Facile Assembly of 11*H*-Indolo[3,2-*c*]quinoline by a Two-Step Protocol Involving a Regioselective 6-*endo*-Cyclization Promoted by the Hendrickson Reagent

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Abstract: An expedient approach was developed to construct the 11*H*-indolo[3,2-*c*]quinoline scaffold starting from acyclic alkyne substrates. The five- and six-membered nitrogen-containing rings in the tetracyclic skeleton were elaborated efficiently by gold(III)-catalyzed 5-*endo*-dig cyclization and Hendrickson reagent promoted regioselective 6-*endo* cyclization.

Key words: alkyne, cyclization, gold, quinoline, Hendrickson reagent

Naturally occurring alkaloids together with their synthetic analogues containing the 11*H*-indolo[3,2-*c*]quinoline scaffold have attracted considerable attention because of their diverse and pronounced biological properties.[1] Isocryptolepine, a methyl-substituted 11*H*-indolo[3,2-*c*]quinoline isolated from *Cryptolepis sanguinolenta*, shows strong antiplasmodial activity[2] (Figure 1), while certain counterparts display high cytotoxicity against cancer cell lines.[3] To further investigate the structure–activity relationship, a variety of strategies based on indole and quinoline formation have been developed to elaborate the tetracyclic skeleton.

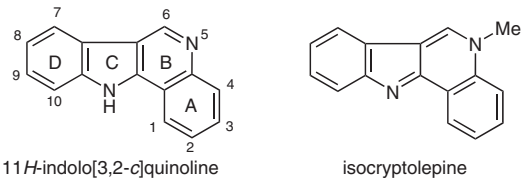
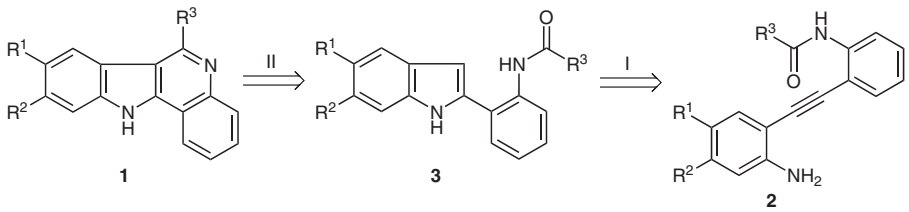


Figure 1 Structure of 11*H*-indolo[3,2-*c*]quinoline and a related alkaloid

Generally, the five-membered ring contained within the fused framework can be incorporated by heteroatom-directed photoannulation,[4] intramolecular insertion of nitrene[5] as well as by palladium-catalyzed Buchwald–Hartwig reaction/C-H activation[6] from quinoline substrates such as anilinoquinoline, 4-(2-azidophenyl)quinoline, and 4-chloroquinoline. The pyridine ring can be installed by Pictet–Spengler reaction[7] and Heck-type cyclization[8] from 2-(1*H*-indol-2-yl)phenylamine and 3-carbamoylindole-2-carboxylic acid. Owing to the limitations of indole and quinoline starting materials, the methodologies mentioned above are relatively inflexible with respect to the introduction of different substituents on the ring. Although Cacchi[9] developed an alternative approach to the construction of 11*H*-indolo[3,2-*c*]quinoline from *o*-(*o*-aminophenyl)trifluoroacetanilide by palladium-catalyzed carbonylative cyclization and subsequent intramolecular condensation, only 6-arylated derivatives were accessible. To further develop an efficient protocol with better flexibility, we designed a two-step strategy to assemble 11*H*-indolo[3,2-*c*]quinoline. As illustrated in Scheme 1, the five- and six-membered nitrogen-containing rings in the skeleton were elaborated through a gold(III)-catalyzed 5-*endo-dig*-cyclization (step I), followed by a Hendrickson reagent promoted regioselective 6-*endo*-cyclization (step II).

The study was initiated with alkyne **2a** as substrate. The amine and amide functional groups were combined by a Sonogashira coupling reaction between 2-ethynylaniline and *N*-(2-iodophenyl)acetamide.[10] Since the characteristic transformation from 2-alkynylaniline into the indole nu-



Scheme 1 A two-step strategy for 11*H*-indolo[3,2-*c*]quinoline assembly

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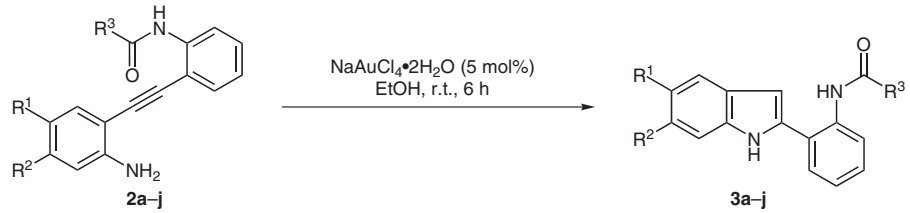


Scheme 2 Au(III)-catalyzed indolization

cleus could be implemented under the catalysis of Lewis acids or transition-metal salts, the conversion from **2a** into *N*-[2-(1*H*-indol-2-yl)phenyl]acetamide (**3a**) was envisioned (R^1,R^2 = H, R^3 = Me; Scheme 2). However, when $InBr_3$ was used according to Sakai's procedure,[11] the indole product was isolated in only 45% yield. It was deduced that competitive cyclization of the amide group was the cause of the low yield. Consequently, milder conditions with better regioselectivity were required. To our delight, when $NaAuCl_4{\cdot}2H_2O$ was employed,[12] the cyclization was completed in 85% yield at room temperature (Table 1, entry 1). In a similar manner, alkynes **2b–g** containing propanamide, formamide, benzamide, and carbamate groups were converted into the corresponding indoles **3b–g** in yields ranging from 58 to 80% (Table 1, entries 2–7). In addition, alkynes **2h–j**, with electron-withdrawing substituents (Cl) and electron-donating substituents (Me, OCH_2O) on the aniline ring, also underwent 5-*endo*-dig cyclization smoothly to afford the indole derivatives **3h–j** in 60–83% yields (Table 1, entries 8–10).

Table 1 Indole Formation by Au(III)-Catalyzed 5-*endo*-dig Cyclization[a]

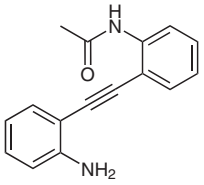
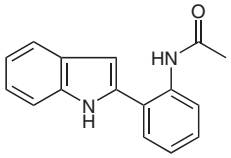
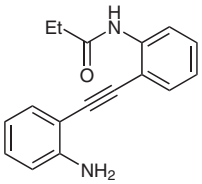
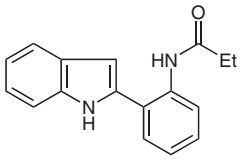
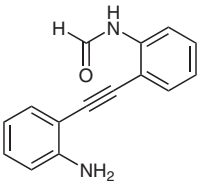
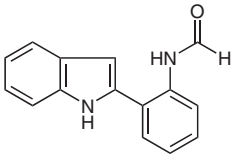
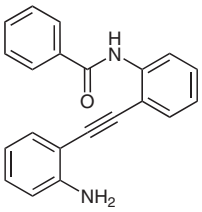
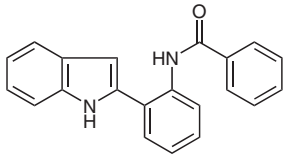
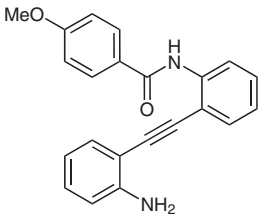
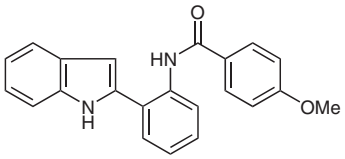
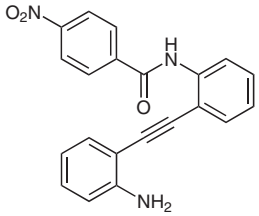
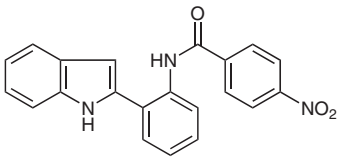
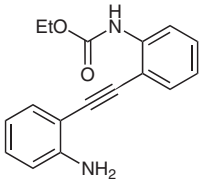
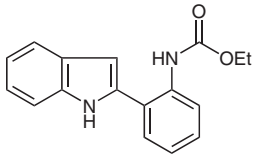
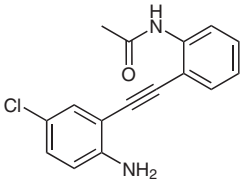
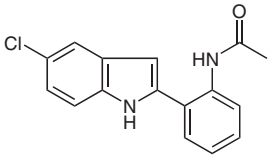
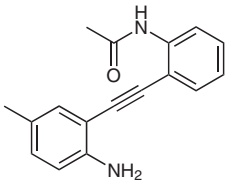
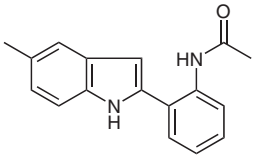
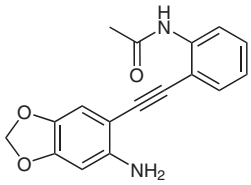
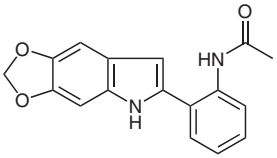
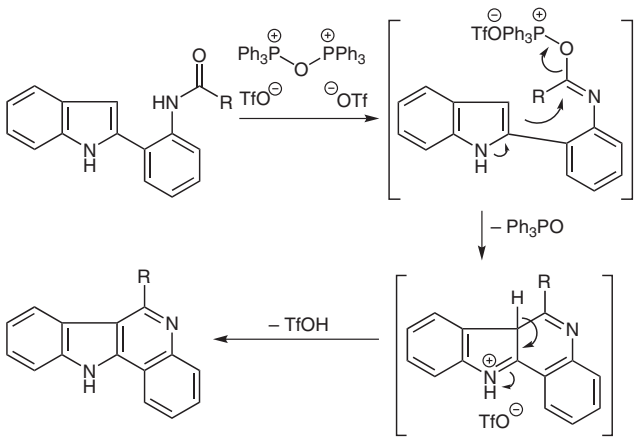
Entry	Alkyne	Indole	Yield (%)
1	 **2a**	 **3a**	85
2	 **2b**	 **3b**	60
3	 **2c**	 **3c**	65
4	 **2d**	 **3d**	80

Table 1 Indole Formation by Au(III)-Catalyzed 5-*endo*-dig Cyclization[a] (continued)

Entry	Alkyne	Indole	Yield (%)
5	 **2e**	 **3e**	80
6	 **2f**	 **3f**	62
7	 **2g**	 **3g**	58
8	 **2h**	 **3h**	83
9	 **2i**	 **3i**	78
10	 **2j**	 **3j**	60

[a] The reaction was performed at a concentration of 0.125 M.

Bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate (Hendrickson reagent), which is derived from triphenylphosphine oxide and triflic anhydride, possesses high oxophilicity.[13] By utilizing this O-bridged bisphosphonium salt, some chemical transformations based on the amide functionality can be realized.[14] In a continuation of our exploration of this reagent, a 6-*endo* cyclization of *N*-[2-(1*H*-indol-2-yl)phenyl]amide triggered by Hendrickson reagent was suggested. As depicted in Scheme 3, the amide group would be selectively activated and transformed into the corresponding imidate. Subsequent intramolecular nucleophilic attack takes place to give 11*H*-indolo[3,2-*c*]quinoline, accompanied by dissociation of triphenylphosphine oxide (Ph_3PO) and trifluoromethanesulfonic acid (TfOH).



Scheme 3 Proposed mechanism for Hendrickson reagent promoted 6-*endo* cyclization

N-[2-(1*H*-Indol-2-yl)phenyl]acetamide (**3a**) was selected to probe the conditions. Under the action of Hendrickson reagent (generated in situ from 1.5 equiv TfOH and 3.0 equiv Ph_3PO in CH_2Cl_2), **3a** was consumed completely within 15 minutes, and the anticipated 11*H*-indolo[3,2-*c*]quinoline (**1a**) was isolated in 88% yield together with a minor amount of byproduct, which was identified as 6-methyl-indolo[1,2-*c*]quinazoline (Table 2, entry 1). Both structures were further confirmed by single crystal X-ray diffraction analysis (Figure 2 and Figure 3).[15] Attempts to ultilize a catalytic amount of Ph_3PO resulted in inversion of the regioselectivity (Table 2, entry 2). In comparison, use of either triflic anhydride or a combination of triflic anhydride (Tf_2O) with amine additives led to similar distributions (Table 2, entries 3–5). To our surprise, when the reaction was performed in xylene, and $POCl_3$ was employed as a dehydrating agent, 6-methylindolo[1,2-*c*]quinazoline became the predominant product, and only a trace amount of 11*H*-indolo[3,2-*c*]quinoline was isolated (Table 2, entry 6).

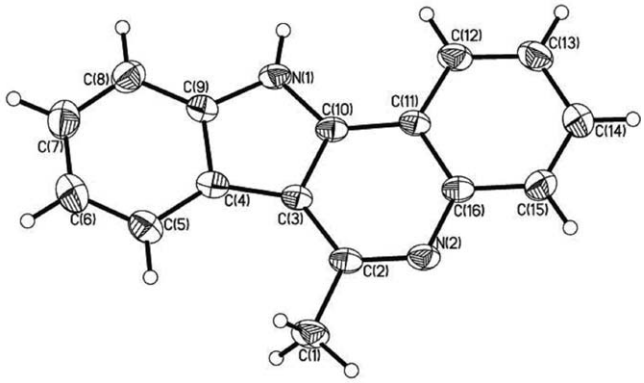


Figure 2 X-ray crystal structure of 11*H*-indolo[3,2-*c*]quinoline **1a**

The high regioselectivity induced by the Hendrickson reagent in the construction of 11*H*-indolo[3,2-*c*]quinoline prompted us to examine the scope of the transformation.

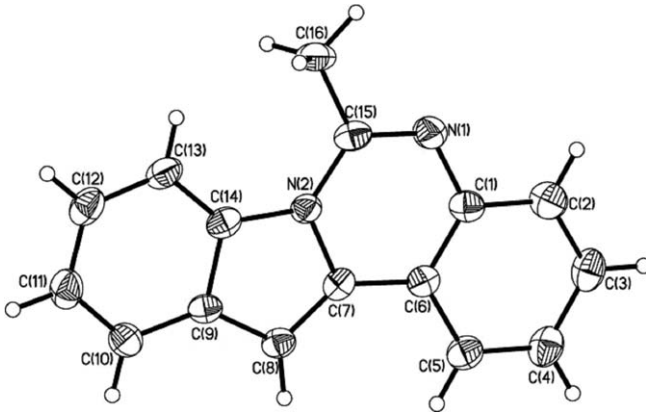
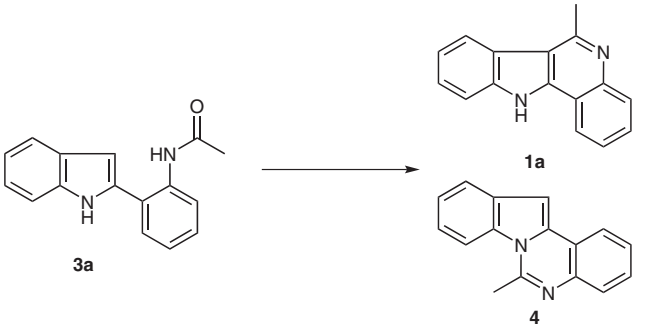


Figure 3 X-ray crystal structure of indolo[1,2-*c*]quinazoline **4**

Table 2 6-*endo*-Cyclization Conditions Screened



Entry	Reagent (equiv)[a]	Temp (°C)	Time (min)	Yield (%)[b]	
				1a	**4**
1	Tf_2O (1.5), Ph_3PO (3.0)	r.t.	15	88	10
2	Tf_2O (1.5), Ph_3PO (0.1)	r.t.	15	13	75
3	Tf_2O (1.5)	r.t.	15	33	63
4	Tf_2O (1.1), 2-ClPy (1.2)	–78 to 45	60	34	60
5	Tf_2O (5.0), DMAP (3.0)	r.t.	12 h	38	53
6[c]	$POCl_3$ (3.0)	120	15	<5	92

[a] CH_2Cl_2 was used as solvent unless otherwise mentioned, and the concentration was 0.125 M.
[b] Isolated yield.
[c] Xylene as solvent.

Analogously, *N*-[2-(1*H*-indol-2-yl)phenyl]propanamide (**3b**) and *N*-[2-(1*H*-indol-2-yl)phenyl]formamide (**3c**) underwent efficient cyclization to afford the tetracyclic products in 83% and 75% yield, respectively (Table 3, entries 1–2). Of particular note is that 11*H*-indolo[3,2-*c*]quinoline (**1c**) has been used as a precursor to synthesize the alkaloid isocryptolepine by selective methylation.

A number of benzamides were screened, and all were converted into the corresponding 6-arylated 11*H*-indolo[3,2-*c*]quinolines **1d–f** as expected (Table 3, entries 3–5). It seemes that the electronic properties of the substituent on the benzoyl moiety affected the outcome of the cyclization. The methoxy group facilitated the conversion, with

the methoxy-substituted indoloquinoline being obtained in 95% yield. The nitro group hindered the cyclization, with the corresponding 11*H*-indolo[3,2-*c*]quinoline **1f** being achieved in only 78% yield. Besides amides, as exemplified above, the carbamate group was also well-tolerated, delivering the 6-ethoxy-11*H*-indolo[3,2-*c*]quinoline in moderate yield (Table 3, entry 6). To further extend the scope, different *N*-[2-(1*H*-indol-2-yl)phenyl]acetamides containing chlorine, methyl, and methylenedioxy substituents on the indole moiety were tested (Table 3, entries 7–9). The corresponding 8-Cl, 8-Me, and 8,9-methylenedioxy-substituted 11*H*-indolo[3,2-*c*]quinolines **1h–j** were achieved in 84–94% yields. The pentacyclic compound **1j** is of particular interest and its biological evaluation is in progress.

Table 3 11*H*-Indolo[3,2-*c*]quinoline Assembly by Hendrickson Reagent Promoted Regioselective 6-*endo* Cyclization[a]

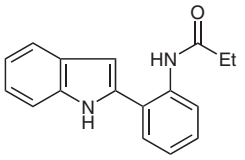
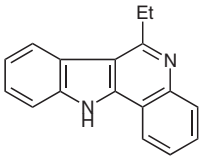
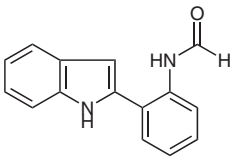
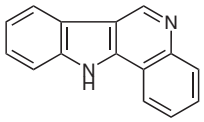
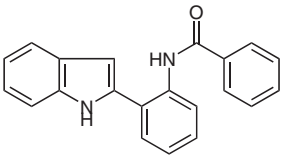
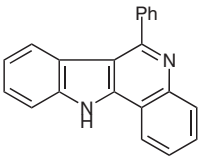
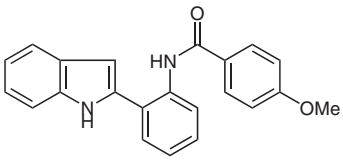
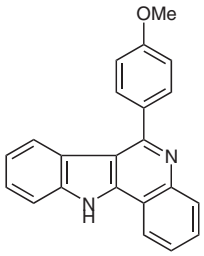
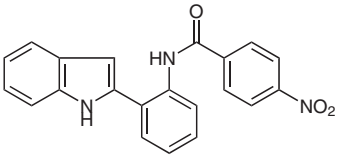
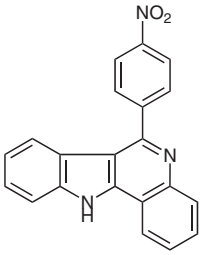
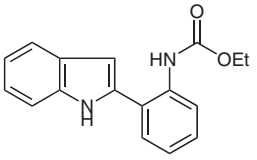
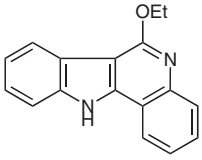
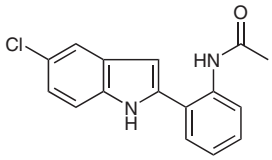
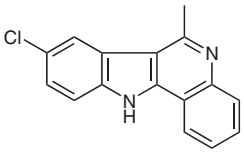
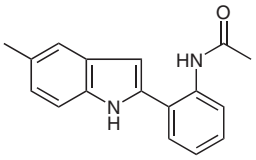
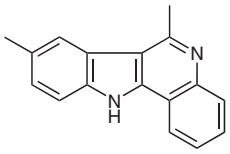
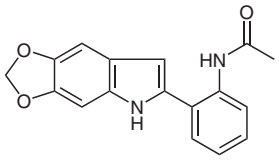
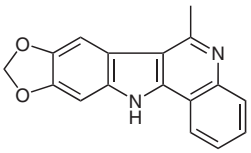
Entry	Indole **3**	Indoloquinoline **1**	Yield (%)
1	 **3b**	 **1b**	83
2	 **3c**	 **1c**	75
3	 **3d**	 **1d**	92
4	 **3e**	 **1e**	95
5	 **3f**	 **1f**	78
6	 **3g**	 **1g**	60

Table 3 11*H*-Indolo[3,2-*c*]quinoline Assembly by Hendrickson Reagent Promoted Regioselective 6-*endo* Cyclization[a] (continued)

Entry	Indole **3**	Indoloquinoline **1**	Yield (%)
7	 **3h**	 **1h**	94
8	 **3i**	 **1i**	84
9	 **3j**	 **1j**	92

[a] The concentration was 0.125 M and the reaction time was 15 min.

In conclusion, a two-step approach that can be used to assemble the 11*H*-indolo[3,2-*c*]quinoline scaffold starting from acyclic alkynes has been developed. The heterocyclic units in the skeleton were constructed successively by a gold(III)-catalyzed 5-*endo*-dig cyclization and Hendrickson reagent promoted regioselective 6-*endo* cyclization. The protocol features mild conditions, functional group compatibility, and high regioselectivity, which is suitable for the preparation of 6-alkyl, aryl, and alkoxy-substituted 11*H*-indolo[3,2-*c*]quinoline derivatives.

Melting points are uncorrected. IR spectra were recorded with a Nicolet FT-IR 5DX spectrometer as KBr pellets. NMR spectra were recorded with a Bruker ACF-300 spectrometer by using tetramethylsilane (TMS) or residue solvent as internal standards; *J* values are given in Hz. Mass spectra were taken with a LCQ Fleet EIS Mass Spectrometer. Elemental analyses were performed with a Perkin–Elmer 240C analyzer. The *o*-ethynylaniline substrates were prepared according to the reported procedure.[10]

_N_-[2-(1*H*-Indol-2-yl)phenyl]amides 3a–j; General Procedure

$NaAuCl_4 \cdot 2H_2O$ (16 mg, 0.04 mmol) was added to a solution of *N*-{2-[(2-aminophenyl)ethynyl]phenyl}amide (1.0 mmol) in EtOH (8 mL). The reaction mixture was stirred at r.t. for 6 h under an argon atmosphere. Then the mixture was diluted with $CHCl_3$ (30 mL), and the obtained solution was washed with brine (15 mL) and H_2O (15 mL) successively. The organic phase was dried (anhydrous $MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc–PE, 1:2) to give *N*-[2-(1*H*-indol-2-yl)phenyl]amide (Table 1).

_N_-[2-(1*H*-Indol-2-yl)phenyl]acetamide (3a)

Yellow solid; mp 130–132 °C (EtOH–PE).

IR (KBr): 3362, 3284, 1680, 1519, 1437, 737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.86 (s, 1 H), 8.25 (d, *J* = 7.8 Hz, 1 H), 7.81 (s, 1 H), 7.67 (d, *J* = 7.5 Hz, 1 H), 7.45 (d, *J* = 8.1 Hz, 1 H), 7.41 (d, *J* = 8.1 Hz, 1 H), 7.32 (td, *J* = 7.8, 1.5 Hz, 1 H), 7.25 (td, *J* = 6.9, 0.9 Hz, 1 H), 7.20–7.14 (m, 2 H), 6.62 (s, 1 H), 2.05 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 136.7, 135.0, 134.2, 129.5, 128.9, 128.6, 124.5, 123.7, 122.5, 122.0, 120.6, 120.3, 111.3, 102.3, 24.5.

ESI-MS: *m*/*z* = 251.1 $[M + H]^+$.

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.71; H, 5.66; N, 11.07.

_N_-[2-(1*H*-Indol-2-yl)phenyl]propanamide (3b)

White solid; mp 158–160 °C (EtOH–PE).

IR (KBr): 3343, 3227, 1631, 1522, 1449, 807 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.97 (s, 1 H), 8.25 (d, *J* = 7.8 Hz, 1 H), 7.83 (s, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.40 (t, *J* = 8.4 Hz, 2 H), 7.30–7.09 (m, 4 H), 6.58 (d, *J* = 1.2 Hz, 1 H), 2.22 (q, *J* = 7.5 Hz, 2 H), 1.09 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 136.7, 135.1, 134.2, 129.4, 128.9, 128.6, 124.3, 123.6, 122.5, 121.8, 120.5, 120.3, 111.2, 102.3, 30.7, 9.4.

ESI-MS: *m*/*z* = 265.1 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.37; H, 6.17; N, 10.64.

_N_-[2-(1*H*-Indol-2-yl)phenyl]formamide (3c)

Yellow solid; mp 112–113 °C (EtOAc–PE).

IR (KBr): 3302, 1674, 745 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.40 (s, 0.63 H), 9.69–9.60 (m, 0.64 H), 9.54 (s, 0.33 H), 8.38–8.35 (m, 1 H), 8.25–8.22 (m, 0.31 H), 8.05 (d, *J* = 7.8 Hz, 0.49 H), 7.85–7.82 (m, 0.31 H), 7.79–7.75 (m, 0.32 H), 7.68–7.53 (m, 2 H), 7.46–7.35 (m, 2.65 H), 7.28 (td, *J* = 7.5, 1.2 Hz, 0.52 H), 7.14 (td, *J* = 8.1, 0.9 Hz, 0.69 H), 7.04 (t, *J* = 7.2 Hz, 0.69 H), 6.72–6.71 (m, 0.68 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.6, 160.7, 138.7, 136.8, 134.4, 134.3, 129.7, 129.3, 128.6, 128.4, 128.1, 127.74, 127.70,

126.0, 125.2, 124.9, 124.4, 123.9, 123.8, 123.5, 122.1, 121.6, 120.6, 120.2, 119.3, 111.5, 111.4, 102.1, 102.0, 94.8.

ESI-MS: m/z = 237.2 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.21; H, 5.17; N, 11.86.

_N_-[2-(1_H_-Indol-2-yl)phenyl]benzamide (3d)
White solid; mp 173–175 °C (EtOH–PE).

IR (KBr): 3359, 1665, 1578, 1517, 1436, 1305, 743 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.84 (s, 1 H), 8.77 (s, 1 H), 8.51 (d, J = 7.8 Hz, 1 H), 7.72 (d, J = 7.8 Hz, 2 H), 7.68 (d, J = 7.8 Hz, 1 H), 7.51–7.45 (m, 3 H), 7.37 (t, J = 7.5 Hz, 3 H), 7.29–7.24 (m, 1 H), 7.19 (td, J = 6.9, 3.6 Hz, 2 H), 6.69 (d, J = 0.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 136.8, 135.7, 134.3, 134.2, 131.9, 129.3, 129.1, 128.8, 127.0, 124.5, 123.6, 122.7, 121.6, 120.7, 120.4, 111.2, 102.5.

ESI-MS: m/z = 313.2 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.82; H, 5.24; N, 8.93.

_N_-[2-(1_H_-Indol-2-yl)phenyl]-4-methoxybenzamide (3e)
Light-yellow solid; mp 177–179 °C (EtOH–PE).

IR (KBr): 3359, 1641, 1505, 1439, 746 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.41 (s, 1 H), 9.81 (s, 1 H), 7.96–7.93 (m, 2 H), 7.72–7.66 (m, 2 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.41–7.37 (m, 3 H), 7.12–7.03 (m, 3 H), 6.97 (td, J = 8.1, 0.9 Hz, 1 H), 6.68 (d, J = 1.2 Hz, 1 H), 3.83 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.9, 161.9, 136.5, 135.2, 129.5, 128.9, 128.5, 128.4, 127.7, 127.6, 126.6, 126.0, 121.5, 120.0, 119.2, 113.7, 111.3, 101.2, 55.4.

ESI-MS: m/z = 343.1 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.21; H, 5.32; N, 8.12.

_N_-[2-(1_H_-Indol-2-yl)phenyl]-4-nitrobenzamide (3f)
Orange solid; mp 192–194 °C (EtOAc–PE).

IR (KBr): 3373, 3251, 1656, 1522, 1439, 1347, 763, 708 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.44 (s, 1 H), 10.36 (s, 1 H), 8.37 (d, J = 8.7 Hz, 2 H), 8.19 (d, J = 8.7 Hz, 2 H), 7.74 (dd, J = 5.9, 3.5 Hz, 1 H), 7.66–7.63 (m, 1 H), 7.50–7.39 (m, 4 H), 7.09 (td, J = 7.2, 1.2 Hz, 1 H), 6.97 (td, J = 7.8, 0.9 Hz, 1 H), 6.69 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.1, 149.2, 140.2, 136.6, 135.0, 134.4, 129.1, 129.0, 128.4, 128.0, 127.8, 126.7, 123.6, 121.5, 120.1, 119.2, 111.3, 101.2.

ESI-MS: m/z = 358.1 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.47; H, 4.24; N, 11.81.

Ethyl 2-(1_H_-Indol-2-yl)phenylcarbamate (3g)
White solid; mp 146–148 °C (EtOAc–PE).

IR (KBr): 3381, 3338, 1714, 1589, 1522, 766 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.46 (s, 1 H), 8.21 (d, J = 8.4 Hz, 1 H), 7.73–7.70 (m, 1 H), 7.46–7.35 (m, 4 H), 7.31–7.18 (m, 2 H), 7.14 (td, J = 7.5, 1.2 Hz, 1 H), 6.69 (dd, J = 2.1, 0.9 Hz, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 1.29 (t, J = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8, 136.5, 135.6, 133.9, 129.3, 129.2, 128.7, 123.3, 122.6, 122.4, 120.7, 120.4, 119.7, 111.1, 102.5, 61.3, 14.4.

ESI-MS: m/z = 281.1 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.81; H, 5.74; N, 10.00.

_N_-[2-(5-Chloro-1_H_-indol-2-yl)phenyl]acetamide (3h)
White solid; mp 160–162 °C ($CHCl_3$).

IR (KBr): 3366, 3602, 1680, 1519, 1436, 759 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.57 (s, 1 H), 9.49 (s, 1 H), 7.65–7.63 (m, 3 H), 7.45 (d, J = 8.7 Hz, 1 H), 7.40–7.31 (m, 2 H), 7.13 (dd, J = 9.0, 2.4 Hz, 1 H), 6.73 (d, J = 1.5 Hz, 1 H), 2.08 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 168.8, 136.8, 135.18, 135.12, 129.6, 129.1, 128.1, 126.7, 125.4, 123.7, 121.3, 119.2, 112.8, 101.1, 23.5.

ESI-MS: m/z = 285.1 $[M + H]^+$.

Anal. Calcd for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.46; H, 4.67; N, 9.81.

_N_-[2-(5-Methyl-1_H_-indol-2-yl)phenyl]acetamide (3i)
White solid; mp 132–134 °C (EtOH–PE).

IR (KBr): 3359, 3292, 1682, 1520, 1434, 755 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.05 (s, 1 H), 8.24 (d, J = 7.8 Hz, 1 H), 7.89 (s, 1 H), 7.48 (s, 1 H), 7.42–7.27 (m, 3 H), 7.18–7.09 (m, 2 H), 6.54 (s, 1 H), 2.52 (s, 3 H), 2.02 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 135.1, 134.9, 134.3, 129.5, 129.4, 128.9, 128.7, 124.4, 124.1, 123.8, 121.9, 120.1, 110.9, 101.7, 24.4, 21.4.

ESI-MS: m/z = 265.2 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.44; H, 6.06; N, 10.66.

_N_-[2-(5,6-Dimethylenedioxy-1_H_-indol-2-yl)phenyl]acetamide (3j)
White solid; mp 158–160 °C (EtOH–PE).

IR (KBr): 3268, 2886, 1622, 1523, 1471, 756 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.19 (s, 1 H), 9.41 (s, 1 H), 7.61–7.58 (m, 2 H), 7.29–7.26 (m, 2 H), 7.05 (s, 1 H), 6.94 (s, 1 H), 6.61 (d, J = 1.2 Hz, 1 H), 5.95 (s, 2 H), 2.07 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 168.8, 144.3, 142.3, 134.5, 133.4, 131.7, 128.3, 127.3, 127.0, 126.8, 125.4, 122.3, 102.0, 100.2, 98.6, 92.0, 23.6.

ESI-MS: m/z = 295.2 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.34; H, 4.84; N, 9.57.

11_H_-Indolo[3,2-_c_]quinoline 1a–j; General Procedure
Tf_2O (0.125 mL, 0.75 mmol) was added dropwise to a stirred solution of Ph_3PO (0.415 g, 1.5 mmol) in anhydrous CH_2Cl_2 (4.0 mL) at 0 °C. After 10 min, the _N_-[2-(1_H_-indol-2-yl)phenyl]amide (0.5 mmol) was added in one portion and the reaction was stirred at r.t. for 15 min. The mixture was diluted with $CHCl_3$ (20 mL) and treated with sat. aq $NaHCO_3$ (10 mL). The organic phase was separated and washed with brine (10 mL), and the obtained organic solution was dried (anhydrous $MgSO_4$), filtered, and concentrated. The residue was purified by chromatography (EtOAc–PE, 2:1) to give the pure 11_H_-indolo[3,2-_c_]quinoline.

6-Methyl-11_H_-indolo[3,2-_c_]quinoline (1a)
White solid; mp 281–283 °C (EtOH).

IR (KBr): 1563, 1515, 1361, 742 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.73 (s, 1 H), 8.50 (d, *J* = 8.1 Hz, 1 H), 8.21 (d, *J* = 8.1 Hz, 1 H), 8.05 (d, *J* = 8.4 Hz, 1 H), 7.75–7.60 (m, 3 H), 7.50 (t, *J* = 7.2 Hz, 1 H), 7.36 (t, *J* = 7.2 Hz, 1 H), 3.08 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 154.2, 144.9, 139.8, 139.7, 128.6, 127.9, 124.9, 124.8, 122.3, 121.7, 121.5, 120.6, 116.2, 112.9, 111.7, 24.4.

ESI-MS: *m*/*z* = 233.2 [M + H]$^+$.

Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.81; H, 5.27; N, 12.01.

6-Ethyl-11*H*-indolo[3,2-*c*]quinoline (1b)
White solid; mp 215–217 °C (EtOAc–PE).

IR (KBr): 1567, 1514, 1361, 742 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.74 (s, 1 H), 8.52 (dd, *J* = 7.8, 1.8 Hz, 1 H), 8.16 (d, *J* = 7.8 Hz, 1 H), 8.09 (dd, *J* = 8.2, 0.9 Hz, 1 H), 7.76–7.60 (m, 3 H), 7.50 (td, *J* = 7.2, 1.2 Hz, 1 H), 7.35 (td, *J* = 7.8, 0.6 Hz, 1 H), 3.43 (q, *J* = 7.8 Hz, 2 H), 1.48 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.9, 144.9, 140.2, 138.8, 128.9, 127.9, 124.9, 124.8, 121.8, 121.5, 120.6, 116.3, 112.1, 111.8, 30.2, 12.2.

ESI-MS: *m*/*z* = 247.2 [M + H]$^+$.

Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.88; H, 5.75; N, 11.41.

11*H*-Indolo[3,2-*c*]quinoline (1c)
White solid; mp >300 °C (EtOH–PE).

IR (KBr): 1513, 1459, 1237, 734 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.73 (s, 1 H), 9.60 (s, 1 H), 8.53 (dd, *J* = 7.8, 1.2 Hz, 1 H), 8.32 (d, *J* = 7.8 Hz, 1 H), 8.24–8.09 (m, 1 H), 7.71–7.66 (m, 3 H), 7.53–7.47 (m, 1 H), 7.34 (t, *J* = 7.8 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 145.4, 144.8, 139.8, 138.8, 129.6, 128.0, 125.7, 125.6, 122.1, 121.9, 120.6, 120.1, 117.1, 114.3, 111.9.

ESI-MS: *m*/*z* = 219.2 [M + H]$^+$.

Anal. Calcd for $C_{15}H_{10}N_2$: C, 82.55; H, 4.62; N, 12.84. Found: C, 82.51; H, 4.77; N, 12.69.

6-Phenyl-11*H*-indolo[3,2-*c*]quinoline (1d)
White solid; mp 249–251 °C (acetone–PE).

IR (KBr): 1557, 1512, 1494, 1359, 737, 698 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.89 (s, 1 H), 8.59 (dd, *J* = 7.8, 1.2 Hz, 1 H), 8.14 (dd, *J* = 8.1, 0.9 Hz, 1 H), 7.86–7.81 (m, 2 H), 7.79–7.70 (m, 3 H), 7.68–7.60 (m, 3 H), 7.52 (d, *J* = 7.8 Hz, 1 H), 7.44 (td, *J* = 7.2, 1.2 Hz, 1 H), 7.13 (td, *J* = 7.7, 0.9 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 155.5, 145.0, 141.0, 140.7, 139.0, 129.4, 128.8, 128.5, 128.4, 125.6, 125.3, 121.9, 121.7, 121.0, 120.3, 116.3, 111.9.

ESI-MS: *m*/*z* = 295.2 [M + H]$^+$.

Anal. Calcd for $C_{21}H_{14}N_2$: C, 85.69; H, 4.79; N, 9.52. Found: C, 85.74; H, 4.79; N, 9.57.

6-(4-Methoxyphenyl)-11*H*-indolo[3,2-*c*]quinoline (1e)
White solid; mp 282–284 °C (EtOH–PE).

IR (KBr): 1610, 1504, 1249, 746 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.92 (s, 1 H), 8.51 (dd, *J* = 8.1, 1.2 Hz, 1 H), 8.12 (dd, *J* = 8.1, 0.9 Hz, 1 H), 7.82–7.66 (m, 5 H), 7.64 (d, *J* = 7.8 Hz, 1 H), 7.48–7.43 (m, 1 H), 7.22–7.14 (m, 3 H), 3.90 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.8, 155.2, 145.0, 141.0, 139.0, 133.1, 130.3, 129.3, 128.4, 125.4, 125.3, 121.9, 121.8, 121.1, 120.2, 116.2, 113.7, 111.9, 55.3.

ESI-MS: *m*/*z* = 325.1 [M + H]$^+$.

Anal. Calcd for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97; N, 8.64. Found: C, 81.33; H, 5.03; N, 8.49.

6-(4-Nitrophenyl)-11*H*-indolo[3,2-*c*]quinoline (1f)
Orange solid; mp >300 °C (acetone–PE).

IR (KBr): 1561, 1519, 1346, 746 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 13.00 (s, 1 H), 8.62–8.60 (m, 1 H), 8.49 (d, *J* = 8.7 Hz, 2 H), 8.19–8.11 (m, 3 H), 7.82–7.72 (m, 3 H), 7.53–7.45 (m, 2 H), 7.17 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.1, 147.7, 146.9, 144.8, 141.2, 139.1, 130.3, 129.5, 128.8, 126.2, 125.7, 123.8, 122.0, 121.1, 121.0, 120.6, 116.4, 112.1, 111.7.

ESI-MS: *m*/*z* = 340.2 [M + H]$^+$.

Anal. Calcd for $C_{21}H_{13}N_3O_2$: C, 74.33; H, 3.86; N, 12.38. Found: C, 74.29; H, 4.01; N, 12.28.

6-Ethoxy-11*H*-indolo[3,2-*c*]quinoline (1g)
White solid; mp 114–116 °C (EtOAc–PE).

IR (KBr): 1574, 1518, 1455, 1219, 744 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.63 (s, 1 H), 8.37–8.34 (m, 1 H), 8.05 (dd, *J* = 8.4, 0.6 Hz, 1 H), 7.96 (dd, *J* = 8.1, 0.9 Hz, 1 H), 7.71–7.55 (m, 1 H), 7.53–7.50 (m, 1 H), 7.47–7.34 (m, 3 H), 4.83 (q, *J* = 7.2 Hz, 2 H), 1.61 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 145.0, 141.8, 137.9, 128.3, 127.5, 124.9, 123.3, 122.6, 122.3, 121.2, 120.5, 115.5, 111.0, 105.0, 61.8, 14.8.

ESI-MS: *m*/*z* = 263.2 [M + H]$^+$.

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.68; H, 5.56; N, 10.42.

8-Chloro-6-methyl-11*H*-indolo[3,2-*c*]quinoline (1h)
White solid; mp >300 °C (EtOAc–PE).

IR (KBr): 1569, 1518, 1438, 1286, 722 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.82 (s, 1 H), 8.43 (d, *J* = 7.2 Hz, 1 H), 8.11 (d, *J* = 1.8 Hz, 1 H), 8.07 (d, *J* = 7.5 Hz, 1 H), 7.72–7.67 (m, 2 H), 7.61 (t, *J* = 6.9 Hz, 1 H), 7.46 (dd, *J* = 8.4, 2.1 Hz, 1 H), 3.01 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 154.3, 145.0, 140.7, 137.2, 128.6, 128.3, 125.0, 124.8, 123.4, 121.8, 120.7, 116.1, 113.2, 112.3, 24.3.

ESI-MS: *m*/*z* = 267.2 [M + H]$^+$.

Anal. Calcd for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.5. Found: C, 72.09; H, 4.24; N, 9.97.

6,8-Dimethyl-11*H*-indolo[3,2-*c*]quinoline (1i)
White solid; mp >300 °C (EtOH–PE).

IR (KBr): 1742, 1563, 1517, 1352, 797, 760 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.57 (s, 1 H), 8.46 (dd, *J* = 7.0, 0.9 Hz, 1 H), 8.05–8.00 (m, 2 H), 7.68 (td, *J* = 6.9, 1.5 Hz, 1 H), 7.62–7.57 (m, 2 H), 7.31 (dd, *J* = 8.1, 1.2 Hz, 1 H), 3.07 (s, 3 H), 2.53 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 154.3, 144.8, 139.9, 137.0, 129.3, 128.6, 127.8, 126.3, 124.7, 122.5, 121.7, 121.3, 116.3, 112.7, 111.4, 24.5, 21.3.

ESI-MS: m/z = 247.2 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.91; H, 5.88; N, 11.21.

8,9-Methylenedioxy-6-methyl-11*H*-indolo[3,2-*c*]quinoline (1j)
White solid; mp >300 °C (EtOH).

IR (KBr): 1570, 1515, 1473, 1298, 760 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.40 (d, J = 7.2 Hz, 1 H), 8.00 (d, J = 8.1 Hz, 1 H), 7.64–7.55 (m, 3 H), 7.23 (s, 1 H), 6.09 (s, 2 H), 2.99 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.6, 146.3, 144.1, 143.1, 139.1, 134.2, 128.6, 127.2, 124.7, 121.3, 116.5, 115.6, 113.5, 101.0, 100.5, 92.8, 24.3.

ESI-MS: m/z = 277.2 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.74; H, 4.46; N, 10.28.

6-Methyl-indolo[1,2-*c*]quinazoline (4)
Pale-yellow solid; mp 113–115 °C (EtOH).

IR (KBr): 1614, 1556, 1384, 756, 739 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (td, J = 8.4, 0.6 Hz, 2 H), 7.75 (d, J = 8.4 Hz, 1 H), 7.69 (dd, J = 8.4, 1.2 Hz, 1 H), 7.49 (td, J = 7.2, 1.5 Hz, 1 H), 7.42–7.36 (m, 2 H), 7.33–7.28 (m, 1 H), 7.04 (s, 1 H), 2.99 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.2, 138.8, 134.6, 131.5, 130.2, 128.7, 126.7, 126.6, 123.2, 122.4, 121.8, 120.5, 120.0, 114.6, 95.2, 25.2.

ESI-MS: m/z = 233.2 $[M + H]^+$.

Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.71; H, 5.27; N, 12.04

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Reference

(1) For a review, see: Lavrado, J.; Moreira, R.; Paulo, A. *Curr. Med. Chem.* **2010**, *17*, 2348.
(2) (a) Pousset, J.-L.; Martin, M.-T.; Jossang, A.; Bodo, B. *Phytochemistry* **1995**, *39*, 735. (b) Van Miert, S.; Hostyn, S.; Maes, B. U. W.; Cimanga, K.; Brun, R.; Kaiser, M.; Matyus, P.; Dommisse, R.; Lemiere, G.; Vlietinck, A.; Pieters, L. *J. Nat. Prod.* **2005**, *68*, 674.
(3) (a) Lu, C.-M.; Chen, Y.-L.; Chen, H.-L.; Chen, C.-A.; Lu, P.-J.; Yang, C.-N.; Tzeng, C.-C. *Bioorg. Med. Chem.* **2010**, *18*, 1948. (b) He, L.; Chang, H.-X.; Chou, T.-C.; Savaraj, N.; Cheng, C.-C. *Eur. J. Med. Chem.* **2003**, *38*, 101. (c) Chen, Y.-L.; Chung, C.-H.; Chen, I.-L.; Chen, P. H.; Jeng, H.-Y. *Bioorg. Med. Chem.* **2002**, *10*, 2705.
(4) (a) Dhanabal, T.; Sangeetha, R.; Mohan, P. S. *Tetrahedron* **2006**, *62*, 6258. (b) Nandha Kumar, R.; Suresh, T.; Mohan, P. S. *Tetrahedron Lett.* **2002**, *43*, 3327.
(5) (a) Kraus, G. A.; Guo, H. *Tetrahedron Lett.* **2010**, *51*, 4137. (b) Beres, M.; Timari, G.; Hajos, G. *Tetrahedron Lett.* **2002**, *43*, 6035. (c) Fresneda, P. M.; Molina, P.; Delgado, S. *Tetrahedron* **2001**, *57*, 6197. (d) Fresneda, P. M.; Molina, P.; Delgado, S. *Tetrahedron Lett.* **1999**, *40*, 7275.
(6) (a) Meyers, C.; Rombouts, G.; Loones, K. T. J.; Coelho, A.; Maes, B. U. W. *Adv. Synth. Catal.* **2008**, *350*, 465. (b) Jonckers, T. H. M.; Maes, B. U. W.; Lemiere, G. L. F.; Rombouts, G.; Pieters, L.; Haemers, A.; Dommisse, R. A. *Synlett* **2003**, 615.
(7) Agarwal, P. K.; Sawant, D.; Sharma, S.; Kundu, B. *Eur. J. Org. Chem.* **2009**, 292.
(8) Miki, Y.; Kuromatsu, M.; Miyatake, H.; Hamamoto, H. *Tetrahedron Lett.* **2007**, *48*, 9093.
(9) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, 620.
(10) Sakai, N.; Annaka, K.; Konakahara, T. *J. Org. Chem.* **2006**, *71*, 3653.
(11) Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 4160.
(12) (a) Alfonsi, M.; Acradi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem.* **2005**, *70*, 2265. (b) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610.
(13) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, *16*, 277.
(14) (a) Wu, M.; Wang, S. *Synthesis* **2010**, 587. (b) Liu, G.-S.; Yao, Y.-S.; Xu, P.; Wang, S.; Yao, Z.-J. *Chem. Asian J.* **2010**, *5*, 1382. (c) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *J. Org. Chem.* **2007**, *72*, 6270. (d) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *Org. Lett.* **2007**, *9*, 2003. (e) You, S.-L.; Kelly, J. W. *Org. Lett.* **2004**, *6*, 1681. (f) You, S.-L.; Kelly, J. W. *J. Org. Chem.* **2003**, *68*, 9506. (g) You, S.-L.; Razavi, H.; Kelly, J. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 83.
(15) CCDC 780631 and 793932 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.