# Tricyclic Quinoxalinediones: 5,6-Dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-diones and 6,7-Dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-diones as Potent Antagonists for the Glycine Binding Site of the NMDA Receptor

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A series of tricyclic quinoxalinediones, 5,6–dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-diones and 6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-diones, were synthesized and was evaluated for their affinity for the glycine binding site of the NMDA receptor using a [$^3$H]-5,7-dichlorokynurenic acid binding assay. The six-membered ring-fused tricyclic quinoxalinedione **18g** ($K_i$ = 9.9 nM) displayed high affinity for the glycine site. The anilide derivative **20g** ($K_i$ = 2.6 nM) was 4-fold more potent than **18g** and as potent as L-689,560, one of the most potent glycine antagonists so far prepared. Although the carboxylic acid derivative of the corresponding five-membered ring-fused tricyclic quinoxalinedione **18e** ($K_i$ = 7.3 nM) had affinity comparable to that of **18g**, the anilide derivative **20e** largely decreased in the affinity in contrast to **20g**. Enantiomers **23g**, **24g**, **25g**, and **26g** were prepared and tested. Only the *S* enantiomer **25g** ($K_i$ = 0.96 nM) retained the affinity among the anilide derivatives, whereas both enantiomers **23g** ($K_i$ = 2.3 nM) and **24g** ($K_i$ = 9.6 nM) were active among the carboxylic acid derivatives. The origin of the high affinity of carboxylic acid derivatives such as **18e** and **18g** would be a charge–charge interaction between the anionic carboxylate residues of the compounds and the cationic proton-donor site in the receptor.

## Introduction

Overexcitation of *N*-methyl-D-aspartate (NMDA) receptor-channel complexes on postsynaptic neurons following excessive release of glutamic acid from synaptosomes and glial cells results in a massive $Ca^{2+}$ influx into the neuronal cells, which leads to their death. This is believed to occur under ischemic or hypoxic conditions such as stroke, hypoglycemia, cardiac arrest, and physical trauma.[1] Therefore, an NMDA receptor antagonist might be therapeutically useful because it should minimize damage of the central nervous system induced by ischemic or hypoxic conditions.[2] The NMDA receptor-channel complex consists of at least three binding domains including glutamic acid (or NMDA) recognition site, channel blocker binding site, and strychinine-insensitive glycine binding site, as confirmed by recent cloning studies.[3] Physiologically, a blockade of at least one of these sites terminates the channel opening of the NMDA receptor to prevent a $Ca^{2+}$ influx. However, several researchers have demonstrated that a compound that acts as a glycine site antagonist might be superior to competitive NMDA antagonists and channel blockers from the perspective of the therapeutic index.[4] Immediately after the discovery of the glycine binding site,[5] three structurally distict antagonists of this site were identified, including kynurenic acids such as **1a**,**b**,[6] indole-2-carboxylic acids such as **2a**,**b**,[7] and quinoxalinediones such as **3a**,**b**.[8] The former two molecules have been extensively modified by several laboratories,[9–11] and antagonists with strong affinity for the glycine site such as **4** (L-689,560)[12] and **5**[13] have been synthesized (Chart 1). However, these antagonists have, unfortunately, shown very weak *in vivo* activities because of their poor blood–brain barrier penetration.[11f,30] On the other hand, a few studies on the development of quinoxalinedione-based glycine antagonists have been reported,[14] although it may have a chance to show *in vivo* activities, since the quinozalinedione-based non-NMDA receptor antagonists, NBQX (6-nitro-7-sulfamoylbenzo[*f*]quinoxaline-2,3-dione) and YM-90K (6-(1*H*-imidazol-1-yl)-7-nitro-2,3(1*H*,4*H*)-quinoxalinedione hydrochloride) are indeed active under systemic administration.[15] Therefore, we synthesized NMDA–glycine antagonists by modifying the quinoxalinedione structure.

According to the known pharmacophore of the glycine antagonist-recognition site,[6c,13] it appeared that there is a lipophilic space in the northern region of the quinoxalinedione molecule which can be occupied by an additional hydrophobic ring system. In this paper, we report a series of novel tricyclic quinoxalinediones, 6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-diones and 5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-diones and describe their properties as NMDA–glycine antagonists. Many known glycine antagonists such as **1b**, **2b**, **3b**, **4**, and **5** have a chlorine atom in the southwestern part of the molecule, and it seems to be crucial for maximizing the affinity. However, during our preliminary study, we found that 6,7-dibromoquinoxaline-2,3-dione slightly

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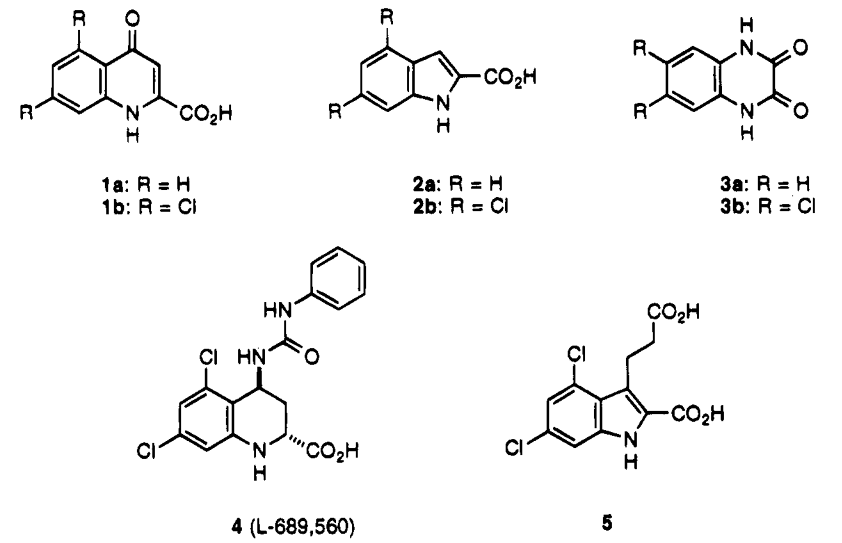
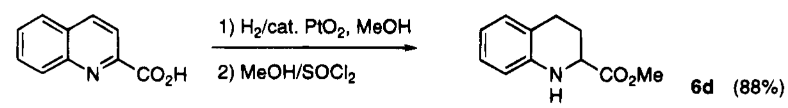
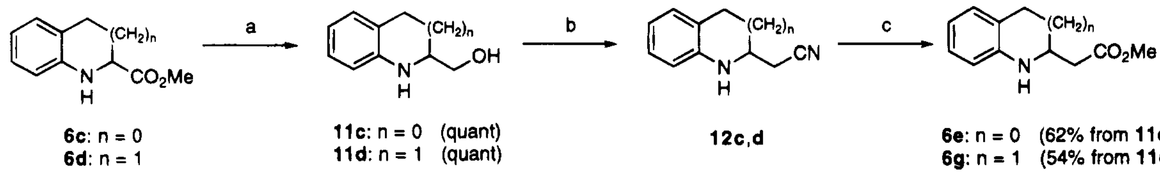
**Chart 1**




**Scheme 1**

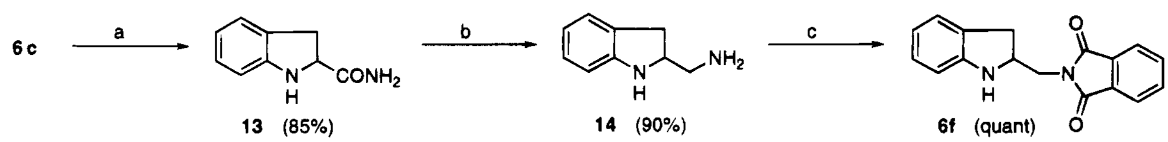



**Scheme 2**[a]




[a] Conditions: (a) $LiAlH_4$, THF; (b) (1) $I_2/PPh_3$/imidazole, toluene/acetonitrile, (2) NaCN, DMF; (c) (1) 12 N HCl, (2) $MeOH/SOCl_2$.

**Scheme 3**[a]



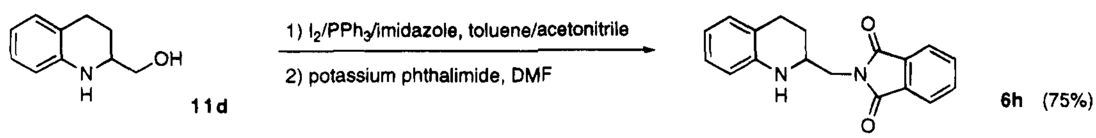

[a]Conditions: (a) $NH_3$, MeOH; (b) $LiAlH_4$, THF; (c) phthalic anhydride, toluene.

improved the affinity for the glycine site compared with 6,7-dichloroquinoxaline-2,3-dione (**3b**).[16] Therefore, in all compounds of this series, a bromine atom instead of a chlorine atom was substituted in the crucial southwestern position.

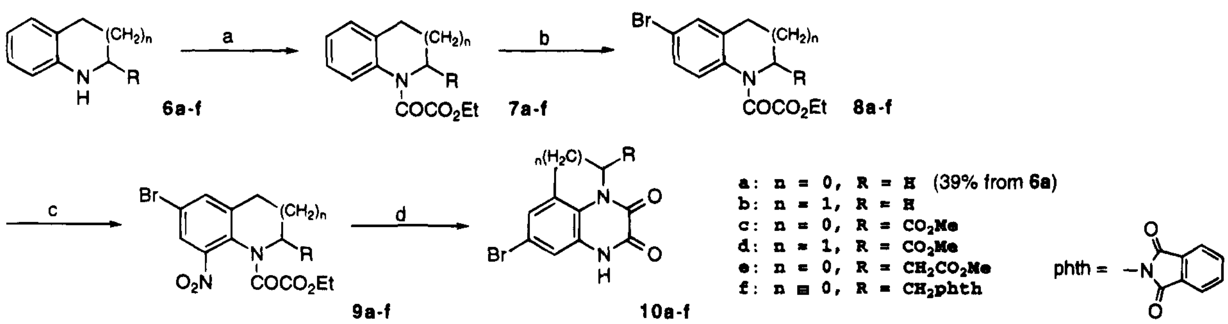
## Synthesis

Starting materials **6d**–**h** were prepared as outlined in Scheme 1–4. Methyl tetrahydroquinoline-2-carboxylate (**6d**) was prepared by hydrogenation of quinaldinic acid in methanol over platinum oxide at ambient temperature under normal pressure of hydrogen followed by methylation with thionyl chloride in methanol (Scheme 1). Methyl ester **6d** was reduced to the corresponding alcohol **11d** with lithium aluminum hydride in quantitative yield. Intermediary crude iodide generated by treatment of **11d** with triphenylphosphine–iodine–imidazole in a mixed solvent of 4:1 toluene/acetonitrile was then reacted with excess sodium cyanide in DMF at 80 °C to give cyanide **12d**. Hydrolysis of **12d** in refluxing 12 N hydrochloric acid followed by methylation with methanol–thionyl chloride afforded **6e** in 54% yield from **11d**. A similar sequence was followed using commercially available **6c** to give **6g** via **11c** and **12c** (Scheme 2). To prepare the phthalimide derivative **6f**, at first, methyl ester **6c** was converted to the corresponding amide **13** by reaction with methanolic ammonia, which was reduced with lithium aluminum hydride in refluxing THF to provide amine **14**. Condensation of **14** with phthalic anhydride in toluene under the azeotropic conditions gave **6f** (Scheme 3). More conveniently, analogous phthalimide **6h** was prepared from alcohol **11d** by iodination with triphenylphosphine–iodine–imidazole followed by condensation with potassium phthalimide in DMF (Scheme 4). Tricyclic quinoxalinediones **10a**–**f** were synthesized as outlined in Scheme 5. Indolines and tetrahydroquinolines **6a**–**f** were acylated with ethyl chloroglyoxalate to give **7a**–**f** which were then brominated by using bromine in methylene chloride in the presence of Fe powder to provide **8a**–**f**. Nitration of **8a**–**f** with isopropyl nitrate in concentrated sulfuric acid followed by purification with silica gel column chromatography gave rise to **9a**–**f**. Reductive ring closure of **9a**–**f** leading to tricyclic quinoxalinediones **10a**–**f** were effected by aqueous titanium trichloride at 0 °C to ambient tem-

**Scheme 4**

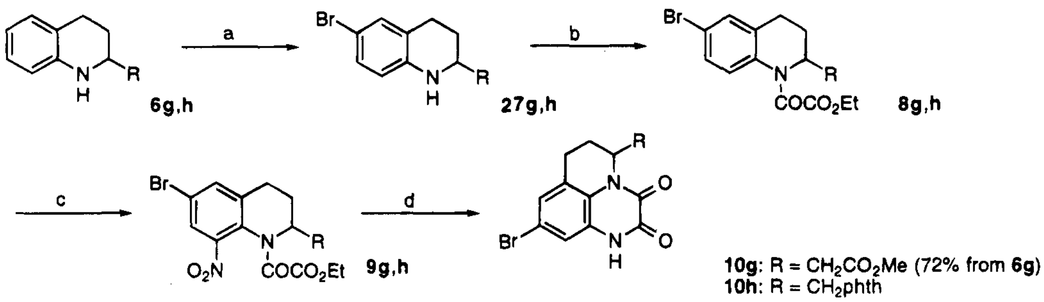



**Scheme 5**[a]



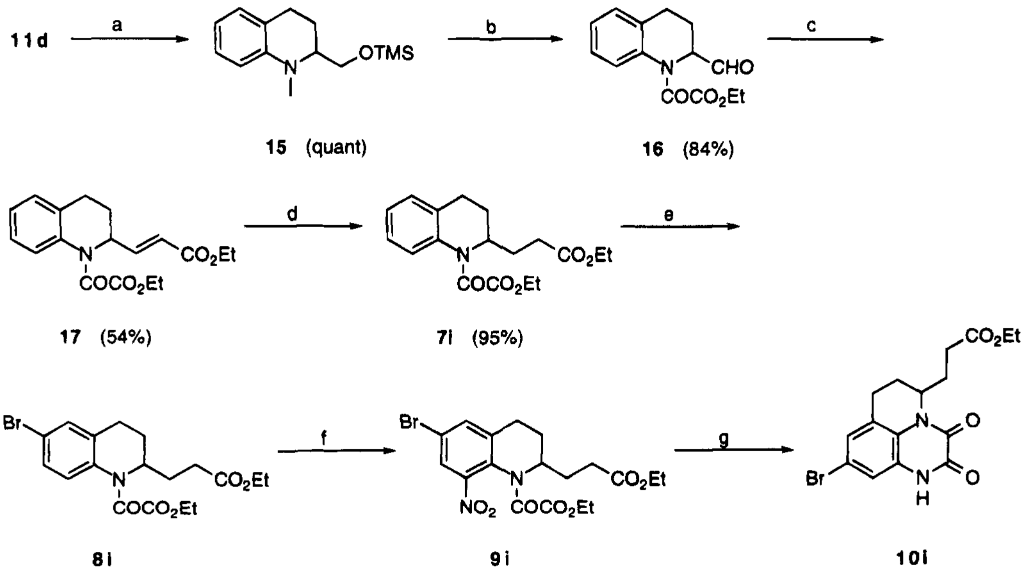

[a] Conditions: (a) $ClCOCO_2Et/NEt_3$, $CH_2Cl_2$; (b) $Br_2$/cat. Fe, $CH_2Cl_2$; (c) isopropyl nitrate, concentrated $H_2SO_4$; (d) $TiCl_3$, $H_2O$/THF.

**Scheme 6**[a]




[a] Conditions: (a) NBS, DMF; (b) $ClCOCO_2Et/NEt_3$, $CH_2Cl_2$; (c) $NO_2^+BF_4^-$, $CH_2Cl_2$; (d) $TiCl_3$; $H_2O$/acetone.

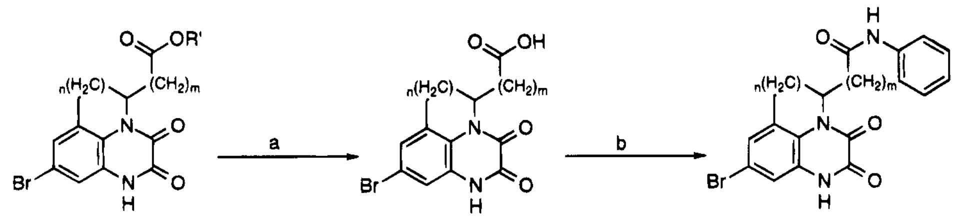
**Scheme 7**[a]




[a] Conditions: (a) TMSCl/$ClCOCO_2Et/NEt_3$, $CH_2Cl_2$; (b) Dess–Martin periodinane/$CF_3CO_2H$, $CH_2Cl_2$; (c) $EtOCOCH_2PO(OEt)_2$-*t*BuOK, THF; (d) $H_2$/Pd–C, EtOH; (e) $Br_2$/cat. Fe, $CH_2Cl_2$; (f) isopropyl nitrate, concentrated $H_2SO_4$; (g) $TiCl_3$, $H_2O$/THF.

perature.[17] We required a large quantity of **10g** and **10h** during the study, and therefore, the synthetic route of these compounds, especially **10g**, was optimized as outlined in Scheme 6. Tetrahydroquinoline **6g** was at first brominated with *N*-bromosuccinimide in DMF at 0 °C selectively at the C-6 position to give **27g**. Acylation of **27g** with ethyl chloroglyoxalate led to **8g** followed by nitration with nitronium tetrafluoroborate in dichloromethane at ambient temperature to afford **9g** in a regiospecific manner. A similar reductive ring closure with aqueous titanium trichloride in a mixed solvent of acetone and water at 0 °C to ambient temperature provided **10g** in 72% overall yield from **6g**. Similarly, **10h** was prepared from **6h**. The tricyclic quinoxlainedione **10i** was synthesized from **11d** as illustrated in Scheme 7. Alcohol **11d** was at first treated with trimethylsilyl chloride in dichloromethane in the presence of excess triethylamine followed by addition of ethyl

**Scheme 8**[a]



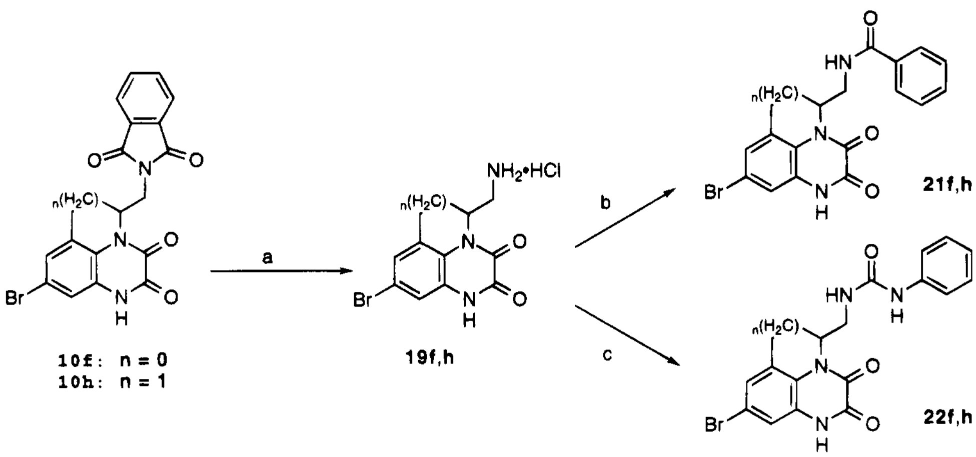
10c: R = Me, n = 0, m = 0
10d: R = Me, n = 1, m = 0
10e: R = Me, n = 0, m = 1
10g: R = Me, n = 1, m = 1
10i: R = Et, n = 1, m = 2

18c,d,e,g,i

20c,d,e,g,i

[a]Conditions: (a) 1 N NaOH, MeOH-THF; (b) $PhNH_2$, WSC-HOBt, DMF.

**Scheme 9**[a]



10f: n = 0
10h: n = 1

19f,h

21f,h

22f,h

[a] Conditions: (a) 12 N HCl, AcOH; (b) $PhCO_2H$, WSC−HOBt, DMF, $NEt_3$; (c) PhNCO, $NEt_3$, DMF.

chloroglyoxalate to give **15**. Direct oxidation of **15** into aldehyde **16** was effected by Dess−Martin periodinane in dichloromethane in the presence of trifluoroacetic acid.[18] A Wittig−Honor−Emmons reaction of aldehyde **16** with (diethylphosphono)acetic acid diethyl ester in THF in the presence of potassium *tert*-butoxide afforded **17**, which was then hydrogenated over palladium on carbon in ethanol at ambient temperature under atmospheric pressure to give **7i**. By the route outlined in Scheme 5, **7i** was transformed into tricyclic quinoxalinedione **10i** via **8i** and **9i**. Schemes 8 and 9 illustrate the synthesis of tricyclic quinoxalinediones evaluated for biological activities. Hydrolysis of **10c−e,g,i** with 1 N aqueous sodium hydroxide in a mixture of methanol and THF provided the corresponding carboxylic acids **18c−e,g,i**, respectively. Condensation of carboxylates **18c,d,g,i,e** with aniline by using a combination of 1-ethyl-3-[3′-(dimethylamino)propyl]carboximide and hydroxybenztriazole in DMF gave anilides **20c,d,g,i,e**, respectively. Hydrolysis of phthalimides **10f** and **10h** was achieved by treatment with 12 N hydrochloric acid in acetic acid under reflux to afford amines **19f** and **19h**, respectively. Anilides **21f** and **21h** were obtained by the similar condensation of **19f** and **19h**, respectively, with benzoic acid. Treating **19f** and **19h** with phenyl isocyanate in DMF in the presence of triethylamine provided **22f** and **22h**. *S* isomers **23g** and **25g** and *R* isomers **24g** and **26g** were prepared starting with (*S*)-2-(methoxycarbonyl)tetrahydroquinoline (**31g**)[19a,b] ($[\alpha]_D = +41.4°$, $c = 1$ in $CHCl_3$, lit.[19a] $[\alpha]_D = +41°$) and (*R*)-2-(methoxycarbonyl)tetrahydroquinoline (**29g**)[19a,b] ($[\alpha]_D = -42.4°$, $c = 1$ in $CHCl_3$, lit.[19a] $[\alpha]_D = -44°$), respectively, without loss of the optical purity according to the procedure described for the corresponding racemic compounds as shown in Scheme 10. The optical purity of the corresponding methyl esters **28g** and **30g** was determined to be 95.7 and 96.5%, respectively, by HPLC analysis using a chiral column (Daicel Chiralpack AD, EtOH as an eluent).

## Pharmacology

The affinity of compounds for the glycine binding site was evaluated by inhibition of [$^3$H]-5,7-dichlorokynurenic acid ([$^3$H]DCKA) binding to rat brain synaptic membrane preparation.[20] The $K_i$ values were calculated according to the general equation: $K_i = IC_{50}/(1 + [L]/K_d)$, where [L] is the concentration of the radio ligand and $K_d$ is the dissociation constant of the radio ligand. In this study, the concentration of [$^3$H]DCKA was always 10 nM, and the dissociation constant of [$^3$H]DCKA ($K_d$ = 27.5 nM) was used.[20] The $IC_{50}$ value, which represents the concentration of the compound required to give 50% inhibition of the radioligand binding, was measured in more than three independent experiments. Full details of this assay have been reported by some of us.[20] The selectivity of **18g** and **20g** was determined by similar binding assays using [$^3$H]CGP-39653[21] for the glutamic acid binding site of the NMDA receptor, and [$^3$H]AMPA[22] and [$^3$H]kainic acid[23] for the non-NMDA receptors. The functional antagonism of the selected compounds for the NMDA receptor was determined by inhibition of [$^3$H]MK-801 binding to the membrane preparation in the presence of the test compound and glutamic acid under the incubation period of 18 h at 30 °C.[24] The prolonged incubation time is necessary for complete equilibrium of MK-801 binding and important for assessing the antagonism. The *in vivo* antagonism of the selected compounds for the NMDA receptor was

**Scheme 10**

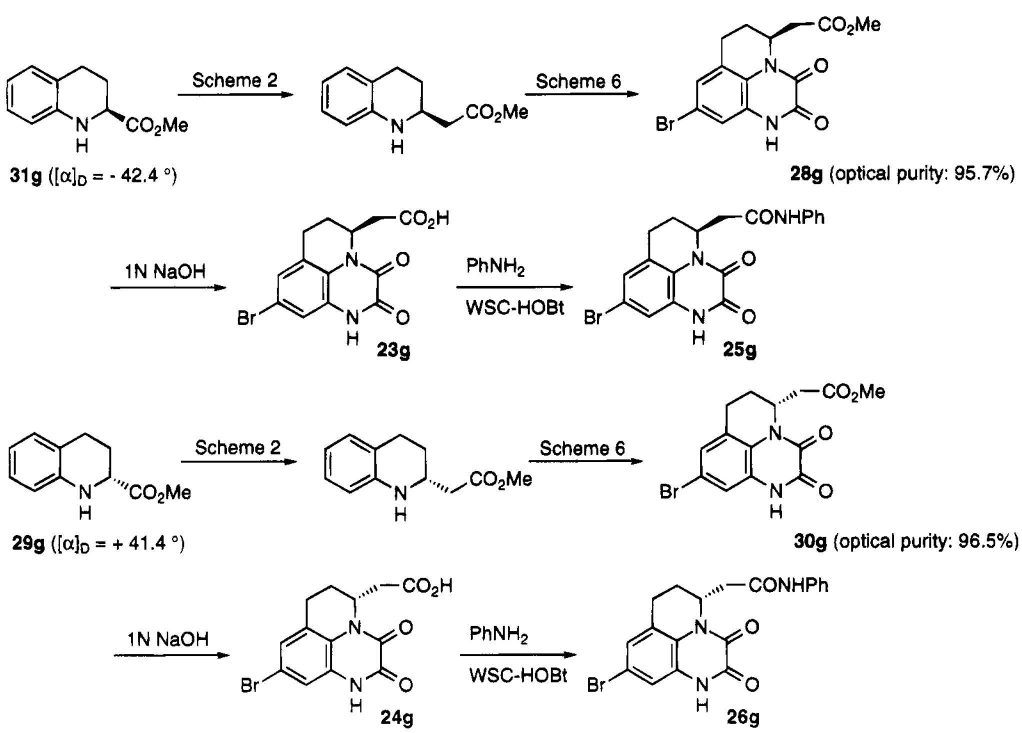
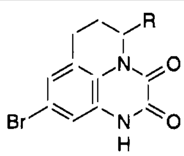
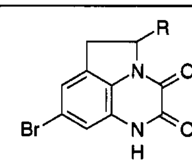



**Table 1.** The Affinity for the Glycine Binding Site[a]





| compd | R = | $K_i$ (nM) vs [$^3$H]DCKA[b] | compd | R = | $K_i$ (nM) vs [$^3$H]DCKA[b] |
|---|---|---|---|---|---|
| **10b** | H | 710 ± 130 | **10a** | H | >3000 |
| **18d** | $CO_2H$ | 30 ± 2.2 | **18c** | $CO_2H$ | >3000 |
| **18g** | $CH_2CO_2H$ | 9.9 ± 0.5 | **18e** | $CH_2CO_2H$ | 7.3 ± 1.9 |
| **18i** | $CH_2CH_2CO_2H$ | 38 ± 5.4 | | | |
| **20d** | CONHPh | 2100 ± 740 | **20c** | CONHPh | 930 ± 310 |
| **20g** | $CH_2CONHPh$ | 2.6 ± 0.6 | **20e** | $CH_2CONHPh$ | 170 ± 18 |
| **20i** | $CH_2CH_2CONHPh$ | 320 ± 51 | | | |
| **21h** | $CH_2NHCOPh$ | 190 ± 9.6 | **21f** | $CH_2NHCOPh$ | >2000 |
| **22h** | $CH_2NHCONHPh$ | 480 ± 260 | **22f** | $CH_2NHCONHPh$ | 430 ± 210 |

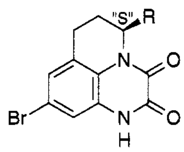
[a] See ref 20 and the text for detail assay procedures. [b] DCKA: 5,7-dichlorokynurenic acid (**1b**).

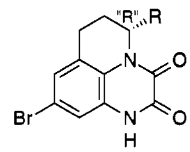
evaluated by using the NMDA-induced seizure model.[25] Namely, the compound was given intraperitoneally to the group of 10 mice, 30 min prior to the intracerebroventricular administration of NMDA (5 nmol). In the absence of the test compound, all the mice exhibit tonic seizure. The mice which did not exhibit tonic seizure after intracerebroventricular (icv) administration of NMDA were considered to be protected. The $ED_{50}$ value represents the dose causing protection from tonic seizure in 50% of the mice.

## Results and Discussion

Tables 1 and 2 summarizes the affinities of the tricyclic quinoxalinediones for the NMDA–glycine binding site by using [$^3$H]DCKA binding inhibition assay. The basic six-memberd ring-fused tricyclic quinoxalinedione **10b** ($K_i$ = 710 nM) had appreciable affinity. As expected, a hydrophobic fused-ring system at the northern region of the parent quinoxalinedione was well-tolerated. Introduction of a carboxylate residue at the C-5 position of **10b** gave **18d**, which drastically improved the affinity ($K_i$ = 30 nM). The enhanced affinity arose from the new interaction between the anionic carboxylate residue and a proton-donor site in the receptor, and this affinity exceeded that of DCQX (**3b**, $K_i$ = 160 nM), a standard quinoxalinedione-based glycine antagonist. Insertion of a methylene group between the C-5 carbon and the carboxylate group of **18d** provided **18g**, which had enhanced affinity ($K_i$ = 9.9 nM). Further homologation of the side chain led to **18i**, which, however, significantly reduced the affinity ($K_i$ = 38 nM). Leeson et al. have discovered that aromatic amide and urea derivatives of 4-amino-5,7-dichloroetetrahydroquinoline-2-carboxylic acid, typically exemplified by L-689,560, **4**,[12] have a nanomolar order of affinity for the glycine binding site. The anilide derivative **20d** ($K_i$ = 2100 nM) was less active than the corresponding carboxylic acid **18d**. However, anilide **20g** ($K_i$ = 2.6 nM) was indeed 4-fold more potent than **18g** and almost as potent as L-689,560, **4** ($K_i$ = 2.0 nM). To examine the effect of the anilide residue more precisely, benzoyl amide **21h** and phenylurea **22h** were prepared. Benzoyl amide **21h** ($K_i$ = 190 nM) significantly reduced the affinity compared to **20g**, and the

**Table 2.** The Affinity for the Glycine Binding Site of Optically Active Tricyclic Quinoxalinediones and Reference Samples[a]





| compd | R = | $K_i$ (nM) vs [$^3$H]DCKA | compd | R = | $K_i$ (nM) vs [$^3$H]DCKA |
|---|---|---|---|---|---|
| **23g** | $CH_2CO_2H$ | 2.3 ± 0.48 | **24g** | $CH_2CO_2H$ | 9.6 ± 2.8 |
| **25g** | $CH_2CONHPh$ | 0.96 ± 0.19 | **26g** | $CH_2CONHPh$ | 82 ± 16 |
| compd | | $K_i$ (nM) vs [$^3$H] DCKA[b] | compd | | $K_i$ (nM) vs [$^3$H] DCKA[b] |
| glycine | $H_2NCH_2CO_2H$ | 170 ± 30[c] | **1b** | DCKA | 40 ± 10[c] |
| **3b** | DCQX | 160 ± 40[c] | **4** | L-689,560 | 2.0 ± 0.3[c] |

affinity of **22h** ($K_i$ = 480 nM) was 3-fold weaker than that of **21h**, suggesting that the positions of both the carbonyl group and the phenyl ring are critical for attaining high affinity. Along these lines, the anilide **20i** ($K_i$ = 320 nM) displayed relatively poor affinity. On the other hand, the five-membered ring-fused tricyclic quinoxalinedione **10a** ($K_i$ > 3000 nM) is less active than the corresponding six-membered ring analog **10b**, indicating that hydrophobic interaction of **10a** with the receptor would not be as strong as that of **10b**. Therefore, the carboxylic acid **18c** ($K_i$ = 83 nM) was somewhat less active than the corresponding six-membered ring analog **18d**, and the affinity of anilide **20c** ($K_i$ = 930 nM) was also not very high. Carboxylic acid **18e** ($K_i$ = 7.3 nM), however, showed comparable affinity to the corresponding six-membered ring analog **18g**, probably due to the strong interaction between the anionic carboxylate group of **18e** and the proton-donor site in the receptor. In contrast to the case of six-membered ring analog **20g**, anilide **20e** ($K_i$ = 170 nM) drastically reduced the affinity, suggesting that the phenyl ring would disturb the correct interaction of the molecule with the receptor. Similarly, amide **21f** ($K_i$ > 2200 nM) as well as urea **22f** ($K_i$ = 430 nM) did not have appreciable affinity. Both enantiomers **23g**, **24g**, **25g**, and **26g** were synthesized starting from optically active methyl tetrahydroquinoline-2-carboxylate according to the route outlined in Scheme 10, and their affinity was tested. Only anilide *S* isomer **25g** ($K_i$ = 0.96 nM) retained the affinity, in agreement with the result of Leeson et al,[12] and this is one of the most active ligands for the NMDA–glycine binding site so far reported. Interstingly, both enantiomers **23g** ($K_i$ = 2.3 nM) and **24g** ($K_i$ = 9.6 nM) were active among carboxylic acid derivatives.

The series of the present tricyclic quinoxalinediones can be divided into two groups. The first group includes compounds having a phenyl ring and an amido or ureido carbonyl at the C-5 side chain such as **20c–e,g,i**, **21h,f**, and **22h,f**, which are non-ionizable at physiological pH. The second group includes compounds having an anionic carboxylate group such as **18c,d,e,g,i**. Both groups provide compounds with nanomolar orders of affinity (**20g** for the first group, **18e** and **18g** for the second group). The affinity of the compounds in the first group changes drastically with subtle structural alterations. For example, just one carbon contraction from **20g** to **20d** and elongation from **20g** to **20i** resulted in 1000- and 100-fold decreases in the affinity, respectively. Conversion from the six-membered ring analog **20g** to the five-membered ring analog **20e** reduced the affinity by 2 orders of magnitude. Simply changing from anilide **20g** to benzamide **2h** again produced a 100-fold decrease in the affinity. Thus, the origin which provides the high affinity to **20g** consists of a combination both of a hydrogen-bonding interaction of the amido carbonyl and of a hydrophorbic interaction of the phenyl ring, which strictly requires conformational restriction. Consequently, only the *S* isomer **25g** retained the affinity. Energy-minimized conformations of **20g** (or **25g**), the most potent tricyclic quinoxalinedione in this series, were generated using a 1000-step Monte Carlo comformational search[28] with AMBER and GB/SA (water)[27] of MacroModel (version 3.5)[26] as shown in Figure 1. The side chain of **20g** was pseudoaxial in the global energy-minimized conformation, and this energy level was 5.7 kcal/mol lower than that of the pseudoeuqatorial conformation. The pseudoaxial conformation was also predicted from $^1$H NMR analysis of **20g**, where the coupling constants, $J[H_5-H_6ax]$ and $J[H_5-H_6eq]$ exhibited 5.5 and 2.5 Hz, respectively, as determined by decoupling experiments. A similar molecular shape has been reported for L-689,560,[12] and this would be important for gaining high affinity for the glycine binding site. However, unlike L-689,560, **20g** is scarcely ionized at physiological pH, since the $pK_a$ value of **20g** was measured to be 8.6–8.7. The cationic recognition site in the receptor which strongly binds the C-2 carboxylate anion of L-689,560 would interact also with the neutral C-2,3 dione group of **20g** to a similar extent. It is noteworthy that **20g** (or **25g**) is the first example, to our knowledge, that a nearly non-ionizable compound at physiological pH exhibited high affinity for the NMDA–glycine binding site. On the other hand, the affinities of the compounds in the second group are not very sensitive to structural changes. For example, the five-membered ring analog **18e** was as potent as the six-membered ring analog **18g**. One carbon contraction from **18g** to **18d** and one carbon elongation from **18g** to **18i** resulted in only 3- and 4-fold decreases in the affinity, respectively. Thus, the origin that provides the high affinities to **18g** and **18e** might consist of a strong charge–charge interaction of the anionic carboxylic residue at the C-5 side chain with the cationic proton-donor site in the receptor rather than a simple hydrogen-bonding interaction. Usually, the distance between a negative and a positive charge where a strong interaction can be formed would be much broader than the hydrogen bond length in a strong hydrogen-bonding interaction. This should reasonably explain why all of compounds in the second group showed good to high affinity despite their structural variance. Although we cannot conclude whether the carboxylate residues both of *S* isomer **23g** and of *R* isomer **24g** interact with the

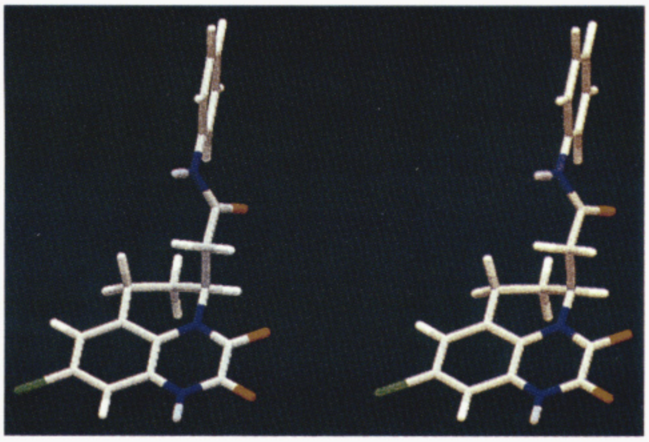


**Figure 1.** The global energy minimized conformation of **20g** (**25g**).

**Table 3.** Selectivities for Various Glutamate Receptor Subtypes[a]

| compd | IC$_{50}$ (nM)[b] vs [$^3$H]CGP-39653[c] | vs [$^3$H]AMPA[d] | vs [$^3$H]kainic acid |
|---|---|---|---|
| **18g** | >30 000 | 4600 ± 800 | >30 000 |
| **20g** | >25 000 | 4600 ± 920 | >25 000 |

[a] See refs 21–23 for detail assay procedures. [b] The values were determined from more than three independent experiments. [c] CGP-39653: (*E*)-2-amino-4-propyl-5-phosphono-3-pentenoic acid. [d] AMPA: 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid.

same cationic proton-donor site of the receptor, it is noteworthy that at least a negative steric interaction between the side chain of *R* isomer **24g** and the receptor would not be present, whereas a negative interaction was evident in the anilide *R* isomer **26g** in the first group. Thus, the properties of compounds in the second group were considerably different from those in the first group. A recent study[29] has demonstrated that [$^3$H]-DCKA binds only to the NR-1a subunit, which is the essential component for producing the NMDA receptor-channel function among the subunits of the heterooligomeric NMDA receptor-channel complex. Since compounds both in the first and second groups uniformly inhibited [$^3$H]DCKA binding to the membrane preparations, the compounds in both groups might bind to the same single protein, the NR-1 subunit, despite differences among their properties. In addition, the C-5 side chains of the compounds in the first and second groups both will bind to the same region in the same receptor, the NR-1 subunit.

The affinities of **18g** and **20g** for the glutamic acid binding site of the NMDA receptor as well as for the non-NMDA receptors were examined by the binding assays using [$^3$H]CGP-39653, [$^3$H]AMPA, and [$^3$H]kainic acid as radioligands. The tricyclic quinoxalinediones **18g** and **20g** have little affinity for the glutamic acid binding site of the NMDA receptor and the kainic acid receptor subtype of the non-NMDA receptors but showed weak affinities for the AMPA receptor subtype of the non-NMDA receptors, as shown in Table 3. The selectivities for the glycine binding site against the AMPA receptor were estimated to be 100-fold for **18g** and 1000-fold for **20g**. Finally, **18g** and **20g** inhibited the binding of [$^3$H]MK-801 to the membrane preparation with IC$_{50}$ values of 4.1 and 1.7 $\mu$M, respectively, under complete equilibrium conditions, and this is evidence that a series of these tricyclic quinoxalinediones would exhibit functional antagonism against the channel opening of the NMDA receptor-channel complex.

Preliminarily, the *in vivo* activities of the tricyclic quinoxalinediones were evaluated using an NMDA-induced seizure model. Although anilide **20g** exhibited poor activity (ED$_{50}$ > 100 mg/kg ip) probably because of its low solubility in water, the carboxylic acid **18g** and *S* isomer **23g** encouragingly inhibited NMDA-induced seizures with moderate activity (ED$_{50}$ = 64 and 26 mg/kg ip, respectively, 30 min prior to NMDA administrations). This *in vivo* activity might result from the modification of the quinoxalinedione skeletone as anticipated, because under these conditions, we confirmed that neither 5,7-dichlorokynurenic acid (**1**), 4,6-dichloroindole-2-carboxylic acid (**5**), nor L-689,560 (**4**) showed more than 50% inhibition against the seizures at doses of 100 mg/kg.

Thus, we successfully generated a novel series of tricyclic quinoxalinediones as potent and selective NMDA-glycine antagonists. Among them, the carboxylic acid derivatives **18e**,**g** and the non-ionizable anilide derivative **20g** had affinity in the nanomolar order. The origin of the high affinities of **18e** and **18g** would be a charge–charge interaction between the anionic carboxylate residues of the compounds and the cationic proton-donor site in the receptor. Anilide **20g** would also bind to the same receptor. With respect to the stereochemical requirement, the anilide *S* isomer **25g** ($K_i$ = 0.96 nM) was recognized by the glycine binding site of the NMDA receptor and is a class of compounds with the highest affinity for the NMDA–glycine binding site known to date. Interestingly, both enantiomers of the carboxylic acid derivatives **23g** ($K_i$ = 2.3 nM) and **24g** ($K_i$ = 9.6 nM) were active. Further modifications of these molecules to improve the *in vivo* activities and the pharmacological evaluations are in progress. The results will be published elsewhere.

## Experimental Section

Melting points were measured on either a Thomas-Hoover or a Yanaco melting point apparatus and were uncorrected. $^1$H NMR spectra were recorded on a JEOL GX-270 spectrometer using tetramethylsilane as an internal standard. Low-resolution mass spectra were obtained on DF/GC/MS M-80 mass spectrometer. Optical rotation was measured on a JASCO DIP-370. Elemental analyses and high resolution mass spectra were obtained from Sumitomo Analytical Center, Inc. Thin-layer chromatography and flash column chromatography was performed on silica gel glass-backed plates (5719, Merck & Co.) and silica gel 60 (230–400 or 70–230 mesh, Merck & Co.), respectively. Optical purity was determined by HPLC using Hitachi L 4000 pump and L 6000 UV detector with a chiral column (Chiralpack AD, Daicel).

**2-(Methoxycarbonyl)tetrahydroquinoline (6d) Hydrochloride.** Quinaldinic acid (100 g, 577 mmol) in methanol (600 mL) was hydrogenated over platinum oxide (3 g) under an atmospheric pressure of hydrogen at ambient temperature until the theoretical amount of hydrogen was consumed. The mixture was filtered through Celite, and to the filtrate was added dropwise thionyl chloride (63 mL, 836 mmol) at 0 °C. The mixture was stirred overnight at ambient temperture and concentrated *in vacuo*. The residue was rinsed with acetone to give 116 g of the title compound (88%): mp 152–154 °C; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 8.46 (br, 2 H), 6.96 (t, 1 H, $J$ = 8.1 Hz), 6.92 (d, 1 H, $J$ = 8.1 Hz), 6.71 (d, 1 H, $J$ = 8.1 Hz), 6.61 (t, 1 H, $J$ = 8.1 Hz), 4.16 (t, 1 H, $J$ = 5.4 Hz), 3.68 (s, 3 H), 2.52–2.80 (m, 2 H), 2.00–2.10 (m, 2 H). The hydrochloride was dissolved in water, and excess saturated sodium bicarbonate was added. The mixture was extracted with ethyl acetate, dried over magnesium sulfate, and concentrated *in vacuo* to give free 2-(methoxycarbonyl)tetrahydroquinoline: MS *m/e* 191 ($M^+$).

**2-(Hydroxymethyl)indoline (11c).** To a suspension of $LiAlH_4$ (4.65 g, 0.122 mol) in THF (100 mL) was added dropwise 2-(methoxycarbonyl)indoline (10.85 g, 0.0613 mol) in THF (260 mL) at room temperature. The mixture was refluxed for 3.5 h, and then excess reagent was decomposed by addition of aqueous THF. To the mixture was added 1 N aqueous NaOH (50 mL), water (100 mL), and diethyl ether (100 mL), successively. The organic layer was separated, washed with brine, dried over magnesium sulfate, and concentrated to give 8.77 g of 2-(hydroxymethyl)indoline (96%): MS *m/e* 149 ($M^+$), $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.08 (d, 1 H, $J$ = 7 Hz), 7.02 (t, 1 H, $J$ = 7 Hz), 6.71 (t, 1 H, $J$ = 7 Hz), 6.64 (d, 1 H, $J$ = 7 Hz), 4.02 (m, 1 H), 3.70 (dd, 1 H, $J$ = 11, 4 Hz), 3.56 (dd, 1 H, $J$ = 11, 7 Hz), 3.09 (dd, 1 H, $J$ = 16, 9 Hz), 2.81 (dd, 1 H, $J$ = 16, 8 Hz).

**2-(Cyanomethyl)indoline (12c).** To a mixture of 2-(hydroxymethyl)indoline (7.77 g, 52.08 mmol), imidazole (8.86 g, 130.2 mmol), and triphenylphosphine (34.15 g, 130.2 mmol) in toluene (500 mL) was added iodine (26.44 g, 104.16 mmol) in acetonitrile (100 mL) at 0 °C. The mixture was stirred for 10 min, and water was added. The organic layer was separated, washed with brine, dried over magnesium sulfate, and concentrated. The residue was triturated with diethyl ether, and insoluble solids were removed by filtration. The filtrate was concentrated to give crude 2-(iodomethyl)indoline. The crude 2-(iodomethyl)indoline was dissolved in DMF (130 mL), and KCN (4.07 g, 62.5 mmol) was added. The mixture was heated at 80 °C for 12 h, and after addition of KCN (4.07 g), the heating was further continued for 5 h. The mixture was poured into saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography with 3:1 to 2:1 hexane/ethyl acetate to give 3.04 g of 2-(cyanomethyl)indoline (37%): MS *m/e* 158 ($M^+$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.03 (m, 2 H), 6.77 (t, 1 H, $J$ = 7 Hz), 6.54 (t, 1 H, $J$ = 7 Hz), 4.42 (m, 1 H), 4.13 (bs, 1 H), 3.07 (m, 1 H), 2.81 (dt, 1 H, $J$ = 16, 4 Hz), 2.22 (m, 2 H).

**2-[(Methoxycarbonyl)methyl]indoline (6e).** A solution of 2-(cyanomethyl)indoline (2.95 g, 18.65 mmol) in concentrated HCl (15 mL) was refluxed for 1 h, and the mixture was concentrated *in vacuo*. The residue was dissolved in methanol (50 mL), and thionyl chloride (2.5 mL, 33.99 mmol) was added slowly at 0 °C. The mixture was heated at 50 °C for 2.5 h, and the solvent was concentrated *in vacuo*. The residue was dispersed between ethyl acetate and saturated aqueous sodium bicarbonate and the organic layer was separated, washed with brine, dried over magnesium sulfate, and concentrated to give 2.22 g of 2-[(methoxycarbonyl)methyl]indoline (62%): $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 6.99 (t, 1 H, $J$ = 7.6 Hz), 6.95 (d, 1 H, $J$ = 7.6 Hz), 6.64 (td, 1 H, $J$ = 7.6, 1 Hz), 6.58 (d, 1 H, $J$ = 7.6 Hz), 4.35 (bs, 1 H), 4.03 (dd, 1 H, $J$ = 8.9, 4 Hz), 3.77 (s, 3 H), 2.74–2.82 (m, 2 H), 2.22–2.33 (m, 1 H), 1.93–2.06 (m, 1 H).

**2-(Hydroxymethyl)tetrahydroquinoline (11d).** Reduction of **6g** (42 g) was performed as described in synthesis of **11c** to give 38.4 g of the title compound (quant): MS *m/e* 163 ($M^+$), 129 ($M^+ - CH_2OH$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 6.95–7.00 (m, 2 H), 6.63 (t, 1 H, $J$ = 7.4 Hz), 6.54 (d, 1 H, $J$ = 7.4 Hz), 3.74 (dd, 1 H, $J$ = 10.2, 3.6 Hz), 3.56 (dd, 1 H, $J$ = 10.2, 8.6 Hz), 3.41–3.49 (m, 1 H), 2.70–2.85 (m, 2 H), 1.85–1.90 (m, 1 H), 1.68–1.77 (m, 1 H).

**2-(Cyanomethyl)tetrahydroquinoline (12d).** To a solution of **11d** (35.9 g, 0.22 mol), imidazole (35.95 g, 0.528 mol), and triphenylphosphine (69.24 g, 0.264 mol) in a mixed solvent of 5:1 toluene/acetonitrile (750 mL) was added iodine (61.42 g, 0.242 mol) at 0 °C. The mixture was stirred for 15 min at 0 °C and for 30 min at room temperature. Aqueous sodium thiosulfate solution (200 mL) was added. The organic layer was separated, washed with brine, dried over magnesium sulfate, and concentrated. The residue was triturated with diethyl ether, and the insoluble materials were removed by filtration. The filtrate was concentrated, and the residual oil was dissolved in DMF (200 mL). To the solution was added sodium cyanide (43.2 g, 0.881 mol), and the mixture was heated at 80 °C for 10 h. The resulting mixture was poured into ice–water and extracted with a mixture of toluene and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography with 1:1 hexane/dichloromethane to 100% dichloromethane as eluents to give 31.6 g of the title compound (94%): MS *m/e* 172 ($M^+$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 6.97–7.04 (m, 2 H), 6.68 (t, 1 H, $J$ = 7.4 Hz), 6.54 (d, 1 H, $J$ = 7.4 Hz), 4.03 (br, 1 H), 3.70 (m, 1 H), 2.70–2.86 (m, 2 H), 2.54 (d, 1 H, $J$ = 6.6 Hz), 2.02–2.13 (m, 1 H), 1.78–1.91 (m, 1 H).

**2-[(Methoxycarbonyl)methyl]tetrahydroquinoline (6g).** 2-(Cyanomethyl)tetrahydroquinoline (**12c**, 28.0 g, 0.163 mol) was dissolved in concentrated hydrochloric acid (200 mL), and the mixture was refluxed for 4 h. The resulting mixture was concentrated, and the residue was dissolved in methanol (500 mL). Thionyl chloride (36 mL, 0.49 mol) was added slowly at 0 °C. The mixture was refluxed for 5 h and concentrated. To the residual solid was added slowly saturated sodium bicarbonate (1 L), and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated to give 31.6 g of the title compound (94%): MS *m/e* 205 ($M^+$). 2-[(Methoxycarbonyl)methyl]tetrahydroquinoline hydrochloride: mp 145–146 °C; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.69–7.72 (m, 1 H), 7.23–7.38 (m, 3 H), 3.96–4.05 (m, 1 H), 3.75 (s, 3 H), 3.48–3.55 (m, 1 H), 2.96–3.12 (m, 3 H), 2.19–2.41 (m, 1 H). Anal. ($C_{12}H_{15}NO_2{\cdot}HCl$): C, H, N.

**2-Carbamoylindoline (13).** To a solution of 2-(methoxycarbonyl)indoline (22.733 g, 0.128 mmol) in methanol (230 mL) was introduced gaseous $NH_3$ at room temperature until the solution was saturated with $NH_3$. The mixture was stirred for 6 h at room temperature. The precipitates formed were collected, washed with methanol, and dried *in vacuo* to give 17.78 g of 2-carbamoylindoline (85%): MS *m/e* 162 ($M^+$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.30 (bs, 1 H), 7.11 (bs, 1 H), 7.01 (d, 1 H, $J$ = 7 Hz), 6.93 (dt, 1 H, $J$ = 1, 7 Hz), 6.56 (m, 2 H), 5.87 (bs, 1 H), 4.12 (dd, 1 H, $H$ = 10, 8 Hz), 3.25 (dd, 1 H, $J$ = 16, 10 Hz), 2.93 (dd, 1 H, $J$ = 16, 8 Hz).

**2-(Aminomethyl)indoline (14).** To a suspension of $LiAlH_4$ (6.0 g, 0.157 mol) in THF (200 mL) was added dropwise a suspension of 2-carbamoylindoline (17.0 g, 0.105 mol) in THF (700 mL) over 50 min. The mixture was refluxed for 5 h, and then $LiAlH_4$ (6.0 g) was added further. The reflux was continued additionally for 6 h, and the mixture was treated with 10% aqueous THF after being cooled with ice bath. Aqueous 1 N NaOH was added, and the mixture was extracted with a mixture of diethyl ether and THF. The organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated to give 13.91 g of 2-(aminomethyl)indoline (90%): MS *m/e* 148 ($M^+$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.11 (dd, 1 H, $J$ = 7, 1 Hz), 7.01 (dt, 1 H, $J$ = 1, 7 Hz), 6.68 (dt, 1 H, $J$ = 1, 7 Hz), 6.61 (d, 1 H, $J$ = 7 Hz), 3.84 (m, 1 H), 3.11 (dd, 1 H, $J$ = 16, 9 Hz), 2.86 (dd, 1 H, $J$ = 13, 5 Hz), 2.70 (m, 2 H).

**2-(Phthalimidomethyl)indoline (6f).** A mixture of 2-(aminomethyl)indoline (6.0 g, 40.48 mmol) and phthalic anhydride (6.30 g, 42.51 mmol) in toluene (600 mL) was refluxed for 4 h, while water generated during the reaction was removed by azeotropic distillation by using a Dean–Stark apparatus. The mixture was concentrated to give crude 2-(phthalimidomethyl)indoline (11.84 g), which was used for the next step without further purification: MS *m/e* 278 ($M^+$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.82 (m, 2 H), 7.71 (m, 2 H), 7.03 (d, 1 H, $J$ = 7 Hz), 6.95 (dt, 1 H, $J$ = 1, 7 Hz), 6.61 (m, 2 H), 4.19 (m, 1 H), 3.86 (d, 2 H, $J$ = 6 Hz), 3.18 (dd, 1 H, $J$ = 16, 9 Hz), 2.93 (dd, 1 H, $J$ = 16, 6 Hz).

**2-(Phthalimidomethyl)tetrahydroquinoline (6h).** To a solution of 2-(hydroxymethyl)tetrahydroquinoline (10 g, 61 mmol), imidazole (10.0 g, 147 mmol), and triphenylphosphine (19.0 g, 72.4 mmol) in a mixed solvent of 5:1 toluene/acetonitrile (360 mL) was added iodine (16.85 g, 66.4 mmol) at 0 °C. The mixture was stirred for 2 h at 0 °C, and aqueous sodium thiosulfate was added. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and concentrated. The residue was triturated with diethyl ether, and insoluble materials were removed by filtration. The filtrate was concentrated, the residue was dissolved in DMF (60 mL), and potassium phthalimide (13.6 g, 73.48 mmol) was added. The mixture was heated at 60 °C for 2 h, diluted with water (200 mL), and extracted with 1:1 toluene/ethyl acetate (200 mL × 2). The organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography with 10:1 to 6:1 hexane/ethyl acetate to give 10.25 g of 2-(phthalimidomethyl)tetrahydroquinoline (75%): MS *m/e* 292 ($M^+$); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 7.86 (m, 2 H), 7.74 (m, 2 H), 6.95 (m, 2 H), 6.59 (t, 1 H, $J$ = 8 Hz), 6.49 (d, 1 H, $J$ = 8 Hz), 3.91 (dd, 1 H, $J$ = 14, 5 Hz), 3.78 (dd, 1 H, $J$ = 14, 5 Hz), 3.68 (m, 1 H), 2.78 (m, 2 H), 2.00 (m, 1 H), 1.69 (m, 1 H).

***N*-Ethoxalylindoline (7a).** To a solution of indoline (2.0 g, 16.8 mmol) and triethylamine (5 mL) in dichloromethane (30 mL) was added slowly ethyl chlorooxalate (2.3 mL, 20.1 mmol) at 0 °C. The mixture was stirred for 10 min at 0 °C and then for 1 h at room temperature. Brine was added, and the organic layer was separated. The organic layer was washed successively with diluted aqueous hydrochloric acid and brine, dried over magnesium sulfate, and concentrated to give 4.0 g of *N*-ethoxalylindoline (100%): MS *m/e* 219 ($M^+$); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 8.18 (dd, 1 H, $J$ = 8, 1 Hz), 7.22 (m, 2 H), 7.10 (dd, 1 H, $J$ = 8, 1 Hz), 4.38 (q, 2 H, $J$ = 7 Hz), 4.22 (t, 2 H, $J$ = 8 Hz), 3.20 (t, 2 H, $J$ = 8 Hz), 1.40 (t, 3 H, $J$ = 7 Hz).

**5-Bromo-*N*-ethoxalylindoline (8a).** To a mixture of *N*-ethoxalylindoline (4 g, 18.3 mmol) and iron powder (0.40 g) in dichloromethane (40 mL) was added dropwise bromine (1.43 mL, 27.7 mmol) at 0 °C. The mixture was stirred for 4 h at room temperature and filtered. The filtrate was washed with aqueous sodium thiosulfate and then brine, dried over magnesium sulfate, and concentrated to give 5.24 g of 5-bromo-*N*-ethoxalylindoline (95%): MS *m/e* 299 ($M^+$ + 2), 297 ($M^+$); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 8.07 (d, 1 H, $J$ = 8 Hz), 7.35 (dd, 2 H, $J$ = 8, 1 Hz), 4.38 (q, 2 H, $J$ = 7 Hz), 4.27 (t, 2 H, $J$ = 8 Hz), 3.20 (t, 2 H, $J$ = 8 Hz), 1.41 (t, 3 H, $J$ = 7 Hz).

**5-Bromo-7-nitro-*N*-ethoxalylindoline (9a).** To a solution of 5-bromo-*N*-ethoxalylindoline (5.23 g, 17.5 mmol) in concentrated sulfuric acid was added slowly isopropyl nitrate (1.87 mL, 18.5 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C and poured into a mixture of water and crushed ice. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The crude residue was purified by silica gel column chromatography to give 5.02 g of 5-bromo-7-nitro-*N*-ethoxalylindoline (83%): MS *m/e* 344 ($M^+$ + 2), 342 ($M^+$); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 7.91 (d, 1 H, $J$ = 1 Hz), 7.62 (d, 1 H, $J$ = 1 Hz), 4.39 (t, 2 H, $J$ = 8 Hz), 4.38 (q, 2 H, $J$ = 7 Hz), 3.22 (t, 2 H, $J$ = 8 Hz), 1.39 (t, 3 H, $J$ = 7 Hz).

**8-Bromo-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione (10a).** To a solution of 5-bromo-7-nitro-*N*-ethoxalylindoline (2.0 g, 5.83 mmol) in a mixture of THF (50 mL), water (10 mL), and acetic acid (10 mL) was added aqueous 20% titanium trichloride (31 mL, 40.8 mmol), and the mixture was stirred for 4 h at room temperature. The precipitates formed were collected by filtration, washed with diluted aqueous hydrochloric acid and then distilled water, and dried *in vacuo* to give 772 mg of the title compound (50%): mp >300 °C; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 11.91 (bs, 1 H), 7.21 (d, 1 H, $J$ = 1 Hz), 7.02 (d, 1 H, $J$ = 1 Hz), 4.22 (t, 2 H, $J$ = 7 Hz), 3.32 (t, 2 H, $J$ = 7 Hz). Anal. ($C_{10}H_7N_2O_2Br$): C, H, N.

**9-Bromo-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (10b).** The title compound was prepared as shown in Scheme 1 starting with tetrahydroquinoline (**6b**): mp >300 °C; $^1$H NMR (270 MHz DMSO-$d_6$) $\delta$ 12.00 (bs, 1 H), 7.17 (d, 1 H, $J$ = 1 Hz), 7.12 (d, 1 H, $J$ = 1 Hz), 3.91 (t, 2 H, $J$ = 5 Hz), 2.84 (t, 2 H, $J$ = 5 Hz), 1.96 (5et, 2 H, J = 5 Hz). Anal. ($C_{11}H_9N_2Br$): C, H, N.

**8-Bromo-5-(methoxycarbonyl)-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione (10c).** The title compound was prepared as shown in Scheme 1 starting with 2-(methoxycarbonyl)indoline (**6c**): mp 266.5−267.5 °C dec; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.11 (bs, 1 H), 7.24 (d, 1 H, $J$ = 1 Hz), 7.09 (d, 1 H, $J$ = 1 Hz), 5.31 (dd, 1 H, $J$ = 11, 5 Hz), 3.79 (dd, 1 H, $J$ = 17, 11 Hz), 3.73 (s, 3 H), 3.39 (dd, 1 H, $J$ = 17, 5 Hz); HRMS calcd for $C_{12}H_9N_2O_4Br$ 323.9746, found 323.9727. Anal. ($C_{11}H_9N_2Br{\cdot}H_2O$): C, H, N.

**9-Bromo-5-(methoxycarbonyl)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (10d).** The title compound was prepared as shown in Scheme 1 starting with 2-(methoxycarbonyl)tetrahydroquinoline (**6d**): mp 240−241 °C; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.24 (bs, 1 H), 7.21 (bs, 2 H), 5.30 (dd, 1 H, $J$ = 4.6 Hz), 3.72 (s, 3 H), 2.88 (bd, 1 H, $J$ = 16 Hz), 2.5−2.63 (m, 1 H), 2.4−2.46 (m, 1 H), 2.03−2.14 (m, 1 H). Anal. ($C_{13}H_{11}N_2O_4Br{\cdot}{}^1/_3H_2O$): C, H, N.

**8-Bromo-5-[(methoxycarbonyl)methyl]-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione (10e).** The title compound was prepared as shown in Scheme 1 starting with 2-[(methoxycarbonyl)methyl]indoline (**6e**): mp 244.5−248 °C dec; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.26 (s, 1 H), 7.21 (s, 2 H), 5.29−5.35 (m, 1 H), 3.70 (s, 3 H), 2.87 (dm, 1 H, $J$ = 18 Hz), 2.60 (dm, 1 H, $J$ = 14 Hz), 2.46 (dm, 1 H, $J$ = 14 Hz), 2.00−2.16 (m, 1 H). Anal. ($C_{13}H_{11}N_2O_4Br{\cdot}{}^3/_2H_2O$): C, H, N.

**8-Bromo-5-(phthalimidomethyl)-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione (10f).** The title compound was prepared as shown in Scheme 1 starting with 2-(phthalimidomethyl)tetrahydroquinoline (**6f**): mp 267 °C dec; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 11.91 (s, 1 H), 7.83 (bs, 4 H), 7.15 (d, 1 H, $J$ = 1 Hz), 6.99 (d, 1 H, $J$ = 1 Hz), 5.13−5.26 (m, 1 H), 4.07 (dd, 1 H, $J$ = 14, 6 Hz), 3.99 (dd, 1 H, 14, 5 Hz), 3.50 (dd, 1 H, $J$ = 17, 10 Hz), 3.11 (dd, 1 H, $J$ = 17, 3 Hz). Anal. ($C_{19}H_{12}N_3O_4Br{\cdot}{}^4/_3H_2O$): C, H, N.

**6-Bromo-2-[(methoxycarbonyl)methyl]tetrahydroquinoline (27g).** To a solution of **6g** (31.5 g, 0.153 mol) in DMF (750 mL) was added dropwise a solution of *N*-bromosuccinimide (27.41 g, 0.154 mol) in DMF (550 mL) at 0 °C. The mixture was stirred for 2 h at the same temperature, poured into water (2 L), and extracted with a mixture of toluene and ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and concentrated to give 44.72 g of the title compound (quant): MS *m/e* 286 ($M^+$ + 3), 284 ($M^+$ + 1); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 7.02−7.06 (m, 2 H), 6.38 (dd, 1 H, $J$ = 1.7, 7.3 Hz), 4.53 (br, 1 H), 3.75 (s, 3 H), 3.72−3.75 (m, 4 H), 2.70−2.85 (m, 2 H), 2.49−2.53 (m, 1 H), 1.89−1.99 (m, 1 H), 1.61−1.75 (m, 1 H).

**6-Bromo-2-[(methoxycarbonyl)methyl]-*N*-ethoxalyltetrahydroquinoline (8g).** A procedure similar to that described in synthesis of **7a** was carried out with **27g** (43.8 g) to give 56.9 g of the title compound (97%): MS *m/e* 386 ($M^+$ + 3), 3.84 ($M^+$ + 1); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 7.36 (s, 1 H), 7.30 (d, 1 H, $J$ = 8.3 Hz), 6.92 (d, 1 H, $J$ = 8.3 Hz), 4.94−5.01 (m, 1 H), 4.13−4.16 (m, 2 H), 3.64 (s, 3 H), 2.43−2.75 (m, 6 H), 1.11−1.26 (m, 3 H).

**6-Bromo-2-[(methoxycarbonyl)methyl]-8-nitro-*N*-ethoxalyltetrahydroquinoline (9g).** A solution of **8g** (56.0 g, 0.146 mol) in dichloromethane (500 mL) was added dropwise to a suspension of nitronium tetrafluoroborate (25.0 g, 0.179 mol) in dichloromethane (500 mL) at 0 °C. The mixture was stirred for 3 h at 0 °C, poured into ice−water, and extracted with dichloromethane. The organic layer washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography with 3:1 to 2:1 hexane/ethyl acetate to give 52.0 of the title compound (83%): MS *m/e* 431 ($M^+$ + 3), 429 ($M^+$ + 1); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 8.11 and 7.99 (d and d, 1 H, $J$ = 2 Hz), 7.66 and 7.61 (d and d, 1 H, $J$ = 2 Hz), 5.03−5.16 and 4.74−4.85 (m and m, 1 H), 4.37−4.49 and 4.13 (m and q, 2 H, $J$ = 7.2 Hz), 3.72 and 3.62 (s and s, 3 H), 2.44−3.02 (m, 5 H), 1.65−1.80 and 1.50−1.60 (m and m, 1 H), 1.42 and 1.23 (t and t, 3 H, $J$ = 7.2 and 7.2 Hz).

**9-Bromo-5-[(methoxycarbonyl)methyl]-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (10g).** To a mixture of 20% aqueous titanium trichloride (6.70 g, 0.867 mol), water (500 mL), and acetone (500 mL) was added dropwise a solution of **9g** (52.0 g, 0.121 mol) in acetone (600 mL) at 0 °C. The mixture was stirred overnight at room temperature, concentrated to ca. 1 L, and diluted with water (1 L). The precipitates formed were collected by filtration, washed with water, and dried *in vacuo* to give 35.2 g of the title compound. The filtrate was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography with ethyl acetate to give 6.0 g of the title compound (total 89%): mp 185–187 °C; $^1H$ NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.04 (bs, 1 H), 7.20 (d, 1 H, $J$ = 2 Hz), 7.15 (d, 1 H, $J$ = 2 Hz), 5.04–5.13 (m, 1 H), 3.62 (s, 3 H), 2.94 (ddd, 1 H, $J$ = 17.1, 13.5, 4.5 Hz), 2.78 (dm, 1 H, $J$ = 17.1 Hz) 2.63 (dd, 1 H, $J$ = 18, 7.2 Hz), 2.57 (dd, 1 H, $J$ = 18, 3.6 Hz), 2.09 (dm, 1 H, $J$ = 13.5 Hz), 1.80–1.95 (m, 1H). Anal. ($C_{14}H_{13}N_2O_4Br{\cdot}^1/_3H_2O$): C, H, N.

**9-Bromo-5-(phthalimidomethyl)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (10h).** The title compound was prepared as shown in Scheme 6 starting with 2-(phthalimidomethyl)tetrahydroquinoline (**6h**): mp >300 °C; $^1H$ NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.02 (bs, 1 H), 7.84 (bs, 4 H), 7.26 (s, 1 H), 7.18 (s, 1 H), 5.21–5.32 (m, 1 H), 3.86 (dd, 1 H, $J$ = 14, 9 Hz), 3.75 (dd, 1 H, $J$ = 14, 5 Hz), 3.10 (ddd, 1 H, $J$ = 17.1, 13.5, 4.5 Hz), 2.86 (dm, 1 H, $J$ = 17.1 Hz), 2.25 (dm, 1 H, $J$ = 13.5 Hz), 1.77–1.95 (m, 1 H). Anal. ($C_{20}H_{14}N_3O_4Br{\cdot}^1/_3H_2O$): C, H, N.

***N*-Ethoxalyl-2-[[(trimethylsilyl)oxy]methyl]tetrahydroquinoline (15).** To a solution of 2-(hydroxymethyl)-tetrahydroquinoline (**11d**, 7.86 g, 48.16 mmol) in dichloromethane (80 mL) containing triethylamine (10 mL, 72.23 mmol) was added trimethylsilyl chloride (6.7 mL, 52.97 mmol) at 0 °C. The mixture was stirred for 10 min at 0 °C followed by addition of triethylamine (10 mL) and ethyl chlorooxalate (5.9 mL, 52.97 mmol). The mixture was stirred for 30 min at 0 °C, and water was added. The organic layer was separated, washed with water, dried over magnesium sulfate, and concentrated to give 15.6 g of *N*-ethoxalyl-2-[[(trimethylsilyl)-oxy]methyl]tetrahydroquinoline (106%): $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 6.97–7.16 (m, 4 H), 4.68 (m, 1 H), 4.09 (q, 2 H, $J$ = 7 Hz), 3.72 (m, 1 H), 3.54 (m, 1 H), 2.65 (m, 2 H), 2.37 (m, 1 H), 1.69 (m, 1 H), 1.06 (t, 3 H, $J$ = 7 Hz), 0.03 (s, 9 H).

***N*-Ethoxalyl-2-formyltetrahydroquinoline (16).** A mixture of **15** (15.55 g, 50.92 mmol) and Dess–Martin reagent (32.4, 76.37 mmol) in dichloromethane (160 mL) in the presence of trifluoroacetic acid (0.8 mL) was stirred for 1 h at room temperature. Aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate were added successively, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated to give 11.23 g of *N*-ethoxalyl-2-formyltetrahydroquinoline (84%): $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 9.57 (s, 1 H), 7.19 (m, 4 H), 5.07 (t, 1 H, $J$ = 8 Hz), 4.19 (q, 2 H, $J$ = 7 Hz), 2.76 (m, 2 H), 2.45 (m, 1 H), 1.96 (m, 1 H), 1.15 (t, 3 H, $J$ = 7 Hz).

***N*-Ethoxalyl-2-[2-(ethoxycarbonyl)ethenyl]tetrahydroquinoline (17).** To a solution of (diethylphosphono)acetic acid diethyl ester (10.6 g, 47.1 mmol) in THF (100 mL) was added potassium *tert*-butoxide (5.04 g, 44.9 mmol) at 0 °C. The mixture was stirred for 20 min at room temperature. To the solution was added dropwise **16** (11.18 g, 42.8 mmol) in THF (120 mL) at 0 °C. After the complete addition, the mixture was stirred for 15 min at room temperature, and water and a small amount of diluted hydrochloric acid were added. The mixture was extracted with ethyl acetate. The organic layer was washed three times with brine, dried over magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography with 4:1 to 3:1 hexane/ethyl acetate to give 7.63 g of *N*-ethoxalyl-2-[2-(ethoxycarbonyl)-ethenyl[tetrahydroquinoline (54%): MS *m/e* 333 ($M^+ + 2$), 332 ($M^+ + 1$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.15 (m, 4 H), 6.79 (dd, 1 H, $J$ = 16, 5 Hz), 5.89 (dd, 1 H, $J$ = 16, 2 Hz), 5.31 (m, 1 H), 4.12 (q, 2 H, $J$ = 7 Hz), 2.73 (t, 2 H, $J$ = 6 Hz), 2.47 (m, 1 H), 1.69 (m, 1 H), 1.25 (t, 3 H, $J$ = 7 Hz), 1.11 (t, 3 H, $J$ = 7 Hz).

***N*-Ethoxalyl-2-[2-(ethoxycarbonyl)ethyl]tetrahydroquinoline (7i).** *N*-Ethoxalyl-2-[2-(ethoxycarbonyl)ethenyl]-tetrahydroquinoline (**17**, 4 g, 12.1 mmol) in ethanol (100 mL) was hydrogenated over 10% palladium on carbon (500 mg) under an atmospheric pressure of hydrogen for 1.5 h at room temperature. The mixture was filtered through Celite, and the filtrate was concentrated to give 3.83 g of *N*-ethoxalyl-2-[2-(ethoxycarbonyl)ethyl]tetrahydroquinoline (95%): MS *m/e* 334 ($M^+ + 1$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.03–7.19 (m, 4 H), 4.78 (m, 1 H), 4.11 (q, 4 H, $J$ = 7 Hz), 2.73 (t, 2 H, $J$ = 6 Hz), 2.47 (m, 1 H), 1.69 (m, 1 H), 1.25 (t, 3 H, $J$ = 7 Hz), 1.11 (t, 3 H, $J$ = 7 Hz).

**9-Bromo-5-[2-(ethoxycarbonyl)ethyl]-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*])quinoxaline-2,3-dione (10i).** The title compound was prepared by a similar procedure as described in synthesis of **10a** from **7a** starting with *N*-ethoxalyl-2-[2-(ethoxycarbonyl)ethyl]tetrahydroquinoline instead of *N*-ethoxalylindoline: mp 185 °C; $^1H$ NMR (270 MHz, $CD_3OD$) $\delta$ 7.23 (s, 1 H), 7.19 (s, 1 H), 5.00–5.09 (m, 1 H), 4.09 (q, 2 H, $J$ = 7.5 Hz), 3.04 (ddd, 1 H, $J$ = 17.1, 13.5, 4.5 Hz), 2.88 (dm, 1 H, $J$ = 17.1 Hz), 2.45 (t, 2 H, $J$ = 7.5 Hz), 2.18 (dm, 1 H, $J$ = 13.5 Hz), 1.80–2.08 (m, 3 H). Anal. ($C_{16}H_{17}N_2O_4Br$): C, H, N.

**8-Bromo-5-carboxy-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]-quinoxaline-2,3-dione (18c).** To a solution of 8-bromo-5-(methoxycarbonyl)-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione (256 mg, 0.76 mmol) in a mixture of THF (5 mL) and methanol (5 mL) was added aqueous 1 N NaOH (2.5 mL), and the mixture was stirred for 12 h at room temperature. Aqueous 1 N HCl was added, and the solvent was concentrated to ca. 5 mL. The precipitates formed were collected by filtration, washed with distilled water, and dried *in vacuo* to give 256 mg of the title compound (quant): mp 285 °C dec; $^1H$ NMR (270 MHz, DMSO-$d_6$) $\delta$ 13.45 (bs, 1 H), 12.09 (s, 1 H), 7.22 (d, 1 H, $J$ = 1 Hz), 7.08 (d, 1 H, $J$ = 1 Hz), 5.18 (dd, 1 H, $J$ = 11, 4 Hz), 3.79 (dd, 1 H, $J$ = 17, 11 Hz), 3.33 (dd, 1 H, $J$ = 17, 4 Hz). Anal. ($C_{11}H_7N_2O_4Br$): C, H, N.

**9-Bromo-5-carboxy-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]-quinoxaline-2,3-dione (18d).** A procedure similar to that described in synthesis of **18c** was carried out with 9-bromo-5-(methoxycarbonyl)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (1.5 g, 4.42 mmol) to give 1.45 g of the title compound (quant): mp >270 °C; $^1H$ NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.23 (bs, 1 H), 7.20 (bs, 2 H), 5.21 (m, 1 H), 2.89 (dm, 1 H, $J$ = 16.8 Hz), 2.37–2.65 (m, 2 H), 1.98–2.11 (m, 1 H). Anal. ($C_{12}H_9N_2O_4Br{\cdot}^2/_3H_2O$): C, H, N.

**8-Bromo-5-(carboxymethyl)-5,6-dihydro-1*H*-pyrido-[1,2,3-*de*]quinoxaline-2,3-dione (18e).** Hydrolysis of 8-bromo-5-[(methoxycarbonyl)methyl]-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]-quinoxaline-2,3-dione (680 mg, 2.01 mmol) was carried out as described in synthesis of **18c** to give 640 mg of the title compound (98%): mp 265 °C dec; $^1H$ NMR (270 MHz, DMSO-$d_6$) $\delta$ 13.38 (br, 1 H), 12.23 (s, 1 H), 7.20 (s, 2 H), 5.19–5.25 (m, 1 H), 2.88 (dm, 1 H, $J$ = 18 Hz), 2.63 (dm, 1 H, $J$ = 14 Hz), 2.43 (m, 1 H, $J$ = 14 Hz), 1.96–2.12 (m, 1 H). Anal. ($C_{12}H_9N_2O_4Br{\cdot}H_2O$): C, H, N.

**9-Bromo-5-(carboxymethyl)-6,7-dihydro-1*H*,5*H*-pyrido-[1,2,3-*de*]quinoxaline-2,3-dione (18g).** Hydrolysis of 9-bromo-5-[(methoxycarbonyl)methyl]-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (10.4 g, 0.03 mol) was carried out as described in synthesis of **18c** to give 9 g of the title compound (90%): mp >270 °C; $^1H$ NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.06 (bs, 1 H), 7.20 (d, 1 H, $J$ = 2 Hz), 7.15 (d, 1 H, $J$ = 2 Hz), 5.02–5.12 (m, 1 H), 2.95 (ddd, 1 H, $J$ = 17.1, 13.5, 4.5 Hz), 2.79 (dm, 1 H, $J$ = 17.1 Hz), 2.43–2.61 (m, 2 H), 2.12 (dm, 1 H, $J$ = 13.5 Hz), 1.78–1.96 (m, 1 H). Anal. ($C_{13}H_{11}N_2O_4Br{\cdot}H_2O$): C, H, N.

**9-Bromo-5-(2-carboxyethyl)-6,7-dihydro-1*H*,5*H*-pyrido-[1,2,3-*de*]quinoxaline-2,3-dione (18i).** The title compound was obtained by hydrolysis of 9-bromo-5-[2-(ethoxycarbonyl)-ethyl]-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione as described in synthesis of **18c**: mp 275–276 °C; $^1H$ NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.03 (bs, 1 H), 7.19 (s, 1 H), 7.14 (s, 1 H), 4.80–4.92 (m, 1 H), 2.93 (ddd, 1 H, $J$ = 17.1, 13.5, 4.5 Hz), 2.77 (dm, 1 H, $J$ = 17.1 Hz), 2.20–2.44 (m, 2 H), 2.10 (dm, 1 H, $J$ = 13.5 Hz), 1.62–1.88 (m, 3 H). Anal. ($C_{14}H_{13}N_2O_4Br{\cdot}^1/_3H_2O$): C, H, N.

**8-Bromo-5-(aminomethyl)-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione Hydrochloride (19f).** A solution of 8-bromo-5-(phthalimidomethyl)-5,6-dihydro-1*H*-pyrrolo-[1,2,3-*de*]quinoxaline-2,3-dione (100 mg) in a mixture of acetic acid (6 mL) and concentrated HCl (6 mL) was refluxed for 4.5

h and concentrated. The residue was triturated with methylene chloride containing a small amount of methanol. The precipitates were collected by filtration, rinsed with methylene chloride, and dried *in vacuo* to give 60 mg of the title compound (60%): mp 268 °C dec; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 11.98 (s, 1 H), 8.07 (br, 3 H), 7.23 (d, 1 H, $J$ = 1 Hz), 7.07 (d, 1 H, $J$ = 1 Hz), 5.02–5.12 (m, 1 H), 3.56 (dd, 1 H, $J$ = 17, 10 Hz), 3.28–3.48 (m, 2 H), 3.11 (dd, 1 H, $J$ = 17, 3 Hz). Satisfactory elemental analysis was not obtained, and the material was used for the next step without further purification.

**9-Bromo-5-(aminomethyl)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione Hydrochloride (19h).** Hydrolysis of 9-bromo-5-(phthalimidomethyl)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (1.64 g, 3.8 mmol) was carried out as described in synthesis of **19f** to give 1.27 g of the title compound (96%): mp 246–255 °C dec; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.10 (bs, 1 H), 8.12 (bs, 3 H), 7.23 (s, 2 H), 5.05–5.17 (m, 1 H), 2.85–3.10 (m, 3 H), 2.78 (dm, 1 H, $J$ = 17.1 Hz), 2.25 (dm, 1 H, $J$ = 13.5 Hz), 1.77–1.95 (m, 1 H). Satisfactory elemental analysis was not obtained, and the material was used for the next step without further purification.

**8-Bromo-5-(phenylcarbamoyl)-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione (20c).** To a solution of 8-bromo-5-carboxy-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione (300 mg, 0.96 mmol) and aniline (97 $\mu$L, 1.061 mmol) in DMF (3 mL) was added 1-ethyl-3-[3′-(dimethylamino)propyl]carbodiimide (164 mg, 1.06 mmol) and *N*-hydroxybenztriazole (162 mg, 1.06 mmol) at 0 °C. The mixture was stirred at room temperature overnight, and aqueous 0.1 N HCl was added. The precipitates formed were collected by filtration, washed with distilled water, and dried *in vacuo* to give 274 mg of the title compound (74%): mp >300 °C; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.09 (s, 1 H), 10.45 (s, 1 H), 7.59 (d, 2 H, $J$ = 75 Hz), 7.34 (t, 2 H, $J$ = 7.5 Hz), 7.23 (d, 1 H, $J$ = 1 Hz), 7.10 (t, 1 H, $J$ = 7.5 Hz), 7.07 (d, 1 H, $J$ = 1 Hz), 5.31 (dd, 1 H, $J$ = 10, 5 Hz), 4.32 (d, 2 H, $J$ = 5.6 Hz), 3.78 (dd, 1 H, $J$ = 17, 10 Hz), 3.35 (dd, 1 H, $J$ = 17, 5 Hz). Anal. ($C_{17}H_{12}N_3O_3Br \cdot {}^2/_3H_2O$): C, H, N.

**9-Bromo-5-(phenylcarbamoyl)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (20d).** A procedure similar to that described in synthesis of **20c** was carried out with 9-bromo-5-carboxy-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (300 mg, 0.92 mmol) and aniline (93 mg, 1.0 mmol) to give 310 mg of the title compound (84%): mp >250 °C; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.25 (s, 1 H), 10.36 (s, 1 H), 7.56 (d, 2 H, $J$ = 8 Hz), 7.33 (t, 2 H, $J$ = 8.0 Hz), 7.24 (bs, 1 H), 7.22 (bs, 1 H), 7.09 (t, 1 H, $J$ = 8 Hz), 5.32–5.36 (m, 1 H), 2.89 (dm, 1 H, $J$ = 16.8 Hz), 2.58–2.81 (m, 2 H), 2.05–2.22 (m, 1 H). Anal. ($C_{18}H_{14}N_3O_3Br \cdot {}^1/_2H_2O$): C, H, N.

**8-Bromo-5-[(phenylcarbamoyl)methyl]-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione (20e).** A procedure similar to that described in synthesis of **20c** was carried out with 8-bromo-5-(carboxymethyl)-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione (130 mg, 0.40 mmol) and aniline (40 $\mu$L, 0.44 mmol) to give 82 mg of the title compound (51%): mp 186 °C dec; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.23 (s, 1 H), 10.34 (s, 1 H), 7.55 (d, 2 H, $J$ = 8 Hz), 7.32 (t, 2 H, $J$ = 8 Hz), 7.22 (s, 2 H), 7.07 (t, 1 H, $J$ = 8 Hz), 5.30–5.36 (m, 1 H), 2.86 (dm, 1 H, $J$ = 18 Hz), 2.75 (dm, 1 H, $J$ = 14 Hz), 2.62 (m, 1 H, $J$ = 14 Hz), 2.02–2.18 (m, 1 H); HRMS calcd for $C_{18}H_{14}N_3O_3Br$ 399.0219, found 399.0148. Anal. ($C_{18}H_{14}N_3O_3Br \cdot 2H_2O$): C, H; N: calcd, 9.63; found, 10.31.

**8-Bromo-5-[(phenylcarbamoyl)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (20g).** The title compound was obtained by a method similar to that described in synthesis of **20c** with 9-bromo-5-(carboxymethyl)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione: mp >270 °C; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.07 (bs, 1 H), 10.01 (s, 1 H), 7.56 (d, 2 H, $J$ = 7.4 Hz), 7.30 (t, 2 H, $J$ = 7.9 Hz), 7.24 (d, 1 H, $J$ = 2 Hz), 7.17 (d, 1 H, $J$ = 2 Hz), 7.05 (t, 1 H, $J$ = 7.5 Hz), 5.16–5.26 (m, 1 H), 3.07 (ddd, 1 H, $J$ = 17.1, 13.5, 4.5 Hz), 2.83 (dm, 1 H, $J$ = 17.1 Hz), 2.63 (dd, 1 H, $J$ = 13.5, 3.6 Hz), 2.57 (dd, 1 H, $J$ = 13.5, 4.5 Hz), 2.12 (dm, 1 H, $J$ = 13.5 Hz), 1.78–1.96 (m, 1 H). Anal. ($C_{19}H_{16}N_3O_3Br$): C, H, N.

**8-Bromo-5-[(benzoylamino)methyl]-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione (21f).** A mixture of 8-bromo-5-(aminomethyl)-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione hydrochloride (134 mg, 0.405 mmol), triethylamine (124 $\mu$L, 0.892 mmol), benzoic acid (54 mg, 0.446 mmol), 1-ethyl-3-[3′-(dimethylamino)propyl]carbodiimide (69 mg, 0.446 mmol) and *N*-hydroxybenztriazole (68 mg, 0.446 mmol) in DMF (6 mL) was stirred for 20 h at room temperature, and 0.1 N hydrochloric acid (20 mL) was added. The precipitates formed were collected by filtration, washed with distilled water, and dried *in vacuo* to give 87 mg of the title compound (52%): mp 180.5–182 °C; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 11.86 (s, 1 H), 8.56 (t, 1 H, $J$ = 6 Hz), 7.34–7.54 (m, 5 H), 7.12 (s, 1 H), 7.17 (s, 2 H), 4.96–5.06 (m, 1 H), 3.90–4.00 (m, 1 H), 3.72–3.82 (m, 1 H), 3.43 (dd, 1 H, $J$ = 17, 10 Hz), 3.19 (dd, 1 H, $J$ = 17, 3 Hz). Anal. ($C_{18}H_{14}N_3O_3Br \cdot {}^1/_2H_2O$): C, H, N.

**9-Bromo-5-[(Benzoylamino)methyl]-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (21h).** A procedure similar to that described in synthesis of **21f** was carried out with 9-bromo-5-(aminomethyl)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione hydrochloride (800 mg, 2.31 mmol) and benzoic acid (312 mg, 2.56 mmol) to give 564 mg of the title compound (59%): mp 169–175 °C dec; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.03 (s, 1 H), 8.66 (t, 1 H, $J$ = 5.4 Hz), 7.77 (d, 2 H, $J$ = 8.6 Hz), 7.41–7.56 (m, 3 H), 7.24 (s, 1 H), 7.19 (s, 1 H), 5.03–5.13 (m, 1 H), 3.62 (dt, 1 H, $J$ = 11, 6.5 Hz), 3.28–3.40 (m, 1 H), 3.10 (ddd, 1 H, $J$ = 17.1, 13.5, 4.5 Hz), 2.78 (dm, 1 H, $J$ = 17.1 Hz), 2.14 (dm, 1 H, $J$ = 13.5 Hz), 1.73–1.89 (m, 1 H). Anal. ($C_{19}H_{16}N_3O_3Br \cdot {}^1/_2H_2O$): C, H, N.

**8-Bromo-5-[(*N*′-phenylureido)methyl]-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione (22f).** A mixture of 8-bromo-5-(aminomethyl)-5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione hydrochloride (134 mg, 0.405 mmol), triethylamine (136 $\mu$L, 0.972 mmol), and phenyl isocyanate (53 $\mu$L, 0.486 mmol) in DMF (2 mL) was stirred for 3 h at ambient temperature, and 0.1 N hydrochloric acid (20 mL) was added. The precipitates formed were collected by filtration, washed with distilled water, and dried *in vacuo*. The precipitates were rinsed with dichloromethane containing a small amount of methanol to give 79 mg of the title compound (47%): mp 175–179 °C dec; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 11.93 (bs, 1 H), 8.31 (s, 1 H), 7.31 (d, 2 H, $J$ = 8 Hz), 7.19 (s, 1 H), 7.18 (t, 2 H, $J$ = 8 Hz), 7.01 (s, 1 H), 6.87 (t, 1 H, $J$ = 8 Hz), 6.42 (t, 1 H, $J$ = 6 Hz), 4.86–4.95 (m, 1 H), 363–3.75 (m, 2 H), 3.45 (dd, 1 H, $J$ = 17, 10 Hz), 3.19 (dd, 1 H, $J$ = 17, 4 Hz). Anal. ($C_{18}H_{15}N_4O_3Br \cdot {}^3/_4H_2O$): C, H, N.

**9-Bromo-5-[(*N*′-phenylureido)methyl]-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (22h).** A mixture of 9-bromo-5-(aminomethyl)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione hydrochloride (52 mg, 0.15 mmol), triethylamine (62.7 $\mu$L, 0.45 mmol), and phenyl isocyanate (20 $\mu$L, 0.18 mmol) in DMF (1.5 mL) was stirred overnight at ambient temperature, and 0.1 N hydrochloric acid (20 mL) was added. The mixture was extracted with a mixture of ethyl acetate and THF, washed with brine, dried over magnesium sulfate, and concentrated. The residual solid was recrystallized from dichloromethane–DMF to give 26 mg of the title compound (40%): mp >270 °C; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 12.03 (s, 1 H), 8.89 (bs, 1 H), 7.39 (d, 1 H, $J$ = 8.6 Hz), 7.21 (t, 1 H, $J$ = 8.6 Hz), 7.19 (s, 1 H), 7.14 (s, 1 H), 6.89 (t, 1 H, $J$ = 8.6 Hz), 6.89 (bs, 1 H), 4.84–4.94 (m, 1 H), 3.10–3.30 (m, 2 H), 3.06 (ddd, 1 H, $J$ = 17.1, 13.5, 4.5 Hz), 2.76 (dm, 1 H, $J$ = 17.1 Hz), 2.18 (dm, 1 H, $J$ = 13.5 Hz), 1.72–1.88 (m, 1 H). Anal. ($C_{19}H_{17}N_4O_3Br \cdot DMF \cdot {}^1/_2H_2O$): C, H, N.

**(*S*)-9-Bromo-5-(carboxymethyl)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (23g).** The title compound was prepared starting with (*S*)-2-(methoxycarbonyl)-tetrahydroquinoline as described for **18g**: mp 174–175 °C; $[\alpha]_D$ = −108.3°, $c$ = 0.1 in MeOH. The spectral properties of the title compound were identical with those of **18g**.

**(*R*)-9-Bromo-5-(carboxymethyl)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (24g).** The title compound was prepared starting with (*R*)-2-(methoxycarbonyl)-tetrahydroquinoline as described for **18g**: mp 173–174 °C; $[\alpha]_D$ = 106.7°, $c$ = 1 in MeOH. The spectral properties of the title compound were identical with those of **18g**.

**(S)-9-Bromo-5-[(phenylcarbamoyl)methyl]-6,7-dihydro-1H,5H-pyrido[1,2,3-de]quinoxaline-2,3-dione (25g).** The title compound was prepared starting with (S)-2-(methoxycarbonyl)tetrahydroquinoline as described for **20g**: mp >270 °C; $[\alpha]_D = 83.3°$, $c = 0.1$ in DMF. The spectral properties of the title compound were identical with those of **20g**.

**(R)-9-Bromo-5-[(phenylcarbamoyl)methyl]-6,7-dihydro-1H,5H-pyrido[1,2,3-de]quinoxaline-2,3-dione (26g).** The title compound was prepared starting with (R)-2-(methoxycarbonyl)tetrahydroquinoline as described for **20g**: mp >270 °C; $[\alpha]_D = 80.1°$, $c = 0.1$ in DMF. The spectral properties of the title compound were identical with those of **20g**.

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