Improved Synthesis and Reaction of 11-Chloroneocryptolepines, Strategic Scaffold for Antimalaria Agent, and Their 6-Methyl Congener from Indole-3-carboxylate

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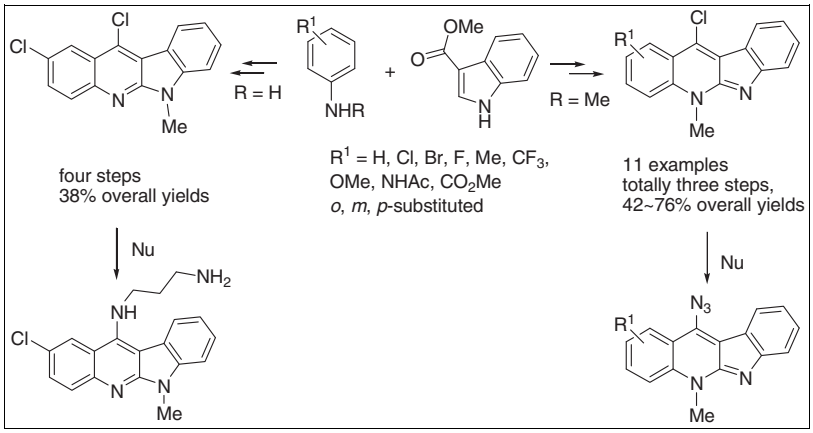

Various 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinolines (neocryptolepines) with different substituents on the quinoline ring, key intermediates for antimalaria agents, are prepared from the substituted *N*-methylanilines, easily accessible by the *N*-methylation of anilines, and indole-3-carboxylate as a counterpart. This protocol is benign in terms of the reduced number of steps to reach the target, compared with the known method using anilines, and easy product purification. Alternatively, their 6-methyl congener is prepared by *N*-methylation of the indole moiety of 2-arylaminoindole-3-carboxylate followed by successive cyclization and chlorination. 11-Chloroneocryptolepines are found more reactive than their 6-methyl congener in the nucleophilic substitution at the C11 position.

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INTRODUCTION

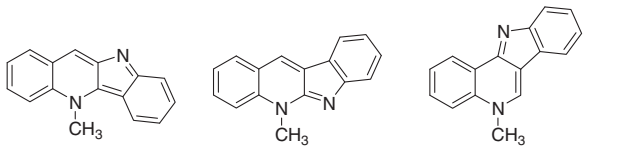
Extracts from the root bark of the African medicinal plant *Cryptolepis sanguinolenta* (Lindl.) Schlechter (Periplocaeae) have traditionally been used for endemic diseases such as malaria fever in west and central Africa [1]. This plant contains several alkaloids with isomeric indoloquinoline skeletons, representative examples of which are cryptolepine (**I**), neocryptolepine (cryptoteckieine) (**II**), and cryptosanguinolentine (**III**) [2,3].

These indoloquinolines **I**–**III** show, in spite of their relatively simple chemical structures, interesting biological activities, namely antiplasmodial [3a], antibacterial [3b], antifungal [3b], and antimalarial [3c,d]. Accordingly, these structural motifs have been used as several drug leads to find more active compounds for human diseases such as cancer and bacteria or protozoal infections [4]. Unfortunately, cryptolepine **I** is a DNA intercalating agent and an inhibitor of topoisomerase II, resulting in a high level of cytotoxicity [5]. On the other hand, neocryptolepine **II**, a minor alkaloid of *C. sanguinolenta*, showed an antiplasmodial activity against chloroquine-resistant *Plasmodium falciparum* and has a lower affinity for DNA and topoisomerase II compared with cryptolepine **I** [5c] (Scheme 1).

Many synthetic approaches to construct the neocryptolepine structure have been developed, which involve the thermal decomposition of enyne–carbodiimides [6], decomposition of 2-(1-benzotriazoyl)quinoline (Graebe–Ullmann reaction) in polyphosphoric acid [7], intramolecular *N*-arylation of chloro-3-(2-aminophenyl)quinolone [8], a Staudinger–aza-Wittig reaction followed by an electrocyclic ring-closure process [9], condensation of isatin and oxindole [10], bromination of 1,3-bis(2-nitrophenyl)propan-2-one followed by Favorskii rearrangement and reductive cyclization [11], intramolecular acylation of 2-(*N*-arylamino)-3-indolecarboxylate [12], and others [13].

In spite of these previous developments in synthetic routes to the indole[2,3-*b*]quinolines, versatile access to this class of compounds deserves to be investigated to find more active ones and gain further insight into the mechanistic rationale of their biological action. Among these reported approaches, the method involving the co-amination of indole-3-carboxylate with anilines and the subsequent intramolecular aromatic

Scheme 1



I, Cryptolepine **II**, Neocryptolepine **III**, Cryptosanguinolentine

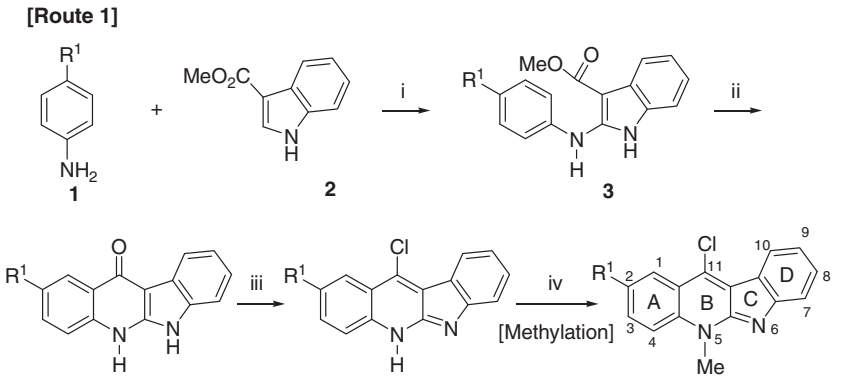
acylation sequence, first reported by Bergman *et al*. [12c], is of value in terms of the availability of various anilines **1** (Scheme 2, Route 1). Thus, the method allows for the formation of the neocryptolepine core with a substitution in position 2 from the 4-substituted anilines **1**.

During our attempts to execute this sequence to prepare various neocryptolepine analogues, however, we have encountered difficulties such as an incompleteness and long reaction time associated with the methylation step due to the low solubility of the intermediate, for example, **5g** (R^1 = OMe) (Route 1, Scheme 2). Therefore, we turned our attention to achieving the methylation at the initial stage or use of the *N*-methylanilines as the starting point [14]. In this paper, we report an improved and versatile protocol for the synthesis of the 2-substituted, 3-substituted, or 4-substituted 11-chloroneocypotolepines **6**, **14**, and **18** starting from indole-3-carboxylate **2** and substituted *N*-methylanilines **7**, **10**, and **15**, respectively. Alternatively, we developed new access to their 6-methyl congener **22** by *N*-methylation at the stage of the intermediate **3**, available from anilines **1** and **2**, followed by the reaction sequence involving cyclization and dehydrative chlorination.

RESULTS AND DISCUSSION

As shown in Route 3 of Scheme 2, we first examined the methylation of the intermediate **4**, obtained by the co-amination of the indole **2** with 4-chloroaniline (**1b**, R^1 = Cl) by the action of *N*-chlorosuccinimide followed by cyclization upon heating at 250°C in diphenyl ether. Thus, the

Scheme 2. Planned routes to 11-chloroneocryptolepines **6**.



a, R^1 = H; **b**, R^1 = Cl; **c**, R^1 = Br; **d**, R^1 = F; **e**, R^1 = Me; **f**, R^1 = CF_3; **g**, R^1 = OMe; **h**, R^1 = NHAc; **i**, R^1 = CO_2Me; **j**, R^1 = NO_2

Reagents and Conditions: (i) a, N-chlorosuccinimide, 1,4-dimethylpiperazine; b, trichloroacetic acid; (ii) diphenyl ether, reflux; (iii) POCl3, toluene, reflux; (iv) a, MeI, THF, reflux; b, NH4OH. Applied equally to Schemes 3 and 4 and Table 1.

treatment of **4b** (R^1 = Cl) with MeI–NaH led exclusively to methylation on the quinolone ring, giving **9b** (R^1 = Cl) in 95% yield. However, this route 3 is still problematic, because the yield of the cyclization of **3b** to **4b** is not very good, only 50%, and the handling of compound **4** is cumbersome because of low solubility.

Accordingly, we examined the synthesis of the neocryptolepine structure **6** using *N*-methylanilines **7** as the source of the structural counterpart [Route 2 in Scheme 2] [15]. Thus, **7b** (R^1 = Cl) was treated with NCS followed by the addition of indole-3-carboxylate **2**, giving the 2-*N*-(*N*-methylanilino) indole-3-carboxylate **8b** (R^1 = Cl) in 75% yield. Upon heating at 250°C in diphenyl ether, **8b** (R^1 = Cl) underwent cyclization, forming the tetracyclic ketone **9b** (R^1 = Cl) in 90% yield, which was much convenient in the implementation and led to higher overall yield compared with Route 1. The chlorination of **9b** (R^1 = Cl) with $POCl_3$ smoothly proceeded to afford the 11-chloroneocrypotolepine **6b** (R^1 = Cl) with high purity.

Subsequently, the procedure for the synthesis of a series of **6** based on Route 2 was applied to various *N*-methylanilines **7** to ensure its utility. Thus, as shown in Table 1, the *N*-methylanilines **7** bearing the substituent R^1, such as halogens, that is, **7c** (R^1 = Br), **7d** (R^1 = F), methyl **7e**, trifluoromethyl **7f**, methoxy **7g**, *N*-acetamido **7h**, and methoxycarbonyl **7i** were successfully converted to the corresponding **6** through the respective intermediates **8** and **9** (entries 1–9). This protocol is versatile in terms of the reduced number of overall steps along with improved overall yields and high purity of the desired 11-chloroneocryptolepines **6**, compared with the ones that were sequentially prepared from **2** through **3**, **4**, and **5** (Scheme 2, Route 1). Conversely, our attempts to combine the *N*-methylaniline **7j** bearing NO_2 with the indole-3-carboxylate **2** were unsuccessful, presumably because of low reactivity of amino group of **7j** (entry 10).

Furthermore, we examined the effect of the substituents of aniline core on the regioselectivity of the cyclization. Thus, 3-chloro-*N*-methylaniline **10** was combined with the indole-3-carboxylate **2** to give 2-anilinoindole **11**. Thermal cyclization of **11** in the same manner as above produced the tetracyclic **12** and **13** as a mixture of 4.3:1 regioisomers. The major isomer **12**, formed by acylation at the 4-position to the Cl substituent, was separated by recrystallization from pyridine and converted to the corresponding 3,11-dichloroneocypotolepine **14** by treatment with $POCl_3$. On the other hand, the cyclization of **16**, derived from 3-chloroaniline **15**, smoothly proceeded to give the desired indoloquinolone **17** by heating at 250°C in diphenyl ether. The chlorination of **17** with $POCl_3$ afforded the 4,11-dichloroneocryptolepine **18** in good yield, as described in Scheme 3.

We then paid our attention to the synthesis of the 6-methyl-6*H*-indole[2,3-*b*]quinoline **22**, a congener of neocryptolepines, from the intermediate **3b** (R^1 = Cl), because their C2-aminoalkylamino or C9-aminoalkylamino derivatives were shown to possess potent cytotoxic DNA topoisomerase II inhibitions by Wietrzyk *et al*.. [15]. As shown in Scheme 4, the successive treatment of **3b** with NaH and MeI produced the *N*-methylated indoles **19** as a major product (61%) along

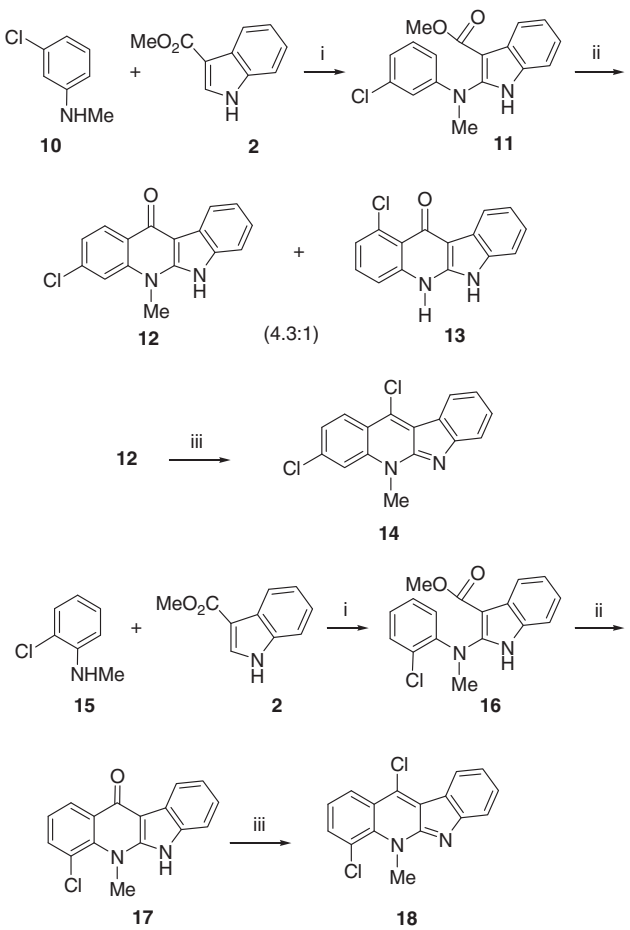
Table 1

Substrate scope for the synthesis of 11-chloroneocryptolepines **6** through **8** and **9** (Route 2 in Scheme 2).

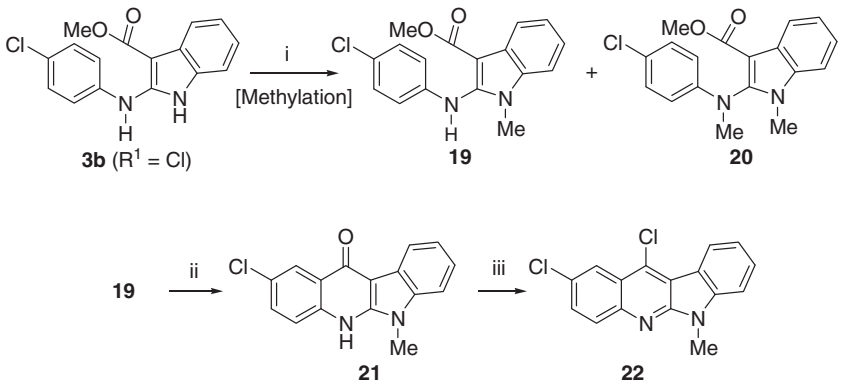
7 + **2** $\xrightarrow{i}$ **8** $\xrightarrow{ii}$ **9** $\xrightarrow{iii}$ **6**

Entry	R^1		Products, yields (%)		
			8	**9**	**6**
1	H	**a**	83	98	94
2	CI	**b**	75	90	94
3	Br	**c**	82	84	90
4	F	**d**	82	75	85
5	Me	**e**	77	72	83
6	CF_3	**f**	80	85	84
7	OMe	**g**	89	87	86
8	NHAc	**h**	88	82	67
9	CO_2Me	**i**	66	68	94
10	NO_2	**j**	nd	nd	nd

Scheme 3. Syntheses of 3,11-dichloroneocryptolepines and 4,11-dichloroneocryptolepines.



Scheme 4. *N*-Methylation of the intermediate **3b** and conversion to 2,11-dichloro-6-methyl-6*H*-indolo[2,3-*b*]quinoline.

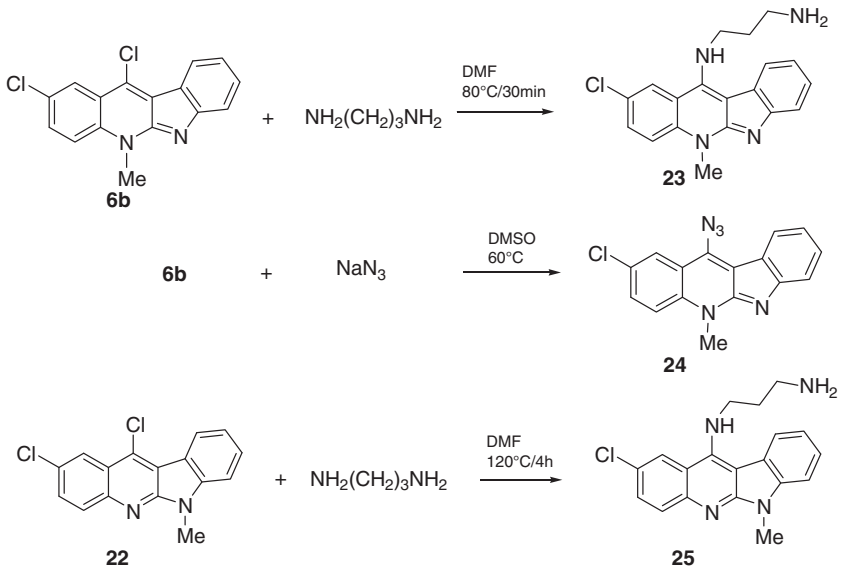


with a small amount of bismethylated **20** (20%). Selective methylation on the indole nitrogen rather than on the nitrogen atom of benzenamine of **3b** can be ascribable to the difference of the *p*Ka value of aniline NH (approximately 30 in DMSO) and indole NH (approximately 21 in DMSO) [16]. Before ring closure, the compound **19** was isolated and then cyclized into the tetracyclic **21** upon heating at 250°C in diphenyl ether. Dehydrative chlorination of **21** with $POCl_3$ gave the desired **22**.

Having succeeded in the benign access to 11-chloroneocryptolepines **6** and their 6-methyl-6*H*-isomer **22**, we examined some nucleophilic substitution reactions on the C11 positions of them and compared their reactivities. Amination of **6b** (R^1 = Cl) with 1,3-propanediamine proceeded at 80°C within 30 min, giving **23** in 97% yield, whereas the same amination reaction of **22** occurred at 120°C for 4 h, giving the corresponding amine **25** in 70% yield [12a]. On the other hand, azidation of **6b** (R^1 = Cl) with sodium azide produced the desired azide **24** in good yield, whereas the reaction of **22** with NaN_3 led to decomposition along with a recovery of the starting material. Namely, **22** is less reactive for nucleophilic substitution compared with **6**, as shown in Scheme 5.

In summary, we developed an efficient procedure for the synthesis of 11-chloroneocryptolepines and their 6-methyl congener from indole-3-carboxylate, which are useful as a scaffold for the preparation of antimalaria and anticancer agents. The protocol for 11-chloroneocryptolepines **6** is successful for the anilines bearing halogens, alkyl, trifluoromethyl, methoxy, *N*-acetamido, and alkoxycarbonyl groups (11 examples with 33–76% overall yield in totally three steps), whereas the aniline substituted with NO_2 was not. Reactivity at the C11-position of these 11-chloroneocryptolepines and their congener toward the nucleophiles were discussed, and 11-chloroneocryptolepines are shown more reactive than their congener, albeit whose aminoalkylamination at the C11 position is shown to be feasible. Preparation of various 11-aminated derivatives from **6** and **22** for bioactive testing is now under active investigation.

Scheme 5. Nucleophilic substitution at the C11 position of **6b** (R^1 = Cl) and **22**.



EXPERIMENTAL

Materials: the starting *N*-methylanilines, **7a–g**, **7j**, **10**, **15**, commercially available, were used as received, and other ones such as **7h** and **7i** were prepared by *N*-methylation of the corresponding anilines.

Synthesis of methyl 2-((4-chlorophenyl)(methyl)amino)-1*H*-indole-3-carboxylate (8b): a typical procedure. To the argon flushed solution of methyl indole-3-carboxylate (438.0 mg, 2.5 mmol) in CH_2Cl_2 (5 mL), a mixture of *N*-chlorosuccinimide (367.1 mg, 2.75 mmol) and *N*,*N*′-dimethylpiperazine (142.7 mg, 1.25 mmol) in CH_2Cl_2 (1 mL) was added dropwise at 0°C. The mixture was stirred at 0°C for 2 h, and a solution of trichloroacetic acid (102.1 mg, 0.625 mmol) and 4-chloro-*N*-methylaniline (708.0 mg, 5 mmol) in CH_2Cl_2 (2 mL) was then added dropwise. The reaction was allowed to warm to room temperature and further stirred for 3.5 h. The mixture was consecutively washed with saturated aqueous $NaHCO_3$, 1*N* HCl, brine, and water. The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 7/1) to give methyl 2-((4-chlorophenyl)(methyl)amino)-1*H*-indole-3-carboxylate 592.6 mg (75% yield). White solid, mp 178.7–181.4°C, R_f = 0.50 (EtOAc/hexanes = 1:3). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.28 (br s, 1H), 8.17–8.09 (m, 1H), 7.33–7.21 (m, 3H), 7.20–7.16 (m, 2H), 6.77–6.73 (m, 2H), 3.82 (s, 3H), 3.41 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 164.5, 146.9, 145.9, 131.9, 129.0, 126.4, 125.0, 123.0, 122.0, 121.5, 116.5, 110.7, 98.6, 50.9, 39.8; IR (KBr, cm^{-1}) 3233, 3188, 1676, 1517, 1437, 1346, 1269, 1233, 1194, 1117, 1067, 781, 754, 716. *Anal*. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 64.81; H, 4.28; N, 8.73.

Methyl 2-(methyl(phenyl)amino)-1H-indole-3-carboxylate (8a). White solid (585.0 mg, 83% yield), mp 133.6–135.1°C; R_f = 0.40 (EtOAc/hexanes = 1:5). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.21 (d, *J* = 15.26 Hz, 1H), 8.13 (d, *J* = 7.34 Hz, 1H), 7.29–7.18 (m, 5H), 6.93 (t, *J* = 7.34 Hz, 1H), 6.91–6.86 (m, 2H), 3.83 (d, *J* = 2.64 Hz, 3H), 3.46 (d, *J* = 2.35 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 164.5, 147.8, 147.0, 131.7, 129.2, 126.7, 122.7, 121.9, 121.5, 120.6, 116.3, 110.4, 98.0, 50.8, 40.0; IR (KBr, cm^{-1}) 3293, 2945, 1668, 1555, 1443, 1337, 1271, 1211, 1086, 746, 716, 694. *Anal*. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.98; H, 5.59; N, 10.00.

Methyl 2-((4-bromophenyl)(methyl)amino)-1H-indole-3-carboxylate (8c). White solid (733.4 mg, 82% yield), mp 164.1–165.7°C; R_f = 0.50 (EtOAc/hexanes = 1:3). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.24 (br s, 1H), 8.17–8.10 (m, 1H), 7.35–7.30 (m, 2H), 7.29–7.19 (m, 4H), 6.72–6.65 (m, 2H), 3.83 (s, 3H), 3.40 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 164.4, 146.7, 146.4, 131.9, 131.8, 126.4, 123.1, 122.1, 121.6, 116.9, 112.3, 110.7, 99.0, 50.3, 39.8; IR (KBr, cm^{-1}) 3279, 2947, 1667, 1557, 1493, 1445, 1329, 1273, 1219, 1163, 1105, 1070, 802, 745. *Anal*. Calcd for $C_{17}H_{15}BrN_2O_2$: C, 56.84; H, 4.21; N, 7.80. Found: C, 56.77; H, 4.11; N, 7.65.

Methyl 2-((4-fluorophenyl)(methyl)amino)-1H-indole-3-carboxylate (8d). White solid (611.5 mg, 82% yield), mp 151.4–152.4°C; R_f = 0.40 (EtOAc/hexanes = 1:3). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 8.10 (d, *J* = 7.63 Hz, 1H), 7.25–7.21 (m, 3H), 6.96 (m, 2H), 6.86–6.84 (m, 2H), 3.82 (d, *J* = 1.80 Hz, 3H), 3.44 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 164.5, 158.5, 156.9, 148.1, 143.4, 131.7, 126.7, 122.7, 122.0, 121.4, 118.1, 118.0, 115.9, 115.8, 110.4, 97.4, 50.8, 40.4; ^{19}F-NMR (564 MHz, $CDCl_3$): δ −123.42; IR (KBr, cm^{-1}) 3192, 2951, 1670, 1555, 1508, 1466, 1273, 1213, 1163, 1098, 1072, 820, 762, 742. *Anal*. Calcd for $C_{17}H_{15}FN_2O_2$: C, 68.45; H, 5.07; N, 9.39. Found: C, 68.62; H, 4.80; N, 9.29.

Methyl 2-(methyl(p-tolyl)amino)-1H-indole-3-carboxylate (8e). White solid (568.5 mg, 77% yield), mp 170.9–171.8°C; R_f = 0.20 (EtOAc/hexanes = 1:5). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.22 Hz, 1H), 7.29–7.12 (m, 3H), 7.12–7.01 (m, 2H), 6.87 (dd, *J* = 8.51, 2.05 Hz, 2H), 3.85 (d, *J* = 2.35 Hz, 3H), 3.55–3.36 (m, 3H), 2.30 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 164.6, 148.8, 144.4, 131.7, 130.9, 129.9, 126.9, 122.3, 121.8, 121.2, 117.6, 110.1, 96.6, 50.8, 40.4, 20.6; IR (KBr, cm^{-1}) 3279, 2945, 1668, 1560, 1518, 1443, 1332, 1275, 1215, 1163, 1105, 1074, 802, 743, 721. *Anal*. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.53. Found: C, 73.41; H, 6.12; N, 9.44.

Methyl 2-(methyl(4-(trifluoromethyl)phenyl)amino)-1H-indole-3-carboxylate (8f). White solid (692.4 mg, 80% yield), mp 142.9–144.7°C; R_f = 0.20 (15% EtOAc/hexanes = 1:5). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.37 (br s, 1H), 8.23–8.12 (m, 1H), 7.45 (d, *J* = 8.80 Hz, 2H), 7.35–7.27 (m, 3H), 6.78 (d, *J* = 8.80 Hz, 2H), 3.81 (s, 3H), 3.43 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 164.3, 150.1, 145.4, 132.0, 126.4, 126.4, 126.4, 126.3, 126.2, 123.7 (d, *J* = 270.41 Hz), 123.5, 122.3, 121.9, 121.0 (q, *J* = 32.42 Hz), 113.7, 111.0, 100.2, 51.0, 39.5; ^{19}F-NMR (564 MHz, $CDCl_3$): δ −61.64; IR (KBr, cm^{-1}) 3358, 3279, 2951, 1741, 1709, 1668, 1616, 1553, 1523, 1458, 1331, 1275, 1196, 1153, 1117, 1061, 829, 754. *Anal*. Calcd for $C_{18}H_{15}F_3N_2O_2$: C, 62.07; H, 4.34; N, 8.04. Found: C, 61.89; H, 4.28; N, 7.52.

Methyl 2-((4-methoxyphenyl)(methyl)amino)-1H-indole-3-carboxylate (8g). White solid (689.1 mg, 89% yield), mp 141.3–143.5°C; R_f = 0.30 (EtOAc/hexanes = 1:3). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.92 Hz, 1H), 7.98 (br s, 1H), 7.24–7.07 (m, 3H), 7.05–6.96 (m, 2H), 6.92–6.79 (m, 2H), 3.86 (d, *J* = 2.05 Hz, 3H), 3.80 (d, *J* = 2.05 Hz, 3H), 3.50 (br s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 164.7, 155.4, 149.9, 140.1, 131.6, 127.2, 121.9, 121.7, 121.0, 120.86, 114.8, 109.9, 94.7, 55.6, 50.7, 41.1; IR (KBr, cm^{-1}) 3314, 2949, 1667, 1550, 1508, 1445, 1327, 1250, 1209, 1074, 1036, 826, 791, 758. *Anal*. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.74; H, 5.69; N, 8.90.

Methyl 2-((4-acetamidophenyl)(methyl)amino)-1H-indole-3-carboxylate (8h). White solid (743.5 mg, 88% yield), mp 189.1–190.9°C; R_f = 0.50 (EtOAc). ^{1}H-NMR (600 MHz, DMSO-d_6): δ 11.82 (s, 1H), 9.76 (s, 1H), 7.96–7.84 (m, 1H), 7.50–7.36 (m, 2H), 7.36–7.24 (m, 1H), 7.20–7.08 (m, 2H), 6.82–6.62 (m, 2H), 3.63 (d, *J* = 1.47 Hz, 3H), 1.99 (d, *J* = 1.47 Hz, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 167.6, 163.6, 148.1, 143.3, 132.5, 132.1, 126.4, 121.8, 121.0, 120.3, 120.2, 115.8, 111.2, 95.8, 50.3, 39.9, 23.8; IR (KBr, cm^{-1}) 3333, 2949, 1674, 1512, 1454, 1389, 1265, 1213, 1115, 1067, 816, 756, 725. *Anal*. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.35; H, 5.66; N, 12.13.

Methyl 2-((4-(methoxycarbonyl)phenyl)(methyl)amino)-1H-indole-3-carboxylate (8i). White solid (556.2 mg, 66% yield), mp 217.9–219.8°C; R_f = 0.20 (EtOAc/hexanes = 1:3). ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.25 (br s, 1H), 8.00 (d, *J* = 7.92 Hz, 1H), 7.81 (d, *J* = 8.80 Hz, 2H), 7.39 (d, *J* = 7.63 Hz, 1H), 7.29–7.15 (m, 2H), 6.73 (d, *J* = 8.80 Hz, 2H), 3.78 (s, 3H), 3.66 (s, 3H), 3.37 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 166.1, 163.5, 151.7, 145.3, 132.6, 130.7, 125.8, 122.7, 121.5, 121.0, 119.0, 112.9, 111.8, 98.4, 51.6, 50.6, 39.1; IR (KBr, cm^{-1}) 3225, 2945, 1719, 1672, 1609, 1545, 1516, 1458, 1284, 1170, 1113, 1069, 835, 764, 741. *Anal*. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.44; H, 5.30; N 8.19.

Methyl 2-((3-chlorophenyl)(methyl)amino)-1H-indole-3-carboxylate (11). White solid (757.6 mg, 96% yield), mp 147.4–149.0°C; R_f = 0.20 (EtOAc/hexanes = 1:5). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.55 (br s, 1H), 8.26–8.07 (m, 1H), 7.35–7.20 (m, 3H), 7.10 (t, *J* = 8.07 Hz, 1H), 6.83 (dt, *J* = 7.92, 0.88 Hz, 1H), 6.76 (t, *J* = 2.05 Hz, 1H), 6.65–6.60 (m, 1H), 3.81 (s, 3H), 3.37 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 164.4, 148.6, 146.2, 135.0, 131.9, 130.0, 126.3, 123.2, 122.1, 121.7, 119.7, 114.8, 113.1, 110.9, 99.4, 50.9, 39.7; IR (KBr, cm^{-1}) 3187, 2947, 1667, 1601, 1551, 1485, 1462, 1333, 1281, 1267, 1217, 1105, 1080, 791, 764, 737, 719. *Anal*. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 64.66; H, 4.65; N, 8.66.

Methyl 2-((2-chlorophenyl)(methyl)amino)-1H-indole-3-carboxylate (16). After the solution of trichloroacetic acid and 2-chloro-*N*-methylaniline in CH_2Cl_2 was added, the reaction was allowed to warm to room temperature and further stirred for 12 h. White solid (657.0 mg, 83% yield), mp 152.3–153.7°C; R_f = 0.20 (EtOAc/hexanes = 1:5). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.28 (d, *J* = 15.85 Hz, 1H), 8.02 (d, *J* = 7.92 Hz, 1H), 7.48–7.36 (m, 1H), 7.28–7.21 (m, 2H), 7.18–7.14 (m, 1H), 7.14–7.10 (m, 2H), 7.10–7.06 (m, 1H), 3.72 (s, 3H), 3.51 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 164.8, 150.3, 144.4, 131.7, 131.0, 130.6, 128.0, 127.7, 126.6, 126.2, 121.7, 121.4, 120.5, 109.9, 92.3, 50.4, 41.3; IR (KBr, cm^{-1}) 3246, 3228, 1636, 1537, 1487, 1458, 1367, 1215, 1188, 1165, 1113, 1051, 791, 758, 731. *Anal*. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 65.03; H, 4.62; N, 8.81.

Methyl 2-(4-chlorophenylamino)-1H-indole-3-carboxylate (3b). White solid (623.2 mg 83% yield), mp 136.0–137.0°C; R_f = 0.45 (EtOAc/hexanes = 1:5). ^{1}H-NMR (600 MHz, CDCl3): δ 8.97 (br s, 1H), 8.29 (d, *J* = 4.99 Hz, 1H), 7.82 (d, *J* = 7.92 Hz, 1H), 7.43–7.30 (m, 2H), 7.23–7.11 (m, 4H), 7.10–7.00 (m, 1H), 3.93 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 167.8, 148.9, 137.0, 131.5, 130.1, 129.9, 126.0, 122.5, 122.1, 121.0, 119.4, 109.9, 86.8, 50.7; IR (KBr, cm^{-1}) 3304, 1663, 1634, 1587, 1568, 1495, 1443, 1393, 1323, 1260, 1207, 1090, 816, 783, 743, 696.

Synthesis of 2-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinolin-11(6*H*)-one (9b): a typical procedure. The methyl 2-((4-chlorophenyl)(methyl)amino)-1*H*-indole-3-carboxylate was refluxed in diphenyl ether (8 mL) at 250°C for 2 h. The solid was filtered and washed with diethyl ether to give 2-chloro-5-methyl-5*H*-indolo [2,3-*b*]quinolin-11(6*H*)-one 479.3 mg (90% yield). Gray solid, mp >370°C; ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.16 (s, 1H), 8.30 (d, *J* = 2.64 Hz, 1H), 8.25–8.20 (m, 1H), 7.90–7.86 (m, 1H), 7.82 (dd, *J* = 9.10, 2.64 Hz, 1H), 7.53 (dt, *J* = 7.92, 0.88 Hz, 1H), 7.35–7.24 (m, 2H), 4.02 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 170.1 146.9, 137.8, 134.8, 130.8, 126.5, 125.9, 124.7, 123.8, 123.2, 121.4, 120.2, 117.8, 110.9, 102.6, 33.6; IR (KBr, cm^{-1}) 3180, 1611, 1576, 1541, 1514, 1460, 1421, 1269, 1202, 806, 743, 706. *Anal*. Calcd for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; N, 9.91. Found: C, 67.80; H, 3.14; N, 9.68.

5-Methyl-5H-indolo[2,3-b]quinolin-11(6H)-one (9a). Pale gray solid (476.0 mg, 98% yield), mp >370°C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.12 (br s, 1H), 8.43 (dd, *J* = 7.92, 2.05 Hz, 1H), 8.29–8.19 (m, 1H), 7.90–7.72 (m, 2H), 7.56–7.50 (m, 1H), 7.44 (ddd, *J* = 7.92, 6.75, 1.17 Hz, 1H), 7.36–7.20 (m, 2H), 4.02 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 171.5, 146.9, 139.2, 134.7, 131.2, 125.8, 124.7, 124.1, 122.8, 121.7, 121.2, 120.1, 115.2, 110.8, 102.3, 33.3; IR (KBr, cm^{-1}) 3136, 3067, 1613, 1578, 1541, 1460, 1391, 1308, 1248, 1213, 878, 723, 679.

2-Bromo-5-methyl-5H-indolo[2,3-b]quinolin-11(6H)-one (9c). Pale gray solid (587.7 mg, 84% yield), mp >370°C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.16 (s, 1H), 8.44 (d, *J* = 2.64 Hz, 1H), 8.19 (d, *J* = 7.63 Hz, 1H), 7.95–7.83 (m, 1H), 7.77 (d, *J* = 8.80 Hz, 1H), 7.53–7.41 (m, 1H), 7.36–7.19 (m, 2H), 3.97 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 170.0, 146.9, 138.1, 134.8, 133.5, 127.8, 126.3, 123.8, 123.2, 121.4, 120.2, 118.0, 114.4, 110.9, 33.5; IR (KBr, cm^{-1}) 3185, 1607, 1574, 1537, 1510, 1460, 1418, 1267, 1248, 1198, 802, 741, 700. *Anal*. Calcd for $C_{16}H_{11}BrN_2O$: C, 58.74; H, 3.39; N, 8.56. Found: C, 58.81; H, 2.98; N, 8.38.

2-Fluoro-5-methyl-5H-indolo[2,3-b]quinolin-11(6H)-one (9d). Pale brown solid (458.4 mg, 75% yield), mp >370°C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ12.13 (s, 1H), 8.23 (dd, *J* = 7.63, 0.59 Hz, 1H), 7.99–8.11 (m, 1H), 7.88 (dd, *J* = 9.24, 3.96 Hz, 1H), 7.72–7.61 (m, 1H), 7.59–7.44 (m, 1H), 7.40–7.20 (m, 2H), 4.01 (d, *J* = 0.88 Hz, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 170.9 (d, *J* = 2.24 Hz), 158.9, 157.3, 147.5, 136.3, 135.4, 126.5, 126.5, 124.3, 123.6, 121.8, 120.7, 119.4 (d, *J* = 24.13 Hz), 118.4, 118.3, 111.4, 110.6 (d, *J* = 22.47 Hz), 102.7, 34.2; ^{19}F-NMR (564 MHz, DMSO-d_6): δ −120.58; IR (KBr, cm^{-1}) 3142, 3098, 2984, 1618, 1587, 1553, 1518, 1460, 1435, 1269, 1233, 802, 781, 740, 708. *Anal*. Calcd for $C_{16}H_{11}FN_2O$: C, 72.17; H, 4.16; N, 10.52. Found: C, 71.82; H, 3.70; N 10.30.

2,5-Dimethyl-5H-indolo[2,3-b]quinolin-11(6H)-one (9e). Pale gray solid (366.4 mg, 72% yield), mp >370°C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.01 (s, 1H), 8.24–8.12 (m, 2H), 7.69 (dd, *J* = 8.80, 0.88 Hz, 1H), 7.58 (d, *J* = 8.51 Hz, 1H), 7.51–7.42 (m, 1H), 7.31–7.17 (m, 2H), 3.96 (d, *J* = 1.47 Hz, 3H), 2.47 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 171.4, 146.8, 137.3, 134.7, 132.3, 130.7, 125.3, 124.6, 124.1, 122.7, 121.1, 120.1, 115.2, 110.7, 102.2, 33.2, 20.5; IR (KBr, cm^{-1}) 3180, 3012, 1614, 1594, 1548, 1520, 1460, 1420, 1271, 1250, 1173, 1065, 806, 772, 743, 708. *Anal*. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.24; H, 5.08; N 10.50.

5-Methyl-2-(trifluoromethyl)-5H-indolo[2,3-b]quinolin-11(6H)-one (9f). Gray solid (557.9 mg, 85% yield), >353.2°C decompose. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.19 (s, 1H), 8.60 (d, *J* = 1.47 Hz, 1H), 8.18 (d, *J* = 7.34 Hz, 1H), 8.03–7.85 (m, 2H), 7.44 (d, *J* = 7.34 Hz, 1H), 7.32–7.18 (m, 2H), 3.96 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 170.4, 146.9, 141.2, 134.7, 127.0, 125.4 (d, *J* = 270.46 Hz), 124.1, 123.5, 123.3, 123.0 (d, *J* = 3.02 Hz), 122.0 (q, *J* = 31.67 Hz), 121.5, 120.3, 116.7, 111.0, 102.9, 33.6; ^{19}F-NMR (564 MHz, DMSO-d_6): δ −59.38; IR (KBr, cm^{-1}) 3175, 1634, 1607, 152, 1549, 1460, 1327, 1296, 1198, 1115, 1082, 816, 748, 687; HRMS (ESI) Calcd for $C_{17}H_{10}F_3N_2O$ $[M-H]^-$ 315.0745. Found: 315.0745.

2-Methoxy-5-methyl-5H-indolo[2,3-b]quinolin-11(6H)-one (9g). Pale gray solid (535.4 mg, 87% yield), mp 353.1–357.2°C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.02 (s, 1H), 8.31–8.18 (m, 1H), 7.88 (d, *J* = 3.23 Hz, 1H), 7.80 (d, *J* = 9.10 Hz, 1H), 7.55–7.46 (m, 1H), 7.46–7.37 (m, 1H), 7.28 (ddd, *J* = 18.63, 7.63, 1.32 Hz, 2H), 4.01 (s, 3H), 3.92 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 171.9, 155.4, 147.6, 135.8, 134.6, 126.6, 125.0, 123.7, 122.0, 121.1, 121.0, 117.8, 111.6, 107.5, 102.9, 56.3, 34.3; IR (KBr, cm^{-1}) 3146, 3096, 1616, 1580, 1549, 1516, 1458, 1238, 1063, 1038, 808, 770, 742, 706. *Anal*. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.25; H, 4.71; N, 9.97.

N-(5-Methyl-11-oxo-6,11-dihydro-5H-indolo[2,3-b]quinolin-2-yl)acetamide (9h). Dark brown solid (552.1 mg, 82% yield), mp >370°C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.01 (s, 1H),

10.18 (s, 1H), 8.51 (d, J = 2.35 Hz, 1H), 8.19 (d, J = 7.04 Hz, 1H), 8.06 (dd, J = 9.10, 2.64 Hz, 1H), 7.75 (d, J = 9.10 Hz, 1H), 7.51–7.41 (m, 1H), 7.31–7.16 (m, 2H), 3.96 (s, 3H), 2.09 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 171.3, 168.2, 146.7, 135.1, 134.8, 133.9, 124.9, 124.1, 123.0, 122.7, 121.1, 120.1, 115.6, 115.0, 110.7, 102.0, 33.3, 24.0; IR (KBr, cm^{-1}) 3237, 1692, 1620, 1582, 1535, 1458, 1418, 1308, 1252, 812, 740. *Anal*. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.81; H, 4.52; N, 13.69.

Methyl 5-methyl-11-oxo-6,11-dihydro-5H-indolo[2,3-b]quinoline-2-carboxylate (9i). Pale gray solid (354.1 mg, 70% yield), >356.6°C decompose. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.21 (s, 1H), 8.96 (d, J = 2.05 Hz, 1H), 8.28–8.12 (m, 2H), 7.84 (d, J = 8.80 Hz, 1H), 7.48 (d, J = 7.63 Hz, 1H), 7.36–7.17 (m, 2H), 3.98 (s, 3H), 3.91 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 171.0, 165.9, 146.9, 142.0, 134.7, 130.9, 127.8, 124.2, 123.7, 123.2, 122.5, 121.5, 120.3, 115.8, 111.0, 102.9, 52.1, 33.7; IR (KBr, cm^{-1}) 3090, 2949, 1714, 1632, 1605, 1576, 1547, 1458, 1287, 1250, 1202, 1113, 764, 743. *Anal*. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.26; H, 4.21; N, 9.07.

3-Chloro-5-methyl-5H-indolo[2,3-b]quinolin-11(6H)-one (12). After recrystallization from pyridine/EtOAc/hexane, the crude product was purified to give the regioisomer **16** as pale gray solid (322.5 mg, 47% yield), mp >370°C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.15 (s, 1H), 8.36 (d, J = 8.51 Hz, 1H), 8.18 (d, J = 7.63 Hz, 1H), 7.87 (d, J = 1.76 Hz, 1H), 7.48 (d, J = 7.92 Hz, 1H), 7.41 (dd, J = 8.51, 1.76 Hz, 1H), 7.31–7.20 (m, 2H), 3.97 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 170.8, 146.9, 140.1, 136.0, 134.7, 127.7, 123.8, 123.4, 123.1, 121.9, 121.4, 120.2, 115.1, 110.9, 102.5, 33.6; IR (KBr, cm^{-1}) 3091, 2978, 1607, 1574, 1533, 1514, 1458, 1383, 1248, 1211, 1099, 909, 781, 743. *Anal*. Calcd for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; N, 9.91. Found: C, 67.42; H, 3.66; N, 9.77.

4-Chloro-5-methyl-5H-indolo[2,3-b]quinolin-11(6H)-one (17). Dark gray solid (300.3 mg, 51% yield), mp >370°C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.22 (s, 1H), 8.36 (dd, J = 7.92, 1.47 Hz, 1H), 8.15 (d, J = 7.34 Hz, 1H), 7.82 (dd, J = 7.63, 1.47 Hz, 1H), 7.50 (d, J = 7.63 Hz, 1H), 7.38 (t, J = 7.78 Hz, 1H), 7.21–7.31 (m, 2H), 4.12 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 170.7, 149.6, 138.3, 134.8, 134.3, 134.2, 128.5, 125.2, 123.3, 123.2, 121.5, 121.3, 120.3, 111.2, 102.7, 41.1; IR (KBr, cm^{-1}) 3057, 1609, 1576, 1537, 1460, 1389, 1258, 1206, 1067, 768, 748; HRMS (ESI) Calcd for $C_{16}H_{10}ClN_2O$ $[M-H]^-$ 281.0482. Found: 281.0469.

2-Chloro-5H-indolo[2,3-b]quinolin-11(6H)-one (4b). Off white solid (276.7 mg, 50% yield), mp >370°C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.48 (s, 1H), 11.79 (s, 1H), 8.29–8.10 (m, 2H), 7.68 (d, J = 1.47 Hz, 2H), 7.55–7.41 (m, 1H), 7.34–7.13 (m, 2H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 170.8, 145.3, 136.9, 135.1, 130.7, 126.0, 124.7, 124.3, 123.5, 123.0, 121.0, 120.1, 119.7, 111.0, 102.0; IR (KBr, cm^{-1}) 3287, 3094, 1645, 1620, 1584, 1520, 1456, 1410, 1337, 912, 806, 727, 698.

2-Chloro-6-methyl-5H-indolo[2,3-b]quinolin-11(6H)-one (21). Off white solid (480.6 mg, 92.4% yield), mp >370°C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.24 (s, 1H), 8.11–8.31 (m, 2H), 7.83–7.72 (m, 1H), 7.69 (dd, J = 8.80, 2.64 Hz, 1H), 7.54 (d, J = 7.92 Hz, 1H), 7.41–7.21 (m, 2H), 3.90 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 170.5, 145.7, 136.8, 136.2, 130.8, 126.3, 124.8, 124.3, 123.0, 122.9, 121.4, 120.1, 119.8, 109.2, 101.4, 29.2; IR (KBr, cm^{-1}) 3142, 3072, 2996, 1641, 1580, 1533, 1470, 1420, 1246, 1130, 812, 745. *Anal*. Calcd for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; N, 9.91. Found: C, 67.78; H, 3.65; N, 9.60.

Synthesis of 2,11-dichloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (6b): a typical procedure. To a suspension of 2-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinolin-11(6*H*)-one (479.3 mg, 1.0 equiv) in toluene (8 mL), phosphoryl chloride (10.4 g, 6.24 mL, 40.0 equiv) was added. The mixture was heated at reflux for 6 h and then poured into an ice–bath with stirring. The temperature should not be higher than 30°C. Removal of the liquid was by filtration, and the solid was sequentially washed with ether, aqueous saturated $NaHCO_3$, and water. The orange product was dried in a vacuum over P_2O_5 (477.8 mg, 94% yield). Orange solid, mp 211.1–215.9°C.; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.30 (d, J = 7.63 Hz, 1H), 8.27 (d, J = 2.35 Hz, 1H), 7.67–7.60 (m, 2H), 7.57–7.50 (m, 2H), 7.23 (t, J = 7.48 Hz, 1H), 4.23 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 154.9, 154.8, 135.1, 134.2, 131.0, 130.2, 128.1, 125.6, 125.0, 124.0, 123.4, 120.5, 119.9, 117.7, 115.7, 33.3; IR (KBr, cm^{-1}) 3410, 3048, 1632, 1560, 1520, 1487, 1444, 1263, 1234, 1194, 1140, 1109, 1072, 961, 789, 756, 737.

11-Chloro-5-methyl-5H-indolo[2,3-b]quinoline (6a). Orange solid (451.0 mg, 94% yield), mp 176.0–177.0°C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 8.45–8.37 (m, 2H), 8.09 (d, J = 8.51 Hz, 1H), 7.97 (ddd, J = 8.51, 7.04, 1.47 Hz, 1H), 7.68–7.61 (m, 2H), 7.57 (td, J = 7.63, 1.17 Hz, 1H), 7.31–7.23 (m, 1H), 4.34 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 154.6, 153.7, 136.7, 136.3, 131.2, 129.8, 126.0, 124.3, 123.8, 123.3, 122.5, 120.5, 119.2, 117.3, 114.3, 33.6; IR (KBr, cm^{-1}) 3399, 1630, 1572, 1522, 1491, 1439, 1416, 1273, 1234, 1074, 750.

2-Bromo-11-chloro-5-methyl-5H-indolo[2,3-b]quinoline (6c). Orange solid (559.6 mg, 90% yield), mp 203.2–205.1°C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.44 (d, J = 2.05 Hz, 1H), 8.31 (d, J = 7.63 Hz, 1H), 7.81 (dd, J = 8.95, 2.20 Hz, 1H), 7.66 (d, J = 7.92 Hz, 1H), 7.59–7.49 (m, 2H), 7.29–7.21 (m, 1H), 4.30 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 153.9, 153.6, 135.4, 134.8, 134.1, 130.3, 128.2, 125.0, 124.0, 122.9, 120.9, 120.6, 117.3, 116.1, 116.0, 33.9; IR (KBr, cm^{-1}) 3393, 3082, 1630, 1560, 1518, 1485, 1464, 1258, 1234, 1192, 1107, 957, 871, 756. *Anal*. Calcd for $C_{16}H_{10}BrClN_2$: C, 55.60; H, 2.92; N, 8.11. Found: C, 55.33; H, 2.85; N, 7.83.

11-Chloro-2-fluoro-5-methyl-5H-indolo[2,3-b]quinoline (6d). Orange solid (417.6 mg, 85% yield), mp 171.6–174.0°C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.32 (d, J = 7.63 Hz, 1H), 8.01 (dd, J = 9.39, 2.05 Hz, 1H), 7.66 (d, J = 7.92 Hz, 1H), 7.60 (dd, J = 9.39, 4.11 Hz, 1H), 7.55 (t, J = 7.48 Hz, 1H), 7.51–7.43 (m, 1H), 7.23 (t, J = 7.34 Hz, 1H), 4.27 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 158.6, 157.0, 154.9 (d, J = 11.2 Hz), 134.5, 133.3, 130.2, 125.7, 124.0, 123.2, 120.4, 120.0 (d, J = 7.54 Hz), 119.4 (d, J = 19.6 Hz), 117.53, 116.0 (d, J = 9.0 Hz), 110.8 (d, J = 24.1 Hz), 33.5; ^{19}F-NMR (564 MHz, $CDCl_3$): δ −119.20; IR (KBr, cm^{-1}) 3366, 1634, 1574, 1528, 1489, 1441, 1344, 1273, 1236, 1184, 1138, 1072, 995, 767, 754. *Anal*. Calcd for $C_{16}H_{10}ClFN_2$: C, 67.50; H, 3.54; N, 9.84. Found: C, 67.46; H, 3.42; N, 9.67.

11-Chloro-2,5-dimethyl-5H-indolo[2,3-b]quinoline (6e). Orange solid (326.1 mg, 83% yield), mp 206.1–209.1°C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 8.57–8.50 (d, J = 7.80 Hz, 1H), 8.39–8.28 (m, 2H), 8.08–8.01 (d, J = 9.00 Hz, 1H), 7.82–7.72 (m, 2H), 7.56–7.49 (t, J = 7.80 Hz, 1H), 4.49 (s, 3H), 2.63 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 147.2, 140.6, 140.4, 136.8, 135.8, 134.5, 130.8, 124.7, 123.8, 123.5, 120.9, 119.4, 119.2, 117.4, 113.0, 37.2, 20.7; IR (KBr, cm^{-1}) 3061, 1634, 1601, 1574, 1524, 1493, 1443, 1418, 1269, 1236, 1192, 1136, 1074, 966, 754, 740.

11-Chloro-5-methyl-2-(trifluoromethyl)-5H-indolo[2,3-b] quinoline (6f). Orange solid (492.0 mg, 84% yield), mp 206.3–209.5°C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.26

(d, J = 7.63 Hz, 1H), 7.90 (dd, J = 8.80, 1.47 Hz, 1H), 7.69–7.64 (m, 1H), 7.62 (d, J = 7.92 Hz, 1H), 7.51 (t, J = 7.63 Hz, 1H), 7.22 (t, J = 7.48 Hz, 1H), 4.26 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 154.8, 154.5, 138.2, 135.1, 130.3, 127.0 (d, J = 2.80 Hz), 125.7, 124.8–124.4 (m), 124.2, 124.0, 123.6 (d, J = 4.49 Hz), 123.2, 121.0, 118.5, 117.8, 115.0 33.5; ^{19}F-NMR (564 MHz, $CDCl_3$): δ −61.75; IR (KBr, cm^{-1}) 3399, 2953, 1626, 1572, 1530, 1497, 1452, 1339, 1254, 1234, 1150, 1123, 1086, 964, 760. *Anal*. Calcd for $C_{17}H_{10}ClF_3N_2$: C, 61.00; H, 3.01; N, 8.37. Found: C, 61.23; H, 2.84; N, 8.21.

11-Chloro-2-methoxy-5-methyl-5H-indolo[2,3-b]quinoline (6g). Red solid (486.1 mg, 86% yield), mp 152.8–156.2°C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 8.48–8.42 (m, 1H), 8.15–8.08 (m, 1H), 7.86–7.79 (m, 1H), 7.71–7.63 (m, 2H), 7.63–7.56 (m, 1H), 7.32–7.24 (m, 1H), 4.38 (s, 3H), 4.02 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 156.2, 155.6, 155.1, 134.9, 132.6, 130.4, 124.9, 124.4, 123.9, 122.3, 120.3, 119.7, 118.2, 106.5, 56.6, 34.2; IR (KBr, cm^{-1}) 3260, 2965, 1634, 1602, 1574, 1493, 1447, 1350, 1269, 1240, 1220, 1194, 1136, 1074, 1038, 839, 756, 737. *Anal*. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; N, 9.44. Found: C, 68.53; H, 4.38; N, 9.19.

N-(11-chloro-5-methyl-5H-indolo[2,3-b]quinolin-2-yl)acetamide (6h). Red solid (390.8 mg, 67% yield), >232°C decompose. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 10.29 (br s, 1H), 8.66 (br s, 1H), 8.33–8.11 (m, 1H), 8.06–7.74 (m, 2H), 7.64–7.36 (m, 2H), 7.23–7.01 (m, 1H), 4.41–3.96 (m, 3H), 2.17–2.03 (m, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 168.5, 155.1, 154.2, 134.4, 134.3, 132.7, 129.3, 123.8, 123.5, 123.3, 123.1, 119.3, 118.1, 117.2, 115.8, 113.2, 32.9, 24.0; IR (KBr, cm^{-1}) 3337, 1630, 1574, 1489, 1466, 1442, 1420, 1265, 1236, 1192, 1134, 1070, 878, 758; HRMS (ESI) Calcd for $C_{18}H_{13}ClN_3O$ $[M-H]^-$ 322.0747. Found: 322.0754.

Methyl 11-chloro-5-methyl-5H-indolo[2,3-b]quinoline-2-carboxylate (6i). Orange solid (326.0 mg, 94% yield), mp 280.9–283.0°C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.29 (d, J = 8.22 Hz, 2H), 7.74–7.57 (m, 2H), 7.52 (t, J = 7.48 Hz, 1H), 7.22 (t, J = 7.48 Hz, 1H), 4.24 (s, 3H), 4.00 (s, 3H); ^{13} C-NMR (150 MHz, $CDCl_3$): δ 166.0, 155.1, 154.5, 139.2, 135.7, 131.3, 130.1, 128.2, 125.4, 123.9, 123.8, 123.5, 120.9, 118.5, 117.8, 114.3, 52.4, 33.4; IR (KBr, cm^{-1}) 2949, 1709, 1616, 1560, 1526, 1495, 1437, 1298, 1246, 1230, 1116, 1071, 766, 743. *Anal*. Calcd for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63. Found: C, 66.31; H, 3.84; N, 8.46.

3,11-Dichloro-5-methyl-5H-indolo[2,3-b]quinoline (14). Orange solid (323.0 mg, 94% yield), mp 214.4–217.2°C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.31 (dd, J = 8.22, 4.99 Hz, 2H), 7.75–7.68 (m, 2H), 7.56 (t, J = 7.63 Hz, 1H), 7.48 (dd, J = 8.80, 1.76 Hz, 1H), 7.30–7.24 (m, 1H), 4.33 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 154.1, 152.9, 137.9, 137.2, 135.9, 130.1 127.3, 124.2, 123.8, 123.3, 123.0, 121.1, 117.8 117.4, 114.3, 33.9; IR (KBr, cm^{-1}) 3399, 1631, 1607, 1557, 1516, 1491, 1443, 1263, 1234, 1105, 1069, 955, 878, 756.

4,11-Dichloro-5-methyl-5H-indolo[2,3-b]quinoline (18). Red solid (246.1 mg, 78% yield), mp 211.4–213.0°C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.36–8.28 (m, 2H), 7.76 (dd, J = 7.92, 1.47 Hz, 1H), 7.69 (d, J = 7.92 Hz, 1H), 7.57–7.52 (m, 1H), 7.34 (t, J = 7.78 Hz, 1H), 7.24 (t, J = 7.48 Hz, 1H), 4.59 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 157.0, 155.0, 135.3 (d, J = 4.5 Hz), 134.4, 130.2, 125.8, 125.3, 124.1, 123.6, 122.6, 122.1, 121.4, 120.8, 117.9, 40.7; IR (KBr, cm^{-1}) 3057, 1640, 1551, 1518, 1483, 1447, 1433, 1261, 1240, 1219, 1142, 1063, 806, 772, 758, 716. *Anal*. Calcd for $C_{18}H_{13}ClN_2O_2$: C, 63.81; H, 3.35; N, 9.30. Found: C, 63.46; H, 3.32; N, 9.07.

2,11-Dichloro-5H-indolo[2,3-b]quinoline (5b). Yellow solid (204.7 mg, 69% yield), >310°C decompose. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 12.15 (br s, 1H), 8.51 (d, J = 7.92 Hz, 1H), 8.31 (s, 1H), 8.05 (dd, J = 9.10, 0.88 Hz, 1H), 7.83–7.78 (m, 1H), 7.66–7.60 (m, 1H), 7.55 (d, J = 7.92 Hz, 1H), 7.35 (t, J = 7.63 Hz, 1H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 152.7, 144.9, 141.8, 132.8, 129.9, 129.6, 129.4, 128.3, 123.8, 122.0, 122.0, 120.4, 118.9, 115.8, 111.3; IR (KBr, cm^{-1}) 3152, 3109, 1638, 1616, 1572, 1485, 1460, 1410, 1344, 1256, 1240, 1223, 1086, 962, 812, 734.

2,11-Dichloro-6-methyl-6H-indolo[2,3-b]quinoline (22). Yellow solid (410.0 mg, 80% yield), mp 170.9–173.3°C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.47 (dd, J = 7.63, 0.59 Hz, 1H), 8.23 (d, J = 2.35 Hz, 1H), 7.94 (d, J = 8.80 Hz, 1H), 7.64–7.52 (m, 2H), 7.36–7.27 (m, 2H), 3.86 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 152.1, 144.9, 142.6, 134.1, 129.9, 129.2, 129.1, 128.8, 124.1, 122.7, 122.6, 120.4, 119.2, 115.8, 108.5, 27.7; IR (KBr, cm^{-1}) 3057, 2930, 1638, 1604, 1560, 1485, 1473, 1397, 1265, 1246, 1126, 1086, 1001, 820, 739. *Anal*. Calcd for $C_{16}H_{10}Cl_2N_2$: C, 63.81; H, 3.35; N, 9.30. Found: C, 63.88; H, 3.36; N 9.14.

Preparation of methyl 2-(4-chlorophenylamino)-1-methyl-1*H*-indole-3-carboxylate (19). To the argon flushed suspension of NaH (52 mg, 1.3 mmol, 1.3 equiv, 60% oil suspension) in THF (5 mL) at 0°C, a solution of methyl 2-(4-chlorophenylamino)-1*H*-indole-3-carboxylate **3b** (300.7 mg, 1 mmol, 1.0 equiv) in THF (5 mL) was added dropwise. The reaction mixture was stirred at 0°C for 0.5 h. Then, MeI (283.9 mg, 2 mmol, 2.0 equiv) was added. The reaction was warmed to room temperature and kept on stirring for 0.5 h. The reaction was quenched with aqueous saturated $NaHCO_3$. The THF was removed under vacuum and extracted with EtOAc for three times. The combined organic layers were washed with brine and water and then dried over anhydrous $MgSO_4$. Further purification was achieved by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 20:1) to give methyl 2-(4-chlorophenylamino)-1-methyl-1*H*-indole-3-carboxylate **19** 192.8 mg (61% yield). White solid, mp 161.9–162.2°C; R_f = 0.50 (EtOAc/hexanes = 1:5).^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.02–7.89 (m, 1H), 7.32–7.16 (m, 5H), 6.95–6.82 (m, 2H), 3.92 (s, 3H), 3.39 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 167.4, 148.5, 141.3, 134.9, 129.5, 128.2, 125.4, 122.2, 121.7, 120.8, 120.3, 109.0, 92.7, 50.9, 31.3; IR (KBr, cm^{-1}) 3289, 3053, 2947, 1659, 1564, 1489, 1439, 1390, 1260, 1215, 1186, 1101, 1022, 833, 806, 785, 742. *Anal*. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 64.83; H, 4.79; N 8.80.

Methyl 2-((4-chlorophenyl)(methyl)amino)-1-methyl-1H-indole-3-carboxylate (20). The reaction was carried out by the same procedure with **19**. Red oil (67.2 mg, 20% yield); R_f = 0.40 (EtOAc/hexanes = 1:5). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.26–8.16 (m, 1H), 7.40–7.30 (m, 3H), 7.18–7.12 (m, 2H), 6.54–6.46 (m, 2H), 3.81 (s, 3H), 3.55 (s, 3H), 3.37 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 164.3, 146.7 146.3, 133.8, 129.0, 128.6, 125.6, 123.6, 123.1, 122.2, 121.9, 114.1, 109.8, 99.95, 50.8, 38.9, 28.8; IR (cm^{-1}) 3053, 2949, 1738, 1697, 1605, 1547, 1495, 1393, 1200, 1099, 1020, 818, 752, 698. *Anal*. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52. Found: C, 65.54; H, 4.84; N, 8.33.

N-(3-aminopropyl)-2-chloro-5-methyl-5,11a-dihydro-4aH-indolo [2,3-b]quinolin-11-amine (23). Yellow solid (32.9 mg, 97% yield); R_f = 0.16 (EtOAc/MeOH = 20:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 1.20, 1H), 7.96 (d, J = 7.60, 1H), 7.75 (d, J = 7.60, 1H), 7.58–7.55 (m, 1H), 7.49 (d, J = 9.20, 1H), 7.42

(t, J = 7.20, 1H), 7.17 (t, J = 7.20, 1H), 4.16 (s, 3H), 3.97 (s, 2H), 3.03 (t, J = 5.20, 2H), 1.80–1.74 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.7, 152.6, 147.3, 136.3, 129.9, 125.8, 125.6, 124.1, 123.7, 121.7, 118.7, 117.3, 117.0, 115.8, 106.4, 49.7, 41.5, 32.7, 32.3; IR (KBr, cm^{-1}) 3433, 1620, 1586, 1557, 1493, 1443, 1418, 1279, 1248, 797, 756, 731.

11-Azido-2-chloro-5-methyl-5H-indolo[2,3-b]quinoline (24). Brown solid (59.2 mg, 96% yield); R_f = 0.56 (EtOAc/MeOH = 20:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 2.00, 1H), 7.96 (d, J = 8.00, 1H), 7.70–7.65 (m, 2H), 7.60–7.52 (m, 2H), 7.27 (t, J = 8.00, 1H), 4.25 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.9, 154.4, 137.3, 135.5, 131.2, 129.3, 127.5, 124.3, 124.0, 121.7, 120.3, 117.8, 117.4, 115.6, 33.2; IR (KBr, cm^{-1}) 3449, 2122, 1626, 1560, 1524, 1489, 1283, 1236, 1109, 804, 760.

N-(3-Aminopropyl)-2-chloro-6-methyl-6H-indolo[2,3-b] quinolin-11-amine (25). Yellow oil (23.7 mg, 70% yield); R_f = 0.50 (EtOAc/MeOH = 4:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 2.40, 1H), 8.06 (d, J = 8.00, 1H), 7.96 (d, J = 9.20, 1H), 7.55 (dd, J = 8.80, 2.40, 1H), 7.52–7.48 (m, 1H), 7.38 (d, J = 7.60, 1H), 7.28 (t, J = 7.60, 1H), 6.03 (br s, 1H), 3.92 (s, 3H), 3.85 (t, J = 4.80, 2H), 2.99 (t, J = 6.40, 2H), 1.90–1.84 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.2, 148.2, 146.3, 141.3, 129.4, 129.2, 126.3, 126.0, 122.2, 122.1, 120.4, 119.7, 118.5, 108.2, 104.1, 48.8, 41.0, 33.7, 27.7; IR (cm^{-1}) 3354, 2931, 1668, 1601, 1566, 1489, 1441, 1395, 1316, 1250, 1123, 822, 743; HRMS (ESI) Calcd for $C_{19}H_{18}ClN_4$ $[M - H]^-$ 337.122. Found: 337.1205.

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