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Designing a sequential Ugi/Ullmann type reaction for the synthesis of indolo[1,2-*a*]quinoxalinones catalyzed by CuI/L-proline

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Dedicated to Prof. Rolf Gleiter on the occasion of his 75th birthday

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ABSTRACT

An efficient strategy for the one-pot syntheses of indolo[1,2-*a*]quinoxalinones catalyzed by CuI have been developed. The procedures combine the Ugi four-component reaction of aldehydes, 2-iodoaniline, 2-indole carboxylic acid, and isocyanides followed by the copper-catalyzed intramolecular *N*-arylation of the Ugi product in one-pot procedure, which afford the desired products in good to very good yields.

1. Introduction

The quinoxalinone core is a privileged heterocyclic scaffold because of a variety of medicinal properties, such as antimicrobial, anticancer, analgesic, antispastic, antiallergic, and antithrombotic activity.[1] Among these nitrogen-containing heterocycles the tetracyclic ring system of indolo[1,2-a]quinoxaline is an interesting skeleton and has attracted the interests of many scientists due to its diverse range of pharmacological properties.[2] The prominence of these molecules has tempted many synthetic chemists to develop efficient synthetic routes to highly functionalized examples of these materials in order to look for structure–activity relationship studies. However, so far, few synthetic methodologies to access indolo[1,2-*a*] quinoxalines are available. Some of general approaches include: (a) intramolecular cyclization of acylaminoacetals in acidic conditions[3] (b) cyclization of *N*-allyl-2-indolcarboxamides in multi-step reactions[4] (c) the use of a Stevens rearrangement of a spiroquinoxaline derived using $FeCl_3$ or MnO_2[5] (d) the reaction of indole with chloroacetone and its utilization in Ugi-4-CR[6] (e) Ugi-4-CR with indole carboxylic acid, β-ketoester, primary amine, and isocyanide as well as the cyclization of the Ugi product under microwave irradiation at 180 °C for 30 min, which was reported by Krasavin[7] (f) Ullmann's coupling of 2-fluoro-nitrobenzene with indole-2-carboxylate and reduction of the nitro group[8] (g) intramolecular C–N bond formation via Buchwald reaction,[9] and (h) a one-pot coupling/-hydrolysis/intra-molecular condensation process using indole-2-carboxylate esters.[10]

2. Results and discussion

The reported approaches have their drawbacks, such as using activated substrates, hazardous reagents, and harsh reaction conditions. The designs of complexity-generating multicomponent sequential processes are desired and are gaining more importance in organic synthesis and drug delivery. In this regard, the use of transition metal catalyzed cyclizations of readily available multifunctional precursors, which could be synthesized through an efficient multicomponent reaction is a straightforward, promising synthetic strategy.[11] In this article, as a part of our ongoing studies on the post-transformation of Ugi-4-CR adducts to synthesize valuable heterocyclic compounds,[12] we report the results of studies

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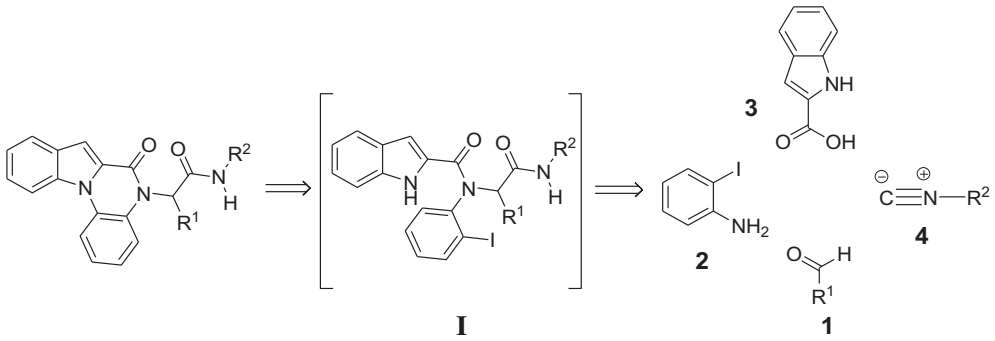
targeting the one-pot synthesis of indolo[1,2-*a*]quinoxalinone skeleton via an Ugi-4-CR condensation. To achieve this goal the retrosynthetic analysis is shown (Scheme 1). First of all, the Ugi product **I** as an intermediate is formed from the reaction of an aliphatic or aromatic aldehyde **1**, 2-iodoaniline **2**, indole carboxylic acid **3**, and an isocyanide **4** and then cyclization leading to the formation of the C–N bond is done using a metal catalyst.

The synthesis of compound **5a** as a model was chosen to study other aspects of this reaction like the variation of conditions. In these examples the corresponding Ugi adduct (**Ia**) was isolated and subsequently intramolecular *N*-arylation was done using $Pd(OAc)_2$ (10%), BINAP (20%), K_2CO_3 (2 equiv) at reflux in toluene in 48% yield. However, this yield was dramatically improved (nearly doubled) by a change of reagents and reaction conditions.



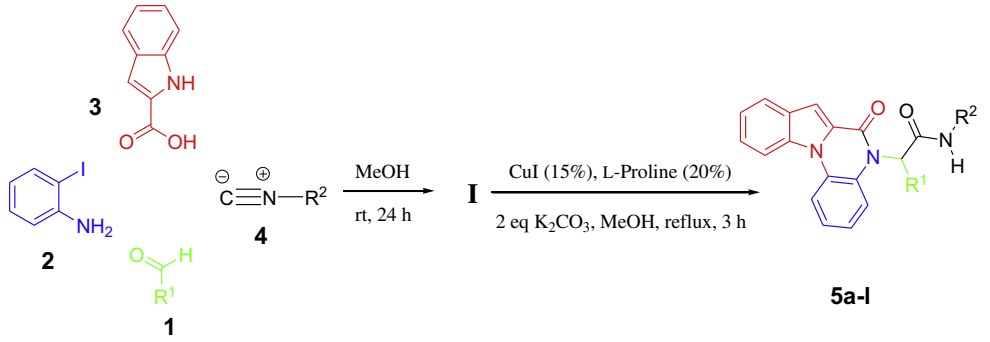
Scheme 1. Retrosynthetic pathway for the synthesis of indolo[1,2-*a*]quinoxalinones.

Ma et al. reported the role of CuI/L-proline as an efficient catalyst for the Ullmann reaction. This system was applied in different reactions, such as coupling of aryl halides with primary and secondary amines,[13] coupling of aryl halides with sulfinic acid salts,[14]azidation of aryl halides and vinyl halides,[15] and coupling of aryl halides with activated methyl compound.[16] Based on this experience, we have developed an efficient protocol for the solution phase synthesis of new indolo[1,2-*a*]quinoxalinone derivatives via a novel four-component sequential Ugi/Ullmann reaction in the presence of an inexpensive copper catalyst in high yields and with high bond-forming efficiency. The reaction was carried out in two steps in a one-pot procedure in MeOH (Scheme 2).

It was accomplished after 3 h in the presence of CuI (15%), L-proline (20%), and K_2CO_3 at reflux in MeOH with a yield of 87% (Scheme 3).

It shows that using palladium acetate in this reaction has serious drawbacks, i.e., low yield, long reaction times, formation of side products, and also the high temperature. The comparison of these experiments showed that so far the superior catalyst for this reaction is CuI/L-proline. According to this finding, we designed this reaction in a one-pot reaction in methanol and without separation of Ugi-4-CR adduct.

The molecular structure of the **5d** and **5f** was determined by X-ray analysis of suitable single crystals (Fig. 1). The products have



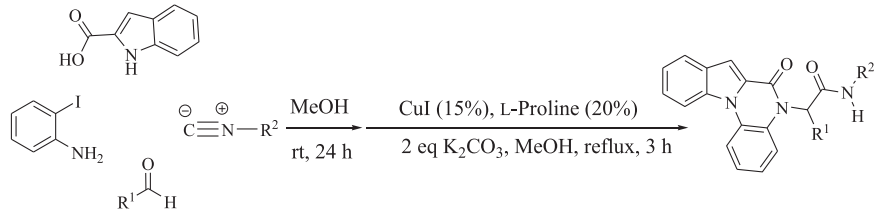
Scheme 2. Synthesis of indolo[1,2-*a*]quinoxalines (**5a**–**l**).

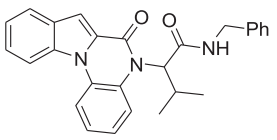
In this approach intermediates **I** were synthesized via the four-component reactions of aldehydes **1**, 2-iodoaniline **2**, 2-indole carboxylic acid **3**, and isocyanides **4** in MeOH at ambient temperature for 24 h. Afterward the Ugi adducts **I** were used without separation in the presence of catalytic amount of CuI (15 mol %), L-proline (20 mol %), and K_2CO_3 (2 equiv) at reflux conditions for 3 h, which resulted in the synthesis of indolo[1,2-*a*]quinoxalines **5a**–**l** in good to very good yields (63–87%). The results are summarized in Table 1. Notably the yield of the products derived from aliphatic aldehydes exceeded the ones obtained from aromatic aldehydes.

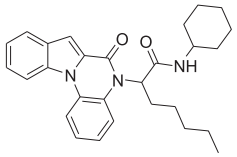
a helicene structure and it could be confirmed that using determination of the torsion angle between two faces, in the compound **5d** and **5f** the torsion angle among C_{16}–C_{11}–N_1–C_{21} are 15.0° and 10.4°, respectively. Also, the intermolecular hydrogen bonding between C=O and N–H groups formed a dimeric structure (Supplementary data).

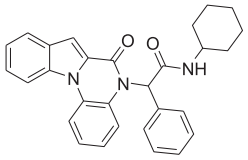
Control experiments indicated that this sequential reaction proceeds in two steps, namely: (i) Ugi-4-MCR between aldehydes **1**, 2-iodoaniline **2**, 2-indolcarboxylic acid **3**, and isocyanides **4**, that is, presumed as the first step of this one-pot process leading to intermediates bearing the structures of compounds **I** and (ii)

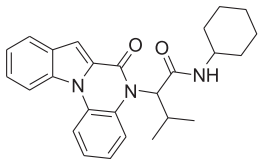
Table 1
Synthesis of indolo[1,2-*a*]quinoxalines **5a**–**l** via sequential Ugi/Ullmann reaction

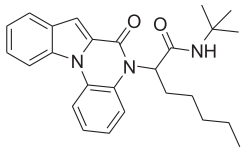


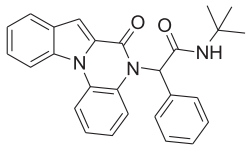

5a (83% yield)

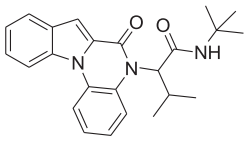

5e (86% yield)

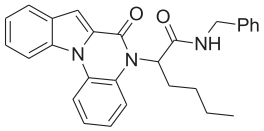

5i (67% yield)

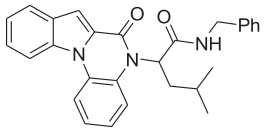

5b (85% yield)

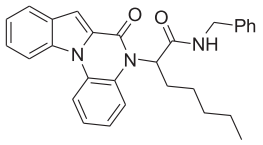

5f (81% yield)

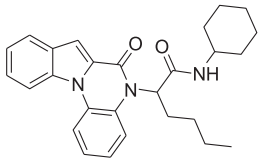

5j (63% yield)

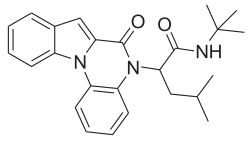

5c (80% yield)

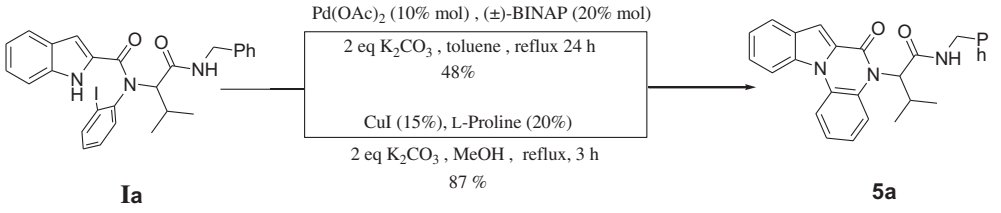

5g (87% yield)


5k (82% yield)


5d (87% yield)


5h (82% yield)


5l (84% yield)



Ia **5a**

Scheme 3.

In an Ullmann type reaction successively the indolo[1,2-*a*]quinoxalinones **5a**–**l** are formed. The proposed mechanism is shown in Scheme 4. The second step of the proposed mechanism is a known Ullman type coupling according to mechanism proposed by Ma.[17] At first, in this process the cuprous ion reacts with L-proline to form the chelate **A**, which coordinates with iodoarenes **I** to provide the π-complex **B**. Next, an intramolecular nucleophilic substitution occurs at the aromatic ring to give intermediate **C**. Finally, HI is eliminated from **C** with the aid of K_2CO_3 to give another π-complex, **D**, which cleaves to afford the indolo[1,2-*a*]quinoxalinones **5a**–**l** as the desired products with concurrent regeneration of the chelate **A**.

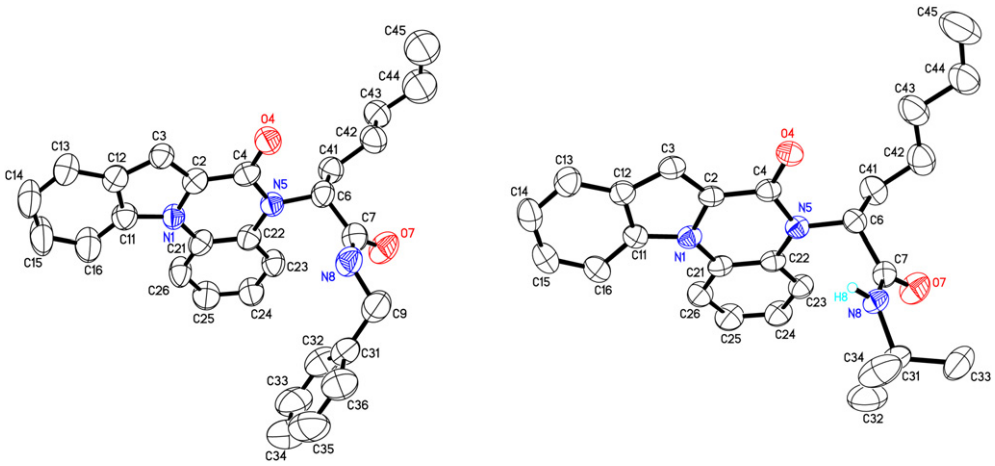
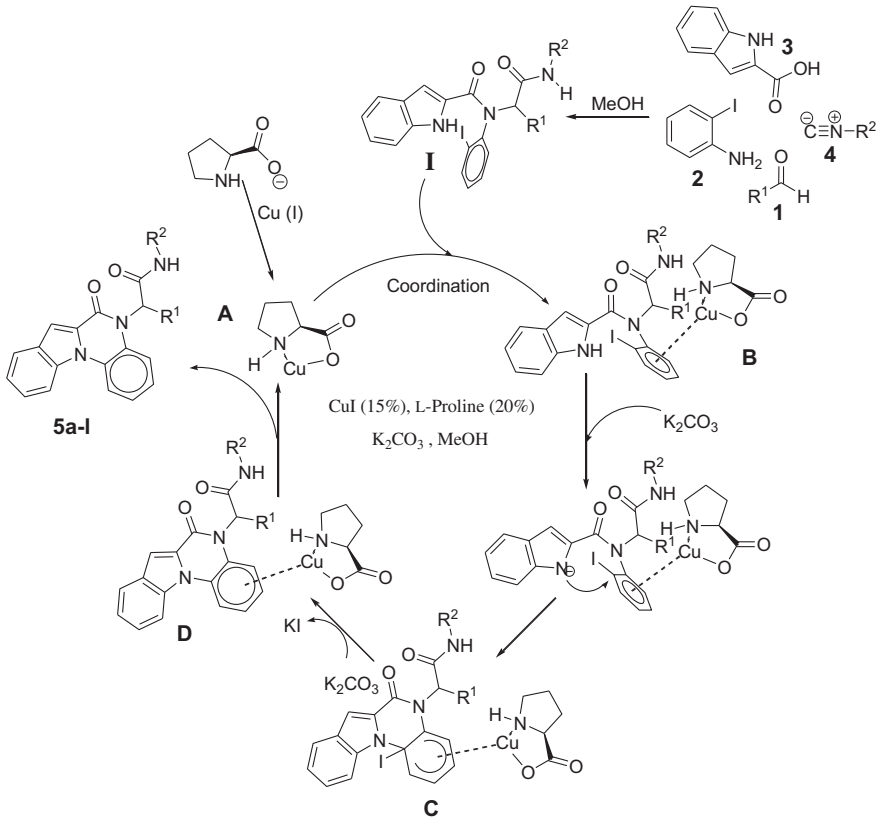


Fig. 1. ORTEP structure of **5d** (left) and **5f** (right).



Scheme 4. Proposed mechanism for the synthesis of indolo[1,2-*a*]quinoxalinones.

3. Conclusions

In summary, we have developed a new, mild strategy to assemble tetracyclic indolo[1,2-*a*]quinoxalinones. This reaction was realized through a novel one-pot Ugi/Ullmann process from readily available starting materials. This sequential process includes a Ugi reaction and subsequent intramolecular *N*-arylation of the Ugi adduct in the presence of catalytic amounts of CuI and L-proline in methanol at reflux. Moreover, it is noteworthy that this four-component one-pot synthesis involved the formation of one C–C, one C–O, and three C–N bonds in a highly selective fashion. This potent methodology will provide new alternatives in the field of drug discovery.

4. Experimental section

4.1. General

Commercially available materials were used without further purification. Melting points were determined on an *Electrothermal 9100* apparatus and were uncorrected. IR spectra were obtained on an ABB FT-IR FTLA 2000 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on Bruker DRX-500 AVANCE spectrometer at 500 MHz for ^{1}H NMR, and 125 MHz for ^{13}C NMR. $CDCl_3$ was used as solvent. HRMS was recorded on Mass-ESI-POS (Apex Qe-FT-ICR instrument) spectrometer.

4.2. General procedure for the synthesis of indolo[1,2-*a*] quinoxalines 5a–l

2-Iodoaniline (219 mg, 1 mmol), aldehyde (1 mmol), and MeOH (5 mL) were stirred for 30 min. Then, indole carboxylic acid (161 mg, 1 mmol) and, after 15 min, isocyanide (1 mmol) were added and the mixture was stirred for 24 h. The progress of reaction was monitored by TLC (eluent hexane/ethyl acetate 5:1). CuI (30 mg, 0.15 equiv), L-proline (23 mg, 0.2 equiv), and K_2CO_3 (276 mg, 2 mmol) were simultaneously added to the solution of Ugi adduct in MeOH. The mixture was stirred at reflux for 3 h. After this time, the reaction mixture was diluted with brine (30 mL) and was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried with sodium sulfate, concentrated to dryness in vacuo, and purification by column chromatography on silica gel (hexane/ethyl acetate) to give **5a**–**l** with 63–87%.

*4.2.1. N-Benzyl-3-methyl-2-(6-oxoindolo[1,2-a]quinoxalin-5(6H)-yl) butanamide (**5a**).* Yield (0.351 g, 83%) as a light yellow solid; mp 197–199 °C; R_f (20% EtOAc/hexane) 0.40;ν_{max} (KBr) 3323, 2957, 1680, 1648 cm^{-1}; δ_H (500 MHz, $CDCl_3$), 0.61 (3H, br s, C*H*$_3$), 1.27 (3H, br s, CH_3), 3.03 (1H, br s, *CH*), 4.50 (1H, br s, CH_2Ph), 4.59 (1H, br s, C*H*$_2$Ph), 5.72 (1H, br s, N*H*), 7.01 (1H, s, =C*H*), 7.19–7.55 (11H, m, Ar), 7.95 (2H, br s, Ar), 8.13 (1H, br s, Ar); δ_C 18.2, 21.7, 26.2, 43.5, 60.9, 107.4, 114.1, 115.7, 118.0, 122.4, 123.2, 124.1, 124.3, 125.7, 126.5, 127.2, 127.7, 128.5, 129.0, 134.1, 138.4, 158.4, 169.7; HRMS (ESI): MH^+ found 424.2020, $C_{27}H_{26}N_3O_2$ requires 424.2019.

*4.2.2. N-Cyclohexyl-3-methyl-2-(6-oxoindolo[1,2-a]quinoxalin-5(6H)-yl)butanamide (**5b**).* Yield (0.357 g, 86%) as a light yellow solid; mp 201–203 °C; R_f (20% EtOAc/hexane) 0.40;ν_{max} (KBr) 3312, 2927, 1674, 1648 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.62 (3H, br s, C*H*$_3$), 0.90–1.93 (13H, m, 5C*H*$_{2Cyclohexyl}$ and C*H*$_{3isopropyl}$), 2.90–3.20 (1H, m, C*H*), 3.78–3.83 (1H, m, C*H*, H$_{Cyclohexyl}$), 5.54 (1H, br s, N*H*), 6.36 (1H, br s, C*H*), 7.29–7.40 (3H, m, Ar), 7.53 (1H, t, *J* 7.9 Hz, Ar), 7.58 (1H, s, *H*C=), 7.88 (1H, d, *J* 7.9 Hz, Ar), 7.95–8.06 (1H, m, Ar), 8.26 (1H, d, *J* 8.9 Hz, Ar), 8.32 (1H, d, *J* 8.9 Hz, Ar); δ_C 18.3, 21.4, 24.6, 24.7, 25.5, 26.0, 32.7, 48.4, 61.5, 107.6, 114.3, 115.6, 118.2, 122.6, 123.3, 124.1, 124.4, 125.7, 126.7, 127.7, 129.3, 134.3, 158.6, 168.7; HRMS (ESI): MH^+ found 416.2332,$C_{26}H_{30}N_3O_2$ requires 416.2332.

*4.2.3. N-tert-Butyl-3-methyl-2-(6-oxoindolo[1,2-a]quinoxalin-5(6H)-yl)butanamide (**5c**).* Yield (0.311 g, 80%) as a light yellow solid; mp 147–149 °C; R_f(20% EtOAc/hexane) 0.40;ν_{max} (KBr) 3327, 2957, 1684, 1648 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.61 (3H, br s, C*H*$_3$), 0.90–1.93 (3H, br s, C*H*$_3$), 1.32 (9H, s, *t*-Bu), 2.96 (1H, br s, C*H*$_{isopropyl}$), 5.46 (1H, br s, N*H*), 6.28 (1H, br s, C*H*), 7.29–7.44 (3H, m, Ar), 7.55 (1H, t, *J* 7.8 Hz, Ar), 7.61 (1H, s, *H*C=), 7.91 (1H, d, *J* 7.9 Hz, Ar), 8.02 (1H, br s, Ar), 8.28 (1H, d, *J* 8.5 Hz, Ar), 8.34 (1H, d, *J* 7.9 Hz, Ar); δ_C 18.3, 21.3, 26.0, 28.6, 51.4, 62.2, 107.6, 114.3, 115.6, 118.3, 122.7, 123.3, 124.1, 124.4, 125.7, 126.9, 129.3, 134.4, 158.6, 169.1; HRMS (ESI): MH^+ found 390.2176, $C_{24}H_{28}N_3O_2$ requires 390.2176.

*4.2.4. N-Benzyl-2-(6-oxoindolo[1,2-a]quinoxalin-5(6H)-yl) heptanamide (**5d**).* Yield (0.393 g, 87%) as a yellow solid; mp 133–135 °C; R_f (20% EtOAc/hexane) 0.40;ν_{max} (KBr) 3291, 2926, 1680, 1643 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.77 (3H, t, *J* 7.3, C*H*$_3$), 1.08–1.31 (6H, m, C*H*$_2$), 2.08 (1H, br s, C*H*$_2$), 2.41–2.49 (1H, m, C*H*$_2$), 4.42 (1H, dd, *J* 15.0, 5.5 Hz, C*H*$_2$Ph), 4.72 (1H, dd, *J* 15.0, 6.6 Hz, C*H*$_2$Ph), 6.15 (1H, br s, N*H*), 6.75 (1H, br s, C*H*), 7.16–7.35 (9H, m, Ar), 7.43 (1H, br s, Ar), 7.58 (1H, d, *J* 7.9 Hz, 1H, Ar),7.65(1H, br s, Ar), 7.81(1H, br s, Ar), 7.99 (1H, d, *J* 7.1 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 13.9, 22.3, 26.1, 27.7, 31.3, 43.7, 55.0, 107.2, 114.0, 115.9, 118.0, 122.2, 123.1, 123.8, 124.1, 125.6, 126.9, 127.2, 128.0, 128.4, 128.8, 134.0, 138.5, 157.8, 170.4; HRMS (ESI): MH^+ found 452.2332, $C_{29}H_{30}N_3O_2$ requires 452.2332.

X-ray structure analysis colorless: colorless crystal (plate), dimensions 0.28×0.24×0.06 mm^3, crystal system triclinic, space group $P\bar{1}$, Z=8, a=10.3791(3) Å, b=21.6975(6) Å, c=23.0136(6) Å, α=73.5020(10)°, β=87.9090(10)°, γ=78.0280(10)°, V=4859.8(2) $Å^3$, ρ=1.234 g/cm^3, T=200(2) K, θ_{max}=21.49°, radiation Mo Kα, λ=0.71073 Å, 0.3°ω-scans with CCD area detector, 1200 frames in two runs covering significantly more than a hemisphere in reciprocal space, 18,883 reflections measured, 11,106 unique (R(int)=0.0450), 6288 observed ($I>2s$(I)), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS based on the Laue symmetry of the reciprocal space, μ=0.08 mm^{-1}, T_{min}=0.98, T_{max}=1.00, structure solved by direct methods and refined against F^2 with a Full-matrix least-squares algorithm using the SHELXTL (Version 2008/4) software package,[2] 1221 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.04 for observed reflections, final residual values $R1(F)$=0.081, $wR(F^2)$=0.213 for observed reflections, residual electron density −0.29 to 0.33 e$Å^{-3}$. CCDC 796306 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

*4.2.5. N-Cyclohexyl-2-(6-oxoindolo[1,2-a]quinoxalin-5(6H)-yl)heptanamide (**5e**).* Yield (0.382 g, 86%) as a yellow solid; mp 155–157 °C; R_f (20% EtOAc/hexane) 0.50;ν_{max} (KBr) 3312, 2927, 1674, 1648 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.76 (3H, t, *J* 7.0 Hz, C*H*$_3$), 0.99–1.93 (16H, m, 8C*H*$_2$), 2.01–2.12 (1H, m, C*H*), 2.39–2.46 (m, 1H, C*H*), 3.81–3.87 (1H, m, C*H*), 5.91 (1H, br s, NH), 6.55 (1H, br s, C*H*), 7.27–7.36 (3H, m, Ar), 7.44 (1H, s, =CH), 7.47 (1H, t, *J* 7.7 Hz, Ar), 7.59 (1H, d, *J* 8.9 Hz, Ar), 7.79 (1H, d, *J* 7.8 Hz, Ar), 8.15 (1H, d, *J* 8.5 Hz, Ar), 8.28 (1H, d, *J* 8.0 Hz, Ar); δ_C 13.8, 22.3, 24.8, 24.9, 25.4, 26.2, 27.7, 31.3, 32.7, 32.8, 48.7, 55.6, 107.6, 114.2, 115.8, 118.2, 122.6, 123.2, 123.9, 124.1, 125.7, 127.0, 127.5, 129.2, 134.3, 158.0, 169.4; HRMS (ESI): MH^+ found 444.2645, $C_{28}H_{34}N_3O_2$ requires 444.2645.

*4.2.6. N-tert-Butyl-2-(6-oxoindolo[1,2-a]quinoxalin-5(6H)-yl)heptanamide (**5f**).* Yield (0.339 g, 81%) as a yellow solid; mp 124–126 °C; R_f (20% EtOAc/hexane) 0.450;ν_{max} (KBr) 3391, 2921, 1683, 1653 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.76 (3H, t, *J* 7.2, C*H*$_3$), 1.17–1.21 (6H, m, C*H*$_2$), 1.30 (9H, s, *t*-Bu), 1.99–2.13 (1H, m, C*H*), 2.35–2.42 (m, 1H, C*H*), 5.92 (1H, br s, N*H*), 6.12 (1H, br s, C*H*), 7.27–7.40 (3H, m, Ar), 7.53 (1H, t, *J* 9.1 Hz, Ar), 7.58 (1H, s, =CH), 7.61 (1H, d, *J* 9.2 Hz, Ar), 7.89 (1H, d, *J* 8.0 Hz, Ar), 8.27 (1H, d, *J* 8.9 Hz, Ar), 8.35 (1H, dd, *J* 8.3, 1.0 Hz, Ar); δ_C 13.8, 22.2, 26.2, 27.5, 28.6, 31.3, 51.5, 56.1, 107.8, 114.3, 115.8, 118.2, 122.7, 123.3, 124.0, 124.1, 125.8, 127.1, 129.3, 134.3, 158.1, 169.6; HRMS (ESI): MH^+ found 418.2489, $C_{26}H_{32}N_3O_2$ requires 418.2488.

X-ray structure analysis colorless: crystal (polyhedron), dimensions 0.30×0.28×0.22 mm^3, crystal system monoclinic, space group $P2_1/n$, Z=8, a=14.1038(1) Å, b=18.1556(1) Å, c=18.2930(2) Å, α=90°, β=93.2240(10)°, γ=90°, V=4676.75(7) $Å^3$, ρ=1.186 g/cm^3, T=200(2) K, θ_{max}=25.03°, radiation Mo, Kα λ=0.71073 Å, 0.3°ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 39,088 reflections measured, 8266 unique (R(int)=0.0488), 5760 observed ($I>2s(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS based on the Laue symmetry of the reciprocal space, μ=0.08 mm^{-1}, T_{min}=0.98, T_{max}=0.98, structure solved by direct methods and refined against F^2 with a Full-matrix least-squares algorithm using the SHELXTL (Version 2008/4) software package, 576 parameters refined, hydrogen atoms were treated using appropriate

riding models, except of the hydrogen at the nitrogen atoms, which were refined isotropically, goodness of fit 1.03 for observed reflections, final residual values $R1(F)$=0.065, $wR(F^2)$=0.156 for observed reflections, residual electron density −0.44 to 0.82 eÅ^{-3}. CCDC 796307 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

*4.2.7. N-Benzyl-2-(6-oxoindolo[1,2-a]quinoxalin-5(6H)-yl)hexanamide (**5g**).* Yield (0.381 g, 87%) as a yellow solid; mp 109–111 °C; R_f (20% EtOAc/hexane) 0.55;ν_{max} (KBr) 3289, 2922, 1668, 1643 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.77 (3H, t, *J* 6.5, CH_3), 1.07–1.33 (4H, m, 2CH_2), 2.09 (1H, br s, C*H*), 2.43–2.50 (1H, m, C*H*), 4.42 (1H, dd, *J* 15.0, 5.5 Hz, C*H*Ph), 4.70 (1H, dd, *J* 15.0, 5.5 Hz, C*H*Ph), 6.13 (1H, br s, NH), 6.77 (1H, s, C*H*), 7.15–7.83 (13H, m, Ar and =CH), 8.01 (1H, d, *J* 7.4 Hz, Ar); δ_C 13.8, 22.2, 27.5, 28.5, 43.7, 55.2, 107.3, 114.0, 115.9, 118.0, 122.3, 123.1, 123.8, 124.1, 125.6, 126.9, 127.2, 127.9, 128.4, 128.8, 134.0, 138.4, 157.8, 170.4; HRMS (ESI): MH$^+$ found 438.2176, $C_{28}H_{28}N_3O_2$ requires 438.2175.

*4.2.8. N-Cyclohexyl-2-(6-oxoindolo[1,2-a]quinoxalin-5(6H)-yl)hexanamide (**5h**).* Yield (0.353 g, 82%) as a light yellow solid; mp 156–158 °C; R_f (20% EtOAc/hexane) 0.50;ν_{max} (KBr) 3296, 2927, 1668, 1638 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.78 (3H, t, *J* 7.0 Hz, CH_3), 0.99–1.93 (14H, m, 7CH_2), 2.02–2.12 (1H, m, C*H*), 2.39–2.46 (1H, m, C*H*), 3.81–3.91 (1H, m, C*H*), 6.02 (1H, br s, N*H*), 6.47 (1H, br s, C*H*), 7.27–7.49 (5H, m, Ar), 7.59 (1H, d, *J* 7.8 Hz, Ar), 7.79 (1H, d, *J* 7.5 Hz, Ar), 8.15 (1H, d, *J* 8.7 Hz, Ar), 8.29 (1H, d, *J* 7.9 Hz, Ar); δ_C 13.8, 22.3, 24.8, 24.9, 25.4, 27.5, 28.7, 32.7, 32.8, 48.7, 55.4, 107.6, 114.2, 115.9, 118.1, 122.6, 123.2, 123.9, 124.1, 125.7, 127.0, 127.5, 129.2, 134.3, 158.0, 169.4; HRMS (ESI): MH$^+$ found 430.2489, $C_{27}H_{32}N_3O_2$ requires 430.2488.

*4.2.9. N-Cyclohexyl-2-(6-oxoindolo[1,2-a]quinoxalin-5(6H)-yl)-2-phenylacetamide (**5i**).* Yield (0.302 g, 67%) as a light yellow solid; mp 183–184 °C; R_f (20% EtOAc/hexane) 0.50;ν_{max} (KBr) 3348, 2927, 1684, 1653 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.06–1.99 (10H, m, 5CH_2), 3.86–3.90 (1H, m, C*H*), 6.21 (1H, d, *J* 7.7 Hz, N*H*), 6.66 (1H, s, C*H*), 7.13 (1H, t, *J* 7.8 Hz, Ar), 7.25–7.46 (8H, m, Ar), 7.54 (1H, t, *J* 7.8 Hz, Ar), 7.64 (1H, s, Ar), 7.90 (1H, d, *J* 8.0 Hz, Ar), 8.29 (1H, d, *J* 8.6 Hz, Ar), 8.35 (1H, d, *J* 8.0 Hz, Ar); δ_C 24.6, 24.7, 25.5, 32.6, 32.7, 48.7, 61.3, 108.0, 114.3, 115.6, 118.4, 122.6, 123.4, 123.9, 124.0, 125.8, 127.0, 127.8, 127.9, 128.0, 128.6, 128.8, 129.3, 134.3, 134.5, 157.6, 167.0; HRMS (ESI): MH$^+$ found 450.2176, $C_{29}H_{28}N_3O_2$ requires 450.2176.

*4.2.10. N-tert-Butyl-2-(6-oxoindolo[1,2-a]quinoxalin-5(6H)-yl)-2-phenylacetamide (**5j**).* Yield (0.267 g, 63%) as a light yellow solid; mp 233–235 °C; R_f (20% EtOAc/hexane) 0.50;ν_{max} (KBr) 3353, 2922, 1678, 1648 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.33 (9H, s, *t*-Bu), 6.17 (1H, br s, N*H*), 6.63 (1H, s, C*H*), 7.11 (1H, td, *J* 7.9, 1.2 Hz, Ar), 7.25–7.55 (8H, m, Ar), 7.53 (1H, td, *J* 7.9, 1.2 Hz, Ar), 7.62 (1H, s, Ar), 7.88 (1H, d, *J* 7.9 Hz, Ar), 8.28 (1H, d, *J* 8.2 Hz, Ar), 8.33 (1H, dd, *J* 8.2, 1.2 Hz, Ar); δ_C 28.6, 51.8, 61.7, 107.9, 114.3, 115.6, 118.5, 122.6, 123.3, 123.8, 123.9, 125.8, 127.0, 127.7, 127.8, 127.9, 128.6, 128.7, 129.3, 134.3, 134.2, 157.6, 167.1; HRMS (FAB$^+$) MH$^+$ found 424.2043, $C_{27}H_{26}N_3O_2$ requires 424.2035.

*4.2.11. N-Benzyl-4-methyl-2-(6-oxoindolo[1,2-a]quinoxalin-5(6H)-yl)pentanamide (**5k**).* Yield (0.360 g, 82%) as a light yellow solid; mp 131–133 °C; R_f (20% EtOAc/hexane) 0.55;ν_{max} (KBr) 3222, 2952, 1674, 1643 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.5 Hz, CH_3), 0.95 (3H, d, *J* 6.5 Hz, CH_3), 1.36–1.41 (1H, m, C*H*), 1.99 (1H, br s, C*H*), 2.36 (1H, br s, C*H*), 4.41 (1H, dd, *J* 14.7, 5.3 Hz, C*H*Ph), 4.75 (1H, dd, *J* 14.7, 5.3 Hz, C*H*Ph), 6.22 (1H, br s, N*H*), 6.67 (1H, br s, C*H*), 7.17–7.37 (9H, m, Ar), 7.41 (1H, br s, Ar), 7.58 (1H, d, *J* 8.5 Hz, Ar), 7.96 (1H, br s, Ar); δ_C 22.0, 23.0, 25.7, 36.7, 43.8, 53.4, 107.2, 113.9, 116.0, 118.1, 122.2, 123.2, 123.8, 124.1, 125.6, 126.9, 127.2, 128.0, 128.4, 128.7, 133.9, 138.5, 157.8, 170.6; HRMS (ESI): MH$^+$ found 438.2176, $C_{28}H_{28}N_3O_{2j}$ requires 438.2176.

*4.2.12. N-tert-Butyl-4-methyl-2-(6-oxoindolo[1,2-a]quinoxalin-5(6H)-yl)pentanamide (**5l**).* Yield (0.340 g, 84%) as a light yellow solid; mp 117–119 °C; R_f (20% EtOAc/hexane) 0.50;ν_{max} (KBr) 3332, 2957, 1678, 1653 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.5 Hz, CH_3), 0.90 (3H, d, *J* 6.5 Hz, CH_3), 1.30 (9H, s, *t*-Bu), 1.40–1.45 (1H, m, C*H*), 1.96 (1H, br s, C*H*), 2.28 (1H, br s, C*H*), 6.04 (2H, br s, N*H* and C*H*), 7.28 (1H, t, *J* 7.9 Hz, Ar), 7.36 (1H, t, *J* 7.7 Hz, Ar), 7.39 (1H, t, *J* 7.7 Hz, Ar), 7.54 (1H, t, *J* 7.7 Hz, Ar), 7.60 (1H, d, *J* 7.9 Hz, Ar), 7.62 (1H, s, =C*H*), 7.90 (1H, d, *J* 8.0 Hz, Ar), 8.27 (1H, d, *J* 8.7 Hz, Ar), 8.35 (1H, d, *J* 8.2 Hz, Ar); δ_C 22.0, 22.9, 25.8, 28.6, 36.5, 51.5, 54.5, 107.8, 114.3, 115.8, 118.4, 120.9, 122.7, 123.3, 124.0, 124.1, 125.5, 125.8, 127.1, 129.3, 134.4, 158.1, 169.7; HRMS (ESI): MH$^+$ found 404.2332, $C_{25}H_{30}N_3O_2$ requires 404.2333.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.052. These data include MOL files and InChiKeys of the most important compounds described in this article.

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