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Stereoselective synthesis and anti-proliferative effects on prostate cancer evaluation of 5-substituted-3,4-diphenylfuran-2-ones

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ABSTRACT

Series of 5-substituted-3,4-diphenylfuran-2-ones were stereoselectively prepared. Their potential anti-proliferative effects on prostate cancer and some of their cyclooxygenases (COXs) inhibitory activities were evaluated. Structure–activity relationship (SAR) data, acquired by substituent modification at the *para*-position and *ortho*-position of the C-3 phenyl ring and 5-substituted modification of the central furanone, showed that 3-(2-chloro-phenyl)-4-(4-methanesulfonyl-phenyl)-5-(1-methoxy-ethyl)-5*H*-furan-2-one (**13p**) was the most potent compound and could effectively reduce the proliferation of prostate cancer cells (PC3 cell IC_{50} = 20 μM; PC3 PCDNA cell IC_{50} = 5 μM; PC3 SKP2 cell IC_{50} = 5 μM; DU145 cell IC_{50} = 25 μM). The cell cycle analysis for **13p** in DU145 indicated that **13p** may induce G1 phase arrest.

1. Introduction

Prostate cancer is a significant public health concern in many regions of the world [1,2]. Compared to other cancer types, prostate cancer is the second leading cause of cancer death in men [3]. Previous literature showed that arachidonic acid (AA) derived from fatty acid and its metabolite prostaglandin E2 (PGE2) stimulated the growth of PC-3 prostate cancer cells [4,5]. These data suggested that AA and its metabolites contributed to carcinogenesis and progression of prostate cancer. Cyclooxygenases (COXs) are bifunctional hemoproteins catalyzing the bisoxygenation of arachidonic acid (AA) to prostaglandin (PG) H2, which serves as a common precursor for the synthesis of prostanoids, such as PGs, prostacyclins, and thromboxanes (TBXs). Cyclooxygenase-2 (COX-2), an inducible isoform of COX, has been observed to be expressed in prostate cancer. A number of preclinical and clinical evidences suggested that COX-2 may be an important molecular target for the chemoprevention of prostate cancer [6–10].

Many studies indicated that COX-2 is a *bona fide* pharmacological target for anticancer therapy. Epidemiological studies showed that the using of non-steroidal anti-inflammatory drugs (NSAIDs), prototypic inhibitors of COX, is associated with a reduced risk of several malignancies, including colorectal cancer [11]. It was also reported that COX-2 inhibitor Celecoxib could block Akt activation in PC-3 cells through the inhibition of phosphoinositide-dependent kinase-1 (PDK-1) with IC_{50} of 48 μM [12]. In recent years, significant achievements have been obtained in drug design regarding selective COX-2 inhibitors and their potential application for the treatment of different disease states [13–17]. For example, the treatments of colon, breast, and prostate cancer have shown promising results [18,19]. Rofecoxib (4-[4-methylsulphonylphenyl]-3-phenylfuran-2(5*H*)-one, **2**) is a highly selective inhibitor of COX-2 [20–22]. It was reported [23] that facile air oxidation of the conjugate base of rofecoxib is a possible contributor to chronic human toxicity. Therefore, we synthesized a series of 5-substituted rofecoxib derivatives to avoid the oxidation reaction, and at the same time to obtain new rofecoxib derivatives with good activity and no or little side effect. Now, a novel series of rofecoxib derivatives, possessing a

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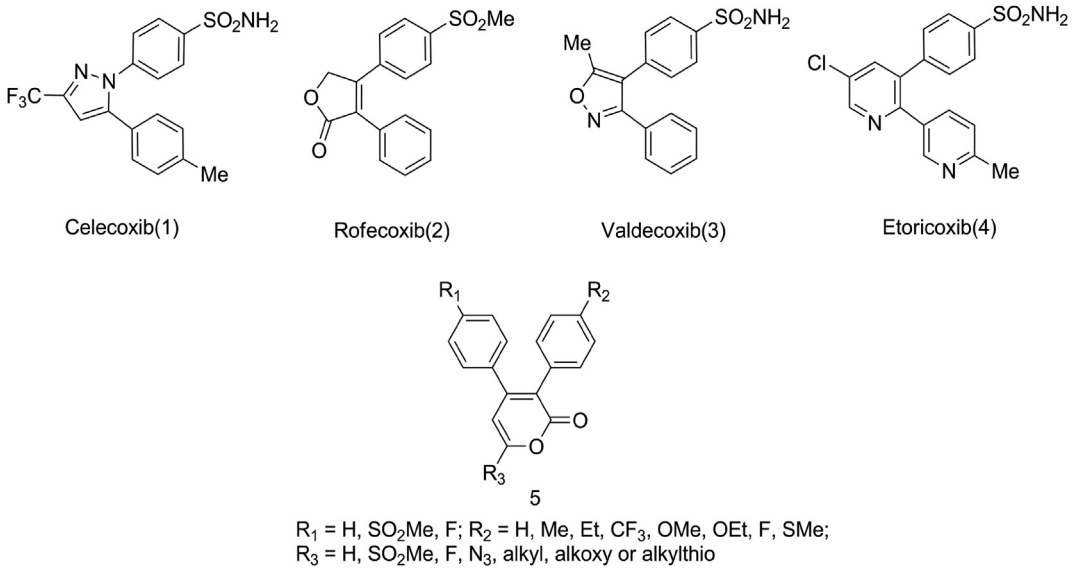


Fig. 1. Representative examples of selective COX-2 inhibitors.

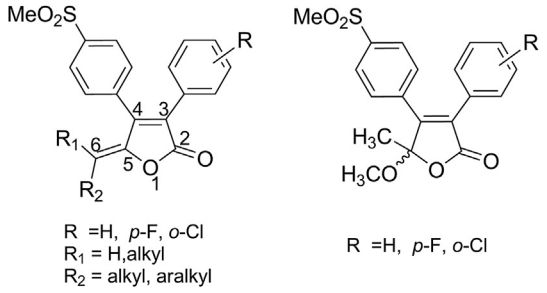


Fig. 2. 5-Substituted-3-phenylfuran-4-(4-methanesulfonylphenyl)-2-ones.

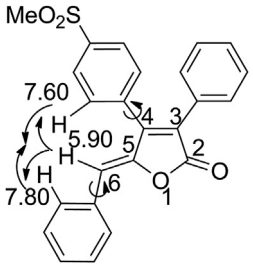
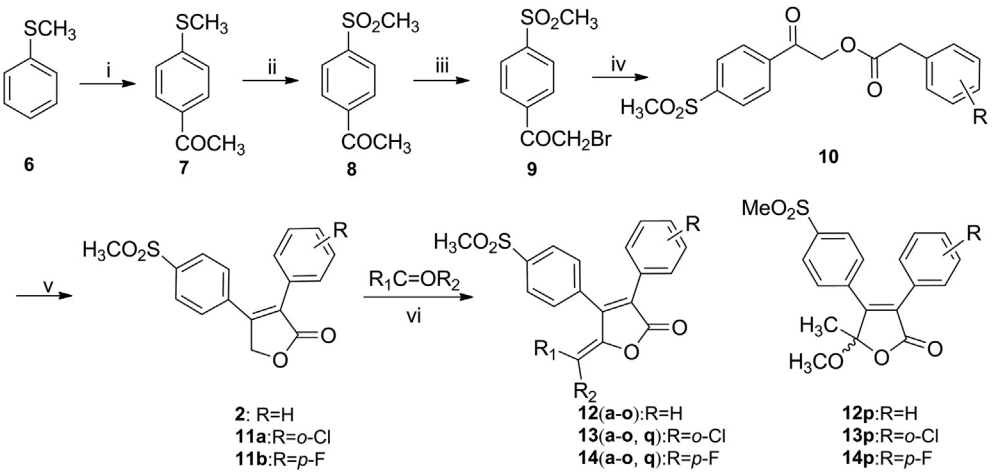


Fig. 3. The NOE spectra of compound **12a**.

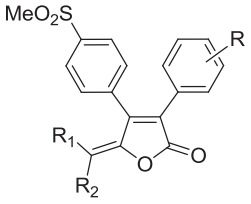
central furan-2-one ring are shown as selective COX-2 inhibitors, which exhibits good anti-proliferative effects on prostate cancer activity profiles. Diarylheterocycles, and other central ring pharmacophore templates, have been extensively studied as cyclooxygenase inhibitors [24] (Fig. 1). SAR studies have shown that for optimum COX-2 selectivity and inhibitory potency, a SO_2Me or SO_2NH_2 substituent at the *para*-position of a phenyl ring, and that the presence of a *p*-F substituent on the nonsulfonyl vicinal phenyl ring improved the *in vivo* activity [25,26].

Based on the above researches and our previous work on the synthesis and bioactivities of γ-alkylidene butenolides [27–31], a series of new 5-substituted-3-phenylfuran-4-(4-methanesulfonylphenyl)-2-ones (Fig. 2) as rofecoxib derivatives were designed and synthesized in the present work. Their prostatic hyperplasia inhibitory activities, the

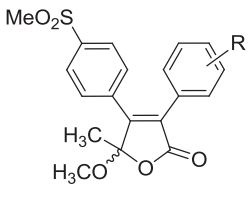


Scheme 1. Synthesis of the 5-substituted-3-phenylfuran-4-(4-methanesulfonylphenyl)-2-ones (**12**, **13**, **14**). Reagents and conditions (i) CH_3COCl, $AlCl_3$, CH_2Cl_2, 97%; (ii) 30% H_2O_2, CH_3COOH, 99%; (iii) Br_2, CH_3COOH, 86%; (iv) R-$PhCH_2COONa$, DMF; (v) $(Me_2CH)_2NH$, DMF, 70%; (vi) CH_3OH, $NH_2CH_2CH_2NH_2$, reflux 70%–100%.

Table 1
Inhibitory results of 5-substituted-3-phenylfuran-4-(4-methanesulfonyl phenyl)-2-ones derivative against prostate cancer cell lines. Bold represents the corresponding compounds of those data show good activity, of which the IC_{50} values less than 50 μM.



R =H, *p*-F, *o*-Cl



(12,13,14)P
R =H, *p*-F, *o*-Cl

Compound	R	R_1	R_2	PC-3PCDNA IC_{50} (μM)[a]	PC-3 SKP2 IC_{50} (μM)	PC-3 IC_{50} (μM)	DU145 IC_{50} (μM)
2	H			>50	>50	200	200
12a	H	H	Ph	>90	>90	Nt[c]	Nt
12b	H	H	*m*-NO_2Ph	>90	>100	Nt	Nt
12c	H	H	*o*-MeOPh	>80	>90	Nt	Nt
12d	H	H	3,4,5-triMeOPh	>90	>100	Nt	Nt
12e	H	H	Furoyl	>100	>100	Nt	Nt
12f	H	H	*m*-MeO–*p*-OHPh	>125	**25.47 ± 1.63**[b]	>50	>50
12g	H	H	*p*-OHPh	**25.88 ± 2.08**	>50	>50	>50
12h	H	H	*p*-BrPh	**25.24 ± 2.27**	>50	>50	>50
12i	H	H	*p*-ClPh	>50	>50	Nt	Nt
12j	H	H	CH=C(CH_3)CH_2CH_2CH=C(CH_3)$_2$	>50	>50	Nt	Nt
12k	H	H	*p*-N(CH_3)$_2$Ph	>50	>50	Nt	Nt
12l	H	H	3,4-(CH_2–O–CH_2)Ph	**37.21 ± 2.38**	**50.63 ± 3.15**	>50	>50
12m	H	H	*p*-MeOPh	>50	>50	Nt	Nt
12n	H	H	α-$C_{10}H_7$Ph	>50	>50	Nt	Nt
12o	H	CH_3	CH_3	>50	>50	Nt	Nt
12p	H	CH_3	OCH_3	**37.09 ± 2.06**	**20.33 ± 2.45**	>50	>50
11a	*o*-Cl			>50	>50	Nt	Nt
13a	*o*-Cl	H	Ph	>50	**5.48 ± 0.91**	>50	>50
13b	*o*-Cl	H	*m*-NO_2Ph	>50	>50	Nt	Nt
13c	*o*-Cl	H	*o*-MeOPh	**25.46 ± 2.30**	**45.75 ± 2.04**	>50	>50
13d	*o*-Cl	H	3,4,5-triMeOPh	>50	>50	Nt	Nt
13e	*o*-Cl	H	Furoyl	>50	>50	Nt	Nt
13f	*o*-Cl	H	*m*-MeO–*p*-OHPh	>50	**25.14 ± 2.16**	>50	>50
13g	*o*-Cl	H	*p*-OHPh	>50	>50	Nt	Nt
13h	*o*-Cl	H	*p*-BrPh	>50	>50	Nt	Nt
13i	*o*-Cl	H	*p*-ClPh	>50	>50	Nt	Nt
13j	*o*-Cl	H	*p*-FPh	>50	>50	Nt	Nt
13k	*o*-Cl	H	*p*-N(CH_3)$_2$Ph	>50	**30.11 ± 2.38**	>50	>50
13l	*o*-Cl	H	3,4-(CH_2–O–CH_2)Ph	>50	>50	Nt	Nt
13m	*o*-Cl	H	*p*-MeOPh	>50	>50	Nt	Nt
13n	*o*-Cl	H	α-$C_{10}H_7$Ph	>50	>50	Nt	Nt
13o	*o*-Cl	CH_3	CH_3	**40.52 ± 2.65**	**15.37 ± 1.04**	>50	>50
13p	*o*-Cl	CH_3	OCH_3	**5.17 ± 0.78**	**5.09 ± 0.80**	20 ± 1.17	25 ± 2.08
13q	*o*-Cl	H	*o*-ClPh	>50	>50	Nt	Nt
11b	*p*-F			>50	>50	Nt	Nt
14a	*p*-F	H	Ph	>50	>50	Nt	Nt
14b	*p*-F	H	*m*-NO_2Ph	>50	>50	Nt	Nt
14c	*p*-F	H	*o*-MeOPh	**18.24 ± 1.92**	**25.13 ± 1.39**	>50	>50
14d	*p*-F	H	3,4,5-triMeOPh	>50	**25.44 ± 2.16**	>50	>50
14e	*p*-F	H	Furoyl	>50	>50	Nt	Nt
14f	*p*-F	H	*m*-MeO-*p*-OHPh	>50	**10.69 ± 1.41**	>50	>50
14g	*p*-F	H	*p*-OHPh	**25.86 ± 1.97**	**25.71 ± 2.16**	>50	>50
14h	*p*-F	H	*p*-BrPh	>50	>50	Nt	Nt
14i	*p*-F	H	*p*-ClPh	>50	>50	Nt	Nt
14j	*p*-F	H	*p*-FPh	>50	>50	Nt	Nt
14k	*p*-F	H	*p*-N(CH_3)$_2$Ph	>50	**47.17 ± 2.04**	>50	>50
14l	*p*-F	H	3,4-(CH_2–O–CH_2)Ph	>50	>50	Nt	Nt
14m	*p*-F	H	*p*-MeOPh	>50	>50	Nt	Nt
14n	*p*-F	H	α-$C_{10}H_7$Ph	**20.04 ± 2.21**	**25.37 ± 2.27**	>50	>50
14o	*p*-F	CH_3	CH_3	>50	>50	Nt	Nt
14p	*p*-F	CH_3	OCH_3	**36.42 ± 3.77**	>50	>50	>50
14q	*p*-F	H	*o*-ClPh	>50	>50	Nt	Nt
5-Fu				31.44 ± 2.37	27.07 ± 4.21	Nt	Nt

[a] Inhibitory activity was assayed by exposure for 72 h to substances and expressed as concentration required to inhibit prostate cancer cell proliferation by 50% (IC_{50}).
[b] Data are presented as the means ± SDs of three independent experiments for those IC_{50} values less than 50 μM.
[c] Nt: no test.

mechanisms of this inhibition effect, and some of their COX inhibitory activities were evaluated and presented.

2. Results and discussion

2.1. Chemistry

The title 5-substituted-3-phenylfuran-4-(4-methanesulfonylphenyl)-2-ones (Fig. 2), possessing a central five-membered lactone ring with a 5-substitution, were prepared by condensation of rofecoxib (**2**) and its analogs **11**(**a**,**b**) with aliphatic or aromatic aldehydes or ketones as illustrated in Scheme 1. Rofecoxib **2** and the two new derivatives **11**(**a**,**b**) were obtained by the simple synthetic method in good yields. Thioanisole (**6**) was reacted with acetyl chloride by a Friedel–Crafts acylation to give compound **7**. Compound **8** was obtained almost quantitatively by hydrogen peroxide oxidation of compound **7**. Compound **9** was obtained by compound **8** after reaction with bromine in ice acetic acid with 86% yield. Then analogs **11**(**a**,**b**) were prepared using a one-pot reaction, starting with condensation of compound **9** and sodium phenylacetate. The reaction was monitored by TLC until completion. Finally, with no further treatment of the reaction, cyclization of intermediate **10** is catalyzed by diisopropylamine to produce **11**(**a**,**b**) with approximate 70% yield.

Rofecoxib derivatives **12**, **13** and **14** were synthesized by reacting **2** and **11**(**a**,**b**) with various aldehydes or ketones using our previously reported procedure [28] (Scheme 1 and Table 1). Based on our previous studies, most of the compounds containing five-membered lactone are sensitive to strong bases and/or high temperature. However, **2** and **11**(**a**,**b**), and their target γ-alkylidene butenolides **12**, **13** and **14** are relatively stable and not very sensitive to organic bases. This might be due to conjugation of two benzene substituents and with the 5-alkylidene substituents in the target compounds. When paraformaldehyde was used as aldehyde source, **12p**, **13p** and **14p** were obtained respectively instead of γ-alkylidene-butenolides. Most of the reaction products precipitated in good yields and high stereoselectivity.

The NMR spectra data showed that single isomers of **12**, **13** and **14** were formed. In the NOE spectrum of **12a** (Fig. 3), the correlation between signals of H-6 (δ_H 5.90) and phenyl H-2, H-6 (δ_H 7.80) and 4-methylsulfanylphenyl H-2, H-6 (δ_H 7.60) showed the geometry of double bond ($\Delta^{5,6}$) in **12a** was *Z* isomer. Similarly, all of the other synthetic compounds **12**, **13** and **14** were confirmed to have *Z* configuration.

In order to understand its high enantioselectivity, theoretical calculations were carried out for a simple model reaction of rofecoxib with benzaldehyde (All calculations were implemented in the Gaussian 03 program). Due to the potential chiral carbonyl C atom of PhCHO, the nucleophile (anion) can attack the carbonyl C atom either from *Re* or *Si* side. Transition structures in the stereo-controlling C–C bond formation were studied using Hartree–Fock (HF) method at 6-31G (d) level and the calculated results were in agreement with experimental results. The calculated barrier energies were 7.8 kJ/mol and 8.6 kJ/mol respectively for *cis*- and *trans*-products respectively. Obviously, the barrier energies for *cis*- is lower than that for *trans*-. This is in great agreement with the experimental results. And the Transition State Structures showed that the cleavage of OH is *trans*-cleavage which is in agreement with the proposed mechanism.

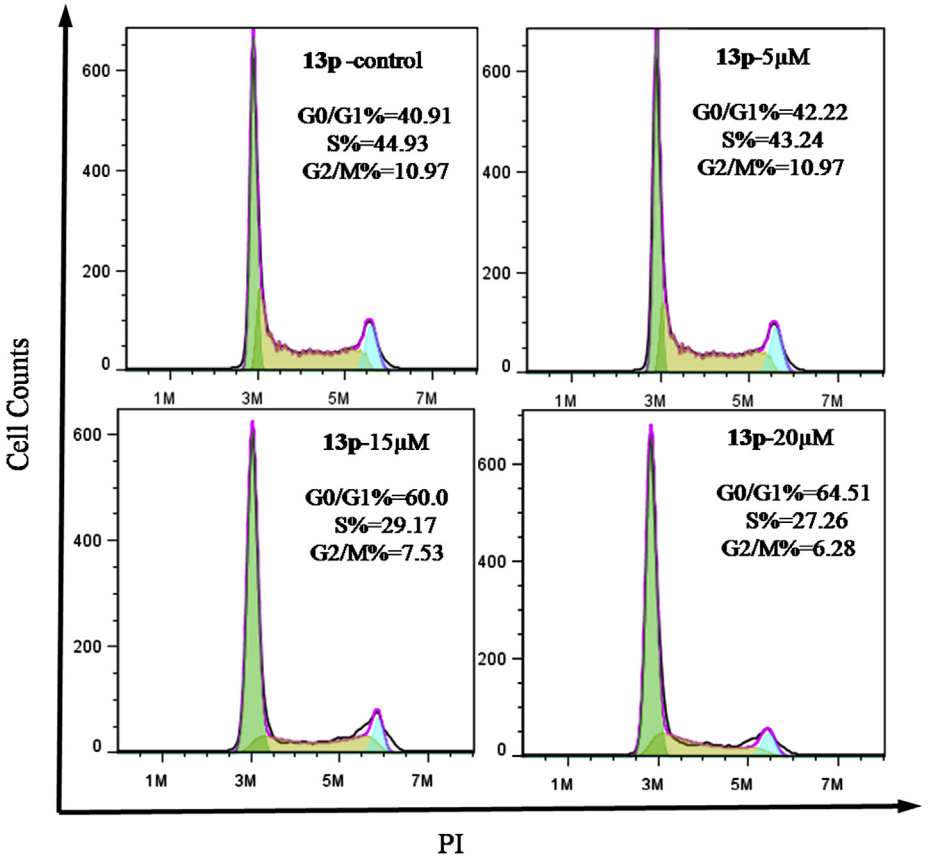


Fig. 4. Effect of compound **13p** on the cell cycle distribution of DU145 cells. Cells were treated with different concentrations (0, 5, 15, 20 μM) for 12 h. Then the cells were fixed and stained with PI to analyze DNA content by flow cytometry. The experiments were performed three times, and a representative experiment is shown.

2.2. Evaluation of biological activities

2.2.1. Prostatic hyperplasia inhibitory activities

Rofecoxib (**2**) and 5-substituted-3-phenylfuran-4-(4-methanesulfonyl phenyl)-2-ones derivatives **12**, **13** and **14** were screened *in vitro* for anti-proliferative effects (IC_{50} values) against prostate cancer cell line PC3 and its transfected cell lines (PC3 PCDNA and PC3 SKP2) and the second prostate cancer cell line DU145. The well-known anticancer drug 5-fluorouracil was used as positive control. All compounds were conducted the MTT assay on PC3 PCDNA and PC3 SKP2 cell lines. Only the active compounds were further conducted by the MTT assays on DU145 and PC3 cells. The results are summarized in Table 1. It can be observed from Table 1 that **12l**, **12p**, **13c**, **13o**, **13p, 14c**, **14g**, and **14n** reduced cell proliferation in both PC3 transfected cells (PC3 PCDNA and PC3 SKP2) by 50% at concentrations less than 50 μM. In addition, **12f**, **12g**, **12h**, **13a**, **13f**, **13k**, **14d**, **14f** and **14p** had IC_{50}s much less than 50 μM for one of the PC3 transfected cell lines.

According to Table 1, **13p** was the most potent compound with good IC_{50} values against PC3 PCDNA and PC3 SKP2 cell lines, and it is much better than the well-known anticancer drug 5-fluorouracil. The MTT assays conducted on the effective compounds on DU145 and PC3 cells indicated that **13p** was the sole compound that consistently had an IC_{50} value below 50 μM, reducing cell viability with an IC_{50} of 20 μM in PC3 cell and 25 μM in DU145 cell. Also, the IC_{50} for **13p** is significantly less than the IC_{50} of rofecoxib (**2**) (PC3 cell $IC_{50} \approx 200$ μM; DU145 cell $IC_{50} \approx 200$ μM).

2.2.2. Cell cycle analysis

Many anticancer drugs interact with cells leading to cell growth arrest. To determine whether the anticancer effects of compound **13p** was caused by cell cycle accumulated at a certain phase, the effects of different concentrations of compound **13p** on cell cycle progression were examined with DU145 cell line. After treatment with compound **13p** at various concentrations (0, 5, 15 and 20 μM) for 12 h, it was observed that the percentage of cells in G0/G1 phase were 40.91%, 42.22%, 60.0% and 64.51%, respectively (Fig. 4). The results suggested that **13p** caused a clear G0/G1 arrest pattern in a concentration dependent manner.

2.2.3. Effect of *13p* on apoptosis of DU145 cells

Further experiments were carried out to determine whether this anti-proliferative effect of **13p** on DU145 cells viability was closely associated with apoptotic cell death. Morphological analysis following DAPI staining was performed to analyze the cells with nuclear chromatin condensation and apoptotic bodies. Cells treated with **13p** displayed chromosomal condensation and formation of apoptotic bodies (Fig. 5).

2.2.4. Cyclooxygenase inhibitory activities

Some of their *in vitro* ability to inhibit the COX-1 and/or COX-2 was evaluated (Table 2). The *in vitro* activity results were reported as a percentage of inhibition of the enzymes at 10 μM for most compounds, several active compounds' and rofecoxib's activity results were reported as IC_{50} values. Most of them exhibited good COX-2 inhibitory activities. In this preliminary study toward new potential COX-2 inhibitor compounds as novel drug candidates for prostatic hyperplasia inhibitory activities, it was well established that 5-substituted-3-phenyl-furan-4-(4-methanesulfonylphenyl)-2-ones was a good template for anti-proliferative effects on prostate cancer.

2.3. Structure activity relationship

Three series of compounds **12a**–**p**, **13a**–**q** and **14a**–**q** were screened for prostatic hyperplasia inhibitory activities. Compounds **12l**, **12p**, **13c**, **13o**, **13p**, **14c**, **14g**, and **14n** exhibited good anti-proliferative effects against both PC3 PCDNA and PC3 SKP2 cell lines, whereas compounds **12f**, **12g**, **12h**, **13a**, **13f**, **13k**, **14d**, **14f** and **14p** had IC_{50}s much lower than 50 μM for one of the PC3 transfected cell lines. The above effective compounds on DU145 and PC3 cells indicated that **13p** was the only compound that consistently had an

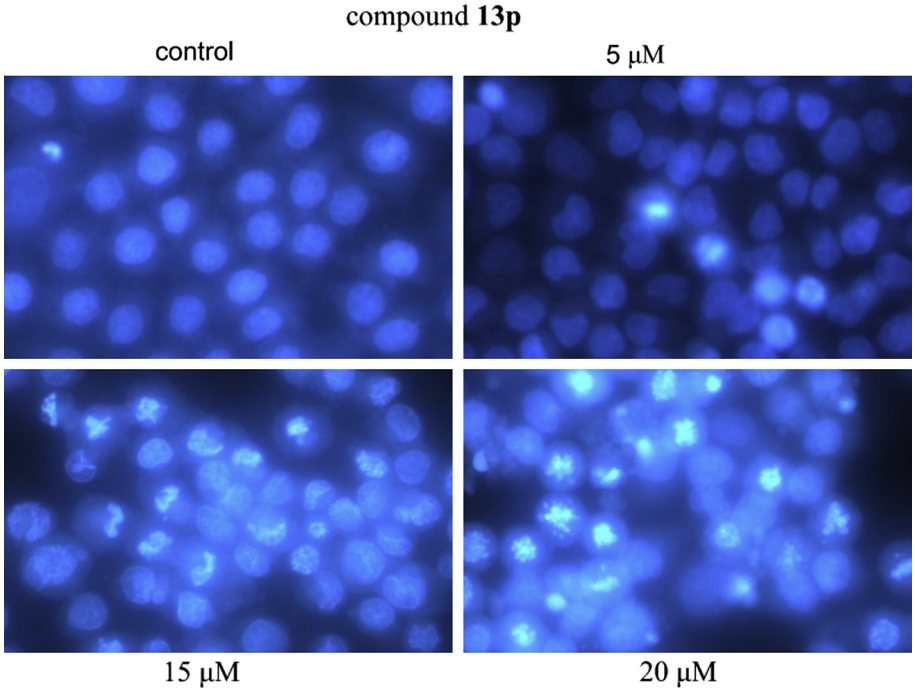


Fig. 5. Compound **13p** treatment induces apoptosis in DU145 cells. Cells were seeded at 2×10^4 cells per 60-mm plate, incubated for 24 h and treated with the indicated concentration of **13p** for 48 h. Stained nuclei with DAPI solution were then photographed with a fluorescent microscope using a blue filter (original magnification 400×).

Table 2
In vitro inhibition of COX-1/COX-2 by some of the 5-substituted-3-phenylfuran-4-(4-methanesulfonyl phenyl)-2-ones derivatives.

Compound	COX-2 inhibition		COX-1 inhibition	
	%[a]	IC_{50}[b] (μM)	%[a]	IC_{50}[b] (μM)
2 (Rofecoxib)	22.15 ± 4.33[c]	0.5	Ni[d]	
12b	Ni		Ni	
12c	72.57 ± 6.69	3.0	71.02 ± 11.18	3.1
12f	36.6 ± 7.91		Nt[e]	
12g	14.4 ± 2.79		Nt	
12h	Ni		Nt	
12l	24.6 ± 6.54		Nt	
12m	16.66 ± 8.19		65.89 ± 8.79	8.2
12e	Ni		Ni	
12i	Ni		14.6 ± 2.07	
11a	7.97 ± 5.68		Ni	
13a	59.1 ± 5.68	7.3	Nt	
13b	59.22 ± 11.20	7.1	7.01 ± 0.50	
13c	44.24 ± 5.61	14.6	Ni	
13f	14.87 ± 3.11		Nt	
13g	2.27 ± 0.53		Nt	
13i	32.68 ± 6.54		Ni	
13k	4.49 ± 1.40		Nt	
13m	Ni		61.21 ± 6.54	8.5
13o	24.14 ± 1.62		18.59 ± 4.35	
13p	43.32 ± 5.46	12.1	Nt	
11b	66.92 ± 8.61	9.2	28.5 ± 9.88	
14b	Ni		Ni	
14c	45.59 ± 5.79	13.9	Ni	
14d	20.8 ± 2.07		Nt	
14f	43.6 ± 3.12	17.6	Nt	
14g	19.5 ± 3.85		Nt	
14k	Ni		Nt	
14i	Ni		Ni	
14m	Ni		10.23 ± 3.41	
14n	Ni		Nt	
14p	32.43 ± 6.79		Nt	

[a] Data are indicated as percentage of inhibition at 10 μM ± SEM ($n = 3$).
[b] Values are mean values of two determinations acquired using an ovine COX-1/COX-2 assay kit, where the deviation from the mean is <10% of the mean value.
[c] Rofecoxib was tested at 0.1 μM ± SEM ($n = 3$).
[d] Ni: no inhibition at the corresponding concentration.
[e] Nt: not tested.

IC_{50} value below 50 μM, and the IC_{50} for **13p** is significantly less than the IC_{50} of rofecoxib (**2**) (PC3 cell $IC_{50} \approx 200$ μM; DU145 cell $IC_{50} \approx 200$ μM). After looking at the structures of these compounds showing good prostatic hyperplasia inhibitory activity, we can conclude that rofecoxib derivatives 5-substituted-3-phenylfuran-4-(4-methanesulfonylphenyl)-2-ones possess sites for interaction with the targeted prostate cancer cells. Compounds **12f**, **13f**, **14f**; **12p**, **13p**, **14p**; **13c**, **14c**, **12g** and **14g** possess good prostatic hyperplasia inhibitory activity. It may due to their 5-phenyl with electron-donating substituents which can effectively interact with the targets both from electronic and stereochemical aspects.

3. Conclusion

The biological evaluation for this novel class of 5-substituted-3-phenylfuran-4-(4-methanesulfonylphenyl)-2-ones have shown that (i) a five-membered lactone (furan-2-one) ring serves as a suitable central ring template to design rofecoxib derivatives as COX-2 inhibitors, which can effectively reduce prostate cancer cell proliferation; (ii) the presence of a *p*-fluoro and/or *o*-chlorine substituent on the C-4 phenyl ring improved *in vitro* prostatic hyperplasia inhibitory activities for this class of compounds; (iii) according to the structure–activity relationships, compounds (**12**, **13**, **14**)**f**, (**12**, **13**, **14**)**p**; (**13**, **14**)**c** and (**12**, **14**)**g** are good modification to rofecoxib for prostatic hyperplasia inhibitory activity; and (iv) the cell cycle analysis for the active compound **13p** in DU145 indicated that **13p** may induce G1 arrest.

4. Experimental protocols

4.1. General methods

Melting points were determined on a Beijing Keyi XT5 apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Thermo Nicolet (IR200) Spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400 and 100 MHz with TMS as internal standard. Mass spectra were taken by Waters Q-Tof micro mass spectrometer.

4.1.1. 4-(Methylthio)acetophenone (*7*)

To a cold (−5 °C) solution of $AlCl_3$ (6.5 g, 0.049 mol) in $CHCl_3$ (50 mL) was added acetyl chloride (205 mL, 2.88 mol) while cooling to maintain the temperature at −5 °C. Thioanisole **6** (5.08 g, 0.041 mol) dissolved in $CHCl_3$ (20 mL) was then dropwise added with cooling to maintain the temperature below 5 °C, the ice bath was then removed, and the mixture was stirred for 1.5 h until finish. Ice H_2O (100 mL) was slowly added, the mixture was well stirred, dropwise added chlorohydric acid, and the layers were separated. The organic layer was washed with H_2O (2 × 100 mL), sat. $NaHCO_3$ (2 × 100 mL), then brine and dried (Na_2SO_4). The solvent was evaporated and the residue was recrystallized in alcohol. The solid was filtered and air-dried to afford 6.66 g (98%) of **7** as a white needle crystal. Mp 80–82 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.91 (d, $J = 1.44$ Hz, 2H, H–Ph), 7.25 (d, $J = 8.52$ Hz, 2H, H–Ph), 2.56 (s, 3H, CH_3), 2.51 (s, 3H, CH_3).

4.1.2. 4-(Methylsulfonyl)acetophenone (*8*)

To a solution of 4-(methylthio)acetophenone (**7**, 5.5 g, 33 mmol) in glacial acetic acid (15 mL) was added 30% H_2O_2 (8.5 mL, 82.5 mmol), 98% H_2SO_4 (1 mL, 5.5 mmol) was then added in drop with cooling to maintain the temperature at 0 °C, the mixture was well stirred over 30 min. The mixture was further stirred at 70 °C for 1.5 h, ice H_2O (100 mL) was slowly added, the mixture was well stirred, then filtered and the filtrate was washed with H_2O (100 mL), and the filtrate was dried under vacuum to give 4-(methylsulfonyl)acetophenone **8** (6.5 g, 99%). Mp 124–125 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.13 (d, $J = 8.48$ Hz, 2H, H–Ph), 8.05 (d, $J = 8.52$ Hz, 2H, H–Ph), 3.09 (s, 3H, CH_3), 2.68 (s, 3H, CH_3).

4.1.3. 2-Bromo-1-(4-(methylsulfonyl)phenyl)ethanone (*9*)

To a solution of 4-(methylsulfonyl)acetophenone (**8**, 2.0 g, 0.01 mol) in glacial acetic acid (10 mL) at r.t. was added 48% HBr a drop, well stirred over 5 min, followed by a solution of bromine (0.5 mL, 0.01 mol) dissolved in 5 mL glacial acetic acid was added in drop about 0.5 mL, the solution was orange yellow, raise the temperature to 58 °C, after 0.5 h the solution changed to white. Then it was cooled to 25 °C and the remaining bromine and glacial acid solution was added in drop. The mixture was stirred for 2 h, after completion of the reaction, ice H_2O (100 mL) was added and solid precipitated then filtered and the filtrate was dried under vacuum to give 2.35 g of **5** (85%). Mp 129–131 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.19 (m, 2H, H–Ph), 8.10 (m, 2H, H–Ph), 4.48 (s, 2H, CH_2), 3.12 (s, 3H, CH_3).

4.1.4. General procedure for the synthesis of rofecoxib (*2*) and its analogs (*11a*,*b*)

50% NaOH (0.8 mL, 15 mmol) was slowly added with stirring to a solution of phenyl acetic acid (2.0 g, 15 mmol) or 2-chlorophenylacetic acid (2.0 g, 12 mmol) or 4-fluorophenylacetic acid (2.0 g, 13 mmol) in DMF (60 mL). Stirring was continued for

1 h at r.t., and 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (**9**, 3.45 g, 12.5 mmol) was added. The mixture was stirred for another 1 h, followed by diisopropylamine (3.8 mL) was slowly added. Stirring was continued for 4 h at 60 °C, and the mixture was acidified with 2 N HCl (a color change from dark brown to light yellow was observed). Then, ice and H_2O (50 mL) were added and the stirring continued for a few minutes. The precipitate was filtered and rinsed with H_2O. The crude wet solid was dried under vacuum to give **2** (3.56 g, 76%). Mp 208–209 °C (lit. 212–214 °C) [22]; IR (KBr): 1747 (C=O), 1149 (C–O),1309 (–CH_3), 1600, 1620, 1580 (C=C, Ph), 3018 (–ArH), 774, 693 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.91 (d, J = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.51 (d, J = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.40 (m, 5H, H–phenyl), 5.20 (s, 2H, CH_2), 3.08 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 172.58 (C_2=O), 153.48, 141.78, 136.16, 129.44, 129.08, 128.94, 128.45, 128.04, 70.34 (C_5), 44.22 (SCH_3); $C_{17}H_{14}O_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 315.0674 (calcd. 315.0691).

11a (2.52 g, 72%). Mp 193–195 °C; IR (KBr): 1741 (C=O), 1150 (C–O), 1308 (–CH_3), 1600, 1620, 1580 (C=C, Ph), 3018 (–ArH), 774, 693 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.92 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.51 (m, 1H, 2-chlorophenyl), 7.42 (d, J = 8.3 Hz, 2H, 4-methylsulfanyl-phenyl, H-2, H-6), 7.40 (m, 2H, 2-chlorophenyl), 7.31 (m, 1H, 2-chlorophenyl), 5.36 (d, J = 18.2 Hz, 2H, CH_2), 3.05 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.80 (C_2=O), 155.36, 142.26, 135.65, 133.52, 131.09, 130.91, 130.36, 129.01, 128.14, 127.91, 127.58 70.39 (C_5), 44.29 (SCH_3); $C_{17}H_{13}ClO_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 349.0299 (calcd. 349.0301).

11b (2.62 g, 73%). Mp 304–306 °C; IR (KBr): 1753 (C=O), 1151 (C–O), 1302 (–CH_3), 1620, 1580, 1424 (C=C, Ph), 3018 (–ArH), 706, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.96 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.51 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.40 (m, 2H, 4-fluorophenyl), 7.10 (m, 2H, 4-fluorophenyl), 5.19 (s, 2H, CH_2), 3.09 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 172.40 (C_2=O), 164.53, 162.04, 153.47, 142.13, 136.15, 131.26, 131.18, 129.57, 128.45, 128.29, 127.99, 125.06, 116.35, 116.13, 70.41 (C_5), 44.29 (SCH_3); $C_{17}H_{13}FO_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 333.0586 (calcd. 333.0597).

4.1.5. General procedure for the synthesis of 5-alkylidene substituted-3-phenylfuran-4-(4-methanesulfonyl phenyl)-2-ones (**12a–p**), (**13a–q**) and (**14a–q**)

Compound **2a** or **11a** or **11b** (0.01 mol) and anhydrous sodium carbonate (0.01 mol) were dissolved in methanol solution, then the corresponding aldehyde or ketone (0.012 mol) was added. The mixture was stirred at 65 °C for 3–8 h and the reaction was monitored by TLC until completion. Most of the target product can be precipitated from the reaction system. Filtration and drying was done to give a series of target compounds **12**, **13** and **14**. When the ketone was acetone the target product cannot be precipitated from reaction system. The reaction solution was evaporated under reduced pressure to steam out of most of the methanol, the reaction mixture was washed with water and ethyl acetate, dried and purified by column chromatography.

4.1.5.1. (5Z)-5-Benzylidene-4-(4-(methylsulfonyl)phenyl)-3-phenylfuran-2(5H)-one (**12a**).

This product was obtained as a yellow crystal in 90% yield. Mp 259–261 °C; IR (KBr) ν: 1780 (C=O), 1600, 1460 (C=C, Ph), 1310 (–CH_3), 1148 (C–O), 3020 (–ArH), 2910 (–CH–), 779, 695 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.07 (d, J = 8.1 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.79 (d, J = 7.5 Hz, 2H, phenyl–H), 7.58 (d, J = 8.1 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.34 (overlap, 8H, phenyl–H), 5.90 (s, 1H, =C_6H), 3.17 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.96 (C_2=O), 147.94, 147.52, 141.59, 136.28, 132.80, 130.73, 130.34, 129.50, 129.35, 129.17, 128.90, 128.64, 128.46, 128.18, 126.38, 113.62 (C_6), 44.35 (SCH_3); $C_{24}H_{18}O_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 403.0999 (calcd. 403.1004).

4.1.5.2. (5Z)-5-(3-Nitrobenzylidene)-4-(4-(methylsulfonyl)phenyl)-3-phenylfuran-2(5H)-one (**12b**).

This product was obtained as a yellow crystal in 90% yield. Mp 289–291 °C; IR (KBr) ν: 1780 (C=O), 1630 (C=C, Ph), 1354 (–CH_3), 1165 (C–O), 1525 (NO_2), 3020 (–ArH), 775, 691 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.44 (s, 1H, 3-nitrobenzylidene, H-2), 8.30 (d, J = 7.9 Hz, 1H, 3-nitrobenzylidene, H-4), 8.18 (d, J = 7.8 Hz, 1H, 3-nitrobenzylidene, H-6), 8.11 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.64 (m, 1H, 3-nitrobenzylidene, H-5), 7.60 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.35 (m, 5H, phenyl), 5.93 (s, 1H, =C_6H), 3.19 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.25 (C_2=O), 149.35, 148.50, 147.42 (C_5), 141.96, 135.75, 134.42, 130.28, 130.00, 129.87, 129.25, 128.80, 128.44, 127.97, 127.74, 125.04, 123.53, 110.25, 44.39 (SCH_3); $C_{24}H_{17}NO_6S$; HR-MS (ESI) m/z: found $[M + H]^+$ 448.0836 (calcd. 448.0855).

4.1.5.3. (5Z)-5-(2-Methoxybenzylidene)-4-(4-(methylsulfonyl) phenyl)-3-phenylfuran-2(5H)-one (**12c**).

This product was obtained as a yellow crystal in 92% yield. Mp 253–255 °C; IR (KBr) ν: 1780 (C=O), 1483, 1464, 1592 (C=C, Ph), 1311 (–CH_3), 1247 (–OCH_3), 1152 (C–O), 3020 (–ArH), 775, 694 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.31 (m, 1H, H–Ph), 8.06 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.60 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.33 (m, 5H, phenyl), 7.26–6.87 (m, 3H, H–Ph), 6.50 (s, 1H, =C_6H), 3.80 (s, 3H, OCH_3), 3.17 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.25 (C_2=O), 157.62, 148.26, 147.22 (C_5), 141.42, 136.47, 131.66, 131.05, 130.49, 129.84, 129.57, 129.24, 129.10, 128.72, 128.62, 128.07, 125.97, 121.83, 121.18, 110.50, 107.71, 55.63, 44.39 (SCH_3); $C_{25}H_{20}O_5S$; HR-MS (ESI) m/z: found $[M + H]^+$ 433.1101 (calcd. 433.1110).

4.1.5.4. (5Z)-5-(3,4,5-Trimethoxybenzylidene)-4-(4-(methylsulfonyl) phenyl)-3-phenylfuran-2(5H)-one (**12d**).

This product was obtained as a yellow crystal in 90% yield. Mp 239–241 °C; IR (KBr) ν: 1780 (C=O), 1640, 1577, 1504, 1449 (C=C, Ph), 1310 (–CH_3), 1256 (–OCH_3), 1124 (C–O), 3020 (–ArH), 778, 663 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.08 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.58 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.33 (m, 5H, phenyl–H), 7.04 (s, 2H, Ph), 5.78 (s, 1H, =C_6H), 3.91 (s, 6H, OCH_3), 3.90 (s, 3H, OCH_3), 3.18 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.23 (C_2=O), 153.73, 148.37, 147.43, 141.98, 139.96, 136.82, 130.78, 129.73, 129.58, 129.08, 128.98, 128.78, 128.62, 126.24, 114.14, 108.37, 101.65, 61.46 (OCH_3), 56.69 (OCH_3), 44.73 (SCH_3); $C_{27}H_{24}O_7S$; HR-MS (ESI) m/z: found $[M + H]^+$ 493.1314 (calcd. 493.1321).

4.1.5.5. (5Z)-5-((Furan-2-yl)methylene)-4-(4-(methylsulfonyl) phenyl)-3-phenylfuran-2(5H)-one (**12e**).

This product was obtained as a yellow crystal in 88% yield. Mp 229–231 °C; IR (KBr) ν: 1770 (C=O), 1647, 1466 (C=C, Ph), 1315 (–CH_3), 1157 (C–O), 3050 (–ArH), 773, 693 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.06 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.57 (d, J = 8.2 Hz, 2H, 4-methylsulfanyl-phenyl, H-2, H-6), 7.52 (d, J = 1.2 Hz, 1H, furan–H), 7.34 (m, 5H, phenyl–H), 7.15 (d, J = 3.5 Hz, 1H, furan–H), 6.58 (m, 1H, furan–H), 5.96 (s, 1H, =C_6H), 3.16 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.60 (C_2=O), 149.16, 146.80 (C_5), 145.52, 144.56, 141.59, 136.02, 130.22, 129.35, 129.10, 128.67, 128.53, 128.26, 126.08, 115.81, 113.36, 101.89 (C_6), 44.40 (SCH_3); $C_{22}H_{16}O_5S$; HR-MS (ESI) m/z: found $[M + H]^+$ 393.0766 (calcd. 393.0797).

*4.1.5.6. (5Z)-5-(4-Hydroxy-3-methoxybenzylidene)-4-(4-(methylsulfonyl)phenyl)-3-phenylfuran-2(5H)-one (**12f**).* This product was obtained as a yellow crystal in 90% yield. Mp 270–271 °C; IR (KBr) ν: 3478 (−OH),1770 (C═O), 1572, 1560, 1517 (C═C, Ph), 1317 (−CH_3), 1266 (−OCH_3), 1147 (C−O), 777, 663 (C═H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.06 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.58 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.47 (d, J = 1.3 Hz, 1H, H−Ph), 7.30 (m, 5H, phenyl−H), 7.22 (d, J = 1.3 Hz, 1H, H−Ph), 6.92 (d, J = 8.3 Hz, 1H, H−Ph), 6.22 (s, 1H, O*H*), 5.82 (s, 1H, ═C_6H), 3.97 (s, 3H, OCH_3), 3.17 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.11 (C_2═O), 148.05, 147.55, 146.88, 145.90, 141.43, 136.55, 130.38, 129.12, 128.74, 128.62, 128.14, 125.54, 125.08, 114.87, 114.19, 112.42, 56.14, 44.37 (SCH_3); $C_{25}H_{20}O_6S$; HR-MS (ESI) m/z: found $[M + H]^+$ 449.1042 (calcd. 449.1059).

*4.1.5.7. (5Z)-5-(4-Hydroxybenzylidene)-4-(4-(methylsulfonyl) phenyl)-3-phenylfuran-2(5H)-one (**12g**).* This product was obtained as a yellow crystal in 84% yield. Mp 287–289 °C; IR (KBr) ν: 3371 (−OH), 1780 (C═O), 1595, 1581, 1511, 1436 (C═C, Ph), 1304 (−CH_3), 1170 (C−O), 2960 (−CH−), 778, 693 (C═H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.07 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.71 (d, J = 8.7 Hz, 2H, H−Ph), 7.61 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.29 (m, 5H, phenyl−H), 6.90 (d, J = 8.7 Hz, 2H, H−Ph), 5.85 (s, 1H, ═C_6H), 3.17 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.70 (C_2═O), 157.73, 148.22, 144.34, 138.11, 137.62, 132.63, 128.7, 128.2, 127.8, 126.4, 122.4, 115.8, 100.6, 44.3. $C_{24}H_{18}O_5S$; HR-MS (ESI) m/z: found $[M + H]^+$ 419.0941 (calcd. 419.0953).

*4.1.5.8. (5Z)-5-(4-Fluorobenzylidene)-4-(4-(methylsulfonyl)phenyl)-3-phenylfuran-2(5H)-one (**12h**).* This product was obtained as a yellow crystal in 86% yield. Mp 301–303 °C; IR (KBr) ν: 1780 (C═O), 1620, 1580, 1482, 1395 (C═C, Ph), 1315 (−CH_3), 1149 (C−O), 3020 (−ArH), 2910 (−CH−), 772, 690 (C═H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.09 (d, J = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.70 (d, J = 8.0 Hz, 2H, Ph), 7.64 (d, J = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.53 (d, J = 8.0 Hz, 2H, Ph), 7.34 (m, 5H, phenyl−H), 5.94 (s, 1H, ═C_6H), 3.21 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.59 (C_2═O), 148.40, 148.02, 141.90, 135.57, 132.20, 132.10, 132.04, 130.40, 129.43, 129.25, 128.65, 128.56, 128.19, 126.51, 123.42, 112.12 (C_6), 44.22 (SCH_3); $C_{24}H_{17}BrO_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 481.0102 (calcd. 481.0109).

*4.1.5.9. (5Z)-5-(4-Chlorobenzylidene)-4-(4-(methylsulfonyl)phenyl)-3-phenylfuran-2(5H)-one (**12i**).* This product was obtained as a yellow crystal in 85% yield. Mp 307–308 °C; IR (KBr) ν: 1780 (C═O), 1637, 1583, 1488, 1406 (C═C, Ph), 1310 (−CH_3), 1149 (C−O), 3020 (−ArH), 2910 (−CH−), 776, 695 (C═H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.09 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.75 (d, J = 8.6 Hz, 2H, H−Ph), 7.64 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.35 (overlap, 7H, H−Ph), 5.92 (s, 1H, ═C_6H), 3.20 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.63 (C_2═O), 148.03, 147.68, 141.58, 135.65, 134.98, 131.81, 131.57, 131.37, 130.24, 129.34, 129.07, 128.97, 128.55, 128.26, 128.17, 126.38, 112.06 (C_6), 44.19 (SCH_3); $C_{24}H_{17}ClO_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 437.0611 (calcd. 437.0614).

*4.1.5.10. (5Z)-5-((Z/E)-3,7-Dimethylocta-2,6-dienylidene)-4-(4-(methylsulfonyl)phenyl)-3-phenylfuran-2(5H)-one (**12j**).* This product was obtained as a yellow crystal in 80% yield. Mp 114–116 °C; IR (KBr) ν: 1780 (C═O), 1625, 1602 (C═C, Ph), 1313 (−CH_3), 1155 (C−O), 2950 (−CH−), 775, 694 (C═H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.11 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.62 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.38 (overlap, 5H, phenyl−H), 6.63 (d, J = 11.8 Hz, 1H, ═C_6H), 6.01 (dd, J = 11.8 Hz, J = 4.4 Hz, 1H, ═C_7H), 5.16 (t, J = 6.4 Hz, 1H, C*H*═C(CH_3)$_2$), 3.22 (s, 3H, SCH_3), 2.25 (m, 4H, CH_2), 1.87 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 1.70 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.70 (C_2═O), 149.39, 146.45, 141.45, 136.54, 132.46, 130.25, 129.15, 129.09, 128.90, 128.56, 128.50, 128.10, 126.04, 123.18, 123.09, 111.00 (C_6), 44.37 (SCH_3), 40.67 (CH_3), 26.49 (CH_3), 25.72 (CH_3), 17.76 (CH_2), 17.61 (CH_2); $C_{27}H_{28}O_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 449.1745 (calcd. 449.1787).

*4.1.5.11. (5Z)-5-(4-(Dimethylamino)benzylidene)-4-(4-(methylsulfonyl)phenyl)-3-phenylfuran-2(5H)-one (**12k**).* This product was obtained as a red crystal in 95% yield. Mp 244–246 °C; IR (KBr) ν: 1770 (C═O), 1590, 1578, 1530 (C═C, Ph), 1314 (−CH_3), 1371 (C−N), 1164 (C−O), 779, 663 (C═H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.04 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.71 (d, J = 8.2 Hz, 2H, 4-methylsulfanyl-phenyl, H-2, H-6), 7.57 (d, J = 8.8 Hz, 2H, H−Ph), 7.33 (m, 5H, phenyl−H), 6.68 (d, J = 8.8 Hz, 2H, H−Ph), 5.84 (s, 1H, ═C_6H), 3.16 (s, 3H, SCH_3), 3.06 (s, 6H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.60 (C_2═O), 147.95, 144.57, 141.18, 137.07, 132.72, 130.44, 129.27, 128.66, 128.52, 128.02, 123.40, 115.21, 111.94 (C_6), 44.40 (SCH_3), 40.10 (NCH_3); $C_{26}H_{23}NO_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 446.1421 (calcd. 446.1426).

*4.1.5.12. (5Z)-5-((Benzo[d][1,3]dioxol-5-yl)methylene)-4-(4-(methylsulfonyl)phenyl)-3-phenylfuran-2(5H)-one (**12l**).* This product was obtained as a yellow crystal in 91% yield. Mp 261–263 °C; IR (KBr) ν: 1750 (C═O), 1610 (C═C, Ph), 1309 (−CH_3), 1163 (C−O), 1232 (−OCH_2−), 3020 (−ArH), 774, 693 (C═H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.06 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.57 (d, J = 8.2 Hz, 2H, 4-methylsulfanyl-phenyl, H-2, H-6), 7.54 (s, 1H, substituent phenyl, H-2), 7.35 (m, 5H, H−phenyl), 7.12 (d, J = 8.2 Hz, 1H, substituent phenyl, H-5), 6.82 (d, J = 8.2 Hz, 1H, substituent phenyl, H-6), 6.03 (s, 2H, CH_2), 5.81 (s, 1H, ═C_6H), 3.17 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.03 (C_2═O), 148.95, 148.40, 147.91, 146.17 (C_5), 141.46, 136.42, 130.36, 129.19, 129.12, 128.63, 128.17, 127.23, 126.52, 125.48, 113.75, 110.00, 108.65, 101.65, 44.37 (SCH_3); $C_{25}H_{18}O_6S$; HR-MS (ESI) m/z: found $[M + H]^+$ 447.0898 (calcd. 447.0902).

*4.1.5.13. (5Z)-5-(4-Methoxybenzylidene)-4-(4-(methylsulfonyl) phenyl)-3-phenylfuran-2(5H)-one (**12m**).* This product was obtained as a yellow crystal in 90% yield. Mp 268–270 °C; IR (KBr) ν: 1780 (C═O), 1599, 1567, 1510 (C═C, Ph), 1330 (−CH_3), 1253 (−OCH_3), 1178 (C−O), 3020 (−ArH), 769, 693 (C═H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.06 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.77 (d, J = 8.8 Hz, 2H, H−Ph), 7.58 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.33 (m, 5H, phenyl−H), 6.93 (d, J = 8.8 Hz, 2H, H−Ph), 5.86 (s, 1H, ═C_6H), 3.85 (s, 3H, OCH_3), 3.17 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.24 (C_2═O), 160.68, 148.01, 146.04, 141.41, 136.53, 132.58, 130.37, 129.12, 128.71, 128.61, 128.15, 125.22, 114.45, 113.74 (C_6), 55.40 (OCH_3), 44.37 (SCH_3); $C_{25}H_{20}O_5S$; HR-MS (ESI) m/z: found $[M + H]^+$ 433.1107 (calcd. 433.1110).

*4.1.5.14. (5Z)-4-(4-(Methylsulfonyl)phenyl)-5-((naphthalen-1-yl) methylene)-3-phenylfuran-2(5H)-one (**12n**).* This product was obtained as a yellow crystal in 88% yield. Mp 236–238 °C; IR (KBr) ν: 1790 (C═O), 1620, 1583, 1452, 1400 (C═C, Ph), 1310 (−CH_3), 1148 (C−O), 3020 (−ArH), 2950 (−CH−), 772, 690 (C═H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.40 (d, J = 7.60 Hz, 1H, H−Ar), 8.14 (d, J = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.88 (m, 2H, H−Ar), 7.82 (m, 1H, H−Ph), 7.69 (d, J = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6),7.60 (m, 1H, H−Ph), 7.40 (m, 2H,

H–Ph), 7.38 (m, 2H, H–Ph), 7.34 (m, 3H, H–Ph), 6.72 (s, 1H, =C_6H), 3.20 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.11 (C_2=O), 148.50, 147.85, 141.79, 136.43, 133.69, 131.58, 130.44, 130.15, 129.98, 129.43, 129.27, 129.17, 128.70, 128.62, 128.52, 128.31, 126.99, 126.76, 126.09, 125.87, 122.69, 109.47 (C_6), 44.40 (SCH_3); $C_{28}H_{20}O_4S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 453.1158 (calcd. 453.1161).

*4.1.5.15. 4-(4-(Methylsulfonyl)phenyl)-3-phenyl-5-(propan-2-ylidene)furan-2(5H)-one (**12o**).* This product was obtained as yellow oil in 70% yield. IR (KBr) *ν*: 1780 (C=O), 1653, 1600, 1580, 1440 (C=C, Ph), 1312 (–CH_3), 1156 (C–O), 2960 (–CH–), 772, 694 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.03 (d, *J* = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.53 (d, *J* = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.23 (s, 5H, phenyl–H), 3.12 (s, 3H, SCH_3), 2.11 (m, 3H, CH_3), 1.44 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.70 (C_2=O), 146.26, 143.37, 141.16, 139.31, 129.89, 129.06, 128.91, 128.63, 128.39, 128.12, 128.09, 126.16, 44.43 (SCH_3), 21.24 (CH_3), 19.52 (CH_3); $C_{20}H_{18}O_4S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 355.1000 (calcd. 355.1004).

*4.1.5.16. 5-Methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenylfuran-2(5H)-one (**12p**).* This product was obtained as yellow oil in 63% yield. IR (KBr) *ν*: 1784 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.92 (d, *J* = 8.8 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.65 (d, *J* = 8.8 Hz, 2H, 4-methylsulfanyl-phenyl, H-2, H-6), 7.39–7.27 (m, 5H, phenyl–H), 3.46 (s, 3H, SCH_3), 3.09 (s, 3H, OCH_3), 1.67 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.82 (C_2=O), 153.32, 141.75, 135.88, 131.23, 129.81, 129.63, 129.43, 128.92, 128.56, 127.87, 107.44, 50.82, 44.24, 23.21; $C_{19}H_{18}O_5S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 359.0950 (calcd. 359.0953).

*4.1.5.17. (Z)-5-Benzylidene-3-(2-chlorophenyl)-4-(4-(methylsulfonyl) phenyl)furan-2(5H)-one (**13a**).* This product was obtained as a yellow crystal in 93% yield. Mp 168–170 °C; IR (KBr) *ν*: 1764 (C=O), 1630, 1620, 1460 (C=C, Ph), 1314 (–CH_3), 1147 (C–O), 3020 (–ArH), 2910 (–CH–), 753, 695 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.00 (d, *J* = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.85 (d, *J* = 7.2 Hz, 2H, phenyl–H), 7.52 (d, *J* = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.43–7.24 (m, 7H, phenyl–H), 6.09 (s, 1H, =C_6H), 3.11 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.19 (C_2=O), 151.46, 147.03, 141.63, 135.66, 133.82, 132.63, 131.61, 130.92, 130.77, 130.14, 129.97, 129.80, 128.97, 127.92, 127.11, 126.37, 114.59 (C_6), 44.32 (SCH_3); $C_{24}H_{17}ClO_4S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 437.0611 (calcd. 437.0614).

*4.1.5.18. (Z)-5-(3-Nitrobenzylidene)-3-(2-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**13b**).* This product was obtained as a yellow crystal in 89% yield. Mp 130–132 °C; IR (KBr) *ν*: 1780 (C=O), 1630 (C=C, Ph), 1311 (–CH_3), 1154 (C–O), 1533 (NO_2), 1349 (C–N), 3020 (–ArH), 780, 669 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.49 (s, 1H, 3-nitrobenzylidene, H-2), 8.33 (d, *J* = 7.8 Hz, 1H, 3-nitrobenzylidene, H-4), 8.22 (d, *J* = 8.2 Hz, 1H, 3-nitrobenzylidene, H-6), 8.03 (d, *J* = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.66 (m, 1H, 3-nitrobenzylidene, H-5), 7.53 (d, *J* = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.44–7.22 (m, 4H, phenyl), 6.13 (s, 1H, =C_6H), 3.12 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 166.38 (C_2=O),151.11, 148.84, 148.55, 142.04, 135.90, 135.07, 134.24, 133.76, 131.49, 131.11, 130.25, 130.05, 129.90, 128.13, 127.85, 127.48, 127.21, 125.22, 123.79, 111.17, 44.33 (SCH_3); $C_{24}H_{16}ClNO_6S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 482.0456 (calcd. 482.0465).

*4.1.5.19. (Z)-5-(2-Methoxybenzylidene)-3-(2-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**13c**).* This product was obtained as a yellow crystal in 90% yield. Mp 211–212 °C; IR (KBr) *ν*: 1780 (C=O), 1610, 1595, 1487, 1465 (C=C, Ph), 1321 (–CH_3), 1237 (–OCH_3), 1151 (C–O), 3020 (–ArH), 756, 648 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.33 (d, *J* = 7.2 Hz, 1H, H–Ph), 7.98 (d, *J* = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.52 (d, *J* = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.41–7.23 (m, 6H, phenyl), 7.08 (m, 1H, phenyl), 6.91 (d, *J* = 8.3 Hz, 1H, H–Ph), 6.68 (s, 1H, =C_6H), 3.82 (s, 3H, OCH_3), 3.11 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.46 (C_2=O), 157.76, 151.60, 146.70, 141.43, 135.89, 133.87, 131.76, 131.67, 131.34, 130.64, 130.11, 130.06, 128.22, 127.80, 127.08, 125.76, 121.62, 121.18, 110.52, 108.65, 55.65 (OCH_3), 44.31 (SCH_3); $C_{25}H_{19}ClO_5S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 467.0713 (calcd. 467.0720).

*4.1.5.20. (Z)-5-(3,4,5-Trimethoxybenzylidene)-3-(2-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**13d**).* This product was obtained as a yellow crystal in 88% yield. Mp 261–263 °C; IR (KBr) *ν*: 1780 (C=O), 1640, 1575, 1504, 1449, 1414 (C=C, Ph), 1323 (–CH_3), 1251 (–OCH_3), 1122 (C–O), 3020 (–ArH), 778, 663 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.00 (d, *J* = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.51 (d, *J* = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.42–7.21 (m, 4H, 2-chlorophenyl), 7.08 (s, 2H, Ph), 5.97 (s, 1H, =C_6H), 3.92 (s, 6H, OCH_3), 3.91 (s, 3H, OCH_3), 3.12 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.23 (C_2=O), 153.35, 151.44, 146.50, 141.62, 135.75, 133.87, 131.63, 130.73, 130.14, 129.98, 128.15, 128.06, 127.91, 127.10, 125.83, 114.62, 108.14, 61.06 (OCH_3), 56.29 (OCH_3), 44.26 (SCH_3); $C_{27}H_{23}ClO_7S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 528.1001 (calcd. 528.1010).

*4.1.5.21. (Z)-3-(2-Chlorophenyl)-5-(furan-2-ylmethylene)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**13e**).* This product was obtained as a yellow crystal in 89% yield. Mp 207–209 °C; IR (KBr) *ν*: 1770 (C=O), 1646, 1616, 1474 (C=C, Ph), 1307 (–CH_3), 1148 (C–O), 3050 (–ArH), 776, 694 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.98 (d, *J* = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.55 (d, *J* = 1.2 Hz, 1H, furan–H), 7.49 (d, *J* = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.39–7.19 (m, 5H, Ar–H), 6.61 (m, 1H, furan–H), 6.16 (s, 1H, =C_6H), 3.10 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 166.82 (C_2=O), 150.31, 149.03, 144.96, 144.83, 141.65, 135.46, 133.80, 131.63, 130.75, 130.17, 129.79, 127.9, 127.11, 125.98, 116.32, 113.44, 102.79 (C_6), 44.35 (SCH_3); $C_{22}H_{15}ClO_5S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 427.0403 (calcd. 427.0407).

*4.1.5.22. (Z)-5-(4-Hydroxy-3-methoxybenzylidene)-3-(2-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**13f**).* This product was obtained as a yellow crystal in 90% yield. Mp 218–220 °C; IR (KBr) *ν*: 3480 (–OH), 1770 (C=O), 1591, 1514, 1450, 1430 (C=C, Ph), 1360 (–CH_3), 1287 (–OCH_3), 1141 (C–O), 777, 663 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.99 (d, *J* = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.53 (s, 1H, phenyl–H), 7.50 (d, *J* = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.41–7.21 (m, 5H, phenyl–H), 6.95 (d, *J* = 8.3 Hz, 1H, H–Ph), 6.01 (s, 1H, =C_6H), 5.4–5.8 (br, 1H, O*H*), 3.99 (s, 3H, OCH_3), 3.11 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.29 (C_2=O), 151.47, 147.67, 146.84, 145.43, 141.50, 135.91, 133.89, 131.68, 130.61, 130.11, 129.98, 128.23, 127.91, 127.86, 127.07, 126.04, 125.44, 125.07, 115.06, 114.81, 112.42, 56.17 (OCH_3), 44.31 (SCH_3); $C_{25}H_{19}ClO_6S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 483.0664 (calcd. 483.0669).

*4.1.5.23. (Z)-5-(4-Hydroxybenzylidene)-3-(2-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**13g**).* This product was obtained as a yellow crystal in 86% yield. Mp 198–200 °C; IR (KBr) *ν*: 3285 (–OH), 1780 (C=O), 1602, 1580, 1480, 1442 (C=C, Ph), 1313 (–CH_3), 1160 (C–O), 2960 (–CH–), 763, 650 (C=H, Ph) cm^{-1}; ^{1}H

NMR (400 MHz, $CDCl_3$, TMS): δ 7.99 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.78 (d, J = 8.6 Hz, 2H, 4-hydroxyphenyl), 7.51 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.47–7.21 (m, 4H, phenyl–H), 6.91 (d, J = 8.6 Hz, 2H, 4-hydroxyphenyl), 5.34 (s, 1H, =C_6H), 3.11 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.49 (C_2=O), 157.01, 148.25, 138.41, 137.66, 135.34, 131.27, 129.47, 128.87, 128.24, 127.89, 127.87, 127.79, 126.85, 122.47, 115.86, 100.69, 44.30. $C_{24}H_{17}ClO_5S$; HR-MS (ESI) m/z: found $[M + H]^+$ 453.0557 (calcd. 453.0563).

*4.1.5.24. (Z)-5-(4-Bromobenzylidene)-3-(2-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**13h**).* This product was obtained as a yellow crystal in 85% yield. Mp 194–196 °C; IR (KBr) ν: 1780 (C=O),1632, 1580, 1481, 1397 (C=C, Ph), 1309 (–CH_3), 1147 (C–O), 3020 (–ArH), 2910 (–CH–), 768, 690 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.00 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.71 (d, J = 8.5 Hz, 2H, Ph), 7.56 (d, J = 8.5 Hz, 2H, Ph), 7.51 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.42–7.21 (m, 4H, phenyl–H), 6.01 (s, 1H, =C_6H), 3.11 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 166.85 (C_2=O), 151.34, 147.47, 141.84, 135.46, 133.81, 132.21, 132.18, 131.59, 131.56, 130.86, 130.17, 129.94, 127.95, 127.87, 127.12, 126.79, 124.21, 113.07 (C_6), 44.30 (SCH_3); $C_{24}H_{16}BrClO_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 514.9713 (calcd. 514.9719).

*4.1.5.25. (Z)-5-(4-Chlorobenzylidene)-3-(2-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**13i**).* This product was obtained as a yellow crystal in 85% yield. Mp 173–175 °C; IR (KBr) ν: 1780 (C=O), 1637, 1580, 1492, 1400 (C=C, Ph), 1311 (–CH_3), 1150 (C–O), 3020 (–ArH), 2910 (–CH–), 776, 695 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.00 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.78 (d, J = 8.5 Hz, 2H, H–Ph), 7.51 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.41 (d, J = 8.5 Hz, 2H, H–Ph), 7.42–7.22 (m, 4H, 2-chlorophenyl), 6.04 (s, 1H, =C_6H), 3.11 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 166.94 (C_2=O), 151.32, 147.30, 141.74, 135.77, 135.49, 133.79, 132.01, 131.57, 131.13, 130.87, 130.18, 129.93, 129.26, 127.98, 127.81, 127.14, 126.66, 113.08 (C_6), 44.32 (SCH_3); $C_{24}H_{16}Cl_2O_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 471.0219 (calcd. 471.0225).

*4.1.5.26. (Z)-5-(4-Fluorobenzylidene)-3-(2-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**13j**).* This product was obtained as a yellow crystal in 88% yield. Mp 257–258 °C; IR (KBr) ν: 1780 (C=O), 1630, 1597, 1506, 1460 (C=C, Ph), 1310 (–CH_3), 1149 (C–O), 3020 (–ArH), 2910 (–CH–), 768, 690 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.00 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.84 (d, J = 3.4 Hz, 2H, Ph), 7.51 (d, J = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.40–7.10 (m, 6H, phenyl–H), 6.05 (s, 1H, =C_6H), 3.11 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.06 (C_2=O), 164.56, 162.05, 151.40, 146.71, 141.72, 135.57, 133.82, 132.94, 132.86, 131.59, 130.81, 130.15, 129.93, 128.99, 128.96, 127.94, 127.11, 126.31, 116.30, 116.08, 113.24 (C_6), 44.30 (SCH_3); $C_{24}H_{16}ClFO_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 455.0517 (calcd. 455.0520).

*4.1.5.27. (Z)-5-(4-(Dimethylamino)benzylidene)-3-(2-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**13k**).* This product was obtained as a red crystal in 87% yield. Mp 250–252 °C; IR (KBr) ν: 1770 (C=O), 1578, 1557, 1526, 1420 (C=C, Ph), 1310 (–CH_3), 1370 (C–N), 1160 (C–O), 770, 665 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.96 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.76 (d, J = 8.9 Hz, 2H, H–Ph), 7.50 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.37–7.23 (m, 4H, phenyl–H), 6.70 (d, J = 8.9 Hz, 2H, H–Ph), 6.02 (s, 1H, =C_6H), 3.10 (s, 3H, SCH_3), 3.06 (s, 6H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.81 (C_2=O), 151.20, 151.11, 143.98, 141.19, 136.45, 133.96, 132.91, 131.83, 131.67, 131.64, 130.25, 130.00, 128.73, 127.70, 127.02, 126.95, 123.10, 120.74, 116.14, 111.88, 110.90, 44.32 (SCH_3), 40.03 (NCH_3), 39.99 (NCH_3); $C_{26}H_{22}ClNO_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 480.1027 (calcd. 480.1036).

*4.1.5.28. (Z)-3-(2-Chlorophenyl)-5-((1,3-dihydroisobenzofuran-5-yl)methylene)-4-(4-(methylsulfonyl)phenyl) furan-2(5H)-one (**13l**).* This product was obtained as a yellow crystal in 87% yield. Mp 164–166 °C; IR (KBr) ν: 1760 (C=O), 1610, 1594, 1502, 1448 (C=C, Ph), 1307 (–CH_3), 1147 (C–O), 1260 (–OCH_2–), 3020 (–ArH), 774, 695 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.00 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.59 (d, J = 1.6 Hz, 2H, H–Ph), 7.52 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.41–7.19 (m, 5H, phenyl–H), 6.87 (d, J = 8.1 Hz, 2H, H–Ph), 6.06 (s, 2H, OCH_2O), 6.02 (s, 1H, =C_6H), 3.12 (s, 3H, SCH_3), 3.06 (s, 6H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.21 (C_2=O), 151.38, 149.21, 148.48, 145.72, 141.58, 135.83, 133.88, 131.67, 130.66, 130.13, 129.97, 129.60, 128.15, 127.88, 127.09, 126.93, 126.80, 125.43, 114.67, 110.15, 108.70, 101.71, 44.33 (SCH_3); $C_{26}H_{19}ClO_5S$; HR-MS (ESI) m/z: found $[M + H]^+$ 479.0716 (calcd. 479.0720).

*4.1.5.29. (Z)-5-(4-Methoxybenzylidene)-3-(2-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**13m**).* This product was obtained as a yellow crystal in 90% yield. Mp 200–202 °C; IR (KBr) ν: 1780 (C=O), 1592, 1580, 1508 (C=C, Ph), 1303 (–CH_3), 1263 (–OCH_3),1159 (C–O), 3020 (–ArH), 773, 649 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.98 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.82 (d, J = 8.8 Hz, 2H, H–Ph), 7.51 (d, J = 8.3 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.41–7.22 (m, 4H, phenyl–H), 6.96 (d, J = 8.8 Hz, 2H, H–Ph), 6.04 (s, 1H, =C_6H), 3.87 (s, 3H, OCH_3), 3.11 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.41 (C_2=O), 160.93, 151.44, 145.58, 141.53, 135.94, 133.89, 132.79, 131.69, 130.60, 130.11, 129.97, 128.24, 127.86, 127.06, 125.56, 125.18, 114.65, 114.53, 55.42 (OCH_3), 44.33 (SCH_3); $C_{25}H_{19}ClO_5S$; HR-MS (ESI) m/z: found $[M + H]^+$ 467.0718 (calcd. 467.0720).

*4.1.5.30. (Z)-3-(2-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-5-(naphthalen-1-ylmethylene)furan-2(5H)-one (**13n**).* This product was obtained as a yellow crystal in 92% yield. Mp 211–213 °C; IR (KBr) ν: 1790 (C=O), 1620, 1583, 1452, 1400 (C=C, Ph), 1314 (–CH_3), 1144 (C–O), 3020 (–ArH), 2950 (–CH–), 766, 690 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.45 (d, J = 7.2 Hz, 1H, H–Ar), 8.05 (d, J = 8.0 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.88 (m, 3H, H–Ar), 7.61 (d, J = 8.0 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.59 (m, 1H, H–Ph), 7.52 (m, 2H, H–Ph), 7.43–7.26 (m, 4H, H–Ar), 6.91 (s, 1H, =C_6H), 3.13 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.29 (C_2=O), 151.34, 148.00, 141.85, 135.81, 133.89, 133.71, 131.65, 130.80, 130.41, 130.19, 130.17, 130.03, 129.21, 128.44, 128.03, 127.13, 127.10, 126.66, 126.14, 125.86, 122.67, 110.33 (C_6), 44.33 (SCH_3); $C_{28}H_{19}ClO_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 487.0767 (calcd. 487.0771).

*4.1.5.31. 3-(2-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-5-(propan-2-ylidene)furan-2(5H)-one (**13o**).* This product was obtained as a yellow oil in 73% yield. IR (KBr) ν: 1770 (C=O), 1596, 1559, 1423 (C=C, Ph), 1312 (–CH_3), 1153 (C–O), 2960 (–CH–), 774, 682 (C=H, Ph) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.92 (d, J = 8.0 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.47 (d, J = 8.0 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.25 (m, 1H, phenyl–H), 7.16 (m, 1H, phenyl–H), 7.04 (m, 1H, phenyl–H), 3.05 (s, 3H, SCH_3), 2.11 (m, 3H, CH_3), 1.52 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.71 (C_2=O), 149.96, 143.40, 141.07, 138.08, 133.89, 131.51, 130.40, 130.32, 129.66, 129.23, 128.35, 127.74, 127.54, 126.81, 44.83

(SCH_3), 21.06 (CH_3), 19.73 (CH_3); $C_{20}H_{17}ClO_4S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 389.0612 (calcd. 389.0614).

*4.1.5.32. 3-(2-Chlorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**13p**).* This product was obtained as yellow oil in 60% yield. IR (KBr) *ν*: 1781 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 7.95 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.61–7.40 (br, 4H, phenyl–H), 3.47 (s, 3H, SCH_3), 3.08 (s, 3H, OCH_3), 1.75 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): *δ* 166.83 (C_2=O), 153.78, 149.37, 141.77, 131.23, 129.81, 129.63, 129.43, 128.92, 128.56, 127.87, 108.25, 98.62, 51.23, 50.73, 44.26, 44.20, 29.66, 24.34; $C_{19}H_{18}ClO_5S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 393.0560 (calcd. 393.0563).

*4.1.5.33. (Z)-5-(2-Chlorobenzylidene)-3-(2-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**13q**).* This product was obtained as a yellow crystal in 86% yield. Mp 200–202 °C; IR (KBr) *ν*: 1777 (C=O), 1596, 1580, 1424 (C=C, Ph), 1314 (–CH_3), 1149 (C–O), 3020 (–ArH), 2910 (–CH–), 769, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 8.32 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H, Ph), 8.11 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.63 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.42–7.37 (m, 4H, phenyl–H), 7.30 (m, 1H, phenyl–H), 6.99 (m, 1H, phenyl–H), 6.44 (s, 1H, =C_6H), 3.16 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): *δ* 167.70 (C_2=O), 164.47, 161.97, 148.35, 147.70, 141.98, 135.79, 134.65, 131.91, 131.34, 131.26, 130.67, 130.41, 130.36, 129.56, 128.35, 126.44, 124.43, 116.11, 115.89, 108.97, 44.38 (SCH_3); $C_{24}H_{16}Cl_2O_4S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 471.0219 (calcd. 471.0225).

*4.1.5.34. (Z)-5-Benzylidene-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14a**).* This product was obtained as a yellow crystal in 90% yield. Mp 245–247 °C; IR (KBr) *ν*: 1765 (C=O), 1596, 1580, 1511, 1423 (C=C, Ph), 1310 (–CH_3), 1148 (C–O), 3020 (–ArH), 2910 (–CH–), 774, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 8.10 (dd, *J* = 6.8 Hz, *J* = 2.0 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.80 (t, *J* = 8.8 Hz, *J* = 1.6 Hz, 2H, 4-fluorophenyl), 7.59 (dd, *J* = 6.8 Hz, *J* = 2.0 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.40 (m, 5H, phenyl), 7.80 (t, *J* = 17.6 Hz, *J* = 8.8 Hz, 2H, 4-fluorophenyl), 5.89 (s, 1H, =C_6H), 3.17 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): *δ* 167.91 (C_2=O), 164.50, 162.97, 147.74, 147.45, 141.85, 136.16, 132.76, 131.24, 131.15, 130.78, 130.31, 129.61, 128.95, 128.33, 125.32, 124.64, 116.04, 115.82, 113.85 (C_6), 44.37 (SCH_3); $C_{24}H_{17}FO_4S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 421.0907 (calcd. 421.0910).

*4.1.5.35. (Z)-5-(3-Nitrobenzylidene)-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14b**).* This product was obtained as a yellow crystal in 90% yield. Mp 275–277 °C; IR (KBr) *ν*: 1769 (C=O), 1596, 1512, 1423 (C=C, Ph), 1307 (–CH_3), 1155 (C–O), 1560 (NO_2), 1354 (C–N), 3020 (–ArH), 706, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 8.44 (d, *J* = 1.6 Hz, 1H, 3-nitrobenzylidene, H-2), 8.28 (d, *J* = 8.0 Hz, 1H, 3-nitrobenzylidene, H-4), 8.19 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz, 1H, 3-nitrobenzylidene, H-6), 8.14 (d, *J* = 8.0 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.63 (m, 1H, 3-nitrobenzylidene, H-5), 7.60 (d, *J* = 8.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.41 (m, 2H, 4-fluorophenyl), 7.03 (m, 2H, 4-fluorophenyl), 5.92 (s, 1H, =C_6H), 3.19 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): *δ* 167.15 (C_2=O), 162.20, 149.27, 148.56, 147.15, 142.21, 135.73, 135.58, 134.35, 131.36, 131.28, 130.21, 130.00, 128.56, 126.65, 125.05, 124.12, 123.59, 116.22, 116.00, 110.41 (C_6), 44.37 (SCH_3); $C_{24}H_{16}FNO_6S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 466.0753 (calcd. 466.0761).

*4.1.5.36. (Z)-5-(2-Methoxybenzylidene)-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14c**).* This product was obtained as a yellow crystal in 88% yield. Mp 259–260 °C; IR (KBr) *ν*: 1751 (C=O), 1596, 1560, 1424 (C=C, Ph), 1309 (–CH_3), 1230 (–OCH_3), 1151 (C–O), 3020 (–ArH), 706, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 8.30 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H, H–Ph), 8.08 (t, *J* = 8.4 Hz, *J* = 6.8 Hz, 2H, 4-methylsulfanyl-phenyl, H-3, H-5), 7.60 (dd, *J* = 6.8 Hz, *J* = 4.2 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.35 (m, 3H, phenyl), 7.06–6.97 (m, 3H, H–Ph), 6.88 (d, *J* = 8.0 Hz, 1H, H–Ph), 6.49 (s, 1H, =C_6H), 3.80 (s, 3H, OCH_3), 3.17 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): *δ* 168.15 (C_2=O), 157.67, 148.05, 147.11, 141.65, 136.31, 131.64, 131.24, 131.16, 130.42, 128.17, 124.86, 124.83, 121.78, 121.19, 115.96, 115.75, 110.55, 107.94, 55.64 (OCH_3), 44.36 (SCH_3); $C_{25}H_{19}FO_5S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 451.1011 (calcd. 451.1015).

*4.1.5.37. (Z)-5-(3,4,5-Trimethoxybenzylidene)-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14d**).* This product was obtained as a yellow crystal in 91% yield. Mp 257–259 °C; IR (KBr) *ν*: 1764 (C=O), 1596, 1560, 1506, 1442 (C=C, Ph), 1314 (–CH_3), 1260 (–OCH_3), 1129 (C–O), 3020 (–ArH), 706, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 8.11 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.59 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.38 (m, 2H, 4-fluorophenyl, H-3, H-5), 7.03 (s, 2H, Ph), 7.02 (m, 2H, 4-fluoro-phenyl, H-2, H-6), 5.77 (s, 1H, =C_6H), 3.91 (s, 6H, OCH_3), 3.90 (s, 3H, OCH_3), 3.18 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): *δ* 167.74 (C_2=O), 153.36, 147.73, 146.92, 141.84, 139.81, 136.27, 131.19, 131.10, 130.32, 128.30, 128.25, 124.75, 124.72, 116.02, 115.80, 113.90, 108.16, 61.02 (OCH_3), 56.31 (OCH_3), 44.29 (SCH_3); $C_{27}H_{23}FO_7S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 511.1221 (calcd. 511.1227).

*4.1.5.38. (Z)-3-(4-Fluorophenyl)-5-(furan-2-ylmethylene)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14e**).* This product was obtained as a yellow crystal in 87% yield. Mp 228–229 °C; IR (KBr) *ν*: 1749 (C=O), 1596, 1580, 1511, 1423 (C=C, Ph), 1310 (–CH_3), 1149 (C–O), 3050 (–ArH), 770, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 8.10 (d, *J* = 8.0 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.57 (d, *J* = 8.0 Hz, 2H, 4-methylsulfanyl-phenyl, H-2, H-6), 7.52 (d, *J* = 1.6 Hz, 1H, furan–H), 7.38 (m, 2H, 4-fluorophenyl, H-3, H-5), 7.14 (d, *J* = 3.6 Hz, 1H, furan–H), 6.99 (m, 2H, 4-fluorophenyl, H-2, H-6), 6.58 (m, 1H, furan–H), 5.95 (s, 1H, =C_6H), 3.16 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): *δ* 167.51 (C_2=O), 149.14, 146.59, 145.46, 144.66, 141.87, 135.88, 131.16, 131.07, 130.18, 128.37, 124.99, 124.75, 124.71, 116.03, 115.94, 115.82, 113.38, 102.03 (C_6), 44.38 (SCH_3); $C_{22}H_{15}FO_5S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 411.0698 (calcd. 411.0702).

*4.1.5.39. (Z)-5-(4-Hydroxy-3-methoxybenzylidene)-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14f**).* This product was obtained as a yellow crystal in 90% yield. Mp 242–243 °C; IR (KBr) *ν*: 3480 (–OH), 1722 (C=O), 1596, 1560, 1432 (C=C, Ph), 1302 (–CH_3),1242 (–OCH_3), 1158 (C–O), 777, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ and DMSO, TMS): *δ* 8.10 (d, *J* = 7.6 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.61 (d, *J* = 7.6 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.38 (m, 3H, phenyl–H), 7.28 (d, *J* = 8.0 Hz, 1H, H–Ph), 7.00 (m, 2H, phenyl–H), 6.91 (d, *J* = 8.4 Hz, 1H, H–Ph), 5.85 (s, 1H, =C_6H), 3.93 (s, 3H, OCH_3), 3.20 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$ and DMSO, TMS): *δ* 167.70 (C_2=O), 148.78, 148.14, 147.79, 145.48, 141.66, 136.23, 131.11, 131.03, 130.31, 128.17, 125.54, 125.12, 125.08, 124.86, 123.51, 115.83, 115.60, 114.76, 113.63, 56.04 (OCH_3), 44.28 (SCH_3); $C_{25}H_{19}FO_6S$; HR-MS (ESI) *m/z*: found $[M + H]^+$ 467.0958 (calcd. 467.0965).

*4.1.5.40. (Z)-5-(4-Hydroxybenzylidene)-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14g**).* This product was obtained as a yellow crystal in 84% yield. Mp 269–271 °C; IR (KBr) *ν*:

3416 (−OH), 1732 (C=O), 1596, 1580, 1432 (C=C, Ph), 1312 (−CH_3), 1173 (C−O), 2960 (−CH−), 845, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ and DMSO, TMS): δ 8.09 (d, *J* = 8.0 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.67 (d, *J* = 8.4 Hz, 2H, 4-hydroxybenzylidene, H-2, H-6), 7.62 (d, *J* = 8.0 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.36 (m, 2H, 4-fluorophenyl, H-3, H-5), 7.03 (m, 2H, 4-fluorophenyl, H-2, H-6), 6.87 (d, *J* = 8.4 Hz, 2H, 4-hydroxybenzylidene, H-3, H-5), 5.89 (s, 1H, =C_6H), 3.20 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$ and DMSO, TMS): δ 167.80 (C_2=O), 159.41, 141.73, 132.82, 131.16, 131.08, 130.33, 128.16, 124.31, 123.39, 116.25, 115.78, 115.57, 114.65, 44.27 (SCH_3); $C_{24}H_{17}FO_5S$; HR-MS (ESI) *m*/*z*: found $[M + H]^+$ 437.0845 (calcd. 437.0859).

*4.1.5.41. (Z)-5-(4-Bromobenzylidene)-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14h**).* This product was obtained as a yellow crystal in 87% yield. Mp 271–272 °C; IR (KBr) *ν*: 1757 (C=O), 1596, 1580, 1423 (C=C, Ph), 1318 (−CH_3), 1160 (C−O), 3020 (−ArH), 2910 (−CH−), 768, 690 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.12 (dd, *J* = 6.8 Hz, *J* = 1.6 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.67 (m, 2H, Ph), 7.61 (dd, *J* = 6.8 Hz, *J* = 2.0 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.56 (m, 2H, Ph), 7.41 (m, 2H, phenyl−H), 7.02 (m, 2H, phenyl−H), 5.83 (s, 1H, =C_6H), 3.19 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.62 (C_2=O), 147.85, 147.54, 141.98, 135.96, 132.18, 132.03, 131.67, 131.24, 131.16, 130.26, 128.37, 125.66, 124.51, 124.01, 116.09, 115.87, 112.35 (C_6), 44.34 (SCH_3); $C_{24}H_{16}BrFO_4S$; HR-MS (ESI) *m*/*z*: found $[M + H]^+$ 499.0009 (calcd. 499.0015).

*4.1.5.42. (Z)-5-(4-Chlorobenzylidene)-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14i**).* This product was obtained as a yellow crystal in 86% yield. Mp 272–274 °C; IR (KBr) *ν*: 1758 (C=O), 1596, 1580, 1511, 1488 (C=C, Ph), 1319 (−CH_3), 1151 (C−O), 3020 (−ArH), 2910 (−CH−), 776, 695 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.12 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.75 (d, *J* = 8.4 Hz, 2H, 4-chlorophenyl), 7.61 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.40 (m, 4H, H−Ph), 7.01 (m, 2H, 4-fluorophenyl), 5.85 (s, 1H, =C_6H), 3.19 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.64 (C_2=O), 147.74, 147.54, 141.97, 135.98, 135.57, 131.85, 131.26, 131.24, 131.16, 130.27, 129.22, 128.37, 125.58, 124.51, 124.48, 116.08, 115.86, 112.31 (C_6), 44.34 (SCH_3); $C_{24}H_{16}ClFO_4S$; HR-MS (ESI) *m*/*z*: found $[M + H]^+$ 455.0515 (calcd. 455.0520).

*4.1.5.43. (Z)-5-(4-Fluorobenzylidene)-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14j**).* This product was obtained as a yellow crystal in 85% yield. Mp 291–292 °C; IR (KBr) *ν*: 1759 (C=O),1596, 1580, 1507, 1422 (C=C, Ph), 1310 (−CH_3), 1148 (C=O), 3020 (−ArH), 2910 (−CH−), 768, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ and DMSO, TMS): δ 8.11 (d, *J* = 6.8 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.85 (m, 2H, Ph), 7.65 (d, *J* = 6.8 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.39 (m, 2H, Ph), 7.18 (m, 2H, phenyl−H), 7.08 (m, 2H, phenyl−H), 6.03 (s, 1H, =C_6H), 3.17 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$ and DMSO, TMS): δ 167.69 (C_2=O), 148.63, 147.28, 147.26, 142.10, 135.35, 133.00, 132.92, 131.56, 131.47, 130.47, 129.68, 129.65, 128.26, 125.15, 125.12, 124.99, 116.26, 116.05, 115.98, 115.76, 112.39 (C_6), 44.11 (SCH_3); $C_{24}H_{16}F_2O_4S$; HR-MS (ESI) *m*/*z*: found $[M + H]^+$ 439.0812 (calcd. 439.0816).

*4.1.5.44. (Z)-5-(4-(Dimethylamino)benzylidene)-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14k**).* This product was obtained as a red crystal in 93% yield. Mp 261–262 °C; IR (KBr) *ν*: 1751 (C=O), 1596, 1560, 1423 (C=C, Ph), 1310 (−CH_3), 1370 (C−N), 1162 (C−O), 842, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.13 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.72 (d, *J* = 8.8 Hz, 2H, 4-dimethylaminobenzylidene, H-2, H-6), 7.58 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.36 (m, 2H, phenyl−H), 6.98 (t, *J* = 17.2 Hz, *J* = 8.4 Hz, 2H, phenyl−H), 6.74 (d, *J* = 8.8 Hz, 2H, 4-(dimethylamino)benzylidene, H-3, H-5), 5.83 (s, 1H, =C_6H), 3.16 (s, 3H, SCH_3), 3.06 (s, 6H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.13 (C_2=O), 148.01, 144.98, 141.50, 136.89, 132.74, 130.99, 130.91, 130.38, 128.13, 125.70, 122.31, 115.82, 115.61, 115.21, 112.32, 111.94 (C_6), 44.38 (SCH_3), 40.29 (N$(CH_3)_2$); $C_{26}H_{22}FNO_4S$; HR-MS (ESI) *m*/*z*: found $[M + H]^+$ 464.1314 (calcd. 464.1332).

*4.1.5.45. (Z)-5-(Benzo[d][1,3]dioxol-5-ylmethylene)-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14l**).* This product was obtained as a yellow crystal in 93% yield. Mp 237–239 °C; IR (KBr) *ν*: 1757 (C=O), 1596, 1560, 1423 (C=C, Ph), 1300 (−CH_3), 1140 (C−O), 1260 (−OCH_2−), 3020 (−ArH), 774, 695 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.10 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.60 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.54 (d, *J* = 1.6 Hz, 1H, substituent phenyl, H-2), 7.40 (m, 2H, 4-fluorophenyl), 7.16 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H, substituent phenyl, H-5), 7.01 (m, 2H, 4-fluorophenyl), 6.85 (d, *J* = 8.0 Hz, 1H, substituent phenyl, H-6), 6.05 (s, 2H, CH_2), 5.82 (s, 1H, =C_6H), 3.19 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.89 (C_2=O), 164.24, 161.75, 149.06, 148.46, 147.70, 146.14, 141.79, 136.30, 131.15, 131.06, 130.30, 128.27, 127.21, 126.57, 124.83, 124.80, 124.42, 115.97, 115.76, 113.90, 110.03, 108.67, 101.65, 44.35 (SCH_3); $C_{25}H_{17}FO_6S$; HR-MS (ESI) *m*/*z*: found $[M + H]^+$ 465.0800 (calcd. 45.0808).

*4.1.5.46. (Z)-5-(4-Methoxybenzylidene)-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14m**).* This product was obtained as a yellow crystal in 86% yield. Mp 226–228 °C; IR (KBr) *ν*: 1742 (C=O), 1596, 1580, 1510, 1424 (C=C, Ph), 1308 (−CH_3), 1254 (−OCH_3), 1177 (C−O), 3020 (−ArH), 843, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.98 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.81 (d, *J* = 8.8 Hz, 2H, 4-methoxyphenyl), 7.50 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.40 (dd, *J* = 8.8 Hz, *J* = 5.2 Hz, 2H, 4-fluorophenyl), 7.02 (t, *J* = 17.2 Hz, *J* = 8.8 Hz, 2H, 4-fluorophenyl), 6.96 (d, *J* = 8.8 Hz, 2H, 4-methoxy-phenyl), 6.04 (s, 1H, =C_6H), 3.86 (s, 3H, OCH_3), 3.10 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.37 (C_2=O), 160.95, 151.46, 145.61, 141.59, 135.92, 133.91, 132.78, 131.71, 130.59, 130.09, 129.98, 128.28, 127.84, 127.05, 125.59, 125.20, 114.62, 114.54, 55.41 (OCH_3), 44.31 (SCH_3); $C_{25}H_{19}FO_5S$; HR-MS (ESI) *m*/*z*: found $[M + H]^+$ 451.1010 (calcd. 451.1015).

*4.1.5.47. (Z)-3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-5-(naphthalen-1-ylmethylene)furan-2(5H)-one (**14n**).* This product was obtained as a yellow crystal in 91% yield. Mp 262–264 °C; IR (KBr) *ν*: 1759 (C=O), 1596, 1580, 1509, 1423 (C=C, Ph), 1309 (−CH_3), 1146 (C−O), 3020 (−ArH), 2950 (−CH−), 771, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.38 (d, *J* = 7.60 Hz, 1H, H−Ar), 8.15 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.89 (d, *J* = 8.8 Hz, 2H, 4-fluorophenyl), 7.79 (m, 1H, H−Ph), 7.69 (d, *J* = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6),7.60 (m, 1H, H−Ph), 7.56 (m, 2H, H−Ph), 7.40 (m, 2H, H−Ph), 7.02 (t, *J* = 17.6 Hz, *J* = 8.8 Hz, 2H, 4-fluorophenyl), 6.71 (s, 1H, =C_6H), 3.20 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.05 (C_2=O), 14.38, 147.62, 141.98, 136.26, 133.69, 131.57, 131.30, 131.22, 130.37, 130.24, 129.98, 129.18, 128.55, 128.43, 127.02, 126.12, 125.85, 125.64, 122.66, 116.07, 115.85, 109.69, 44.38 (SCH_3); $C_{28}H_{19}FO_4S$; HR-MS (ESI) *m*/*z*: found $[M + H]^+$ 471.1058 (calcd. 471.1066).

*4.1.5.48. 3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-5-(propan-2-ylidene)furan-2(5H)-one (**14o**).* This product was

obtained as a yellow oil in 75% yield. IR (KBr) ν: 1748 (C=O), 1596, 1580, 1511, 1423 (C=C, Ph), 1312 (−CH_3), 1156 (C−O), 2960 (−CH−), 769, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.05 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H, 4-methylsulfanylphenyl, H-3, H-5), 7.53 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.24 (s, 2H, 4-fluorophenyl), 6.91 (s, 2H, 4-fluorophenyl), 3.13 (s, 3H, SCH_3), 2.10 (m, 3H, CH_3), 1.44 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 167.63 (C_2=O), 146.19, 143.27, 141.35, 139.08, 131.05, 130.96, 129.81, 128.19, 127.46, 126.60, 125.06, 125.02, 115.65, 115.44, 44.37 (SCH_3), 21.21 (CH_3), 19.48 (CH_3); $C_{20}H_{17}FO_4S$; HR-MS (ESI) m/z: found $[M + H]^+$373.0997 (calcd. 373.0910).

*4.1.5.49. 3-(2-Fluorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14p**).* This product was obtained as yellow oil in 60% yield. IR (KBr) ν: 1778 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.95 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.39 (m, 2H),7.06 (m, 2H), 3.45 (s, 3H, SCH_3), 3.10 (s, 3H, OCH_3), 1.66 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.84 (C_2=O),164.63, 162.14, 153.44, 141.82, 135.72, 131.59, 130.58, 129.57, 128.06, 124.52, 124.49, 116.26, 116.05, 107.55, 50.89, 44.22, 23.02; $C_{19}H_{18}FO_5S$; HR-MS (ESI) m/z: found $[M + H]^+$ 377.0853 (calcd. 377.0859).

*4.1.5.50. (Z)-5-(2-Chlorobenzylidene)-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (**14q**).* This product was obtained as a yellow crystal in 89% yield. Mp 204–206 °C; IR (KBr) ν: 1765 (C=O), 1596, 1580, 1424 (C=C, Ph), 1305 (−CH_3), 1142 (C−O), 3020 (−ArH), 2910 (−CH−), 769, 682 (C=H, Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ and DMSO, TMS): δ 8.32 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H, Ph), 8.11 (d, J = 8.4 Hz, 2H, 4-methylsulfanyl-phenyl, H-3, H-5), 7.63 (d, J = 8.4 Hz, 2H, 4-methylsulfanylphenyl, H-2, H-6), 7.42–7.38 (m, 4H, Ph), 7.30 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H, Ph), 7.03 (m, 2H, phenyl−H), 6.44 (s, 1H, =C_6H), 3.17 (s, 3H, SCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$ and DMSO, TMS): δ 167.71 (C_2=O), 148.35, 141.98, 135.79, 134.65, 131.91, 131.34, 131.26, 131.04, 130.67, 130.41, 130.37, 130.32, 129.75, 128.35, 127.37, 127.04, 126.01, 116.11, 115.0, 108.9, 44.38 (SCH_3); $C_{24}H_{16}ClFO_4S$; HR-MS (ESI) m/z: found $[M + H]^+$ 455.0519 (calcd. 455.0520).

4.2. General procedure for prostatic hyperplasia inhibitory activity assay [2,12,32–34]

4.2.1. Cell culture

Two different prostate cancer cell lines were cultured. One prostate cancer cell line was PC3 and its transfected cell lines (PC3 PCDNA and PC3 SKP2). PC3, PC3 PCDNA, and PC3 SKP2 cells were cultured in 10 mL RMPI 1640 medium with 10% fetal bovine serum. Since the transfected cells express resistance to antibiotics, 50 μL of G418 antibiotic also was added to the PC3 PCDNA and PC3 SKP2 plates to screen for the transfected cells. The second prostate cancer cell line was DU145, which were cultured in 10 mL RMPI 1640 with 10% fetal bovine serum.

4.2.2. MTT assays

Exponentially growing cells were seeded into 96-well plates at a concentration of 1×10^4 cells per well. After 24 h incubation at 37 °C, the culture medium was removed and replaced with fresh medium containing the candidate compounds in different concentrations. The cells were incubated for another 72 h. Afterward, 0.5 mL of MTT assay solution was added to all wells and incubated for 1–3 h at 37 °C to generate crystal violet. When a sufficient amount of crystal violet had been generated, the MTT assay solution was removed. Then 0.5 mL of an MTT dissolve solution consisting of 4% hydrochloric acid in 96% isopropanol were added to the plates before shaking for 5–10 min (average 7 min) to create the crystal violet solution. Then 200 μL of crystal violet solution from each well was then transferred to a 96 well plate. The crystal violet concentration could then be determined by spectrometry absorbance at 570 nm wavelength. The relative absorbance detected by the spectrometer revealed the cell viability. The viability was plotted and analyzed. MTT assays were conducted for the candidate compounds to determine whether they had IC_{50}s that were less than 50 μM. Additional MTT assays were conducted on the candidate compounds that had approximate IC_{50}s that were less than 50 μM. The average 50% inhibitory concentration (IC_{50}) was determined from the dose–response curves according to the inhibition ratio for each concentration. Each concentration was analyzed in triplicate. (IC_{50s} was calculated using the software SPSS 16.0).

4.2.3. Flow cytometric analysis of cell cycle distribution

For flow cytometric analysis of DNA content, 5×10^5 DU145 cells in exponential growth were treated with different concentrations of the test compounds for 12 h. After an incubation period, the cells were collected, centrifuged and fixed with ice-cold ethanol (70%). The cells were then treated with buffer containing RNAse A and 0.1% Triton X-100 and then stained with PI. Samples were analyzed on Accuri C6 flow cytometer (Becton, Dickinson). Data obtained from the flow cytometer was analyzed using the FlowJo software (Tree Star, Inc., Ashland, OR, USA).

4.2.4. Nuclear staining with DAPI

After treatment of **13P** on DU145 cells for 48 h, the cells were washed twice with PBS and then fixed with 3.7% paraformaldehyde (Sigma) in PBS for 10 min at room temperature. Fixed cells were washed with PBS, and stained with 4,6-diamidino-2-phenylindole (DAPI, Sigma) solution for 10 min at room temperature. The cells were washed two more times with PBS and analyzed via a fluorescence microscope.

4.3. Cyclooxygenase inhibition studies

The ability of the tested compounds to inhibit ovine COX-1 and COX-2 was determined using an enzyme immunoassay (EIA) kit (catalog number 560101, Cayman Chemical, Ann Arbor, MI) according to the manufacturer's instructions. Cyclooxygenase catalyzes the first step in the biosynthesis of arachidonic acid (AA) to PGH2. PGF2, produced from PGH2 by reduction with stannous chloride, is measured by enzyme immunoassay (ACE competitive EIA). Stock solutions of test compounds were dissolved in a minimum volume of DMSO. Briefly, to a series of supplied reaction buffers (960 μL, 0.1 M Tris–HCl pH 8.0 containing 5 mM EDTA and 2 mM phenol) with either COX-1 or COX-2 (10 μL) enzyme in the presence of heme (10 μL) was added 10 μL of various concentrations of test drug solutions (0.001, 0.1, 1, 10, 50, and 100 μM in a final volume of 1 mL). These solutions were incubated for a period of 5 min at 37 °C after which 10 μL of AA (100 μM) solution was added and the COX reaction was stopped by the addition of 50 μL of 1 M HCl after 2 min. $PGF_{2\alpha}$, produced from PGH2 by reduction with stannous chloride, was measured by enzyme immunoassay. This assay is based on the competition between PGs and a PG acetylcholinesterase conjugate (PG tracer) for a limited amount of PG antiserum. The amount of PG tracer that is able to bind to the PG antiserum is inversely proportional to the concentration of PGs in the wells since the concentration of PG tracer is held constant while the concentration of PGs varies. This antibody PG complex binds to a mouse anti-rabbit monoclonal antibody that had been previously attached to the well. The plate is washed to remove any unbound reagents and then Ellman's reagent, which contains the substrate to acetylcholine esterase, is added to the well. The product of this enzymatic reaction produces a distinct yellow color that absorbs at

412 nm. The intensity of this color, determined spectrophotometrically, is proportional to the amount of PG tracer bound to the well, which is inversely proportional to the amount of PGs present in the well during the incubation: Absorbance [Bound PG Tracer] 1/PGs. Percent inhibition was calculated by the comparison of compound-treated to various control incubations.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.04.062.

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