DOI: 10.1002/ejoc.201101508

Synthesis of Paullone and Kenpaullone Derivatives by Photocyclization of 2-(2-Chloro-1*H*-indol-3-yl)-*N*-arylacetamides

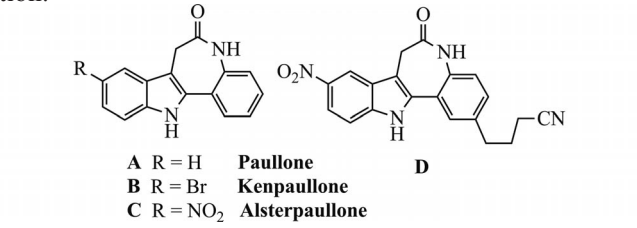
Zhanshan Li,[a] Nianhong Lu,[a] Lihong Wang,[a] and Wei Zhang*[a]

Keywords: Natural products / Alkaloids / Nitrogen heterocycles / Photochemistry / Cyclization

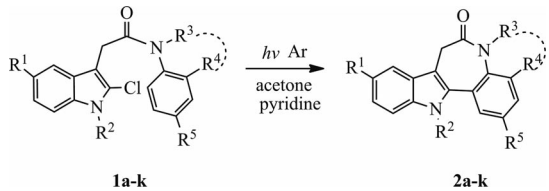
An efficient synthesis of paullone and kenpaullone derivatives in moderate to high yields has been achieved through photocyclizations of (2-chloro-1*H*-indole-3-yl)-*N*-arylacetamides in acetone at room temperature. Paullone and kenpaullone have been obtained easily and in high yields by deprotection of the photocyclization products.

Introduction

Paullone (**A**), kenpaullone (**B**), and alsterpaullones (**C**, **D**) are a series of fused tetracyclic compounds containing the indolo[3,2-*d*][1]benzazepin-6(5*H*)-one structure. They have been described as potent, ATP-competitive inhibitors of the cell cycles regulating cyclin-dependent kinases (CDKs), glycogen-synthase kinases (GSKs), and mitochondrial malate dehydrogenase (mMDH) and have become a class of very useful agents for the treatment of neurodegenerative and proliferative disorders.[1a–1h] The synthesis of paullone and analogues has thus attracted great interest over the last decade.[2,3] Several synthetic strategies to access the paullone system have been reported. The first synthetic pathway involved the construction of the fused 1*H*-indole moiety through a Fischer indolization of benzazepinone.[2] Another pathway proceeded through the initial construction of an indole precursor and subsequent extension to the paullone structure through intramolecular coupling or condensation. Examples of this approach include rhodium(III)-catalyzed cycloadditions between acetanilides and methyl 4-(2-aminophenyl)but-3-ynoate and subsequent lactamization,[3a] copper-catalyzed borylative cyclizations of 2-alkenylaryl isocyanides and Suzuki–Miyaura couplings with subsequent lactamization,[3b] a Strecker reaction between a protected 2-aminobenzaldehyde and a 2-aminocinnamate and further cyclization of the deprotonated *N*-monosubstituted amino nitrile,[3c] and a Bu_3SnH-mediated radical cyclization of an *o*-alkenyl arylisonitrile followed by a Stille coupling with *N*-Boc-2-iodoaniline to give the methyl 2-arylindoacetate with subsequent lactamization.[3d] Strategies starting directly from an indole precursor have also been widely used; they include a Pd-catalyzed intramolecular Heck reaction of *N*-(ethoxymethyl)-2-[1-(ethoxymethyl)-indol-3-yl]-*N*-(2-iodophenyl)acetamide,[4a] a Bu_3SnH-mediated radical cyclization of *N*-[2-(indol-2-yl)phenyl]-*N*-methylchloroacetamide,[4b] and palladium-catalyzed borylation/Suzuki coupling reactions between 2-bromindole-3-acetonitriles and 2-haloacetanilides with subsequent lactamization.[4c]



All of these syntheses, however, required the use of metallic catalysts and multi-step reactions, so a concise and metal-free process was still required. We found that no syntheses of paullone or kenpaullone derivatives through photochemical reactions had been reported in the literature, although photoinduced couplings between haloarenes and arenes have been used extensively in the synthesis of alkaloids and polycyclic compounds.[5] We have recently reported on the synthesis of indolo[2,1-*a*]isoquinolines and indolo[2,1-*a*][2]benzazepines through intramolecular photochemical cross-coupling reactions between 3-acyl-2-haloindoles and their tethered arene units.[6] Here we report a new synthesis of paullone derivatives through photoinduced intramolecular cross-coupling reactions of 2-(2-chloro-1*H*-indol-3-yl)-*N*-arylacetamides in acetone (Scheme 1).



Scheme 1. Photocyclizations of 2-(2-chloro-1*H*-indol-3-yl)-*N*-arylacetamides in acetone.

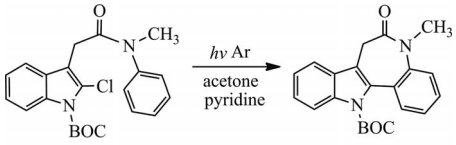
[a] State Key Laboratory of Applied Organic Chemistry and College of Chemistry and Chemical Engineering, Lanzhou University,
Lanzhou 730000, P. R. China
Fax: +86-931-8625657
E-mail: zhangwei6275@yahoo.com

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101508.

Results and Discussion

We first optimized the photoreaction conditions by using the 2-(indol-3-yl)acetamide derivative **1a** (see Table 1) as a model substrate. The reaction was examined in different solvents in a Pyrex flask ($\lambda > 280$ nm) because the ultraviolet absorption of **1a** was below 300 nm (λ_{max} = 292 nm, 280 nm, 223 nm). The photoreaction efficiency of **1a** in acetone was clearly higher than those in other solvents such as dichloromethane, acetonitrile, or benzene, as shown in Table 1. This result may be attributed to the photosensitization effect of acetone, because the triplet energy of acetone (E_T = 326 kJ mol^{-1})[7a] was higher than that of 1-acylindole (E_T = 288 kJ mol^{-1}).[7b] In addition, it could be seen that polar solvents favored the photocyclization reaction, because higher levels of conversion of **1a** could be reached in shorter time in more polar solvents. For these two reasons, acetone was selected as the solvent in the photoreactions of all substrates.

Table 1. Optimization of photoreaction conditions for the synthesis of **2a**.[a]



1a **2a**

Entry	Solvent	Time [h]	Conv. of **1a**[b] [%]	Yield of **2a**[c] [%]
1	Me_2CO	5	95	90
2	CH_3CN	16	62	71
3	CH_2Cl_2	22	57	68
4	C_6H_6	30	53	62

[a] Compound **1a** (0.5 mmol) and pyridine (79 mg, 1.0 mmol) were dissolved in acetone (25 mL). The solution was irradiated at $\lambda \geq 280$ nm with a medium-pressure mercury lamp (500 W) under argon at ambient temperature. [b] Conversions calculated on the basis of substrate. [c] Yields of isolated product based on consumed substrate.

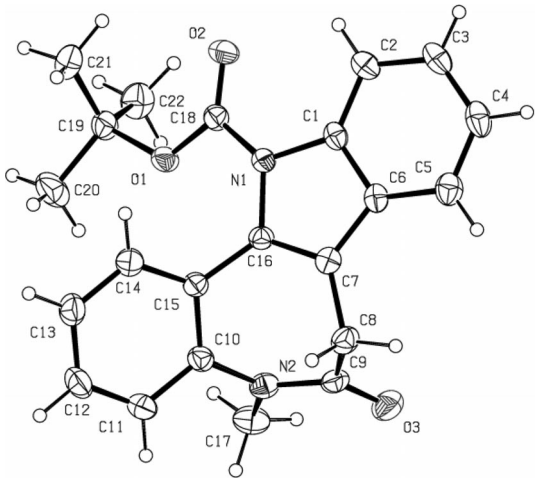
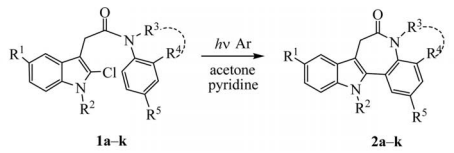


Figure 1. X-ray crystal structure of **2a**.

Table 2. Photocyclizations of 2-(2-chloro-1*H*-indol-3-yl)-*N*-aryl-acetamides **1a**–**k** in acetone.[a]



1a–k **2a–k**

Entry	Substrate	Time (h)	Conv.[b] (%)	Product	Yield[a] (%)
1	**1a**	5	95	**2a**	90
2	**1b**	5	92	**2b**	87
3	**1c**	8	90	**2c**	72
4	**1d**	24	63	**2d**	15
5	**1e**	8	95	**2e**	75
6	**1f**	12	90	**2f**	63
7	**1g**	12	92	**2g**	60
8	**1h**	8	95	**2h**	65
9	**1i**	10	92	**2i**	52
10	**1j**	12	90	**2j**	68
11	**1k**	10	93	**2k**	75

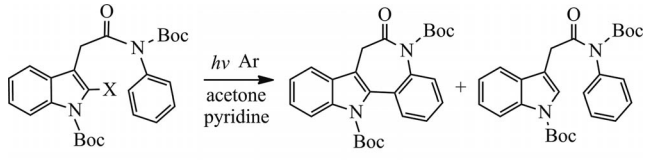
[a] Compounds **1a**–**1k** (0.5 mmol) and pyridine (79 mg, 1.0 mmol) were dissolved in acetone (25 mL). The solutions were irradiated at $\lambda \geq 280$ nm with a medium-pressure mercury lamp (500 W) under argon at ambient temperature. [b] Levels of conversion were calculated on the basis of substrate. [c] Yields of isolated products based on consumed substrate.

We then examined the photoreactions of a group of 2-(2-chloro-1*H*-indol-3-yl)-*N*-arylacetamides with different substituents on both indolyl and aryl groups under the optimized conditions. Photoreactions of all these substrates afforded the corresponding cyclization products – paullone derivatives – in moderate to high yields after 5–30 h irradiation at room temperature. All products were fully identified by ^{1}H NMR, ^{13}C NMR, and HRMS, and the structure of **2a** was further confirmed by X-ray analysis as depicted in Figure 1.[8] It was found that the photocyclization of **1d** (Table 2), in which there were no substituents on the nitrogen atoms, was difficult; substituents on both nitrogen atoms were therefore necessary to improve both the levels of conversion of substrates and the yields of products. The 1-Boc-substituted substrates (**1a** and **1e**) were more reactive than 1-alkyl-substituted substrates (**1c**, **1f**, and **1g**) and the photoreaction efficiencies were higher. The differences in reactivity for **1a**, **1c**, and **1d** originated from the different properties of their triplet excited states: the triplet form of the 1-acylindole system, for example, was diradical and reacted easily with olefins at the 2-position to form triplet 1,4-biradicals,[7b] but the triplet form of 1-methylindole showed some triplet charge transfer as well as the diradical,[7c] so the indole could react with acetone through H-abstraction from the N–H bond.[7c] It was also found that the presence of a BOC group at the amide nitrogen atom retarded the photocyclization in **1h** and **1k** relative to the presence of the alkyl groups at the amide nitrogen atoms in **1a**, **1e**, and **1j**. In addition, the reactions of **1e** and **1f**, in which the *N*-phenyl group was replaced by tetrahydroquinoline, were slow and the yields of products **2e** and **2f** were lower than in the cases of **1a**–**c**.

Because the synthesis of paullone by direct photocyclization of **1d** in acetone was much more difficult than those of its derivatives **2h** and **2k** from **1h** and **1k**, the syntheses of paullone and kenpaullone were achieved in high yields by the removal of the *tert*-butoxycarbonyl groups from the photocyclization products **2h** and **2k** through two-step mild hydrolysis reactions[9] (Scheme 2).

Although the photocyclizations of 2-(2-chloro-1*H*-indol-3-yl)-*N*-arylacetamides had proceeded successfully, we wanted to know whether or not photocyclizations of other 2-(2-halo-1*H*-indol-3-yl)-*N*-arylacetamide derivatives would be more efficient, because the bond dissociation energies of C–Br and C–I bonds were lower than that of the C–Cl bond. Two other substrates – **1l** and **1m** (Table 3) – were therefore prepared and the photoreactions of the two substrates were examined under the same conditions. The results for **1l** and **1m** were compared with that for **1h** and all are listed in Table 3. It was found by comparison of levels of conversion and reaction times that the photoreaction efficiency decreased gradually from **1h** to **1m**. In particular, it could be seen that the photoreaction products of **1m** were different from those of **1h** and **1l**, the main product being not the cyclization product but the deiodination product **3**, which was obviously derived from a hydrogen-abstraction reaction of the 2-indoyl radical. It was therefore clear that the photoreactions of 2-chloro-substituted *N*-arylindole-3-acetamides gave the best results for the synthesis of paullone derivatives.

Table 3. Photoreactions of different halogen-substituted 2-(1*H*-indol-3-yl)-*N*-arylacetamides.[a]

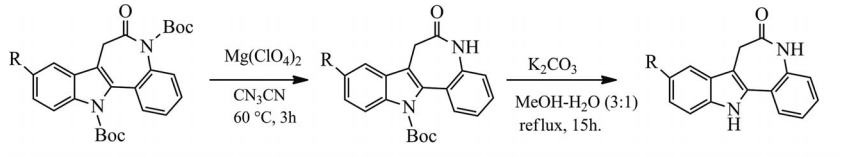


1h, **1l**, **1m** **2h** **3**

Entry	Substrate	X	Time [h]	Conv.[b] [%]	Product	Yield[c] [%]	
						2h	**3**
1	**1h**	Cl	8	95	**2h**	65	
2	**1l**	Br	30	60	**2h**	50	
3	**1m**	I	30	35	**2h** + **3**	8	51

[a] Compound **1l** or **1m** (0.5 mmol) and pyridine (79 mg, 1.0 mmol) were dissolved in acetone (25 mL). The solution was irradiated at $\lambda \geq 280$ nm with a medium-pressure mercury lamp (500 W) under argon at ambient temperature. [b] Levels of conversion calculated on the basis of substrate. [c] Yields of isolated products based on consumed substrate.

No further reaction was detectable in the acetone solution of **3** after prolonged irradiation (48 h), so it was clear that the presence of the 2-chlorine atom on the indole ring was essential for the photocyclizations of **1a**–**k**. However, it was also impossible that the photocyclizations of **1a**–**k** were initiated by the photoinduced homolysis of the C–Cl bonds to produce the free 2-indolyl radicals because of three facts: 1) no solvent-incorporated product – 2-(2-phenylindol-3-yl)-*N*-phenylacetamide – was detected from the photoreaction of **1a** in benzene, 2) the triplet energy of the 1-acylindole system (E_T = 288 kJ mol^{-1})[7b] was not sufficient for the cleavage of the C–Cl and C–Br bonds [the bond dissociation energies (D_{C-X}) for C–Cl and C–Br are 339 and



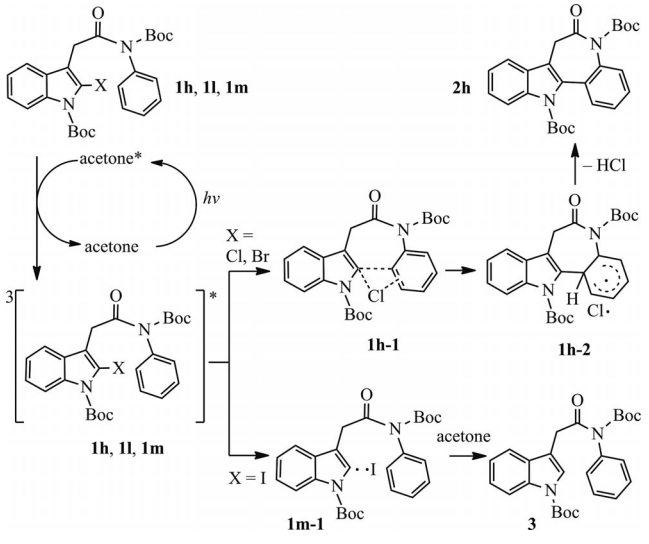
R = H **2h**
R = Br **2k**

2h-1 (98%)
2k-1 (96 %)

R = H **Paullone**, (90 %)
R = Br **Kenpaullone** (95 %)

Scheme 2. Synthesis of paullone and kenpaullone by hydrolysis of **2h** and **2k**.

289 kJ mol^{-1}, respectively[10]], and 3) although the free 2-indolyl radical could be produced from photolysis of 2-iodo-indol-3-yl-*N*-phenylacetamide (**1m**; the bond dissociation energy for C–I was 222 kJ mol^{-1}[10]), the main product was not the cyclization product **1h** as shown in Table 3. There might therefore be another, lower-energy path to induce the cyclization. Grimshaw[11a] and Park[11b] proposed a novel mechanism to explain the photocyclizations of 2-chlorobenzanilide and 2-halo-*N*-pyridinylbenzamides. Cyclic transition states could be formed from the complexing of the π-clouds of the *N*-phenyl or *N*-pyridinyl rings with the developing aryl radical centers and chlorine atoms, stretching the C–Cl bonds and thus lowering the transition energies for the reactions. Such a low-energy pathway would also be reasonable to explain the photocyclizations of **1a**–**k**, because the photoreactions were more efficient in the triplet states of **1a**–**k** (Table 2) and the triplet states of the indole rings in **1a**–**k** each have the diradical structure,[7b] which should be favorable for coupling of the C-2 moiety in the 2-chloroindole system with tethered *N*-aryl groups. Chlorine and bromine atoms are electron-deficient species with high electron affinities,[12] their complexation by aromatic molecules is well known, and anchimeric assistance to C–X bond cleavage by radical complexation has also been confirmed by dynamic methods[13] and flash photolysis studies.[11b,14] A plausible mechanism based on the above suggestions is shown in Scheme 3. This mechanism also affords an explanation of why the chlorine-substituted substrate **1h** reacts more rapidly than the bromine-substituted substrate **1l** even though $D_{C-Cl} > D_{C-Br}$, because the transition state **1h**–**1** is reached earlier along the reaction coordinate for X = Cl than for X = Br, due to the higher electron affinity of the chlorine atom. Photocyclization of **1m** might proceed by homolysis of the C–I bond to give a free 2-indolyl radical and an iodine atom and subsequent coupling of the 2-indolyl radical with the *N*-aryl group.



Scheme 3. A plausible mechanism for the photoreactionsof **1h**, **1l**, and **1m** in acetone.

Conclusions

In conclusion, an efficient synthesis of paullone derivatives through photocyclizations of 2-(2-chloro-1*H*-indol-3-yl)-*N*-arylacetamides in acetone has been developed. The photocyclizations of 2-(1-acyl-2-chloro-1*H*-indol-3-yl)-*N*-arylacetamides are more efficient than those of 2-(1-alkyl-2-chloro-1*H*-indol-3-yl)-*N*-arylacetamides and the photocyclizations of 2-chlorine-substituted (1*H*-indol-3-yl)-*N*-arylacetamides are more efficient than those of 2-bromine- or 2-iodine-substituted (1*H*-indol-3-yl)-*N*-arylacetamides. Paullone and kenpaullone can be obtained in high yields by deprotection of the photocyclization products.

Experimental Section

General: Melting points were measured with a micro melting point apparatus. ^{1}H NMR and ^{13}C NMR (400 MHz and 100 MHz, respectively) spectra were recorded with a Bruker AM 400 NMR spectrometer in $CDCl_3$ or [D_6]DMSO. Chemical shifts (δ) are reported in ppm with use of TMS as internal standard and spin–spin coupling contants (J) are given in Hz. IR spectra were recorded with a BOMEM MB-100 FTIR instrument. The high-resolution mass spectra (HRMS) were measured by ESI with a Bruker Daltonics APEX II 47e spectrometer. The X-ray crystallographic analysis was performed with a Bruker APEX II CCD instrument. Analytical TLC was performed with silica gel GF254 plates and the products were visualized by UV detection. Flash chromatography was carried out on silica gel (200–300 mesh) eluted with hexane/acetone 8:1 to 14:1 (v/v).

General Procedure for the Photocyclizations of 2-(2-chloro-1*H*-indol-3-yl)-*N*-arylacetamides: Compound **1a** (156 mg, 0.5 mmol) and pyridine (79 mg, 1.0 mmol) were dissolved in anhydrous acetone (25 mL) in a reaction flask. The solution was deaerated by bubbling with Ar for half an hour and irradiated at $\lambda \geq 280$ nm with a medium-pressure mercury lamp (500 W) at ambient temperature. The progress of the reaction was monitored by TLC at regular intervals. After the solvent had been removed under reduced pressure, the residue was separated by silica gel column chromatography to give the product **2a**.

***tert*-Butyl 5-Methyl-6-oxo-6,7-dihydroindolo[3,2-*d*][1]benzazepine-12(5*H*)-carboxylate (2a):** Colorless solid, m.p. 169–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.46 (s, 9 H, *t*Bu), 2.96 and 3.87 (AB system, J = 14.4 Hz, 2 H, CH_2), 3.38 (s, 3 H, NCH_3), 7.23–7.33 (m. 2 H, ArH), 7.36–7.46 (m, 3 H, ArH), 7.45 (d, J = 7.6 Hz, 1 H, ArH), 7.65 (d, J = 7.6 Hz, 1 H, ArH), 8.19 (d, J = 8.0 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 27.7, 32.0, 37.2, 83.9, 115.5, 118.6, 120.5, 123.2, 123.4, 124.0, 125.4, 127.2, 127.7, 127.8, 129.9, 132.5, 138.1, 140.2, 149.9 (C=O), 172.1 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3057, 2930, 1731, 1666, 1423, 1363, 1154, 698 cm^{-1}. ESI-HRMS: calcd. for $C_{22}H_{22}N_2O_3$ + H^+ 363.1709; found 363.1703.

12-Acetyl-5-methyl-7,12-dihydroindolo[3,2-*d*][1]benzazepin-6(5*H*)-one (2b): Colorless solid, m.p. 223–226 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.33 (s, 3 H, CH_3), 2.98 and 3.93 (AB system, J = 14.0 Hz, 2 H, CH_2), 3.43 (s, 3 H, NCH_3), 7.31 (td, J = 8.4, 1.6 Hz, 1 H, ArH), 7.35 (td, J = 8.0, 0.8 Hz, 1 H, ArH), 7.40–7.49 (m, 4 H, ArH), 7.66 (d, J = 7.6 Hz, 1 H, ArH), 8.32 (d, J = 8.4 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 27.9, 32.2, 37.2, 115.8, 118.7, 122.6, 123.9, 124.1, 125.1, 126.3, 127.0, 127.6, 128.4, 129.4, 131.9, 138.3, 140.4, 170.7 (C=O), 172.1

(C=O) ppm. IR (KBr): ṽ = 3059, 2925, 2854, 1708, 1663, 1453, 1368, 1297, 752 cm^{-1}. ESI-HRMS: calcd. for $C_{19}H_{16}N_2O_2$ + H^+ 305.129; found 305.134.

5,12-Dimethyl-7,12-dihydroindolo[3,2-*d*][1]benzazepin-6(5*H*)-one (2c): Pale yellow solid, m.p. 134–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.05 (d, J = 14.0 Hz, 1 H, C*H*H), 3.34 (s, 3 H, NCH_3), 3.90 (s, 3 H, NCH_3), 3.95 (dd, J = 14.0, 0.4 Hz, 1 H, CH*H*), 7.19 (t, J = 8.0 Hz, 1 H, ArH), 7.28–7.35 (m, 2 H, ArH), 7.38–7.41 (m, 1 H, ArH), 7.45 (t, J = 8.0 Hz, 2 H, ArH), 7.54 (d, J = 8.0 Hz, 1 H, ArH), 7.72 (d, J = 7.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 31.7, 32.2, 37.6, 109.7, 112.3, 118.6, 119.9, 122.7, 124.2, 124.6, 124.9, 125.6, 127.9, 128.5, 133.6, 139.2, 141.7, 172.7 (C=O) ppm. IR (KBr): ṽ = 3057, 2931, 2850, 1670, 1493, 1385, 1321, 754 cm^{-1}. ESI-HRMS: calcd. for $C_{19}H_{16}N_2O$ + H^+ 277.1341; found 277.1347.

***tert*-Butyl 8-Oxo-5,6,8,9-tetrahydro-4*H*,14*H*-indolo[2′,3′:4,5]-azepino[3,2,1-*ij*]quinoline-14-carboxylate (2e):** Colorless solid, m.p. 169–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.43 (s, 9 H, *t*Bu), 1.78–1.88 (m, 1 H), 2.17–2.28 (m, 1 H), 2.77–2.85 (m, 1 H), 2.89–3.00 (m, 2 H), 3.01 and 3.91 (AB system, J = 14.0 Hz, 2 H, CH_2), 4.57–4.63 (m, 1 H), 7.14–7.19 (m, 2 H, ArH), 7.29–7.33 (m, 2 H, ArH), 7.37 (td, J = 7.6, 1.2 Hz, 1 H, ArH), 7.67 (d, J = 7.2 Hz, 1 H, ArH), 8.17 (d, J = 8.0 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 23.9, 27.6, 27.7, 32.2, 43.0, 83.7, 115.3, 118.6, 119.9, 123.1, 123.2, 125.2, 126.1, 127.2, 127.7, 127.9, 132.8, 133.0, 135.9, 138.3, 150.0 (C=O), 171.4 (C=O) ppm. IR (KBr): ṽ = 3058, 2975, 2929, 1732, 1664, 1452, 1362, 1152, 754 cm^{-1}. ESI-HRMS: calcd. for $C_{24}H_{24}N_2O$ + H^+ 389.1865; found 389.1870.

14-Methyl-5,6,9,14-tetrahydro-4*H*,8*H*-indolo[2′,3′:4,5]azepino-[3,2,1-*ij*]quinolin-8-one (2f): Pale yellow solid, m.p. 188–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.82–1.91 (m, 1 H), 2.18–2.25 (m, 1 H), 2.81–2.97 (m, 3 H), 3.09 and 4.00 (AB system, J = 14.0 Hz, 2 H), 3.87 (s, 3 H, NCH_3), 4.60–4.67 (m,1 H), 7.17–7.25 (m, 3 H), 7.29 (td, J = 7.6, 1.2 Hz, 1 H, ArH), 7.37–7.42 (m, 2 H, ArH), 7.30 (d, J = 8.0 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 23.9, 27.7, 31.7, 32.5, 42.8, 109.6, 111.8, 118.6, 119.9, 122.6, 123.8, 124.0, 125.5, 126.5, 127.7, 133.6, 133.9, 137.4, 139.3, 171.9 (C=O) ppm. IR (KBr): ṽ = 3055, 2970, 2930, 1668, 1452, 1365, 1152, 754 cm^{-1}. ESI-HRMS: calcd. for $C_{20}H_{18}N_2O$ + H^+ 303.1497; found 303.1500.

14-Benzyl-5,6,9,14-tetrahydro-4*H*,8*H*-indolo[2′,3′:4,5]azepino-[3,2,1-*ij*]quinolin-8-one (2g): Yellow solid, m.p. 210–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.79–1.88 (m, 1 H), 2.17–2.26 (m, 1 H), 2.76–2.95 (m, 3 H), 3.15 and 4.04 (AB system, J = 13.6 Hz, 2 H, azepine CH_2), 4.61–4.67 (m, 1 H), 5.46 (q, J = 17.2 Hz, 2 H, benzyl CH_2), 7.06–7.18 (m, 3 H, ArH), 7.19–7.23 (m, 5 H, ArH), 7.27–7.32 (m, 3 H, ArH), 7.78 (m, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 23.8, 27.6, 32.5, 42.7, 48.3, 110.6, 112.3, 118.7, 120.2, 122.8, 123.9, 124.0, 125.8, 125.9, 126.0, 127.2, 127.9, 128.8, 133.6, 134.2, 137.4, 137.9, 139.1, 171.9 (C=O) ppm. IR (KBr): ṽ = 3057, 2979, 2940, 1661, 1446, 1355, 1149, 753 cm^{-1}. ESI-HRMS: calcd. for $C_{26}H_{22}N_2O$ + H^+ 379.181; found 379.1795.

Di-*tert*-butyl 6-Oxo-6,7-dihydroindolo[3,2-*d*][1]benzazepine-5,12-dicarboxylate (2h): Pale yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.41 (s, 9 H, *t*Bu), 1.43 (s, 9 H, *t*Bu), 3.04 and 3.89 (AB system, J = 14.0 Hz, 2 H, azepine CH_2), 7.29–7.42 (m, 5 H, ArH), 7.47–7.49 (m, 1 H, ArH), 7.63 (d, J = 7.6 Hz, 1 H, ArH), 8.29 (d, J = 8.4 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 27.7, 27.8, 33.9 (azepine *C*H_2), 83.6, 84.0, 115.7, 118.3, 118.5, 123.3, 125.6, 125.9, 127.1, 127.6, 127.7, 129.1, 130.0, 132.6, 135.1, 138.1, 149.7 (C=O), 151.4 (C=O), 171.7 (C=O) ppm. IR (KBr): ṽ = 3058, 2971, 2928, 1769, 1731, 1391, 1240, 1159, 753 cm^{-1}. ESI-HRMS: calcd. for $C_{26}H_{28}N_2O_5$ + H^+ 449.2076; found 449.2077.

***tert*-Butyl 3-{2-[(*tert*-Butoxycarbonyl)(phenyl)amino]-2-oxoethyl}-1*H*-indole-1-carboxylate (3):** Pale yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.36 (s, 9 H, *t*Bu), 1.64 (s, 9 H, *t*Bu), 4.39 (s, 2 H, CH_2), 6.98–7.00 (m, 2 H, ArH), 7.21–7.25 (m, 1 H, ArH), 7.27–7.36 (m, 4 H, ArH), 7.57 (d, J = 8.0 Hz, 1 H, ArH), 7.60 (s, 1 H, ArH), 8.15 (d, J = 8.0 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 27.7, 28.1, 34.4 (azepine *C*H_2), 83.2, 83.4, 113.6, 115.1, 119.2, 122.6, 124.4, 124.9, 127.7. 128.0, 128.8, 130.4, 135.3, 138.8, 149.6 (C=O), 152.7 (C=O), 173.2 (C=O) ppm. IR (KBr): ṽ = 3059, 2970, 2931, 1759, 1730, 1391, 1160, 752 cm^{-1}. ESI-HRMS: calcd. for $C_{26}H_{30}N_2O_5$ + H^+ 451.2233; found 451.2236.

Di-*tert*-butyl 2-Methoxy-6-oxo-6,7-dihydroindolo[3,2-*d*][1]benzazepine-5,12-dicarboxylate (2i): Colorless solid, m.p. 166–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.41 (s, 9 H, *t*Bu), 1.46 (s, 9 H, *t*Bu), 3.08 (d, J = 14.4 Hz, 1 H azepine CH), 3.87 (d, J = 13.6 Hz, 4 H, azepine CH, OCH_3), 6.90–6.92 (m, 2 H, ArH), 7.26–7.33 (m, 2 H, ArH), 7.40 (t, J = 8.0 Hz, 1 H, ArH), 7.62 (d, J = 8.0 Hz, 1 H, ArH), 8.29 (d, J = 8.4 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 27.7, 27.9, 34.1, 55.5, 83.4, 83.9, 113.7, 113.8, 115.6, 118.4, 118.6, 123.3, 125.7, 127.7, 128.5, 129.0, 130.3, 132.7, 138.1, 149.7, 151.5 (C=O), 157.1 (C=O), 172.2 (C=O) ppm. IR (KBr): ṽ = 3055, 2979, 2932, 1773, 1733, 1395, 1315, 1150, 755 cm^{-1}. ESI-HRMS: calcd. for $C_{27}H_{30}N_2O_6$ + H^+ 479.2182; found 479.2177.

9-Bromo-5,12-dimethyl-7,12-dihydroindolo[3,2-*d*][1]benzazepin-6(5*H*)-one (2j): Pale yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.04 and 3.88 (AB system, J = 14.0 Hz, 2 H azepine CH_2), 3.34 (s, 3 H, NCH_3), 3.88 (s, 3 H, NCH_3), 7.25 (d, J = 8.4 Hz, 1 H, ArH), 7.33–7.38 (m, 2 H, ArH), 7.47 (d, J = 3.6 Hz, 2 H, ArH), 7.54 (d, J = 8.0 Hz, 1 H, ArH), 7.84 (d, J = 1.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 31.8 (azepine *C*H_2), 32.1, 37.6, 111.1, 111.6, 132.2, 121.2, 124.3, 124.5, 124.7, 125.5, 127.1, 128.4, 128.5, 134.7, 137.7, 141.8, 172.4 (C=O) ppm. IR (KBr): ṽ = 3059, 2920, 2850, 1656, 1360, 1290, 759 cm^{-1}. ESI-HRMS: calcd. for $C_{18}H_{15}BrN_2O$ + H^+ 355.0446; found 355.0449.

Di-*tert*-butyl 9-Bromo-6-oxo-6,7-dihydroindolo[3,2-*d*][1]benzazepine-5,12-dicarboxylate (2k): Pale yellow solid, m.p. 184–185 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.41 (s, 9 H, *t*Bu), 1.42 (s, 9 H, *t*Bu), 3.01 and 3.81 (AB system, J = 14.0 Hz, 2 H, azepine CH_2), 7.33–7.38 (m, 3 H, ArH), 7.44–7.48 (m, 2 H, ArH), 7.74 (d, J = 2.0 Hz, 1 H, ArH), 8.16 (d, J = 8.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 27.6, 27.7, 33.7 (azepine *C*H_2), 83.7, 84.4, 116.5, 117.1, 117.2, 121.2, 125.9, 127.5, 127.6, 128.3, 128.5, 129.2, 130.0, 133.6, 135.2, 136.7, 149.3 (C=O), 151.2 (C=O), 171.2 (C=O) ppm. IR (KBr): ṽ = 3058, 2971, 2922, 1778, 1735, 1389, 1325, 1156, 752 cm^{-1}. ESI-HRMS: calcd. for $C_{26}H_{27}BrN_2O_5$ + H^+ 527.1182; found 527.1187.

***tert*-Butyl 6-Oxo-6,7-dihydroindolo[3,2-*d*][1]benzazepine-12(5*H*)-carboxylate (2h–1):** White solid, m.p. > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.42 (s, 9 H, *t*Bu), 3.50 (m, 2 H, azepine CH_2), 7.18 (d, J = 8.0 Hz, 1 H, ArH), 7.23 (td, J = 7.6, 0.8 Hz, 1 H, ArH), 7.29–7.470 (m, 3 H, ArH), 7.47 (dd, J = 8.0, 1.2 Hz, 1 H, ArH), 7.64 (d, J = 7.6 Hz, 1 H, ArH), 8.19 (d, J = 8.4 Hz, 1 H, ArH), 8.36 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 27.7, 31.3 (azepine *C*H_2), 84.0, 115.3, 118.4, 118.8, 122.3, 123.2, 123.6, 125.0, 125.4, 127.8, 128.1, 130.4, 132.8, 134.1, 138.4, 150.1 (C=O), 173.9 (C=O) ppm. IR (KBr): ṽ = 3150,

2975, 1730 (C=O), 1661 (C=O), 751 cm^{-1}. ESI-HRMS: calcd. for $C_{21}H_{20}N_2O_3 + H^+$ 349.1552; found 349.1557.

***tert*-Butyl 9-Bromo-6-oxo-6,7-dihydroindolo[3,2-*d*][1]benzazepin-12(5*H*)-carboxylate (2k–1):** Colorless solid, m.p. > 300 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.40 (s, 9 H, *t*Bu), 3.43 (m, 2 H, azepine CH_2), 7.21–7.25 (m, 2 H, ArH), 7.37 (td, J = 8.0, 1.2 Hz, 1 H, ArH), 7.44–7.46 (m, 2 H, ArH), 7.76 (d, J = 1.2 Hz, 1 H, ArH), 8.06 (d, J = 8.8 Hz, 1 H, ArH), 9.03 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 27.6, 31.2 (azepine CH_2), 84.5, 116.4, 116.8, 117.6, 121.1, 122.4, 123.5, 124.4, 128.1, 128.5, 129.4, 130.3, 134.0, 134.5, 137.1, 149.7 (C=O), 173.8 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3151 (NH), 2972, 1732 (C=O), 1660 (C=O), 753 cm^{-1}. ESI-HRMS: calcd. for $C_{21}H_{19}BrN_2O_3 + H^+$ 427.0657; found 427.0652.

Paullone (2d): Colorless solid, m.p. > 300 °C. ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 3.50 (s, 2 H, azepine CH_2), 7.07 (td, J = 7.6, 0.8 Hz, 1 H, ArH), 7.17 (td, J = 8.0, 1.2 Hz, 1 H, ArH), 7.24–7.29 (m, 2 H, ArH), 7.37 (td, J = 8.0, 1.2 Hz, 1 H, ArH), 7.43 (d, J = 8.4 Hz, 1 H, ArH), 7.65 (d, J = 7.6 Hz, 1 H, ArH), 7.74 (dd, J = 7.6, 1.2 Hz, 1 H, ArH), 10.08 (s, 1 H, NH), 11.57 (s, 1 H, indole NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 31.6 (CH_2), 107.5, 111.4, 117.9, 119.0, 122.0, 122.2, 122.8, 123.6, 126.5, 126.8, 127.9, 132.4, 135.4, 137.4, 171.5 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3410 (br., NH), 1666 (C=O), 1025, 999, 764 cm^{-1}. ESI-HRMS: calcd. for $C_{16}H_{12}N_2O + H^+$ 249.1022; found 249.1019.

Kenpaullone (6): Pale yellow solid, m.p. > 300 °C. ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 3.52 (s, 2 H, azepine CH_2), 7.25–7.30 (m, 3 H, ArH), 7.37–7.41 (m, 2 H, ArH), 7.74 (dd, J = 8.0, 1.6 Hz, 1 H, ArH), 7.91 (d, J = 1.6 Hz, 1 H, ArH), 10.11 (s, 1 H, NH), 11.80 (s, 1 H, indole NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 31.3 (CH_2), 107.1, 111.6, 113.3, 120.3, 122.2, 122.3, 123.6, 124.4, 126.9, 128.3, 128.4, 134.0, 135.6, 136.0, 171.4 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3415 (br., NH), 1655 (C=O), 1025, 1000, 764 cm^{-1}. ESI-HRMS: calcd. for $C_{16}H_{11}BrN_2O + H^+$:327.0133; found 327.0140.

Supporting Information (see footnote on the first page of this article): procedures for the preparation of the photoreaction substrates and copies of the ^1H and ^{13}C NMR spectra for all new compounds.

Acknowledgments

We are grateful to the National Nature Science Foundation of China (NSFC) (grant number 20872056) for financial support.

[1] a) N. Tolle, C. Kunick, *Curr. Top. Med. Chem.* **2011**, *11*, 1320; b) D. P. Power, O. Lozach, L. Meijer, D. H. Grayson, S. J. Connon, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4940; c) A. Becker, S. Kohfeld, A. Lader, L. Preu, T. Pies, K. Wieking, Y. Ferandin, M. Knockaert, L. Meijer, C. Kunick, *Eur. J. Med. Chem.* **2010**, *45*, 335; d) L. Flohe, in: *Antiparasitic and Antibacterial Drug Discovery* (Ed.: P. M. Selzer), Wiley-VCH, Weinheim, Germany, **2009**, p. 211; e) C. Kunick, T. Lemcke, L. Meijer, in: *Inhibitors of Cyclin-Dependent Kinases as Anti-Tumor Agents* (Ed.: P. J. Smith, E. W. Yue), CRC Press, New York, **2007**, 227; f) C. Kunick, K. Lauenroth, K. Wieking, X. Xie, C. E. Schultz, R. Gussio, D. Zaharevitz, M. Leost, L. Meijer, A. Weber, F. S. Jorgensen, T. Lemcke, *J. Med. Chem.* **2004**, *47*, 22; g) R. Gussio, D. W. Zaharevitz, C. F. McGrath, N. Pattabiraman, G. E. Kellogg, C. Schultz, A. Link, C. Kunick, M. Leost, L. Meijer, E. A. Sausville, *Anti-Cancer Drug Des.* **2000**, *15*, 53; h) C. Schultz, A. Link, M. Leost, D. W. Zaharevitz, R. Gussio, E. A. Sausville, L. Meijer, C. Kunick, *J. Med. Chem.* **1999**, *42*, 2909.

[2] C. Schultz, A. Link, M. Leost, D. W. Zaharevitz, R. Gussio, E. A. Sausville, L. Meijer, C. Kunick, *J. Med. Chem.* **1999**, *42*, 2909.

[3] a) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326; b) M. Tobisu, H. Fujihara, K. Koh, N. Chatani, *J. Org. Chem.* **2010**, *75*, 4841; c) T. Opatz, D. Ferenc, *Synthesis* **2008**, 3941; d) N. Henry, J. Blu, V. Beneteau, J.-Y. Merour, *Synthesis* **2006**, 3895.

[4] a) L. Joucla, F. Popowycz, O. Lozach, L. Meijer, B. Joseph, *Helv. Chim. Acta* **2007**, *90*, 753; b) J. B. Bremner, W. Sengpracha, *Tetrahedron* **2005**, *61*, 5489; c) O. Baudoin, M. Cesario, D. Guenard, F. Gueritte, *J. Org. Chem.* **2002**, *67*, 1199.

[5] a) S. V. Kessar, S. Mankotia, in: *CRC Handbook of Organic Photochemistry and Photobiology* (Eds.: W. H. Horspool, P.-S. Song), CRC Press, New York, **1995**, **1218**; b) Y. Kanaoka, *Acc. Chem. Res.* **1978**, *11*, 407; c) S. M. Barolo, X. Teng, G. D. Cuny, R. A. Rossi, *J. Org. Chem.* **2006**, *71*, 8493; M. A. Clyne, F. Aldabbagh, *Org. Biomol. Chem.* **2006**, *4*, 268; d) M. M. V. Ramana, R. H. Sharma, J. A. Parihar, *Tetrahedron Lett.* **2005**, *46*, 4385; e) T.-I. Ho, C.-K. Ku, R. S. H. Liu, *Tetrahedron Lett.* **2001**, *42*, 715; f) Y.-T. Park, C.-H. Jung, M. S. Kim, N. W. Kim, N. W. Song, D. Kim, *J. Org. Chem.* **2001**, *66*, 2197; g) Y.-T. Park, N. W. Song, Y.-H. Kim, C.-G. Hwang, S. K. Kim, D. Kim, *J. Am. Chem. Soc.* **1996**, *118*, 11399.

[6] S. Lu, X. Zhang, Z. Shi, Y. Ren, B. Li, W. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 2839.

[7] a) R. O. Loutfy, R. W. Yip, *Can. J. Chem.* **1973**, *51*, 1881; b) D. L. Oldroyd, N. C. Payne, J. J. Vittal, A. C. Weedon, B. Zhang, *Tetrahedron Lett.* **1993**, *34*, 1087; c) K. Kasama, A. Takematsu, S. Aral, *J. Phys. Chem.* **1982**, *86*, 2420.

[8] Crystal data for compound **2a** (recrystallized from acetone/hexane). $C_{22}H_{22}N_2O_3$, M_r = 362.42. Monoclinic, a = 11.171(4) Å, b = 11.202(4) Å, c = 14.889(5) Å, β = 92.732(3), V = 1861.1(11) $Å^3$, colorless plates, ρ = 1.293 $g\,cm^{-3}$, T = 296(2) K, space group $P2_1/n$, Z = 4, μ (Mo-K_α) = 0.71073 mm^{-1}, $2\theta_{max}$ = 51.0°, 3443 reflections measured, 2203 unique (R_{int} = 0.0914) which were used in all calculation. the final w$R(F^2)$ was 0.1112 (for all data), R_1 = 0.0516. CCDC-842943 contains 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.

[9] a) J. A. Stafford, *Tetrahedron Lett.* **1993**, *34*, 7873; b) M. Chakrabarty, T. Kundu, *Synth. Commun.* **2006**, *36*, 2069.

[10] J. A. Kerr, *Chem. Rev.* **1966**, *66*, 465.

[11] a) J. Grimshaw, *J. Chem. Soc., Chem. Commun.* **1981**, 181; b) Y.-T. Park, C.-H. Jung, M. S. Kim, N. W. Kim, N. W. Song, D. Kim, *J. Org. Chem.* **2001**, *66*, 2197.

[12] R. S. Berry, C. W. Reimann, *J. Chem. Phys.* **1963**, *38*, 1540.

[13] J. A. Rimshaw, P. Silva, *Can. J. Chem.* **1980**, *58*, 1880.

[14] R. E. Bühler, *Helv. Chim. Acta* **1968**, *51*, 1558.

Received: October 16, 2011
Published Online: December 21, 2011

