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Quinoxalino[2,3-*c*]cinnolines and Their 5-*N*-Oxide: Alkoxylation of Methyl-Substituted Quinoxalino[2,3-*c*]cinnolines to Acetals and Orthoesters

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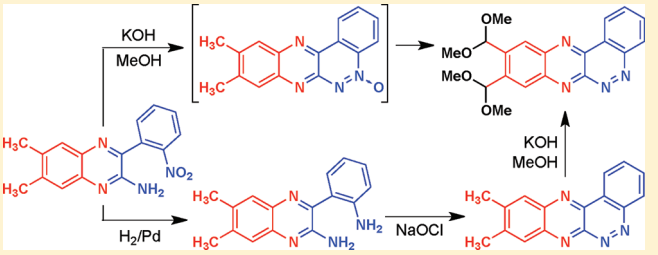
Supporting Information

ABSTRACT: We report the alkoxylation of methyl-substituted quinoxalino[2,3-*c*]cinnolines to give acetals and orthoesters in high yields. Routes to the precursors of this alkoxylation reaction as well as other quinoxalino[2,3-*c*]cinnoline and their 5-oxide derivatives are reported. Most of these quinoxalino[2,3-*c*]cinnolines were prepared by cyclization of the corresponding 2-amino-3-(2-nitrophenyl)quinoxaline, which, in turn, result from an unusual Beirut reaction from benzofurazan oxides plus 2-nitrobenzylcyanides. Mechanistic explanations for these intriguing reactions are presented.



INTRODUCTION

Current interest in the chemistry of heterocyclic di-*N*-oxides stems from their biological activities as they are known to be effective growth-promoting additives in animal feed as exemplified by quinoxaline 1,4-dioxides **1**.[1] Some of these compounds are reported to have antimalarial, anti-Chagas disease, and anticancer properties.[2−7] We have established the anticancer activity of **1b**.[8] Tirapazamine (**2**; SR 4223) is currently in stage 3 clinical trials (Figure 1).[9] It is believed that the anticancer activities of both **1b** and **2** are initiated by bioreductive processing of the nitrone moiety in these compounds. Therefore, we envisaged that synthetic access to additional *N*-oxides might broaden and enhance the activity profile of such heterocycles.[10]

As a continuation of our efforts in this field, we predicted that quinoxaline 1,4-dioxides with an amino group at position 2 would bear a resemblance to tirapazamine (**2**). Furthermore, the synthesis of 2-amino-3-(2-nitrophenyl)quinoxaline 1,4-dioxides such as **5a** and subsequent cyclization to quinoxalino[2,3-*c*]cinnoline 5,7,12-tri-*N*-oxide (**7a**) would result in an unknown and potentially more active tri-*N*-oxide. However, as reported here, this objective (**5a** → **7a**; Scheme 1) was not realized experimentally, even in refluxing 10% KOH in MeOH for 3 h, presumably because of the poor nucleophilicity of the 2-amino group in **5a**. The failure of this transformation (**5a** → **7a**) caused us to focus our attention on the second unexpected product (**6a**−**i**) of the Beirut reaction as detailed below.

RESULTS AND DISCUSSION

The Beirut reaction of a number of benzofurazan oxides (**3**) with 2-nitrobenzylcyznides (**4**) in acetonitrile with pyrrolidine as a catalyst, at room temperature, gave the corresponding 2-amino-3-(2-nitrophenyl)quinoxaline 1,4-dioxide (**5a**). It was surprising to find that the second product of this reaction, formed in almost equivalent amount, was the deoxygenated 2-amino-3-(2-nitrophenyl)quinoxaline (**6a**; Scheme 1).

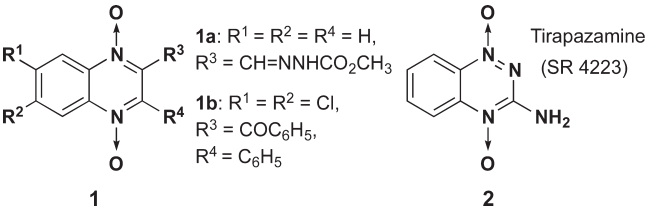


Figure 1. Bioactive heterocyclic di-*N*-oxides.

Because the Beirut reaction of **3** + **4** has taken an unusual course, namely, the formation of 2-aminoquinoxaline derivatives **6a**−**i** in addition to the 2-aminoquioxaline 1,4-dioxide derivative **5a**, this paper focuses on the chemistry of these 2-amino-3-(2-phenyl)quinoxaline products **6a**−**i**. The possibility that the unusual quinoxaline **6a** could have arisen from deoxygenation of the quionxaline 1,4-dioxide **5a** was dismissed when it was found that **5a**, when subjected to these reaction conditions, was unchanged even after one week. Mechanistic considerations led us to speculate that formation of quinoxaline **6a** was caused by the generation of 2-nitrosoaniline (**8**) which, in turn, reacted with 2-nitrobenzylcyanide (**4**) to give 2-amino-3-(2-nitrophenyl)quinoxalines (Scheme 2).

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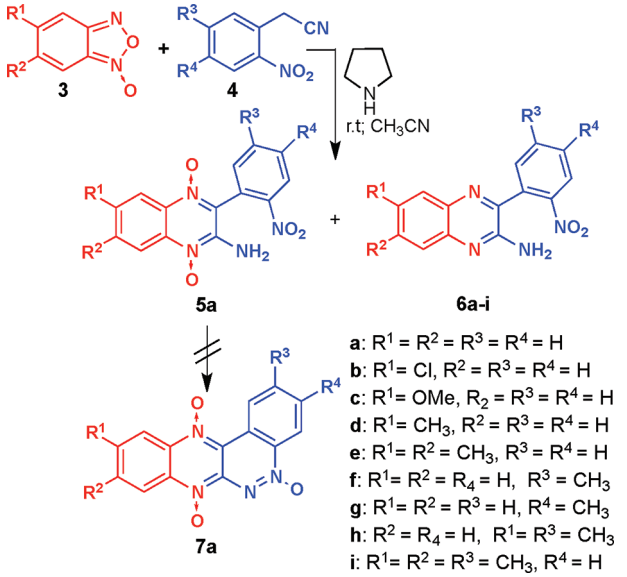
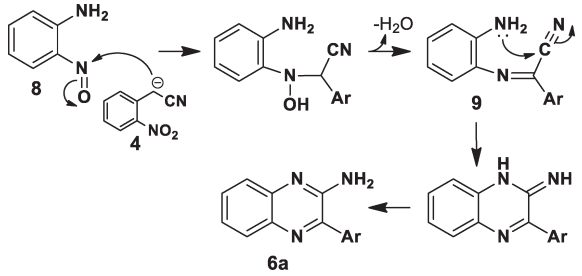
Scheme 1. Beirut Reaction to Quinoxaline Derivatives



Scheme 2. Formation of 6a: Mechanistic Considerations[a]

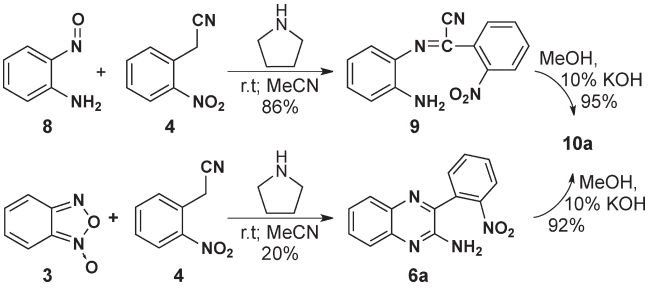


[a] Formation of **8** from **3** and **4** is detailed in the Supporting Information (Scheme 2[SI]).

Indeed, the mother liquor from **3** + **4** showed the presence of trace amounts of 2-nitrosoaniline (**8**), the identity of which was confirmed by comparison with an authentic sample. Furthermore, reaction of independently prepared 2-nitrosoaniline (**8**)[11] with 2-nitrobenzyl cyanide, under the same reaction conditions (Scheme 3), yielded quinoxaline **6a** in high yield. The postulated mechanism is supported by the fact that the reaction of 2-nitrosoaniline with cyanide **4** gave intermediate **9** as a deep red solid. Upon heating in 10% methanolic KOH, **9** gave quinoxaline **6a**. The structures of quinoxaline 1,4-dioxide **5a** and quinoxalines **6a**−**i** are supported by full spectral data (IR, ^{1}H NMR, ^{13}C NMR, and HRMS).

This easy formation of a series of 2-amino-3-(2-nitrophenyl)quinoxalines (**6a**−**c**,**g**) prompted us to investigate their cyclization to the novel corresponding quioxalino[2,3-*c*]cinnoline 5-oxides (**10a**−**d**,**h**). Indeed, this type of cyclization to form cinnoline *N*-oxides is well-known.[12] Heating methanolic KOH solutions of quinoxalines **6a**−**c**,**g** gave novel quioxalino[2,3-*c*]cinnoline 5-oxides **10a**−**c**,**g** in high yields (80−90%). Smith and co-workers have published elegant work on the preparation and reactions of quinoxalino[2,3-*c*]cinnolines using a different method that proceeded in relatively low yields. They also reported the preparation of three quioxalino[2,3-*c*]cinnoline 5-*N*-oxide

Scheme 3. Independent Route to Quinoxaline 6a



derivatives, which did not include the parent ring system. They stated that these quinoxalinocinnoline 5-*N*-oxides were impure and obtained in small quantities which "precluded further work on these compounds".[13,14] As outlined in Scheme 4, we report the preparation of the parent system (**10a**) and a number of derivatives via a new, simple, and efficient sythetic route. Structures for quinoxalino[2,3-*c*]cinnoline 5-*N*-oxides **10a**−**c**,**g** were corroborated by full spectral data (IR/^{1}H NMR/^{13}C NMR/HRMS), and the structure of **10a** was confirmed by X-ray crystallography (see the Supporting Information, Figure 2[SI]).

During the course of this work, a serendipitous reaction was found to occur with some methyl-substituted 2-aminoquinoxalines (**6d**−**f**,**h**,**i**). These analogues underwent cyclization and alkoxylation at the benzylic carbon with subsequent deoxygenation of the anticipated 5-*N*-oxide to yield an acetal, an orthoester (using methanol/10% KOH), or a 1,3-dioxolane (using ethylene glycol/10% KOH) (**11**−**16**; Scheme 5). The structure of diacetal **11** was established by X-ray crystallography (see the Supporting Information, Figure 2[SI]), and a postulated mechanism for its formation is presented in Scheme 6. In contrast, when **6i** was heated with ethylene glycol, under the same reaction conditions but for 10 min, alkoxylation occurred at the methyl carbon of the 2-nitrophenyl group to give **17**, whereas when the reaction was extended to 30 min, a di- and tri-1,3-dioxolane-containing mixture was obtained (**18**).

It is intriguing to speculate whether the 5-*N*-oxide functionality is lost during or after the alkoxylation reaction (Scheme 5). Although we have no solid evidence to indicate at which step deoxygenation takes place, it is believed that this deoxygenation occurs during the alkoxylation reaction because the formation of quinoxalino[2,3-*c*]cinnoline **10a** and its further heating under cyclization conditions (10% KOH/MeOH) did not result in deoxygenation. This postulate is supported by the fact that the 5-*N*-oxide bond length in **10a** is quite short (Supporting Information, Figure 2[SI]) and there is a similar shortness in the 5N−6N bond indicating substantial conjugation with the 5-*N*-oxide.

Another aspect of this alkoxylation reaction requires comment: namely, the absence of monoalkoxylated products. It seems that introduction of the first alkoxy group (methoxy) at the benzylic carbon enhances the acidity of the remaining benzylic hydrogens and renders the next alkoxylation faster than the first. However, where two adjacent methyl groups are found (i.e., **6e** and **6i**), steric hindrance limits alkoxylation to two methoxylations at each of the two benzylic carbons (i.e., acetal formation: positions 9 and 10) compared to three methoxylations (i.e., ortho ester formation) at the benzylic carbon at position 2 in quinoxalino[2,3-*c*]cinnoline (**6i** → **17**).

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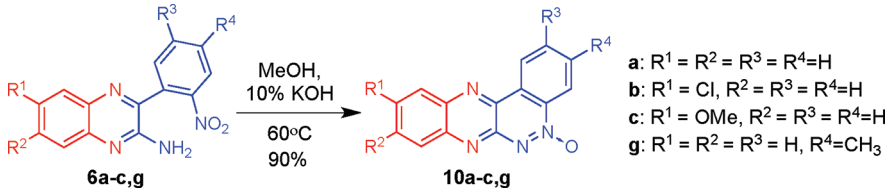
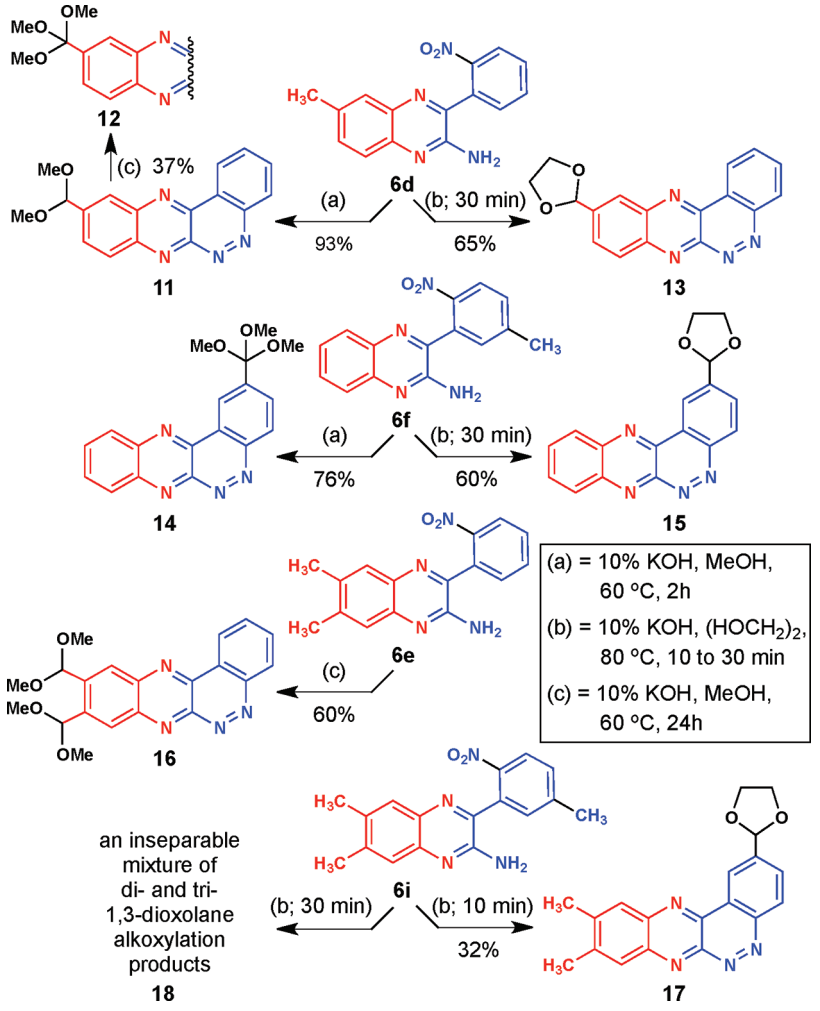
Scheme 4. Synthesis of Quinoxalino[2,3-*c*]cinnoline 5-*N*-Oxides



Scheme 5. Benzylic Alkoxylation of Methyl-Substituted 2-Aminoquioxalines



It is intriguing that the 5-*N*-oxide functionality does not appear to be essential for benzylic methoxylation. As outlined in Scheme 7, this assumption is supported by the fact that 9,10-dimethylquinoxalino-[2,3-*c*]cinnoline (**20**), which was prepared by reduction (H_2/Pd) of 2-amino-3-(2-nitrophenyl)-4,5-dimethylquinoxaline (**6e**) followed by subsequent ring cyclization of **19** with Clorox, underwent alkoxylation under the same conditions to give diacetal **16** in a high yield. It is interesting to note that the alkoxylation reaction proceeds well with primary alcohols, such as methanol, ethanol, or ethylene glycol in 10% KOH, but fails with isopropyl or *tert*-butyl alcohols presumably because of decreased nuceophlicity.

In conclusion, a new route for the Beirut reaction is revealed in which a number of novel 2-amino-3-(2-nitrophenyl)quinoxalines, in addition to their expected 1,4-dioxides, can be easily prepared and converted to novel quinoxalino[2,3-*c*]cinnoline 5-*N*-oxide which are rare in the literature. The highlight of this report is the fortuitous finding that the methyl substituents of some of quinoxalino[2,3-*c*]cinnolines, or their presumed 5-*N*-oxides intermediates, can be easily converted to acetals or orthoesters which we believe to be unprecedented.

EXPERIMENTAL SECTION

All chemicals and solvents were purchased from commercial suppliers. The ^{1}H NMR and ^{13}C NMR spectra were recorded in solution of $CDCl_3$ or DMSO-d_6 with tetramethylsilane (TMS) as the internal standard.

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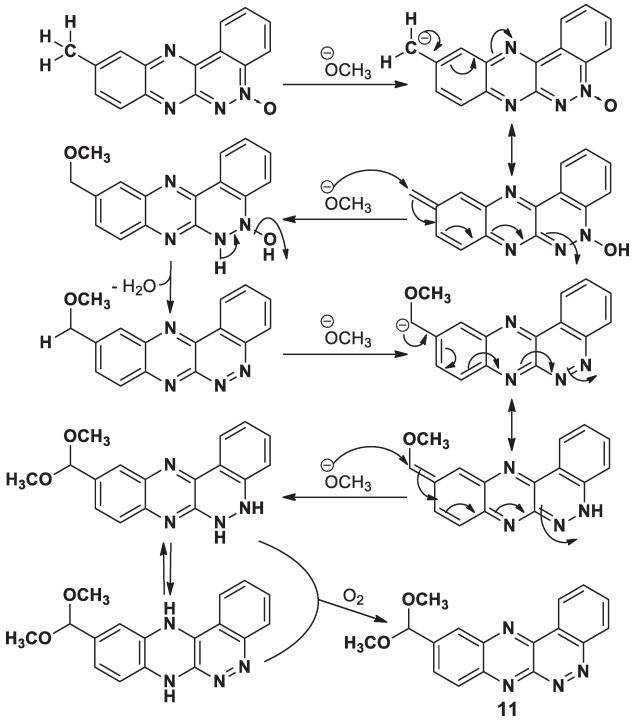
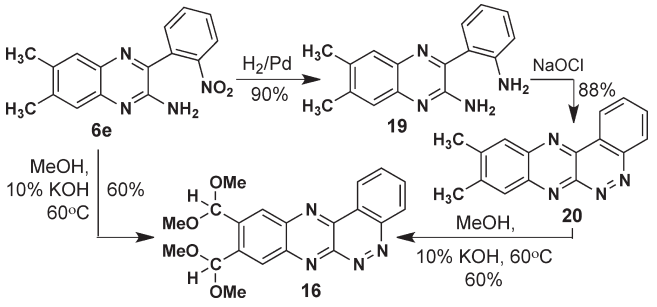
Scheme 6. Postulated Mechanism for the Formation of 11



Scheme 7. Evidence that the 5-*N*-Oxide Moiety Is Not Essential for Benzylic Alkoxylation



^{1}H NMR spectra often include a water peak. Mass spectra were measured using high-resolution MS. Benzofurazan oxide (**3**) and its derivatives were synthesized according to a modified literature procedure.

General Procedure A. Derivatives of benzofurazan oxide (15 mmol) were dissolved in acetonitrile. A solution of 2-nitrobenzylcyanide (1 equiv) dissolved in acetonitrile was added. Dropwise addition of pyrrolidine (5 mL) resulted in a solution color change from yellow to dark blue-black. Water (10 mL) was added, and the reaction was left at room temperature for 12 h. The base was quenched with acetic acid. The resulting yellow solid was filtered to afford products **6a**−**i**. Product **5a** remained in solution, and its purification required column chromatography.

2-Amino-3-(2-nitrophenyl)quinoxaline 1,4-Dioxide (5a). This product was synthesized according to general procedure A as a yellow solid in 20% yield: hygroscopic; ^{1}H NMR ($CDCl_3$) δ 7.37 (2H, s), 7.65(t, J = 1.2 Hz, 1H), 7.81 (d, J = 7.65 Hz, 1H), 7.89 (q, J = 12.7 Hz, 2H), 8.00 (t, J = 7.6 Hz, 1H), 8.31 (t, J = 8.4 Hz, 1H), 8.38 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 117.5, 123.1, 124.9, 131.8, 132.2, 135.2, 148.2, 170.3, 174.6; FTIR (KBr) 3426.0 (s, b), 1652.8 (w), 1635.3 (m, b), 668.0 (w), 533.2 (w, b) cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{11}N_4O_4$ [M + 1] m/z 299.07775, found 299.0775.

General Procedure B. *o*-Nitrosoaniline (**8**; 2 g, 16.4 mmol) and 2-nitrobenzylcyanide (**4**; 2.65 g, 16.4 mmol) were dissolved in acetonitrile (25−30 mL) at room temperature. Pyrrolidine (3 mL) was added dropwise, resulting in a solution color change from light to deep black. Water (10 mL) was added. The reaction mixture was allowed to stand at room temperature for 12 h. The basic solution was quenched with either acetic acid or dilute hydrochloric acid. The yellow solid was filtered to afford the desired product.

3-(2-Nitrophenyl)quinoxalin-2-amine (6a). This product was synthesized as a yellow solid according to general procedure A (20% yield) or B (93% yield): mp 260 °C (lit. mp 260−261 °C); ^{1}H NMR (DMSO-d_6) δ 6.66 (s, 2H, s), 7.45 (m,1H), 7.66 (d, J = 3.6 Hz, 2H), 7.77 (m, 2H), 7.87 (m, 1H), 8.02 (m, 1H), 8.34 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 123.9, 125.0, 125.1, 128.3, 129.8, 130.5, 131.6, 132.1, 134.7, 136.0, 141.6, 144.8, 147.7, 151.5; FTIR (KBr) 3458.5 (s), 3304.5 (w), 3104.6 (m, b), 1647.4 (m), 1522.1 (s), 1437.2 (m), 1433.1 (m). 1344.1 (s), 756.7 (m) cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{11}N_4O_2$ [M + 1] m/z 267.0877, found 267.0878.

6-Chloro-3-(2-nitrophenyl)quinoxalin-2-amine (6b). This product was synthesized according to general procedure A as a yellow solid in 12% yield: mp 270 °C; ^{1}H NMR (DMSO-d_6) δ 6.72 (2H, s), 7.65 (m, 3H), 7.82 (m, 2H), 7.93 (t, J = 7.2 Hz, 1H), 8.29 (d, J = 8.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 125.1, 126.9, 126.9, 127.6, 130.2, 130.8, 131.5, 131.6, 134.9, 136.2, 140.3, 146.1, 147.5, 151.7; FTIR (KBr) 3466.4 (s), 3299.8 (w,b), 3140.2 (m, b), 1642.7 (s), 1613.3 (w), 1572.0 (w), 1561.6 (w), 1529.6 (s), 1489.3 (w), 1453.8 (m), 1427.7 (w), 1342.2 (s), 1301.8 (w), 1012.1 (m), 871.6 (w), 830.3 (m), 789.2 (m), 754.0 (w), 721.4 (w), 696.9 (w) cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{10}N_4O_2Cl$ [M + 1] m/z 301.0487, found 301.0494.

6-Methoxy-3-(2-nitrophenyl)quinoxalin-2-amine (6c). This product was synthesized according to general procedure A as a yellow solid in 26% yield: mp 214 °C; ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H), 6.31 (bs, 2H), 7.21(s, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 9.3 Hz, 1H), 7.69 (d, J = 6.6 Hz, 1H), 7.79 (m, 1H), 7.92(m, 1H), 8.26 (d, J = 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 48.6, 107.6, 121.4, 125.0, 126.2, 130.4, 131.6, 132.3, 134.5, 136.7, 136.8, 144.3, 147.8, 150.4, 156.0; FTIR (KBr) 3450.1 (s), 2924.0 (w, b), 1643.0 (w), 1522.7 (w), 1499.2 (w), 1457.4 (w), 1449.7 (m), 1437.6 (m), 1430.9 (m), 1380.2 (w), 1358.2 (w), 1032.3 (m), 468.1 (w) cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}N_4O_3$ [M + 1] m/z 297.0982, found 297.0983.

6-Methyl-3-(2-nitrophenyl)quinoxalin-2-amine (6d). This product was synthesized according to general procedure A as a yellow solid in 17% yield or procedure B in 84% yield: mp 235 °C; ^{1}H NMR ($CDCl_3$) δ 4.69 (bs, 2H), 7.49 (dd, J = 1.2, 8.4 Hz, 1H), 7.69 (m, 4H), 7.83 (td, J = 1.2, 7.5 hz, 1H), 8.25 (d, J = 1.2, 7.5 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.7, 124.9, 125.0, 127.4, 130.5, 131.6, 131.7, 132.2, 133.3, 134.6, 136.0, 139.7, 144.4, 147.8, 151.1; FTIR (KBr) 3466.0 (s, b), 2923.2 (m), 2852.5 (w), 1653.6 (w), 1458.3 (m), 1450.2 (m), 1448.4 (m), 1437.1 (m), 1419.8 (m), 1345.0 (w), 1032.8 (m, b), 465.8 (w) cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}N_4O_2$ [M + 1] m/z 281.1039, found 281.1033.

6,7-Dimethyl-3-(2-nitrophenyl)quinoxalin-2-amine (6e). This product was synthesized according to general procedure A as a yellow solid in 21% yield: mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H), 2.38 (s, 3H), 6.39 (s, 2H), 7.39 (s, 1H), 7.50 (m, 1H), 7.80 (m, 1H), 7.90 (m, 1H), 8.24 (d, J = 8.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 19.2, 19.9, 124.7, 124.9, 127.6, 130.3, 131.6, 132.3, 133.2, 134.4, 134.9, 139.5, 140.1, 143.2, 147.9, 151.1; FTIR (KBr) 3448.1 (s), 1643.1 (w), 1521.2 (m), 1433.0 (m), 1352.4 (w), 1031.0 (w), 874.9 (w) cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}N_4O_2$ [M + 1] m/z 295.1190, found 295.1190.

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3-(5-Methyl-2-nitrophenyl)quinoxalin-2-amine (6f). This product was synthesized according to general procedure A as a yellow solid in 23% yield or procedure B in 87% yield: mp 245 °C; ^{1}H NMR ($CDCl_3$) δ 8.17−8.20 (1H, d, J = 8.4 Hz), 7.88−7.91 (1H, dd, J = 7.8, 0.9 Hz), 7.71−7.74 (1H, dd, J = 8.1, 1.2 Hz), 7.61−7.67 (1H, td, J = 6.9, 1.5 Hz), 7.42−7.50 (3H, m), 4.81 (2H, s, b), 2.53 (3H, s); ^{13}C NMR ($CDCl_3$) δ 150.19, 146.26, 145.63, 144.14, 141.36, 137.46, 132.05, 132.02, 131.16, 130.38, 128.86, 126.01, 125.58, 125.44, 21.56; FTIR (KBr) 3457.69 (m), 3308.37 (w, b), 3135.92 (m, s), 1586.93 (m), 1650 (w), 1516.38 (m), 1470.75 (w), 1441.44 (m), 1338.99 (w), 1253.51 (s), 1187.06 (s), 1143.47 (s), 1093.30 (s), 1037.68 (s), 954.15 (s), 916.49 (s), 839.58 (m), 755.52 (m), 698.75 (s), 614.24 (s) cm^{-1}; HRMS (EI) calcd for $C_{15}H_{12}N_4O_2$ m/z 280.0960, found 280.0957.

3-(4-Methyl-2-nitrophenyl)quinoxalin-2-amine (6g). This product was synthesized according to general procedure A as a yellow solid in 20% yield: mp 279 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (1H, s), 7.87−7.90 (1H, dd, J = 8.4, 1.2 Hz), 7.72−7.75 (1H, dd, J = 8.4 Hz, 1.2 Hz), 7.61−7.67 (2H, dt, J = 6.9, 1.5 Hz), 7.46−7.53 (2H, m), 4.72 (2H, s, b), 2.56 (3H, s); ^{13}C NMR ($CDCl_3$) δ 150.2, 148.0, 143.8, 141.6, 141.4, 137.6, 135.0, 131.3, 130.4, 129.2, 128.9, 126.0, 125.6, 125.6, 21.3; FTIR (KBr) 3453.81 (s), 3106.04 (w, b), 1646.46 (s), 1568.10 (m), 1530 (s), 1495.23 (s), 1430 (s), 1361.11 (s), 1146.64 (m), 1011.77 (m), 838.32 (m), 799.91 (m), 760.01 (s) cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}N_4O_2$ [M + 1] m/z 281.1033, found 281.1031.

6-Methyl-3-(5-methyl-2-nitrophenyl)quinoxalin-2-amine (6h). This product was synthesized according to general procedure A as a yellow solid in 18% yield: mp 264 °C; ^{1}H NMR ($CDCl_3$) δ 8.16−8.19 (1H, d, J = 8.4 Hz), 7.68 (1H, s), 7.62−7.65 (1H, d, J = 8.4 Hz), 7.46−7.50 (2H, m), 7.42 (1H, s), 4.66 (2H, s, b), 2.53 (3H, s), 2.51 (3H, s); ^{13}C NMR ($CDCl_3$) δ 149.7, 146.1, 145.7, 143.9, 139.5, 137.5, 135.7, 132.5, 132.2, 132.0, 131.0, 128.0, 125.6, 125.4, 21.6, 21.4; FTIR (KBr) 3457.38 (m), 3123.15 (m, b), 1649.31 (m), 1587.29 (w), 1584.71 (w), 1517.96 (s), 1420 (m), 1357.91 (s), 1227.29 (w), 1039.95 (m), 819.47 (s) cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}N_4O_2$ [M + 1] m/z 295.1190, found 294.1190.

6,7-Dimethyl-3-(5-methyl-2-nitrophenyl)quinoxalin-2-amine (6i). This product was synthesized according to general procedure A as a yellow solid in 22% yield: mp >264 °C; ^{1}H NMR ($CDCl_3$) δ 8.15−8.18 (1H, d, J = 8.4 Hz), 7.65 (1H, s), 7.50 (1H, s), 7.45−7.48 (1H, dd, J = 9.6, 1.2 Hz), 7.41−7.42 (1H, d, J = 1.2 Hz), 4.60 (2H, s, b), 2.52 (3H, s), 2.45 (3H, s), 2.41 (3H, s); ^{13}C NMR ($CDCl_3$) δ 149.8, 146.0, 145.8, 142.8, 140.7, 134.0, 136.4, 135.5, 132.3, 132.1, 130.9, 128.2, 125.6, 125.4, 21.6, 20.5, 19.9; FTIR (KBr) 3453.24 (m), 3307.81 (w), 3131.63 (m, b), 1620 (m), 1609.00 (w), 1588.16 (w), 1562.41 (w), 1516.47 (s), 1440.53 (m), 1354.07 (s), 1308.40 (w), 1236.69 (w), 1177.88 (w), 1040.00 (w), 1002.91 (w), 872.28 (m), 826.71 (m), 758.58 (w), 701.52 (w), 453.83 (w) cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}N_4O_2$ [M + 1] m/z 309.1352, found 309.1349.

General Procedure C. *o*-Nitrosoaniline (**8**; 2 g, 16.4 mmol) and 2-nitrobenzylcyanide (**4**; 2.65 g, 16.4 mmol) were dissolved in acetonitrile (25−30 mL) at room temperature. Pyrrolidine (3 mL) was added dropwise resulting in a solution color change from light to deep black. Water (10 mL) was added, and the reaction mixture was allowed to stand at room temperature for 30 min. The basic solution was quenched with either acetic acid or dilute hydrochloric acid, and the resulting deep red solid was collected by filtration, washed with cold methanol, dried, and identified as *N*-(2-aminophenyl)-2-nitrobenzimidoylcyanide (**9**). This deep red solid can be converted to the corresponding quinoxaline by dissolving it in 10% MeOH/KOH and heating for 2 min; the resulting yellow solid was collected by filtration, washed with cold methanol, dried, and identified as 2-amino-3-(2-nitrophenyl)quinoxaline (**6a**).

***N*-(2-Aminophenyl)-2-nitrobenzimidoyl Cyanide (9).** This product was synthesized according to general procedure C as a deep red solid in 86% yield: mp 96 °C; ^{1}H NMR ($CDCl_3$) δ 7.95−7.98 (1H, dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.84−7.87 (1H, dd, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 7.73−7.78 (1H, dt, J_1 = 7.5 Hz, J_2 = 1.2 Hz), 7.64−7.70 (1H, dt, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.58−7.61 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.2 Hz), 7.18−7.28 (1H, dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz), 6.74−6.81 (2H, m), 4.26 (2H, s, b); ^{13}C NMR ($CDCl_3$) δ 148.30, 144.42, 132.57, 132.10, 132.05, 131.74, 130.90, 129.98, 129.11, 124.51, 118.95, 117.88, 116.18, 111.90; FTIR (KBr) 3493.50 (m), 3452.21 (s), 3386.91 (s), 3356.80 (s), 3032.24 (w), 2209.89 (m), 1617.46 (s), 1550 (m), 1479.74 (m) cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{10}N_4O_2$ [M + 1] m/z 267.0882, found 267.0877.

General Procedure D. The appropriate 2-amino-3-(2-nitrophenyl) quinoxaline **6** (2.60 mmol) was dissolved in 10% methanolic base (KOH, 30 mL). The yellow solution was heated at 60 °C for 2 h, and then the reaction mixture was cooled to room temperature affording a yellow-orange solid. In cases where no solid precipitated, the solvent was removed at reduced pressure and the residue was extracted with dichloromethane (50 mL × 4). The organic extracts were combined, dried over $MgSO_4$, and purified by silica gel column chromatography.

Quinoxalino[2,3-*c*]cinnoline 5-Oxide (10a). This product was synthesized according to general procedure D as a yellow solid in 92% yield: mp 246 °C; ^{1}H NMR ($CDCl_3$) δ 9.20−9.23 (1H, dd, J = 7.8, 1 Hz), 8.78−8.81 (1H, d, J = 8.4 Hz), 8.31−8.38 (2H, m), 8.04−8.14 (1H, td, J = 8.1, 1.2 Hz), 7.92−8.03 (3H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 121.7, 124.1, 128.1, 129.0, 129.4, 131.9, 132.1, 133.0, 133.2, 134.0, 140.3, 141.6, 143.3, 146.6; FTIR (KBr) 3447.2 (m, b), 1469.4 (m), 1409.5 (w), 1344.2 (m), 1016.9 (s), 771.2 (m), 656.4 (s), 596.2 (s), 524.9 (s) cm^{-1}; UV (methanol) λ_{max} (nm) (ε_{max} M^{-1} cm^{-1} × 10^3) 287 (113), 401 (78.49); HRMS (ESI) calcd for $C_{14}H_9N_4O$ [M + 1] m/z 249.0776, found 249.0768. The structure of **10a** was confirmed by X-ray crystallography as indicated in the Supporting Information.

10-Chloroquinoxalino[2,3-c]cinnoline 5-Oxide (10b). This product was synthesized according to general procedure D as a yellow solid in 74% yield: mp 260 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.71 (m, 2H), 8.18 (m, 1H), 8.68 (d, J = 8.4 Hz, 1H), 9.08 (d, J = 7.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 105.7, 121.7, 124.0, 126.5, 128.1, 130.6, 132.9, 133.8, 140.1, 143.6, 145.1, 161.8; FTIR (KBr) 3447.6 (m, b), 1623.9 (w), 1481.7 (m), 1402.0 (s), 1208.6 (w), 1199.5 (w), 1128.5 (w), 1016.0 (w) cm^{-1}; HRMS (ESI) calcd for $C_{14}H_8N_4OCl$ [M + 1] m/z 283.0387, found 283.0377.

10-Methoxyquinoxalino[2,3-c]cinnoline 5-Oxide (10c). This product was synthesized according to general procedure D as a yellow solid in 98% yield: mp 274 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.10 (3H, s), 7.70 (1H, m), 7.74 (1H, d, J = 3 Hz), 8.13 (1H, t, J = 1.5 Hz), 8.23 (2H, m), 8.68 (1H, d, J = 8.55 Hz), 9.08 (1H, d, J = 7.35 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ56.34, 105.73, 121.64, 123.98, 126.45, 128.08, 130.61, 132.89, 133.79, 140.10, 143.62, 161.84; FTIR (KBr) 3447.5 (m, b), 1623.6 (m), 1480.9 (s), 1401.6 (s), 1208.4 (m), 1198.8 (m), 1127.7 (w), 1014.3 (w), 834.9 (w), 541.3 (w), 527.4 (w) cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{11}N_4O_2$ [M + 1] m/z 279.0882, found 279.0876.

3-Methylquinoxalino[2,3-c]cinnoline 5-Oxide (10g). This product was synthesized according to general procedure D as a yellow solid in 88% yield: mp 279 °C; ^{1}H NMR ($CDCl_3$) δ 9.07−9.09 (1H, d, J = 8.1 Hz), 8.59 (1H, s), 8.24−8.35 (2H, m), 7.88−7.94 (3H, m), 2.70 (3H, s); ^{13}C NMR ($CDCl_3$) δ 145.4, 143.1, 141.7, 139.6, 134.1, 131.8, 130.6, 130.5, 129.2, 128.2, 125.0, 123.4, 120.9, 21.2; FTIR (KBr) 3082.20 (w), 2921.93 (w, b), 1520.82 (m), 1483.70 (m), 1473.04 (m), 1411.44 (m), 1394.74 (s), 1335.85 (w), 1295.89 (m), 1216.88 (m), 1141.28 (m), 1036.19 (s), 820 (s), 781.08 (w), 768.77 (s), 595.05 (m), 548.74 (m), 529.05 (m) cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{11}N_4O$ [M + 1] m/z 263.0933, found 263.0925; UV (methanol) λ_{max} (nm) (ε_{max} M^{-1} cm^{-1} × 10^3) 289 (53.99), 405 (29.34), 427 (24.19).

10-(Dimethoxymethyl)quinoxalino[2,3-c]cinnoline (11). This product was synthesized according to general procedure D as a

yellow solid in 93% yield: mp 190 °C; ^{1}H NMR ($CDCl_3$) δ 9.29−9.32 (1H, dd, J = 5.7, 2.4 Hz), 8.94−8.97 (1H, dd, J = 5.7, 2.1 Hz), 8.55−8.59 (2H, m), 8.11−8.19 (3H, m), 5.74 (1H, s), 3.49 (6H, s); ^{13}C NMR ($CDCl_3$) δ 53.1, 102.1, 121.3, 123.1, 127.3, 130.8, 131.0, 131.6, 132.0, 133.1, 133.4, 143.7, 143.9, 145.5, 145.6, 146.7; FTIR (KBr) 3438.7 (w, b), 2934.8 (s, b), 1438.0 (m), 1095.2 (m), 1075.6 (w), 1005.1 (s) cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}N_4O_2$ [M + 1] m/z 307.1195, found 307.1191; UV (methanol) λ_{max} (nm) (ε_{max} M^{-1} cm^{-1} × 10^3) 282 (309), 382 (87.86). The structure of **11** was confirmed by X-ray crystallography as indicated in the Supporting Information.

10-(Trimethoxymethyl)quinoxalino[2,3-*c*]cinnoline (12). This product was synthesized according to general procedure D as a yellow solid in 37% yield, but the reflux was continued for 24 h: mp 162 °C; ^{1}H NMR ($CDCl_3$) δ 9.2−9.21 (1H, m), 8.84−8.87 (1H, m), 8.72 (1H, s), 8.34−8.48 (1H, d, J = 8.7 Hz), 8.05−8.11(3H, m), 3.20 (9H, s); ^{13}C NMR ($CDCl_3$) δ 145.6, 144.5, 144.2, 142.8, 141.5, 132.4, 132.2, 131.1, 130.6, 130.1, 129.9, 127.9, 122.0, 120.2, 113.2, 49.1; FTIR (KBr) 2956.9 (w, b), 2838.6 (w), 1726.9 (s), 1474.8 (w), 1379.8 (w), 1342.4 (m), 1306.1 (m), 1249.8 (s), 1223.2 (w), 1185.4 (m), 1092.9 (m), 1059.7 (s), 1004.2 (w), 978.0 (w), 925.1 (m), 894.1 (w), 817.5 (m), 773.7 (s), 604.2 (m), 528.9 (m) cm^{-1}; HRMS (EI) calcd for $C_{18}H_{16}N_4O_3$ m/z 336.1222, found 336.1224; UV (methanol) λ_{max} (nm) (ε_{max} M^{-1} cm^{-1} × 10^3) 282 (118.6), 381(33.27).

2-(Trimethoxymethyl)quinoxalino[2,3-*c*]cinnoline (14). This product was synthesized according to general procedure D as a yellow solid. The reaction mixture was extracted with dichloromethane/water and purified through a short column of silica gel using hexane/ethyl acetate (1:1 ratio) as eluent (76% yield): mp 215 °C; ^{1}H NMR ($CDCl_3$) δ 9.53−9.54 (1H, d, J = 1.5 Hz), 8.95−8.98 (1H, d, J = 8.4 Hz), 8.57−8.60 (1H, dt, J = 8.1, 0.9 Hz), 8.47−8.50 (1H, dt, J = 8.1 Hz, 0.6 Hz), 8.33 (1H, dd, J 8.4 Hz, 1.8 Hz), 8.05−8.14 (2H, m), 3.27 (9H, s); ^{13}C NMR ($CDCl_3$) δ 146.5, 145.9, 145.6, 143.8, 142.2, 133.6, 133.2, 132.0, 131.7, 131.1, 131.0, 129.4, 122.7, 121.0, 114.4, 50.1; FTIR (KBr) 3079.5 (w, b), 2948.1 (w, b), 1725.8 (s), 1594.0 (w), 1531.1 (w), 1489.8 (w), 1462.4 (w), 1433.5 (w), 1395.1 (w), 1370.4 (w), 1334.4 (w), 1272.0 (m), 1207.1 (m), 1165.5 (m), 1117.8 (m), 1086.5 (w), 1023.4 (w), 982.8 (w), 921.9 (w), 898.6 (w), 869.0 (w), 799.1 (w), 762.3 (s), 655.7 (m), 605.4 (m), 561.1 (w) cm^{-1}; HRMS (EI) calcd for $C_{18}H_{16}N_4O_3$ m/z 336.1222, found 336.1218; UV (methanol) λ_{max} (nm) (ε_{max} M^{-1} cm^{-1} × 10^3) 286 (74.13), 384 (31.87).

9,10-Bis(dimethoxymethyl)quinoxalino[2,3-*c*]cinnoline (16). This product was synthesized according to general procedure D as a yellow solid. The reaction mixture was extracted with dichloromethane/water and purified through a short column of silica gel using hexane/ethyl acetate (1:1 ratio) as eluent (60% yield): mp 168 °C; ^{1}H NMR ($CDCl_3$) δ 9.27−9.30 (1H, dd, J = 6 Hz, 2.1 Hz), 8.91−8.94 (1H, dd, J = 6.6,2.4 Hz), 8.80 (1H, s), 8.70 (1H, s), 8.06−8.16 (2H, m), 6.02 (1H, s), 5.97 (1H, s), 3.47 (12H, s); ^{13}C NMR ($CDCl_3$) δ 146.7, 145.8, 145.3, 143.3, 141.9, 140.1, 133.7, 133.0, 131.9, 131.6, 129.5, 127.9, 123.1, 121.4, 100.3, 100.1, 53.4, 53.4; FTIR (KBr) 3447.5 (m, b), 2961.6 (w, b), 2923.7 (w, b), 2850.1 (w, b), 1437.6 (w), 1261.3 (m), 1087.1 (w), 1049.2 (w), 1030.6 (w), 801.8 (w, b) cm^{-1}; UV (methanol) λ_{max} (nm) (ε_{max} M^{-1} cm^{-1} × 10^3): 284 (146), 384 (38.29); HRMS (ESI) calcd for $C_{20}H_{21}N_4O_4$ [M + 1] m/z 381.1563, found 381.1539.

General Procedure E. The appropriate 2-amino-3-(2-nitrophenyl)quinoxaline **6** (2.60 mmol) was dissolved in 10% *tert*-butyl alcohol/KOH (30 mL). Ethylene glycol (10 mL) was added, and the blackish solution was heated at 80 °C for 30 min. After cooling, the solvent was removed at reduced pressure, and the brown residue was extracted with dichloromethane (50 mL × 4). The organic extracts were combined, dried over $MgSO_4$, and purified by silica gel column chromatography (1:1 ethyl acetate/hexane) to obtain the corresponding quinoxalino[2,3-*c*]cinnoline as a yellow-orange solid.

10-(1,3-Dioxolan-2-yl)quinoxalino[2,3-*c*]cinnoline (13). This product was synthesized according to general procedure E as a yellow solid in 65% yield: mp 198 °C; ^{1}H NMR ($CDCl_3$) δ 9.12−9.15 (1H, dd, J = 7.8, 1.2 Hz), 8.70−8.73 (1H, dd, J = 8.4, 0.9 Hz), 8.36 (2H, d, J = 1.8 Hz), 8.28−8.32 (2H, d, J = 9.0 Hz), 7.91−8.09 (4H, m), 6.06 (1H, s), 4.10−4.18 (5H, m); ^{13}C NMR ($CDCl_3$) δ 146.9, 144.6, 144.2, 142.9, 142.3, 142.1, 141.8, 140.7, 133.7, 132.9, 132.7, 130.5, 130.1, 129.8, 129.7, 128.3, 128.1, 127.1, 124.7, 124.7, 122.4, 102.9, 65.7; FTIR (KBr) 2890.19 (w, b), 1466.16 (m), 1405 (s), 1349.36 (w), 1177.96 (m), 1080.59 (m), 1017.11 (w), 896.52 (w), 776.26 (w) cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{13}N_4O_2$ [M + 1] m/z 305.1039, found 305.1036.

2-(1,3-Dioxolan-2-yl)quinoxalino[2,3-*c*]cinnoline (15). This product was synthesized according to general procedure E as a yellow solid in 60% yield: ^{1}H NMR ($CDCl_3$) δ 9.40−9.41 (1H, d, J = 1.8 Hz), 8.95 (1H, d, J = 8.1 Hz), 8.56−8.59 (1H, dd, J = 8.1, 1.8 Hz),8.45 (1H, dd, J = 7.8, 1.5 Hz), 8.24 (1H, dd, J = 8.4, 1.5 Hz), 8.02−8.13 (2H, m), 6.22 (1H, s), 4.25−4.28 (4H, m), 4.20−4.23 (4H, m); ^{13}C NMR ($CDCl_3$) δ 146.6, 146.0, 142.8, 142.3, 132.5, 130.9, 130.8, 130.0, 129.0, 128.4, 123.4, 123.0, 120.2, 118.1, 101.9, 64.7; FTIR (KBr) 3453.2 (w, b), 2889.8 (w, b), 1585.8 (m), 1485.9 (w), 1464.3 (m), 1405.6 (s), 1348.8 (m), 1292.7 (w), 1177.7 (m), 1075.5 (s), 1016.7 (m), 941.0 (w), 895.8 (w), 803.4 (w), 777.1 (m), 745.1 (w), 726.7 (w), 672.5 (w), 658.3 (m), 606.4 (w), 531.9 (m) cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{13}N_4O_2$ [M + 1] m/z 305.1039, found 305.1035.

2-(1,3-Dioxolan-2-yl)-9,10-dimethylquinoxalino[2,3-*c*]-cinnoline (17). This product was synthesized according to general procedure E (reflux was done only for 10 min) as a yellow solid in 32% yield: mp 207 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (1H, s), 8.71−8.73 (1H, d, J = 8.4 Hz), 8.51 (1H, s), 8.24 (1H, s), 7.83−7.87 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 6.19 (1H, s), 4.11−4.21 (4H, m), 2.72 (3H, s), 2.71 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.87, 145.55, 144.42, 143.83, 143.62, 142.99, 141.72, 133.31, 132.84, 131.35, 130.65, 125.99, 122.24, 121.44, 101.50, 65.51, 22.68, 22.43; FTIR (KBr) 2910 (m), 2853.30 (w), 1466.06 (w), 1383.76 (w), 1345.16 (m),1260 (m), 1177.08 (w), 1146.93 (m), 1067.33 (m), 971.09 (w), 940.99 (w), 872.94 (w), 814.97 (w) cm^{-1}; UV (methanol) λ_{max} (nm) (ε_{max} M^{-1} cm^{-1} × 103) 287 (22.69), 390 (6.82); MS (ESI) calcd for$C_{19}H_{17}N_4O_2$ [M + 1] m/z 333.4, found 333.1

3-(2-Aminophenyl)-6,7-dimethylquinoxalin-2-amine (19). To a 100 mL round-bottom flask containing 6,7-dimethyl-2-amino-3-(2-nitrophenyl)quinoxaline (**6e**; 0.5 g, 1.9 mmol) were added methanol (50 mL) and 5% pd/carbon (0.1 g). The mixture was placed in the hydrogenator (3−4 bar) for 8 h. The mixture was subjected to suction filtration through Celite, and the filtrate (10 mL) was diluted with water (20 mL), whereby a green-yellow solid was formed. The latter was collected by suction filtration, washed with cold ethanol, dried under vacuum, and identified as 3-(2-aminophenyl)-6,7-dimethylquinoxalin-2-amine (**19**) (90% yield): ^{1}H NMR ($CDCl_3$) δ 7.66 (1H, s), 7.44−7.46 (2H, m), 7.22−7.28 (1H, m), 6.84−6.89 (2H, m), 5.05 (2H, s, b), 4.38 (2H, s,b), 2.44 (3H, s), 2.41 (3H, s); ^{13}C NMR ($CDCl_3$) δ 150.66, 145.38, 143.50, 140.33, 139.65, 136.38, 135.02, 130.54, 129.26, 127.93, 125.21, 121.02, 118.63, 117.31, 20.42, 19.90; HRMS (ESI) calcd for $C_{16}H_{17}N_4$ [M + 1] m/z 265.1453, found 265.1447.

9,10-Dimethylquinoxalino[2,3-*c*]cinnoline (20). To a 100 mL round-bottom flask containing 3-(2-aminophenyl)-6,7-dimethylquinoxalin-2-amine (**19**; 0.2 g, 0.76 mmol) was added methanol (30 mL) followed by Clorox (10 mL). The dark red solution was allowed to stand at room temperature for 5 min. The reaction was quenched by addition of water and extracted with dichloromethane. The organic layer was dried and evaporated, and the crude product was purified by chromatography over a short column of silica. The obtained yellow product was identified as 9,10-dimethylquinoxalino[2,3-*c*]cinnoline (**20**) (88% yield): mp 190 °C; ^{1}H NMR ($CDCl_3$) δ 9.25−9.26 (1H, m), 8.89−8.92 (1H, m), 8.28 (1H, s), 8.17 (1H, s), 8.08−8.11 (2H, m), 2.66 (7H, s); ^{13}C NMR ($CDCl_3$) δ 146.61, 145.82, 145.56, 145.12, 143.58, 143.13, 132.75, 132.40, 131.47,

131.39, 129.20, 127.79, 122.92, 121.75, 21.08, 20.83; FTIR (KBr) 2923.46 (w, b), 1477.78 (m), 1462.63 (m), 1375.65 (s), 1341.83 (s), 1166.86 (w), 1025.54 (w), 1001.40 (m), 865.12 (m), 782.06 (m), 720.87 (w), 594.83 (w), 530.54 (m) cm^{-1}; UV (methanol) λ_{max} (nm) (ε_{max} M^{-1} cm^{-1} $\times$ 10^3) 287 (81.62), 392 (25.28); HRMS (ESI) calcd for $C_{16}H_{13}N_4$ [M + 1] m/z 261.1140, found 261.1134.

■ ASSOCIATED CONTENT

Supporting Information. ^1H NMR and ^{13}C NMR spectra as well as crystallographic data for **10a** and **11**, including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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