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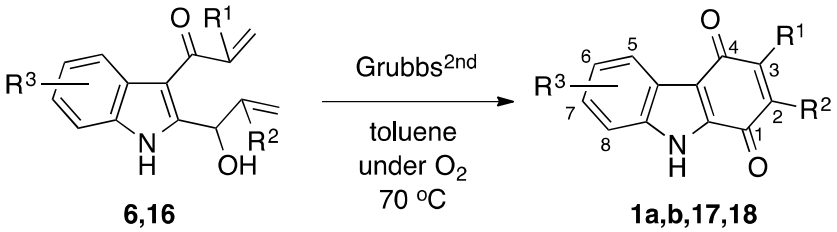
**Graphical Abstract**




**6,16** **1a,b,17,18**

# Concise Synthesis of Carbazole-1,4-quinones and Evaluation of Their Antiproliferative Activity against HCT-116 and HL-60 Cells

Takashi Nishiyama[a], Noriyuki Hatae[b]*, Teruki Yoshimura[b], Sawa Takaki[a], Takumi Abe[b], Minoru Ishikura[b], Satoshi Hibino[a], and Tominari Choshi[a]*

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Keyword: carbazole-1,4-quinone, koeniginequinone A, koeniginequinone B, antiproliferative activity

Abstract: We report a convenient synthesis of carbazole-1,4-quinone alkaloid koeniginequinones A and B using a tandem ring-closing metathesis with the dehydrogenation reaction sequence under an $O_2$ atmosphere as an important step. Using this method, carbazole-1,4-quinones substituted at the 5-, 6-, 7-, and/or 8-positions have been synthesized. Moreover, 24 compounds, including koeniginequinones A and B, have been evaluated for their antiproliferative activity against HCT-116 and HL-60 cells, and the 6-nitro analog exhibited the most potent activity against both tumor cell types.

## 1. Introduction

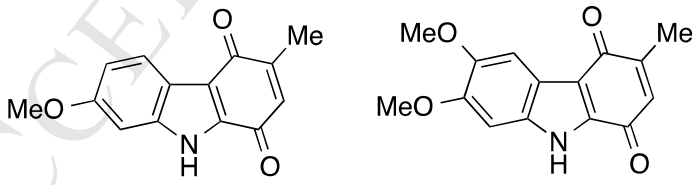
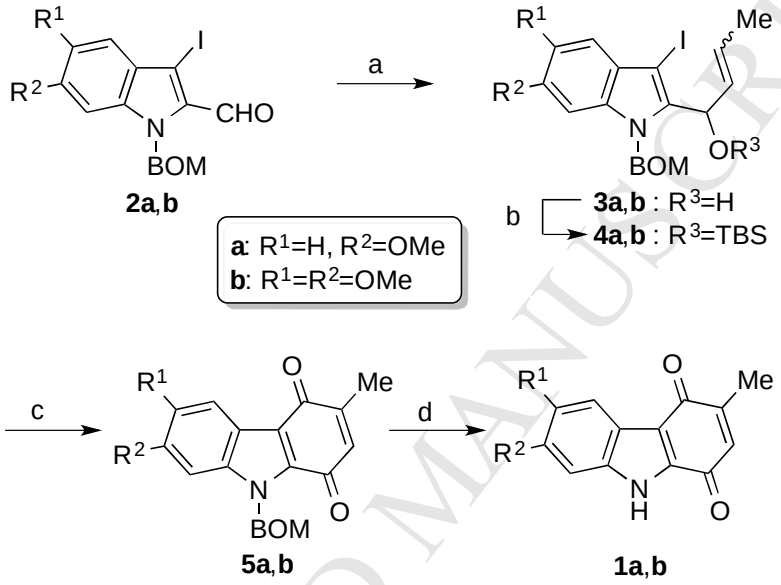



**Figure 1**. Structure of koeniginequinones A (**1a**) and B (**1b**)

The carbazole-1,4-quinone alkaloid koeniginequinones A (**1a**) and B (**1b**) were isolated from *Murraya koenigii* by Chowdhury et al. (Figure 1) who also reported the first total synthesis of these compounds [1]. This was accomplished via Fremy's salt oxidation of 1-hydroxycarbazoles, which were obtained from 1-oxotetrahydrocarbazoles. Note that koeniginequinone A (**1a**) has been also synthesized by construction of quinone moiety via either direct oxidation of 1-oxotetrahydrocarbazole with DDQ, which was reported by Kapil 's group et al. [2a], and/or CAN,

which was reported by Saha's group et al. [2b], respectively. Recently, the McErlean's group et al. described the total synthesis of **1a** using an in-water oxidation with an on-water conjugate addition process, followed by palladium-mediated ring closure [2c]. Furthermore, the Knölker's group et al. achieved the total synthesis of both **1a** and **1b** based on using a palladium(II)-catalyzed oxidative C–C bond formation of arylamino-1,4-benzoquinones [3]. We recently reported a one-pot synthesis of the carbazole-1,4-quinone framework using a cyclocarbonylation reaction, followed by desilylation and oxidation reactions [4] and completed the total synthesis of koeniginequinones A (**1a**) and B (**1b**) from *N*-BOM-3-iodoindole-2-carbaldehyde **2** in four steps (Scheme 1) [5].




**Scheme 1**. Synthesis of koeniginequinones A and B using one-pot cyclocarbonylation. Reagents and conditions: (a) propenylmagnesium bromide, THF, 0 °C; (b) TBSCl, *i*$Pr_2$NEt, $CH_2Cl_2$; (c) tributyl(vinyl)tin, CO (1 atm), BHT, $PdCl_2$(dppf), DMF, 70 °C; (d) Na, liq.$NH_3$, −78 °C .

The quinone ring system is an important core in many drugs such as mitomycin and doxorubicin, which are used clinically in cancer therapy [6]. Among the quinone-containing therapeutic agents, the carbazolequinone alkaloids exhibit cardiotonic [7], antitumor [8], neuronal cell-protecting [9], and antimalarial activities [10], in addition to other biological activities. Therefore, currently, these compounds are the focus of intensive research. The biological activities of both synthetic and natural carbazolequinones have been examined by numerous research groups.

We have been interested in the unique structure and pharmacological action of carbazolequinone alkaloids and have achieved the total synthesis of several carbazolequinones (murrayaquinone A [11], carbazomycin G [12], carquinostatin A [13], carbazoquinocins [14], carbazomadurins [15], and calothrixins [16]) using an allene-mediated electrocyclic reaction of the 6π-electron system as our original method. Moreover, we have been searching for highly active compounds that are based on these naturally occurring compounds and their derivatives [17]. Recently, we developed an efficient synthetic method for the carbazole-1,4-quinone framework using a tandem ring-closing

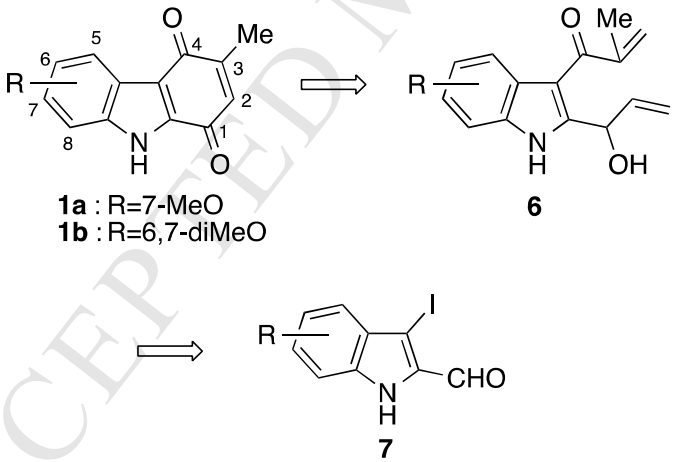
metathesis (RCM) and dehydrogenation reaction sequence and achieved the total synthesis of murrayaquinone A [18, 11c].

Herein, we describe a facile total synthesis of koeniginequinones A (**1a**) and B (**1b**) by constructing a carbazole-1,4-quinone core using a tandem RCM and dehydrogenation reaction sequence, starting from the appropriate 3-acryloyl-2-propenylindoles. In addition, we report the synthesis of carbazole-1,4-quinones substituted at the 5-, 6-, 7-, and/or 8-positions using this method. The antiproliferative activity of these synthetic compounds, and several natural products, against HCT-116 colon tumor cells and HL-60 promyelocytic leukemia cells were evaluated using the MTT and WST-1 assays, respectively.

## 2. Results and Discussion

### *2.1. Chemistry*

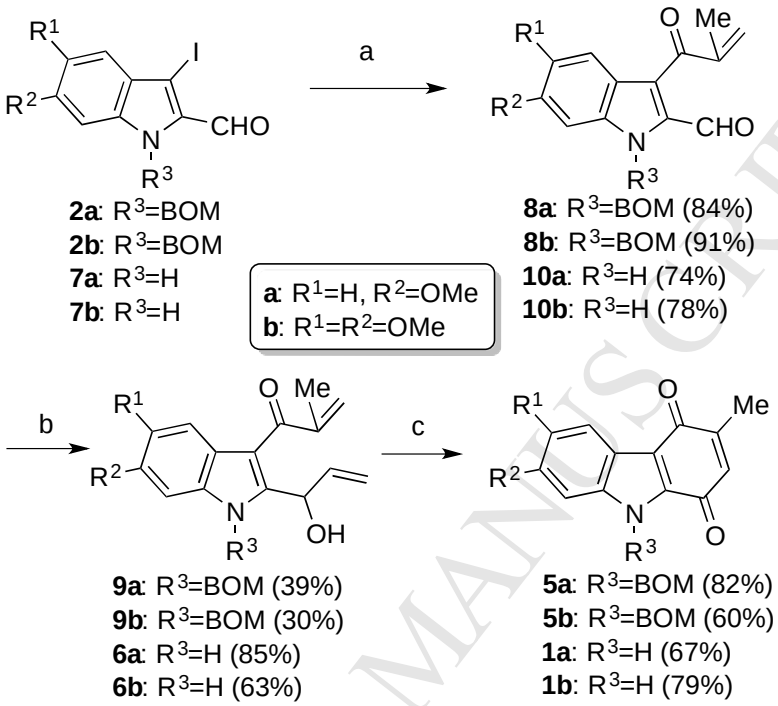
Our retrosynthetic strategy for synthesizing carbazole-1,4-quinones is illustrated in Scheme 2. In our previous study [11c], the construction of carbazole-1,4-quinone **1** from 3-acryloyl-2-propenylindole **6** was accomplished using tandem RCM and dehydroxylation reactions; furthermore, the indoles **6** could be derived from the appropriate 3-iodoindole-3-carbaldehydes **7**.




**Scheme 2**. Retrosynthetic analysis of koeniginequinones A and B

To synthesize the carbazole-1,4-quinone alkaloid koeniginequinones A and B, we prepared two *N*-BOM-3-iodoindole-2-carbaldehydes as starting materials [5]. Based on the sequence in Scheme 3, a three-component Pd-catalyzed cross-coupling reaction [19] of the 3-iodoindoles **2a**,**b** with tributyl(isopropenyl)tin under a CO (1 atm) atmosphere was executed in DMF at 70 °C to afford 3-acryloylindoles **8a**,**b** in 84% and 91% yields, respectively. Subsequently, the Grignard reaction of the 3-acryloylindoles **8a**,**b** with vinylmagnesium bromide resulted in the 2-allyl alcohols **9a**,**b** in 39% and 30% yields, respectively. Subsequent treatment of the 2-allyl alcohols **9a**,**b** with the Grubbs 2$^{nd}$ generation catalyst in toluene at 70 °C under an $O_2$ atmosphere afforded the desired

*N*-BOM-koeniginequinones A (**5a**) and B (**5b**) in 82% and 60% yields, respectively. Note that the deprotection of the BOM group of **5a**,**b** has previously been reported using Birch reduction [5]. Thus, completing the formal synthesis of koeneginequinones A and B was possible; however, improving the yield of the allyl alcohols **9a**,**b** that were formed via the Grignard reaction was not possible because of the steric hindrance of the BOM and 3-acryloyl groups.



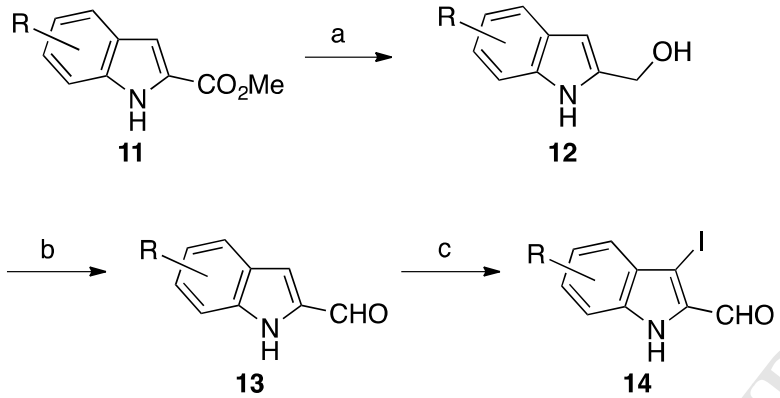

**Scheme 3**. Synthesis of koeniginequinones A (**1a**) and B (**1b**). Reagents and conditions: (a) tributyl(isopropenyl)tin, CO (1 atm), BHT, $PdCl_2$(dppf), DMF, 70 °C; (b) vinylmagnesium bromide, THF, 0 °C; (c) Grubbs$^{2nd}$, under $O_2$, toluene, 70 °C.

Next, we attempted the total synthesis of koeniginequinones from 3-iodoindole-2-carbaldehydes **7a**,**b**, which do not possess the BOM protecting group. As shown in Scheme 3, treating the 3-iodoindole-2-carbaldehydes **7a**,**b** with tributyl(isopropenyl)tin and a Pd-catalyst under a CO (1 atm) atmosphere afforded the 3-acryloylindoles **10a**,**b** in 74% and 78% yields, respectively. Subsequently, the Grignard reaction of **10a**,**b** with vinylmagnesium bromide afforded the 2-allyl alcohols **6a**,**b** in 85% and 63% yields, respectively. Finally, treating the 2-allyl alcohols **6a**,**b** with Grubbs 2$^{nd}$ generation catalyst in toluene at 70 °C under an $O_2$ atmosphere afforded the koeniginequinones A (**1a**) and B (**1b**) in 67% and 79% yields, respectively. Therefore, we completed the total synthesis of koeniginequinones A and B from 3-iodoindole-2-carbaldehydes in three steps and in 42% and 39% overall yields, respectively. The spectroscopic data of our synthetic koeniginequinones A and B were identical to those of naturally occurring materials [1].

Based on the above results, we then attempted to synthesize new carbazole-1,4-quinones that possess several substitutions on the benzene ring to prepare compounds, which display high antiproliferative activity.

As shown in Scheme 4 and Table 1, the indole-2-carboxylates **11** were purchased as commercial reagents and/or synthesized according to reported procedures [20]. The reduction of the esters **11** with $LiAlH_4$ afforded the alcohols **12** in 50%–99% yields. Subsequent oxidation of **12** with activated $MnO_2$ afforded the indole-2-carbaldehydes **13** in 28%–99% yields. Subsequently, the treatment of the aldehydes **13** with $I_2$ and KOH afforded the 3-iodoindoles **14** in 40%–87% yields.

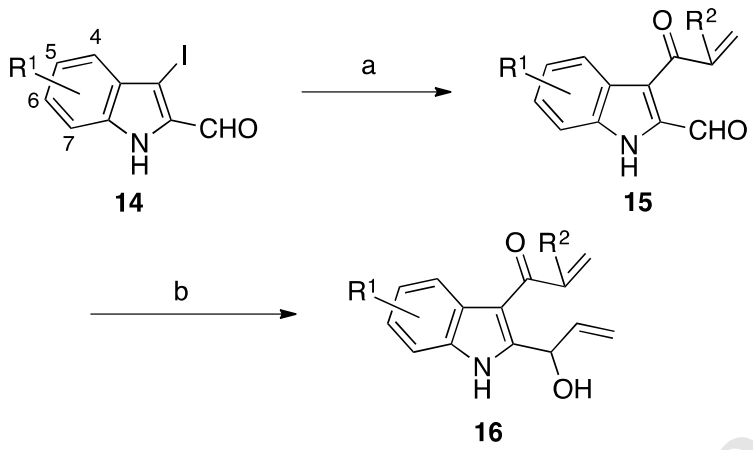
We then prepared the important substrates **16** for synthesizing the carbazole-1,4-quinones (Scheme 5 and Table 2). The three-component Pd-catalyzed cross-coupling reaction of the 3-iodoindoles **14** with alkenyl tributyltin under a CO (1 atm) atmosphere was performed in DMF at 70 °C to provide the 3-acryloylindoles **15** in 23%–90% yields. Subsequently, the Grignard reaction of the 3-acryloylindoles **15** with vinylmagnesium bromide afforded the desired 2-allyl alcohols **16** in 36%–90% yields. Finally, we synthesized the carbazole-1,4-quinones **1**, **17**, and **18** in 53%–93% yields using a tandem RCM and dehydrogenation reaction sequence from the alcohols **6** and **16** (Table 3). The structures of the carbazole-1,4-quinones were supported by $^{1}H$ and $^{13}C$ NMR spectra as well as the mass spectra.




**Scheme 4**. Synthesis of 3-iodoindole-2-carbaldehydes **14**. Reagents and conditions: (a) $LiAlH_4$, THF, rt; (b) act. $MnO_2$, DMF, rt; (c) $I_2$, KOH, DMF, rt.

**Table 1**. Yields of indole derivatives **12**, **13**, and **14**.

| No. | **11** | **12** | **13** | **14** |
|---|---|---|---|---|
| | R | Yield (%) | Yield (%) | Yield (%) |
| **a** | 5-MeO | 72 | 70 | 63 |
| **b** | 4,5-diMeO | 68 | 44 | 40 |
| **c** | 4,7-diMeO | 70 | 60 | 51 |
| **d** | 4,6-diMeO | 71 | 81 | 83 |
| **e** | 5,7-diMeO | 54 | 40 | 62 |
| **f** | 5-Me | 76 | 63 | 72 |
| **g** | 6-Me | 96 | 90 | 86 |
| **h** | 5-Cl | 80 | 76 | 80 |
| **i** | 6-Cl | 50 | 79 | 74 |
| **j** | 5-$NO_2$ | 71 | 98 | 56 |
| **k** | 5-$NO_2$ | 65 | 62 | 48 |
| **l** | 5-$CF_3$ | 87 | 98 | 85 |
| **m** | 6-$CF_3$ | 83 | 78 | 56 |
| **n** | 5-F | 76 | 84 | 54 |
| **o** | 6-F | 77 | 99 | 87 |
| **p** | 4,5-fused benzene | 81 | 28 | 61 |
| **q** | 5,6-fused benzene | 99 | 67 | 85 |




**Scheme 5.** Synthesis of 2-allylindoles **16.** Reagents and conditions: (a) tributyl(isopropenyl)tin or tributyl(vinyl)tin, CO (1 atm), BHT, $PdCl_2$(dppf), DMF, 70 °C; (b) vinylmagnesium bromide, THF, 0 °C.

**Table 2**. Synthesis of 3-acryloylindoles **15** and 2-allylindoles **16**

| No. | $R^1$ | $R^2$ | **15** | | **16** | |
|---|---|---|---|---|---|---|
| | | | Time (h) | Yield (%) | Time (h) | Yield (%) |
| **a** | 5-MeO | Me | 6 | 61 | 1 | 70 |
| **b** | 4,5-diMeO | Me | 13 | 70 | 1 | 56 |
| **c** | 4,7-diMeO | Me | 13 | 75 | 1 | 79 |
| **d** | 4,6-diMeO | Me | 13 | 83 | 1 | 53 |
| **e** | 5,7-diMeO | Me | 13 | 90 | 2 | 37 |
| **f** | 5-Me | Me | 7 | 79 | 2 | 43 |
| **g** | 6-Me | Me | 7 | 65 | 2 | 44 |
| **h** | 5-Cl | Me | 7 | 75 | 1 | 74 |
| **i** | 6-Cl | Me | 7 | 62 | 1 | 70 |
| **j** | 5-$NO_2$ | Me | 13 | 55 | 2 | 50 |
| **k** | 5-$NO_2$ | Me | 13 | 70 | 2 | 43 |
| **l** | 5-$CF_3$ | Me | 13 | 67 | 2 | 44 |
| **m** | 6-$CF_3$ | Me | 13 | 75 | 2 | 40 |
| **n** | 5-F | Me | 13 | 75 | 1 | 60 |
| **o** | 6-F | Me | 13 | 71 | 1 | 57 |
| **p** | 4,5-fused benzene | Me | 13 | 60 | 1 | 52 |
| **q** | 5,6-fused benzene | Me | 13 | 84 | 1 | 67 |
| **r** | H | Me | 13 | 64 | 1 | 90 |
| **s** | H | H | 1 | 23 | 1 | 36 |

*2.2. Antiproliferative studies*

The results of the antiproliferative studies are shown in Table 3. The $IC_{50}$ values for the antiproliferative activity of murrayaquinone A (**17a**) against HCT-116 and HL-60 cells were found to be 3.716 and 3.022 μM (Entry 1 in Table 3), respectively, which was in good agreement with the findings of a previous report [8b]. Koeniginequinone A (**1a**) has been reported to display moderate antiproliferative activity against KB, SK-MEL-5, Colo-205, and HCT-8 tumor cells [8b]; however, the $IC_{50}$ values reported against these tumor cells were quite different when compared with our findings of 0.992 and 1.751 □M for HCT-116 and HL-60 cells, respectively (Entry 7 in Table 3). This discrepancy could be the result of differences in the tumor cell types. Koeniginequinone B (**1b**) was shown to be active against both tumor cell types, but its potency was diminished compared with that of koeniginequinone A (**1a**). The reduction potential of chemical has been reviewed to correlate with bioactive properties as a consequence of facile electron acceptance from biological donors [21]. In contrast to this review, some of carbazole-1,4-quinone analogs like as *N*-MOM calothrixin B and *N*-MOM ellipticine quinones, which are more easily reduced compared to the corresponding *N*–H compounds, showed no direct correlation between their reduction potentials and antiproliferative activity [8c]. Moreover, our studies of *N*-MOM murrayaquinone A **17b** and *N*-MOM carbazole-1,4-quinone **17d** indicated that there could be no correlation between the reduction potential and antiproliferative activity of a compound because of their decreased activity compared with murrayaquinone A (**17a**) and carbazole-1,4-quinone (**17c**).

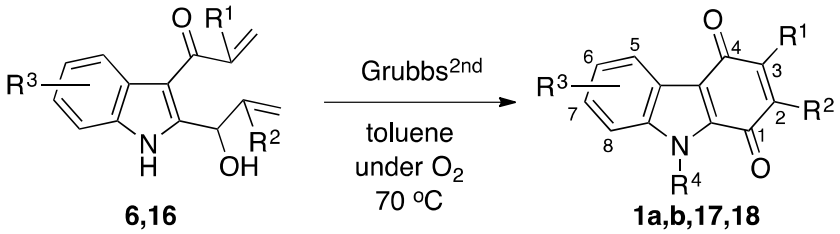
Based on the differences in the activity between koeniginequinone A (**1a**) and murrayaquinone A (**17a**), we hypothesized that the substituents on the phenyl ring in carbazole-1,4-quinone might lead to changes in the biological activities of the compounds. The monoMeO derivatives **1a** and **18a** exhibited greater activity against both tumor cells than the diMeO derivatives **1b** and **18b**–**e**, with the exception of the 5,8-diMeO derivative **18c** against HL-60 cells. Furthermore, the sterically hindered phenyl-fused derivatives **18p**,**q** displayed weak activity against both tumor cell types. These findings suggested that the mono-substituted derivatives might display higher antiproliferative activity than the corresponding di-substituted derivatives. Therefore, the mono-substituted derivatives **18f**–**o** were synthesized and their antiproliferative activity was assessed. The derivatives **1a**, **18a**, and **18f**,**g**, which possessed MeO and Me groups as electron donating groups (EDGs), exhibited increased activity against HCT-116 tumor cells compared to unsubstituted **17a**; however, only the MeO derivative **1a** demonstrated better activity against HL-60 cells than compound **17a**. Of the derivatives that contained EDGs, the 7-substituted derivatives **1a** and **18g** exhibited more potent activity than the corresponding 6-substituted derivatives **18a** and **18f**. However, with the exception of the 7-substituted derivative **18m**, the derivatives **18j**–**l** that possessed $NO_2$ and $CF_3$ groups as electron withdrawing groups (EWGs) exhibited good activity against both HCT-116 and HL-60 tumor cells. Note that the 6-$NO_2$ derivative **18j** demonstrated the

most potent activity of all of the tested compounds. Of the derivatives that contained EWGs, the 6-substituted derivatives **18j** and **18l** were better than the corresponding 7-substituted derivatives **18k** and **18m**.

The halogenated derivatives **18h**,**i** and **18n**,**o** demonstrated increased activity against HCT-116 tumor cells compared to unsubstituted **17a**. In contrast, the derivatives **18i** (7-Cl) and **18n** (6-F) exhibited decreased activity against HL-60 cells compared to **17a**.

Based on the antiproliferative activity data for all of the tested carbazole-1,4-quinones, several generalizations may be made about the activity of these compounds against HCT-116 tumor cells. Except in the case of the 7-$CF_3$ derivative **18m**, mono-substitution resulted in increased activity against HCT-116 cells compared to un- or di-substituted analogs; however, there was no direct correlation between the type of substituent and the biological activity. In addition, some preliminary correlations between the substitution position and the antiproliferative activity against HCT-116 cells were observed; these can be summarized as follows: substitution at the C7-position resulted in higher antiproliferative activity than substitution at C6-position among derivatives possessing single EDG or halogen substituents. However, among derivatives bearing single EWGs, substitution at the C6-position resulted in higher antiproliferative activity than substitution at C7-position. To better understand the effect of the substitution position, $E_{HOMO}$ values were calculated for each mono-substituent compound (see Supplementary data). With the aid of □B97X-D/6-31G(d) calculations in Spartan 14 [22], the compounds that exhibited higher antiproliferative activity against HCT-116 cells were found to have higher $E_{HOMO}$ values than those compounds that exhibit low activity.

**Table 3**. Synthesis of poly-substituted carbazole-1,4-quinones by tandem RCM reaction and evaluation of antiproliferative activity against HCT-116 and HL-60 cells




**6,16** **1a,b,17,18**

| Entry | Compd. No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Time (min) | Compd. No. | Yield (%) | $IC_{50}$ (μM) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | HCT-116 | HL-60 |
| 1 | **16r** | Me | H | H | H | – | **17a** | 70 | 3.716 | 3.022 |
| 2 | | Me | H | H | MOM | – | **17b**[a)] | – | 6.494 | 3.919 |
| 3 | **16s** | H | H | H | H | – | **17c** | 53 | 0.763 | 1.001 |
| 4 | | H | H | H | MOM | – | **17d**[a)] | – | 1.311 | 1.384 |
| 5 | | H | Me | H | MOM | – | **17e**[b)] | – | >10 | >10 |
| 6 | **16a** | Me | H | 6-MeO | H | 60 | **18a** | 80 | 1.597 | 3.414 |
| 7 | **6a** | Me | H | 7-MeO | H | 30 | **1a** | 67 | 0.992 | 1.751 |
| 8 | **6b** | Me | H | 6,7-diMeO | H | 30 | **1b** | 79 | 4.094 | 8.946 |
| 9 | **16b** | Me | H | 5,6-diMeO | H | 10 | **18b** | 82 | >10 | >10 |
| 10 | **16c** | Me | H | 5,8-diMeO | H | 30 | **18c** | 78 | 1.842 | 2.274 |
| 11 | **16d** | Me | H | 5,7-diMeO | H | 30 | **18d** | 78 | >10 | 7.259 |
| 12 | **16e** | Me | H | 6,8-diMeO | H | 30 | **18e** | 92 | 3.602 | 3.818 |
| 13 | **16f** | Me | H | 6-Me | H | 30 | **18f** | 93 | 2.033 | >10 |
| 14 | **16g** | Me | H | 7-Me | H | 30 | **18g** | 80 | 1.005 | 6.928 |
| 15 | **16h** | Me | H | 6-Cl | H | 30 | **18h** | 74 | 2.208 | 1.283 |
| 16 | **16i** | Me | H | 7-Cl | H | 30 | **18i** | 70 | 0.895 | >10 |
| 17 | **16j** | Me | H | 6-$NO_2$ | H | 30 | **18j** | 67 | 0.569 | 1.026 |
| 18 | **16k** | Me | H | 7-$NO_2$ | H | 30 | **18k** | 72 | 1.370 | 1.579 |
| 19 | **16l** | Me | H | 6-$CF_3$ | H | 30 | **18l** | 74 | 0.921 | 1.131 |
| 20 | **16m** | Me | H | 7-$CF_3$ | H | 30 | **18m** | 77 | >10 | 6.018 |
| 21 | **16n** | Me | H | 6-F | H | 30 | **18n** | 78 | 2.701 | 4.401 |
| 22 | **16o** | Me | H | 7-F | H | 30 | **18o** | 72 | 1.000 | 1.466 |
| 23 | **16p** | Me | H | 5,6-fused benzene | H | 20 | **18p** | 60 | >10 | >10 |
| 24 | **16q** | Me | H | 6,7-fused benzene | H | 20 | **18q** | 72 | >10 | 5.269 |
| | | | | Camptothecin | | | | | 0.159 | 0.019 |

a) **17b,d** synthesized by the other method in ref.11c. b) **17e** synthesized by the other method in ref.4.

## 3. Conclusion

In summary, we achieved the total synthesis of the carbazole-1,4-quinone alkaloid koeniginequinones A (**1a**) and B (**1b**) in three steps using our previously reported tandem RCM and dehydrogenation reactions. Furthermore, 24 carbazole-1,4-quinones substituted at the 5-, 6-, 7-, and/or 8-positions have been synthesized using this method. 24 compounds, including naturally occurring compounds, have been evaluated for their antiproliferative activity against HCT-116 and HL-60 cells. The mono-substituted derivatives were found to possess good antiproliferative activity against both tumor cell types, and the 6-nitro derivative **18j** exhibited $IC_{50}$ values about 1.7-fold higher against both HCT-116 and HL-60 cells compared with koeniginequinone A (**1a**). This is the first report describing the development of synthetic carbazole-1,4-quinone derivatives that display more potent antiproliferative activity than the corresponding naturally occurring alkaloids. Thus, the findings of the present study suggest that the carbazole-1,4-quinone structure is an important potential candidate for use in antitumor medicinal chemistry. The method reported here provides an efficient synthesis of carbazole-1,4-quinones from 3-iodoindole-2-carbaldehydes using readily available starting materials. Extension of this method to the synthesis of other biologically interesting heterocyclic compounds is currently being investigated.

## 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.

#### *4.2.1. N-(Benzyloxymethyl)-6-methoxy-3-(2-methylpropenoyl)indole-2-carbaldehyde (**8a**)*

Carbon monoxide was bubbled for 5 min to a mixture of the iodoindole **2a** (200 mg, 514 mmol),

isopropenyltributyltin (315 mg, 617 mmol), BHT (210 mg, 617 mmol), and $PdCl_2$(dppf) (777 mg, 26 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 **8a** (330 mg, 84%). mp 66–67 ºC (EtOAc-hexane). IR (ATR) ν = 1662 (CO), 1616 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 9.94 (s, 1H; CHO), 7.63 (d, *J* = 9.6 Hz, 1H; ArH), 7.26–7.27 (m, 5H; ArH), 6.90–6.93 (m, 2H; ArH), 6.15 (s, 2H; N-$CH_2$-O), 6.05 (s, 1H; =$CH_2$), 5.79 (s, 1H; =$CH_2$), 4.59 (s, 2H; O-$CH_2$), 3.87 (s, 3H; $OCH_3$), 2.15 (s, 3H; $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 193.3, 182.7, 160.5, 147.0, 140.4, 137.3, 133.7, 129.9, 128.4, 128.4, 127.9, 127.7, 123.8, 120.2, 115.1, 93.0, 73.8, 70.6, 55.7, 17.7. MS *m/z*: 363 ($M^+$). HRMS (EI): calcd for $C_{22}H_{21}NO_4$ 363.1471; found 363.1452.

*4.2.2. N-(Benzyloxymethyl)-5,6-dimethoxy-3-(2-methylpropenoyl)indole-2-carbaldehyde (**8b**)*

3-Acryloylindole **8b** was prepared according to a synthetic method for **8a**.

Yield 91%. mp 75–76 ºC (EtOAc-hexane). IR (ATR) ν = 1658 (CO), 1619 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 9.92 (s, 1H; CHO), 7.22–7.32 (m, 5H; ArH), 7.14 (s, 1H; ArH), 6.93 (s, 1H; ArH), 6.15 (s, 2H; N-$CH_2$-O), 6.04 (s, 1H; =$CH_2$), 5.79 (s, 1H; =$CH_2$), 4.56 (s, 2H; $OCH_2$), 3.95 (s, 3H; $OCH_3$), 3.91 (s, 3H; $OCH_3$), 2.16 (s, 3H; $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 193.5, 182.2, 151.9, 147.9, 147.4, 137.2, 134.7, 133.2, 129.6, 128.4, 127.9, 127.7, 127.4, 119.3, 102.1, 93.0, 74.0, 70.5, 56.3, 56.2, 17.7. MS *m/z*: 393 ($M^+$). HRMS (EI): calcd for $C_{23}H_{23}NO_5$ 393.1576; found 393.1597.

*4.2.3. N-(Benzyloxymethyl)-2-(1-hydroxyprop-2-en-1-yl)-6-methoxy-3-(2-methylpropenoyl)indole (**9a**)*

A solution of vinylmagnesium bromide (1 M in THF, 0.35 mL, 0.35 mmol) was added dropwise to a solution of 3-acryloylindole **8a** (90 mg, 0.23 mmol) in THF (20 mL) under cooling with ice-water. After stirring at rt for 4 h, 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 **9a** (32 mg, 39%) as yellow oil. IR (ATR) ν = 3260 (OH), 1620 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 7.63 (d, *J* = 8.9 Hz, 1H; ArH), 7.32–7.36 (m, 5H; ArH), 6.85 (dd, *J* = 8.9, 2.2 Hz, 1H; ArH), 6.81 (d, *J* = 2.2 Hz, 1H; ArH), 6.12 (ddd, *J* =17.2, 10.6, 3.6 Hz, 1H; CH=$CH_2$), 5.79 (s, 1H; =$CH_2$), 5.71 (s, 1H; =$CH_2$), 5.56–5.67 (m, 4H; N-$CH_2$-O, CHOH), 5.28 (d, *J* = 17.2 Hz, 1H; CH=$CH_2$), 5.13 (d, *J* = 10.6 Hz, 1H;

CH=$CH_2$), 4.56 (d, *J* = 11.7 Hz, 1H; $OCH_2$), 4.50 (d, *J* = 11.7 Hz, 1H; $OCH_2$), 3.81 (s, 3H; $OCH_3$), 2.12 (s, 3H; $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 191.1, 157.1, 146.6, 146.2, 137.5, 137.4, 136.6, 128.6, 128.2, 127.9, 125.0, 122.1, 120.7, 115.2, 114.9, 112.0, 93.8, 72.1, 70.0, 67.0, 55.6, 18.3. MS *m/z*: 391 ($M^+$). HRMS (EI): calcd for $C_{24}H_{25}NO_4$ 391.1784; found 391.1796.

*4.2.4.*

*N-(Benzyloxymethyl)-2-(1-hydroxyprop-2-en-1-yl)-5,6-dimethoxy-3-(2-methylpropenoyl)indole (**9b**)*

Allyl alcohol **9b** was prepared according to a synthetic method for **9a**.

Yield 30%. IR (ATR) ν = 3262 (OH), 1633 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 7.29–7.39 (m, 5H; ArH), 7.24 (s, 1H; ArH), 6.77 (s, 1H; ArH), 6.10 (ddd, *J* = 17.2, 10.3, 4.1 Hz, 1H; CH=$CH_2$), 5.53–5.81 (m, 6H; =$CH_2$, N-$CH_2$-O, CHOH), 5.28 (d, *J* = 17.0 Hz, 1H; CH=$CH_2$), 6.14 (d, *J* = 10.3 Hz, 1H; CH=$CH_2$), 4.55 (d, *J* = 12.4 Hz, 1H; $OCH_2$), 4.47 (d, *J* = 12.4 Hz, 1H; $OCH_2$), 3.89 (s, 3H; $OCH_3$), 3.86 (s, 3H; $OCH_3$), 2.14 (s, 3H; $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 184.5, 180.1, 151.1, 149.4, 146.2, 137.0, 134.5, 133.4, 132.1, 128.4, 128.0, 127.9, 127.8, 118.2, 117.5, 102.3, 93.7, 73.8, 70.8, 56.3, 56.2 15.5. MS *m/z*: 421 ($M^+$). HRMS (EI): calcd for $C_{25}H_{27}NO_5$ 421.1889; found 421.1877.

*4.2.5. N-(Benzyloxymethyl)-6-methoxy-3-methylcarbazole-1,4-quinone (**5a**)*

A suspension of the allyl alcohol **9a** (53 mg, 0.15 mmol) and Grubbs$^{2nd}$ catalyst (13 mg, 0.015 mml) in toluene (20 mL) was heated at 70 ºC for 5 min 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 *N*-BOM-koeniginequinone **5a** (40 mg, 82%) as red solid. mp 117–118 ºC (EtOAc-hexane). IR (ATR) ν = 1639 (CO), 1624 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 8.13 (d, *J* = 8.8 Hz, 1H; ArH), 7.20–7.28 (m, 5H; ArH), 7.02 (dd, *J* = 8.8, 2.2 Hz, 1H; ArH), 6.96 (d, *J* = 2.2 Hz, 1H; ArH), 6.42 (q, *J* = 1.6 Hz, 1H; ArH), 6.11 (s, 2H; N-$CH_2$-O), 4.57 (s, 2H; $OCH_2$), 3.87 (s, 3H; $OCH_3$), 2.13 (d, *J* = 1.6 Hz, 3H; $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 184.3, 180.6, 160.1, 146.4, 140.6, 137.1, 133.0, 132.9, 128.4, 127.9, 127.7, 123.9, 118.6, 118.0, 116.1, 93.8, 73.6, 70.8, 55.7, 15.5. MS *m/z*: 361 ($M^+$). HRMS (EI): calcd for $C_{22}H_{19}NO_4$ 361.1314; found 361.1299.

*4.2.6. N-(Benzyloxymethyl)-6,7-dimethoxy-3-methylcarbazole-1,4-quinone (**5b**)*

Carbazole-14,-quinone **5b** was prepared according to a synthetic method for **5a**.

Yield 60%. mp 143–145 ºC (EtOAc-hexane). IR (ATR) ν = 1635 (CO), 1612 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 7.64 (s, 1H; ArH), 7.20–7.30 (m, 5H; ArH), 6.95 (s, 1H; ArH), 6.42 (q, *J* = 1.6 Hz, 1H; ArH), 6.12 (s, 2H; N-$CH_2$-O), 4.55 (s, 2H; $OCH_2$), 4.00 (s, 3H; $OCH_3$), 3.94 (s, 3H; $OCH_3$), 2.13 (d, *J* = 1.6 Hz, 3H; $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 184.5, 180.1, 151.1, 149.4,

146.2, 137.0, 134.5, 133.4, 132.1, 128.4, 128.0, 127.9, 127.8, 118.2, 117.5, 102.3, 93.7, 73.8, 70.8, 56.3, 15.5. MS *m/z*: 391 ($M^+$). HRMS (EI): calcd for $C_{23}H_{21}NO_5$ 391.1420; found 391.1446.

*4.2.7. 6-Methoxy-3-(2-methylpropenoyl)indole-2-carbaldehyde (**10a**)*

3-Acryloylindole **10a** was prepared according to a synthetic method for **8a**

Yield 74%. mp 126–128 ºC (EtOAc-hexane). IR (ATR) ν = 3273 (NH), 1620 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.99 (s, 1H; CHO), 9.43 (br s, 1H; NH), 7.78 (d, *J* = 9.2 Hz, 1H; ArH), 6.91 (dd, *J* = 9.2, 2.3 Hz, 1H; ArH), 6.85 (d, *J* = 2.3 Hz, 1H; ArH), 6.03 (s, 1H; $=CH_2$), 5.85 (s, 1H; $=CH_2$), 3.89 (s, 3H; $OCH_3$), 2.17 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 192.8, 182.3, 160.3, 147.1, 137.5, 135.3, 128.6, 124.3, 123.5, 121.1, 114.8, 93.4, 55.6, 18.0. MS *m/z*: 243 ($M^+$). HRMS (EI): calcd for $C_{14}H_{13}NO_3$ 243.0895; found 243.0907.

*4.2.8. 5,6-Dimethoxy-3-(2-methylpropenoyl)indole-2-carbaldehyde (**10b**)*

3-Acryloylindole **10b** was prepared according to a synthetic method for **8a**.

Yield 78%. mp 182–183 ºC (EtOAc-hexane). IR (ATR) ν = 3297 (NH), 1620 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.96 (s, 1H; CHO), 9.64 (br s, 1H; NH), 7.32 (s, 1H; ArH), 6.88 (s, 1H; ArH), 6.01 (s, 1H; $=CH_2$), 5.85 (s, 1H; $=CH_2$), 3.97 (s, 3H; $OCH_3$), 3.93 (s, 3H; $OCH_3$), 2.19 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 192.9, 181.6, 151.8, 147.9, 147.8, 134.8, 131.9, 128.1, 122.6, 120.4, 102.6, 93.4, 56.2, 18.2. MS *m/z*: 273 ($M^+$). HRMS (EI): calcd for $C_{15}H_{15}NO_4$ 273.1001; found 273.1011.

*4.2.9. 2-(1-Hydroxyprop-2-en-1-yl)-6-methoxy-3-(2-methylpropenoyl)indole (**6a**)*

3-Acryloyl-2-allylindole **6a** was prepared according to a synthetic method for **9a**.

Yield 85%. IR (ATR) ν = 3494 (OH), 1624 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.38 (br s, 1H; NH), 7.66 (d, *J* = 9.5 Hz, 1H; ArH), 6.79–6.82 (m, 2H; ArH), 6.12 (ddd, *J* = 17.3, 10.3, 5.3 Hz, 1H; $CH=CH_2$), 5.75 (s, 1H; $=CH_2$), 5.69 (s, 1H; $=CH_2$), 5.48–5.69 (m, 1H, CH), 5.45 (d, *J* = 17.3 Hz, 1H; $CH=CH_2$), 5.27 (m, 2H; OH, $CH=CH_2$), 3.79 (s, 3H; $OCH_3$), 2.11 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 195.5, 156.7, 146.3, 146.1, 136.1, 135.3, 123.8, 121.9, 121.1, 116.9, 112.9, 111.7, 94.8, 68.1, 55.6, 18.5. MS *m/z*: 271 ($M^+$). HRMS (EI): calcd for $C_{16}H_{17}NO_3$ 271.1208; found 271.1194.

*4.2.10 2-(1-Hydroxyprop-2-en-1-yl)-5,6-dimethoxy-3-(2-methylpropenoyl)indole (**6b**)*

3-Acryloyl-2-allylindole **6b** was prepared according to a synthetic method for **9a.**

Yield 63%. IR (ATR) ν = 3298 (OH), 1597 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 8.81 (br s, 1H; NH), 7.29 (s, 1H; ArH), 6.86 (s, 1H; ArH), 6.16 (ddd, *J* = 17.2, 10.4, 5.3 Hz, 1H; $CH=CH_2$), 5.77 (s, 1H; $=CH_2$), 5.74 (s, 1H; $=CH_2$), 5.60 (br s, 1H; CH), 5.65 (td, *J* = 17.2, 1.4 Hz, 1H;

CH=$CH_2$), 5.38 (td, *J* = 10.4, 1.4 Hz, 1H; CH=$CH_2$), 4.68 (br s, 1H; OH), 3.89 (s, 3H; $OCH_3$), 3.88 (s, 3H; $OCH_3$), 2.14 (s, 3H; $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 195.1, 147.6, 146.3, 146.3, 145.3, 136.1, 128.6, 123.5, 120.1, 117.3, 113.3, 103.2, 94.5, 67.8, 56.3, 56.1, 18.6. MS *m/z*: 301 ($M^+$). HRMS (EI): calcd for $C_{17}H_{19}NO_4$ 301.1314; found 301.1304.

*4.2.11. Koniginequinone A (**1a**)*

Koniginequinone A (**1a**) was prepared according to a synthetic method for **5a**. $^1$H NMR spectrum data of synthetic **1a** by $CDCl_3$ were identical with those of natural **1a** [1]. However, the spectrum data of our synthetic **1a** was measured again in DMSO-$d_6$, because its solubility was lower against $CDCl_3$.

Yield 67%. mp 241–242 ºC (EtOAc-hexane) (lit. [1] mp 241 ºC). IR (ATR) ν = 3221 (NH), 1651 (CO), 1631 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 9.00 (br s, 1H; NH), 8.09 (d, *J* = 8.9 Hz, 1H; ArH), 7.00 (dd, *J* = 8.9, 2.2 Hz, 1H; ArH), 6.86 (d, *J* = 2.2 Hz, 1H; ArH), 6.46 (q, *J* = 1.7 Hz, 1H; ArH), 3.88 (s, 3H; $OCH_3$), 2.15 (d, *J* = 1.7 Hz, 3H; $CH_3$). $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 12.63 (br s, 1H; NH), 7.90 (d, *J* = 8.9 Hz, 1H; ArH), 6.96 (dd, *J* = 8.9, 2.2 Hz, 1H; ArH), 6.92 (d, *J* = 2.2 Hz, 1H; ArH), 6.56 (q, *J* = 1.6 Hz, 1H; ArH), 3.82 (s, 3H; $OCH_3$), 2.04 (d, *J* = 1.6 Hz, 3H; $CH_3$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 183.3, 179.4, 158.7, 147.1, 138.8, 135.0, 131.6, 122.4, 117.7, 115.9, 115.1, 95.0, 55.3, 15.5. MS *m/z*: 241 ($M^+$). HRMS (EI): calcd for $C_{14}H_{11}NO_3$ 241.0739; found 241.0721.

*4.2.12. Koniginequinone B (**1b**)*

Koniginequinone B (**1b**) was prepared according to a synthetic method for **5b**. $^1$H NMR spectrum data of synthetic **1b** by $CDCl_3$ were identical with those of natural **1b** [1]. However, the spectrum data of our synthetic **1b** was measured again in DMSO-$d_6$, because its solubility was lower against $CDCl_3$.

Yield 79%. mp 245–246 ºC (EtOAc-hexane) (lit. [1] mp 246–247 ºC). IR (ATR) ν = 3286 (NH), 1631 (CO), 1619 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 8.88 (br s, 1H; NH), 7.59 (s, 1H; ArH), 6.86 (s, 1H; ArH), 6.46 (1H, q, *J* = 1.4 Hz; ArH), 3.99 (s, 3H; $OCH_3$), 3.96 (s, 3H; $OCH_3$), 2.15 (d, *J* = 1.4 Hz, 3H; $CH_3$). $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 12.60 (br s, 1H; NH), 7.40 (s, 1H; ArH), 6.92 (s, 1H; ArH), 6.54 (q, *J* = 1.6 Hz, 1H; ArH), 3.83 (s, 6H; $OCH_3 \times 2$), 2.04 (d, *J* = 1.6 Hz, 3H; $CH_3$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 183.3, 178.8, 150.2, 148.5, 147.0, 134.0, 132.8, 131.9, 117.1, 115.8, 101.3, 95.2, 79.1, 55.6, 15.4. MS *m/z*: 271 ($M^+$). HRMS (EI): calcd for $C_{15}H_{13}NO_4$ 271.0845; found 271.0873.

*4.3. General procedure for the synthesis of indol-2-ylmethanol (**12a–12q**)*

A solution of indole-2-carboxylate **11** (1 mmol) in THF (10 mL) was added dropwise to a

suspension of $LiAlH_4$ (0.8 mmol) in THF (20 mL) under cooling with ice-water. After stirring at rt for 5 h, the reaction mixture was quenched with water, and then was filtrated through a Celite pad. The filtrate 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 as an eluent to give the alcohol **12**.

*4.3.1. 5-Methoxyindol-2-ylmethanol (**12a**)*

Yield 72%. mp 67–69 ºC (EtOAc-hexane). IR (ATR) ν = 3194 (OH) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 8.24 (br s, 1H; NH), 7.24 (d, *J* = 8.8 Hz, 1H; ArH), 7.04 (d, *J* = 2.5 Hz, 1H; ArH), 6.77 (dd, *J* = 8.8, 2.5 Hz, 1H; ArH), 6.34 (s, 1H; ArH), 4.81 (s, 2H; $CH_2$), 3.84 (s, 3H; $OCH_3$), 1.79 (br s, 1H; OH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 154.2, 138.3, 131.4, 128.5, 112.3, 111.6, 102.4, 100.3, 58.8, 55.8. MS *m/z*: 177 ($M^+$). HRMS (EI): calcd for $C_{10}H_{11}NO_2$ 177.0790; found 177.0810.

*4.3.2. 4,5-Dimethoxyindol-2-ylmethanol (**12b**)*

Yield 68%. mp 76–78 ºC (EtOAc-hexane). IR (ATR) ν = 3289 (OH) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 8.34 (br s, 1H; NH), 6.98 (d, *J* = 8.9 Hz, 1H; ArH), 6.90 (d, *J* = 8.9 Hz, 1H; ArH), 6.47 (s, 1H; ArH), 4.77 (s, 2H; $CH_2$), 4.03 (s, 3H; $OCH_3$), 3.89 (s, 3H; $OCH_3$), 2.14 (br s, 1H; OH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 144.6, 141.7, 138.2, 133.7, 122.4, 111.5, 105.8, 97.7, 60.7, 58.6, 58.2. MS *m/z*: 207 ($M^+$). HRMS (EI): calcd for $C_{11}H_{13}NO_3$ 207.0895; found 207.0877.

*4.3.3. 4,7-Dimethoxyindol-2-ylmethanol (**12c**)*

Yield 70%. mp 78–80 ºC (EtOAc-hexane). IR (ATR) ν = 3228 (OH) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 8.73 (br s, 1H; NH), 6.50 (d, *J* = 8.3 Hz, 1H; ArH), 6.48 (d, *J* = 2.4 Hz, 1H; ArH), 6.37 (d, *J* = 8.3 Hz, 1H; ArH), 4.76 (d, *J* = 5.0 Hz, 2H; ArH), 3.90 (s, 3H; $OCH_3$), 3.89 (s, 3H; $OCH_3$), 2.06 (br s, 1H; OH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 147.6, 140.9, 136.1, 128.0, 120.0, 101.8, 98.9, 98.4, 58.6, 55.7, 55.7. MS *m/z*: 207 ($M^+$). HRMS (EI): calcd for $C_{11}H_{13}NO_3$ 207.0895; found 207.0890.

*4.3.4. 4,6-Dimethoxyindol-2-ylmethanol (**12d**)*

Yield 71%. mp 74–76 ºC (EtOAc-hexane). IR (ATR) ν = 3298 (OH) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 8.31 (br s, 1H; NH), 6.40 (d, *J* = 1.6 Hz, 1H; ArH), 6.26–6.43 (m, 1H; ArH), 6.20 (d, *J* = 1.6 Hz, 1H; ArH), 4.68 (s, 2H; $CH_2$), 3.88 (s, 3H; $OCH_3$), 3.80 (s, 3H; $OCH_3$), 2.29 (br s, 1H; OH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 157.6, 153.6, 137.8, 134.6, 112.9, 98.1, 91.7, 86.8, 58.5, 55.6, 55.3. MS *m/z*: 207 ($M^+$). HRMS (EI): calcd for $C_{11}H_{13}NO_3$ 207.0895; found 207.0903.

*4.3.5. 5,7-Dimethoxyindol-2-ylmethanol (**12e**)*

Yield 54%. mp 68–69 ºC (EtOAc-hexane). IR (ATR) ν = 3290 (OH) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 8.63 (br s, 1H; NH), 6.61 (d, *J* = 2.2 Hz, 1H; ArH), 6.33 (d, *J* = 2.2 Hz, 1H; ArH), 6.28 (d, *J* = 2.2 Hz, 1H; ArH), 4.72 (s, 2H; $CH_2$), 3.88 (s, 3H; $OCH_3$), 3.82 (s, 3H; $OCH_3$), 2.25 (br s, 1H; OH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 154.9, 146.3, 137.5, 128.6, 122.1, 100.8, 94.2, 93.7, 58.6, 55.8, 55.3. MS *m/z*: 207 ($M^+$). HRMS (EI): calcd for $C_{11}H_{13}NO_3$ 207.0895; found 207.0913.

*4.3.6. 5-Methylindol-2-ylmethanol (**12f**)*

Yield 76%. mp 82–84 ºC (EtOAc-hexane). IR (ATR) ν = 3278 (OH) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 8.24 (br s, 1H; NH), 7.36 (s, 1H; ArH), 7.22 (d, *J* = 8.3 H, 1H; ArH), 7.00 (d, *J* = 8.3 Hz, 1H; ArH), 6.32 (s, 1H; ArH), 4.78 (d, *J* = 5.8 Hz, 2H; $CH_2$), 2.43 (s, 3H; $OCH_3$), 1.89 (t, *J* = 5.8 Hz, 1H; OH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 137.6, 134.6, 129.1, 128.2, 123.7, 120.2, 110.6, 100.1, 58.6, 21.4. MS *m/z*: 161 ($M^+$). HRMS (EI): calcd for $C_{10}H_{11}NO$ 161.0841; found 161.0833.

*4.3.7. 6-Methylindol-2-ylmethanol (**12g**)*

Yield 96%. mp 74–76 ºC (EtOAc-hexane). IR (ATR) ν = 3263 (OH) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 8.22 (br s, 1H; NH), 7.45 (d, *J* = 8.1 Hz, 1H; ArH), 7.08 (s, 1H; ArH), 6.93 (d, *J* = 8.1 Hz, 1H; ArH), 6.34 (s, 1H; ArH), 4.75 (s, 2H; $CH_2$), 2.44 (s, 3H; $OCH_3$), 2.04 (br s, 1H; OH). $^{13}C$ NMR (300 MHz, $CDCl_3$) δ = 136.9, 136.8, 132.0, 125.6, 121.7, 120.2, 111.0, 100.5, 58.4, 21.7. MS *m/z*: 161 ($M^+$). HRMS (EI): calcd for $C_{10}H_{11}NO$ 161.0841; found 161.0825.

*4.3.8. 5-Chloroindol-2-ylmethanol (**12h**)*

Yield 80%. mp 110–111 ºC (EtOAc-hexane). IR (ATR) ν = 3305 (OH) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 8.41 (br s, 1H; NH), 7.54 (s, 1H; ArH), 7.24–7.28 (m, 1H; ArH), 7.13 (dd, *J* = 8.6, 2.0 Hz, 1H; ArH), 6.34 (s, 1H; ArH), 4.84 (d, *J* = 5.3 Hz, 2H; $CH_2$), 1.86 (br s, 1H; OH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 139.0, 134.6, 129.2, 125.5, 122.4, 120.0, 111.9, 100.0, 58.6. MS *m/z*: 181 ($M^+$), 183 ($M^+$+2). HRMS (EI): calcd for $C_9H_8ClNO$ 181.0294; found 181. 0288.

*4.3.9. 6-Chloroindol-2-ylmethanol (**12i**)*

Yield 50%. mp 108–109 ºC (EtOAc-hexane). IR (ATR) ν = 3386 (NH), 3294 (OH) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 8.37 (br s, 1H; NH 7.46 (d, *J* = 8.3 Hz, 1H; ArH), 7.34 (d, *J* = 1.8 Hz, 1H; ArH), 7.07 (dd, *J* = 8.3, 1.8 Hz, 1H; ArH), 6.37 (s, 1H; ArH), 4.83 (s, 2H; $CH_2$), 1.83 (br s, 1H; OH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 138.2, 136.7, 127.9, 126.6, 121.4, 120.6, 110.9, 100.5, 58.6. MS *m/z*: 181 ($M^+$), 183 ($M^+$+2). HRMS (EI): calcd for $C_9H_8ClNO$ 181.0294; found 181.0279.

*4.3.10. 5-Nitroindol-2-ylmethanol (**12j**)*

Yield 71%. mp 125–127 ºC (EtOAc-hexane). IR (ATR) ν = 3197 (OH), 1518 ($NO_2$), 1362 ($NO_2$)

cm$^{-1}$. $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ = 11.81 (br s, 1H; NH), 8.50 (d, *J* =2.3 Hz, 1H; ArH), 7.96 (dd, *J* = 8.8, 2.3 Hz, 1H; ArH), 7.49 (d, *J* = 8.8 Hz, 1H; ArH), 6.57 (s, 1H; ArH), 5.46 (t, *J* = 5.5 Hz, 1H; OH), 4.66 (d, *J* = 5.5 Hz, 2H; $CH_2$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 144.4, 140.5, 139.5, 127.3, 116.8, 116.2, 111.4, 100.8, 56.7. MS *m/z*: 192 ($M^+$). HRMS (EI): calcd for $C_9H_8N_2O_3$ 192.0535; found 192.0552.

*4.3.11. 6-Nitroindol-2-ylmethanol (**12k**)*

Yield 65%. mp 121–123 ºC (EtOAc-hexane). IR (ATR) ν = 3194 (OH), 1585 ($NO_2$), 1304 ($NO_2$) cm$^{-1}$. $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ = 11.85 (br s, 1H; NH), 8.27 (d, *J* =2.6 Hz, 1H; ArH), 7.86 (dd, *J* =8.8, 2.6 Hz, 1H; ArH), 7.63 (d, *J* = 8.8 Hz, 1H; ArH), 6.50 (s, 1H; ArH), 5.56 (t, *J* = 6.0 Hz, 1H; OH), 4.70 (d, *J* = 6.0 Hz, 2H; $CH_2$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 147.8, 141.3, 134.4, 133.2, 119.6, 114.2, 107.7, 99.3, 56.8. MS *m/z*: 192 ($M^+$). HRMS (EI): calcd for $C_9H_8N_2O_3$ 192.0535; found 192.0543.

*4.3.12. 5-Trifluoromethylindol-2-ylmethanol (**12l**)*

Yield 87%. mp 96–98 ºC (EtOAc-hexane). IR (ATR) ν = 3217 (OH) cm$^{-1}$. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.60 (br s, 1H; NH), 7.87 (s, 1H; ArH), 7.41 (m, 2H; ArH), 6.48 (s, 1H; ArH), 4.88 (s, 2H; $CH_2$), 1.88 (br s, 1H; OH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 139.3, 137.5, 127.5, 123.8 (q, $J_{C–F}$ = 271.2 Hz), 122.4 (q, $J_{C–F}$ = 32.2 Hz), 118.8 (q, $J_{C–F}$ = 3.7 Hz), 118.3 (q, $J_{C–F}$ = 3.7 Hz), 111.1, 101.0, 58.6. MS *m/z*: 215 ($M^+$). HRMS (EI): calcd for $C_{10}H_8F_3NO$ 215.0558; found 215.0546.

*4.3.13. 6-Trifluoromethylindol-2-ylmethanol (**12m**)*

Yield 83%. mp 100–101 ºC (EtOAc-hexane). IR (ATR) ν = 3290 (OH) cm$^{-1}$. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.71 (br s, 1H; NH), 7.63 (d, *J* = 8.3 Hz, 1H; ArH), 7.61 (s, 1H; ArH), 7.33 (d, *J* = 8.3 Hz, 1H; ArH), 6.44 (s, 1H; ArH), 4.87 (s, 2H; $CH_2$), 2.13 (br s, 1H; OH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 140.2, 135.1, 130.5, 124.1 (q, $J_{C–F}$ = 32.5 Hz), 121.6 (q, $J_{C–F}$ = 271.2 Hz), 120.9, 116.7 (q, $J_{C–F}$ = 3.7 Hz), 105.5 (q, $J_{C–F}$ = 5.0 Hz), 100.4, 58.6. MS *m/z*: 215 ($M^+$). HRMS (EI): calcd for $C_{10}H_8F_3NO$ 215.0558; found 215.0568.

*4.3.14. 5-Fluoroindol-2-ylmethanol (**12n**)*

Yield 76%. mp 113–115 ºC (EtOAc-hexane). IR (ATR) ν = 3390 (OH) cm$^{-1}$. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.41 (br s, 1H; NH), 7.13-7.25 (m, 2H; ArH), 6.85–6.95 (m, 1H; ArH), 6.34 (s, 1H; ArH), 4.75 (s, 2H; $CH_2$), 2.12 (br s, 1H; OH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 158.0 (d, $J_{C–F}$ = 234.2 Hz), 139.2, 132.8, 128.4 (d, $J_{C–F}$ = 11.1 Hz), 111.5 (d, $J_{C–F}$ = 10.0 Hz), 110.5 (d, $J_{C–F}$ = 26.2 Hz), 105.4 (d, $J_{C–F}$ = 23.7 Hz), 100.5 (d, $J_{C–F}$ = 4.8 Hz), 58.6. MS *m/z*: 165 ($M^+$). HRMS (EI): calcd for $C_9H_8FNO$ 165.0590; found 165.0610.

*4.3.15. 6-Fluoroindol-2-ylmethanol (**12o**)*

Yield 77%. mp 119–120 ºC (EtOAc-hexane). IR (ATR) ν = 3310 (OH) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 8.45 (br s, 1H; NH), 7.47 (dd, *J* = 8.7, 5.5 Hz, 1H; ArH), 6.97-7.01 (m, 1H; ArH), 6.86 (ddd, *J* = 8.7, 2.3, 0.9 Hz, 1H; ArH), 6.36 (s, 1H; ArH), 4.77 (s, 2H; $CH_2$), 2.11 (br s, 1H; OH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 159.9 (d, $J_{C–F}$ = 238.2 Hz), 137.8 (d, $J_{C–F}$ = 3.7 Hz), 136.3 (d, $J_{C–F}$ = 12.6 Hz), 124.5, 121.3 (d, $J_{C–F}$ = 10.0 Hz), 108.7 (d, $J_{C–F}$ = 24.8 Hz), 100.6 (d, $J_{C–F}$ = 2.7 Hz), 97.3 (d, $J_{C–F}$ = 26.2 Hz), 58.6. MS *m/z*: 165 ($M^+$). HRMS (EI): calcd for $C_9H_8FNO$ 165.0590; found 165.0601.

*4.3.16. Benzo[e]indol-2-ylmethanol (**12p**)*

Yield 81%. mp 118–119 ºC (EtOAc-hexane). IR (ATR) ν = 3263 (OH) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 8.70 (br s, 1H; NH), 8.17 (d, *J* = 8.2 Hz, 1H; ArH), 7.79 (d, *J* = 8.2 Hz, 1H; ArH), 7.51–7.59 (m, 2H; ArH), 7.47 (d, *J* = 8.7 Hz, 1H; ArH), 7.41 (dt, *J* = 8.2, 1.1 Hz, 1H; ArH), 6.93 (s, 1H; ArH), 4.89 (s, 2H; $CH_2$), 1.68 (br s, 1H; OH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 135.6, 132.7, 129.1, 128.6, 128.1, 125.8, 123.3, 123.2, 122.9, 122.8, 112.6, 100.0, 58.8. MS *m/z*: 197 ($M^+$). HRMS (EI): calcd $C_{13}H_{11}NO$ 197.0841; found 197.0841.

*4.3.17. Benzo[f]indol-2-ylmethanol (**12q**)*

Yield 99%. mp 123–125 ºC (EtOAc-hexane). IR (ATR) ν = 3236 (OH) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 9.25 (br s, 1H; NH), 7.98 (d, *J* = 8.1 Hz, 1H; ArH), 7.92 (d, *J* = 8.1 Hz, 1H; ArH), 7.65 (d, *J* = 8.6 Hz, 1H; ArH), 7.48–7.54 (m, 2H; ArH), 7.39–7.45 (m, 1H; ArH), 6.54 (d, *J* = 2.2 Hz, 1H; ArH), 4.90 (s, 2H; $CH_2$), 1.97 (br s, 1H; OH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 135.5, 131.1, 130.5, 128.9, 125.5, 123.9, 123.9, 121.6, 120.8, 120.6, 119.4, 102.4, 58.8. MS *m/z*: 197 ($M^+$). HRMS (EI): calcd for $C_{13}H_{11}NO$ 197.0841; found 197.0857.

*4.4. General procedure for the synthesis of indole-2-carbaldehyde (**13a–13q**)*

A suspension of the alcohol **12** (1 mmol) and active $MnO_2$ (10 mmol) in DMF (30 mL) was stirred at rt for 12 h. The reaction mixture was filtrated through a Celite pad. The filtrate was evaporated in vacuo. The residue was purified by column chromatography using EtOAc-hexane as an eluent to give the indole-2-carbaldehyde **13**.

*4.4.1. 5-Methoxyindole-2-carbaldehyde (**13a**)*

Yield 70%. mp 178–179 ºC (EtOAc-hexane). IR (ATR) ν = 3188 (NH), 1639 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 9.80 (s, 1H; CHO), 9.25 (br s, 1H; NH), 7.36 (d, *J* = 8.8 Hz, 1H; ArH), 7.19 (d, *J* = 2.2 Hz, 1H; ArH), 7.11 (s, 1H; ArH), 7.08 (dd, *J* = 8.8, 2.2 Hz, 1H; ArH), 3.86 (s, 3H; $OCH_3$).

$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 181.9, 155.1, 136.3, 133.6, 127.7, 119.4, 114.3, 113.5, 102.8, 55.7. MS *m/z*: 175 ($M^+$). HRMS (EI): calcd for $C_{10}H_9NO_2$ 175.0633; found 175.0656.

*4.4.2. 4,5-Dimethoxyindole-2-carbaldehyde (**13b**)*

Yield 44%. mp 142–144 ºC (EtOAc-hexane). IR (ATR) ν = 3186 (NH), 1662 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 9.80 (s, 1H; CHO), 9.02 (br s, 1H; NH), 7.36–7.37 (m, 1H; ArH), 7.17 (d, *J* = 9.0 Hz, 1H; ArH), 7.09 (d, *J* = 9.0 Hz, 1H; ArH), 4.10 (s, 3H; $OCH_3$), 3.91 (s, 3H; $OCH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 182.1, 144.7, 143.3, 136.2, 135.3, 122.4, 118.3, 112.4, 107.2, 60.9, 58.4. MS *m/z*: 205 ($M^+$). HRMS (EI): calcd for $C_{11}H_{11}NO_3$ 205.0739; found 205.0756.

*4.4.3. 4,7-Dimethoxyindole-2-carbaldehyde (**13c**)*

Yield 60%. mp 137–138 ºC (EtOAc-hexane). IR (ATR) ν = 3313 (NH), 1670 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 9.78 (s, 1H; CHO), 9.23 (br s, 1H; NH), 7.33 (m, 1H; ArH), 6.66 (d, *J* = 8.2 Hz, 1H; ArH), 6.36 (d, *J* = 8.2 Hz, 1H; ArH), 3.92 (s, 3H; $OCH_3$), 3.91 (s, 3H; $OCH_3$). $^{13}$C NMR ($CDCl_3$) δ = 181.5, 149.0, 141.1, 134.9, 130.3, 120.2, 112.6, 106.2, 99.0, 55.8, 55.5. MS *m/z*: 205 ($M^+$). HRMS (EI): calcd for $C_{11}H_{11}NO_3$ 205.0739; found 205.0744.

*4.4.4. 4,6-Dimethoxyindole-2-carbaldehyde (**13d**)*

Yield 81%. mp 148–149 ºC (EtOAc-hexane). IR (ATR) ν = 3282 (NH), 1639 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 9.80 (s, 1H; CHO), 8.91 (br s, 1H; NH), 7.36 (dd, *J* = 2.2, 0.9 Hz, 1H; ArH), 7.16 (d, *J* = 8.8 Hz, 1H; ArH), 7.09 (d, *J* = 8.8, 0.9 Hz, 1H; ArH), 4.10 (s, 3H; $OCH_3$), 3.91 (s, 3H; $OCH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 182.0, 144.7, 143.3, 136.2, 135.3, 122.4, 118.3, 112.4, 107.1, 60.9, 58.4. MS *m/z*: 205 ($M^+$). HRMS (EI): calcd for $C_{11}H_{11}NO_3$ 205.0739; found 205.0714.

*4.4.5. 5,7-Dimethoxyindole-2-carbaldehyde (**13e**)*

Yield 40%. mp 143–146 ºC (EtOAc-hexane). IR (ATR) ν = 3321 (NH), 1651 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 9.78 (s, 1H; CHO), 9.11 (br s, 1H; NH), 7.14 (d, *J* = 2.1 Hz, 1H; ArH), 6.67 (d, *J* = 1.7 Hz, 1H; ArH), 6.48 (d, *J* = 2.1 Hz, 1H; ArH), 3.93 (s, 3H; $OCH_3$), 3.84 (s, 3H; $OCH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 181.6, 155.8, 147.2, 135.7, 127.8, 125.3, 114.1, 99.1, 93.9, 55.7, 55.6. MS *m/z*: 205 ($M^+$). HRMS (EI): calcd for $C_{11}H_{11}NO_3$: 205.0739; found 205.0727.

*4.4.6. 5-Methylindole-2-carbaldehyde (**13f**)*

Yield 63%. mp 123–125 ºC (EtOAc-hexane). IR (ATR) ν = 3233 (NH), 1641 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 9.82 (s, 1H; CHO), 9.21 (br s, 1H; NH), 7.51 (d, *J* = 0.7 Hz, 1H; ArH), 7.36 (d, *J* = 8.5 Hz, 1H; ArH), 7.23 (dd, *J* = 8.5, 1.6 Hz, 1H; ArH), 7.19 (dd, *J* = 1.6, 0.7 Hz, 1H; ArH), 2.45 (s, 3H; $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 182.0, 136.4, 136.0, 130.6, 129.4, 127.6, 122.5,

114.3, 112.0, 21.4. MS *m/z*: 159 ($M^+$). HRMS (EI): calcd for $C_{10}H_9NO$: 159.0684; found 159.0671.

*4.4.7. 6-Methylindole-2-carbaldehyde (**13g**)*

Yield 90%. mp 133–137 ºC (EtOAc-hexane). IR (ATR) ν = 3178 (NH), 1643 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.79 (s, 1H; CHO), 9.06 (br s, 1H; NH), 7.62 (dd, *J* = 8.4, 2.4 Hz, 1H; ArH), 7.23–7.26 (m, 2H; ArH), 7.02 (d, *J* = 8.4 Hz, 1H; ArH), 2.48 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 182.0, 138.9, 137.9, 135.6, 125.2, 123.4, 122.9, 115.4, 112.1, 22.1. MS *m/z*: 159 ($M^+$). HRMS (EI): calcd for $C_{10}H_9NO$ 159.0684; found 159.0669.

*4.4.8. 5-Chloroindole-2-carbaldehyde (**13h**)*

Yield 76%. mp 139–142 ºC (EtOAc-hexane). IR (ATR) ν = 3290 (NH), 1655 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 9.85 (s, 1H; CHO), 9.12 (br s, 1H; NH), 7.73 (d, *J* = 9.0 Hz, 1H; ArH), 7.40 (d, *J* = 8.8 Hz, 1H; ArH), 7.36 (dd, *J* = 8.8, 1.9 Hz, 1H; ArH), 7.21 (d, *J* = 1.9 Hz, 1H; ArH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 183.3, 137.4, 136.7, 127.7, 126.4, 124.9, 122.0, 114.6, 113.2. MS *m/z*: 179 ($M^+$), 181 ($M^+$+2). HRMS (EI): calcd for $C_9H_6ClNO$ 179.0138; found 179.0125.

*4.4.9. 6-Chloroindole-2-carbaldehyde (**13i**)*

Yield 79%. mp 144–147 ºC (EtOAc-hexane). IR (ATR) ν = 3205 (NH), 1635 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.84 (s, 1H; CHO), 9.16 (br s, 1H; NH), 7.67 (d, *J*=8.5 Hz, 1H; ArH), 7.47 (s, 1H; ArH), 7.25–7.26 (m, 1H; ArH), 7.16 (dd, *J*=8.5, 1.7 Hz, 1H; ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 182.0, 138.3, 136.5, 133.3, 125.8, 124.4, 122.4, 114.7, 112.3. MS *m/z*: 179 ($M^+$), 181 ($M^+$+2). HRMS (EI): calcd for $C_9H_6ClNO$ 179.0138; found 179.0149.

*4.4.10. 5-Nitroindole-2-carbaldehyde (**13j**)*

Yield 98%. mp 162–164 ºC (EtOAc-hexane). IR (ATR) ν = 3316 (NH), 1678 (CO), 1521 ($NO_2$), 1338 ($NO_2$) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.66 (br s, 1H; NH), 9.96 (s, 1H; CHO), 8.84 (s, 1H; ArH), 8.19 (dd, *J* = 9.0 Hz, 1H; ArH), 7.69 (s, 1H; ArH), 7.62 (d, *J* = 9.0 Hz, 1H; ArH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 183.8, 141.7, 140.8, 139.0, 126.0, 120.8, 120.7, 116.0, 113.6. MS *m/z*: 190 ($M^+$). HRMS (EI): calcd for $C_9H_6N_2O_3$ 190.0378; found 190.0362.

*4.4.11. 6-Nitroindole-2-carbaldehyde (**13k**)*

Yield 62%. mp 155–157 ºC (EtOAc-hexane). IR (ATR) ν = 3305 (NH), 1651(CO), 1508 ($NO_2$), 1338 ($NO_2$) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.66 (br s, 1H; NH), 10.00 (s, 1H; CHO), 8.33 (s, 1H; ArH), 7.92-8.01 (m, 2H; ArH), 7.56 (s, 1H; ArH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 183.9, 145.2, 140.3, 136.4, 131.1, 124.0, 114.9, 113.0, 109.5. MS *m/z*: 190 ($M^+$). HRMS (EI): calcd for $C_9H_6N_2O_3$ 190.0378; found 190.0374.

*4.4.12. 5-Trifluoromethylindole-2-carbaldehyde (**13l**)*

Yield 98%. mp 132–135 ºC. IR (ATR) ν = 3282 (NH), 1651 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 9.92 (s, 1H; CHO), 9.55 (br s, 1H; NH), 8.08 (s, 1H; ArH), 7.56–7.64 (m, 2H; ArH), 7.37 (s, 1H; ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 182.3, 138.9, 137.1, 124.7 (q, $J_{C–F}$ = 271.5 Hz), 126.5, 123.8 (q, $J_{C–F}$ = 32.5 Hz), 123.7 (q, $J_{C–F}$ = 2.5 Hz), 121.4 (q, $J_{C–F}$ = 3.9 Hz), 115.1, 113.1. MS *m/z*: 213 ($M^+$). HRMS (EI): calcd for $C_{10}H_6F_3NO$ 213.0401; found 213.0411.

*4.4.13. 6-Trifluoromethylindole-2-carbaldehyde (**13m**)*

Yield 78%. mp 138–140 ºC (EtOAc-hexane). IR (ATR) ν = 3294 (NH), 1666 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 9.92 (s, 1H; CHO), 9.22 (br s, 1H; NH), 7.87 (d, *J* = 8.7 Hz, 1H; ArH), 7.76 (s, 1H; ArH), 7.42 (d, *J*= 8.7 Hz, 1H; ArH), 7.33 (s, 1H; ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 182.6, 137.6, 136.8, 129.2, 128.9 (q, $J_{C–F}$ = 32.4 Hz), 124.4 (q, $J_{C–F}$ = 272.6 Hz), 124.1, 117.6 (q, $J_{C–F}$ = 3.7 Hz), 114.3, 110.4 (q, $J_{C–F}$ = 4.7 Hz). MS *m/z*: 213 ($M^+$). HRMS (EI): calcd for $C_{10}H_6F_3NO$ 213.0401; found 213.0423.

*4.4.14. 5-Fluorolindole-2-carbaldehyde (**13n**)*

Yield 84%. mp 122–123 ºC (EtOAc-hexane). IR (ATR) ν = 3302 (NH), 1670 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 9.85 (s, 1H; CHO), 9.36 (br s, 1H; NH), 7.36–7.44 (m, 2H; ArH), 7.24–7.25 (m, 1H; ArH), 7.17 (dt, *J* = 9.2, 2.5 Hz, 1H; ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 182.2, 158.3 (d, $J_{C–F}$ = 237.8 Hz), 137.1, 134.6, 127.5 (d, $J_{C–F}$ = 10.0 Hz), 116.6 (d, $J_{C–F}$ = 27.3 Hz), 114.4 (d, $J_{C–F}$ = 5.0 Hz), 113.5 (d, $J_{C–F}$ = 8.9 Hz), 107.5 (d, $J_{C–F}$ = 22.4 Hz). MS *m/z*: 163 ($M^+$). HRMS (EI): calcd for $C_9H_6FNO$ 163.0433; found 163.0412.

*4.4.15. 6-Fluorolindole-2-carbaldehyde (**13o**)*

Yield 99%. mp 132–135 ºC. IR (ATR) ν = 3298 (NH), 1651 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 9.81 (s, 1H; CHO), 9.50 (br s, 1H; NH), 7.70 (dd, *J* = 8.9, 5.4 Hz, 1H; ArH), 7.26–7.28 (m, 1H; ArH), 7.14 (dd, *J* = 9.4, 2.2 Hz, 1H; ArH), 6.96 (dt, *J* = 9.4, 2.2 Hz, 1H; ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 181.7, 162.9 (d, $J_{C–F}$ = 245.4 Hz), 138.4, (d, $J_{C–F}$ = 12.6 Hz), 136.7 (d, $J_{C–F}$ = 3.9 Hz), 124.9, 124.4 (d, $J_{C–F}$ = 57.0 Hz), 115.1, 111.2 (d, $J_{C–F}$ = 26.2 Hz), 98.3 (d, $J_{C–F}$ = 26.5 Hz). MS *m/z*: 163 ($M^+$). HRMS (EI): calcd for $C_9H_6FNO$ 163.0433; found 163.0439.

*4.4.16. Benzo[e]indole-2-carbaldehyde (**13p**)*

Yield 28%. mp 163–165 ºC (EtOAc-hexane). IR (ATR) ν = 3313 (NH), 1639 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 9.86 (s, 1H; CHO), 9.43 (br s, 1H; NH), 8.26 (d, *J* = 8.2 Hz, 1H; ArH), 7.91 (d, *J* = 8.2 Hz, 1H; ArH), 7.77–7.80 (m, 2H; ArH), 7.63 (dt, *J* = 7.0, 1.2 Hz, 1H; ArH), 7.47–7.53

(m, 2H; ArH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 181.0, 135.7, 134.5, 130.3, 129.4, 129.3, 129.0, 127.5, 127.3, 124.8, 122.8, 113.4, 113.1. MS *m/z*: 195 ($M^+$). HRMS (EI): calcd for $C_{13}H_9NO$ 195.0684; found 195.0692.

*4.4.17. Benzo[f]indole-2-carbaldehyde (**13q**)*

Yield 67%. mp 158–160 ºC (EtOAc-hexane). IR (ATR) ν = 3298 (NH), 1651 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 10.44 (br s, 1H; NH), 9.87 (s, 1H; CHO), 8.27 (d, *J* = 7.6, 1.3 Hz, 1H; ArH), 7.90–7.93 (m, 1H; ArH), 7.68 (d, *J* = 8.7 Hz, 1H; ArH), 7.53-7.64 (m, 3H; ArH), 7.39 (d, *J* = 2.2 Hz, 1H; ArH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 181.4, 134.9, 134.7, 132.9, 128.9, 126.6, 126.4, 123.9, 122.7, 121.9, 121.3, 121.2, 116.3. MS *m/z*: 195 ($M^+$). HRMS (EI): calcd for $C_{13}H_9NO$ 195.0684; found 195.0682.

*4.5. General procedure for the synthesis of 3-iodoindole-2-carbaldehyde (**14a–14q**)*

A solution of indole-2-carbaldehyde (6.6 mmol) in DMF (10 mL) was added to a suspension of powdered KOH (23.8 mmol) in DMF (10 mL) under cooling with ice-water, and then stirred at same temperature for 30 min. A solution of $I_2$ (6.6 mmol) in DMF (30 mL) was added dropwise to the reaction mixture under cooling with ice-water. After stirring at rt for 4 h, the mixture was poured into a solution of 28% $NH_4OH$ (100 mL) and $NaHSO_3$ (9.6 mmol) in water (1.5 L). The precipitates were separated by filtration to give the 3-iodoindole.

*4.5.1. 3-Iodo-5-methoxyindole-2-carbaldehyde (**14a**)*

Yield 63%. mp 174–177 ºC (EtOAc-hexane). IR (ATR) ν = 3209 (NH), 1793 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 12.31 (br s, 1H; NH), 9.76 (s, 1H; CHO), 7.39 (d, *J* = 8.9 Hz, 1H; ArH), 7.07 (dd, *J* = 8.9, 2.4 Hz, 1H; ArH), 6.87 (d, *J* = 2.4 Hz, 1H; ArH), 3.84 (s, 3H; $OCH_3$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 182.7, 155.0, 133.9, 133.3, 130.3, 119.7, 114.7, 101.6, 71.6, 55.4. MS *m/z*: 301 ($M^+$). HRMS (EI): calcd for $C_{10}H_8INO_2$ 300.9600; found 300.9616.

*4.5.2. 3-Iodo-4,5-dimethoxylindole-2-carbaldehyde (**14b**)*

Yield 40%. mp 167–170 ºC (EtOAc-hexane). IR (ATR) ν = 3290 (NH), 1778 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ □ 12.32 (br s, 1H; NH), 9.81 (s, 1H; CHO), 7.33 (d, *J* = 9.1 Hz, 1H; ArH), 7.24 (d, *J* = 9.1 Hz, 1H; ArH), 3.92 (s, 3H; $OCH_3$), 3.89 (s, 3H; $OCH_3$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 183.5, 145.6, 142.6, 134.8, 134.2, 122.8, 117.8, 108.8, 65.6, 61.3, 57.7. MS *m/z*: 331 ($M^+$). HRMS (EI): calcd for $C_{11}H_{10}INO_3$ 330.9705; found 330.9727.

*4.5.3. 3-Iodo-4,7-dimethoxylindole-2-carbaldehyde (**14c**)*

Yield 51%. mp 160–163 ºC (EtOAc-hexane). IR (ATR) ν = 3259 (NH), 1666 (CO) $cm^{-1}$.$^1$H NMR

(300 MHz, DMSO-$d_6$) δ = 12.15 (br s, 1H; NH), 9.48 (s, 1H; CHO), 6.77 (d, *J* = 8.4 Hz, 1H; ArH), 6.38 (d, *J* = 8.4 Hz, 1H; ArH), 3.90 (s, 3H; $OCH_3$), 3.50 (s, 3H; $OCH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 181.8, 149.2, 141.3, 133.3, 129.2, 119.3, 117.4, 105.9, 99.6, 55.8, 55.1. MS *m/z*: 331 ($M^+$). HRMS (EI): calcd for $C_{11}H_{10}INO_3$ 330.9705; found 330.9703.

*4.5.4. 3-Iodo-4,6-dimethoxylindole-2-carbaldehyde (**14d**)*

Yield 83%. mp 166–170 ºC (EtOAc-hexane). IR (ATR) ν = 3271 (NH), 1612 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.14 (br s, 1H; NH), 9.57 (s, 1H; CHO), 6.42 (d, *J* = 2.0 Hz, 1H; ArH), 6.20 (d, *J* = 2.0 Hz, 1H; ArH), 3.84 (s, 3H; $OCH_3$), 3.77 (s, 3H; $OCH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 181.8, 160.8, 155.6, 140.7, 132.4, 114.2, 93.6, 86.5, 68.6, 55.4, 55.4. MS *m/z*: 331 ($M^+$). HRMS (EI): calcd for $C_{11}H_{10}INO_3$ 330.9705; found 330.9711.

*4.5.5. 3-Iodo-5,7-dimethoxylindole-2-carbaldehyde (**14e**)*

Yield 62%. mp 154–157 ºC (EtOAc-hexane). IR (ATR) ν = 3367 (NH), 1628 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.77 (s, 1H; CHO), 9.33 (br s, 1H; NH), 6.50 (d, *J* = 2.0 Hz, 1H; ArH), 6.48 (d, *J* = 2.0 Hz, 1H; ArH), 3.93 (s, 3H; $OCH_3$), 3.89 (s, 3H; $OCH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 182.4, 156.5, 147.2, 133.2, 131.3, 124.6, 100.1, 93.7, 71.6, 55.8, 55.8. MS *m/z*: 331 ($M^+$). HRMS (EI): calcd for $C_{11}H_{10}INO_3$ 330.9705; found 330.9729.

*4.5.6. 3-Iodo-5-methylindole-2-carbaldehyde (**14f**)*

Yield 72%. mp 169–171 ºC (EtOAc-hexane). IR (ATR) ν = 3294 (NH), 1647 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.30 (br s, 1H; NH), 9.77 (s, 1H; CHO), 7.36 (d, *J* = 8.3 Hz, 1H; ArH), 7.28 (s, 1H; ArH), 7.24 (d, *J* = 8.3 Hz, 1H; ArH), 2.42 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 182.9, 136.5, 133.7, 130.6, 130.1, 129.7, 121.5, 113.2, 72.1, 21.0. MS *m/z*: 285 ($M^+$). HRMS (EI): calcd for $C_{10}H_8INO$ 284.9651; found 284.9663.

*4.5.7. 3-Iodo-6-methylindole-2-carbaldehyde (**14g**)*

Yield 86%. mp 154–157 ºC (EtOAc-hexane). IR (ATR) ν = 3275 (NH), 1643 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 9.78 (s, 1H; CHO), 9.10 (br s, 1H; NH), 7.47 (d, *J* = 8.3 Hz, 1H; ArH), 7.19–7.23 (m, 1H; ArH), 7.09 (d, *J* = 8.0 Hz, 1H; ArH), 2.50 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 182.8, 139.3, 137.9, 133.2, 128.8, 124.4, 123.0, 112.2, 73.2, 22.1. MS *m/z*: 285 ($M^+$). HRMS (EI): calcd for $C_{10}H_8INO$ 284.9651; found 284.9653.

*4.5.8. 5-Chloro-3-iodoindole-2-carbaldehyde (**14h**)*

Yield 80%. mp 132–135 ºC (EtOAc-hexane). IR (ATR) ν = 3275 (NH), 1643 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.58 (br s, 1H; NH), 9.81 (s, 1H; CHO), 7.46-7.52 (m, 2H; ArH),

7.39–7.43 (m, 1H; ArH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 183.2, 136.4, 135.0, 131.0, 127.7, 126.1, 121.4, 115.4, 71.3. MS *m/z*: 304 ($M^+$), 306 ($M^+$+2). HRMS (EI): calcd for $C_9H_5ClINO$ 304.9104; found 304.9126.

*4.5.9. 6-Chloro-3-iodoindole-2-carbaldehyde (**14i**)*

Yield 74%. mp 137–139 ºC (EtOAc-hexane). IR (ATR) ν = 3267 (NH), 1651 (CO) cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 12.58 (br s, 1H; NH), 9.80 (s, 1H; CHO), 7.36–7.52 (m, 3H; ArH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 183.3, 136.4, 135.0, 131.0, 127.7, 126.1, 121.4, 115.4, 71.3. MS *m/z*: 304 ($M^+$), 306 ($M^+$+2). HRMS (EI): calcd for $C_9H_5ClNO$ 304.9104; found 304.9116.

*4.5.10. 3-Iodo-5-nitroindole-2-carbaldehyde (**14j**)*

Yield 56%. mp 171–173 ºC (EtOAc-hexane). IR (ATR) ν = 3310 (NH), 1687 (CO), 1561 ($NO_2$), 1357 ($NO_2$) cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 13.05 (br s, 1H; NH), 9.85 (s, 1H; CHO), 8.40 (d, *J* = 1.7 Hz, 1H; ArH), 8.23 (dd, *J* = 9.1, 1.7 Hz, 1H; ArH), 7.22 (d, *J* = 9.1 Hz, 1H; ArH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 183.6, 142.3, 140.7, 137.0, 129.4, 121.9, 119.7, 114.5, 74.8. MS *m/z*: 316 ($M^+$). HRMS (EI): calcd for $C_9H_5IN_2O_3$ 315.9345; found 315.9369

*4.5.11. 3-Iodo-6-nitroindole-2-carbaldehyde (**14k**)*

Yield 48%. mp 184–186 ºC (EtOAc-hexane). IR (ATR) ν = 3359 (NH), 1658 (CO), 1508 ($NO_2$), 1331 ($NO_2$) cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 12.51 (br s, 1H; NH), 9.80 (s, 1H; CHO), 7.50 (dd, *J* = 8.9, 4.6 Hz, 1H; ArH), 7.23–7.33 (m, 2H; ArH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 183.2, 159.5, 156.4, 134.7, 130.4, 116.9, 115.3, 106.8, 71.6. MS *m/z*: 316 ($M^+$). HRMS (EI): calcd for $C_9H_5IN_2O_3$ 315.9345; found 315.9349.

*4.5.12. 3-Iodo-5-trifluromethylindole-2-carbaldehyde (**14l**)*

Yield 85%. mp 176–178 ºC (EtOAc-hexane). IR (ATR) ν = 3286 (NH), 1651 (CO) cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 12.79 (br s, 1H; NH), 9.83 (s, 1H; CHO), 7.64–7.80 (m, 3H; ArH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 183.5, 139.3, 135.7, 129.3, 124.6 (q, $J_{C–F}$ = 270.9 Hz), 123.4 (q, $J_{C–F}$ = 2.5 Hz), 122.2 (q, $J_{C–F}$ = 31.5 Hz), 120.3 (q, $J_{C–F}$ = 3.9 Hz), 114.8, 73.2. MS *m/z*: 339 ($M^+$). HRMS (EI): calcd for $C_{10}H_5F_3INO$ 338.9368; found 338.9376.

*4.5.13. 3-Iodo-6-trifluromethylindole-2-carbaldehyde (**14m**)*

Yield 56%. mp 168–170 ºC (EtOAc-hexane). IR (ATR) ν = 3278 (NH), 1658 (CO) cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 12.83 (br s, 1H; NH), 9.87 (s, 1H; CHO), 7.75–7.78 (m, 2H; ArH), 7.49 (d, *J* = 8.6 Hz, 1H; ArH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 183.7, 136.6, 136.1, 132.3, 127.2 (q, $J_{C–F}$ = 31.6 Hz), 124.4 (q, $J_{C–F}$ = 271.9 Hz), 124.1, 117.3 (q, $J_{C–F}$ = 3.6 Hz), 110.9 (q, $J_{C–F}$ = 4.8 Hz),

71.9. MS *m/z*: 339 ($M^+$). HRMS (EI): calcd for $C_{10}H_5F_3INO$ 338.9368; found 338.9348.

*4.5.14. 5-Fluoro-3-iodoindole-2-carbaldehyde (**14n**)*

Yield 54%. mp 148–149 ºC (EtOAc-hexane). IR (ATR) ν = 3297 (NH), 1639 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.50 (br s, 1H; NH), 9.78 (s, 1H; CHO), 7.46–7.50 (m, 1H; ArH), 7.22–7.30 (m, 2H; ArH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 183.2, 159.5 (d, $J_{C–F}$ = 235.3 Hz), 135.0 (d, $J_{C–F}$ = 37.7 Hz), 130.3 (d, $J_{C–F}$ = 9.5 Hz), 121.8, 116.8 (d, $J_{C–F}$ = 27.6 Hz), 115.3 (d, $J_{C–F}$ = 10.0 Hz), 106.5 (d, $J_{C–F}$ = 26.5 Hz), 71.6. MS *m/z*: 289 ($M^+$). HRMS (EI): calcd for $C_9H_5FINO$ 288.9400; found 288.9411.

*4.5.15. 6-Fluoro-3-iodoindole-2-carbaldehyde (**14o**)*

Yield 87%. mp 140–142 ºC (EtOAc-hexane). IR (ATR) ν = 3286 (NH), 1651 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.77 (s, 1H; CHO), 9.60 (br s, 1H; NH), 7.57 (dd, *J* = 9.0, 5.4 Hz, 1H; ArH), 7.12 (d, *J* = 9.0 Hz, 1H; ArH), 6.99–7.05 (m, 1H; ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 182.6, 165.2, 137.6 (d, $J_{C–F}$ = 13.4 Hz), 134.4 (d, $J_{C–F}$ = 3.4 Hz), 127.4, 125.1 (d, $J_{C–F}$ = 11.2 Hz), 98.7, 98.3, 72.9. MS *m/z*: 289 ($M^+$); HRMS (EI): calcd for $C_9H_5FINO$ 288.9400; found 288.9411.

*4.5.16. 3-Iodobenzo[e]indole-2-carbaldehyde (**14p**)*

Yield 61%. mp 170–172 ºC (EtOAc-hexane). IR (ATR) ν = 3244 (NH), 1627 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.94 (br s, 1H; NH), 9.84 (s, 1H; CHO), 9.41 (d, *J* = 8.6 Hz, 1H; ArH), 8.01 (d, *J* = 7.9 Hz, 1H; ArH), 7.86 (d, *J* = 8.6 Hz, 1H; ArH), 7.72 (t, *J* = 7.9 Hz, 1H; ArH), 7.52–7.61 (m, 2H; ArH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 182.7, 136.5, 132.5, 129.8, 129.5, 129.1, 128.8, 126.5, 124.8, 120.6, 120.4, 114.1, 70.0. MS *m/z*: 321 ($M^+$). HRMS (EI): calcd for $C_{13}H_8INO$ 320.9651; found 320.9667.

*4.5.17. 3-Iodobenzo[f]indole-2-carbaldehyde (**14q**)*

Yield 85%. mp 161–162 ºC (EtOAc-hexane). IR (ATR) ν = 3267 (NH), 1612 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 13.34 (br s, 1H; NH), 9.79 (s, 1H; CHO), 8.75 (d, *J* = 7.9 Hz, 1H; ArH), 7.97 (d, *J* = 7.9 Hz, 1H; ArH), 7.5–7.64 (m, 3H; ArH), 7.47 (d, *J* = 8.7 Hz, 1H; ArH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 182.0, 134.8, 132.8, 132.8, 128.8, 126.8, 126.6, 126.6, 123.1, 122.5, 122.0, 120.6, 74.9. MS *m/z*: 321 ($M^+$). HRMS (EI): calcd for $C_{13}H_8INO$ 320.9651; found 320.9651.

*4.6. General procedure for the synthesis of 3-Acryloylindole-2-carbaldehyde (**15a–15s**)*

Carbon monoxide was bubbled for 5 min to a mixture of the iodoindole **14** (514 mmol), isopropenyltributyltin (617 mmol), BHT (617 mmol), and $PdCl_2$(dppf) (26 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 as an eluent to give the 3-acryloylindole **15**.

*4.6.1. 5-Methoxy-3-(2-methylpropenoyl)indole-2-carbaldehyde (**15a**)*

Yield 61%. mp 152–153 ºC (EtOAc-hexane). IR (ATR) ν = 3305 (NH), 1655 (CO), 1620 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 10.07 (s, 1H; CHO), 9.62 (br s, 1H, NH), 7.38 (d, *J* = 9.0 Hz, 1H; ArH), 7.35 (d, *J* = 2.4 Hz, 1H; ArH), 7.10 (dd, *J* = 9.0, 2.4 Hz, 1H; ArH), 6.01 (s, 1H; $=CH_2$), 5.84 (s, 1H; $=CH_2$), 3.85 (s, 3H; $OCH_3$), 2.19 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 192.9, 182.8, 156.3, 147.7, 136.3, 131.5, 127.9, 127.5, 122.0, 119.7, 113.5, 102.9, 55.7, 18.2. MS *m/z*: 243 ($M^+$). HRMS (EI): calcd for $C_{14}H_{13}NO_3$ 243.0895; found 243.0908.

*4.6.2. 4,5-Dimethoxy-3-(2-methylpropenoyl)indole-2-carbaldehyde (**15b**)*

Yield 70%. mp 166–168 ºC (EtOAc-hexane). IR (ATR) ν = 3263 (NH), 1658 (CO), 1647 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.75 (s, 1H; CHO), 9.30 (br s, 1H; NH), 7.19 (d, *J* = 8.9 Hz, 1H; ArH), 7.13 (d, *J* = 8.9 Hz, 1H; ArH), 5.96 (s, 1H; $=CH_2$), 5.63 (s, 1H; $=CH_2$), 3.89 (s, 3H; $OCH_3$), 3.86 (s, 3H; $OCH_3$), 2.15 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 194.8, 181.8, 146.9, 146.3, 143.0, 134.4, 133.1, 129.1, 124.6, 122.2, 118.5, 107.6, 60.5, 58.0, 17.5. MS *m/z*: 273 ($M^+$). HRMS (EI): calcd for $C_{15}H_{15}NO_4$ 273.1001; found 273.1019.

*4.6.3. 4,7-Dimethoxy-3-(2-methylpropenoyl)indole-2-carbaldehyde (**15c**)*

Yield 75%. mp 157–158 ºC (EtOAc-hexane). IR (ATR) ν = 3263 (NH), 1646 (CO), 1620 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.73 (s, 1H; CHO), 9.37 (br s, 1H; NH), 6.69 (d, *J* = 8.5 Hz, 1H; ArH), 6.39 (d, *J* = 8.5 Hz, 1H; ArH), 5.91 (s, 1H; $=CH_2$), 5.57 (s, 1H; $=CH_2$), 3.93 (s, 3H; $OCH_3$), 3.79 (s, 3H; $OCH_3$), 2.12 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 194.6, 181.2, 148.7, 147.0, 146.9, 140.8, 133.1, 128.7, 125.4, 118.6, 106.5, 100.5, 55.8, 55.7, 17.5. MS *m/z*: 273 ($M^+$). HRMS (EI): calcd for $C_{15}H_{15}NO_4$ 273.1001; found 273.1008.

*4.6.4. 4,6-Dimethoxy-3-(2-methylpropenoyl)indole-2-carbaldehyde (**15d**)*

Yield 83%. mp 149–151 ºC (EtOAc-hexane). IR (ATR) ν = 3263 (NH), 1658 (CO), 1647 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.60 (s, 1H; CHO), 9.13 (br s, 1H; NH), 6.42 (d, *J* = 1.8 Hz, 1H; ArH), 6.19 (d, *J* = 1.8 Hz, 1H; ArH), 5.91 (s, 1H; $=CH_2$), 5.60 (s, 1H; $=CH_2$), 3.86 (s, 3H; $OCH_3$), 3.81 (s, 3H; $OCH_3$), 2.11 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 194.8, 180.4, 162.2, 155.5, 146.9, 138.7, 132.6, 128.9, 126.4, 112.9, 94.3, 86.0, 55.7, 55.4, 17.2. MS *m/z*: 273 ($M^+$). HRMS

(EI): calcd for $C_{15}H_{15}NO_4$ 273.1001; found 273.1022.

*4.6.5. 5,7-Dimethoxy-3-(2-methylpropenoyl)indole-2-carbaldehyde (**15e**)*

Yield 90%. mp 155–157 ºC (EtOAc-hexane). IR (ATR) ν = 3263 (NH), 1662 (CO), 1647 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 10.04 (s, 1H; CHO), 9.49 (br s, 1H; NH), 6.90 (d, *J* = 1.8 Hz, 1H; ArH), 6.49 (d, *J* = 1.8 Hz, 1H; ArH), 5.98 (s, 1H; $=CH_2$), 5.83 (s, 1H; $=CH_2$), 3.95 (s, 3H; $OCH_3$), 3.84 (s, 3H; $OCH_3$), 2.18 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 193.0, 182.5, 157.2, 147.4, 147.0, 135.7, 127.8, 127.7, 123.4, 122.0, 99.3, 94.0, 55.8, 55.7, 18.1. MS *m/z*: 273 ($M^+$). HRMS (EI): calcd for $C_{15}H_{15}NO_4$ 273.1001; found 273.1003

*4.6.6. 5-Methyl-3-(2-methylpropenoyl)indole-2-carbaldehyde (**15f**)*

Yield 79%. mp 137–139 ºC (EtOAc-hexane). IR (ATR) ν = 3294 (NH), 1651 (CO), 1620 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 10.07 (s, 1H; CHO), 9.45 (br s, 1H; NH), 7.37 (d, *J* = 8.6 Hz, 1H; ArH), 7.24–7.26 (m, 2H; ArH), 6.02 (s, 1H; $=CH_2$), 5.85 (s, 1H; $=CH_2$), 2.45 (s, 3H; $OCH_3$), 2.19 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 193.1, 183.3, 147.2, 136.0, 134.8, 132.5, 129.6, 128.4, 126.9, 122.6, 122.4, 112.3, 21.6, 18.0. MS *m/z*: 227 ($M^+$). HRMS (EI): calcd for $C_{14}H_{13}NO_2$ 227.0946; found 227.0962.

*4.6.7. 6-Methyl-3-(2-methylpropenoyl)indole-2-carbaldehyde (**15g**)*

Yield 65%. mp 124–126 ºC (EtOAc-hexane). IR (ATR) ν = 3298 (NH), 1651 (CO), 1619 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 10.06 (s, 1H; CHO), 9.42 (br s, 1H; NH), 7.79 (d, *J* = 8.3 Hz, 1H; ArH), 7.13–7.33 (m, 1H; ArH), 7.09 (dd, *J* = 8.3, 1.2 Hz, 1H; ArH), 6.02 (s, 1H; $=CH_2$), 5.84 (s, 1H; $=CH_2$), 2.49 (s, 3H; $CH_3$), 2.18 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 192.9, 183.0, 147.1, 138.2, 136.6, 135.7, 128.3, 125.1, 124.7, 123.1, 123.0, 112.0, 22.0, 18.0. MS *m/z*: 227 ($M^+$). HRMS (EI): calcd for $C_{14}H_{13}NO_2$ 227.0946; found 227.0924.

*4.6.8. 5-Chloro-3-(2-methylpropenoyl)indole-2-carbaldehyde (**15h**)*

Yield 75%. mp 142–144 ºC (EtOAc-hexane). IR (ATR) ν = 3290 (NH), 1658 (CO), 1631 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 10.10 (s, 1H; CHO), 9.64 (br s, 1H; NH), 7.90 (d, *J* = 1.9 Hz, 1H; ArH), 7.44 (dd, *J* = 8.9, 0.6 Hz, 1H; ArH), 7.38 (dd, *J* = 8.9, 1.9 Hz, 1H; ArH), 6.06 (s, 1H; $=CH_2$), 5.84 (s, 1H; $=CH_2$), 2.19 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 192.2, 183.0, 147.1, 136.9, 134.3, 128.8, 128.6, 128.1, 127.5, 122.6, 122.1, 113.7, 18.0. MS *m/z*: 247 ($M^+$), 249 ($M^+$+2). HRMS (EI): calcd for $C_{13}H_{10}ClNO_2$ 247.0400; found 247.0382.

*4.6.9. 6-Chloro-3-(2-methylpropenoyl)indole-2-carbaldehyde (**15i**)*

Yield 62%. mp 149–151 ºC (EtOAc-hexane). IR (ATR) ν = 3278 (NH), 1651 (CO), 1612 (CO) $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$) δ = 10.11 (s, 1H; CHO), 9.84 (br s, 1H; NH), 7.90 (d, *J* = 1.8 Hz, 1H; ArH), 7.46 (d, *J* = 8.8 Hz, 1H; ArH), 7.38 (dd, *J* = 8.8, 1.8 Hz, 1H; ArH), 6.06 (s, 1H; $=CH_2$), 5.84 (s, 1H; $=CH_2$), 2.19 (s, 3H; $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 192.3, 183.1, 147.1, 136.9, 134.4, 128.7, 128.6, 128.1, 127.5, 122.6, 122.2, 113.8, 18.0. MS *m/z*: 247 ($M^+$), 249 ($M^+$+2). HRMS (EI): calcd for $C_{13}H_{10}ClNO_2$ 247.0400; found 247.0411.

*4.6.10. 3-(2-Methylpropenoyl)-5-nitroindole-2-carbaldehyde (**15j**)*

Yield 55%. mp 156–158 ºC (EtOAc-hexane). IR (ATR) ν = 3261 (NH), 1663 (CO), 1620 (CO), 1553 ($NO_2$), 1330 ($NO_2$) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 10.15 (s, 1H; CHO), 9.93 (br s, 1H; NH), 8.88 (d, *J* = 2.2 Hz, 1H; ArH), 8.32 (dd, *J* = 8.9, 2.2 Hz, 1H; ArH), 7.62 (d, *J* = 8.9 Hz, 1H; ArH), 6.15 (s, 1H; $=CH_2$), 5.87 (s, 1H; $=CH_2$), 2.23 (s, 3H; $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 191.4, 182.7, 147.2, 143.9, 138.3, 138.2, 129.5, 125.9, 124.2, 122.3, 120.7, 113.1, 17.9. MS *m/z*: 258 ($M^+$). HRMS (EI): calcd for $C_{13}H_{10}N_2O_4$ 258.0641; found 258.0638.

*4.6.11. 3-(2-Methylpropenoyl)-6-nitroindole-2-carbaldehyde (**15k**)*

Yield 70%. mp 164–166 ºC (EtOAc-hexane). IR (ATR) ν = 3282 (NH), 1662 (CO), 1620 (CO), 1512 ($NO_2$), 1342 ($NO_2$) $cm^{-1}$.$^1$H NMR (300 MHz, $CDCl_3$) δ = 10.22 (br s, 1H; CHO), 10.19 (s, 1H; NH), 8.50 (d, *J* = 1.9 Hz, 1H; ArH), 8.32 (dd, *J* = 9.2, 1.9 Hz, 1H; ArH), 8.16 (d, *J* = 9.2 Hz, 1H; ArH), 6.12 (s, 1H; $=CH_2$), 5.85 (s, 1H; $=CH_2$), 2.22 (s, 3H; $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 191.8, 183.0, 147.1, 146.7, 139.3, 134.5, 130.6, 129.2, 124.1, 122.3, 117.5, 109.5, 17.9. MS *m/z*: 258 ($M^+$). HRMS (EI): calcd for $C_{13}H_{10}N_2O_4$ 258.0641; found 258.0615.

*4.6.12. 3-(2-Methylpropenoyl)-5-trifluoromethylindole-2-carbaldehyde (**15l**)*

Yield 67%. mp 145–146 ºC (EtOAc-hexane). IR (ATR) ν = 3290 (NH), 1661 (CO), 1620 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 10.13 (s, 1H; CHO), 9.78 (s, 1H; NH), 8.24 (d, *J* = 0.8 Hz, 1H; ArH), 7.65 (dd, *J* = 8.9, 1.8 Hz, 1H; ArH), 7.60 (d, *J* = 8.8 Hz, 1H; ArH), 6.10 (s, 1H; $=CH_2$), 5.85 (s, 1H; $=CH_2$), 2.21 (s, 3H; $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 192.0, 182.9, 147.3, 137.2, 137.1, 134.4 (q, $J_{C–F}$ = 272.8 Hz), 129.1, 125.9, 125.3 (q, $J_{C–F}$ = 32.7 Hz), 124.0 (q, $J_{C–F}$ = 3.6 Hz), 123.3, 121.4 (q, $J_{C–F}$ = 4.2 Hz), 113.2, 18.0. MS *m/z*: 281 ($M^+$). HRMS (EI): calcd for $C_{14}H_{10}F_3NO_2$ 281.0664; found 281.0673.

*4.6.13. 3-(2-Methylpropenoyl)-6-trifluoromethylindole-2-carbaldehyde (**15m**)*

Yield 75%. mp 152–153 ºC (EtOAc-hexane). IR (ATR) ν = 3290 (NH), 1666 (CO), 1616 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ = 10.15 (s, 1H; CHO), 9.83 (br s, 1H; NH), 8.04 (d, *J* = 8.6 Hz, 1H; ArH), 7.72–7.94 (m, 1H; ArH), 7.48 (dd, *J* = 8.6, 1.1 Hz, 1H; ArH), 6.08 (s, 1H; $=CH_2$), 5.84 (s, 1H; $=CH_2$), 2.20 (s, 3H; $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ= 192.2, 183.0, 147.1, 137.7, 134.8,

129.1, 128.9, 128.6, 124.3, 123.9 (q, $J_{C–F}$ = 272.9 Hz), 122.4, 119.2 (q, $J_{C–F}$ = 3.9 Hz), 119.2 (q, $J_{C–F}$ = 4.1 Hz), 18.0. MS *m/z*: 281 ($M^+$). HRMS (EI): calcd for $C_{14}H_{10}F_3NO_2$: 281.0664; found 281.0688.

*4.6.14. 5-Fluoro-3-(2-methylpropenoyl)indole-2-carbaldehyde (**15n**)*

Yield 75%. mp 141–143 ºC (EtOAc-hexane). IR (ATR) ν = 3298 (NH), 1658 (CO), 1620 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 10.12 (s, 1H; CHO), 9.71 (br s, 1H; NH), 7.58 (dd, *J* = 9.4, 2.4 Hz, 1H; ArH), 7.47 (dd, *J* = 8.9, 4.3 Hz, 1H; ArH), 7.20 (dt, *J* = 8.9, 2.4 Hz, 1H; ArH), 6.04 (s, 1H; $=CH_2$), 5.84 (s, 1H; $=CH_2$), 2.19 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 192.4, 183.1, 159.2 (d, $J_{C–F}$ = 239.6 Hz), 147.1, 137.3, 132.7, 128.3, 127.1 (d, $J_{C–F}$ = 4.2 Hz), 122.7, 116.9 (d, $J_{C–F}$ = 27.6 Hz), 113.8 (d, $J_{C–F}$ = 8.9 Hz), 108.0 (d, $J_{C–F}$ = 24.1 Hz), 18.0. MS *m/z*: 231 ($M^+$). HRMS (EI): calcd for $C_{13}H_{10}FNO_2$ 231.0696; found 231.0682.

*4.6.15. 6-Fluoro-3-(2-methylpropenoyl)indole-2-carbaldehyde (**15o**)*

Yield 71%. mp 149–151 ºC (EtOAc-hexane). IR (ATR) ν = 3301 (NH), 1655 (CO), 1620 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 10.06 (s, 1H; CHO), 9.74 (br s, 1H; NH), 7.89 (dd, *J* = 9.2, 5.3 Hz, 1H; ArH), 7.17 (dd, *J* = 9.0, 2.2 Hz, 1H; ArH), 7.04 (dt, *J* = 9.1, 2.2 Hz, 1H; ArH), 6.05 (s, 1H; $=CH_2$), 5.84 (s, 1H; $=CH_2$), 2.19 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 192.5, 182.6, 162.6 (d, $J_{C–F}$ = 247.7 Hz, 1H), 147.3, 136.6 (d, $J_{C–F}$ = 4.7 Hz), 136.5 (d, $J_{C–F}$ = 5.0 Hz), 128.7, 125.0 (d, $J_{C–F}$ = 10.0 Hz), 123.4, 123.1, 112.7 (d, $J_{C–F}$ = 24.9 Hz), 98.4 (d, $J_{C–F}$ = 26.0 Hz), 18.0. MS *m/z*: 231 ($M^+$). HRMS (EI): calcd for $C_{13}H_{10}FNO_2$ 231.0696; found 231.0692.

*4.6.16. 3-(2-Methylpropenoyl)benzo[e]indole-2-carbaldehyde (**15p**)*

Yield 60%. mp 166–168 ºC (EtOAc-hexane). IR (ATR) ν = 3267 (NH), 1651 (CO), 1635 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 11.14 (br s, 1H; NH), 10.10 (s, 1H; CHO), 8.39 (d, *J* = 7.3 Hz, 1H; ArH), 7.88–7.91 (m, 1H; ArH), 7.80 (d, *J* = 8.9 Hz, 1H; ArH), 7.54–7.65 (m, 3H; ArH), 6.07 (s, 1H; $=CH_2$), 5.90 (s, 1H; $=CH_2$), 2.22 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 193.1, 182.7, 140.0, 134.5, 133.2, 132.7, 129.1, 128.9, 127.0, 126.8, 125.0, 124.2, 123.4, 121.5, 121.4, 120.7, 18.0. MS *m/z*: 263 ($M^+$). HRMS (EI): calcd for $C_{17}H_{13}NO_2$ 263.0946; found 263.0933.

*4.6.17. 3-(2-Methylpropenoyl)benzo[f]indole-2-carbaldehyde (**15q**)*

Yield 84%. mp 173–174 ºC (EtOAc-hexane). IR (ATR) ν = 3270 (NH), 1658 (CO), 1628 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 10.04 (br s, 1H; NH), 9.74 (s, 1H; CHO), 7.88–7.91 (m, 2H; ArH), 7.82 (d, *J* = 8.9 Hz, 1H; ArH), 7.45-7.56 (m, 3H; ArH), 6.07 (s, 1H; $=CH_2$), 5.90 (s, 1H; $=CH_2$), 2.27 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 197.3, 183.1, 147.0, 138.0, 134.2, 132.7, 129.5, 128.9, 127.0, 126.8, 125.3, 124.2, 123.4, 121.5, 121.4, 120.7, 18.0. MS *m/z*: 263($M^+$). HRMS (EI): calcd for $C_{17}H_{13}NO_2$ 263.0946; found 263.0941.

*4.6.18. 3-(2-Methylpropenoyl)indole-2-carbaldehyde (**15r**)*

Yield 64%. mp 118–119 ºC (EtOAc-hexane). IR (ATR) ν = 3289 (NH), 1651 (CO), 1622 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 10.11 (s, 1H; CHO), 9.63 (br s, 1H; NH), 7.93 (d, *J* = 8.3 Hz, 1H; ArH), 7.51 (d, *J* = 8.3 Hz, 1H; ArH), 7.44 (dt, *J* = 6.8, 1.1 Hz, 1H; ArH), 7.26 (dt, *J* = 6.8, 1.1 Hz, 1H; ArH), 6.04 (s, 1H; $=CH_2$), 5.86 (s, 1H; $=CH_2$), 2.19 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 192.8, 183.2, 147.1, 136.0, 136.0, 128.6, 127.5, 126.7, 123.4, 123.0, 122.8, 112.5, 18.0. MS *m/z*: 213 ($M^+$). HRMS (EI): calcd for $C_{13}H_{11}NO_2$: 213.0790; found 213.0812.

*4.6.19. 3-Propenoylindole-2-carbaldehyde (**15s**)*

Yield 23%. mp 113–115 ºC (EtOAc-hexane). IR (ATR) ν = 3298 (NH), 1658 (CO), 1619 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 10.35 (s, 1H; CHO), 9.62 (br s, 1H; NH), 7.53 (d, *J* = 8.3 Hz, 1H; ArH), 7.46 (dt, *J* = 6.8, 1.1 Hz, 1H; ArH), 7.33 (dt, *J* = 6.8, 1.1 Hz, 1H; ArH), 7.19 (dd, *J* = 17.2, 10.5 Hz, 1H; $CH=CH_2$), 6.48 (dd, *J* = 17.2, 1.3 Hz, 1H; $CH=CH_2$), 6.04 (dd, *J* = 10.5, 1.3 Hz, 1H; $CH=CH_2$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 188.1, 184.0, 136.5, 136.5, 136.2, 130.2, 127.4, 125.8, 123.3, 123.0, 122.8, 112.9. MS *m/z*: 199 ($M^+$). HRMS (EI): calcd for $C_{12}H_9NO_2$ 199.0633; found 199.0658.

*4.7. General procedure for the synthesis of 3-acryloyl-2-allylindole (**16a–16s**)*

A solution of vinylmagnesium bromide (1 M in THF, 0.35 mmol) was added dropwise to a solution of 3-acryloylindole **15** (0.23 mmol) in THF (20 mL) under cooling with ice-water. After stirring at rt for 4 h, 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 as an eluent to give the allyl alcohol **16**.

*4.7.1. 2-(1-Hydroxyprop-2-en-1-yl)-5-methoxy-3-(2-methylpropenoyl)indole (**16a**)*

Yield 70%. IR (ATR) ν = 3194 (OH), 1651 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 8.91 (br s, 1H; NH), 7.30 (d, *J* = 2.4 Hz, 1H; ArH), 7.24–7.27 (m, 1H; ArH), 6,87 (dd, *J* = 8.8, 2.4 Hz, 1H; ArH), 6.16 (ddd, *J* = 17.2, 10.5, 5.3 Hz, 1H; $CH=CH_2$), 5.76 (s, 1H; $=CH_2$), 5.73 (s, 1H; $=CH_2$), 5.54–5.73 (m, 1H; CH), 5.54 (td, *J* = 17.2, 1.5 Hz, 1H; $CH=CH_2$), 5.37 (td, *J* = 10.5, 1.5 Hz, 1H; $CH=CH_2$), 4.81 (d, *J* = 4.6 Hz, 1H; OH), 3.82 (s, 3H; $OCH_3$), 2.14 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 195.3, 155.5, 147.7, 146.2, 135.9, 129.3, 127.9, 123.5, 117.5, 113.0, 112.7, 112.3, 103.7, 68.0, 55.8, 18.6. MS *m/z*: 271 ($M^+$). HRMS (EI): calcd for $C_{16}H_{17}NO_3$ 271.1208; found 271.1223

*4.7.2. 2-(1-Hydroxyprop-2-en-1-yl)-4,5-dimethoxy-3-(2-methylpropenoyl)indole (**16b**)*

Yield 56%. IR (ATR) ν = 3267 (OH), 1620 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 8.59 (br s, 1H; NH), 7.05 (d, *J* = 9.0 Hz, 1H; ArH), 6.95 (d, *J* = 9.0 Hz, 1H; ArH), 6.11 (ddd, *J* = 17.1, 10.2, 5.0 Hz, 1H; $CH=CH_2$), 5.70 (s, 1H; $=CH_2$), 5.52 (d, *J* = 17.1 Hz, 1H; $CH=CH_2$), 5.51 (s, 1H; $=CH_2$), 5.43 (br s, 1H; CH), 5.34 (d, *J* = 10.2 Hz, 1H; $CH=CH_2$), 4.10 (br s, 1H; OH), 3.88 (s, 3H; $OCH_3$), 3.77 (s, 3H; $OCH_3$), 2.10 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 197.4, 158.2, 153.8, 147.1, 141.2, 136.3, 135.7, 124.2, 116.8, 113.7, 93.5, 86.8, 67.3, 55.6, 54.9, 29.7, 17.9. MS *m/z*: 301 ($M^+$). HRMS (EI): calcd for $C_{17}H_{19}NO_4$ 301.1314; found 301.1322.

*4.7.3. 2-(1-Hydroxyprop-2-en-1-yl)-4,7-dimethoxy-3-(2-methylpropenoyl)indole (**16c**)*

Yield 79%. IR (ATR) ν = 3259 (OH), 1647 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 8.76 (br s, 1H; NH), 6.56 (d, *J* = 8.5 Hz, 1H; ArH), 6.44 (d, *J* = 8.5 Hz, 1H; ArH), 6.13 (ddd, *J* = 17.3, 10.5, 5.2 Hz, 1H; $CH=CH_2$), 5.62 (s, 1H; $=CH_2$), 5.53 (d, *J* = 17.3 Hz, 1H; $CH=CH_2$), 5.43 (br s, 1H; CH), 5.41 (s, 1H; $=CH_2$), 5.34 (d, *J* = 10.5 Hz, 1H; $CH=CH_2$), 4.01–4.20 (m, 1H; OH), 3.91 (s, 3H; $OCH_3$), 377 (s, 3H; $OCH_3$), 2.08 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 197.4, 147.5, 147.2, 142.3, 140.7, 136.1, 125.8, 124.3, 118.7, 117.1, 114.1, 102.7, 101.4, 67.4, 55.7, 55.3, 17.9. MS *m/z*: 301 ($M^+$). HRMS (EI): calcd for $C_{17}H_{19}NO_4$ 301.1314; found 301.1346.

*4.7.4. 2-(1-Hydroxyprop-2-en-1-yl)-4,6-dimethoxy-3-(2-methylpropenoyl)indole (**16d**)*

Yield 53%. IR (ATR) ν = 3259 (OH), 1646 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 8.50 (br s, 1H; NH), 6.46 (d, *J* = 2.0 Hz, 1H; ArH), 6.24 (d, *J* = 2.0 Hz, 1H; ArH), 6.11 (ddd, *J* = 17.2, 10.5, 5.2 Hz, 1H; $CH=CH_2$), 5.62 (s, 1H; $=CH_2$), 5.52 (td, *J* = 17.2, 1.4 Hz, 1H; $CH=CH_2$), 5.40–5.43 (m, 2H; $=CH_2$, CH), 5.33 (td, *J* = 10.5, 1.4 Hz, 1H; $CH=CH_2$), 3.92–3.98 (m, 1H; OH), 3.82 (s, 3H; $OCH_3$), 3.78 (s, 3H; $OCH_3$), 2.07 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 197.4, 158.2, 153.8, 147.1, 141.2, 136.3, 135.7, 124.2, 116.8, 113.7, 93.5, 86.8, 67.3, 55.6, 54.9, 29.7, 17.9. MS *m/z*: 301 ($M^+$). HRMS (EI): calcd for $C_{17}H_{19}NO_4$ 301.1314; found 301.1310.

*4.7.5. 2-(1-Hydroxyprop-2-en-1-yl)-5,7-dimethoxy-3-(2-methylpropenoyl)indole (**16e**)*

Yield 37%. IR (ATR) ν = 3209 (OH), 1597 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 8.87 (br s, 1H; NH), 6.86 (d, *J* = 2.0 Hz, 1H; ArH), 6.36 (d, *J* = 2.0 Hz, 1H; ArH), 6.17 (ddd, *J* = 17.3, 10.6, 5.2 Hz, 1H; $CH=CH_2$), 5.75 (s, 1H; $=CH_2$), 5.73 (s, 1H; CH), 5.59 (s, 1H; $=CH_2$), 5.55 (td, *J* = 17.3, 1.4 Hz, 1H; $CH=CH_2$), 5.39 (td, *J* = 10.6, 1.4 Hz, 1H; $CH=CH_2$), 4.74 (br d, 1H; OH), 3.92 (s, 3H; $OCH_3$), 3.81 (s, 3H; $OCH_3$), 2.13 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 195.4, 156.3, 146.5, 146.1, 135.8, 128.1, 123.4, 120.0, 117.5, 113.6, 94.9, 94.8, 67.9, 55.8, 55.5, 29.7, 18.6. MS *m/z*: 301 ($M^+$). HRMS (EI): calcd for $C_{17}H_{19}NO_4$ 301.1314; found 301.1318.

*4.7.6. 2-(1-Hydroxyprop-2-en-1-yl)-5-methyl-3-(2-methylpropenoyl)indole (**16f**)*

Yield 43%. IR (ATR) ν = 3235 (OH), 1619 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.38 (br s, 1H; NH), 7.57 (s, 1H; ArH), 7.23 (d, *J* = 8.1 Hz, 1H; ArH), 7.01 (d, *J* = 8.1 Hz, 1H; ArH), 6.12 (ddd, *J* = 17.2, 10.7, 5.5 Hz, 1H; $CH=CH_2$), 5.75 (s, 1H; $=CH_2$), 5.70 (s, 1H; $=CH_2$), 5.57–5.59 (m, 1H; CH), 5.45 (dd, *J* = 17.2, 1.5 Hz, 1H; $CH=CH_2$), 5.31 (br s, 1H; OH), 5.27 (dd, *J* = 10.7, 1.5 Hz, 1H; $CH=CH_2$), 2.42 (s, 3H; $CH_3$), 2.13 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 195.7, 147.4, 146.0, 136.0, 132.7, 131.2, 127.3, 124.5, 123.9, 120.8, 117.0, 112.5, 111.4, 68.1, 21.7, 18.6. MS *m/z*: 255 ($M^+$). HRMS (EI): calcd for $C_{16}H_{17}NO_2$ 255.1259; found 255.1272.

*4.7.7. 2-(1-Hydroxyprop-2-en-1-yl)-6-methyl-3-(2-methylpropenoyl)indole (**16g**)*

Yield 44%. IR (ATR) ν = 3274 (OH), 1597 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 8.94 (br s, 1H; NH), 7.68 (d, *J* = 8.2 Hz, 1H; ArH), 7.14 (s, 1H; ArH), 7.00 (d, *J* = 8.2 Hz, 1H; ArH), 6.16 (ddd, *J* = 17.2, 10.4, 5.1 Hz, 1H; $CH=CH_2$), 5.77 (s, 1H; $=CH_2$), 5.71 (s, 1H; $=CH_2$), 5.59–5.62 (m, 1H; CH), 5.52 (d, *J* = 17.2 Hz, 1H; $CH=CH_2$), 5.35 (d, *J* = 10.4 Hz, 1H; $CH=CH_2$), 4.82–4.99 (m, 1H; OH), 2.43 (s, 3H; $CH_3$), 2.13 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 195.4, 146.7, 146.0, 135.9, 134.6, 133.0, 124.9, 123.9, 123.6, 120.9, 117.3, 113.0, 111.5, 68.0, 21.5, 18.6. MS *m/z*: 255 ($M^+$). HRMS (EI): calcd for $C_{16}H_{17}NO_2$ 255.1259; found 255.1266.

*4.7.8. 5-Chloro-2-(1-hydroxyprop-2-en-1-yl)-3-(2-methylpropenoyl)indole (**16h**)*

Yield 74%. IR (ATR) ν = 3169 (OH), 1701 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.12 (br s, 1H; NH), 7.75 (d, *J* = 1.9 Hz, 1H; ArH), 7.29 (d, *J* = 8.6 Hz, 1H; ArH), 7.17 (dd, *J* = 8.6, 1.9 Hz, 1H; ArH), 6.15 (ddd, *J* = 17.2, 10.5, 5.0 Hz, 1H; $CH=CH_2$), 5.83 (s, 1H; $=CH_2$), 5.71 (s, 1H; $=CH_2$), 5.60–5.71 (m, 1H; CH), 5.52 (td, *J* = 17.2, 1.4 Hz, 1H; $CH=CH_2$), 5.37 (td, *J* = 10.5, 1.4 Hz, 1H; $CH=CH_2$), 4.62 (br s, 1H; OH), 2.13 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 194.9, 148.1, 145.9, 135.7, 132.6, 128.2, 127.7, 124.7, 123.4, 120.7, 120.6, 117.6, 112.7, 67.8, 18.4. MS *m/z*: 275 ($M^+$), 277 ($M^+$+2). HRMS (EI): calcd for $C_{15}H_{14}ClNO_2$ 275.0713; found 275.0727.

*4.7.9.* 6-*Chloro-2-(1-hydroxyprop-2-en-1-yl)-3-(2-methylpropenoyl)indole (**16i**)*

Yield 70%. IR (ATR) ν = 3163 (OH), 1651 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 8.97 (br s, 1H; NH), 7.76 (d, *J* = 1.8 Hz, 1H; ArH), 7.31 (d, *J* = 8.6 Hz, 1H; ArH), 7.18 (dd, *J* = 8.6, 1.8 Hz, 1H; ArH), 6.16 (ddd, *J* = 17.0, 10.3, 4.9 Hz, 1H; $CH=CH_2$), 5.84 (s, 1H; $=CH_2$), 5.71 (s, 1H; $=CH_2$), 5.64–5.69 (m, 1H; CH), 5.56 (td, *J* = 17.0, 1.5 Hz, 1H; $CH=CH_2$), 5.40 (td, *J* = 10.3, 1.5 Hz, 1H; $CH=CH_2$), 4.45 (d, *J* = 3.3 Hz, 1H; OH), 2.14 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 194.8, 148.0, 145.9, 145.1, 135.7, 132.6, 129.7, 124.6, 123.5, 122.7, 124.8, 117.7, 112.6, 67.7, 18.4. MS *m/z*: 275 ($M^+$), 277 ($M^+$+2). HRMS (EI): calcd for $C_{15}H_{14}ClNO_2$ 275.0713; found 275.0717.

*4.7.10. 2-(1-Hydroxyprop-2-en-1-yl)-3-(2-methylpropenoyl)-5-nitroindole (**16j**)*

Yield 50%. IR (ATR) ν = 3263 (OH), 1619 (CO), 1531 ($NO_2$), 1335 ($NO_2$) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.29 (br s, 1H; NH), 8.73 (d, *J* = 2.2 Hz, 1H; ArH), 8.14 (dd, *J* = 8.9, 2.2 Hz, 1H; ArH), 7.47 d, *J* = 8.9 Hz, 1H; ArH), 6.18 (ddd, *J* = 17.1, 10.4, 5.0 Hz, 1H; $CH=CH_2$), 5.96 (s, 1H; $=CH_2$), 5.71–5.78 (m, 2H: $=CH_2$, CH), 5.56–5.62 (m, 2H; $CH=CH_2$, OH), 5.42 (d, *J* = 10.4 Hz, 1H; $CH=CH_2$), 2.17 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 193.8, 149.3, 145.9, 143.5, 137.1, 135.5, 126.7, 126.0, 118.5, 118.1, 111.9, 98.7, 67.8, 29.6, 18.3. MS *m/z*: 286 ($M^+$). HRMS (EI): calcd for $C_{15}H_{14}N_2O_4$ 286.0954; found 286.0954.

*4.7.11. 2-(1-Hydroxyprop-2-en-1-yl)-3-(2-methylpropenoyl)-6-nitroindole (**16k**)*

Yield 43%. IR (ATR) ν = 3253 (OH), 1697 (CO), 1574 ($NO_2$), 1330 ($NO_2$) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.33 (br s, 1H; NH), 7.45 (dd, *J* = 10.4, 5.5 Hz, 1H; ArH), 7.28 (dd, *J* = 8.9, 4.6 Hz, 1H; ArH), 6.95 (dt, *J* = 8.9, 2.4 Hz, 1H; ArH), 6.13 (ddd, *J* = 17.2, 10.5, 5.0 Hz, 1H; $CH=CH_2$), 5.80 (s, 1H; $=CH_2$), 5.69 (s, 1H; $=CH_2$), 5.63 (br s, 1H; CH), 5.52 (td, *J* = 17.2, 1.4 Hz, 1H; $CH=CH_2$), 5.32 (td, *J* = 10.5, 1.4 Hz, 1H; $CH=CH_2$), 5.02 (br d, 1H; OH), 2.12 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 194.1, 151.3, 145.9, 143.7, 135.4, 132.8, 131.7, 125.4, 121.3, 118.0, 117.0, 113.4, 108.4, 67.8, 18.2. MS *m/z*: 275 ($M^+$). HRMS (EI): calcd for $C_{15}H_{14}ClNO_2$ 275.0713; found 275.0733.

*4.7.12. 2-(1-Hydroxyprop-2-en-1-yl)-3-(2-methylpropenoyl)-5-trifluoromethylindole (**16l**)*

Yield 44%. IR (ATR) ν = 3217 (OH), 1593 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.24 (br s, 1H; NH), 8.07 (s, 1H; ArH), 7.46–7.48 (m, 2H; ArH), 6.15 (ddd, *J* = 17.2, 10.5, 5.3 Hz, 1H; $CH=CH_2$), 5.88 (s, 1H; $=CH_2$), 5.63–5.73 (m, 2H; CH, $=CH_2$), 5.55 (td, *J* = 17.2, 1.1 Hz, 1H; $CH=CH_2$), 5.37 (td, *J* = 10.5, 1.1 Hz, 1H; $CH=CH_2$), 4.38 (br s, 1H; OH), 2.15 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 194.7, 148.2, 146.0, 135.7, 135.6, 126.5, 125.2, 124.9 (q, $J_{C–F}$ = 272.4 Hz), 124.2 (q, $J_{C–F}$ = 32.5 Hz), 119.8 (q, $J_{C–F}$ = 3.7 Hz), 118.9 (q, $J_{C–F}$ = 4.1 Hz), 117.6, 113.5, 112.0, 67.7, 18.3. MS *m/z*: 309 ($M^+$). HRMS (EI): calcd for $C_{16}H_{14}F_3NO_2$ 309.0977; found 309.0990.

*4.7.13. 2-(1-Hydroxyprop-2-en-1-yl)-3-(2-methylpropenoyl)-6-trifluoromethylindole (**16m**)*

Yield 40%. IR (ATR) ν = 3217 (OH), 1593 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.44 (br s, 1H; NH), 7.86 (d, *J* = 8.6 Hz, 1H; ArH), 7.65 (s, 1H; ArH), 7.38 (d, *J* = 8.6 Hz, 1H; ArH), 6.15 (ddd, *J* = 17.3, 10.5, 5.4 Hz, 1H; $CH=CH_2$), 5.84 (s, 1H; $=CH_2$), 5.68–5.74 (m, 2H; CH, $=CH_2$), 5.54 (dd, *J* = 17.3, 1.2 Hz, 1H; $CH=CH_2$), 5.37 (dd, *J* = 10.5, 1.2 Hz, 1H; $CH=CH_2$), 4.62 (br s, 1H; OH), 2.15 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 194.9, 149.1, 145.9, 135.7, 133.2, 129.4, 125.1 (q, $J_{C–F}$ = 32.4 Hz), 124.3 (q, $J_{C–F}$ = 271.0 Hz), 121.6, 118.4 (q, $J_{C–F}$ = 2.7 Hz), 117.6, 113.0, 109.2 (q, $J_{C–F}$ = 3.9 Hz), 67.9, 18.3. MS *m/z*: 309 ($M^+$). HRMS (EI): calcd for $C_{16}H_{14}F_3NO_2$ 309.0977; found 309.0963.

*4.7.14. 5-Fluoro-2-(1-hydroxyprop-2-en-1-yl)-3-(2-methylpropenoyl)indole (**16n**)*

Yield 60%. IR (ATR) ν = 3178 (OH), 1589 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 9.03 (br s, 1H; NH), 7.46 (d, *J* = 10.2 Hz, 1H; ArH), 7.30 (dd, *J* = 8.8, 4.6 Hz, 1Hv), 6.97 (d, *J* = 8.8 Hz, 1H; ArH), 6.16 (ddd, *J* = 17.2, 10.4, 5.3 Hz, 1H; $CH=CH_2$), 5.80 (s, 1H; $=CH_2$), 5.70 (s, 1H; $=CH_2$), 5.60–5.68 (m, 1H; CH), 5.52–5.54 (m, 1H; $CH=CH_2$), 5.36–5.41 (m, 1H; $CH=CH_2$), 4.65 (br s, 1H; OH), 2.13 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 195.1, 158.8 (q, $J_{C–F}$ = 236.4 Hz), 148.7, 145.8, 135.7, 130.7, 127.8 (d, $J_{C–F}$ = 9.8 Hz), 124.0, 117.5, 113.1 (d, $J_{C–F}$ = 4.2 Hz), 112.5 (d, $J_{C–F}$ = 10.0 Hz), 111.5 (d, $J_{C–F}$ = 26.2 Hz), 106.6 (d, $J_{C–F}$ = 25.1 Hz), 68.0, 18.5. MS *m/z*: 259 ($M^+$). HRMS (EI): calcd for $C_{15}H_{14}FNO_2$ 259.1009; found 259.1021.

*4.7.15. 6-Fluoro-2-(1-hydroxyprop-2-en-1-yl)-3-(2-methylpropenoyl)indole (**16o**)*

Yield 57%. IR (ATR) ν = 3305 (OH), 1651 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 8.90 (br s, 1H; NH), 7.70–7.75 (m, 1H; ArH), 7.07 (dd, *J* = 9.0, 2.4 Hz, 1H; ArH), 6.90–6.97 (m, 1H; ArH), 6.15 (ddd, *J* = 17.0, 10.4, 5.1 Hz, 1H; $CH=CH_2$), 5.81 (s, 1H; $=CH_2$), 5.71 (s, 1H; $=CH_2$), 5.64 (br s, 1H; CH), 5.57 (d, *J* = 17.0 Hz, 1H; $CH=CH_2$), 5.39 (d, *J* = 10.4 Hz, 1H; $CH=CH_2$), 4.45 (br s, 1H; OH), 2.13 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 194.9, 159.9 (d, $J_{C–F}$ = 239.2 Hz), 147.1, 146.1, 135.8, 132.5, 124.4, 123.5, 122.3 (d, $J_{C–F}$ = 10.4 Hz), 117.5, 112.9 (d, $J_{C–F}$ = 36.6 Hz), 110.6 (d, $J_{C–F}$ = 25.1 Hz), 98.0 (d, $J_{C–F}$ = 26.0 Hz), 67.7, 18.4. MS *m/z*: 259 ($M^+$). HRMS (EI): calcd for $C_{15}H_{14}FNO_2$ 259.1009; found 259.1003.

*4.7.16. 2-(1-Hydroxyprop-2-en-1-yl)-3-(2-methylpropenoyl)benzo[e]indole (**16p**)*

Yield 52%. IR (ATR) ν = 3275 (OH), 1608 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 8.92 (br s, 1H; NH), 7.89 (t, *J* = 7.9 Hz, 1H; ArH), 7.63 (d, *J* = 8.9 Hz, 1H; ArH), 7.37–7.50 (m, 3H; ArH), 6.11 (ddd, *J* = 17.4, 10.4, 5.2 Hz, 1H; $CH=CH_2$), 5.85 (s, 1H; $=CH_2$), 5.78 (s, 1H; $=CH_2$), 5.48–5.54 (m, 2H; CH, $CH=CH_2$), 5.35 (d, *J* = 10.4 Hz, 1H; $CH=CH_2$), 3.32 (br d, 1H; OH), 2.21 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 197.6, 146.0, 139.7, 136.6, 131.3, 130.3, 129.3, 128.9, 127.4, 125.6, 125.4, 124.9, 123.7, 121.0, 116.9, 115.9, 112.5, 67.5, 17.5. MS *m/z*: 291 ($M^+$). HRMS (EI): calcd for $C_{19}H_{17}NO_2$ 291.1259; found 291.1269.

*4.7.17. 2-(1-Hydroxyprop-2-en-1-yl)-3-(2-methylpropenoyl)benzo[f]indole (**16q**)*

Yield 67%. IR (ATR) ν = 3213 (OH), 1593 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 9.85 (br s, 1H; NH), 8.03 (d, *J* = 8.1 Hz, 1H; ArH), 7.91 (d, *J* = 7.9 Hz, 1H; ArH), 7.82 (d, *J* = 8.8 Hz, 1H; ArH), 7.44–7.57 (m, 3H; ArH), 6.21 (ddd, *J* = 17.1, 10.4, 5.1 Hz, 1H; $CH=CH_2$), 5.81 (s, 1H; $=CH_2$), 5.77 (s, 1H; $=CH_2$), 5.72 (br s, 1H; CH), 5.53 (td, *J* = 17.1, 1.4 Hz, 1H; $CH=CH_2$), 5.35 (td, *J* = 10.4, 1.4 Hz, 1H; $CH=CH_2$), 4.92 (br d, 1H; OH), 2.17 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz,

$CDCl_3$) δ = 195.7, 146.1, 144.4, 136.3, 130.4, 129.1, 128.7, 126.1, 125.2, 124.7, 123.3, 122.4, 121.3, 120.3, 119.7, 117.0, 114.8, 68.2, 18.4. MS *m/z*: 291 ($M^+$). HRMS (EI): calcd for $C_{19}H_{17}NO_2$ 291.1259; found 291.1273.

*4.7.18. 2-(1-Hydroxyprop-2-en-1-yl)-3-(2-methylpropenoyl)indole (**16r**)*

Yield 90%. IR (ATR) ν = 3251 (OH), 1735 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.07 (br s, 1H; NH), 7.81 (d, *J* = 8.6 Hz, 1H; ArH), 7.37 (d, *J* = 7.3 Hz, 1H; ArH), 7.14–7.24 (m, 2H; ArH), 6.17 (ddd, *J* = 17.2, 10.4, 5.3 Hz, 1H; $CH=CH_2$), 5.78 (s, 1H; $=CH_2$), 5.72 (s, 1H; $=CH_2$), 5.65 (br d, 1H; CH), 5.54 (td, *J* = 17.2, 1.4 Hz, 1H; $CH=CH_2$), 5.36 (td, *J* = 10.4, 1.4 Hz, 1H; $CH=CH_2$), 4.84 (br s, 1H; OH), 2.14 (s, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 195.4, 147.2, 146.1, 135.9, 134.2, 127.1, 124.0, 123.0, 121.8, 121.2, 117.4, 113.1, 111.7, 67.9, 18.5. MS *m/z*: 241 ($M^+$). HRMS (EI): calcd for $C_{15}H_{15}NO_2$ 241.1103; found 241.1119.

*4.7.19. 2-(1-Hydroxyprop-2-en-1-yl)-3-propenoylindole (**16s**)*

Yield 36%. IR (ATR) ν = 3220 (OH), 1635 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 9.52 (br s, 1H; NH), 7.85 (d, *J* = 8.3 Hz, 1H; ArH), 7.23–7.40 (m, 4H; ArH, $COCH=CH_2$), 6.47 (dd, *J* = 17.1, 1.5 Hz, 1H; $COCH=CH_2$), 6.16 (ddd, *J* = 17.1, 10.5, 5.5 Hz, 1H; $CH=CH_2$), 5.89 (dd, *J* = 10.5, 1.5 Hz, 1H; $COCH=CH_2$), 5.68 (br s, 1H; CH), 5.52 (br s, 1H; OH), 5.47 (d, *J* = 17.1 Hz, 1H; $CH=CH_2$), 5.36 (d, *J* = 10.5 Hz, 1H; $CH=CH_2$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 188.5, 148.9, 136.0, 135.8, 134.5, 128.3, 126.4, 123.2, 122.4, 120.8, 117.4, 114.1, 112.1, 68.6. MS *m/z*: 227 ($M^+$). HRMS (EI): calcd for $C_{14}H_{13}NO_2$ 227.0946; found 227.0942.

*4.8. General procedure for the synthesis of carbazole-1,4-quinones (**18a–18q, 17a, 17c**)*

A suspension of allyl alcohol **16** (0.15 mmol) and Grubbs$^{2nd}$ catalyst (0.015 mmol) in toluene (20 mL) was heated at 70 °C for 5 min under an $O_2$ atmosphere. After cooling to an ambient temperature, the reaction solvent was evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane as an eluent to give the carbazole-1,4-quinone **18**.

*4.8.1. 6-Methoxy-3-methylcarbazole-1,4-quinone (**18a**)*

Yield 80%. mp 246–247 ºC (EtOAc-hexane). IR (ATR) ν = 3233 (NH), 1661 (CO), 1641 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.75 (br s, 1H; NH), 7.45 (s, 1H; ArH), 7.43 (d, *J* = 9.4 Hz, 1H; ArH), 7.03 (d, *J* = 9.4 Hz, 1H; ArH), 6.59 (q, *J* = 1.5 Hz, 1H; ArH), 3.82 (s, 3H; $OCH_3$), 2.06 (d, *J* = 1.5 Hz, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 182.9, 179.7, 156.9, 148.0, 135.8, 132.6, 131.8, 124.5, 117.5, 115.1, 115.0, 101.6, 55.3, 15.6. MS *m/z*: 241 ($M^+$). HRMS (EI): calcd for $C_{14}H_{11}NO_3$ 241.0739; found 241.0744.

*4.8.2. 5,6-Dimethoxy-3-methylcarbazole-1,4-quinone (**18b**)*

Yield 82%. mp 242–243 ºC (EtOAc-hexane). IR (ATR) ν = 3321 (NH), 1641 (CO), 1623 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.79 (br s, 1H; NH), 7.23–7.27 (m, 2H; ArH), 6.63 (q, *J* = 2.3 Hz, 1H; ArH), 3.85 (s, 3H; $OCH_3$), 3.79 (s, 3H; $OCH_3$), 2.08 (d, *J* = 2.3 Hz, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 180.5, 180.0, 149.3, 145.6, 142.6, 137.2, 134.2, 130.5, 119.5, 115.4, 114.9, 109.4, 61.5, 57.2, 16.5. MS *m/z*: 271 ($M^+$). HRMS (EI): calcd for $C_{15}H_{13}NO_4$ 271.0845; found 271.0863.

*4.8.3. 5,8-Dimethoxy-3-methylcarbazole-1,4-quinone (**18c**)*

Yield 78%. mp 245–246 ºC (EtOAc-hexane). IR (ATR) ν = 3351 (NH), 1676 (CO), 1646 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.93 (br s, 1H; NH), 6.81 (d, *J* = 8.5 Hz, 1H; ArH), 6.50–6.64 (m, 2H; ArH), 3.87 (s, 3H; $OCH_3$), 3.81 (s, 3H; $OCH_3$), 2.05 (d, *J* = 1.4 Hz, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 180.7, 179.6, 148.6, 148.5, 141.6, 135.9, 130.7, 129.8, 116.7, 115.9, 106.6, 103.8, 56.1, 55.9, 16.4. MS *m/z*: 271 ($M^+$). HRMS (EI): calcd for $C_{15}H_{13}NO_4$ 271.0845; found 271.0833.

*4.8.4. 5,7-Dimethoxy-3-methylcarbazole-1,4-quinone (**18d**)*

Yield 78%. mp 241–243 ºC (EtOAc-hexane). IR (ATR) ν = 3229 (NH), 1661 (CO), 1623 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.60 (br s, 1H; NH), 6.50–6.60 (m, 1H; ArH), 6.45–6.55 (m, 1H; ArH), 6.34 (q, *J* = 1.4 Hz, 1H; ArH), 3.83 (s, 3H; $OCH_3$), 3.78 (s, 3H; $OCH_3$), 2.02 (d, *J* = 1.4 Hz, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 182.2, 179.3, 160.1, 155.5, 140.1, 134.9, 130.4, 109.0, 100.1, 95.4, 87.2, 86.1, 55.5, 55.4, 16.5. MS *m/z*: 271 ($M^+$). HRMS (EI): calcd for $C_{15}H_{13}NO_4$ 271.0845; found 271.0827.

*4.8.5. 6,8-Dimethoxy-3-methylcarbazole-1,4-quinone (**18e**)*

Yield 92%. mp 249–250 ºC (EtOAc-hexane). IR (ATR) ν = 3216 (NH), 1659 (CO), 1,630 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.93 (br s, 1H; NH), 7.01 (s, 1H; ArH), 6.50–6.60 (m, 2H; ArH), 3.90 (s, 3H; $OCH_3$), 3.81 (s, 3H; $OCH_3$), 2.03 (d, *J* = 1.8 Hz, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 183.0, 179.3, 158.5, 148.1, 147.5, 135.3, 132.0, 125.2, 123.9, 115.7, 98.4, 93.1, 55.7, 55.4, 15.5. MS *m/z*: 271 ($M^+$). HRMS (EI): calcd for $C_{15}H_{13}NO_4$ 271.0845; found 271.0849.

*4.8.6. 3,6-Dimethylcarbazole-1,4-quinone (**18f**)*

Yield 93%. mp 232–233 ºC (EtOAc-hexane). IR (ATR) ν = 3331 (NH), 1636 (CO), 1621 (CO) $cm^{-1}$. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.73 (br s, 1H; NH), 7.82 (s, 1H; ArH), 7.42 (d, *J* = 8.4 Hz, 1H; ArH), 7.20 (d, *J* = 8.4 Hz, 1H; ArH), 6.59 (q, *J* = 1.5 Hz, 1H; ArH), 2.42 (s, 3H; $CH_3$), 2.05 (d,

*J* = 1.5 Hz, 3H; $CH_3$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 183.0, 180.0, 147.9, 135.9, 135.8, 133.2, 131.6, 128.1, 123.9, 120.9, 114.9, 113.5, 21.3, 15.7. MS *m/z*: 225 ($M^+$). HRMS (EI): calcd for $C_{14}H_{11}NO_2$ 225.0790; found 225.0788.

*4.8.7. 3,7-Dimethylcarbazole-1,4-quinone (**18g**)*

Yield 80%. mp 225–226 ºC (EtOAc-hexane). IR (ATR) ν = 3259 (NH), 1658 (CO), 1631 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 12.67 (br s, 1H; NH), 7.92 (d, *J* = 8.3 Hz, 1H; ArH), 7.31 (s, 1H; ArH), 7.14 (d, *J* = 8.3 Hz, 1H; ArH), 6.58 (q, *J* = 1.7 Hz, 1H; ArH), 2.42 (s, 3H; $CH_3$), 2.05 (d, *J* = 1.7 Hz, 3H; $CH_3$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 183.1, 179.9, 147.7, 137.9, 136.0, 135.5, 131.6, 125.8, 121.5, 121.2, 115.5, 113.2, 21.5, 15.6. MS *m/z*: 225 ($M^+$). HRMS (EI): calcd for $C_{14}H_{11}NO_2$ 225.0790; found 225.0776.

*4.8.8. 6-Chloro-3-methylcarbazole-1,4-quinone (**18h**)*

Yield 74%. mp 251–252 ºC (EtOAc-hexane). IR (ATR) ν = 3228 (NH), 1635 (CO), 1608 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 13.06 (br s, 1H; NH), 8.00 (d, *J* = 2.1 Hz, 1H; ArH), 7.57 (d, *J* = 8.8 Hz, 1H; ArH), 7.41 (dd, *J* = 8.8, 2.1 Hz, 1H; ArH), 6.67 (q, *J* = 1.7 Hz, 1H; ArH), 2.08 (d, *J* = 1.7 Hz, 3H; $CH_3$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 182.8, 179.9, 148.1, 137.0, 135.9, 131.8, 128.4, 126.4, 124.4, 120.5, 115.7, 114.8, 15.6. MS *m/z*: 245 ($M^+$), 247 ($M^+$+2). HRMS (EI): calcd for $C_{13}H_8ClNO_2$ 245.0244; found 245.0272.

*4.8.9. 7-Chloro-3-methylcarbazole-1,4-quinone (**18i**)*

Yield 70%. mp 257–258 ºC (EtOAc-hexane). IR (ATR) ν = 3213 (NH), 1662 (CO), 1635 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 12.65 (br s, 1H; NH), 8.03 (d, *J* = 8.6 Hz, 1H; ArH), 7.54 (d, *J* = 1.9 Hz, 1H; ArH), 7.34 (dd, *J* = 8.6, 1.9 Hz, 1H; ArH), 6.65 (q, *J* = 1.7 Hz, 1H; ArH), 2.07 (d, *J* = 1.7 Hz, 3H; $CH_3$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 183.0, 180.0, 148.0, 137.9, 136.8, 131.8, 130.6, 124.3, 123.1, 122.3, 115.4, 113.4, 15.6. MS *m/z*: 245 ($M^+$), 247 ($M^+$+2). HRMS (EI): calcd for $C_{13}H_8ClNO_2$ 245.0244; found 245.0248.

*4.8.10. 3-Methyl-6-nitrocarbazole-1,4-quinone (**18j**)*

Yield 67%. mp 246–247 ºC (EtOAc-hexane). IR (ATR) ν = 3321 (NH), 1658 (CO), 1621 (CO), 1544 ($NO_2$), 1329 ($NO_2$) $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 13.46 (br s, 1H; NH), 8.86 (d, *J* = 2.1 Hz, 1H; ArH), 8.23 (dd *J* = 9.0, 2.1 Hz, 1H; ArH), 7.73 (d, *J* = 9.0 Hz, 1H; ArH), 6.74 (q, *J* = 1.5 Hz, 1H; ArH), 2.06 (d, *J* = 1.5 Hz, 3H; $CH_3$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 183.1, 178.3, 161.1, 148.4, 137.1, 135.2, 131.8, 124.0, 115.7, 114.9, 106.1, 15.6. MS *m/z*: 256 ($M^+$). HRMS (EI): calcd for $C_{13}H_8N_2O_4$ 256.0484; found 256.0472.

*4.8.11. 3-Methyl-7-nitrocarbazole-1,4-quinone (**18k**)*

Yield 72%. mp 239–240 ºC (EtOAc-hexane). IR (ATR) ν = 3326 (NH), 1653 (CO), 1626 (CO), 1553 ($NO_2$), 1343 ($NO_2$) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.98 (br s, 1H; NH), 7.67 (dd, *J* = 9.2, 2.5 Hz, 1H; ArH), 7.53–7.57 (m, 1H; ArH), 7.27 (dt, *J* = 9.2, 2.5 Hz, 1H; ArH), 6.63 (q, *J* = 1.5 Hz, 1H; ArH), 2.06 (d, *J* = 1.5 Hz, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 182.8, 179.9, 161.1, 157.9, 148.1, 137.2, 134.2, 131.8, 124.0, 115.7, 114.9, 106.1, 15.6. MS *m/z*: 256 ($M^+$). HRMS (EI): calcd for $C_{13}H_8N_2O_4$ 256.0484; found 256.0496.

*4.8.12. 3-Methyl-6-trifluoromethylcarbazole-1,4-quinone (**18l**)*

Yield 74%. mp 221–222 ºC (EtOAc-hexane). IR (ATR) ν = 3251 (NH), 1635 (CO), 1608 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 13.15 (br s, 1H; NH), 8.17 (d, *J* = 8.3 Hz, 1H; ArH), 7.78 (s, 1H; ArH), 7.57 (d, *J* = 8.3 Hz, 1H; ArH), 6.66 (q, *J* = 1.5 Hz, 1H; ArH), 2.06 (d, *J* = 1.5 Hz, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 182.7, 179.9, 148.4, 138.1, 136.2, 131.8, 127.6 (q, $J_{C–F}$ = 271.6 Hz), 126.1 (q, $J_{C–F}$ = 32.4 Hz), 125.9, 122.8, 119.7 (q, $J_{C–F}$ = 2.8 Hz), 115.0, 111.2 (q, $J_{C–F}$ = 4.2 Hz), 15.6. MS *m/z*: 279 ($M^+$). HRMS (EI): calcd for $C_{14}H_8F_3NO_2$ 279.0507; found 279.0523.

*4.8.13. 3-Methyl-7-trifluoromethylcarbazole-1,4-quinone (**18m**)*

Yield 77%. mp 233–234 ºC (EtOAc-hexane). IR (ATR) ν = 3228 (NH), 1639 (CO), 1539 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 13.25 (br s, 1H; NH), 8.23 (d, *J* = 8.5 Hz, 1H; ArH), 7.81 (s, 1H; ArH), 7.60 (d, *J* = 8.5 Hz, 1H; ArH), 6.69 (q, *J* = 1.5 Hz, 1H; ArH), 2.08 (d, *J* = 1.5 Hz, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 182.8, 180.0, 148.4, 138.1, 136.2, 131.9, 126.1 (q, $J_{C–F}$ = 31.0 Hz), 125.9, 124.2 (q, $J_{C–F}$ = 271.1 Hz), 122.8, 119.7 (q, $J_{C–F}$ = 3.0 Hz), 115.1, 111.2 (q, $J_{C–F}$ = 5.0 Hz), 15.6. MS *m/z*: 279 ($M^+$). HRMS (EI): calcd for $C_{14}H_8F_3NO_2$ 279.0507; found 279.0513.

*4.8.14. 6-Fluoro-3-methylcarbazole-1,4-quinone (**18n**)*

Yield 78%. mp 237–238 ºC (EtOAc-hexane). IR (ATR) ν = 3217 (NH), 1635 (CO), 1601 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.97 (br s, 1H; NH), 7.67 (dd, *J* = 9.1, 2.6 Hz, 1H; ArH), 7.56 (dd, *J* = 9.1, 4.6 Hz, 1H; ArH), 7.56 (dt, *J* = 9.1, 2.6 Hz, 1H; ArH), 6.64 (q, *J* = 1.7 Hz, 1H; ArH), 2.07 (d, *J* = 1.7 Hz, 3H; $CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ = 182.9, 180.1, 160.1 (d, $J_{C–F}$ = 237.4 Hz), 148.3, 137.4, 134.3, 131.9, 124.0 (d, $J_{C–F}$ = 11.1 Hz), 115.9 (d, $J_{C–F}$ = 10.1 Hz), 115.5 (d, $J_{C–F}$ = 5.6 Hz), 115.2 (d, $J_{C–F}$ = 26.7 Hz), 106.0 (d, $J_{C–F}$ = 24.0 Hz), 15.7. MS *m/z*: 229 ($M^+$). HRMS (EI): calcd for $C_{13}H_8FNO_2$ 229.0539; found 229.0541.

*4.8.15. 7-Fluoro-3-methylcarbazole-1,4-quinone (**18o**)*

Yield 72%. mp 233–235 ºC (EtOAc-hexane). IR (ATR) ν = 3244 (NH), 1624 (CO), 1581 (CO) $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ = 12.97 (br s, 1H; NH), 8.01 (dd, *J* = 9.1, 6.1 Hz, 1H; ArH),

7.15–7.26 (m, 2H; ArH), 6.60 (q, *J* = 1.5 Hz, 1H; ArH), 2.04 (d, *J* = 1.5 Hz, 3H; $CH_3$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 184.7, 181.3, 149.3, 139.4 (d, $J_{C–F}$ = 12.0 Hz), 138.3 (d, $J_{C–F}$ = 3.7 Hz), 133.2, 124.9 (d, $J_{C–F}$ = 9.7 Hz), 121.9, 117.1, 114.7, 114.4, 101.2, 17.1 (d, $J_{C–F}$ = 26.3 Hz). MS *m/z*: 229 ($M^+$). HRMS (EI): calcd for $C_{13}H_8FNO_2$ 229.0539; found 229.0554.

*4.8.16. 3-Methylbenzo[g]carbazole-1,4-quinone (**18p**)*

Yield 60%. mp 253–254 ºC (EtOAc-hexane). IR (ATR) ν = 3321 (NH), 1662 (CO), 1548 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 13.31 (br s, 1H; NH), 9.72 (d, *J* = 8.3 Hz, 1H; ArH), 7.99 (d, *J* = 7.8 Hz, 1H; ArH), 7.87 (d, *J* = 8.3 Hz, 1H; ArH), 7.51–7.68 (m, 3H; ArH), 6.69 (q, *J* = 1.5 Hz, 1H; ArH), 2.15 (d, *J* = 1.5 Hz, 3H; $CH_3$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ = 182.8, 179.3, 148.9, 135.7, 135.0, 131.3, 130.7, 128.9, 128.6, 128.2, 126.8, 126.7, 125.6, 120.0, 118.2, 114.0, 16.5. MS *m/z*: 261 ($M^+$). HRMS (EI): calcd for $C_{17}H_{11}NO_2$ 261.0790; found 261.0772.

*4.8.17. 3-Methylbenzo[h]carbazole-1,4-quinone (**18q**)*

Yield 72%. mp 261–262 ºC (EtOAc-hexane). IR (ATR) ν = 3229 (NH), 1658 (CO), 1551 (CO) $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ = 13.58 (br s, 1H; NH), 8.66 (d, *J* = 7.7 Hz, 1H; ArH), 7.97–8.05 (m, 2H; ArH), 7.71–7.75 (m, 1H; ArH), 7.54–7.65 (m, 2H; ArH), 6.58 (q, *J* = 1.5 Hz, 1H; ArH), 2.03 (d, *J* = 1.5 Hz, 3H; $CH_3$). $^{13}$C NMR (75 MHz, DMSO-*d*) δ = 183.6, 179.2, 147.3, 134.2, 133.7, 132.3, 131.8, 128.7, 126.8, 126.4, 125.2, 122.2, 120.5, 119.8, 119.7, 116.9, 15.5. MS *m/z*: 261 ($M^+$). HRMS (EI): calcd for $C_{17}H_{11}NO_2$ 261.0790, found 261.0781.

*4.8.18. 3-Methylcarbazole-1,4-quinone (murrayaquinone A) (**17a**)*

Carbazole-1,4-quinone **17a** (yield 70%) was prepared according to a synthetic method for **18**. The spectroscopic data of **17a** were identical to those of our reported murrayaquinone A [11].

*4.8.19. Carbazole-1,4-quinone (**17c**)*

Carbazole-1,4-quinone **17c** (yield 53%) was prepared according to a synthetic method for **18**. The spectroscopic data of **17c** were identical to those of our reported compound [4].

4.9. Biochemistry

*4.9.1. 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% $CO_2$.

*4.9.2. Cell viability assays*

The HCT-116 cells' viability assay was conducted using the MTT method based on the procedure described by Mosmann [23]. Briefly, cells were placed in 96-well flat bottomed tissue culture plates with 3.0 x $10^3$ 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 [24]. 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.

*4.9.3. 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.2016.03.XXX.

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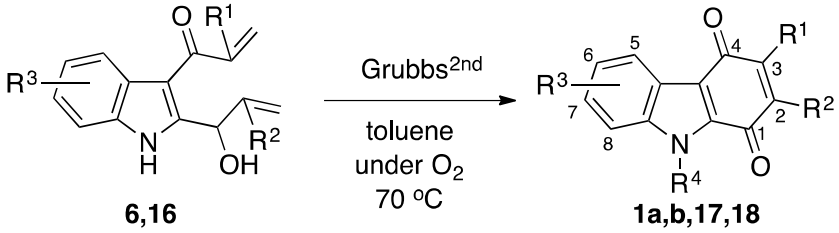
**Table 1**. Yields of indole derivatives **12**, **13**, and **14**.

| No. | **11** R | **12** Yield (%) | **13** Yield (%) | **14** Yield (%) |
|---|---|---|---|---|
| **a** | 5-MeO | 72 | 70 | 63 |
| **b** | 4,5-diMeO | 68 | 44 | 40 |
| **c** | 4,7-diMeO | 70 | 60 | 51 |
| **d** | 4,6-diMeO | 71 | 81 | 83 |
| **e** | 5,7-diMeO | 54 | 40 | 62 |
| **f** | 5-Me | 76 | 63 | 72 |
| **g** | 6-Me | 96 | 90 | 86 |
| **h** | 5-Cl | 80 | 76 | 80 |
| **i** | 6-Cl | 50 | 79 | 74 |
| **j** | 5-$NO_2$ | 71 | 98 | 56 |
| **k** | 5-$NO_2$ | 65 | 62 | 48 |
| **l** | 5-$CF_3$ | 87 | 98 | 85 |
| **m** | 6-$CF_3$ | 83 | 78 | 56 |
| **n** | 5-F | 76 | 84 | 54 |
| **o** | 6-F | 77 | 99 | 87 |
| **p** | 4,5-fused benzene | 81 | 28 | 61 |
| **q** | 5,6-fused benzene | 99 | 67 | 85 |

**Table 2**. Synthesis of 3-acryloylindoles **15** and 2-allylindoles **16**

| No. | $R^1$ | $R^2$ | **15** | | **16** | |
|---|---|---|---|---|---|---|
| | | | Time (h) | Yield (%) | Time (h) | Yield (%) |
| **a** | 5-MeO | Me | 6 | 61 | 1 | 70 |
| **b** | 4,5-diMeO | Me | 13 | 70 | 1 | 56 |
| **c** | 4,7-diMeO | Me | 13 | 75 | 1 | 79 |
| **d** | 4,6-diMeO | Me | 13 | 83 | 1 | 53 |
| **e** | 5,7-diMeO | Me | 13 | 90 | 2 | 37 |
| **f** | 5-Me | Me | 7 | 79 | 2 | 43 |
| **g** | 6-Me | Me | 7 | 65 | 2 | 44 |
| **h** | 5-Cl | Me | 7 | 75 | 1 | 74 |
| **i** | 6-Cl | Me | 7 | 62 | 1 | 70 |
| **j** | 5-$NO_2$ | Me | 13 | 55 | 2 | 50 |
| **k** | 5-$NO_2$ | Me | 13 | 70 | 2 | 43 |
| **l** | 5-$CF_3$ | Me | 13 | 67 | 2 | 44 |
| **m** | 6-$CF_3$ | Me | 13 | 75 | 2 | 40 |
| **n** | 5-F | Me | 13 | 75 | 1 | 60 |
| **o** | 6-F | Me | 13 | 71 | 1 | 57 |
| **p** | 4,5-fused benzene | Me | 13 | 60 | 1 | 52 |
| **q** | 5,6-fused benzene | Me | 13 | 84 | 1 | 67 |
| **r** | H | Me | 13 | 64 | 1 | 90 |
| **s** | H | H | 1 | 23 | 1 | 36 |

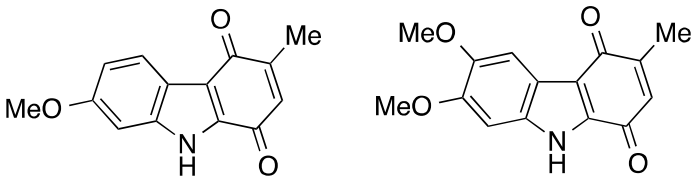
**Table 3**. Synthesis of poly-substituted carbazole-1,4-quinones by tandem RCM reaction and evaluation of antiproliferative activity against HCT-116 and HL-60 cells




**6,16** **1a,b,17,18**

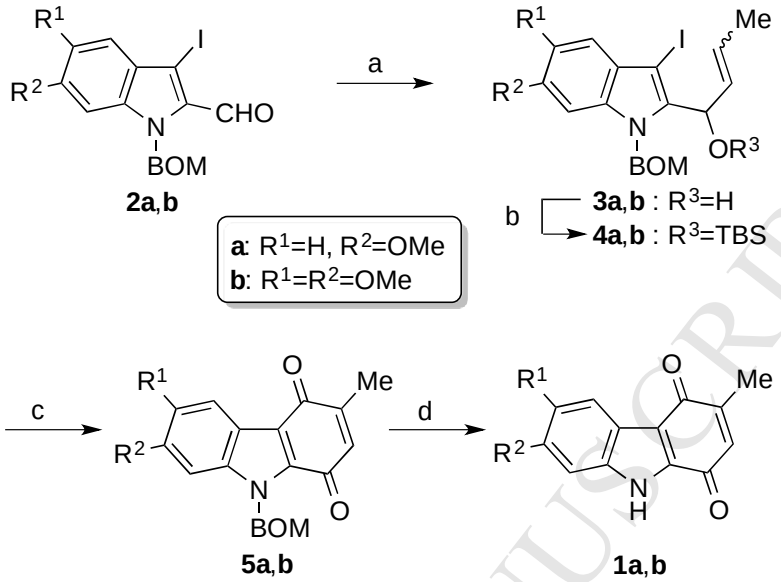
| Entry | Compd. No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Time (min) | Compd. No. | Yield (%) | $IC_{50}$ (μM) HCT-116 | $IC_{50}$ (μM) HL-60 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **16r** | Me | H | H | H | – | **17a** | 70 | 3.716 | 3.022 |
| 2 | | Me | H | H | MOM | – | **17b**[a)] | – | 6.494 | 3.919 |
| 3 | **16s** | H | H | H | H | – | **17c** | 53 | 0.763 | 1.001 |
| 4 | | H | H | H | MOM | – | **17d**[a)] | – | 1.311 | 1.384 |
| 5 | | H | Me | H | MOM | – | **17e**[b)] | – | >10 | >10 |
| 6 | **16a** | Me | H | 6-MeO | H | 60 | **18a** | 80 | 1.597 | 3.414 |
| 7 | **6a** | Me | H | 7-MeO | H | 30 | **1a** | 67 | 0.992 | 1.751 |
| 8 | **6b** | Me | H | 6,7-diMeO | H | 30 | **1b** | 79 | 4.094 | 8.946 |
| 9 | **16b** | Me | H | 5,6-diMeO | H | 10 | **18b** | 82 | >10 | >10 |
| 10 | **16c** | Me | H | 5,8-diMeO | H | 30 | **18c** | 78 | 1.842 | 2.274 |
| 11 | **16d** | Me | H | 5,7-diMeO | H | 30 | **18d** | 78 | >10 | 7.259 |
| 12 | **16e** | Me | H | 6,8-diMeO | H | 30 | **18e** | 92 | 3.602 | 3.818 |
| 13 | **16f** | Me | H | 6-Me | H | 30 | **18f** | 93 | 2.033 | >10 |
| 14 | **16g** | Me | H | 7-Me | H | 30 | **18g** | 80 | 1.005 | 6.928 |
| 15 | **16h** | Me | H | 6-Cl | H | 30 | **18h** | 74 | 2.208 | 1.283 |
| 16 | **16i** | Me | H | 7-Cl | H | 30 | **18i** | 70 | 0.895 | >10 |
| 17 | **16j** | Me | H | 6-$NO_2$ | H | 30 | **18j** | 67 | 0.569 | 1.026 |
| 18 | **16k** | Me | H | 7-$NO_2$ | H | 30 | **18k** | 72 | 1.370 | 1.579 |
| 19 | **16l** | Me | H | 6-$CF_3$ | H | 30 | **18l** | 74 | 0.921 | 1.131 |
| 20 | **16m** | Me | H | 7-$CF_3$ | H | 30 | **18m** | 77 | >10 | 6.018 |
| 21 | **16n** | Me | H | 6-F | H | 30 | **18n** | 78 | 2.701 | 4.401 |
| 22 | **16o** | Me | H | 7-F | H | 30 | **18o** | 72 | 1.000 | 1.466 |
| 23 | **16p** | Me | H | 5,6-fused benzene | H | 20 | **18p** | 60 | >10 | >10 |
| 24 | **16q** | Me | H | 6,7-fused benzene | H | 20 | **18q** | 72 | >10 | 5.269 |
| | | | | Camptothecin | | | | | 0.159 | 0.019 |

a) **17b,d** synthesized by the other method in ref.11c. b) **17e** synthesized by the other method in ref.4.

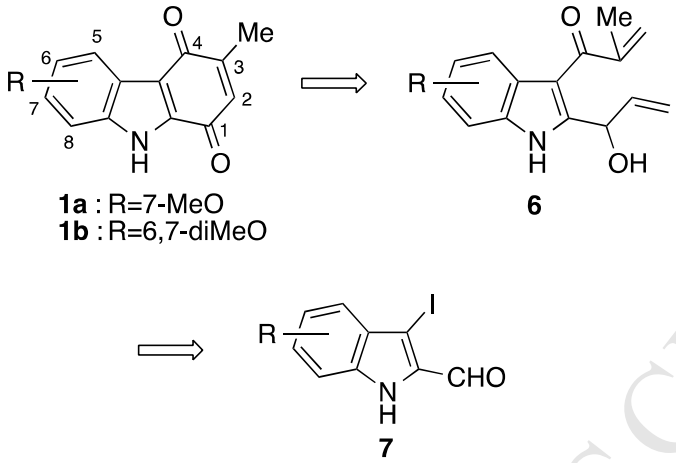



**1a** **1b**

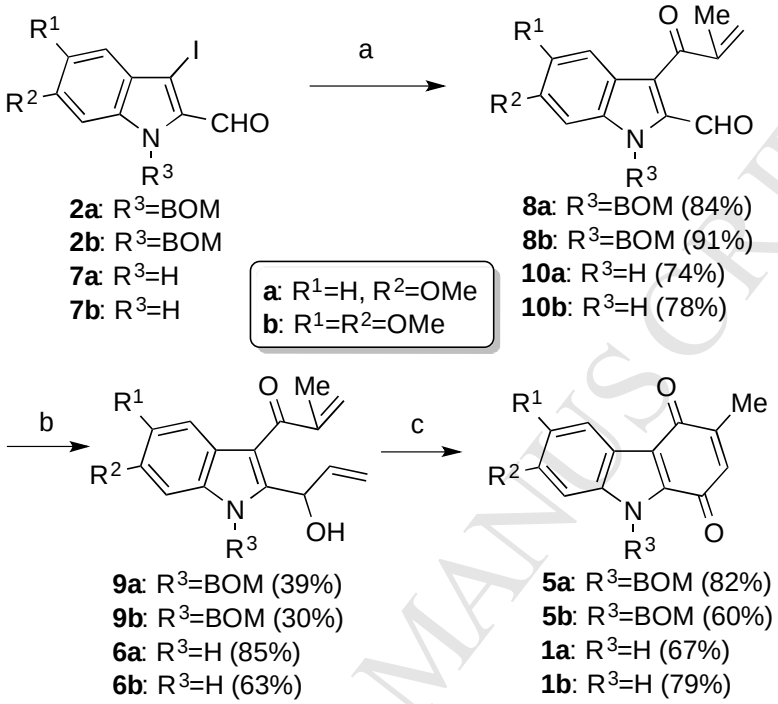
**Figure 1.** Structure of koeniginequinones A (**1a**) and B (**1b**)



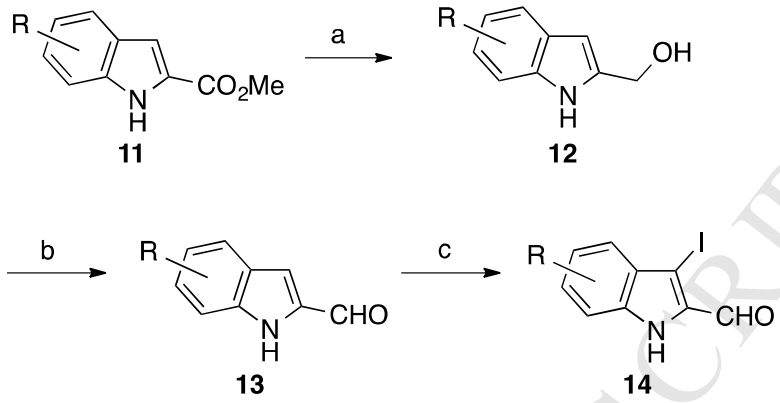

**Scheme 1**. Synthesis of koeniginequinones A and B using one-pot cyclocarbonylation. Reagents and conditions: (a) propenylmagnesium bromide, THF, 0 °C; (b) TBSCl, *i*$Pr_2$NEt, $CH_2Cl_2$; (c) tributyl(vinyl)tin, CO (1 atm), BHT, $PdCl_2$(dppf), DMF, 70 °C; (d) Na, liq.$NH_3$, −78 °C .



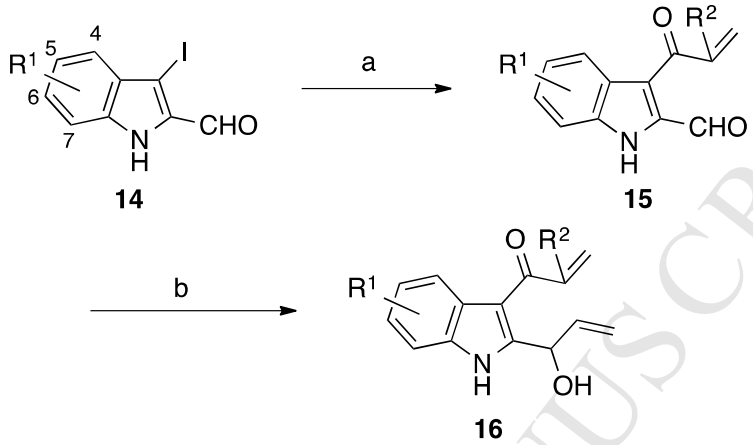

**Scheme 2**. Retrosynthetic analysis of koeniginequinones A and B




**Scheme 3**. Synthesis of koeniginequinones A (**1a**) and B (**1b**). Reagents and conditions: (a) tributyl(isopropenyl)tin, CO (1 atm), BHT, $PdCl_2$(dppf), DMF, 70 °C; (b) vinylmagnesium bromide, THF, 0 °C; (c) Grubbs$^{2nd}$, under $O_2$, toluene, 70 °C.




**Scheme 4**. Synthesis of 3-iodoindole-2-carbaldehydes **14**. Reagents and conditions: (a) $LiAlH_4$, THF, rt; (b) act. $MnO_2$, DMF, rt; (c) $I_2$, KOH, DMF, rt.




**Scheme 5**. Synthesis of 2-allylindoles **16**. Reagents and conditions: (a) tributyl(isopropenyl)tin or tributyl(vinyl)tin, CO (1 atm), BHT, $PdCl_2$(dppf), DMF, 70 °C; (b) vinylmagnesium bromide, THF, 0 °C.

♦The total synthesis of the carbazole-1,4-quinone alkaloid koeniginequinones A and B in three steps using tandem RCM and dehydrogenation reactions have been achieved.

♦24 carbazole-1,4-quinones substituted at the 5-, 6-, 7-, and/or 8-positions have been synthesized using this method.

♦The carbazole-1,4-quinones have been evaluated for their antiproliferative activity against HCT-116 and HL-60 cells.

♦The 6-nitro analog exhibited the most potent activity against both tumor cell types.