European Journal of Medicinal Chemistry 62 (2013) 222–231

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and biological evaluation of some novel resveratrol amide derivatives as potential anti-tumor agents

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ARTICLE INFO

Article history:
Received 31 May 2012
Received in revised form
19 October 2012
Accepted 14 November 2012
Available online 20 November 2012

Keywords:
Resveratrol derivatives
COX-2 inhibitor
Anti-tumor
Molecular docking

ABSTRACT

Three series of novel resveratrol amide derivatives (**1a**–**q**, **2a**–**h**, **3a**–**l**) were synthesized and evaluated for their biological activities. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. Furthermore, compound **3e** was also characterized by X-ray crystallography. All the compounds were evaluated for their anti-tumor activity against MCF-7, A549 and B16-F10 tumor cell lines as well as cyclooxygenase-2 (COX-2)-derived prostaglandin E2 (PGE_2) inhibitory activity of murine macrophage RAW 264.7 cell line. Among them, compounds **1c**, **1g** and **3e** displayed the most potent COX-2 inhibitory activity with the IC_{50} values of 1.02, 1.27 and 1.98 μM, respectively. Molecular docking studies were performed to position compounds **1c** and **3e** into the active site of COX-2 to determine the probable binding modes.

1. Introduction

Cyclooxygenase (COX) enzymes have the key role in catalyzing biotransformation of arachidonic acid (AA) to prostaglandins (PGs), prostacyclin (PGI_2), and thromboxane A_2 (TXA_2) [1]. COX activity originates from two distinct and independently regulated enzymes, termed COX-1 and COX-2. COX-1 is the constitutive isoform and is mainly responsible for the synthesis of cytoprotective prostaglandins in the gastrointestinal (GI) tract and thromboxane which triggers platelet aggregation in blood platelets. COX-2 is inducible and short-lived; its expression is stimulated in response to endotoxins, cytokines, and mitogens [2].

The role of COX-2 is very important. COX-2 has been implicated in human carcinogenesis, and thus, inhibition of COX-2 might have the dual effect on controlling both inflammation and cancer [3]. Numerous studies have demonstrated the overexpression of COX-2 in solid malignancies [4]. Epidemiological, clinical, and preclinical investigations also provide compelling evidence that COX-2 inhibitors could act as chemopreventive agents [5]. Recent data have demonstrated the involvement of COX-2 in both *in vitro* proliferation and *in vivo* tumor growth rate [6,7]. Other works have highlighted the role played by COX-2 in disturbing the balance between matrix metalloproteinases (MMPs) and the tissue inhibitors of metalloproteinases (TIMPs) in prostate cancer cells [8,9].

Several selective COX-2 inhibitors are currently used in the clinics (e.g. celecoxib, valdecoxib, parecoxib, rofecoxib, etoricoxib, and lumiracoxib) which provide effective treatment of inflammatory disease states such as rheumatoid arthritis and osteoarthritis [10]. Several lines of evidence suggest that these selective COX-2 inhibitors may also provide an opportunity for both cancer prevention and therapy [11].

Natural products in general and medicinal plants in particular, are believed to be an important source of new chemical substances with a potential therapeutic efficacy. Thus many researchers have investigated selective COX-2 inhibitors in natural products. Among them, resveratrol (3,4,5′-trihydroxy-*trans*-stilibene) is a phytoalexin found mainly in the skin of grapes and red wine and exhibits anticancer, antioxidation, anti-inflammatory, cardiovascular protection properties. It has also been shown to be a non-selective inhibitor of COX-1 and COX-2 [12,13]. In order to find more selective COX-2 inhibitors, three series of resveratrol derivatives (**1a**–**q**, **2a**–**h** and **3a**–**l**) were synthesized and evaluated for their anticancer, anti-inflammatory and COX-2 inhibition activities. In order to identify the possible binding mode, molecular docking studies were consequently performed.

2. Chemistry

Three series of compounds were synthesized via the route outlined in Scheme 1. The intermediate (*E*)-2,4-dimethoxy-6-(4-

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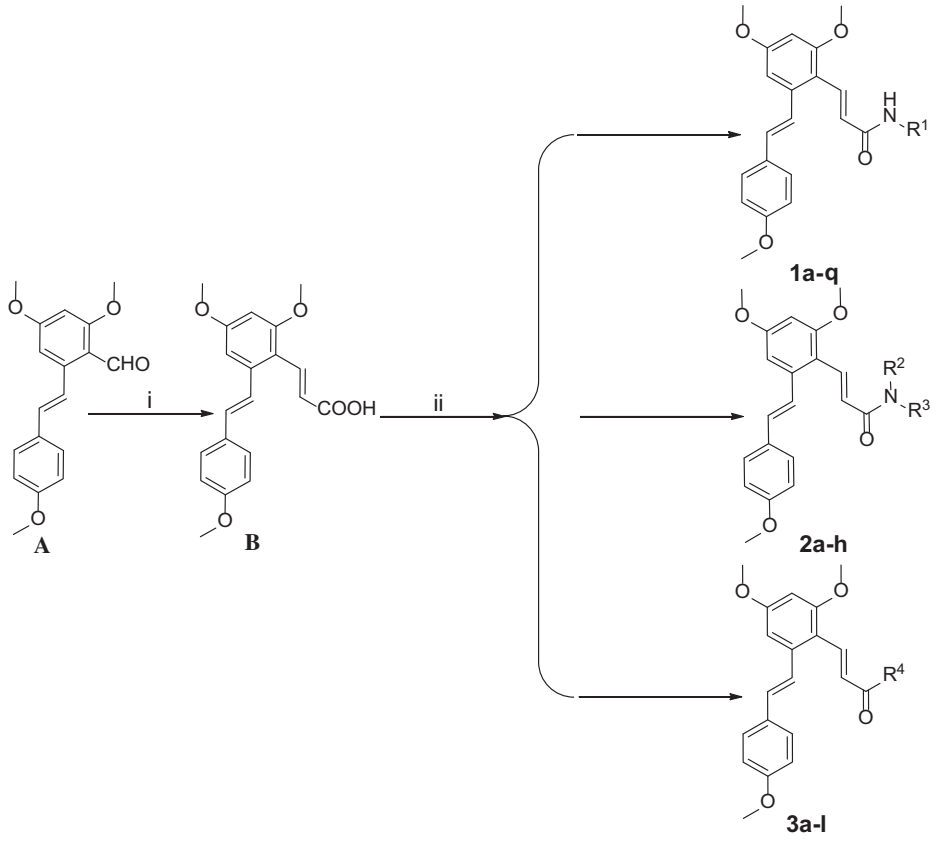
http://dx.doi.org/10.1016/j.ejmech.2012.11.021



Scheme 1. Reagents and conditions: (i) malonate, pyridine, piperidine, 95 °C; (ii) EDCI, HOBt, DCM, appropriate substituted amines, room temperature.

methoxystyryl) benzaldehyde (**A**) was obtained as reported [14]. (*E*)-3-(2,4-dimethoxy-6-((*E*)-4-methoxystyryl)phenyl)acrylic acid (**B**) was obtained in 92.1% yield by Knoevenagel condensation. The target compounds (**1a**–**q**, **2a**–**h** and **3a**–**l**) were prepared by reaction of **B** with primary, secondary and cyclic amines in good yields, respectively.

All the obtained compounds gave satisfactory elementary analytical and spectroscopic data. ^{1}H NMR, ^{13}C NMR and ESI MS spectra were consistent with the assigned structures (Table 1). Furthermore, compound **3e** was also determined by single crystal X-ray diffraction analysis.

3. Results and discussion

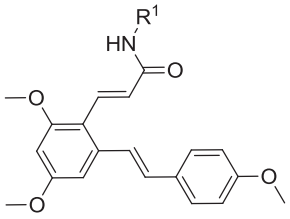
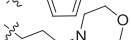
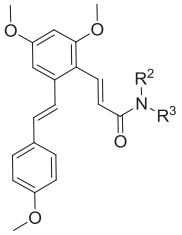
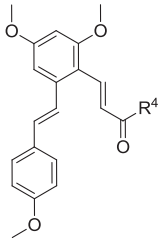
3.1. Biological activity

It is well known that COX-2 is overexpressed in many human cancer entities such as breast cancer, hepatic carcinoma and melanoma. Thirty-seven target compounds were evaluated for the antiproliferative activities against human breast cancer MCF-7 cells, human non-small cell lung cancer A549 cells and melanoma B16-F10 cells. The results were presented in Table 2. All compounds showed obvious activities with IC_{50} values between 1.33 and 13.63 μM, and they were much better than that of the positive control celecoxib. Compounds **1c**, **1g** and **3e** had significant activities.

Subsequently SAR studies were performed to determine how the substituents (R^1–R^4) affected the antiproliferative activities. Among the first series of compounds **1a**–**q**, **1c** (R^1 = butyl) displayed the most potent activity (IC_{50} = 1.33 μM for MCF-7; 1.88 μM for A549; 2.08 μM for B16-F10). It can be seen that the activities would be reduced by the increase or decrease of the length of butyl as well as the addition of branched groups. Compound **1g** has the comparable activity to **1c**, probably because of the similar length of 3-chloropropal to butyl. So the length of the side chain (R^1) played a key role in the activities. Compounds **2a**–**h** showed almost the same moderate anticancer activities, and they were not as good as **1c**. This demonstrated that the substitution of secondary amines had little effect on the activities. The difference among compounds **3a**–**e** lies in the position and number of methyl on piperidinyl. Among them, **3e** (R^4 = 3, 5-dimethylpiperidinyl) showed the potent activity with IC_{50} value of 1.57, 2.27 and 3.26 μM when tested against MCF-7, A549 and B16-F10, respectively. And they follow the sequence of 3,5-dimethyl > ortho-methyl > para-methyl > meta-methyl. The change of methyl to other groups (**3f**–**h**) or piperidine to other cyclic amines (**3i**–**l**) could not increase the activities. These changes of R^4 were associated with great differences in activity, which suggested a possible critical binding role for this group in the binding site of the molecular target [15].

To study the effect of the synthesized compounds on COX-2 selectivity and potency, we determined the ability of compounds to inhibit the COX-1 and COX-2 isozymes using chemiluminescent enzyme assays kit. The efficacies of compounds were determined as the concentration causing 50% enzyme inhibition (IC_{50}). The results were summarized in Table 2. These data showed that most of the synthesized compounds exhibited remarkable and selective inhibition of COX-2 isozyme, while weak to COX-1, and particularly, compound **1c**, **1g**, **3e** and **3j** showed significant activities comparable to celecoxib. Among them, **1c** was the most potent (IC_{50} = 1.02 μM) COX-2 inhibitor. Furthermore, the results of western blotting assay shown in Fig. 1 confirmed that compound **1c** with the concentration above 0.5 μM could obviously inhibit lipopolysaccharide (LPS)-induced COX-2 expression in murine macrophage RAW 264.7 cell line.

Table 1
Chemical structures of the synthetic compounds.

Structure	Comp. no	R^1
	**1a**	
	1b	
	1c	
	1d	
	1e	
	1f	
	1g	
	1h	
	1i	
	1j	
	1k	
	1l	
	1m	
	1n	
	1o	
	1p	
	1q	
		R^2 R^3
	2a	
	2b	
	2c	
	2d	
	2e	
	2f	
	2g	
	2h	
		R^4
	3a	
	3b	
	3c	
	3d	
	**3e**	
	3f	
	3g	
	3h	
	3i	
	3j	
	3k	
	3l	

Prostaglandin E2 (PGE_2) is biosynthesized via COX-2 enzymes, which is one of the principal mediators of inflammation. Compound **1c** exhibited promising inhibitory against PGE_2 with IC_{50} value of 0.28 μM as shown in Table 2, which was approximate to that of celecoxib (IC_{50} = 0.10 μM). These data suggested that these synthesized compounds inhibited the inflammatory activity via the COX-2 pathway and were devoid of toxicity due to the absence of COX-1 inhibition which maintains normal physiological functions.

3.2. Crystal structure of compound *3e*

Compound **3e** crystallizes in the monoclinic space group P2(1)/n. The crystal data and refinement data are listed in Table 3. Selected bond lengths and angles are given in Table 4. All bond lengths are within normal ranges [16]. As shown in Fig. 2a, C10–C9 and C19–C20 are both in *trans* form and the bond lengths of 1.332(4) and 1.326(5) Å conform to the value for double C–C bond, respectively. Similarly, the C8–O1 bond length of 1.225(5) conforms to the value for double C–O bond. The dihedral angle between the two phenyl rings is 56.7(1)° (C21–C22–C23–C24–C25–C26 and C11–C12–C13–C14–C15–C16). The six-membered piperidine ring is in a standard chair form. As shown in Fig. 2b, intermolecular H bonds (H27B···O1) between adjacent molecules lead to a 1D chain structure. Furthermore, intermolecular H bonds (H26···O1 and H23···O2) between adjacent 1D chains generate a 2D layer.

3.3. Molecular docking

In order to get a better insight into the binding affinity and guide further SAR studies, molecular docking studies of compounds **1c** and **3e** were performed using the crystal structure of COX-2 enzymes given in PDB code 1cx2. All docking runs were applied the Lamarckian genetic algorithm of Auto-Dock 4.0. The binding modes of **1c** and **3e** were depicted in Fig. 3. It can be seen that the C=O of compound **1c**, formed a hydrogen bonding interaction with the backbone NH of Arg120 (bond length: Arg120 N–H···O = 2.037Å; bond angle: Arg120 N–H···O = 160.073°). Compound **3e** as well as **1c**, interacts with Arg120 (bond length: Arg120 N–H···O = 1.968Å; bond angle: Arg120 N–H···O = 152.713°), and **3e** had one more interaction. The oxygen atom of one of the methoxyl groups on benzene ring formed a hydrogen bond with Lys83 (bond length: Lys83 N–H···O = 1.637Å; bond angle: Lys83 N–H···O = 131.135°). The 3D binding modes of **1c** and **3e** were exhibited in Fig. 4. They also showed well binding affinity to the target via hydrogen bonds and hydrophobic interactions.

These results of molecular docking studies proved that compounds **1c** and **3e** had high binding potency of COX-2.

4. Conclusion

Three series of amide derivatives of resveratrol were synthesized and evaluated for the anti-tumor and COX-1/COX-2 inhibition activity. Compounds **1c**, **1g** and **3e** exhibited the most potent anti-tumor activity against MCF-7, A549 and B16-F10 tumor cell lines. Furthermore, compounds **1c**, **1g** and **3e** also exhibited optimal COX-2 inhibitory potency and selectivity compared with celecoxib. Molecular docking studies further help in understanding the interactions between the ligands and enzyme active sites in detail and thereby help to design novel potent inhibitors from natural product. It is clear that compounds **1c** and **3e** interact with the binding site of COX-2 by forming strong hydrogen bond(s) and hydrophobic interactions. The results of this work might be helpful for discovering novel class of potent anti-tumor agents.

Table 2
Inhibition (IC_{50}) of MCF-7, A549 and B16-F10 tumor cell lines as well as the inhibition of COX-1, PGE_2 and COX-2 in lipopolysaccharide (LPS)-activated murine macrophage RAW 264.7 cells.

Comp. no	IC_{50} (μM)					
	MCF-7	A549	B16-F10	COX-1	COX-2	PGE_2
1a	7.06 ± 0.21	7.86 ± 0.81	6.99 ± 0.44	35.36 ± 1.86	12.36 ± 1.50	7.06 ± 1.50
1b	5.61 ± 0.15	5.17 ± 0.34	9.08 ± 1.06	>50	6.75 ± 0.26	2.08 ± 0.12
1c	1.33 ± 0.06	1.88 ± 0.31	2.08 ± 0.27	>50	1.02 ± 0.30	0.28 ± 0.04
1d	5.53 ± 0.13	6.23 ± 0.48	7.18 ± 0.62	34.68 ± 2.48	8.99 ± 0.91	5.01 ± 0.82
1e	4.28 ± 0.08	8.66 ± 0.56	8.06 ± 1.07	>50	20.09 ± 2.85	13.82 ± 1.95
1f	2.30 ± 0.14	2.00 ± 0.23	3.45 ± 0.29	32.26 ± 2.64	1.36 ± 0.43	0.45 ± 0.07
1g	1.98 ± 0.08	1.98 ± 0.11	2.78 ± 0.31	38.39 ± 3.28	1.27 ± 0.08	0.39 ± 0.14
1h	4.56 ± 0.96	6.93 ± 1.13	8.28 ± 0.94	>50	9.08 ± 1.17	5.08 ± 0.67
1i	2.56 ± 1.25	2.36 ± 0.25	4.02 ± 0.42	40.39 ± 2.89	2.01 ± 0.49	0.72 ± 0.06
1j	13.63 ± 0.06	8.67 ± 0.42	7.98 ± 0.87	>50	11.12 ± 1.84	5.29 ± 0.89
1k	5.29 ± 0.36	10.44 ± 1.14	12.65 ± 1.24	>50	15.09 ± 2.04	6.12 ± 0.64
1l	3.43 ± 0.73	3.95 ± 0.28	4.38 ± 0.54	>50	4.56 ± 0.46	2.09 ± 0.26
1m	3.94 ± 0.02	8.81 ± 0.68	10.16 ± 1.48	>50	12.96 ± 2.74	7.05 ± 1.15
1n	2.63 ± 0.11	3.61 ± 0.62	5.48 ± 0.69	>50	5.09 ± 1.12	1.98 ± 0.38
1o	5.42 ± 0.15	6.42 ± 0.46	10.09 ± 1.16	29.09 ± 3.58	9.67 ± 1.36	3.15 ± 0.57
1p	4.15 ± 0.08	4.22 ± 1.00	6.83 ± 0.76	>50	8.92 ± 1.03	3.68 ± 0.48
1q	7.01 ± 0.03	5.14 ± 10.6	8.15 ± 0.81	>50	6.66 ± 0.98	2.10 ± 0.07
2a	6.86 ± 0.16	6.00 ± 0.76	5.78 ± 0.52	>50	12.98 ± 1.88	4.36 ± 0.26
2b	6.55 ± 0.01	3.35 ± 0.49	3.98 ± 0.23	>50	4.67 ± 0.45	2.15 ± 0.31
2c	2.00 ± 0.22	5.58 ± 0.15	5.98 ± 0.47	45.88 ± 2.96	8.06 ± 1.58	3.88 ± 0.10
2d	3.99 ± 0.03	6.16 ± 0.38	9.03 ± 0.96	>50	10.08 ± 2.04	4.12 ± 0.29
2e	2.39 ± 0.05	3.35 ± 0.51	4.85 ± 0.12	>50	6.84 ± 1.04	2.56 ± 0.72
2f	6.13 ± 0.23	7.49 ± 0.84	9.27 ± 0.82	>50	16.43 ± 1.78	7.19 ± 1.06
2g	4.03 ± 0.02	5.34 ± 0.61	8.02 ± 0.94	>50	9.08 ± 0.91	3.10 ± 0.83
2h	3.22 ± 0.11	5.89 ± 0.63	8.18 ± 0.78	34.98 ± 2.74	8.01 ± 1.47	3.28 ± 0.54
3a	6.05 ± 0.11	10.62 ± 1.28	9.75 ± 1.04	>50	23.16 ± 2.68	15.29 ± 2.81
3b	4.35 ± 0.13	5.77 ± 0.74	7.66 ± 1.24	>50	6.69 ± 0.74	2.44 ± 0.43
3c	11.92 ± 0.12	5.82 ± 0.33	8.25 ± 0.79	>50	7.09 ± 1.28	3.16 ± 0.46
3d	6.45 ± 0.38	7.20 ± 0.88	7.76 ± 1.36	>50	10.28 ± 2.07	8.09 ± 1.04
3e	1.57 ± 0.10	2.27 ± 0.14	3.26 ± 0.27	45.06 ± 3.58	1.98 ± 0.09	0.58 ± 0.03
3f	5.24 ± 0.21	5.60 ± 0.16	7.38 ± 0.69	>50	10.28 ± 2.08	6.27 ± 0.48
3g	4.95 ± 0.11	2.08 ± 0.38	4.69 ± 0.64	40.56 ± 4.26	1.45 ± 0.11	0.46 ± 0.08
3h	4.23 ± 0.07	6.69 ± 0.45	9.18 ± 1.52	>50	8.57 ± 1.58	3.55 ± 0.46
3i	2.29 ± 0.06	4.51 ± 0.14	5.67 ± 0.91	39.06 ± 2.81	5.78 ± 0.44	1.62 ± 0.32
3j	3.31 ± 0.70	2.32 ± 0.28	3.08 ± 0.28	>50	1.88 ± 0.14	0.85 ± 0.06
3k	2.76 ± 0.06	5.40 ± 0.93	8.10 ± 1.04	45.19 ± 4.68	8.01 ± 1.06	3.18 ± 0.40
3l	4.2 ± 0.34	6.35 ± 0.98	9.28 ± 0.93	>50	8.87 ± 1.28	3.76 ± 0.47
B	6.10 ± 0.36	5.46 ± 0.39	6.78 ± 0.64	>50	6.89 ± 0.91	3.01 ± 0.29
Celecoxib	40.8 ± 0.42	15.6 ± 1.38	85.9 ± 2.34	27.5 ± 2.46	0.10 ± 0.02	0.12 ± 0.01

5. Experimental

5.1. General

All the chemicals used were commercial products employed without further purification. The ^1H NMR spectra were recorded on a Bruker DRX 300 model spectrometer in $CDCl_3$ solutions at room temperature with TMS as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker DRX 600 model spectrometer in $CDCl_3$ solutions at room temperature with TMS as an internal standard. Chemical shifts (δ) for ^1H NMR and ^{13}C NMR spectra were reported in parts per million to residual solvent protons. Melting points were measured on a Boetius micro melting point apparatus.

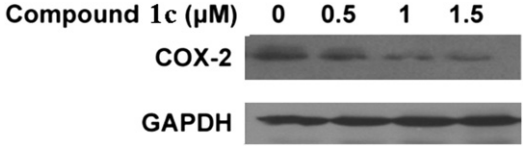


Fig. 1. Inhibitory effect of compound **1c** on COX-2 protein expression. Raw 264.7 cells (5×10^5) were incubated in 12 well culture plate for 24 h, and then treated with compounds and LPS (1 μg/mL) for 18 h. After incubation, cells were lysed, and protein was applied on SDS–polyacrylamide gel. The level of COX-2 protein expression was examined by western blotting analysis.

Table 3
Crystallographic data and structure refinements for compound **3e**.

Compound	**3e**
Formula	$C_{27}H_{33}NO_4$
Formula wt	435.54
Crystal system	monoclinic
Space group	P2(1)/n
Crystal size (mm^3)	0.30 × 0.20 × 0.20
a (Å)	13.273(5)
b (Å)	8.619(5)
c (Å)	22.032(5)
α (°)	90.000(5)
β (°)	99.450(5)
γ (°)	90.000(5)
V ($Å^3$)	2486.3(18)
Z	4
D_c (g cm^{-3})	1.164
μ (mm^{-1})	0.077
F (000)	936
θ range (°)	2.54–21.20
Reflns collected	16,842
Reflns unique	4381
Parameters	294
Goodness-of-fit on F^2	1.137
R_1, wR_2 [$I > 2\sigma(I)$]	0.0696, 0.1968
R_1, wR_2 [all data]	0.1173, 0.2323

Table 4
Selected bond lengths (Å) and angles (°) for compound **3e**.

Bond lengths			
C16–C19	1.469(5)	C19–C20	1.326(5)
C20–C21	1.464(5)	C11–C10	1.466(4)
C10–C9	1.332(4)	C9–C8	1.477(4)
C8–N1	1.344(5)	C8–O1	1.225(5)
C3–N1	1.481(5)	C4–N1	1.470(5)
C12–O2	1.363(4)	C14–O3	1.372(4)
C24–O4	1.366(5)	C17–O2	1.426(5)
C18–O3	1.411(5)	H27–O1	2.393(3)
H26···O1	2.513(3)	H23···O2	2.625(3)
Bond angles			
C15–C16–C19	118.8(3)	C11–C16–C19	121.2(3)
C16–C19–C20	126.2(3)	C19–C20–C21	126.5(3)
C20–C21–C22	122.6(3)	C20–C21–C26	120.3(3)
C16–C11–C10	124.0(30)	C12–C11–C10	118.0(3)
C11–C10–C9	128.4(3)	C10–C9–C8	120.4(3)
O1–C8–C9	121.4(3)	C27–H27B–O1	160.6(3)
C26–H26···O1	157.0(2)	C23–H23···O2	158.8(3)

The ESI-MS spectra were recorded on a Mariner System 5304 Mass spectrometer. Carbon, hydrogen and nitrogen assays were carried out with a CHN–O-Rapid instrument and were within ±0.4% of the theoretical values. TLC was run on the silica gel coated aluminum sheets (Silica Gel 60 GF254, E. Merk, Germany) and visualized in UV light (254 nm). Compound **A** was prepared as previously reported.

5.2. Synthesis (Scheme 1)

5.2.1. Procedure for the preparation of (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)acrylic acid (*B*)

To a solution of (*E*)-2,4-dimethoxy-6-(4-methoxystyryl)benzaldehyde (**A**) (2.98 g, 10 mmol) and malonic acid (3.12 g, 30 mmol) in 100 mL of pyridine was added 2 mL of piperidine, and the reaction mixture was stirred for 2 h at 95 °C, followed by adjustment of pH = 2 with HCl solution. A yellow crude product was obtained and purified by silica gel chromatography to afford the target product **B**. Yellow solid; Yield: 92.1%; m.p. 150–152 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.84 (s, 3H), 3.89 (s, 6H), 6.42 (d, 1H, J = 2.4 Hz), 6.51 (d, 1H, J = 15.9 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.89–6.94 (m, 3H), 7.27 (d, 1H, J = 16.2 Hz), 7.47–7.48 (m, 2H), 8.13 (d, 1H, J = 15.9 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.4, 97.5, 103.5, 114.2, 119.6, 124.8, 128.0, 132.1, 140.7, 160.7, 172.9. MS (ESI): 341.4 ($C_{20}H_{20}O_5$, $[M + H]^+$). Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92%; Found: C, 75.42; H, 5.94%.

5.2.2. General procedure for the preparation of compounds ***1a–q***, ***2a–h***, ***3a–l***

Compounds **1a–q**, **2a–h**, **3a–l** were synthesized by the known procedure as previously reported [14].

*5.2.2.1. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N-ethylacrylamide (**1a**).* White solid. Yield: 78.3%. m.p. 178–180 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18 (t, 3H, J = 5.4 Hz), 3.40 (q, 2H,

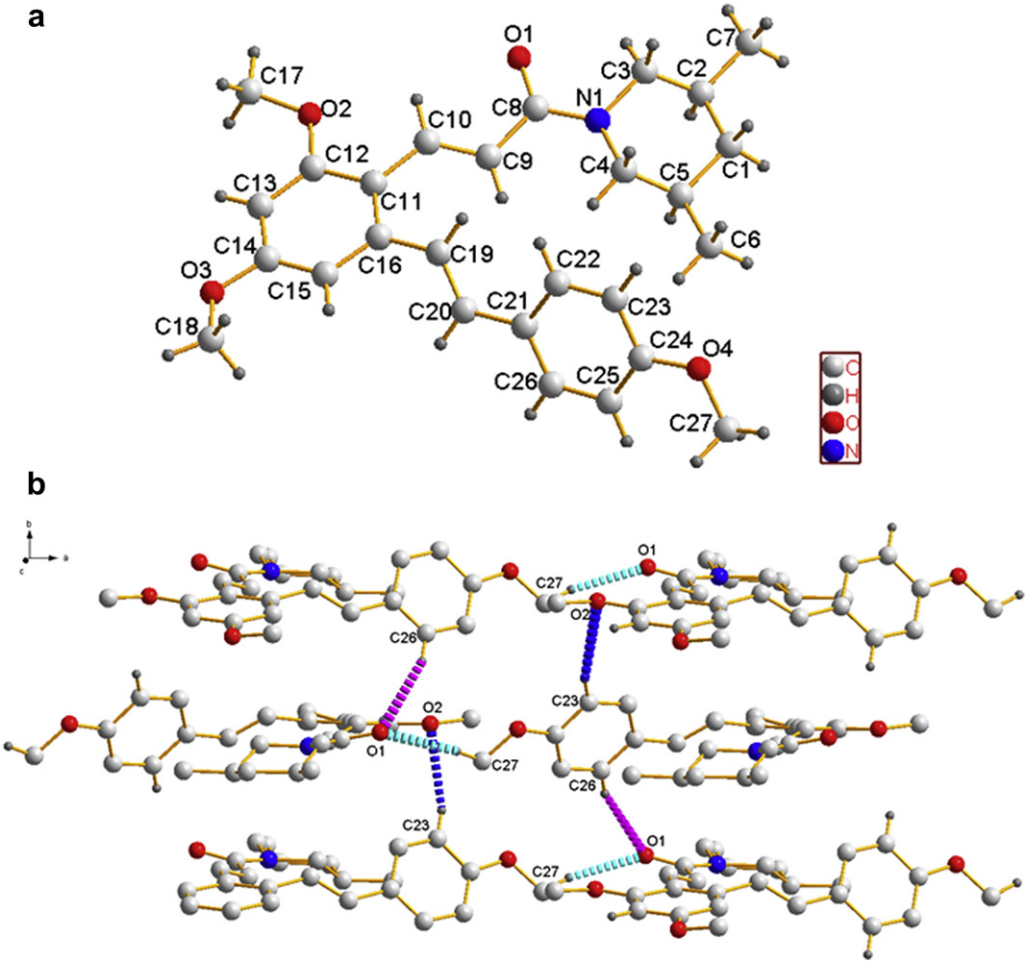


Fig. 2. Crystal structure of compound **3e.**

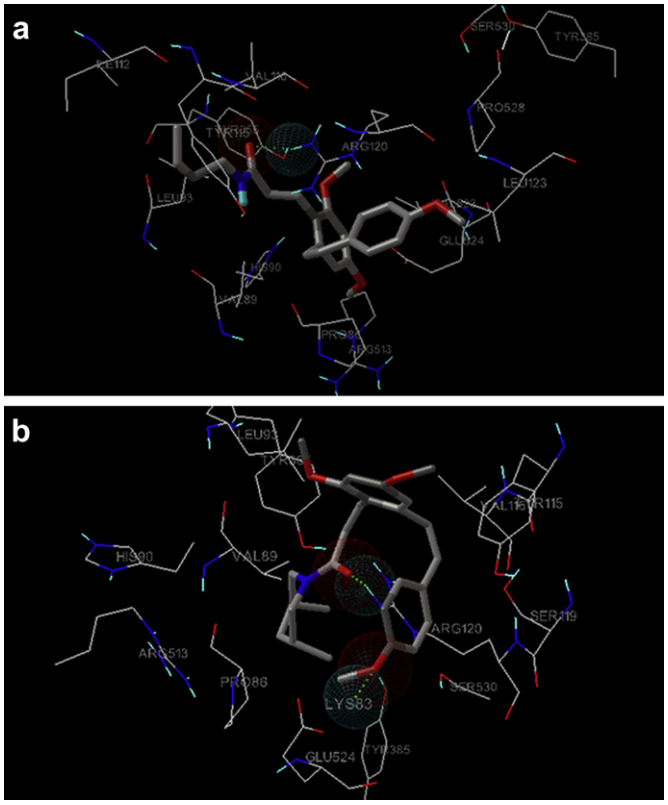


Fig. 3. (a) Binding mode of compound **1c** with COX-2; (b) Binding mode of compound **3e** with COX-2. The hydrogen bonds were displayed as green dotted lines. Hydrophobic interactions were shown as red balls (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

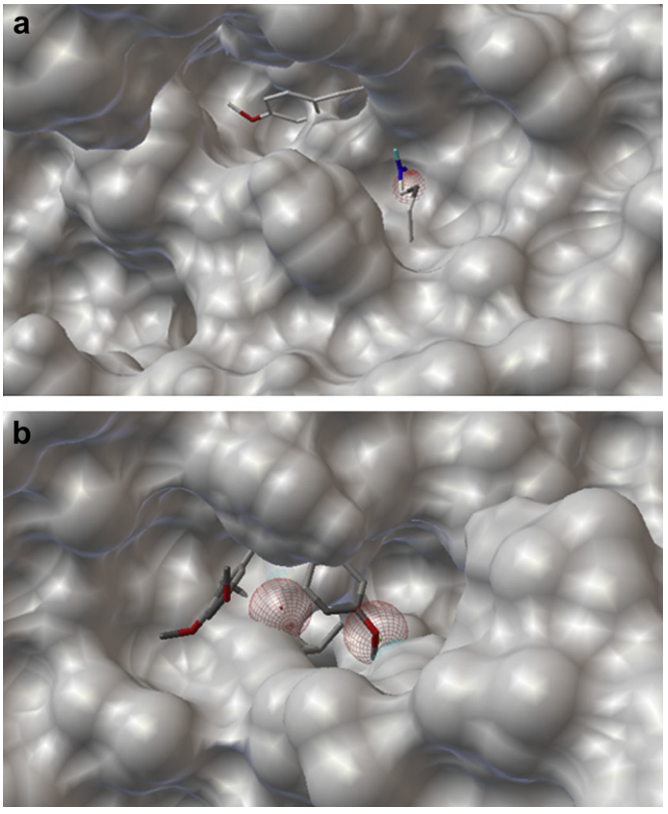


Fig. 4. (a) 3D mode of compound **1c** binding with COX-2; (b) 3D mode of compound **3e** binding with COX-2. The protein was represented by surface and the compounds were depicted by sticks and balls.

J = 5.4 Hz), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 5.50 (bras, 1H), 6.31 (d, 1H, J = 11.7 Hz), 6.41 (d, 1H, J = 1.8 Hz), 6.70 (d, 1H, J = 1.8 Hz), 6.89–6.93 (m, 3H), 7.27 (d, 1H, J = 12.0 Hz), 7.44–7.46 (m, 2H), 7.93 (d, 1H, J = 11.7 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.9, 34.5, 97.6, 103.0, 114.1, 125.5, 127.9, 130.9, 134.6, 159.5, 166.6. MS (ESI): 368.4 ($C_{22}H_{25}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81%; Found: C, 71.73; H, 6.88; N, 3.82%.

*5.2.2.2. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N-propylacrylamide (**1b**).* White solid. Yield: 83.1%. m.p. 142–145 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.95 (t, 3H, J = 7.5 Hz), 1.54–1.63 (m, 2H), 3.33 (q, 2H, J = 6.6 Hz), 3.83 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 5.55 (bras, 1H), 6.33 (d, 1H, J = 15.6 Hz), 6.40 (d, 1H, J = 2.1 Hz), 6.70 (d, 1H, J = 2.1 Hz), 6.88–6.93 (m, 3H), 7.28 (d, 1H, J = 15.9 Hz), 7.44–7.46 (m, 2H), 7.94 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 11.4, 22.9, 41.4, 55.3, 97.6, 103.0, 114.1, 124.2, 125.5, 127.9, 130.9, 134.6, 159.9, 166.7. MS (ESI): 382.5 ($C_{23}H_{27}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67%; Found: C, 72.30; H, 7.15; N, 3.68%.

*5.2.2.3. (E)-N-butyl-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl) phenyl)acrylamide (**1c**).* White solid. Yield: 87.2%. m.p. 153–155 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.93 (t, 3H, J = 7.2 Hz), 1.34–1.41 (m, 2H), 1.49–1.56 (m, 2H), 3.34–3.40 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 5.49 (bras, 1H), 6.32 (d, 1H, J = 15.6 Hz), 6.41 (d, 1H, J = 2.4 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.88–6.93 (m, 3H), 7.28 (d, 1H, J = 16.2 Hz), 7.43–7.46 (m, 2H), 7.93 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.7, 20.1, 31.7, 39.4, 55.4, 97.6, 103.0, 114.1, 125.5, 127.9, 130.9, 134.7, 140.4, 159.4, 160.7, 166.7. MS (ESI): 396.5 ($C_{24}H_{29}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54%; Found: C, 72.73; H, 7.41; N, 3.55%.

*5.2.2.4. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N-hexylacrylamide (**1d**).* White solid. Yield: 84.6%. m.p. 129–131 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, 3H, J = 6.6 Hz), 1.26–1.36 (m, 6H), 1.49–1.57 (m, 2H), 3.33–3.39 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 5.53 (bras, 1H), 6.32 (d, 1H, J = 15.6 Hz), 6.41 (d, 1H, J = 2.4 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.88–6.93 (m, 3H), 7.28 (d, 1H, J = 16.2 Hz), 7.43–7.46 (m, 2H), 7.94 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.0, 22.5, 26.7, 29.6, 31.5, 39.7, 55.4, 97.6, 114.1, 128.0, 130.9, 134.6, 140.4, 160.1, 166.7. MS (ESI): 424.5 ($C_{26}H_{33}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31%; Found: C, 73.55; H, 7.88; N, 3.32%.

*5.2.2.5. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N-octylacrylamide (**1e**).* White solid. Yield: 78.4%. m.p. 142–134 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, 3H, J = 6.6 Hz), 1.27–1.30 (m, 10H), 1.49–1.56 (m, 2H), 3.32–3.39 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 5.52 (bras, 1H), 6.32 (d, 1H, J = 15.6 Hz), 6.41 (d, 1H, J = 2.4 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.87–6.93 (m, 3H), 7.28 (d, 1H, J = 16.2 Hz), 7.43–7.46 (m, 2H), 7.93 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.1, 22.6, 27.0, 29.2, 29.7, 31.8, 39.7, 55.6, 97.6, 114.1, 127.9, 130.9, 134.6, 140.4, 160.1, 166.7. MS (ESI): 452.6 ($C_{28}H_{37}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{28}H_{37}NO_4$: C, 74.47; H, 8.26; N, 3.10%; Found: C, 74.32; H, 8.28; N, 3.11%.

*5.2.2.6. (E)-N-(2-chloroethyl)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)acrylamide (**1f**).* Yellow solid. Yield: 81.9%. m.p. 146–148 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.68–3.73 (m, 4H), 3.83

(s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 5.93 (bras, 1H), 6.39 (d, 1H, J = 11.7 Hz), 6.42 (d, 1H, J = 1.5 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.88–6.93 (m, 3H), 7.27 (d, 1H, J = 15.9 Hz), 7.44–7.47 (m, 2H), 7.97 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.7, 41.4, 44.2, 55.3, 97.6, 114.2, 123.2, 125.3, 127.9, 131.3, 135.6, 140.7, 160.1, 161.0, 166.9. MS (ESI): 402.1 ($C_{22}H_{24}ClNO_4$, $[M + H]^+$). Anal. Calcd for $C_{22}H_{24}ClNO_4$: C, 65.75; H, 6.02; N, 3.49%; Found: C, 65.91; H, 6.03; N, 3.48%.

*5.2.2.7. (E)-N-(3-chloropropyl)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)acrylamide (**1g**).* White solid. Yield: 65.3%. m.p. 147–149 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.03–2.10 (m, 2H), 3.53 (t, 2H, J = 6.3 Hz), 3.61 (t, 2H, J = 6.3 Hz), 3.83 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 5.74 (bras, 1H), 6.36 (d, 1H, J = 15.6 Hz), 6.41 (d, 1H, J = 2.4 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.87–6.92 (m, 3H), 7.27 (d, 1H, J = 16.2 Hz), 7.43–7.46 (m, 2H), 7.95 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.1, 22.7, 29.7, 32.2, 37.1, 42.6, 55.3, 97.5, 103.0, 114.1, 127.9, 131.0, 134.9, 140.6, 160.8, 167.2. MS (ESI): 416.9 ($C_{23}H_{26}ClNO_4$, $[M + H]^+$). Anal. Calcd for $C_{23}H_{26}ClNO_4$: C, 66.42; H, 6.30; N, 3.37%; Found: C, 66.62; H, 6.32; N, 3.36%.

*5.2.2.8. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N-(prop-2-yn-1-yl)acrylamide (**1h**).* White solid. Yield: 67.8%. m.p. 172–174 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.22–2.24 (t, 1H, J = 2.4), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.16–4.19 (m, 2H), 5.69 (bras, 1H), 6.37 (d, 1H, J = 15.6 Hz), 6.41 (d, 1H, J = 2.4 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.87–6.93 (m, 3H), 7.26 (d, 1H, J = 15.9 Hz), 7.43–7.46 (m, 2H), 7.97 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.3, 55.4, 97.6, 103.2, 114.2, 128.0, 131.3, 135.7, 140.7, 160.9, 166.5. MS (ESI): 378.4 ($C_{23}H_{23}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71%; Found: C, 73.38; H, 6.13; N, 3.70%.

*5.2.2.9. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N-isopropylacrylamide (**1i**).* White solid. Yield: 66.3%. m.p. 174–176 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20 (d, 6H, J = 3.6 Hz), 3.84 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.17–4.28 (m,1H), 5.36 (bras, 1H), 6.31 (d, 1H, J = 15.6 Hz), 6.41 (d, 1H, J = 2.4 Hz), 6.70 (d, 1H, J = 2.1 Hz), 6.88–6.93 (m, 3H), 7.28 (d, 1H, J = 15.6 Hz), 7.44–7.47 (m, 2H), 7.94 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 22.9, 41.4, 55.3, 97.6, 114.1, 128.0, 131.0, 134.6, 160.7, 165.9. MS (ESI): 382.5 ($C_{23}H_{27}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67%; Found: C, 72.26; H, 7.16; N, 3.68%.

*5.2.2.10. (E)-N-(tert-butyl)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)acrylamide (**1j**).* White solid. Yield: 65.9%. m.p. 145–147 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.42 (s, 9H), 3.84 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 5.36 (bras, 1H), 6.32 (d, 1H, J = 15.6 Hz), 6.41 (d, 1H, J = 2.4 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.88–6.93 (m, 3H), 7.31 (d, 1H, J = 15.9 Hz), 7.44–7.47 (m, 2H), 7.90 (d, 1H, J = 15.3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 28.9, 51.3, 55.3, 97.6, 114.1, 125.4, 128.0, 131.0, 133.9, 140.5, 160.0, 166.2. MS (ESI): 396.5 ($C_{24}H_{29}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54%; Found: C, 72.79; H, 7.41; N, 3.55%.

*5.2.2.11. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N-isobutylacrylamide (**1k**).* White solid. Yield: 62.8%. m.p. 162–164 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (d, 6H, J = 6.6 Hz), 1.79–1.88 (m, 1H), 3.20 (t, 2H, J = 6.6 Hz), 3.83 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 5.57 (bras, 1H), 6.34 (d, 1H, J = 15.6 Hz), 6.41 (d, 1H, J = 2.4 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.88–6.93 (m, 3H), 7.29 (d, 1H, J = 16.2 Hz), 7.44–7.47 (m, 2H), 7.95 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.1, 28.6, 47.0, 55.3, 97.6, 103.0, 114.1, 127.9, 130.8, 134.7, 140.4, 159.9, 166.8. MS (ESI): 396.2 ($C_{24}H_{29}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54%; Found: C, 72.77; H, 7.37; N, 3.55%.

*5.2.2.12. (E)-N-(sec-butyl)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)acrylamide (**1l**).* White solid. Yield: 69.3%. m.p. 158–160 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.93 (t, 3H, J = 7.2 Hz), 1.17 (d, 3H, J = 6.6 Hz), 1.49–1.56 (m, 2H), 3.83 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.01–4.11 (m, 1H), 5.30 (bras, 1H), 6.33 (d, 1H, J = 15.6 Hz), 6.41 (d, 1H, J = 2.1 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.88–6.93 (m, 3H), 7.30 (d, 1H, J = 15.9 Hz), 7.44–7.47 (m, 2H), 7.94 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 10.4, 20.5, 29.7, 46.7, 55.3, 97.6, 103.0, 114.1, 127.9, 130.9, 134.6, 140.5, 160.7, 166.1. MS (ESI): 396.2 ($C_{24}H_{29}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54%; Found: C, 73.09; H, 7.38; N, 3.55%.

*5.2.2.13. (E)-N-cyclopropyl-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)acrylamide (**1m**).* White solid. Yield: 72.7%. m.p. 204–206 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.52–0.58 (m, 2H), 0.78–0.84 (m, 2H), 2.81–2.87 (m, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 5.64 (bras, 1H), 6.28 (d, 1H, J = 15.6 Hz), 6.40 (d, 1H, J = 2.1 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.87–6.93 (m, 3H), 7.27 (d, 1H, J = 15.9 Hz), 7.43–7.47 (m, 2H), 7.96 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 45.9, 55.6, 97.6, 103.8, 136.6, 140.2, 160.7, 166.2. MS (ESI): 380.4 ($C_{23}H_{25}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69%; Found: C, 72.72; H, 6.63; N, 3.70%.

*5.2.2.14. (E)-N-cyclohexyl-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)acrylamide (**1n**).* White solid. Yield: 73.5%. m.p. 187–189 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.04–1.25 (m, 4H), 1.33–1.45 (m, 2H), 1.59–1.71 (m, 2H), 1.95–2.00 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.92–3.96 (m, 1H), 5.43 (bras, 1H), 6.32 (d, 1H, J = 15.6 Hz), 6.40 (d, 1H, J = 2.1 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.87–6.93 (m, 3H), 7.29 (d, 1H, J = 16.50 Hz), 7.44–7.47 (m, 2H), 7.93 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 25.6, 33.2, 48.3, 55.3, 97.6, 103.0, 125.4, 127.9, 130.9, 134.5, 140.4, 159.9, 165.7. MS (ESI): 422.5 ($C_{26}H_{31}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32%; Found: C, 74.26; H, 7.36; N, 3.31%.

*5.2.2.15. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N-(furan-2-ylmethyl)acrylamide (**1o**).* White solid. Yield: 76.5%. m.p. 164–166 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.77–3.94 (m, 9H), 4.55–4.59 (m, 2H), 5.85 (bras, 1H), 6.26–6.43 (m, 3H), 6.70–6.72 (m, 1H), 6.88–6.93 (m, 3H), 7.25–7.48 (m, 5H), 7.96–8.04 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.6, 36.6, 55.3, 97.6, 103.1, 107.4, 110.4, 123.3, 125.3, 128.2, 128.0, 131.2, 135.4, 142.1, 151.4, 160.1, 160.8, 166.6. MS (ESI): 420.5 ($C_{25}H_{25}NO_5$, $[M + H]^+$). Anal. Calcd for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34%; Found: C, 71.79; H, 5.99; N, 3.35%.

*5.2.2.16. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N-(3-morpholinopropyl)acrylamide (**1p**).* White solid. Yield: 74.9%. m.p. 145–147 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.70–1.74 (m, 2H), 2.40–2.43 (m, 4H), 2.48 (t, 2H, J = 6.0 Hz), 3.45–3.51 (m, 2H), 3.56–3.59 (m, 4H), 3.83 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 6.30 (d, 1H, J = 15.6 Hz), 6.42 (d, 1H, J = 2.1 Hz), 6.71(d, 1H, J = 2.4 Hz), 6.88–6.94 (m, 3H), 7.28 (d, 1H, J = 15.9 Hz), 7.44–7.46 (m, 2H), 7.92 (d, 1H, J = 15.9 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 24.5, 39.5, 53.4, 55.4, 57.8, 66.7, 97.6, 103.1, 114.1, 125.5, 127.9, 130.9, 134.3, 140.3, 159.9, 166.6. MS (ESI): 467.6 ($C_{27}H_{34}N_2O_5$, $[M + H]^+$). Anal. Calcd for $C_{27}H_{34}N_2O_5$: C, 69.51; H, 7.35; N, 6.00%; Found: C, 69.70; H, 7.36; N, 5.98%.

*5.2.2.17. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N-(3,4,5-trimethoxyphenyl)acrylamide (**1q**).* White solid. Yield: 65.3%. m.p. 155–157 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.80 (s, 3H), 3.81 (s, 3H), 3.82 (s, 6H), 3.85 (s, 3H), 3.88 (s, 3H), 6.41 (d, 1H, *J* = 2.1 Hz), 6.53 (d, 1H, *J* = 15.6 Hz), 6.69 (d, 1H, *J* = 2.4 Hz), 6.87–6.95 (m, 4H), 7.28 (d, 1H, *J* = 15.9 Hz), 7.42–7.46 (m, 3H), 8.08 (d, 1H, *J* = 15.3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.3, 56.5, 97.7, 103.2, 114.1, 125.3, 128.0, 129.9, 131.3, 133.5, 140.8, 159.5, 164.5. MS (ESI): 506.6 ($C_{29}H_{31}NO_7$, $[M + H]^+$). Anal. Calcd for $C_{29}H_{31}NO_7$: C, 68.90; H, 6.18; N, 2.77%; Found: C, 69.06; H, 6.17; N, 2.78%.

*5.2.2.18. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N,N-dimethylacrylamide (**2a**).* Light white oil. Yield: 83.2%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.04 (s, 6H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 6.42 (d, 1H, *J* = 2.4 Hz), 6.71 (d, 1H, *J* = 2.4 Hz), 6.81 (d, 1H, *J* = 15.6 Hz), 6.87–6.93 (m, 3H), 7.30 (d, 1H, *J* = 16.2 Hz), 7.44–7.47 (m, 2H), 7.97 (d, 1H, *J* = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.3, 55.6, 97.6, 103.1, 114.1, 116.1, 121.4, 125.8, 127.8, 130.7, 136.0, 140.2, 159.4, 160.6. MS (ESI): 368.4 ($C_{22}H_{25}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81%; Found: C, 72.07; H, 6.87; N, 3.80%.

*5.2.2.19. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N,N-diethylacrylamide (**2b**).* Light white oil. Yield: 81.3%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.07 (t, 3H, *J* = 6.9 Hz), 1.17 (t, 3H, *J* = 7.2 Hz), 3.34 (q, 2H, *J* = 7.2 Hz), 3.47 (q, 2H, *J* = 7.2 Hz), 3.81 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 6.41 (d, 1H, *J* = 2.4 Hz), 6.70 (d, 1H, *J* = 2.4 Hz), 6.76 (d, 1H, *J* = 15.6 Hz), 6.86–6.93 (m, 3H), 7.29 (d, 1H, *J* = 15.9 Hz), 7.43–7.46 (m, 2H), 8.00 (d, 1H, *J* = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.2, 40.9, 55.2, 97.6, 103.2, 114.0, 116.7, 121.8, 125.9, 127.8, 130.8, 135.8, 140.2, 159.8, 160.3, 166.4. MS (ESI): 396.5 ($C_{24}H_{29}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54%; Found: C, 73.06; H, 7.41; N, 3.53%.

*5.2.2.20. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N,N-dipropylacrylamide (**2c**).* Light white oil. Yield: 87.6%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.68–0.93 (m, 6H), 1.55–1.64 (m, 4H), 3.24–3.37 (m, 4H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 6.42 (d, 1H, *J* = 2.4 Hz), 6.70 (d, 1H, *J* = 2.4 Hz), 6.77 (d, 1H, *J* = 15.3 Hz), 6.86–6.93 (m, 3H), 7.31 (d, 1H, *J* = 15.9 Hz), 7.43–7.48 (m, 2H), 8.03 (d, 1H, *J* = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 10.9, 22.1, 22.9, 48.5, 49.8, 55.2, 97.4, 103.2, 109.3, 113.9, 116.5, 121.6, 125.8, 127.8, 130.7, 135.7, 140.2, 160.6, 166.7. MS (ESI): 424.5 ($C_{26}H_{33}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31%; Found: C, 73.89; H, 7.88; N, 3.30%.

*5.2.2.21. (E)-N,N-dibutyl-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)acrylamide (**2d**).* Light white oil. Yield: 85.4%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.75 (t, 3H, *J* = 5.4 Hz), 0.94 (t, 3H, *J* = 5.4 Hz), 1.09–1.15 (m, 2H), 1.32–1.37 (m, 2H), 1.46–1.59 (m, 4H), 3.24 (t, 2H, *J* = 5.7 Hz), 3.40 (t, 2H, *J* = 5.7 Hz), 3.81 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 6.41 (d, 1H, *J* = 1.8 Hz), 6.70 (d, 1H, *J* = 1.5 Hz), 6.78 (d, 1H, *J* = 11.4 Hz), 6.86–6.93 (m, 3H), 7.30 (d, 1H, *J* = 12.0 Hz), 7.43–7.45 (m, 2H), 8.01 (d, 1H, *J* = 11.7 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.5, 19.9, 30.1, 46.7, 55.2, 97.6, 103.2, 114.0, 116.7, 121.7, 125.9, 127.9, 135.8, 140.2, 160.6, 166.7. MS (ESI): 452.3 ($C_{28}H_{37}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{28}H_{37}NO_4$: C, 74.47; H, 8.26; N, 3.10%; Found: C, 74.62; H, 8.28; N, 3.09%.

*5.2.2.22. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N,N-diisobutylacrylamide (**2e**).* Light white oil. Yield: 72.2%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.72 (d, 6H, *J* = 5.1 Hz), 0.90 (d, 6H, *J* = 5.1 Hz), 1.82–1.89 (m, 1H), 2.04–2.11 (m, 1H), 3.09 (d, 2H, *J* = 5.7 Hz), 3.28 (d, 2H, *J* = 5.7 Hz), 3.82 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 6.41 (d, 1H, *J* = 1.8 Hz), 6.70 (d, 1H, *J* = 1.8 Hz), 6.80 (d, 1H, *J* = 11.7 Hz), 6.86–6.93 (m, 3H), 7.28 (d, 1H, *J* = 12.0 Hz), 7.42–7.45 (m, 2H), 8.00 (d, 1H, *J* = 11.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.3, 27.0, 29.2, 55.2, 97.5, 103.2, 114.0, 116.6, 121.8, 125.9, 127.9, 129.9, 130.7, 135.7, 140.2, 160.6, 167.2. MS (ESI): 452.6 ($C_{28}H_{37}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{28}H_{37}NO_4$: C, 74.47; H, 8.26; N, 3.10%; Found: C, 74.68; H, 8.24; N, 3.11%.

*5.2.2.23. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N,N-dipentylacrylamide (**2f**).* Light white oil. Yield: 74.7%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.71–0.92 (m, 12H), 1.05–1.61 (m, 6H), 2.99–3.41 (m, 4H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 6.42 (d, 1H, *J* = 2.4 Hz), 6.70 (d, 1H, *J* = 1.5 Hz), 6.73–6.80 (m, 1H), 6.86–6.94 (m, 3H), 7.25–7.34 (m, 1H), 7.42–7.46 (m, 2H), 8.00 (d, 1H, *J* = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 11.4, 13.9, 16.7, 22.6, 27.1, 29.6, 55.3, 97.6, 103.2, 114.0, 125.9, 127.9, 130.8, 159.4, 160.6. MS (ESI): 480.7 ($C_{30}H_{41}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{30}H_{41}NO_4$: C, 75.12; H, 8.62; N, 2.92%; Found: C, 74.93; H, 8.61; N, 2.93%.

*5.2.2.24. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-N,N-dihexylacrylamide (**2g**).* Light white oil. Yield: 79.1%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.82 (t, 3H, *J* = 7.2 Hz), 0.89 (t, 3H, *J* = 6.9 Hz), 1.08–1.31 (m, 12H), 1.49–1.58 (m, 4H), 3.23 (t, 2H, *J* = 7.50 Hz), 3.39 (t, 2H, *J* = 7.5 Hz), 3.82 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 6.42 (d, 1H, *J* = 2.4 Hz), 6.70 (d, 1H, *J* = 2.4 Hz), 6.76 (d, 1H, *J* = 15.3 Hz), 6.86–6.93 (m, 3H), 7.30 (d, 1H, *J* = 16.2 Hz), 7.43–7.46 (m, 2H), 8.01 (d, 1H, *J* = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.8, 22.5, 26.4, 26.7, 27.9, 29.7, 31.2, 31.6, 47.0, 48.2, 55.2, 97.5, 103.2, 114.0, 116.6, 121.7, 125.8, 127.8, 129.9, 130.7, 135.8, 140.2, 159.4, 160.6, 166.7. MS (ESI): 508.7 ($C_{32}H_{45}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{32}H_{45}NO_4$: C, 75.70; H, 8.93; N, 2.76%; Found: C, 75.97; H, 8.91; N, 2.77%.

*5.2.2.25. (E)-N,N-diallyl-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)acrylamide (**2h**).* Light white oil. Yield: 75.6%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.83 (s, 3H), 3.83 (s, 3H), 3.83–3.87 (m, 5H), 4.07–4.09 (m, 2H), 4.97–5.18 (m, 4H), 5.77–5.90 (m, 1H), 5.59–5.71 (m, 1H), 6.41 (d, 1H, *J* = 2.4 Hz), 6.69 (d, 1H, *J* = 2.4 Hz), 6.73 (d, 1H, *J* = 15.3 Hz), 6.87–6.92 (m, 3H), 7.25 (d, 1H, *J* = 15.9 Hz), 7.42–7.44 (m, 2H), 8.03 (d, 1H, *J* = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 48.7, 55.6, 97.6, 103.2, 114.0, 116.5, 117.1, 121.3, 125.8, 127.9, 130.9, 133.5, 136.7, 140.3, 159.4, 160.7, 167.4. MS (ESI): 420.5 ($C_{26}H_{29}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34%; Found: C, 74.22; H, 6.99; N, 3.35%.

*5.2.2.26. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-1-(piperidin-1-yl)prop-2-en-1-one (**3a**).* White solid. Yield: 83.7%. m.p. 92–93 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.50–1.66 (m, 6H), 3.45 (bras, 2H), 3.65 (bras, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 6.41 (d, 1H, *J* = 2.4 Hz), 6.70 (d, 1H, *J* = 2.4 Hz), 6.80 (d, 1H, *J* = 15.6 Hz), 6.87–6.93 (m, 3H), 7.28 (d, 1H, *J* = 16.2 Hz), 7.43–7.46 (m, 2H), 7.94 (d, 1H, *J* = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 24.6, 55.3, 97.6, 103.0, 114.1, 121.5, 125.9, 127.8, 130.6, 136.0, 140.1, 160.6, 166.1. MS (ESI): 408.5 ($C_{25}H_{29}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44%; Found: C, 73.49; H, 7.20; N, 3.43%.

*5.2.2.27. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-1-(2-methylpiperidin-1-yl)prop-2-en-1-one (**3b**).* Light white oil. Yield: 65.2%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.16 (d, 3H, *J* = 6.9 Hz), 1.39–1.64 (m, 7H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 6.41 (d, 1H, *J* = 2.4 Hz), 6.70 (d, 1H, *J* = 2.4 Hz), 6.78 (d, 1H, *J* = 15.6 Hz), 6.87–6.93 (m, 3H), 7.28 (d, 1H, *J* = 16.2 Hz), 7.43–7.46 (m, 2H), 7.94 (d, 1H, *J* = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 18.8, 55.3, 97.5, 103.1, 114.0, 116.7, 122.0, 127.8, 130.5, 135.7, 139.9, 159.7, 160.5, 166.2. MS (ESI): 422.5 ($C_{26}H_{31}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32%; Found: C, 74.35; H, 7.43; N, 3.31%.

*5.2.2.28. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-1-(3-methylpiperidin-1-yl)prop-2-en-1-one (**3c**).* White solid. Yield: 71.4%. m.p. 115–117 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.71–0.93 (m, 3H), 1.10–1.82 (m, 6H), 2.28–2.97 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.46–4.57 (m, 1H), 6.41 (d, 1H, J = 2.4 Hz), 6.71 (d, 1H, J = 2.4 Hz), 6.80 (d, 1H, J = 15.3 Hz), 6.87–6.93 (m, 3H), 7.28 (d, 1H, J = 16.2 Hz), 7.43–7.46 (m, 2H), 7.94 (d, 1H, J = 15.1 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 33.1, 55.4, 97.6, 103.1, 114.1, 121.7, 127.8, 130.6, 135.9, 140.1, 160.6, 166.0. MS (ESI): 422.2 ($C_{26}H_{31}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32%; Found: C, 73.97; H, 7.40; N, 3.34%.

*5.2.2.29. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-1-(4-methylpiperidin-1-yl)prop-2-en-1-one (**3d**).* Light white oil. Yield: 74.5%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.93 (d, 3H, J = 6.3 Hz), 1.07–1.17 (m, 2H), 1.56–1.76 (m, 4H), 2.60–2.68 (m, 1H), 2.93–3.01 (m, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.66–4.71 (m, 1H), 6.41 (d, 1H, J = 2.4 Hz), 6.71 (d, 1H, J = 2.4 Hz), 6.80 (d, 1H, J = 15.3 Hz), 6.87–6.93 (m, 3H), 7.28 (d, 1H, J = 16.2 Hz), 7.43–7.46 (m, 2H), 7.94 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.7, 31.1, 55.3, 97.6, 103.1, 114.1, 116.8, 121.7, 125.9, 127.8, 130.6, 135.9, 140.0, 160.6, 166.0. MS (ESI): 422.3 ($C_{26}H_{31}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32%; Found: C, 73.99; H, 7.39; N, 3.32%.

*5.2.2.30. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-1-(3,5-dimethylpiperidin-1-yl)prop-2-en-1-one (**3e**).* White solid. Yield: 76.1%. m.p. 118–120 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.69–0.91 (m, 8H), 1.53–1.62 (m, 2H), 1.77–1.91 (m, 2H), 2.03–2.09 (m, 1H), 2.41–2.47 (m, 1H), 3.82 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 6.41 (d, 1H, J = 1.5 Hz), 6.70 (d, 1H, J = 1.8 Hz), 6.79 (d, 1H, J = 11.7 Hz), 6.87–6.93 (m, 3H), 7.26 (d, 1H, J = 12.0 Hz), 7.43–7.46 (m, 2H), 7.93 (d, 1H, J = 11.7 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.0, 42.5, 55.4, 97.6, 103.1, 114.1, 121.6, 126.0, 127.8, 130.6, 136.0, 140.1, 159.7, 160.6, 165.8. MS (ESI): 436.6 ($C_{27}H_{33}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22%; Found: C, 74.33; H, 7.67; N, 3.21%.

*5.2.2.31. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-1-(2-ethylpiperidin-1-yl)prop-2-en-1-one (**3f**).* White solid. Yield: 77.4%. m.p. 91–92 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.68–0.90 (m, 3H), 1.46–1.77 (m, 9H), 2.61–3.03 (m, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.62–4.84 (m, 1H), 6.42 (d, 1H, J = 2.1 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.79 (d, 1H, J = 15.6 Hz), 6.86–6.93 (m, 3H), 7.28 (d, 1H, J = 15.9 Hz), 7.42–7.45 (m, 2H), 7.94 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 10.7, 19.1, 55.3, 97.6, 103.0, 114.0, 127.8, 130.5, 135.7, 160.5. MS (ESI): 436.4 ($C_{27}H_{33}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22%; Found: C, 74.71; H, 7.62; N, 3.23%.

*5.2.2.32. (E)-1-(4-chloropiperidin-1-yl)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)prop-2-en-1-one (**3g**).* White solid. Yield: 72.8%. m.p. 61–62 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.77–1.86 (m, 2H), 2.01–2.07 (m, 2H), 3.52–3.59 (m, 2H), 3.79–3.88 (m, 11H), 4.24–4.29 (m, 1H), 6.42 (d, 1H, J = 2.4 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.80 (d, 1H, J = 15.3 Hz), 6.88–6.93 (m, 3H), 7.27 (d, 1H, J = 15.9 Hz), 7.43–7.46 (m, 2H), 7.97 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.4, 56.9, 97.6, 103.2, 114.1, 120.6, 125.8, 127.8, 130.9, 136.8, 140.3, 160.8, 166.2. MS (ESI): 442.9 ($C_{25}H_{28}ClNO_4$, $[M + H]^+$). Anal. Calcd for $C_{25}H_{28}ClNO_4$: C, 67.94; H, 6.39; N, 3.17%; Found: C, 67.83; H, 6.37; N, 3.18%.

*5.2.2.33. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-1-(4-phenylpiperidin-1-yl)prop-2-en-1-one (**3h**).* White solid. Yield: 67.4%. m.p. 127–129 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.11–1.24 (m, 2H), 1.69–1.80 (m, 2H), 2.50–2.96 (m, 4H), 3.82 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.49–4.74 (m, 1H), 6.41 (d, 1H, J = 2.4 Hz), 6.70 (d, 1H, J = 2.1 Hz), 6.80 (d, 1H, J = 15.3 Hz), 6.86–6.93 (m, 3H), 7.11–7.14 (m, 2H), 7.21–7.25 (m, 1H), 7.25–7.31 (m, 3H), 7.42–7.45 (m, 2H), 7.94 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 38.3, 42.9, 55.3, 97.6, 103.1, 114.1, 125.1, 128.2, 136.1, 140.0, 160.6, 166.0. MS (ESI): 484.6 ($C_{31}H_{33}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{31}H_{33}NO_4$: C, 76.99; H, 6.88; N, 2.90%; Found: C, 76.87; H, 6.90; N, 2.91%.

*5.2.2.34. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-1-(4-methylpiperazin-1-yl)prop-2-en-1-one (**3i**).* White solid. Yield: 84.7%. m.p. 73–74 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.29 (s, 3H), 2.36–2.41 (m, 4H), 3.54–3.76 (m, 4H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 6.42 (d, 1H, J = 2.4 Hz), 6.70 (d, 1H, J = 2.1 Hz), 6.79 (d, 1H, J = 15.6 Hz), 6.87–6.93 (m, 3H), 7.26 (d, 1H, J = 16.2 Hz), 7.43–7.46 (m, 2H), 7.96 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 6.7, 22.8, 55.3, 97.6, 103.0, 114.1, 123.6, 125.4, 127.9, 131.0, 134.8, 140.5, 159.4, 168.1. MS (ESI): 423.5 ($C_{25}H_{30}N_2O_4$, $[M + H]^+$). Anal. Calcd for $C_{25}H_{30}N_2O_4$: C, 71.07; H, 7.16; N, 6.63%; Found: C, 70.91; H, 7.15; N, 6.65%.

*5.2.2.35. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-1-morpholinoprop-2-en-1-one (**3j**).* White solid. Yield: 88.2%. m.p. 103–105 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.45–3.69 (m, 8H), 3.83 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 6.42 (d, 1H, J = 2.4 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.77 (d, 1H, J = 15.6 Hz), 6.88–6.93 (m, 3H), 7.26 (d, 1H, J = 15.9 Hz), 7.42–7.45 (m, 2H), 7.99 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.6, 36.5, 39.5, 55.3, 66.8, 97.6, 103.2, 114.1, 120.2, 125.8, 127.8, 130.9, 136.9, 140.4, 160.8, 166.4. MS (ESI): 410.5 ($C_{24}H_{27}NO_5$, $[M + H]^+$). Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42%; Found: C, 70.23; H, 6.66; N, 3.43%.

*5.2.2.36. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-1-thiomorpholinoprop-2-en-1-one (**3k**).* White solid. Yield: 83.6%. m.p. 138–140 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.48–2.69 (m, 4H), 3.77–3.82 (m, 4H), 3.83 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 6.42 (d, 1H, J = 2.4 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.75 (d, 1H, J = 15.3 Hz), 6.88–6.93 (m, 3H), 7.25 (d, 1H, J = 16.2 Hz), 7.43–7.46 (m, 2H), 7.98 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.3, 97.6, 103.2, 114.1, 120.7, 125.8, 127.8, 130.9, 136.9, 140.3, 160.8, 166.4. MS (ESI): 426.5 ($C_{24}H_{27}NO_4S$, $[M + H]^+$). Anal. Calcd for $C_{24}H_{27}NO_4S$: C, 67.74; H, 6.40; N, 3.29%; Found: C, 67.63; H, 6.41; N, 3.30%.

*5.2.2.37. (E)-3-(2,4-dimethoxy-6-((E)-4-methoxystyryl)phenyl)-1-(pyrrolidin-1-yl)prop-2-en-1-one (**3l**).* White solid. Yield: 76.7%. m.p. 100–101 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.84–1.93 (m, 4H), 3.45 (t, 2H, J = 6.6 Hz), 3.59 (t, 2H, J = 6.6 Hz), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 6.42 (d, 1H, J = 2.1 Hz), 6.64 (d, 1H, J = 15.6 Hz), 6.71 (d, 1H, J = 2.4 Hz), 6.88–6.94 (m, 3H), 7.29 (d, 1H, J = 15.9 Hz), 7.44–7.46 (m, 2H), 7.99 (d, 1H, J = 15.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 24.3, 26.1, 46.4, 97.6, 103.0, 114.1, 122.8, 125.8, 127.9, 130.6, 135.3, 140.2, 160.6, 165.5. MS (ESI): 394.5 ($C_{24}H_{27}NO_4$, $[M + H]^+$). Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56%; Found: C, 73.45; H, 6.91; N, 3.57%.

5.3. X-ray crystallography

The crystallographic data for compound **3e** were collected on a Bruker Smart 1000 CCD area detector diffractometer. Equipped with Mo $K\alpha$ (λ = 0.71073Å) radiation using ω-scan mode. Empirical absorption correction was applied to the data. The structures were solved by direct methods and refined by full-matrix least-squares methods on F^2. All non-hydrogen atoms were located from the trial structure and then refined anisotropically. All hydrogen atoms were

generated in idealized positions and were assigned fixed isotropic thermal parameters at 1.2 times the equivalent isotropic U of the atoms to which they are attached and allowed to ride on their respective parent atoms. The contributions of these hydrogen atoms were included in the structure-factors calculations. Other relevant parameters of the crystal structure are listed in Table 3. Table 4 shows some selected bond lengths (Å) and angles for **3e**.

5.4. Antiproliferation assay

The antiproliferative activity of the prepared compounds against B16-F10, MCF-7 and A549 cell lines was evaluated as described elsewhere with some modifications [17]. Target tumor cell lines were grown to log phase in RPMI 1640 medium supplemented with 10% fetal bovine serum. After diluting to 2×10^4 cells mL^{-1} with the complete medium, 100 μL of the obtained cell suspension was added to each well of 96-well culture plates. The subsequent incubation was permitted at 37 °C, 5% CO_2 atmosphere for 24 h before the cytotoxicity assessments. Tested samples at pre-set concentrations were added to 6 wells with celecoxib coassayed as positive reference. After 48 h exposure period, 40 μL of PBS containing 2.5 mg mL^{-1} of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)) was added to each well. 4 h later, 100 μL extraction solution (10% SDS–5% isobutyl alcohol–0.01 M HCl) was added. After an overnight incubation at 37 °C, the optical density was measured at a wavelength of 570 nm on an ELISA microplate reader. In all experiments three replicate wells were used for each drug concentration. Each assay was carried out at least three times. The results were summarized in Table 2.

5.5. In vitro cyclooxygenase (COX) inhibition assays

The ability of the test compounds to inhibit COX-1 and COX-2 was determined using chemiluminescent enzyme assays kit (Cayman Chemical, Ann Arbor, MI, USA) according to previously reported method [18].

5.6. Anti-inflammatory assay

The inhibitory effects of samples on PGE_2 expression were evaluated in lipopolysaccharide (LPS)-activated murine macrophage RAW 264.7 cells, using a method modified from that previously reported [19].

5.7. Western immunoblot analysis

RAW 264.7 cells were pretreated with **1c** at the concentrations of 0.5, 1.0, 1.5 μM for 15 min before treatment with 1 μg mL^{-1} LPS for 18 h and examining the expression of COX-2 protein. Cells were lysed with lysis buffer. Western immunoblot analysis was performed using a method described by Cheenpracha *et al.* [20].

5.8. Molecular modeling (docking) studies

Molecular docking of compounds into the three dimensional COX-2 complex structure (PDB code: 1cx2) was carried out using the Molsoft ICM-Pro software package (version 3.5-0a) [21,22].

Acknowledgments

This work was supported by the Fundamental Research Funds for the Central Universities (2012HGZY0021, 2012HGCX0003 and 2012HGQC0034).

Appendix A. Supplementary material

CCDC 845819 contains the supplementary crystallographic data for compound **3e**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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