Regiospecific Oxidative Nitration of 3,4-Dihydro-6,7-disubstituted Quinoxalin-2(1*H*)-ones Gives 1,4-Dihydro-5-nitro-6,7-disubstituted Quinoxaline-2,3-diones, Potent Antagonists at the NMDA/Glycine Site

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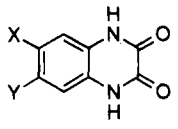
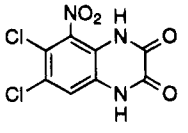
The regiospecific oxidative nitration of 3,4-dihydro-6,7-disubstituted quinoxalin-2(1*H*)-ones (**15a–h, 20**) utilizing fuming nitric acid in TFA gave 1,4-dihydro-5-nitro-6,7-disubstituted quinoxaline-2,3-diones (**6a–i**), respectively, in good yields. Compounds **15a–h** were prepared from commercially available 1-halo-3,4-disubstituted benzenes **12a–h** in three steps. These were nitration, nucleophilic substitution of the halogen ortho to the nitro group with sodium glycinate, and finally, reduction of the nitro group and concomitant cyclization. Compound **20** was prepared from **16** by a different route involving alkylation of substituted *o*-nitroaniline **18**. The final oxidative nitration yields a single, predictable nitro isomer and is a significant improvement over the direct nitration of 6,7-disubstituted quinoxaline-2,3-diones.

Introduction

The *N*-methyl-D-aspartic acid (NMDA) receptor is involved in a number of pathophysiological conditions including ischemia, brain, and spinal cord trauma that lead to neuronal death and degeneration.[1] The receptor is known to be regulated by several distinct sites, providing a variety of mechanistic approaches for therapeutic intervention.[2] The discovery that the presence of glycine is required for the opening of the NMDA receptor ion channel[3] has stimulated research in the development of antagonists for the glycine site as a promising approach for control of glutamate excitotoxicity expressed through the NMDA receptor.[4] Two 1,4-dihydroquinoxaline-2,3-diones (QXs), **1** (DNQX) and **2** (CNQX), were shown earlier to act as antagonists at the glycine site, although potency and selectivity were modest.[5] We have therefore synthesized several substituted QXs and identified 6,7-dichloro-5-nitro QX **4**[6] as a highly potent and selective glycine site antagonist (K_b = 0.0033 μM[7]). QX **4** was prepared by direct nitration of the symmetrical 6,7-dichloro QX **3**.[6]



1, X = Y = NO_2
2, X = CN; Y = NO_2
3, X = Y = Cl



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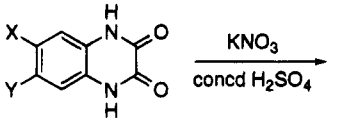
Based on these results, we wished to prepare the 5-nitro-6,7-disubstituted QXs **6a–i** for evaluation as glycine site ligands. As anticipated, direct nitration of the unsymmetrically substituted QXs **5a** and **5b** led to mixtures of the corresponding mono nitro derivatives **6a**, **7a** and **6b**, **7b**, respectively, which were difficult to separate (eq 1).



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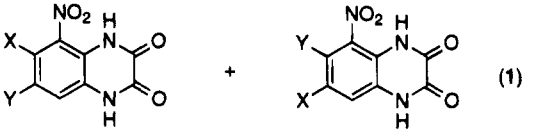

6 + **7** (1)

a, X = F; Y = Br
b, X = F; Y = Cl

Herein, we report a regiospecific pathway termed "oxidative nitration" to 5-nitro-6,7-disubstituted QXs **6a–i**. The route was discovered during an attempted preparation of the 3,4-dihydro-5-nitroquinoxalin-2(1*H*)-one **11** from 3,4-dihydroquinoxalin-2(1*H*)-one **9** (Scheme 1). **9** was prepared by the catalytic hydrogenation of the known quinoxalinone **8**.[8] Treatment of **9** with 1 equiv of fuming nitric acid in TFA resulted in oxidation back to **8** in 84% yield. Treatment of **9** with 2 equiv of fuming nitric acid in TFA gave regiospecifically **10** in near quantitative yield. The structure of **10** was assigned on

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(1) Meldrum, B.; Carthwaite, J. *Trends Pharmacol. Sci.* **1990**, *11*, 379–387.
(2) Wong, E. H. F.; Kemp, J. A. *Annu. Rev. Pharmacol. Toxicol.* **1991**, *31*, 401–425.
(3) Johnson, J. W.; Ascher, P. *Nature* **1987**, *325*, 529–531.
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(6) (a) Cai, S. X.; Dinsmore, C.; Gee, K. R.; Glenn, A. G.; Huang, J.-C.; Johnson, B. J.; Kher, S. M.; Lu, Y.; Oldfield, P. L.; Marek, P.; Zheng, H.; Weber, E.; Keana, J. F. W. *Soc. Neurosci. Abst.* **1993**, *718*, 296.11. (b) Keana, J. F. W.; Kher, S. M.; Cai, S. X.; Dinsmore, C. M.; Glenn, A. G.; Guastella, J.; Huang, J.-C.; Ilyin, V.; Lü, Y.; Mouser, P. L.; Woodward, R. M.; Weber, E. *J. Med. Chem.*, submitted.
(7) Woodward, R. M.; Huettner, J. E.; Guastella, J.; Keana, J. F. W.; Weber, E. *Mol. Pharmacol.* **1995**, *47*, 568–581.
(8) Kazimierczuk, Z.; Pfleiderer, W. *Liebigs Ann. Chem.* **1982**, 754–761.

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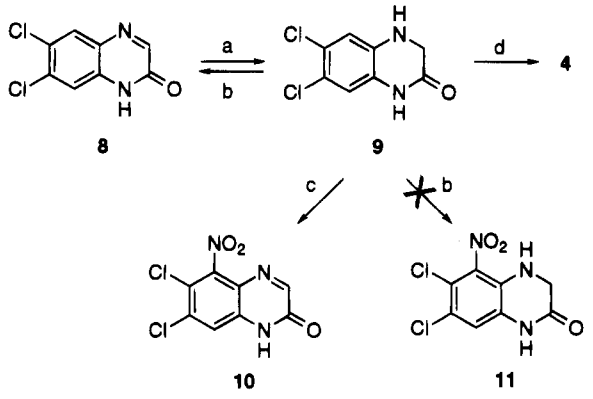
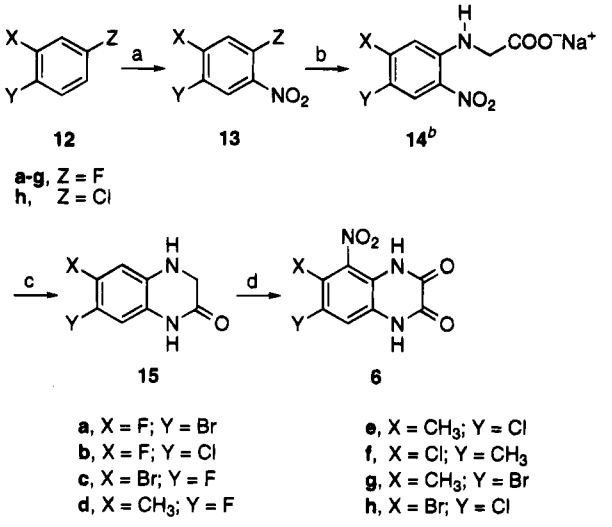
Scheme 1[a]



[a] Key: (a) H_2, Pd–C, DMF; (b) 1 equiv fuming HNO_3, TFA; (c) 2 equiv fuming HNO_3, TFA; (d) excess fuming HNO_3, TFA.

Scheme 2[a]



a, X = F; Y = Br
b, X = F; Y = Cl
c, X = Br; Y = F
d, X = CH_3; Y = F
e, X = CH_3; Y = Cl
f, X = Cl; Y = CH_3
g, X = CH_3; Y = Br
h, X = Br; Y = Cl

[a] Key: (a) KNO_3, concd H_2SO_4; (b) sodium glycinate, DMF, water; (c) $SnCl_2 \cdot 2H_2O$, EtOH; (d) excess fuming HNO_3, TFA. [b] **14a** was isolated as a free acid.

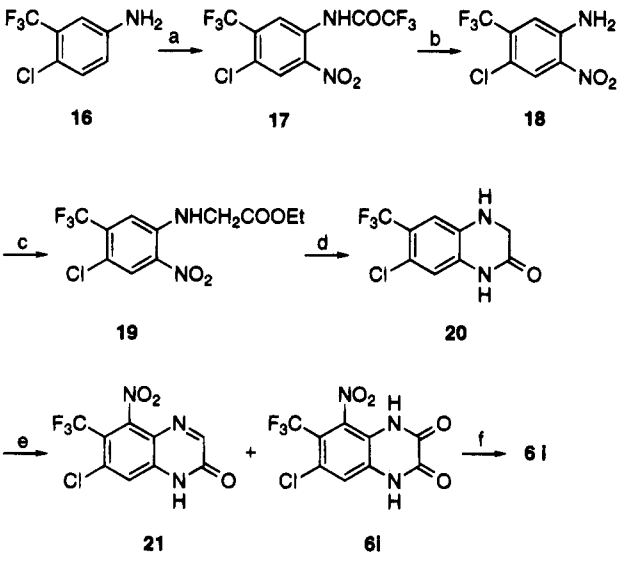
the basis of an NOE experiment. **10** exhibited a 21% NOE enhancement between the single aromatic proton and the peri N-1 amide proton. The nitration of **9** with an excess (10–20 equiv) of fuming nitric acid in TFA yielded the previously described **4**.[6] These results indicate that **8** and **10** are intermediates in the direct conversion of **9** to **4** with excess nitrating agent.

Our results are consistent with related studies by Cheeseman.[9] He reported that the nitration of unsubstituted quinoxalin-2(1*H*)-one with KNO_3 in concd H_2SO_4 gave 6-nitroquinoxalin-2(1*H*)-one while nitration in acetic acid with fuming HNO_3 gave 7-nitroquinoxalin-2(1*H*)-one. He also observed that nitration of quinoxalin-2(1*H*)-one with excess fuming HNO_3 in acetic acid gave 6-nitro QX.

To determine whether the regiospecificity of the reaction producing **10** could be advantageously extended to cases in which the 6 and 7 positions are differently substituted, we undertook the synthesis of compounds **6a–h** (Scheme 2) and **6i** (Scheme 3). For the synthesis of **6a–h**, commercially available 1-halo-3,4-disubstituted benzenes **12a–h** were regioselectively nitrated (KNO_3, H_2SO_4) to give the corresponding nitro derivatives **13a–h**

(9) Cheeseman, G. H. W. *J. Chem. Soc.* **1961**, 1246–1251.

Scheme 3[a]



[a] Key: (a) KNO_3, TFAA; (b) K_2CO_3, EtOH, water; (c) $BrCH_2COOEt$, K_2CO_3, 150 °C; (d) $SnCl_2 \cdot 2H_2O$, EtOH; (e) excess fuming HNO_3, TFA, rt; (f) excess fuming HNO_3, TFA, 40 °C.

in 90–95% yield. Treating **13a–h** with aqueous sodium glycinate in DMF at 70 °C gave the desired *N*-phenylglycine derivatives **14a–h**. Nucleophilic substitution of the fluorine para to the nitro group of **13a** and **13b** was also observed to an extent of 25–40%. Compounds **14a–h** were reduced with tin(II) chloride dihydrate in refluxing ethanol to the desired 3,4-dihydroquinoxalin-2(1*H*)-ones **15a–h**. The minor isomeric impurity found with **14a** and **14b** was eliminated during the alkaline workup. Stirring **15a–h** with an excess of fuming nitric acid (10–20 equiv) in TFA overnight at rt resulted in the formation of analytically pure nitrated QXs **6a–h** in 80–90% yield.

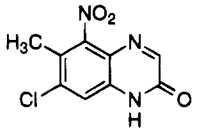
For the synthesis of **6i** (Scheme 3), **16** was nitrated (KNO_3, TFAA) to give nitro derivative **17** in 87% yield. Treatment of **17** with K_2CO_3 generated the free amine **18** in 92% yield. Aniline **18** was alkylated with ethyl bromoacetate in the presence of K_2CO_3 at 150 °C for 36 h to give a mixture of **19** and **18** in a ratio of 9:1, respectively, in 86% yield. The mixture as such was reduced with tin(II) chloride dihydrate in refluxing ethanol to obtain 3,4-dihydroquinoxalin-2(1*H*)-one **20** in 61% yield. Compound **20** was subjected to oxidative nitration with excess of fuming HNO_3 in TFA at rt to give a mixture of partially oxidized quinoxalin-2(1*H*)-one **21** and QX **6i**. Subjecting this mixture to the same reagents at 40 °C resulted in complete conversion to **6i** in 84% yield.

The 5- versus 8-position regiochemistry of the nitration sequence was confirmed as follows. In the case of fluorine-containing compounds **6a–d**, the structural assignments were based on H–F coupling constants (J) in the ^1H NMR.[10] QXs **6c** and **6d** exhibited doublets at 7.18 (J = 9.0 Hz) and 7.06 (J = 9.9 Hz), respectively. This established that the fluorine atom was adjacent to the single aromatic proton and therefore meta to the nitro group. On the other hand, QXs **6a** and **6b** exhibited doublets at 7.37 (J = 6.9 Hz) and 7.46 (J = 6.3 Hz), respectively, thus demonstrating that the fluorine atom

(10) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley: New York, 1981; p 236.

was meta to the single aromatic proton and, therefore, ortho to the nitro group.

The structure of **6e** was established through an NOE study of quinoxalinone **22**, an intermediate in the conversion of **15e** to **6e**. Compound **22** was prepared by treating **15e** with 2 equiv of fuming nitric acid in TFA. As expected, **22** exhibited a 16% NOE enhancement between the single aromatic proton and the peri N-1 amide proton. Therefore, nitration must have occurred next to the methyl group. A similar NOE experiment on **21** allowed the assignment of structure of **6i**.



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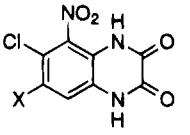
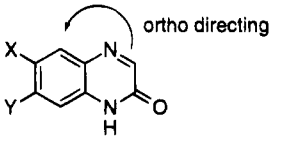


23, X = Br
24, X = H

The physical and spectral properties of **6h**, the product obtained from the oxidative nitration of **15h**, were different from those for the isomeric compound **23**. Nitro compound **23** was earlier prepared by the bromination of 5-nitro-6-chloro QX **24**.[6,11] Since the identities of **6a–e** and **6h,i** were now established, the structures of **6f,g** were assigned by analogy.

The regiospecificity observed in the formation of QXs **6a–i** indicates that the nitration is not governed by the substituents on the aromatic ring. Instead, the N=C unit of the quinoxalin-2(1*H*)-one intermediates of type **25**, formed by the action of 1 equiv of fuming HNO_3 on 3,4-dihydroquinoxalin-2(1*H*)-ones (Scheme 1), apparently directs the nitration specifically to the 5 position in these compounds. This observation holds even when a meta directing group is present in the 6 position as seen by the preparation of QX **6i**.



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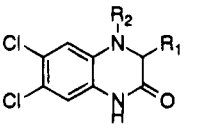
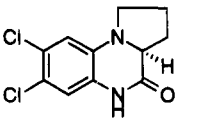
A limitation of the oxidative nitration sequence as revealed by preliminary experiments is that a substituent other than H may not be present in the 3 and/or 4 position of the 3,4-dihydroquinoxalin-2(1*H*)-one. Multiple products were obtained when **26–28** were treated with excess fuming nitric acid in TFA.



26, $R_1 = CH_3$; $R_2 = H$
27, $R_1 = H$; $R_2 = CH_3$



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Experimental Section

General. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. The ^1H NMR spectra were recorded at 300 MHz. Elemental analyses were performed by Desert Analytics, Tucson, AZ. Reverse phase HPLCs were obtained at 254 nm on a 4.6 × 250 mm Microsorb-MV C18 column using as solvents 0.1% TFA in water (A) and 0.1% TFA in acetonitrile (B). A linear gradient from 20% → 95% B in A was used at a flow rate of 1 mL/min. Compounds **12a–d**, **12f,g**, **16**, sodium glycinate, tin(II) chloride, ethyl bromoacetate, and TFA were obtained from Aldrich, while **12e** and **12h** were obtained from Lancaster and Pfaltz & Bauer, respectively. Fuming HNO_3 was obtained from Baker. All reagents were used as received. Reagent grade solvents were used without distillation. The preparation of QX **6c** is representative. Similar procedures were used for the preparation of other QXs.

6,7-Dichloro-3,4-dihydroquinoxalin-2(1*H*)-one (9). A solution of **8**[8] (0.392 g, 1.82 mmol) in DMF (5 mL) was hydrogenated (Parr hydrogenator, 20 psi) over 10% Pd–C (0.040 g) for 5 h. The catalyst was removed by filtration through Celite, and the filtrate was poured into water (40 mL). The solid was collected by vacuum filtration, washed with water (5 mL), and dried *in vacuo* to give 0.356 g (90%, >97% pure by HPLC) of **9** as a light purple powder: mp 240–242 °C dec; ^1H NMR (DMSO-d_6) δ 3.74 (s, 2H), 6.33 (s, 1H), 6.76 (s, 1H), 6.80 (s, 1H), 10.40 (s, 1H); MS (EI) *m/e* (relative intensity) 216 (100, M^+), 187 (80), 152 (15); HRMS calcd for $C_8H_6Cl_2N_2O$ 215.9857, found 215.9864.

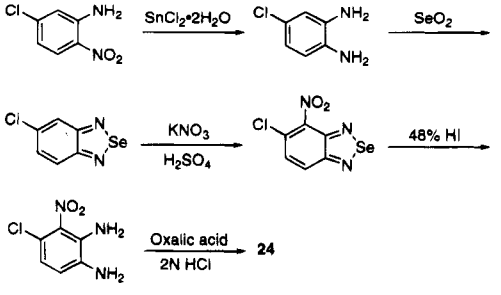
6,7-Dichloroquinoxalin-2(1*H*)-one (8). To a stirred solution of **9** (0.050 g, 0.23 mmol) in TFA (1 mL) was added fuming nitric acid (10 μL, 0.23 mmol), and stirring was continued overnight at rt. The resulting suspension was poured into water (5 mL), and the solid was collected by vacuum filtration, washed with water (5 mL), and dried *in vacuo* to give 0.042 g (84%) of **8** as a cream powder: mp 297 °C dec (lit.[8] mp 300 °C); ^1H NMR (DMSO-d_6) δ 7.41 (s, 1H), 8.02 (s, 1H), 8.18 (s, 1H), 12.519 (s, 1H).

6,7-Dichloro-5-nitroquinoxalin-2(1*H*)-one (10). To a stirred solution of **9** (0.050 g, 0.23 mmol) in TFA (1 mL) was added fuming nitric acid (20 μL, 0.46 mmol), and stirring was continued overnight at rt. The resulting suspension was cooled in an ice-bath and diluted with water (5 mL). The solid was collected by vacuum filtration, washed with water (5 mL), and dried *in vacuo* to give 58 mg (97%, >98% pure by HPLC) of **10** as a light yellow powder: mp 331–332 °C dec; ^1H NMR (DMSO-d_6) δ 7.59 (s, 1H), 8.28 (s, 1H), 12.90 (s, 1H); MS (EI) *m/e* (relative intensity) 259 (100, M^+), 213 (10), 201 (10), 185 (20), 173 (40), 158 (20); HRMS calcd for $C_8H_3Cl_2N_3O_3$ 258.9551, found 258.9552.

6,7-Dichloro-1,4-dihydro-5-nitroquinoxaline-2,3-dione (4). To a stirred solution of **9** (0.050 g, 0.23 mmol) in TFA (1 mL) was added fuming nitric acid (0.200 mL), and stirring was continued for 3 days at rt. The resulting suspension was poured into water (5 mL), and the solid was collected by vacuum filtration, washed with water (5 mL), and dried *in vacuo* to give 0.058 mg (91%) of **4** as a light yellow powder: mp 338–41 °C dec (lit.[6] mp 342–44 °C); ^1H NMR (DMSO-d_6) δ 7.36 (s, 1H), 12.26 (s overlapped by a br s, 2H).

1-Bromo-2,5-difluoro-4-nitrobenzene (13c). To a stirred solution of **12c** (1.000 g, 5.181 mmol) in concd H_2SO_4 (8 mL) at 0 °C was added KNO_3 (0.525 g, 5.19 mmol) in one portion.

(11) The synthesis of QX **24** from commercially available 5-chloro-2-nitroaniline is outlined below. Experimental details will be published elsewhere (see ref 6).



For the regiospecific nitration of (2,1,3)benzoselenadiazole, see: (a) Tian, W.; Grivas, S. *J. Heterocycl. Chem.* **1992**, *29*, 1305–1308. (b) Tian, W.; Grivas, S.; Olsson, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 257–261.

The resulting yellow solution was allowed to warm to rt, and then it was stirred overnight at rt. It was poured into ice (80 g) and extracted with ethyl acetate (75 mL). The ethyl acetate extract was washed with water and brine, dried over anhyd Na_2SO_4, and concentrated. The residual solid was dried *in vacuo* to give 1.105 g (89%) of **13c** as a white powder of sufficient purity (^{1}H NMR) for the next reaction: mp 58–60 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (dd, 1H, J_1 = 9.6 Hz, J_2 = 5.4 Hz), 7.89 (t, 1H, J = 6.9 Hz).

***N*-(5-Bromo-4-fluoro-2-nitrophenyl)glycine Sodium Salt (14c).** A modified procedure of St. Clair *et al.*[12] was employed. To a stirred solution of **13c** (1.100 g, 4.622 mmol) in DMF (11 mL) at 70 °C was added dropwise a solution of sodium glycinate (0.451 g, 4.65 mmol) in water (5 mL). The resulting solution was stirred overnight at 70 °C. The solution was then cooled to rt, and the bright orange solid was collected by vacuum filtration, washed with $CHCl_3$ (10 mL), and dried *in vacuo* to give 0.690 g (51%) of **14c** as bright orange powder of sufficient purity (^{1}H NMR) for the next reaction: mp 252 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.46 (d, 2H, J = 3.9 Hz), 7.15 (d, 1H, J = 6.0 Hz), 7.94 (d, 1H, J = 9.3 Hz), 8.74 (s, 1H).

6-Bromo-7-fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (15c). The procedure of Bellamy *et al.*[13] was adapted. A solution of **14c** (0.650 g, 2.22 mmol) and tin(II) chloride dihydrate (1.501 g, 6.66 mmol) in ethanol (10 mL) was refluxed for 30 min. It was then cooled to rt, and the solvent was removed *in vacuo*. The residual slurry was diluted with water (15 mL), and the pH was adjusted with 10% Na_2CO_3 to 8. The resulting suspension was extracted with ethyl acetate (100 mL). The ethyl acetate extract was washed with water and brine, dried over anhyd Na_2SO_4, and concentrated. The residual solid was dried *in vacuo* to give 0.348 g (64%) of **15c** as yellow powder of sufficient purity for the next reaction: mp 214–216 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.68 (s, 2H), 6.06 (s, 1H), 6.63 (d, 1H, J = 9.3 Hz), 6.83 (d, 1H, J = 6.6 Hz), 10.30 (s, 1H).

6-Bromo-7-fluoro-1,4-dihydro-5-nitroquinoxaline-2,3-dione (6c). To a stirred solution of **15c** (0.050 g, 0.20 mmol) in TFA (0.5 mL) was added excess fuming HNO_3 (0.20 mL), and the red solution was stirred overnight at rt. The resulting yellow suspension was poured into ice–water (3 mL). The solid was collected by vacuum filtration, washed with water (3 mL), and dried *in vacuo* to give 0.053 g (85%, 24.7% overall) of **6c** as yellow powder: mp 323–327 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.18 (d, 1H, J = 9.0 Hz), 12.21 (s, 1H), 12.32 (s, 1H). Anal. Calcd for $C_8H_3BrFN_3O_4$: C, 31.60; H, 0.99; N, 13.82. Found: C, 31.30; H, 0.87; N, 13.66.

7-Bromo-6-fluoro-1,4-dihydro-5-nitroquinoxaline-2,3-dione (6a). QX **6a** was prepared in four steps from **12a** in a manner similar to **6c** and was isolated as light brown powder (5.1% overall yield): mp 316–321 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.46 (d, 1H, J = 6.3 Hz), 12.01 (br s, 1H), 12.18 (s, 1H). Anal. Calcd for $C_8H_3BrFN_3O_4$: C, 31.60; H, 0.99; N, 13.82. Found: C, 31.78; H, 0.84; N, 13.49.

7-Chloro-6-fluoro-1,4-dihydro-5-nitroquinoxaline-2,3-dione (6b). QX **6b** was prepared in four steps from **12b** in a manner similar to **6c** and was isolated as light yellow powder (7.6% overall yield): mp 308–310 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.37 (d, 1H, J = 6.9 Hz), 12.02 (br s, 1H), 12.22 (s, 1H). Anal. Calcd for $C_8H_3ClFN_3O_4{\cdot}H_2O$: C, 34.61; H, 1.09; N, 15.14. Found: C, 34.66; H, 1.09; N, 15.16.

7-Fluoro-1,4-dihydro-6-methyl-5-nitroquinoxaline-2,3-dione (6d). QX **6d** was prepared in four steps from **12d** in a manner similar to **6c** and was isolated as yellow powder (7.4% overall yield): mp 308–311 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.11 (s, 3H), 7.06 (d, 1H, J = 9.9 Hz), 11.77 (br s, 1H), 12.17 (s, 1H). Anal. Calcd for $C_9H_6FN_3O_4{\cdot}0.19H_2O$: C, 44.56; H, 2.49; N, 17.32. Found: C, 44.96; H, 2.33; N, 16.89.

7-Chloro-1,4-dihydro-6-methyl-5-nitroquinoxaline-2,3-dione (6e). QX **6e** was prepared in four steps from **12e** in a manner similar to **6c** and was isolated as light yellow powder (37.4% overall yield): mp darkens at 340 °C; ^{1}H NMR (DMSO-d_6) δ 2.18 (s, 3H), 7.26 (s, 1H), 11.95 (s, 1H), 12.14 (s, 1H). Anal. Calcd for $C_9H_6ClN_3O_4{\cdot}H_2O$: C, 40.85; H, 2.28; N, 15.87. Found: C, 40.63; H, 2.05; N, 15.75.

6-Chloro-1,4-dihydro-7-methyl-5-nitroquinoxaline-2,3-dione (6f). QX **6f** was prepared in four steps from **12f** in a manner similar to **6c** and was isolated as light yellow powder (7% overall yield): mp > 340 °C; ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H), 7.15 (s, 1H), 12.11 (s, 1H), 12.19 (s, 1H). Anal. Calcd for $C_9H_6ClN_3O_4$: C, 42.29; H, 2.37; N, 16.44. Found: C, 42.46; H, 2.10; N, 16.33.

7-Bromo-1,4-dihydro-6-methyl-5-nitroquinoxaline-2,3-dione (6g). QX **6g** was prepared in four steps from **12g** in a manner similar to **6c** and was isolated as light yellow powder (15.8% overall yield): mp > 340 °C; ^{1}H NMR (DMSO-d_6) δ 2.23 (s, 3H), 7.44 (s, 1H), 11.98 (s, 1H), 12.14 (s, 1H). Anal. Calcd for $C_9H_6BrN_3O_4{\cdot}0.45H_2O$: C, 35.07; H, 1.96; N, 13.63. Found: C, 35.44; H, 1.92; N, 13.23.

6-Bromo-7-chloro-1,4-dihydro-5-nitroquinoxaline-2,3-dione (6h). QX **6h** was prepared in four steps from **12h** in a manner similar to **6c** and was isolated as cream powder (15.6% overall yield): mp 338–343 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.35 (s, 1H), 12.25 (s overlapped by a br s, 2H). Anal. Calcd for $C_8H_3BrClN_3O_4$: C, 29.98; H, 0.94; N, 13.11. Found: C, 29.79; H, 0.77; N, 12.71.

2-Chloro-5-(trifluoroacetamido)-4-nitrobenzotrifluoride (17). To trifluoroacetic anhydride (50 mL) stirred in an ice bath was added dropwise **16** (5.98 g, 30.6 mmol). To the resulting solution was added, in portion, KNO_3 (3.38 g, 33.4 mmol), and the solution was stirred in ice bath for 1 h and then at 25 °C overnight. The solution was diluted with ice–water (150 mL). The solid was collected by vacuum filtration, washed with water, and dried *in vacuo* to give 8.97 g (87%) **17** as yellow powder: mp 80–81 °C; ^{1}H NMR ($CDCl_3$) δ 8.46 (s, 1H), 9.20 (s, 1H), 11.22 (br s, 1H).

5-Amino-2-chloro-4-nitrobenzotrifluoride (18). A solution of **17** (8.30 g, 24.7 mmol) in 7% (w/w) aqueous K_2CO_3 (20 mL) and methanol (30 mL) was stirred at 25 °C for 1 h. The resulting mixture was diluted with water (50 mL). The solid was collected by vacuum filtration, washed with water, and dried *in vacuo* to give 5.50 g (92%) **18** as yellow powder: mp 84–85 °C; ^{1}H NMR ($CDCl_3$) δ 6.21 (br s, 2H), 7.21 (s, 1H), 8.26 (s, 1H).

Ethyl *N*-[4-chloro-5-(trifluoromethyl)-2-nitro]phenylglycinate (19). A suspension of **18** (0.445 g, 1.85 mmol) and K_2CO_3 (0.310 g, 2.24 mmol) in ethyl bromoacetate (2.0 mL) was heated at 150 °C for 36 h. The resulting suspension was cooled to 25 °C, diluted with water (3 mL) followed by 1 M NaOH (18 mL), and stirred for 1 h. The supernatant liquid was decanted, and the residual oily solid was washed with water and dried *in vacuo* to give 0.524 g (86%) **19** as black powder: ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3H, J = 7.1 Hz), 4.11 (d, 2H, J = 5.2 Hz), 4.32 (q, 2H, J = 7.1 Hz), 7.04 (s, 1H), 8.34 (s, 1H), 8.42 (br s, 1H). This material was contaminated by 10% of **18**.

7-Chloro-6-(trifluoromethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (20). A solution of **19** (0.520 g, 1.59 mmol) and tin(II) chloride dihydrate (1.30 g, 5.70 mmol) in ethanol (4 mL) was refluxed for 4 h and cooled to 25 °C. The solvent was removed under vacuum, and the residual slurry was basified with 1 M NaOH to pH = 10. The resulting suspension was filtered, washed with water, and dried *in vacuo* to give 0.430 g of a brown solid. This solid was stirred as a suspension in $CHCl_3$ (15 mL), filtered, washed with $CHCl_3$ and dried *in vacuo* to give 0.254 g of a brown solid. It was dissolved in ethyl acetate (10 mL) and filtered to remove a small amount of insoluble material. The filtrate was evaporated *in vacuo* and the residue dried *in vacuo* to leave 0.247 g (61%) **20** as brown powder: ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 2H), 6.49 (br s, 1H), 6.88 (s, 1H), 7.03 (s, 1H), 10.64 (s, 1H).

7-Chloro-6-(trifluoromethyl)-1,4-dihydro-5-nitroquinoxaline-2,3-dione (6i). To a solution of **20** (0.235 g, 0.919 mmol) in TFA (5.0 mL) stirred in an ice bath was added fuming HNO_3 (1.0 mL) dropwise. The resulting solution was stirred in an ice bath for 1 h and at 25 °C overnight. A small aliquot was removed from the reaction mixture and worked up by pouring into water (1 mL), collecting the solid by vacuum

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filtration, and drying *in vacuo*. The ^{1}H NMR revealed it to be a 10:1 mixture of **21** and **6i**, respectively, as shown in Scheme 3. As a result, fuming HNO_3 (1 mL) was added to the reaction mixture and heated at 40 °C for 48 h. The resulting suspension was poured into ice–water (40 mL), and the solid was collected by vacuum filtration and dried *in vacuo* to give 0.247 g of a yellow powder. It was purified by dissolving in 1 M NaOH (5 mL), filtering, and then acidifying the filtrate with 2 M HCl to pH = 3. The yellow suspension was vacuum filtered, washed with water, and dried *in vacuo* to give 0.240 g (84%, >98% pure by HPLC) of **6i** as a yellow powder: mp > 375 °C; ^{1}H NMR (DMSO-d_6) δ 7.42 (s, 1H), 12.52 (br s, 2H); MS (EI) *m/e* (relative intensity) 309 (90, M^+), 235 (100); HRMS calcd for $C_9H_3ClF_3N_3O_4$ 308.9760, found 308.9768.

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Supporting Information Available: ^{1}H NMR data and experimental details for compounds **13a,b**, **13d–h**, **14a,b**, **14d–h**, **15a,b**, and **15d–h** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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