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Design, synthesis and biological evaluation of a series of pyrano chalcone derivatives containing indole moiety as novel anti-tubulin agents

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ABSTRACT

A new series of pyrano chalcone derivatives containing indole moiety (**3**–**42**, **49a**–**49r**) were synthesized and evaluated for their antiproliferative activities. Among all the compounds, compound **49b** with a propionyloxy group at the 4-position of the left phenyl ring and *N*-methyl-5-indoly on the right ring displayed the most potent cytotoxic activity against all tested cancer cell lines including multidrug resistant phenotype, which inhibits cancer cell growth with IC_{50} values ranging from 0.22 to 1.80 μM. Furthermore, **49b** significantly induced cell cycle arrest in G2/M phase and inhibited the polymerization of tubulin. Molecular docking analysis demonstrated the interaction of **49b** at the colchicine binding site of tubulin. In experiments in vivo, **49b** exerted potent anticancer activity in HepG2 human liver carcinoma in BALB/c nude mice. These results indicated these compounds are promising inhibitors of tubulin polymerization for the potential treatment of cancer.

1. Introduction

Microtubules are essential cytoskeletal polymers in all eukaryotic cells controlling various cellular functions, including cell signaling, cell division, secretion, cell architecture in interphase, and intracellular transport[1–3] and are recognized as important targets for the development of compounds useful in anticancer chemotherapy. The three characterized binding sites of tubulin are the taxane,[4] vinca alkaloid[5] and colchicine sites.[6] Anti-mitotic compounds such as taxanes and vinca alkaloids have been widely used in the clinical treatment of different human cancers over the past decade.[7] However, the development of drug resistance, side effects, complex synthesis, and low bioavailability render these drugs suboptimum for clinical treatment of cancer.[8] This has encouraged scientists and industry to develop novel antimitotic agents for cancer therapy.

Indole-based derivatives have been found to exhibit a variety of biological activities such as antiproliferative,[9] anti-inflammatory,[10] antimalarial,[11] anti-bacterial,[12] and antifungal activities.[13] The indole moiety emerged as a versatile molecular skeleton for the development of compounds with antitubulin activity.[14,15] Over the last few years, numbers of tubulin polymerization inhibitors containing indole moiety have been obtained from natural sources or have been prepared by chemical synthesis. Among them, vinblastine[16] and vincristine,[16] which have been used in clinical and indibulin,[17] MKC-1[18] and LP-261,[19] which are in clinical trials showed good antiproliferative activities (Fig. 1).

Recently, we have reported the synthesis and biological evaluation of three different series of pyrano chalcone derivatives,[20–22] based on the molecular skeleton of nature occurring pyrano chalcone millepachine which isolated from *Millettia pachycarpa* for the first time in our group.[23] These compounds strongly inhibited the growth of cancer cell lines and tubulin polymerization by binding to the colchicine site of tubulin and caused cells to arrest in the G2/M phase of the cell cycle. As a part of our search for novel tubulin polymerization inhibitors, these encouraging results prompted us to synthesize a new series of pyrano chalcone derivatives containing indole moiety.

In the present investigation, a new series of pyrano chalcone derivatives containing indole moiety (**3**–**42**, **49a**–**49r**) were synthesized and evaluated for their cytotoxic activities. Among all the compounds, compound **49b** displayed the most potent cytotoxic

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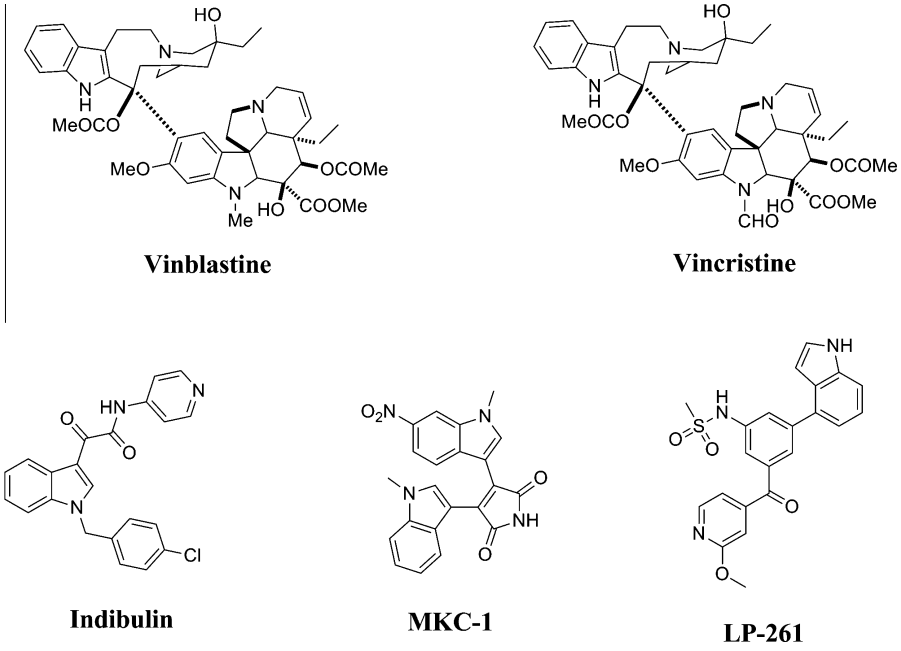


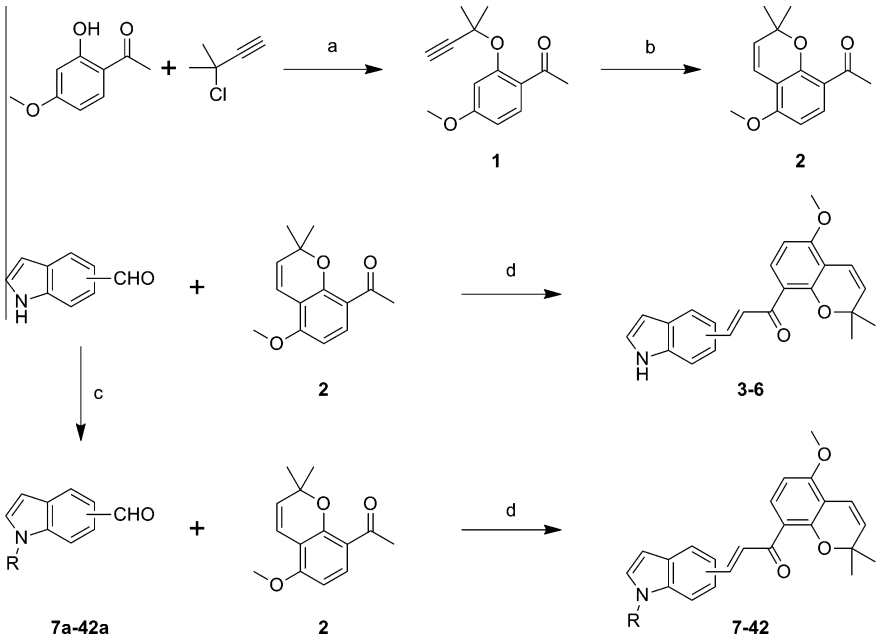
Figure 1. Structures of some indole-based molecules as anti-tubulin agents.

activity against all tested cancer cell lines including multidrug resistant phenotype, which inhibits cancer cell growth with IC_{50} values ranging from 0.22 to 1.80 μM. Furthermore, **49b** significantly induced cell cycle arrest in G2/M phase and inhibit the polymerization of tubulin. Molecular docking analysis demonstrated the interaction of compound **49b** at the colchicine binding site of tubulin.

2. Chemistry

Pyrano chalcone derivatives containing indole moiety **3**–**42** were prepared by the synthetic route outlined in Scheme 1. Treatment of paeonol with 3-chloro-3-methyl-1-butyne in the presence of DBU and catalytic amounts of $CuCl_2{\cdot}H_2O$ proceeded smoothly to afforded 1,1-dimethylpropargyl ether **1** in good yield, which, upon heating in pyridine at 120 °C for overnight, underwent Claisen rearrangement, leading to key intermediate **2**. Having appropriate quantities intermediate **2**, we focus on the synthesis of N-alkyl indole aldehydes **7a**–**42a**, which were synthesized, in moderate to good yields, by heating indole aldehydes with various alkyl halides in the presence of Cs_2CO_3 in CH_3CN. Condensation of **2** and N–H indole aldehydes or *N*-alkyl indole aldehydes **7a**–**42a** under Claisen–Schmidt conditions using 50% KOH in methanol provided the desired compounds **3**–**42**.

Compounds **49a**–**49r** were synthesized by the method shown in Scheme 2. The 4-hydroxyl of 1-(2,4-dihydroxyphenyl)ethanone **43** was protected with 3,4-dihydro-2*H*-Pyran in dichloromethane in the presence of pyridinium p-toluenesulfonate (PPTS) to give the



Scheme 1. Reagents and conditions: (a) DBU, $CuCl_2{\cdot}H_2O$, CH_3CN, 0 °C, 5 h; (b) pyridine, 120 °C, 12 h; (c) Cs_2CO_3, CH_3CN, 60 °C, 2 h; (d) KOH, methanol, 48 h, room temperature.

THP ether **44**, which condensation with 3-chloro-3-methyl-1-butyne in the presence of DBU and catalytic amounts of $CuCl_2 \cdot H_2O$ provided the 1,1-dimethylpropargyl ether **45**, The crude **45** was directly heating in pyridine at 120 °C for overnight, underwent Claisen rearrangement, leading to key intermediate **46**. Condensation of **46** and 1-methyl-1*H*-indole-5-carbaldehyde **31a** under Claisen–Schmidt conditions using 50% KOH in methanol provided the desired compound **47**. Deprotection of the THP groups using *p*-toluenesulfonic acid in CH_3OH–THF (1:1) solution at 60 °C for 5 h yielded key intermediate **48**, followed by an esterification or etherification of the liberated phenol with acid anhydride, alkyl halide and sulfonyl halide to afford the final desired products **49a**–**49r**.

3. Results and discussion

3.1. Antiproliferative activity in vitro

The synthesized pyrano chalcone derivatives **3**–**42** were evaluated for their antiproliferative activities against human hepatocellular liver carcinoma cell line HepG2, which has widely been used for the screening of potential antitumor compounds, by using MTT method. Millepachine was chosen as reference molecules. The compounds that exhibit $IC_{50} > 10.0$ μM are considered to be inactive on the respective cancer cell lines. The cytotoxicities were expressed as IC_{50} values presented in Table 1.

With respect to the study of structure–activity relationship (SAR), we first evaluated the effect of the position of the indole ring and the N1-substitution group on the indole ring for cytotoxic activity. Date from cytotoxicity assay of compounds **3**–**42** suggested that α,β-unsaturated ketone located at the C-3, or C-5 position of the indole ring resulted in the best activity. Shifting α,β-unsaturated ketone group to the C-4 or C-6 position resulted in moderate activity, while changing to the C-7 position decreased the activity drastically. It is interesting to point out that compound **31**, with a N1-methyl group, displayed the most potent antiproliferative activity with an IC_{50} value of 0.84 μM. However, compound **4**, with a N1–H group, slightly decrease of cytotoxicity, but increase in the bulkiness of the substituent (**32**) resulted in a remarkable decrease of cytotoxicity, thus revealing that the steric effect of the substitutions at the N1-position of 5-indole ring influences cell growth inhibitory activities. On the basis of these results, the *N*-methyl-5-indoly ring seems to be the optimal group on the right ring.

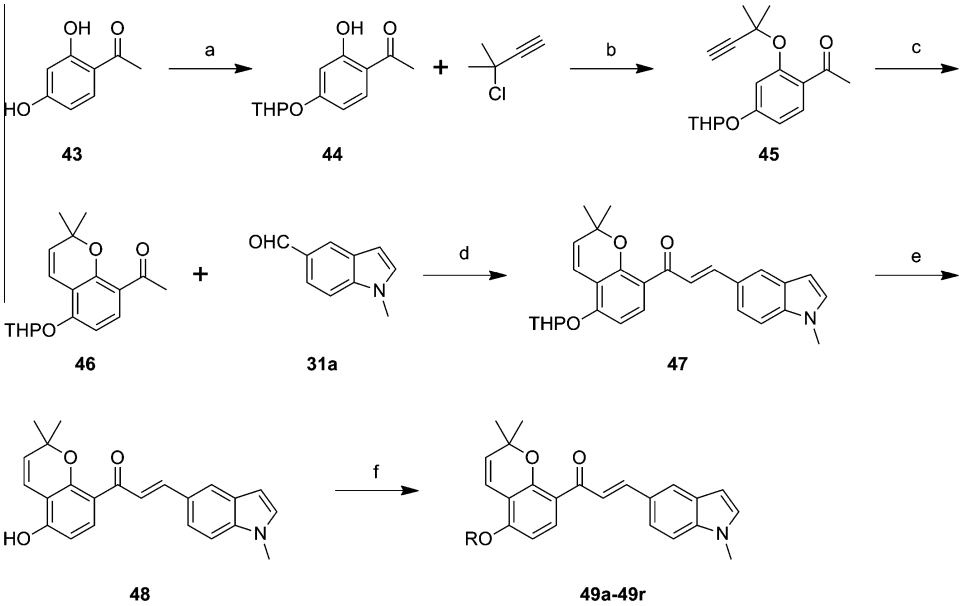
To understand the effect of substituents at the C-4 position of the left phenyl ring, compounds **49a**–**49r** were prepared and evaluated for their antiproliferative activities. As shown in Table 2, introduction ester groups (**49a**–**49d**), alkoxy groups (**49e**–**49j**) or sulfonate ester groups (**49k**–**49r**) at the C-5 position, resulted in slightly increase of cytotoxicity. Among all the compounds, compound **49b** with a propionyloxy group at the 4-position of the left phenyl ring displayed the most potent cytotoxic activity.

To further evaluate the antiproliferative properties, the most potent compound **49b** was chosen to be further evaluated by MTT assay against various tumor cell lines (SMMC-7221, HepG2, PC-3, A549, K562, HCT116, SKOV3 and MCF-7), vincristine resistant HCT-8 (HCT-8/V), taxol resistant HCT-8 (HCT-8/T) and normal human cell line (LO2). The results were presented in Table 3. Compound **49b** showed strong antiproliferative activity with IC_{50} values in the range of 0.22–1.80 μM against all tested cancer cell lines and low cytotoxicity on normal human cell line (LO2).

Although many anticancer drugs in clinical use are effective, their potentials are limited by the development of drug resistance. Multiple drug resistance cell lines have been reported overexpression of transmembrane cellular pumps P-glycoprotein (Pgp).[24] To investigate whether these derivatives are substrates of P-glycoprotein, the antiproliferative activity of **49b** against tumor cell lines with different resistance phenotypes was evaluated by MTT assay. As showed in Table 3, **49b** was effective against the tested cell lines and retained activity in cell lines with various multiple drug resistance phenotypes. These results indicating that this type of compound has great potential to overcome resistance to anti-tubulin drugs.

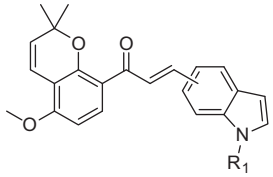
3.2. Tubulin polymerization assay

To investigate whether the antiproliferative activities of these compounds were related to the interaction with the microtubule system, the effect of compound **49b** on the polymerization of



Scheme 2. Reagents and conditions: (a) DHP, PPTS, CH_2Cl_2, 5 h, room temperature; (b) DBU, $CuCl_2 \cdot H_2O$, CH_3CN, 0 °C, 5 h; (c) pyridine, 120 °C, 12 h; (d) KOH, methanol, 48 h, room temperature; (e) TsOH, THF–CH_3OH = 1:1, 60 °C, 5 h; (f) compounds **49a**–**49e**: pyridine, 12 h, room temperature; compounds **49f**–**49j**: Cs_2CO_3, acetone, 12 h, room temperature; compounds **49k**–**49r**: Cs_2CO_3, acetone, 12 h, room temperature.

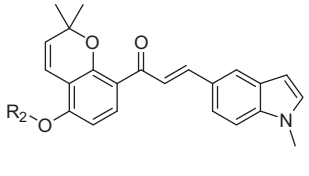
Table 1
The in vitro antiproliferative activities of pyrano chalcone derivatives **3**–**42** and millepachine against human cancer cell lines HepG2



3-43

Compound	R_1	Indole position	IC_{50} (μM)
Millepachine			1.51 ± 0.03
3	H	4	8.38 ± 0.04
4	H	5	1.06 ± 0.02
5	H	6	4.95 ± 0.02
6	H	7	7.62 ± 0.03
7	Methoxymethyl	3	4.70 ± 0.05
8	Methyl	3	2.23 ± 0.04
9	Ethyl	3	3.01 ± 0.02
10	Isobutyl	3	>10.0
11	Prenyl	3	2.81 ± 0.22
12	2-Morpholinoethyl	3	3.23 ± 0.06
13	Benzyl	3	1.78 ± 0.02
14	2-Fluorobenzyl	3	2.75 ± 0.02
15	3-Fluorobenzyl	3	3.09 ± 0.04
16	4-Fluorobenzyl	3	>10.0
17	2-Chlorobenzyl	3	1.94 ± 0.04
18	3-Chlorobenzyl	3	2.13 ± 0.03
19	4-Chlorobenzyl	3	>10.0
20	2-Bromobenzyl	3	>10.0
21	3-Bromobenzyl	3	1.38 ± 0.04
22	4-Bromobenzyl	3	>10.0
23	2-Trifluoromethylbenzyl	3	>10.0
24	3-Trifluoromethylbenzyl	3	2.18 ± 0.02
25	4-Trifluoromethylbenzyl	3	3.46 ± 0.08
26	Methyl	4	2.75 ± 0.03
27	Ethyl	4	5.54 ± 0.04
28	3-Fluorobenzyl	4	>10.0
29	3-Chlorobenzyl	4	>10.0
30	3-Bromobenzyl	4	>10.0
31	Methyl	5	0.84 ± 0.12
32	2-(Piperidin-1-yl)ethyl	5	4.45 ± 0.05
33	Methyl	6	8.85 ± 0.06
34	Ethyl	6	>10.0
35	3-Fluorobenzyl	6	>10.0
36	3-Chlorobenzyl	6	>10.0
37	3-Bromobenzyl	6	>10.0
38	Methyl	7	>10.0
39	Ethyl	7	>10.0
40	3-Fluorobenzyl	7	>10.0
41	3-Chlorobenzyl	7	>10.0
42	3-Bromobenzyl	7	>10.0

Table 2
The in vitro antiproliferative activities of pyrano chalcone derivatives **49a**–**49r** against human cancer cell lines HepG2



49a-49r

Compound	R_2	IC_{50} (μM)
49a	Acetyl	0.52 ± 0.05
49b	Propionyl	0.22 ± 0.03
49c	Isobutyryl	0.37 ± 0.04
49d	Pentanoyl	0.92 ± 0.08
49e	Ethyl	0.75 ± 0.10
49f	Isopropyl	0.78 ± 0.03
49g	*n*-Propyl	0.46 ± 0.05
49h	*n*-Butyl	0.63 ± 0.02
49i	*n*-Amyl	0.67 ± 0.06
49j	Isobutyl	0.97 ± 0.04
49k	3,5-Difluorobenzenesulfonyl	0.69 ± 0.05
49l	4-Bromo-2-(trifluoromethyl)benzenesulfonyl	0.62 ± 0.03
49m	2,3,4,5,6-Pentafluorobenzenesulfonyl	1.53 ± 0.12
49n	4-Methylbenzenesulfonyl	0.86 ± 0.05
49o	3-Methoxybenzenesulfonyl	0.75 ± 0.03
49p	4-Isopropylbenzenesulfonyl	1.87 ± 0.22
49q	3-(Trifluoromethyl)benzenesulfonyl	1.55 ± 0.03
49r	2-Methoxy-4-nitrobenzenesulfonyl	0.57 ± 0.04

Table 3
The in vitro antiproliferative activities of selected compound **49b** against various human tumor cell lines and normal human liver cell line LO2

Cell lines		IC_{50} (μM)
Liver	SMMC-7221	1.8 ± 0.04
	HepG2	0.22 ± 0.03
Prostate	PC-3	0.65 ± 0.01
Lung	A549	0.68 ± 0.01
Leukemia	K562	0.8 ± 0.01
Colon	HCT116	1.28 ± 0.01
Ovarian	SKOV3	0.23 ± 0.04
Breast	MCF-7	1.5 ± 0.02
Drug resistant	HCT-8/T	1.6 ± 0.04
	HCT-8/V	0.45 ± 0.02
Normal	LO2	>10.0

purified tubulin was evaluated at a concentration of 10.0 μM. Colchicine (2.5 μM) and paclitaxel (2.5 μM) were used as a reference. Figure 2 shows that compound **49b** proved to be a strong inhibitor of tubulin polymerization and indicates the rational relationship between the inhibition of tubulin and the corresponding antiproliferative activity. The results demonstrated that tubulin is a possible target for these compounds.

3.3. Cell cycle analysis

Because the anti-mitotic drugs induced cell cycle arrest at G2/M phase in various cancer cell lines and led to an increment of the relative peak in the DNA histogram.[25,26] The effect of the most active compound **49b** on cell cycle progression was investigated in HepG2 (human hepatocellular liver carcinoma) cells by flow cytometry at various concentrations. As shown in Figure 3, the percentage of cells in the G2/M phase were 26.2%, 60.7%, 75.0% and 86.0% when the cells were treated with **49b** for 24 h at concentrations of 0.125 μM, 0.25 μM, 0.375 μM and 0.50 μM, respectively. In control (untreated cells) 25.5% of accumulation in G2/M phase was observed. These results clearly demonstrated that **49b** could arrest cells in G2/M phase in a dose-dependent manner, which is consistent with the behavior of tubulin-binding agents.

3.4. Effects on apoptosis

Cell-cycle arrest in the G2/M phase is frequently followed by DNA fragmentation and other morphological features of apoptosis. To determine whether compound **49b** exhibiting high antitumor activity induce apoptosis of HepG2 cells, the potency of **49b** to induce apoptosis was further characterized by apoptosis assay. HepG2 cells were treated with 0.125 μM, 0.25 μM, 0.375 μM and 0.50 μM of **49b** for 48 h. As shown in Figure 4, the results showed that the effect was observed in a dose-dependent manner and the apoptotic rates of HepG2 cells increased with the increase of concentration of **49b**. The results demonstrated that **49b**, in addition to its antiproliferative properties, also induced apoptosis in the tested cancer cell lines.

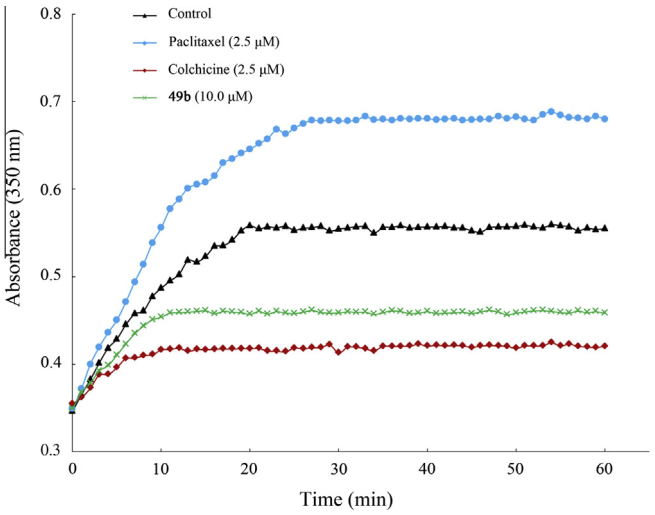


Figure 2. Effects of **49b** on in vitro tubulin polymerization assay. Purified tubulin of rat and ATP were mixed in a 96-well plate. The reaction was started by warming the solution from 4 to 37 °C. Colchicine (2.5 μM) and paclitaxel (2.5 μM) were used as a reference, while DMSO (0.1% v/v) was used as a vehicle control. The effect on tubulin assembly was monitored in a Spectramax M5 Microtiter Plate Luminometer (Molecular Devices, USA) at 350 nm at 60 s intervals for 60 min at 37 °C.

3.5. Immunofluorenscence staining

Accumulative evidence showed that microtubule-targeting drugs disrupt the cellular microtubule network and formation of the mitotic spindle, subsequently resulting in the blockage of the cell cycle in G2/M phase.[27] In order to confirm the antiproliferative activity of **49b** derived from an interaction with tubulin, we investigated microtubule structure in human hepatocellular liver carcinoma cell line HepG2 exposed to **49b** by immunofluorescence using α-tubulin monoclonal antibody. As shown in Figure 5, in control cells, we observed a well-organized microtubule network throughout the cells. However, cells treatment with **49b** showed disrupted microtubule organization. These results confirm that tubulin is an effective target for its anti-tumor activity.

3.6. Docking study

To further elucidate the interactions between compound **49b** and tubulin, a molecular docking study was performed by simulation of compound **49b** into the colchicine binding site of tubulin. The molecular docking study was carried out by genetic optimization of ligand docking (GOLD)[28] that docks flexible ligands into protein binding sites. The 3D structure of tubulin was gained from Protein Data Bank (PDB ID: 3N2G).[29] All water molecules were deleted, and Charmm force field was assigned by using Accelrys Discovery Studio 3.1. The binding site was defined as a sphere containing the residues within 10 Å from the ligand. The Goldscore was used as fitness function. And the rest parameters were kept at their default values. The results of the molecular docking study are summarized in Figure 6. The binding site of tubulin is a semi-enclosed pocket. N-methyl indole moiety of the compound **49b** is surrounded by residues Tyr52, Gln136, Glu200, Tyr202, Val238 and Ile378 which form a hydrophobic domain. Residues Thr179, Ala180, Ala250, Leu255, Asn258, Ala316, Val318, Lys352 and Ala354 form a polar domain, which locate the other part of the compound **49b** of which the oxygen atom connecting with benzopyran ring can form a hydrogen bond with the hydroxyl group of Thr179. Overall, the result of the molecular docking study suggested that compound **49b** was a potential inhibitor of tubulin.

3.7. In vivo antitumor activity of compound 49b

To further evaluate the antitumor effect of **49b** in vivo, we performed an animal study using a hepatocarcinoma HepG2 mice model. As shown in Figure 7, the results demonstrated that the growth of tumors in mice treated with **49b** (30 mg/kg) was reduced by 56.58% compared with that in control mice treated with vehicle only at day 35. By comparison, positive control anticancer drug 5-Fu reduced the growth of tumors by 25.93%. Meanwhile, we did not observe significant growth inhibition of mice in the **49b** and 5-Fu treated groups compared to the vehicle group. These results indicated that **49b** had a significant in vivo antitumor activity in mice, with little effect on the normal growth of the animals.

4. Conclusions

In conclusion, the synthesis and biological evaluation of a series of pyrano chalcone derivatives containing indole moiety was discussed. Most of these synthesized compounds showed moderate to potent cytotoxic activity against HepG2 cancer cell lines. The SAR study demonstrated that *N*-methyl-5-indoly on right ring and propionyloxy group at the 4-position of the left phenyl ring had beneficial effect on the cytotoxicity activity. Flow cytometry analysis and Immunofluorenscence staining assay showed that compound **49b** led to cell cycle arrest at the G2/M phase by effectively inhibit microtubule polymerization. Finally, molecular docking analysis demonstrated the interaction of **49b** at the colchicine binding site of tubulin. These results indicated pyrano chalcone derivatives containing indole moiety are promising inhibitors of tubulin polymerization for the potential treatment of cancer.

5. Experimental section

5.1. Chemistry

All starting materials and reagents were purchased from commercial suppliers. TLC was performed on 0.20 mm Silica Gel 60 F_{254} plates (Qingdao Ocean Chemical Factory, Shandong, China). Nuclear magnetic resonance spectra (NMR) were recorded at 400 MHz on a Varian spectrometer (Varian, Palo Alto, CA) and reported in parts per million. Mass spectra (MS) were measured by Q-TOF Priemier mass spectrometer (Micromass, Manchester, UK).

5.1.1. 1-(4-Methoxy-2-((2-methylbut-3-yn-2-yl)oxy)phenyl) ethanone (1)

To a solution of 1-(2-hydroxy-4-methoxyphenyl)ethanone (1.66 g, 10 mmol) in CH_3CN (100 mL) at 0 °C was added DBU (1.5 mL, 15 mmol), $CuCl_2{\cdot}H_2O$ (5 mg, 0.3% mol), and 3-chloro-3-methyl-1-butyne (1.53 g, 15 mmol). The mixture was stirred at 0 °C for 5 h and monitored by TLC. After completed, 1 N HCl (aq) was added to adjust pH = 2. After removing the solvent under reduced pressure, the residue was poured into water (50 mL) and the white precipitate was collected by filtration to obtain **1** (1.97 g, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.75 (s, 6H), 2.58 (s, 3H), 2.69 (s, 1H), 3.84 (s, 3H), 6.58 (dd, 1H, J = 8.8 Hz, 2.0 Hz), 7.19 (d, 1H, J = 2.0 Hz), 7.75 (d, 1H, J = 8.8 Hz); MS (ESI, m/z): 255.05 $[M+Na]^+$.

5.1.2. 1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-8-yl)ethanone (2)

A suspension of **1** (2.32 g, 10 mmol) in pyridine (50 mL) was stirred at 120 °C for 12 h. After cooling to room temperature, the mixture concentrated under reduced pressure to give **2** as black

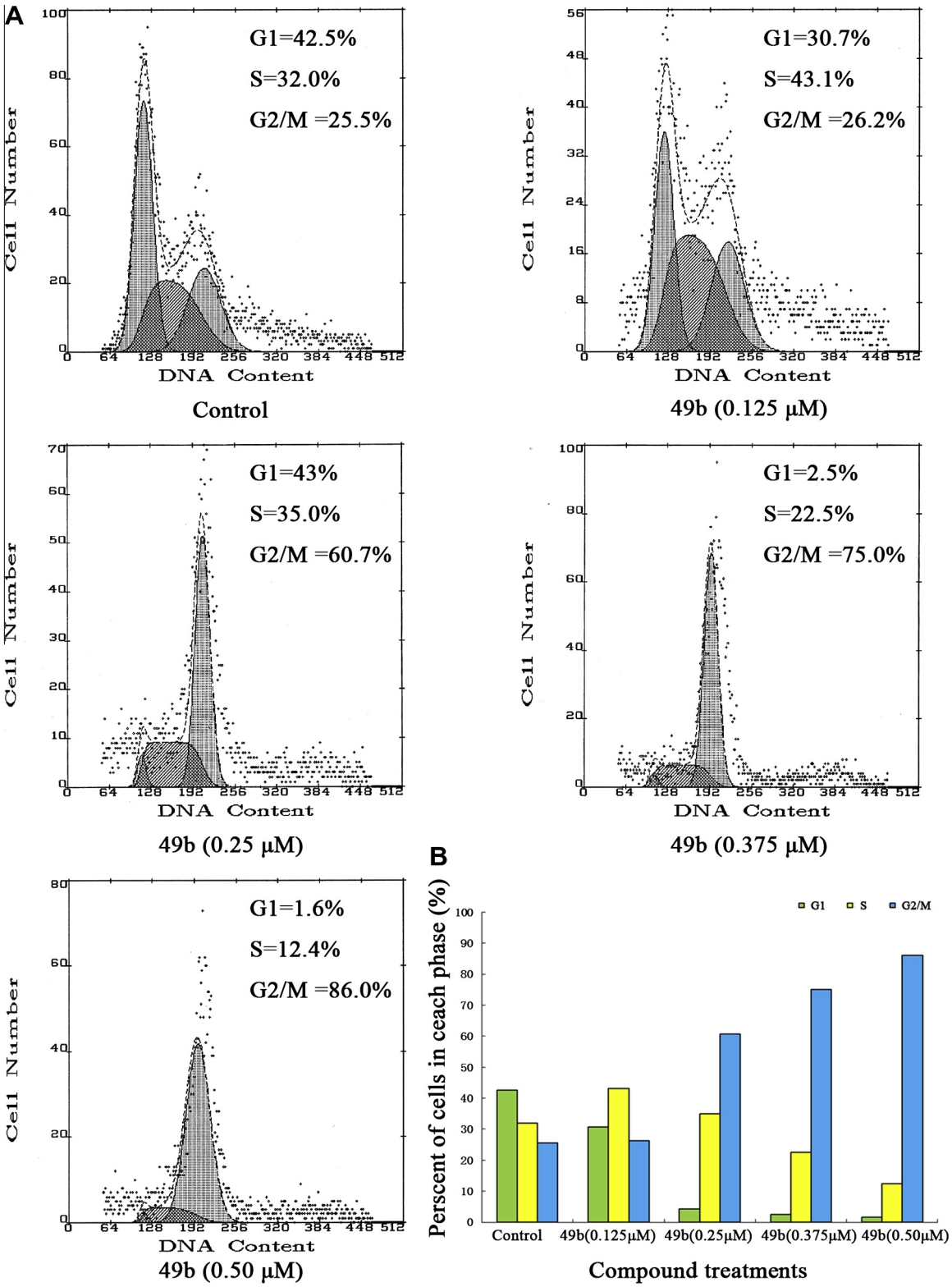


Figure 3. Flow cytometry analysis of compound **49b** in HepG2 cells. (A) Cell cycle distribution of HepG2 cells after treatment with **49b** at different concentrations (0.125 μM, 0.25 μM, 0.375 μM and 0.50 μM) for 24 h. An increased proportion of cells at G_2/M phase were observed in cells treated with **49b**. (B) The statistical graph of cell cycle distribution.

oil, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.49 (s, 6H), 2.62 (s, 3H), 3.87 (s, 3H), 5.61 (d, 1H, J = 10.0 Hz), 6.47 (d, 1H, J = 8.8 Hz), 6.66 (d, 1H, J = 10.0 Hz), 7.73 (d, 1H, J = 8.8 Hz); MS (ESI, m/z): 255.14 $[M+Na]^+$.

5.1.3. General procedure A for the synthesis of 7a–42a

To a solution of indole-aldehyde (435 mg 3 mmol) in CH_3CN (30 mL) was added Cs_2CO_3 (829 mg, 6 mmol), and the mixture was refluxed for 2 h. To this solution, alkyl halide (3.3 mmol) was

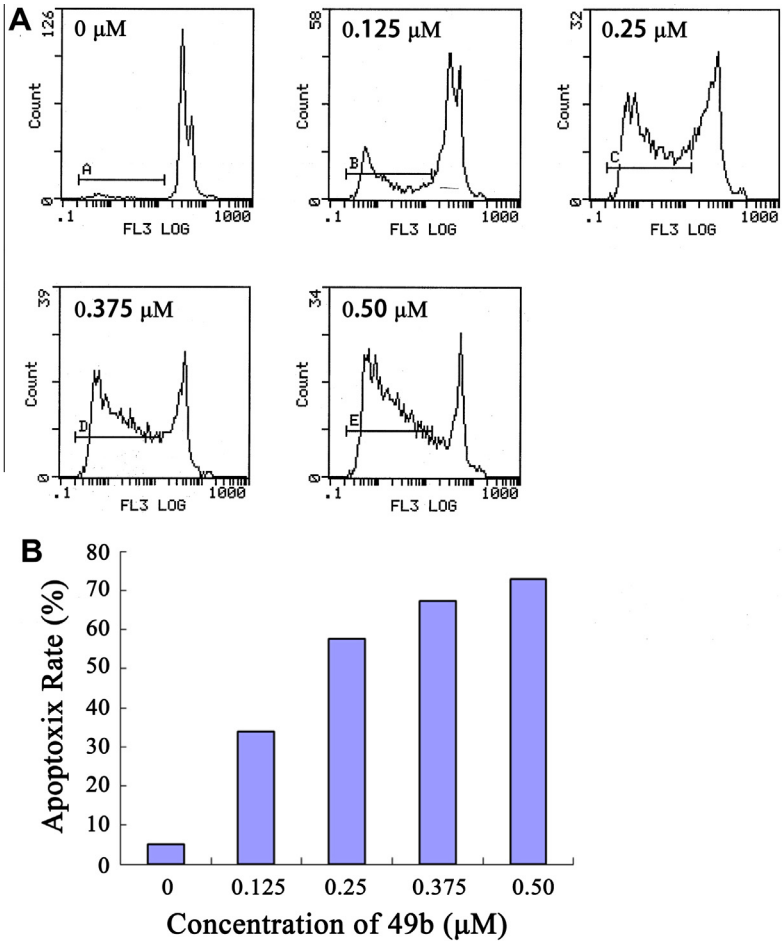


Figure 4. Apoptotic effects of **49b** in HepG2 cells. (A) The results are expressed in the percentage of apoptotic cells detected following 48 h of treatment with **49b** at different concentrations (0.125 μM, 0.25 μM, 0.375 μM and 0.50 μM). (B) The rate of apoptotic cells as detected by flow cytometry.

added, and the mixture was heated under reflux for 1 h. After the completion of the reaction, the solvent was evaporated under reduced pressure and water was added to the reaction mixture and extracted 3 times for ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography.

5.1.3.1. 1-(Methoxymethyl)-1*H*-indole-3-carbaldehyde (7a). The compound **7a** was prepared from indole-3-aldehyde and chloro (methoxy)methane according to general procedure A. The residue was purified by flash chromatography to give 465 mg (82%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.30 (s, 3H), 5.50 (s, 2H), 7.33–7.39 (m, 2H), 7.52 (d, 1H, J = 8.0 Hz), 7.80 (s, 1H), 8.31 (d, 1H, J = 7.2 Hz), 10.05 (s, 1H); MS (ESI, m/z): 212.2 $[M+Na]^+$.

5.1.3.2. 1-Methyl-1*H*-indole-3-carbaldehyde (8a). The compound **8a** was prepared from indole-3-aldehyde and iodomethane according to general procedure A. The residue was purified by flash chromatography to give 358 mg (75%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.76 (s, 3H), 7.27–7.30 (m, 3H), 7.55–7.57 (m, 1H), 8.26–8.28 (m, 1H), 9.88 (s, 1H); MS (ESI, m/z): 182.2 $[M+Na]^+$.

5.1.3.3. 1-Ethyl-1*H*-indole-3-carbaldehyde (9a). The compound **9a** was prepared from indole-3-aldehyde and iodoethane according to general procedure A. The residue was purified by flash chromatography to give 442 mg (85%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.55 (t, 3H, J = 7.2 Hz), 4.20 (q, 2H, J = 7.2 Hz), 7.26–7.34 (m, 2H), 7.38 (t, 1H, J = 7.2 Hz), 7.74 (s, 1H), 8.30 (d, 1H, J = 8.0 Hz), 10.0 (s, 1H); MS (ESI, m/z): 196.1 $[M+Na]^+$.

5.1.3.4. 1-Isopropyl-1*H*-indole-3-carbaldehyde (10a). The compound **10a** was prepared from indole-3-aldehyde and 2-iodopropane according to general procedure A. The residue was purified by flash chromatography to give 387 mg (69%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.57 (d, 6H, J = 6.8 Hz), 4.69 (heptet, 1H, J = 6.8 Hz), 7.28–7.35 (m, 2H), 7.40 (d, 1H, J = 8.0 Hz), 7.84 (s, 1H), 8.31 (d, 1H, J = 7.2 Hz), 10.0 (s, 1H); MS (ESI, m/z): 210.1 $[M+Na]^+$.

5.1.3.5. 1-(3-Methylbut-2-en-1-yl)-1*H*-indole-3-carbaldehyde (11a). The compound **11a** was prepared from indole-3-aldehyde and 1-bromo-3-methylbut-2-ene according to general procedure A. The residue was purified by flash chromatography to give 371 mg (58%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.82 (s, 3H), 1.84 (s, 3H), 4.71 (d, 2H, J = 7.2 Hz), 5.42 (t, 1H, J = 7.2 Hz), 7.29–7.38 (m, 3H), 7.72 (s, 1H), 8.29 (d, 1H, J = 8.0 Hz), 9.97 (s, 1H); MS (ESI, m/z): 236.1 $[M+Na]^+$.

5.1.3.6. 1-(2-Morpholinoethyl)-1*H*-indole-3-carbaldehyde (12a). The compound **12a** was prepared from indole-3-aldehyde and 4-(2-chloroethyl)morpholine hydrochloride according to general procedure A. The residue was purified by flash chromatography to give 379 mg (49%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.49 (t, 4H, J = 4.4 Hz), 2.80 (t, 2H, J = 6.4 Hz), 3.70 (t, 4H,

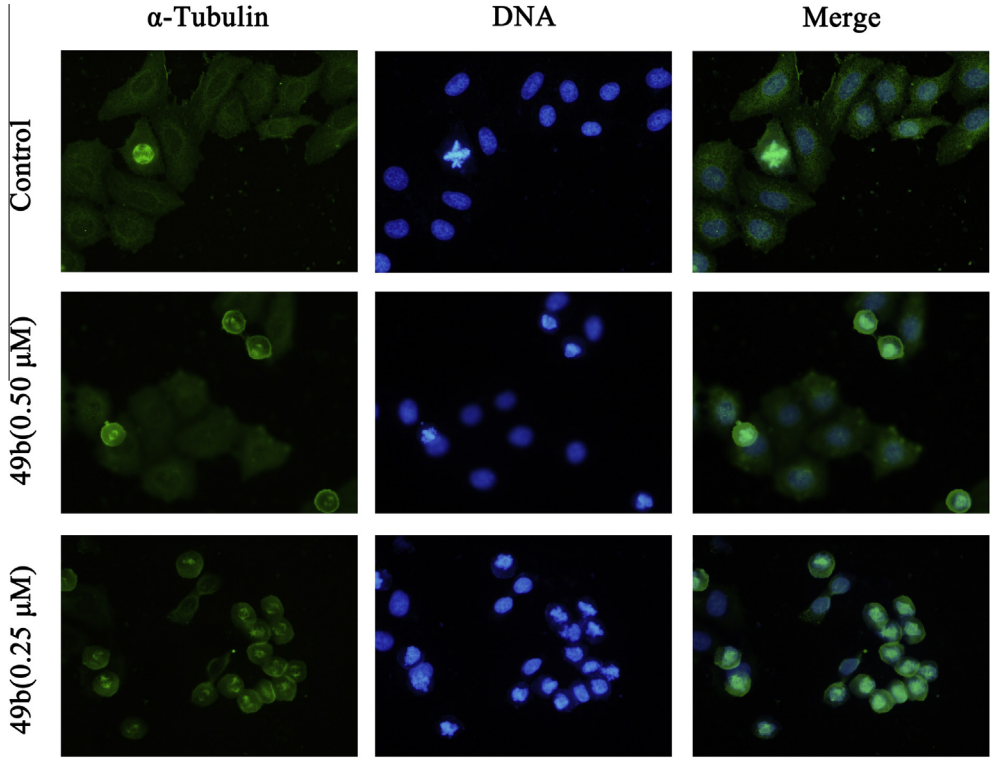


Figure 5. Effect of **49b** on the organization of cellular microtubule network. HepG2 cells treated with **49b** were fixed and stained with α-tubulin, and then counterstained with 4,6-diamidino-2-phenylindole (DAPI). Microtubules and unassembled tubulin are shown in green. DNA, stained with DAPI, is shown in blue.

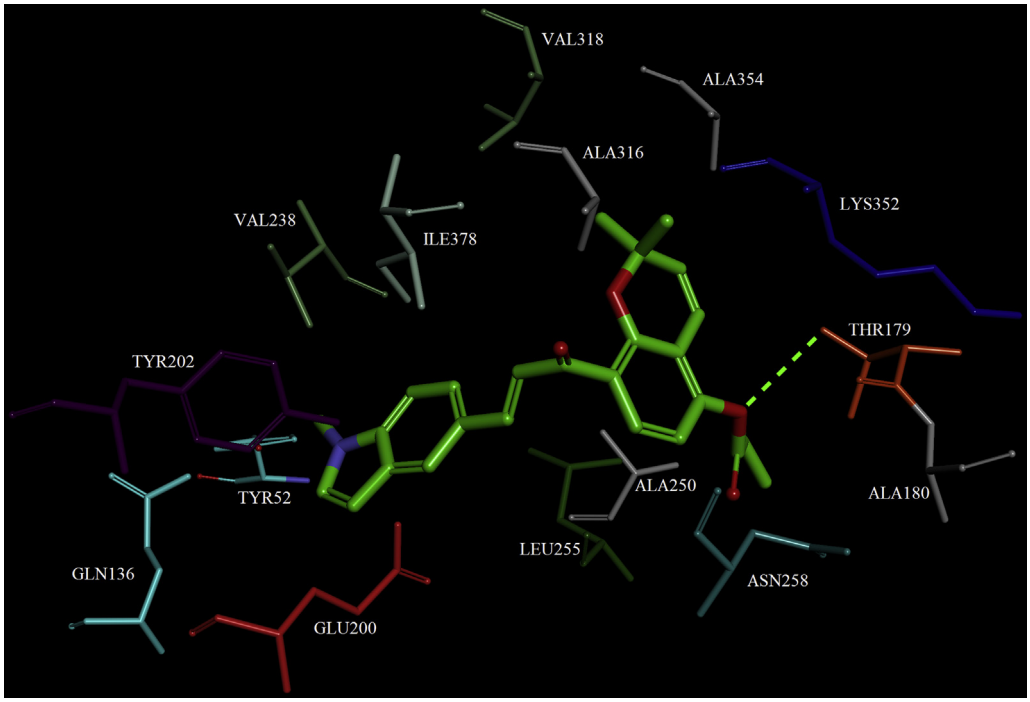


Figure 6. The interaction mode of compound **49b** within the binding site of tubulin (PDB ID: 3N2G). Ligand is represented with thick stick and carbon atoms are depicted with green color. Residues within the binding site were expressed with thin stick and colored by their types.

J = 4.4 Hz), 4.28 (t, 2H, *J* = 6.4 Hz), 7.30–7.35 (m, 2H), 7.38 (t, 1H, *J* = 7.2 Hz), 7.81 (s, 1H), 8.30 (d, 1H, *J* = 8.0 Hz), 10.01 (s, 1H); MS (ESI, *m*/*z*): 281.1 $[M+Na]^+$.

5.1.3.7. 1-Benzyl-1*H*-indole-3-carbaldehyde (13a). The compound **13a** was prepared from indole-3-aldehyde and (bromomethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 600 mg (85%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.35 (s, 2H), 7.17 (d, 1H, *J* = 7.2 Hz), 7.31–7.35 (m, 6H), 7.70 (s, 1H), 8.32 (d, 1H, *J* = 7.2 Hz), 10.00 (s, 1H); MS (ESI, *m*/*z*): 258.1 $[M+Na]^+$.

5.1.3.8. 1-(2-Fluorobenzyl)-1*H*-indole-3-carbaldehyde (14a). The compound **14a** was prepared from indole-3-aldehyde

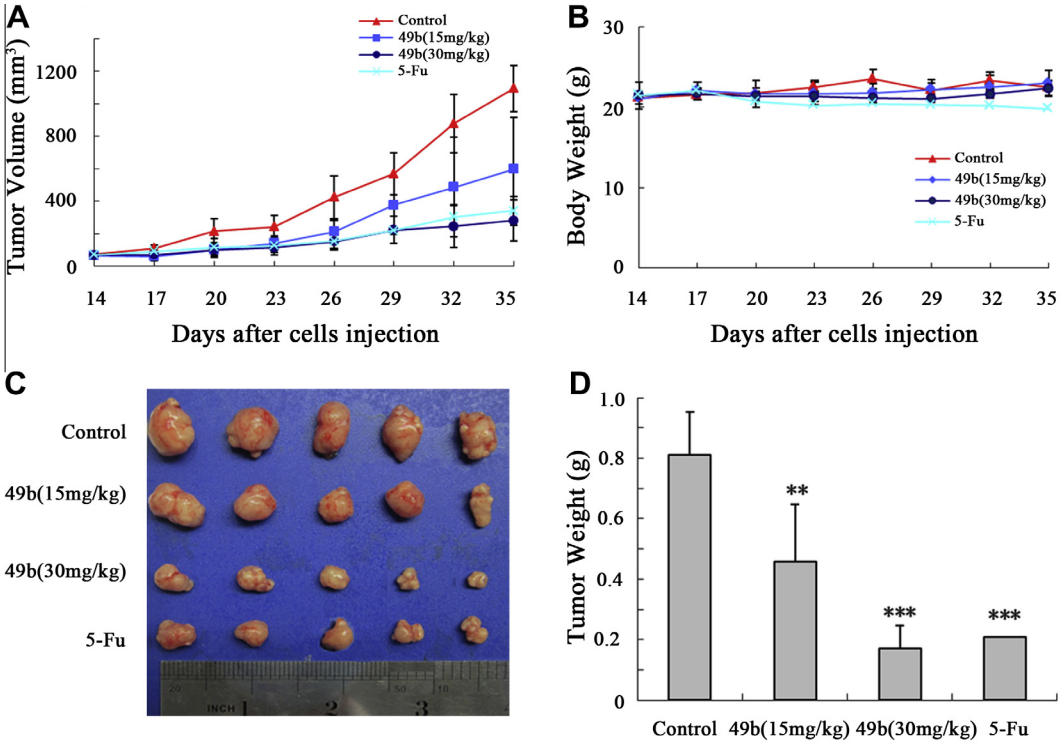


Figure 7. The in vivo antitumor activity of compound **49b** against HepG2 xenografts in BALB/c nude mice. (A) The curves of inhibition of tumors. HepG2 tumor-bearing nude mice were administered vehicle alone, or 15 mg/kg or 30 mg/kg of **49b** once every two days for 21 days, the positive group received injections of 5-Fu at a dose of 5 mg/kg once a day. Each group contained six mice; bars, ±SD. (B) Effects of **49b** and 5-Fu on mice body weight, bars, ±SD. (C) The picture of the stripping tumor from mice. (D) Effects of **49b** and 5-Fu on tumor weight.$^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$, significantly different compared with control by *t* test.

and 1-(bromomethyl)-2-fluorobenzene according to general procedure A. The residue was purified by flash chromatography to give 631 mg (83%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.40 (s, 2H), 7.05–7.15 (m, 4H), 7.27–7.46 (m, 3H), 7.77 (s, 1H), 8.32 (d, 1H, J = 8.0 Hz), 10.01 (s, 1H); MS (ESI, m/z): 254.1 $[M+H]^+$.

5.1.3.9. 1-(3-Fluorobenzyl)-1*H*-indole-3-carbaldehyde (15a). The compound **15a** was prepared from indole-3-aldehyde and 1-(bromomethyl)-3-fluorobenzene according to general procedure A. The residue was purified by flash chromatography to give 615 mg (81%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.35 (s, 2H), 6.84 (d, 1H, J = 8.8 Hz), 6.93 (d, 1H, J = 8.0 Hz), 7.01 (t, 1H, J = 8.0 Hz), 7.27–7.34 (m, 4H), 7.72 (s, 1H), 8.32 (d, 1H, J = 8.0 Hz), 10.02 (s, 1H); MS (ESI, m/z): 276.0 $[M+Na]^+$.

5.1.3.10. 1-(4-Fluorobenzyl)-1*H*-indole-3-carbaldehyde (16a). The compound **16a** was prepared from indole-3-aldehyde and 1-(bromomethyl)-4-fluorobenzene according to general procedure A. The residue was purified by flash chromatography to give 577 mg (76%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.33 (s, 2H), 7.04 (t, 2H, J = 8.0 Hz), 7.16 (t, 2H, J = 8.0 Hz), 7.31–7.33 (m, 3H), 7.70 (s, 1H), 8.32 (d, 1H, J = 8.0 Hz), 10.00 (s, 1H); MS (ESI, m/z): 276.0 $[M+Na]^+$.

5.1.3.11. 1-(2-Chlorobenzyl)-1*H*-indole-3-carbaldehyde (17a). The compound **17a** was prepared from indole-3-aldehyde and 1-chloro-2-(chloromethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 680 mg (84%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.46 (s, 2H), 6.83 (d, 1H, J = 8.0 Hz), 7.18 (t, 1H, J = 8.0 Hz), 7.27–7.34 (m, 4H), 7.45 (d, 1H, J = 8.0 Hz), 7.72 (s, 1H), 8.33 (d, 1H, J = 8.8 Hz), 10.02 (s, 1H); MS (ESI, m/z): 292.0 $[M+Na]^+$.

5.1.3.12. 1-(3-Chlorobenzyl)-1*H*-indole-3-carbaldehyde (18a). The compound **18a** was prepared from indole-3-aldehyde and 1-chloro-3-(chloromethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 574 mg (71%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.33 (s, 2H), 6.09 (d, 2H, J = 8.0 Hz), 7.26–7.32 (m, 5H), 7.70 (s, 1H), 8.31 (d, 1H, J = 8.8 Hz), 10.00 (s, 1H); MS (ESI, m/z): 292.0 $[M+Na]^+$.

5.1.3.13. 1-(4-Chlorobenzyl)-1*H*-indole-3-carbaldehyde (19a). The compound **19a** was prepared from indole-3-aldehyde and 1-chloro-4-(chloromethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 639 mg (79%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.31 (s, 2H), 7.01 (d, 1H, J = 7.2 Hz), 7.17 (s, 1H), 7.24–7.34 (m, 5H), 7.70 (s, 1H), 8.32 (d, 1H, J = 8.8 Hz), 10.00 (s, 1H); MS (ESI, m/z): 292.0 $[M+Na]^+$.

5.1.3.14. 1-(2-Bromobenzyl)-1*H*-indole-3-carbaldehyde (20a). The compound **20a** was prepared from indole-3-aldehyde and 1-bromo-2-(bromomethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 631 mg (67%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.45 (s, 2H), 6.78 (t, 1H, J = 8.0 Hz), 7.19–7.21 (m, 2H), 7.32–7.36 (m, 3H), 7.65 (t, 1H, J = 8.0 Hz), 7.71 (s, 1H), 8.33 (d, 1H, J = 8.8 Hz), 10.01 (s, 1H); MS (ESI, m/z): 337.0 $[M+Na]^+$.

5.1.3.15. 1-(3-Bromobenzyl)-1*H*-indole-3-carbaldehyde (21a). The compound **21a** was prepared from indole-3-aldehyde and 1-bromo-3-(bromomethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 575 mg (61%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.33 (s, 2H), 7.05 (d, 1H, J = 8.0 Hz), 7.18–7.23 (m, 1H), 7.29–7.35 (m, 4H), 7.45

(d, 1H, J = 7.2 Hz), 7.72 (s, 1H), 8.32 (d, 1H, J = 8.8 Hz), 10.02 (s, 1H); MS (ESI, m/z): 337.0 $[M+Na]^+$.

5.1.3.16. 1-(4-Bromobenzyl)-1*H*-indole-3-carbaldehyde (22a). The compound **22a** was prepared from indole-3-aldehyde and 1-bromo-4-(bromomethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 726 mg (77%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.30 (s, 2H), 7.02 (d, 2H, J = 8.0 Hz), 7.27–7.34 (m, 3H), 7.45 (d, 2H, J = 8.0 Hz), 7.69 (s, 1H), 8.31 (d, 1H, J = 8.8 Hz), 9.99 (s, 1H); MS (ESI, m/z): 337.0 $[M+Na]^+$.

5.1.3.17. 1-(2-(Trifluoromethyl)benzyl)-1*H*-indole-3-carbaldehyde (23a). The compound **23a** was prepared from indole-3-aldehyde and 1-(bromomethyl)-2-(trifluoromethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 536 mg (59%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.57 (s, 2H), 6.70 (d, 1H, J = 8.0 Hz), 7.19 (d, 1H, J = 8.0 Hz), 7.25–7.34 (m, 2H), 7.36–7.43 (m, 2H), 7.71 (s, 1H), 7.74 (d, 2H, J = 8.0 Hz), 8.31 (d, 1H, J = 8.8 Hz), 10.01 (s, 1H); MS (ESI, m/z): 326.0 $[M+Na]^+$.

5.1.3.18. 1-(3-(Trifluoromethyl)benzyl)-1*H*-indole-3-carbaldehyde (24a). The compound **24a** was prepared from indole-3-aldehyde and 1-(bromomethyl)-3-(trifluoromethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 573 mg (63%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.43 (s, 2H), 7.26–7.34 (m, 4H), 7.46 (t, 1H, J = 8.0 Hz), 7.51 (s, 1H), 7.59 (d, 1H, J = 8.0 Hz), 7.74 (s, 1H), 8.33 (d, 1H, J = 8.8 Hz), 10.03 (s, 1H); MS (ESI, m/z): 326.1 $[M+Na]^+$.

5.1.3.19. 1-(4-(Trifluoromethyl)benzyl)-1*H*-indole-3-carbaldehyde (25a). The compound **25a** was prepared from indole-3-aldehyde and 1-(bromomethyl)-4-(trifluoromethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 491 mg (54%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.44 (s, 2H), 7.25–7.29 (m, 3H), 7.30–7.35 (m, 2H), 7.59 (d, 2H, J = 8.0 Hz), 7.74 (s, 1H), 8.33 (d, 1H, J = 8.8 Hz), 10.03 (s, 1H); MS (ESI, m/z): 302.3 $[M-H]^-$.

5.1.3.20. 1-Methyl-1*H*-indole-4-carbaldehyde (26a). The compound **26a** was prepared from indole-4-aldehyde and iodomethane according to general procedure A. The residue was purified by flash chromatography to give 491 mg (70%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.84 (s, 3H), 7.23–7.26 (m, 2H), 7.34 (t, 1H, J = 8.0 Hz), 7.57 (d, 1H, J = 8.0 Hz), 7.61 (d, 1H, J = 7.2 Hz), 10.23 (s, 1H); MS (ESI, m/z): 182.2 $[M+Na]^+$.

5.1.3.21. 1-Ethyl-1*H*-indole-4-carbaldehyde (27a). The compound **27a** was prepared from indole-4-aldehyde and iodoethane according to general procedure A. The residue was purified by flash chromatography to give 405 mg (78%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.48 (t, 3H, J = 7.2 Hz), 4.21 (q, 2H, J = 7.2 Hz), 7.25–7.36 (m, 4H), 7.61 (d, 2H, J = 7.2 Hz), 10.24 (s, 1H); MS (ESI, m/z): 196.1 $[M+Na]^+$.

5.1.3.22. 1-(3-Fluorobenzyl)-1*H*-indole-4-carbaldehyde (28a). The compound **28a** was prepared from indole-4-aldehyde and 1-(bromomethyl)-3-fluorobenzene according to general procedure A. The residue was purified by flash chromatography to give 539 mg (71%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.38 (s, 2H), 6.74 (d, 1H, J = 8.0 Hz), 6.85 (d, 1H, J = 8.0 Hz), 6.96 (t, 1H, J = 8.0 Hz), 7.24–7.36 (m, 4H), 7.50 (d, 1H, J = 8.0 Hz), 7.63 (d, 1H, J = 7.2 Hz), 10.25 (s, 1H); MS (ESI, m/z): 276.0 $[M+Na]^+$.

5.1.3.23. 1-(3-Chlorobenzyl)-1*H*-indole-4-carbaldehyde (29a). The compound **29a** was prepared from indole-4-aldehyde and 1-chloro-3-(chloromethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 615 mg (76%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.34 (s, 2H), 6.74 (d, 1H, J = 7.8 Hz), 7.08 (s, 1H), 7.19–7.36 (m, 5H), 7.49 (d, 1H, J = 8.0 Hz), 7.62 (d, 1H, J = 7.2 Hz), 10.24 (s, 1H); MS (ESI, m/z): 292.0 $[M+Na]^+$.

5.1.3.24. 1-(3-Bromobenzyl)-1*H*-indole-4-carbaldehyde (30a). The compound **30a** was prepared from indole-4-aldehyde and 1-bromo-3-(bromomethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 622 mg (66%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.34 (s, 2H), 6.95 (d, 1H, J = 7.6 Hz), 7.15 (t, 1H, J = 7.6 Hz), 7.26 (s, 1H), 7.29 (d, 1H, J = 7.6 Hz), 7.33 (s, 1H), 7.36 (s, 1H), 7.39 (d, 1H, J = 8.0 Hz), 7.49 (d, 1H, J = 8.0 Hz), 7.62 (d, 1H, J = 7.2 Hz), 10.24 (s, 1H); MS (ESI, m/z): 337.0 $[M+Na]^+$.

5.1.3.25. 1-Methyl-1*H*-indole-5-carbaldehyde (31a). The compound **31a** was prepared from indole-5-aldehyde and iodomethane according to general procedure A. The residue was purified by flash chromatography to give 401 mg (84%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.84 (s, 3H), 6.64 (d, 1H, J = 2.8 Hz), 7.15 (d, 1H, J = 2.8 Hz), 7.39 (d, 1H, J = 8.8 Hz), 7.79 (d, 1H, J = 8.8 Hz), 8.15 (s, 1H), 10.03 (s, 1H); MS (ESI, m/z): 182.2 $[M+Na]^+$.

5.1.3.26. 1-(2-(Piperidin-1-yl)ethyl)-1*H*-indole-5-carbaldehyde (32a). The compound **32a** was prepared from indole-5-aldehyde and 1-(2-chloroethyl)piperidine hydrochloride according to general procedure A. The residue was purified by flash chromatography to give 361 mg (47%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.44–1.45 (m, 2H), 1.55–1.59 (m, 4H), 2.34–2.50 (m, 4H), 2.70 (t, 2H, J = 6.8 Hz), 4.26 (t, 2H, J = 6.8 Hz), 6.64 (d, 1H, J = 2.4 Hz), 7.25 (d, 1H, J = 2.4 Hz), 7.42 (d, 1H, J = 8.8 Hz), 7.46 (d, 1H, J = 8.8 Hz), 8.13 (s, 1H), 10.01 (s, 1H); MS (ESI, m/z): 255.4 $[M-H]^-$.

5.1.3.27. 1-Methyl-1*H*-indole-6-carbaldehyde (33a). The compound **33a** was prepared from indole-6-aldehyde and iodomethane according to general procedure A. The residue was purified by flash chromatography to give 363 mg (76%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.88 (s, 3H), 6.56 (d, 1H, J = 2.4 Hz), 7.28 (d, 1H, J = 2.4 Hz), 7.62 (d, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 8.0 Hz), 7.90 (s, 1H), 10.07 (s, 1H); MS (ESI, m/z): 182.2 $[M+Na]^+$.

5.1.3.28. 1-Ethyl-1*H*-indole-6-carbaldehyde (34a). The compound **33a** was prepared from indole-6-aldehyde and iodoethane according to general procedure A. The residue was purified by flash chromatography to give 379 mg (73%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.49 (t, 3H, J = 7.2 Hz), 4.21 (q, 2H, J = 7.2 Hz), 6.55 (d, 1H, J = 2.4 Hz), 7.33 (d, 1H, J = 2.4 Hz), 7.60 (d, 1H, J = 8.0 Hz), 7.69 (d, 1H, J = 8.0 Hz), 7.91 (s, 1H), 10.05 (s, 1H); MS (ESI, m/z): 196.2 $[M+Na]^+$.

5.1.3.29. 1-(3-Fluorobenzyl)-1*H*-indole-6-carbaldehyde (35a). The compound **35a** was prepared from indole-6-aldehyde and 1-(bromomethyl)-3-fluorobenzene according to general procedure A. The residue was purified by flash chromatography to give 570 mg (75%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.36 (s, 2H), 6.65 (d, 1H, J = 2.4 Hz), 6.96 (d, 1H, J = 6.8 Hz), 7.09 (s, 1H), 7.21–7.29 (m, 2H), 7.33 (d, 1H, J = 2.4 Hz), 7.64 (d, 1H, J = 8.0 Hz), 7.74 (d, 1H, J = 8.0 Hz), 7.81 (s, 1H), 10.01 (s, 1H); MS (ESI, m/z): 276.0 $[M+Na]^+$.

5.1.3.30. 1-(3-Chlorobenzyl)-1*H*-indole-6-carbaldehyde (36a). The compound **36a** was prepared from indole-6-aldehyde and 1-chloro-3-(chloromethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 510 mg (63%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.40 (s, 2H), 6.64 (d, 1H, J = 2.4 Hz), 6.75 (d, 1H, J = 8.8 Hz), 6.88 (d, 1H, J = 8.0 Hz), 6.97 (t, 1H, J = 8.0 Hz), 7.21–7.31 (m, 1H), 7.35 (d, 1H, J = 2.4 Hz), 7.64 (d, 1H, J = 8.0 Hz), 7.74 (d, 1H, J = 8.0 Hz), 7.82 (s, 1H), 10.01 (s, 1H); MS (ESI, m/z): 292.0 $[M+Na]^+$.

5.1.3.31. 1-(3-Bromobenzyl)-1*H*-indole-6-carbaldehyde (37a). The compound **37a** was prepared from indole-6-aldehyde and 1-bromo-3-(bromomethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 565 mg (60%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.35 (s, 2H), 6.64 (d, 1H, J = 2.4 Hz), 6.98 (d, 1H, J = 8.0 Hz), 7.16 (t, 1H, J = 8.0 Hz), 7.25–7.26 (m, 1H), 7.33 (d, 1H, J = 2.4 Hz), 7.40 (d, 1H, J = 7.2 Hz), 7.63 (d, 1H, J = 8.0 Hz), 7.73 (d, 1H, J = 8.0 Hz), 7.81 (s, 1H), 10.00 (s, 1H); MS (ESI, m/z): 337.0 $[M+Na]^+$.

5.1.3.32. 1-Methyl-1*H*-indole-7-carbaldehyde (38a). The compound **38a** was prepared from indole-7-aldehyde and iodomethane according to general procedure A. The residue was purified by flash chromatography to give 401 mg (84%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.13 (s, 3H), 6.58 (d, 1H, J = 2.4 Hz), 7.07 (d, 1H, J = 2.4 Hz), 7.22 (t, 1H, J = 8.0 Hz), 7.68 (d, 1H, J = 8.0 Hz), 7.86 (d, 1H, J = 8.0 Hz), 10.21 (s, 1H); MS (ESI, m/z): 182.2 $[M+Na]^+$.

5.1.3.33. 1-Ethyl-1*H*-indole-7-carbaldehyde (39a). The compound **39a** was prepared from indole-7-aldehyde and iodoethane according to general procedure A. The residue was purified by flash chromatography to give 395 mg (76%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.37 (t, 3H, J = 7.2 Hz), 4.64 (q, 2H, J = 7.2 Hz), 6.60 (d, 1H, J = 2.4 Hz), 7.10 (d, 1H, J = 2.4 Hz), 7.23 (t, 1H, J = 8.0 Hz), 7.68 (d, 1H, J = 8.0 Hz), 7.88 (d, 1H, J = 8.0 Hz), 10.14 (s, 1H); MS (ESI, m/z): 196.1 $[M+Na]^+$.

5.1.3.34. 1-(3-Fluorobenzyl)-1*H*-indole-7-carbaldehyde (40a). The compound **40a** was prepared from indole-7-aldehyde and 1-(bromomethyl)-3-fluorobenzene according to general procedure A. The residue was purified by flash chromatography to give 509 mg (67%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.92 (s, 2H), 6.70 (d, 1H, J = 2.4 Hz), 6.94–7.00 (m, 2H), 7.07–7.19 (m, 2H), 7.28–7.33 (m, 2H), 7.64 (d, 1H, J = 8.0 Hz), 7.92 (d, 1H, J = 8.0 Hz), 9.94 (s, 1H); MS (ESI, m/z): 276.0 $[M+Na]^+$.

5.1.3.35. 1-(3-Chlorobenzyl)-1*H*-indole-7-carbaldehyde (41a). The compound **41a** was prepared from indole-7-aldehyde and 1-chloro-3-(chloromethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 550 mg (68%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.91 (s, 2H), 6.70 (d, 1H, J = 2.4 Hz), 6.92–6.93 (m, 2H), 7.13–7.16 (m, 3H), 7.19–7.20 (m, 1H), 7.65 (d, 1H, J = 8.0 Hz), 7.92 (d, 1H, J = 8.0 Hz), 9.95 (s, 1H); MS (ESI, m/z): 292.0 $[M+Na]^+$.

5.1.3.36. 1-(3-Bromobenzyl)-1*H*-indole-7-carbaldehyde (42a). The compound **42a** was prepared from indole-7-aldehyde and 1-bromo-3-(bromomethyl)benzene according to general procedure A. The residue was purified by flash chromatography to give 660 mg (70%) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.81 (s, 2H), 6.61 (d, 1H, J = 2.4 Hz), 6.73 (d, 1H, J = 8.0 Hz), 6.97 (d, 1H, J = 8.0 Hz), 7.00–7.03 (m, 1H), 7.09 (d, 1H, J = 2.4 Hz), 7.18 (d, 1H, J = 8.0 Hz), 7.22 (d, 1H, J = 8.0 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.83 (d, 1H, J = 8.0 Hz), 9.85 (s, 1H); MS (ESI, m/z): 337.0 $[M+Na]^+$.

5.1.4. General procedure B for the synthesis of 3–42

A solution of 50% KOH (2 mL, aq) was added dropwise to a stirred solution of **2** (1 mmol, 1 equiv) and indole-aldehyde (1 mmol, 1 equiv) in methanol (10 mL) at 0 °C. The resulting mixture was stirred at room temperature for 48 h under N_2 atmosphere. After the end of reaction, the mixture was poured into ice water and pH was brought back to 7.0 by the careful addition of 1 N HCl solution. The aqueous layer was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and then concentrated in vacuo. The residue was purified by silica gel column chromatography to provide **3**–**42** as a yellow solid.

5.1.4.1. (*E*)-3-(1*H*-Indol-4-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (3). The reaction was carried out following the general procedure B with 1*H*-indole-4-carbaldehyde (145 mg, 1 mmol) to give **3** as a yellow solid (158 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 3.89 (s, 3H), 5.62 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.70 (d, 1H, J = 10.0 Hz), 6.95 (s, 1H), 7.22 (t, 1H, J = 8.0 Hz), 7.32 (t, 1H, J = 2.8 Hz), 7.43 (d, 1H, J = 8.0 Hz), 7.46 (d, 1H, J = 8.0 Hz), 7.75 (d, 1H, J = 8.8 Hz), 7.91 (d, 1H, J = 15.6 Hz), 8.13 (d, 1H, J = 15.6 Hz), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 55.8, 77.0, 101.7, 103.5, 110.5, 113.1, 116.8, 120.5, 122.0, 122.0, 125.5, 127.3, 127.3, 127.7, 128.9, 131.8, 136.4, 140.8, 153.7, 158.4, 190.5; HRMS (ESI) calcd for $[M+H]^+$ $C_{23}H_{22}NO_3$: 360.1600, found: 360.1605.

5.1.4.2. (*E*)-3-(1*H*-Indol-5-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (4). The reaction was carried out following the general procedure B with 1*H*-indole-5-carbaldehyde (145 mg, 1 mmol) to give **4** as a yellow solid (209 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 3.89 (s, 3H), 5.64 (d, J = 10.0 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 6.60 (s, 1H), 6.71 (d, J = 10.0 Hz, 1H), 7.25–7.22 (m, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.52 (dd, J = 8.5, 1.2 Hz, 1H), 7.71 (dd, J = 12.2, 10.1 Hz, 2H), 7.86 (d, J = 15.2 Hz, 2H), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 55.8, 76.8, 103.4, 103.5, 110.5, 111.6, 116.8, 121.7, 122.1, 122.8, 124.8, 125.2, 127.7, 128.3, 128.7, 131.6, 136.9, 143.8, 153.5, 158.2, 190.5; HRMS (ESI) calcd for $[M+H]^+$ $C_{23}H_{22}NO_3$: 360.1600, found: 360.1605.

5.1.4.3. (*E*)-3-(1*H*-Indol-6-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (5). The reaction was carried out following the general procedure B with 1*H*-indole-6-carbaldehyde (145 mg, 1 mmol) to give **5** as a yellow solid (243 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 3.89 (s, 3H), 5.63 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.57 (s, 1H), 6.69 (d, 1H, J = 10.0 Hz), 7.29 (s, 1H), 7.46 (d, 1H, J = 8.8 Hz), 7.61 (s, 1H), 7.63 (d, 1H, J = 8.8 Hz), 7.71–7.75 (m, 2H), 7.83 (d, 1H, J = 15.6 Hz), 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.1, 28.1, 55.8, 76.9, 103.1, 103.4, 110.5, 113.2, 116.8, 119.0, 121.1, 122.0, 125.3, 126.4, 128.8, 129.6, 131.6, 136.0, 143.6, 153.6, 158.3, 190.4; HRMS (ESI) calcd for $[M+H]^+$ $C_{23}H_{22}NO_3$: 360.1600, found: 360.1600.

5.1.4.4. (*E*)-3-(1*H*-Indol-7-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (6). The reaction was carried out following the general procedure B with 1*H*-indole-7-carbaldehyde (145 mg, 1 mmol) to give **6** as a yellow solid (215 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 3.90 (s, 3H), 5.65 (d, 1H, J = 10.0 Hz), 6.54 (d, 1H, J = 8.8 Hz), 6.61 (t, 1H, J = 2.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 7.17 (t, 1H, J = 8.0 Hz), 7.25–7.26 (m, 1H), 7.51 (d, 1H, J = 8.0 Hz), 7.69 (d, 1H, J = 8.0 Hz), 7.77 (d, 1H, J = 8.8 Hz), 7.83 (d, 1H, J = 15.6 Hz), 8.14 (d, 1H, J = 15.6 Hz), 8.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 55.9, 77.2, 102.9, 103.6, 110.6, 116.8, 119.5, 120.0, 121.2, 121.9, 123.0, 125.0, 126.8, 128.9, 128.9, 131.8, 135.2, 138.1, 153.8, 158.6, 190.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{23}H_{22}NO_3$: 360.1600, found: 360.1658.

5.1.4.5. (*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-(methoxymethyl)-1*H*-indol-3-yl)prop-2-en-1-one (7). The reaction was carried out following the general procedure B with **7a** (189 mg, 1 mmol) to give **7** as a yellow solid (149 mg, 37%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.53 (s, 6H), 3.28 (s, 3H), 3.89 (s, 3H), 5.47 (s, 2H), 5.64 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 7.28 (d, 1H, J = 8.0 Hz), 7.34 (t, 1H, J = 8.0 Hz), 7.51 (s, 1H), 7.52 (d, 1H, J = 8.0 Hz), 7.60 (d, 1H, J = 8.0 Hz), 7.81 (d, 1H, J = 16.0 Hz), 7.97 (d, 1H, J = 16.0 Hz), 8.08 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 55.8, 56.2, 77.0, 77.8, 103.4, 110.5, 110.8, 114.6, 116.9, 121.2, 121.7, 122.2, 123.5, 123.8, 126.7, 128.8, 131.8, 133.2, 135.4, 137.6, 153.5, 158.1, 190.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{25}H_{26}NO_4$: 404.1862, found: 404.1858.

5.1.4.6. (*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-methyl-1*H*-indol-3-yl)prop-2-en-1-one (8). The reaction was carried out following the general procedure B with **8a** (189 mg, 1 mmol) to give **8** as a yellow solid (153 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 3.83 (s, 3H), 3.89 (s, 3H), 5.63 (d, 1H, J = 10.0 Hz), 6.51 (d, 1H, J = 8.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 7.23 (d, 1H, J = 7.2 Hz), 7.30–7.37 (m, 2H), 7.39 (s, 1H), 7.74 (d, 1H, J = 8.8 Hz), 7.75 (d, 1H, J = 16.0 Hz), 7.97 (d, 1H, J = 16.0 Hz), 8.07 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 33.2, 55.8, 76.9, 103.3, 110.0, 110.5, 113.5, 116.9, 121.1, 121.1, 122.4, 122.7, 122.9, 126.2, 128.8, 131.7, 134.2, 135.9, 138.2, 153.4, 158.0, 190.2; HRMS (ESI) calcd for $[M+H]^+$ $C_{24}H_{24}NO_3$: 374.1756, found: 374.1752.

5.1.4.7. (*E*)-3-(1-Ethyl-1*H*-indol-3-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (9). The reaction was carried out following the general procedure B with **9a** (189 mg, 1 mmol) to give **9** as a yellow solid (154 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21 (t, 3H, J = 7.2 Hz), 1.52 (s, 6H), 3.45 (q, 2H, J = 7.2 Hz), 3.88 (s, 3H), 3.63 (d, 1H, J = 10.0 Hz), 6.51 (d, 1H, J = 8.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 7.22 (d, 1H, J = 8.0 Hz), 7.30 (t, 1H, J = 8.0 Hz), 7.37 (d, 1H, J = 8.0 Hz), 7.45 (s, 1H), 7.75 (d, 1H, J = 8.8 Hz), 7.76 (d, 1H, J = 15.6 Hz), 7.98 (d, 1H, J = 15.6 Hz), 8.07 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.2, 28.0, 28.0, 41.4, 55.8, 76.9, 103.3, 110.1, 110.5, 113.5, 116.9, 121.0, 121.2, 122.4, 122.6, 122.8, 126.3, 128.8, 131.7, 132.6, 136.1, 137.3, 153.4, 158.0, 190.2; HRMS (ESI) calcd for $[M+H]^+$ $C_{25}H_{26}NO_3$: 388.1913, found: 388.1907.

5.1.4.8. (*E*)-3-(1-Isopropyl-1*H*-indol-3-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (10). The reaction was carried out following the general procedure B with **10a** (189 mg, 1 mmol) to give **10** as a yellow solid (132 mg, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.63 (s, 6H), 1.55 (d, 6H, J = 6.8 Hz), 3.88 (s, 3H), 4.67 (heptet, 1H, J = 6.8 Hz), 5.63 (d, 1H, J = 10.0 Hz), 6.51 (d, 1H, J = 8.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 7.22 (d, 1H, J = 8.0 Hz), 7.29 (t, 1H, J = 8.0 Hz), 7.55 (s, 1H), 7.75 (d, 1H, J = 8.8 Hz), 7.76 (d, 1H, J = 15.6 Hz), 7.99 (d, 1H, J = 15.6 Hz), 8.07 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.7, 22.7, 27.9, 27.9, 47.5, 55.8, 76.9, 103.3, 110.2, 110.5, 113.7, 116.9, 121.1, 121.2, 122.5, 122.5, 122.7, 126.3, 128.8, 129.5, 131.7, 136.2, 137.2, 153.4, 157.9, 190.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{26}H_{28}NO_3$: 402.2069, found: 402.2066.

5.1.4.9. (*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-(3-methylbut-2-en-1-yl)-1*H*-indol-3-yl)prop-2-en-1-one (11). The reaction was carried out following the general procedure B with **11a** (189 mg, 1 mmol) to give **11** as a yellow solid (167 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 1.80 (s, 3H), 1.83 (s, 3H), 3.89 (s, 3H), 4.69 (d, 2H, J = 6.8 Hz), 5.40 (t, 1H, J = 6.8 Hz), 5.63 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.0 Hz), 6.71 (d, 1H, J = 10.0 Hz), 7.22 (d, 1H, J = 8.0 Hz), 7.29 (t, 1H, J = 8.0 Hz), 7.36 (d, 1H, J = 8.0 Hz), 7.46 (s, 1H), 7.75–7.78 (m, 2H), 7.99 (d, 1H, J = 15.6 Hz), 8.06 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.1, 25.7, 27.9, 27.9, 44.4, 55.8, 76.9, 103.3, 110.3, 110.5, 113.4, 116.9, 118.7, 121.1, 122.3, 122.8, 126.5, 128.8, 131.8, 133.0, 136.4, 137.6, 138.0, 153.4, 158.0, 190.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{28}H_{30}NO_3$: 428.2226, found: 428.2221.

5.1.4.10. (*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-(2-morpholinoethyl)-1*H*-indol-3-yl)prop-2-en-1-one (12). The reaction was carried out following the general procedure B with **12a** (189 mg, 1 mmol) to give **12** as a yellow solid (111 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (s, 6H), 2.49 (t, 4H, J = 4.4 Hz), 2.77 (t, 2H, J = 6.4 Hz), 3.70 (t, 4H, J = 4.4 Hz), 3.89 (s, 3H), 4.25 (t, 2H, J = 6.4 Hz), 5.64 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 7.22 (d, 1H, J = 8.0 Hz), 7.30 (t, 1H, J = 8.0 Hz), 7.38 (d, 1H, J = 8.0 Hz), 7.52 (s, 1H), 7.75 (d, 1H, J = 8.8 Hz), 7.76 (d, 1H, J = 15.6 Hz), 7.98 (d, 1H, J = 15.6 Hz), 8.07 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 44.1, 53.8, 53.8, 55.8, 55.8, 57.8, 66.9, 76.9, 103.4, 110.0, 110.5, 113.6, 116.9, 121.1, 121.3, 122.4, 122.7, 122.9, 126.2, 128.8, 131.8, 133.9, 136.0, 137.5, 153.4, 158.0, 190.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{29}H_{33}N_2O_4$: 473.2440, found: 473.2445.

5.1.4.11. (*E*)-3-(1-Benzyl-1*H*-indol-3-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (13). The reaction was carried out following the general procedure B with **13a** (189 mg, 1 mmol) to give **13** as a yellow solid (189 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 3.88 (s, 3H), 5.32 (s, 2H), 5.63 (d, 1H, J = 10.0 Hz), 6.51 (d, 1H, J = 8.8 Hz), 6.70 (d, 1H, J = 10.0 Hz), 7.15–7.16 (m, 2H), 7.22–7.25 (m, 2H), 7.27–7.32 (m, 4H), 7.44 (s, 1H), 7.74 (d, 1H, J = 8.8 Hz), 7.97 (d, 1H, J = 16.0 Hz), 8.08 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 50.5, 55.8, 76.9, 103.4, 110.5, 110.5, 114.0, 116.9, 121.2, 121.3, 122.3, 123.0, 123.1, 126.4, 127.0, 127.0, 128.1, 128.8, 129.0, 129.0, 131.8, 133.5, 135.9, 136.2, 137.8, 153.4, 158.0, 190.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{28}NO_3$: 450.2069, found: 450.2061.

5.1.4.12. (*E*)-3-(1-(2-Fluorobenzyl)-1*H*-indol-3-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (14). The reaction was carried out following the general procedure B with **14a** (189 mg, 1 mmol) to give **14** as a yellow solid (215 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 3.88 (s, 3H), 5.37 (s, 2H), 5.63 (d, 1H, J = 10.0 Hz), 6.51 (d, 1H, J = 8.8 Hz), 6.70 (d, 1H, J = 10.0 Hz), 6.98 (t, 1H, J = 7.2 Hz), 7.05 (t, 1H, J = 7.2 Hz), 7.10 (t, 1H, J = 8.8 Hz), 7.23–7.30 (m, 3H), 7.37 (d, 1H, J = 7.2 Hz), 7.50 (s, 1H), 7.75 (d, 1H, J = 8.8 Hz), 7.77 (d, 1H, J = 16.0 Hz), 7.98 (d, 1H, J = 16.0 Hz), 8.07 (d, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 44.2, 55.8, 76.9, 103.4, 110.3, 110.5, 114.2, 115.6, 115.8, 116.9, 121.2, 121.3, 122.2, 123.1, 123.2, 124.7, 126.4, 128.8, 129.2, 130.0, 130.1, 131.8, 133.4, 135.8, 137.6, 153.5, 158.1, 190.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}FNO_3$: 468.1975, found: 468.1976.

5.1.4.13. (*E*)-3-(1-(3-Fluorobenzyl)-1*H*-indol-3-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (15). The reaction was carried out following the general procedure B with **15a** (189 mg, 1 mmol) to give **15** as a yellow solid (187 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 3.88 (s, 3H), 5.32 (s, 2H), 5.63 (d, 1H, J = 10.0 Hz), 6.51 (d, 1H, J = 8.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 6.82 (d, 1H, J = 8.0 Hz), 6.91 (d, 1H, J = 8.0 Hz), 6.96 (t, 1H, J = 8.0 Hz), 7.27–7.31 (m, 4H), 7.45 (s, 1H), 7.75 (d, 1H, J = 8.8 Hz), 7.79 (d, 1H, J = 15.6 Hz), 7.98 (d, 1H, J = 15.6 Hz), 8.09 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 49.9, 55.8, 76.9, 103.4, 110.4, 110.5, 113.8, 114.0, 114.2, 114.9, 115.1, 116.9,

121.3, 121.4, 122.3, 122.4, 123.3, 126.4, 128.8, 130.6, 131.8, 133.3, 135.5, 137.6, 138.8, 153.4, 158.1, 190.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}FNO_3$: 468.1975, found: 468.1978.

5.1.4.14. (*E*)-3-(1-(4-Fluorobenzyl)-1*H*-indol-3-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (16). The reaction was carried out following the general procedure B with **16a** (189 mg, 1 mmol) to give **16** as a yellow solid (145 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 3.89 (s, 3H), 5.30 (s, 2H), 5.63 (d, 1H, J = 10.0 Hz), 6.51 (d, 1H, J = 8.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 7.01 (d, 2H, J = 8.0 Hz), 7.14 (d, 2H, J = 8.0 Hz), 7.23–7.30 (m, 5H), 7.43 (s, 1H), 7.75–7.81 (m, 2H), 7.96 (d, 1H, J = 15.6 Hz), 8.08 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.9, 27.9, 49.8, 55.8, 76.9, 103.4, 110.4, 110.5, 114.1, 115.8, 116.0, 116.9, 121.2, 121.3, 122.2, 123.1, 123.2, 126.5, 128.7, 128.8, 128.8, 131.8, 132.0, 132.0, 133.3, 135.7, 137.6, 153.4, 158.1, 190.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}FNO_3$: 468.1975, found: 468.1977.

5.1.4.15. (*E*)-3-(1-(2-Chlorobenzyl)-1*H*-indol-3-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (17). The reaction was carried out following the general procedure B with **17a** (189 mg, 1 mmol) to give **17** as a yellow solid (189 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 3.88 (s, 3H), 5.43 (s, 2H), 5.63 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.0 Hz), 6.71 (d, 1H, J = 10.0 Hz), 6.75 (d, 1H, J = 8.0 Hz), 7.13 (t, 1H, J = 8.0 Hz), 7.22–7.30 (m, 4H), 7.42 (d, 1H, J = 8.0 Hz), 7.44 (d, 1H, J = 8.0 Hz), 7.75 (d, 1H, J = 8.0 Hz), 7.79 (d, 1H, J = 16.0 Hz), 7.98 (d, 1H, J = 16.0 Hz), 8.10 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 48.0, 55.8, 76.9, 103.4, 110.4, 110.5, 114.2, 116.9, 121.2, 121.4, 122.3, 123.2, 123.3, 126.4, 127.4, 128.3, 128.8, 129.3, 129.8, 131.8, 132.7, 133.5, 133.9, 135.6, 137.7, 153.4, 158.1, 190.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}ClNO_3$: 484.1679, found: 484.1674.

5.1.4.16. (*E*)-3-(1-(3-Chlorobenzyl)-1*H*-indol-3-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (18). The reaction was carried out following the general procedure B with **18a** (189 mg, 1 mmol) to give **18** as a yellow solid (218 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 3.89 (s, 3H), 5.31 (s, 2H), 5.63 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 6.99 (d, 1H, J = 8.0 Hz), 7.11 (s, 1H), 7.23–7.31 (m, 5H), 7.45 (s, 1H), 7.75 (d, 1H, J = 8.8 Hz), 7.79 (d, 1H, J = 16.0 Hz), 7.97 (d, 1H, J = 16.0 Hz), 8.09 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 49.9, 55.8, 76.9, 103.4, 110.4, 110.5, 114.3, 116.9, 121.3, 121.4, 122.2, 123.3, 123.3, 125.0, 126.4, 127.0, 128.3, 128.8, 130.3, 131.8, 133.3, 134.9, 135.6, 137.6, 138.3, 153.5, 158.1, 190.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}ClNO_3$: 484.1679, found: 484.1679.

5.1.4.17. (*E*)-3-(1-(4-Chlorobenzyl)-1*H*-indol-3-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (19). The reaction was carried out following the general procedure B with **19a** (189 mg, 1 mmol) to give **19** as a yellow solid (203 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 3.89 (s, 3H), 5.30 (s, 2H), 5.63 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 7.07 (d, 1H, J = 8.0 Hz), 7.22–7.27 (m, 5H), 7.28 (d, 1H, J = 8.0 Hz), 7.44 (s, 1H), 7.75 (d, 1H, J = 8.8 Hz), 7.78 (d, 1H, J = 15.6 Hz), 7.96 (d, 1H, J = 15.6 Hz), 8.08 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 49.9, 55.8, 76.9, 103.4, 110.4, 110.5, 114.2, 116.9, 121.3, 121.4, 122.2, 123.2, 123.2, 126.5, 128.3, 128.3, 128.8, 129.2, 129.2, 131.8, 133.3, 133.9, 134.7, 135.6, 137.6, 153.5, 158.1, 190.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}ClNO_3$: 484.1679, found: 484.1674.

5.1.4.18. (*E*)-3-(1-(2-Bromobenzyl)-1*H*-indol-3-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (20). The reaction was carried out following the general procedure B with **20a** (189 mg, 1 mmol) to give **20** as a yellow solid (180 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (s, 6H), 3.88 (s, 3H), 5.40 (s, 2H), 5.63 (d, 1H, J = 10.0 Hz), 6.51 (d, 1H, J = 8.8 Hz), 6.68 (d, 1H, J = 4.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 7.22–7.31 (m, 5H), 7.45 (s, 1H), 7.62 (t, 1H, J = 4.8 Hz), 7.75 (d, 1H, J = 8.8 Hz), 7.79 (d, 1H, J = 15.6 Hz), 7.98 (d, 1H, J = 15.6 Hz), 8.10 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 50.5, 55.8, 76.9, 103.4, 110.5, 110.5, 114.3, 116.9, 121.2, 121.4, 122.2, 122.6, 123.2, 123.3, 126.3, 128.0, 128.3, 128.8, 129.6, 131.8, 133.0, 133.5, 135.5, 135.6, 137.7, 153.5, 158.1, 190.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}BrNO_3$: 528.1174, found: 528.1171.

5.1.4.19. (*E*)-3-(1-(3-Bromobenzyl)-1*H*-indol-3-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (21). The reaction was carried out following the general procedure B with **21a** (189 mg, 1 mmol) to give **21** as a yellow solid (248 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 3.88 (s, 3H), 5.29 (s, 2H), 5.63 (d, 1H, J = 10.0 Hz), 6.51 (d, 1H, J = 8.8 Hz), 6.70 (d, 1H, J = 10.0 Hz), 7.02 (d, 1H, J = 8.0 Hz), 7.17 (t, 1H, J = 8.0 Hz), 7.23–7.29 (m, 3H), 7.34 (s, 1H), 7.41–7.44 (m, 2H), 7.75 (d, 1H, J = 8.8 Hz), 7.78 (d, 1H, J = 15.6 Hz), 7.97 (d, 1H, J = 15.6 Hz), 8.08 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 49.8, 55.8, 76.9, 103.4, 110.4, 110.5, 114.3, 116.9, 121.3, 121.4, 122.2, 123.1, 123.3, 123.3, 125.5, 126.4, 128.8, 129.9, 130.6, 131.3, 131.8, 133.3, 135.6, 137.6, 138.6, 153.5, 158.1, 190.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}BrNO_3$: 528.1174, found: 528.1178.

5.1.4.20. (*E*)-3-(1-(4-Bromobenzyl)-1*H*-indol-3-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (22). The reaction was carried out following the general procedure B with **22a** (189 mg, 1 mmol) to give **22** as a yellow solid (190 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 3.88 (s, 3H), 5.28 (s, 2H), 5.63 (d, 1H, J = 10.0 Hz), 6.51 (d, 1H, J = 8.8 Hz), 6.70 (d, 1H, J = 10.0 Hz), 7.00 (d, 2H, J = 8.0 Hz), 7.22–7.29 (m, 3H), 7.43–7.45 (m, 3H), 7.74 (d, 1H, J = 8.8 Hz), 7.78 (d, 1H, J = 16.0 Hz), 7.96 (d, 1H, J = 16.0 Hz), 8.08 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.9, 27.9, 49.9, 55.8, 76.9, 103.4, 110.4, 110.5, 114.2, 116.9, 121.3, 121.4, 122.0, 122.2, 123.2, 123.2, 126.4, 128.6, 128.6, 128.8, 131.8, 132.1, 132.1, 133.3, 135.3, 135.6, 137.6, 153.4, 158.1, 190.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}BrNO_3$: 528.1174, found: 528.1170.

5.1.4.21. (*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-(2-(trifluoromethyl)benzyl)-1*H*-indol-3-yl)prop-2-en-1-one (23). The reaction was carried out following the general procedure B with **23a** (189 mg, 1 mmol) to give **23** as a yellow solid (150 mg, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (s, 6H), 3.89 (s, 3H), 5.57 (s, 2H), 5.64 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.68 (d, 1H, J = 4.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 7.20–7.31 (m, 3H), 7.34–7.40 (m, 2H), 7.47 (s, 1H), 7.73 (d, 1H, J = 4.8 Hz), 7.76 (d, 1H, J = 8.8 Hz), 7.81 (d, 1H, J = 15.6 Hz), 7.99 (d, 1H, J = 15.6 Hz), 8.11 (d, 1H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 46.8, 55.8, 76.9, 103.4, 110.4, 110.5, 114.5, 116.9, 121.3, 121.5, 122.2, 123.4, 123.4, 126.2, 126.2, 126.4, 127.1, 127.5, 127.9, 128.8, 131.8, 132.6, 133.6, 135.1, 135.5, 137.7, 153.5, 158.1, 190.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{31}H_{27}F_3NO_3$: 518.1943, found: 518.1943.

5.1.4.22. (*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-(3-(trifluoromethyl)benzyl)-1*H*-indol-3-yl)prop-2-en-1-one (24). The reaction was carried out following the general procedure B with **24a** (189 mg, 1 mmol) to give **24** as a yellow solid (181 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 3.88 (s,

3H), 5.39 (s, 2H), 5.63 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 7.23–7.27 (m, 5H), 7.41 (d, 1H, J = 8.0 Hz), 7.45 (d, 1H, J = 8.0 Hz), 7.50 (s, 1H), 7.76 (d, 1H, J = 8.8 Hz), 7.79 (d, 1H, J = 15.6 Hz), 7.99 (d, 1H, J = 15.6 Hz), 8.09 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.9, 27.9, 50.0, 55.8, 76.9, 103.4, 110.3, 110.5, 114.4, 116.9, 121.3, 121.5, 122.2, 123.4, 123.4, 123.7, 123.7, 125.0, 125.0, 126.5, 128.8, 129.7, 130.2, 131.8, 133.1, 135.5, 137.4, 137.6, 153.5, 158.1, 190.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{31}H_{27}F_3NO_3$: 518.1943, found: 518.1948.

5.1.4.23. (*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-(4-(trifluoromethyl)benzyl)-1*H*-indol-3-yl)prop-2-en-1-one (25). The reaction was carried out following the general procedure B with **25a** (189 mg, 1 mmol) to give **25** as a yellow solid (166 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 3.89 (s, 3H), 5.40 (s, 2H), 5.63 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.71 (d, 1H, J = 10.0 Hz), 7.21–7.29 (m, 5H), 7.46 (s, 1H), 7.57 (d, 2H, J = 8.0 Hz), 7.75 (d, 1H, J = 8.8 Hz), 7.80 (d, 1H, J = 15.6 Hz), 7.97 (d, 1H, J = 15.6 Hz), 8.10 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.9, 27.9, 50.0, 55.8, 76.9, 103.4, 110.3, 110.5, 114.4, 116.9, 121.3, 121.5, 122.2, 123.4, 123.4, 125.9, 126.0, 126.0, 126.0, 126.4, 127.1, 127.1, 128.8, 131.8, 133.2, 135.4, 137.6, 140.4, 153.5, 158.1, 190.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{31}H_{27}F_3NO_3$: 518.1943, found: 518.1942.

5.1.4.24. (*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-methyl-1*H*-indol-4-yl)prop-2-en-1-one (26). The reaction was carried out following the general procedure B with **26a** (189 mg, 1 mmol) to give **26** as a yellow solid (175 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 3.83 (s, 3H), 3.89 (s, 3H), 5.62 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.69 (d, 1H, J = 10.0 Hz), 6.87 (d, 1H, J = 2.8 Hz), 7.15 (d, 1H, J = 2.8 Hz), 7.23–7.27 (m, 2H), 7.36 (d, 1H, J = 8.0 Hz), 7.45 (d, 1H, J = 8.0 Hz), 7.74 (d, 1H, J = 8.8 Hz), 7.89 (d, 1H, J = 15.6 Hz), 8.11 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 33.1, 55.8, 77.0, 100.2, 103.5, 110.5, 111.1, 116.8, 120.2, 121.6, 122.0, 127.4, 127.9, 128.8, 130.0, 131.8, 137.2, 140.6, 153.7, 158.3, 190.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{24}H_{24}NO_3$: 374.1756, found: 374.1754.

5.1.4.25. (*E*)-3-(1-Ethyl-1*H*-indol-4-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (27). The reaction was carried out following the general procedure B with **27a** (189 mg, 1 mmol) to give **27** as a yellow solid (190 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49 (t, 3H, J = 7.2 Hz), 1.51 (s, 6H), 3.89 (s, 3H), 4.18 (q, 2H, J = 7.2 Hz), 5.62 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.69 (d, 1H, J = 10.0 Hz), 6.88 (d, 1H, J = 2.8 Hz), 7.22–7.23 (m, 2H), 7.38 (d, 1H, J = 8.0 Hz), 7.45 (d, 1H, J = 8.0 Hz), 7.74 (d, 1H, J = 8.8 Hz), 7.89 (d, 1H, J = 15.6 Hz), 8.12 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.5, 28.0, 28.0, 41.2, 55.8, 77.0, 100.3, 103.4, 110.5, 111.1, 116.8, 120.0, 121.4, 122.1, 127.3, 128.0, 128.1, 128.2, 128.8, 131.8, 136.2, 140.7, 153.7, 158.3, 190.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{25}H_{26}NO_3$: 388.1913, found: 388.1918.

5.1.4.26. (*E*)-3-(1-(3-Fluorobenzyl)-1*H*-indol-4-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (28). The reaction was carried out following the general procedure B with **28a** (189 mg, 1 mmol) to give **28** as a yellow solid (164 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 3.89 (s, 3H), 5.34 (s, 2H), 5.62 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.69 (d, 1H, J = 10.0 Hz), 6.77 (d, 1H, J = 8.0 Hz), 6.87 (d, 1H, J = 8.0 Hz), 6.93–6.96 (m, 2H), 7.18–7.29 (m, 4H), 7.47 (d, 1H, J = 8.0 Hz), 7.75 (d, 1H, J = 8.8 Hz), 7.91 (d, 1H, J = 15.6 Hz), 8.13 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 49.8, 55.8, 77.0, 101.2, 103.5, 110.5, 111.4, 113.6, 113.8, 114.6, 114.8, 116.8, 120.2, 122.0, 122.2, 127.5, 128.2, 128.3, 128.8, 129.3, 130.5, 131.8, 136.7, 139.8, 140.2, 153.7, 158.4, 190.2; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}FNO_3$: 468.1975, found: 468.1971.

5.1.4.27. (*E*)-3-(1-(3-Chlorobenzyl)-1*H*-indol-4-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (29). The reaction was carried out following the general procedure B with **29a** (189 mg, 1 mmol) to give **29** as a yellow solid (213 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 3.89 (s, 3H), 5.33 (s, 2H), 5.63 (d, 1H, J = 10.0 Hz), 6.53 (d, 1H, J = 8.8 Hz), 6.70 (d, 1H, J = 10.0 Hz), 6.94–6.96 (m, 2H), 7.13 (s, 1H), 7.21–7.29 (m, 5H), 7.47 (d, 1H, J = 8.0 Hz), 7.75 (d, 1H, J = 8.8 Hz), 7.91 (d, 1H, J = 15.6 Hz), 8.13 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 49.7, 55.8, 77.0, 101.2, 103.5, 110.5, 111.4, 116.8, 120.2, 122.0, 122.0, 124.8, 126.8, 127.5, 128.0, 128.2, 128.3, 128.8, 129.3, 130.2, 131.8, 134.8, 136.7, 139.3, 140.2, 153.7, 158.4, 190.2; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}ClNO_3$: 484.1679, found: 484.1679.

5.1.4.28. (*E*)-3-(1-(3-Bromobenzyl)-1*H*-indol-4-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (30). The reaction was carried out following the general procedure B with **30a** (189 mg, 1 mmol) to give **30** as a yellow solid (217 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 3.89 (s, 3H), 5.33 (s, 2H), 5.62 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.69 (d, 1H, J = 10.0 Hz), 6.95–6.99 (m, 2H), 7.14–7.30 (m, 5H), 7.39 (d, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 8.0 Hz), 7.75 (d, 1H, J = 8.8 Hz), 7.91 (d, 1H, J = 15.6 Hz), 8.13 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 49.7, 55.8, 77.0, 101.2, 103.5, 110.5, 111.4, 116.8, 120.2, 122.0, 122.1, 123.0, 125.3, 127.6, 128.2, 128.3, 128.8, 129.3, 129.7, 130.5, 130.9, 131.8, 136.7, 139.6, 140.2, 153.7, 158.4, 190.2; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}BrNO_3$: 528.1174, found: 528.1179.

5.1.4.29. (*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-methyl-1*H*-indol-5-yl)prop-2-en-1-one (31). The reaction was carried out following the general procedure B with **31a** (189 mg, 1 mmol) to give **31** as a yellow solid (179 mg, 48%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.52 (s, 6H), 3.81 (s, 3H), 3.89 (s, 3H), 5.62 (d, 1H, J = 10.0 Hz), 6.51–6.53 (m, 2H), 6.69 (d, 1H, J = 10.0 Hz), 7.07 (d, 1H, J = 2.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.54 (d, 1H, J = 8.8 Hz), 7.67–7.72 (m, 2H), 7.84–7.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 33.0, 55.8, 76.8, 102.0, 103.4, 109.8, 110.5, 116.8, 121.2, 122.2, 123.0, 124.6, 127.2, 128.7, 128.8, 129.9, 131.6, 137.8, 134.9, 153.5, 158.1, 190.4; HRMS (ESI) calcd for $[M+H]^+$ $C_{24}H_{24}NO_3$: 374.1756, found: 374.1758.

5.1.4.30. (*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-(2-(piperidin-1-yl)ethyl)-1*H*-indol-5-yl)prop-2-en-1-one (32). The reaction was carried out following the general procedure B with **32a** (189 mg, 1 mmol) to give **32** as a yellow solid (99 mg, 21%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.47–1.41 (m, 2H), 1.52 (s, 6H), 1.59 (dt, J = 11.0, 5.6 Hz, 4H), 2.45 (s, 4H), 2.70 (t, J = 7.2 Hz, 2H), 3.88 (s, 3H), 4.24 (t, J = 7.2 Hz, 2H), 5.63 (d, J = 10.0 Hz, 1H), 6.51 (dd, J = 6.0, 2.7 Hz, 2H), 6.70 (d, J = 10.0 Hz, 1H), 7.16 (d, J = 3.1 Hz, 1H),7.36 (d, J = 8.6 Hz, 1H), 7.57–7.49 (m, 1H),7.70 (dd, J = 12.2, 10.4 Hz, 2H), 7.86 (d, J = 15.5 Hz, 2H); HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{35}N_2O_3$: 471.2648, found: 471.2646.

5.1.4.31. (*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-methyl-1*H*-indol-6-yl)prop-2-en-1-one (33). The reaction was carried out following the general procedure B with **33a** (189 mg, 1 mmol) to give **33** as a yellow solid (172 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (s, 6H), 3.81 (s, 3H), 3.88 (s, 3H), 5.63 (d, 1H, J = 10.0 Hz), 6.49 (d, 1H, J = 2.8 Hz), 6.51 (d, 1H, J = 8.8 Hz), 6.70 (d, 1H, J = 10.0 Hz), 7.12 (d, 1H, J = 2.8 Hz), 7.42 (d, 1H, J = 8.8 Hz), 7.54 (s, 1H), 7.60 (d, 1H, J = 8.8 Hz), 7.72–7.79 (m, 2H), 7.85 (d, 1H, J = 15.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.1, 28.1, 32.9, 55.8, 76.8, 101.5, 103.4, 110.5, 110.8, 116.8,

118.9, 121.2, 122.0, 125.4, 128.7, 129.3, 130.2, 130.9, 131.7, 136.9, 143.5, 153.6, 158.2, 190.2; HRMS (ESI) calcd for $[M+H]^+$ $C_{24}H_{24}NO_3$: 374.1756, found: 374.1761.

5.1.4.32. (*E*)-3-(1-Ethyl-1*H*-indol-6-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (34). The reaction was carried out following the general procedure B with **34a** (189 mg, 1 mmol) to give **34** as a yellow solid (120 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49 (t, 3H, J = 7.2 Hz), 1.53 (s, 6H), 3.89 (s, 3H), 4.18 (q, 2H, J = 7.2 Hz), 5.63 (d, 1H, J = 10.0 Hz), 6.50 (d, 1H, J = 2.8 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.70 (d, 1H, J = 10.0 Hz), 7.19 (d, 1H, J = 2.8 Hz), 7.42 (d, 1H, J = 8.0 Hz), 7.57 (s, 1H), 7.61 (d, 1H, J = 8.0 Hz), 7.72–7.78 (m, 2H), 7.85 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.5, 28.0, 28.0, 41.1, 55.8, 76.8, 101.6, 103.4, 110.4, 110.8, 116.8, 118.9, 121.3, 122.1, 125.3, 128.7, 129.2, 129.2, 130.4, 131.7, 135.8, 143.6, 153.6, 158.2, 190.2; HRMS (ESI) calcd for $[M+H]^+$ $C_{25}H_{26}NO_3$: 388.1913, found: 388.1911.

5.1.4.33. (*E*)-3-(1-(3-Fluorobenzyl)-1*H*-indol-6-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (35). The reaction was carried out following the general procedure B with **35a** (189 mg, 1 mmol) to give **35** as a yellow solid (182 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 6H), 3.88 (s, 3H), 5.35 (s, 2H), 5.60 (d, 1H, J = 10.0 Hz), 6.50 (d, 1H, J = 8.8 Hz), 6.59 (s, 1H), 6.68 (d, 1H, J = 10.0 Hz), 6.75 (d, 1H, J = 8.8 Hz), 6.87 (d, 1H, J = 8.0 Hz), 6.96 (t, 1H, J = 8.0 Hz), 7.26–7.30 (m, 3H), 7.44–7.46 (m, 2H), 7.64–7.71 (m, 2H), 7.77 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 49.7, 55.8, 76.6, 102.6, 103.4, 110.4, 111.0, 113.4, 113.6, 114.7, 114.9, 116.8, 119.4, 121.5, 121.9, 122.1, 125.5, 128.7, 129.7, 130.3, 130.5, 131.7, 136.4, 139.7, 143.3, 153.6, 158.3, 190.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}FNO_3$: 468.1975, found: 468.1975.

5.1.4.34. (*E*)-3-(1-(3-Chlorobenzyl)-1*H*-indol-6-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (36). The reaction was carried out following the general procedure B with **36a** (189 mg, 1 mmol) to give **36** as a yellow solid (237 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 6H), 3.87 (s, 3H), 5.32 (s, 2H), 5.60 (d, 1H, J = 10.0 Hz), 6.50 (d, 1H, J = 8.8 Hz), 6.58 (d, 1H, J = 2.8 Hz), 6.68 (d, 1H, J = 10.0 Hz), 6.94 (d, 1H, J = 6.4 Hz), 7.10 (s, 1H), 7.19 (d, 1H, J = 6.4 Hz), 7.22 (d, 2H, J = 6.4 Hz), 7.44 (d, 2H, J = 6.4 Hz), 7.64–7.71 (m, 3H), 7.77 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 49.6, 55.8, 76.8, 102.7, 103.4, 110.4, 110.9, 116.8, 119.4, 121.5, 121.9, 124.6, 125.5, 126.6, 128.1, 128.7, 129.7, 130.2, 130.3, 130.5, 131.7, 134.9, 136.4, 139.2, 143.2, 153.6, 158.3, 190.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}ClNO_3$: 484.1679, found: 484.1684.

5.1.4.35. (*E*)-3-(1-(3-Bromobenzyl)-1*H*-indol-6-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (37). The reaction was carried out following the general procedure B with **37a** (189 mg, 1 mmol) to give **37** as a yellow solid (164 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 6H), 3.87 (s, 3H), 5.31 (s, 2H), 5.60 (d, 1H, J = 10.0 Hz), 6.50 (d, 1H, J = 8.8 Hz), 6.58 (d, 1H, J = 2.8 Hz), 6.68 (d, 1H, J = 10.0 Hz), 6.97 (d, 1H, J = 8.0 Hz), 7.16 (t, 1H, J = 8.0 Hz), 7.18 (d, 1H, J = 2.8 Hz), 7.27 (s, 1H), 7.39 (d, 1H, J = 8.0 Hz), 7.44 (d, 2H, J = 8.0 Hz), 7.64 (d, 1H, J = 8.8 Hz), 7.68–7.72 (m, 2H), 7.77 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 49.5, 55.8, 76.8, 102.7, 103.5, 110.4, 110.9, 116.8, 119.4, 121.5, 121.9, 123.0, 125.1, 125.5, 128.7, 129.5, 129.7, 130.3, 130.5, 130.5, 131.0, 131.7, 136.4, 139.5, 143.2, 153.6, 158.3, 190.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}BrNO_3$: 528.1174, found: 528.1170.

5.1.4.36. (*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-methyl-1*H*-indol-7-yl)prop-2-en-1-one (38). The reaction was carried out following the general procedure B with **38a** (189 mg, 1 mmol) to give **38** as a yellow solid (168 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (s, 6H), 3.89 (s, 3H), 4.10 (s, 3H), 5.63 (d, 1H, J = 10.0 Hz), 6.49 (d, 1H, J = 2.8 Hz), 6.53 (d, 1H, J = 8.8 Hz), 6.69 (d, 1H, J = 10.0 Hz), 7.00 (d, 1H, J = 2.8 Hz), 7.11 (t, 1H, J = 8.0 Hz), 7.51 (d, 1H, J = 8.0 Hz), 7.64 (d, 1H, J = 8.0 Hz), 7.71 (d, 1H, J = 15.6 Hz), 7.75 (d, 1H, J = 8.8 Hz), 8.58 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 37.9, 55.8, 77.0, 101.3, 103.6, 110.5, 116.8, 119.7, 121.1, 121.5, 121.7, 123.0, 128.4, 128.8, 130.5, 131.4, 131.8, 134.7, 138.6, 153.9, 158.5, 189.5; HRMS (ESI) calcd for $[M+H]^+$ $C_{24}H_{24}NO_3$: 374.1756, found: 374.1752.

5.1.4.37. (*E*)-3-(1-Ethyl-1*H*-indol-7-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (39). The reaction was carried out following the general procedure B with **39a** (189 mg, 1 mmol) to give **39** as a yellow solid (155 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (t, 3H, J = 2.8 Hz), 1.52 (s, 6H), 3.89 (s, 3H), 4.38 (q, 2H, J = 2.8 Hz), 5.63 (d, 1H, J = 10.0 Hz), 6.51 (d, 1H, J = 2.8 Hz), 6.53 (d, 1H, J = 8.8 Hz), 6.69 (d, 1H, J = 10.0 Hz), 7.09–7.13 (m, 2H), 7.47 (d, 1H, J = 8.0 Hz), 7.64 (d, 1H, J = 8.0 Hz), 7.68 (d, 1H, J = 15.6 Hz), 7.75 (d, 1H, J = 8.8 Hz), 8.44 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.7, 28.0, 28.0, 44.5, 55.8, 77.0, 101.7, 103.6, 110.5, 116.8, 119.6, 121.2, 121.4, 121.6, 122.9, 128.8, 128.9, 129.6, 130.5, 131.7, 133.7, 139.1, 153.8, 158.5, 189.7; HRMS (ESI) calcd for $[M+H]^+$ $C_{25}H_{26}NO_3$: 388.1913, found: 388.1908.

5.1.4.38. (*E*)-3-(1-(3-Fluorobenzyl)-1*H*-indol-7-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (40). The reaction was carried out following the general procedure B with **40a** (189 mg, 1 mmol) to give **40** as a yellow solid (135 mg, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 6H), 3.89 (s, 3H), 5.53 (s, 2H), 5.60 (d, 1H, J = 10.0 Hz), 6.49 (d, 1H, J = 8.8 Hz), 6.62 (d, 1H, J = 2.8 Hz), 6.67 (d, 1H, J = 10.0 Hz), 6.98–6.99 (m, 2H), 7.12–7.16 (m, 2H), 7.18–7.22 (m, 2H), 7.39 (d, 1H, J = 8.0 Hz), 7.45 (d, 1H, J = 15.6 Hz), 7.65–7.70 (m, 2H), 8.13 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 52.6, 55.8, 77.0, 102.5, 103.5, 110.5, 112.9, 113.2, 114.5, 114.7, 116.7, 120.2, 121.6, 121.8, 121.8, 122.9, 128.8, 129.6, 130.4, 130.5, 130.9, 131.5, 133.9, 139.1, 140.8, 153.5, 158.3, 190.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}FNO_3$: 468.1975, found: 468.1980.

5.1.4.39. (*E*)-3-(1-(3-Chlorobenzyl)-1*H*-indol-7-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (41). The reaction was carried out following the general procedure B with **41a** (189 mg, 1 mmol) to give **41** as a yellow solid (155 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 6H), 3.88 (s, 3H), 5.55 (s, 2H), 5.59 (d, 1H, J = 10.0 Hz), 6.49 (d, 1H, J = 8.8 Hz), 6.62 (d, 1H, J = 2.8 Hz), 6.66 (d, 1H, J = 10.0 Hz), 6.87–6.89 (m, 2H), 7.08–7.15 (m, 3H), 7.21–7.24 (m, 1H), 7.39 (d, 1H, J = 8.0 Hz), 7.44 (d, 1H, J = 15.6 Hz), 7.63 (d, 1H, J = 8.8 Hz), 7.68 (d, 1H, J = 8.0 Hz), 8.11 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 52.6, 55.8, 77.0, 102.6, 103.5, 110.5, 116.7, 120.2, 121.6, 121.6, 121.8, 122.9, 124.5, 126.2, 127.9, 128.8, 129.6, 130.1, 130.5, 130.9, 131.6, 133.9, 134.8, 139.0, 140.2, 153.6, 158.3, 189.8; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}ClNO_3$: 484.1679, found: 484.1674.

5.1.4.40. (*E*)-3-(1-(3-Bromobenzyl)-1*H*-indol-7-yl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)prop-2-en-1-one (42). The reaction was carried out following the general procedure B with **42a** (189 mg, 1 mmol) to give **42** as a yellow solid (206 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (s, 6H), 3.88 (s, 3H), 5.52 (s, 2H), 5.60 (d, 1H, J = 10.0 Hz), 6.49 (d, 1H, J = 8.8 Hz), 6.61 (d, 1H, J = 2.8 Hz), 6.66 (d, 1H, J = 10.0 Hz), 7.01 (d, 1H, J = 8.0 Hz), 7.13 (d,

2H, *J* = 8.0 Hz), 7.22 (d, 1H, *J* = 8.0 Hz), 7.32 (d, 1H, *J* = 8.0 Hz), 7.40 (d, 1H, *J* = 8.0 Hz), 7.46 (d, 1H, *J* = 15.6 Hz), 7.53 (s, 1H), 7.65 (d, 1H, *J* = 8.8 Hz), 7.68 (d, 1H, *J* = 8.0 Hz), 8.13 (d, 1H, *J* = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.0, 28.0, 52.5, 55.8, 77.0, 102.6, 103.5, 110.5, 116.7, 120.2, 121.5, 121.8, 123.0, 125.0, 125.3, 128.8, 129.2, 129.5, 130.1, 130.4, 130.5, 130.9, 131.6, 133.9, 139.1, 140.4, 143.3, 153.6, 158.4, 189.9; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}BrNO_3$: 528.1174, found: 528.1182.

5.1.5. 1-(2-Hydroxy-4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)-ethanone (44)

A solution of DHP (18 mL, 197 mmol) in CH_2Cl_2 (100 mL) was added dropwise to a solution of 1-(2,4-dihydroxyphenyl)ethanone **43** (10 g, 65 mmol) and PPTS (600 mg) at room temperature. The resulting mixture was stirred for 4 h at room temperature and monitored by TLC, then washed with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The collected organic extracts were dried over anhydrous $NaSO_4$, filtered, and concentrated under reduced pressure to give **44** as white solid, which was used in the next step without further purification.

5.1.6. 1-(2-((2-Methylbut-3-yn-2-yl)oxy)-4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)ethanone (45)

To a solution of **44** (4.43 g, 10 mmol) in CH_3CN (100 mL) at 0 °C was added DBU (1.5 mL, 15 mmol), $CuCl_2{\cdot}2H_2O$ (5 mg, 0.3% mol), and 3-chloro-3-methyl-1-butyne (1.53 g, 15 mmol). The mixture was stirred at 0 °C for 5 h and monitored by TLC. After completed, 1 N HCl (aq) was added to adjust pH = 2. The reaction mixture was poured into ice-cold water and extracted with ethyl acetate (3 × 200 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give **45** as an red oil (40%), which was used in the next step without further purification.

5.1.7. 1-(2,2-Dimethyl-5-((tetrahydro-2*H*-pyran-2-yl)oxy)-2*H*-chromen-8-yl)ethanone (46)

A mixture of **45** (17.5 g) and pyridine (75 mL) was stirred at 120 °C for 12 h. After cooling to room temperature, the mixture concentrated under reduced pressure to give **46** as black oil, which was used in the next step without further purification.

5.1.8. (*E*)-1-(2,2-Dimethyl-5-((tetrahydro-2*H*-pyran-2-yl)oxy)-2*H*-chromen-8-yl)-3-(1-methyl-1*H*-indol-5-yl)prop-2-en-1-one (47)

To a solution (140 mL) of **46** (3.02 g, 10 mmol) and **31a** (8.40 g, 10 mmol) in methanol was added 50% KOH (20 mL, aq) and the mixture was stirred for overnight. The reaction mixture was poured into ice water and extracted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give **47** as a yellow solid (51%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.52 (s, 3H), 1.53 (s, 3H), 1.57–2.08 (m, 6H), 3.62–3.65 (m, 1H), 3.81 (s, 3H), 3.85–3.90 (m, 1H), 5.51–5.53 (m, 1H), 5.64 (d, 1H, *J* = 10.0 Hz), 6.52 (s, 1H), 6.75 (t, 2H, *J* = 8.8 Hz), 7.07 (s, 1H), 7.32 (d, 1H, *J* = 8.8 Hz), 7.54 (d, 1H, *J* = 8.8 Hz), 7.64–7.68 (m, 2H), 7.83–7.87 (m, 2H); MS (ESI, *m*/*z*): 444.5 $[M+H]^+$.

5.1.9. (*E*)-1-(5-Hydroxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-methyl-1*H*-indol-5-yl)prop-2-en-1-one (48)

To a solution of **47** (6.65 g, 15 mmol) in CH_3OH (150 mL) and THF (150 mL) at room temperature was added pTsOH (258 mg, 1.5 mmol). The resulting mixture was stirred at 60 °C for 1 h. After cooling to room temperature, the mixture concentrated under reduced. The residue was dissolved in EtOAc (300 mL) and washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under reduce pressure to give a yellow solid **48** (5.0 g, 93%). ^{1}H NMR (d^6 DMSO, 400 MHz) δ: 1.49 (s, 6H), 3.82 (s, 3H), 5.74 (d, 1H, *J* = 10.0 Hz), 6.51–6.54 (m, 2H), 6.64 (d, 1H, *J* = 10.0 Hz), 7.39 (s, 1H), 7.47 (d, 1H, *J* = 8.8 Hz), 7.55 (s, 2H), 7.65 (d, 1H, *J* = 16.0 Hz), 7.69 (d, 1H, *J* = 16.0 Hz), 7.87 (s, 1H), 10.50 (s, 1H); MS (ESI, *m*/*z*): 360.3 $[M+H]^+$.

5.1.10. General procedure C for the synthesis of 49a–49d

The appropriate acid anhydride (5 mmol) was added to a solution of **48** (179.7 mg, 0.5 mmol) in pyridine. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography.

5.1.10.1. (*E*)-2,2-Dimethyl-8-(3-(1-methyl-1*H*-indol-5-yl)acryloyl)-2*H*-chromen-5-yl acetate (49a). The title compound was synthesized according to the general procedure C using **48** (179.7 mg, 0.5 mmol), acetic anhydride (610 μL, 5 mmol), and pyridine (5 mL). The product was purified by silica gel column chromatography to give **49a** (78 mg, 39%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 2.35 (s, 3H), 3.81 (s, 3H), 5.72 (d, 1H, *J* = 10.0 Hz), 6.39 (d, 1H, *J* = 10.0 Hz), 6.53 (d, 1H, *J* = 2.8 Hz), 6.71 (d, 1H, *J* = 8.8 Hz), 7.08 (d, 1H, *J* = 2.8 Hz), 7.33 (d, 1H, *J* = 8.8 Hz), 7.49–7.54 (m, 2H), 7.58 (d, 1H, *J* = 8.0 Hz), 7.82–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.9, 28.1, 28.1, 33.0, 77.3, 102.1, 109.9, 114.5, 114.6, 116.2, 121.2, 123.2, 124.1, 126.5, 126.8, 128.8, 130.0, 130.2, 131.4, 137.9, 145.2, 148.7, 152.9, 168.8, 191.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{25}H_{24}NO_4$: 402.1705, found: 402.1702.

5.1.10.2. (*E*)-2,2-Dimethyl-8-(3-(1-methyl-1*H*-indol-5-yl)acryloyl)-2*H*-chromen-5-yl propionate (49b). The title compound was synthesized according to the general procedure C using **48** (179.7 mg, 0.5 mmol), propionic anhydride (650 μL, 5 mmol), and pyridine (5 mL). The product was purified by silica gel column chromatography to give **49b** (137 mg, 66%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (t, 3H, *J* = 6.8 Hz), 1.53 (s, 6H), 3.81 (s, 3H), 4.08 (q, 2H, *J* = 6.8 Hz), 5.62 (d, 1H, *J* = 10.0 Hz), 6.49 (d, 1H, *J* = 8.8 Hz), 6.52 (d, 1H, *J* = 2.8 Hz), 6.73 (d, 1H, *J* = 10.0 Hz), 7.07 (d, 1H, *J* = 2.8 Hz), 7.32 (d, 1H, *J* = 8.0 Hz), 7.54 (d, 1H, *J* = 8.0 Hz), 7.69–7.73 (m, 2H), 7.85–7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.17, 27.65, 28.14, 28.14, 33.03, 77.25, 102.11, 109.87, 114.56, 114.67, 116.18, 121.24, 123.19, 124.18, 126.43, 126.80, 128.79, 130.02, 130.21, 131.30, 137.90, 145.15, 148.85, 152.94, 172.29, 191.27. HRMS (ESI) calcd for $[M+H]^+$ $C_{26}H_{26}NO_4$: 416.1862, found: 416.1860.

5.1.10.3. (*E*)-2,2-Dimethyl-8-(3-(1-methyl-1*H*-indol-5-yl)acryloyl)-2*H*-chromen-5-yl isobutyrate (49c). The title compound was synthesized according to the general procedure C using **48** (179.7 mg, 0.5 mmol), isobutyric anhydride (400 μL, 5 mmol), and pyridine (5 mL). The product was purified by silica gel column chromatography to give **49c** (136 mg, 63%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (d, 6H, *J* = 7.2 Hz), 1.51 (s, 6H), 2.87 (heptet, 1H, *J* = 7.2 Hz), 3.81 (s, 3H), 5.71 (d, 1H, *J* = 10.0 Hz), 5.36 (d, 1H, *J* = 10.0 Hz), 6.53 (d, 1H, *J* = 2.8 Hz), 6.69 (d, 1H, *J* = 8.8 Hz), 7.07 (d, 1H, *J* = 2.8 Hz), 7.33 (d, 1H, *J* = 8.8 Hz), 7.50–7.54 (m, 2H), 7.58 (d, 1H, *J* = 8.8 Hz), 7.81–7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.1, 19.1, 28.2, 28.2, 33.0, 34.3, 77.3, 102.1, 109.9, 114.5, 114.7, 116.1, 121.2, 123.2, 124.2, 126.4, 126.8, 128.8, 130.0, 130.2, 131.3, 137.9, 145.2, 149.0, 153.0, 174.9, 191.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{27}H_{28}NO_4$: 430.2018, found: 430.2012.

5.1.10.4. (*E*)-2,2-Dimethyl-8-(3-(1-methyl-1*H*-indol-5-yl)acryloyl)-2*H*-chromen-5-yl pentanoate (49d). The title compound was synthesized according to the general procedure C using **48** (179.7 mg, 0.5 mmol), pentanoic anhydride (500 μL, 5 mmol), and

pyridine (5 mL). The product was purified by silica gel column chromatography to give **49d** (156 mg, 70%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.00 (t, 3H, J = 7.2 Hz), 1.42 (sext, 2H, J = 7.2 Hz), 1.51 (s, 6H), 1.77 (quint, 2H, J = 7.2 Hz), 2.61 (t, 2H, J = 7.2 Hz), 3.81 (s, 3H), 5.71 (d, 1H, J = 10.0 Hz), 5.37 (d, 1H, J = 10.0 Hz), 6.53 (d, 1H, J = 2.8 Hz), 6.70 (d, 1H, J = 8.8 Hz), 7.07 (d, 1H, J = 2.8 Hz), 7.33 (d, 1H, J = 8.8 Hz), 7.49–7.53 (m, 2H), 7.58 (d, 1H, J = 8.8 Hz), 7.81–7.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 22.3, 27.0, 28.1, 28.1, 33.0, 34.0, 77.2, 102.1, 109.9, 114.6, 114.7, 116.2, 121.2, 123.2, 124.2, 126.4, 126.8, 128.8, 130.0, 130.2, 131.3, 137.9, 145.1, 148.9, 152.9, 171.6, 191.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{28}H_{30}NO_4$: 444.2175, found: 444.2171.

5.1.11. General procedure D for the synthesis of 49e–49j

A mixture of appropriate alkyl halide (0.75 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL) was stirred at room temperature for overnight. The mixture was filtered to remove Cs_2CO_3 and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography.

5.1.11.1. (*E*)-1-(5-Ethoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-methyl-1*H*-indol-5-yl)prop-2-en-1-one (49e). The title compound was synthesized according to the general procedure D using iodoethane (125 μL, 0.75 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49e** (143 mg, 74%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (t, 3H, J = 6.8 Hz), 1.52 (s, 6H), 3.80 (s, 3H), 4.08 (q, 2H, J = 6.8 Hz), 5.62 (d, 1H, J = 10.0 Hz), 6.49 (d, 1H, J = 8.8 Hz), 6.52 (d, 1H, J = 2.8 Hz), 6.72 (d, 1H, J = 10.0 Hz), 7.07 (d, 1H, J = 2.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.54 (d, 1H, J = 8.8 Hz), 7.69–7.73 (m, 2H), 7.85–7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 28.1, 28.1, 31.0, 33.0, 64.1, 102.0, 104.2, 109.8, 110.5, 117.0, 121.2, 121.9, 123.0, 124.6, 127.2, 128.6, 128.8, 129.9, 131.6, 137.7, 143.8, 153.6, 157.6, 190.4; HRMS (ESI) calcd for $[M+H]^+$ $C_{25}H_{26}NO_3$: 388.1913, found: 388.1915.

5.1.11.2. (*E*)-1-(5-Isopropoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-methyl-1*H*-indol-5-yl)prop-2-en-1-one (49f). The title compound was synthesized according to the general procedure D using 2-iodopropane (98 μL, 0.75 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49f** (158 mg, 79%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (d, 6H, J = 6.0 Hz), 1.52 (s, 6H), 3.81 (s, 3H), 4.63 (heptet, 1H, J = 6.0 Hz), 5.61 (d, 1H, J = 10.0 Hz), 6.50–6.52 (m, 2H), 6.71 (d, 1H, J = 10.0 Hz), 7.07 (d, 1H, J = 2.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.54 (d, 1H, J = 8.8 Hz), 7.68 (d, 1H, J = 8.8 Hz), 7.69 (d, 1H, J = 16.0 Hz), 7.85–7.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.2, 22.2, 28.1, 28.1, 31.0, 33.0, 70.7, 102.0, 105.6, 109.8, 111.3, 117.2, 121.2, 121.6, 122.9, 124.7, 127.2, 128.4, 128.8, 129.9, 131.4, 137.7, 143.7, 153.8, 156.8, 190.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{26}H_{28}NO_3$: 402.2069, found: 402.2061.

5.1.11.3. (*E*)-1-(2,2-Dimethyl-5-propoxy-2*H*-chromen-8-yl)-3-(1-methyl-1*H*-indol-5-yl)prop-2-en-1-one (49g). The title compound was synthesized according to the general procedure D using 1-iodopropane (95 μL, 0.75 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49g** (138 mg, 69%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.06 (t, 3H, J = 7.2 Hz), 1.53 (s, 6H), 1.80 (sext, 2H, J = 7.2 Hz), 3.80 (s, 3H), 3.99 (t, 2H, J = 7.2 Hz), 5.61 (d, 1H, J = 10.0 Hz), 6.48 (d, 1H, J = 8.8 Hz), 6.52 (d, 1H, J = 2.8 Hz), 6.73 (d, 1H, J = 10.0 Hz), 7.06 (d, 1H, J = 2.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.54 (d, 1H, J = 8.8 Hz), 7.69–7.73 (m, 2H), 7.85–7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.6, 22.6, 28.1, 28.1, 31.0, 33.0, 69.9, 102.0, 104.3, 109.8, 110.5, 117.0, 121.2, 121.9, 123.0, 124.7, 127.2, 128.5, 128.8, 129.9, 131.6, 137.7, 143.8, 153.6, 157.7, 190.4; HRMS (ESI) calcd for $[M+H]^+$ $C_{26}H_{28}NO_3$: 402.2069, found: 402.2065.

5.1.11.4. (*E*)-1-(5-Butoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-methyl-1*H*-indol-5-yl)prop-2-en-1-one (49h). The title compound was synthesized according to the general procedure D using 1-iodobutane (114 μL, 0.75 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49h** (160 mg, 77%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.99 (t, 3H, J = 7.2 Hz), 1.49 (sext, 2H, J = 7.2 Hz), 1.52 (s, 6H), 1.80 (quint, 2H, J = 7.2 Hz), 3.80 (s, 3H), 4.04 (t, 2H, J = 7.2 Hz), 5.61 (d, 1H, J = 10.0 Hz), 6.49 (d, 1H, J = 8.8 Hz), 6.52 (d, 1H, J = 2.8 Hz), 6.72 (d, 1H, J = 10.0 Hz), 7.06 (d, 1H, J = 2.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.54 (d, 1H, J = 8.8 Hz), 7.69 (d, 1H, J = 8.8 Hz), 7.69 (d, 1H, J = 16.0 Hz), 7.85–7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 19.3, 28.1, 28.1, 31.0, 31.3, 33.0, 68.2, 102.0, 104.2, 109.8, 110.5, 117.0, 121.2, 121.9, 123.0, 124.6, 127.2, 128.5, 128.8, 129.9, 131.6, 137.7, 143.7, 153.6, 157.8, 190.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{27}H_{30}NO_3$: 416.2226, found: 416.2228.

5.1.11.5. (*E*)-1-(2,2-Dimethyl-5-(pentyloxy)-2*H*-chromen-8-yl)-3-(1-methyl-1*H*-indol-5-yl)prop-2-en-1-one (49i). The title compound was synthesized according to the general procedure D using 1-iodopentane (130 μL, 0.75 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49i** (170 mg, 79%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.95 (t, 3H, J = 7.2 Hz), 1.37–1.49 (m, 4H), 1.53 (s, 6H), 1.82 (quint, 2H, J = 7.2 Hz), 3.80 (s, 3H), 4.03 (t, 2H, J = 7.2 Hz), 5.62 (d, 1H, J = 10.0 Hz), 6.48 (d, 1H, J = 8.8 Hz), 6.52 (d, 1H, J = 2.8 Hz), 6.72 (d, 1H, J = 10.0 Hz), 7.06 (d, 1H, J = 2.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.54 (d, 1H, J = 8.8 Hz), 7.69–7.73 (m, 2H), 7.85–7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.5, 28.1, 28.1, 28.2, 28.9, 29.7, 33.0, 68.5, 102.0, 104.2, 109.8, 110.5, 117.0, 121.2, 121.9, 123.0, 124.7, 127.2, 128.5, 128.8, 129.9, 131.6, 137.7, 143.7, 153.6, 157.8, 190.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{28}H_{32}NO_3$: 430.2382, found: 430.2386.

5.1.11.6. (*E*)-1-(5-Isobutoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-(1-methyl-1*H*-indol-5-yl)prop-2-en-1-one (49j). The title compound was synthesized according to the general procedure D using 1-iodo-2-methylpropane (115 μL, 0.75 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49j** (133 mg, 64%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (d, 6H, J = 6.8 Hz), 1.53 (s, 6H), 2.10–2.17 (m, 1H, J = 6.8 Hz), 3.79–3.81 (m, 5H), 5.62 (d, 1H, J = 10.0 Hz), 6.48 (d, 1H, J = 8.8 Hz), 6.52 (d, 1H, J = 2.8 Hz), 6.73 (d, 1H, J = 10.0 Hz), 7.07 (d, 1H, J = 2.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.54 (d, 1H, J = 8.8 Hz), 7.69–7.73 (m, 2H), 7.85–7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.3, 19.3, 28.1, 28.1, 28.4, 31.0, 33.0, 74.7, 102.0, 104.3, 109.8, 110.5, 117.0, 121.2, 121.9, 122.9, 124.7, 127.2, 128.5, 128.8, 129.9, 131.6, 137.7, 143.8, 153.6, 157.8, 190.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{27}H_{30}NO_3$: 416.2226, found: 416.2226.

5.1.12. General procedure E for the synthesis of 49k–49r

A mixture of appropriate aryl sulfonyl chloride (0.6 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL) was stirred at room temperature for overnight. The mixture was filtered to remove Cs_2CO_3 and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography.

5.1.12.1. (*E*)-2,2-Dimethyl-8-(3-(1-methyl-1*H*-indol-5-yl)acryloyl)-2*H*-chromen-5-yl 3,5-difluorobenzenesulfonate (49k). The title compound was synthesized according to the general procedure E using 3,5-difluorobenzene-1-sulfonyl chloride (127.5 mg, 0.6 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49k** (132 mg, 49%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.43 (s, 6H), 3.81 (s, 3H), 5.64 (d, 1H, J = 10.0 Hz), 6.33 (d, 1H, J = 10.0 Hz), 6.53 (d, 1H, J = 2.8 Hz), 6.69 (d, 1H, J = 8.8 Hz), 7.08 (d, 1H, J = 2.8 Hz), 7.13–7.17 (m, 1H), 7.33 (d, 1H, J = 8.8 Hz), 7.40–7.45 (m, 3H), 7.50 (d, 2H, J = 8.8 Hz), 7.78–7.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.9, 27.9, 33.1, 77.4, 102.2, 109.9, 110.2, 112.2, 112.4, 114.5, 115.7, 115.8, 121.3, 123.4, 123.7, 126.5, 128.1, 128.8, 130.1, 130.2, 132.1, 138.0, 138.3, 146.0, 146.8, 152.8, 161.6, 164.1, 191.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{29}H_{24}F_2NO_5S$: 536.1343, found: 536.1348.

5.1.12.2. (*E*)-2,2-Dimethyl-8-(3-(1-methyl-1*H*-indol-5-yl)acryloyl)-2*H*-chromen-5-yl 4-bromo-2-(trifluoromethyl)benzenesulfonate (49l). The title compound was synthesized according to the general procedure E using 4-bromo-2-(trifluoromethyl)benzene-1-sulfonyl chloride (194 mg, 0.6 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49l** (157 mg, 48%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 6H), 3.81 (s, 3H), 5.68 (d, 1H, J = 10.0 Hz), 6.47 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 2.8 Hz), 6.55 (d, 1H, J = 8.8 Hz), 7.08 (d, 1H, J = 2.8 Hz), 7.33 (d, 1H, J = 8.8 Hz), 7.40 (d, 1H, J = 16.0 Hz), 7.44 (d, 1H, J = 8.8 Hz), 7.50 (d, 2H, J = 8.8 Hz), 7.77 (d, 1H, J = 16.0 Hz), 7.83 (s, 1H), 7.84 (d, 1H, J = 8.8 Hz), 7.91 (d, 1H, J = 8.8 Hz), 8.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.0, 28.0, 33.1, 57.3, 102.2, 107.7, 109.9, 113.9, 115.1, 115.8, 116.2, 121.2, 123.3, 123.7, 126.5, 127.8, 128.8, 129.0, 130.1, 130.1, 131.8, 133.2, 138.0, 145.9, 147.0, 152.6, 152.9, 158.3, 191.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{24}BrF_3NO_5S$: 646.0511, found: 646.05113.

5.1.12.3. (*E*)-2,2-Dimethyl-8-(3-(1-methyl-1*H*-indol-5-yl)acryloyl)-2*H*-chromen-5-yl 2,3,4,5,6-pentafluorobenzenesulfonate (49m). The title compound was synthesized according to the general procedure E using 2,3,4,5,6-pentafluorobenzene-1-sulfonyl chloride (160 mg, 0.6 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49m** (149 mg, 51%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (s, 6H), 3.81 (s, 3H), 5.76 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 2.8 Hz), 6.55 (d, 1H, J = 10.0 Hz), 6.81 (d, 1H, J = 8.8 Hz), 7.08 (d, 1H, J = 2.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.38 (d, 1H, J = 16.0 Hz), 7.50 (d, 1H, J = 8.8 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.76 (d, 1H, J = 16.0 Hz), 7.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.9, 27.9, 33.0, 77.6, 102.2, 109.9, 113.6, 115.5, 115.6, 121.3, 123.4, 123.6, 126.5, 128.5, 128.8, 130.2, 130.4, 132.5, 132.6, 138.0, 146.2, 146.3, 152.9, 191.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{29}H_{21}F_5NO_5S$: 590.1061, found: 590.1059.

5.1.12.4. (*E*)-2,2-Dimethyl-8-(3-(1-methyl-1*H*-indol-5-yl)acryloyl)-2*H*-chromen-5-yl 4-methylbenzenesulfonate (49n). The title compound was synthesized according to the general procedure E using 4-methylbenzene-1-sulfonyl chloride (114 mg, 0.6 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49n** (174 mg, 68%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (s, 6H), 2.45 (s, 3H), 3.81 (s, 3H), 5.59 (d, 1H, J = 10.0 Hz), 6.40 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 2.8 Hz), 6.63 (d, 1H, J = 8.8 Hz), 7.08 (d, 1H, J = 2.8 Hz), 7.32–7.34 (m, 3H), 7.41 (d, 1H, J = 16.0 Hz), 7.45 (d, 1H, J = 8.8 Hz), 7.50 (d, 1H, J = 8.8 Hz), 7.74 (d, 2H, J = 8.0 Hz), 7.78 (d, 1H, J = 16.0 Hz), 7.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 28.0, 28.0, 33.0, 77.3, 102.1, 109.9, 114.7, 116.0, 116.2, 121.2, 123.3, 123.8, 126.6, 127.5, 128.6, 128.6, 128.6, 128.8, 130.0, 130.0, 130.1, 131.5, 132.2, 138.0, 145.6, 145.7, 147.3, 152.8, 191.2; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{28}NO_5S$: 514.1688, found: 514.1685.

5.1.12.5. (*E*)-2,2-Dimethyl-8-(3-(1-methyl-1*H*-indol-5-yl)acryloyl)-2*H*-chromen-5-yl 3-methoxybenzenesulfonate (49o). The title compound was synthesized according to the general procedure E using 3-methoxybenzene-1-sulfonyl chloride (142 mg, 0.6 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49o** (183 mg, 69%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41 (s, 6H), 3.81 (s, 3H), 3.83 (s, 3H), 5.60 (d, 1H, J = 10.0 Hz), 6.38 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 2.8 Hz), 6.66 (d, 1H, J = 8.8 Hz), 7.08 (d, 1H, J = 2.8 Hz), 7.18–7.21 (m, 1H), 7.32 (d, 2H, J = 8.8 Hz), 7.41–7.45 (m, 3H), 7.47 (d, 1H, J = 8.8 Hz), 7.50 (d, 1H, J = 8.8 Hz), 7.77 (d, 1H, J = 16.0 Hz), 7.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.0, 28.0, 31.0, 33.1, 55.8, 102.1, 109.9, 112.8, 114.6, 116.0, 116.1, 120.8, 121.1, 121.2, 123.3, 123.8, 126.6, 127.6, 128.8, 130.0, 130.1, 130.4, 131.6, 136.2, 138.0, 145.7, 147.3, 152.8, 160.0, 191.2; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{28}NO_6S$: 530.1637, found: 530.1633.

5.1.12.6. (*E*)-2,2-Dimethyl-8-(3-(1-methyl-1*H*-indol-5-yl)acryloyl)-2*H*-chromen-5-yl 4-isopropylbenzenesulfonate (49p). The title compound was synthesized according to the general procedure E using 4-isopropylbenzene-1-sulfonyl chloride (131 mg, 0.6 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49p** (162 mg, 60%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (d, 6H, J = 6.8 Hz), 1.39 (s, 6H), 3.00 (heptet, 1H, J = 6.0 Hz), 3.81 (s, 3H), 5.55 (d, 1H, J = 10.0 Hz), 6.35 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 2.8 Hz), 6.69 (d, 1H, J = 8.8 Hz), 7.08 (d, 1H, J = 2.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.37 (d, 2H, J = 8.8 Hz), 7.41 (d, 1H, J = 15.6 Hz), 7.47 (d, 1H, J = 8.8 Hz), 7.50 (d, 1H, J = 8.8 Hz), 7.77 (d, 2H, J = 8.8 Hz), 7.78 (d, 1H, J = 15.6 Hz), 7.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.7, 23.7, 28.0, 28.0, 33.1, 34.3, 77.2, 102.1, 109.9, 114.8, 116.0, 116.1, 121.2, 123.3, 123.9, 126.6, 127.5, 127.5, 127.5, 128.8, 128.8, 128.8, 130.0, 130.1, 131.3, 132.4, 138.0, 145.6, 147.3, 152.8, 156.4, 191.2; HRMS (ESI) calcd for $[M+H]^+$ $C_{32}H_{32}NO_5S$: 542.2001, found: 542.2006.

5.1.12.7. (*E*)-2,2-Dimethyl-8-(3-(1-methyl-1*H*-indol-5-yl)acryloyl)-2*H*-chromen-5-yl 3-(trifluoromethyl)benzenesulfonate (49q). The title compound was synthesized according to the general procedure E using 3-(trifluoromethyl)benzene-1-sulfonyl chloride (147 mg, 0.6 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49p** (201 mg, 71%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 6H), 3.81 (s, 3H), 5.66 (d, 1H, J = 10.0 Hz), 6.50–6.54 (m, 3H), 7.08 (d, 1H, J = 2.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.41 (d, 1H, J = 15.6 Hz), 7.42 (d, 1H, J = 8.8 Hz), 7.50 (d, 1H, J = 8.8 Hz), 7.72 (t, 1H, J = 8.0 Hz), 7.77 (d, 1H, J = 16.0 Hz), 7.83–7.85 (m, 2H), 8.00 (d, 1H, J = 8.0 Hz), 8.09 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.0, 28.0, 33.1, 77.5, 102.1, 109.9, 114.3, 116.0, 116.2, 121.2, 123.3, 123.8, 126.5, 127.8, 128.8, 128.9, 130.0, 130.1, 131.9, 132.5, 132.9, 134.0, 134.6, 138.0, 145.9, 147.0, 152.9, 191.2; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{25}F_3NO_5S$: 568.1406, found: 568.1414.

5.1.12.8. (*E*)-2,2-Dimethyl-8-(3-(1-methyl-1*H*-indol-5-yl)acryloyl)-2*H*-chromen-5-yl 2-methoxy-4-nitrobenzenesulfonate (49r). The title compound was synthesized according to the general procedure E using 2-methoxy-4-nitrobenzene-1-sulfonyl chloride (151 mg,

0.6 mmol), **48** (179.7 mg, 0.5 mmol), Cs_2CO_3 (325 mg, 1 mmol) and acetone (5 mL). The product was purified by silica gel column chromatography to give **49r** (176 mg, 71%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 6H), 3.81 (s, 3H), 4.12 (s, 3H), 5.71 (d, 1H, J = 10.0 Hz), 6.52 (d, 1H, J = 2.8 Hz), 6.61 (d, 1H, J = 10.0 Hz), 6.69 (d, 1H, J = 8.8 Hz), 7.08 (d, 1H, J = 2.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.39 (d, 1H, J = 16.0 Hz), 7.45 (d, 1H, J = 8.8 Hz), 7.49 (d, 1H, J = 8.8 Hz), 7.76 (d, 1H, J = 16.0 Hz), 7.82 (s, 1H), 7.88–7.91 (m, 2H), 8.06 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.0, 28.0, 31.0, 33.1, 77.5, 102.2, 109.9, 114.3, 115.9, 116.1, 121.3, 123.4, 123.7, 126.5, 128.0, 128.8, 129.9, 130.1, 130.1, 132.1, 132.2, 132.2, 133.0, 134.3, 135.5, 138.0, 146.0, 146.8, 152.9, 191.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{30}H_{27}N_2O_8S$: 575.1488, found: 575.1484.

5.2. Biological evaluation

5.2.1. Cytotoxicity assay

1×10^4 cells per well were plated in 96-well culture plates and incubated for 24 h. After incubation, Tetrazolium dye [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazo-lium bromide, MTT] solution (20 μL of 5 mg/mL) in PBS was added to each well. This was incubated until a purple precipitate was visible. Then, the precipitates were dissolved in 150 μL of DMSO, after the medium was carefully removed, shaken mechanically for 10 min, and then absorbance values at a wavelength of 570 nm were determined with the Spectramax M5 Microtiter Plate Luminometer (Molecular Devices, USA). Values were calculated using percentage of growth versus untreated control.

5.2.2. Tubulin polymerization assay

MAP-rich tubulin (2 mg/mL) was preincubated in polymerization buffer (0.1 M MES, 1 mM EGTA, pH 6.5, 0.5 mM $MgCl_2$) with various compound at 4 °C for 2 min before the addition of 1 mM GTP. The samples were then rapidly warmed to 37 °C in a 96-well plate thermostatically controlled Spectramax M5 Microtiter Plate Luminometer, and the change in absorbance at 350 nm was periodically measured. Colchicine and Paclitaxel were used as reference.

5.2.3. Flow cytometric analysis

HepG2 tumor cells (2×10^5) were cultured in 6-well cell culture plates for 24 h, then treated with vehicle alone (0.1% DMSO) or various concentrations of **49b** (0.125 μM, 0.25 μM, 0.375 μM and 0.50 μM). The untreated and treated cells were incubated for 24 h, fixed in ice chilled methanol for at least 30 min in 4 °C, then washed twice with PBS, and incubated for 0.5 h at 37 °C in a PBS solution containing 1 mg/mL RNase A and propidium iodide (PI). The cells Cycle were analyzed by flow cytometer (TASC240, USA). The date was analyzed using Modfit 2.8 software.

5.2.4. Apoptosis assay

HepG2 tumor cells were treated with compound **49b** for 48 h at concentrations of 0.125 μM, 0.25 μM, 0.375 μM and 0.5 μM, respectively. Then, the cells were harvested and stained with PI (propidium iodide) for 20 min. The samples were analyzed by flow cytometer.

5.2.5. Immunofluorescence staining of tubulin

HepG2 tumor cells (1×10^5) were seeded in 6-well culture plate and incubated for 12 h at 37 °C and 5% CO_2. Cells were treatment with DMSO, **49b** (0.25 μM) or **49b** (0.50 μM) for 12 h. The cells were fixed with methanol and then permeabilized with 0.5% Triton X-100/PBS. After blocking for 45 min in 5% BSA/PBS, cells were washed with PBS and incubated with α-tubulin for 2 h, and then tubulin was immunostained with monoclonal antibody to α-tubulin followed by fluorescence antibody. Nuclei were labeled with DAPI. Cells were visualized using a fluorescence microscope.

5.2.6. The in vivo antitumor activity

Six weeks old, female BALB/c nude mice (16–18 g) were purchased from the animal breeding laboratories of Sichuan University Animal Center (Sichuan, Chengdu, China). HepG2 cells (1×10^7) were collected in 0.1 mL of DMEM and these cell suspensions were inoculated into the right gluteal region of each nude mouse. Once the HepG2 xenografts reached a size of 100 mm^3, twenty-four female BALB/c nude mice were randomly divided into four groups: a vehicle control group, a positive group, and two tested groups. The mice in the test group received tail intravenous once every other day at the dosage of 15 mg/kg or 30 mg/kg of **49b** for 21 days. The positive group received tail intravenous once a day of 5-Fu at a dose of 5 mg/kg, and the control group received injection of vehicle alone following the time schedule for the test groups. Tumor burden was measured every 3 days with a caliper (calculated volume (mm^3) = $\pi/6 \times$ length $\times$ width $\times$ width). After completing the treatment schedule, tumor-bearing mice were euthanized.

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