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One-Pot Access to Indolo[2,3-*b*]quinolines by Electrophile-Triggered Cross-Amination/Friedel−Crafts Alkylation of Indoles with 1-(2-Tosylaminophenyl)ketones

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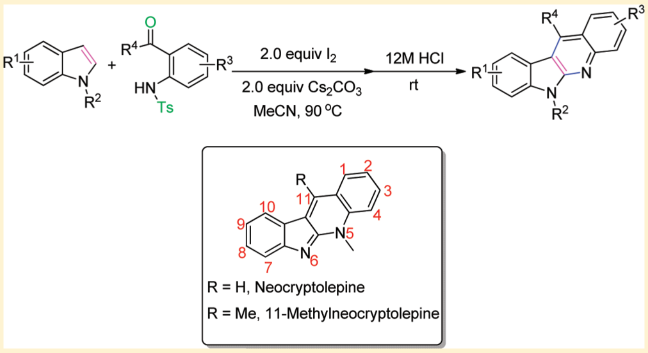
Supporting Information

ABSTRACT: Activation of C2 and C3 of indoles by molecular iodine (I_2) and base followed by in situ reaction with 1-(2-tosylaminophenyl)ketones or 2-tosylaminobenzaldehyde can afford highly substituted indolo(2,3-*b*)quinolines in moderate to excellent yields (up to 99%). The reaction provides a metal-free selective difunctionalization of indoles. The synthetic potential of the protocol has been illustrated by the synthesis of neocryptolepine and its 11-methyl analogue.



INTRODUCTION

Indoloquinolines have been well established to be useful as antibacterial, antifungal, antimalarial, anticancer, antiplatelet, aggregation, analgesic, antihypertensive agents as well as exhibiting several other activities.[1] It is believed that they act as DNA intercalating agents[2] and topoisomerase **II** inhibitors,[3] and thereby one structure can exhibit an array of activities. The interesting biological activities of indoloquinolines (Figure 1) has stimulated the interest of synthetic chemists in developing new synthetic pathways to these polyheteroaromatic ring systems.[4−9] However, most of these syntheses suffer from lack of substrate generality, use of metal catalysts, and/or involve two or more steps with exhaustive isolation/purification efforts resulting in low overall yields and hence of little interest to the pharmaceutical industry. Very recently, Seidel's group reported an excellent methodology for neocryptolepines and analogues.[10,11] This reaction is extremely efficient for preparing a variety of substituted neocryptolepines. It is, however, not possible to synthesize 11-substituted neocryptolepines and 6*H*-indolo(2,3-*b*)quinolines by Seidel's method. In our laboratory, we were interested in exploring a more general method for a one-pot/cascade synthesis of indoloquinolines from readily available substrates. We have previously described a metal-free cascade synthesis of functionalized quinolines.[12] In pursuit of a protocol for preparing functionalized quinolines with diverse pharmacological properties, we envisioned that the readily available indoles can be activated by iodonium to undergo cross-amination with 1-(2-tosylaminophenyl)ketones at position-2. Elimination of HI promoted by a suitable base would then leave position 3 again prone to electrophilic attack by the keto group (see Schemes 1 and 3) . In this way a new sequential reaction could be developed to affect selective difunctionalization of indoles. Herein, we report a metal-free cascade coupling of indoles with 1-(2-tosylaminophenyl)ketones affording indolo[2,3-*b*]quinolines and its application to the synthesis of neocryptolepine and 11-methylneocryptolepine natural products.

RESULTS AND DISCUSSION

Our study began with the coupling reaction of an equal amount of *N*-methylindole **1a** with 2-(tosylamino)benzophenone **2a** in the presence of 2.0 equiv of iodine (I_2) and 2.0 equiv of K_2CO_3 in acetonitrile at room temperature. After 6 h, an examination of the reaction mixture revealed 25% of the expected indolo[2,3-*b*]quinolines **3a**, 60% of the cross-aminated product **4** and 15% recovery of the starting materials. This initial investigation showed that the cross-amination step was going well but the cyclization via Friedel−Crafts alkylation did not occur smoothly. Changing the amount of iodine or base was not successful. When the nature of the base was changed, Cs_2CO_3 was found to be best (Table 1, entry 2), but the cyclization step was only 30% complete along with 62% of the cross-aminated product **4** and 8% starting materials. In order to promote the cyclization step a number of Lewis and Bronsted acids were screened. Of them only $AlCl_3$, HCl and $AlCl_3$/TfOH were found to promote the cyclization step (Table 1 entries 9, 10, and 13). Of course, we were interested to produce a

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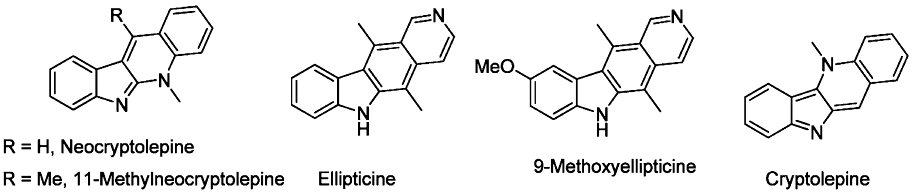
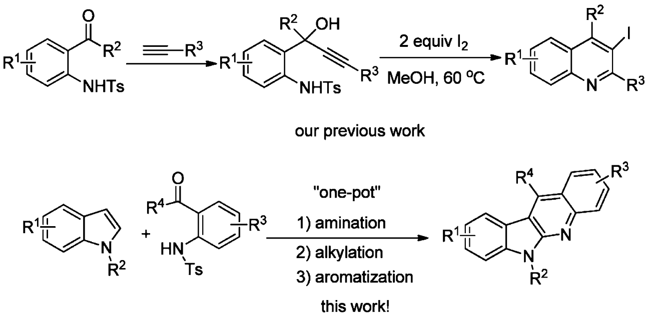


Figure 1. Selected indoloquinoline natural products.

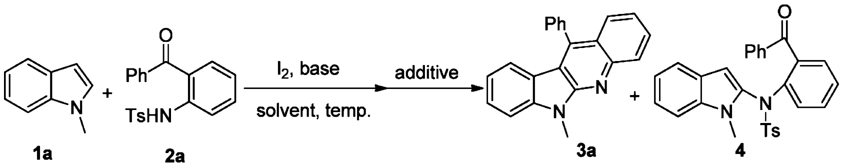
Scheme 1. Design of a One-Pot Access to Indolo(2,3-*b*)quinolines



metal-free protocol, and thus, the use of HCl for further screening was continued. By using excess of HCl as additive, a 70% yield of **3a** was obtained with no cross-aminated product **4** but again conversion was not complete (Table 1 entry 10). Turning to stoichiometry of the reaction revealed that by using 1.5 equiv of indole **1a** with respect to ketone **2a** **3a** was furnished in 83% yield (Table 1 entry 14), but there were still some traces of substrates. When the reaction was carried out at 90 °C, a complete disappearance of starting materials was observed, and the highest yield of **3a** (88%) was obtained (Table 1 entry 15).

With the standard reaction conditions in hand, we then explored the scope and generality of the method. We first examined the use of different protecting groups for the indolic *N*-atom. A variety of protecting groups such as alkyl, benzyl, and allyl groups was well tolerated (Scheme 2, products **3a**–**3c**). However, in the case of a tosyl group and *N*-unsubstituted indoles we observed no reaction. We then examined the effect of substituents in the indole moiety of indolo[2,3-*b*]quinolines (Scheme 2, products **3d**–**3i**). In general, we found that the presence of substituents with different electronic and steric properties in various positions did not have a significant effect on the formation of the indoloquinolines; all provided good to excellent yields. Similarly, the change of substituents in the 2-(tosylamino)phenyl ketones upon the efficiency of indolo[2,3-*b*]quinolines formation (Scheme 2, products **3j and 3k**) revealed no effect on the formation of the indoloquinolines. The structure of product **3j** was also confirmed by single-crystal X-ray crystallography (see the Supporting Information for details). Afterward, we examined the influence of R^4 in the starting ketones **2** on the outcome of the reaction and yields of

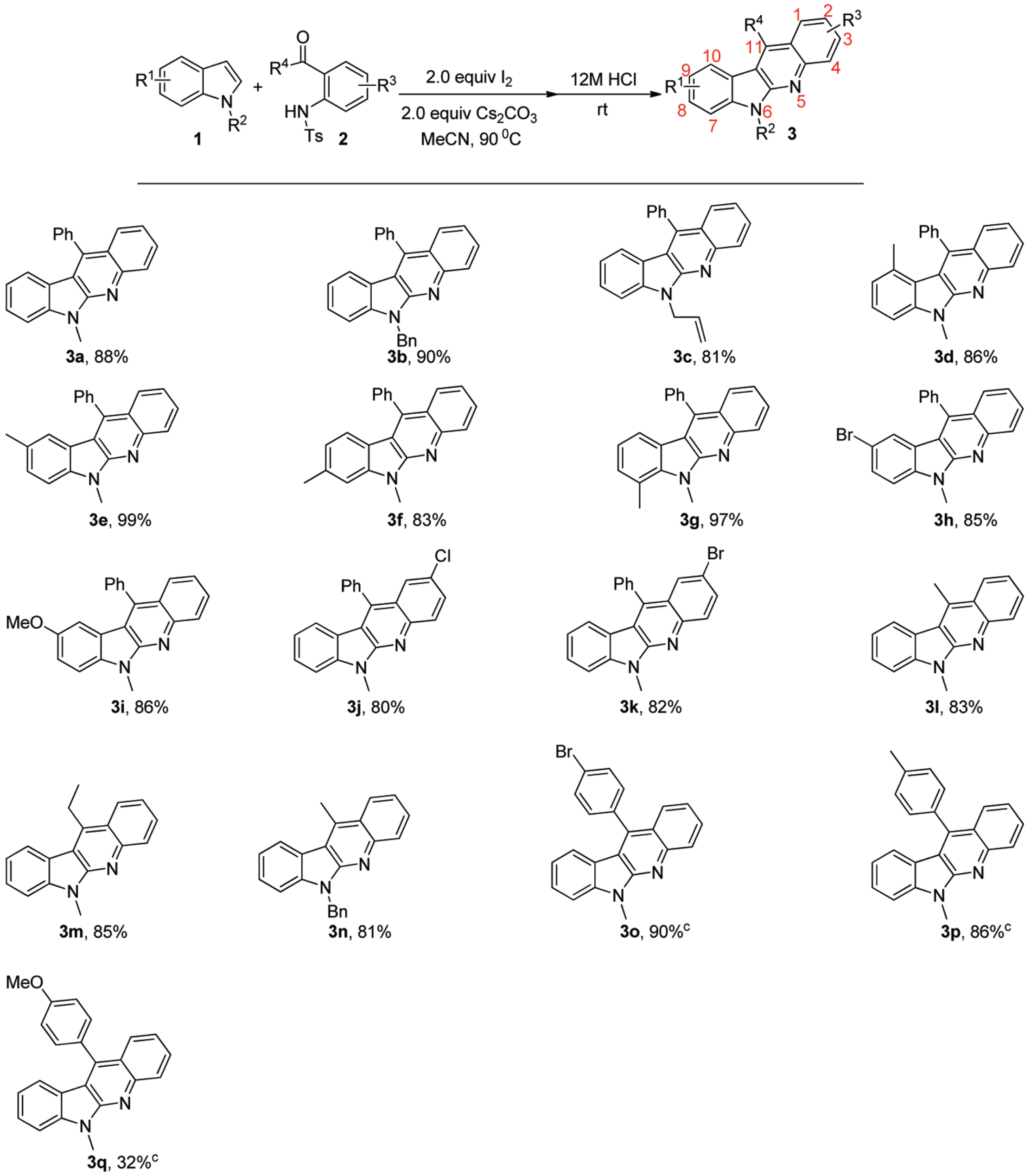
Table 1. Optimization of Reaction Conditions



entry	base	solvent	additive[a] (equiv)	temp (°C)	yield (%)[b] 3a/4
1	K_2CO_3	CH_3CN		rt	25/60
2	Cs_2CO_3	CH_3CN		rt	30/62
3	K_3PO_4	CH_3CN		rt	7/10
4	Cs_2CO_3	CH_3OH		rt	6/40
5	Cs_2CO_3	DMF		rt	traces
6	Cs_2CO_3	DCM		rt	10/30
7	Cs_2CO_3	CH_3CN		90	32/63
8	Cs_2CO_3	CH_3OH		70	6/45
9	Cs_2CO_3	CH_3CN	$AlCl_3$ (2)	rt	65/–
10	Cs_2CO_3	CH_3CN	HCl[c]	rt	70/–
11	Cs_2CO_3	CH_3CN	TfOH (0.1)	rt	33/62
12	Cs_2CO_3	CH_3CN	$HSbF_6$ (0.1)	rt	37/62
13	Cs_2CO_3	CH_3CN	$AlCl_3$ (0.5)/ TfOH (0.1)	rt	60/–
14	Cs_2CO_3	CH_3CN	HCl[c]	rt	83/–[d]
15	**Cs_2CO_3**	**CH_3CN**	**HCl[c]**	**90**	**88/–[d]**
16[e]	Cs_2CO_3	CH_3CN	HCl[c]	90	86/–
17[f]	Cs_2CO_3	CH_3CN	HCl[c]	90	84/–

[a] All reactions were run under the following conditions, unless otherwise indicated: 0.2 M **1a**, 0.2 M **2a**, 0.4 M I_2, and 0.4 M base in wet solvent. Additive was added to the reaction mixture at room temperature after 9 h and further stirred at room temperature for 6 h. [b] Based on isolation of products after column chromatography. [c] 250 μL (25 equiv) of 12 M HCl was used as additive. [d] 0.3 M **1a**, 0.6 M I_2 and 0.6 M base was used. [e] 0.61 M I_2 was used. [f] 0.59 M I_2 was used.

Scheme 2. Scope of Metal-Free Cross-Amination/Alkylation Cascade of Indoles with 1-(2-Tosylaminophenyl)ketones[a,b,c]



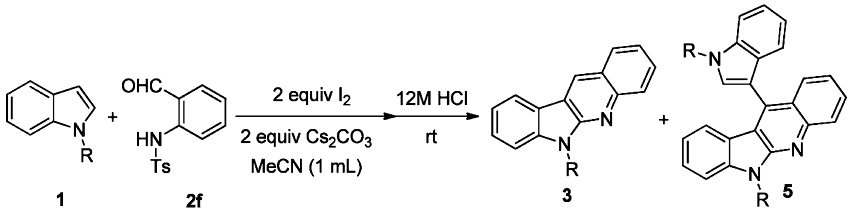
[a] All reactions were run under the following conditions, unless otherwise indicated: 0.3 M **1**, 0.2 M **2**, 0.6 M I_2, and 0.6 M base in wet solvent for 9 h at 90 °C and then 250 μL of 12 M HCl was added at room temperature and further stirred at room temperature for 6 h. The equiv of iodine and Cs_2CO_3 corresponds to 1. [b] The yields are based on isolation of products after column chromatography. [c] After adding HCl the reaction was stirred for 12 h.

the various 11-substituted indolo[2,3-*b*]quinolines (Scheme 2, products **3l**–**3m** and **3o**–**3q**). With an electron-withdrawing group such as 4-ClC_6H_5, we observed only 5% of the corresponding indolo[2,3-*b*]quinoline. However, 4-BrC_6H_5 gave 90% yield of the corresponding indolo[2,3-*b*]quinoline (Scheme 2, product **3q**), although Cl and Br differ only slightly in electronegativity. With a more electron-rich but rather bulky group such as 4-$MeOC_6H_5$, the reaction time was increased to 21 h, and only 32% yield of the product was obtained. Also, when 3,4-$Me_2C_6H_4$ was used, only traces of product was generated. These findings show that the yields of products **3** are evidently susceptible to subtle changes in the nature of the C-11 substituent (or, correctly, R^4 in **2**).

Knowing the importance of neocryptolepines as antimalarial and antitumor agents, we also investigated the reaction of 2-tosylaminobenzaldehyde **2f** with *N*-methyl and *N*-benzyl indoles **1a** and **1b** under initially optimized conditions. The corresponding indolo[2,3-*b*]quinolines **3r** and **3s** were obtained in moderate yields of 32% and 40% along with dialkylated products (or more properly 11-indolylindolo[2,3-*b*]quinolines) **5a** and **5b** in 63% and 52% yields, respectively. The dialkylated products were suppressed, and the yields of the desired products were improved by carrying out the reactions at room temperature with 3 equiv of the indole derivative (see Table 2).

The mechanism of this reaction involves electrophilic addition of iodonium to the 3-position of indole **1** to give

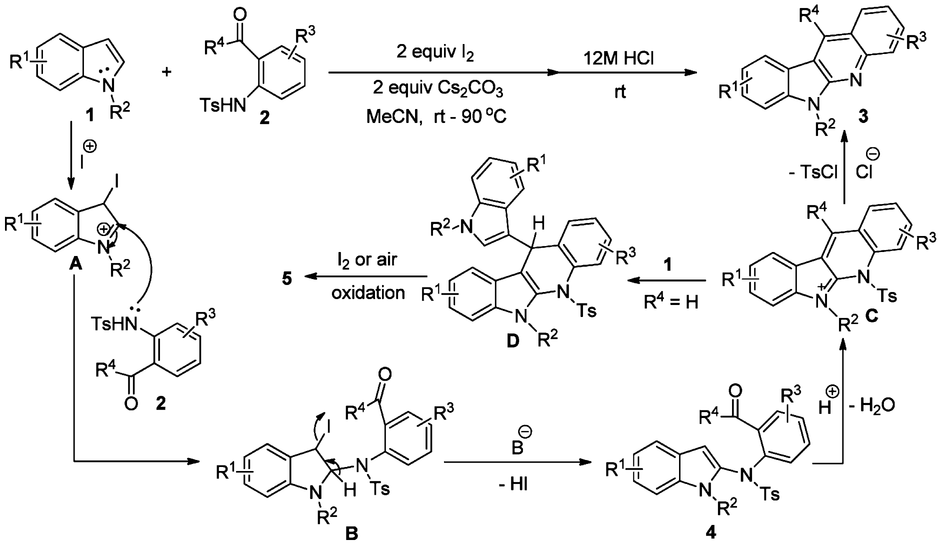
Table 2. Cross-Amination/Alkylation of *N*-Methyl Indole (1a) and *N*-Benzyl Indole (1b) with 2-Tosylaminobenzaldehyde (2f)[a,b]



entry	R	1 (mmol)	2f(mmol)	temp. (°C)	yield (%) 3	yield (%) 5
1	Me	**1a** (0.3)	0.2	90	**3r** (32)	**5a** (63)
2	Bn	**1b** (0.3)	0.2	90	**3s** (40)	**5b** (52)
3	Me	**1a** (0.2)	0.2	90	**3r** (20)	**5a** (73)
4	Me	**1a** (0.4)	0.2	90	**3r** (55)	**5a** (15)
5	Me	**1a** (0.6)	0.2	rt	**3r** (71)	–
6	Bn	**1b** (0.6)	0.2	rt	**3s** (78)	–

[a] All reactions were run for 9 h, and then 250 μL of 12 M HCl was added at room temperature and further stirred at room temperature for 6 h. The equiv of iodine and Cs_2CO_3 corresponds to 1. [b] The yields are based on isolation of products after column chromatography.

Scheme 3. Proposed Mechanism



cation **A**, which undergoes 2-amination with **2** to afford **B**. The intermediate **B** eliminates a molecule of HI in the presence of base to give **4**. Alkylation and subsequent detosylation of **4** in the prescence of HCl gives **3**. The formation of 11-indolylindolo[2,3-*b*]quinolines **5** can be explained as follows. When the intermediate carbocation **C** has a *H*-atom on the 11-position (R^4 = H), due to less steric hindrance and more reactivity it is attacked by a second molecule of **1** to give **D**. Finally, **D** gains full aromaticity via oxidation by molecular iodine (I_2) or air[13,14] to give **5** (see Scheme 3).

The application of the new annulation strategy to the synthesis of the neocryptolepine, a linear 5-*N*-methyl-5*H*-indolo[2,3-*b*]quinoline alkaloid isolated from the West African shrub *Cryptolepis sanguinolenta* which has been reported to exhibit strong antiplasmodial activity,[15] illustrates the utility of this methodology. 11-Methylneocryptolepine which has been found to display strong antimicrobial and cytotoxic activities in vitro and significant antitumor properties in vivo[16] can also be prepared by using our protocol. Products **3s** and **3n** were prepared on 10 mmol scale. To our delight; the reactions proceeded without change in reaction yields. Debenzylation[17] with $AlCl_3$ in refluxing benzene and then regioselective methylation[18] of quinoline *N*-atom with Me_2SO_4 afforded neocryptolepine **7a** and 11-methylneocryptolepine **7b** in overall 68% and 64% yields, respectively (Scheme 4).

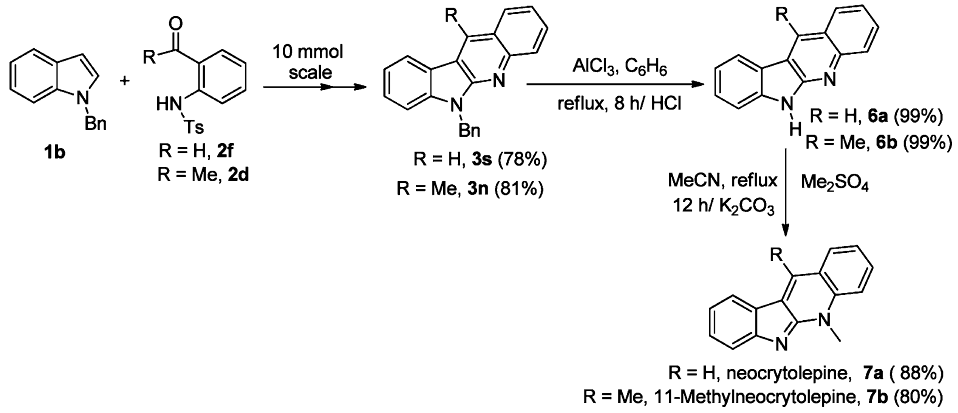
■ CONCLUSION

In short, we have described a useful annulation strategy of readily available indoles to indolo(2,3-b)quinolines. The reaction is metal-free and can produce substituted indolo(2,3-*b*)quinolines in a one-pot manner. Our simple approach to indolo(2,3-*b*)quinolines complements existing routes and allows access to some novel C-11-substituted derivatives. Synthesis of neocryptolepine and its various analogues can be carried out in overall moderate yields.

■ EXPERIMENTAL SECTION

General Methods Used for Preparing Starting Materials 1a–1i and 2a–2i. Starting materials **1a**–**1i** were prepared by methylation, benzylation, or allylation of the corresponding indoles

Scheme 4. Synthesis of Neocryptolepine and 11-Methylneocryptolepine



according to the literature procedure.[19] Starting materials **2a**–**2i** were prepared by tosylation of the corresponding 2-aminobenzoketones or 2-aminobenzaldehyde according to the literature procedure.[20,21] 2-Aminobenzaldehyde was prepared by reduction of 2-nitrobenzaldehyde according to the literature procedure[22] and used immediately. The respective characterization data of all the starting materials match those reported in the literature.

General Procedure A. *Preparation of Indolo(2,3-b)quinolines (3a–3s) and (5a–5b).* Iodine (152.4 mg, 2.0 equiv) was added to a solution of **1a** (0.3 mmol, 39.3 mg), **2a** (0.2 mmol, 70.2 mg) and Cs$_2$CO$_3$ (195.6 mg, 2.0 equiv) in acetonitrile (1.0 mL). The resulting mixture was stirred for 9 h at 90 °C. Then the reaction mixture was cooled to room temperature, and 250 μL (25 equiv) of 12 M HCl was added, and the mixture further stirred at room temperature for 6 h. The reaction was then quenched by adding saturated aq solution of Na$_2$S$_2$O$_3$ and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with aq NaHCO$_3$ and brine, and dried over anhyd. Na$_2$SO$_4$. After removal of solvent the crude product was purified by column chromatography with silica gel using a mixture of petroleum ether (bp 40–80 °C) and ethyl acetate (20: 1) to give 54.5 mg of **3a** (88%).

In case of indolo(2,3-*b*)quinolines **3r** and **3s** the amount of indole **1b** was 0.6 mmol, 124.3 mg, and the reaction was conducted at room temperature. The rest of procedure remains the same.

Characterization Data of Products (3a–3s) and (5a–5b). *6-Methyl-11-phenyl-6H-indolo[2,3-b]quinoline (3a):* yield 88%; light-green solid; mp 152–154 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.17 (1H, d, J = 8.4 Hz), 7.68–7.74 (2H, m), 7.61–7.66 (3H, m), 7.52–7.53 (2H, m), 7.45–7.51 (1H, m), 7.32–7.38 (2H, m), 7.05 (1H, d, J = 7.6 Hz), 6.96–7.00 (1H, m), 4.02 (3H, s) ; ^{13}C NMR (CDCl$_3$, 100 MHz): δ 152.4, 146.8, 142.9, 142.3, 136.6, 129.8, 129.3, 128.9, 128.4, 127.7, 127.2, 126.3, 123.7, 123.0, 122.7, 120.5, 119.6, 115.9, 108.3, 27.7; IR (neat) ν: 3399, 3056, 2925, 2862, 1598, 1480, 1392, 1319, 1252, 1122, 1024, 746, 703 cm^{-1} ; HRMS (ESI) calcd for C$_{22}$H$_{17}$N$_2$ (M$^+$ + H): 309.1386, found: 309.1388.

6-Benzyl-11-phenyl-6H-indolo[2,3-b]quinoline (3b): yield 90%; light-yellow solid; mp 148–150 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.16 (1H, d, J = 8.4 Hz), 7.73 (1H, d, J = 8.0 Hz), 7.67–7.71 (1H, m), 7.61–7.64 (3H, m), 7.53 (2H, dd, J = 2.0, 7.6 Hz), 7.33–7.37 (4H, m), 7.24–7.28 (3H, t, J = 6.4 Hz), 7.21–7.23 (1H, t, J = 4.0 Hz), 7.05 (1H, d, J = 7.6 Hz), 6.93- 6.97 (1H, t, J = 7.6 Hz), 5.79 (2H, s) ; ^{13}C NMR (CDCl$_3$, 100 MHz): δ 152.2, 146.8, 142.3, 142.1, 137.3, 136.6, 129.3, 128.9, 128.6, 128.5, 127.8, 127.6, 127.3, 127.2, 126.4, 126.3, 124.0, 123.0, 122.8, 120.8, 119.8, 115.8, 109.3, 44.9; IR (neat) ν: 3664, 3394, 3070, 2922, 1595, 1464, 1404, 1320, 1120, 1068, 1025, 865, 751, 702, 614 cm^{-1}; HRMS (ESI) calcd for C$_{28}$H$_{21}$N$_2$ (M$^+$ + H): 385.1699, found: 385.1697.

6-Allyl-11-phenyl-6H-indolo[2,3-b]quinoline (3c): yield 81%; light-green solid; mp 100–102 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.15 (1H, d, J = 8.8 Hz), 7.67–7.74 (2H, m), 7.62–7.64 (3H, q, J = 5.2 Hz), 7.51–7.54 (2H, m), 7.41–7.45 (1H, m), 7.32–7.37 (2H, m), 7.05 (1H, d, J = 7.6 Hz), 6.96 (1H, t, J = 7.6 Hz), 6.06–6.15 (1H, m), 5.17 (4H, q, J = 5.2 Hz) ; ^{13}C NMR (CDCl$_3$, 100 MHz): δ 151.8, 146.7, 142.3, 142.2, 136.6, 132.7, 129.3, 128.9, 128.6, 128.4, 127.7, 127.6, 123.0, 122.8, 120.7, 119.7, 116.8, 115.8, 109.2, 43.6, 31.9, 22.6; IR (neat) ν: 3393, 3059, 2923, 1594, 1473, 1403, 1357, 1324, 1259, 1215, 1180, 1154, 1120, 1068, 1027, 765, 742, 701, 663, 613 cm^{-1}; HRMS (ESI) calcd for C$_{24}$H$_{19}$N$_2$ (M$^+$ + H): 335.1543, found: 335.1545.

6,10-Dimethyl-11-phenyl-6H-indolo[2,3-b]quinoline (3d): yield 86%; light green solid; mp 184–186 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.11 (1H, d, J = 8.0 Hz), 7.64–7.68 (1H, m), 7.49–7.55 (6H, m), 7.37 (1H, t, 7.6 Hz), 7.23–7.28 (2H, m), 6.84 (1H, d, J = 7.2 Hz), 4.02 (3H, s), 1.7 (3H, s) ; ^{13}C NMR (CDCl$_3$, 100 MHz): δ 152.2, 145.8, 143.7, 142.5, 139.7, 135.5, 131.2, 128.6, 128.2, 127.8, 127.7, 127.2, 127.1, 124.2, 123.3, 122.4, 119.5, 117.3, 105.9, 27.7, 22.1; IR (neat) ν: 3395, 3053, 2925, 1579, 1464, 1446, 1383, 1307, 1248, 1155, 1108, 1066, 1026, 961, 754, 702 cm^{-1}; HRMS (ESI) calcd for C$_{23}$H$_{19}$N$_2$ (M$^+$ + H): 323.1543, found: 323.1546.

6,9-Dimethyl-11-phenyl-6H-indolo[2,3-b]quinoline (3e): yield 99%; yellow solid; mp 108–110 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.16 (1H, d, J = 8.4 Hz), 7.67–7.73 (2H, m), 7.50–7.52 (2H, m), 7.31–7.35 (1H, m), 7.27 (2H, t, J = 1.2 Hz), 7.24 (1H, d, J = 4.8 Hz), 6.83 (1H, s), 3.99 (3H, s), 2.27 (3H, s) ; ^{13}C NMR (CDCl$_3$, 100 MHz): δ 152.5, 146.6, 142.2, 141.0, 136.6, 130.8, 128.9, 128.6, 128.4, 128.3, 127.4, 126.3, 123.6, 123.2, 123.2, 122.6, 120.6, 115.9, 108.1, 27.7, 21.3; IR (neat) ν: 3398, 3060, 2922, 2851, 1634, 1596, 1567, 1484, 1447, 1385, 1332, 1295, 1252, 1164, 1119, 1068, 1020, 761, 703 cm^{-1}; HRMS (ESI) calcd for C$_{23}$H$_{19}$N$_2$ (M$^+$ + H): 323.1543, found: 323.1550.

6,8-Dimethyl-11-phenyl-6H-indolo[2,3-b]quinoline (3f): yield 83%; light-yellow solid; mp 136–140 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.15 (1H, d, J = 8.4 Hz), 7.69 (2H, q, J = 8.4 Hz), 7.61–7.68 (2H, m), 7.50 (2H, q, J = 2.0 Hz), 7.31–7.40 (2H, m), 6.92(1H, d, J = 8.0 Hz), 6.79 (1H, d, J = 8.0 Hz), 3.98 (3H, s), 2.5 (3H, s) ; ^{13}C NMR (CDCl$_3$, 100 MHz): δ 152.6, 146.5, 143.3, 142.2, 141.4, 140.9, 138.3, 136.7, 129.8, 128.9, 127.2, 126.2, 124.9, 123.7, 122.6, 120.9, 118.1, 116.0, 108.8, 27.6, 22.2; IR (neat) ν: 3399, 3059, 2923, 2854, 1597, 1466, 1423, 1391, 1307, 1251, 1161, 1114, 1067, 1027, 765,703 cm^{-1}; HRMS (ESI) calcd for C$_{23}$H$_{19}$N$_2$ (M$^+$ + H): 323.1543, found: 323.1547

6,7-Dimethyl-11-phenyl-6H-indolo[2,3-b]quinoline (3g): yield 97%; light-green solid; mp 196–200 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.14 (1H, d, J = 8.4 Hz), 7.67 (2H, t, J = 4.0 Hz), 7.60 (3H, d, J = 6.8 Hz), 7.47 (2H, d, J = 8.0 Hz), 7.30 (1H, t, J = 7.2 Hz), 7.15 (1H, d, J = 6.8 Hz), 6.81 (2H, m), 4.32 (3H, s), 2.85 (3H, s); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 152.8, 146.6, 141.9, 136.7, 130.9, 129.3, 128.5, 127.5, 126.3, 124.8, 123.9, 122.6, 121.2, 121.0, 120.4, 119.6, 118.2, 115.7, 102.2, 29.3, 22.6; IR (neat) ν: 3400, 3046, 2923, 2854, 1607, 1580, 1492, 1459, 1389, 1297, 1222, 1163, 1131, 1080, 1025, 771, 745, 704, 403 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}N_2$ (M^+ + H): 323.1543, found: 323.1548

9-Bromo-6-methyl-11-phenyl-6H-indolo[2,3-b]quinoline (***3h***): yield 85%; light-green solid; mp 180−184 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (1H, d, J = 8.4 Hz), 7.67−7.72 (2H, m), 7.62−7.65 (3H, m), 7.50 (1H, dd, J = 2.0, 8.8 Hz), 7.45−7.47(2H, m), 7.31−7.35 (1H, m), 7.16 (1H, d, J = 8.4 Hz), 7.09 (1H, s), 3.94 (3H, s) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.1, 147.0, 142.9, 141.4, 135.8, 130.2, 129.2, 129.1, 129.0, 128.8, 127.6, 126.4, 125.5, 123.6, 123.0, 122.1, 114.8, 112.2, 109.7, 27.7; IR (neat) ν: 3397, 3062, 2922, 2840, 1626, 1585, 1477, 1442, 1383, 1330, 1278, 1122, 1069, 1027, 765, 767, 711, 613, 402 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{16}N_2Br$ (M^+ + H): 387.0491, found: 387.0497.

9-Methoxy-6-methyl-11-phenyl-6H-indolo[2,3-b]quinoline (***3i***): yield 86%; yellow solid; mp 152−154 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (1H, d, J = 8.4 Hz), 7.66−7.74 (2H, m), 7.59−7.64 (3H, m), 7.50−7.52 (2H, m), 7.30−7.34 (1H, m), 7.22 (1H, d, J = 8.4 Hz), 7.05 (1H, dd, J = 2.4, 8.8 Hz), 6.54 (1H, s), 3.96 (3H, s), 3.57 (3H, s) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.6, 152.6, 146.8, 142.2, 137.5, 136.4, 130.8, 129.4, 128.6, 128.4, 128.2, 127.5, 126.3, 123.3, 122.5, 120.8, 115.9, 108.8, 107.0, 55.5, 27.7; IR (neat) ν: 3393, 3058, 2923, 2854, 1594, 1483, 1386, 1331, 1289, 1263, 1223, 1118, 1067, 1029, 801, 769, 703, 653, 614, 402 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}ON_2$ (M^+ + H): 339.1492, found: 339.1498.

2-Chloro-6-methyl-11-phenyl-6H-indolo[2,3-b]quinoline (***3j***): yield 80%; light-green solid; mp 260−263 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (1H, d, J = 9.2 Hz), 7.59−7.67 (5H, m), 7.36 (1H, d, J = 8.4 Hz), 6.98−7.05 (2H, m) 3.99 (3H, s) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.4, 145.1, 143.0, 141.3, 135.9, 129.4, 129.3, 129.2, 129.1, 128.7, 128.2, 128.1, 124.9, 124.3, 123.2, 120.2, 119.9, 116.5, 108.5, 27.6; IR (neat) ν: 3400, 3047, 2918, 2849, 2279, 1595, 1466, 1443, 1387, 1340, 1308, 1118, 1070, 1025, 812, 772, 735, 708, 403 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{16}N_2Cl$ (M^+ + H): 343.0997, found: 343.1003.

2-Bromo-6-methyl-11-phenyl-6H-indolo[2,3-b]quinoline (***3k***): yield 82%; yellow solid; mp 248−251 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (1H, d, J = 9.2 Hz), 7.83 (1H, s), 7.72 (1H, dd, 2, 8.8 Hz), 7.64 (3H, t, J = 5.6 Hz), 7.37 (1H, d, J = 8 Hz) 6.98−7.04 (2H, m), 3.99 (3H, s) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.4, 145.3, 143.0, 141.3, 135.8, 131.8, 129.3, 129.1, 128.8, 128.5, 128.3, 128.2, 128.1, 127.2, 120.2, 119.9, 116.5, 116.1, 108.5, 27.7; IR (neat) ν: 3794, 3664, 3407, 3053, 2921, 2851, 1060, 1463, 1443, 1385, 1309, 1220, 1158, 1110, 1066, 1023, 771, 738, 705 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{16}N_2Br$ (M^+ + H): 387.0491, found: 387.0497.

6,11-Dimethyl-6H-indolo[2,3-b]quinoline (***3l***): yield 83%; yellow solid; mp 96−98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (1H, d, J = 8 Hz), 8.23 (1H, dd, J = 0.8, 8.4 Hz)), 8.12 (1H, d, J = 8.8 Hz), 7.69−7.73 (1H, m), 7.55−7.60 (1H, m), 7.46−7.50 (1H, m) 7.41 (1H, d, J = 8 Hz), 7.30−7.34 (1H, m), 3.98 (3H, s), 3.19 (3H, s) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.4, 146.7, 145.0, 142.7, 128.5, 128.1, 127.3, 123.6, 123.3, 122.9, 122.6, 120.7, 119.9, 115.3, 108.5, 27.6, 15.1; IR (neat) ν: 3399, 3060, 2852, 2245, 1685, 1626, 1602, 1578, 1472, 1430, 1390, 1319, 1285, 1245, 1120, 1089, 1065, 1025, 747, 403 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}N_2$ (M^+ + H): 247.1230, found: 247.1236.

11-Ethyl-6-methyl-6H-indolo[2,3-b]quinoline (***3m***): yield 85%; yellow solid; mp 126−130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19−8.25 (2H, m), 8.13 (1H, d, J = 8.4 Hz), 7.68−7.73 (1H, m), 7.54−7.59 (1H, m), 7.45−7.49 (1H, m), 7.40 (1H, d, J = 8 Hz), 7.29−7.33 (1H, m), 3.97 (3H, s), 3.63 (2H, q, J = 7.6 Hz), 1.51 (3H, t, J = 7.6 Hz) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.4, 146.7, 145.0, 142.7, 128.5, 128.1, 127.3, 123.6, 123.3, 122.9, 122.6, 120.7, 119.9, 115.3, 108.5, 27.6, 22.1, 13.6; IR (neat) ν: 3664, 3398, 3060, 2963, 2923, 2851, 1626, 1601, 1567, 1473, 1428, 1393, 1319, 1275, 1245, 1121, 1057, 1024, 748, 402 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}N_2$ (M^+ + H): 261.1386, found: 261.1380.

6-Benzyl-11-methyl-6H-indolo[2,3-b]quinoline (***3n***): yield 81%; light-green solid; mp 144−147 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (1H, dd, J = 0.8, 8.4 Hz), 7.67−7.71 (1H, m), 7.41−7.49 (2H, m), 7.20−7.30 (3H, m), 5.71 (2H, s), 3.18 (3H, s) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.1, 146.6, 144.1, 141.9, 138.9, 137.0, 128.2, 127.1, 126.4, 124.3, 123.5, 122.6, 121.6, 120.1, 119.9, 118.9, 116.2, 109.6, 109.4, 44.7, 15.1; IR (neat) ν: 3395, 3060, 2923, 2854, 1722, 1621, 1602, 1577, 1471, 1404, 1379, 1321, 1286, 1263, 1213, 1153, 1122, 1072, 745, 702, 462 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}N_2$ (M^+ + H): 323.1543, found: 323.1539.

11-(4-Bromophenyl)-6-methyl-6H-indolo[2,3-b]quinoline (***3o***): yield 90%; light-green solid; mp 156−160 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (1H, d, J = 8.4 Hz), 7.77 (2H, d, J = 8.4 Hz), 7.66−7.70 (2H, m), 7.47−7.52 (1H, m), 7.37 (4H, q, J = 8.4 Hz), 7.10 (1H, d, J = 7.6 Hz), 7.01−7.05 (1H, m), 4.00 (3H, s) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.2, 146.7, 142.9, 140.7, 135.5, 132.2, 132.5, 131.1, 129.6, 128.7, 127.7, 127.2, 125.9, 123.3, 122.8, 120.2, 119.8, 115.8, 108.5, 27.6; IR (neat) ν: 3732, 3393, 2922, 2857, 1591, 1455, 1429, 1387, 1156, 1107, 1065, 1025, 826, 767, 717, 582 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{16}N_2Br$ (M^+ + H): 387.0491, found: 387.0486.

6-Methyl-11-(p-tolyl)-6H-indolo[2,3-b]quinoline (***3p***): yield 86%; light-green solid; mp 119−121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16−8.18 (1H, m), 7.75 (1H, dd, J = 0.8, 8.4 Hz), 7.67−7.71 (1H, m), 7.32−7.50 (7H, m), 7.13 (1H, d, J = 8.0 Hz), 6.98−7.02 (1H, m), 4.01 (3H, s), 2.56 (3H, s) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.4, 146.8, 142.9, 142.5, 138.2, 133.4, 129.6, 129.2, 128.6, 127.6, 127.5, 126.4, 123.9, 123.0, 122.6, 120.7, 119.6, 116.0, 108.3, 27.6, 21.5; IR (neat) ν: 3403, 3057, 2923, 2862, 1592, 1479, 1429, 1392, 1322, 1251, 1160, 1119, 1068, 1027, 818, 755, 634 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}N_2$ (M^+ + H): 323.1543, found: 323.1547.

11-(4-Methoxyphenyl)-6-methyl-6H-indolo[2,3-b]quinoline (***3q***): yield 32%; yellow solid; mp 90−92 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (1H, d, J = 8.0 Hz), 7.64 (1H, d, J = 7.6 Hz), 7.35 (2H, t, J = 8.4 Hz), 7.28−7.32 (3H, m), 7.20−7.24 (2H, m), 7.17−7.19 (2H, m), 7.11−7.15 (1H, m), 6.61 (1H, brs), 3.86 (3H, s), 3.74 (3H, s) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.0, 137.9, 136.9, 135.0, 130.1, 128.3, 127.6, 122.3, 120.9, 120.3, 120.1, 119.9, 119.5, 116.1, 115.9, 109.4, 109.3, 107.3, 101.3, 22.6, 14.1; IR (neat) ν: 3733, 3402, 3049, 2923, 2855, 1583, 1461, 1382, 1320, 1243, 1071, 1023, 743, 667, 571 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}ON_2$ (M^+ + H): 339.1492, found: 339.1497.

6-Methyl-6H-indolo[2,3-b]quinoline (***3r***): yield 71%; light-green solid; mp 42−45 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (1H, s), 8.11 (2H, q, J = 4.4 Hz), 7.9 (1H, d, J = 8 Hz), 7.69 (1H, t, J = 7.6 Hz), 7.55 (1H, t, J = 7.6 Hz), 7.42 (1H, t, J = 7.6 Hz), 7.38 (1H, d, J = 8.0 Hz), 7.27 (1H, t, J = 7.2 Hz), 3.97 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.7, 146.7, 142.8, 128.8, 128.5, 128.0, 127.4, 127.3, 124.1, 122.8, 121.4, 120.4, 119.9, 118.2, 108.7, 27.7; IR (neat) ν: 3401, 3054, 2924, 2856, 1606, 1573, 1481, 1431, 1395, 1362, 1321, 1254, 1148, 1118, 779, 743 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{13}N_2$ (M^+ + H): 233.1073, found: 233.1075.

6-Benzyl-6H-indolo[2,3-b]quinoline (***3s***): yield 78%; white solid; mp 160−163 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.74 (1H, s), 8.12 (2H, t, J = 8.4 Hz), 8.00 (1H, d, J = 7.2 Hz), 7.68−7.73 (1H, m), 7.44−7.48 (2H, m), 7.22−7.36 (H, m), 5.76 (2H, s) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.06, 137.3, 136.7, 128.6, 128.0, 127.7, 127.0, 126.9, 125.1, 123.3, 122.6, 122.5, 121.1, 120.8, 120.3, 119.6, 117.1, 110.1, 109.1, 50.4; IR (neat) ν: 3390, 2918, 1604, 1570, 1470, 1408, 1382, 1262, 1205, 1146, 1066, 1024, 737, 702 cm^{-1} ; HRMS (ESI) calcd for $C_{22}H_{17}N_2$ (M^+ + H): 309.1386, found: 309.1388.

6-Methyl-11-(1-methyl-1H-indol-3-yl)-6H-indolo[2,3-b]quinoline (***5a***): yield 73%; yellow solid; mp 230−233 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (1H, d, J = 8.4 Hz), 7.99 (1H, dd, J = 1.2, 8.4 Hz), 7.67−7.71 (1H, m), 7.52 (1H, d, J = 8.4 Hz), 7.42−7.46 (1H, m), 7.29−7.38 (5H, m), 7.16 (2H, t, J = 8.8 Hz), 7.03 (1H, t, J = 7.2 Hz), 6.88−6.92 (1H, m), 4.04 (3H, s), 4.01 (3H, s) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.7, 146.8, 142.8, 137.1, 135.9, 128.6, 127.6, 127.5, 127.4, 126.9, 124.9, 123.4, 122.4, 122.3, 120.9, 120.7, 120.0, 119.4, 117.1, 110.1, 109.9, 109.6, 108.1, 33.2, 27.7; IR (neat) ν: 3413, 3058, 2923, 2856, 1586, 1556, 1468, 1430, 1390, 1321, 1246, 1214, 1157, 1118, 1073, 1023, 752, 666 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{20}N_3$ (M^+ + H): 362.1652, found: 362.1658.

6-Benzyl-11-(1-benzyl-1H-indol-3-yl)-6H-indolo[2,3-b]quinoline (***5b***): yield 52%; light-green solid; mp 110−112 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (1H, d, J = 8.4 Hz), 7.99 (1H, d, J = 8.4 Hz), 7.67 (1H, t, J = 7.2 Hz), 7.51 (1H, d, J = 8.4 Hz), 7.43 (1H, s), 7.20−7.37 (16H, m), 7.04 (1H, t, J = 7.6 Hz), 6.81 (1H, t, J = 7.6 Hz), 5.74 (2H, q, J = 16 Hz), 5.43 (2H, q, J = 16 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.4, 146.9, 142.0, 137.4, 137.4, 137.3, 136.7, 128.9, 128.6, 128.0, 127.9, 127.8, 127.7, 127.4, 127.2, 127.0, 126.9, 125.1, 123.3, 122.6, 122.5, 121.1, 120.8, 120.3, 119.6, 117.1, 110.7, 110.1, 109.1, 50.4, 44.9; IR (neat) ν: 3394, 3058, 2922, 2857, 1598, 1542, 1461, 1393, 1320, 1254, 1158, 1067, 1023, 916, 752, 663, 602 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{28}N_3$ (M$^+$ + H): 514.2278, found: 514.2280.

General Procedure for Preparing 6*H*-Indolo[2,3-*b*]quinolines, 6a and 6b. Anhydrous $AlCl_3$ (754.3 mg, 5.65 equiv) was added to a solution of **3s** (1 mmol, 308 mg) in dry benzene (10.0 mL) and then refluxed for 9 h. On completion, 30 mL of 0.15 M HCl was added and extracted with ethyl acetate. The combined organic phases were washed with aq $NaHCO_3$ and brine and were dried over anhyd. Na_2SO_4. After removal of solvent the crude product was purified by column chromatography with silica gel using a mixture of petroleum ether (bp 40−80 °C) and ethyl acetate (4:1) to give 217 mg of **6a** (99%).

Characterization Data of Products (6a−6b). *6H-Indolo[2,3-b]quinoline (**6a**):* yield 99%; light-yellow solid; mp 276−280 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.68 (1H, s), 9.04 (1H, s), 8.25 (1H, d, J = 7.6 Hz), 8.09 (1H, dd, J = 0.8, 8.0 Hz), 7.96 (1H, d, J = 8.4 Hz), 7.69−7.73 (1H, m), 7.45−7.55 (3H, m), 7.24−7.28 (1H, m) ; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 152.8, 146.3, 141.4, 128.6, 128.1, 127.4, 126.9, 123.6, 122.6, 121.7, 120.2, 119.6, 117.8, 111.5, 110.8; IR (neat) ν: 3400, 3131, 2922, 2852, 1609, 1457, 1379, 1261, 1230, 1157, 1071, 1014, 947, 781, 731, 692, 472 cm^{-1} ; HRMS (ESI) calcd for $C_{15}H_{11}N_2$ (M$^+$ + H): 219.0917, found: 219.0913.

*11-Methyl-6H-indolo[2,3-b]quinoline (**6b**):* yield 99%; light-yellow solid; mp 260−262 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.67 (1H, s), 8.31−8.34 (2H, m), 7.94 (1H, dd, J = 0.8, 8.4 Hz), 7.69−7.73 (1H, m), 7.47−7.54 (3H, m), 7.25−7.29 (1H, m) ; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 152.2, 146.0, 141.3, 138.7, 128.4, 127.4, 127.3, 124.3, 123.6, 123.4, 122.4, 121.0, 119.6, 115.9, 110.7, 14.8; IR (neat) ν: 3781, 3691, 3401, 3159, 3086, 2922, 2856, 1668, 1602, 1453, 1385, 1240, 1062, 1025, 738, 594, 403 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{13}N_2$ (M$^+$ + H): 233.1073, found: 233.1078.

General Procedure for Preparing Neocryptolepine (7a) and 11-Methylneocryptolepine (7b). Dimethyl sulfate (150.7 mg, 1.2 equiv) was added to a solution of **6a** (0.9954 mmol, 217 mg) in dry acetonitrile (5 mL) under argon and then refluxed for 12 h. On completion, the reaction was quenched with aq solution of K_2CO_3 and extracted with ethyl acetate. The combined organic phases were washed with aq K_2CO_3 and brine and dried over anhyd. Na_2SO_4. After removal of solvent the crude product was purified by column chromatography with silica gel using mixture of petroleum ether (bp 40−80 °C) and ethyl acetate (20: 1) to give 204 mg of **7a** (88%).

Characterization Data of Products (7a and 7b). *5-Methyl-5H-indolo[2,3-b]quinoline (**7a**):* yield 88%; red solid; mp 101−103 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.71 (1H, s), 8.12 (2H, t, J = 6.8 Hz), 7.99 (1H, d, J = 8.0 Hz), 7.69 (1H, m), 7.56−7.60 (1H, m), 7.41−7.47 (2H, m), 7.29 (1H, t, J = 7.6 Hz), 3.99 (3H, s) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.8, 142.8, 128.8, 128.5, 128.0, 127.5, 127.3, 124.1, 122.8, 121.4, 120.4, 119.9, 118.2, 118.0, 108.7, 27.7; IR (neat) ν: 3396, 3054, 2924, 2853, 1724, 1637, 1606, 1574, 1491, 1474, 1430, 1396, 1360, 1321, 1255, 1118, 1019, 787, 744, 600, 476 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{13}N_2$ (M$^+$ + H): 233.1073, found: 233.1066.

*5,11-Dimethyl-5H-indolo[2,3-b]quinoline (**7b**):* yield 81%; pale-yellow solid; mp 222−224 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (1H, d, J = 8.0 Hz), 8.23 (1H, d, J = 8.4 Hz), 7.69 (1H, t, J = 7.2 Hz), 7.56 (1H, t, J = 7.6 Hz), 7.46 (1H, t, J = 8.0 Hz), 7.42 (1H, d, J = 8.0 Hz), 7.30 (1H, t, J = 7.6 Hz), 3.08 (3H, s), 3.20 (3H, s) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.7, 130.2, 130.0, 128.5, 128.0, 127.9, 127.3, 124.1, 124.0, 123.5, 122.5, 121.4, 119.8, 108.5, 62.1, 31.9, 14.1; IR (neat) ν: 3407, 2922, 2852, 1742, 1632, 1603, 1460, 1383, 1215, 1155, 1090, 1067, 1025, 758, 667 cm^{-1} ; HRMS (ESI) calcd for $C_{17}H_{15}N_2$ (M$^+$ + H): 247.1230, found: 247.1234.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, analytical data for all new compounds, and X-ray crystallography data of **3j** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org

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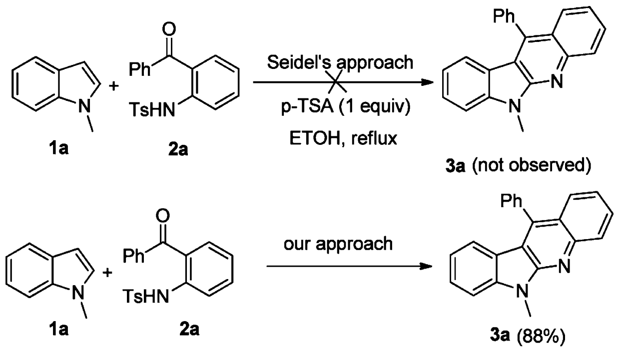
(11) During our study of this annulation approach of indoles to indolo(2,3-*b*)quinolines, a similar approach[10] to neocryptolepine and analogues has been developed by Seidel's group using free indoles and secondary aminobenzaldehydes as coupling partners. However, Siedel's approach is limited to the use of secondary aminobenzaldehydes and the inertness of aminobenzophenones indicates the lack of substrate generality. Moreover, when Siedel's approach was applied to our model substrates, we did not obtain the expected product (see scheme below for inertness of aminobenzophenones to Seidel's approach).



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