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Synthesis and anticancer evaluation of certain indolo[2,3-*b*]quinoline derivatives

Yeh-Long Chen,* Hsien-Ming Hung, Chih-Ming Lu, Kuang-Chieh Li and Cherng-Chyi Tzeng

Faculty of Medicinal and Applied Chemistry, College of Life Science, Kaohsiung Medical University, Kaohsiung City 807, Taiwan

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Abstract—The present report describes the synthesis and anticancer evaluation of certain 11-substituted 6*H*-indolo[2,3-*b*]quinolines and their methylated derivatives. These 6*H*-indolo[2,3-*b*]quinoline derivatives **11**–**13** were prepared from the commercially available 1,4-dihydroxyquinoline through alkylation, chlorination, nucleophilic reaction, and ring cyclization. Depending on the ratio of **11**, $(MeO)_2SO_2$, and K_2CO_3, alkylation occurred primarily on N-5 (1:0.8:0.8) or N-6 (1:1.5:1.5) leading to the isolation of **14a** or **14b** as a major product. Accordingly, major product **15a** (**2**/$(MeO)_2SO_2$/K_2CO_3 = 1:2:2) or **15b** (1:1:1), respectively, was obtained by alkylation of **12** while **16a** (**13**/$(MeO)_2SO_2$/K_2CO_3 = 1:2:2) or **16b** (1:1:1), respectively, was obtained by alkylation of **13**. The in vitro anticancer assay indicated 5-methylated derivatives **14a**, **15a**, **16a** are more cytotoxic than their respective 6-methylated counterparts **14b**, **15b**, **16b** and 6*H*-indolo[2,3-*b*]quinoline precursors **11**, **12**, **13**. Among them, 11-(4-methoxyanilino)-6-methyl-6*H*-indolo[2,3-*b*]quinoline (**16a**) was the most cytotoxic with a mean GI_{50} value of 0.78 μM and also exhibited selective cytotoxicities for HL-60 (TB), K-562, MOLT-4, RPMI-8226, and SR with GI_{50} values of 0.11, 0.42, 0.09, 0.14, and 0.19 μM, respectively.

1. Introduction

Acridine derivatives, especially 9-anilinoacridines have been extensively studied as potential chemotherapeutic agents due to their capability of intercalating DNA leading to the inhibition of mammalian topoisomerase II.[1–10] Among such derivatives, 4′-(9-acridinylamino)methanesulfonyl-*m*-anisidine (amsacrine, *m*-AMSA) has been clinically used for the treatment of leukemia and lymphoma.[1] Further structural modification lead to the discovery of an improved broad spectrum antitumor agent, 3-(9-acridinylamino)-5-(hydroxymethyl)aniline (AHMA), which is capable of inhibiting the growth of certain solid tumors such as mammary adenocarcinoma, melanoma, and Lewis lung carcinoma in mice.[10] These results prompted us to synthesize and evaluate the anticancer activity of bioisosteric 4-anilinofuro[2,3-*b*]quinoline derivatives.[11,12] Some of them were found to possess potent and broad anticancer activities. To further explore the structure–activity relationships, the tricyclic furo[2,3-*b*]quinoline was replaced with cryptotackieine (neocryptolepine), a tetracyclic indolo[2,3-*b*]quinoline alkaloid, which proved to be an effective DNA intercalator.[13–15] We expect these 4-anilino substituents to form hydrogen bonding with DNA molecule during the intercalation process of tetracyclic indolo[2,3-*b*]quinoline ring. Since *m*-AMSA has been clinically used for the treatment of leukemia, the antileukemia activity of certain indolo[2,3-*b*]quinoline derivatives is also described (Fig. 1).

2. Chemistry

Preparation of the indolo[2,3-*b*]quinoline derivatives **11**–**13** is outlined in Scheme 1.[15,16] The commercially available 2,4-dihydroxyquinoline (**1**) was methylated with $(MeO)_2SO_2$ and K_2CO_3 in acetone to afford 4-methoxy-1*H*-quinolin-2-one (**2**) in 76% yield. Reflux of **1** with aniline (neat) or *p*-anisidine (in Ph_2O) afforded 4-anilino-2-quinolinones (**3**) or its 4-methoxy derivative **4**, respectively. Chlorination of **2** was with $POCl_3$ followed by the treatment with benzotriazole in refluxed ethoxyethanol afforded 2-benzotriazol-1-yl-4-methoxyquinoline (**8**) in a 49% overall yield. Accordingly, **9** and **10** were prepared from the respective quinolinyl chlorides **6** and **7**, which in turn were obtained from **3**

Keywords: 6*H*-Indolo[2,3-*b*]quinoline; Cytotoxicity; Anticancer agents.
* Corresponding author. Tel.: +886 7 3121101x2684; fax: +886 7 3125339; e-mail: yeloch@kmu.edu.tw

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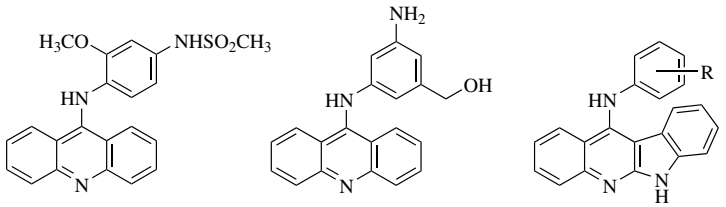
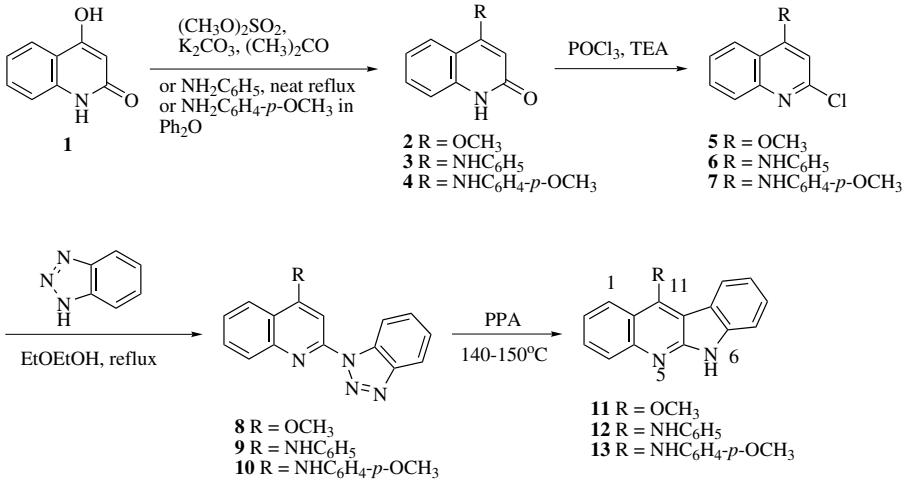


m-AMSA AHMA Indolo[2,3-*b*]quinolines

Figure 1. Chemical structures of *m*-AMSA, AHMA, and indolo[2,3-*b*]quinoline derivatives.



1

2 R = OCH_3
3 R = NHC_6H_5
4 R = NHC_6H_4-*p*-OCH_3

5 R = OCH_3
6 R = NHC_6H_5
7 R = NHC_6H_4-*p*-OCH_3

8 R = OCH_3
9 R = NHC_6H_5
10 R = NHC_6H_4-*p*-OCH_3

11 R = OCH_3
12 R = NHC_6H_5
13 R = NHC_6H_4-*p*-OCH_3

Scheme 1.

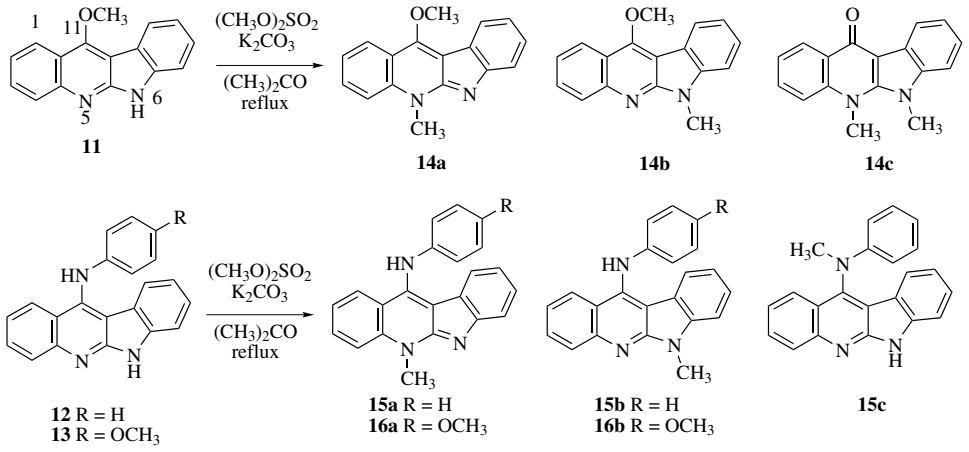
and **4**, respectively, in moderate overall yields (41–54%). Decomposition of triazole **8** in polyphosphoric acid (PPA) gave the tetracyclic 11-methoxy-6*H*-indolo[2,3-*b*]quinoline (**11**) in 33% yield. The structure of **11** was confirmed by ^{1}H NMR, which showed a methoxy singlet at δ 4.24 and an indolyl-NH broad singlet at δ 11.78 (Table 1). From the NOESY spectrum, the NOE interactions were observed among methoxy protons (δ 4.24), H–C(1) (δ 8.29), and H–C(10) (δ 8.21). Accordingly, 11-anilinoindolo[2,3-*b*]quinolines **12** and **13** were prepared by the thermal decomposition of triazoles **9** and **10**, respectively.

Refluxed of **11**, $(MeO)_2SO_2$, and K_2CO_3 in a ratio of 1:0.8:0.8 in acetone afforded a sole product of 11-methoxy-5-methyl-5*H*-indolo[2,3-*b*]quinoline **14a** in 50% yield along with the recovery of 24% starting material (Table 2, entry 1). With a ratio of 1:1.5:1.5, the mixture of **14a**,**b**, and **14c**, was obtained in 7%, 52%, and 15% yield, respectively, (entry 2). The position of methyl

Table 1. NMR spectral data of compounds **11**–**13** in DMSO-d_6

H	**11**		**12**		**13**	
	δ_H[a]	NOE[b]	δ_H[a]	NOE[b]	δ_H[a]	NOE[b]
1-H	8.29 (dd, 8.0, 1.8)	2-H, OCH_3	8.38 (dd, 8.4, 1.2)	2-H NH–C(11)	8.42 (d, 8.0)	2-H NH–C(11)
2-H	7.51 (m)	1, 3-H	7.43 (m)	1, 3-H	7.40 (m)	1, 3-H
3-H	7.75 (m)	2, 4-H	7.72 (m)	2, 4-H	7.69 (m)	2, 4-H
4-H	7.99 (d, 8.4)	3-H	7.96 (dd, 8.8, 1.2)	3-H	7.92 (d, 8.0)	3-H
6-NH	11.78	7-H	11.66	7-H	11.58	7-H
7-H	7.51 (m)	6-NH, 8-H	7.43 (m)	6-NH, 8-H	7.40 (m)	6-NH, 8-H
8-H	7.51 (m)	7, 9-H	7.37 (m)	7, 9-H	7.32 (m)	7, 9-H
9-H	7.31 (m)	8, 10-H	6.92 (m)	8, 10-H	6.89 (m)	8, 10-H
10-H	8.21 (d, 8.0)	9-H, OCH_3	7.14 (d, 8.0)	9-H, NH–C(11)	6.99 (d, 7.6)	9-H, NH–C(11)
C(11)	4.33 (OCH_3)	1, 10-H	9.21 (NH–C(11))	1, 10-H	9.00 (NH–C(11))	1, 10-H
			6.83 (m, 3 Ar–H)	[c]	3.68 (OCH_3)	[c]
			7.18 (m, 2 Ar–H)	[c]	6.82 (m, 4 Ar–H)	[c]

[a] Multiplicity and *J* values in Hz are given in parentheses.
[b] Protons observed NOE interactions in NOESY spectrum.
[c] The NOE interactions with other aromatic protons.



Scheme 2.

Table 2. Methylation reaction of 11-substituted-6*H*-indolo[2,3-*b*]quinoline (**11**–**13**) by various conditions

Entry	Reaction condition	Recovery (%)	Product yield (%)		
1	**11**/$(CH_3O)_2SO_2/K_2CO_3$ (1:0.8:0.8)	**11** (24)	**14a** (50)	**14b** (0)	**14c** (0)
2	**11**/$(CH_3O)_2SO_2/K_2CO_3$ (1:1.5:1.5)	—	**14a** (7)	**14b** (52)	**14c** (15)
3	**12** (R = H)/CH_3I/K_2CO_3 (1:2:1)	**12** (48)	**15a** (21)	**15b** (11)	**15c** (0)
4	**12** (R = H)/$(CH_3O)_2SO_2/K_2CO_3$ (1:1:1)	—	**15a** (20)	**15b** (49)	**15c** (trace)
5	**12** (R = H)/$(CH_3O)_2SO_2/K_2CO_3$ (1:2:2)	—	**15a** (44)	**15b** (18)	**15c** (14)
6	**13** (R = OCH_3)/$(CH_3O)_2SO_2/K_2CO_3$ (1:1:1)	**13** (27)	**16a** (12)	**16b** (40)	—
7	**13** (R = OCH_3)/$(CH_3O)_2SO_2/K_2CO_3$ (1:2:2)	**13** (14)	**16a** (45)	**16b** (15)	—

group in **14a**–**c** was confirmed by NOESY experiments in which the NOE interactions was observed between Me–N(5) protons (δ 4.29) and H–C(4) (δ 8.01) in **14a**; Me–N(6) protons (δ 3.94) and H–C(7) (δ 7.63) in **14b**; Me–N(5) protons (δ 4.18) and H–C(4) (δ 7.82), and Me–N(6) protons (δ 4.11) and H–C(7) (δ 7.58) in **14c**. Accordingly, refluxed of 4-anilino-6*H*-indolo[2,3-*b*]quinoline (**1 2**), $(MeO)_2SO_2$, and K_2CO_3 in a ratio of 1:2:1 gave a mixture of **15a** and **15b** in 21% and 11% yield, respectively, along with the recovery of 48% starting material (entry 3). With a ratio of 1:1:1, a mixture of **15a** and **15b** was obtained in 20% and 49% yield, respectively, (entry 4) while a ratio of 1:2:2 gave **15a**, **15b**, and **15c** in 44%, 18%, and 14% yield, respectively, (entry 5). With a ratio of **13**:$(MeO)_2SO_2$:K_2CO_3 = 1:1:1, compounds **13**, **16a**, and **16b** were obtained in 27%, 12%, and 40% yield, respectively, while a ration of 1/2/2 gave **13**, **16a**, and **16b** in 14%, 45%, and 15% yield, respectively, (entry 6) and (entry 7) (Scheme 2).

3. Pharmacological results and discussion

All compounds were evaluated in vitro against a 3-cell line panel consisting of MCF7 (Breast), NCI-H460 (Lung), and SF-268 (CNS).[17] Results from Table 3 indicated all the methylated 6*H*-indolo[2,3-*b*]quinoline derivatives **14**–**16** are active with exception of **14b** while their precursors **11**–**13** are inactive with exception of **13**, which exhibited a weak inhibitory activity on the growth of NCI-H460. Those active compounds were evaluated in the full panel of 60 human tumor cell lines derived from nine cancer cell types (leukemia, nonsmall cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer). For each compound, dose–response curves for each cell line were measured with five different drug concentration, the concentration causing 50% cell growth inhibition (GI_{50}) compared with the control were calculated.[18] 11-Methoxy-6*H*-indolo[2,3-*b*]quinoline (**11**) and its 6-methyl derivative **14b** were inactive, the 5,6-dimethyl derivative **14c** (40.74 μM) exhibited a moderate activity, while the 5-methyl derivative **14a** (mean GI_{50} = 10.72 μM) demonstrated a fairly good cytotoxicity. Similar structure–activity relationships were observed in which 11-anilino-6*H*-indolo[2,3-*b*]quinoline (**12**) was inactive, its 6-methyl derivative **15b** (16.98 μM) exhibited a marginal cytotoxicity, while the 5-methyl derivative **15a** (1.95 μM) proved to be the most cytotoxic; 11-(4-methoxyanilino)-6*H*-indolo[2,3-*b*]quinoline (**13**) and its 6-methyl derivative **16b** (22.91 μM) were weakly active while the 5-methyl derivative **16a** (0.78 μM) was the most cytotoxic. These indolo[2,3-*b*]quinoline derivatives demonstrated selective activity against the growth of leukemia cells in which the GI_{50} value for the individual cell line was less than the mean GI_{50} as shown in Table 4. Compounds **15a**,**c**, and **16a** are especially cytotoxic for MOLT-4 with GI_{50} values of 0.32, 0.66, and 0.09 μM, respectively. Compound **16a** also demonstrated selective cytotoxicities for HL-60 (TB), K-562, MOLT-4, RPMI-8226, and SR with GI_{50} values of 0.11, 0.42, 0.09, 0.14, and 0.19 μM, respectively.

Table 3. In vitro primary anticancer assay of indolo[2,3-*b*]quinoline derivatives

Compound	Growth percentages (at 100 μM)[a]			Mean GI_{50} (μM)[b,c]
	NCI-H460 (Lung)	MCF7 (Breast)	SF-268 (CNS)	
8	83	75	91	Nd[d]
11	70	47	58	Nd
12	55	51	59	Nd
13	16	63	108	12.88
14a	16	21	67	10.72
14b	82	73	98	Nd
14c	24	34	50	40.74
15a	−1	−1	0	1.95
15b	11	16	76	16.98
15c	−1	−1	−1	1.51
16a	0	7	55	0.78
16b	20	44	68	22.91
m-AMSA	Nd	Nd	Nd	0.46

[a] In this protocol, each cell line is inoculated and preincubated on a microtiter plate. Test agents are then added at a single concentration (100 μM) and the culture incubated for 48 h. End-point determinations are made with alamar blue.[17] Results for each test agent are reported as the percent of growth of the treated cells when compared to the untreated control cells. Compounds which reduced the growth of any one of the cell lines to 32% or less (negative numbers indicate cell kill) are passed on for evaluation in the full panel of 60 cell lines over a 5-log dose range.

[b] Data obtained from NCI's in vitro disease-oriented tumor cell screen.[18] GI_{50}: Drug molar concentration causing 50% cell growth inhibition.

[c] Mean values over all cell lines tested. These cell lines are: leukemia (CCRF-CEM, HL-60 (TB), K-562, MOLT-4, PRMI-8226, and SR); nonsmall cell lung cancer (A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, and NCI-H522); colon cancer (COLC 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, and SW-620); CNS cancer (SF-268, SF-295, SF-539, SNB-19, SNB-75, and U251); melanoma (LOX IMVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-5, and UACC-257); ovarian cancer (IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OV-3); renal cancer (786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, and UO-31); prostate cancer (PC-3 and DU-145); and breast cancer (MCF7, MCF7/ADR-RES, MDA-MB-231/ATCC, HS 578T, MDA-MB-435, MDA-N, and T-47D).

[d] Not determined.

4. Conclusion

A number of 11-substituted 6*H*-indolo[2,3-*b*]quinoline and their methylated derivatives were synthesized and evaluated for their cytotoxic activities. The preliminary anticancer assay indicated 5-methylated derivatives **14a**, **15a**, **16a** are more cytotoxic than their respective 6-methylated counterparts **14b**, **15b**, **16b** and 6*H*-indolo[2,3-*b*]quinoline precursors **11**, **12**, **13**. Among them, 11-(4-methoxyanilino)-6-methyl-6*H*-indolo[2,3-*b*]quinoline (**16a**) is the most cytotoxic with a mean GI_{50} of 0.78 μM. Compounds **15a**,**c**, and **16a** are especially cytotoxic for MOLT-4 with GI_{50} values of 0.32, 0.66, and 0.09 μM respectively.

5. Experimental

5.1. General

TLC: precoated (0.2 mm) silica gel 60 F_{254} plates from EM Laboratories, Inc.; detection by UV light (254 nm). All chromatographic separations were performed using silica gel (Merck 60 230–400 mesh). Mp: Yamato MP-21 melting-point apparatus; uncorrected. UV spectra (λ_{max} (log ε) in nm): Hitachi U-3210 spectrophotometer. IR spectra (cm^{-1}): Nicolet Magana-IR 550 infrared spectrophotometer. ^1H and ^{13}C NMR spectra: Varian-Unity-400 spectrometer at 400 and 100 MHz or Varian-Gemini-200 spectrometer at 200 and 50 MHz, chemical shifts δ in ppm with $SiMe_4$ as an internal standard (= 0 ppm), coupling constants *J* in Hz. Elemental analyses were carried out on a Heraeus CHN-O-Rapid elemental analyzer, and results were within ±0.4% of calculated values.

5.1.1. 4-Methoxy-1*H*-quinolin-2-one (2). A mixture of 4-hydroxy-1*H*-quinolin-2-one (**1**, 3.20 g, 20 mmol) and K_2CO_3 (5.5 g, 40 mmol) in acetone (50 mL) was refluxed for 3 h. The mixture was cooled to room temperature, dimethylsulfate (5.1 g, 40 mmol) was added, and the mixture was refluxed for another 2 h (TLC monitoring). Most of the solvent was removed in vacuo, and the resulting precipitate that separated was collected by filtration, washed with H_2O, and dried to give **2** (2.66 g, 76%) as a pale-yellow solid. Mp: 253–255 °C (lit:[19] 254–255 °C); UV_{max} nm (log ε): 226.4 (4.61), 265.0 (3.77), 274.0 (3.76), 313.8 (3.70) in MeOH; IR ν_{max} cm^{-1}: 1236, 1391, 1609, 1674, 3324 in KBr; ^1H NMR (200 MHz, DMSO): 3.93 (s, OCH_3), 5.89 (s, H–C(3)), 7.16 (m, H–C(6)), 7.29 (m, H–C(5)), 7.51 (m, H–C(7)), 7.77 (m, H–C(8)), 11.35 (br s, NH). ^{13}C NMR (50 MHz, DMSO): 56.05, 96.61, 114.49, 115.15, 121.30, 122.15, 130.90, 138.58, 163.13 (C(2)), 163.19 (C(4)).

Table 4. Antileukemia activity of indolo[2,3-*b*]quinoline derivatives [GI_{50} (μM)]

Compound	Cell lines					Mean GI_{50} (μM)
	HL-60(TB)	K-562	MOLT-4	RPMI-8226	SR	
13	4.98	7.17	2.35	2.33	3.83	12.88
14a	9.88	11.5	4.70	6.04	7.10	10.72
15a	Nd	1.84	0.32	1.08	Nd	1.95
15b	Nd	5.11	7.89	3.34	Nd	16.98
15c	0.99	2.23	0.66	1.58	0.34	1.51
16a	0.11	0.42	0.09	0.14	0.19	0.78
16b	3.99	5.57	1.88	3.77	2.75	22.91
m-AMSA	0.025	0.79	0.016	0.20	0.016	0.46

Anal. Calcd for $C_{10}H_9NO_2$: C 68.56, H 5.18, N 8.00. Found: C 68.42, H 5.30, N 7.91.

5.1.2. 4-Anilino-1*H*-quinolin-2-one (3). A mixture of **1** (8.05 g, 50 mmol) and aniline (150 g, 1.61 mol) was refluxed for 18 h. After the mixture was cooled to room temperature, the precipitate that separated was collected by filtration. The filter cake was poured into 5% $NaHCO_3$ aqueous (200 mL) with vigorous stirring for 1 h, the solid was separated was filtered and washed with H_2O, and dried. Crystallization of the crude product from MeOH to give **3** (8.86 g, 75%). Mp: 316–318 °C; UV λ_{max} nm ($\log\varepsilon$): 226.6 (4.67), 314.9 (4.16) in MeOH; IR_{max} cm^{-1}: 1263, 1395, 1589, 1643, 3277 in KBr; ^1H NMR (200 MHz, DMSO): 5.68 (s, H–C(3)), 7.16–7.55 (m, 8 arom. H), 8.11 (d, $J = 7.6$ Hz, H–C(8)), 8,63 (br s, NH–C(4)), 11.05 (br s, NH). ^{13}C NMR (50 MHz, DMSO): 94.38, 113.91, 115.62, 120.74, 122.41, 123.68 (2C), 124.21, 129.25 (2C), 130.51, 139.37, 140.07, 150.02 (C(4)), 162.83 (C(2)). Anal. Calcd for $C_{15}H_{12}N_2O$: C 76.25, H 5.12, N 6.77. Found: C 76.08, H 5.24, N 6.87.

5.1.3. 4-(4-Methoxyanilino)-1*H*-quinolin-2-one (4). A mixture of **1** (1.93 g, 12 mmol) and *p*-anisidine (1.48 g, 12 mol) in diphenyl ether (10 mL) was refluxed for 8 h (by TLC monitoring). After the mixture was cooled to room temperature and added *n*-hexane (80 mL), the precipitate that separated was collected by filtration. The filter cake was with *n*-hexane, 5% $NaHCO_3$, and dried. Crystallization of the crude product from MeOH to give **4** (2.18 g, 68%). Mp: 306 °C (dec); UV λ_{max} nm ($\log\varepsilon$): 224.6 (4.68), 314.0 (4.15) in MeOH; IR_{max} cm^{-1}: 1239, 1509, 1642, 3439 in KBr; ^1H NMR (400 MHz, DMSO): 3.79 (s, OCH_3), 5.41 (s, H–C(3)), 7.00 (m, 2 arom. H), 7.17 (m, H–C(6)), 7.23 (m, 2 arom. H), 7.28 (d, $J = 8.0$ Hz, H–C(5)), 7.50 (m, H–C(7)), 8.11 (d, $J = 8.0$ Hz, H–C(8)), 8.52 (br s, NH–C(4)), 10.97 (br s, NH). ^{13}C NMR (100 MHz, DMSO): 55.31, 92.95, 113.72, 114.59 (2C), 115.66, 120.73, 122.30, 126.53 (2C), 130.47, 132.38, 139.36, 151.21, 156.66 (C(4)), 162.99 (C(2)). Anal. Calcd for $C_{16}H_{14}N_2O_2$: C 72.16, H 5.30, N 10.52. Found: C 72.07, H 5.36, N 10.52.

5.1.4. 2-Chloro-4-methoxyquinoline (5). A solution of **2** (5.1 g, 29.2 mmol) in $POCl_3$ (50 mL) and trimethylamine (3.0 g, 29.6 mmol) was heated at 90 °C for 2 h (TLC monitoring). After cooling, the mixture was poured into ice water (150 mL) and neutralized with saturated Na_2CO_3 until pH 7 resulted. The resulting precipitate that separated was collected by filtration, washed with H_2O, and dried to give a brown solid, which was recrystallized with MeOH to give **5** (4.93 g, 87%). Mp: 78–80 °C; UV λ_{max} nm ($\log\varepsilon$): 227.6 (4.85), 276.0 (3.89), 311.2 (3.28) in MeOH; IR ν_{max} cm^{-1}: 1318, 1417, 1568, 1581 in KBr; ^1H NMR ($CDCl_3$): 4.05 (s, OCH_3), 6.73 (s, H–C(3)), 7.50 (m, H–C(6)), 7.70 (m, H–C(7)), 7.95 (d, $J = 8.6$ Hz, H–C(5)), 8.12 (dd, $J = 8.2$, 1.4 Hz, H–C(8)). ^{13}C NMR ($CDCl_3$): 56.25, 101.21, 120.37, 122.01, 126.09, 127.99, 130.95, 147.99, 151.52 (C(2)), 163.87 (C(4)). Anal. Calcd for $C_{10}H_8ClNO$: C 62.03, H 4.16, N 7.23. Found: C 61.97, H 4.19, N 7.22.

5.1.5. 4-Anilino-2-chloroquinoline (6). Compound **6** was obtained from **3** as described for **5** in 72% yield. Mp: 166–168 °C; UV_{max} nm ($\log\varepsilon$): 223.0 (4.59), 244.0 (4.40), 328.4 (4.17) in MeOH; IR ν_{max} cm^{-1}: 1265, 1359, 1445, 1573, 3199 in KBr; ^1H NMR (400 MHz, DMSO): 6.66 (s, H–C(3)), 7.26 (m, H–C(6)), 7.41 (m, 2 arom. H), 7.49 (m, 2 arom. H), 7.59 (m, 1 arom. H), 7.76 (m, H–C(7)), 7.80 (dd, $J = 8.4$, 1.6 Hz, H–C(5)), 8.42 (d, $J = 8.0$ Hz, H–C(8)), 9.32 (br s, NH–C(4)). ^{13}C NMR (100 MHz, DMSO): 99.72, 118.50, 122.26, 123.78 (2C), 125.09, 125.28, 128.20, 129.64 (2C), 130.66, 139.40, 148.06, 150.80 (C(4)), 150.84 (C(2)). Anal. Calcd for $C_{15}H_{11}ClN_2$: C 70.73, H 4.35, N 11.00. Found: C 70.64, H 4.50, N 11.04.

5.1.6. 2-Chloro-4-(4-methoxyanilino)quinoline (7). Compound **7** was obtained from **4** as described for **5** in 75% yield. Mp: 211–213 °C; UV $_{max}$ nm ($\log\varepsilon$): 222.6 (4.65), 244.0 (4.36), 328.4 (4.14) in MeOH; IR ν_{max} cm^{-1}: 1261, 1432, 1573, 3196 in KBr; ^1H NMR (200 MHz, DMSO): 3.81 (s, OCH_3), 6.39 (s, H–C(3)), 7.06 (m, 2 arom. H), 7.32 (m, 2 arom. H), 7.56 (m, H–C(6)), 7.74 (m, 2 H–C(5, 7)), 8.40 (d, $J = 8.2$ Hz, H–C(8)), 9.22 (br s, NH–C(4)). ^{13}C NMR (50 MHz, DMSO): 55.31, 98.83, 114.93 (2C), 118.14, 122.13, 125.12, 126.55 (2C), 128.14, 130.56, 131.69, 147.97, 150.86, 151.95 (C(2)), 157.15 (C(4)). Anal. Calcd for $C_{16}H_{111}ClN_2O$: C 67.49, H 4.60, N 9.84. Found: C 67.36, H 4.56, N 9.88.

5.1.7. 2-(Benzotriazol-1-yl)-4-methoxyquinoline (8). A mixture of **5** (1.00 g, 5.16 mmol) and benzotriazole (0.63 g, 5.29 mmol) was heated at 110 °C for 1 h (TLC monitoring). After the mixture was cooled to room temperature, the residue was precipitated from ammonia water and stirred for 30 min. The resulting precipitate that separated was collected by filtration, washed with H_2O, and dried to give a crude solid, which was recrystallized with MeOH to give **8** (0.8 g, 56%): mp: 176–178 °C; UV λ_{max} nm ($\log\varepsilon$): 205.4 (4.60), 244.8 (4.63), 310.4 (4.25), 323.0 (4.15) in MeOH; IR ν_{max} cm^{-1}: 1292, 1404, 1452, 1591 in KBr; ^1H NMR (200 MHz, DMSO): 4.23 (s, OCH_3), 7.59 (m, 2 arom. H), 7.82 (m, 3 arom. H), 8.16 (m, 3 arom. H), 8.93 (d, $J = 8.4$ Hz, H–C(8)). ^{13}C NMR (50 MHz, DMSO): 56.75, 92.29, 115.35, 119.65, 119.98, 121.76, 125.55, 126.19, 128.22, 129.48, 131.07, 131.21, 146.26, 146.56, 151.12, 164.01. Anal. Calcd for $C_{16}H_{12}N_4O$: C 69.55, H 4.38, N 20.28. Found: C 69.42, H 4.29, N 20.44.

5.1.8. 4-Anilino-2-(benzotriazol-1-yl)quinoline (9). Compound **9** was obtained from **6** as described for **8** in 74% yield. Mp: 244–245 °C; UV $_{max}$ nm ($\log\varepsilon$): 202.4 (4.74), 243.2 (4.57), 306.4 (4.33) in MeOH; IR ν_{max} cm^{-1}: 1283, 1411, 1541, 1588, 3335 in KBr; ^1H NMR (400 MHz, DMSO): 7.28 (m, 1 arom. H), 7.53 (m, H–C(6) and 4 arom. H), 7.61 (m, 1 arom. H), 7.74 (m, 2H–C(3, 7)), 7.82 (m, 1 arom. H), 8.05 (d, $J = 7.6$ Hz, 1 arom. H), 8.17 (d, $J = 8.0$ Hz, H–C(5)), 8.50 (d, $J = 7.6$ Hz, 1 arom. H), 8.91 (d, $J = 8.4$ Hz, H–C(8)), 9.39 (br s, NH–C(4)). ^{13}C NMR (50 MHz, DMSO): 90.84, 115.41, 118.82, 119.46, 122.26, 123.74 (2C), 124.94, 125.10, 125.24, 128.79, 129.12, 129.64 (2C),

130.67, 131.11, 139.79, 146.12, 147.19, 151.00, 151.13. Anal. Calcd for $C_{21}H_{15}N_5$: C 74.76, H 4.48, N 20.76. Found: C 74.78, H 4.63, N 20.80.

5.1.9. 2-(Benzotriazol-1-yl)-4-(4-methoxyanilino)quinoline (10). Compound **10** was obtained from **7** as described for **8** in 55% yield. Mp: 236–238 °C; UV_{max} nm ($\log\varepsilon$): 202.8 (4.58), 242.4 (4.43), 305.2 (4.16) in MeOH; IR ν_{max} cm^{-1}: 1242, 1411, 1534, 1585, 3275 in KBr; ^1H NMR (400 MHz, DMSO): 7.12 (m, 2 arom. H), 7.42 (m, 2 arom. H), 7.49 (s, H–C(3)), 7.55 (m, H–C(6)), 7.60 (m, 1 arom. H), 7.75 (m, H–C(7)), 7.82 (m, 1 arom. H), 8.04 (dd, J = 8.4, 2.4 Hz, 1 arom. H), 8.18 (d, J = 8.4 Hz, H–C(5)), 8.50 (d, J = 8.4 Hz, 1 arom. H), 8.92 (d, J = 8.0 Hz, H–C(8)), 9.29 (br s, NH–C(4)). ^{13}C NMR (100 MHz, DMSO): 55.23, 89.81, 114.87 (2C), 115.40, 118.40, 119.40, 122.07, 124.90, 125.16, 126.47 (2C), 128.69, 129.05, 130.53, 131.08, 131.99, 146.04, 147.05, 151.01, 152.07, 157.03. Anal. Calcd for $C_{22}H_{17}N_5O$: C 71.92, H 4.66, N 19.06. Found: C 71.90, H 4.72, N 19.10.

5.1.10. 11-Methoxy-6*H*-indolo[2,3-*b*]quinoline (11). A mixture of **8** (1.78 g, 6.44 mmol) in PPA (18 mL) was heated at 140–150 °C for 2 h (TLC monitoring). After cooling, the mixture was poured into ice water (100 mL) and neutralized with saturated Na_2CO_3 until pH 8.5 resulted. The resulting precipitate that separated was collected by filtration, washed with H_2O, and dried to give a crude solid, which was purified by flash column chromatography (FC, silica gel CH_2Cl_2/MeOH 20:1) and recrystallized from EtOH to give **11** (0.53 g, 33%). Mp: 231–232 °C; UV λ_{max} nm ($\log\varepsilon$): 223.8 (4.50), 270.4 94.93), 314.0 (4.14), 327.8 (4.31), 365.2 (3.62) in MeOH; IR ν_{max} cm^{-1}: 1233, 1291, 1406, 1584, 1616, 1647 in KBr; ^1H NMR (400 MHz, DMSO): 4.24 (s, OCH_3), 7.31 (m, H–C(9)), 7.51 (m, 3H–C(2, 7, 8)), 7.75 (m, H–C(3)), 7.99 (d, J = 8.4 Hz, H–C(4)), 8.21 (d, J = 8.0 Hz, H–C(10)), 8.29 (dd, J = 8.0, 1.6 Hz, H–C(1)), 11.78 (br s, H–N(6)). ^{13}C NMR (100 MHz, DMSO): 61.83 (OCH_3–C(11)), 108.22, 110.81, 118.65, 118.82, 120.06, 122.10, 122.54, 123.49, 127.21, 127.71, 129.18, 140.67, 148.09, 154.84, 157.88. Anal. Calcd for $C_{16}H_{12}N_2O$ $0.1H_2O$: C 76.84, H 4.92, N 11.20. Found: C 76.71, H 4.94, N 11.17.

5.1.11. 11-Anilino-6*H*-indolo[2,3-*b*]quinoline (12). Compound **12** was obtained from **9** as described for **11** in 56% yield. Mp: 312–314 °C; UV_{max} nm ($\log\varepsilon$): 219.8 (4.55), 233.8 (4.52), 274.2 (4.90), 346.6 (4.07), 381.6 (4.05), 399.0 (4.11) in MeOH; IR ν_{max} cm^{-1}: 1231, 1251, 1501, 1578, 1614, 3398 in KBr; ^1H NMR (400 MHz, DMSO): 6.83 (m, 3 arom. H), 6.92 (m, H–C(9)), 7.14 (d, J = 8.0 Hz, H–C(10)), 7.18 (m, 2 arom. H), 7.37 (m, H–C(8)), 7.43 (m, 2H-(2, 7)), 7.72 (m, H–C(3)), 7.96 (dd, J = 8.8, 1.2 Hz, H–C(4)), 8.38 (dd, J = 8.4, 1.2 Hz, H–C(1)), 9.21 (br s, NH–C(11)), 11.66 (br s, H–N(6)). ^{13}C NMR (100 MHz, DMSO): 108.85, 109.99, 115.97 (2C), 118.84, 119.69, 119.73, 119.81, 121.70, 123.58, 124.57, 126.60, 127.26, 128.77, 129.09 (2C), 139.77, 140.56, 143.93, 147.54, 154.29. Anal. Calcd for $C_{21}H_{15}N_3$: C 81.53, H 4.89, N 13.58. Found: C 81.44, H 4.96, N 13.61.

5.1.12. 11-(4-Methoxyanilino)-6*H*-indolo[2,3-*b*]quinoline (13). Compound **13** was obtained from **10** as described for **11**, which was purified by flash column chromatography (FC, CH_2Cl_2/MeOH = 100:7) and recrystallized from MeOH in 32% yield. Mp: 280–282 °C; UV λ_{max} nm ($\log\varepsilon$): 202.4 (4.19), 220.2 (4.18), 235.0 (4.17), 275.6 (4.44), 348.6 (3.58), 400.0 (3.73) in MeOH; IR ν_{max} cm^{-1}: 1033, 1236, 1510, 1575, 1612, 1419 in KBr; ^1H NMR (400 MHz, DMSO): 3.68 (s, OCH_3), 6.82 (m, 4 arom. H), 6.89 (m, H–C(9)), 6.99 (d, J = 7.6 Hz, H–C(10)), 7.32 (m, H–C(8)), 7.40 (m, 2H–C(2, 7)), 7.69 (m, H–C(3)), 7.92 (d, J = 8.0 Hz, H–C(4)), 8.42 (d, J = 8.0 Hz, H–C(1)), 9.00 (br s, NH–C(11)), 11.58 (br s, H–N(6)). ^{13}C NMR (100 MHz, DMSO): 55.14 (OCH_3), 106.73, 109.73, 114.36 (2C), 118.39 (2C), 118.65, 119.02, 119.81, 121.31, 123.36, 124.43, 126.06, 127.15, 128.62, 137.05, 140.20, 140.82, 147.49, 153.49, 154.38. Anal. Calcd for $C_{22}H_{17}N_3O$: C 77.86, H 5.05, N 12.38. Found: C 77.91, H 5.00, N 12.42.

5.1.13. 11-Methoxy-5-methyl-5*H*-indolo[2,3-*b*]quinoline (14a), 11-methoxy-6-methyl-6*H*-indolo[2,3-*b*]quinoline (14b), and 5,6-dimethyl-5,6-dihydroindolo[2,3-*b*]quinolin-11-one (14c). General procedure A for the methylation reactions of 11–13 by dimethylsulfate and K_2CO_3 in acetone (Table 2, entry 1). A mixture of **11** (150 mg, 0.6 mmol), K_2CO_3 (66 mg, 0.48 mmol), and dimethylsulfate (61 mg, 0.48 mmol) in acetone (5 mL) was refluxed for 24 h. The solvent was removed in vacuo, and the residue was poured into water (50 mL), neutralized with 5% HCl until pH 7 resulted, and extracted with EtOAc (50 mL × 3). The organic layer was washed with a saturated $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated in vacuo. Purification by FC (CH_2Cl_2/MeOH = 100:7) to give the reactant **11** (36 mg, 24% recovered) first and then **14a** (79 mg, 50%). Compound **14a** mp: 184–186 °C (recrystallized from MeOH); UV_{max} nm ($\log\varepsilon$): 207.4 (4.35), 277.0 (4.73), 281.4 (4.73), 332.6 (4.21), 347.4 (4.20) in MeOH; IR ν_{max} cm^{-1}: 1241, 1281, 1492, 1520, 1569, 1638 in KBr; ^1H NMR (400 MHz, DMSO): 4.29 (two s, CH_3–N(5), OCH_3), 7.22 (m, H–C(9)), 7.48 (m, H–C(2)), 7.54 (m, H–C(8)), 7.60 (dd, J = 8.0, 0.8 Hz, H–C(7)), 7.90 (m, H–C(3)), 8.01 (d, J = 8.4 Hz, H–C(4)), 8.12 (ddd, J = 7.6, 1.2, 0.8 Hz, H–C(10)), 8.32 (dd, J = 8.4, 1.2 Hz, H–C(1)). ^{13}C NMR (100 MHz, DMSO): 32.71 (CH_3–N(5)), 62.11 (11-OCH_3), 114.81, 115.27, 116.66, 117.14, 119.43, 121.74, 122.03, 123.10, 123.73, 127.86, 131.34, 137.97, 153.80, 157.54, 157.65 (C(5a or 11)). Anal. Calcd for $C_{10}H_9NO_2$: C 68.56, H 5.18, N 8.00. Found: C 68.42, H 5.30, N 7.91.

(Table 2, entry 2). The reaction was performed from **11** (199 mg, 0.8 mmol), K_2CO_3 (165 mg, 1.2 mmol), and dimethylsulfate (151 mg, 1.2 mmol) in acetone (10 mL) according to general procedure A described above to give **14a** (15 mg, 7%), **14b** (109 mg, 52%), and **14c** (31 mg, 15%). Compound **14b** mp: 130–132 °C (recrystallized from MeOH); UV λ_{max} nm ($\log\varepsilon$): 222.0 (4.31), 273.2 (4.77), 313.4 (3.92), 327.6 (4.10), 371.2 (3.41) in MeOH; IR ν_{max} cm^{-1}: 1290, 1394, 1569, 1606, 1636 in KBr; ^1H NMR (400 MHz, DMSO): 3.94 (s, CH_3–N(6)), 4.25 (s, OCH_3), 7.37 (m, H–C(9)), 7.53 (m, H–

C(2)), 7.63 (m, 2H–C(7, 8)), 7.78 (m, H–C(3)), 8.06 (d, $J = 8.4$ Hz, H–C(4)), 8.25 (dd, $J = 7.8$, 0.8 Hz, H–C(10)), 8.31 (dd, $J = 8.4$, 1.2 Hz, H–C(1)). ^{13}C NMR (100 MHz, DMSO): 27.67 (CH_3–N(6)), 61.86 (OCH_3), 107.96, 109.20, 117.92, 118.86, 120.34, 122.13, 122.58, 123.32, 127.24, 127.71, 129.34, 141.58, 147.77, 153.88, 157.95. Anal. Calcd for $C_{17}H_{14}N_2O$: C 77.84, H 5.38, N 10.68. Found: C 77.92, H 5.45, N 10.76. Compound **14c** mp: 271–273 °C (recrystallized from EtOH); UV λ_{max} nm ($\log\varepsilon$): 235.3 (4.44), 282.3 (4.48), 316.5 (3.88), 341.2 (3.96), 362.5 (3.71) in MeOH; IR ν_{max} cm^{-1}: 1242, 1387, 1466, 1511, 1537, 1579, 1589, 1616, 3424 in KBr; ^{1}H NMR (400 MHz, DMSO): 4.11 (s, CH_3–N(6)), 4.18 (s, CH_3–N(5)), 7.28 (m, H–C(9)), 7.33 (m, H–C(8)), 7.58 (d, $J = 8.0$ Hz, H–C(7)), 7.77 (m, 1H–C(3)), 7.82 (d, $J = 8.0$ Hz, H–C(4)), 8.26 (dd, $J = 8.4$, 1.6 Hz, H–C(10)), 8.34 (dd, $J = 7.6$, 1.2 Hz, H–C(1)). ^{13}C NMR (100 MHz, DMSO): 34.02 (CH_3–N(6)), 37.58 (CH_3–N(5)), 103.60, 109.77, 116.39, 119.88, 121.71, 122.00, 122.92, 123.16, 124.88, 125.23, 131.28, 137.55, 141.37, 148.49, 171.83 (C=O). Anal. Calcd for $C_{17}H_{14}N_2O$: C 77.84, H 5.38, N 10.68. Found: C 77.88, H 5.52, N 10.70.

5.1.14. 11-Anilino-5-methyl-5*H*-indolo[2,3-*b*]quinoline (15a), 11-anilino-6-methyl-6*H*-indolo[2,3-*b*]quinoline (15b), and 11-(*N*-methylanilino)indolo[2,3-*b*]quinolin-11-one (15c). The methylation reaction of 12 by CH_3I and K_2CO_3 in acetone (Table 2, entry 3). A mixture of **12** (108 mg, 0.35 mmol), K_2CO_3 (48 mg, 0.35 mmol), and CH_3I (99 mg, 0.7 mmol) in acetone (10 mL) was refluxed for 18 h. The solvent was removed in vacuo, and the residue was poured into water (50 mL), neutralized with 5% HCl until pH 7 resulted, and extracted with CH_2Cl_2 (50 mL×3). The organic layer was washed with a saturated $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated in vacuo. Purification by FC (CH_2Cl_2/MeOH = 40:3–5:1) to give **15b** (13 mg, 11%) first, the reactant **12** (52 mg, 48% recovered) second, and then **15a** (24 mg, 21%). Compound **15a** mp: 255–257 °C (recrystallized from EtOH); UV λ_{max} nm ($\log\varepsilon$): 213.2 (4.34), 244.1 (4.36), 272.1 (4.60), 338.2 (3.90), 375.0 (4.08) in MeOH; IR ν_{max} cm^{-1}: 1241, 1262, 1496, 1588, 1620, 3395 in KBr; ^{1}H NMR (400 MHz, DMSO): 4.34 (s, CH_3 -N(5)), 6.58 (d, $J = 7.6$ Hz, H–C(10)), 6.83 (m, H–C(9)), 7.05 (m, 3 arom. H), 7.28 (m, 2 arom. H), 7.33 (m, H–C(8)), 7.57 (d, $J = 8.0$ Hz, H–C(7)), 7.63 (m, H–C(2)), 7.98 (m, H–C(3)), 8.13 (d, $J = 8.8$ Hz, H–C(4)), 8.71 (d, $J = 8.0$ Hz, H–C(1)), 10.00 (br s, NH–C(11)). ^{13}C NMR (100 MHz, DMSO): 34.34 (CH_3 –N(5)), 113.67, 116.07, 117.60, 119.51 (2C), 119.86, 121.11, 122.76, 122.87, 124.16, 124.94, 126.49, 127.32, 129.09, 129.13 (2C), 132.03, 137.01, 141.60, 143.62, 152.06. Anal. Calcd for $C_{22}H_{17}N_3$: C 81.71, H 5.30, N 12.99. Found: C 81.86, H 5.43, N 13.06. Compound **15b** mp: 198–200 °C (recrystallized from EtOH); UV λ_{max} nm ($\log\varepsilon$): 222.4 (4.50), 234.4 (4.47), 275.8 (4.83), 347.6 (4.00), 384.0 (3.94), 403.0 (4.02) in MeOH; IR ν_{max} cm^{-1}: 1250, 1320, 1397, 1488, 1563, 1598, 3218 in KBr; ^{1}H NMR (400 MHz, DMSO): 3.94 (s, CH_3–N(6)), 6.84 (m, 3 arom. H), 6.98 (m, H–C(9)), 7.13 (d, $J = 7.8$ Hz, H–C(10)), 7.18 (m, 2 arom. H), 7.45 (m, 2H–C(2, 8)), 7.56 (d, $J = 8.0$ Hz, H–C(7)), 7.74 (m, H–C(3)), 8.04 (dd, $J = 8.4$, 1.2 Hz, H–C(4)), 8.42 (dd, $J = 8.4$, 0.8 Hz, H–C(1)), 9.26 (br s, NH–C(11)). ^{13}C NMR (100 MHz, DMSO): 27.62 (CH_3–N(6)), 108.23, 108.46, 116.20 (2C), 118.43, 119.06, 119.26, 119.91, 121.92, 123.68, 124.50, 126.70, 127.41, 129.08, 129.14 (2C), 140.05, 141.52, 143.81, 147.27, 153.43. Anal. Calcd for $C_{22}H_{17}N_3$: C 81.71, H 5.30, N 12.99. Found: C 81.76, H 5.45, N 12.91.

(Table 2, entry 4). The reaction was performed from **12** (186 mg, 0.6 mmol), K_2CO_3 (83 mg, 0.6 mmol), and dimethylsulfate (76 mg, 0.6 mmol) in acetone (10 mL) according to general procedure A described above to give **15a** (38 mg, 20%), and **15b** (96 mg, 49%).

(Table 2, entry 5). The reaction was performed from **12** (186 mg, 0.6 mmol), K_2CO_3 (166 mg, 1.2 mmol), and dimethylsulfate (151 mg, 1.2 mmol) in acetone (10 mL) according to general procedure A described above to give **15a** (85 mg, 44%), **15b** (35 mg, 18%), and **15c** (27 mg, 14%). Compound **15c** mp: 164–165 °C (recrystallized from MeOH); UV λ_{max} nm ($\log\varepsilon$): 226.9 (4.36), 249.6 (4.26), 280.9 (4.63), 368.4 (3.96), 398.1 (3.98) in MeOH; IR ν_{max} cm^{-1}: 1242, 1440, 1486, 1570, 1590, 1620, 3292 in KBr; ^{1}H NMR (400 MHz, DMSO): 4.31 (s, NCH_3–C(11)), 6.78 (m, 2H–C(9, 10)), 6.94 (m, 3 arom. H), 7.24 (m, 2 arom. H), 7.27 (m, H–C(8)), 7.49 (m, 2H–C(2, 7)), 7.88 (m, H–C(3)), 7.99 (d, $J = 8.4$ Hz, H–C(4)), 8.51 (dd, $J = 8.0$, 0.8 Hz, H–C(1)), 9.45 (br s, H–N(6)). ^{13}C NMR (100 MHz, DMSO): 33.08 (NCH_3-C(11)), 113.21, 116.84, 117.60, 118.24 (2C), 118.46, 121.47, 121.51, 123.61, 124.68, 125.33, 126.76, 129.56 (2C), 131.38, 138.03, 140.78, 143.35, 153.85, 157.01. Anal. Calcd for $C_{22}H_{17}N_3$: C 81.71, H 5.30, N 12.99. Found: C 81.61, H 5.33, N 12.84.

5.1.15. 11-(4-Methoxyanilino)-5-methyl-5*H*-indolo[2,3-*b*]quinoline (16a) and 11-(4-methoxyanilino)-6-methyl-6*H*-indolo[2,3-*b*]quinoline (16b) (Table 2, entry 6). The reaction was performed from **13** (204 mg, 0.6 mmol), K_2CO_3 (83 mg, 0.6 mmol), and dimethylsulfate (76 mg, 0.6 mmol) in acetone (10 mL) according to general procedure A described above. Purification by FC (CH_2Cl_2/MeOH = 10:1–1:1) to give **16a** (26 mg, 12%) first, the reactant **13** (56 mg, 27% recovered) second, and then **16b** (85 mg, 40%). Compound **16a** mp: 155–157 °C (recrystallized from EtOH); UV λ_{max} nm ($\log\varepsilon$): 235.3 (4.38), 248.5 (4.44), 282.4 (4.57), 332.4 (3.86), 386.8 (4.04) in MeOH; IR ν_{max} cm^{-1}: 1243, 1384, 1512, 1541, 1591, 3392 in KBr; ^{1}H NMR (400 MHz, DMSO): 3.74 (s, OCH_3), 4.30 (s, CH_3–N(5)), 6.47 (d, $J = 8.0$ Hz, H–C(10)), 6.83 (m, H–C(9)), 6.90 (m, 2 arom. H), 7.10 (m, 2 arom. H), 7.31 (m, H–C(8)), 7.55 (d, $J = 8.0$ Hz, H–C(7)), 7.63 (m, H–C(2)), 7.98 (m, H–C(3)), 8.12 (d, $J = 8.8$ Hz, H–C(4)), 8.76 (d, $J = 8.0$ Hz, H–C(1)), 10.00 (br s, HN–C(11)). ^{13}C NMR (100 MHz, DMSO): 33.77 (CH_3–N(5)), 55.36 (OCH_3), 106.65, 114.32, 114.42 (2C), 114.53, 115.82, 116.99, 119.30, 121.88 (2C), 122.26, 124.08, 124.73, 125.95, 131.68, 134.98, 137.19, 143.77, 146.50, 153.28, 155.37. Anal. Calcd for $C_{23}H_{19}N_3O$: C 78.16, H 5.42, N 11.89. Found: C 78.19, H 5.49, N 11.62. Compound **16b** mp: 173–175 °C (recrystallized from EtOH); UV λ_{max} nm

(log ε): 223.5 (4.42), 238.2 (4.43), 273.5 (4.56), 352.9 (3.49), 404.4 (3.99) in MeOH; IR ν_{max} cm^{-1}: 1242, 1291, 1384, 1419, 1441, 1509, 1619, 3239 in KBr; ^1H NMR (400 MHz, DMSO): 3.68 (s, OCH_3), 3.91 (s, CH_3–N(6)), 6.82 (m, 4 arom. H), 6.95 (m, H–C(9)), 7.00 (d, $J = 7.2$ Hz, H–C(10)), 7.42 (m, 2H–C(2, 8)), 7.52 (d, $J = 8.0$ Hz, H–C(7)), 7.72 (m, H–C(3)), 7.99 (dd, $J = 8.4$, 1.2 Hz, H–C(4)), 8.45 (dd, $J = 8.4$, 1.2 Hz, H–C(1)), 9.06 (br s, NH–C(11)). ^{13}C NMR (100 MHz, DMSO): 27.46 (CH_3–N(6)), 55.13 (OCH_3), 106.06, 108.16, 114.34 (2C), 118.60 (2C), 119.03, 119.13, 119.17, 121.48, 123.42, 124.32, 126.11, 127.32, 128.87, 136.90, 141.04, 141.14, 147.21, 153.50, 153.60. Anal. Calcd for $C_{23}H_{19}N_3O$: C 78.16, H 5.42, N 11.89. Found: C 78.04, H 5.46, N 11.76.

(Table 2, entry 7). The reaction was performed from **13** (204 mg, 0.6 mmol), K_2CO_3 (166 mg, 1.2 mmol), and dimethylsulfate (151 mg, 1.2 mmol) in acetone (10 mL) according to general procedure A described above to give **16a** (96 mg, 45%), the reactant **13** (28 mg, 14% recovered), and **16b** (32 mg, 15%).

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