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J. Org. Chem., Just Accepted Manuscript • DOI: 10.1021/acs.joc.6b03084 • Publication Date (Web): 03 Mar 2017 Downloaded from http://pubs.acs.org on March 3, 2017

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# One-Pot, Three-Component Assembly of Indoloquinolines: Total Synthesis of Isocryptolepine

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**ABSTRACT**: Indolo[3,2-c]quinolones are efficiently synthesized via an acid-mediated, one-pot, threecomponent condensation of arylhydrazines, *ortho*-aminoacetophenones, and triazines or nitriles. Synthetic application of this method is showcased by the concise synthesis of isocryptolepine alkaloid and a series of its synthetic analogs with demonstrated cancer cell antiproliferative activities.

# Introduction

The indoloquinoline heterocyclic system is frequently found in natural products isolated from plants used in traditional medicine.<sup>1</sup> Due to the broad spectrum of biological and pharmacological activities associated with compounds incorporating this structural skeleton, it has been recognized as an important privileged scaffold in drug discovery.<sup>2</sup> For example, isocryptolepine (cryptosanguinolentine, **1aa**), one of the four types of indoloquinoline

alkaloids isolated from West African plant *Cryptolepis sanguinolenta*,<sup>3</sup> has been investigated as a promising antimalarial and anticancer agent (Figure 1).<sup>4</sup> Due to its potential pharmacological applications, it has been the target of numerous synthetic efforts. The majority of the total syntheses of isocryptolepine and analogs reported to date exploited stepwise assembly of the two heterocyclic rings. Typically, a quinoline precursor would be used as a platform for installation of the pyrrole moiety,<sup>4d,5</sup> although alternate disconnection approaches are also known, including iodine-mediated intramolecular coupling, <sup>6</sup> electrocyclic cyclization, <sup>7</sup> transition metal-catalyzed tandem reactions,<sup>8</sup> and various acid-mediated annulations.<sup>9</sup> All previously reported synthetic routes required multistep linear sequences with isolation and purification of intermediate products, with the shortest known approach consisting of 3 steps from commercially available materials.<sup>10</sup> Herein we wish to report a metal-free threecomponent synthesis of isocryptolepine and its bioactive analogs, that involves sequential assembly of the indoloquinoline core in one-pot with single isolation operation.



Figure 1. Naturally indoloquinoline alkaloids isolated from Cryptolepis sanguinolenta.



**Scheme 1**. Kundu's retrosynthetic analysis of isocryptolepine involving formation of the quinoline and indole rings via modified Pictet-Spengler protocol and Fisher indolization, respectively.



**Scheme 2**. Synthetic approach to isocryptolepine analogs involving one-pot acylation of indoles with carboxylic acids or nitriles

# **Results and Discussion**

In 2009 Kundu and co-workers reported a novel and interesting synthetic approach to the indoloquinoline core of isocryptolepine alkaloid, which involved installation of the quinoline ring via oxidative Pictet-Spengler type reaction of *N*-arylmethanimine **3**.<sup>11</sup> The indole moiety in the latter compound was assembled via Fisher indolization of hydrazone **5**, prepared from ketone **7** and hydrazine **6** (Scheme 1). Although this strategy featured 4 linear steps involving isolation and purification of intermediate products (starting from commercially available precursors) and provided ~50% overall yield,<sup>11,12</sup> we felt that it can be greatly simplified and significantly shortened through designing of a cascade or sequential one-pot transformation protocol.

We have previously reported a sequential three-component heteroannulation reaction

leading to 3-aryl-2-quinolones that proceeds via a cascade transformation involving Fisher indole synthesis from hydrazines 2 and involves the use of polyphosphoric acid (PPA) as the reaction medium.<sup>13</sup> We have found that the P<sub>2</sub>O<sub>5</sub>-water ratio can be accurately tuned to optimal values (which usually range between 75 and 85%) to achieve the necessary acidity and anhydride activity of the medium. PPA also efficiently phosphorylates amino and hydroxyl groups in situ and converts them into good nucleofuges, facilitating cascade cationic transformations. Furthermore, it was demonstrated that carboxylic acids in the presence of PPA could serve as electrophiles in acylation reactions and related cyclization cascades.<sup>14</sup> We envisioned that these previously developed tools could be combined to craft a convenient route to indologuinolines **1**. Thus, hydrazone **9** readily available from acetophenone **8** and hydrazine **6** (step **A**, Scheme 2) would undergo the Fisher reaction (step **B**) to produce indole **10**. Next, acylation of the aniline moiety with carboxylic acid 13 or nitrile 14 (see Scheme 3) would afford amide (X = 0) or amidine (X = NH) **11**, which would spontaneously undergo a PPAassisted intramolecular Vilsmeier reaction to furnish indologuinoline **1**. Given our previous successful experience with PPA-assisted indole synthesis from hydrazines and acetophenones,<sup>10</sup> we anticipated that all of the steps in the proposed transformation could be performed in PPA in a sequential, one-pot mode. However, our attempts to engage ketones 8 in a condensation reaction with hydrazines 6 in PPA medium were unproductive. Formation of 9 was accompanied by significant polymerization processes, possibly originating from intermolecular homocondensation of *ortho*-aminosubstituted acetophenones **6**. Accordingly, a classical reaction medium, such as ethanol with catalytic amounts of acetic acid,<sup>12</sup> was employed in the first step to enable the desired cross-condensation to form hydrazones (9a-d). The latter, isolated and purified by crystallization, were exposed to PPA to produce the corresponding indoles **11**, which were subsequently treated *in situ* with acetic (**13b**), benzoic (**13c**), or caproic (13d) acids to provide isocryptolepine analogs 1ab-1bd in high yields (Scheme 3, Method I). Likewise, the reaction of hydrazones **9a**,**b** with nitriles **14b**,**c**,**e** afforded the corresponding indologuinolines as sole products in good yields (Scheme 3, Method II). After the successful preparation of substituted analogs, we attempted the synthesis of isocryptolepine via this method. To obtain a product such as **1aa** with the unsubstituted C6-position, it was necessary to use formic acid (13a) as the electrophile. Unfortunately, formic acid was incompatible with

the reaction conditions:<sup>15</sup> all our efforts resulted in decomposition of the starting materials. To overcome this limitation, we searched for an alternative electrophilic component that would permit the installation of the unsubstituted C-6 in the indoloquinoline core. Our previous work on PPA-assisted  $S_EAr$ -type cyclizations with triazines<sup>16</sup> inspired us to probe this heterocycle as a formic acid surrogate. To this end, a purified sample of indole **11a**, obtained as described above, was treated with triazine **15a** in PPA under the standard reaction conditions. Gratifyingly, isocryptolepine (**1aa**) was produced as the sole product in 83% yield. Furthermore, the PPA-mediated reaction between triazine **15a** and various hydrazones (**9a-g**) proceeded smoothly in one pot affording the corresponding indoloquinoline products in high yields (Scheme 3, Method **III**). An analogous reaction with symmetric 2,4,6-trisubstituted 1,3,5-triazines **15b-c** gave indoloquinolines substituted at C-6 (Scheme 3).



**Figure 2**. ORTEP drawing of compounds **1ea** (CCDC 1510030, left) and **1fa** (CCDC 1510031, right): showing atom-labeling schemes and 50% probability amplitude displacement ellipsoids (See SI for details)



**Scheme 3.** One-Step Synthesis of Isocryptolepine and Analogs from Hydrazones. Isolated yields of purified products are shown. Carboxylic acids **13** are employed in Method **I**, nitriles **14** are in Method **II**, triazines **15** in Method **III**. Methods **Ia** and **IIIa** employ a one-pot protocol

 starting directly from hydrazines **6** and acetophenones **8** without isolation of intermediate hydrazones **9**, but otherwise identical to Methods **I** and **III**, respectively.



**Scheme 4**. Synthetic approach to isocryptolepine analogs involving one-pot reaction of indoles with 1,3,5-triazines.

Formation of the indoloquinoline core was unambiguously proved by single crystal X-ray crystallography of compounds **1fa** and **1ea** (Figure 2). The proposed mechanism of this trans formation is outlined in Scheme 3. First, addition of triazine to the mixture of indole and PPA

produces species **16** (step **C**, Scheme 4). Ring opening of the dihydrotriazine (step **D**) and the subsequent intramolecular electrophilic attack of the resulting linear species **17** at C-3 of the indole (step **E**) furnishes the six-membered heterocyclic ring in **18**. Finally, proton transfer (step **F**), followed by neighboring group-assisted elimination (step **G**), affords isocryptolepine **1aa** (Scheme 4). Alternatively, species **18** could experience deprotonation at C-6a (step **H**) to provide intermediate product **20** further undergoing elimination and deprotonation sequence (Scheme 4).

With the two-linear step, two-pot triazine-based synthesis of isocryptolepine in hand, we next challenged ourselves to develop a single pot approach to this natural product. We reasoned that sub-stoichiometric amounts of acetic acid (13b) employed as a catalyst in step A would compromise step **C** in the synthesis by competing with triazine and producing 6-methylisocryptolepine analog 1ab (Scheme 2). On the other hand, formic acid (13a) would not survive exposure to PPA, as noted above. An attempt to use weaker non-nucleophilic acids, such as TFA also proved unfruitful, as the Fisher indolization (step **B**) did not proceed at all under these conditions. This prompted us to probe the condensation of commercially available 6a and 8a in refluxing ethanol in the presence of catalytic amounts of HCOOH. The reaction proceeded uneventfully and, upon completion, ethanol was evaporated to give crude hydrazone **9a**. The subsequent Fisher indolization was carried out in the same pot at 80 °C for 2 hrs, during which time all residual amounts of ethanol were chemically destroyed in the PPA medium via facile dehydration and liberation of ethylene gas. Likewise, formic acid (13a) was tracelessly decomposed by PPA. Using this modified one-pot approach, isocryptolepine alkaloid (1aa) was obtained in 81% overall yield. Further optimization revealed that the condensation step A could be performed in the absence of solvent and catalyst by simply stirring neat reactants at 120 °C for 10 min. Subsequent addition of PPA, followed by triazine (6a) shortly after, provided the natural product **1aa** in 82% yield. Several analogs were also prepared using this one-pot protocol, with yields comparable to those obtained using the twostep method (Scheme 3, Methods Ia, IIIa).

Because isocryptolepine is investigated as a potential anticancer agent, we evaluated this alkaloid and several of its synthetic analogs against a panel of six cancer cell lines that included the murine B16F10 melanoma and the human MCF-7 breast carcinoma, HS683 oligodendro-glioma as well as A549 non-small cell lung cancer, U373 glioblastoma and SKMEL-28

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melanoma cell lines (Table 1). The latter three cell lines have been shown to display various degrees of resistance to pro-apoptotic insults<sup>17</sup> and are thus good models of chemotherapy-resistant cancers associated with dismal prognoses. Isocryptolepine (**1aa**) exhibited the mean antiproliferative IC<sub>50</sub> value of 0.8  $\mu$ M, while its demethylated (R<sup>2</sup> = H) synthetic analogues **1ea** and **1fa** had the mean IC<sub>50</sub>'s of 1.2 mM each. Of note, analogue **1ga**, differing from isocryptolepine by the presence of two methoxy groups in the quinoline part of the molecule (R<sub>4</sub> = R<sub>5</sub> = OMe), was more potent than the natural alkaloid showing the mean IC<sub>50</sub> of 0.4  $\mu$ M.

Table 1. 50% in vitro growth inhibitory concentration (IC<sub>50</sub>;  $\mu$ M<sup>a</sup>) determined by the colorimetric MTT assay.

Compound	carcinoma		glioma		melanoma		Mean + SEM
	A549	MCF-7	U373	HS683	SKMEL-28	B16F10	
<b>1aa</b>	0.6	1.0	1.3	0.4	0.9	0.7	$0.8 \pm 0.1$
1ba	8	27	16	4	24	7	$14 \pm 4$
1ea	0.7	2.0	1.2	0.3	2.2	0.7	$1.2 \pm 0.3$
1fa	0.7	2.3	0.8	0.5	2.3	0.5	$1.2 \pm 0.4$
1ga	0.4	0.5	0.6	0.3	0.4	0.3	$0.4 \pm 0.05$

<sup>a</sup> Average concentration required to reduce the cell viability by 50% after 72 h treatment relative to a control as determined by MTT assay. Each experiment was performed once in sextuplicates.

# Conclusion

In conclusion, an expeditious metal-free approach to indoloquinolines involving a PPA-assisted cascade twofold heteroannulation has been developed. Three alternate routes for quinolone ring closure were demonstrated employing carboxylic acids, nitriles, and triazines as electrophilic components. The developed method was used for an efficient and concise (a single pot operation starting from inexpensive commercially available precursors) total synthesis of alkaloid isocryptolepine. A rapid increase of molecular complexity with up to three points of diversification allowed by this method presents a promising avenue for drug

discovery. The initial structure-activity studies made possible through our synthetic approach demonstrated the possibility of obtaining analogues more potent than the natural alkaloid.

# **Experimental Part**

#### **General Information**

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance-III spectrometer (400 or 100 MHz, respectively) equipped with BBO probe in CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub>, using TMS as internal standard. High-resolution mass spectra were registered with a Bruker Maxis spectrometer (electrospray ionization, in MeCN solution, using HCO<sub>2</sub>Na–HCO<sub>2</sub>H for calibration). Melting points were measured with a Stuart smp30 apparatus. All reactions were performed in oven-dried 5 mL round-bottomed flasks open to the atmosphere, employing overhead stirring. Reaction progress and purity of isolated compounds were controlled by TLC on Silufol UV-254 plates, eluting with EtOAc. Hydrazones **4a-g** were obtained from the corresponding arylhydrazines and *ortho*-aminoacetophenones according to published literature procedures.<sup>12</sup> All other reagents and solvents were purchased from commercial vendors and used as received.

#### **Experimental Procedures**

*General procedure for preparation of indoloquinolines* **1** *from arylhydrazones* **9** (General protocol **A**, combining Methods **I**, **II**, and **III**): Mixture of hydrazone **9** (1.0 mmol) and 80% polyphosphoric acid (PPA, 2.0 g) was stirred at 100 °C and acylating agent (**13**, **14** or **14**, 1.2 mmol) was added. The mixture was stirred at 100 °C for 30 min, then at 130 °C for 90 min (heating should be continued for 5 hr at 150 °C when nitriles **14** used as acylating agents or for 2 hr at 150 °C in reactions with 1,3,5-triphenyltriazine **15c**). The reaction mixture was poured out into water (50 mL) and neutralized with 25% aqueous ammonia. Formed precipitate was filtered out. Usually this material is sufficiently pure for further application, but for analytical purposes it can be additionally purified by Flash column chromatography on Silica gel, eluting with mixture acetone-benzene (1:3) doped with ammonia (one drop of per 10 mL of eluent).

 General procedure for preparation of indoloquinoline 1 from arylhydrazines 6 and acetophenones (7 or 8) (performing first step in ethanol/formic acid mixture, General protocol B): Reaction vessel was charged with arylhydrazine 2 (1.0 mmol) and *ortho*-amino-acetophenone (7 or 8) (1.0 mmol), ethanol (700  $\mu$ L) and formic acid (20 mg). The mixture was stirred at reflux for 30 min, and then the solvent was removed in vacuum. Polyphosphoric acid (80% PPA, 2.0 g) was added, after which the reaction, post-reaction work up, and isolation of the products were carried out in the same manner as described above in the procedure for General protocol **A**.

General procedure for preparation of indoloquinolines 1 from arylhydrazines 6 and acetophenones (7 or 8) (performing first step in neat, General protocol C, combining Methods Ia and IIIa): Reaction vessel was charged with arylhydrazine 6 (1.0 mmol) and *ortho*-aminoacetophenone (7 or 8) (1.0 mmol), and the mixture was heated at 120 °C for 10 min. Then, the mixture was cooled down to 100 oC, and polyphosphoric acid (80% PPA, 2.0 g) was added. The reaction, post-reaction work up, and isolation of the products were carried out in the same manner as described above in the procedure for General protocol **A**.

**5-Methyl-5***H***-indolo[3,2-c]quinoline** (isocryptolepine, **1aa**): <sup>18</sup> yield 193 mg (0.83 mmol, 83%) via Method **III**, 190 mg (0.82 mmol, 82%) via Method **IIIa**. Physical and spectral properties listed below are measured for the sample obtained via Method **III**. Yellowish crystals, m.p. 198-199 °C (EtOH),  $R_f$  0.17 (EtOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.91 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.23 (s, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.70 – 7.62 (m, 1H), 7.61 – 7.55 (m, 2H), 7.55 – 7.49 (m, 1H), 7.31 – 7.26 (m, 1H), 4.02 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 155.1, 153.9, 135.6, 135.4, 129.4, 126.5, 125.5, 125.2, 125.2, 121.4, 120.7, 119.2, 119.2, 117.6, 116.0, 77.2, 42.5; FT IR (NaCl, cm<sup>-1</sup>): 2372, 2340, 1650, 1597, 1451, 1347, 1320, 1226, 1111, 745; HRMS (TOF-ES): Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>2</sub> (M+H)<sup>+</sup> 233.1073, found 233.1075 (0.7 ppm).

**5,6-Dimethyl-5***H***-indolo[3,2-***c***]quinoline (1ab):<sup>19</sup> yield 194 mg (0.79 mmol, 79%) via Method I, 180 mg (0.73 mmol, 73%) via Method II. Physical and spectral properties listed below are measured for the sample obtained via Method I. Yellowish crystals, m.p. 235 °C (EtOH), R<sub>f</sub> 0.34 (EtOH); <sup>1</sup>H NMR (400 MHz, DMSO) \delta 8.75 (d,** *J* **= 7.9 Hz, 1H), 8.32 (dd,** *J* **= 13.1,** 

8.5 Hz, 2H), 7.96 (t, J = 7.8 Hz, 1H), 7.83 (t, J = 7.1 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 4.27 (s, 3H), 3.30 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO)  $\delta$  154.6, 152.0, 149.4, 137.1, 129.8, 126.7, 125.3, 125.2, 124.4, 121.5, 121.2, 120.2, 118.9, 118.1, 116.0, 36.2, 19.0; FT IR (NaCl, cm<sup>-1</sup>): 2924, 2848, 1735, 1587, 1456, 1432, 1342, 1243, 1077; HRMS (TOF-ES): Calcd. for C<sub>17</sub>H<sub>15</sub>N<sub>2</sub> (M+H)<sup>+</sup>: 247.1230, found 247.1233 (1.4 ppm).

 **5-Methyl-6-phenyl-5***H***-indolo[3,2-***c***]quinoline (1ac)**: yield 253 mg (0.82 mmol, 82%) via Method **I**, 225 mg (0.73 mmol, 73%) via Method **II**, 228 mg (0.74 mmol, 74%) via Method **III**. Physical and spectral properties listed below are measured for the sample obtained via Method **III**. Yellowish crystals, m.p. 258-262 °C (benzene), R<sub>f</sub> 0.27 (EtOAc/EtOH 2:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.76 (d, *J* = 7.9 Hz, 1H), 8.09 (d, *J* = 8.9 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.85 – 7.79 (m, 3H), 7.76 – 7.71 (m, 2H), 7.63 – 7.57 (m, 1H), 7.48 – 7.42 (m, 1H), 7.35 – 7.29 (m, 1H), 7.09 – 7.04 (m, 1H), 6.41 (d, *J* = 8.1 Hz, 1H), 4.32 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl3) δ 152.4, 145.4, 136.8, 132.4, 132.0, 131.4, 130.2 (2C), 130.1, 128.5 (2C), 128.3, 127.7, 127.3, 125.2, 122.8, 122.7, 120.7, 118.2, 115.5, 114.9, 54.8; FT IR (NaCl, cm<sup>-1</sup>): 3441, 3054, 2975, 1589, 1540, 1447, 1349, 1261, 1202, 1060, 1011; HRMS (TOF-ES): Calcd. for C<sub>22</sub>H<sub>17</sub>N<sub>2</sub> (M+H)<sup>+</sup>: 309.1386, found 309.1385 (0.4 ppm).

**5-Methyl-6-pentyl-5***H***-indolo[3,2-***c***]quinoline (1ad)**: yield 230 mg (0.76 mmol, 76%) via Method I. Yellowish crystals, m.p. 340-341 °C (EtOH), R<sub>f</sub> 0.02 (petroleum ether/ EtOAc, 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.33 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.56 – 7.40 (m, 3H), 7.26 – 7.16 (m, 2H), 4.26 (s, 3H), 3.33 (t, *J* = 8.2 Hz, 2H), 1.72 – 1.61 (m, 2H), 1.59 – 1.48 (m, 2H), 1.45 – 1.31 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  156.2, 144.2, 142.6, 136.4, 131.7, 127.3, 126.9, 124.7, 123.0, 121.9, 120.7, 117.8, 116.0, 115.3, 113.2, 37.2, 32.0, 32.0, 27.4, 22.4, 14.0.; FT IR (NaCl, cm<sup>-1</sup>): 2945, 2869, 1666, 1583, 1546, 1439, 1339, 1239, 1188, 1098; HRMS (TOF-ES): Calcd. for C<sub>21</sub>H<sub>23</sub>N<sub>2</sub> (M+H)<sup>+</sup>: 303.1856, found 303.1865 (2.9 ppm).

**11***H***-Indolo[3,2-***c***]<b>quinoline** (**1ba**):<sup>20</sup> yield 177 mg (0.81 mmol, 81%) via Method III, 174 mg (0.80 mmol, 80%) via Method IIIa. Physical and spectral properties listed below are measured for the sample obtained via Method III. Colorless crystals, m.p. 340-341 °C (EtOH), R<sub>f</sub> 0.19

 (EtOAc); <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  12.73 (s, 1H), 8.53 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.32 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 7.9 Hz, 1H), 7.78 – 7.65 (m, 3H), 7.55 – 7.45 (m, 1H), 7.34 (t, *J* = 7.3 Hz, 1H); <sup>13</sup>C NMR (101 MHz, DMSO)  $\delta$  145.4, 144.8, 139.8, 138.8, 129.5, 128, 125.7, 125.5, 122.1, 121.9, 120.6, 120.1, 117.1, 114.3, 111.8, 39.5; FT IR (NaCl, cm<sup>-1</sup>): 3047, 2775, 1571, 1519, 1462, 1373, 1341, 1242, 1158, 933, 771, 740; HRMS (TOF-ES): Calcd. for C<sub>15</sub>H<sub>11</sub>N<sub>2</sub> (M+H)<sup>+</sup> 219.0917, found 219.0917 (0.1 ppm).

**6-Methyl-11***H***-indolo[3,2-***c***]quinoline (1bb)**:<sup>18</sup> yield 179 mg (0.77 mmol, 77%) via Method I, 165 mg (0.71 mmol, 71%) via Method II, 181 mg (0.78 mmol, 78%) via Method III. Physical and spectral properties listed below are measured for the sample obtained via Method III. Colorless crystals, m.p. 208-210 °C (EtOH); R<sub>f</sub> 0.5 (EtOAc); <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.90 (s, 1H), 8.52 (dd, *J* = 8.0, 0.9 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.67 – 7.63 (m, 1H), 7.52 (dd, *J* = 11.2, 4.0 Hz, 1H), 7.37 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.10 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO) δ 154.0, 143.3, 140.3, 138.9, 128.6, 127.3, 125.4, 125.3, 122.3, 122.1, 121.6, 121.0, 116.0, 113.0, 112.0, 22.5; FT IR (NaCl, cm<sup>-1</sup>): 3054, 2932, 2853, 1599, 1555, 1452, 1359, 1114; HRMS (TOF-ES): Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>2</sub> (M+H)<sup>+</sup> 233.1073, found 233.1074 (0.2 ppm).

**6-Phenyl-11***H***-indolo[3,2-c]quinoline (1bc)**:<sup>21</sup> yield 238 mg (0.81 mmol, 81%) via Method I, 209 mg (0.71 mmol, 71%) via Method II, 223 mg (0.76 mmol, 76%) via Method III. Physical and spectral properties listed below are measured for the sample obtained via Method III. Colorless crystals, m.p. 248-250 °C (EtOH),  $R_f$  0.30 (petroleum ether/ EtOAc 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.24 (s, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 8.24 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.94 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.62 – 7.57 (m, 2H), 7.50 – 7.33 (m, 6H), 7.17 – 7.12 (m, 1H); <sup>13</sup>C NMR (101 MHz, DMSO) δ 156.9, 145.3, 141.8, 140.3, 139.4, 129.1, 129.0 (2C), 128.9, 128.7, 128.6 (2C), 125.6, 125.6, 122.8, 121.9, 121.8, 120.8, 116.8, 113.4, 111.8; FT IR (NaCl, cm<sup>-1</sup>): 3172, 3054, 2917, 2843, 1560, 1530, 1501, 1501, 1452, 1359, 1320, 1241, 1222; HRMS (TOF-ES): Calcd. for C<sub>21</sub>H<sub>15</sub>N<sub>2</sub> (M+H)<sup>+</sup>: 295.1230, found 295.1237 (2.4 ppm).

**6-Pentyl-11***H***-indolo[3,2-***c***]quinoline (1bd)**: yield 233 mg (0.81 mmol, 81%) via Method I. Colorless crystals, m.p. 147-152 °C (benzene), R<sub>f</sub> 0.32 (petroleum ether/EtOAc 1:1); <sup>1</sup>H NMR

 $(400 \text{ MHz}, \text{CDCl}_3) \delta 11.92 \text{ (s, 1H)}, 8.33 \text{ (dd, } J = 21.9, 8.2 \text{ Hz}, 2\text{H}), 8.19 \text{ (d, } J = 7.6 \text{ Hz}, 1\text{H}), 7.61 \text{ (t, } J = 7.0 \text{ Hz}, 2\text{H}), 7.52 - 7.36 \text{ (m, 3H)}, 3.58 \text{ (t, } J = 7.9 \text{ Hz}, 2\text{H}), 2.10 - 1.96 \text{ (m, 2H)}, 1.57 - 1.43 \text{ (m, 2H)}, 1.35 - 1.24 \text{ (m, 2H)}, 0.80 \text{ (t, } J = 7.2 \text{ Hz}, 3\text{H}); ^{13}\text{C} \text{ NMR} (101 \text{ MHz}, \text{CDCl}_3) \delta 159.9, 145.3, 141.4, 139.2, 128.6, 128.5, 125.4, 125.3, 123.0, 122.0, 121.5, 121.4, 116.7, 113.7, 111.9, 38.1, 32.4, 28.9, 22.7, 14.1; FT IR (NaCl, cm<sup>-1</sup>): 3069, 2959, 2862, 1563, 1515, 1449, 1360, 1249; HRMS (TOF-ES): Calcd. for C<sub>20</sub>H<sub>21</sub>N<sub>2</sub> (M+H)<sup>+</sup>: 289.1699, found 289.1703 (1.4 ppm).$ 

**6-(Pyridin-3-yl)-11***H***-indolo[3,2-***c***]quinoline (1be)**: yield 186 mg (0.63 mmol, 63%) via Method **II**. Colorless crystals, m.p. 300-302 °C (EtOH), R<sub>f</sub> 0.24 (EtOAc), <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.98 (s, 1H), 9.04 (d, *J* = 2.0 Hz, 1H), 8.83 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.60 (dd, *J* = 8.2, 1.1 Hz, 1H), 8.26 (dt, *J* = 7.8, 1.9 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.83 – 7.66 (m, 4H), 7.47 (dd, *J* = 12.2, 5.5 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H); <sup>13</sup>C NMR (101 MHz, DMSO) δ 152.5, 149.9, 149.4, 145.0, 141.1, 139.1, 136.4, 136.3, 129.5, 128.7, 126.0, 125.6, 123.6, 122.0, 121.4, 120.6, 120.5, 116.3, 112.1; FT IR (NaCl, cm<sup>-1</sup>): 3054, 2936, 2373, 2255, 1560, 1520, 1457, 1364, 1251, 1212, 1026; HRMS (TOF-ES): Calcd. for C<sub>20</sub>H<sub>14</sub>N<sub>3</sub> (M+H)<sup>+</sup>: 296.1182, found 296.1188 (2.03 ppm).

**8-Methyl-11***H***-indolo[3,2-***c***]<b>quinoline** (**1ca**):<sup>22</sup> yield 200 mg (0.86 mmol, 86%) via Method III. Colorless crystals, m.p. 305-311 °C (EtOH), R<sub>f</sub> 0.24 (petroleum ether/ EtOAc 4:1); <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.59 (s, 1H), 9.54 (s, 1H), 8.50 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 7.77 – 7.64 (m, 2H), 7.61 (dd, *J* = 8.1, 4.6 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 2.52 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO) δ 145.4, 144.7, 139.8, 137.0, 129.5, 129.4, 127.9, 126.9, 125.6, 122.1, 122.0, 119.8, 117.2, 114.1, 111.5, 21.2; FT IR (NaCl, cm<sup>-1</sup>): 3042, 2773, 2366, 1570, 1363, 1239; HRMS (TOF-ES): Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>2</sub> (M+H)<sup>+</sup>: 233.1073, found 233.1076 (1.3 ppm);

**6,8-Dimethyl-11***H***-indolo**[**3,2-***c***]<b>quinoline** (**1cb**):<sup>23</sup> yield 202 mg (0.82 mmol, 82%) via Method I. Colorless crystals, m.p. 270-272 °C (benzene), R<sub>f</sub> 0.15 (EtOAc); <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.58 (s, 1H), 8.45 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.02 (d, *J* = 7.4 Hz, 2H), 7.76 – 7.56 (m, 4H), 7.32 (dd, *J* = 8.2, 1.0 Hz, 1H), 3.07 (s, 3H), 2.54 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO) δ 154.7, 144.9, 140.5, 137.5, 130.0, 128.7, 128.5, 126.9, 125.3, 123.0, 122.3, 121.8, 116.7, 113.2, 112.0, 24.8, 21.8; FT IR (NaCl, cm<sup>-1</sup>): 3157, 3059, 2922, 2775, 1594, 1569, 1516, 1442, 1359, 1300,

1251, 1207, 1021, 1002; HRMS (TOF-ES): Calcd. for C<sub>17</sub>H<sub>15</sub>N<sub>2</sub> (M+H)+: 247.1230, found 247.1236 (2.42 ppm).

8-Methyl-6-phenyl-11*H*-indolo[3,2-c]quinoline (1cc): yield 231 mg (0.75 mmol, 75%) via Method I, 222 mg (0.72 mmol, 72%) via Method Ia. Physical and spectral properties listed below are measured for the sample obtained via Method I. Colorless crystals, m.p. 231-233 °C (EtOH); R<sub>f</sub> 0.56 (petroleum ether/EtOAc 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.83 (br. s, 1H), 8.30 (d, *J* = 8.1 Hz, 1H), 8.20 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.88 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.67 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.60 – 7.49 (m, 5H), 7.36 (d, *J* = 0.7 Hz, 1H), 7.24 (dd, *J* = 8.3, 1.2 Hz, 1H), 2.37 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 156.6, 145.4, 141.4, 140.8, 137.2, 130.4, 129.8, 129.2, 129.1(2C), 128.6(2C), 128.6, 127.1, 125.7, 123.1, 122.0, 120.9, 116.4, 113.2, 111.1, 21.8; FT IR (NaCl, cm<sup>-1</sup>): 2931, 2366, 1642, 1563, 1442, 1336, 1225, 1119; HRMS (TOF-ES): Calcd. for C<sub>22</sub>H<sub>17</sub>N<sub>2</sub> (M+H)<sup>+</sup>: 309.1386, found 309.1391 (1.5 ppm).

**5,8-Dimethyl-5***H***-indolo[3,2-c]quinoline** (**1da**): yield 194 mg (0.79 mmol, 79%) via Method **III**. Yellowish crystals, m.p. 184-188 °C (benzene),  $R_f 0.07$  (EtOH); <sup>1</sup>H NMR (400 MHz, CDCl3)  $\delta$ 8.84 (d, *J* = 7.8 Hz, 1H), 8.32 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.67 – 7.43 (m, 4H), 7.24 (d, *J* = 8.3 Hz, 1H), 3.99 (s, 3H), 2.44 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl3)  $\delta$  151.3, 149.9, 136.6, 135.4, 130.6, 129.6, 128.1, 125.6, 125.4, 124.6, 120.3, 119.4, 117.5, 116.4, 116.2, 42.7, 21.8; FT IR (NaCl, cm<sup>-1</sup>): 3049, 2917, 1653, 1609, 1452, 1334, 1227, 1124; HRMS (TOF-ES): Calcd. for C<sub>17</sub>H<sub>15</sub>N<sub>2</sub> (M+H)+: 247.1230, found 247.1236 (2.4 ppm).

**5,6,8-Trimethyl-5***H***-indolo[3,2-***c***]quinoline (1db):<sup>19</sup> yield 231 mg (0.75 mmol, 75%) via Method I. Yellowish crystals, m.p. 182-184 °C (benzene), R\_f 0.10 (EtOH); <sup>1</sup>H NMR (400 MHz, DMSO) \delta 8.72 (dd,** *J* **= 7.9, 0.9 Hz, 1H), 8.07 (d,** *J* **= 8.6 Hz, 1H), 7.95 (s, 1H), 7.77 (t,** *J* **= 7.7 Hz, 1H), 7.64 (dd,** *J* **= 17.2, 7.8 Hz, 2H), 7.24 (d,** *J* **= 8.0 Hz, 1H), 4.09 (s, 3H), 3.16 (s, 3H), 2.51 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO) \delta 152.3, 151.2, 148.6, 136.5, 129.1, 128.5, 126.3, 126.3, 124.6, 123.8, 121.1, 120.7, 118.0, 117.5, 115.3, 35.6, 21.6, 18.4; FT IR (NaCl, cm<sup>-1</sup>): 3062, 2897, 1590, 1435, 1429, 1336, 1243, 1215; HRMS (TOF-ES): Calcd. for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub> (M+H)+: 261,1386 found 261.1393 (2.7 ppm).** 

**5,8-Dimethyl-6-phenyl-5***H***-indolo[3,2-***c***]quinoline (1dc): yield 229 mg (0.71 mmol, 71%) via Method I, 219 mg (0.68 mmol, 68%) via Method Ia. Physical and spectral properties listed below are measured for the sample obtained via Method I. Yellowish crystals, m.p. 234-236 °C (benzene), R\_f 0.15 (petroleum ether/EtOAc, 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 9.04 (dd,** *J* **= 8.0, 1.0 Hz, 1H), 7.85 (d,** *J* **= 8.2 Hz, 1H), 7.78 (d,** *J* **= 8.4 Hz, 1H), 7.75 – 7.59 (m, 5H), 7.48 (dd,** *J* **= 7.7, 1.6 Hz, 2H), 7.24 (dd,** *J* **= 8.1, 1.2 Hz, 1H), 6.26 (s, 1H), 3.84 (s, 3H), 2.26 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) \delta 153.1, 147.7, 136.5, 134.0, 130.1, 129.6, 129.6 (2C), 129.3, 128.6 (2C), 128.3, 127.5, 126.4, 125.2, 125.0, 121.6, 120.4, 118.5, 117.2, 116.5, 37.1, 21.7; FT IR (NaCl, cm<sup>-1</sup>): 2931, 2366, 1659, 1439, 1339, 1260, 1032; HRMS (TOF-ES): Calcd. for C<sub>23</sub>H<sub>19</sub>N<sub>2</sub> (M+H)<sup>+</sup>: 323.1543, found 323.1550 (2.2 ppm).** 

**2-Methoxy-11***H***-indolo[3,2-***c***]quinoline (1ea):<sup>9a</sup> yield 176 mg (0.71 mmol, 71%) via Method III, 166 mg (0.67 mmol, 67%) via Method IIIa.** Physical and spectral properties listed below are measured for the sample obtained via Method III. Colorless crystals, m.p. 300-301 °C (EtOH), Rf 0.21 (EtOAc); <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.56 (s, 1H), 9.45 (s, 1H), 8.29 (d, *J* = 7.7 Hz, 1H), 8.04 (d, *J* = 9.1 Hz, 1H), 7.96 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.49 (t, *J* = 8.1 Hz, 1H), 7.41 – 7.26 (m, 2H), 3.99 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO) δ 157.0, 142.2, 140.0, 139.4, 138.7, 130, 125.5, 121.9, 120.4, 120.1, 119.4, 117.7, 114.3, 111.8, 101.3, 55.6; FT IR (NaCl, cm<sup>-1</sup>): 3042, 2827, 1529, 1462, 1378, 1247, 1211, 949, 818, 740, 557; HRMS (TOF-ES): Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>2</sub>O (M+H)<sup>+</sup>: 249.1022, found 249.1026 (1.6 ppm).

**2,3-Dimethoxy-11***H***-indolo**[**3,2-***c***]<b>quinoline** (**1fa**):<sup>9a</sup> yield 222 mg (0.80 mmol, 80%) via Method III, 214 mg (0.77 mmol, 77%) via Method IIIa. Physical and spectral properties listed below are measured for the sample obtained via Method III. Colorless crystals, m.p. 320-321 °C (EtOH), R<sub>f</sub> 0.05 (EtOAc); <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  12.37 (s, 1H), 9.38 (s, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 7.93 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.53 (s, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO)  $\delta$  150.6, 148.7, 142.2, 142.0, 139.7, 138.7, 125.1, 122.1, 120.2, 119.8, 113.5, 111.5, 111.1, 109.2, 101.2, 55.7, 55.5; FT IR (NaCl, cm<sup>-1</sup>): 3005, 838,2367,2346, 1629, 1493, 1425, 1263, 1226, 1200, 1179, 834, 751; HRMS (TOF-ES): Calcd. for C<sub>17</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 279.1128, found 279.1122, (2.1 ppm).

**2,3-Dimethoxy-5-methyl-5***H***-indolo[3,2-***c***]quinoline (1ga): yield 237 mg (0.81 mmol, 81%) via Method III, 231 mg (0.79 mmol, 79%) via Method IIIa. Physical and spectral properties listed below are measured for the sample obtained via Method III. Yellowish crystals, m.p. 276-278 °C (EtOH), R<sub>f</sub> 0.13 (EtOH); <sup>1</sup>H NMR (400 MHz, DMSO) δ 9.28 (s, 1H), 8.11 (s, 1H), 8.09 (d,** *J* **= 7.7 Hz, 1H), 7.73 (d,** *J* **= 8.0 Hz, 1H), 7.43 (s, 1H), 7.40 (d,** *J* **= 7.8 Hz, 1H), 7.20 (t,** *J* **= 7.4 Hz, 1H), 4.29 (s, 3H), 4.04 (s, 3H), 4.01 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO) δ 155.1, 152.9, 151.3, 148.1, 136.7, 131.1, 125.5, 125.1, 120.4, 119.6, 119.3, 117.9, 115.4, 103.5, 99.6, 56.1, 55.8, 42.6; FT IR (NaCl, cm<sup>-1</sup>): 3005, 2361, 2340, 1639, 1514, 1430, 1352, 1273, 1226, 1054, 813; HRMS (TOF-ES): Calcd. for C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 293.1285, found 293.1282 (0.8 ppm).** 

# **Cancer Cell Growth Inhibition**

Material and Methods (Cell culture and growth inhibitory evaluation).

Cell lines used to evaluate the growth inhibitory effects of the compounds were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA), the European Collection of Cell Culture (ECACC, Salisbury, UK) and the Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ, Braunschweig, Germany). The human cell lines breast carcinoma MCF-7 (DSMZ ACC107), oligodendroglioma Hs683 (ATCC HTB138), non-small cell lung cancer A549 (DSMZ ACC107), glioblastoma U373 cells (ECACC 08061901), melanoma SKMEL-28 (ATCC HTB72) and the murine melanoma B16F10 (ATCC CRL-6475) cells were cultured in RPMI supplemented with 10% FBS (GIBCO code 10270106), 4mM glutamine (Lonza code BE17-605E), 100 µg/mL gentamicin (Lonza code 17-5182), and penicillin-streptomycin (200 units/ml and 200 µg/ml) (Lonza code 17-602E). Cell lines were cultured in flasks, maintained and grown at 370 C, 95% humidity, 5% CO2. Antiproliferative effects of the compounds on these cell lines were evaluated through the colorimetric assay MTT.<sup>24</sup> Briefly, cells were trypsinized and seeded in 96 well plates. Prior to treatment compounds were dissolved in DMSO at a concentration of 10mM. After 24h, cells were treated with the compounds at different concentrations ranging from 10nM to 100 µM or left untreated for 72 h. Cell viability was estimated by means of the MTT - (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (Sigma, Bornem, Belgium) mitochondrial reduction into formazan in living cells as

previously described (Mosmann, 1983). The optical density of the untreated control was normalized as 100% of viable cells allowing determination of the concentration that reduced their global growth by 50%. The results are shown in Table 1.

## Acknowledgements

This project received financial support from the Ministry of Education and Science of the Russia in the framework of the State Assignment to the Higher Education Institutions (grant  $#4.1196.2017/\Pi$ 4). Financial support from the Russian Science Foundation (grant #14-13-01108, Chemistry) is gratefully acknowledged.

# **Supporting Information**

<sup>1</sup>H, <sup>13</sup>C NMR, and HRMS spectral charts for new compounds, X-ray crystallography information, and CIF files. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

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# One-Pot, Three-Component Assembly of Indoloquinolines: Total Synthesis of Isocryptolepine

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# TOC graphics for jo-2016-03084

