Synthesis and Functionalization of 3-Azolylquinoxalin-2(1*H*)-ones

Oleksandr V. Geraschenko,*[a,b] Pavel V. Khodakovskiy,[a,b] Oleg V. Shishkin,[c] Andrey A. Tolmachev,[a,b] Pavel K. Mykhailiuk*[a,b]

[a] Enamine Ltd., Aleksandra Matrosova Street, 23, Kyiv 01103, Ukraine

[b] Department of Chemistry, Kyiv National Taras Shevchenko University, Volodymyrska Street, 64, Kyiv 01033, Ukraine
Fax +380(44)2351273; E-mail: Geraschenko.Aleksandr@gmail.com; E-mail: Pavel.Mykhailiuk@gmail.com

[c] STC, Institute for Single Crystals, National Academy of Science of Ukraine, 60 Lenina Ave., Kharkiv 61001, Ukraine

Accepted after revision: 21.02.2014; Received: 23.12.2013

Abstract: Ethyl 2-azolylglyoxylates react smoothly with *o*-phenylenediamines and 1,2-diaminocyclohexane in acetonitrile at room temperature to give the corresponding 3-azolylquinoxalin-2(1*H*)-ones and their saturated analogues in good to excellent yields.

Key words: quinoxalin-2(1*H*)-ones, 2-azolylglyoxylates, condensation, *o*-phenylenediamine, 1,2-diaminocyclohexane

In recent decades derivatives of quinoxaline have gained widespread application in organic chemistry, medicinal chemistry, and drug discovery.[1] Substituted quinoxalines exhibit a broad spectrum of biological activity, e.g. antagonists of NMDA glutamate receptor,[2] agents to treat insulin-independent diabetes,[3] and matrix metalloproteinase inhibitors[4] There are also compounds possessing antibacterial[5] and antiviral[6] properties.

Scientists have synthesized derivatives of quinoxalin-2(1*H*)-ones that are potent thrombin inhibitors,[7] anticancer,[8] anxiolytic,[9] antiallergic,[10] and analgesic and antispastic[11] agents. FDA-approved antiasthmatic drug bamaquimast and spasmolytic drug caroverine are worth special mention (Figure 1).

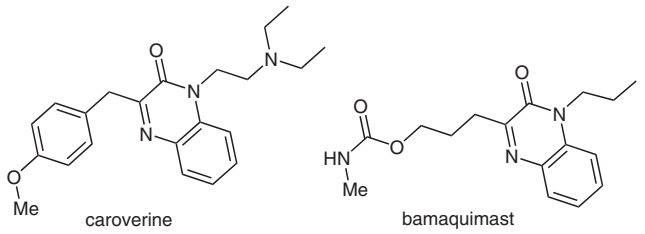
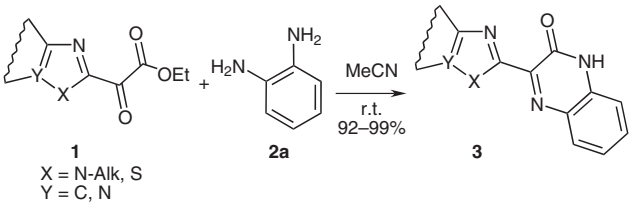


Figure 1 Two marketed drugs bearing the quinoxalin-2(1*H*)-one fragment: bamaquimast (antiasthmatic agent), caroverine (spasmolytic agent)

Indeed, the mode of biological activity of various quinoxalin-2(1*H*)-ones depends strongly on the nature and position of the substituents. Therefore, the elaboration of novel strategies aimed at the synthesis of diversely substituted quinoxalin-2(1*H*)-ones is of true practical importance for drug discovery.

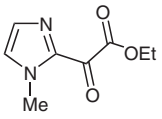
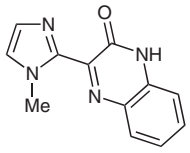
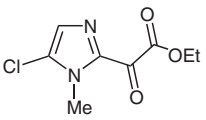
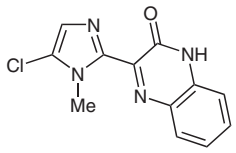
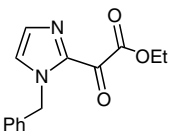
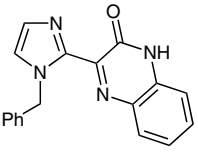
Among many synthetic approaches to quinoxalin-2(1*H*)-ones,[12–16] direct condensation of 1,2-diaminobenzenes with 2-ketocarboxylic acid is probably the most popular. As a part of our research project aimed at the preparation[17] and subsequent functionalization[18] of ethyl azolylglyoxylates, herein we report on their use to obtain the correspondingly substituted quinoxalin-2(1*H*)-ones.

First we examined the condensation of various ethyl 2-azolylglyoxylates **1a–k** with *o*-phenylenediamine (**2a**) (Scheme 1, Table 1).



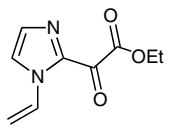
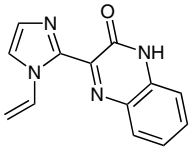
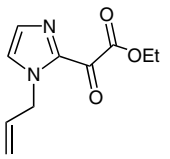
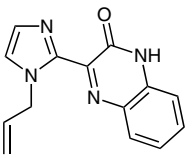
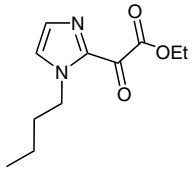
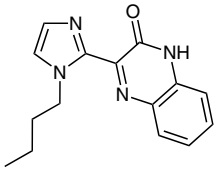
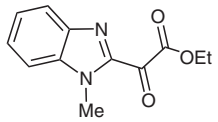
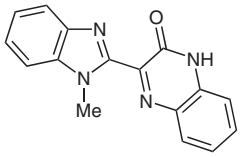
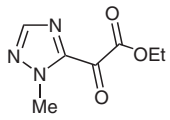
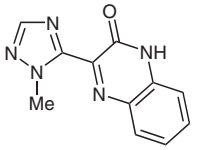
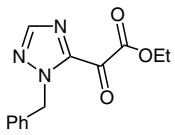
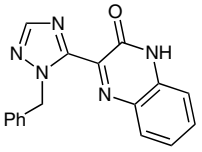
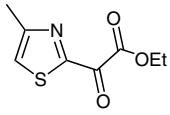
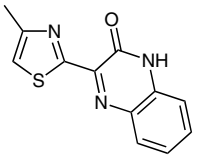
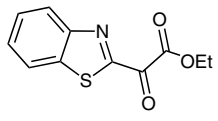
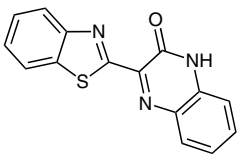
Scheme 1 Reaction of compounds **1a–k** with *o*-phenylenediamine (**2a**)

Table 1 Reaction Compounds **1a–k** with *o*-Phenylenediamine (**2a**)

Starting material	Product	Yield (%)
 **1a**	 **3a**	95
 **1b**	 **3b**	98
 **1c**	 **3c**	95

SYNTHESIS 2014, 46, 000A–000F
Advanced online publication: 03.04.2014
DOI: 10.1055/s-0033-1340983; Art ID: SS-2012-Z0370-OP

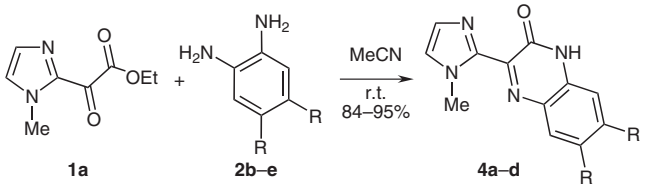
Table 1 Reaction Compounds **1a**–**k** with *o*-Phenylenediamine (**2a**) (continued)

Starting material	Product	Yield (%)
 **1d**	 **3d**	94
 **1e**	 **3e**	94
 **1f**	 **3f**	92
 **1g**	 **3g**	99
 **1h**	 **3h**	92
 **1i**	 **3i**	97
 **1j**	 **3j**	97
 **1k**	 **3k**	98

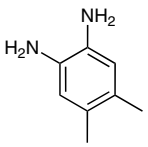
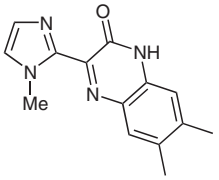
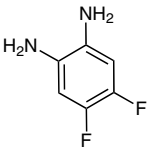
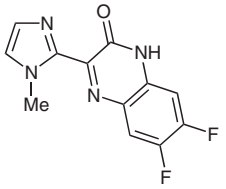
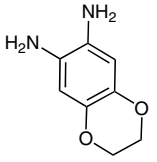
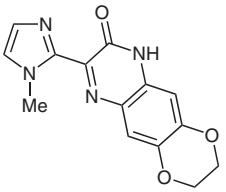
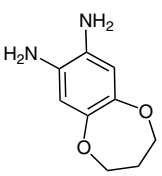
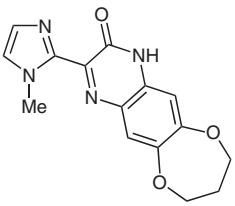
The reaction proceeded smoothly in acetonitrile at room temperature (Table 1). It was slightly exothermic, but no external cooling was required when working on micromolar quantities. Cooling, however, became necessary when working on a molar scale. After mixing both reagents together in acetonitrile, the rapid formation of a precipitate was observed. To complete the transformation, the reaction mixture was stirred at room temperature for an additional 12 h. After recrystallization, all products **3a**–**k** were obtained as solids in excellent yields of 92–98%.

To expand the scope of the performed transformation, we next challenged the reaction of the simplest glyoxylate **1a** with substituted *o*-phenylenediamines **2b**–**e**. We used symmetric diamines in order to avoid the formation of stereoisomers. The target products **4a**–**d** were obtained in 84–95% isolated yields (Table 2).

Table 2 Reaction of Ketone **1a** with *o*-Phenylenediamines **2b**–**e**

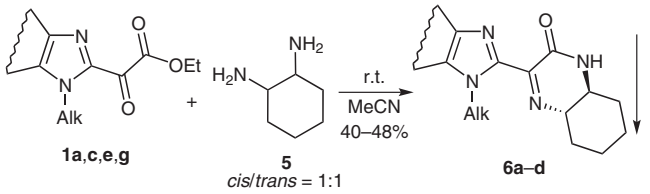


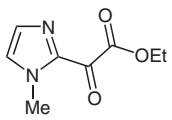
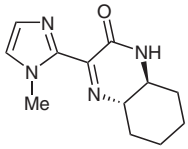
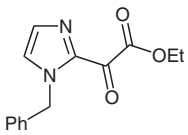
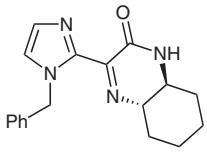
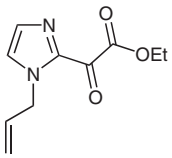
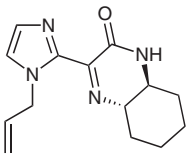
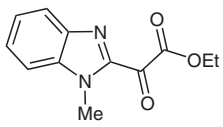
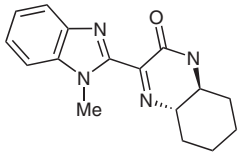
1a **2b–e** **4a–d**

Starting material	Product	Yield (%)
 **2b**	 **4a**	93
 **2c**	 **4b**	95
 **2d**	 **4c**	91
 **2e**	 **4d**	84

We also studied the condensation of some glyoxylates **1a**,**c**,**e**,**g** with 1,2-diaminocyclohexane (**5**) (Table 3); products **6a**–**d** were isolated in moderate yields of 40–85%. It is interesting to note that though 1,2-diaminocyclohexane was used as a 1:1 mixture of *cis* and *trans* isomers, the formed products precipitated from the reaction mixture as a single stereoisomer. Presumably, epimerization occurred during the formation of the intermediate Schiff base.[19,20] The *trans* stereoconfiguration of the obtained compounds was determined by X-ray crystallographic analysis of product **6c** (Figure 2).

Table 3 Reaction of Compounds **1a**,**c**,**e**,**g** with 1,2-Diaminocyclohexane (**5**)



Starting material	Product	Yield (%)
 **1a**	 **6a**	40
 **1c**	 **6b**	48
 **1e**	 **6c**	85
 **1g**	 **6d**	45

Unexpectedly, attempts to purify product **6c** by column chromatography led to aromatization to form compound **7** (Scheme 2).

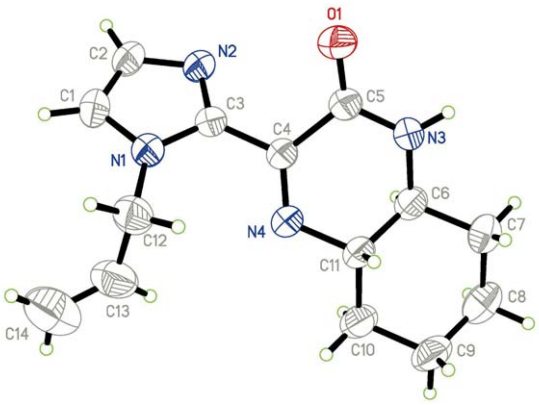
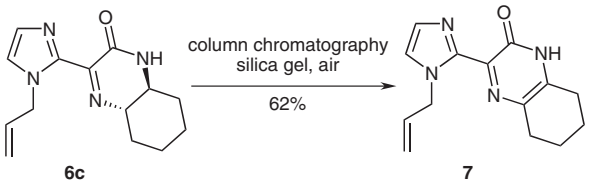
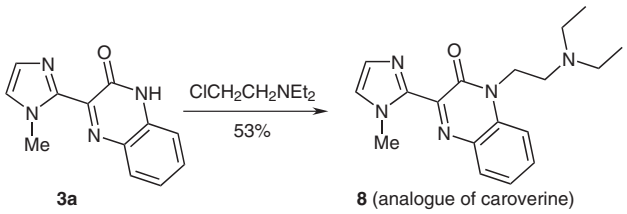


Figure 2 X-ray diffraction structure of compound **6c**[21]



Scheme 2 Synthesis of compound **7**

Finally, to demonstrate the practical importance of the developed procedure, we performed the synthesis of compound **8**, an analogue of the launched drug caroverine (Figure 1). In fact, alkylation of quinoxalinone **3a** with 2-chloro-*N*,*N*-diethylethylamine in dimethyl sulfoxide using sodium hydride as the base led to a mixture of N- and O-alkylated products, from which the major N-alkylated isomer **8** was isolated by column chromatography in 53% yield (Scheme 3).



Scheme 3 Synthesis of compound **8**, an analogue of the launched drug caroverine (Figure 1)

In summary, we have developed a practical approach to novel 3-azolylquinoxalin-2(1*H*)-ones and their saturated derivatives from 2-azolylglyoxylates **1** and 1,2-diaminobenzenes and -cyclohexanes. The reaction is practical, it proceeds smoothly in acetonitrile at room temperature, it gives products in excellent yields that requires no purification by column chromatography. The conceptual importance of the developed reaction was demonstrated by the preparation of compound **8**, an analogue of the launched drug caroverine.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer at 499.9 MHz and 124.9 MHz, respectively. ^{19}F NMR spectra were recorded on a Varian 400 instrument at 376 MHz. Internal standard from TMS (^{1}H, ^{13}C) and C_6F_6 (^{19}F). Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument by chemical ionization (CI).

3-Hetarylquinoxalin-2(1*H*)-ones 3, 4, 6; General Procedure
Glyoxylate **1** (10 mmol) was dissolved in MeCN (1 mL). The solution of 1,2-diamine **2** or **5** (10 mmol) in MeCN (20 mL) was added. The mixture was stirred at r.t. overnight. The formed precipitate was filtered off and was washed with MeCN (2 × 10 mL) on the filter. The pure product was obtained by recrystallization (DMF).

3-(1-Methyl-1*H*-imidazol-2-yl)quinoxalin-2(1*H*)-one (3a)
White solid; yield: 4.3 g (95%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.78 (s, 3 H), 7.07 (s, 1 H), 7.36 (m, 3 H), 7.59 (t, *J* = 7.2 Hz, 1 H), 7.82 (d, *J* = 7.3 Hz, 1 H), 12.76 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 34.87, 116.49, 124.13, 124.58, 128.43, 129.36, 131.47, 132.43, 133.29, 142.64, 148.55, 154.43.

MS (APCI): *m*/*z* = 244 [M + 1].

Anal. Calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.4; N, 24.76. Found: C, 63.94; H, 4.75; N, 24.83.

3-(5-Chloro-1-methyl-1*H*-imidazol-2-yl)quinoxalin-2(1*H*)-one (3b)
Yellow solid; yield: 5.2 g (98%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.67 (s, 3 H), 7.20 (s, 1 H), 7.36 (s, 2 H), 7.61 (t, *J* = 7.3 Hz, 1 H), 7.83 (d, *J* = 7.3 Hz, 1 H), 12.73 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 32.52, 115.95, 119.76, 124.08, 125.76, 129.52, 131.86, 132.11, 133.0, 142.73, 148.78, 154.20.

MS (APCI): *m*/*z* = 261 [M + 1].

Anal. Calcd for $C_{12}H_9ClN_4O$: C, 55.29; H, 3.48; Cl, 13.60; N, 21.49. Found: C, 55.47; H, 3.61; Cl, 13.52; N, 21.68.

3-(1-Benzyl-1*H*-imidazol-2-yl)quinoxalin-2(1*H*)-one (3c)
Yellow solid; yield: 3.8 g (95%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.46 (s, 2 H), 7.10–7.17 (m, 3 H), 7.21 (m, 1 H), 7.23–7.29 (m, 2 H), 7.34 (s, 2 H), 7.43 (s, 1 H), 7.57 (t, *J* = 7.2 Hz, 1 H), 7.75 (d, *J* = 7.2 Hz, 1 H), 12.67 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 50.77, 116.34, 123.47, 123.88, 124.18, 127.79, 127.97, 128.86, 128.93, 129.25, 131.55, 132.27, 133.13, 138.15, 142.19, 154.36.

MS (APCI): *m*/*z* = 303 [M + 1].

Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.75; H, 4.95; N, 18.71.

3-(1-Vinyl-1*H*-imidazol-2-yl)quinoxalin-2(1*H*)-one (3d)
Brown solid; yield: 4.2 g (94%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.87 (d, *J* = 8.3 Hz, 1 H), 5.50 (d, *J* = 15.4 Hz, 1 H), 7.18 (s, 1 H), 7.24 (m, 1 H), 7.34–7.38 (m, 2 H), 7.61 (t, *J* = 7.5 Hz, 1 H), 7.82 (d, *J* = 7.5 Hz, 1 H), 7.89 (s, 1 H), 12.71 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 102.56, 116.09, 118.26, 124.05, 129.57, 129.99, 130.95, 131.91, 132.24, 133.19, 142.07, 149.16, 154.50.

MS (APCI): *m*/*z* = 239 [M + 1].

Anal. Calcd for $C_{13}H_{10}N_4O$: C, 65.54; H, 4.23; N, 23.52. Found: C, 65.81; H, 4.38; N, 23.68.

3-(1-Allyl-1*H*-imidazol-2-yl)quinoxalin-2(1*H*)-one (3e)
Brown solid; yield: 3.1 g (94%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.84 (s, 2 H), 5.01 (d, *J* = 16.9 Hz, 1 H), 5.09(d, *J* = 10.1 Hz, 1 H), 5.97 (m, 1 H), 7.11 (s, 1 H), 7.36 (s, 3 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.81 (d, *J* = 7.5 Hz, 1 H), 12.70 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.85, 116.29, 117.91, 123.30, 124.17, 128.68, 129.35, 131.56, 132.32, 133.21, 134.86, 142.12, 149.04, 154.40.

MS (APCI): *m*/*z* = 253 [M + 1].

Anal. Calcd for $C_{14}H_{12}N_4O$: C, 66.66; H, 4.79; N, 22.21. Found: C, 66.92; H, 4.85; N, 22.15.

3-(1-Butyl-1*H*-imidazol-2-yl)quinoxalin-2(1*H*)-one (3f)
Brown solid; yield: 3.5 g (92%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.82 (t, *J* = 7.4 Hz, 3 H), 1.23 (m, *J* = 7.1 Hz, 2 H), 1.70 (m, *J* = 6.7 Hz, 2 H), 4.15 (m, 2 H), 7.09 (s, 1 H), 7.38 (s, 2 H), 7.42 (s, 1 H), 7.60 (t, *J* = 7.5 Hz, 1 H), 7.80 (d, *J* = 7.5 Hz, 1 H), 12.63 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.88, 19.66, 33.20, 47.07, 115.62, 123.43, 124.25, 126.09, 128.47, 129.23, 131.46, 132.51, 133.51, 141.95, 154.50.

MS (APCI): *m*/*z* = 269 [M + 1].

Anal. Calcd for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.88. Found: C, 67.31; H, 6.25; N, 21.05.

3-(1-Methyl-1*H*-benzimidazol-2-yl)quinoxalin-2(1*H*)-one (3g)
Brown solid; yield: 4.7 g (99%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.87 (s, 3 H), 7.30 (t, *J* = 7.0 Hz, 1 H), 7.36–7.43 (m, 3 H), 7.66 (d, *J* = 7.6 Hz, 2 H), 7.73 (d, *J* = 7.3 Hz, 1 H), 7.90 (d, *J* = 7.3 Hz, 1 H), 12.84 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ =31.68, 111.10, 116.31, 120.17, 122.72, 123.80, 124.27, 129.80, 132.35, 133.30, 136.22, 142.71, 148.54, 149.82, 154.45, 154.46.

MS (APCI): *m*/*z* = 277 [M + 1].

Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.72; H, 4.53; N, 20.22.

3-(2-Methyl-2*H*-1,2,4-triazol-3-yl)quinoxalin-2(1*H*)-one (3h)
Yellow solid; yield: 3.8 g (92%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.94 (s, 3 H), 7.37–7.41 (m, 2 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.87 (d, *J* = 7.6 Hz, 1 H), 8.01 (s, 1 H), 12.87 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 37.36, 116.16, 124.24, 129.80, 132.10, 132.55, 133.25, 148.05, 149.99, 150.96, 153.95.

MS (APCI): *m*/*z* = 228 [M + 1].

Anal. Calcd for $C_{11}H_9N_5O$: C, 58.15; H, 3.99; N, 30.82. Found: C, 58.32; H, 4.11; N, 30.76.

3-(2-Benzyl-2*H*-1,2,4-triazol-3-yl)quinoxalin-2(1*H*)-one (3i)
Yellow solid; yield: 4.4 g (97%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.52 (s, 2 H), 7.25 (m, 3 H), 7.30 (m, 2 H), 7.38 (m, 2 H), 7.66 (t, *J* = 7.3 Hz, 1 H), 7.82 (d, *J* = 7.3 Hz, 1 H), 8.15 (s, 1 H), 12.86 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 53.16, 116.18, 124.26, 128.20, 128.45, 128.85, 129.74, 132.03, 132.63, 133.31, 136.70, 148.02, 150.02, 151.43, 154.0.

MS (APCI): *m*/*z* = 304 [M + 1].

Anal. Calcd for $C_{17}H_{13}N_5O$: C, 67.32; H, 4.32; N, 23.09. Found: C, 67.40; H, 4.38; N, 23.17.

3-(4-Methylthiazol-2-yl)quinoxalin-2(1*H*)-one (3j)
Black solid; yield: 5.7 g (97%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.51 (s, 3 H), 7.40 (m, 2 H), 7.60 (m, 2 H), 7.94 (d, *J* = 7.8 Hz, 1 H), 12.96 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.42, 116.03, 120.87, 124.44, 129.75, 131.52, 132.16, 132.66, 147.28, 153.89, 154.14, 158.08.

MS (APCI): m/z = 244 [M + 1].

Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27; S, 13.18. Found: C, 59.43; H, 3.85; N, 17.23; S, 13.22.

3-Benzothiazol-2-ylquinoxalin-2(1*H*)-one (3k)
Black solid; yield: 4.9 g (98%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.44 (m, 2 H), 7.55 (t, J = 7.5 Hz, 1 H), 7.62 (t, J = 7.6 Hz, 1 H), 7.67 (t, J = 7.6 Hz, 1 H), 8.01 (d, J = 8.1 Hz, 1 H), 8.22 (m, 2 H), 13.08 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 116.14, 122.68, 124.36, 124.65, 126.80, 127.18, 130.16, 132.56, 132.68, 132.82, 137.16, 147.81, 152.89, 154.34, 160.48.

MS (APCI): m/z = 280 [M + 1].

Anal. Calcd for $C_{15}H_9N_3OS$: C, 64.50; H, 3.25; N, 15.04; S, 11.48. Found: C, 64.72; H, 3.48; N, 15.12; S, 11.64.

6,7-Dimethyl-3-(1-methyl-1*H*-imidazol-2-yl)quinoxalin-2(1*H*)-one (4a)
Yellow solid; yield: 3.4 g (93%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.32 (s, 3 H), 2.35 (s, 3 H), 3.79 (s, 3 H), 7.07 (s, 1 H), 7.16 (s, 1 H), 7.35 (s, 1 H), 7.60 (s, 1 H), 12.66 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.43, 20.38, 34.86, 116.80, 124.39, 128.15, 129.03, 131.21, 131.71, 133.14, 141.40, 142.81, 146.93, 154.57.

MS (APCI): m/z = 255 [M + 1].

Anal. Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.30; H, 5.68; N, 22.18.

6,7-Difluoro-3-(1-methyl-1*H*-imidazol-2-yl)quinoxalin-2(1*H*)-one (4b)
Grey solid; yield: 3.6 g (95%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.91 (s, 3 H), 7.14 (s, 1 H), 7.43 (m, 2 H), 7.95 (s, 1 H), 13.24 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 35.51, 105.84, 116.47, 116.61, 125.51, 128.09, 129.73, 132.17, 142.03, 147.12 (d, J_{CF} = 260.3 Hz), 151.57 (dd, J_{CF} = 252.1 Hz, $^3J_{CF}$ = 14.5 Hz), 154.62.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –142.24 (br s, 1 F), –132.20 (m, 1 F).

MS (APCI): m/z = 263 [M + 1].

Anal. Calcd for $C_{12}H_8F_2N_4O$: C, 54.97; H, 3.08; N, 21.37. Found: C, 55.13; H, 3.27; N, 21.45.

8-(1-Methyl-1*H*-imidazol-2-yl)-2,3-dihydro[1,4]dioxino[2,3-*g*]quinoxalin-7(6*H*)-one (4c)
Black solid; yield: 3.8 g (91%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.83 (s, 3 H), 4.32 (s, 2 H), 4.38 (s, 2 H), 6.85 (s, 1 H), 7.09 (s, 1 H), 7.30 (s, 1 H), 7.36 (s, 1 H), 12.53 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 35.08, 64.30, 65.22, 103.37, 115.29, 124.52, 127.69, 128.23, 129.71, 141.60, 142.69, 144.26, 147.63, 154.42.

MS (APCI): m/z = 285 [M + 1].

Anal. Calcd for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.25; N, 19.71. Found: C, 59.34; H, 4.36; N, 19.62.

3-(1-Methyl-1*H*-imidazol-2-yl)-8,9-dihydro-7*H*-[1,4]dioxepino[2,3-*g*]quinoxalin-2(1*H*)-one (4d)
Black solid; yield: 2.9 g (84%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.18 (m, J = 5.1 Hz, 2 H), 3.80 (s, 3 H), 4.20 (t, J = 5.1 Hz, 2 H), 4.28 (t, J = 5.1 Hz, 2 H), 6.94 (s, 1 H), 7.08 (s, 1 H), 7.36 (s, 1 H), 7.41 (s, 1 H), 12.63 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 31.58, 34.98, 71.29, 71.38, 107.84, 120.44, 124.55, 127.97, 128.94, 130.57, 142.61, 145.87, 148.62, 154.41, 154.97.

MS (APCI): m/z = 299 [M + 1].

Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78. Found: C, 60.53; H, 4.85; N, 18.67.

3-(1-Methyl-1*H*-imidazol-2-yl)-4a,5,6,7,8,8a-hexahydroquinoxalin-2(1*H*)-one (6a)
White solid; yield: 2.4 g (40%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.25–1.46 (m, 4 H), 1.71 (m, 1 H), 1.78 (m, 1 H), 1.95 (m, 1 H), 2.23 (m, 1 H), 3.14 (m, 1 H), 3.25 (m, 1 H), 3.68 (s, 3 H), 6.94 (s, 1 H), 7.23 (s, 1 H), 8.60 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.75, 25.23, 30.65, 31.87, 34.48, 53.83, 63.06, 123.96, 127.93, 142.36, 156.05, 156.61.

MS (APCI): m/z = 233 [M + 1].

Anal. Calcd for $C_{12}H_{16}N_4O$: C, 62.05; H, 6.94; N, 24.12. Found: C, 62.27; H, 7.11; N, 24.18.

3-(1-Benzyl-1*H*-imidazol-2-yl)-4a,5,6,7,8,8a-hexahydroquinoxalin-2(1*H*)-one (6b)
White solid; yield: 2.9 g (48%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.20–1.42 (m, 4 H), 1.68 (m, 1 H), 1.75 (m, 1 H), 1.91 (m, 1 H), 2.19 (m, 1 H), 2.97 (m, 1 H), 3.18 (m, 1 H), 5.30 (d, J = 15.2 Hz, 1 H), 5.30 (d, J = 15.2 Hz, 1 H), 7.00 (s, 1 H), 7.18 (m, 2 H), 7.25–7.36 (m, 4 H), 8.56 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.71, 25.17, 30.58, 31.81, 50.22, 53.71, 62.93, 123.26, 127.98, 128.01, 128.32, 128.92, 138.08, 142.0, 156.02, 156.51.

MS (APCI): m/z = 309 [M + 1].

Anal. Calcd for $C_{18}H_{20}N_4O$: C, 70.11; H, 6.54; N, 18.17. Found: C, 70.29; H, 6.72; N, 18.09.

3-(1-Allyl-1*H*-imidazol-2-yl)-4a,5,6,7,8,8a-hexahydroquinoxalin-2(1*H*)-one (6c)
White solid; yield: 8.2 g (85%); 90% purity. The analytical sample was obtained by crystallization (DMF); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.22–1.45 (m, 4 H), 1.72 (m, 1 H), 1.77 (m, 1 H), 1.96 (m, 1 H), 2.25 (m, 1 H), 3.12 (m, 1 H), 3.23 (m, 1 H), 4.68 (dd, ^2J = 15.6 Hz, ^3J = 5.2 Hz, 1 H), 4.78 (dd, ^2J = 15.6 Hz, ^3J = 5.2 Hz, 1 H), 5.05 (d, J = 17.2 Hz, 1 H), 5.14 (d, J = 10.1 Hz, 1 H), 5.91 (m, 1 H), 6.98 (s, 1 H), 7.24 (s, 1 H), 8.58 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.54, 25.20, 30.64, 31.85, 53.77, 55.49, 63.02, 117.94, 122.75, 128.11, 134.68, 141.93, 156.54, 159.09.

MS (APCI): m/z = 259 [M + 1].

Anal. Calcd for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 65.27; H, 7.24; N, 21.50.

3-(1-Allyl-1*H*-imidazol-2-yl)-5,6,7,8-tetrahydroquinoxalin-2(1*H*)-one (7)
Compound **6c** (100 mg) was dissolved in MeOH (5mL) and silica gel (5 g) was added. The solvent was evaporated in vacuo. The solid was transferred into to the column charged with silica gel (*t*-BuOMe). Evaporation of the solvent afforded the pure compound **7** as a brown solid; yield: 52 mg (62%); mp 85 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.88 (m, 4 H), 2.83 (m, 2 H), 2.86 (m, 2 H), 5.11 (d, J = 16.7 Hz, 1 H), 5.20 (d, J = 10 Hz, 1 H), 5.35 (d, J = 5.5 Hz, 2 H), 6.02 (m, 1 H), 7.0 (s, 1 H), 7.10 (s, 1 H), 13.90 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.21, 22.59, 30.52, 31.43, 50.54, 117.35, 122.26, 125.17, 126.99, 133.13, 141.40, 142.35, 149.38, 156.97.

MS (APCI): *m*/*z* = 257 [M + 1].

Anal. Calcd for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.74; H, 6.38; N, 21.79.

3-(1-Methyl-1*H*-benzimidazol-2-yl)-4a,5,6,7,8,8a-hexahydroquinoxalin-2(1*H*)-one (6d)
White solid; yield: 2.6 g (45%); mp >200 °C (DMF).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.21–1.49 (m, 4 H), 1.72 (m, 1 H), 1.79 (m, 1 H), 1.99 (m, 1 H), 2.29 (m, 1 H), 3.27 (m, 1 H), 3.41 (m, 1 H), 3.82 (s, 3 H), 7.28 (t, *J* = 7.7 Hz, 1 H), 7.35 (t, *J* = 7.7 Hz, 1 H), 7.60 (d, *J* = 7.7 Hz, 1 H), 7.69 (d, *J* = 7.7 Hz, 1 H), 8.80 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.17, 25.27, 30.67, 31.43, 31.71, 53.92, 63.50, 111.01, 120.06, 122.63, 123.65, 135.96, 142.36, 148.25, 156.52, 156.78.

MS (APCI): *m*/*z* = 283 [M + 1].

Anal. Calcd for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.84. Found: C, 68.21; H, 6.57; N, 19.72.

1-[2-(Diethylamino)ethyl]-3-(1-methyl-1*H*-imidazol-2-yl)quinoxalin-2(1*H*)-one (8)
NaH (80 mg, 60% in mineral oil, 2 mmol) was added to a solution of **3a** (226.2 mg, 1 mmol) in DMSO (5 mL). After stirring the mixture for 1 h at r.t., 2-chloro-*N*,*N*-diethylethylamine hydrochloride (172.1 mg, 1 mmol) was added. The mixture was stirred overnight at r.t. for 12 h. It was then poured into H_2O (100 mL) and extracted with EtOAc (2 × 20 mL). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The solvent was distilled off under reduced pressure. The residue was purified by column chromatography (hexane–EtOAc, 1:1) to give **8** (172 mg, 0.53 mol, 53%) as an yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 6.7 Hz, 6 H), 2.67 (q, *J* = 6.7 Hz, 4 H), 2.80 (t, *J* = 7.5 Hz, 2 H), 3.91 (s, 3 H), 4.40 (t, *J* = 7.5 Hz, 2 H), 7.02 (s, 1 H), 7.23 (s, 1 H), 7.33 (t, *J* = 7.8 Hz, 1 H), 7.42 (d, *J* = 7.8 Hz, 1 H), 7.58 (t, *J* = 7.8 Hz, 1 H), 7.88 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.95, 35.52, 41.16, 47.61, 49.29, 113.73, 123.72, 124.16, 129.51, 130.68, 131.18, 132.66, 132.86, 142.29, 146.55, 153.43.

MS (APCI): *m*/*z* = 326 [M + 1].

Anal. Calcd for $C_{18}H_{23}N_5O$: C, 66.44; H, 7.12; N, 21.52. Found: C, 66.58; H, 7.30; N, 21.63.

Acknowledgement

All authors are grateful to Dr. Oleg Lozinski for help with the manuscript preparation.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) Carta, A.; Piras, S.; Loriga, G.; Paglietti, G. *Mini-Rev. Med. Chem.* **2006**, *6*, 1179; and references therein.
(2) Nikam, S. S.; Bigge, C. F. *Drugs Future* **1999**, *24*, 1107.
(3) Hyae-Gyeong, C.; Chul-Min, L.; Beom-Tae, K.; Ki-jun, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2661.
(4) Xun, L.; Yonggang, L.; Wenfang, X.; Jian, Z.; Huawei, Z. *Bioorg. Med. Chem.* **2010**, *18*, 1516.
(5) El-Sabbagh, O. I.; El-Sadek, M. E.; Lashine, S. M.; Yassin, S. H.; El-Nabtity, S. M. *Med. Chem. Res.* **2009**, *18*, 782.
(6) Patel, M.; Mchugh, R. J.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Trainor, G. L.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1729.
(7) Willardsen, J. A.; Dudley, D. A.; Cody, W. L.; Chi, L.; McClanahan, T. B.; Mertz, T. E.; Potoczak, R. E.; Narasimhan, L. S.; Holland, D. R.; Rapundalo, S. T.; Edmunds, J. J. *J. Med. Chem.* **2004**, *47*, 4089.
(8) Carta, A.; Sanna, P.; Loriga, M.; Setzu, M. G.; La Colla, P.; Loddo, R. *Farmaco* **2002**, *57*, 19.
(9) Tang, A. H.; Franklin, S. R.; Himes, C. S.; Ho, P. M. *J. Pharmacol. Exp. Ther.* **1991**, *259*, 248.
(10) Ager, I. R.; Barnes, A. C.; Danswan, G. W.; Hairsine, P. W.; Kay, D. P.; Kennewell, P. D.; Matharu, S. S.; Miller, P.; Robson, P.; Rowlands, D. A.; Tully, W. R.; Westwood, R. *J. Med. Chem.* **1988**, *31*, 1098.
(11) Manca, P.; Peana, A.; Savelli, F.; Mule, A.; Pirisino, G. *Farmaco* **1992**, *47*, 519.
(12) Brown, D. J. In *Quinoxalines: Supplement II*; Taylor, E. C.; Wipf, P.; Weissberger, A., Eds.; John Wiley & Sons: New Jersey, **2004**, 92; 1–189-239.
(13) Gris, J.; Glisoni, R.; Fabian, L.; Fernández, B.; Moglioni, A. *Tetrahedron Lett.* **2008**, *49*, 1053.
(14) Andrioletti, B.; Rose, E.; Szydlo, F.; Duhayon, C. *Tetrahedron Lett.* **2008**, *49*, 3749.
(15) Mukherjee, C.; Watanabe, K.; Biehl, E. *Tetrahedron Lett.* **2012**, *53*, 6008.
(16) Shi, F.; Tan, W.; Zhang, H.; Li, M.; Ye, Q.; Ma, G.; Tu, S.; Li, G. *Adv. Synth. Catal.* **2013**, *355*, 3715.
(17) Geraschenko, O. V.; Khodakovskiy, P.; Shishkin, O.; Mykhailiuk, P.; Zaporozhets, O.; Tolmachev, A. *Synthesis* **2011**, 1633.
(18) Geraschenko, O. V.; Khodakovskiy, P. V.; Shivanyuk, O. N.; Shishkin, O. V.; Mykhailiuk, P. K.; Tolmachev, A. A. *Synthesis* **2012**, *44*, 1263.
(19) Soloshonok, V. A.; Ono, T. *J. Org. Chem.* **1997**, *62*, 3030.
(20) Unfortunately, all attempts to isolate the *cis* isomers from the mother liquor failed.
(21) CCDC number for compound **6c** is 913386.

