Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 7351

www.rsc.org/obc

PAPER

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]

Received 10th June 2011, Accepted 4th August 2011
DOI: 10.1039/c1ob05936j

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-HT_3 receptor agonists **F** (Fig. 1).[2]

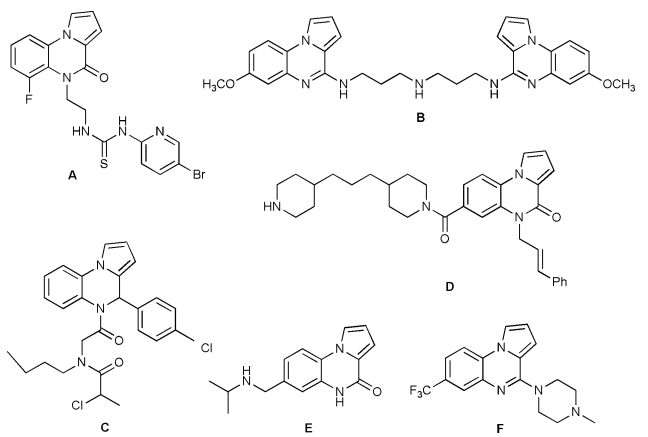
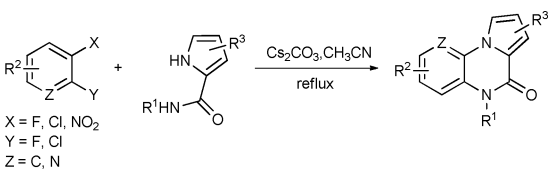


Fig. 1 Some important pyrrolo[1,2-*a*]quinoxalines.

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 triphsogene.[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-halotrifluoroacetanilides 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 rearrangement[6] 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.

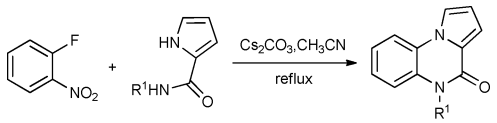
Results and discussion

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).

[a]*School of Chemistry and Chemical Engineering, Shandong University, Jinan, 250100, P R China. E-mail: chenma@sdu.edu.cn*
[b]*State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing, 100191, P R China*

† Electronic supplementary information (ESI) available. CCDC reference numbers 829636 and 834986. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05936j

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



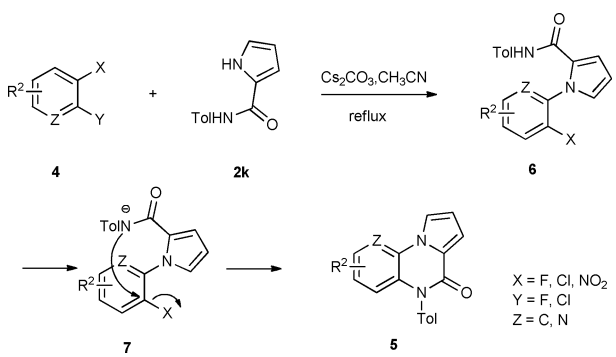
1 2 3

Entry	R^1	2	Time (h)	Product	Yield (%)[b]
1	Et	**2a**	14	**3a**	99
2	Pr	**2b**	16	**3b**	72
3	*i*-Pr	**2c**	12	**3c**	74
4	*c*-Hex	**2d**	8	**3d**	96
5	Bn	**2e**	13	**3e**	93
6	3,4-$(MeO)_2$-$C_6H_3(CH_2)_2$	**2f**	9	**3f**	80
7	Ph	**2g**	9	**3g**	93
8	4-FC_6H_4	**2h**	8	**3h**	94
9	4-ClC_6H_4	**2i**	13	**3i**	94
10	4-BrC_6H_4	**2j**	16	**3j**	98
11	4-MeC_6H_4	**2k**	4	**3k**	83
12	4-$MeOC_6H_4$	**2l**	6	**3l**	89

[a] Reaction conditions: pyrrole-2-carboxamide **2** (1.0 equiv), 1-fluoro-2-nitrobenzene **1** (1.2 equiv), Cs_2CO_3 (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).

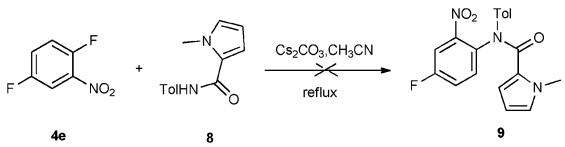
A plausible mechanism for these results is shown in Scheme 2. Compound **6** was formed by nucleophilic substitution of compound **2k** on 1,2-dihalobenzenes or 2-halonitroarenes **4**. The next step was the formation of carboxamide anion **7**. Finally,



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).



4e 8 9

Scheme 3 Reaction of *N*-ethyl-1-methyl-1*H*-pyrrole-2-carboxamide **8** with 1,4-difluoro-2-nitrobenzene **4e**.

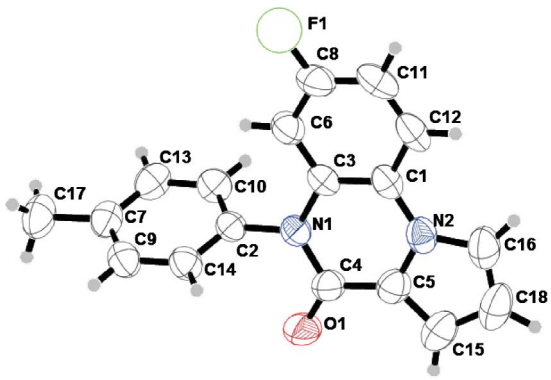


Fig. 2 X-ray structure of compound **5e**.

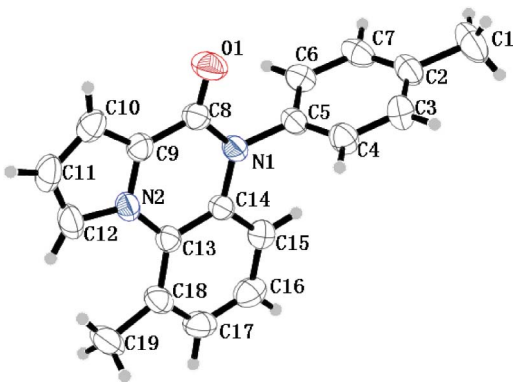
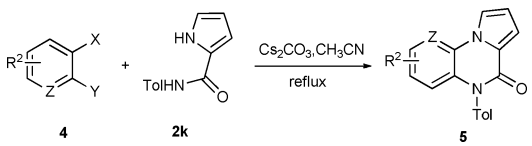


Fig. 3 X-ray structure of compound **5g**.

To expand the applicability of this methodology, We then investigated a number of indole-2-carboxamides[11] **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]



4 **2k** **5**

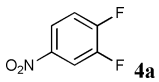
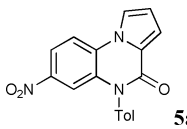
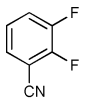
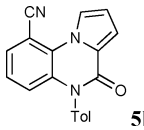
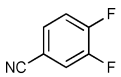
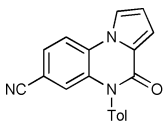
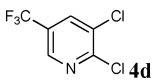
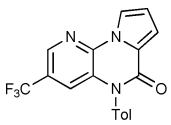
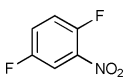
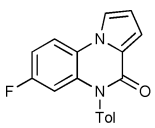
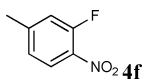
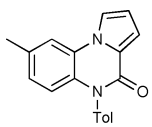
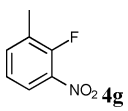
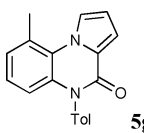
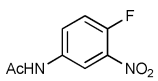
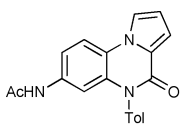
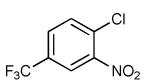
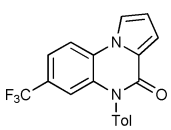
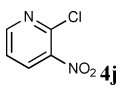
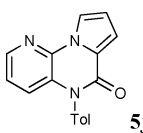
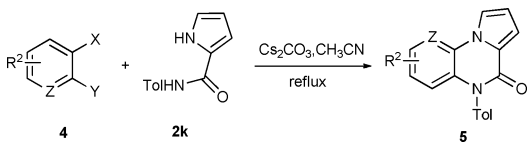
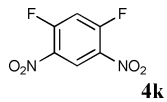
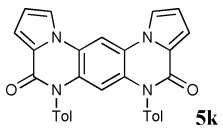
Entry	4	Time (h)	Product	Yield (%)[c]
1	 **4a**	4	 **5a**	92
2	 **4b**	8	 **5b**	75
3	 **4c**	6	 **5c**	70
4	 **4d**	7	 **5d**	97
5	 **4e**	3	 **5e**	82
6	 **4f**	7	 **5f**	85
7	 **4g**	7	 **5g**	95
8	 **4h**	11	 **5h**	77
9	 **4i**	10	 **5i**	86
10	 **4j**	6	 **5j**	68

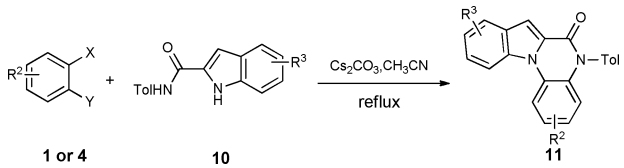
Table 2 (*Contd.*)

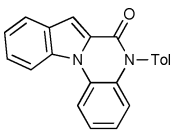
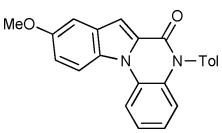
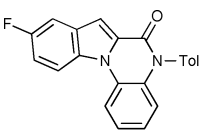
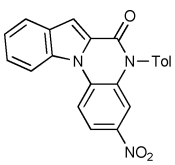
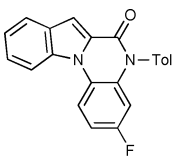


Entry	4	Time (h)	Product	Yield (%)[c]
11[b]	 **4k**	7	 **5k**	60

[a] Reaction conditions: **2k** (1.0 equiv), **4** (1.2 equiv), Cs_2CO_3 (3.5 equiv), CH_3CN (15 mL). [b] **2k** (1.7 equiv), **4k** (1.0 equiv), Cs_2CO_3 (5.95 equiv), CH_3CN (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), Cs_2CO_3 (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 medicinally relevant compounds.

Experimental section

General information

Pyrrole-2-carboxamides, *N*-ethyl-1-methyl-1*H*-pyrrole-2-carboxamide[8,9] and indole-2-carboxamides[11] 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). ^{1}H NMR spectra were recorded on a Bruker Avance 400 or 300 spectrometer at 400 or 300 MHz, using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. ^{13}C 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 spectrograph (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 Cs_2CO_3 (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 $MgSO_4$ 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.^{1}H NMR (400 MHz, $CDCl_3$) 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, 2 H), 1.34 (t, J = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{13}H_{12}N_2O$ 212.0950; found: 212.0962.

5-Propylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3b). Pale yellow solid (72%). mp 78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 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, 2 H), 6.65 (dd, J = 3.84, 3.01 Hz, 1H), 4.21 (t, J = 7.72 Hz, 2 H), 1.78 (m, 2H), 1.05 (t, J = 7.44 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{14}H_{14}N_2O$ 226.1106; found: 226.1095.

5-Isopropylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3c). Brown oil (74%). ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{14}H_{14}N_2O$ 226.1106; found: 226.1136.

5-Cyclohexylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3d). Brown solid (96%). mp 99–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{17}H_{18}N_2O$ 266.1419; found: 266.1425.

5-Benzylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3e). White solid (93%). mp 136–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 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);^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{18}H_{14}N_2O$ 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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);^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{21}H_{20}N_2O_3$ 348.1474; found: 348.1486.

5-Phenylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3g). White solid (93%). mp 173–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{17}H_{12}N_2O$ 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{17}H_{11}FN_2O$ 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.^{1}H 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); ^{13}C 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 $C_{17}H_{11}ClN_2O$ 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.^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{17}H_{11}BrN_2O$ 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.^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{14}N_2O$ 274.1106: 274.1105.

5-(4-Methoxyphenyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3l). White solid (89%). mp 208–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{18}H_{14}N_2O$ 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. ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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. ^{1}H 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. ^{1}H 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, 2 H), 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. ^{1}H 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. ^{1}H 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. ^{1}H 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}CNMR (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. ^{1}H 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. ^{1}H 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. ^{1}H 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. ^{1}H 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. ^{1}H 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. ^{1}H 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. ^{1}H 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 $C_{23}H_{18}N_2O_2$ 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. ^{1}H 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 $C_{22}H_{15}FN_2O$ 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. ^{1}H NMR (300 MHz, 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 $C_{22}H_{15}N_3O_3$ 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. ^{1}H NMR (300 MHz, 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 $C_{22}H_{15}FN_2O$ 342.1168; found: 342.1172.

Acknowledgements

We are grateful to National Science Foundation of China (No. 20872079), the Natural Science Foundation of Shandong Province (2009ZRB019YA), and State Key Laboratory of Natural and Biomimetic Drugs of Peking University (K20090205) for financial support of this research.

References

1 (*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.
2 (*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.
3 G. Abbiati, E. M. Beccalli and G. Broggini, *Synthesis*, 2005, 2881.
4 Q. Yuan and D. Ma, *J. Org. Chem.*, 2008, **73**, 5159.
5 J. T. Reeves, D. R. Fandrick, Z. Tan and C. H. Senanayake, *J. Org. Chem.*, 2010, **75**, 992.
6 (*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. Oble, *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.
7 (*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.
8 (*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.
9 (*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.
10 D. Jaramillo, Q. Liu, J. Aldrich-Wright and Y. Tor, *J. Org. Chem.*, 2004, **69**, 8151.
11 S. Koeller, J. Kadota, F. Peruch, A. Deffieux, N. Pinaud, J.-P. Desvergne and B. Bibal, *Chem.–Eur. J.*, 2010, **16**, 4196.