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The synthesis of anticancer sulfonated indolo[2,1-*a*]isoquinoline and benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones derivatives *via* a free radical cascade pathway†

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A facile $CuBr_2$ induced radical relay addition/cyclization of activated alkenes with substituted-thiosulfonates has been achieved, leading to a broad range of sulfonated indolo[2,1-*a*]isoquinolines and benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones in moderate to good yields. In particular, some compounds exhibit bioactivity against cancer cell lines. This protocol shows advantages of low-cost, base-free, simple operation, and broad functional group tolerance.

Introduction

Nitrogen-containing heterocycles, for example, fused-indole and fused-benzimidazo derivatives, are commonly found in natural products and bioactive molecules.[1] In particular, indolo[2,1-*a*]isoquinoline and benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones derivatives containing the tetracyclic core structure (Fig. 1),[2] with a wide range of biological properties, have attracted increasing attention from both synthetic and medicinal chemists. As indolo[2,1-*a*]isoquinoline and benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones derivatives are an important series of molecules, huge efforts have been devoted to the assembly of these two special types of heterocyclic skeleton.

In general, the traditional approach to prepare indolo[2,1-*a*]isoquinoline derivatives containing the tetracyclic core by using 2-arylindoles as materials is involved in a radical cyclization process, which is simple and convenient. For example, Xu's group developed a $Fe(OTf)_3$-promoted tandem selenylation/cyclization to gain indolo[2,1-*a*]isoquinolin derivatives (Scheme 1a).[3] Very recently, Lei's group disclosed an electrochemical radical cascade by applying Mn as the catalyst for the synthesis of indolo[2,1-*a*]isoquinoline derivatives from 2-arylindoles and boronic acid (Scheme 1b).[1e] On the other side, as for benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones derivatives, it has been reported that a tandem phosphinoylation/cyclization of 2-arylbenzimidazoles with disubstituted phosphine oxides by using manganese(III) as the catalyst.[4] Besides, Yu's group also reported a silver-catalyzed decarboxylative radical cascade cyclization toward benzimidazo[2,1-*a*]isoquinolin6(5*H*)-ones (Scheme 1c).[5] Nevertheless, an unique approach for introducing a sulfone group into the indolo[2,1-*a*]isoquinolines and benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones moiety has not been adequately studied.

As an extremely valuable functional group, sulfonyl-containing compounds have obtained considerable interest due to their well-known biological activities and wide applications in pharmaceutical and food chemistry.[6] Hence, the development of novel, versatile strategies to construct different useful skeletons bearing sulfonyl groups would be highly significant.[7] Recently, the studies revealed that heterocyclic molecules containing sulfonyl-substituents exhibit unique bioactivities and chemical properties, and widely adopted in drug design.[6d,8] Among the various sulfonate reagents, the incorporation of sulfonyl radicals, which generated *in situ* from thiosulfonates, have been disclosed in the literature.[9] However, to the best of our knowledge, methods for the construction of molecules bearing

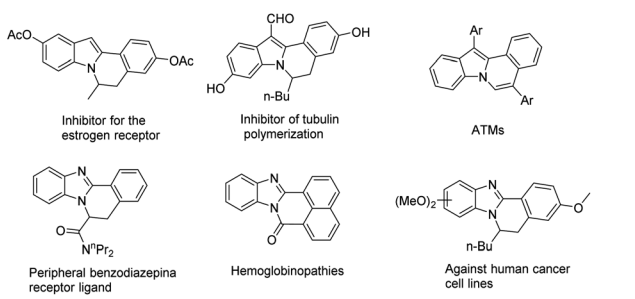

Fig. 1 Representative nature products and biologically active molecules.

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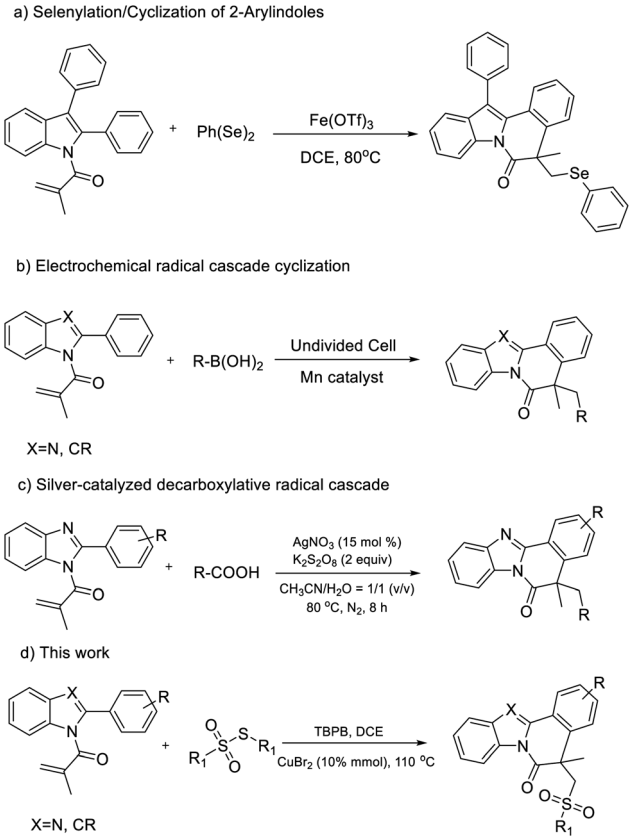


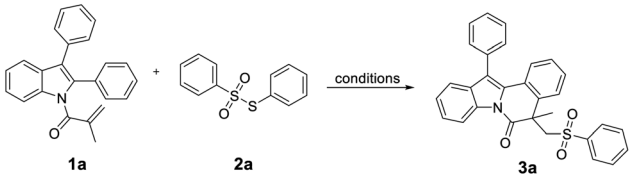
Scheme 1 (a)–(c) The previous work to prepare the different derivatives of indolo[2,1-*a*]isoquinolines and benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones; (d) the representative equation of our work.

both a sulfonyl group and a indolo[2,1-*a*]isoquinoline or benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones motif by the usage of thiosulfonates have not yet been reported. Based on the significance of the sulfonyl group and our continued interest in the free radical process,[10] in this article, we present an efficient $CuBr_2$-catalysed sulfonation/cyclization with substituted-thiosulfonates for the synthesis of sulfonyl-substituted indolo[2,1-*a*]isoquinolines and benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones, in which a C–S bond and C–C bond were constructed simultaneously under the oxidizing condition (TBPB).

Results and discussion

As shown in Table 1, the reaction was carried out between 1-(2,3-diphenyl-1*H*-indol-1-yl)-2-methylprop-2-en-1-one (**1a**) and *S*-phenyl benzenesulfonothioate (**2a**) to optimize the reaction condition. At first, **1a** and **2a** were dissolved in 1,2-dichloroethane (DCE) and treated with $NiCl_2$ (catalyst, 10% mmol) and *tert*-butyl peroxybenzoate (TBPB, 3.0 equiv.) at 110 °C in pressure tube. However, just trace amounts of product **3a** were detected (Table 1, entry 1). Subsequently, different catalysts were screened (Table 1, entries 2–4), and encouragingly, we obtained the product **3a** in an isolated yield of 31% (Table 1, entry 4).

Table 1 Optimization of reaction condition[a]



Entry	Catalyst (10% mmol)	Oxidant	Solvent	T (°C)	Yield[b] (%)
1	$NiCl_2$	TBPB	DCE	110	Trace
2	$(CH_3COO)_2Co$	TBPB	DCE	110	N.R.[c]
3	CuI	TBPB	DCE	110	23
4	CuBr	TBPB	DCE	110	31
5	$CuBr_2$	TBPB	DCE	110	85
6	$CuCl_2$	TBPB	DCE	110	62
7	CuO	TBPB	DCE	110	41
8	—	TBPB	DCE	110	25
9	$CuBr_2$	TBHP[d]	DCE	110	56
10	$CuBr_2$	DTBP	DCE	110	28
11	$CuBr_2$	$K_2S_2O_8$	DCE	110	N.R.
12	$CuBr_2$	$(NH_4)_2S_2O_8$	DCE	110	N.R.
13	$CuBr_2$	TBPB	ACN	110	63
14	$CuBr_2$	TBPB	DMF	110	35
15	$CuBr_2$	TBHP	Benzene	110	21
16	$CuBr_2$	TBHP	$PhCF_3$	110	48
17	$CuBr_2$	TBPB	EtOH	110	27
18	$CuBr_2$	TBPB	DMSO	110	55
19	$CuBr_2$	TBPB	DCE	80	43
20	$CuBr_2$	TBPB[e]	DCE	110	42
21	$CuBr_2$	TBPB	DCE	110	72[f]

[a] Reaction condition: **1a** (0.1 mmol, 1.0 eq.), **2a** (0.1 mmol, 1.0 eq.), catalyst (10% mmol), oxidant (3.0 eq.), N_2, pressure tube. [b] Isolated yield. [c] N.R.: no reaction. [d] TBHP: 5.0–6.0 mol L^{-1} in decane. [e] TBPB (2.0 eq.). [f] Large scale: **1a** (1.0 mmol, 1.0 eq.), **2a** (1.0 mmol, 1.0 eq.), $CuBr_2$ (10% mmol), TBPB (3.0 eq.), N_2, pressure tube.

Then, we further optimized the reaction condition to increase the yield of **3a**. Initially, different copper catalysts, like $CuBr_2$, $CuCl_2$ and CuO, were screened to replace CuBr (Table 1, entries 5–7) for the reaction. Delightfully, $CuBr_2$ was demonstrated to be the best choice for the reaction, with a dramatically increased yield of 85%. However, while the $CuBr_2$ was absent from the reaction, the yield would be significantly decreased to 25%, indicating $CuBr_2$ playing an essential role in the reaction process (Table 1, entry 8). Furthermore, different oxidants, such as *tert*-butyl hydroperoxide (TBHP), 2-(*tert*-butylperoxy)-2-methylpropane (DTBP), $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ (Table 1, entries 9–12), were also screened. Nevertheless, there was no better yield obtained than $CuBr_2$. As exhibited in Table 1, different solvents, including acetonitrile (ACN), *N*,*N*-dimethylformamide (DMF), benzene, benzotrifluoride ($PhCF_3$), ethanol and dimethyl sulfoxide (DMSO), were also employed into the reaction (entries 13–18). However, lower yields were gained and the results demonstrated that DCE was the best choice in our reaction. Additionally, while the reaction temperature was decreased to 80 °C, the yield of **3a** was down to 43% (Table 1, entry 19), suggesting that proper temperature being required to initiate the chemical reaction. At last, when

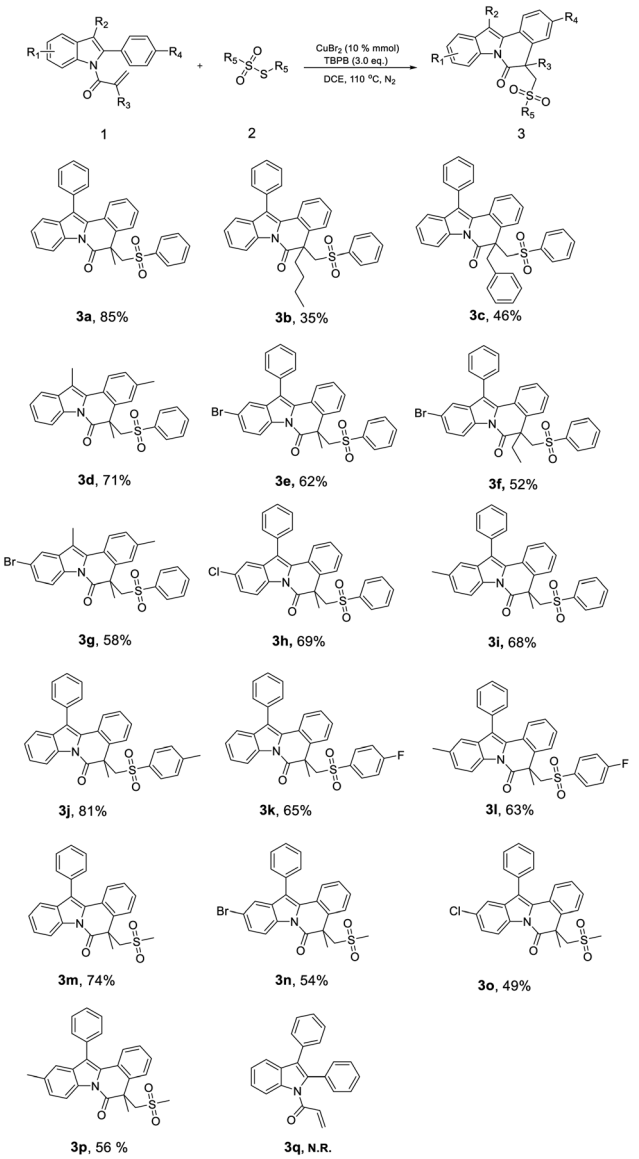
the amount of TBPB was reduced to 2.0 equiv., it would have a negative effect on the reaction (Table 1, entry 20). Hence, the adequate peroxide would promote the reaction process. According to the best condition screened above (Table 1, entry 5), we conducted the reaction of **1a** on a large scale (1.0 mmol), and **3a** was gained in an acceptable yield of 72% (Table 1, entry 21), demonstrating the good scalability of the developed reaction. In summary, the optimized reaction conditions were achieved for the $CuBr_2$-catalysed sulfonation/cyclization, utilizing the oxidants TBPB in DCE at the temperature of 110 °C.

With the above optimized reaction conditions in hand, substrate scope studies were further performed, focusing on various 1-(2,3-diphenyl-1*H*-indol-1-yl)-2-methylprop-2-en-1-ones (Scheme 2). As exhibited in Scheme 2, the reaction was carried out between substituted 2-methyl-1-(2-phenyl-1*H*-indol-1-yl) prop-2-en-1-one (**1**) and various thiosulfonates (**2**) under our optimized reaction conditions to achieve the corresponding products in good yields. For example, we obtained the product **3a** in a high yield of 85%. Nevertheless, when R_3 is *n*-Bu or benzyl, it would produce **3b** and **3c** in a relatively lower yield of 35% and 46%, respectively, indicating the steric hindrance showing a negative role in the reaction. As displayed in Scheme 2, we got product **3d** in a yield of 71%, and it suggested that the phenyl bearing 3-position of indole is better than methyl. Besides, while the –Br, –Cl and $–CH_3$ was introduced at the 5-position of indole, it would acquire the corresponding products in a moderate yield (**3e–3i**).

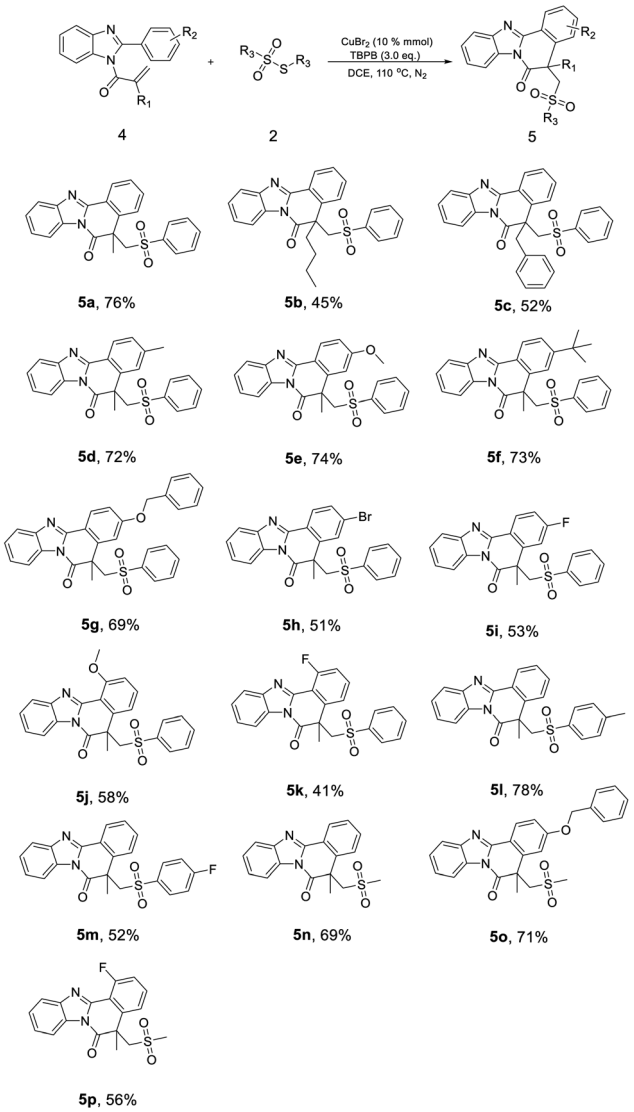
On the other hand, substituted thiosulfonates were also reacted with compound **1a**, and obviously, the electron-donating group (**3j**, 81%) would show more activity than the electron-withdrawing group (**3k**, 65%). At last, the reaction was performed between substituted indoles and *S*-methyl methanesulfonothioate. As displayed in Scheme 2, the yields of compounds **3m** (74%), **3n** (54%), **3o** (49%) and **3p** (56%) were lower than **3a** (85%), **3e** (62%), **3h** (69%) and **3i** (68%), respectively, indicating aromatic-substituted thiosulfonates maybe possess more activity than aliphatic group. Notably, while the starting material **1** was replaced by 1-(2,3-diphenyl-1*H*-indol-1-yl)prop-2-en-1-one (**3q**), there was no reaction occurred, demonstrating that acryl being unable to form crucial intermediate with another reagent under our reaction condition.

In addition to the above-mentioned, the reactions of 2-methyl-1-(2-phenyl-1*H*-benzo[*d*]imidazol-1-yl)prop-2-en-1-ones (**4**) with different thiosulfonates were also performed (Scheme 3). Obviously, the substituted compound **4** reacted with thiosulfonates also could achieve corresponding product in a relatively high yield, for example, product **5a** (76%). In the beginning, two products **5b** (45%) and **5c** (52%) were produced in a moderate yield near 50%, which was lower than **5a**. Subsequently, while the electron-donating group, like $–CH_3$, $–OCH_3$, –*t*-Bu and $–OCH_2Ph$, was introduced at the *para*-position of benzene, we also could obtain the corresponding products, **5d** (72%), **5e** (74%), **5f** (73%) and **5g** (69%), respectively, in a relatively high yield (Scheme 3). By contrast, –Br and –F substituent groups would make the yield decreased, like **5h** (51%) and **5i** (53%). The results indicated that the electron-withdrawing groups at the *para*-position of phenyl would have a negative effect on the reaction process. Additionally, the *ortho*-substituted compound **4** also could react with thiosulfonates to produce corresponding products **5j** (58%) and **5k** (41%) in a moderate yield.

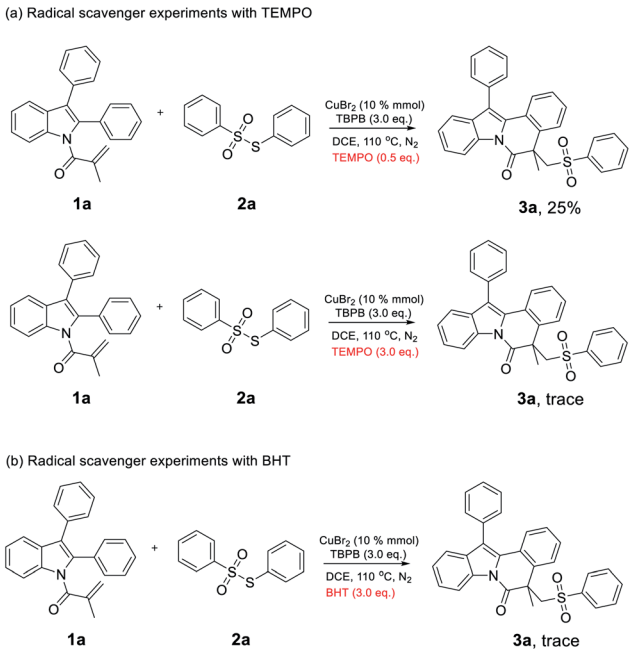
On the other side, while the –Me and –F was introduced at *para*-position of phenyl in *S*-phenyl benzenesulfonothioate, the reaction also occurred to obtain products **5l** (78%) and **5m** (52%), demonstrating the electron-donating substituent group bearing *S*-phenyl benzenesulfonothioate also would promote the reaction process. At last, we also tested the *S*-methyl methanesulfonothioate as the sulfonate agent, and the products, **5n** (69%), **5o** (71%) and **5p** (56%), were achieved in a moderate to high yield, indicating the reaction condition could be appropriate for a large scope of substrates.



Scheme 2 The reaction between different 2-methyl-1-(2-phenyl-1*H*-indol-1-yl)prop-2-en-1-ones (**1**) and sulfonothioates (**2**).



Scheme 3 The reaction between different 2-methyl-1-(2-phenyl-1*H*-benzo[*d*]imidazol-1-yl)prop-2-en-1-ones (**4**) and various sulfonothioates (**2**).

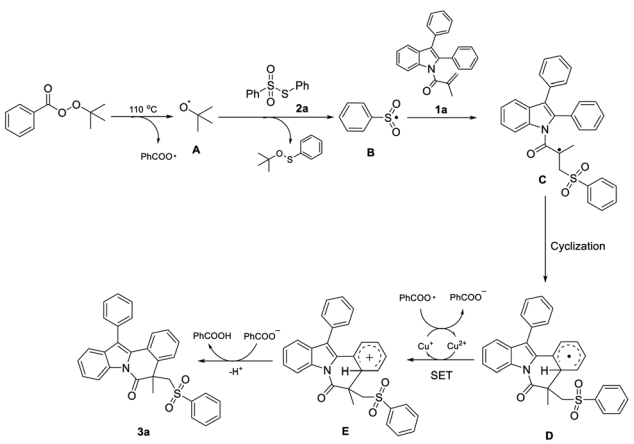


Scheme 4 Control experiments. (a) The TEMPO in the reaction, (b) the BHT in the reaction.

Based on the results discussed above, we carried out the primary control experiments to propose a possible mechanism. Initially, we added 0.5 equiv. of radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine) into the reaction under standard conditions and gave product **3a** in a decreased yield of 25% (Scheme 4a). Subsequently, 3.0 equiv. of TEMPO was added into the reaction and only trace amount of product **3a** was detected (Scheme 4a). Additionally, another radical scavenger BHT (2,6-di-*tert*-butyl-4-methylphenol) with 3.0 equiv. was also mixed into the reaction and no good result was obtained (Scheme 4b).

On the basis of control experiments and previous results,[5,8c,11] a plausible mechanism for this transformation is proposed and shown in Scheme 5. Initially, in the presence of TBPB under heating conditions, *tert*-butoxyl radical **A** is formed *via* single electron transfer (SET) with the aid of a copper catalyst. Then, the *S*-phenyl benzenesulfonothioate is activated by the radical **A** to generate the radical **B**. Furthermore, the radical **C** was produced *via* the radical addition of 1-(2,3-diphenyl-1*H*-indol-1-yl)-2-methylprop-2-en-1-one (**1a**) with radical **B**. Subsequently, the radical **C** underwents an intramolecular cyclization to form intermediate **D**, which was further oxidized to form carbocation **E** through SET process. Finally, loss of a proton from **E** affords the desired product **3a**.

At last, the biological activities of these series of sulfonated indolo[2,1-*a*]isoquinolines and benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones were explored *in vitro*, and antitumor activities of representative synthesized compounds were evaluated *via* the CCK8 assays of the MGC-803, T-24 and HeLa tumor cell lines. Paclitaxel (PTX) was applied as the positive control. As shown in Fig. 2, some representative compounds exhibited significant



Scheme 5 Plausible mechanism.

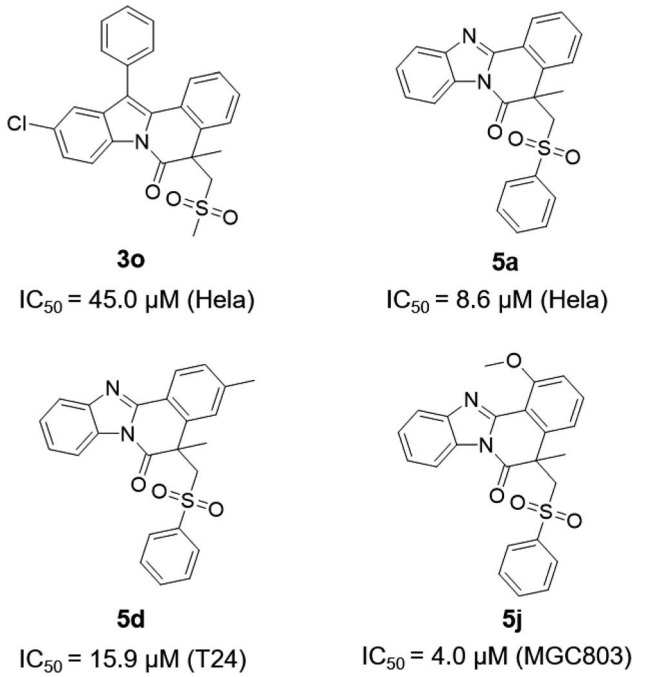


Fig. 2 Anticancer activity of some representative compounds.

antitumor activities against the tumor cell lines. Notably, compound **5j** displayed potent inhibitory bioactivity against MGC803 cell lines with IC_{50} values of 4.0 μM.

Conclusions

In summary, we have disclosed a practical TBPB induced radical relay addition/cyclization of activated alkenes with different thiosulfonates to synthesize various sulfonated indolo[2,1-*a*]isoquinolines and benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones. Notably, some compounds exhibited bioactivity against different cancer cell lines. This reaction was performed in an easy operation, giving the target compounds in moderate to excellent yields. Further studies on the applications of these sulfonated derivatives in drug design are currently ongoing in our laboratory.

Experimental section

General information

All reagents and solvents were commercially available and used directly without further purification. NMR spectra were recorded at room temperature on a Bruker Avance-400 or 500 spectrometer operating for ^{1}H NMR and ^{13}C NMR, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in hertz. The peaks were internally referenced to $CDCl_3$ (7.26 ppm) or residual undeuterated solvent signal (77.20 ppm for ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, brs = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent 6200 LC/MS TOF using APCI or ESI in positive mode.

Materials

The derivatives of substituted 2-methyl-1-(3-methyl-2-phenyl-1*H*-indol-1-yl)prop-2-en-1-ones were prepared *via* the reported methods,[12] and the derivatives of substituted 2-methyl-1-(2-phenyl-1*H*-benzo[*d*]imidazol-1-yl)prop-2-en-1-ones were also prepared thought the previous published articles.[4,13] Additionally, the substituted of acryloyl chlorides was synthesized following the published approaches.[14]

General procedure A for the preparation of the sulfonated indolo[2,1-*a*]isoquinolines. A mixture of substituted 2-methyl-1-(3-methyl-2-phenyl-1*H*-indol-1-yl)prop-2-en-1-ones (0.1 mmol), an substituted *S*-methyl methanesulfonothioates (0.1 mmol), TBHP (0.3 mmol) and $CuBr_2$ (10% mol) in DCE (3 mL) was stirred at preheated oil bath (110 °C) for 10 h. The reaction mixture was then cooled to room temperature, and quenched with saturated sodium chloride. The aqueous phase was extracted with DCM and dried over Na_2SO_4. After concentration, the resulting residue was purified by flash chromatography on silica gel with a gradient eluent of petroleum ether/ethyl acetate to afford the desired product.

General procedure B for the preparation of the sulfonated benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones. The substituted 2-methyl-1-(2-phenyl-1*H*-benzo[*d*]imidazol-1-yl)prop-2-en-1-ones (0.1 mmol), substituted *S*-methyl methanesulfonothioates (0.1 mmol), TBHP (0.3 mmol) and $CuBr_2$ (10% mol) were dissolved into the DCE (3 mL), and the mixture was stirred at preheated oil bath (110 °C) for 10 h. The reaction mixture was then cooled to room temperature, and quenched with saturated sodium chloride. The aqueous phase was extracted with DCM and dried over Na_2SO_4. After concentration, the resulting residue was purified by flash chromatography on silica gel with a gradient eluent of petroleum ether/ethyl acetate to afford the final product.

Cell culture

The cell lines (HeLa, MGC803 and T24) and medium were purchased from American type culture collection (ATCC). HeLa and T24 were cultured in DMEM and McCOy's 5A medium, respectively. Besides, MGC803 was cultured in RPMI-1640 medium. All media were supplemented with 10% fetal bovine serum (EXCELL, FND500) and maintained at 37 °C in a humidified atmosphere of 5% CO_2. The cell line was authenticated by STR profiling. Cell lines were monitored for mycoplasma contamination every 6 months.

CCK-8 assay

Cell growth inhibition was typically assessed using the enhanced cell counting kit-8 (CCK-8, #C0042, Beyotime) assay. Cancer cells were first counted, and approximately 2500 cells per well were seeded in a 96-well cell culture plate (Corning Inc.). Then, after incubation at 37 °C in a humidified atmosphere with 5% CO_2 for 24 h, the culture medium was replaced by a series of concentrations of drugs diluted with the corresponding culture fluid. Three replicates were made for each measurement. After co-incubation for 24 h, 10 μL of the CCK-8 reagent was added into each well, and OD at 450 nm was

measured using a multifunction microplate reader (EnSpire) after incubation for 2 h at 37 °C. The percentage each concentration accounted for of the control was presented as cell viability. The IC_{50} value was calculated using SPSS.

Characterization data of products

5-Methyl-12-phenyl-5-((phenylsulfonyl)methyl)indolo[2,1-*a*]isoquinolin-6(5*H*)-one (3a)

Colorless oil (40.6 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, J = 8.2 Hz, 1H), 7.53–7.41 (m, 6H), 7.37 (dd, J = 8.1, 1.1 Hz, 1H), 7.34–7.28 (m, 2H), 7.22–7.18 (m, 4H), 7.13 (dd, J = 7.9, 0.8 Hz, 1H), 6.99 (td, J = 7.7, 1.3 Hz, 1H), 6.95–6.85 (m, 1H), 4.52 (d, J = 14.5 Hz, 1H), 3.90 (d, J = 16.3 Hz, 1H), 1.61 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.59, 140.25, 134.49, 134.34, 134.06, 133.24, 132.42, 130.22, 129.35, 129.15, 128.86, 128.23, 128.05, 127.76, 127.40, 126.86, 126.01, 125.48, 125.19, 124.77, 120.98, 119.52, 116.89, 64.40, 46.69, 31.54. HRMS (ESI): calcd for $C_{30}H_{24}NO_3S$ $[M + H]^+$ 478.1478, found 478.1460.

5-Butyl-12-phenyl-5-((phenylsulfonyl)methyl)indolo[2,1-*a*]isoquinolin-6(5*H*)-one (3b)

Yellow oil (18.2 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 8.2 Hz, 1H), 7.63–7.48 (m, 7H), 7.45 (dd, J = 8.0, 1.0 Hz, 1H), 7.43–7.37 (m, 1H), 7.35–7.27 (m, 3H), 7.23 (t, J = 7.7 Hz, 2H), 7.17–7.12 (m, 1H), 7.05 (td, J = 7.6, 1.3 Hz, 1H), 7.01–6.96 (m, 1H), 4.57 (d, J = 14.6 Hz, 1H), 3.92 (d, J = 14.6 Hz, 1H), 2.34–2.11 (m, 1H), 1.89–1.72 (m, 1H), 1.19–1.00 (m, 2H), 0.97–0.79 (m, 2H), 0.67 (t, J = 7.3 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 170.20, 140.22, 134.10, 133.10, 133.00, 132.40, 130.24, 129.33, 128.77, 128.20, 128.04, 127.69, 127.33, 126.73, 126.65, 125.93, 125.23, 124.76, 120.91, 119.45, 116.99, 64.97, 50.47, 44.82, 25.27, 22.40, 13.57. HRMS (ESI): calcd for $C_{33}H_{30}NO_3S$ $[M + H]^+$ 520.1947, found 520.1913.

5-Benzyl-12-phenyl-5-((phenylsulfonyl)methyl)indolo[2,1-*a*]isoquinolin-6(5*H*)-one (3c)

Colorless oil (25.5 mg, 46%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 8.2 Hz, 1H), 7.58–7.52 (m, 2H), 7.44–7.34 (m, 4H), 7.33–7.29 (m, 1H), 7.25 (dd, J = 14.9, 7.5 Hz, 3H), 7.17–7.13 (m, 1H), 7.14–7.08 (m, 1H), 7.08–7.01 (m, 2H), 6.88 (ddd, J = 11.2, 9.1, 4.2 Hz, 2H), 6.69 (t, J = 7.7 Hz, 2H), 6.69 (t, J = 7.7 Hz, 2H), 6.37 (d, J = 7.1 Hz, 2H), 4.78 (d, J = 14.6 Hz, 1H), 4.12 (d, J = 14.6 Hz, 1H), 3.33 (d, J = 12.4 Hz, 1H), 2.94 (d, J = 12.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.44, 140.76, 133.96, 133.90, 133.33, 133.12, 131.92, 131.82, 130.00, 129.50, 129.08, 128.91, 128.72, 127.95, 127.62, 127.56, 127.39, 127.28, 127.12, 127.02, 125.79, 125.21, 124.51, 120.44, 119.24, 116.58, 63.23, 52.79, 50.85. HRMS (ESI): calcd for $C_{36}H_{28}NO_3S$ $[M + H]^+$ 554.1791, found 554.1775.

3,5,12-Trimethyl-5-((phenylsulfonyl)methyl)indolo[2,1-*a*]isoquinolin-6(5*H*)-one (3d)

Colorless oil (30.5 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56–8.51 (m, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.62–7.54 (m, 1H), 7.48–7.42 (m, 2H), 7.40–7.32 (m, 3H), 7.27–7.22 (m, 2H), 7.14 (d, J = 8.1 Hz, 1H), 6.91 (s, 1H), 4.59 (d, J = 14.8 Hz, 1H), 3.96 (d, J = 14.7 Hz, 1H), 2.65 (s, 3H), 2.17 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.26, 140.43, 137.44, 134.29, 134.15, 133.08, 132.56, 129.44, 128.80, 128.66, 127.65, 125.58, 125.10, 124.36, 123.75, 118.27, 116.91, 114.24, 64.45, 46.46, 31.61, 21.31, 11.58. HRMS (ESI): calcd for $C_{26}H_{24}NO_3S$ $[M + H]^+$ 430.1478, found 430.1477.

10-Bromo-5-methyl-12-phenyl-5-((phenylsulfonyl)methyl)indolo[2,1-*a*]isoquinolin-6(5*H*)-one (3e)

Colorless oil (34.5 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.7 Hz, 1H), 7.65–7.37 (m, 11H), 7.29 (t, J = 7.7 Hz, 2H), 7.21 (d, J = 7.6 Hz, 1H), 7.12–7.06 (m, 1H), 6.99 (dt, J = 17.8, 5.3 Hz, 1H), 4.59 (d, J = 14.6 Hz, 1H), 3.99 (d, J = 14.6 Hz, 1H), 1.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.65, 140.18, 134.67, 134.22, 133.34, 132.98, 130.30, 130.13, 129.52, 128.91, 128.71, 128.51, 128.46, 127.73, 127.54, 126.89, 125.65, 124.74, 122.16, 119.93, 118.30, 118.25, 64.45, 46.64, 31.49. HRMS (ESI): calcd for $C_{30}H_{23}BrNO_3S$ $[M + H]^+$ 556.0584, found 556.0532.

10-Bromo-5-ethyl-12-phenyl-5-((phenylsulfonyl)methyl)indolo[2,1-*a*]isoquinolin-6(5*H*)-one (3f)

Yellow oil (29.7 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 8.7 Hz, 1H), 7.44 (tdd, J = 17.8, 15.7, 6.6 Hz, 8H), 7.33–7.28 (m, 2H), 7.23–7.18 (m, 3H), 7.07 (d, J = 7.4 Hz, 1H), 7.03–6.97 (m, 1H), 6.94 (dd, J = 11.1, 4.1 Hz, 1H), 4.49 (d, J = 14.6 Hz, 1H), 3.88 (d, J = 14.6 Hz, 1H), 2.21 (dt, J = 14.5, 7.3 Hz, 1H), 1.82 (dq, J = 14.8, 7.4 Hz, 1H), 0.49 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.21, 140.21, 134.17, 133.35, 133.25, 132.85, 132.70, 130.48, 130.15, 129.50, 128.85, 128.67, 128.49, 128.45, 127.70, 127.49, 126.74, 126.49, 125.40, 122.12, 119.87, 118.32, 118.28, 64.67, 51.09, 38.31, 7.99. HRMS (ESI): calcd for $C_{31}H_{25}BrNO_3S$ $[M + H]^+$ 570.0739, found 570.0732.

10-Bromo-3,5,12-trimethyl-5-((phenylsulfonyl)methyl)indolo[2,1-*a*]isoquinolin-6(5*H*)-one (3g)

Yellow oil (29.4 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.7 Hz, 1H), 7.92 (t, J = 13.7 Hz, 1H), 7.75–7.64 (m, 1H), 7.49–7.37 (m, 3H), 7.25 (dd, J = 8.5, 7.0 Hz, 2H), 7.20–7.11 (m, 1H), 7.19–7.08 (m, 1H), 6.91 (d, J = 13.9 Hz, 1H), 4.54 (d, J = 12.3 Hz, 1H), 3.96 (d, J = 14.8 Hz, 1H), 2.59 (s, 3H), 2.13 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.38, 140.35, 137.99, 134.47, 134.32, 133.18, 132.93, 130.66, 128.93, 128.72, 128.19, 127.70, 127.59, 125.27, 123.26, 121.15, 118.28, 117.81, 113.21, 64.49, 46.42, 31.54, 21.33, 11.54. HRMS (ESI): calcd for $C_{26}H_{23}BrNO_3S$ $[M + H]^+$ 508.0583, found 508.0588.

10-Chloro-5-methyl-12-phenyl-5-((phenylsulfonyl)methyl)indolo[2,1-*a*]isoquinolin-6(5*H*)-one (3h)

Colorless oil (35.3 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, J = 8.7 Hz, 1H), 7.55–7.40 (m, 7H), 7.39–7.31 (m, 2H), 7.27 (ddd, J = 8.7, 4.0, 2.1 Hz, 1H), 7.24–7.19 (m, 2H), 7.16–7.11 (m, 2H), 7.03–6.99 (m, 1H), 6.95–6.89 (m, 1H), 4.50 (d, J = 14.8 Hz, 1H), 3.90 (d, J = 14.8 Hz, 1H), 1.61 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.61, 140.19, 134.66, 133.79, 133.36, 133.33, 132.62, 130.49, 130.43, 130.12, 129.51, 128.90, 128.50, 128.44, 127.72, 127.53, 126.89, 125.99, 125.63, 124.79, 120.05, 119.13, 117.93, 64.46, 46.62, 31.49. HRMS (ESI): calcd for $C_{30}H_{23}ClNO_3S$ $[M + H]^+$ 512.1088, found 512.1029.

5,10-Dimethyl-12-phenyl-5-((phenylsulfonyl)methyl)indolo[2,1-*a*]isoquinolin-6(5*H*)-one (3i)

Yellow oil (33.4 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.3 Hz, 1H), 7.53–7.41 (m, 7H), 7.31 (dd, J = 20.8, 7.7 Hz, 2H), 7.20–7.16 (m, 2H), 7.13 (t, J = 8.0 Hz, 2H), 7.02–6.95 (m, 2H), 6.90 (t, J = 7.6 Hz, 1H), 4.53 (d, J = 14.7 Hz, 1H), 3.90 (d, J = 14.6 Hz, 1H), 2.32 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$)

δ 169.24, 139.12, 133.44, 133.36, 133.12, 132.17, 131.51, 131.42, 129.15, 128.28, 128.11, 127.77, 127.10, 126.85, 126.70, 126.30, 126.21, 125.77, 124.33, 124.20, 123.70, 119.73, 118.30, 115.45, 76.21, 63.26, 59.38, 45.51, 30.50, 28.67, 20.44, 20.05. HRMS (ESI): calcd for $C_{31}H_{26}NO_3S$ $[M + H]^+$ 492.1633, found 492.1640.

5-Methyl-12-phenyl-5-(tosylmethyl)indolo[2,1-*a*]isoquinolin-6(5*H*)-one (3j)

Colorless oil (39.8 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (t, J = 33.1 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.64–7.35 (m, 9H), 7.27 (dd, J = 10.8, 5.7 Hz, 2H), 7.16 (t, J = 7.6 Hz, 1H), 7.01 (dd, J = 16.5, 8.0 Hz, 3H), 4.67 (d, J = 14.6 Hz, 1H), 3.95 (d, J = 14.6 Hz, 1H), 2.32 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.35, 144.57, 136.51, 134.49, 134.27, 134.05, 133.71, 132.34, 130.17, 129.37, 129.31, 129.25, 129.18, 128.50, 128.23, 128.07, 127.99, 127.35, 127.15, 125.92, 125.40, 125.07, 124.72, 120.85, 119.44, 116.86, 64.41, 46.53, 31.86, 21.33. HRMS (ESI): calcd for $C_{31}H_{26}NO_3S$ $[M + H]^+$ 492.1634, found 492.1642.

5-(((4-Fluorophenyl)sulfonyl)methyl)-5-methyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (3k)

Colorless oil (32.2 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (t, J = 36.9 Hz, 1H), 7.53–7.41 (m, 7H), 7.37 (dt, J = 7.7, 3.8 Hz, 1H), 7.35 (s, 1H), 7.25–7.19 (m, 2H), 7.13 (dt, J = 6.8, 3.4 Hz, 1H), 7.03 (tt, J = 10.3, 5.1 Hz, 1H), 6.96–6.91 (m, 1H), 6.88–6.79 (m, 2H), 4.49 (dd, J = 48.0, 23.0 Hz, 1H), 3.91 (d, J = 14.7 Hz, 1H), 1.61 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.42, 165.49, 163.45, 135.08, 133.36, 133.22, 132.89, 131.31, 129.72, 129.64, 129.11, 128.34, 127.94, 127.45, 127.24, 127.05, 126.43, 125.78, 125.10, 124.46, 124.17, 123.84, 120.11, 118.55, 115.74, 115.12, 114.94, 63.53, 45.65, 30.51. HRMS (ESI): calcd for $C_{30}H_{23}FNO_3S$ $[M + H]^+$ 496.1383, found 496.1349.

5-(((4-Fluorophenyl)sulfonyl)methyl)-5,10-dimethyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (3l)

Yellow oil (32.1 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.3 Hz, 1H), 7.57–7.39 (m, 8H), 7.37–7.31 (m, 1H), 7.14 (dd, J = 9.9, 8.2 Hz, 2H), 7.05–6.89 (m, 3H), 6.83 (t, J = 8.5 Hz, 2H), 4.53 (d, J = 14.7 Hz, 1H), 3.90 (d, J = 14.6 Hz, 1H), 2.33 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.17, 169.12, 165.69, 163.14, 135.01, 134.98, 133.61, 133.29, 133.00, 131.46, 131.34, 129.70, 129.61, 129.10, 128.33, 127.95, 127.17, 126.91, 126.37, 125.76, 124.35, 124.23, 119.91, 118.38, 115.37, 115.11, 114.89, 76.21, 63.46, 59.39, 45.50, 30.50, 28.67, 20.44, 20.05. HRMS (ESI): calcd for $C_{31}H_{25}FNO_3S$ $[M + H]^+$ 510.1539, found 510.1540.

5-Methyl-5-((methylsulfonyl)methyl)-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (3m)

Colorless oil (30.7 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79–8.38 (m, 1H), 7.51–7.30 (m, 8H), 7.26–7.19 (m, 3H), 7.02–6.95 (m, 1H), 4.44 (dd, J = 52.9, 15.1 Hz, 1H), 3.78 (dd, J = 35.6, 14.2 Hz, 1H), 2.74 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.87, 134.33, 133.28, 132.82, 131.37, 129.16, 128.26, 127.98, 127.39, 127.18, 126.53, 125.12, 125.00, 124.90, 124.24, 123.79, 120.24, 118.61, 115.62, 61.85, 46.03, 43.07, 30.06. HRMS (ESI): calcd for $C_{25}H_{22}NO_3S$ $[M + H]^+$ 416.1321, found 416.1307.

10-Bromo-5-methyl-5-((methylsulfonyl)methyl)-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (3n)

Yellow oil (26.7 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.4 Hz, 1H), 7.50–7.35 (m, 8H), 7.32 (d, J = 1.6 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 6.99 (t, J = 3.6 Hz, 1H), 4.36 (d, J = 14.8 Hz, 1H), 3.84 (d, J = 14.8 Hz, 1H), 2.59 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.90, 134.47, 133.18, 132.12, 131.94, 129.13, 129.08, 128.44, 127.80, 127.47, 126.67, 125.09, 125.05, 123.83, 121.23, 119.16, 117.27, 117.06, 61.97, 45.92, 43.04, 30.00. HRMS (ESI): calcd for $C_{25}H_{21}BrNO_3S$ $[M + H]^+$ 494.0426, found 494.0426.

10-Chloro-5-methyl-5-((methylsulfonyl)methyl)-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (3o)

Yellow oil (22.0 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68–8.37 (m, 1H), 7.52–7.33 (m, 7H), 7.31–7.21 (m, 2H), 7.16 (d, J = 1.9 Hz, 1H), 7.04–6.92 (m, 1H), 4.35 (d, J = 14.7 Hz, 1H), 3.74 (d, J = 14.7 Hz, 1H), 2.60 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.86, 134.46, 132.74, 132.15, 131.58, 129.52, 129.24, 129.07, 128.43, 127.77, 127.46, 126.67, 125.10, 125.05, 123.87, 119.30, 118.21, 116.69, 61.95, 45.91, 43.05, 30.03. HRMS (ESI): calcd for $C_{25}H_{21}ClNO_3S$ $[M + H]^+$ 450.0931, found 450.0929.

5,10-Dimethyl-5-((methylsulfonyl)methyl)-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (3p)

Yellow oil (24.1 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.4 Hz, 1H), 7.61–7.47 (m, 5H), 7.44 (dd, J = 8.1, 4.9 Hz, 2H), 7.34–7.27 (m, 1H), 7.23 (dd, J = 8.4, 1.7 Hz, 1H), 7.10–7.02 (m, 2H), 4.44 (d, J = 14.7 Hz, 1H), 3.89 (d, J = 14.8 Hz, 1H), 2.69 (s, 3H), 2.39 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.64, 135.36, 134.63, 134.02, 132.61, 132.50, 130.22, 129.31, 129.08, 128.32, 128.18, 127.54, 127.44, 126.02, 125.88, 125.38, 121.13, 119.52, 116.30, 62.88, 60.45, 46.99, 44.09, 31.13, 29.73, 21.49, 21.11. HRMS (ESI): calcd for $C_{26}H_{24}NO_3S$ $[M + H]^+$ 430.1477, found 430.1476.

5-Methyl-5-((phenylsulfonyl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5a)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 7.8 Hz, 1H), 8.31–8.19 (m, 1H), 7.75 (t, J = 11.4 Hz, 1H), 7.40–7.29 (m, 7H), 7.22–7.14 (m, 2H), 7.12 (d, J = 7.9 Hz, 1H), 4.57–4.32 (m, 1H), 4.10–3.83 (m, 1H), 1.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.61, 148.21, 142.82, 138.75, 136.14, 132.38, 130.45, 130.30, 128.36, 127.99, 127.49, 126.59, 125.66, 125.25, 125.05, 124.75, 122.51, 121.84, 118.83, 114.80, 63.55, 45.94, 30.16. HRMS (ESI): calcd for $C_{23}H_{19}N_2O_3S$ $[M + H]^+$ 403.1117, found 403.1109.

5-Butyl-5-((phenylsulfonyl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5b)

Yellow oil (20.0 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 7.0 Hz, 1H), 8.31–8.21 (m, 1H), 7.85–7.69 (m, 1H), 7.43–7.28 (m, 6H), 7.24–7.15 (m, 2H), 7.08 (d, J = 7.9 Hz, 1H), 4.45 (d, J = 14.7 Hz, 1H), 4.05 (m, J = 14.7 Hz, 1H), 2.28–2.08 (m, 1H), 1.88–1.68 (m, 1H), 1.05–0.91 (m, 2H), 0.87–0.74 (m, 2H), 0.64–0.53 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.36, 148.32, 142.59, 138.79, 134.78, 132.30, 130.40, 130.14, 127.96, 127.49, 126.53, 125.35, 125.10, 124.79, 123.33, 118.74, 114.85, 64.12, 50.01, 43.40, 24.18, 21.26, 12.43. HRMS (ESI): calcd for $C_{26}H_{25}N_2O_3S$ $[M + H]^+$ 445.1587, found 445.1585.

5-Benzyl-5-((phenylsulfonyl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5c)

Colorless oil (24.9 mg, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28–8.13 (m, 2H), 7.61 (dd, J = 5.8, 3.0 Hz, 1H), 7.44 (d, J = 7.5 Hz, 2H), 7.40–7.20 (m, 8H), 6.81 (t, J = 7.4 Hz, 1H), 6.68 (t, J = 7.7 Hz, 2H), 6.32 (t, J = 22.6 Hz, 2H), 4.69 (d, J = 14.7 Hz, 1H), 4.11 (t, J = 14.7 Hz, 1H), 3.34 (t, J = 18.0 Hz, 1H), 3.04 (d, J =

12.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.70, 147.79, 139.0, 133.76, 132.47, 131.08, 129.87, 128.15, 128.0, 127.58, 126.85, 126.77, 126.67, 126.14, 124.92, 124.84, 124.57, 123.68, 118.62, 114.47, 62.50, 51.95, 49.48. ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.70, 147.79, 139.00, 133.76, 132.47, 131.08, 129.87, 128.15, 128.0, 127.58, 126.85, 126.77, 126.67, 126.14, 124.92, 124.84, 124.57, 123.68, 118.62, 114.47, 62.50, 51.95, 49.48. HRMS (ESI): calcd for $C_{29}H_{23}N_2O_3S$ $[M + H]^+$ 479.1430, found 479.1400.

3,5-Dimethyl-5-((phenylsulfonyl)methyl)benzo[4,5]imidazo [2,1-*a*]isoquinolin-6(5*H*)-one (5d)

Colorless oil (29.9 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35–8.24 (m, 2H), 7.75–7.74 (m, 1H), 7.45–7.26 (m, 5H), 7.20–7.13 (m, 3H), 6.77 (s, 1H), 4.49 (d, J = 14.9 Hz, 1H), 3.95 (d, J = 14.9 Hz, 1H), 2.08 (s, 3H), 1.64 (d, J = 49.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.76, 149.44, 143.94, 141.98, 139.92, 136.97, 133.31, 131.47, 129.61, 128.85, 127.53, 127.19, 126.17, 126.00, 125.58, 120.36, 119.77, 115.80, 64.56, 46.86, 31.15, 21.65. HRMS (ESI): calcd for $C_{24}H_{21}N_2O_3S$ $[M + H]^+$ 417.1274, found 417.1271.

3-Methoxy-5-methyl-5-((phenylsulfonyl)methyl)benzo[4,5] imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5e)

Colorless oil (32.0 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44–8.28 (m, 1H), 8.28 (s, 1H), 7.85–7.64 (m, 1H), 7.41–7.30 (m, 5H), 7.23 (d, J = 8.0 Hz, 2H), 6.89 (dd, J = 8.8, 2.4 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 4.50 (d, J = 14.8 Hz, 1H), 4.00–3.79 (m, 1H), 3.64 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.58, 160.99, 148.35, 142.99, 138.88, 137.99, 132.24, 130.37, 127.89, 127.11, 126.59, 124.93, 124.26, 118.42, 114.72, 114.65, 113.38, 111.25, 63.53, 54.35, 46.08, 30.29. HRMS (ESI): calcd for $C_{24}H_{21}N_2O_4S$ $[M + H]^+$ 433.1223, found 433.1212.

3-(*tert*-Butyl)-5-methyl-5-((phenylsulfonyl)methyl)benzo[4,5] imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5f)

Colorless oil (33.5 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 8.3 Hz, 1H), 8.27–8.22 (m, 1H), 7.76–7.71 (m, 1H), 7.43–7.25 (m, 7H), 7.15 (dd, J = 9.4, 7.9 Hz, 2H), 4.51 (d, J = 14.8 Hz, 1H), 4.00 (d, J = 14.8 Hz, 1H), 1.63 (s, 3H), 1.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.89, 154.09, 148.39, 142.95, 138.84, 135.98, 132.47, 130.42, 127.90, 126.70, 125.00, 124.93, 124.48, 122.28, 119.23, 118.66, 114.72, 63.86, 46.20, 34.12, 30.40, 29.98. HRMS (ESI): calcd for $C_{27}H_{27}N_2O_3S$ $[M + H]^+$ 459.1743, found 459.1710.

3-(Benzyloxy)-5-methyl-5-((phenylsulfonyl)methyl)benzo[4,5] imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5g)

Yellow oil (35.1 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.7 Hz, 1H), 8.26–8.16 (m, 1H), 7.78–7.64 (m, 1H), 7.40–7.27 (m, 10H), 7.19 (dd, J = 9.5, 5.9 Hz, 2H), 7.01–6.89 (m, 1H), 6.56 (t, J = 10.8 Hz, 1H), 4.82 (q, J = 11.2 Hz, 2H), 4.45 (d, J = 18.3 Hz, 1H), 3.87 (d, J = 18.3 Hz, 1H), 1.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.56, 160.22, 148.31, 142.98, 138.90, 138.02, 134.77, 132.25, 130.37, 127.90, 127.74, 127.42, 127.08, 126.58, 124.93, 124.28, 118.43, 114.94, 114.66, 114.11, 112.09, 69.20, 63.56, 46.05, 30.16. HRMS (ESI): calcd for $C_{30}H_{25}N_2O_4S$ $[M + H]^+$ 509.1536, found 509.1536.

3-Bromo-5-methyl-5-((phenylsulfonyl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5h)

Colorless oil (24.5 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33–8.24 (m, 2H), 7.77–7.75 (m, 1H), 7.48–7.45 (m, 1H), 7.43–7.35 (m, 5H), 7.26 (t, J = 7.8 Hz, 2H), 7.14 (d, J = 1.6 Hz, 1H), 4.48 (d, J = 14.9 Hz, 1H), 3.90 (d, J = 14.9 Hz, 1H), 1.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.87, 147.34, 142.81, 138.58, 137.73, 133.36, 132.88, 130.96, 130.43, 128.96, 128.40, 128.10, 127.21, 126.57, 126.31, 125.23, 125.07, 124.92, 121.01, 118.93, 114.84, 63.33, 45.82, 29.86. HRMS (ESI): calcd for $C_{23}H_{18}BrN_2O_3S$ $[M + H]^+$ 481.0222, found 481.0251.

3-Fluoro-5-methyl-5-((phenylsulfonyl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5i)

Colorless oil (22.3 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (dd, J = 8.8, 5.7 Hz, 1H), 8.28–8.20 (m, 1H), 7.80–7.67 (m, 1H), 7.44–7.33 (m, 5H), 7.25 (t, J = 7.7 Hz, 2H), 7.07 (td, J = 8.6, 2.4 Hz, 1H), 6.79 (dd, J = 9.5, 2.4 Hz, 1H), 4.45 (d, J = 14.8 Hz, 1H), 4.01 (d, J = 14.8 Hz, 1H), 1.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.07, 165.66, 163.13, 148.47, 143.86, 139.90, 139.82, 139.70, 133.71, 131.40, 129.12, 128.79, 128.70, 127.54, 126.18, 125.84, 119.85, 119.45, 119.42, 116.71, 116.49, 115.79, 113.96, 113.72, 64.40, 47.12, 31.06. HRMS (ESI): calcd for $C_{23}H_{18}FN_2O_3S$ $[M + H]^+$ 421.1023, found 421.1021.

1-Methoxy-5-methyl-5-((phenylsulfonyl)methyl)benzo[4,5] imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5j)

Colorless oil (25.1 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38–8.14 (m, 1H), 8.01–7.76 (m, 1H), 7.56–7.39 (m, 2H), 7.41–7.28 (m, 2H), 7.31–7.30 (m, 4H), 6.98–6.83 (m, 1H), 6.83 (s, 1H), 4.47 (d, J = 14.8 Hz, 1H), 4.05 (s, 3H), 3.91 (d, J = 14.8 Hz, 1H), 1.58 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.51, 157.83, 146.32, 143.06, 138.87, 138.74, 132.38, 130.86, 129.30, 127.92, 126.63, 124.79, 124.74, 119.43, 118.05, 114.61, 110.94, 110.16, 63.58, 55.66, 45.93, 30.74. HRMS (ESI): calcd for $C_{24}H_{21}N_2O_4S$ $[M + H]^+$ 433.1233, found 433.1213.

1-Fluoro-5-methyl-5-((phenylsulfonyl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5k)

Colorless oil (17.2 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32–8.20 (m, 1H), 7.95–7.83 (m, 1H), 7.45 (t, J = 7.2 Hz, 2H), 7.42–7.34 (m, 3H), 7.24 (dd, J = 15.0, 7.7 Hz, 3H), 7.14 (dd, J = 10.5, 8.4 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 4.50 (d, J = 14.7 Hz, 1H), 4.00 (dd, J = 36.8, 10.9 Hz, 1H), 1.62 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.02, 160.79, 158.18, 144.44, 144.36, 143.17, 138.75, 138.68, 132.60, 130.98, 130.89, 129.43, 128.08, 126.60, 125.26, 125.12, 121.74, 121.70, 119.64, 115.49, 115.27, 114.69, 111.34, 111.24, 63.54, 45.96, 30.47. HRMS (ESI): calcd for $C_{23}H_{18}FN_2O_3S$ $[M + H]^+$ 421.1023, found 421.0998.

5-Methyl-5-(tosylmethyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5l)

Colorless oil (32.5 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 7.8 Hz, 1H), 8.18 (d, J = 7.3 Hz, 1H), 7.72 (t, J = 20.2 Hz, 1H), 7.37 (tt, J = 20.2, 7.5 Hz, 4H), 7.22 (d, J = 8.2 Hz, 3H), 6.85 (t, J = 40.5 Hz, 2H), 4.48 (d, J = 14.7 Hz, 1H), 4.07–3.64 (d, J = 14.7 Hz, 1H), 2.11 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.44, 148.21, 143.83, 142.81, 136.16, 135.07, 130.44, 130.32, 128.46, 127.43, 126.89, 125.97, 125.17, 125.00, 124.68, 121.80, 118.83, 114.74, 63.45, 45.88, 30.54, 20.29. HRMS (ESI): calcd for $C_{24}H_{21}N_2O_3S$ $[M + H]^+$ 417.1274, found 417.1265.

5-(((4-Fluorophenyl)sulfonyl)methyl)-5-methylbenzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5m)

Yellow oil (21.9 mg, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (dd, J = 7.9, 1.1 Hz, 1H), 8.29–8.19 (m, 1H), 7.82–7.71 (m, 1H),

7.42–7.33 (m, 5H), 7.29–7.23 (m, 1H), 7.12 (dd, J = 17.2, 7.6 Hz, 1H), 6.91–6.82 (m, 2H), 4.46 (t, J = 25.1 Hz, 1H), 4.02–3.85 (m, 1H), 1.63 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.94, 169.52, 165.58, 163.53, 148.09, 142.88, 136.09, 134.77, 130.41, 130.31, 129.59, 129.52, 127.56, 125.62, 125.31, 125.15, 124.87, 121.95, 118.92, 115.37, 115.19, 114.72, 63.70, 45.95, 30.14. HRMS (ESI): calcd for $C_{23}H_{18}FN_2O_3S$ $[M + H]^+$ 421.1023, found 421.1017.

5-Methyl-5-((methylsulfonyl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5n)

Yellow oil (23.5 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 7.8 Hz, 1H), 8.33–8.18 (m, 1H), 7.81–7.71 (m, 1H), 7.59–7.42 (m, 3H), 7.37 (p, J = 7.4 Hz, 2H), 4.33 (d, J = 14.8 Hz, 1H), 3.87 (d, J = 14.8 Hz, 1H), 2.39 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.89, 148.16, 142.97, 136.97, 130.72, 130.42, 127.75, 125.77, 125.07, 125.02, 124.82, 122.07, 118.97, 114.65, 62.23, 46.14, 42.87, 29.79. HRMS (ESI): calcd for $C_{18}H_{17}N_2O_3S$ $[M + H]^+$ 341.0961, found 341.0954.

3-(Benzyloxy)-5-methyl-5-((methylsulfonyl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5o)

Yellow oil (31.7 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.7 Hz, 1H), 8.34–8.27 (m, 1H), 7.81–7.75 (m, 1H), 7.40 (tdd, J = 14.0, 11.2, 7.1 Hz, 7H), 7.17 (dd, J = 8.8, 2.2 Hz, 1H), 7.05 (d, J = 2.1 Hz, 1H), 5.32–5.04 (m, 2H), 4.35 (d, J = 14.8 Hz, 1H), 3.75 (t, J = 35.0 Hz, 1H), 2.48 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.88, 161.54, 149.31, 144.05, 140.07, 135.95, 131.34, 128.86, 128.75, 128.52, 127.68, 126.01, 125.38, 119.59, 115.99, 115.54, 115.21, 112.93, 70.51, 63.24, 47.33, 43.83, 30.95. HRMS (ESI): calcd for $C_{25}H_{23}N_2O_4S$ $[M + H]^+$ 447.1379, found 447.1369.

1-Fluoro-5-methyl-5-((methylsulfonyl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (5p)

Colorless oil (20.1 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33–8.23 (m, 1H), 7.90–7.84 (m, 1H), 7.52 (td, J = 8.1, 5.2 Hz, 1H), 7.42–7.37 (m, 2H), 7.31–7.21 (m, 2H), 4.40 (d, J = 14.7 Hz, 1H), 4.09–3.71 (d, J = 14.7 Hz, 1H), 2.78 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.50, 158.45, 143.29, 143.26, 139.68, 131.45, 131.35, 129.38, 125.31, 125.17, 120.88, 120.84, 119.76, 115.77, 115.56, 114.48, 61.83, 46.40, 43.27, 30.29. HRMS (ESI): calcd for $C_{18}H_{16}FN_2O_3S$ $[M + H]^+$ 359.0866, found 359.0859.

Conflicts of interest

There are no conflicts to declare.

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