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Synthesis of novel indolo[2,3-*c*]quinolinones via Ugi-4CR/palladium-catalyzed arylation

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ABSTRACT

In this letter, an expedient method was developed for the construction of novel indolo[2,3-*c*]quinolinone derivatives via palladium-catalyzed arylation of Ugi adducts obtained from the reaction of indole-2-carboxylic acid, various aromatic aldehydes, 2-bromoanilines, and isocyanides. The reaction proceeded efficiently with various starting materials to produce the indoloquinolinone scaffolds in good yields.

1. Introduction

Fused indole-quinoline derivatives are significant heterocyclic compounds due to their abundance in a wide spectrum of pharmaceuticals and natural products. For instance, naturally occurring indoloquinoline alkaloids; cryptolepine (Fig. 1, **A**), neocryptolepine (Fig. 1, **B**), and 5,10-dihydro-11*H*-indolo[3,2-*b*]quinolin-11-one (Fig. 1, **C**) extracted from the roots of *Cryptolepis sanguinolenta*[1,2] have shown various biological properties, such as antimalarial,[3,4] antibacterial, and antifungal,[5,6] cytotoxicity, and antiplasmodial activities.[7] On the other hand, studying this class of heterocyclic rings elucidated the importance and necessity of indoloquinolines in drug discovery[8] and among them indolo[2,3-*c*]quinolinone derivatives (Fig. 1, **D**) attracted our attention because they possess remarkable properties. Some derivatives prepared by Fryer et al.[9] exhibited anti-tumor activity by suppressing the growth of transplantable tumors. Also antitumor activity of these heterocycles has been separately proved by Fukushima et al.[10] and Grunberg et al.[11] In addition, indolo[2,3-*c*]quinolinone derivatives have shown good inhibition towards tubulin polymerization.[12]

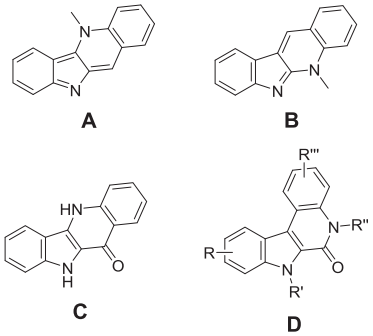

Fig. 1. Cryptolepine **A**, neocryptolepine **B**, 10-dihydro-11*H*-indolo[3,2-*b*]quinolin-11-one **C**, and indolo[2,3-*c*]quinolinone derivatives **D**.

In spite of the fact that indolo[2,3-*c*]quinolinones are very important, few efficient synthetic methods have been reported. Some of them are based on photochemical reactions;[13] oxidative photochemical cyclization of amides by Kanaoka et al.,[13a] photostimulated intramolecular S_{RN}^1 reactions with *N*-(2-chlorophenyl)-1*H*-indole-2-carboxamides by Vaillard et al.,[13b] and recently, sequential photocyclizations of 3-(2-azidophenyl)-*N*-phenylacrylamides by Li et al.[13c] 5,7-Dihydro-6*H*-indolo[2,3-*c*]quinolin-6-one derivatives were synthesized through the reaction of 1-methyl-3-formyloxindole with phenylhydrazines by Tokmakov et al.[14] Apart from these methods, Hostyn et al.[15] described a procedure

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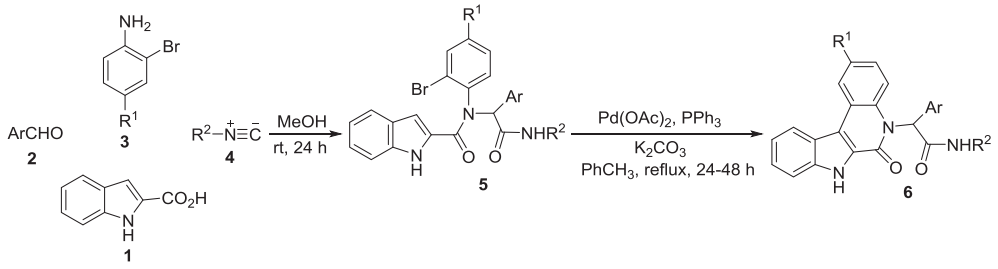
based on Pd-catalyzed intramolecular arylation of 3-(2-bromophenylamino)quinolones under microwave irradiation.

Focusing on the above mentioned properties of indolo[2,3-*c*]quinolinones[9–12] and also lack of diverse reports in the literature reveals that they are still highly desired. Therefore, following our previous works on the multicomponent reactions and synthesis of new *N*-heterocyclic compounds,[16] a two-step approach toward the synthesis of novel indolo[2,3-*c*]quinolinone derivatives **6** is reported via palladium-catalyzed arylation of Ugi adducts obtained from the reaction of indole-2-carboxylic acid **1**, aromatic aldehydes **2**, 2-bromoanilines **3**, and isocyanides **4** (Scheme 1).



Scheme 1. Synthesis of indolo[2,3-*c*]quinolinone derivatives **6**.

2. Results and discussion

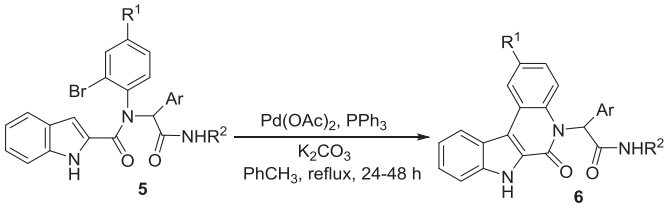
To obtain the title compounds **6**, we began our studies by the preparation of several Ugi adducts **5**. It was found that all compounds **5** were easily prepared by the reaction of indole-2-carboxylic acid **1**, various aromatic aldehydes **2**, 2-bromoanilines **3**, and isocyanides **4** in methanol at ambient temperature in the absence of any catalysts or additives within 24 h (Scheme 1). It is worthy to mention that after completion of the reaction, the precipitated products **5** were filtered off and used for further reaction without any purification (Table 1, **5a**–**j**).

this regard, a wide range of metal-catalyzed procedures have been developed.[17] Considering our previous experience in Pd-catalyzed intramolecular preparation of novel quinolinones;[16b] herein, we investigated Pd-catalyzed synthesis of indolo[2,3-*c*]quinolinone derivatives **6a**–**j** from versatile starting materials bearing indole moiety **5a**–**j** (Table 1).

In the search for optimized conditions, we selected *N*-(2-bromophenyl)-*N*-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-1*H*-indole-2-carboxamide (**5a**) as a model substrate and the C-arylation reaction was conducted in the presence of different palladium sources, such as palladium acetate $Pd(OAc)_2$, palladium(II) chloride $PdCl_2$, and tetrakis(triphenylphosphine)palladium(0) $Pd[(PPh)_3]_4$ in various solvents as summarized in Table 2. Our studies demonstrated that using triphenyl phosphine (PPh_3) and potassium carbonate (K_2CO_3) is essential for the desired C3-arylation of indole ring to proceed. As can be seen in Table 2, it was perceived that $Pd(OAc)_2$ catalyzed the reaction much better than $PdCl_2$ and Pd $[(PPh)_3]_4$ and 5 mol % of catalyst was enough for the above mentioned reaction.

Our solvent screening indicated the significance of solvent and its effect on the yield of reaction. Among tested solvents; dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile

Table 1
Synthesis of indolo[2,3-*c*]quinolinone derivatives **6a**–**j**



Entry	R^1	Ar	R^2	Ugi adduct **5**	Yield (%)[a]	Product **6**	Yield (%)[a]	Mp (°C)
1	H	C_6H_5–	Cyclohexyl	**5a**	92	**6a**	85	205–206
2	H	3-OMe–C_6H_4–	Cyclohexyl	**5b**	95	**6b**	67	233–235
3	Me	3,4-diOMe–C_6H_3–	1,1,3,3-Tetramethylbutyl	**5c**	83	**6c**	65	249–250
4	Me	3,5-diOMe–C_6H_3–	Cyclohexyl	**5d**	93	**6d**	52	243–245
5	H	4-Me–C_6H_4–	Cyclohexyl	**5e**	86	**6e**	55	202–203
7	Me	4-Br–C_6H_4–	Cyclohexyl	**5f**	88	**6f**	82	>250
8	Me	4-Br–C_6H_4–	1,1,3,3-Tetramethylbutyl	**5g**	66	**6g**	51	>250
8	H	4-Cl–C_6H_4–	Cyclohexyl	**5h**	90	**6h**	76	>250
9	H	3-Cl–C_6H_4–	Cyclohexyl	**5i**	94	**6i**	55	>250
10	H	1-Naphthyl	Cyclohexyl	**5j**	83	**6j**	69	208–210

[a] Isolated yields.

In the next step, we investigated the further C-3 arylation reaction of compounds **5**. Selective C-2 and C-3 arylation of indoles is one of the most significant and attractive tools for carbon–carbon bond formation. At this juncture, direct C-arylation of free indoles have led to many pioneering advances and is a fundamental objective for the advancement of substituted indole synthesis.[17] In

(CH_3CN), and toluene ($PhCH_3$); toluene was the best choice. It is worth mentioning that in all cases, temperature had a key role and the reaction needed to be heated at reflux. In this manner, carrying out the model reaction in the presence of 5 mol % of $Pd(OAc)_2$ in toluene under reflux conditions led to the formation of **6a** within 24 h in 85% yield. The structure of **6a** was confirmed by analytical

Table 2
Optimization of reaction conditions to synthesize compound **6a**

Entry	Solvent	Pd source[a]	Yield (%)[b]
1	DMSO	$Pd(OAc)_2$	12
2	DMF	$Pd(OAc)_2$	62
3	DMF	$Pd[(PPh)_3]_4$	43
4	CH_3CN	$Pd(OAc)_2$	42
5	$PhCH_3$	$Pd(OAc)_2$	85
6	$PhCH_3$	$PdCl_2$	22
7	$PhCH_3$	$Pd[(PPh_3)]_4$	47

[a] The model reaction was carried out in the presence of Pd catalyst (5 mol %), PPh_3 (15 mol %), and K_2CO_3 (3 mmol) under reflux.
[b] Isolated yields.

information obtained from mass spectrometry, IR, and NMR spectroscopies.

Then, in order to show the generality and scope of this effective protocol, we utilized various Ugi adducts **5** and achieved the C-3 arylation reaction under the optimized conditions to obtain different indolo[2,3-*c*]quinolinones **6** (Table 1, Scheme 1). As can be seen in Table 1, all derivatives underwent facile C-arylation and electronic effects of substituents attached to the aromatic rings did not influence the arylation reaction significantly.

3. Conclusion

In conclusion, we have described a facile, efficient, and user-friendly method for the synthesis of indolo[2,3-*c*]quinolinone derivatives. At first, various Ugi adducts were prepared by the 4-CR of indole-2-carboxylic acid, aromatic aldehydes, 2-bromoanilines, and isocyanides. Then, palladium-catalyzed C-3 arylation of indole moiety led to the formation of corresponding products in good yields. It should be noted that all reactions showed a good tolerance toward various starting materials having electron-donating and electron-withdrawing substituents. Also it is worth mentioning that C-3 arylation of indole derivatives was successfully achieved without disturbance and protection of the N–H function.

4. Experimental section

4.1. General

Melting points were taken on a *Kofler* hot stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on *Bruker FT-500* and *FT-400*, using TMS as an internal standard. The IR spectra were obtained on a *Nicolet Magna FTIR 550* spectrophotometer (in KBr). Mass spectra were determined on an *Agilent Technology* (HP) mass spectrometer operating at an ionization potential of 70 eV. The elemental analysis was performed with an Elementar Analysensystem GmbH *VarioEL* CHNS mode. All reagents and solvents were obtained from Merck and Aldrich and used without any purification. Silica gel 60 (0.040–0.063 mm) were used for column chromatography. Thin layer chromatography (TLC) was performed using silica gel 60/Kieselguhr F_{254} precoated on Aluminum sheets (thickness 0.2 mm), commercially available from Merck.

4.2. Synthesis of indolo[2,3-*c*]quinolinone derivatives 6

4.2.1. General procedure. A mixture of indole-2-carboxylic acid **1** (1 mmol), 2-bromo aniline **2** (1 mmol), aromatic aldehyde **3** (1 mmol), and isocyanide **4** (1.2 mmol) were dissolved in methanol (10 mL) and stirred at room temperature for 24 h. After completion of reaction, the precipitated Ugi product **5** was filtered off, washed with petroleum ether, and used for further reactions. Then, a mixture of Ugi product **5** (1 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (15 mol %), and K_2CO_3 (3 mmol) in toluene (10 mL) was heated at reflux for 24–48 h. After that the mixture was filtered off and the solvent was removed under reduced pressure. The resulting residue was extracted with ethyl acetate and purified by column chromatography (ethyl acetate/petroleum ether=1/3 as eluent and silica gel as stationary phase).

*4.2.1.1. N-Cyclohexyl-2-(6-oxo-6,7-dihydro-5H-indolo[2,3-c]quinolin-5-yl)-2-phenylacetamide **6a**.* Yield: 85%; mp 205–206 °C; IR (KBr, cm^{-1}) ν: 3406, 3254 (NH), 1662, 1634 (CO). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.21–1.96 (m, 10H, cyclohexyl), 4.07 (m, 1H, NCH, cyclohexyl), 5.95 (s, 1H, CH), 6.76–7.63 (m, 13H, ArH), 7.96 (br s, 1H, NH), 10.90–11.00 (br s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 24.6, 24.8, 25.1, 31.8, 32.1, 48.2, 57.1, 105.5, 111.8, 113.7, 118.4, 120.8, 121.2, 121.7, 122.5, 124.2, 124.8, 126.9, 127.8, 128.0, 128.8, 136.3, 137.7, 137.8, 140.3, 159.6, 166.8. MS (*m*/*z*): 449 (M^+, 9), 350 (100), 324 (83), 293 (32), 217 (93), 205 (16), 190 (47), 83 (27), 55 (38). Anal. Calcd for $C_{29}H_{27}N_3O_2$: C, 77.51; H, 6.06; N, 9.35. Found: C, 77.57; H, 6.03; N, 9.32.

*4.2.1.2. N-Cyclohexyl-2-(3-methoxyphenyl)-2-(6-oxo-6,7-dihydro-5H-indolo[2,3-c]quinolin-5-yl)acetamide **6b**.* Yield: 67%; mp 235–236 °C; IR (KBr, cm^{-1}) ν: 3421, 3275 (NH), 1631, 1620 (CO). ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 0.98–1.81 (m, 10H, cyclohexyl), 3.68 (s, 3H, OMe), 3.68 (m, 1H, NCH, cyclohexyl), 6.72 (d, *J*=8.0 Hz, 1H, ArH), 6.82 (d, *J*=7.3 Hz, 1H, ArH), 6.86 (s, 1H, CH), 7.18 (t, *J*=8.0 Hz, 1H, ArH), 7.29–7.35 (m, 5H, ArH), 7.40 (t, *J*=8.0 Hz, 1H, ArH), 7.66 (d, *J*=8.0 Hz, 1H, ArH), 7.94 (1H, NH), 8.24 (d, *J*=8.0 Hz, 1H), 8.28 (s, 1H, ArH), 12.67 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 24.8, 24.9, 25.7, 30.0, 32.6, 51.7, 56.1, 71.1, 106.2, 112.6, 113.0, 113.5, 114.3, 119.4, 120.5, 121.4, 122.6, 123.1, 125.0, 125.9, 130.0, 130.1, 131.4, 136.7, 139.1, 141.0, 144.8, 149.4, 161.5, 168.8. MS (*m*/*z*): 479 (M^+, 3), 380 (39), 354 (13), 323 (9), 217 (66), 205 (12), 190 (40), 135 (25), 121 (42), 83 (89), 55 (100). Anal. Calcd for $C_{30}H_{29}N_3O_3$: C, 75.16; H, 6.10; N, 8.77. Found: C, 75.26; H, 6.19; N, 8.72.

*4.2.1.3. 2-(3,4-Dimethoxyphenyl)-2-(2-methyl-6-oxo-6,7-dihydro-5H-indolo[2,3-c]quinolin-5-yl)-N-(2,4,4-trimethylpentan-2-yl)acetamide **6c**.* Yield: 65%; mp 249–250 °C; IR (KBr, cm^{-1}) ν: 3435, 3277 (NH), 1629, 1619 (CO). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 0.85 (s, 9H, 3×Me), 1.34 (s, 6H, 2×Me), 1.68 (d, *J*=1–2 Hz, CH), 1.72 (d, *J*=1–2 Hz, CH), 2.40 (s, 3H, Me), 3.65 (s, 3H, OMe), 3.69 (s, 3H, OMe), 6.67 (d, *J*=5.7 Hz, 1H, ArH), 6.85 (d, *J*=6.3 Hz, 1H, ArH), 6.97 (s, 1H, CH), 7.13–7.19 (m, 3H, ArH), 7.29 (d, *J*=5.7, 1H, ArH), 7.39 (d, *J*=6.3 Hz, 1H, ArH), 7.63 (d, *J*=6.3 Hz, 1H, ArH), 8.06 (s, 1H, NH), 8.23 (d, *J*=5.7 Hz, 1H, ArH), 12.59 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 20.8, 29.0, 29.1, 31.6, 31.7, 51.6, 55.1, 55.9, 56.0, 105.9, 112.1, 112.3, 112.6, 113.9, 119.3, 120.4, 121.3, 121.6, 122.6, 124.6, 125.2, 129.5, 129.8, 131.2, 136.5, 138.3, 140.6, 148.3, 148.8, 160.0, 167.6. MS (*m*/*z*): 553 (M^+, 7), 424 (100), 398 (24), 367 (14), 248 (13), 231 (60), 219 (16), 204 (16), 166 (15), 151 (37), 57 (65). Anal. Calcd for $C_{34}H_{39}N_3O_4$: C, 73.78; H, 7.11; N, 7.59. Found: C, 73.82; H, 7.15; N, 7.53.

*4.2.1.4. N-Cyclohexyl-2-(3,5-dimethoxyphenyl)-2-(2-methyl-6-oxo-6,7-dihydro-5H-indolo[2,3-c]quinolin-5-yl)acetamide **6d**.* Yield: 52%; mp 243–245 °C; IR (KBr, cm^{-1}) ν: 3446, 3272 (NH), 1626, 1595 (CO). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.01–1.61 (m, 10H, cyclohexyl), 2.57 (s, 3H, Me), 3.55 (m, 1H, NCH, cyclohexyl), 3.92 (s, 3H, OMe), 3.97 (s, 3H, OMe), 5.85 (s, 1H, CH), 6.58–6.65 (m, 3H, ArH), 7.38 (t, *J*=7.5 Hz, 1H, ArH), 7.53 (t, *J*=7.5 Hz, 1H, ArH), 7.65 (s, 1H, ArH), 7.91 (d, *J*=7.5 Hz, 1H, ArH), 8.08 (s, 1H, ArH), 8.27 (s, 1H, ArH), 8.33 (d, *J*=8.0 Hz, 1H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 20.9, 24.8, 25.3, 25.6, 31.4, 32.8, 48.7, 55.6, 55.6, 95.9, 104.9, 106.8, 107.1, 113.2, 118.1, 120.2, 122.8, 123.5, 126.4, 126.7, 129.3, 132.1, 138.5, 144.4, 156.5, 160.4, 160.6, 160.9, 162.6, 166.7. MS (*m*/*z*): 523 (M^+, 4), 501 (5), 424 (67), 398 (43), 325 (37), 299 (100), 284 (20), 192 (15),

165 (28), 152 (13), 91 (39), 83 (15), 55 (32). Anal. Calcd for $C_{32}H_{33}N_3O_4$: C, 73.42; H, 6.36; N, 8.03. Found: C, 73.49; H, 6.27; N, 7.99.

4.2.1.5. N-Cyclohexyl-2-(6-oxo-6,7-dihydro-5H-indolo[2,3-c]quinolin-5-yl)-2-(p-tolyl)acetamide ***6e***. Yield: 55%; mp 202–203 °C; IR (KBr, cm^{-1}) ν: 3406, 3253 (NH), 1660, 1633 (CO). ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 0.87–2.0 (m, 10H, cyclohexyl), 2.37 (s, 3H, Me), 3.97 (m, 1H, NCH, cyclohexyl), 5.91 (s, 1H, CH), 7.31–7.56 (m, 12H, ArH), 11.60 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 21.9, 24.8, 24.9, 26.6, 31.7, 32.1, 48.1, 57.8, 104.6, 112.1, 120.0, 122.0, 123.4, 125.5, 126.7, 127.2, 128.0, 129.5, 130.4, 132.6, 133.0, 133.6, 134.4, 137.7, 139.0, 159.0, 164.3. MS (m/z): 461 (M^+, 2), 395 (5), 387 (15), 384 (8), 368 (16), 362 (25), 353 (9), 339 (14), 336 (28). Anal. Calcd for $C_{30}H_{29}N_3O_2$: C, 78.01; H, 6.34; N, 9.11. Found: C, 77.91; H, 6.45; N, 9.05.

4.2.1.6. 2-(4-Bromophenyl)-N-cyclohexyl-2-(2-methyl-6-oxo-6,7-dihydro-5H-indolo[2,3-c]quinolin-5-yl)acetamide ***6f***. Yield: 82%; mp>250 °C; IR (KBr, cm^{-1}) ν: 3408, 3249 (NH), 1643, 1560. ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 0.96–1.82 (m, 10H, cyclohexyl), 2.28 (s, 3H, Me), 3.58 (m, 1H, NCH, cyclohexyl), 6.15 (s, 1H, CH), 6.90 (t, J=7.5 Hz, 1H, ArH), 7.11–7.40 (m, 10H, ArH), 11.66 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 20.8, 24.8, 25.0, 25.6, 32.6, 32.7, 48.4, 64.8, 105.0, 112.6, 120.1, 122.0, 122.1, 124.3, 126.1, 127.3, 129.5, 130.5, 130.9, 133.1, 133.4, 133.5, 133.8, 136.1, 141.1, 161.7, 168.9; MS (m/z): 543 (2), 541 (M^+, 2), 498 (27), 444 (7), 442 (7), 418 (80), 416 (80), 354 (85), 286 (26), 284 (26), 262 (34), 248 (26), 172 (38), 170 (38), 144 (100), 116 (51), 89 (92), 55 (55). Anal. Calcd for $C_{30}H_{28}N_3O_2Br$: C, 66.42; H, 5.21; N, 7.75. Found: C, 66.46, H, 5.18; N, 7.66.

4.2.1.7. 2-(4-Bromophenyl)-2-(2-methyl-6-oxo-6,7-dihydro-5H-indolo[2,3-c]quinolin-5-yl)-N-(2,4,4-trimethylpentan-2-yl)acetamide ***6g***. Yield: 51%, mp>250 °C; IR (KBr, cm^{-1}) ν: 3407, 3242 (NH), 1641, 1575 (CO). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 0.89 (s, 9H, 3×Me), 1.31 (s, 6H, 2×Me), 1.69 (d, J=1–2 Hz, CH), 1.73 (d, J=1–2 Hz, CH), 2.30 (s, 3H, Me), 6.19 (s, 1H, CH), 6.90 (t, J=7.5 Hz, 1H, ArH), 7.13–7.47 (m, 10H, ArH), 11.69 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 20.8, 29.0, 29.1, 31.5, 31.7, 48.9, 51.9, 104.9, 112.6, 120.1, 122.0, 122.1, 124.3, 126.1, 127.2, 129.5, 130.4, 130.9, 133.1, 133.4, 133.5, 133.8, 136.1, 141.0, 161.3, 168.6. MS (m/z): 573 (17), 571 (M^+, 17), 444 (32), 442 (34), 418 (15), 416 (15), 314 (13), 270 (26), 236 (74), 205 (36), 175 (100), 57 (8). Anal. Calcd for $C_{32}H_{34}N_3O_2Br$: C, 67.13; H, 5.99; N, 7.34. Found: C, 67.20; H, 6.07; N, 7.27.

4.2.1.8. 2-(4-Chlorophenyl)-N-cyclohexyl-2-(6-oxo-6,7-dihydro-5H-indolo[2,3-c]quinolin-5-yl)acetamide ***6h***. Yield: 76%; mp>250 °C; IR (KBr, cm^{-1}) ν: 3421, 3231 (NH), 1623, 1612 (CO). ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 0.99–1.83 (m, 10H, cyclohexyl), 3.60 (m, 1H, NCH, cyclohexyl), 6.19 (s, 1H, CH), 6.90 (t, J=5.7 Hz, 1H, ArH), 7.13 (t, J=5.7 Hz, 1H, ArH), 7.19–7.27 (m, 6H, ArH), 7.39 (d, J=6.3 Hz, 2H, ArH), 7.45 (d, J=6.3 Hz, 2H, ArH), 11.69 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 24.8, 25.0, 25.6, 32.6, 32.7, 48.4, 64.7, 105.0, 112.6, 120.2, 122.1, 124.3, 126.5, 127.2, 128.0, 128.9, 130.4, 131.2, 132.6, 133.0, 133.3, 134.4, 136.1, 138.8, 161.5, 168.9. MS (m/z): 485 (0.7), 483 (M^+, 2), 386 (3), 384 (8), 360 (14), 358 (40), 294 (28), 240 (17), 144 (100), 125 (51), 115 (42), 89 (91), 55 (91). Anal. Calcd for $C_{29}H_{26}N_3O_2Cl$: C, 71.97; H, 5.42; N, 8.69. Found: C, 72.06; H, 5.49; N, 8.73.

4.2.1.9. 2-(3-Chlorophenyl)-N-cyclohexyl-2-(6-oxo-6,7-dihydro-5H-indolo[2,3-c]quinolin-5-yl)acetamide ***6i***. Yield: 55%; mp>250 °C; IR (KBr, cm^{-1}) ν: 3411, 3257 (NH), 1634, 1572 (CO). ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 1.00–1.82 (m, 10H, cyclohexyl), 3.60 (m, 1H, NCH, cyclohexyl), 6.20 (s, 1H, CH), 6.91 (t, J=7.2 Hz, 1H, ArH), 7.12 (t, J=7.2 Hz, ArH), 7.20–7.48 (m, 10H), 11.68 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 24.6, 25.3, 25.4, 31.6, 32.7, 48.8, 86.3, 105.8, 108.3, 114.3, 115.3, 115.8, 117.2, 122.7, 123.0, 123.4, 124.1, 124.2, 124.7, 125.8, 127.2, 128.7, 129.7, 130.5, 133.0, 148.1, 151.9, 165.6, 169.7. MS (m/z): 485 (M^+, 3), 483 (9), 386 (33), 384 (100), 360 (10), 358 (29), 327 (14), 234 (21), 217 (99), 205 (28), 190 (45), 83 (61), 55 (92). Anal. Calcd for $C_{29}H_{26}N_3O_2Cl$: C, 71.97; H, 5.42; N, 8.69. Found: C, 72.03; H, 5.37; N, 8.64.

4.2.1.10. N-Cyclohexyl-2-(naphthalen-1-yl)-2-(6-oxo-6,7-dihydro-5H-indolo[2,3-c]quinolin-5-yl)acetamide ***6j***. Yield: 69%; mp 208–210 °C; IR (KBr, cm^{-1}) ν: 3427, 3226 (NH), 1647, 1572 (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.13–1.75 (m, 10H, cyclohexyl), 4.09 (m, 1H, NCH, cyclohexyl), 5.72 (s, 1H, CH), 6.27 (s, 1H, ArH), 7.10 (t, J=5.7 Hz, 1H, ArH), 7.18–7.60 (m, 8H, ArH), 7.67 (t, J=5.7 Hz, 1H, ArH), 7.81–8.02 (m, 4H, ArH), 8.24 (d, J=6.5 Hz, 1H, NH), 11.91 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 24.7, 25.5, 29.7, 30.9, 32.3, 49.7, 71.6, 110.2, 111.0, 113.1, 115.0, 120.6, 121.5, 122.4, 123.5, 124.2, 124.9, 126.1, 126.3, 127.1, 128.3, 128.8, 129.0, 129.6, 130.9, 131.4, 132.8, 133.9, 135.7, 138.0, 140.4, 160.2, 168.1. MS (m/z): 499 (M^+, 2), 414 (33), 400 (74), 387 (11), 374 (82), 357 (6), 248 (7), 231 (24), 218 (13), 204 (13), 141 (24), 83 (88), 55 (100). Anal. Calcd for $C_{33}H_{29}N_3O_2$: C, 79.36; H, 5.86; N, 8.42. Found: C, 79.74; H, 5.91; N, 8.34.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.079.

References and notes

1. Alajarin, M.; Molina, P.; Vidal, A. *J. Nat. Prod.* **1997**, *60*, 747.
2. Crouch, R. C.; Davis, A. O.; Spitzer, T. D.; Martin, G. E.; Sharaf, M. M. H.; Schiff, P. L., Jr.; Phoebe, C. H., Jr.; Tackie, A. N. *J. Heterocycl. Chem.* **1995**, *32*, 1077.
3. (a) Cimanga, K.; De Bruyne, T.; Lasure, A.; Van Poel, B.; Pieters, L.; Claeys, M.; Berghe, D. V.; Kambu, K.; Tona, L.; Vlietinck, A. J. *Planta Med.* **1996**, *62*, 22; (b) Cimanga, K.; De Bruyne, T.; Pieters, L.; Claeys, M.; Vlietinck, A. *Tetrahedron Lett.* **1996**, *37*, 1703; (c) Cimanga, K.; De Bruyne, T.; Pieters, L.; Vlietinck, A. J.; Turger, C. A. *J. Nat. Prod.* **1997**, *60*, 688.
4. Lu, W.-J.; Wicht, K. J.; Wang, L.; Imai, K.; Mei, Z.-W.; Kaiser, M.; El Sayed, I. E. T.; Egan, T. J.; Inokuchi, T. *Eur. J. Med. Chem.* **2013**, *64*, 498.
5. Cimanga, K.; De Bruyne, T.; Pieters, L.; Totte, J.; Tona, L.; Kambu, K.; Berghe, D. V.; Vlietinck, A. J. *Phytomedicine* **1998**, *5*, 209.
6. Boakye-Yiadom, K.; Heman-Ackah, S. M. *J. Pharm. Sci.* **1979**, *68*, 1510.
7. Van Miert, S.; Jonckers, T.; Maes, L.; Vlietinck, A.; Dommisse, R.; Lemière, G.; Pieters, L. *Acta Hortic.* **2005**, *677*, 91.
8. Lavrado, J.; Moreira, R.; Paulo, A. *Curr. Med. Chem.* **2010**, *17*, 2348.
9. Fryer, R. I.; Ning, R. Y.-F.; Sternbach, L. H.; Walser, A. U.S. Patent 4,014,883, 1977; *Chem. Abstr.* **1977**, 39450s.
10. Fukushima, K.; Teller, M. N.; Mountain, I. M.; Tarnowski, G. S.; Stock, C. C. *J. Reticuloendothel. Soc.* **1979**, *26*, 187.
11. Grunberg, E.; Kramer, M. J.; Buck, M.; Trown, P. W. *Chemotherapy* **1978**, *24*, 77.
12. Putey, A.; Popowycz, F.; Do, Q.-T.; Bernard, P.; Talapatra, S. K.; Kozielski, F.; Galmarini, C. M.; Joseph, B. *J. Med. Chem.* **2009**, *52*, 5916.
13. (a) Kanaoka, Y.; Itoh, K. *Synthesis* **1972**, 36; (b) Vaillard, V. A.; Budén, M. E.; Martín, S. E.; Rossi, R. A. *Tetrahedron Lett.* **2009**, *50*, 3829; (c) Li, Z.; Wang, W.; Zhang, X.; Hu, C.; Zhang, W. *Synlett* **2013**, 73.
14. Tokmakov, G. P.; Zemlyanova, T. G.; Grandberg, I. I. *Chem. Heterocycl. Compd.* **1994**, *30*, 434.
15. Hostyn, S.; Maes, B. U. W.; Baelen, G. V.; Gulevskaya, A.; Meyers, C.; Smits, K. *Tetrahedron* **2006**, *62*, 4676.
16. (a) Rasouli, M. A.; Mahdavi, M.; Ranjbar, P. R.; Saeedi, M.; Shafiee, A.; Foroumadi, A. *Tetrahedron Lett.* **2012**, *53*, 7088; (b) Rasouli, M. A.; Mahdavi, M.; Saeedi, M.; Ranjbar, P. R.; Shafiee, A.; Foroumadi, A. *J. Heterocycl. Chem.* http://dx.doi.org/10.1002/jhet.2053. (c) Saeedi, M.; Mahdavi, M.; Foroumadi, A.; Shafiee, A. *Tetrahedron* **2013**, *69*, 3506.
17. (a) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996; (b) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476; (c) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.