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Synthesis and SAR of Novel Di- and Trisubstituted 1,4-Dihydroquinoxaline-2,3-diones Related to Licostinel (Acea 1021) as NMDA/Glycine Site Antagonists

Zhang-Lin Zhou,[a] Sunil M. Kher,[a] Sui Xiong Cai,[b] Edward R. Whittemore,[b] Stephen A. Espitia,[b] Jon E. Hawkinson,[b] Minhtam Tran,[b] Richard M. Woodward,[b] Eckard Weber[b] and John F. W. Keana[a,*]

[a]*Department of Chemistry, University of Oregon, Eugene, OR 97403, USA*
[b]*CoCensys, Inc., 201 Technology Drive, Irvine, CA 92618, USA*

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Abstract—A series of novel di- and trisubstituted 1,4-dihydroquinoxaline-2,3-diones (QXs) related to licostinel (Acea 1021) was synthesized and evaluated as antagonists for the glycine site of the *N*-methyl-D-asparate (NMDA) receptor. The in vitro potency of these antagonists was determined by displacement of the glycine site radioligand [^{3}H]-5,7-dichlorokynurenic acid ([^{3}H]DCKA) in rat brain cortical membranes. Structure–activity relationship studies indicate that a cyano group is a good replacement for the nitro group in the 5-position of licostinel while 5-carboxy, 5-ester, 5-ketone and 5-amide derivatives showed reduced potency. 5,6-Cyclized analogues of licostinel also showed significantly reduced potency. Among the trisubstituted QXs investigated, 5-cyano-6,7-dichloro QX and 5-cyano-7-chloro-6-methyl QX are the most potent with IC_{50} values of 32 nM and 26 nM, respectively.

Introduction

N-Methyl-D-asparate (NMDA) receptors are a subclass of ionotropic glutamate receptors. Overstimulation of NMDA receptors has been implicated in a number of pathophysiological conditions including CNS ischemia and trauma that lead to neuronal death and degeneration.[1] Since the discovery that glycine is an essential co-agonist for NMDA receptor activation,[2] considerable effort has been directed toward the discovery of NMDA receptor glycine site antagonists useful for the treatment of CNS disorders.

Several structurally different classes of potent glycine site antagonists have been identified (Chart 1). Examples include 4-hydroxy-3-(3-phenoxyphenyl)quinoline-2(1*H*)-ones such as **1**[3] and 1,2,3,4-tetrahydroquinoline-2,3,4-trione-3-oximes (QTOs) such as **2**.[4]

We recently reported on the structure–activity relationship (SAR) of substituted 1,4-dihydroquinoxaline-2,3-diones (QXs) leading to licostinel (Acea 1021, **3**), 7-chloro-6-methyl-5-nitro QX (**4**) and 7-bromo-6-methyl-5-nitro QX (**5**) (Chart 1).[5,6] As a continuation of these studies, we report herein the synthesis of a series of novel di- and trisubstituted QXs **7** and their evaluation as NMDA/glycine site antagonists.

Chemistry

QXs **7a–k** were prepared by condensation of oxalic acid or diethyl oxalate with the corresponding 1,2-diaminobenzenes **6a–k** (Scheme 1). Diamines **6a**,**c**,**e** were prepared from the corresponding anilines **8** as follows. The amino group of **8** was first protected by reaction with acetic anhydride or trifluoroacetic anhydride to give the corresponding amide, which was then nitrated in H_2SO_4 with KNO_3 or HNO_3. The nitrated amide **9** was then hydrolyzed to give the corresponding *o*-nitroaniline **10**, which was then reduced to give the corresponding 1,2-diaminobenzene **6**. 1,2-Diaminobenzene **6b** was prepared by selective reduction of **10b** using ammonium sulfide. Intermediate **10b** was prepared[7] (Scheme 2) by dinitration of 2-fluorobenzoic acid (**11**) with fuming

*Corresponding author. Tel.: +1-541-346-4609; fax: +1-541-346-0487; e-mail: jkeana@oregon.uoregon.edu

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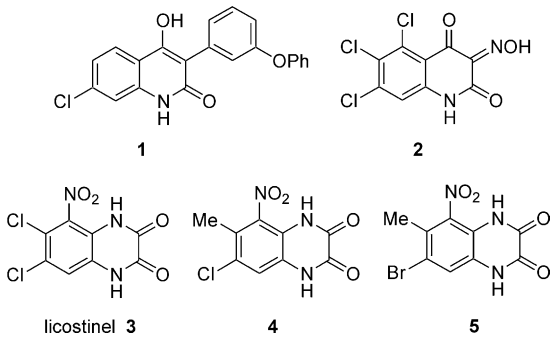
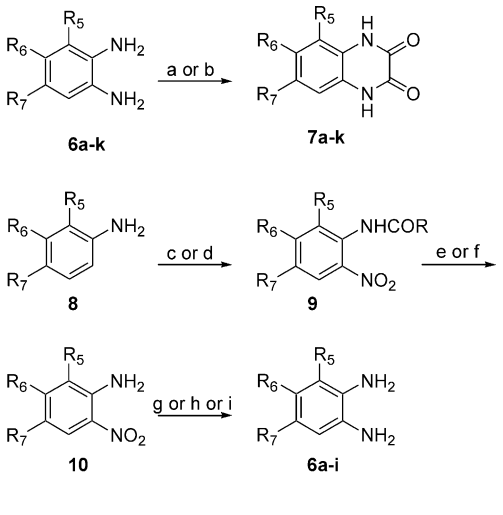
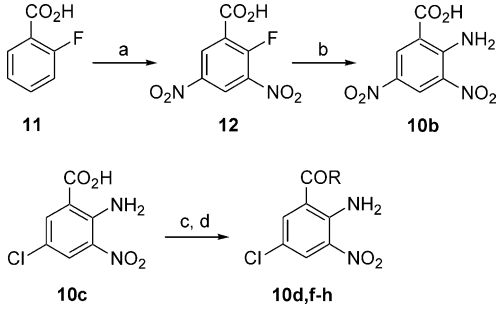


Chart 1.



a, $R_5 = CO_2H$, $R_6 = H$, $R_7 = Me$
b, $R_5 = CO_2H$, $R_6 = H$, $R_7 = NO_2$
c, $R_5 = CO_2H$, $R_6 = H$, $R_7 = Cl$
d, $R_5 = CO_2Me$, $R_6 = H$, $R_7 = Cl$
e, $R_5 = COPh$, $R_6 = H$, $R_7 = Cl$
f, $R_5 = CONH_2$, $R_6 = H$, $R_7 = Cl$
g, $R_5 = CONMe_2$, $R_6 = H$, $R_7 = Cl$
h, $R_5 = CONEt_2$, $R_6 = H$, $R_7 = Cl$
i, $R_5 = CO_2Me$, $R_6 = Me$, $R_7 = Br$
j, $R_5, R_6 = C(O)CH_2CH_2$, $R_7 = Cl$
k, $R_5, R_6 = C(O)OCH_2$, $R_7 = Cl$

Scheme 1. (a) $(CO_2H)_2$, 2N HCl; (b) $(CO_2Et)_2$, EtOH; (c) (i) $(CH_3CO)_2O$; (ii) KNO_3/H_2SO_4; (d) $(CF_3CO)_2O$, CF_3CO_2H, then KNO_3; (e) 2 N HCl; (f) K_2CO_3 or NaOH; (g) $SnCl_2{\cdot}2H_2O$; (h) $(NH_4)_2S$; (i) H_2, Pd/C.



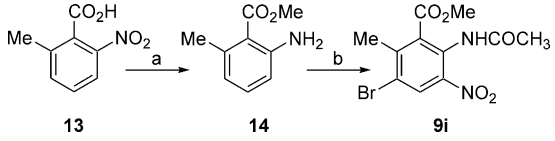
Scheme 2. (a) 90% HNO_3, H_2SO_4 (fuming, 15% SO_3), 145 °C, 73%; (b) 30% NH_4OH, HCl, rt, 97%; (c) $SOCl_2$, relfux; (d) CH_3OH or NH_3 or $HN(CH_3)_2$ or $HN(CH_2CH_3)_2$, rt, 81–98%.

nitric acid in fuming sulfuric acid to give dinitro compound **12**, which was then reacted with aqueous NH_4OH to give **10b** in 97% yield.

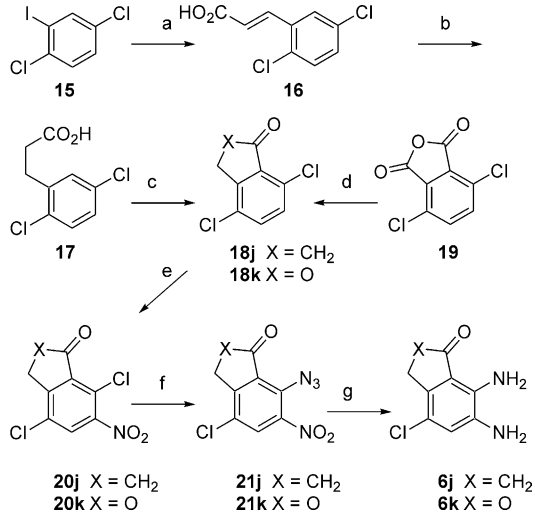
Diamines **6d**,**f**–**h** were obtained from intermediates **10d**,**f**–**h**, which were prepared from 2-amino-5-chloro-3-nitro-benzoic acid (**10c**). Refluxing **10c** in thionyl chloride gave the corresponding acid chloride, which was treated with methanol to give ester **10d** or alternatively, with ammonia, dimethylamine or diethylamine to give the corresponding amides **10f**–**h** in excellent yields.

Diamine **6i** was prepared from methyl 2-acetylamino-5-bromo-6-methyl-3-nitro-benzoate (**9i**) by way of **10i**. Ester **9i** was prepared as shown in Scheme 3. Esterification of benzoic acid **13** with methyl iodide, followed by reduction by catalytic hydrogenation gave amino ester **14**, which was then *N*-protected with acetic anhydride, brominated and nitrated to give **9i**.

Diamines **6j**,**k** were prepared as described in Scheme 4. Heck coupling of 1,4-dichloro-2-iodobenzene (**15**) with acrylic acid gave acrylic acid **16**, which was reduced to 3-(2,5-dichlorophenyl)propanoic acid (**17**). Acid **17** underwent an intramolecular Friedel–Crafts acylation to give indanone **18j**. Lactone **18k** was prepared by selective reduction of 4,7-dichloro-isobenzofuran-1,3-dione (**19**) with sodium borohydride. Nitration of **18j**,**k** gave the corresponding nitro compounds **20j**,**k**, which were then treated with sodium azide to give the corresponding azides **21j**,**k**. Concomitant reduction of the nitro and azide groups in these latter molecules led to the desired diamines **6j**,**k**, respectively.



Scheme 3. (a) (i) K_2CO_3, MeI, acetone; (ii) 10% Pd/C, H_2; (b) (i) $(CH_3CO)_2O$, rt; (ii) Br_2, AcOH; (iii) 90% HNO_3, TFA.



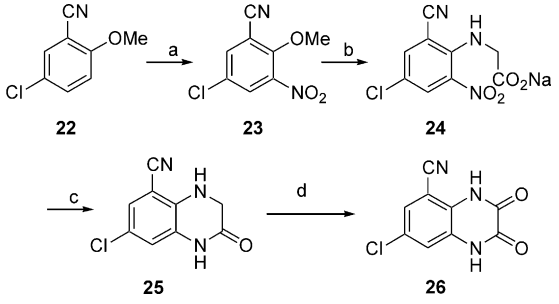
Scheme 4. (a) $CH_2{=}CHCO_2H$, $Pd(OAc)_2$, TEA, CH_3CN, 94%; (b) PtO_2, H_2, EtOAc; (c) (i) $SOCl_2$; (ii) $AlCl_3$, CS_2, 71%; (d) $NaBH_4$, DMF rt, 75%; (e) 90% HNO_3, 43% or KNO_3, H_2SO_4, 86%; (f) NaN_3, acetone, H_2O, 75%; (g) 10% Pd/C, H_2, EtOAc.

7-Chloro-5-cyano QX **26** was prepared as shown in Scheme 5. Nitration of benzonitrile **22** with 70% HNO_3 at 5 °C gave nitro derivative **23** in 97% yield. Nucleophilic substitution of the methoxy group of **23** with sodium glycinate yielded glycinate **24**. Reduction followed by cyclization led to quinoxalin-2(1*H*)-one **25**, which was oxidized to the desired QX **26** using nitric acid.[8]

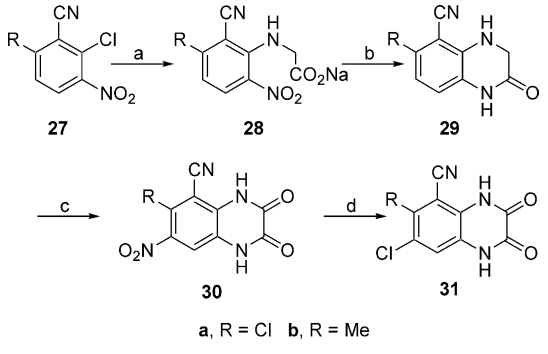
5-Cyano-6,7-dichloro QX (**31a**) and 7-chloro-5-cyano-6-methyl QX (**31b**) were prepared by a regiospecific oxidative nitration procedure (Scheme 6).[8] Nucleophilic substitution of 2,6-dichloro-3-nitrobenzonitrile (**27a**) and 2-chloro-6-methyl-3-nitrobenzonitrile (**27b**) by sodium glycinate gave the respective substituted *N*-phenylglycinate **28a**,**b**. These were separately reduced and cyclized to give the respective 5-cyano-3,4-dihydroquinoxalin-2(1*H*)-one **29a**,**b**. Oxidative nitration of **29a**,**b** gave 5-cyano-7-nitro QX **30a**,**b**, respectively. The nitro group in each compound was reduced to give the corresponding amine, which was diazotized and chlorinated to give QX **31a**,**b**.

Pharmacology

The affinity of the QXs for the NMDA receptor glycine site was measured by inhibition of [^{3}H] 5,7-dichlorokynurenic acid ([^{3}H]DCKA) binding to rat brain cortical membranes as described previously.[9] Affinity is expressed as $IC_{50} \pm SEM$ ($n = 3$–4) estimated from displacement of [^{3}H]DCKA binding to the membrane.



Scheme 5. (a) HNO_3, 5 °C, 97%; (b) $NH_2CH_2CO_2Na$, EtOH, reflux, 66%; (c) $Na_2S_2O_4$, H_2O, 70 °C, 79%; (d) TFA, HNO_3, rt, 75%.



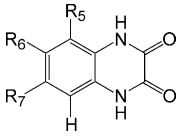
Scheme 6. (a) $NH_2CH_2CO_2Na$, EtOH, reflux; (b) $SnCl_2 \cdot 2H_2O$, EtOH, reflux; (c) TFA HNO_3, rt; (d) (i) $SnCl_2 \cdot 2H_2O$, EtOH, reflux; (ii) $NaNO_2$, CuCl, HCl.

Results and Discussion

The structure–activity relationships of QXs in this series as antagonists at NMDA/glycine site follow from the IC_{50} values given in Table 1. Considering first the 5-carboxylic acid-substituted QXs, 5,7-disubstituted QXs **7a** and **7b** are both about 2-fold less potent than **7c**, suggesting that 7-chloro is slightly favored over 7-methyl and 7-nitro for high potency. We next varied the substituent at the 5-position while retaining a 7-chloro group. The potencies of disubstituted QXs **7e**,**f**,**g**,**h** containing a carbonyl group at the 5-position were all within a factor of two to four of that of **7c**, with the exception of methyl ester **7d**, which was about 10-fold less potent than **7c**. Most strikingly, a 100-fold increase in potency over **7c** was seen when the 5-carboxy group was replaced by 5-cyano to give 7-chloro-5-cyano QX **26**. These results confirm the importance of having an electron withdrawing group at the 5-position of the QX. Interestingly, replacement of the 5-cyano group in **26** by a nitro group resulted in disubstituted QX **32**,[5] which was only 10-fold more potent than **7c** and 10-fold *less* potent than **26**. This result was unexpected given the generally high potency of the (trisubstituted) 5-nitro Qxs **3**, **4** and **5**.

We next investigated the effect on potency of adding a third substituent to selected QXs discussed above. We were also interested to see the effect of forming a ring between positions 5 and 6 while retaining a carbonyl group at position 5 and a chlorine atom at position 7. Thus, tricyclic QXs **7j** and **7k** were prepared and evaluated. Disappointingly, these QXs were 2- to 4-fold less potent than **7c**. This result is surprising given that a methyl group is well tolerated at the 6-position in **4** and **5**. We speculate that the loss in potency may be because

Table 1. SAR of QXs at the NMDA receptor glycine site



Compd	R_5	R_6	R_7	[^{3}H]DCKA IC_{50} (μM)
7a	CO_2H	H	Me	13±3
7b	CO_2H	H	NO_2	10±3
7c	CO_2H	H	Cl	6.4±0.5
7d	CO_2Me	H	Cl	65±9
7e	COPh	H	Cl	6.7±0.8
7f	$CONH_2$	H	Cl	3.1±0.2
7g	$CONMe_2$	H	Cl	13±2
7h	$CONEt_2$	H	Cl	24±3
7i	CO_2Me	Me	Br	0.40±0.08
7j	C(O)	CH_2CH_2	Cl	4.6±0.5
7k	C(O)	OCH_2	Cl	2.9±0.4
26	CN	H	Cl	0.067±0.009
31a	CN	Cl	Cl	0.032±0.003
31b	CN	Me	Cl	0.026±0.007
3[a]	NO_2	Cl	Cl	0.0059±0.001
4[b]	NO_2	Me	Cl	0.0047±0.0006
5[b]	NO_2	Me	Br	0.0087±0.0004
32[a]	NO_2	H	Cl	0.65±0.04

[a]Ref 5.
[b]Ref 6.

the 5-carbonyl group in **7j,k** is confined approximately to the plane of the QX ring system whereas in licostinel the nitro group is twisted out of the plane of the ring.[5]

The effect of adding a third substituent to 7-chloro-5-cyano QX **26** is illustrated by 6-chloro QX **31a** and 6-methyl QX **31b**. 5-Cyano QXs **31a** and **31b** have IC_{50} values of 32 and 26 nM, respectively. Although both are less potent than their 5-nitro counterparts **3** and **4**, QXs **31a** and **31b** remain highly potent compounds in the QX series. The results indicate that, in terms of potency, CN and NO_2 are comparable substituents in the 5-position. Trisubstituted QX **7i** is 200-fold less potent than its 5-nitro analogue **5**, demonstrating again (cf. **7d**) that introduction of an ester group at the 5-position is not well tolerated.

Administered iv, several of these substituted QXs were active anticonvulsants in the maximum electroshock-induced seizure (MES) test in mice. Compound **31b** has an ED_{50} of 6.5 mg/kg, which is 6-fold less active than its 5-nitro counterpart **4**. In contrast, 7-chloro-5-cyano QX **26** is highly active in vivo with an ED_{50} of 0.9 mg/kg, which is 5 times more potent than licostinel (**3**). The most obvious explanations would be increased blood–brain permeability or a lower plasma-protein binding.

In summary, a series of novel di- and trisubstituted QXs related to licostinel (**3**) was synthesized and evaluated as NMDA/glycine site antagonists. SAR of 5,7-disubstituted QXs shows that a cyano group is a reasonable replacement for a nitro group in the 5-position. Among those trisubstituted QXs investigated, 5-cyano-6,7-dichloro QX (**31a**) and 7-chloro-5-cyano-6-methyl QX (**31b**) are the two most potent glycine site antagonists with IC_{50} values of 32 and 26 nM, respectively. 7-Chloro-5-cyano QX (**26**) is highly active as an anticonvulsant (iv) in MES test in mice with an ED_{50} of 0.9 mg/kg, a value 5-fold more potent than licostinel (**3**).

Experimental

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. Chemical shifts are reported in ppm (δ), and *J* coupling constants are reported in Hz. Elemental analyses were performed by Desert Analytics, Tucson, AZ, USA. Mass spectra (MS) were obtained with a VG 12-250 or VG ZAB-2FHF mass spectrometer. Reagent grade solvents were used without further purification unless otherwise specified. Reverse phase HPLC analyses were monitored at 254 nM on a 4.6 × 250 mM microsorb-MV C18 column, using as solvents 0.1% trifluoroacetic acid in water (A) and 0.1% trifluoroacetic acid in acetonitrile (B). The linear gradient was 20% B in A to 95% B in A with a flow rate of 1 mL/min.

Preparation of 7a

5-Methyl-3-nitro-2-(2,2,2-trifluoro-acetylamino)-benzoic acid (9a). 2-Amino-5-methyl-benzoic acid (**8a**) (1.0 g, 6.6 mmol) was dissolved into 5 mL of THF. To this solution was added dropwise 5 mL of trifluoroacetic anhydride at 0 °C. The resulting solution was allowed to stir at room temperature for 12 h. The solution was poured into ice-water. The mixture was filtered, washed with water and dried to give 1.60 g (70%) of 2-[bis-(2,2,2-trifluoro-acetyl)-amino]-5-methyl-benzoic acid as a white solid, mp 200–202 °C. ^1H NMR ($CDCl_3$) δ 2.53 (s, 3H), 7.68 (m, 2H), 8.07 (s, 1H).

To 7 mL of fuming nitric acid was added the above anilide (1.6 g, 4.66 mmol) in one portion at 4 °C. The resulting solution was allowed to stir at 4 °C for 1 h. The solution was poured into ice-water (5 g), filtered, washed with water and dried to give 1.18 g (87%) of the title compound as a yellow solid, mp 198–200 °C. ^1H NMR ($CDCl_3$) δ 8.09 (s, 1H), 8.22 (s, 1H), 10.99 (s, 1H).

2-Amino-5-methyl-3-nitro-benzoic acid (10a). To a solution of 5-methyl-3-nitro-2-(2,2,2-trifluoro-acetylamino)-benzoic acid (**9a**) (0.146 g, 0.5 mmol) in absolute alcohol (3 mL) was added 10% aqueous sodium hydroxide solution (3 mL). The solution was allowed to stir at 80 °C (oil bath) for 3 h. Ethanol was evaporated in vacuo to leave an orange solid, which was collected by suction filtration and washed with water and dried in vacuo, giving 90 mg (92%) of the title compound as an orange solid, mp 245–246 °C. ^1H NMR (DMSO-d_6) δ 2.20 (s, 3H), 8.03 (s, 1H), 8.10 (s, 1H), 8.30 (brs, 2H), 13.50 (brs, 1H).

2,3-Diamino-5-methyl-benzoic acid (6a). 2-Amino-5-methyl-3-nitro-benzoic acid (**10a**) (80 mg, 0.38 mmol) was dissolved into methanol (7 mL). To this solution was added 5% Pd/C (20 mg, 20%). The mixture was then stirred at room temperature under H_2 at 45 psi for 3 h. The catalyst was removed through a column of Celite (5 g) and washed with ethyl acetate under nitrogen. The extracts were combined and the solvent was removed to give diamine **6a** as a brown solid. ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.65 (brs, 4H), 6.16 (s, 1H), 6.64 (s, 1H).

7-Methyl-1,4-dihydro-quinoxaline-2,3-dione-5-carboxylic acid (7a). 2,3-Diamino-5-methyl-benzoic acid (**6a**) (300 mg, 1.68 mmol) was dissolved in 4 N hydrochloric acid (30 mL), and oxalic acid dihydrate (352.8 mg, 2.8 mmol; Fisher) was added to this solution in one portion with stirring under N_2. The mixture was refluxed using a 130–135 °C oil bath for 3 h. A brown solid came out which was collected by suction filtration and dried in vacuo overnight and recrystallized from DMF/H_2O to give 240 mg (65%) of the title compound as a white solid, mp > 350 °C. ^1H NMR (DMSO-d_6) δ 2.28 (s, 3H), 7.14 (s, 1H), 7.53 (s, 1H), 11.49 (s, 1H), 12.06 (s, 1H). EI–MS *m/e* 220 (100, M^+), 174 (98, $M^+ - CO_2H$). HR-MS calcd for $C_{10}H_5N_2O_4$: 220.1863. Found: 220.1865 (HPLC 100%)

Preparation of 7b

2-Fluoro-3,5-dinitro-benzoic acid (12). Fuming nitric acid (5 mL) was added dropwise into fuming sulfuric

acid (15% SO_3, 10 mL) cooled in an ice bath. The temperature rise was limited to 40 °C. After all the nitric acid was added; the ice bath was removed and 2 g (14.3 mmol) of 2-fluoro-benzoic acid (**11**) was added. The resulting mixture was heated to 145 °C for 1.5 h. Then the mixture was cooled to room temperature and poured into 60 g of crushed ice. The white solid was collected, washed with water and dried to give 2.4 g (73%) of the product, mp 196–198 °C (dec.) (lit.[11] mp 197–198 °C). ^{1}H NMR ($CDCl_3$–DMSO-d_6) δ 8.77 (m, 2H).

2-Amino-3,5-dinitro-benzoic acid (10b). Ammonium hydroxide solution (30%, 9 mL) was added dropwise into 1 g (4.35 mmol) of 2-fluoro-3,5-dinitro-benzoic acid (**12**). The resulting mixture was allowed to stir at room temperature for 10 min. The precipitate was collected by suction filtration and dried in the air, recrystallized from water and then was acidified to pH 4 with 4 N HCl to give 0.96 g (97%) of the product as a yellow solid, mp 266–268 °C (lit.[10] mp 268 °C). ^{1}H NMR ($CDCl_3$–DMSO-d_6) δ 8.398 (brs, 1H), 8.756 (dd, 1H, J = 2.4 Hz), 8.884 (d, 1H,J = 2.4 Hz), 9.398 (brs, 1H).

2,3-Diamino-5-nitro-benzoic acid (6b). The procedure of Gillespie[7] was adapted for this reaction. To 14 mL of freshly prepared 6% of ammonium sulfide was added 0.9 g (3.7 mmol) of 2-amino-3,5-dinitro-benzoic acid (**10b**). The resulting mixture was allowed to stir at 90 °C for 2 h. and then boiled to remove the bulk of ammonia. The hot solution was filtered to remove sulfur. After cooling to 5 °C, the filtrate was acidified with acetic acid. The precipitate was filtered off, washed with water, and recrystallized from 75% ethanol to give 495 mg (68%) of the product as a red solid, mp 244–246 °C (dec.) (lit.[7] mp 245 °C). ^{1}H NMR (DMSO-d_6) δ 5.40 (brs, 2H), 7.42 (brs, 2H), 7.433(d, 1H, J = 2.7 Hz), 8.04 (d, 1H, J = 2.7 Hz).

7-Nitro-1,4-dihydro-quinoxaline-2,3-dione-5-carboxylic acid (7b). 2,3-Diamino-5-nitro-benzoic acid (**6b**) (170 mg, 0.79 mmol) was dissolved in 4 N hydrochloric acid (10 mL), and oxalic acid dihydrate (150 mg, 1.2 mmol; Fisher) was added to this solution in one portion with stirring under N_2. The mixture was refluxed at 130–135 °C (oil bath) for 3 h. A brown solid came out which was collected by suction filtration and dried in vacuo overnight and recrystallized from DMF/H_2O to give 240 mg (65%) of the title compound as a yellow solid, mp > 350 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 8.09 (d, 1H, J = 2.7 Hz), 8.40 (d, 1H, J = 2.7 Hz), 11.79 (s, 1H), 12.36 (s, 1H). EI–MS m/e 251 (100, M^+), 205 (78, $M^+ - CO_2H$). HR-MS calcd for $C_9H_5N_3O_6$: 251.1567. Found: 251.1563.

Preparation of 7c

5-Chloro-3-nitro-2-(2,2,2-trifluoro-acetylamino)-benzoic acid (9c). 2-Amino-5-chloro-benzoic acid (**8c**) (1.716 g, 10 mmol) was dissolved in 6 mL of dioxane. To this solution was added dropwise 2 mL of trifluoroacetic anhydride at 0 °C. The resulting solution was allowed to stir at room temperature for 12 h. The solution was poured into ice-water (10 g). The mixture was filtered and washed with water and dried to give 1.8 g (67%) of 5-chloro-2-(2,2,2-trifluoro-acetylamino)benzoic acid as a white solid, mp 198–200 °C. ^{1}H NMR ($CDCl_3$) δ 7.41 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.7 Hz), 7.94 (d, 1H, J = 2.7 Hz), 8.44 (d, 1H, J = 8.6 Hz), 12.50 (s, 1H).

The above anilide was dissolved into 3 mL of concentrated sulfuric acid. To this solution was added potassium nitrate (121 mg, 1.2 mmol) at 0 °C. The resulting mixture was allowed to stir at room temperature for 12 h. The mixture was poured into ice-water (5 g), filtered, washed with water and dried to give 256 mg (82%) of **9c** as a yellow solid, mp 179–180 °C. ^{1}H NMR (DMSO-d_6) δ 8.17 (d, 1H, J = 2.4 Hz), 8.37 (d, 1H, J = 2.4 Hz), 11.90 (s, 1H).

2-Amino-5-chloro-3-nitro-benzoic acid (10c). To a solution of 5-chloro-3-nitro-2-(2,2,2-trifluoro-acetylamino)-benzoic acid (**9c**) (0.157 g, 0.5 mmol) in absolute alcohol (3 mL) was added 10% aqueous sodium hydroxide solution (3 mL). The solution was allowed to stir at 80 °C (oil bath) for 3 h. Ethanol was evaporated in vacuo to leave an orange solid, which was collected by suction filtration and washed with water and dried in vacuo, giving 90 mg (82%) of the title compound as an orange solid, mp 230–232 °C. ^{1}H NMR (DMSO-d_6) δ 8.10 (d, 1H, J = 2.7 Hz), 8.28 (d, 1H, J = 2.7 Hz), 8.45 (brs, 2H), 13.90 (brs, 1H).

7-Chloro-1,4-dihydro-quinoxaline-2,3-dione-5-carboxylic acid (7c) (from 10c two steps). 2-Amino-5-chloro-3-nitro-benzoic acid (**10c**) (300 mg, 1.4 mmol) was dissolved in ethyl acetate (30 mL). To this solution was added 5% Pd/C (75 mg, 20%; Aldrich). The mixture was then stirred at room temperature under H_2 at 45 psi for 3 h. The catalyst was removed through a column of Celite (5 g) and washed with ethyl acetate (3 × 15 mL) under nitrogen. The extracts were combined and the solvent was removed to give diamine **6c** as a black solid. The ^{1}H NMR spectrum was consistent with the assigned structure. Diamine **6c** was dissolved in 4 N hydrochloric acid (15 mL) and oxalic acid dihydrate (252 mg, 2.00 mmol; Fisher) was added to this solution in one portion with stirring under N_2. The mixture was refluxed using a 130–135 °C oil bath for 3 h. A yellow solid came out which was collected by suction filtration and dried in vacuo overnight and recrystallized from DMF/H_2O to give 210 mg (62% based on **10c**) of the title compound as a red solid, mp > 350 °C. ^{1}H NMR (DMSO-d_6) δ 7.31 (d, 1H, J = 2.1 Hz), 7.62 (d, 1H, J = 2.1 Hz), 11.49 (s, 1H), 12.17 (s, 1H). EI–MS m/e 240 (100, M^+, ^{35}Cl). HR-MS calcd for $C_9H_5ClN_2O_4$: 240.6042. Found: 240.6045 (HPLC > 95%).

Preparation of 7d

Methyl 2-amino-5-chloro-3-nitro-benzoate (10d). To a 25-mL round-bottomed flask was placed 2-amino-5-chloro-3-nitro-benzoic acid (**10c**) (165 mg, 0.76 mmol) and then was added 5 mL of thionyl chloride. The resulting mixture was refluxed for 3 h. The mixture was evaporated in vacuo to dryness and methanol (5 mL)

was added. The resulting solution was allowed to stir at room temperature for 12 h. Methanol was evaporated and water (6 mL) was added. A yellow solid was collected by filtration, washed with water and dried to give 172 mg (98%) of **10d**, mp 93–95 °C. ^{1}H NMR ($CDCl_3$) δ 3.99(s, 3H). 8.20 (d, J = 2.7 Hz, 1H), 8.38 (d, J = 2.7 Hz, 1H), 8.40 (brs, 2H).

Methyl 7-chloro-1,4-dihydro-quinoxaline-2,3-dione-5-carboxylate (7d) (from 10d two steps). Methyl 2-amino-5-chloro-3-nitro-benzoate (**10d**) (115 mg, 0.50 mmol) was dissolved in methanol (25 mL). To this solution was added 5% Pd/C (30 mg, 20%; Aldrich). The mixture was then stirred at room temperature under H_2 at 40 psi for 3 h. The catalyst was removed through a column of Celite (5 g) and washed with ethyl acetate (3 × 15 mL) under nitrogen. The extracts were combined and the solvent was removed to give diamine **6d** as a black solid. The ^{1}H NMR spectrum was consistent with the assigned structure. Diamine **6d** was mixed with diethyl oxalate (4 mL; Fisher) with stirring under N_2. The mixture was allowed to stir at 120 °C for 15 h. A brown solid came out which was collected by suction filtration, washed with ethyl acetate and dried in vacuo overnight to give 51 mg (40% based on **10d**) of the title compound as a pale yellow solid, mp 244–246 °C. ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H), 7.33 (s, 1H), 7.61 (d, J = 2.1 Hz, 1H), 11.14 (s, 1H), 12.19 (s, 1H). EI–MS m/e 239 (254, 40, M^+, ^{35}Cl), 194 (100). HR-MS calcd for $C_{10}H_7ClN_2O_4$: 254.0066. Found: 254.0080 (HPLC > 96%).

Preparation of 7e

***N*-(2-Benzoyl-4-chloro-6-nitro-phenyl)-2,2,2-trifluoroacetamide (9e).** (2-Amino-5-chloro-phenyl)-phenyl-methanone (**8e**) (4.634 g, 20 mmol) was dissolved in 6 mL of THF. To this solution was added dropwise 5 mL of trifluoroacetic anhydride at 0 °C. The resulting solution was allowed to stir at room temperature for 12 h. The solution was poured into ice-water (10 g). The mixture was filtered and washed with water and dried to give 6.5 g (99%) of *N*-(2-benzoyl-4-chloro-phenyl)-2,2,2-trifluoroacetamide as a white solid, mp 95–97 °C. ^{1}H NMR ($CDCl_3$) δ 7.55–7.71 (m, 7H), 8.61 (d, 1H, J = 8.4 Hz), 11.88 (s, 1H).

N-(2-Benzoyl-4-chloro-phenyl)-2,2,2-trifluoroacetamide (710 mg, 2.16 mmol) was dissolved into 8 mL of trifluoroacetic acid. To this solution was added 0.432 mL (4.32 mmol) of fuming nitric acid at room temperature. The resulting solution was allowed to stir at 50 °C for 24 h. The mixture was poured into ice-water (5 g), filtered, washed with water and dried. Recrystallization from ethyl acetate/hexanes gave 300 mg (39%) of **9e** as a white solid, mp 166–168 °C. ^{1}H NMR ($CDCl_3$) δ 7.52–7.57 (m, 2H), 7.67–7.69 (m, 2H), 7.77 (d, 1H, J = 2.1 Hz), 7.84 (d, 1H, J = 7.5 Hz), 8.28 (d, 1H, J = 2.1 Hz), 10.36 (s, 1H). EI–MS m/e 372 (50, M^+), 105 (100, PhCO).

(2-Amino-5-chloro-3-nitro-phenyl)-phenyl-methanone (10e). To a solution of **9e** (0.30 g, 0.8 mmol) in absolute alcohol (4 mL) was added 10% aqueous sodium hydroxide solution (4 mL). The solution was allowed to stir at room temperature for 24 h. Ethanol was evaporated in vacuo to leave an orange solid, which was collected by suction filtration and washed with water (3 × 5 mL) and dried in vacuo, giving 200 mg (90%) of the title compound as an orange solid, mp 110–112 °C. ^{1}H NMR ($CDCl_3$) δ 7.50–7.54 (m, 3H), 7.62–7.63 (m, 2H), 7.73 (d, 1H, J = 2.4 Hz), 8.41 (d, 1H, J = 2.4 Hz), 8.53 (brs, 2H).

5-Benzoyl-7-chloro-1,4-dihydro-quinoxaline-2,3-dione (7e) (from 10e two steps). (2-Amino-5-chloro-3-nitro-phenyl)-phenyl-methanone (**10e**) (100 mg, 0.36 mmol) was dissolved in ethyl acetate (5 mL). To this solution was added 5% Pd/C (25 mg, 20%; Aldrich). The mixture was then stirred at room temperature under H_2 at 45 psi for 3 h. The catalyst was removed through a column of Celite (5 g) and washed with ethyl acetate (3 × 15 mL) under nitrogen. The extracts were combined and the solvent was removed to give diamine **6e** as a black solid. The ^{1}H NMR spectrum was consistent with the assigned structure. Diamine **6e** was dissolved in 4 N hydrochloric acid (15 mL) and oxalic acid dihydrate (75.6 mg, 0.6 mmol; Fisher) was added to this solution in one portion with stirring under N_2. The mixture was refluxed using a 130–135 °C oil bath for 3 h. A yellow solid came out which was collected by suction filtration, washed with ethyl acetate and dried in vacuo overnight to give 65 mg (60% based on **10e**) of the title compound as a pale yellow solid, mp 256–258 °C. ^{1}H NMR (DMSO-d_6) δ 7.13 (d, 1H, J = 2.1 Hz), 7.31 (d, 1H, J = 2.1 Hz), 7.54 (m, 2H), 7.71 (m, 3H), 11.34 (s, 1H), 12.19 (s, 1H). EI–MS m/e 300 (100, M^+, ^{35}Cl). HR-MS calcd for $C_{15}H_9ClN_2O_3$: 300.0300. Found: 300.0301 (HPLC > 98%).

Preparation of 7f

2-Amino-5-chloro-3-nitro-benzamide (10f). To a 25-mL round-bottomed flask was placed 2-amino-5-chloro-3-nitro-benzoic acid (**10c**) (165 mg, 0.76 mmol) and then was added 5 mL of thionyl chloride. The resulting mixture was refluxed for 3 h. The mixture was evaporated in vacuo to dryness and then 5 mL of THF was added. To this solution was added a solution 5 mL of 30% aqueous ammonium hydroxide solution. The resulting solution was allowed to stir at room temperature for 12 h. Water (10 mL) was added. The yellow precipitate was collected by filtration and dried to give 147 mg (90%) of **10f**, mp 240–242 °C. ^{1}H NMR (DMSO-d_6) δ 6.46 (brs, 1H), 7.68 (d, 1H, J = 1.8 Hz), 7.80 (brs, 1H), 7.91 (d, 1H, J = 2.1 Hz), 8.21 (s, 2H).

7-Chloro-1,4-dihydro-quinoxaline-2,3-dione-5-carboxylic acid amide (7f) (from 10f two steps). 2-Amino-4-chloro-3-nitro-benzamide (**10f**) (85 mg, 0.394 mmol) was dissolved in methanol (25 mL). To this solution was added 5% Pd/C (25 mg, 20%; Aldrich). The mixture was then stirred at room temperature under H_2 at 40 psi for 3 h. The catalyst was removed through a column of Celite (5 g) and washed with ethyl acetate (3 × 15 mL) under nitrogen. The extracts were combined and the solvent

was removed to give diamine **6f** as a black solid. The ^{1}H NMR spectrum was consistent with the assigned structure. Diamine **6f** was mixed with diethyl oxalate (4 mL; Fisher) with stirring under N_2. The mixture was allowed to stir at 120 °C for 15 h. A brown solid came out which was collected by suction filtration, washed with ethyl acetate and dried in vacuo overnight to give 25 mg (50% based on **10f**) of the title compound as a pale yellow solid, mp 330–332 °C. ^{1}H NMR (DMSO-d_6) δ 7.25 (s, 1H), 7.75 (s, 1H), 8.04 (s, 1H), 8.49 (s, 1H), 12.09 (s, 1H), 12.48 (s, 1H). EI–MS *m*/*e* 239 (40, M^+, ^{35}Cl). HR-MS calcd for $C_9H_6ClN_3O_3$: 239.0110. Found: 239.0104 (HPLC >91%).

Preparation of 7g

2-Amino-5-chloro-*N,N*-dimethyl-3-nitro-benzamide (10g). To a 25-mL round-bottomed flask was placed 2-amino-4-chloro-3-nitro-benzoic acid (**10c**) (320 mg, 1.48 mmol) and then was added 7.5 mL of thionyl chloride. The resulting mixture was refluxed for 3 h. The mixture was evaporated in vacuo to dryness and then 5 mL of THF was added. To this solution was added a solution 5 mL of 40% aqueous dimethylamine solution. The resulting solution was allowed to stir at room temperature for 12 h and then water (10 mL) was added. The yellow precipitate was collected by filtration and dried to give 317 mg (81%) of **10g**, mp 134–136 °C. ^{1}H NMR ($CDCl_3$) δ 3.08 (brs, 6H), 6.82 (brs, 2H), 7.31 (d, 1H, J = 2.1 Hz), 8.20 (d, 1H, J = 2.1 Hz).

7-Chloro-1,4-dihydro-quinoxaline-2,3-dione-5-carboxylic acid dimethylamide (7g) (from 10g two steps). 2-Amino-5-chloro-*N,N*-dimethyl-3-nitro-benzamide (**10g**) (100 mg, 0.41 mmol) was dissolved in ethyl acetate (5 mL). To this solution was added 5% Pd/C (25 mg, 20%; Aldrich). The mixture was then stirred at room temperature under H_2 at 40 psi for 3 h. The catalyst was removed through a column of Celite (5 g) and washed with ethyl acetate (3 × 15 mL) under nitrogen. The extracts were combined and the solvent was removed to give diamine **6g** as a black solid. The ^{1}H NMR spectrum was consistent with the assigned structure. Diamine **6g** was dissolved in ethanol (2 mL), and diethyl oxalate (4 mL) was added to this solution in one portion with stirring under N_2. The mixture was refluxed for 15 h. A yellow solid came out which was collected by suction filtration, washed with ethyl acetate and dried in vacuo overnight to give 25 mg (23% based on compound **10g**) of the title compound as a pale yellow solid, mp 254–256 °C. ^{1}H NMR (DMSO-d_6) δ 2.764 (s, 3H), 2.92 (s, 3H), 7.00 (d, 1H, J = 1.8 Hz), 7.11 (d, 1H, J = 1.8 Hz), 11.42 (s, 1H), 12.03 (s, 1H). EI–MS *m*/*e* 267 (40, M^+, ^{35}Cl). HR-MS calcd for $C_{11}H_{10}ClN_3O_3$: 267.0411. Found: 267.0411 (HPLC >99%).

Preparation of 7h

2-Amino-5-chloro-*N,N*-diethyl-3-nitro-benzamide (10h). To a 25-mL round-bottomed flask was placed 2-amino-4-chloro-3-nitro-benzoic acid (**10c**) (216.5 mg, 1.0 mmol) and then was added 5 mL of thionyl chloride. The resulting mixture was refluxed for 3 h. The mixture was evaporated in vacuo to dryness and then 5 mL of THF was added. To this solution was added a solution 0.52 mL of diethylamine in 2 mL of THF. The resulting resolution was allowed to stir at room temperature for 12 h and then water (10 mL) was added. The yellow precipitate was collected by filtration and dried to give 220 mg (81%) of **10h**, mp 110–112 °C. ^{1}H NMR ($CDCl_3$) δ 1.22 (brs, 6H), 3.45 (brs, 4H), 6.60 (brs, 2H), 7.27 (d, 1H, J = 2.4 Hz), 8.18 (d, 1H, J = 2.4 Hz).

7-Chloro-1,4-dihydro-quinoxaline-2,3-dione-5-carboxylic acid diethylamide (7h) (from 10h two steps). 2-Amino-5-chloro-*N,N*-diethyl-3-nitro-benzamide (**10h**) (100 mg, 0.37 mmol) was dissolved in ethyl acetate (5 mL). To this solution was added 5% Pd/C (25 mg). The mixture was then stirred at room temperature under H_2 at 40 psi for 3 h. The catalyst was removed through a column of Celite (5 g) and washed with ethyl acetate (3 × 15 mL) under nitrogen. The extracts were combined and the solvent was removed to give diamine **6h** as a black solid. The ^{1}H NMR spectrum was consistent with the assigned structure. Diamine **6h** was dissolved in ethanol (2 mL), and diethyl oxalate (4 mL) was added to this solution in one portion with stirring under N_2. The mixture was refluxed for 15 h. A yellow solid came out which was collected by suction filtration, washed with ethyl acetate and dried in vacuo overnight to give 79 mg (72% based on **10h**) of the title compound as a pale yellow solid, mp 274–276 °C. ^{1}H NMR (DMSO-d_6) δ 0.96 (m, 3H), 1.13 (m, 3H), 3.09 (m, 2H), 3.40 (m, 2H), 6.95 (d, 1H, J = 2.1 Hz), 7.11 (d, 1H, J = 2.1 Hz), 11.43 (s, 1H), 12.04 (s, 1H). EI–MS *m*/*e* 295 (60, M^+, ^{35}Cl). HR-MS calcd for $C_{13}H_{14}ClN_3O_3$: 295.0710. Found: 295.0717 (HPLC >99%).

Preparation of 7i

Methyl 2-amino-6-methyl-benzoate (14). A suspension of 2-methyl-6-nitro-benzoic acid (**13**) (2.000 g, 11.04 mmol), anhydrous K_2CO_3 (1.830 g, 13.24 mmol) and iodomethane (2.50 mL, 40.2 mmol) in acetone (40 mL) was refluxed for 20 h. The solvent was removed in vacuo and the residual slurry was diluted with water (40 mL) and extracted with ethyl acetate (2 × 40 mL). The extract was washed with brine, dried over anhydrous Na_2SO_4 and removed in vacuo. The residual solid was dried and purified on silica gel (5% EtOAc in hexane) to give 2.061 g (96%) of pure methyl 2-methyl-6-nitro-benzoate as yellow powder, mp 45–47 °C. ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.96 (s, 3H), 7.46 (dd, 1H, J = 8.1 Hz), 7.54 (d, 1H, J = 7.5 Hz), 7.99 (d, 1H, J = 8.1 Hz).

A suspension of methyl 2-methyl-6-nitro-benzoate (1.500 g, 7.685 mmol) and 10% Pd/C (50 mg) in EtOH (50 mL) was stirred under H_2 (maintained by a balloon filled with H_2) for 18 h. The catalyst was filtered and the solvent was removed in vacuo. The residue was dried further to give 1.146 g (90%) of the title compound as a light red liquid which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.89 (s, 3H), 5.45 (brs, 2H), 6.53 (d, 2H, J = 7.8 Hz), 7.08 (d, 1H, J = 7.8 Hz).

Methyl 2-acetylamino-5-bromo-6-methyl-3-nitro-benzoate (9i). A solution of methyl 2-amino-6-methyl-benzoate (1.000 g, 6.054 mmol) in Ac_2O (9 mL) was stirred overnight at room temperature. It was then poured into water (100 mL) and stirred at room temperature for 30 min. The white solid was collected by vacuum filtration, dried and purified on silica gel (10% EtOAc in hexane) to give 1.154 g (92%) of pure methyl 2-acetylamino-6-methyl-benzoate as white powder, mp 76–78 °C. ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H), 2.46 (s, 3H), 3.95 (s, 3H), 6.96 (d, 1H, J = 7.5 Hz), 7.34 (d, 1H, J = 7.5 Hz), 8.23 (d, 1H, J = 7.8 Hz), 9.65 (br s, 1H).

To a stirred solution of methyl 2-acetylamino-6-methyl-benzoate (0.584 g, 2.82 mmol) in acetic acid (6.8 mL), a solution of Br_2 (0.17 mL, 3.3 mmol) in acetic acid (1.5 mL) was added dropwise. The resulting orange solution was allowed to stand overnight at room temperature. The stirred orange suspension was diluted with water followed by 10% aqueous sodium metabisulfite to remove the yellow color. The white solid was collected by vacuum filtration, washed with water (100 mL) and dried in vacuo to give 0.709 (88%) of methyl 6-acetylamino-3-bromo-2-methyl-benzoate as a white powder, mp 66–69 °C. ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.45 (s, 3H), 3.96 (s, 3H), 7.61 (d, 1H, J = 9.0 Hz), 8.03 (d, 1H, J = 9.0 Hz), 8.85 (br s, 1H).

To a stirred solution of methyl 6-acetylamino-3-bromo-2-methyl-benzoate (0.262 g, 0.916 mmol) in TFA (5 mL) at 0 °C, 90% HNO_3 (0.080 mL) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight at room temperature. It was then poured into water (50 mL) and the solid was collected by vacuum filtration, washed with water and dried in vacuo to give 0.273 g (90%) of pure methyl 2-acetylamino-5-bromo-6-methyl-3-nitro-benzoate (**9i**) as cream colored powder, mp 164–167 °C. ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H), 2.51 (s, 3H), 3.93 (s, 3H), 8.30 (s, 1H), 8.78 (brs, 1H).

Methyl 2-Amino-5-bromo-6-methyl-3-nitro-benzoate (10i). A solution of **9i** (0.296 g, 0.894 mmol) and concentrated HCl (1.4 mL) in EtOH (7 mL) was refluxed for 18 h. The solvent was removed in vacuo and the residue was diluted with water (10 mL). The pH was adjusted with 2 M NaOH to 5 and the shiny yellow solid was collected by vacuum filtration, washed with water and dried in air to give 0.223 g (86%) of the title compound as shiny yellow needles, mp 121–124 °C. ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 3.97 (s, 3H), 7.13 (brs, 2H), 8.46 (s, 1H).

Methyl 2,3-diamino-5-bromo-6-methyl-benzoate (6i). The wine red solution of methyl 2-amino-5-bromo-6-methyl-3-nitro-benzoate (0.105 g, 0.363 mmol) and $SnCl_2{\cdot}2H_2O$ (0.300 g, 1.33 mmol) in EtOH (4 mL) was refluxed for 2 h. The solution was poured into water (6 mL) and the pH adjusted to ~8 with 5% aq $NaHCO_3$ (13.5 mL). The suspension was extracted with EtOAc. The extract was washed with brine, dried and removed in vacuo to give 0.086 g (91%) of the title compound as a light red powder. ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.92 (s, 3H), 6.99 (s, 1H).

Methyl 7-bromo-6-methyl-1,4-dihydro-quinoxaline-2,3-dione-5-carboxylate (7i). A mixture of methyl 2,3-diamino-5-bromo-6-methyl-benzoate (0.073 g, 0.28 mmol) and oxalic acid dihydrate (0.053 g, 0.42 mmol) was refluxed in 2 M HCl (4 mL) for 6 h. It was then cooled to room temperature and the solid was collected by vacuum filtration, washed with water (10 mL) and dried in vacuo to give 0.047 g (53%) of crude product as a brick red powder. A 0.043 g sample was purified by refluxing in acetone (2 mL) for 10 min and then filtering while hot. The residual solid was washed with hot acetone and dried in vacuo to give 0.031 g (35%) of pure title compound as a light burgundy powder, mp 282 °C (dec). ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 3H), 3.87 (s, 3H), 7.37 (s, 1H), 11.53 (s, 1H), 11.99 (s, 1H). Anal. calcd for $C_{11}H_9BrN_2O_4$: C, 42.19; H, 2.90; N, 8.95. Found: C, 41.89; H, 2.89; N, 9.01. (HPLC 100%)

Preparation of 7j

3-(2,5-Dichloro-phenyl)-acrylic acid (16). A suspension of 1,4-dichloro-2-iodo-benzene (**15**) (2.931 g, 10.74 mmol), acrylic acid (0.96 mL, 14 mmol), Pd(II) acetate (0.022 g, 0.10 mmol), triethylamine (3.5 mL) and acetonitrile (4.0 mL) was heated in a sealed tube at 110 °C for 1 h. The suspension was cooled to room temperature and the catalyst was removed by filtration. The filtrate was poured into 10% HCl (250 mL) and the precipitated solid was collected by vacuum filtration, washed with water until the pH of the filtrate was ~6 (pH paper). It was further dried in vacuo to give 2.190 g (94%) of the title compound as a light cream colored powder. ^{1}H NMR (DMSO-d_6) δ 6.69 (d, 1H, J = 15.0 Hz), 7.47–7.55 (m, 2H), 7.73 (d, 1H, J = 15.9 Hz), 8.01 (s, 1H), 12.71 (brs, 1H).

3-(2,5-Dichlorophenyl)-propanoic acid (17). A suspension of **16** (1.825 g, 8.408 mmol) and Pt(IV) oxide (0.025 g) was stirred in EtOAc (80 mL) under H_2 (maintained by a balloon) at room temperature for 24 h. The catalyst was removed by filtration and solvent from the filtrate was removed on a rotavapor. The residue was dried further in vacuo to give 1.734 g (95%) of the title compound as white powder. ^{1}H NMR ($CDCl_3$) δ 2.71 (t, 2H, J = 8.1 Hz), 3.04 (t, 2H, J = 8.1 Hz), 7.14–7.30 (m, 3H) 10.5–12 (br s, 1H).

4,7-Dichloro-indan-1-one (18j). A solution of **17** (1.542 g, 7.039 mmol) in $SOCl_2$ (15 mL) was refluxed for 4 h and then cooled to room temperature and the excess $SOCl_2$ was distilled off. The residual liquid was dried at water aspirator pressure and dissolved in CS_2 (18 mL). Then $AlCl_3$ (1.200 g, 9.000 mmol) was added and the reaction mixture was refluxed for 24 h under N_2. The CS_2 was distilled off and the residual solid was cooled in an ice-bath and worked up by slow addition of cold 10% HCl (25 mL). The resulting suspension was stirred at room temperature for 30 min and extracted with EtOAc. The combined EtOAc was washed with 5% $NaHCO_3$, water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotavapor and drying the residue under high vacuum gave 1.001 g (71%) of the title compound as a yellow powder. ^{1}H NMR ($CDCl_3$) δ

2.77 (t, 2H, $J=6.3$ Hz), 3.09 (t, 2H, $J=6.3$ Hz), 7.28 (d, 1H, $J=8.1$ Hz), 7.48 (d, 1H, $J=8.1$ Hz).

4,7-Dichloro-6-nitro-indan-1-one (20j). To stirred fuming HNO_3 (3.0 mL) at 0 °C, **18j** (0.582 g, 2.89 mmol) was added in one portion. The reaction mixture was stirred in an ice-bath for 30 min and then stored in the freezer (−20 °C) for 2 days. The orange-red solution was added dropwise to ice (50 g) and the precipitated solid was collected by vacuum filtration and washed with water until the filtrate was pH 7. The resulting solid was dried under high vacuum to give 0.712 g (81%) of the title compound as a light-yellow powder. ^{1}H NMR ($CDCl_3$) δ 2.86–2.91 (m, 2H), 3.16–3.18 (m, 2H), 8.04 (s, 1H).

7-Azido-4-chloro-6-nitro-indan-1-one (21j). To a stirred solution of **20j** (0.268 g, 1.09 mmol) in acetone (2.0 mL) at 45 °C, NaN_3 (0.105 g, 1.62 mmol) in water (1.5 mL) was added and the resulting suspension was stirred at 45 °C for 24 h. TLC indicated the absence starting material. The volatiles were removed on a rotavapor and the residue was diluted with water (5 mL). The precipitated solid was collected by vacuum filtration, washed with water (5 mL) and dried in vacuo to give 0.206 g (75%) of the title compound as a brown powder. ^{1}H NMR ($CDCl_3$) δ 2.88 (t, 2H, $J=6.0$ Hz), 3.19 (t, 2H, $J=6.0$ Hz), 8.09 (s, 1H).

6,7-Diamino-4-chloro-indan-1-one (6j). A suspension of **21j** (0.200 g, 0.792 mmol) and 10% Pd/C (0.025 g) in EtOAc (7.0 mL) was stirred under H_2 (maintained by a balloon) at room temperature for 24 h. The catalyst was removed by filtration and the solvent from the filtrate was removed on a rotavapor. The residue was dried further in vacuo to give 0.140 g (90%) of the title compound as a brown powder. ^{1}H NMR ($CDCl_3$) δ 2.68 (t, 2H, $J=6.0$ Hz), 2.96 (t, 2H, $J=6.0$ Hz), 3.2–4.0 (brs, 4H), 6.87 (s, 1H).

6 - Chloro - 1,4,7,8 - tetrahydro - cyclopenta[f]quinoxaline - 2,3,9-trione (7j). A suspension of **6j** (0.131 g, 0.666 mmol) in diethyl oxalate (1.5 mL) was refluxed for 24 h. It was then cooled to room temperature and diluted with hexane (15 mL). The precipitated solid was collected by vacuum filtration, washed with hexane and dried in vacuo to give 0.123 g of crude product as a brown powder. A 0.120 g sample was stirred in 1 M NaOH (40 mL) at room temperature for 30 min. The solid was mostly undissolved and was removed by vacuum filtration. The bright yellow filtrate was acidified with concentrated HCl (4 mL) to pH ~2 to give a suspension, which was filtered in vacuo, washed with water and dried to give 0.028 g (17%) of pure (97.7% by HPLC) title compound as an off-white powder, mp 322 °C (dec). ^{1}H NMR (DMSO-d_6) δ 2.76–2.77 (m, 2H), 2.99 (t, 1H, $J=4.5$ Hz), 7.36 (s, 1H), 10.36 (s, 1H), 12.15 (s, 1H). HRMS calcd for $C_{11}H_7ClN_2O_3$: 250.0145. Found: 250.0151.

Preparation of 7k

4,7-Dichloro-3*H*-isobenzofuran-1-one (18k). To a stirred solution of sodium borohydride (0.175 g, 4.63 mmol) in DMF (1 mL) in an ice-bath, a solution of 4,7-dichloroisobenzofuran-1,3-dione (1.007 g, 4.64 mmol) in DMF (3.5 mL) was added dropwise to it. The solution was allowed to warm to room temperature and stirred for 1 h at room temperature. The yellow solution was again cooled in ice-bath and decomposed with 6 N HCl (2 mL) followed by water (10 mL). The white solid was collected by vacuum filtration, washed with water and dried in vacuo to give 0.708 g (75%) of the title compound as a white powder, mp 150–159 °C. ^{1}H NMR ($CDCl_3$) δ 5.24 (s, 2H), 7.46 (d, 1H, $J=8.4$ Hz), 7.56 (d, 1H, $J=8.4$ Hz).

4,7-Dichloro-6-nitro-3*H*-isobenzofuran-1-one (20k). To a stirred solution of **18k** (0.700 g, 3.45 mmol) in concentrated H_2SO_4 (10 mL) in an ice-bath, KNO_3 (0.418 g, 4.13 mmol) was added in one portion. The yellow solution was then stirred overnight at room temperature and poured into ice-water. The white solid was collected by vacuum filtration, washed with water and dried in vacuo to give 0.738 g (86%) of **20k** as a white powder, mp 153–612 °C. ^{1}H NMR ($CDCl_3$) δ 5.31 (s, 2H), 8.13 (s, 1H).

7-Azido-4-chloro-6-nitro-3*H*-isobenzofuran-1-one (21k). To a stirred solution of **20k** (0.730 g, 2.94 mmol) in acetone (12 mL) at room temperature, a solution of NaN_3 (0.285 g, 4.38 mmol) was added dropwise. The resulting suspension was stirred overnight at room temperature. The suspension was concentrated on a rotavapor and diluted with water (20 mL). The solid was collected by vacuum filtration, washed with water (20 mL) and dried in vacuo to give 0.690 g (92%) of the title compound as a light yellow powder, mp 118–122 °C. ^{1}H NMR ($CDCl_3$) δ 5.34 (s, 2H), 8.04 (s, 1H); IR (KBr, cm^{-1}) 2173, 2139, 1770, 1525, 1327, 1088.

6,7-Diamino-4-chloro-3*H*-isobenzofuran-1-one (6k). To a suspension of **21k** (0.666 g, 2.62 mmol) in EtOH (15 mL), 10% Pd/C (0.080 g) was added and the mixture was stirred under the H_2 (maintained by a balloon) for 18 h. The insoluble material was filtered and washed with EtOAc. The filtrate was removed in vacuo and the residual solid was dried further to give 0.48 g of a mixture of **6k** and 7-amino-4-chloro-6-nitro-3*H*-isobenzofuran-1-one (~3:1 by NMR) as a red powder; ^{1}H NMR ($CDCl_3$) δ 5.14 (s, 2H), 6.88 (s, 1H) and 5.25 (s, 2H), 8.42 (s, 1H).

A solution of the mixture (0.168 g) and $SnCl_2{\cdot}2H_2O$ (0.290 g, 1.29 mmol) in EtOH (5 mL) was refluxed for 45 min. The suspension was cooled to room temperature and poured into water (5 mL). The pH was adjusted to ~7 with 2 M aqueous NaOH (1.5 mL). The suspension was extracted with EtOAc. The combined extract was washed with brine, dried over anhydrous Na_2SO_4 and removed in vacuo to give 0.139 g (73% for two steps) of **6k** as a cream colored powder, mp 172–178 °C. ^{1}H NMR ($CDCl_3$) δ 3.48 (brs, 2H), 4.89 (brs, 2H), 5.14 (s, 2H), 6.88 (s, 1H).

4-Chloro-6,9-dihydro-3*H*-2-oxa-6,9-diaza-cyclopenta[a]-naphthalene-1,7,8-trione (7k). A solution of **6k** (0.130 g, 0.655 mmol) in diethyl oxalate (3 mL) was stirred at

150 °C for 3 h. The suspension was cooled to room temperature and diluted with hexane (15 mL). The solid was collected vacuum filtration and dried in vacuo to give 0.082 g (50%) of crude **7k** as a dark brown powder. A 0.043 g sample was suspended in DMSO (2.5 mL) and heated with a heat gun to a gentle boil. The resulting red solution was allowed to stand overnight at room temperature. The precipitated solid was collected by vacuum filtration, washed with water (5 mL) and dried to give 0.034 g (38%) of pure (purity by HPLC 100%) title compound as a shiny cream powder, mp 342–346 °C. ^{1}H NMR (DMSO-d_6) δ 5.41 (s, 2H), 7.39 (s, 1H). Anal. calcd for $C_{10}H_5ClN_2O_4 \cdot 0.1H_2O$: C, 47.21; H, 2.06; N, 11.01. Found: C, 46.87; H, 1.69; N, 10.93.

Preparation of 26

5-Chloro-2-methoxy-3-nitro-benzonitrile (23). To 15 mL of fuming nitric acid at 0 °C was added portionwise 5-chloro-2-methoxy-benzonitrile (**22**) (2.51 g, 15.0 mmol). After addition, the solution was allowed to stir at 5 °C for 3 h and then it was poured into ice-water (50 g). A pale-yellow solid was collected by filtration and dried to give 3.08 g (97%) of the title compound, mp 97–99 °C. ^{1}H NMR ($CDCl_3$) δ 4.18 (s, 3H), 7.79 (d, J = 2.7 Hz, 1H), 8.01 (d, J = 2.7 Hz, 1H).

(4-Chloro-2-cyano-6-nitro-phenylamino)-acetic acid sodium salt (24). To a stirred solution of **23** (0.319 g, 1.5 mmol) in methanol (5 mL) was added dropwise an aqueous solution of sodium glycinate (0.291 g, 3.0 mmol) in water (3.0 mL) at room temperature. The resulting solution was stirred at 60 °C for 3 h. The suspension was cooled to room temperature and the precipitated yellow solid was filtered, washed with chloroform (20 mL) and dried under vacuum to furnish 0.277 g (67%) of the title compound, mp 220 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 3.84 (s, 2H), 8.08 (d, J = 2.1 Hz, 1H), 8.29 (d, J = 2.1 Hz, 1H), 9.39 (s, 1H).

7-Chloro-2-oxo-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile (25). To a solution of **24** (0.277 g, 1.0 mmol) in 25 mL of water at 70 °C was added 1.4 g (8.0 mmol) of sodium dithionite in five equal portions at an interval of 5 min each. The resulting white suspension was allowed to stir at 70 °C for 1 h. The suspension was cooled to room temperature and the precipitated white solid was filtered and dried under vacuum to furnish 0.125 g (60%) of the title compound, mp 288–290 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 3.88 (s, 2H), 6.80 (s, 1H), 6.86 (d, J = 2.1 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 10.67 (s, 1H).

7-Chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile (26). To a suspension of **25** (50 mg, 0.24 mmol) in CF_3COOH (1.0 mL), fuming nitric acid (84 μL) was added to give a dark red solution. The resulting solution was then stirred overnight at room temperature. The volatiles were removed under vacuum and the residue was diluted with water (9.0 mL). The yellow solid was filtered, washed with water (6.0 mL) and dried under vacuum to furnish 32 mg (60%) of the title compound, mp 338–340 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 7.32 (d, J = 2.1 Hz, 1H), 7.68 (d, J = 2.1 Hz, 1H), 12.18 (s, 1H).

Preparation of 31a

(3-Chloro-2-cyano-6-nitro-phenylamino)-acetic acid sodium salt (28a). To a stirred solution of 2,6-dichloro-3-nitrobenzonitrile (**27a**) (3.935 g, 18.13 mmol) in DMF (25 mL) at 70 °C, an aqueous solution of sodium glycinate (1.760 g, 18.13 mmol) in water (25.0 mL) was added dropwise. The resulting solution was stirred at 70 °C for 48 h. The suspension was cooled to room temperature and the precipitated yellow solid was filtered, washed with chloroform and dried under vacuum to furnish 2.020 g (44%) of the title compound as a yellow powder. ^{1}H NMR (DMSO-d_6) δ 3.89 (d, 2H, J = 3.9 Hz), 6.86 (d, 1H, J = 9.0 Hz), 8.28 (d, 1H, J = 9.3 Hz), 9.57 (s, 1H).

6-Chloro-2-oxo-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile (29a). A suspension of **28a** (2.000 g, 7.824 mmol) and tin (II) chloride dihydrate (6.000 g, 26.59 mmol) in ethanol (40 mL) was refluxed for 30 min. The resulting suspension was cooled to room temperature and the solid was filtered, washed with ethanol and dried under vacuum to give 1.261 g (78%) of the title compound as light yellow solid. ^{1}H NMR (DMSO-d_6) δ 3.67 (s, 1H), 6.72 (d, 1H, J = 8.4 Hz), 6.84 (d, 1H, J = 8.1 Hz), 6.91 (s, 1H), 10.68 (s, 1H).

6-Chloro-7-nitro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile (30a). To a suspension of **29a** (0.300 g, 1.45 mmol) in CF_3COOH (3.0 mL), fuming nitric acid (0.50 mL) was added to give a dark red solution. (Lesser amounts of fuming nitric acid gave a suspension, which gave a mixture of partially oxidized and fully oxidized products.) The resulting solution was then stirred overnight at room temperature. The volatiles were removed under vacuum and the residue was diluted with water (9.0 mL). The yellow solid was filtered, washed with water and dried under vacuum to furnish 0.207 g (54%) of the title compound as yellow powder. ^{1}H NMR (DMSO-d_6) δ 7.95 (s, 1H), 12.38 (s, 1H).

6,7-Dichloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile (31a). A suspension of **30a** (0.100 g, 0.38 mmol) and tin(II) chloride dihydrate (0.508 g, 2.25 mmol) in ethanol (4.0 mL) was refluxed for 24 h. The resulting suspension was then cooled to room temperature and the yellow solid was filtered, washed with ethanol and dried under vacuum to obtain 0.078 g (88%) of 7-amino-6-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile as yellow powder; ^{1}H NMR (DMSO-d_6) δ 5.76 (brs, 2H), 6.82 (s, 1H), 11.69 (s, 1H), 12.03 (s, 1H).

To a stirred solution of 7-amino-6-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile (0.035 g, 0.15 mmol) in concentrated HCl (1.5 mL) at 0 °C, an aqueous solution of $NaNO_2$ (0.060 g, 0.87 mmol) in water (0.20 mL) was added and the resulting turbid mixture was stirred in an ice bath for 2 h. An ice-cold solution of CuCl (0.100 g, 1.01 mmol) in concentrated HCl (1.0 mL) was added while cooling the flask in an ice bath. An instant evolution of N_2 ensued and the resulting dark green suspension was stirred at 0 °C for 2 h. Water (1.0 mL) was added and then the mixture was

stirred overnight at room temperature. To the light green suspension so formed, water (4.0 mL) was added and again the mixture was stirred at room temperature for 1 h. The precipitated solid was filtered, washed with water (2.0 mL) and dried under vacuum to furnish 0.029 g (77%, 96% by HPLC) of the title compound as a cream colored solid, mp 327–335 °C (dec). ^{1}H NMR (DMSO-d_6) δ 7.46 (d, 1H, J = 1.2 Hz), 12.31 (s, 2H). IR (KBr, cm^{-1}): 3574, 3479, 2237, 1737, 1710, 1392, 1271, 1183. HRMS calcd for $C_9H_3Cl_2N_3O_2$: 254.9602. Found: 254.9609.

Preparation of 31b

2 - Chloro - 6 - methyl - 3 - nitrobenzonitrile (27b) and 2-chloro-6-methyl-5-nitrobenzonitrile (27b′). To a solution of 4.70 g (31.0 mmol) of 2-chloro-6-methylbenzonitrile in 30 mL of CF_3CO_2H stirred in ice-bath was added dropwise 2 mL of fuming HNO_3 and the solution was stirred at room temperature overnight. To the solution was added dropwise 2 mL of fuming HNO_3 and the solution was heated at 60 °C for 5 days. The solution was added into 200 mL of ice-water and stirred for 1 h. The precipitate was filtered, washed by water and dried to give 5.5 g of pale-yellow mixture, which was separated by chromatography over silica gel. Elution with 1:20 (200 mL), 3:40 (200 mL), 1:10 (200 mL), 2:10 (200 mL) and 3:10 (500 mL) ethyl acetate/hexane gave 1.61 g of **27b** as white solid, ^{1}H NMR ($CDCl_3$) δ 2.68 (s, 3H), 7.41 (d, 1H, J = 8.5 Hz), 8.01 (d, 1H, J = 8.5 Hz), and 3.80 g of **27b′** as white solid, ^{1}H NMR ($CDCl_3$) δ 2.83 (s, 3H), 7.54 (d, 1H, J = 8.8 Hz), 8.08 (d, 1H, J = 8.8 Hz).

(2-Cyano-3-methyl-6-nitro-phenylamino)-acetic acid sodium salt (28b). To a solution of 810 mg (4.12 mmol) of **27b** in 6 mL of DMF kept at 70 °C was added a solution of 802 mg (6.97 mmol) of sodium glycinate in 5 mL of water. The solution turned yellow and a precipitate was observed. It was heated at 70 °C for 18 h and a TLC showed no more **27b**. The solution was cooled to room temperature and the resulting precipitate was filtered and washed with water (2 mL) and dried to leave 416 mg of crude **28b** as a yellow solid, which was used for the next reaction without further purification.

6-Methyl-2-oxo-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile (29b). A solution of 401 mg (1.70 mmol) of **28b**, 1.41 g (6.24 mmol) of tin(II) chloride dihydrate and 8 mL of absolute alcohol was refluxed for 2 h to give a yellow precipitate. The mixture was cooled to room temperature, filtered and washed with water and dried to leave 149 mg (47%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 1H), 3.84 (s, 1H), 6.52 (d, 1H, J = 7.7 Hz), 6.79 (d, 1H, J = 7.7 Hz), 10.46 (s, 1H).

6-Methyl-7-nitro-2-oxo-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile (30b). To a mixture of 515 mg (2.75 mmol) of **29b** in 6 mL of CF_3CO_2H stirred in an ice bath was added dropwise 2.4 mL of fuming HNO_3. The resulting red solution was stirred in an ice bath for 2 h and at room temperature for 2 days. It was then added to 50 mL of ice-water and the precipitate was allowed to stand at room temperature for 2 days. It was filtered and washed with water and dried to leave 390 mg (57%) of the title compound as a yellow solid, mp > 340 °C. ^{1}H NMR (DMSO-d_6) δ 2.66 (s, 3H), 7.95 (s, 1H), 12.27 (mb, 2H).

7-Chloro-6-methyl-2,3-dioxo-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile (31b). A mixture of 243 mg (0.988 mmol) of **30b**, 972 mg (4.31 mmol) of tin (II) chloride dihydrate and 6 mL of absolute alcohol was refluxed for 20 h. It was cooled to room temperature, filtered and washed by water, dried to leave 202 mg (94%) of 7-amino-6-methyl-2,3-dioxo-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile as a yellow solid, mp > 360 °C. ^{1}H NMR (DMSO-d_6) δ 2.20 (s, 3H), 5.35 (brs, 2H), 6.67 (s, 1H), 11.38 (s, 1H), 11.91 (s, 1H).

To a mixture of 115 mg (0.532 mmol) of 7-amino-6-methyl-2,3-dioxo-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile in 6 mL of 8 N HCl stirred in an ice bath was added dropwise a solution of 78 mg (1.13 mmol) of $NaNO_2$ in 0.5 mL of water and then the mixture was stirred in ice bath for 4 h. The mixture was added dropwise into a mixture of 115 mg of CuCl in 2 mL of concentrated HCl stirred in ice-bath. It was stirred in an ice-bath for 3 h and at room temperature overnight. The mixture was diluted by 4 mL of water, filtered, washed with water and dried to leave 49 mg (39%) of the title compound as a yellow solid, mp > 370 °C. ^{1}H NMR (DMSO-d_6) δ 2.47 (s, 3H), 7.35 (s, 1H), 12.04 (s, 1H), 12.12 (s, 1H). Anal. calcd for $C_{10}H_6ClN_3O_2.H_2O$: C, 47.35; H, 3.17; N, 16.56. Found: C, 46.94; H, 2.62; N, 16.87.

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