Hz, ArH), 7.64 (2H, d, $^3J_{H,H}$ = 8.4 Hz, ArH), 7.89 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.16, 26.21, 33.54, 35.66, 37.58, 55.42, 113.64, 124.00 (q, $^1J_{C\text{-}F}$ = 270.4 Hz), 125.33 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 129.20, 129.74 (q, $^2J_{C\text{-}F}$ = 32.4 Hz), 130.06, 130.22, 132.16, 136.69, 139.59, 143.68, 163.22, 197.46 ppm. HRMS (ES): M + Na^+, found 425.1690. $C_{24}H_{25}F_3NaO_2$ requires 425.1699.

*8.2.4.25. (E)-N-(3-(2,4-Dichlorophenyl)-2-(4-methoxybenzoyl)allyl)-N-methylbenzamide (**3ib**).* Yellowish oil. Yield 51%. IR (KBr): ν_{max} = 1643, 1633 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.91 (3H, s, NCH_3), 3.85 (3H, s, OCH_3), 4.59 (2H, br. s, CH_2NMeCOPh), 6.95 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.04–7.08 (2H, m, ArH, =CH), 7.20–7.37 (5H, m, ArH), 7.43 (1H, d, $^4J_{H,H}$ = 1.6 Hz, ArH), 7.61–7.74 (1H, m, ArH), 7.99 (2H, d, $^3J_{H,H}$ = 7.6 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.39, 46.54, 55.40, 113.75, 113.87, 126.67, 127.08, 128.14, 129.29, 129.41, 129.81, 131.25, 132.12, 132.34, 134.38, 134.76, 135.80, 139.59, 163.65, 171.72, 196.32 ppm. HRMS (ES): M + Na^+, found 476.0787. $C_{25}H_{21}Cl_2NNaO_3$ requires 476.0791.

*8.2.4.26. (E)-N-(3-cyclohexyl-2-(4-methoxybenzoyl)allyl)-N-methylbenzamide (**3if**).* Yellow oil. Yield 49%. IR (KBr): ν_{max} = 1640, 1632 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.06–1.17 (4H, m, *c*Hex), 1.54–1.87 (6H, m, *c*Hex), 2.80 (1H, br. s, *c*Hex), 2.95 (3H, br. s, NCH_3), 3.83 (3H, s, OCH_3), 4.43–4.57 (2H, m, CH_2NMeCOPh), 6.11 (1H, d, $^4J_{H,H}$ = 9.6 Hz, =CH), 6.90 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.27–7.35 (5H, m, ArH), 7.64–7.80 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.19, 25.65, 32.16, 37.75, 38.68, 44.27, 55.34, 113.45, 113.81, 126.66, 128.23, 129.34, 130.57, 131.90, 136.36, 151.65, 162.96, 171.69, 197.38 ppm. HRMS (ES): M + Na^+, found 414.2043. $C_{25}H_{29}NNaO_3$ requires 414.2040.

*8.2.4.27. (Z)-3-(2-Chlorophenyl)-2-(4-methoxybenzoyl)allyl benzoate (**4 dl**).* Colorless oil. Yield 20%. IR (KBr): ν_{max} = 1715, 1651 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.76 (3H, s, OCH_3), 5.26 (2H, d, $^3J_{H,H}$ = 1.2 Hz, CH_2OCOPh), 6.74 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 6.93

(1H, td, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,H}$ = 0.8 Hz, ArH), 7.04 (1H, td, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,H}$ = 1.6 Hz, ArH), 7.13 (1H, dd, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,H}$ = 1.6 Hz, ArH), 7.24 (1H, dd, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 0.8 Hz, ArH), 7.30 (1H, br. s, =CH), 7.34–7.38 (2H, m, ArH), 7.51 (1H, t, $^3J_{H,H}$ = 7.6 Hz, ArH), 7.82 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.89–7.92 (2H, m, ArH) ppm. HRMS (ES): M + Na^+, found 429.0870. $C_{24}H_{19}ClNaO_4$ requires 429.0864.

*8.2.4.28. 1-(2-Fluorophenyl)-2-(4-methoxybenzoy)lallyl acetate (**5ba**).* Colorless oil. Yield 31%. IR (KBr): ν_{max} = 1744, 1651 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.09 (3H, s, $OCOCH_3$), 3.84 (3H, s, OCH_3), 5.76 (1H, d, $^4J_{H,H}$ = 0.8 Hz, =CH), 5.87 (1H, d, $^4J_{H,H}$ = 1.2 Hz, =CH), 6.91 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.01–7.06 (2H, m, CHOCOMe, ArH), 7.13 (1H, td, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,H}$ = 0.8 Hz, ArH), 7.25–7.29 (1H, m, ArH), 7.43 (1H, td, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 1.6 Hz, ArH), 7.79 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.85, 55.40, 69.29 (d, $^3J_{C,F}$ = 2.8 Hz), 113.56, 115.74 (d, $^2J_{C,F}$ = 21.2 Hz), 124.13 (d, $^3J_{C,F}$ = 3.6 Hz), 124.19, 125.00 (d, $^2J_{C,F}$ = 13.1 Hz), 129.27 (d, $^3J_{C,F}$ = 3.6 Hz), 129.72, 130.13 (d, $^4J_{C,F}$ = 8.3 Hz), 131.90, 145.57, 160.39 (d, $^1J_{C,F}$ = 248.1 Hz), 143.41, 169.33, 194.06 ppm. HRMS (ES): M + Na^+, found 351.1005. $C_{19}H_{17}FNaO_4$ requires 351.1003.

*8.2.4.29. 4-Ethyl-2-(4-methoxybenzoyl)hex-1-en-3-yl acetate (**5be**).* Yellowish oil. Yield 36%. IR (KBr): ν_{max} = 1741, 1650 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.85 (3H, t, $^3J_{H,H}$ = 7.2 Hz,$CH(CH_2\underline{CH_3})_2$), 0.89 (3H, t, $^3J_{H,H}$ = 7.2 Hz,$CH(CH_2\underline{CH_3})_2$), 1.23–1.34 (2H, m, $\underline{CH_2}CH_3$), 1.37–1.44 (1H, m, $\underline{CH_2}CH_3$), 1.46–1.53 (1H, m, $\underline{CH_2}CH_3$), 1.56–1.63 (1H, m, $\underline{CH}(CH_2CH_3)_2$), 2.07 (3H, s, $OCOCH_3$), 3.84 (3H, s, OCH_3), 5.64 (1H, s, =CH), 5.78 (1H, s, =CH), 5.83 (1H, d, $^3J_{H,H}$ = 4.8 Hz, CHOCOMe), 6.91 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH) 7.79 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.28, 11.33, 20.92, 20.93, 22.12, 43.44, 55.38, 74.47, 113.51, 123.24, 129.87, 131.92, 146.36, 163.28, 170.07, 194.81 ppm. HRMS (ES): M + Na^+, found 327.1567. $C_{18}H_{24}NaO_4$ requires 327.1567.

*8.2.4.30. 1-Cyclohexyl-2-(4-methoxybenzoyl)allyl acetate (**5bf**).* Yellowish oil. Yield 29%. IR (KBr): ν_{max} = 1732, 1651 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.03–1.24 (5H, m, *c*Hex), 1.62–1.81 (6H, m, *c*Hex), 2.05 (3H, s, $OCOCH_3$), 3.85 (3H, s, OCH_3), 5.52 (1H, d, $^3J_{H,H}$ = 6.0 Hz, CHOCOMe), 5.63 (1H, s, =CH), 5.80 (1H, s, =CH), 6.91 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.79 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.93, 25.85, 25.96, 26.21, 27.97, 29.27, 40.70, 55.39, 77.42, 113.51, 123.75, 129.93, 131.98, 145.95, 163.28, 170.18, 194.85 ppm. HRMS (ES): M + Na^+, found 339.1571. $C_{19}H_{24}NaO_4$ requires 339.1567.

*8.2.4.31. 1-(2-Fluorophenyl)-2-(4-methoxybenzoyl)allyl benzoate (**5da**).* Yellowish oil. Yield 42%. IR (KBr): ν_{max} = 1721, 1650 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.84 (3H, s, OCH_3), 5.82 (1H, d, $^4J_{H,H}$ = 1.2 Hz, =CH), 6.01 (1H, d, $^4J_{H,H}$ = 1.2 Hz, =CH), 6.92 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.04–7.09 (1H, m, ArH), 7.14 (1H, td, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 0.8 Hz, ArH), 7.31 (1H, br. s., CHOCOPh), 7.41 (2H, t, $^3J_{H,H}$ = 7.6 Hz, ArH), 7.52–7.57 (2H, m, ArH), 7.84 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 8.05–8.08 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.38, 70.04 (d, $^3J_{C,F}$ = 2.5 Hz), 113.57, 115.81 (d, $^2J_{C,F}$ = 21.2 Hz), 124.12, 124.17 (d, $^3J_{C,F}$ = 3.6 Hz), 124.95 (d, $^2J_{C,F}$ = 13.0 Hz), 128.36, 129.39 (d, $^3J_{C,F}$ = 3.5 Hz), 129.53, 129.68, 129.70, 130.20 (d, $^4J_{C,F}$ = 8.2 Hz), 131.90, 133.15, 145.54, 160.50 (d, $^3J_{C,F}$ = 248.2 Hz), 163.40, 164.88, 194.09 ppm. HRMS (ES): M + Na^+, found 413.1162. $C_{24}H_{19}FNaO_4$ requires 413.1160.

*8.2.4.32. 2-((2-Fluorophenyl) (hydroxy)methyl)-1-phenylprop-2-en-1-one (**5'da**).* Yellowish oil. Yield 9%. IR (KBr): ν_{max} = 3433 (OH), 1643 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.85 (3H, s, OCH_3), 5.70 (1H, s, CHOH),5.89 (1H, br. s, =CH), 5.93 (1H, d, $^3J_{H,H}$ = 5.2 Hz, =CH), 6.90 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 6.99–7.04 (1H, m, ArH), 7.15 (1H, td, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,H}$ = 0.8 Hz, ArH), 7.22–7.28 (1H, m, ArH), 7.57 (1H, td, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,H}$ = 1.6 Hz, ArH), 7.75 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.47, 69.42 (d, $^3J_{C,F}$ = 3.2 Hz), 113.62, 115.18 (d, $^2J_{C,F}$ = 21.2 Hz), 124.30 (d, $^3J_{C,F}$ = 3.5 Hz), 125.63, 128.09 (d, $^3J_{C,F}$ = 3.9 Hz), 128.27 (d, $^2J_{C,F}$ = 13.0 Hz), 129.29 (d, $^4J_{C,F}$ = 8.2 Hz), 129.62, 132.16, 147.12, 159.82 (d, $^1J_{C,F}$ = 244.9 Hz), 163.68, 197.52 ppm. HRMS (ES): M + Na^+, found 309.0896. $C_{17}H_{15}FNaO_3$ requires 309.0897.

*8.2.4.33. 2-((2,4-Dichlorophenyl) (hydroxy)methyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**5'db**).* Orange oil. Yield 32%. IR (KBr): ν_{max} = 3431 (OH), 1645 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.85 (3H, s, OCH_3), 5.70 (1H, s, =CH),5.73 (1H, d, $^4J_{H,H}$ = 0.9 Hz, =CH), 5.91 (1H, s, CHOH), 6.91 (2H, d, $^3J_{H,H}$ = 9.0 Hz, ArH), 7.29 (1H, dd, $^3J_{H,H}$ = 8.4 Hz, $^4J_{H,H}$ = 2.1 Hz, ArH), 7.36 (1H, d, $^4J_{H,H}$ = 2.1 Hz, ArH), 7.63 (1H, d, $^3J_{H,H}$ = 8.4 Hz, ArH), 7.77 (2H, d, $^3J_{H,H}$ = 9.0 Hz, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.49, 71.11, 113.72, 126.56, 127.36, 129.13, 129.15, 129.35, 132.24, 132.83, 133.92, 137.13, 146.43, 163.83, 197.60 ppm. HRMS (ES): M + Na^+, found 359.0220. $C_{17}H_{14}Cl_2NaO_3$ requires 359.0212.

*8.2.4.34. 4-Ethyl-2-(4-methoxybenzoyl)hex-1-en-3-yl benzoate (**5de**).* Yellowish oil. Yield 37%. IR (KBr): ν_{max} = 1718, 1650 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.92–0.98 (6H, m, $CH(CH_2\underline{CH_3})_2$), 1.36–1.53 (3H, m, $\underline{CH_2}CH_3$), 1.64–1.77 (2H, m, $\underline{CH_2}CH_3$, $\underline{CH}(CH_2CH_3)_2$), 3.85 (3H, s, $\overline{OCH_3}$), 5.69 (1H, s, =CH), 5.86 (1H, d, $^4J_{H,H}$ = 0.8 Hz, =CH), 6.14 (1H, d, $^3J_{H,H}$ = 4.4 Hz, CHOCOPh), 6.93 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.45 (2H, t, $^3J_{H,H}$ = 7.2 Hz, ArH), 7.57 (1H, t, $^3J_{H,H}$ = 7.2 Hz, ArH), 7.85 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 8.08–8.10 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.44, 11.55, 21.16, 22.43, 43.77, 55.39, 74.89, 113.56, 128.41, 129.58, 129.93, 130.14, 131.96, 133.02, 146.44, 163.30, 165.49, 194.84 ppm. HRMS (ES): M + Na^+, found 389.1722. $C_{23}H_{26}NaO_4$ requires 389.1723.

*8.2.4.35. 1-Cyclohexyl-2-(4-methoxybenzoyl)allyl benzoate (**5df**).* White solid, m. p. = 87–89 °C. Yield 55%. IR (KBr): ν_{max} = 1702, 1649 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.13–1.28 (5H, m, *c*Hex), 1.65–1.93 (6H, m, *c*Hex), 3.84 (3H, s, OCH_3), 5.68 (1H, s, =CH), 5.82 (1H, d, $^3J_{H,H}$ = 5.6 Hz, CHOCOPh), 5.90 (1H, s, =CH), 6.91 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.45 (2H, t, $^3J_{H,H}$ = 7.2 Hz, ArH), 7.56 (1H, t, $^3J_{H,H}$ = 7.2 Hz, ArH), 7.83 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 8.07–8.09 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.91, 25.99, 26.23, 27.86, 29.48, 40.95, 55.36, 77.65, 113.50, 123.92, 128.35, 129.53, 129.87, 130.18, 131.99, 132.95, 145.95, 163.22, 165.54, 194.86 ppm. HRMS (ES): M + Na^+, found 401.1718. $C_{24}H_{26}NaO_4$ requires 401.1723.

*8.2.4.36. 2-((2,3,4,5,6-Pentafluorophenyl) (hydroxy)methyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**5'di**).* Yellow oil. Yield 38%. IR (KBr): ν_{max} = 3431 (OH), 1654 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.86 (3H, s, CH_3O), 5.89 (1H, d, $^4J_{H,H}$ = 1.6 Hz, =CH), 6.15 (1H, br. s, CHOH), 6.20 (1H, d, $^4J_{H,H}$ = 1.6 Hz, =CH), 6.92 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.75 (2H, d, $^3J_{H,H}$ = 9.2 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.48, 65.07, 113.74, 114.90 (m), 125.31, 128.43, 129.37, 130.11, 131.99, 136.24, 138.76, 139.66, 143.83, 146.01, 146.28, 163.75, 195.52 ppm. HRMS (ES): M + H^+, found 381.0524. $C_{17}H_{11}F_5NaO_3$ requires 381.0521.

*8.2.4.37. 1-(2-Nitrophenyl)-2-(4-methoxybenzoyl)allyl benzoate (**5dj**).* Yellowish solid; m.p. = 120–122 °C. Yield 22%. IR (KBr): ν_{max} = 1726, 1651 (C=O) cm^{-1}.^1H NMR (400 MHz, $CDCl_3$) δ: 3.85 (3H, s, OCH_3), 5.81 (1H, d, $^4J_{H,H}$ = 1.2 Hz, =CH), 5.86 (1H, d, $^4J_{H,H}$ = 0.4 Hz, =CH), 6.93 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.42 (2H, t,

$^3J_{H,H}$ = 7.6 Hz, ArH), 7.46–7.51 (1H, m, ArH), 7.56 (1H, t, $^3J_{H,H}$ = 7.6 Hz, ArH), 7.60 (1H, br. s, CHOCOPh), 7.63 (1H, td, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,H}$ = 1.2 Hz, ArH), 7.77 (1H, dd, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 1.2 Hz, ArH), 7.84 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 8.01–8.04 (3H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.44, 71.10, 113.67, 124.94, 126.01, 128.46, 129.14, 129.21, 129.33, 129.58, 129.76, 131.95, 133.36, 133.43, 145.59, 148.23, 163.49, 164.88, 193.97 ppm. HRMS (ES): M + Na^+, found 440.1089. $C_{24}H_{19}NNaO_6$ requires 440.1105.

*8.2.4.38. 3-Benzoylbut-3-en-2-yl benzoate (**5dk**).* Colorless oil. Yield 23%. IR (KBr): ν_{max} = 1715, 1649 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.60 (3H, d, $^3J_{H,H}$ = 6.4 Hz, CH_3), 3.86 (3H, s, OCH_3), 5.63 (1H, s, =CH), 5.99 (1H, d, $^4J_{H,H}$ = 1.2 Hz, =CH), 6.02 (1H, q, $^3J_{H,H}$ = 6.4 Hz, CHOCOPh), 6.93 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.42 (2H, t, $^3J_{H,H}$ = 7.6 Hz, ArH), 7.55 (1H, t, $^3J_{H,H}$ = 7.6 Hz, ArH), 7.84 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 8.03–8.05 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.29, 55.43, 70.19, 113.55, 122.04, 128.33, 129.56, 129.90, 130.19, 132.00, 132.97, 148.46, 163.38, 165.41, 195.14 ppm. HRMS (ES): M + Na^+, found 333.1094. $C_{19}H_{18}NaO_4$ requires 333.1097.

*8.2.4.39. 2-((2-Chlorophenyl) (hydroxy)methyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**5'dl**).* Yellow oil. Yield 13%. IR (KBr): ν_{max} = 3435 (OH), 1645 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.86 (3H, s, OCH_3), 5.69 (1H, s, =CH),5.73 (1H, s, =CH), 5.98 (1H, s, CHOH), 6.91 (2H, d, $^3J_{H,H}$ = 8.7 Hz, ArH), 7.20–7.25 (1H, m, ArH), 7.29–7.37 (2H, m, ArH), 7.70 (1H, dd, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.5 Hz, ArH), 7.79 (2H, d, $^3J_{H,H}$ = 8.7 Hz, ArH) ppm. HRMS (ES): M + Na^+, found 325.0606. $C_{17}H_{15}ClNaO_3$ requires 325.0602.

*8.2.4.40. 2-((2,4-Dinitrophenyl) (hydroxy)methyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**5'dm**).* Yellow oil. Yield 59%. IR (KBr): ν_{max} = 3436 (OH), 1639 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.85 (3H, s, CH_3O), 5.74 (1H, d, $^4J_{H,H}$ = 0.6 Hz, =CH), 5.75 (1H, s, =CH), 6.31 (1H, br. s, CHOCOPh), 6.89 (2H, d, $^3J_{H,H}$ = 9.0 Hz, ArH), 7.70 (2H, d, $^3J_{H,H}$ = 9.0 Hz, ArH), 8.24 (1H, d, $^3J_{H,H}$ = 8.7 Hz, ArH), 8.48 (1H, dd, $^3J_{H,H}$ = 8.7 Hz, $^4J_{H,H}$ = 2.4 Hz, ArH), 8.79 (1H, d, $^4J_{H,H}$ = 2.4 Hz, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.50, 69.75, 113.81, 120.04, 126.93, 127.37, 128.67, 130.71, 132.20, 143.15, 146.31, 147.14, 147.57, 164.00, 196.72 ppm. HRMS (ES): M + Na^+, found 381.0698. $C_{17}H_{14}N_2NaO_7$ requires 381.0693.

*8.2.4.41. (E)-4-(2,4-Dibenzoylpenta-1,4-dien-1-yl)phenyl benzoate (**6ad**).* Yellowish oil. Yield 14%. IR (KBr): ν_{max} = 1738, 1659, 1651 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.95 (2H, br. s, $=CCH_2C=$), 5.71 (1H, br. s, =CHH), 5.91 (1H, t, br. s, =CHH), 7.28 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.40–7.44 (3H, m, =CH, ArH), 7.46–7.59 (8H, m, ArH), 7.63–7.67 (1H, m, ArH), 7.75–7.77 (2H, m, ArH), 7.80–7.83 (2H, m, ArH), 8.19–8.22 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.55, 122.08, 126.00, 128.19, 128.32, 128.58, 129.19, 129.55, 129.61, 130.16, 130.62, 131.97, 132.32, 132.62, 133.73, 137.33, 137.77, 138.19, 143.25, 145.14, 151.39, 164.86, 197.76, 198.15 ppm. HRMS (ES): M + Na^+, found 495.1563. $C_{32}H_{24}NaO_4$ requires 495.1567.

*8.2.4.42. (E)-4-(2,4-Bis(4-methoxybenzoyl)penta-1,4-dien-1-yl) phenyl benzoate (**6bd**).* Yellowish oil. Yield 12%. IR (KBr): ν_{max} = 1737, 1658, 1650 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.84 (3H, s, OCH_3), 3.88 (3H, m, OCH_3), 3.91 (2H, br. s, $=CCH_2C=$), 5.59 (1H, br. s, =CHH), 5.80 (1H, br. s, =CHH), 6.89 (2H, d, $^3J_{H,H}$ = 9.2 Hz, ArH), 6.96 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.27 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH),7.30 (1H, s, =CH), 7.52–7.55 (4H, m, ArH), 7.65 (1H, t, $^3J_{H,H}$ = 7.6 Hz, ArH), 7.78 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.85 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 8.19–8.21 (2H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.43, 55.39, 55.45, 113.48, 113.59, 122.02, 123.94, 128.59, 129.28, 129.77, 130.17, 130.49, 130.55, 132.07, 132.10, 132.84, 133.71, 137.94, 141.22, 145.30, 151.19, 162.96, 163.21, 164.92, 196.00, 196.98 ppm. HRMS (ES): M + Na^+, found 555.1776. $C_{34}H_{28}NaO_6$ requires 555.1778.

*8.2.4.43. (E)-2-(4-Methylbenzylidene)-4-methylene-1,5-diphenylpentane-1,5-dione (**6bg**).* Yellow oil. Yield 17%. IR (KBr): ν_{max} = 1651 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.85 (3H, s, OCH_3), 3.87–3.88 (5H, m, $=C\underline{CH_2}C=$, OCH_3), 5.57 (1H, br. s, =CHH), 5.78 (1H, br. s, =CHH), 6.88 (2H, d, $^3J_{H,H}$ = 9.2 Hz, ArH), 6.95 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.30 (1H, s, =CH), 7.34–7.41 (3H, m, ArH), 7.44–7.46 (2H, m, ArH), 7.78 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.85 (2H, d, $^3J_{H,H}$ = 9.2 Hz, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.40, 55.42, 55.46, 113.46, 113.57, 123.77, 128.65, 128.83, 129.21, 130.60, 132.07, 132.11, 135.16, 137.81, 142.42, 145.57, 162.92, 163.20, 196.69, 197.09 ppm. HRMS (ES): M + H^+, found 413.1743. $C_{27}H_{25}O_4$ requires 413.1747.

*8.2.4.44. (E)-2-(4-Methylbenzylidene)-4-methylene-1,5-di(4-methoxyphenyl)pentane-1,5-dione (**6dc**).* Yellowish oil. Yield 26%. IR (KBr): ν_{max} = 1715, 1644 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.36 (3H, s, $\underline{CH_3}C_6H_4$), 3.85 (3H, s, OCH_3), 3.87–3.88 (5H, m, $=C\underline{CH_2}C=$ and OCH_3), 5.56 (1H, br. s, =CHH), 5.76 (1H, br. s, =CHH), 6.89 (2H, d, $^3J_{H,H}$ = 8.7 Hz, ArH), 6.94 (2H, d, $^3J_{H,H}$ = 8.7 Hz, ArH), 7.20 (2H, d, $^3J_{H,H}$ = 8.1 Hz, ArH), 7.30 (1H, s, =CH), 7.35 (2H, d, $^3J_{H,H}$ = 8.1 Hz, ArH), 7.78–7.84 (4H, m, ArH) ppm. HRMS (ES): M + Na^+, found 449.1416. $C_{28}H_{26}NaO_4$ requires 449.1723.

*8.2.4.45. (E)-2-((Diethylamino)methyl)-1-(4-methoxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one (**7a**).* Yellow solid, m. p. = 69–71 °C. Yield 48%. IR (KBr): ν_{max} = 1650 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (6H, t, $^3J_{H,H}$ = 6.4 Hz, $N(CH_2CH_3)_2$), 2.48 (4H, q, $^3J_{H,H}$ = 6.4 Hz, $N(CH_2CH_3)_2$), 3.58 (2H, s, CH_2NEt_2), 3.88 (3H, s, OCH_3), 6.97 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.06 (1H, s, =CH), 7.73 (2H, d, $^3J_{H,H}$ = 8.4 Hz, ArH), 7.90 (2H, d, $^3J_{H,H}$ = 8.4 Hz, ArH), 8.24 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.24, 46.63, 50.59, 55.48, 113.69, 123.47, 129.71, 130.55, 131.98, 135.97, 142.17, 144.10, 147.28, 163.34, 196.65 ppm. HRMS (ES): M + H^+, found 369.1806. $C_{21}H_{25}N_2O_4$ requires 369.1809.

*8.2.4.46. (E)-1-(4-Methoxyphenyl)-2-(morpholinomethyl)-3-(4-nitrophenyl)prop-2-en-1-one (**7c**).* Yellow solid, m. p. = 107–109 °C. Yield 77%. IR (KBr): ν_{max} = 1656 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.45 (4H, br. s, $N(\underline{CH_2}CH_2)_2O$), 3.49 (2H, s, $\underline{CH_2}N(CH_2CH_2)_2O$), 3.62 (4H, br. s, $N(CH_2\underline{CH_2})_2O$), 3.87 (3H, s, OCH_3), 6.96 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.17 (1H, s, =CH), 7.76 (2H, d, $^3J_{H,H}$ = 8.4 Hz, ArH), 7.87 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 8.24 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.37, 55.22, 55.47, 66.82, 113.77, 123.52, 129.35, 130.57, 131.98, 138.33, 141.57, 141.79, 147.40, 163.42, 196.12 ppm. HRMS (ES): M + H^+, found 383.1607. $C_{21}H_{23}N_2O_5$ requires 383.1601.

*8.2.4.47. (E)-3-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-2-(morpholinomethyl)prop-2-en-1-one (**7f**).* Yellow solid, m. p. = 117–118 °C. Yield 53%. IR (KBr): ν_{max} = 1643 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.39 (4H, br. s, $N(\underline{CH_2}CH_2)_2O$), 3.44 (2H, s, $\underline{CH_2}N(CH_2CH_2)_2O$), 3.57 (4H, br. s, $N(CH_2\underline{CH_2})_2O$), 3.88 (3H, s, OCH_3), 6.97 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH), 7.14 (1H, s, =CH), 7.29 (1H, dd, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 2.0 Hz, ArH), 7.44 (1H, d, $^4J_{H,H}$ = 2.0 Hz, ArH), 7.61 (1H, d, $^3J_{H,H}$ = 8.0 Hz, ArH), 7.94 (2H, d, $^3J_{H,H}$ = 8.8 Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.33, 55.03, 55.45, 66.82, 113.70, 126.91, 129.27, 129.54, 131.91, 132.14, 132.55, 134.58, 134.89, 163.41, 196.22 ppm. HRMS (ES): M + H^+, found 406.0977. $C_{21}H_{22}Cl_2NO_3$ requires 406.0971.

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Appendix A. Supplementary data

Supplementary data contains notation and short description of the QSAR molecular descriptors involved in the models and copies of ^{1}H and ^{13}C NMR spectra of all synthesized compounds can be found at http://dx.doi.org/10.1016/j.ejmech.2015.05.012.

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