

One-pot synthesis of pyrrolo[1,2-*a*]quinoxalines†Aiping Huang,^a Feng Liu,^a Chunjing Zhan,^a Yanli Liu^a and Chen Ma^{*a,b}

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A transition metal-free process for the regioselective synthesis of pyrrolo[1,2-*a*]quinoxalines under mild conditions in one-pot is described. The reaction afforded a variety of products in good to excellent yields. Indolo[1,2-*a*]quinoxalines were also synthesized from indole-2-carboxamides under the same conditions.

Introduction

The pyrrolo[1,2-*a*]quinoxaline subunit is present in various biologically and medicinally useful molecules,¹ and many pyrrolo[1,2-*a*]quinoxaline derivatives are anti-HIV agents **A**,^{1a} antimalarial agents **B**,^{1b} antagonist agents **C**,^{1c} anticancer agents **D**,^{1d,1e} and PARP-1 inhibitors **E**.^{1f} Additionally, pyrrolo[1,2-*a*]quinoxalines are also important intermediates for the construction of 5-HT₃ receptor agonists **F** (Fig. 1).²

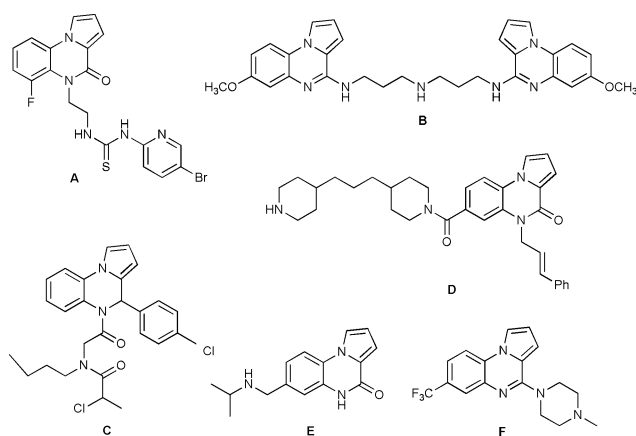
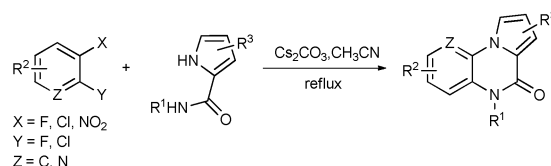


Fig. 1 Some important pyrrolo[1,2-*a*]quinoxalines.

The conventional method reported for the synthesis of pyrrolo[1,2-*a*]quinoxalines proceeded through three steps: formation of pyrrole ring, reduction of nitro group and cyclization with triphosgene.² This method employs hazardous reagents, harsh reaction conditions, or inconvenient operations. Additionally, the azole arylation procedure limits the scope of suitable substrates. Beccalli described a palladium catalyzed C–N bond formation

method to construct these tricyclic compounds.³ However, the methylation of 2-haloanilines limits the scope of this method. Ma and Yuan developed a CuI/L-proline catalyzed strategy to assemble these compounds from 2-halo-trifluoroacetanilides and pyrrole-2-carboxylate esters, but this method needs a multistep synthesis.⁴ Recently, Reeves presented a CuI and sparteine catalyzed strategy for the annulation of 2-formylpyrroles with *o*-aminoiodoarenes to assemble these compounds, but a costly ligand was required.⁵

Bai and Xiang described the synthesis of these tricyclic compounds through Smiles rearrangement⁶ without transition metal catalyst, although a multistep synthesis was needed.^{6c,7} Therefore, a direct and facile approach for the synthesis of pyrrolo[1,2-*a*]quinoxalines became more desirable. Herein, we report a simple, efficient, and metal-free process for the synthesis of pyrrolo[1,2-*a*]quinoxalines under mild conditions. We used 1,2-dihalobenzenes or 2-halonitroarenes as substrates and pyrrole-2-carboxamides^{8,9} as reagents. The reaction was carried out in the presence of cesium carbonate, and acetonitrile as solvent in one-pot (Scheme 1).



Scheme 1 The reaction of 1,2-dihalobenzenes or 2-halonitroarenes with pyrrole-2-carboxamides.

Results and discussion

The expected pyrrolo[1,2-*a*]quinoxalines **3** were obtained by the reactions of pyrrole-2-carboxamides **2** and 1-fluoro-2-nitrobenzene **1** in refluxing acetonitrile. The experimental results are collected in Table 1. As observed in Table 1, a variety of aliphatic or aromatic pyrrole-2-carboxamides afforded good to excellent yields of these tricyclic products. However, pyrrole-2-carboxamides with an electron-withdrawing group (Table 1, entries 8–10) gave higher yields than those with an electron-donating group (Table 1, entries 11, 12).

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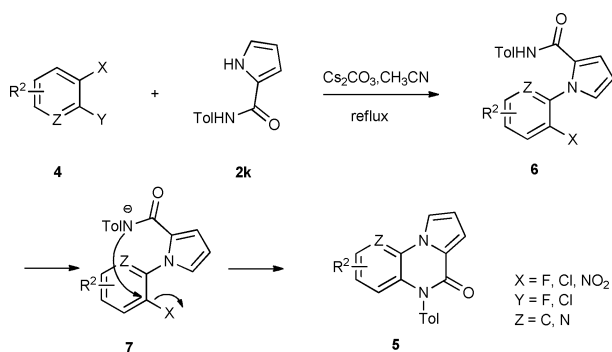
Table 1 Synthesis of pyrrolo[1,2-*a*]quinoxalines **3**^a

Entry	R ¹	2	Time (h)	Product	Yield (%) ^b
1	Et	2a	14	3a	99
2	Pr	2b	16	3b	72
3	<i>i</i> -Pr	2c	12	3c	74
4	<i>c</i> -Hex	2d	8	3d	96
5	Bn	2e	13	3e	93
6	3,4-(MeO) ₂ -C ₆ H ₃ (CH ₂) ₂	2f	9	3f	80
7	Ph	2g	9	3g	93
8	4-FC ₆ H ₄	2h	8	3h	94
9	4-ClC ₆ H ₄	2i	13	3i	94
10	4-BrC ₆ H ₄	2j	16	3j	98
11	4-MeC ₆ H ₄	2k	4	3k	83
12	4-MeOC ₆ H ₄	2l	6	3l	89

^a Reaction conditions: pyrrole-2-carboxamide **2** (1.0 equiv), 1-fluoro-2-nitrobenzene **1** (1.2 equiv), Cs₂CO₃ (3.5 equiv), reflux. ^b Isolated yield.

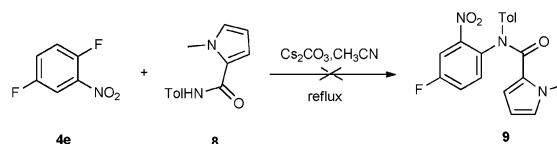
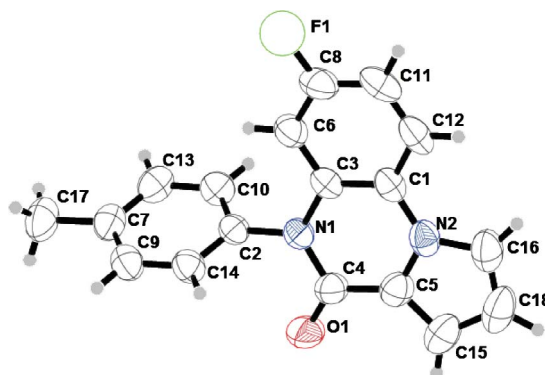
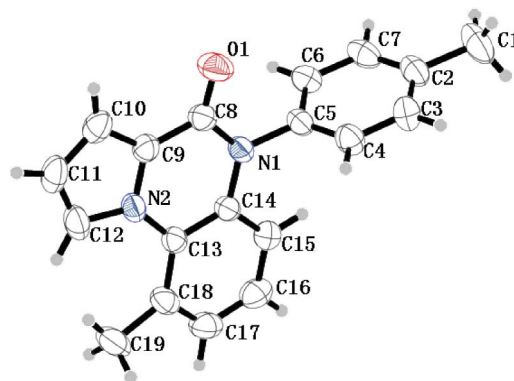
To explore the scope of this methodology, a variety of 1,2-dihalobenzenes or 2-halonitroarenes **4** were studied under the same reaction conditions (Table 2). As shown in Table 2, 1,2-dihalobenzenes or 2-halonitroarenes with an electron-withdrawing group (entries 1–5 and 9–11) or an electron-donating group (entries 6–8) afforded good yields of pyrrolo[1,2-*a*]quinoxalines **5**. It is noteworthy that all substrates have a strong electron-withdrawing group. These results indicate that the strong electron-withdrawing group plays a key role in the process. These phenomena can also be seen from reactions of different 2-fluoronitroarenes (entries 5–8). However, the reactant with nitro group (entry 1) afforded a higher yield of **5** than those with a cyano group (entries 2 and 3). 2,3-Dichloro-5-(trifluoromethyl)pyridine afforded the desired product in excellent yield (entry 4). 1-Chloro-2-nitro-4-(trifluoromethyl)benzene and 2-chloro-3-nitropyridine also gave the desired products in good yields (entries 9, 10). 1,5-Difluoro-2,4-dinitrobenzene also worked well and afforded the product in good yield (entry 11).

A plausible mechanism for these results is shown in Scheme 2. Compound **6** was formed by nucleophilic substitution of compound **2k** on 1,2-dihalobenzenes or 2-halonitroarenes **4**. The next step was the formation of carboxamide anion **7**. Finally,

**Scheme 2** Plausible mechanism for formation of pyrrolo[1,2-*a*]quinoxalines in one-pot.

an intramolecular nucleophilic reaction of **7** with displacement of the leaving group by carboxamide anion led to pyrrolo[1,2-*a*]quinoxaline **5**.

In order to demonstrate this mechanism, we used *N*-ethyl-1-methyl-1*H*-pyrrole-2-carboxamide^{9,10} **8** and **4e** as substrates in refluxing acetonitrile in the presence of cesium carbonate (Scheme 3). However, we did not detect any new product even when the reaction was refluxed for 8 h. This experiment suggested that the first step of the reaction of **4e** and **2k** was replacement of fluoride anion with pyrrolyl anion. Subsequently, **6e** underwent an intramolecular nucleophilic substitution to yield **5e**. We supposed that the formation of the six-centred structure made the activation energy of the second nucleophilic substitution reduce dramatically. The structures of products **5e** and **5g** were identified by X-ray diffraction analysis (Fig. 2, 3).

**Scheme 3** Reaction of *N*-ethyl-1-methyl-1*H*-pyrrole-2-carboxamide **8** with 1,4-difluoro-2-nitrobenzene **4e**.**Fig. 2** X-ray structure of compound **5e**.**Fig. 3** X-ray structure of compound **5g**.

To expand the applicability of this methodology, we then investigated a number of indole-2-carboxamides¹¹ **10**. As shown in Table 3, reactions of 1-fluoro-2-nitrobenzene with indole-2-carboxamide, 5-fluoro- and 5-methoxyindole-2-carboxamides

Table 2 Synthesis of pyrrolo[1,2-*a*]quinoxalines **5**^a

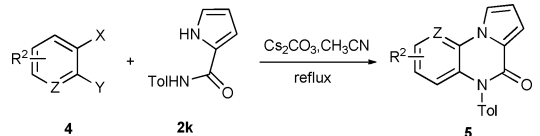
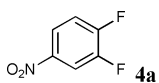
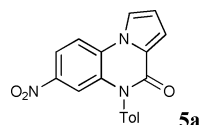
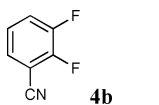
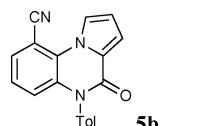
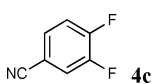
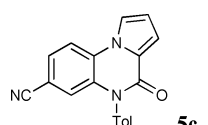
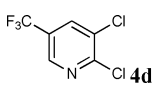
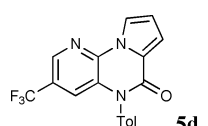
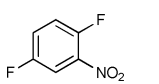
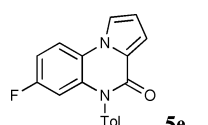
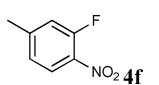
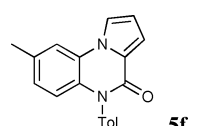
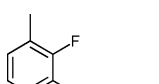
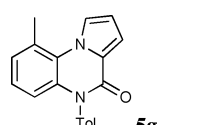
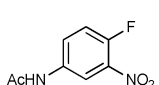
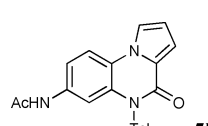
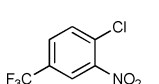
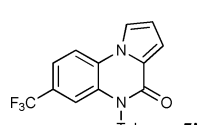
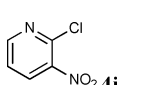
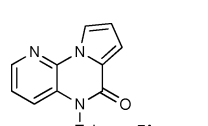
				
Entry	4	Time (h)	Product	Yield (%) ^c
1	 4a	4	 5a	92
2	 4b	8	 5b	75
3	 4c	6	 5c	70
4	 4d	7	 5d	97
5	 4e	3	 5e	82
6	 4f	7	 5f	85
7	 4g	7	 5g	95
8	 4h	11	 5h	77
9	 4i	10	 5i	86
10	 4j	6	 5j	68

Table 2 (Contd.)

Entry	4	Time (h)	Product	Yield (%) ^c
11 ^b	 4k	7	 5k	60

^a Reaction conditions: **2k** (1.0 equiv), **4** (1.2 equiv), Cs₂CO₃ (3.5 equiv), CH₃CN (15 mL). ^b **2k** (1.7 equiv), **4k** (1.0 equiv), Cs₂CO₃ (5.95 equiv), CH₃CN (15 mL). ^c Isolated yield.

Table 3 Synthesis of indolo[1,2-*a*]quinoxalines **11**^a

Entry	1 or 4	R ³	Time (h)	Product	Yield (%) ^b
1	1	H	4	 11a	92
2	1	5-MeO	8	 11b	82
3	1	5-F	6	 11c	92
4	4a	H	7	 11d	73
5	4e	H	3	 11e	83

^a Reaction conditions: **10** (1.0 equiv), **1** or **4** (1.2 equiv), Cs₂CO₃ (3.5 equiv), reflux. ^b Isolated yield.

worked well to afford indolo[1,2-*a*]quinoxalines **11** in good to excellent yields (entries 1–3). The reactions of indole-2-carboxamide **10** with 1,2-difluoro-4-nitrobenzene or 1,4-difluoro-2-nitrobenzene under the same conditions also gave the products in good yields (entries 4 and 5).

Conclusions

In conclusion, we have developed an efficient and economical method for the synthesis of pyrrolo-[1,2-*a*]quinoxalines under mild conditions. A variety of pyrrolo[1,2-*a*]quinoxaline derivatives were synthesized from pyrrole-2-carboxamides in good to excellent yields. Indole-2-carboxamides were compatible with this approach, giving indolo[1,2-*a*]quinoxalines in high yields. This transition metal-free process has potential applications in the synthesis of biologically and medically relevant compounds.

Experimental section

General information

Pyrrole-2-carboxamides, *N*-ethyl-1-methyl-1*H*-pyrrole-2-carboxamide^{8,9} and indole-2-carboxamides¹¹ were prepared according to literature procedures. Acetonitrile was distilled from calcium hydride prior to use. Other reagents were commercially available and were used without further purification. All reactions were monitored by thin-layer chromatography (TLC). ¹H NMR spectra were recorded on a Bruker Avance 400 or 300 spectrometer at 400 or 300 MHz, using CDCl₃ or DMSO-*d*₆ as solvent and tetramethylsilane (TMS) as internal standard. ¹³C NMR spectra were run in the same instrument at 100 or 75 MHz. Melting points were determined on an XD-4 digital micro melting point apparatus. HRMS spectra were determined on a Q-TOF6510 spectrometer (Agilent).

General experimental procedure for pyrrolo[1,2-*a*]quinoxalines **3**.

A mixture of pyrrolamide **2** (1.0 mmol), 1-fluoro-2-nitrobenzene **1** (1.2 mmol) and Cs₂CO₃ (3.5 mmol) in acetonitrile (15 mL) was refluxed, and TLC monitored the end of the reaction. Then the mixture was cooled to room temperature and diluted with brine (60 mL) and extracted with dichloromethane twice (2 × 30 mL). The combined organic layers were dried with MgSO₄ and the

solvent was removed *in vacuo* to afford a residue. The residue was purified by column chromatography on silica gel to afford 3.

5-Ethylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3a). Pale yellow solid (99%). mp 76–79 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 8.08 Hz, 1H), 7.61 (dd, *J* = 2.64, 1.48 Hz, 1H), 7.28 (d, *J* = 3.84 Hz, 2H), 7.20 (dd, *J* = 4.08, 1.48 Hz, 1H), 7.18 (q, *J* = 3.96 Hz, 1H), 6.63 (dd, *J* = 3.84, 2.88 Hz, 1H), 4.29 (q, *J* = 7.12 Hz, 2H), 1.34 (t, *J* = 7.16 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 12.59, 36.14, 111.99, 112.36, 113.15, 115.12, 116.16, 120.89, 122.34, 125.25, 129.04, 134.63, 155.12. HRMS calcd for C₁₃H₁₂N₂O 212.0950; found: 212.0962.

5-Propylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3b). Pale yellow solid (72%). mp 78–80 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, *J* = 7.96 Hz, 1H), 7.64 (dd, *J* = 2.40, 1.44 Hz, 1H), 7.28–7.31 (m, 2H), 7.20 (m, 2H), 6.65 (dd, *J* = 3.84, 3.01 Hz, 1H), 4.21 (t, *J* = 7.72 Hz, 2H), 1.78 (m, 2H), 1.05 (t, *J* = 7.44 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 11.32, 20.80, 42.70, 112.49, 113.19, 114.74, 115.72, 115.79, 122.64, 123.28, 124.14, 125.51, 129.40, 155.42. HRMS calcd for C₁₄H₁₄N₂O 226.1106; found: 226.1095.

5-Isopropylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3c). Brown oil (74%). ¹H NMR (400 MHz, CDCl₃) δ 7.68 (dd, *J* = 8.04, 1.40 Hz, 1H), 7.61 (dd, *J* = 2.68, 1.48 Hz, 1H), 7.53 (d, *J* = 8.40 Hz, 1H), 7.25–7.30 (m, 1H), 7.20 (m, 2H), 6.64 (dd, *J* = 3.76, 2.84 Hz, 1H), 5.42 (s, 1H), 1.66 (d, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 20.03, 46.40, 112.35, 113.35, 115.06, 115.50, 116.64, 122.57, 123.82, 124.54, 124.99, 155.97. HRMS calcd for C₁₄H₁₄N₂O 226.1106; found: 226.1136.

5-Cyclohexylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3d). Brown solid (96%). mp 99–101 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.65 (dd, *J* = 8.04, 1.40 Hz, 1H), 7.60 (dd, *J* = 2.64, 1.52 Hz, 1H), 7.56 (d, *J* = 8.24 Hz, 1H), 7.25–7.29 (m, 1H), 7.16–7.20 (m, 2H), 6.62 (dd, *J* = 3.68, 2.80 Hz, 1H), 4.76 (s, br, 1H), 2.62 (t, *J* = 4.84 Hz, 2H), 1.74–1.95 (m, 5H), 1.26–1.48 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 25.51, 26.71, 29.34, 56.40, 112.26, 113.20, 115.01, 115.44, 122.57, 124.05, 124.50, 124.99, 129.50, 156.12. HRMS calcd for C₁₇H₁₈N₂O 266.1419; found: 266.1425.

5-Benzylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3e). White solid (93%). mp 136–139 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.67–7.70 (m, 2H), 7.29–7.32 (m, 5H), 7.16–7.23 (m, 4H), 6.70 (dd, *J* = 3.76, 2.80 Hz, 1H), 5.52 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 45.00, 113.23, 113.39, 114.58, 116.24, 116.66, 122.96, 123.07, 124.17, 125.57, 126.65, 127.32, 128.82, 129.53, 136.51, 155.83. HRMS calcd for C₁₈H₁₄N₂O 274.1106; found: 274.1142.

5-(3,4-Dimethoxyphenethyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3f). Orange solid (80%). mp 146–148 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (dd, *J* = 7.68, 1.40 Hz, 1H), 7.66 (dd, *J* = 2.76, 1.48 Hz, 1H), 7.34–7.36 (m, 2H), 7.24–7.27 (m, 2H), 6.83–6.89 (m, 3H), 6.68 (dd, *J* = 3.80, 2.84 Hz, 1H), 4.45 (m, 2H), 3.87 (d, *J* = 0.92 Hz, 6H), 2.99 (q, *J* = 5.88 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 33.42, 42.99, 55.96, 111.49, 112.17, 112.65, 113.34, 114.90, 115.53, 115.98, 120.72, 122.85, 123.24, 124.18, 125.66, 129.31, 130.96, 147.92, 149.16, 155.32. HRMS calcd for C₂₁H₂₀N₂O₃ 348.1474; found: 348.1486.

5-Phenylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3g). White solid (93%). mp 173–174 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.71–7.73

(m, 2H), 7.57–7.61 (m, 2H), 7.50–7.54 (m, 1H), 7.32–7.34 (m, 2H), 7.28 (dd, *J* = 3.84, 1.44 Hz, 1H), 7.19–7.23 (m, 1H), 7.08–7.12 (m, 1H), 6.71 (dd, *J* = 3.76, 2.92 Hz, 1H), 6.65 (dd, *J* = 8.28, 1.08 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 113.34, 113.42, 114.39, 116.40, 117.57, 123.05, 123.46, 125.20, 128.94, 129.48, 130.11, 131.56, 136.76, 155.43. HRMS calcd for C₁₇H₁₂N₂O 260.0950; found: 260.0969.

5-(4-Fluorophenyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3h). White solid (94%). mp 222–224 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.72–7.74 (m, 2H), 7.27–7.32 (m, 5H), 7.21–7.25 (m, 1H), 7.12–7.15 (m, 1H), 6.72 (dd, *J* = 3.80, 2.84 Hz, 1H), 6.65 (dd, *J* = 9.40, 1.04 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 113.51, 114.50, 116.57, 117.06, 117.32 (d, *J* = 7.0 Hz), 123.23, 123.74, 125.28, 131.27 (d, *J* = 8.1 Hz), 131.44, 132.52 (d, *J* = 3.0 Hz), 155.50, 161.37, 163.84. HRMS calcd for C₁₇H₁₁FN₂O 278.0855; found: 278.0865.

5-(4-Chlorophenyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3i). Pale yellow solid (94%). mp 249–250 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.30 (q, *J* = 1.48 Hz, 1H), 8.18 (dd, *J* = 8.08, 1.00 Hz, 1H), 7.67–7.71 (m, 2H), 7.45–7.49 (m, 2H), 7.26–7.30 (m, 1H), 7.18–7.22 (m, 1H), 7.11 (dd, *J* = 3.84, 1.36 Hz, 1H), 6.76 (dd, *J* = 3.60, 2.96 Hz, 1H), 6.54 (dd, *J* = 8.28, 0.92 Hz, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 113.08, 113.73, 115.84, 117.25, 118.89, 123.10, 123.62, 126.10, 130.54, 131.31, 132.17, 133.94, 136.16, 154.82, 159.04. HRMS calcd for C₁₇H₁₁ClN₂O 294.0560; found: 294.0562.

5-(4-Bromophenyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3j). Yellow solid (98%). mp 258–260 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.73 (dd, *J* = 8.52, 6.64 Hz, 4H), 7.29 (dd, *J* = 3.88, 1.36 Hz, 1H), 7.22 (d, *J* = 8.56 Hz, 3H), 7.10–7.15 (m, 1H), 6.71–6.73 (m, 1H), 6.66 (dd, *J* = 8.24, 0.88 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 113.54, 113.63, 114.54, 116.65, 117.31, 123.04, 123.16, 123.32, 123.73, 125.31, 131.14, 131.27, 133.41, 135.74, 155.27. HRMS calcd for C₁₇H₁₁BrN₂O 338.0055; found: 338.0044.

5-(*p*-Tolyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3k). White solid (83%). mp 217–220 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (m, 2H), 7.38 (d, *J* = 8.08 Hz, 1H), 7.28 (dd, *J* = 3.88, 1.36 Hz, 1H), 7.18–7.22 (m, 3H), 7.08–7.12 (m, 1H), 6.68–6.72 (m, 2H), 2.47 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 21.32, 113.24, 113.35, 114.33, 116.31, 117.63, 122.95, 123.50, 123.71, 125.14, 129.10, 130.78, 131.66, 134.00, 138.88, 155.55. HRMS calcd for C₁₈H₁₄N₂O 274.1106; found: 274.1105.

5-(4-Methoxyphenyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3l). White solid (89%). mp 208–209 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 7.32 Hz, 2H), 7.21–7.29 (m, 4H), 7.08–7.11 (m, 3H), 6.70–6.72 (m, 2H), 3.89 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 55.57, 113.28, 113.37, 114.36, 115.41, 116.32, 117.65, 122.96, 123.57, 123.78, 125.18, 129.23, 130.41, 131.90, 155.71, 159.78. HRMS calcd for C₁₈H₁₄N₂O 290.1055; found: 290.1082.

7-Nitro-5-(*p*-tolyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (5a). Brown solid (92%). mp 258–261 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.09 (dd, *J* = 9.0, 2.40 Hz, 1H), 8.81 (d, *J* = 9.0 Hz, 1H), 7.75 (q, *J* = 1.5 Hz, 1H), 7.59 (d, *J* = 2.4 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.36 (dd, *J* = 3.9, 1.5 Hz, 1H), 7.19 (dd, *J* = 4.20, 2.4 Hz, 1H), 6.81 (dd, *J* = 3.6, 3.0 Hz, 1H), 2.50 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 21.39, 113.10, 114.88, 115.06, 115.15, 117.50, 118.34,

123.51, 127.89, 128.71, 131.31, 132.17, 132.78, 139.85, 144.54, 154.99. HRMS calcd for $C_{18}H_{13}N_3O_3$ 319.0957; found: 319.0949.

4-Oxo-5-(*p*-tolyl)-4,5-dihydropyrrolo[1,2-*a*]quinoxaline-9-carbonitrile (5b). White solid (75%). mp 280–284 °C. 1H NMR (400 MHz, $CDCl_3$) δ 8.88 (dd, J = 3.08, 1.36 Hz, 1H), 7.51 (dd, J = 7.68, 1.36 Hz, 1H), 7.38–7.41 (m, 3H), 7.12–7.17 (m, 3H), 6.95 (dd, J = 8.48, 1.24 Hz, 1H), 6.80 (t, J = 3.16 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.32, 99.75, 114.47, 114.81, 118.58, 120.18, 122.31, 124.39, 124.65, 124.88, 128.94, 129.38, 131.15, 133.26, 133.45, 139.53, 154.77. HRMS calcd for $C_{19}H_{13}N_3O$ 299.1059; found: 299.1062.

4-Oxo-5-(*p*-tolyl)-4,5-dihydropyrrolo[1,2-*a*]quinoxaline-7-carbonitrile (5c). White solid (70%). mp 267–270 °C. 1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 1H), 7.73 (dd, J = 3.0, 1.5 Hz, 1H), 7.48 (dd, J = 8.4, 1.5 Hz, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.33 (dd, J = 3.9, 1.2 Hz, 1H), 7.17 (d, J = 8.1 Hz, 2H), 6.96 (d, J = 1.5 Hz, 1H), 6.78 (dd, J = 3.6, 3.0 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.33, 108.64, 114.82, 114.84, 115.21, 117.09, 118.15, 121.23, 123.63, 126.51, 126.67, 128.81, 131.29, 132.37, 132.94, 139.81, 154.92. HRMS calcd for $C_{19}H_{13}N_3O$ 299.1059; found: 299.1056.

5-(*p*-Tolyl)-3-(trifluoromethyl)pyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one (5d). White solid (97%). mp 187–190 °C. 1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 0.68 Hz, 1H), 8.19 (dd, J = 2.84, 1.60 Hz, 1H), 7.42 (d, J = 8.08 Hz, 2H), 7.36 (dd, J = 3.72, 1.48 Hz, 1H), 7.19 (d, J = 8.20 Hz, 2H), 7.14 (d, J = 1.64 Hz, 1H), 6.76 (t, J = 3.28 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.37, 114.64, 115.87, 118.59, 121.03 (d, J = 3.0 Hz), 123.53 (q, J = 22.3 Hz), 123.97, 124.51, 127.45, 128.68, 131.30, 132.32, 137.74, 138.60 (d, J = 4.1 Hz), 139.90, 154.69. HRMS calcd for $C_{18}H_{12}F_3N_3O$ 343.0932; found: 343.0932.

7-Fluoro-5-(*p*-tolyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (5e). Orange solid (82%). mp 219–222 °C. 1H NMR (300 MHz, $CDCl_3$) δ 7.64–7.68 (m, 2H), 7.39 (d, J = 8.1 Hz, 1H), 7.27 (dd, J = 3.9, 1.5 Hz, 1H), 7.19 (dd, J = 4.2, 2.4 Hz, 1H), 6.88–6.94 (m, 1H), 6.70 (dd, J = 3.9, 3.0 Hz, 1H), 6.40 (dd, J = 10.5, 2.7 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.33, 104.82 (d, J = 29.2 Hz), 109.78 (d, J = 24.1 Hz), 113.46, 115.52 (d, J = 9.1 Hz), 116.43, 120.26, 123.02, 128.90, 130.98, 133.28, 133.63, 139.28, 155.45, 158.60, 161.02. HRMS calcd for $C_{18}H_{13}FN_2O$ 292.1012; found: 292.1030.

8-Methyl-5-(*p*-tolyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (5f). Orange solid (85%). mp 201–203 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 2.64, 1.48 Hz, 1H), 7.51 (s, 1H), 7.37 (d, J = 8.04 Hz, 2H), 7.27 (d, J = 1.40 Hz, 1H), 7.19 (d, J = 8.20 Hz, 2H), 6.90 (dd, J = 8.48, 1.04 Hz, 1H), 6.69 (dd, J = 3.72, 2.96 Hz, 1H), 6.57 (d, J = 8.44 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.93, 21.32, 113.10, 113.23, 114.66, 116.15, 117.50, 123.51, 123.64, 125.95, 129.10, 129.47, 130.72, 132.93, 134.15, 138.76, 155.47. HRMS calcd for $C_{18}H_{14}N_2O$ 288.1263; found: 288.1271.

9-Methyl-5-(*p*-tolyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (5g). Orange solid (95%). mp 247–249 °C. 1H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, J = 2.7, 1.5 Hz, 1H), 7.34–7.39 (m, 3H), 7.18 (d, J = 8.1 Hz, 2H), 6.94–7.03 (m, 2H), 6.69 (dd, J = 3.9, 3.0 Hz, 1H), 6.58 (dd, J = 7.8, 1.5 Hz, 1H), 2.87 (s, 3H), 2.46 (s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 21.34, 24.11, 112.59, 112.95, 116.29, 122.30, 123.96, 124.34, 124.85, 126.08, 127.31, 129.09, 130.85, 132.98, 134.63, 138.79, 155.48. HRMS calcd for $C_{18}H_{14}N_2O$ 288.1263; found: 288.1258.

***N*-(4-Oxo-5-(*p*-tolyl)-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-acetamide (5h).** Yellow solid (77%). mp 291–294 °C. 1H NMR (300 MHz, $DMSO-d_6$) δ 9.96 (s, 1H), 8.18 (dd, J = 1.5 Hz, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.62 (dd, J = 9.0, 2.1 Hz, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.05 (dd, J = 3.9, 1.5 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.71 (dd, J = 3.9, 3.0 Hz, 1H), 2.44 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (100 Hz, $DMSO-d_6$) δ 21.35, 24.35, 107.55, 112.53, 113.39, 114.21, 115.93, 118.27, 119.18, 122.83, 129.76, 130.95, 131.92, 134.57, 137.41, 138.57, 155.09, 168.76. HRMS calcd for $C_{20}H_{17}N_3O_2$ 331.1321; found: 331.1312.

5-(*p*-Tolyl)-7-(trifluoromethyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (5i). Brown solid (86%). mp 250–253 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.48 Hz, 1H), 7.74 (dd, J = 2.80, 1.44 Hz, 1H), 7.43–7.46 (m, 1H), 7.40 (d, J = 8.00 Hz, 2H), 7.31 (dd, J = 3.84, 1.36 Hz, 1H), 7.18 (d, J = 8.20 Hz, 2H), 6.93 (m, 1H), 6.75 (dd, J = 3.72, 2.96 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.36, 109.63, 113.54, 114.32 (d, J = 4.0 Hz), 114.74, 114.89, 116.97, 119.85 (q, J = 3.1 Hz), 120.13 (d, J = 34.7 Hz), 122.02, 123.94, 128.84, 129.49, 131.91, 133.13, 139.51, 155.29. HRMS calcd for $C_{19}H_{13}F_3N_2O$ 342.0980; found: 342.0972.

5-(*p*-Tolyl)pyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one (5j). White solid (68%). mp 239–242 °C. 1H NMR (300 MHz, $CDCl_3$) δ 8.17–8.21 (m, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.32 (dd, J = 3.9, 1.5 Hz, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.07 (dd, J = 8.4, 4.8 Hz, 1H), 6.98 (dd, J = 8.1, 1.5 Hz, 1H), 6.73 (dd, J = 3.6, 3.0 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.32, 113.69, 114.71, 117.86, 120.71, 123.41, 124.34, 127.46, 128.93, 130.95, 133.11, 135.75, 139.28, 141.66, 155.04. HRMS calcd for $C_{17}H_{13}N_3O$ 275.1059; found: 275.1062.

5,7-Di-*p*-tolylpyrrolo[1,2-*a*]pyrrolo[1',2':4,5]pyrazino[2,3-*g*]quinoxaline-4,8(5*H*,7*H*)-dione (5k). Orange solid (60%). mp 273–278 °C. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.82 (s, 1H), 8.45 (d, J = 1.08 Hz, 2H), 7.19 (d, J = 8.04 Hz, 4H), 7.10 (dd, J = 3.8, 1.2 Hz, 2H), 7.00 (d, J = 8.12 Hz, 4H), 6.80 (t, J = 3.04 Hz, 2H), 5.57 (s, 1H), 2.36 (s, 6H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ 21.15, 102.20, 105.88, 113.23, 113.73, 119.29, 119.43, 123.12, 129.24, 129.36, 130.42, 133.96, 138.51, 154.53. HRMS calcd for $C_{30}H_{22}N_4O_2$ 470.1743, found: 470.1736.

5-(*p*-Tolyl)indolo[1,2-*a*]quinoxalin-6(5*H*)-one (11a). Yellow solid (92%). mp 208–209 °C. 1H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, J = 8.32 Hz, 1.04 Hz, 1H), 8.32 (d, J = 8.72 Hz, 1H), 7.90 (d, J = 7.96 Hz, 1H), 7.65 (d, J = 0.44 Hz, 1H), 7.51–7.56 (m, 1H), 7.36–7.42 (m, 3H), 7.27–7.31 (m, 1H), 7.23–7.25 (m, 2H), 7.06–7.11 (m, 1H), 6.75 (dd, J = 8.32, 1.32 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.33, 107.47, 114.32, 115.38, 117.73, 122.47, 123.33, 123.78, 125.48, 126.50, 128.42, 128.96, 129.36, 130.87, 131.28, 133.96, 134.47, 139.05, 156.55. HRMS calcd for $C_{22}H_{16}N_2O$ 324.1263; found: 324.1282.

9-Methoxy-5-(*p*-tolyl)indolo[1,2-*a*]quinoxalin-6(5*H*)-one (11b). White solid (82%). mp 255–256 °C. 1H NMR (300 MHz, $CDCl_3$) δ 8.32 (dd, J = 8.4 Hz, 1H), 8.22 (d, J = 9.3 Hz, 1H), 7.57 (s, 1H),

7.41 (d, $J = 8.1$ Hz, 2H), 7.25–7.31 (m, 2H), 7.23–7.25 (m, 2H), 7.18 (dd, $J = 9.3$, 2.4 Hz, 1H), 7.05–7.11 (m, 1H), 6.74 (dd, $J = 8.1$, 1.2 Hz, 1H), 3.93 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.34, 55.62, 103.19, 106.86, 114.95, 115.13, 116.56, 117.70, 123.32, 123.58, 126.35, 128.74, 128.95, 129.66, 130.27, 130.86, 131.09, 133.96, 139.03, 155.53, 156.40. HRMS calcd for $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_2$ 354.1368; found: 354.1367.

9-Fluoro-5-(*p*-tolyl)indolo[1,2-*a*]quinoxalin-6(5*H*)-one (11c). Yellow solid (92%). mp 271–272 °C. ^1H NMR (300 MHz, CDCl_3) δ 8.32 (d, $J = 8.4$ Hz, 1H), 8.28 (dd, $J = 9.3$, 4.2 Hz, 1H), 7.60 (s, 1H), 7.53 (dd, $J = 8.7$, 2.4 Hz, 1H), 7.41 (d, $J = 7.8$ Hz, 2H), 7.28–7.33 (m, 2H), 7.24 (d, $J = 8.4$ Hz, 2H), 7.08–7.14 (m, 1H), 6.76 (dd, $J = 8.4$, 1.5 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.34, 107.02 (d, $J = 5.0$ Hz), 107.68 (d, $J = 23.1$ Hz), 114.24 (d, $J = 26.2$ Hz), 115.02, 115.28 (d, $J = 4.1$ Hz), 117.88, 123.44, 124.06, 126.16, 128.91, 129.86, 130.12 (d, $J = 10.1$ Hz), 130.92, 131.17 (d, $J = 8.0$ Hz), 133.82, 139.18, 156.18, 157.53, 159.92. HRMS calcd for $\text{C}_{22}\text{H}_{15}\text{FN}_2\text{O}$ 342.1168; found: 342.1182.

3-Nitro-5-(*p*-tolyl)indolo[1,2-*a*]quinoxalin-6(5*H*)-one (11d). Yellow solid (73%). mp 276–277 °C. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.79 (d, $J = 9.3$ Hz, 1H), 8.63 (d, $J = 8.4$ Hz, 1H), 8.17 (dd, $J = 9.3$, 2.7 Hz, 1H), 8.02 (d, $J = 7.5$ Hz, 1H), 7.70 (s, 1H), 7.64–7.68 (m, 1H), 7.48–7.53 (m, 3H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 2.7$ Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3) δ 21.43, 109.96, 112.91, 114.22, 115.22, 118.86, 123.81, 123.86, 126.68, 127.98, 128.58, 129.82, 130.86, 131.42, 131.90, 132.74, 134.72, 140.02, 143.07, 155.98. HRMS calcd for $\text{C}_{22}\text{H}_{15}\text{N}_3\text{O}_3$ 369.113; found: 369.112.

3-Fluoro-5-(*p*-tolyl)indolo[1,2-*a*]quinoxalin-6(5*H*)-one (11e)

Orange solid (83%). mp 211–212 °C. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.34 (q, $J = 5.1$ Hz, 1H), 8.28 (d, $J = 8.4$ Hz, 1H), 7.92 (d, $J = 7.8$ Hz, 1H), 7.66 (s, 1H), 7.55 (dd, $J = 8.4$, 7.2 Hz, 1H), 7.37–7.44 (m, 3H), 7.23 (d, $J = 8.1$ Hz, 2H), 6.97–7.04 (m, 1H), 6.48 (dd, $J = 10.5$, 2.7 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.34, 105.15 (d, $J = 29.2$ Hz), 107.62, 109.71 (d, $J = 23.14$ Hz), 113.75, 116.39 (d, $J = 9.1$ Hz), 122.56, 122.98 (d, $J = 3.0$ Hz), 123.49, 125.73, 127.86, 128.78, 129.22, 131.07, 132.84 (d, $J = 10.1$ Hz), 133.58, 134.32, 139.46, 156.48, 157.46, 159.87. HRMS calcd for $\text{C}_{22}\text{H}_{15}\text{FN}_2\text{O}$ 342.1168; found: 342.1172.

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References

- (a) G. Maga, S. Gemma, C. Fattorusso, G. A. Locatelli, M. Persico and G. Campiani, *Biochemistry*, 2005, **44**, 9637; (b) J. Guillon, P. Grellier, M. Labaied, P. Sonnet and C. Jarry, *J. Med. Chem.*, 2004, **47**, 1997; (c) G. Szabó, R. Kiss, D. Páyer-Lengyel, K. Vukics and J. Szikra, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3471; (d) V. Desplat, A. Geneste, M.-A. Begorre and J. Guillon, *J. Enzyme Inhib. Med. Chem.*, 2008, **23**, 648; (e) J. Milne, K. D. Normington and M. Milburn, WO2006094210; (f) J. Miyashiro, K. W. Woods, C. H. Park, X. Liu, Y. Shi, E. F. Johnson and T. D. Penning, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4050; (g) F. Grande, F. Aiello and N. Neamati, *Bioorg. Med. Chem.*, 2007, **15**, 288.
- (a) R. A. Glennon, M. K. Daoud, M. Dukat and H. Syed, *Bioorg. Med. Chem.*, 2003, **11**, 4449; (b) H. S. Parihar and K. S. Kirschbaum, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2743; (c) G. Campiani, E. Morelli, S. Gemma, V. Nacci and T. Mennini, *J. Med. Chem.*, 1999, **42**, 4362; (d) T. Katounina, L. Besret, M. Dhilly, M.-C. Petit-Taboue, A. Barbelivien, J.-C. Baron, F. Dauphin and L. Barre, *Bioorg. Med. Chem.*, 1998, **6**, 789.
- G. Abbiati, E. M. Beccalli and G. Brogini, *Synthesis*, 2005, 2881.
- Q. Yuan and D. Ma, *J. Org. Chem.*, 2008, **73**, 5159.
- J. T. Reeves, D. R. Fandrick, Z. Tan and C. H. Senanayake, *J. Org. Chem.*, 2010, **75**, 992.
- (a) H. Sun, J. Li, D. Zhang, C. Ma and C. Liu, *J. Phys. Org. Chem.*, 2008, **21**, 215; (b) L. E. Kaim, M. Gizolme, L. Grimaud and J. Obie, *Org. Lett.*, 2006, **8**, 4019; (c) J. Xiang, L. Zheng, F. Chen, Q. Dang and X. Bai, *Org. Lett.*, 2007, **9**, 765; (d) S. Brauch, L. Gabriel and B. Westermann, *Chem. Commun.*, 2010, **46**, 3387; (e) M. Nielsen, C. B. Jacobsen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2009, **131**, 10581.
- (a) J. Xiang, T. Zhu, Q. Dang and X. Bai, *J. Org. Chem.*, 2010, **75**, 8147; (b) J. Xiang, H. Xie, D. Wen, Q. Dang and X. Bai, *J. Org. Chem.*, 2008, **73**, 3281; (c) J. Xiang, L. Zheng, H. Xie, X. Hu, Q. Dang and X. Bai, *Tetrahedron*, 2008, **64**, 9101.
- (a) J. W. Harbuck and H. Rapoport, *J. Org. Chem.*, 1972, **37**, 3618; (b) C. Schmuck, V. Bickert, M. Merschky, L. Geiger and U. Machon, *Eur. J. Org. Chem.*, 2008, 324; (c) A. T. Dubis and S. J. Grabowski, *New J. Chem.*, 2010, **34**, 556.
- (a) V. S. Thoi, J. R. Stork, E. T. Niles, E. C. Depperman, D. L. Tierney and S. M. Cohen, *Inorg. Chem.*, 2008, **47**, 10533; (b) G. L. Regina, R. Silvestri, M. Artico, A. Lavecchia and E. Novellino, *J. Med. Chem.*, 2007, **50**, 922.
- D. Jaramillo, Q. Liu, J. Aldrich-Wright and Y. Tor, *J. Org. Chem.*, 2004, **69**, 8151.
- S. Koeller, J. Kadota, F. Peruch, A. Deffieux, N. Pinaud, J.-P. Desvergne and B. Bibal, *Chem.–Eur. J.*, 2010, **16**, 4196.