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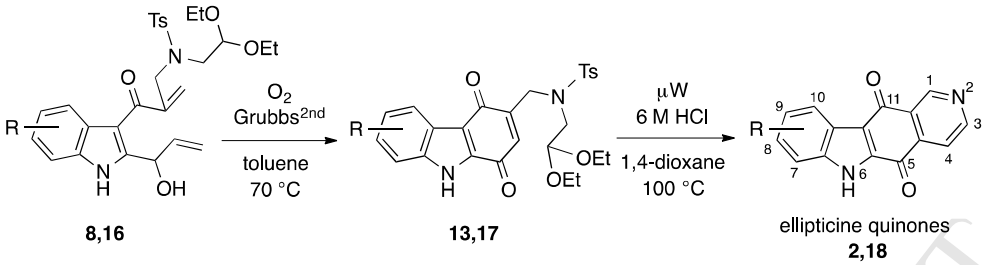
Graphical Abstract



8,16 **13,17** ellipticine quinones **2,18**

Concise Synthesis and Antiproliferative Activity Evaluation of Ellipticine Quinone and its Analogs

Takashi Nishiyama[a], Noriyuki Hatae[b]**, Masataka Mizutani[b], Teruki Yoshimura[b], Tsuyoshi Kitamura[a], Mana Miyano[a], Mami Fujii[a], Nanase Satsuki[a], Minoru Ishikura[b], Satoshi Hibino[a], and Tominari Choshi[a]*

[a]*Graduate School of Pharmacy Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-0292, Japan*
[b]*Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan*
Corresponding author. E-mail address: choshi@fupharm.fukuyama-u.ac.jp (T. Choshi)

Keyword: carbazole-1,4-quinone, Ring-Closing Metathesis, pyrido[4,3-*b*]carbozole-5,11-quinone, ellipticine quinone, antiproliferative activity

Abstract: We developed a concise protocol for the synthesis of ellipticine quinone from the appropriate 3-iodoindole-2-carbaldehydes in four steps. The key step is the construction of carbazole-1,4-quinone through tandem Ring-Closing Metathesis (RCM) and dehydrogenation under oxygen atmosphere. Therefore, the ellipticine quinone analogs possessing substitution at the 8- and/or 9-positions were synthesized using this method. In total, 14 compounds were evaluated for antiproliferative activity against HCT-116 and HL-60 cell lines; 9-nitroellipticine quinone was found to have superior activity compared to calothrixin B.

1. Introduction

Pyrido[4,3-*b*]carbazole alkaloid, an ellipticine, was isolated from the leaves of *Ochrosia elliptica Labill* by Goodwin et al. in 1959 [1]. The alkaloid's biological activity was suggested to primarily occur through DNA intercalation and topoisomerase II inhibition [2]. In addition, ellipticine and its derivatives have attracted broad interest in chemistry, biology, and pharmacology. Many synthetic approaches to their formation has been investigated and summarized in the literature [3].

Ellipticine quinone (**2**) has been reported as a key intermediate in ellipticine synthesis by Gribble et al. (Chart 1) [4]. Since then, **2** has been synthesized by many research groups [5] and revealed to show antitumor activity by Bernardo et al. [6]. Moreover, the pentacyclic quinolino[4,3-*b*]carbazole alkaloid and calothrixins A and B including the carbazole-1,4-quinone framework were isolated from *cyanobacteria Calothrix* by Rickards et al. in 1999 [7]. These compounds have been reported to exhibit antimalarial activity as well as activity against human HeLa cancer cells. In this way,

heterocyclic quinones are currently the focus of intensive research because of their several biological activities such as anticancer [6,8], neuronal cell-protecting [9], and antimalarial activities [6,10].

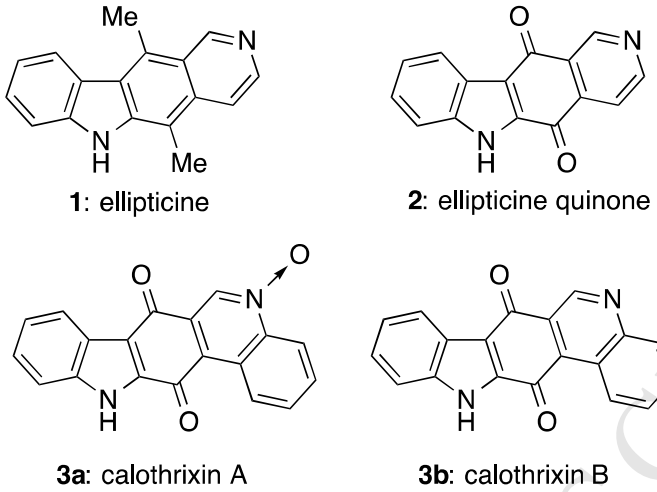
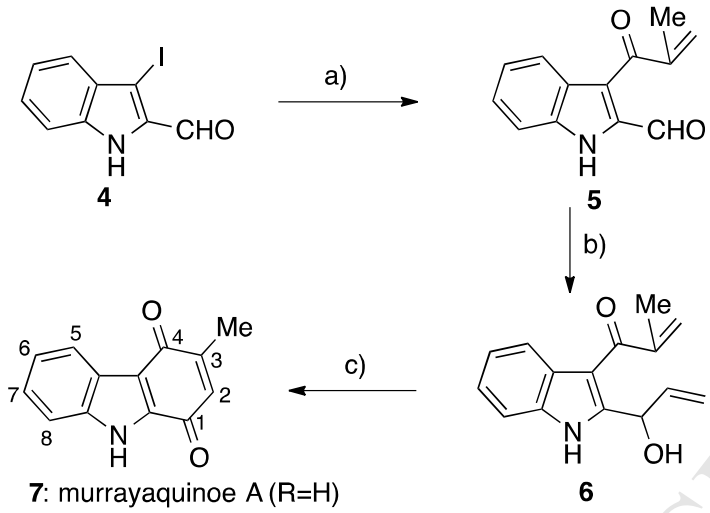


Figure 1. Structure of pyridocarbzoles

We are interested in the unique structure and pharmacological action of carbazolequinone alkaloids. To date, we have achieved the total synthesis of carbazolequonones (murrayaquinone A [11], koeniginequinones [12], carbazomycin G [13], carquinostatin A [14], carbazoquinocins [15], carbazomadurins [16], and calothrixins [17]) based on our original two methods of allene-mediated electrocyclic reaction of a 6π-electron system [11a,b,13–17] or one-pot cyclocarbonylation, desilylation, and oxidation reaction [11c,12]. Furthermore, we have been searching for stronger biologically active compounds using these natural compounds and their derivatives. Recently, we developed an efficient synthetic method for the carbazole-1,4-quinone framework from the appropriate 3-acryloyl-2-propenylindoles using a tandem RCM [18] and dehydrogenation reaction, and achieved the total synthesis of murrayaquinone A (**7**) (Scheme 1) [19]. In addition, we evaluated the antiproliferative activity of these derivatives [20].



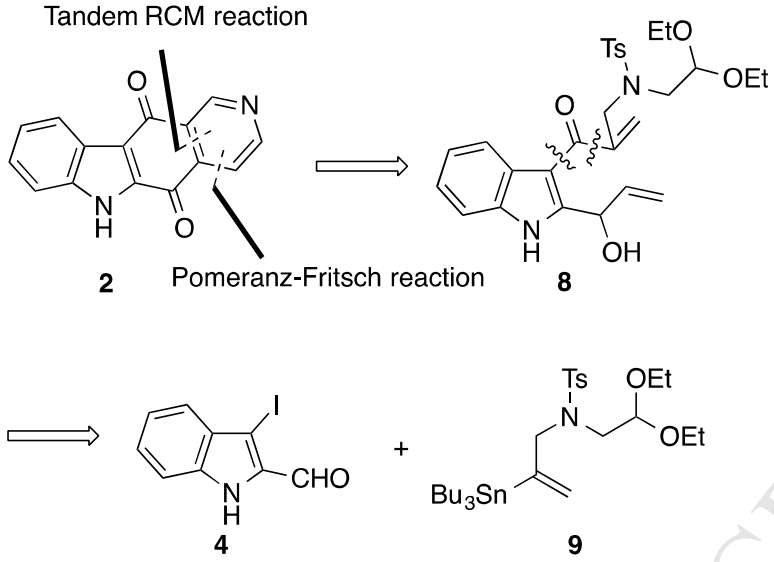
Scheme 1. Synthesis of murrayaquinone A. Reagents and conditions: (a) isopropenyltributyltin, CO (1 atm), BHT, $PdCl_2$(dppf), DMF, 70 °C; (b) vinylmagnesium bromide, THF, 0 °C; (c) Grubbs^{2nd}, O_2 (1 atm), toluene, 70 °C.

Herein, we describe a concise total synthesis of ellipticine quinone based on the construction of a carbazole-1,4-quinone using a tandem RCM and dehydrogenation reaction. In addition, we synthesize its analogs that possess substitution in the 8- and/or 9-positions using this method and aim at developing new drug candidates or lead compounds. We then evaluate the antiproliferative activity of the new compounds and natural products against HCT-116 and HL-60 cell lines.

2. Results and Discussion

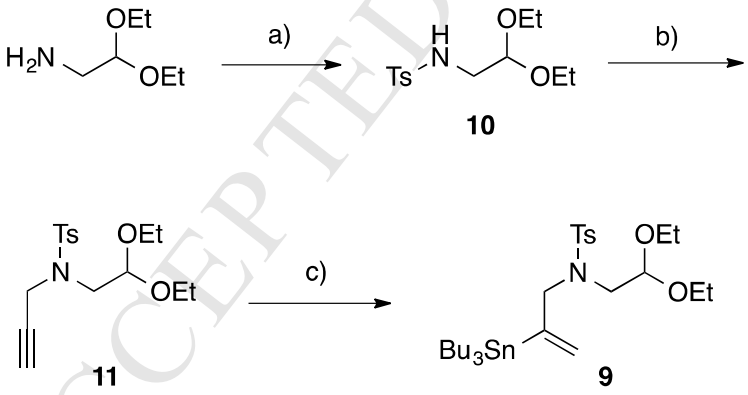
2.1. Chemistry

Our retrosynthetic strategy for ellipticine quinones is illustrated in Scheme 2. We envisioned that the fused pyridine moiety of **2** could be constructed through a Pomeranz–Fritsch reaction [21]. The carbazole-1,4-quinone framework of **2** was prepared from 3-acryloyl-2-propenylindole **8** using a tandem RCM and dehydrogenation reaction as a key step. The 3-acryloyl-2-propenylindole **8** would be provided by a three-component Pd-catalyzed cross-coupling reaction between 3-iodoindole-2-carbaldehyde (**4**), CO (1 atm), and alkenyl tributyltin **9**, followed by a Grignard reaction toward the formyl group.

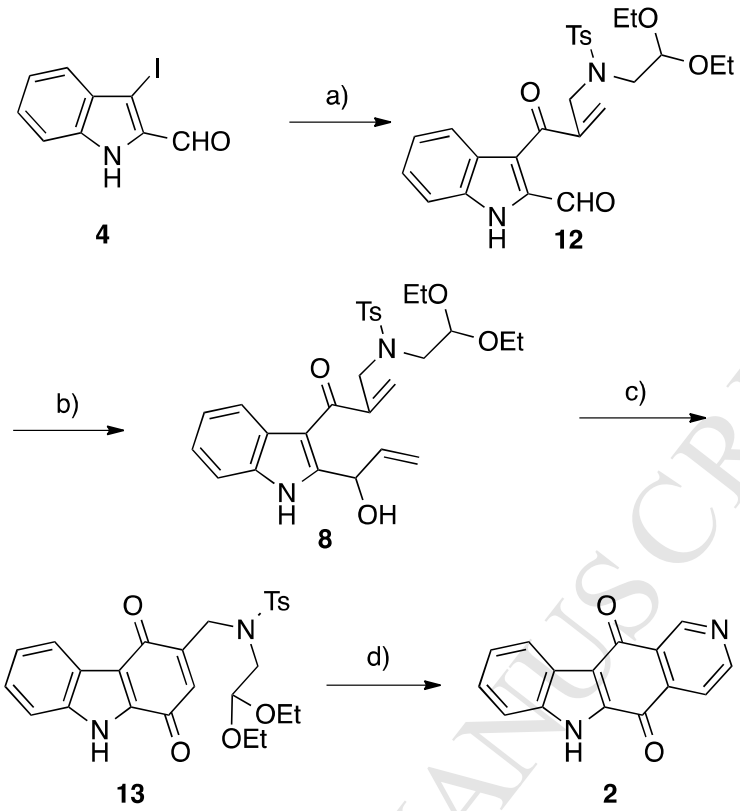


Scheme 2. Retrosynthetic Analysis of Ellipticine quinone

Initially, to obtain a required alkenyl tributyltin **9** (Scheme 3), treatment of aminoacetaldehyde diethyl acetal with *p*-toluenesulfonyl chloride and Et_3N afforded the *p*-toluenesulfonamide **10** [22] in 76% yield, which was subjected to alkylation with propargyl bromide in the presence of K_2CO_3 to give the propargylamine **11** in 74% yield. Subsequently, **11** was subjected to Pd-catalyzed hydrostannylation [23] with tributyltin hydride to afford the desired alkenyl tributyltin **9** in 97% yield.



Scheme 3. Synthesis of alkenyl tributyltin. Reagents and conditions: (a) TsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 76%; (b) propargyl bromide, K_2CO_3, DMF, rt, 12 h, 74%; (c) Bu_3SnH, $PdCl_2(PPh_3)_2$, THF, 0 °C, 1 h, 97%.

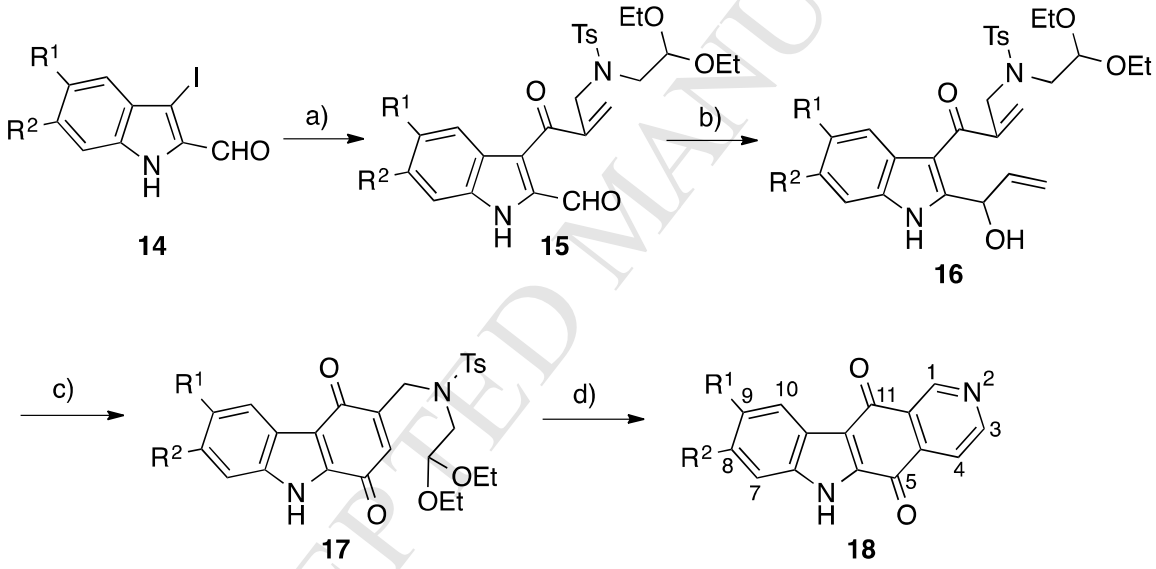


Scheme 4. Synthesis of ellipticine quinone. Reagents and conditions: (a) **9**, CO (1 atm), BHT, $PdCl_2$(dppf), DMF, 70 °C (64%); (b) vinylmagnesium bromide, THF, 0 °C, (91%); (c) Grubbs^{2nd}, O_2, toluene, 70 °C (66%); (d) conc. HCl, 1,4-dioxane, MW, 100 °C (90%).

The synthesis of ellipticine quinone was performed as outlined in Scheme 4. The three-component Pd-catalyzed cross-coupling reaction [24] between 3-iodoindole-2-carbaldehyde (**4**) and alkenyl tributyltin **9** under CO (1 atm) atmosphere was conducted in DMF at 70 °C to provide 3-acryloylindole **12** in 64% yield. Subsequently, the Grignard reaction of **12** with vinylmagnesium bromide afforded the allyl alcohol **8**. Treatment of **8** with Grubbs 2nd generation catalyst under oxygen atmosphere in toluene at 70 °C for 2 h directly afforded the carbazole-1,4-quinone **13** in 66% yield. Finally, we investigated the construction of a fused pyridine moiety through a Pomerantz–Fritsch reaction. Compound **13** was subjected to cyclization with 6 M HCl in 1,4-dioxane at 70 °C by conventional heating. The desired ellipticine quinone (**2**) was obtained in 35% yield. Next, according to Chern's method [21f], we examined cyclization with 6 M HCl in 1,4-dioxane at 150 °C under microwave irradiation (in a sealed microwave tube). Under these conditions, the yield improved and **2** was obtained in 67% yield. Furthermore, cyclization of **13** with 6 M HCl in 1,4-dioxane at 100 °C under microwave irradiation gave ellipticine quinone (**2**) as the sole product in 90% yield. Thus, a concise synthesis of ellipticine quinone (**2)** was achieved from 3-iodoindole-2-carbaldehyde (**4**) in 34.6% overall yield in four steps.

Next, based on the above precedents, we attempted to synthesize new ellipticine quinone analogs possessing several substitutions in the 8- and/or 9-positions to evaluate their in vitro antiproliferative activity against HCT-116 and HL-60 cell lines.

As shown in Scheme 5 and Table 1, the starting material, indole-2-carbaldehyde **14**, was synthesized according to our reported procedure [20]. A three-component Pd-catalyzed cross-coupling reaction of 3-iodoindole **14** and alkenyl tributyltin **9** under CO (1 atm) atmosphere performed in DMF at 70 °C provided 3-acryloylindole **15** in 42%–66% yields. Subsequently, the Grignard reaction of **15** with vinylmagnesium bromide gave the desired 2-allyl alcohol **16** in 53%–70% yields. We synthesized the carbazole-1,4-quinone **17** in 52%–72% yields using a tandem RCM and dehydrogenation reaction against **16**. Finally, cyclization of the obtained carbazole-1,4-quinone **17** with HCl in 1,4-dioxane under microwave irradiation gave the ellipticine quinone **18** in 60%–80% yields. The structures of these ellipticine quinone **18** are supported by the ^{1}H, ^{13}C NMR, and mass spectra.



Scheme 5. Synthesis of ellipticine quinones. Reagents and conditions: (a) **9**, CO (1 atm), BHT, $PdCl_2$(dppf), DMF, 70 °C; (b) vinylmagnesium bromide, THF, 0 °C; (c) Grubbs^{2nd}, O_2, toluene, 70 °C; (d) 6 M HCl, 1,4-dioxane, MW, 100 °C.

Table 1. Yield of **15**, **16, 17**, and **18**

Compd. No.	R^1	R^2	Yield (%)			
			15	**16**	**17**	**18**
a	MeO	MeO	43	57	65	65
b	MeO	H	54	63	64	71
c	Me	H	52	56	61	65
d	Cl	H	45	60	58	63
e	F	H	60	66	62	80
f	NO_2	H	41	64	66	62
g	CF_3	H	54	65	61	72
h	H	MeO	66	60	60	72
i	H	Me	42	53	53	72
j	H	Cl	58	56	52	68
k	H	F	45	64	60	70
l	H	NO_2	46	72	72	66
m	H	CF_3	48	53	53	60

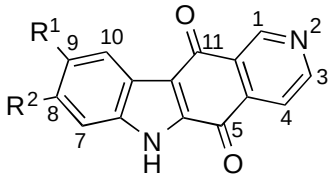
2.2. Antiproliferative studies

The HCT-116 and HL-60 cell viabilities treated with ellipticine quinone analogs were assessed by the MTT [25] and WST-1 [26] method, respectively, and the data is shown in Table 2. Antiproliferative activity by ellipticine quinone (**2**) has only been reported against the HeLa cell line, showing an IC_{50} value of 0.15 μM [6]. Against HCT-116 and HL-60 cells, the IC_{50} values were 0.877 and 3.286 μM, respectively. Our previous report [8d] regarding the antiproliferative activity against HCT-116 and HL-60 cells treated with calothrixin B and *N*-MOM calothrixin B that included a pyrido[4,3-*b*]carbazole-5,11-quinone structure similar to ellipticine quinone also exhibited weaker activity compared to that against HeLa cells in a report by Bernardo et al. [6]. Furthermore, all our synthetic pyrido[4,3-*b*]carbozole-5,11-quinone analogs, such as the current ellipticine quinone analogs and previously reported calothrixin B analogs [8d], displayed weaker activity against HL-60 cells than against HCT-116 cells.

Based on our previous report regarding the increasing effect of mono-MeO substitution on the phenyl ring of murrayaquinone A on antiproliferative activity [20], mono-MeO ellipticine quinones **18b** and **18h** were predicted to show an increase in activity. Unlike mono-MeO murrayaquinone A, the mono- and di-MeO analogs **18a**, **18b**, and **18h** exhibited weaker activity compared to unsubstituted ellipticine quinone **2**. All our 8-monosubstituted analogs **18h**–**18m** showed a decrease

in antiproliferative activity compared to unsubstituted **2**. For 9-monosubstituted analogs **18c**–**18g**, with the exception of 9-MeO analog **18b**, the activity increased compared to the corresponding 8-monosubstituted analogs **18i**–**18m**. Finally, we developed the 9-NO_2 derivative **18f** that showed the most potent antiproliferative activity against HCT-116 and HL-60 cells with IC_{50} values of 0.187 and 1.350 μM, respectively. The values of 9-NO_2 ellipticine quinone **18f** were superior to those of calothrixin B (**3b**), whose IC_{50} values are 0.32 μM against HCT-116 cells and over 10 μM against HL-60 cells [8d]. Then, based on current antiproliferative activity against tumor cells, we will be assessed to their selectivity index test using normal cells in the near future.

Table 2. Evaluation of Cell Growth Inhibitory activity against HCT-116 and HL-60 cell lines



Compd. No.	R^1	R^2	HCT-116 IC_{50} (μM)	HL-60 IC_{50} (μM)
2	H	H	0.877	3.286
18a	MeO	MeO	3.721	7.487
18b	MeO	H	5.430	>10
18c	Me	H	0.849	4.268
18d	Cl	H	1.380	3.881
18e	F	H	1.127	4.500
18f	NO_2	H	0.187	1.350
18g	CF_3	H	1.641	5.084
18h	H	MeO	3.137	9.005
18i	H	Me	5.795	>10
18j	H	Cl	4.066	>10
18k	H	F	1.600	4.500
18l	H	NO_2	1.254	4.429
18m	H	CF_3	4.619	>10
Camptothecin			0.159	0.019

3. Conclusion

In conclusion, we developed a concise protocol for the total synthesis of ellipticine quinone and achieved the formal synthesis of ellipticine. Furthermore, we synthesized 13 analogs using our protocol for evaluating their in vitro antiproliferative activity against HCT-116 and HL-60 cell lines. The 9-monosubstituted analogs, with the exception of 9-MeO derivative **18b**, were found to possess good activity compared to the corresponding 8-monosubstituted compounds; notably, 9-NO_2 ellipticine quinone **18f** exhibited IC_{50} values 4.7-fold higher against HCT-116 cells and 2.4-fold higher against HL-60 cells. This is the first report of an ellipticine quinone analog with higher IC_{50} values than calothrixin B (**3b**), which displayed extremely strong antiproliferative activity in natural products with a carbazole-1,4-quinone structure. The current findings are considered to be important for the development of antitumor carbazole-1,4-quinone analogs.

4. Experimental section

4.1. Chemistry

All non-aqueous reactions were carried out under an atmosphere of nitrogen in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Analytical thin-layer chromatography was performed with Silica gel 60PF_{254} (Merck). Silica gel column chromatography was performed with Silica gel 60 (70–230 mesh, Canto Co. Lit.). All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL AL-300 at 300 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00). Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL AL-300 at 75 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0) and DMSO-d_6 (δ 39.7). Infrared spectra were recorded with ATR method using a Shimadzu FTIR-8000 spectrophotometer and Technologies DuraScop. Low and High-resolution mass spectra were recorded on JEOL JMS-700 spectrometers by direct inlet system.

*4.2. N-(2,2-Diethoxyethyl)-4-methylbenzenesulfonamide (**10**)*

A mixture of aminoacetaldehyde diethyl acetal (10.0 g, 75 mmol), Et_3N (21.0 mL, 150 mmol), and *p*-toluenesulfonyl chloride (17.1 g, 90 mmol) in CH_2Cl_2 (80 mL) was stirred at rt for 1.5 h. After water was added to the mixture, the mixture was extracted with CH_2Cl_2. The organic extract was washed with water, 1 M HCl, 20% $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated under reduced pressure to give **10** (17.1 g, 79%) as white solid. mp 63–64 °C (EtOAc-hexane). IR (ATR) ν = 3251 (NH), 1323 (SO_2), 1122 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 8.2 Hz,

2H; ArH), 7.29 (d, *J* = 8.2 Hz, 2H; ArH), 5.13–5.18 (m, 1H; NH), 4.47 (t, *J* = 5.5 Hz, 1H; CH), 3.57–3.67 (m, 2H; OCH_2), 3.40–3.50 (m, 2H; OCH_2), 2.99–3.05 (m, 2H; CH_2), 2.40 (s, 3H; CH_3), 1.15 (t, *J* = 7.0 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.1, 136.7, 129.4, 126.8, 100.4, 62.8, 45.2, 21.2, 14.9. MS *m/z*: 287 (M^+, 5), 155 (25), 103 (100). HRMS (EI): calcd for $C_{13}H_{21}NO_4S$ 287.1191; found 287.1123.

*4.3. N-(2,2-Diethoxyethyl)-N-(2-propynyl)-4-methylbenzenesulfonamide (**11**)*

A mixture of **10** (17.0 g, 59 mmol), 3-bromopropyne (7.0 g, 59 mmol), and K_2CO_3 (16.3 g, 118 mmol) in DMF (60 mL) was stirred at rt for 3 h. After water was added to the mixture, the mixture was extracted with EtOAc. The organic extract was washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure to give **11** (16.1 g, 83%) as colorless crystals. mp 58–59 °C (EtOAc-hexane). IR (ATR) ν = 3275 (NH), 1335 (SO_2), 1161 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 8.3 Hz, 2H; ArH), 7.28 (d, *J* = 8.3 Hz, 2H; ArH), 4.69 (t, *J* = 5.6 Hz, 1H; CH), 4.29 (d, *J* = 2.4 Hz, 2H; CH_2), 3.69–3.80 (m, 2H; OCH_2), 3.52–3.62 (m, 2H; OCH_2), 3.26 (d, *J* = 5.6 Hz, 2H; CH_2), 2.42 (s, 3H; CH_3), 1.99 (t, *J*= 2.4 Hz, 1H; CH), 1.22 (t, *J*= 7.0 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.5, 136.0, 129.4, 127.7, 102.7, 73.4, 63.4, 48.5, 38.3, 21.5, 15.3. MS *m/z*: 325 (M^+, 2), 155 (17), 103 (100). HRMS (EI): calcd for $C_{16}H_{23}NO_4S$ 325.1348; found 325.1348.

*4.4. N-(2,2-Diethoxyethyl)-N-[2-(tributylstannyl)allyl]-4-methylbenzenesulfonamide (**9**)*

A solution of tributyltin hydride (12.3 ml, 47 mmol) was added dropwise to a suspension of propargylamine **11** (14 g, 43 mmol) and $PdCl_2(PPh_3)_2$ (0.31 g, 0.43 mmol) in THF (50 mL) under cooling with ice-water. After stirring at same temperature for 1 h, the mixture was evaporated in vacuo. The residue was purified by column chromatography using EtOAc-hexane (1:9, v/v) as an eluent to give the alkenyl tributyltin **9** (25.7 g, 97%). IR (ATR) ν =1342 (SO_2), 1157 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 7.9 Hz, 2H; ArH), 7.26 (d, *J* = 7.9 Hz, 2H; ArH), 5.51 (d, *J* = 1.8 Hz, 1H; =CH_2), 5.18 (d, *J* = 1.8 Hz, 1H; =CH_2), 4.54 (t, *J* = 5.3 Hz, 1H; CH), 4.21 (s, 2H; CH_2), 3.57–3.67 (m, 2H; OCH_2), 3.34–3.44 (m, 2H; OCH_2), 3.26 (d, *J* = 5.3 Hz, 2H; CH_2), 2.41 (s, 3H; CH_3), 1.42–1.50 (m, 6H; $CH_2CH_2CH_2$), 1.27–1.37 (m, 6H; $CH_2CH_2CH_2$), 1.22 (t, *J*= 7.0 Hz, 6H; CH_3 × 2), 0.87–0.94 (m, 9H; CH_3 × 3). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.8, 142.9, 138.1, 129.4, 127.2, 125.7, 102.0, 63.1, 56.4, 49.0, 29.0, 27.3, 21.5, 15.3, 13.7, 9.3. MS *m/z*: 617 (M^+, 3), 155 (30), 103 (100). HRMS (EI): calcd for $C_{28}H_{51}NO_4SSn$ 617.2561; found 617.2555.

*4.5. N-(2,2-Diethoxyethyl)-N-{[2-(2-formylindol-3-yl)carbonyl]prop-2-en-1-yl}-4-methylbenzenesulfonamide (**12**)*

Carbon monoxide was bubbled for 5 min to a mixture of the iodoindole **4** (500 mg, 1.85 mmol), alkenyl tributyltin **9** (1.71 g, 2.77 mmol), BHT (448 mg, 2.04 mmol), and $PdCl_2$(dppf) (75 mg, 0.093 mmol) in DMF (20 mL) at rt. The resulting mixture was stirred at 70 °C for 12 h under a CO atmosphere. After cooling to an ambient temperature, 30% aq. KF solution (20 mL) was added to the mixture and then the mixture was stirred at the same temperature for 1 h. The mixture was quenched with water and then the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (2:8, v/v) as an eluent to give the 3-acryloylindole **12** (778 mg, 64%). mp 127–128 °C (EtOAc-hexane). IR (ATR) ν = 3302 (NH), 1658 (CO), 1616 (CO), 1334 (SO_2), 1157 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 10.08 (s, 1H; CHO), 9.49 (br s, 1H; NH), 7.94 (d, *J*=8.1 Hz, 1H; ArH), 7.76 (d, *J* = 8.0 Hz, 2H; ArH), 7.40–7.51 (m, 2H; ArH), 7.24–7.31 (m, 3H; ArH), 6.29 (s, 1H; $=CH_2$), 6.08 (s, 1H; $=CH_2$), 4.64 (t, *J* = 5.6 Hz, 1H; CH), 4.42 (s, 2H; CH_2), 3.63–3.73 (m, 2H; OCH_2), 3.43–3.53 (m, 2H; OCH_2), 3.39 (d, *J* = 5.6 Hz, 2H; CH_2), 2.41 (s, 3H; CH_3), 1.16 (t, *J* = 6.9 Hz, 6H; CH_3 × 2); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.4, 183.3, 146.2, 143.6, 136.6, 136.3, 135.9, 129.8, 129.7, 127.5, 127.3, 126.6, 123.6, 123.1, 122.2, 112.4, 101.7, 63.0, 51.3, 49.6, 21.5, 15.3. MS *m/z*: 498 (M^+, 1), 155 (23), 103 (100). HRMS (EI): calcd for $C_{26}H_{30}N_2O_6S$ 498.1825; found 498.1833.

*4.6. N-(2,2-diethoxyethyl)-N-((2-(2-(1-hydroxyprop2-en-1-yl)indol-3-yl)carbonyl)prop-2-en-1-yl)-4-methylbenzenesulfonamide (**8**)*

A solution of vinylmagnesium bromide (1 M in THF, 3.2 mL, 3.2 mmol) was added dropwise to a solution of 3-acryloylindole **12** (1.00 g, 0.23 mmol) in THF (30 mL) under cooling with ice-water. After stirring at rt for 30 min, the reaction mixture was quenched with aqueous NH_4Cl solution (saturated), and then was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (1:9, v/v) as an eluent to give the allyl alcohol **8** (960 mg, 91%) as yellow oil. IR (ATR) ν = 3336 (OH), 1608 (CO), 1330 (SO_2), 1153 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 9.19 (br s, 1H; NH), 7.79 (d, *J* = 7.9 Hz, 1H; ArH), 7.73 (d, *J* = 8.4 Hz, 2H; ArH), 7.36 (d, *J* = 7.9 Hz, 1H; ArH), 7.22 (d, *J* = 8.4 Hz, 2H; ArH), 7.12–7.20 (m, 2H; ArH), 6.13 (ddd, *J* = 17.1, 10.5, 5.0 Hz, 1H; $CH=CH_2$), 6.02 (s, 1H; $=CH_2$), 5.95 (s, 1H; $=CH_2$), 5.64 (br s, 1H; CH), 5.50 (td, *J* = 17.1, 1.5 Hz, 1H; $CH=CH_2$), 5.32 (td, *J* = 10.5, 1.5 Hz, 1H; $CH=CH_2$), 4.69 (br s, 1H; OH), 4.65 (t, *J* = 5.5 Hz, 1H; CH), 4.40 (s, 2H; CH_2), 3.62–3.72 (m, 2H; OCH_2), 3.42–3.51 (m, 2H; OCH_2), 3.41 (d, *J* = 5.5 Hz, 2H; CH_2), 2.37 (s, 3H; CH_3), 1.15 (t, *J* = 7.2 Hz, 6H; CH_3 × 2).^{13}C NMR (75 MHz, $CDCl_3$) δ = 193.1, 147.5, 144.8, 143.4, 136.9, 136.1, 134.3, 129.6, 127.2, 126.9, 126.1, 123.0, 122.0, 121.3, 117.1, 112.8, 111.6, 101.7, 67.8, 63.0, 50.6, 49.6, 21.4, 15.2. MS *m/z*: 526 (M^+, 2), 155 (24), 103 (100). HRMS (EI): calcd for $C_{28}H_{34}N_2O_6S$ 526.2138; found 526.2142.

*4.7. N-(2,2-diethoxyethyl)-N-(1,4-dioxocarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**13**)*

A suspension of the allyl alcohol **8** (100 mg, 0.19 mmol) and Grubbs^{2nd} catalyst (17 mg, 0.02 mmol) in toluene (20 mL) was heated at 70 °C for 2 h under an O_2 atmosphere. After cooling to an ambient temperature, reaction solvent was evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (3:7, v/v) as an eluent to give the carbazole-1,4-quinone **13** (62 mg, 66%) as red solid. mp 190–192 °C (EtOAc-hexane). IR (ATR) ν = 3181 (NH), 1643 (CO), 1612 (CO), 1342 (SO_2), 1161 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.51 (br s, 1H; NH), 8.16 (d, *J* = 7.6 Hz, 1H; ArH), 7.73 (d, *J* = 8.4 Hz, 2H; ArH), 7.52 (d, *J* = 7.6 Hz, 1H; ArH), 7.42 (t, *J* = 7.6 Hz, 1H; ArH), 7.37 (t, *J* = 7.6 Hz, 1H; ArH), 7.29 (d, *J* = 8.4 Hz, 2H; ArH), 6.71 (t, *J* = 1.7 Hz, 1H; ArH), 4.62 (t, *J* = 5.0 Hz, 1H; CH), 4.42 (d, *J* = 1.7 Hz, 2H; CH_2), 3.61–3.71 (m, 2H; OCH_2), 3.41–3.51 (m, 2H; OCH_2), 3.36 (d, *J* = 5.0 Hz, 2H; CH_2), 2.36 (s, 3H; CH_3), 1.13 (t, *J* = 7.0 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.7, 179.9, 146.7, 143.8, 137.1, 136.3, 135.2, 131.4, 129.8, 127.3, 127.2, 124.4, 124.0, 122.8, 116.8, 113.0, 101.9, 63.1, 52.3, 48.5, 21.4, 15.2. MS *m/z*: 496 (M^+, 2), 210 (4), 155 (15), 103 (100). HRMS (EI): calcd for $C_{26}H_{28}N_2O_6S$ 496.1668; found 496.1674.

*4.8. ellipticine quinone (**2**)*

A stirred solution of **13** (100 mg, 0.202 mmol) in dioxane/6 M HCl (3:2) (5 mL) under N_2 atmosphere, was heated under microwave irradiation at 100 °C for 10 min. After cooling to an ambient temperature, the pH of the reaction mixture was adjusted to 8 with Na_2CO_3 and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (5:5, v/v) as an eluent to give ellipticine quinone (**2**) (45 mg, 90%). mp 316–318 °C (EtOAc-hexane) (lit. [4] mp 317–320 °C). IR (ATR) ν = 3078 (NH), 1662 (CO), 1651 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 13.2 (br s, 1H; NH), 9.24 (s, 1H; ArH), 9.06 (d, *J* = 4.8 Hz, 1H; ArH), 8.21 (d, *J* = 8.0 Hz, 1H; ArH), 7.93 (d, *J* = 4.8 Hz, 1H; ArH), 7.61 (d, *J* = 8.0 Hz, 1H; ArH), 7.48 (t, *J* = 8.0 Hz, 1H; ArH), 7.39 (t, *J* = 8.0 Hz, 1H; ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.3, 176.9, 155.2, 147.4, 138.5, 138.4, 137.0, 128.1, 127.6, 124.4, 123.7, 122.5, 118.4, 117.5, 114.0. MS *m/z*: 248 (M^+, 100). HRMS (EI): calcd for $C_{15}H_8N_2O_2$ 248.0586; found 248.0573.

*4.9. Synthesis of 3-Acryloylindoles (**15a**–**15m**)*

3-Acryloylindole **15a**–**15m** were prepared according to a synthetic method for **12**.

*4.9.1. N-(2,2-diethoxyethyl)-N-{[2-(2-formyl-5,6-dimethoxyindol-3-yl)carbonyl]prop-2-en-1-yl}-4-methylbenzenesulfonamide (**15a**)*

Yield 43%. mp 78–79 °C (EtOAc-hexane). IR (ATR) ν = 3332 (NH), 1666 (CO), 1628 (CO), 1342 (SO_2), 1122 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 10.48 (br s, 1H; NH), 10.00 (s, 1H; CHO), 7.76 (d, *J* = 7.5 Hz, 2H; ArH), 7.43 (s, 1H; ArH), 7.30 (d, *J* = 7.5 Hz, 2H; ArH), 6.94 (s, 1H; ArH), 6.31 (s, 1H, $=CH_2$), 6.09 (s, 1H, $=CH_2$), 4.61 (t, *J* = 5.1 Hz, 1H; CH), 4.41 (s, 2H; CH_2), 3.97 (s, 3H; OCH_3), 3.93 (s, 3H; OCH_3), 3.62–3.72 (m, 2H; OCH_2), 3.42–3.49 (m, 2H; OCH_2), 3.40 (d, *J* = 5.1 Hz, 2H; CH_2), 2.42 (s, 3H; CH_3), 1.14 (t, *J* = 6.9 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.9, 182.4, 151.8, 148.0, 146.6, 143.7, 136.4, 135.1, 132.3, 129.7, 128.9, 127.3, 122.3, 120.5, 102.9, 101.4, 93.4, 62.9, 56.3, 56.2, 51.4, 49.8, 21.5, 15.1. MS *m/z*: 558 (M^+, 2), 403 (10), 155 (14), 103 (100). HRMS (EI): calcd for $C_{28}H_{34}N_2O_8S$ 558.2036; found 558.2023.

*4.9.2. N-(2,2-diethoxyethyl)-N-{[2-(2-formyl-5-methoxyindol-3-yl)carbonyl]prop-2-en-1-yl}-4-methylbenzenesulfonamide (**15b**)*

Yield 54%. mp 121–122 °C (EtOAc-hexane). IR (ATR) ν = 3294 (NH), 1651 (CO), 1612 (CO), 1342 (SO_2), 1134 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 10.06 (s, 1H; CHO), 9.41 (br s, 1H; NH), 7.75 (d, *J* = 8.4 Hz, 2H; ArH), 7.45 (d, *J* = 2.6 Hz, 1H; ArH), 7.37 (d, *J* = 9.2 Hz, 1H; ArH), 7.30 (d, *J* = 8.4 Hz, 2H; ArH), 7.09 (dd, *J* = 9.2, 2.6 Hz, 1H; ArH), 6.29 (s, 1H; $=CH_2$), 6.06 (s, 1H; $=CH_2$), 4.61 (t, *J* = 5.3 Hz, 1H; CH), 4.40 (s, 2H; CH_2), 3.86 (s, 3H; OCH_3), 3.61–3.69 (m, 2H; OCH_2), 3.42–3.50 (m, 2H; OCH_2), 3.39 (d, *J* = 5.3 Hz, 2H; CH_2), 2.41 (s, 3H; CH_3), 1.15 (t, *J* = 7.0 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.8, 179.6, 157.7, 146.6, 143.8, 136.3, 135.2, 132.3, 131.6, 129.8, 127.3, 125.1, 119.0, 116.5, 114.0, 102.3, 102.0, 63.2, 55.7, 52.2, 48.4, 21.4, 15.2. MS *m/z*: 528 (M^+, 1), 373 (14), 155 (6), 103 (100). HRMS (EI): calcd for $C_{27}H_{32}N_2O_7S$ 528.1930; found 528.1943.

*4.9.3. N-(2,2-diethoxyethyl)-N-{[2-(2-formyl-5-methylindol-3-yl)carbonyl]prop-2-en-1-yl}-4-methylbenzenesulfonamide (**15c**)*

Yield 52%. mp 104–105 °C (EtOAc-hexane). IR (ATR) ν = 3294 (NH), 1654 (CO), 1616 (CO), 1331 (SO_2), 1153 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 10.04 (s, 1H; CHO), 9.39 (br s, 1H; NH), 7.74–7.77 (m, 3H; ArH), 7.37 (d, *J* = 8.3 Hz, 1H; ArH), 7.24–7.30 (m 3H; ArH), 6.27 (s, 1H; $=CH_2$), 6.07 (s, 1H; $=CH_2$), 4.64 (t, *J* = 5.5 Hz, 1H; CH), 4.42 (s, 2H; CH_2), 3.63–3.73 (m, 2H; OCH_2), 3.42–3.53 (m, 2H; OCH_2), 3.39 (d, *J* = 5.5 Hz, 2H; CH_2), 2.45 (s, 3H; CH_3), 2.41 (s, 3H; CH_3), 1.16 (t, *J* = 7.1 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.5, 183.2, 146.4, 143.6, 136.6, 136.3, 134.4, 132.8, 129.7, 129.6, 129.5, 127.3, 126.9, 122.6, 121.6, 112.1, 101.6, 62.9, 51.3, 49.6, 21.6, 21.5, 15.3. MS *m/z*: 512 (M^+, 1), 357 (14), 155 (7), 103 (100). HRMS (EI): calcd for $C_{27}H_{32}N_2O_6S$ 512.1981; found 512.1996.

4.9.4. N-(2,2-diethoxyethyl)-N-{[2-(5-chloro-2-formylindol-3-yl)carbonyl]prop-2-en-1-yl}-

*4-methylbenzenesulfonamide (**15d**)*

Yield 45%. mp 123–125 °C (EtOAc-hexane). IR (ATR) ν = 3278 (NH), 1658 (CO), 1635 (CO), 1369 (SO_2), 1149 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 10.10 (s, 1H; CHO), 9.58 (br s, 1H; NH), 7.95 (s, 1H; ArH), 7.76 (d, *J* = 8.2 Hz, 2H; ArH), 7.43 (d, *J* = 8.8 Hz, 1H; ArH), 7.38 (d, *J* = 8.8 Hz, 1H; ArH), 7.30 (d, *J* = 8.2 Hz, 2H; ArH), 6.28 (s, 1H; $=CH_2$), 6.04 (s, 1H; $=CH_2$), 4.66 (t, *J* = 5.2 Hz, 1H; CH), 4.41 (s, 2H; CH_2), 3.63–3.73 (m, 2H; OCH_2), 3.42–3.53 (m, 2H; OCH_2), 3.40 (d, *J* = 5.2 Hz, 2H; CH_2), 2.41 (s, 3H; CH_3), 1.17 (t, *J* = 7.1 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 190.8, 183.3, 146.5, 143.7, 137.1, 136.5, 134.2, 129.9, 129.8, 129.0, 128.2, 127.5, 127.3, 122.8, 121.2, 113.7, 101.6, 62.9, 51.4, 49.6, 21.5, 15.3. MS *m/z*: 534 (M^++2, 1), 532 (M^+, 3), 377 (12), 155 (16), 103 (100). HRMS (EI): calcd for $C_{26}H_{29}ClN_2O_6S$ 532.1435; found 532.1421.

*4.9.5. N-(2,2-diethoxyethyl)-N-{[2-(5-fluoro-2-formylindol-3-yl)carbonyl]prop-2-en-1-yl}-4-methylbenzenesulfonamide (**15e**)*

Yield 60%. mp 142–143 °C (EtOAc-hexane). IR (ATR) ν = 3301 (NH), 1651 (CO), 1616 (CO), 1342 (SO_2), 1146 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 10.10 (s, 1H; CHO), 9.58 (br s, 1H; NH), 7.75 (d, *J* = 8.4 Hz, 2H; ArH), 7.62 (dd, *J* = 9.1, 2.6 Hz, 1H; ArH), 7.44 (dd, *J* = 9.1, 4.2 Hz, 1H; ArH), 7.31 (d, *J* = 8.4 Hz, 2H; ArH), 7.16–7.23 (m, 1H; ArH), 6.27 (s, 1H; $=CH_2$), 6.04 (s, 1H; $=CH_2$), 4.65 (t, *J* = 5.2 Hz, 1H; CH), 4.40 (s, 2H; CH_2), 3.64–3.74 (m, 2H; OCH_2), 3.44–3.54 (m, 2H; OCH_2), 3.39 (d, *J* = 5.2 Hz, 2H; CH_2), 2.41 (s, 3H; CH_3), 1.17 (t, *J* = 6.6 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.4, 183.9, 159.2 (d, $J_{C–F}$ = 240.6 Hz), 146.7, 144.1, 137.5, 136.4, 132.6, 129.7, 129.4, 127.2, 126.9, 121.8, 117.4 (d, $J_{C–F}$ = 27.4 Hz), 113.7 (d, $J_{C–F}$ = 10.0 Hz), 108.1 (d, $J_{C–F}$ = 24.9 Hz), 101.6, 63.4, 51.8, 50.4, 21.9, 15.6. MS *m/z*: 516 (M^+, 1), 361 (23), 155 (8), 103 (100). HRMS (EI): calcd for $C_{26}H_{29}FN_2O_6S$ 516.1730; found 516.1718.

*4.9.6. N-(2,2-diethoxyethyl)-N-{[2-(2-formyl-5-nitroindol-3-yl)carbonyl]prop-2-en-1-yl}-4-methylbenzenesulfonamide (**15f**)*

Yield 41%. mp 125–126 °C (EtOAc-hexane). IR (ATR) ν = 3274 (NH), 1654 (CO), 1616 (CO), 1535 (NO_2), 1352 (SO_2), 1338 (NO_2), 1153 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 10.18 (s, 1H; CHO), 9.99 (br s, 1H; NH), 8.94 (d, *J* = 2.2 Hz, 1H; ArH), 8.30 (dd, *J* = 9.0, 2.2 Hz, 1H; ArH), 7.77 (d, *J* = 8.5 Hz, 2H; ArH), 7.59 (d, *J* = 9.0 Hz, 1H; ArH), 7.32 (d, *J* = 8.5 Hz, 2H; ArH), 6.37 (s, 1H; $=CH_2$), 6.05 (s, 1H; $=CH_2$), 4.66 (t, *J* = 5.3 Hz, 1H; CH), 4.41 (s, 2H; CH_2), 3.65–3.75 (m, 2H; OCH_2), 3.45–3.55 (m, 2H; OCH_2), 3.41 (d, *J* = 5.3 Hz, 2H; CH), 2.42 (s, 3H; CH_3), 1.16 (t, *J* = 7.1 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 190.1, 183.2, 147.2, 144.0, 143.8, 138.4, 138.2, 136.1, 130.2, 129.8, 127.3, 125.9, 123.1, 122.4, 120.9, 113.0, 101.6, 62.9, 51.4, 49.6, 21.5, 15.3. MS *m/z*: 543 (M^+, 2), 387 (18), 155 (10), 103 (100). HRMS (EI): calcd for $C_{26}H_{29}N_3O_8S$ 543.1675; found 543.1687.

*4.9.7. N-(2,2-diethoxyethyl)-N-{[2-(2-formyl-5-trifluoromethylindol-3-yl)carbonyl]prop-2-en-1-yl}-4-methylbenzenesulfonamide (**15g**)*

Yield 54%. mp 134–135 °C (EtOAc-hexane). IR (ATR) ν = 3286 (NH), 1651 (CO), 1635 (CO), 1327 (SO_2), 1153 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ□= 10.14 (s, 1H; CHO), 9.83 (br s, 1H; NH), 8.31 (s, 1H; ArH), 7.75 (d, *J* = 8.4 Hz, 2H; ArH), 7.64 (d, *J* = 8.8 Hz, 1H; ArH), 7.59 (d, *J* = 8.8 Hz, 1H; ArH), 7.30 (d, *J* = 8.4 Hz, 2H; ArH), 6.33 (s, 1H; $=CH_2$), 6.04 (s, 1H; $=CH_2$), 4.65 (t, *J* = 5.5 Hz, 1H; CH), 4.41 (s, 2H; CH_2), 3.63–3.73 (m, 2H; OCH_2), 3.43–3.53 (m, 2H; OCH_2), 3.39 (d, *J* = 5.5 Hz, 2H; CH_2), 2.41 (s, 3H; CH_3), 1.16 (t, *J* = 7.2 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 190.8, 183.5, 146.9, 143.8, 137.4, 137.2, 136.3, 130.0, 129.8, 127.3, 125.8, 125.4 (q, $J_{C–F}$ = 32.5 Hz), 124.4 (q, $J_{C–F}$ = 272.8 Hz), 123.9 (q, $J_{C–F}$ = 3.1 Hz), 122.4, 121.4 (q, $J_{C–F}$ = 5.1 Hz), 113.4, 101.5, 62.8, 51.3, 49.6, 21.4, 15.2. MS *m/z*: 566 (M^+, 1), 366 (14), 155 (13), 103 (100). HRMS (EI): calcd for $C_{27}H_{29}F_3N_2O_6S$ 566.1698; found 566.1678.

*4.9.8. N-(2,2-diethoxyethyl)-N-{[2-(2-formyl-6-methoxyindol-3-yl)carbonyl]prop-2-en-1-yl}-4-methylbenzenesulfonamide (**15h**)*

Yield 66%. mp 116–117 °C (EtOAc-hexane). IR (ATR) ν = 3294 (NH), 1651 (CO), 1639 (CO), 1342 (SO_2), 1134 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 9.97 (s, 1H; CHO), 9.42 (br s, 1H; NH), 7.74–7.80 (m, 3H; ArH), 7.30 (d, *J* = 8.2 Hz, 2H; ArH), 6.92 (dd, *J* = 9.0, 2.3 Hz, 1H; ArH), 6.84 (d, *J* = 2.3 Hz, 1H; ArH), 6.28 (s, 1H; $=CH_2$), 6.07 (s, 1H; $=CH_2$), 4.63 (t, *J* = 5.6 Hz. 1H; CH), 4.40 (s, 2H; CH_2), 3.88 (s, 3H; OCH_3), 3.64–3.74 (m, 2H; OCH_2), 3.44–3.54 (m, 2H; OCH_2), 3.38 (d, *J* = 5.6 Hz, 2H; CH_2), 2.41 (s, 3H; CH_3), 1.16 (t, *J* = 6.9 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.4, 182.5, 160.3, 146.2, 143.6, 137.4, 136.6, 135.6, 129.8, 129.7, 127.3, 124.5, 122.7, 121.0, 115.0, 101.6, 93.5, 63.0, 55.6, 51.3, 49.6, 21.5, 15.2. MS *m/z*: 528 (M^+, 2), 373 (17), 155 (15), 103 (100). HRMS (EI): calcd for $C_{27}H_{32}N_2O_7S$ 528.1930; found 528.1942.

*4.9.9. N-(2,2-diethoxyethyl)-N-{[2-(2-formyl-6-methylindol-3-yl)carbonyl]prop-2-en-1-yl}-4-methylbenzenesulfonamide (**15i**)*

Yield 42%. mp 115–116 °C (EtOAc-hexane). IR (ATR) ν = 3302 (NH), 1655 (CO), 1620 (CO), 1331 (SO_2), 1153 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 10.04 (s, 1H; CHO), 9.55 (br s, 1H; NH), 7.75–7.81 (m, 3H; ArH), 7.26–7.31 (m, 3H; ArH), 7.09 (d, *J* = 8.3 Hz, 1H; ArH), 6.27 (s, 1H; $=CH_2$), 6.07 (s, 1H; $=CH_2$), 4.64 (t, *J* = 5.3 Hz, 1H; CH), 4.42 (s, 2H; CH_2), 3.63–3.73 (m, 2H; OCH_2), 3.42–3.52 (m, 2H; OCH_2), 3.40 (d, *J* = 5.3 Hz, 2H; CH_2), 2.49 (s, 3H; CH_3), 2.41 (s, 3H; CH_3), 1.16 (t, *J* = 6.8 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.5, 183.4, 146.1, 143.6, 138.2, 136.7, 136.6, 135.9, 129.7, 129.6, 127.3, 125.3, 124.5, 123.0, 122.4, 112.1, 101.6, 63.0, 51.2,

49.6, 22.0, 21.5, 15.2. MS *m/z*: 512 (M^+, 2), 357 (7), 155 (11), 103 (100). HRMS (EI): calcd for $C_{27}H_{32}N_2O_6S$ 512.1981; found 512.1986.

*4.9.10. N-(2,2-diethoxyethyl)-N-{[2-(6-chloro-2-formylindol-3-yl)carbonyl]prop-2-en-1-yl}-4-methylbenzenesulfonamide (**15j**)*

Yield 58%. mp 131–132 °C (EtOAc-hexane). IR (ATR) ν = 3278 (NH), 1651 (CO), 1635 (CO), 1327 (SO_2), 1149 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 10.08 (s, 1H; CHO), 9.73 (br s, 1H; NH), 7.88 (d, *J* = 9.0 Hz, 1H; ArH), 7.76 (d, *J* = 7.8 Hz, 2H; ArH), 7.50 (s, 1H; ArH), 7.31 (d, *J* = 7.8 Hz, 2H; ArH), 7.22 (d, *J* = 9.0 Hz, 1H; ArH), 6.32 (s, 1H; $=CH_2$), 6.05 (s, 1H; $=CH_2$), 4.63 (t, *J* = 5.5 Hz, 1H; CH), 4.40 (s, 2H; CH_2), 3.63–3.73 (m, 2H; OCH_2), 3.42–3.52 (m, 2H; OCH_2), 3.38 (d, *J* = 5.5 Hz, 2H; CH), 2.42 (s, 3H; CH_3), 1.16 (t, *J* = 7.2 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.0, 183.2, 146.4, 143.7, 136.7, 136.4, 136.2, 133.6, 129.8, 129.7, 127.3, 125.1, 124.6, 124.2, 122.1, 112.3, 101.6, 63.0, 51.4, 49.6, 21.5, 15.2. MS *m/z*: 534 (M^++ 2, 1), 532 (M^+, 3), 377 (4), 155 (13), 103 (100). HRMS (EI): calcd for $C_{26}H_{29}ClN_2O_6S$ 532.1435; found: 532.1447.

*4.9.11. N-(2,2-diethoxyethyl)-N-{[2-(6-fluoro-2-formylindol-3-yl)carbonyl]prop-2-en-1-yl}-4-methylbenzenesulfonamide (**15k**)*

Yield 45%. mp 126–127 °C (EtOAc-hexane). IR (ATR) ν = 3302 (NH), 1651 (CO), 1616 (CO), 1342 (SO_2), 1146 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 10.05 (s, 1H; CHO), 9.77 (br s, 1H; NH), 7.89-7.94 (m, 1H; ArH), 7.76 (d, *J* = 8.2 Hz, 2H; ArH), 7.31 (d, *J* = 8.2 Hz, 2H; ArH), 7.18 (dd, *J* = 8.9, 2.1 Hz, 1H; ArH), 7.18 (dt, *J* = 9.1, 2.1 Hz, 1H; ArH), 6.32 (s, 1H, $=CH_2$), 6.06 (s, 1H; $=CH_2$), 4.63 (t, *J* = 5.4 Hz, 1H; $=CH_2$), 4.40 (s, 2H; CH_2), 3.63–3.73 (m, 2H; OCH_2), 3.42–3.52 (m, 2H; OCH_2), 3.39 (d, *J* = 5.4 Hz, 2H; CH_2), 2.42 (s, 3H; CH_3), 1.16 (t, *J* = 7.0 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.1, 183.0, 163.5 (d, $J_{C–F}$ = 246.9 Hz), 146.5, 143.7, 136.9 (d, $J_{C–F}$ = 3.9 Hz), 136.4 (d, $J_{C–F}$ = 5.0 Hz), 136.3, 129.8, 129.7, 127.3, 125.2 (d, $J_{C–F}$ = 10.7 Hz), 123.2, 122.3, 112.9 (d, $J_{C–F}$ = 24.9 Hz), 101.6, 98.3 (d, $J_{C–F}$ = 26.5 Hz), 63.0, 51.4, 49.6, 21.5, 15.2. MS *m/z*: 516 (M^+, 1), 361 (22), 155 (8), 103 (100). HRMS (EI): calcd for $C_{26}H_{29}FN_2O_6S$ 516.1730; found 516.1736.

*4.9.12. N-(2,2-diethoxyethyl)-N-{[2-(2-formyl-6-nitroindol-3-yl)carbonyl]prop-2-en-1-yl}-4-methylbenzenesulfonamide (**15l**)*

Yield 46%. mp 135–136 °C (EtOAc-hexane). IR (ATR) ν = 3278 (NH), 1655 (CO), 1620 (CO), 1543 (NO_2), 1348 (SO_2), 1338 (NO_2), 1153 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 10.15 (s, 1H; CHO), 9.81 (br s, 1H; NH), 8.08 (d, *J* = 8.1 Hz, 1H; ArH), 7.79 (s, 1H; ArH), 7.75 (d, *J* = 8.4 Hz, 2H; ArH), 7.47 (d, *J* = 8.1 Hz, 1H; ArH), 7.30 (d, *J* = 8.4 Hz, 2H; ArH), 6.35 (s, 1H, $=CH_2$), 6.05 (s, 1H; $=CH_2$), 4.64 (t, *J* = 5.2 Hz, 1H; CH), 4.40 (s, 2H; CH_2), 3.63–3.71 (m, 2H; OCH_2),

3.42–3.49 (m, 2H; OCH_2), 3.39 (d, *J* = 5.2 Hz, 2H; CH_2), 2.42 (s, 3H; CH_3), 1.16 (t, *J* = 6.8 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ =190.1, 183.0, 147.2, 144.1, 148.3, 138.4, 138.1, 136.2, 130.2, 129.8, 127.4, 125.9, 123.0, 122.4, 120.9, 113.0, 101.6, 62.9, 51.4, 49.6, 21.5, 15.3. MS *m/z*: 543 (M^+, 1), 387 (10), 155 (8), 103 (100). HRMS (EI): Calcd for $C_{26}H_{29}N_3O_8S$ 543.1675; found 543.1693.

4.9.13.

*N-(2,2-diethoxyethyl)-N-{[2-(2-formyl-6-trifluoromethylindol-3-yl)carbonyl]prop-2-en-1-yl}-4-methylbenzenesulfonamide (**15m**)*

Yield 48%. mp 130-132 °C (EtOAc-hexane). IR (ATR) ν = 3290 (NH), 1651 (CO), 1635 (CO), 1330 (SO_2), 1153 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 10.15 (s, 1H; CHO), 9.73 (br s, 1H; NH), 8.09 (d, *J* = 8.7 Hz, 1H; ArH), 7.79 (s, 1H; ArH), 7.76 (d, *J* = 7.9 Hz, 2H; ArH), 7.49 (d, *J* = 8.7 Hz, 1H; ArH), 7.23 (d, *J* = 7.9 Hz, 2H; ArH), 6.35 (s, 1H; $=CH_2$), 6.05 (s, 1H; $=CH_2$), 4.63 (t, *J* = 5.3 Hz, 1H; CH), 4.40 (s, 2H; CH_2), 3.63–3.73 (m, 2H; OCH_2), 3.42–3.52 (m, 2H; OCH_2), 3.39 (d, *J* = 5.3 Hz, 2H; CH), 2.42 (s, 3H; CH_3), 1.15 (t, *J* = 7.2 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 190.8, 183.3, 146.5, 143.8, 138.0, 136.4, 134.6, 129.9, 129.8, 128.9 (q, $J_{C–F}$ = 37.9 Hz), 127.5 (q, $J_{C–F}$ = 271.1 Hz), 127.3, 127.1, 124.5, 121.6, 119.4 (q, $J_{C–F}$ = 3.6 Hz), 110.2 (q, $J_{C–F}$ = 5.5 Hz), 101.6, 63.0, 51.5, 49.6, 21.5, 15.2. MS *m/z*: 566 (M^+, 1), 387 (12), 155 (9), 103 (100). HRMS (EI): calcd for $C_{27}H_{29}F_3N_2O_6S$ 566.1698; found 566.1688.

*4.10. Synthesis of 3-Acryloyl-2-allylindoles (**16a**–**16m**)*

3-Acryloyl-2-allylindole **16a**–**16m** were prepared according to a synthetic method for **8**.

*4.10.1. N-(2,2-diethoxyethyl)-N-((2-(2-(1-hydroxyprop2-en-1-yl)-5,6-dimethoxyindol-3-yl)carbonyl) prop-2-en-1-yl)-4-methylbenzenesulfonamide (**16a**)*

Yield 57%. IR (ATR) ν = 3332 (OH), 1601 (CO), 1338 (SO_2), 1119 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 9.05 (br s, 1H; NH), 7.73 (d, *J* = 8.2 Hz, 2H; ArH), 7.47 (s, 1H; ArH), 7.26 (d, *J* = 8.2 Hz, 2H; ArH), 6.84 (s, 1H; ArH), 6.13 (ddd, *J* = 17.0, 10.0, 5.0 Hz, 1H; $CH=CH_2$), 6.10 (s, 1H; $=CH_2$), 5.97 (s, 1H; $=CH_2$), 5.60 (d, *J* = 5.0 Hz, 1H; CH), 5.50 (d, *J* = 17.0 Hz, 1H; $CH=CH_2$), 5.32 (d, *J* = 10.0 Hz, 1H; $CH=CH_2$), 4.62–4.84 (m, 1H; OH), 4.59 (t, *J* = 5.8 Hz, 1H; CH), 4.35 (s, 2H; CH_2), 3.91 (s, 3H; OCH_3), 3.87 (s, 3H; OCH_3), 3.59–3.68 (m, 2H; OCH_2), 3.39–3.47 (m, 2H; OCH_2), 3.39 (d, *J* = 5.8 Hz, 2H; CH_2), 2.39 (s, 3H; CH_3), 1.12 (t, *J* = 7.5 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 193.3, 147.5, 146.4, 145.6, 145.3, 143.5, 136.6, 136.2, 129.6, 128.5, 127.2, 125.2, 120.2, 117.0, 113.3, 103.2, 101.3, 94.3, 67.7, 62.8, 56.4, 56.1, 50.9, 50.1, 21.4, 15.2. MS *m/z*: 586 (M^+, 2), 155 (29), 103 (100). HRMS (EI): calcd for $C_{30}H_{38}N_2O_8S$ 586.2349; found 586.2336.

*4.10.2. N-(2,2-diethoxyethyl)-N-((2-(2-(1-hydroxyprop2-en-1-yl)-5-methoxyindol-3-yl)carbonyl) prop-2-en-1-yl)-4-methylbenzenesulfonamide (**16b**)*

Yield 63%. IR (ATR) ν = 3373 (OH), 1620 (CO), 1338 (SO_2), 1153 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 9.03 (br s, 1H; NH), 7.73 (d, *J* = 8.0 Hz, 2H; ArH), 7.43 (d, *J* = 1.5 Hz, 1H; ArH), 7.22–7.26 (m, 3H; ArH), 6.85 (dd, *J* = 8.2, 1.5 Hz, 1H; ArH), 6.13 (ddd, *J* = 17.3, 10.5, 5.1 Hz, 1H; $CH=CH_2$), 6.07 (s, 1H; $=CH_2$), 5.97 (s, 1H; $=CH_2$), 5.59–5.62 (m, 1H; CH), 5.52 (d, *J* = 17.3 Hz, 1H; $CH=CH_2$), 5.34 (d, *J* = 10.5 Hz, 1H; $CH=CH_2$), 4.68–4.86 (m, 1H; OH), 4.60 (t, *J* = 5.6 Hz, 1H; CH), 4.36 (s, 2H; CH_2), 3.83 (s, 3H; OCH_3), 3.60–3.70 (m, 2H; $=CH_2$), 3.42–3.49 (m, 2H; $=CH_2$), 3.40 (d, *J*= 5.6 Hz, 2H; CH_2), 2.38 (s, 3H; CH_3), 1.13 (t, *J*= 7.5 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 193.3, 155.7, 147.7, 145.1, 143.5, 136.7, 136.0, 129.6, 129.1, 127.9, 127.3, 125.3, 117.3, 113.5, 113.1, 112.3, 103.3, 101.4, 67.8, 62.9, 55.9, 50.8, 50.0, 21.5, 15.2. MS *m/z*: 556 (M^+, 3), 401 (6), 155 (14), 103 (100). HRMS (EI): calcd for $C_{29}H_{36}N_2O_7S$ 556.2243; found 556.2258.

*4.10.3. N-(2,2-diethoxyethyl)-N-((2-(2-(1-hydroxyprop2-en-1-yl)-5-methylindol-3-yl)carbonyl)prop-2-en-1-yl)-4-methylbenzenesulfonamide (**16c**)*

Yield 56%. IR (ATR) ν = 3324 (OH), 1608 (CO), 1639 (CO), 1338 (SO_2), 1157 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 9.53 (br s, 1H; NH), 7.72 (d, *J* = 8.9 Hz, 2H; ArH), 7.62 (s, 1H; ArH), 7.19–7.24 (m, 3H; ArH), 6.99 (d, *J* = 8.3 Hz, 1H; ArH), 6.08 (ddd, *J* = 15.2, 11.0, 4.8 Hz, 1H; $CH=CH_2$), 5.99 (s, 1H; $=CH_2$), 5.92 (s, 1H; $=CH_2$), 5.60–5.63 (m, 1H; CH), 5.42 (d, *J* = 15.2 Hz, 1H; $CH=CH_2$), 5.22 (d, *J* = 11.0 Hz, 1H; $CH=CH_2$), 5.06–5.12 (m, 1H; OH), 4.65 (t, *J* = 5.3 Hz, 1H; CH), 4.40 (s, 2H; CH_2), 3.61–3.71 (m, 2H; OCH_2), 3.41–3.50 (m, 2H; OCH_2), 3.40 (d, *J* = 5.3 Hz, 2H; CH_2), 2.40 (s, 3H; CH_3), 2.34 (s, 3H; CH_3), 1.14 (t, *J* = 6.7 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 193.2, 147.5, 144.8, 143.4, 136.8, 136.0, 132.6, 131.4, 129.6, 129.5, 127.2, 125.9, 124.6, 120.9, 117.1, 112.5, 111.3, 101.4, 67.8, 62.9, 50.5, 49.7, 21.6, 21.4, 15.2 MS *m/z*: 540 (M^+, 2), 385 (10), 155 (17), 103 (100). HRMS (EI): calcd for $C_{29}H_{36}N_2O_6S$ 540.2294; found 540.2286.

*4.10.4. N-(2,2-diethoxyethyl)-N-((2-(2-(5-chloro-1-hydroxyprop2-en-1-yl)indol-3-yl)carbonyl)prop-2-en-1-yl)-4-methylbenzenesulfonamide (**16d**)*

Yield 60%. IR (ATR) ν = 3345 (OH), 1616 (CO), 1338 (SO_2), 1153 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 9.17 (br s, 1H; NH), 7.77 (d, *J* = 2.0 Hz, 1H; ArH), 7.73 (d, *J* = 8.2 Hz, 2H; ArH), 7.28 (d, *J* = 8.5 Hz, 1H; ArH), 7.25 (d, *J* = 8.2 Hz, 2H; ArH), 7.16 (dd, *J* = 8.5, 2.0 Hz, 1H; ArH), 6.12 (ddd, *J* = 17.0, 10.5, 5.0 Hz, 1H; $CH=CH_2$), 5.99 (s, 1H; $=CH_2$), 5.91 (s, 1H; $=CH_2$), 5.58–5.66 (m, 1H; CH), 5.52 (d, *J* = 17.0 Hz, 1H; $CH=CH_2$), 5.34 (d, *J* = 10.5 Hz, 1H; $CH=CH_2$), 4.65 (t, *J* = 5.8 Hz, 1H; CH), 4.38 (s, 2H; CH_2), 3.63–3.73 (m, 2H; OCH_2), 3.45–3.53 (m, 2H; OCH_2), 3.39 (d,

J = 5.8 Hz, 2H; CH_2), 2.37 (s, 3H; CH_3), 1.16 (t, J = 7.5 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 192.6, 148.3, 144.9, 143.5, 136.8, 135.9, 132.7, 129.7, 128.0, 127.8, 127.2, 126.4, 123.6, 120.8, 117.4, 112.6, 101.6, 67.5, 62.9, 62.8, 50.6, 49.7, 21.4, 15.2. MS *m/z*: 562 (M^++2, 1), 560 (M^+, 2), 405 (1), 155 (10), 103 (100). HRMS (EI): calcd for $C_{28}H_{33}ClN_2O_6S$ 560.1748; found 560.1762.

*4.10.5. N-(2,2-diethoxyethyl)-N-((2-(2-(5-fluoro-1-hydroxyprop2-en-1-yl)indol-3-yl)carbonyl)prop-2-en-1-yl)-4-methylbenzenesulfonamide (**16e**)*

Yield 66%. IR (ATR) ν = 3733 (OH), 1612 (CO), 1338 (SO_2), 1153 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.89 (br s, 1H; NH), 7.72 (d, J = 8.2 Hz, 2H; ArH), 7.42 (dd, J = 10.3, 2.3 Hz, 1H; ArH), 7.26–7.31 (m, 1H; ArH), 7.26 (d, J = 8.2 Hz, 2H; ArH), 6.95 (dt, J = 8.9, 2.3 Hz, 1H; ArH), 6.07 (ddd, J = 16.0, 10.8, 5.4 Hz, 1H; $CH{=}CH_2$), 5.93 (s, 1H; $=CH_2$), 5.86 (s, 1H; $=CH_2$), 5.66–5.68 (m, 1H; CH), 5.40 (d, J = 16.0 Hz, 1H; $CH{=}CH_2$), 5.19 (d, J = 10.8 Hz, 1H; $CH{=}CH_2$), 5.06–5.12 (m, 1H; OH), 4.66 (t, J = 5.4 Hz, 1H; CH), 4.40 (s, 2H; CH_2), 3.62–3.72 (m, 2H; OCH_2), 3.43–3.51 (m, 2H; OCH_2), 3.41 (d, J = 5.4 Hz, 2H; CH_2), 2.36 (s, 3H; CH_3), 1.14 (t, J = 6.3 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 192.7, 159.4 (d, $J_{C–F}$ = 239.0 Hz), 148.8, 144.7, 143.6, 136.8, 135.7, 130.7, 129.7, 127.5, 127.2, 126.1, 117.5, 113.1 (d, $J_{C–F}$ = 5.6 Hz), 112.4 (d, $J_{C–F}$ = 10.0 Hz), 111.6 (d, $J_{C–F}$ = 26.2 Hz), 106.7 (d, $J_{C–F}$ = 25.1 Hz), 101.7, 67.6, 63.0, 50.7, 49.7, 21.5, 15.2 MS *m/z*: 544 (M^+, 1), 389 (7), 155 (22), 103 (100). HRMS (EI): calcd for $C_{28}H_{33}FN_2O_6S$ 544.2043; found 544.2056.

*4.10.6. N-(2,2-diethoxyethyl)-N-((2-(2-(1-hydroxyprop2-en-1-yl)-5-nitroindol-3-yl)carbonyl)prop-2-en-1-yl)-4-methylbenzenesulfonamide (**16f**)*

Yield 64%. IR (ATR) ν = 3237 (OH), 1619 (CO), 1523 (NO_2), 1348 (SO_2), 1334 (NO_2), 1153 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.68 (br s, 1H; NH), 8.70 (d, J = 1.5 Hz, 1H; ArH), 8.06 (dd, J = 8.5, 1.5 Hz, 1H; ArH), 7.74 (d, J = 8.3 Hz, 2H; ArH), 7.43 (d, J = 8.5 Hz, 1H; ArH), 7.25 (d, J = 8.3 Hz, 2H; ArH), 6.10 (ddd, J = 17.0, 10.3, 5.0 Hz, 1H; $CH{=}CH_2$), 6.05 (s, 1H; $=CH_2$), 5.88 (s, 1H; $=CH_2$), 5.78–5.81 (m, 1H; CH), 5.52 (d, J = 17.0 Hz, 1H; $CH{=}CH_2$), 5.32 (d, J = 10.3 Hz, 1H; $CH{=}CH_2$), 4.65 (t, J = 5.5 Hz, 1H; CH), 4.40 (s, 2H; CH_2), 4.25 (br s, 1H; OH), 3.63–3.73 (m, 2H; OCH_2), 3.45–3.53 (m, 2H; OCH_2), 3.44 (d, J = 5.5 Hz, 2H; CH_2), 2.37 (s, 3H; CH_3), 1.15 (t, J = 7.5 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 192.0, 149.9, 145.4, 143.6, 143.1, 137.3, 136.5, 135.9, 129.7, 127.3, 126.9, 126.4, 118.5, 118.1, 117.4, 113.9, 111.8, 101.6, 67.4, 62.9, 50.5, 49.7, 21.4, 15.2. MS *m/z*: 571 (M^+, 2), 416 (5), 155 (57), 103 (100). HRMS (EI): calcd for $C_{28}H_{33}N_3O_8S$ 571.1988; found 571.1982.

*4.10.7. N-(2,2-diethoxyethyl)-N-((2-(2-(1-hydroxyprop2-en-1-yl)-5-trifluoromethylindol-3-yl) carbonyl)prop-2-en-1-yl)-4-methylbenzenesulfonamide (**16g**)*

Yield 65%. IR (ATR) ν□= 3270 (OH), 1651 (CO), 1326 (SO_2), 1111 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ□= 9.08 (br s, 1H; NH), 8.13 (s, 1H; ArH), 7.71 (d, *J* = 7.9 Hz, 2H; ArH), 7.45–7.46 (m 2H; ArH), 7.22 (d, *J* = 7.9 Hz, 2H; ArH), 6.15 (ddd, *J* = 17.1, 10.2, 4.8 Hz, 1H; $CH=CH_2$), 6.07 (s, 1H; $=CH_2$), 5.93 (s, 1H; $=CH_2$), 5.75–5.78 (m, 1H; CH), 5.58 (d, *J* = 17.1 Hz, 1H; $CH=CH_2$), 5.39 (d, *J* = 10.2 Hz, 1H; $CH=CH_2$), 4.65 (t, *J* = 5.5 Hz, 1H; CH), 4.39 (d, *J* = 4.8 Hz, 2H; CH_2), 4.04 (br s, 1H; OH), 3.62–3.72 (m, 2H; OCH_2), 3.44–3.52 (m, 2H; OCH_2), 3.39 (d, *J* = 5.5 Hz, 2H; CH_2), 2.35 (s, 3H; CH_3), 1.15 (t, *J* = 7.2 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ□= 192.0, 147.8, 144.9, 143.0, 136.3, 135.4, 135.2, 129.2, 126.8, 126.3, 126.0, 125.9 (q, $J_{C–F}$ = 32.2 Hz), 124.6 (q, $J_{C–F}$ = 271.4 Hz), 124.1, 119.6 (q, $J_{C–F}$ = 3.6 Hz), 118.7 (q, $J_{C–F}$ = 3.6 Hz), 117.1, 111.5, 101.2, 66.9, 62.4, 50.1, 49.2, 21.0, 15.2. MS *m/z*: 594 (M^+, 1), 439 (7), 155 (25), 103 (100). HRMS (EI): calcd for $C_{29}H_{33}F_3N_2O_6S$ 594.2011; found 594.2023.

*4.10.8. N-(2,2-diethoxyethyl)-N-((2-(2-(1-hydroxyprop2-en-1-yl)-6-methoxyindol-3-yl)carbonyl) prop-2-en-1-yl)-4-methylbenzenesulfonamide (**16h**)*

Yield 60%. IR (ATR) ν□= 3232 (OH), 1620 (CO), 1338 (SO_2), 1157 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ□= 8.86 (br s, 1H), 7.66–7.73 (d, *J* = 8.1 Hz, 2H; ArH), 7.67 (d, *J* = 8.6 Hz, 1H; ArH), 7.23–7.26 (m, 2H; ArH), 6.80–6.84 (m, 2H; ArH), 6.13 (ddd, *J* = 16.9, 10.7, 5.1 Hz, 1H; $CH=CH_2$), 6.03 (s, 1H; $=CH_2$), 5.96 (s, 1H; $=CH_2$), 5.58-5.62 (m, 1H; CH), 5.54 (d, *J* = 16.9 Hz, 1H; $CH=CH_2$), 5.35 (d, *J* = 10.7 Hz, 1H; $CH=CH_2$), 4.64 (t, *J* = 5.1 Hz, 1H; CH), 4.54–4.57 (m, 1H; OH), 4.36 (s, 2H; CH_2), 3.82 (s, 3H; OCH_3), 3.64–3.82 (m, 2H; OCH_2), 3.43–3.49 (m, 2H; OCH_2), 3.40 (d, *J* = 5.1 Hz, 2H; CH_2), 2.38 (s, 3H CH_3), 1.14 (t, *J*= 7.5 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ□= 192.9, 156.6, 146.7, 144.7, 143.4, 136.7, 136.2, 135.3, 129.6, 127.1, 125.8, 121.9, 120.9, 116.7, 112.6, 111.7, 101.5, 94.8, 67.9, 63.0, 55.4, 50.6, 49.6, 21.4, 15.2. MS *m/z*: 556 (M^+, 2), 401 (5), 155 (10), 103 (100). HRMS (EI): calcd for $C_{29}H_{36}N_2O_7S$ 556.2243; found 556.2248.

*4.10.9. N-(2,2-diethoxyethyl)-N-((2-(2-(1-hydroxyprop2-en-1-yl)-6-methylindol-3-yl)carbonyl) prop-2-en-1-yl)-4-methylbenzenesulfonamide (**16i**)*

Yield 53%. IR (ATR) ν□= 3294 (OH), 1612 (CO), 1338 (SO_2), 1157 (SO_2) cm^{-1}. ^1H NMR ($CDCl_3$) δ□= 8.67 (br s, 1H; NH), 7.73 (d, *J* = 8.6 Hz, 2H; ArH), 7.68 (d, *J* = 8.3 Hz, 1H; ArH), 7.25 (d, *J* = 8.6 Hz, 2H; ArH), 7.15 (s, 1H; ArH), 7.00 (d, *J* = 8.3 Hz, 1H; ArH), 6.15 (ddd, *J* = 17.2, 10.4, 5.0 Hz, 1H; $CH=CH_2$), 6.04 (s, 1H; $=CH_2$), 5.97 (s, 1H; $=CH_2$), 5.59–5.61 (m, 1H; CH), 5.56 (d, *J* = 17.2 Hz, 1H; $CH=CH_2$), 5.39 (d, *J* = 10.4 Hz, 1H; $CH=CH_2$), 4.65 (t, *J* = 5.5 Hz, 1H; CH), 4.39–4.42 (m, 1H; OH), 4.39 (s, 2H; CH_2), 3.62–3.70 (m, 2H; OCH_2), 3.43–3.52 (m, 2H; OCH_2), 3.40 (d, *J* = 5.5 Hz, 2H; CH_2), 2.44 (s, 3H; CH_3), 2.38 (s, 3H; CH_3), 1.16 (t, *J* = 7.2 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ□= 193.0, 147.0, 144.8, 143.4, 136.9, 136.1, 134.7, 133.0, 129.6, 127.2,

126.0, 124.7, 123.7, 121.0, 117.0, 112.8, 111.5, 101.6, 67.8, 63.0, 50.6, 49.6, 21.5, 21.4, 15.2. MS *m/z*: 540 (M^+, 1), 385 (7), 155 (10), 103 (100). HRMS (EI): calcd for $C_{29}H_{36}N_2O_6S$ 540.2294; found 540.2286.

*4.10.10. N-(2,2-diethoxyethyl)-N-((2-(2-(6-chloro-1-hydroxyprop-2-en-1-yl)indol-3-yl)carbonyl) prop-2-en-1-yl)-4-methylbenzenesulfonamide (**16j**)*

Yield 56%. IR (ATR) ν□= 3294 (OH), 1612 (CO), 1328 (SO_2), 1154 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ□= 9.75 (br s, 1H; NH), 7.71 (d, *J* = 8.4 Hz, 2H; ArH), 7.67 (d, *J* = 8.9 Hz, 1H; ArH), 7.30 (d, *J* = 1.9 Hz, 1H; ArH), 7.24 (d, *J* = 8.4 Hz, 2H; ArH), 7.06 (dd, *J* = 8.9, 1.9 Hz, 1H; ArH), 6.08 (ddd, *J* = 17.2, 10.5, 5.3 Hz, 1H; $CH=CH_2$), 6.01 (s, 1H; $=CH_2$), 5.88 (s, 1H; $=CH_2$), 5.57–5.68 (m, 1H; CH), 5.42 (d, *J* = 17.2 Hz, 1H; $CH=CH_2$), 5.22 (d, *J* = 10.5 Hz, 1H; $CH=CH_2$), 4.91–4.95 (m, 1H; OH), 4.62 (t, *J* = 5.0 Hz, 1H; CH), 4.38 (s, 2H; CH_2), 3.61–3.71 (m, 2H; OCH_2), 3.42–3.50 (m, 2H; OCH_2), 3.39 (d, *J*= 5.0 Hz, 2H; CH_2), 2.37 (s, 3H; CH_3), 1.14 (t, *J* = 7.5 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ□= 192.8, 148.2, 144.8, 143.6, 136.6, 136.1, 134.8, 129.6, 128.6, 127.1, 126.1, 125.4, 122.4, 122.1, 116.9, 112.4, 111.6, 101.5, 67.8, 63.0, 50.7, 49.7, 21.4, 15.2. MS *m/z*: 562 (M^++2, 1), 560 (M^+, 2), 405 (3), 155 (10), 103 (100). HRMS (EI): calcd for $C_{28}H_{33}ClN_2O_6S$ 560.1748; found 560.1753.

*4.10.11. N-(2,2-diethoxyethyl)-N-((2-(2-(6-fluoro-1-hydroxyprop-2-en-1-yl)indol-3-yl)carbonyl) prop-2-en-1-yl)-4-methylbenzenesulfonamide (**16k**)*

Yield 64%. IR (ATR) ν□= 3734 (OH), 1620 (CO), 1338 (SO_2), 1153 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ□= 9.40 (br s, 1H; NH), 7.71–7.74 (m, 3H; ArH), 7.24 (d, *J* = 8.5 Hz, 2H; ArH), 7.03 (dd, *J* = 9.0, 2.2 Hz, 1H; ArH), 6.89 (dt, *J* = 9.0, 2.2 Hz, 1H; ArH), 6.09 (ddd, *J* = 16.8, 10.7, 5.2 Hz, 1H; $CH=CH_2$), 6.04 (s, 1H; $=CH_2$), 5.91 (s, 1H; $=CH_2$), 5.64–5.66 (m, 1H; CH), 5.47 (d, *J* = 16.8 Hz, 1H; $CH=CH_2$), 5.27 (d, *J* = 10.7 Hz, 1H; $CH=CH_2$), 4.71 (br s, 1H; OH), 4.65 (t, *J* = 5.5 Hz, 1H; CH), 4.39 (s, 2H; CH_2), 3.62–3.70 (m, 2H; OCH_2), 3.44–3.52 (m, 2H; OCH_2), 3.40 (d, *J* = 5.5 Hz, 2H; CH_2), 2.35 (s, 3H; CH_3), 1.16 (t, *J* = 7.2 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 192.8, 159.7 (d, $J_{C–F}$ = 243.8 Hz), 148.2, 144.7, 143.5, 136.4, 136.2 (d, $J_{C–F}$ = 4.8 Hz), 134.6 (d, $J_{C–F}$ = 11.2 Hz), 129.5, 127.0, 125.7, 123.2, 122.0 (d, $J_{C–F}$ = 9.7 Hz), 116.5, 112.1, 110.2 (d, $J_{C–F}$ = 24.3 Hz), 101.4, 97.9 (d, $J_{C–F}$ = 27.4 Hz), 67.9, 62.9, 50.6, 49.6, 21.2 15.0. MS *m/z*: 544 (M^+, 3), 389 (4), 155 (40), 103 (100). HRMS (EI): calcd for $C_{28}H_{33}FN_2O_6S$ 544.2043; found 544.2048.

*4.10.12. N-(2,2-diethoxyethyl)-N-((2-(2-(1-hydroxyprop-2-en-1-yl)-6-nitroindol-3-yl)carbonyl) prop-2-en-1-yl)-4-methylbenzenesulfonamide (**16l**)*

Yield 72%. IR (ATR) ν□= 3733 (OH), 1620 (CO), 1523 (NO_2), 1348 (SO_2), 1334 (NO_2), 1153 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 8.98 (br s, 1H; NH), 7.71–7.74 (m, 3H; ArH), 7.36 (d,

J = 1.8 Hz, 1H; ArH), 7.25 (d, *J* = 8.2 Hz, 2H; ArH), 7.13 (dd, *J* = 8.6, 1.8Hz, 1H; ArH), 6.12 (ddd, *J* = 16.5, 10.3, 5.1 Hz, 1H; $CH=CH_2$), 6.06 (s, 1H; $=CH_2$), 5.94 (s, 1H; $=CH_2$), 5.64–5.66 (m, 1H; CH), 5.55 (d, *J* = 16.5 Hz, 1H; $CH=CH_2$), 5.37 (d, *J* = 10.3 Hz, 1H; $CH=CH_2$), 4.63 (t, *J* = 5.3 Hz, 1H; CH), 4.37 (s, 2H; CH_2), 4.26 (br s, 1H; OH), 3.62–3.69 (m, 2H; OCH_2), 3.44–3.49 (m, 2H; OCH_2), 3.38 (d, *J* = 5.3 Hz, 2H; CH_2), 2.39 (s, 3H; CH_3), 1.15 (t, *J* = 6.9 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ□= 192.1, 149.8, 145.3, 143.6, 143.1, 137.3, 136.5, 135.9, 129.7, 127.3, 126.9, 126.4, 118.5, 118.1, 117.4, 113.9, 111.8, 101.5, 67.4, 62.9, 50.5, 49.7, 21.4, 15.2. MS *m/z*: 571 (M^+, 1), 416 (1), 155 (30), 103 (100). HRMS (EI): calcd for $C_{28}H_{33}N_3O_8S$ 571.1988; found 571.1998.

*4.10.13. N-(2,2-diethoxyethyl)-N-((2-(2-(1-hydroxyprop2-en-1-yl)-6-trifluoromethylindol-3-yl) carbonyl)prop-2-en-1-yl)-4-methylbenzenesulfonamide (**16m**)*

Yield 53%. IR (ATR) ν□= 3116 (OH), 1635 (CO), 1331 (SO_2), 1115 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ□= 9.60 (br s, 1H; NH), 7.85 (d, *J* = 8.5 Hz, 1H; ArH), 7.72 (d, *J* = 8.3 Hz, 2H; ArH), 7.64 (s, 1H; ArH), 7.36 (d, *J* = 8.5 Hz, 1H; ArH), 7.25 (d, *J* = 8.3 Hz, 2H; ArH), 6.11 (ddd, *J* = 17.0, 10.4, 4.8 Hz, 1H; $CH=CH_2$), 6.07 (s, 1H; $=CH_2$), 5.91 (s, 1H; $=CH_2$), 5.57–5.73 (m, 1H; CH), 5.49 (d, *J* = 17.0 Hz, 1H; $CH=CH_2$), 5.30 (d, *J* = 10.4 Hz, 1H; $CH=CH_2$), 4.63 (t, *J* = 5.2 Hz, 1H; CH), 4.58 (br s, 1H; OH), 4.39 (s, 2H; CH_2), 3.62–3.72 (m, 2H; OCH_2), 3.43–3.51 (m, 2H; OCH_2), 3.40 (d, *J* = 5.2 Hz, 2H, CH_2), 2.38 (s, 3H; CH_3), 1.15 (t, *J* = 7.2 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 192.7, 149.5, 145.0, 143.6, 136.6, 135.8, 133.2, 129.7, 129.2, 127.2, 126.7, 125.1 (q, $J_{C–F}$ = 32.9 Hz), 124.4 (q, $J_{C–F}$ = 272.5 Hz), 121.8, 118.5 (q, $J_{C–F}$ = 5.0 Hz), 117.4, 112.8, 109.1 (q, $J_{C–F}$ = 5.0 Hz), 101.6, 67.6, 63.1, 50.8, 49.7, 21.5, 15.2. MS *m/z*: 594 (M^+, 1), 439 (5), 155 (32), 103 (100). HRMS (EI): calcd for $C_{29}H_{33}F_3N_2O_6S$ 594.2011; found 594.2032.

*4.11. Synthesis of Carbazole-1,4-quinones (**17a–17m**)*

Carbazole-1,4-quinones **17a**–**17m** were prepared according to a synthetic method for **13**.

*4.11.1. N-(2,2-diethoxyethyl)-N-(6,7-dimethoxyl-1,4-dioxocarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**17a**)*

Yield 65%. mp 210–212 °C (EtOAc-hexane). IR (ATR) ν = 3263 (NH), 1627 (CO), 1601 (CO), 1350 (SO_2), 1161 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.05 (br s, 1H; NH), 7.72 (d, *J* = 8.2 Hz, 2H; ArH), 7.46 (s, 1H; ArH), 7.28 (d, *J* = 8.2 Hz, 2H; ArH), 6.93 (s, 1H; ArH), 6.66 (t, *J* = 1.8 Hz, 1H; ArH), 4.61 (t, *J* = 5.5 Hz, 1H; CH), 4.39 (d, *J* =1.8 Hz 2H; CH_2), 3.98 (s, 3H; OCH_3), 3.97 (s, 3H; OCH_3), 3.60–3.71 (m, 2H; OCH_2), 3.43–3.51 (m, 2H; OCH_2), 3.36 (d, *J* = 5.5 Hz, 2H; CH_2), 2.38 (s, 3H; CH_3), 1.13 (t, *J* = 7.2 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.1, 178.9, 155.1, 149.1, 145.7, 143.8, 136.2, 133.5, 133.0, 132.1, 129.8, 127.3, 117.9, 117.1, 101.9,

101.8, 94.6, 63.1, 56.2, 56.1, 52.1, 48.3, 21.4, 15.2. MS *m/z*: 556 (M^+, 3), 270 (10), 155 (40), 103 (100). HRMS (EI): calcd for $C_{28}H_{32}N_2O_8S$ 556.1879; found 556.1887.

*4.11.2. N-(2,2-diethoxyethyl)-N-(6-methoxy-1,4-dioxocarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**17b**)*

Yield 64%. mp 186–188 °C (EtOAc-hexane). IR (ATR) ν = 3244 (NH), 1635 (CO), 1608 (CO), 1342 (SO_2), 1165 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 9.54 (br s, 1H; NH), 7.73 (d, *J* = 8.5 Hz, 2H; ArH), 7.54 (d, *J* = 2.0 Hz, 1H; ArH), 7.41 (d, *J* = 8.2 Hz, 1H; ArH), 7.29 (d, *J* = 8.5 Hz, 2H; ArH), 7.05 (dd, *J* = 8.2, 2.0 Hz, 1H; ArH), 6.67 (t, *J* = 2.0 Hz, 1H; ArH), 4.62 (t, *J* = 5.5 Hz, 1H; CH), 4.42 (d, *J* = 2.0 Hz, 2H; CH_2), 3.89 (s, 3H; OCH_3), 3.61–3.71 (m, 2H; OCH_2), 3.43–3.51 (m, 2H; OCH_2), 3.35 (d, *J* = 5.5 Hz, 2H; CH_2), 2.37 (s, 3H; CH_3), 1.14 (t, *J* = 7.2 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.8, 179.6, 157.7, 146.6, 143.8, 136.3, 135.2, 132.3, 131.6, 129.8, 127.3, 125.1, 119.0, 116.5, 114.0, 102.3, 102.0, 63.2, 55.7, 52.2, 48.4, 21.4, 15.2. MS *m/z*: 526 (M^+, 1), 240 (7), 155 (19), 103 (100). HRMS (EI): calcd for $C_{27}H_{30}N_2O_7S$ 526.1774; found 526.1782.

*4.11.3. N-(2,2-diethoxyethyl)-N-(6-methyl-1,4-dioxocarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**17c**)*

Yield 61%. mp 151–153 °C (EtOAc-hexane). IR (ATR) ν = 3217 (NH), 1651 (CO), 1647 (CO), 1338 (SO_2), 1161 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 9.92 (br s, 1H; NH), 7.92 (s, 1H; ArH), 7.74 (d, *J* = 8.1 Hz, 2H; ArH), 7.44 (d, *J* = 8.4 Hz, 1H; ArH), 7.29 (d, *J* = 8.1 Hz, 2H; ArH), 7.23 (d, *J* = 8.4 Hz, 1H; ArH), 6.69 (t, *J* = 1.8 Hz, 1H; ArH), 4.62 (t, *J* = 5.4 Hz, 1H; CH), 4.42 (d, *J* = 1.8 Hz, 2H; CH_2), 3.61–3.71 (m, 2H; OCH_2), 3.41–3.51 (m, 2H; OCH_2), 3.37 (d, *J* = 5.4 Hz, 2H; CH_2), 2.48 (s, 3H, CH_3), 2.36 (s, 3H; CH_3), 1.14 (t, *J* = 7.2 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.8, 180.0, 146.7, 143.8, 136.2, 135.7, 135.1, 134.4, 131.5, 129.8, 129.1, 127.3, 124.3, 122.1, 116.3, 122.8, 101.9, 101.8, 63.1, 52.2, 48.5, 21.4, 15.3. MS *m/z*: 510 (M^+, 6), 224 (5), 155 (10), 103 (100). HRMS (EI): calcd for $C_{27}H_{30}N_2O_6S$ 510.1825; found 510.1849.

*4.11.4. N-(2,2-diethoxyethyl)-N-(6-chloro-1,4-dioxocarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**17d**)*

Yield 58%. mp 183–184 °C (EtOAc-hexane). IR (ATR) ν = 3286 (NH), 1662 (CO), 1648 (CO), 1338 (SO_2), 1157 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 9.72 (br s, 1H; NH), 8.14 (d, *J* = 1.8 Hz, 1H; ArH), 7.74 (d, *J* = 8.3 Hz, 2H; ArH), 7.46 (d, *J* = 8.9 Hz, 1H; ArH), 7.37 (dd, *J* = 8.9, 1.8 Hz, 1H; ArH), 7.30 (d, *J* = 8.3 Hz, 2H; ArH), 6.76 (t, *J* = 2.0 Hz, 1H; ArH), 4.60 (t, *J* = 5.6 Hz, 1H; CH), 4.41 (d, *J* = 2.0 Hz, 2H; CH_2), 3.61–3.71 (m, 2H; OCH_2), 3.40–3.50 (m, 2H; OCH_2), 3.35 (d, *J* = 5.6 Hz, 2H; CH_2), 2.39 (s, 3H, CH_3), 1.13 (t, *J* = 7.7 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.3, 179.8, 147.1, 143.9, 136.1, 136.0, 135.4, 131.6, 130.4, 129.9, 127.8, 127.3, 124.8,

122.2, 116.2, 114.2, 101.8, 63.1, 52.2, 48.5, 21.5, 15.2. MS *m/z*: 532 (M^++2, 1), 530 (M^+, 4), 244 (9), 155 (23), 103 (100). HRMS (EI): calcd for $C_{26}H_{27}ClN_2O_6S$ 530.1278; found 530.1296.

*4.11.5. N-(2,2-diethoxyethyl)-N-(6-fluoro-1,4-dioxocarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**17e**)*

Yield 62%. mp 199–200 °C (EtOAc-hexane). IR (ATR) ν = 3236 (NH), 1639 (CO), 1628 (CO), 1338 (SO_2), 1157 (SO_2) cm^{-1}. H NMR (300 MHz, $CDCl_3$) δ = 9.35 (br s, 1H; NH), 7.81 (dd, *J* = 8.8, 2.5 Hz, 1H; ArH), 7.73 (d, *J* = 8.5 Hz, 2H; ArH), 7.47 (dd, *J* = 9.1, 4.3 Hz, 1H; ArH), 7.30 (d, *J* = 8.5 Hz, 2H; ArH), 7.18 (dt, *J* = 9.1, 2.5 Hz, 1H; ArH), 6.75 (t, *J* = 2.1 Hz, 1H; ArH), 4.60 (t, *J* = 5.0 Hz, 1H; CH), 4.41 (d, *J* = 2.1 Hz, 2H; CH_2), 3.61–3.70 (m, 2H; OCH_2), 3.40–3.50 (m, 2H; OCH_2), 3.34 (d, *J* = 5.0 Hz, 2H; CH_2), 2.38 (s, 3H; CH_3), 1.13 (t, *J* = 7.1 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.4, 179.6, 158.8, 147.0, 143.9, 136.4, 136.2, 133.5, 131.5, 129.9, 127.3, 124.6 (d, $J_{C–F}$ = 11.1 Hz), 116.3 (d, $J_{C–F}$ = 27.7 Hz), 114.1 (d, $J_{C–F}$ = 10.1 Hz), 107.7 (d, $J_{C–F}$ = 26.5 Hz), 101.9, 63.2, 52.3, 48.5, 21.5, 15.2. MS *m/z*: 514 (M^+, 3), 228 (6), 155 (14), 103 (100). HRMS (EI): calcd for $C_{26}H_{27}FN_2O_6S$ 514.1574; found 514.1566.

*4.11.6. N-(2,2-diethoxyethyl)-N-(6-nitro-1,4-dioxocarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**17f**)*

Yield 66%. mp 113–115 °C (EtOAc-hexane). IR (ATR) ν = 3236 (NH), 1643 (CO), 1624 (CO), 1543 (NO_2), 1342 (SO_2), 1323 (NO_2), 1157 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.47 (br s, 1H, NH), 9.00 (d, *J* = 1.5 Hz, 1H; ArH), 8.29 (dd, *J* = 8.4, 1.5 Hz, 1H; ArH), 7.79 (d, *J* = 8.8 Hz, 2H; ArH), 7.67 (d, *J* = 8.4 Hz, 1H; ArH), 7.36 (d, *J* = 8.8 Hz, 2H; ArH), 6.88 (t, *J* = 2.0 Hz, 1H; ArH), 4.61 (t, *J* = 5.4 Hz, 1H; CH), 4.41 (d, *J* = 2.0 Hz, 2H; CH_2), 3.61–3.71 (m, 2H; OCH_2), 3.40–3.48 (m, 2H; OCH_2), 3.36 (d, *J* = 5.4 Hz, 2H; CH_2), 2.43 (s, 3H, CH_3), 1.12 (t, *J* = 7.5 Hz, 6H, CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ =181.9, 179.6, 147.4, 144.9, 144.2, 139.6, 137.8, 135.7, 131.6, 130.0, 127.3, 123.1, 122.1, 119.6, 117.9, 113.7, 101.6, 63.1, 52.2, 48.4, 21.5, 15.2. MS *m/z*: 541 (M^+, 2), 255 (9), 155 (56), 103 (100). HRMS (EI): calcd for $C_{26}H_{27}N_3O_8S$ 541.1519; found 541.1531.

*4.11.7. N-(2,2-diethoxyethyl)-N-(1,4-dioxo-6-trifluoromethylcarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**17g**)*

Yield 61%. mp 102–104 °C (EtOAc-hexane). IR (ATR) ν = 3251 (NH), 1666 (CO), 1643 (CO), 1346 (SO_2), 1119 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.74 (br s, 1H; NH), 8.48 (s, 1H; ArH), 7.74 (d, *J* = 8.3 Hz, 2H; ArH), 7.56–7.68 (m, 2H; ArH), 7.31 (d, *J* = 8.3 Hz, 2H; ArH), 6.81 (t, *J* = 2.0 Hz, 1H; ArH), 4.61 (t, *J* = 5.4 Hz, 1H; CH), 4.42 (d, *J* = 2.0 Hz, 2H; CH_2), 3.61–3.71 (m, 2H; OCH_2), 3.40–3.51 (m, 2H; OCH_2), 3.35 (d, *J* = 5.4 Hz, 2H; CH_2), 2.39 (s, 3H; CH_3), 1.13 (t, *J* =

7.2 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.4, 179.7, 147.1, 144.0, 138.1, 136.6, 135.9, 131.6, 129.9, 127.3, 128.6 (q, $J_{C–F}$ = 31.1 Hz), 126.9, 126.2, 124.6 (q, $J_{C–F}$ = 276.2 Hz), 123.8 (q, $J_{C–F}$ = 3.1 Hz), 123.2, 120.8 (q, $J_{C–F}$ = 4.6 Hz), 117.1, 63.1, 52.3, 48.5, 21.5, 15.2□ MS *m/z*: 564 (M^+, 7), 278 (13), 155 (44), 103 (100). HRMS (EI): calcd for $C_{27}H_{27}F_3N_2O_6S$ 564.1542; found 564.1536.

*4.11.8. N-(2,2-diethoxyethyl)-N-(7-methoxy-1,4-dioxocarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**17h**)*

Yield 60%. mp 101–103 °C (EtOAc-hexane). IR (ATR) ν = 3232 (NH), 1639 (CO), 1624 (CO), 1346 (SO_2), 1157 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.18 (br s, 1H; NH), 8.02 (d, *J* = 8.5 Hz, 1H; ArH), 7.72 (d, *J* = 8.5 Hz, 2H; ArH), 7.28 (d, *J* = 8.5 Hz, 2H; ArH), 6.99 (dd, *J* = 8.5, 2.0 Hz, 1H; ArH), 6.87 (d, *J* = 2.0 Hz, 1H; ArH), 6.64 (t, *J* = 2.0 Hz, 1H; ArH), 4.61 (t, *J* = 5.5 Hz, 1H; CH), 4.39 (d, *J* = 2.0 Hz, 2H; CH_2), 3.89 (s, 3H; OCH_3), 3.61–3.71 (m, 2H; OCH_2), 3.41–3.51 (m, 2H; OCH_2), 3.34 (d, *J* = 5.5 Hz, 2H; CH_2), 2.37 (s, 3H; CH_3), 1.13 (t, *J* = 6.8 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.0, 179.3, 160.0, 145.9, 143.8, 138.7, 136.2, 134.4, 131.6, 129.8, 127.3, 123.5, 118.3, 117.3, 115.8, 101.9, 94.5, 63.1, 55.6, 52.2, 48.4, 21.4, 15.2. MS *m/z*: 526 (M^+, 3), 240 (6), 155 (20), 103 (100). HRMS (EI): calcd for $C_{27}H_{30}N_2O_7S$ 526.1774; found 526.1778.

*4.11.9. N-(2,2-diethoxyethyl)-N-(7-methyl-1,4-dioxocarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**17i**)*

Yield 53%. mp 107–108 °C (EtOAc-hexane). IR (ATR) ν = 3228 (NH), 1647 (CO), 1631 (CO), 1338 (SO_2), 1161 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.40 (br s, 1H; NH), 8.02 (d, *J* = 8.7 Hz, 1H; ArH), 7.72 (d, *J* = 8.1 Hz, 2H; ArH), 7.26–7.30 (m, 3H; ArH), 7.17 (dd, *J* = 8.7, 1.2 Hz, 1H; ArH), 6.68 (t, *J* = 1.9 Hz, 1H; ArH), 4.61 (t, *J* = 5.2 Hz, 1H; CH), 4.41 (d, *J* = 2.0 Hz, 2H; CH_2), 3.61–3.71 (m, 2H; OCH_2), 3.41–3.48 (m, 2H; CH_2), 3.35 (d, *J* = 5.2 Hz. 2H; CH_2), 2.50 (s, 3H; CH_3), 2.36 (s, 3H; CH_3), 1.13 (t, *J* = 7.0 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.8, 179.9, 146.4, 143.8, 137.8, 136.2, 134.8, 131.5, 129.8, 127.4, 127.3, 126.5, 122.3, 121.9, 116.9, 112.7, 101.9, 63.1, 52.2, 48.4, 22.0, 21.4, 15.2. MS *m/z*: 510 (M^+, 3), 224 (2), 155 (17), 103 (100). HRMS (EI): calcd for $C_{27}H_{30}N_2O_6S$ 510.1825; found 510.1833.

*4.11.10. N-(2,2-diethoxyethyl)-N-(7-chloro-1,4-dioxocarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**17j**)*

Yield 52%. mp 139–140 °C (EtOAc-hexane). IR (ATR) ν = 3290 (NH), 1647 (CO), 1620 (CO), 1338 (SO_2), 1157 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.74 (br s, 1H; NH), 8.06 (d, *J* = 8.9 Hz, 1H; ArH), 7.74 (d, *J* = 8.2 Hz, 2H; ArH), 7.55 (s, 1H; ArH), 7.27–7.33 (m, 3H; ArH), 6.75 (t, *J* = 1.9 Hz, 1H; ArH), 4.62 (t, *J* = 5.8 Hz, 1H; CH), 4.41 (d, *J* = 1.9 Hz, 2H; CH_2), 3.62–3.72 (m, 2H;

OCH_2), 3.41–3.51 (m, 2H; OCH_2), 3.35 (d, J = 5.8 Hz, 2H; CH_2), 2.39 (s, 3H; CH_3), 1.14 (t, J = 7.7 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.5, 179.8, 146.8, 144.0, 137.6, 136.0, 135.6, 133.2, 131.5, 129.9, 127.4, 125.3, 1238, 122.4, 116.7, 113.0, 101.7, 63.2, 52.2, 48.5, 21.5, 15.2. MS *m/z*: 532 (M^++2, 2), 530 (M^+, 4), 244 (3), 155 (10), 103 (100). HRMS (EI): calcd for $C_{26}H_{27}ClN_2O_6S$ 530.1278; found 530.1263.

*4.11.11. N-(2,2-diethoxyethyl)-N-(7-fluoro-1,4-dioxocarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**17k**)*

Yield 60%. mp 130–131 °C (EtOAc-hexane). IR (ATR) ν = 3236 (NH), 1639 (CO), 1628 (CO), 1338 (SO_2), 1157 (SO_2) cm^{-1}. H NMR (300 MHz, $CDCl_3$) δ = 9.91 (br s, 1H; NH), 8.07–8.11 (m, 1H; ArH), 7.74 (d, J = 7.6 Hz, 2H; ArH), 7.31 (d, J = 7.6 Hz, 2H; ArH), 7.21–7.23 (m, 1H; ArH), 7.11 (t, J = 8.8 Hz, 1H; ArH), 6.72 (t, J = 1.8 Hz, 1H; ArH), 4.62 (t, J = 4.9 Hz, 1H; CH), 4.41 (d, J = 1.8 Hz, 2H; CH_2), 3.62–3.71 (m, 2H; OCH_2), 3.43–3.51 (m, 2H; OCH_2), 3.34 (d, J = 5.0 Hz, 2H; CH_2), 2.38 (s, 3H; CH_3), 1.13 (t, J = 7.1 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.6, 179.7, 162.1 (d, $J_{C–F}$ = 246.0 Hz), 146.6, 143.9, 137.8 (d, $J_{C–F}$ = 12.6 Hz), 136.0, 135.6 (d, $J_{C–F}$ = 2.8 Hz), 131.4, 129.9, 127.3, 124.0 (d, $J_{C–F}$ = 9.7 Hz), 120.4, 116.8, 113.8 (d, $J_{C–F}$ = 25.9 Hz), 101.8, 99.4 (d, $J_{C–F}$ = 26.0 Hz), 63.2, 52.2, 48.4, 21.4, 15.2. MS *m/z*: 514 (M^+, 2), 228 (8), 155 (22), 103 (100). HRMS (EI): calcd for $C_{26}H_{27}FN_2O_6S$ 514.1574; found 514.1568.

*4.11.12. N-(2,2-diethoxyethyl)-N-(7-nitro-1,4-dioxocarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**17l**)*

Yield 72%. mp 168–171 °C (EtOAc-hexane). IR (ATR) ν = 3236 (NH), 1643 (CO), 1624 (CO), 1543 (NO_2), 1346 (SO_2), 1335 (NO_2), 1161 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.44 (br s, 1H; NH), 8.12 (dd, J = 8.7, 5.3 Hz, 1H; ArH), 7.72 (d, J = 8.2 Hz, 2H; ArH), 7.28 (d, J = 8.2 Hz, 2H; ArH), 7.08–7.19 (m, 2H; ArH), 6.70 (t, J = 1.8 Hz, 1H; ArH), 4.61 (t, J = 5.1 Hz, 1H; CH), 4.41 (d, J = 1.8 Hz;, 2H; CH_2), 3.61–3.69 (m, 2H; OCH_2), 3.43–3.51 (m, 2H; OCH_2), 3.34 (d, J = 5.1 Hz, 2H; CH_2), 2.38 (s, 3H; CH_3), 1.13 (t, J = 7.3 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.5, 179.8, 146.8, 144.0, 137.6, 136.0, 135.6, 133.2, 131.5, 129.9, 127.4, 125.3, 123.8, 122.4, 116.7, 113.0, 101.7, 63.2, 52.2, 48.4, 21.5, 15.2. MS *m/z*: 541 (M^+, 5), 255 (8), 155 (36), 103 (100). HRMS (EI): calcd for $C_{26}H_{27}N_3O_8S$ 541.1519; found 541.1526.

*4.11.13. N-(2,2-diethoxyethyl)-N-(1,4-dioxo-7-trifluoromethylcarbazol-3-ylmethyl)-4-methylbenzenesulfonamide (**17m**)*

Yield 53%. mp 108–109 °C (EtOAc-hexane). IR (ATR) ν = 3255 (NH), 1666 (CO), 1647 (CO), 1335 (SO_2), 1153 (SO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.85 (br s, 1H; NH), 8.28 (d, J = 9.0 Hz, 1H; ArH), 7.82 (s, 1H; ArH), 7.75 (d, J = 8.3 Hz, 2H; ArH), 7.57 (d, J = 9.0 Hz, 1H; ArH), 7.31

(d, *J* = 8.3 Hz, 2H; ArH), 6.81 (t, *J* = 2.0 Hz, 1H; ArH), 4.61 (t, *J* = 5.4 Hz, 1H; CH), 4.42 (d, *J* = 2.0 Hz, 2H; CH_2), 3.61–3.71 (m, 2H; OCH_2), 3.41–3.49 (m, 2H; OCH_2), 3.34 (d, *J* = 5.4 Hz, 2H; CH_2), 2.39 (s, 3H; CH_3), 1.13 (t, *J* = 6.9 Hz, 6H; CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.4, 179.7, 147.3, 144.0, 137.1, 136.0, 135.9, 131.6, 129.9, 128.5 (q, $J_{C–F}$ = 31.8 Hz), 127.3, 126.0, 123.6 (q, $J_{C–F}$ = 274.8 Hz), 120.8, 120.7 (q, $J_{C–F}$ = 3.7 Hz), 116.0, 110.3 (q, $J_{C–F}$ = 3.9 Hz), 101.4, 62.7, 51.9, 48.1, 21.0, 13.7. MS *m/z*: 564 (M^+, 3), 278 (2), 155 (17), 103 (100). HRMS (EI): calcd for $C_{27}H_{27}F_3N_2O_6S$ 564.1542; found 564.1548.

*4.12. Synthesis of Ellipticine quinones (**18a**–**18m**)*

Ellipticine quinones **18a**–**18m** were prepared according to a synthetic method for **2**.

*4.12.1. 8,9-dimethoxyellipticine quinone (**18a**)*

Yield 65%. mp 310–312 °C (EtOAc-hexane). IR (ATR) ν = 3097 (NH), 1666 (CO), 1650 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 13.05 (br s, 1H; NH), 9.21 (s, 1H; ArH), 9.04 (d, *J* = 4.7 Hz, 1H; ArH), 7.90 (d, *J* = 4.7 Hz, 1H; ArH), 7.54 (s, 1H; ArH), 6.96 (s, 1H; ArH), 3.88 (s, 3H; OCH_3), 3.87 (s, 3H; OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.1, 176.5, 157.3, 155.1, 147.4, 138.6, 136.7, 133.9, 126.7, 124.7, 122.9, 119.1, 118.4, 115.2, 102.1, 55.5 (× 2). MS *m/z*: 308 (M^+, 100), 247 (52). HRMS (EI): calcd for $C_{17}H_{12}N_2O_4$ 308.0797; found 308.0788.

*4.12.2. 9-methoxyellipticine quinone (**18b**)*

Yield 71%. mp 323–325 °C (EtOAc-hexane). IR (ATR) ν = 3012 (NH), 1666 (CO), 1631 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 13.17 (br s, 1H; NH), 9.23 (s, 1H; ArH), 9.04 (d, *J* = 5.0 Hz, 1H; ArH), 7.91 (d, *J* = 5.0 Hz, 1H; ArH), 7.59 (d, *J* = 2.6 Hz, 1H; ArH), 7.51 (d, *J* = 8.6 Hz, 1H; ArH), 7.11 (dd, *J* = 8.6, 2.6 Hz, 1H; ArH), 3.85 (s, 3H; OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.1, 176.4, 157.2, 155.0, 147.4, 138.6, 136.7, 133.9, 126.6, 125.4, 124.7, 119.1, 118.4, 115.2, 102.1, 55.4. MS *m/z*: 278 (M^+, 100), 263 (57), 247 (66). HRMS (EI): calcd for $C_{16}H_{10}N_2O_3$ 278.0691; found 278.0672.

*4.12.3. 9-methylellipticine quinone (**18c**)*

Yield 65%. mp 317–319 °C (EtOAc-hexane). IR (ATR) ν = 3059 (NH), 1666 (CO), 1651 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 13.10 (br s, 1H; NH), 9.21 (s, 1H; ArH), 9.04 (d, *J* = 4.8 Hz, 1H; ArH), 7.95 (s, 1H; ArH), 7.89 (d, *J* = 4.8 Hz, 1H; ArH), 7.46 (d, *J* = 8.9 Hz, 1H; ArH), 7.27 (d, *J* = 8.9 Hz, 1H; ArH), 2.44 (s, 3H; CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.3, 176.8, 155.1, 147.4, 138.5, 137.1, 136.9, 133.9, 129.5, 126.6, 124.1, 121.7, 118.4, 117.0, 113.7, 21.4. MS *m/z*: 262 (M^+, 100). HRMS (EI): calcd for $C_{16}H_{10}N_2O_2$ 262.0742; found 262.0751.

*4.12.4. 9-chloroellipticine quinone (**18d**)*

Yield 63%. mp 325–328 °C (EtOAc-hexane). IR (ATR) ν = 3081 (NH), 1651 (CO), 1639 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 13.40 (br s, 1H; NH), 9.23 (s, 1H; ArH), 9.06 (d, *J*=4.8 Hz, 1H; ArH), 8.11 (d, *J*=2.0 Hz, 1H; ArH), 7.92 (d, *J*=4.8 Hz, 1H; ArH), 7.60 (d, *J*=8.9 Hz, 1H; ArH), 7.47 (dd, *J*=8.9, 2.0 Hz, 1H; ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.0, 176.8, 155.2, 147.4, 138.3, 137.9, 136.8, 128.9, 127.6, 126.3, 124.5, 121.2, 118.4, 116.7, 115.8. MS *m/z*: 284 (M^++2, 33), 282 (M^+, 100), 247 (5). HRMS (EI): calcd for $C_{15}H_7ClN_2O_2$ 282.0196; found 282.0183.

*4.12.5. 9-fluoroellipticine quinone (**18e**)*

Yield 80%. mp 320–323 °C (EtOAc). IR (ATR) ν = 3033 (NH), 1670 (CO), 1651 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 13.39 (br s, 1H; NH), 9.22 (s, 1H; ArH), 9.05 (d, *J* = 4.7 Hz, 1H; ArH), 8.10 (d, *J* = 2.0 Hz, 1H; ArH), 7.90 (d, *J* = 4.7 Hz, 1H; ArH), 7.58 (d, *J* = 9.0 Hz, 1H; ArH), 7.47 (dd, *J* = 9.0, 2.0 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.5, 176.7, 160.4, 155.5, 147.6, 139.3, 138.6, 138.0, 126.6, 124.9, 124.6 (d, $J_{C–F}$ =10.4 Hz), 120.7, 118.7 (d, $J_{C–F}$ = 25.4 Hz), 113.9 (d, $J_{C–F}$ = 20.8 Hz), 99.9 (d, $J_{C–F}$ = 25.3 Hz). MS *m/z*: 266 (M^+, 100), 247 (10). HRMS (EI): calcd for $C_{15}H_7FN_2O_2$ 266.0492; found 266.0486.

*4.12.6. 9-nitroellipticine quinone (**18f**)*

Yield 62%. mp 322–325 °C (EtOAc). IR (ATR) ν = 3077 (NH), 1656 (CO), 1648 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 13.41 (br s, 1H; NH), 9.24 (s, 1H; ArH), 9.08 (d, *J* = 4.5 Hz, 1H; ArH), 8.12 (d, *J* = 1.9 Hz, 1H; ArH), 7.93 (d, *J* = 4.5 Hz, 1H; ArH), 7.59 (d, *J* = 8.8 Hz, 1H; ArH), 7.47 (dd, *J* = 8.8, 1.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.0, 176.8, 155.2, 147.4, 138.3, 137.9, 136.8, 128.8, 127.6, 126.3, 124.4, 121.2, 118.4, 116.7, 115.7. MS *m/z*: 293 (M^+, 100), 247 (4). HRMS (EI): calcd for $C_{15}H_7N_3O_4$ 293.0437; found 293.0449.

*4.12.7. 9-trifluoromethylellipticine quinone (**18g**)*

Yield 72%. mp 310–313 °C (EtOAc-hexane). IR (ATR) ν = 3051 (NH), 1674 (CO), 1651 (CO) cm^{-1}. H NMR (300 MHz, DMSO-d_6) δ = 13.63 (br s, 1H; NH), 9.28 (s, 1H; ArH), 9.10 (d, *J* = 4.9 Hz, 1H; ArH), 8.48 (s, 1H; ArH), 7.96 (d, *J* = 5.2 Hz, 1H; ArH), 7.76-7.83 (m, 2H; ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.2, 177.0, 155.4, 147.4, 139.7, 138.8, 138.3, 126.3, 125.0 (q, $J_{C–F}$ = 31.9 Hz), 124.8 (q, $J_{C–F}$ = 271.4 Hz), 123.5 (q, $J_{C–F}$ = 3.9 Hz), 122.8, 119.7 (q, $J_{C–F}$ = 3.9 Hz), 118.5, 117.7, 115.2. MS *m/z*: 316 (M^+, 100), 247 (23). HRMS (EI): calcd for $C_{16}H_7F_3N_2O_2$ 316.0460; found 316.0472.

*4.12.8. 8-methoxyellipticine quinone (**18h**)*

Yield 72%. mp 319–321 °C (EtOAc-hexane). IR (ATR) ν = 3105 (NH), 1666 (CO), 1631 (CO) cm^{-1}. H NMR (300 MHz, DMSO-d_6) δ = 13.35 (br s, 1H; NH), 9.21 (d, *J* = 1.0 Hz, 1H; ArH), 9.04 (d, *J* = 5.0 Hz, 1H; ArH), 8.06 (d, *J* = 8.9 Hz, 1H; ArH), 7.90 (dd, *J* = 5.0, 1.0 Hz, 1H; ArH), 7.04 (dd, *J* = 8.9, 2.3 Hz, 1H; ArH), 6.97 (d, *J* = 2.3 Hz, 1H; ArH), 3.84 (s, 3H; OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.4, 175.9, 159.8, 155.2, 147.2, 140.4, 138.7, 136.2, 126.5, 123.4, 118.4, 118.1, 117.9, 116.1, 95.1, 55.5. MS *m/z*: 278 (M^+, 100), 263 (50), 248 (50). HRMS (EI): calcd for $C_{16}H_{10}N_2O_3$ 278.0691; found 278.0682.

*4.12.9. 8-methylellipticine quinone (**18i**)*

Yield 72%. mp 317–320 °C (EtOAc-hexane). IR (ATR) ν = 3032 (NH), 1670 (CO), 1651 (CO) cm^{-1}. H NMR (300 MHz, DMSO-d_6) δ = 13.10 (br s, 1H; NH), 9.23 (s, 1H; ArH), 9.05 (d, *J* = 4.7 Hz, 1H; ArH), 8.08 (d, *J* = 8.2 Hz, 1H; ArH), 7.92 (d, *J* = 4.7 Hz, 1H; ArH), 7.38 (s, 1H; ArH), 7.23 (d, *J* = 8.2 Hz, 1H; ArH), 2.45 (s, 3H; CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.3, 176.7, 155.1, 147.3, 139.1, 138.5, 137.7, 136.6, 126.5, 126.4, 122.1, 121.6, 118.4, 117.6, 113.3, 21.6. MS *m/z*: 262 (M^+, 100), 247 (2). HRMS (EI): calcd for $C_{16}H_{10}N_2O_2$ 262.0742; found 262.0766.

*4.12.10. 8-chloroellipticine quinone (**18j**)*

Yield 68%. mp 323–325 °C (EtOAc-hexane). IR (ATR) ν = 3055 (NH), 1651 (CO), 1639 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ = 13.34 (br s, 1H; NH), 9.25 (s, 1H; ArH), 9.07 (d, *J* = 3.7 Hz, 1H; ArH), 8.19 (d, *J* = 8.7 Hz, 1H; ArH), 7.92 (d, *J* = 3.7 Hz, 1H; ArH), 7.60 (d, *J* = 2.0 Hz, 1H; ArH), 7.41 (dd, *J* = 8.7, 2.0 Hz, 1H; ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.2, 176.8, 155.3, 147.4, 138.8, 138.4, 137.8, 132.0, 126.4 124.9, 124.0, 122.3, 118.5, 117.4, 113.4. MS *m/z*: 284 (M^++2, 33), 282 (M^+, 100), 247 (9). HRMS (EI): calcd for $C_{15}H_7ClN_2O_2$ 282.0196; found 282.0193.

*4.12.11. 8-fluoroellipticine quinone (**18k**)*

Yield 70%. mp 320–322 °C (EtOAc-hexane). IR (ATR) ν = 3081 (NH), 1662 (CO), 1651 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ = 13.33 (br s, 1H; NH), 9.25 (s, 1H; ArH), 9.08 (d, *J* = 5.5 Hz, 1H; ArH), 8.22 (dd, *J* = 8.9, 5.8 Hz, 1H; ArH), 7.94 (d, *J* = 5.5 Hz, 1H; ArH), 7.26–7.35 (m, 2H; ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.3, 176.5, 160.1, 155.2, 147.4, 138.5 (d, $J_{C–F}$ = 32.5 Hz), 137.7 (d, $J_{C–F}$ = 2.5 Hz), 126.3 (d, $J_{C–F}$ = 4.4 Hz), 124.3 (q, $J_{C–F}$ = 9.8 Hz), 120.4, 118.4, 117.5, 113.8, 113.5, 99.8 (d, $J_{C–F}$ = 26.0 Hz). MS *m/z*: 266 (M^+, 100), 247 (6). HRMS (EI): calcd for $C_{15}H_7FN_2O_2$ 266.0492; found 266.0488.

*4.12.12. 8-nitroellipticine quinone (**18l**)*

Yield 66%. mp 320–322 °C (EtOAc-hexane). IR (ATR) ν = 3060 (NH), 1683 (CO), 1652 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ = 13.32 (br s, 1H; NH), 9.24 (s, 1H; ArH), 9.07 (d, *J* = 5.0 Hz, 1H; ArH), 8.21 (dd, *J* = 9.2, 5.6 Hz, 1H; ArH), 7.94 (d, *J* = 5.0 Hz, 1H; ArH), 7.25–7.34 (m, 2H; ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.5, 177.1, 155.6, 147.7, 139.1, 138.7, 138.0, 132.3, 126.7, 125.2, 124.3, 122.6, 118.7, 117.7, 113.7. MS *m/z*: 293 (M^+), 247 (21). HRMS (EI): calcd for $C_{15}H_7N_3O_4$ 293.0437; found 293.0421.

*4.12.13. 8-trifluoromethylellipticine quinone (**18m**)*

Yield 60%. mp 313–315 °C (EtOAc). IR (ATR) ν = 3055 (NH), 1670 (CO), 1651 (CO) cm^{-1}. H NMR (300 MHz, DMSO-d_6) δ = 13.62 (br s, 1H; NH), 9.25 (s, 1H; ArH), 9.07 (d, *J* = 4.9 Hz, 1H; ArH), 8.36 (d, *J* = 7.5 Hz, 1H; ArH), 7.93 (d, *J* = 4.9 Hz, 1H; ArH), 7.85 (s, 1H; ArH), 7.65 (d, *J* = 7.5 Hz, 1H; ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 180.1, 177.1, 155.3, 147.5, 139.1, 138.3, 137.2, 127.2 (q, $J_{C–F}$ = 31.5 Hz), 126.4, 126.0, 123.7, 123.4 (q, $J_{C–F}$ = 273.2 Hz), 120.1 (q, $J_{C–F}$ = 3.3 Hz), 118.4, 116.9, 111.2 (q, $J_{C–F}$ = 4.4 Hz). MS *m/z*: 316 (M^+), 247 (12). HRMS (EI): calcd for $C_{16}H_7F_3N_2O_2$ 316.0460; found 316.0448.

4.13. Biochemistry

4.13.1. Cell lines and cell cultures

For testing the antiproliferative cell activities, two types of cancer cell lines were used in this study: HCT-116 cells (human colon cancer) and HL-60 cells (human promyelocytic leukemia), which were purchased from the American Type Culture Collection (VA, USA). The HCT-116 and HL-60 cells were maintained in a McCOY's 5A medium with L-glutamine and 10% heat inactivated (55 °C for 30 min) fetal bovine serum (FBS) and in a RPMI-1640 medium with L-glutamine and 10% heat-inactivated FBS, respectively, at 37 °C in an atmosphere of 5% CO_2.

4.13.2. Cell viability assays

The HCT-116 cells' viability assay was conducted using the MTT method based on the procedure described by Mosmann [25]. Briefly, cells were placed in 96-well flat bottomed tissue culture plates with 3.0×10^3 cells per well in a 100 μL culture medium. This was followed by incubation at 37 °C in an atmosphere of 5% CO_2 for 24 h to allow the cells to attach onto the wells. The cells were treated with the indicated concentrations of test agents in a culture medium without FBS. Following a further 48 h incubation, 10 μL of MTT (5 mg/mL in phosphate-buffered saline) were added per well, and the plate was incubated for 4 h to allow the MTT to metabolize by cellular mitochondrial dehydrogenases. The excess MTT was aspirated and the produced formazan crystals were dissolved by adding 100 μL dimethyl sulfoxide. The absorbance of the purple formazan was read at 570 nm

using a microplate reader. The results following the test agents' exposure were calculated as a percentage relative to untreated controls.

The HL-60 cells' viability assay was conducted using the WST-1 method based on the procedure described by Ishiyama [26]. The cells were seeded in 96-well flat bottomed tissue culture plates with 2.0 x 10^4 cells per well in a 100 μL of the FBS containing culture medium with the indicated concentrations of test agents. Following a further 48 h incubation, 10 μL of a mixture of WST-1/1-methoxy phenazine methosulfate (1-methoxy PMS) solution containing 5 mM WST-1 and 0.2 mM 1-methoxy PMS in 20 mM HEPES-NaOH (pH 7.4) were added per well, and the plate was incubated for 3 h to allow the WST-1/1-methoxy PMS to metabolize by cellular mitochondrial dehydrogenases. The absorbance of the yellow formazan was read at 415 nm using a microplate reader. The results following the test agents' exposure were calculated as a percentage relative to untreated controls.

4.13.3. Statistical calculation

The concentration-cells' viability curves were fitted to a four-parametric logistic equation using a nonlinear curve-fitting program that derived the IC_{50} values (Kaleida-graph; Synergy Software, Reading, PA). Wherever appropriate, the results were expressed as means ± sem, with n = 3 or higher in at least one out of three similar experiments.

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Appendix A. Supplementary data

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

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♦The total synthesis of ellipticine quinone in four steps using tandem RCM and dehydrogenation reactions as key step have been achieved.

♦13 ellipticine quinones substituted at the 8- and/or 9-positions have been synthesized using this method.

♦The ellipticine quinones have been evaluated for their antiproliferative activity against HCT-116 and HL-60 cells.

♦The 9-nitro analog exhibited the most potent activity against both tumor cell types.