Bioorganic & Medicinal Chemistry xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Anti-proliferative effect of chalcone derivatives through inactivation of NF-κB in human cancer cells

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ARTICLE INFO

Article history:
Received 18 February 2014
Revised 22 April 2014
Accepted 23 April 2014
Available online xxxx

Keywords:
Chalcones
Inactivation of NF-κB
Anti-proliferative activity

ABSTRACT

To investigate the anti-proliferative effect of NF-κB inhibitor, a series of analogs of (*E*)-1-(2-hydroxy-6-(isopentyloxy)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (**5a**) were prepared and evaluated for their NF-κB inhibition and anti-proliferative activity against various human cancer cell lines. Compounds (*E*)-1-(2-(3,3-dimethylbutoxy)-6-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (**5e**) and (*E*)-4-(3-(2-(3,3-dimethylbutoxy)-6-hydroxyphenyl)-3-oxoprop-1-enyl)benzenesulfonamide (**5p**) showed good NF-κB inhibition as well as potent anti-proliferative activity. SAR studies showed that all the compounds with potent or moderate NF-κB inhibition displayed good anti-proliferative activity. All the analogs (**5b**–**r**) maintained a good correlation between their NF-κB inhibition and anti-proliferative activity though the extent is not directly proportional to each other.

1. Introduction

Eukaryotic transcription factor NF-κB is not only essential for regulating the immune and inflammatory processes but also plays an important role in cell proliferation and survival.[1,2] It is also involved in processes of synaptic plasticity and memory.[3–7] Therefore, an inappropriate regulation of NF-κB may lead to various discrepancies and diseases such as inadequate immune development, cancer, inflammatory and autoimmune diseases, septic shock and viral infection. The above discussion confirms that NF-κB signaling pathway is important for pharmacological intervention, especially on the situations of chronic inflammation and cancer, where the pathway is often constitutively active. Thus NF-κB could be an important target for the discovery of new anti-cancer or anti-inflammatory agents. Although the correlation between initiation of inflammation and abnormal cell proliferation is not yet completely understood, approximately 15% of all malignancies are instigated by chronic and prolonged inflammatory diseases.[8–14]

Flavonoids and chalcones (flavonoid precursors) are abundantly[15–17] present in many fruits and vegetables. Chalcones are associated with remarkably diverse biologic properties like anti-inflammatory,[18,19] anti-oxidative,[20] anti-fungal,[21] anti-bacterial,[22] chemo-preventive and anti-cancer activities.[23–27] As chalcone derivatives show numerous pharmacological properties, these compounds have been an important target for the research.

Till date, a number of natural products[28–30] (Fig. 1) has been identified as chemotherapeutic agents through inhibition of NF-κB activity. Specially, compounds like curcumin,[28] 3-dihydro-3,5-dihydroxy-6-methyl-4*H*-pyranone (DDMP)[29] isolated from onion and thiacremonone[30] from garlic exerted anti-carcinogenic properties by inhibiting the activation of NF-κB. In another study[31] the researchers observed that complete abolition of NF-κB activity was responsible for the combined anti-proliferative effect of thiacremonone and docetaxel in colon cancer cells. The compound SK 2009, an analog of simplactone[32] (Fig. 1), was most effective in suppressing NF-κB activation in KBM-5 leukemic cells. Recently, *N*-substituted phenyl amide derivatives of indoline-2-carboxylic acid were studied for their NF-κB inhibitory activity as well as anti-proliferative activity.[33] These results indicated that compounds having NF-κB inhibitory activity displayed anti-proliferative effect in various cancer cell lines. However, the anti-proliferative activity was not directly proportional to the NF-κB inhibitory activity.

Previously, we have discovered a novel small molecule, (*E*)-1-(2-hydroxy-6-(isopentyloxy)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (**5a**, Fig. 1) and successfully established it as an inhibitor of LPS induced NF-κB activation in macrophages with an IC_{50} value of about 10 μM.[34] It is a non-lipid chalcone which not only inhibited the TLR4-mediated NF-κB activating pathway but also suppressed the NF-κB regulated expression of iNOS, COX-2 or pro-inflammatory cytokine genes. Thus, to explore structure activity correlation of NF-κB inhibition and anti-proliferative activity of

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http://dx.doi.org/10.1016/j.bmc.2014.04.045
0968-0896/

5a analogs, here in the current article we have designed and synthesized analogs (**5b–r)** of **5a** and evaluated their inhibitory activity against NF-κB and in vitro anti-proliferative activity against various human cancer cell lines namely, ACHN (renal), NCI-H23 (lung), MDA-MB-231 (breast), HCT-15 (colon), NUGC-3 (stomach) and PC-3 (prostate).

2. Chemistry

The syntheses of the desired compounds **5a–r** were accomplished as outlined in Scheme 1. The key intermediate mono-alkylated hydroxyacetophenone **3** was synthesized from dihydroxyacetophenone **1** by reacting with various alkyl bromides **2** in the presence of potassium carbonate and catalytic amount of sodium iodide.[35] Later the mono-alkylated hydroxyacetophenones **3** were subjected to aldol condensation with 4-substituted benzaldehydes **4** to get the final compounds **5a–q**. The compound **5r** was obtained from **5e** using catalytic hydrogenation under H_2 pressure at 30 psi. All these synthesized compounds were characterized by physical and spectral analysis data that confirmed their assigned structures.

3. Biologic evaluations

The NF-κB inhibitory activity of compounds **5a–r** was evaluated by previously reported procedure (SEAP assay).[34] In brief, the RAW 264.7 cells harboring pNF-κB-SEAP-NPT reporter construct or THP-1 cells transfected with pNF-kB-SEAP reporter construct were treated with **5a–r** for 2 h and then stimulated with LPS (1 μg/ml) for 16 h. SEAP activity was measured as described previously.[36] Accordingly, the aliquots of the culture media were heated at 65 °C for 5 min and reacted with 4-methylumbellifery phosphate (500 μM) in the dark for 1 h. SEAP activity was measured as relative fluorescence units (RFUs) with emission at 449 nm and excitation at 360 nm. The results from these tests are summarized as IC_{50} values in Table 1.

The anti-proliferative activity was measured against ACHN (renal), NCI-H23 (lung), MDA-MB-231 (breast), HCT-15 (colon), NUGC-3 (stomach) and PC-3 (prostate) human cell lines using sulforhodamine B (SRB) colorimetric assay.[37] The results from these tests are given as IC_{50} values in Table 2.

4. Results and discussion

In our previous study we have observed that **5a** inhibited LPS induced NF-κB activation with an IC_{50} value of 10.0 μM.[34] The length of alkoxy chain at 6th position of ring A in chalcones might play an important role in the inhibition of LPS induced NF-κB activation. Therefore, to optimize the size of alkoxy group in the current set of experiment analogs **5b–r** were prepared with varied lipophilic alkoxy chain.

Initially, we want to investigate the effect of alkoxy chain length and branch at 6th position of ring A in chalcones. Accordingly, various chalcone analogs with varied alkoxy groups such as

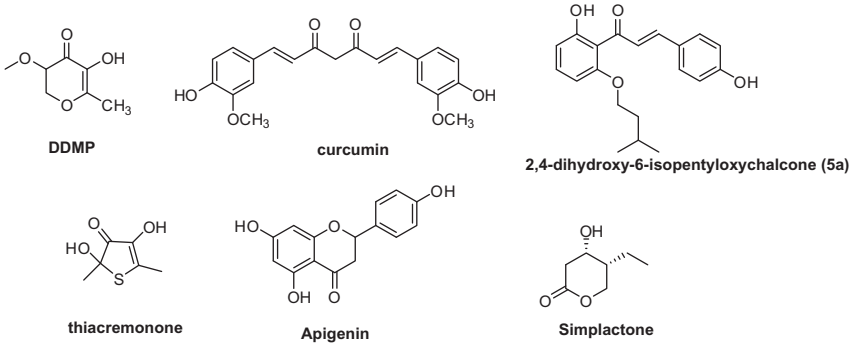
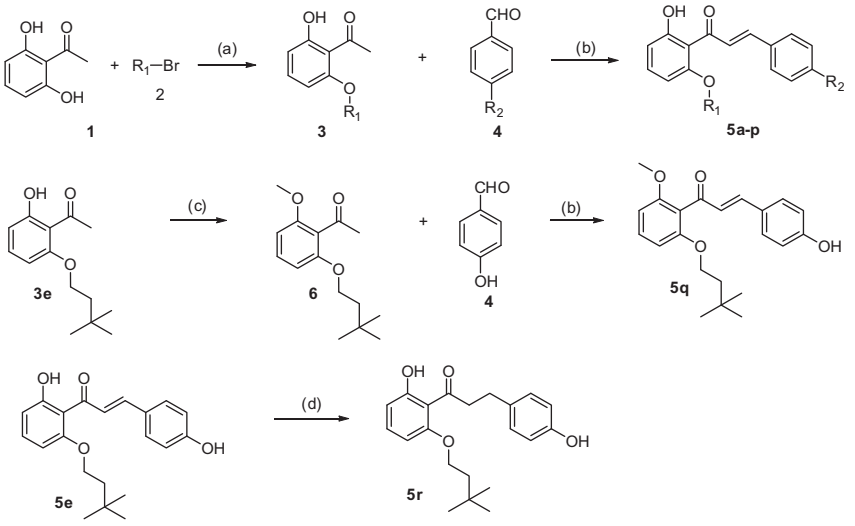


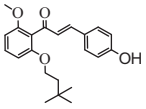
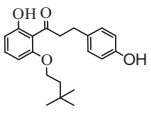
Figure 1. Known chemotherapeutic agents through inactivation of NF-κB.



Scheme 1. Synthesis of 2,4-dihydroxy-6-isopentyloxychalcone analogs **5b–r**. Reagents and conditions: (a) K_2CO_3, NaI, acetonitrile, reflux at 80–82 °C; (b) **3**, substituted benzaldehyde, piperidine, EtOH, reflux at 78 °C; (c) NaH, CH_3I; (d) $H_2$30psi, Pd/C, methanol, rt for 3 h. *Note* = substituents are indicated in Table 1.

Please cite this article in press as: Venkateswararao, E.; et al. *Bioorg. Med. Chem.* (2014), http://dx.doi.org/10.1016/j.bmc.2014.04.045

Table 1
In vitro NF-κB inhibitory activity of chalcone analogs **5a–r**

Compd no.	R	R_2	IC_{50} (μM)[a]	*C*log*P*[b]	Compd no.	R	R_1	IC_{50} (μM)[a]	*C*log*P*[b]
5a[34]		OH	10.0	5.349	**5j**		OH	18.0	5.983
5b		OH	11.0	5.878	**5k**[35]		OH	>30	6.013
5c		OH	>30	4.949	**5l**		OH	>30	6.542
5d[35]		OH	>30	6.007	**5m**[35]		OH	>30	5.131
5e		OH	3.0	5.748	**5n**		OH	>30	7.680
5f		OH	8.0	4.819	**5o**		–COOH	2.8	6.212
5g		OH	12.0	5.878	**5p**		$–SO_2NH_2$	1.2	4.632
5h		OH	>30	5.064	**5q**			>30	5.589
5i		OH	13.0	5.454	**5r**			>30	5.802

[a] IC_{50} values are taken as a mean from three experiments.
[b] *C*log*P* values were calculated by Chem Draw version 11.0.

Table 2
In vitro anti-proliferative activity of chalcone analogs **5a–r** against human cancer cell lines

Compd no.	Anti-proliferative activity: GI_{50} (μM)[a]					
	ACHN	NCI-H23	MDA-MB231	HCI-15	NUGC-3	PC-3
5a	11.33	12.12	10.28	10.58	12.36	11.45
5b	3.63	11.35	3.48	11.58	3.52	3.60
5c	>30	>30	>30	>30	>30	>30
5d	>30	>30	>30	>30	>30	>30
5e	3.14	3.13	2.38	3.43	3.30	3.22
5f	3.29	3.22	3.52	2.60	2.98	2.97
5g	3.37	3.21	3.13	3.42	1.96	3.39
5h	>30	>30	>30	>30	>30	>30
5i	3.51	3.16	3.41	3.41	2.14	3.04
5j	3.40	3.37	3.34	3.31	3.20	3.48
5k	>30	>30	>30	>30	>30	>30
5l	>30	>30	>30	>30	>30	>30
5m	>30	>30	>30	>30	>30	>30
5n	>30	4.77	>30	>30	>30	>30
5o	8.45	4.77	11.23	2.17	5.44	6.50
5p	3.30	2.95	2.11	2.93	1.17	3.25
5q	>30	>30	>30	>30	>30	>30
5r	>30	>30	>30	>30	>30	>30
ADR[b]	1.63	1.66	1.79	1.34	1.00	1.65

[a] GI_{50} values are taken as a mean from three experiments.
[b] ADR: Adriamycin.

methylpentyloxy (**5b**, IC_{50} = 11.0 μM, *C*log*P* = 5.878), butoxy (**5c**, IC_{50} = >30 μM, *C*log*P* = 4.949), hexyloxy (**5d**, IC_{50} = >30 μM, *C*log*P* = 6.007), 3,3-dimethylbutoxy (**5e**, IC_{50} = 3.0 μM, *C*log*P* = 5.748), isobutoxy (**5f**, IC_{50} = 8.0 μM, *C*log*P* = 4.819), ethylbutoxy (**5g**, IC_{50} = 12.0 μM, *C*log*P* = 5.878) and methylbut-2-enyloxy (**5h**, IC_{50} = >30 μM, *C*log*P* = 5.064) were studied for their NF-κB inhibitory activity. Among these derivatives, 3,3-dimethylbutoxy analog **5e** showed highly potent inhibitory activity while **5c**, **5d** and **5h** failed to show any activity. The compounds **5b** and **5f** showed almost similar activity as **5a**. The above results emphasized that an increment in the chain length does not have considerable effect on the activity whereas the activity is enhanced with an increase in the volume of alkoxy group as in **5e**. In the next set of experiment, the cycloalkyloxy groups at the 6th position of the ring A were introduced. Accordingly, cyclopentylmethoxy (**5i**, IC_{50} = 13 μM, *C*log*P* = 5.454), cyclopentylethoxy (**5j**, IC_{50} = 18.0 μM, *C*log*P* = 5.983), cyclohexylmethoxy (**5k**, IC_{50} = >30 μM, *C*log*P* =6.013), cyclohexylethoxy (**5l**, IC_{50} = >30 μM, *C*log*P* = 6.542), benzyloxy (**5m**, IC_{50} = >30 μM, *C*log*P* = 5.131) and adamantylmethoxy (**5n**, IC_{50} = >30 μM, *C*log*P* = 7.680) analogs were prepared and studied for their NF-κB activity. As shown in Table 1, less bulky cyclopentylmethoxy analog **5i** had far better activity than cyclohexylmethoxy analog **5k**. In addition, on increasing the chain length as in **5j**, activity decreased as compared to **5i**. The bulky cyclohexyl derivative (**5k)** and (**5l)** did not show any activity possibly due to increase in hydrophobicity or bulkiness. Similarly, the bulkier adamantylmethoxy **5n** derivatives did not turn up with any activity. Planar benzyl analog **5m** did not show any activity. These results implicate that the suitable size of branched alkoxy group at 6th position of ring A would be important for binding to the active site and 3,3-dimethylbutoxy would be optimum.

To rationalize the above bioactivity results with the change in alkoxy groups at 6th position of ring A, a selected set of chalcones derivatives was chosen for the analysis of steric parameters (E_s, *MR*, B1, B5 and *L*).[38] It was observed that the steric parameters E_s *MR* and B1 do not have the correlation with the activity (Table 3). However, the B5 and the *L* parameter together showed some correlation with the activity. As shown in Table 3 the most potent compound **5e** has values of 4.54 for B5 and 6.17 for *L*. As on changing either of the B5 or *L* values as shown in **5a** (B5 = 3.49, *L* = 6.17), **5b** (B5 = 5.59, *L* = 6.97), **5d** (B5 = 5.96, *L* = 8.22), **5f** (B5 = 4.45,

L = 4.92), **5k** (B5 = 6.02, L = 4.62) and **5m** (B5 = 5.42, L = 6.09), the activity decreased (**5a**, **5b** and **5f**) or completely lost (**5d**, **5k** and **5m**). The above results confirmed the importance of optimum volume of alkoxy group at 6th position of ring A, in which the optimum values of steric parameters for alkoxy group should be B5 = 4.54 and L = 6.17. This infers that the hydrophobic binding of this group to putative receptor would be important for the activity.

As was observed in our previous studies, substitution at 4th position of ring B greatly affected the activity. Interestingly, replacement of hydroxyl group of **5e** with electron withdrawing group such as carboxylic acid (**5o**, IC_{50} = 2.8 μM, $C\log P$ = 6.212) or sulfonamide (**5p**, IC_{50} = 1.2 μM, $C\log P$ = 4.632) showed compatible level of NF-κB inhibitory activity. These results imply that hydrogen bonding capability of substituents at 4th position of ring B is important for NF-κB inhibitory activity of chalcones regardless of their size.

The masking of hydroxyl function at 2nd position of ring A in **5e** by methylation as shown in **5q** led to complete loss of activity. This might indicate that intramolecular hydrogen bonding of this hydroxyl group with carbonyl oxygen of α,β-unsaturated ketone unit of these chalcones enhance the activity.

Reduction of double bond of **5e** to saturated ketone shown in **5r** abolished the activity. This result indicates that α,β-unsaturated ketone unit of these chalcones is critically important for their NF-κB inhibitory activity.

For finding the correlation between inhibitory activity of NF-κB and anti-proliferative activity, all the compounds **5a**–**r** were evaluated for their anti-proliferative against various cancer cell lines such as ACHN (renal), NCI-H23 (lung), MDA-MB-231 (breast), HCT-15 (colon), NUGC-3 (stomach) and PC-3 (prostate) cancer cell lines as shown in Table 2 (GI_{50} values are listed in parenthesis below along with this sequence of these cell lines written here).

The compounds with variable alkoxy chain length and branch (**5a**–**b**, **5e**–**g**) showed good anti-proliferative activity against all cancer cell lines. Even though compounds **5a**–**b** showed similar level of NF-κB activity, their anti-proliferative activities were somewhat different as compound **5b** was better compared to **5a** especially against ACHN, MDA-MB231, NUGC-3 and PC-3 cell lines. As expected for inhibitory activity of NF-κB, compounds **5c**–**d** did not show any activity. Interestingly, the compound **5e** (3.14, 3.13, 2.38, 3.43, 3.30, 3.22 μM) showed good anti-proliferative activity as well as good NF-κB inhibition. In addition, the compounds **5f** (3.29, 3.22, 3.52, 2.60, 2.98, 2.97 μM), **5g** (3.37, 3.21, 3.13, 3.42, 1.96, 3.39 μM), **5i** (3.51, 3.16, 3.41, 3.41, 2.14, 3.04 μM) and **5j** (3.40, 3.37, 3.34, 3.31, 3.20, 3.48 μM) showed good anti-proliferative activity and moderate NF-κB inhibition. However, compounds **5h** and **5k**–**n** did not show any anti-proliferative activity against any cancer cell lines and their NF-κB inhibition was almost negligible. The carboxylic (**5o**, 8.45, 4.77, 11.23, 2.17, 5.44, 6.50 μM) and sulfonamide (**5p**, 3.30, 2.95, 2.11, 2.93, 1.17, 3.25 μM) derivatives showed potent anti-proliferative activity, especially compound **5p** was more potent than the previous one. These activities also indicate the role of hydrogen bonding ability by functional group at 4th position of ring B of these chalcones.

As shown by NF-κB inhibitory activity profile, masking of hydroxyl function at 2nd position of ring A of **5e** with methylation (as in **5q**) and saturation of double bond of **5e** to ketone (as in **5r**) led to complete loss of anti-proliferative activity. These results indicate that intramolecular hydrogen bonding of hydroxyl function at 2nd position of ring A and α,β-unsaturated ketone unit of these chalcones are critically important for their anti-proliferative activity as well as NF-κB inhibitory activity.

Table 3
Descriptors for alkyl substituents on oxygen at 6th position of ring A for chalcone analogs **5a–b**, **5d–f**, **5k** and **5m**

Compd no.	Substituents	Descriptors[a]					IC_{50}[b] (μM)
		E_s	*MR*	B1	B5	*L*	
5a		−1.59	2.43	1.52	3.49	6.17	10.0
5b		−1.67	2.89	1.52	5.59	6.97	11.0
5d		−1.54	2.89	1.52	5.96	8.22	>30
5e		−1.58	2.90	1.52	4.54	6.17	3.0
5f		−2.17	1.96	1.52	4.45	4.92	8.0
5k		−2.22	3.13	1.52	5.42	6.09	>30
5m		−1.61	3.00	1.52	6.02	4.62	>30

[a] Descriptors E_s, *MR*, B1, B5 and *L* are taken from Ref. 38.
[b] In vitro NF-κB inhibitory activity of chalcone analogs.

5. Conclusion

For defining the correlation between NF-κB inhibition and anti-proliferative activity a number of analogs of 2,4′-dihydroxy-6-isopentyloxychalcone (**5a**) have been prepared and tested for their anti-proliferative activity against cancer cell lines. Among these analogs compounds **5e** and **5p** showed potent NF-κB inhibition as well as anti-proliferative activity. The structure activity relationship showed that 6-branched alkoxy-2-hydroxychalcone with hydrogen bonding capable substituents at 4th position of ring B should be essential scaffold for the inhibition of NF-κB. The optimum size of 6-branched alkoxy and the intramolecular hydrogen bonding of the hydroxyl group at 2nd position of ring A with carbonyl oxygen of α,β-unsaturated ketone unit of these chalcones should be critical factors for NF-κB inhibitory activity. All the compounds with potent or moderate NF-κB inhibitory activity showed good anti-proliferative activity. Taken together, all the chalcone analogs (**5a–r**) maintained a good correlation between their NF-κB inhibition and anti-proliferative activity, though the extent was not directly proportional to each other.[23] This might indicate that these chalcones achieve their anti-proliferative activity through inactivation of NF-κB.

6. Materials and methods

6.1. Chemistry

Melting points (mp) were determined on Electro thermal 1A 9100 MK2 apparatus and are uncorrected. All commercial chemicals were used as obtained and all solvents were purified by the standard procedures prior to use. Flash column chromatography was performed with E Merck silica gel (230–400 mesh). FT-IR spectrum was recorded by Nicolet-380 model. NMR spectra were measured against the peak of tetramethylsilane by JNM-AL 400 NMR (400 MHz, JEOL, Japan) spectrometers. High resolution mass spectra (HRMS) were measured by using Shimadzu LCMS-IT-TOF spectrometer.

6.1.1. General procedure for preparation of compounds (3)

The solution of dihydroxyacetophenone (**1**, 1.0 equiv), anhydrous potassium carbonate (2.0 equiv) and corresponding alkyl

bromides (**2**, 1.1 equiv) in acetonitrile was stirred at 70–80 °C for 4–5 h. After evaporation of acetonitrile, the reaction mixture was diluted with dichloromethane and washed with water three times. The organic layer was dried with anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography to give **3**.

6.1.1.1. 1-(2-Hydroxy-6-(isopentyloxy)phenyl)ethanone (3a). Data associated to the compound **3a** was reported in our previous work.[34]

6.1.1.2. 1-(2-Hydroxy-6-(4-methylpentyloxy)phenyl)ethanone (3b). Yield 45%; light green liquid; R_f 0.60 (1:9 EA: HX); IR (KBr) 3335, 2917, 2850, 1618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.26 (s, 1H), 7.31 (t, J = 8.2 Hz, 1H), 6.54 (dd, J = 0.8, 8.4 Hz, 1H), 6.36 (d, J = 8.2 Hz, 1H), 4.01 (t, J = 6.5 Hz, 2H), 2.70 (s, 3H), 1.92–1.85 (m, 2H), 1.58–1.51 (m, 1H), 1.38–1.31 (m, 2H) 0.84 (d, J = 6.5 Hz, 6H).

6.1.1.3. 1-(2-Butoxy-6-hydroxyphenyl)ethanone (3c). Yield 80%; colorless liquid; R_f 0.55 (0.5:9.5 EA: HX); IR (KBr) 3333, 2917, 2852, 1616 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.22 (s, 1H), 7.30 (t, J = 8.4 Hz, 1H), 6.55–6.57 (m, 1H), 6.38 (d, J = 8.2 Hz, 1H), 4.08 (t, J = 6.1 Hz, 2H), 2.70 (s, 3H), 1.80–1.92 (m, 2H), 1.53–1.51 (m, 2H), 0.92 (t, J = 1.8, Hz, 3H).

6.1.1.4. 1-(2-(Hexyloxy)-6-hydroxyphenyl)ethanone (3d). Data associated to the compound **3d** was reported in our previous work.[34]

6.1.1.5. 1-(2-(3,3-Dimethylbutoxy)-6-hydroxyphenyl)ethanone (3e). Yield 38%; light yellow liquid; R_f 0.52 (0.5:9.5 EA: HX); IR (KBr) 3233, 2919, 2852, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.28 (s, 1H), 7.33 (t, J = 8.4 Hz, 1H), 6.55 (dd, J = 0.8, 8.4 Hz, 1H), 6.38 (d, J = 8.2 Hz, 1H), 4.13 (t, J = 7.4 Hz, 2H), 2.68 (2, 3H), 1.89 (t, J = 7.4 Hz, 2H), 0.98 (s, 9H).

6.1.1.6. 1-(2-Hydroxy-6-isobutoxyphenyl)ethanone (3f). Yield 65%; colorless liquid; R_f 0.45 (0.5:9.5 EA: HX); IR (KBr) 3298, 2910, 2855, 1616 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.27 (s, 1H), 7.32 (t, J = 8.4 Hz, 1H), 6.53–6.57 (m, 1H), 6.36 (d, J = 8.2 Hz, 1H) 3.85 (d, J = 6.5 Hz, 2H), 2.71 (s, 3H), 2.12–2.28 (m, 1H), 1.08 (d, J = 6.5 Hz, 6H).

6.1.1.7. 1-(2-(2-Ethylbutoxy)-6-hydroxyphenyl)ethanone (3g). Yield 68%; white semi solid; R_f 0.58 (0.5:9.5 EA: HX); IR (KBr) 3235, 2917, 2852, 1619 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.29 (s, 1H), 7.31 (t, J = 8.4 Hz, 1H), 6.53 (dd, J = 0.8, 8.4 Hz, 1H), 6.39 (d, J = 8.2 Hz, 1H), 3.93 (d, J = 6.4 Hz, 2H), 2.69 (s, 3H), 1.68–1.75 (m, 1H), 1.49–1.52 (m, 4H), 0.95 (t, J = 7.6 Hz, 6H).

6.1.1.8. 1-(2-Hydroxy-6-(3-methylbut-2-enyloxy)phenyl)ethanone (3h). Yield 24%; light green liquid; R_f 0.46 (1:9 EA: HX); ^1H NMR (DMSO-d_6) δ 10.78 (s, 1H), 7.46 (t, J = 8.2 Hz, 1H), 6.99 (d, J = 15.1 Hz, 1H), 6.83–6.90 (m, J = 08.5 Hz, 2H), 4.55 (d, J = 6.3 Hz, 2H), 4.26–4.41 (m, 1H), 2.69 (s, 3H), 1.54–1.64 (m, 6H).

6.1.1.9. 1-(2-(Cyclopentylmethoxy)-6-hydroxyphenyl)ethanone (3i). Yield 50%; white semi solid; R_f 0.61 (0.5:9.5 EA: HX); IR (KBr) 3239, 2911, 2840, 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.23 (s, 1H), 7.29 (t, J = 8.4 Hz, 1H), 6.52 (dd, J = 0.8, 8.4 Hz, 1H), 6.39 (d, J = 8.2 Hz, 1H), 3.94 (d, J = 7.07 Hz, 2H), 2.70 (s, 3H), 2.33–2.57 (m, 1H), 1.85 (dd, J = 5.73, 6.95 Hz, 2H), 1.52–1.63 (m, 4H), 1.31–1.45 (m, 2H).

6.1.1.10. 1-(2-(2-Cyclopentylethoxy)-6-hydroxyphenyl)ethanone (3j). Yield 47%; light green liquid; R_f 0.66 (0.5:9.5 EA: HX); IR (KBr) 3239, 2915, 2840, 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.28 (s, 1H), 7.32 (t, J = 8.4 Hz, 1H), 6.53 (dd, J = 0.8, 8.4 Hz, 1H), 6.34 (d, J = 8.2 Hz, 1H), 4.09 (t, J = 6.3 Hz, 2H), 2.68 (s, 3H), 2.02 (d, J = 7.8 Hz, 1H), 1.90 (q, J = 6.7 Hz, 2H), 1.72–1.82 (m, 2H), 1.55–1.66 (m, 2H), 1.42–1.55 (m, 2H), 1.06–1.20 (m, 2H).

6.1.1.11. 1-(2-(Cyclohexylmethoxy)-6-hydroxyphenyl)ethanone (3k). Data associated to the compound **3k** was reported in our previous work.[35]

6.1.1.12. 1-(2-(2-Cyclohexylethoxy)-6-hydroxyphenyl)ethanone (3l). Yield 50%; colorless liquid; R_f 0.63 (0.5:9.5 EA: HX); IR (KBr) 3230, 2919, 2848, 1618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.27 (s, 1H), 7.32 (t, J = 8.4 Hz, 1H), 6.53 (dd, J = 0.8, 8.4 Hz, 1H), 6.34 (d, J = 8.2 Hz, 1H), 4.11 (t, J = 6.4 Hz, 2H), 2.70 (s, 3H), 1.78 (q, J = 6.5 Hz, 2H), 1.60–1.74 (m, 5H), 1.55–1.49 (m, 1H), 1.05–1.20 (m, 3H), 0.93 (d, J = 9.0 Hz, 2H).

6.1.1.13. 1-(2-(Benzyloxy)-6-hydroxyphenyl)ethanone (3m). Data associated to the compound **3m** was reported in our previous work.[35]

6.1.1.14. 1-(2-(Adamantylmethoxy)-6-hydroxyphenyl)ethanone (3n). Yield 38%; light green liquid; R_f 0.60 (1:9 EA: HX); ^1H NMR ($CDCl_3$) δ 12.69 (s, 1H), 7.33 (t, J = 8.4 Hz, 1H), 6.59 (d, J = 8.2 Hz, 1H), 6.42 (d, J = 8.2 Hz, 1H), 5.29 (s, br s, 1H), 3.60 (s, 2H), 2.66 (s, 3H), 1.85 (s, 3H), 1.56–1.62 (m, 8H), 1.41 (m, 3H).

6.1.2. General procedure for the preparation of compound (5)

The corresponding alkyl substituted-2-hydroxyacetophenone **3** (1.0 equiv) was dissolved in ethanol and piperidine (2.0 equiv) and benzaldehydes **4** (1.02 equiv) were added. The resulting mixture was stirred for 5 h at 78 °C. After completion of reaction, the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane and washed with 1*N*-HCl followed by water. The organic layer was dried with anhydrous sodium sulfate and evaporated under reduced pressure to get the crude product, which was further purified by flash column chromatography to give **5b**–**p**.

6.1.2.1. (*E*)-1-(2-Hydroxy-6-(4-methylpentyloxy)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5b). Yield 88%; yellow solid; R_f 0.43 (3:7 EA: HX); mp 131–134 °C; IR (KBr) 3255.1, 2959.4, 1610.5, 1439.9, 1202.6, 831.3 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.25 (s, 1H), 7.85 (d, J = 16.0 Hz, 1H), 7.78 (d, J = 16.0 Hz, 1H), 7.52 (d, J = 8.7 Hz, 2H), 7.33 (t, J = 8.0 Hz, 1H), 6.86 (d, J = 8 8.5 Hz, 2H), 6.60 (d, J = 8.5 Hz, 1H), 6.41 (d, J = 8.2 Hz, 1H), 5.33 (s, 1H), 4.06 (t, J = 6.5 Hz, 2H), 1.92–1.85 (m, 2H), 1.58–1.51 (m, 1H), 1.38–1.31 (m, 2H) 0.84 (d, J = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 194.8, 164.9, 160.7, 157.8, 143.0, 135.9, 130.6, 128.3, 125.6, 116.0, 110.7, 102.4, 77.4, 77.1, 76.7, 76.7, 69.4, 35.2, 27.9, 22.4; HRMS calculated for $C_{21}H_{24}O_4$: m/z 340.1675, found: 340.1671.

6.1.2.2. (*E*)-1-(2-Butoxy-6-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one (5c). Yield 85%; yellow solid; R_f 0.40 (3:7 EA: HX); mp 129–132 °C; IR (KBr) 3343.2, 2956.1, 1616.4, 1202.6, 831.6 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.37 (s, 1H), 7.86 (d, J = 16.0 Hz, 1H), 7.79 (d, J = 16.0 Hz, 1H), 7.50 (d, J = 8.5 Hz, 2H), 7.33 (t, J = 8.0 Hz, 1H), 6.87 (dd, J = 8.4 Hz, 2H), 6.59 (d, J = 8.0 Hz, 1H), 6.41 (d, J = 8.0 Hz, 1H), 5.69 (br s, 1H) 4.08 (t, J = 6.1 Hz, 2H), 1.80–1.92 (m, 2H), 1.53–1.51 (m, 2H), 0.92 (t, J = 1.8, Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 194.9, 165.0, 160.8, 157.9, 143.1, 136.0, 130.6, 128.3, 125.6, 116.1, 110.7, 102.4, 77.4, 76.8, 68.9, 31.5, 19.6, 13.8; HRMS calculated for $C_{19}H_{20}O_4$: m/z 312.3597, found: 312.3595.

6.1.2.3. (*E*)-1-(2-(Hexyloxy)-6-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5d). Data associated to the compound **5d** was reported in our previous work.[35]

6.1.2.4. (*E*)-1-(2-Hydroxy-6-(3,3-dimethylbutoxy)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5e). Yield 77%; yellow solid; R_f 0.49 (3:7 ethyl acetate: hexane); mp 118–121 °C; IR (KBr) 3293.8, 2954.5, 1614.6, 1469.2, 1205.5, 825.2 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.34 (s, 1H), 7.88 (d, J = 15.6 Hz, 1H), 7.77 (d, J = 15.6 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 8.2 Hz, 1H), 6.88 (d, J = 8.0 Hz, 2H), 6.60 (d, J = 8.2 Hz, 1H), 6.43 (d, J = 8.2 Hz, 1H), 5.20 (s, 1H), 4.13 (t, J = 7.4 Hz, 2H), 1.87 (t, J = 7.4 Hz, 2H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 194.7, 165.0, 160.6, 157.7, 142.7, 135.9, 130.5, 128.3, 125.7, 115.9, 112.0, 110.7, 102.3, 76.7, 66.4, 42.7, 29.7, 29.6; HRMS calculated for $C_{21}H_{24}O_4$: m/z 340.4129, found: 340.4126.

6.1.2.5. (*E*)-1-(2-Hydroxy-6-isobutoxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5f). Yield 81%; yellow solid; R_f 0.37 (3:7 EA: HX); mp 128–131 °C; IR (KBr) 3192.3, 3033.0, 1680.9, 1201.9, 828.9 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.22 (s, 1H), 7.88 (d, J = 16.0 Hz, 1H), 7.79 (d, J = 16.0 Hz, 1H), 7.52 (d, J = 8.2 Hz, 2H), 7.33 (t, J = 8.2 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.60 (dd, J = 0.9, 8.2 Hz, 1H), 6.41 (d, J = 8.2 Hz, 1H), 5.48 (br s, 1H), 3.85 (d, J = 6.5 Hz, 2H), 2.12–2.28 (m, 1H), 1.04 (d, J = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 194.8, 164.7, 160.6, 157.8, 143.0, 135.8, 130.6, 128.2, 125.5, 115.9, 112.1, 110.6, 102.3, 77.3, 76.7, 75.6, 28.4, 19.4; HRMS calculated for $C_{21}H_{24}O_4$: m/z 340.1675, found: 340.1671.

6.1.2.6. (*E*)-1-(2-(2-Ethylbutoxy)-6-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5g). Yield 88%; yellow solid; R_f 0.47 (3:7 EA: HX); mp 69–72 °C; IR (KBr) 3333.5, 2956.9, 1615.7, 1465.8, 1199.8, 831.0 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.15 (s, 1H), 7.81 (d, J = 16.0 Hz, 1H), 7.76 (d, J = 16.0 Hz, 1H), 7.52 (d, J = 8.7 Hz, 2H), 7.33 (t, J = 8.4 Hz, 1H), 6.86 (d, J = 8.5 Hz, 2H), 6.60 (d, J = 8.2 Hz, 1H), 6.44 (d, J = 8.5 Hz, 1H), 5.50 (br s, 1H), 3.97 (d, J = 5.6 Hz, 2H), 1.73 (m, 1H), 1.48 (m, 4H), 0.89 (t, J = 7.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 194.8, 164.9, 160.7, 157.8, 143.0, 135.9, 130.6, 128.3, 125.6, 116.0, 110.7, 102.4, 77.4, 77.1, 76.7, 76.7, 69.4, 35.2, 24.9, 11.4; HRMS calculated for $C_{21}H_{24}O_4$: m/z 340.4129, found: 340.4125.

6.1.2.7. (*E*)-1-(2-Hydroxy-6-(3-methylbut-2-enyloxy)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5h). Yield 27%; yellow color solid; R_f 0.13 (3:7 EA: HX); mp 246–247 °C; IR (KBr) 3200, 2952, 2358, 1559, 1463, 1225, 740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.73 (s, 1H), 7.68–7.77 (m, 3H), 7.41 (t, J = 8.2 Hz, 1H), 6.99 (d, J = 15.1 Hz, 1H), 6.83–6.90 (m, J = 8.5 Hz, 2H), 6.71–6.78 (m, J = 8.2 Hz, 2H), 5.20–5.30 (m, 1H), 4.55 (d, J = 6.3 Hz, 2H), 4.26–4.41 (m, 1H), 1.54–1.64 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 171.2, 162.7, 155.9, 155.5, 155.2, 138.1, 133.1, 125.1, 119.2, 116.3, 114.5, 108.8, 107.0, 103.8, 65.0, 55.1, 26.7, 25.2, 22.8, 17.9; HRMS: calculated for $C_{20}H_{20}O_4$: m/z 324.3704, found: 324.3700.

6.1.2.8. (*E*)-1-(2-(Cyclopentylmethoxy)-6-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5i). Yield 92%; yellow solid; R_f 0.42 (3:7 EA: HX); mp 127–129 °C; IR (KBr) 3367.8, 2959.4, 1659.9, 1202.7, 836.0 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.27 (s, 1H), 7.85 (d, J = 16.0 Hz, 1H), 7.78 (d, J = 16.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 8.41 Hz, 1H), 6.86 (d, J = 8.0 Hz, 2H), 6.59 (dd, J = 0.85, 8.41 Hz, 1H), 6.42 (d, J = 8.0 Hz, 1H), 5.55 (s, 1H), 3.94 (d, J = 7.07 Hz, 2H), 2.33–2.57 (m, 1H), 1.85 (dd, J = 5.73, 6.95 Hz, 2H), 1.52–1.63 (m, 4H), 1.31–1.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 194.8, 164.8, 160.7, 157.7, 142.9, 135.9, 130.5, 128.3, 125.7, 115.9, 112.0, 110.6, 102.3, 77.2, 76.7, 73.2, 39.2, 29.6, 25.2; HRMS calculated for $C_{21}H_{22}O_4$: m/z 338.3970, found: 338.3966.

6.1.2.9. (*E*)-1-(2-(2-Cyclopentylethoxy)-6-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5j). Yield 88%; yellow solid; R_f 0.45 (3:7 EA: HX); mp 149–151 °C; IR (KBr) 3264.5, 1613.2, 1441.9, 1203.7, 831.7 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.36 (s, 1H), 7.87 (d, J = 15.6 Hz, 1H), 7.78 (d, J = 15.6 Hz, 1H), 7.48–7.56 (m, J = 8.5 Hz, 2H), 7.33 (t, J = 8.2 Hz, 1H), 6.82–6.91 (m, J = 8.5 Hz, 2H), 6.60 (d, J = 8.5 Hz, 1H), 6.42 (d, J = 8.2 Hz, 1H), 5.57 (br s, 1H), 4.09 (t, J = 6.3 Hz, 2H), 2.02 (d, J = 7.8 Hz, 1H), 1.90 (q, J = 6.7 Hz, 2H), 1.72–1.82 (m, 2H), 1.55–1.66 (m, 2H), 1.42–1.55 (m, 2H), 1.06–1.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 194.8, 164.9, 160.6, 157.8, 142.9, 135.9, 130.5, 128.3, 125.6, 115.9, 110.6, 102.3, 76.7, 68.3, 36.6, 35.5, 32.5, 24.9; HRMS calculated for $C_{22}H_{24}O_4$: m/z 352.4326, found: 352.4322.

6.1.2.10. (*E*)-1-(6-Cyclohexylmethoxy-2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one (5k). Data associated to the compound **5k** was reported in our previous work.[35]

6.1.2.11. (*E*)-1-(2-(2-Cyclohexylethoxy)-6-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5l). Yield 92%; yellow solid; R_f 0.43 (2:8 EA: HX); mp 166–168 °C; IR (KBr) 3254.1, 2959.4, 1610.5, 1439.9, 1202.6, 831.3 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.39 (s, 1H), 7.88 (d, J = 15.6 Hz, 1H), 7.79 (d, J = 15.6 Hz, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.33 (t, J = 8.2 Hz, 1H), 6.87 (d, J = 8.0 Hz, 2H), 6.60 (d, J = 8.0 Hz, 1H), 6.42 (d, J = 8.2 Hz, 1H), 5.23 (s, 1H), 4.11 (t, J = 6.4 Hz, 2H), 1.78 (q, J = 6.5 Hz, 2H), 1.60–1.74 (m, 5H), 1.55–1.49 (m, 1H), 1.05–1.20 (m, 3H), 0.93 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 194.3, 165.0, 160.6, 157.8, 143.1, 135.9, 130.5, 128.3, 125.6, 115.9, 110.6, 102.3, 76.7, 68.3, 33.2, 36.6, 35.5, 32.5, 28.1, 25.1; HRMS calculated for $C_{23}H_{26}O_4$: m/z 366.4501, found: 366.4498.

6.1.2.12. (*E*)-1-(2-(Benzyloxy)-6-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5m). Data associated to the compound **5m** was reported in our previous work.[35]

6.1.2.13. (*E*)-1-(2-(Adamantylmethoxy)-6-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5n). Yield 48%; yellow color solid; R_f 0.39 (3:7 EA: HX); mp 104–108 °C; IR (KBr) 3280, 2897, 2845, 1574, 1445, 1165, 829 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.67 (s, 1H), 7.80 (d, J = 15.6 Hz, 1H), 7.65 (d, J = 15.6 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.33 (t, J = 8.4 Hz, 1H), 6.84 (d, J = 8.5 Hz, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.42 (d, J = 8.2 Hz, 1H), 5.29 (s, br s, 1H), 3.60 (s, 2H), 1.85 (s, 3H), 1.56–1.62 (m, 8H), 1.41 (m, 3H); ^{13}C NMR δ 194.7, 167.4, 163.9, 160.9, 158.2, 157.7, 148.3, 142.5, 135.6, 130.7, 128.2, 126.4, 115.8, 112.9, 110.3, 102.6, 80.0, 44.6, 39.5, 36.6, 34.8, 33.7, 27.9, 24.3, 21.4; HRMS: calculated for $C_{26}H_{28}O_4$: m/z 404.4981, found: 404.4978.

6.1.2.14. 4-((*E*)-3-(2-Hydroxy-6-(3,3-dimethylbutoxy)phenyl)-3-oxoprop-1-enyl)benzoic acid (5o). Yield 28%; yellow color solid; R_f 0.18 (3:7 EA: HX); mp 185–187 °C; IR (KBr) 2947, 2541, 1684, 1557, 1465, 1227, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.03 (s, 1H), 8.12–8.18 (m, J = 8.2 Hz, 2H), 8.03 (d, J = 15.6 Hz, 1H), 7.77 (d, J = 15.8 Hz, 1H), 7.68–7.73 (m, J = 8.2 Hz, 2H), 7.37 (t, J = 8.2 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 6.44 (d, J = 8.2 Hz, 1H), 4.15 (t, J = 7.4 Hz, 2H), 1.85 (t, J = 7.3 Hz, 2H), 0.98 (s, 9H); ^{13}C NMR δ 194.4, 165.1, 160.7, 140.6, 140.5, 136.5, 130.8, 130.2, 128.3, 112.0, 110.8, 102.3, 66.5, 42.8, 29.7, 29.6; HRMS: calculated for $C_{22}H_{24}O_5$: m/z 368.4230, found: 368.4226.

6.1.2.15. 4-((*E*)-3-(2-Hydroxy-6-(3,3-dimethylbutoxy)phenyl)-3-oxoprop-1-enyl)benzenesulfonamide (5p). Yield 49%; yellow color solid; R_f 0.11 (1:9 EA: HX); mp 170–172 °C; IR (KBr) 3413, 2955, 2358, 1588, 1449, 1226, 724 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.54 (s, 1H), 7.86–7.90 (m, 2H), 7.81–7.86 (m, 2H), 7.42 (s, 2H), 7.37 (d, J = 5.37 Hz, 2H), 7.27 (t, J = 8.29 Hz, 1H), 6.62 (d, J = 8.54 Hz, 1H), 6.54 (d, J = 8.29 Hz, 1H), 4.04 (t, J = 7.07 Hz, 2H), 1.58 (t, J = 6.95 Hz, 2H), 0.83–0.90 (m, 9H); ^{13}C NMR (DMSO-d_6) δ

194.3, 158.0, 157.7, 145.2, 141.1, 137.8, 132.5, 130.8, 128.8, 126.2, 115.5, 109.0, 103.3, 65.8, 41.9, 29.4, 29.3; HRMS: calculated for $C_{21}H_{25}NO_5S$: *m*/*z* 403.4919, found: 403.4916.

6.1.2.16. (*E*)-1-(2-(3,3-Dimethylbutoxy)-6-methoxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5q). To a mixture of compound **3e** (1.0 equiv) in THF was added sodium hydride (1.2 equiv) at 0–5 °C under nitrogen. Reaction mixture stirred for 10 min at the same temperature then added CH_3I (2.0 equiv) and continued stirring until TLC shows completion of reaction. Reaction mixture was quenched with ethyl acetate and washed with water. Organic layer was dried and evaporated to get 1-(2-(3,3-dimethylbutoxy)-6-methoxyphenyl)ethanone intermediate (**6**) which was converted to compound **5q** using above mentioned procedure for the preparation of **5e**.

Yield 27%; white color solid; R_f 0.22 (3:7 EA: HX); mp 58–60 °C; IR (KBr) 3286, 2952, 2358, 1560, 1510, 1465, 1232, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (d, J = 8.4 Hz, 2H), 7.30 (s, 1H), 6.79–6.85 (m, 3H), 6.59 (t, J = 8.9 Hz, 2H), 6.03 (s, 1H), 4.00 (t, J = 7.06 Hz, 2H), 3.76 (s, 3H), 1.59 (t, J = 7.15 Hz, 2H), 0.87 (s, 9H); ^{13}C NMR δ 206.5, 164.4, 160.6, 153.5, 135.6, 133.3, 129.2, 114.9, 111.0, 110.3, 101.7, 66.1, 46.2, 41.9, 29.3, 29.2, 28.9; ^{13}C NMR ($CDCl_3$) δ 196.1, 158.2, 157.6, 157.1, 145.7, 130.7, 130.4, 127.5, 126.6, 118.8, 116.0, 105.0, 103.9, 66.1, 55.9, 42.1, 29.6; HRMS: calculated for $C_{22}H_{26}O_4$: *m*/*z* 354.4394, found: 354.4390.

6.1.2.17. 1-(2-(3,3-Dimethylbutoxy)-6-hydroxyphenyl)-3-(4-hydroxyphenyl)propan-1-one (5r). Compound **5e** (1 mmol) was dissolved in methanol and 10% Pd/C was added in Parr's hydrogenation bottle. After 30 psi hydrogen gas was charged, the reaction mixture was shaken for 3 h at room temperature. TLC profile of the reaction indicated completion of reaction. The catalyst was removed by the filtration using celite aid. The filtrate was evaporated and the residue was purified by flash column chromatography to give **5r**.

Yield 54%; white color solid; R_f 0.50 (3:7 EA: HX); mp 104–106 °C; IR (KBr) 3409, 2953, 2358, 1588, 1513, 1449, 1200, 803 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.21 (s, 1H), 7.32 (t, J = 8.2 Hz, 1H), 7.07–7.14 (m, J = 8.2 Hz, 2H), 6.73–6.80 (m, J = 8.2 Hz, 2H), 6.56 (d, J = 8.2 Hz, 1H), 6.39 (d, J = 8.2 Hz, 1H), 4.67 (s, 1H), 4.08 (t, J = 7.5 Hz, 2H), 3.41 (t, J = 7.5 Hz, 2H), 2.96 (t, J = 7.5 Hz, 2H), 1.74 (t, J = 7.5 Hz, 2H), 0.96 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 206.5, 164.4, 160.6, 153.5, 135.6, 133.3, 129.2, 114.9, 111.0, 110.3, 101.7, 66.1, 46.2, 41.9, 29.3, 29.2, 28.9; HRMS: calculated for $C_{21}H_{26}O_4$: *m*/*z* 342.4287, found: 342.4283.

Acknowledgment

This work was supported by Priority Research Centers Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2009-0093815).

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