2-Carboxytetrahydroquinolines. Conformational and Stereochemical Requirements for Antagonism of the Glycine Site on the NMDA Receptor

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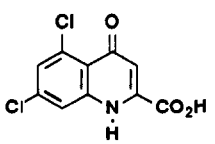
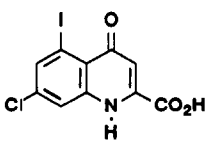
2-Carboxy-1,2,3,4-tetrahydroquinoline derivatives, derived from kynurenic acid, have been synthesized and evaluated for in vitro antagonist activity at the glycine site on the NMDA receptor. 2,3-Dihydrokynurenic acids show reduced potency relative to the parent lead compounds (Table I) possibly as a result of conformational effects. Removal of the 4-oxo group results in further reduced potency, but introduction of a *cis*-carboxymethyl group to the 4-position restores antagonist activity (Tables III and IV). Replacement of the keto group of 5,7-dichloro-2,3-dihydrokynurenic acid with other alternative H-bonding groups, for example *cis*- and *trans*-benzyloxycarbonyl and *cis*- and *trans*-carboxamido (Table V), gives comparable activity, but there is negligible stereoselectivity. A significant increase in potency and stereoselectivity is seen within the 4-acetate series (Table VI). The *trans*-4-acetic acid is significantly more potent than the corresponding lead kynurenic acid and has 100-fold greater affinity than the cis isomer. The results are consistent with a requirement in binding for a pseudoequatorially placed 2-carboxylate and clearly demonstrate the importance for binding of a correctly positioned hydrogen-bond-accepting group at the 4-position. The high-affinity binding of an anionic group in the 4-substituent binding pocket suggests that the glycine site and the neurotransmitter recognition (NMDA) site may have some features in common.

Introduction

Overactivation of the *N*-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptors has been implicated in several neurodegenerative disorders including epilepsy, stroke, and Alzheimer's disease.[1] As a result, NMDA antagonists may be of therapeutic benefit, since these compounds have been shown to be neuroprotective and anticonvulsant in a variety of animal models. The receptor complex consists of distinct binding regions,[2] including a neurotransmitter (probably glutamate) recognition site; a strychnine-insensitive glycine site; a site-recognizing phencyclidine, MK-801, and related molecules; sites for zinc and magnesium ions; and a polyamine site.[3] Competitive NMDA antagonists such as [3-(2-carboxypiperazin-4-yl)propyl]phosphonic acid[4] (CPP), which act at the neurotransmitter binding site, and uncompetitive NMDA antagonists, for example (+)-5-methyl-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5,10-imine[5] (MK-801), which act by blockade of the open state of the ion channel, both show undesirable in vivo behavioural effects.[6] Since the discovery of the role of glycine[7,8] in promoting NMDA receptor activation, compounds which would block the effect of glycine have been sought as potentially superior NMDA antagonists.[9] We have previously reported on the optimization of the lead compound kynurenic acid (**1a**),[10] where studying the effect of aromatic substitution resulted in potent 5,7-disubstituted derivatives (**1d**, **1h**). We



1d



1h

proposed a model[10] to account for glycine-site NMDA receptor antagonist binding which comprised (a) size-limited, hydrophobic binding of the benzene ring, (b) hydrogen-bond acceptance by the 4-oxo group, (c) hydrogen-bond donation by the 1-amino group, and (d) a Coulombic attraction of the 2-carboxylate. We proposed that the tautomer of the kynurenates which was recognized by the glycine/NMDA site was the 4-keto-1-amino form as illustrated by **1d** and **1h**. In this paper we have tested the model by modifications of the heterocyclic ring and 4-substituents of the kynurenic acid nucleus (compounds 1-18). 4-Substituted-2-carboxytetrahydroquinolines in

† Department of Biochemistry.
‡ Department of Pharmacology.

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(3) Ransom, R. W.; Stec, N. C. Cooperative modulation of [^{3}H]-MK-801 binding to the N-methyl-D-aspartate receptor-ion channel complex by L-glutamate, glycine, and polyamines. *J. Neurochem.* **1988**, *51*, 830.

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(9) Koek, W.; Colpaert, F. C. Selective blockade of N-methyl-D-aspartate (NMDA)-induced convulsions by NMDA antagonists and putative glycine antagonists: Relationship with phencyclidine-like behavioural effects. *J. Pharm. Exp. Ther.* **1990**, *252*, 349.

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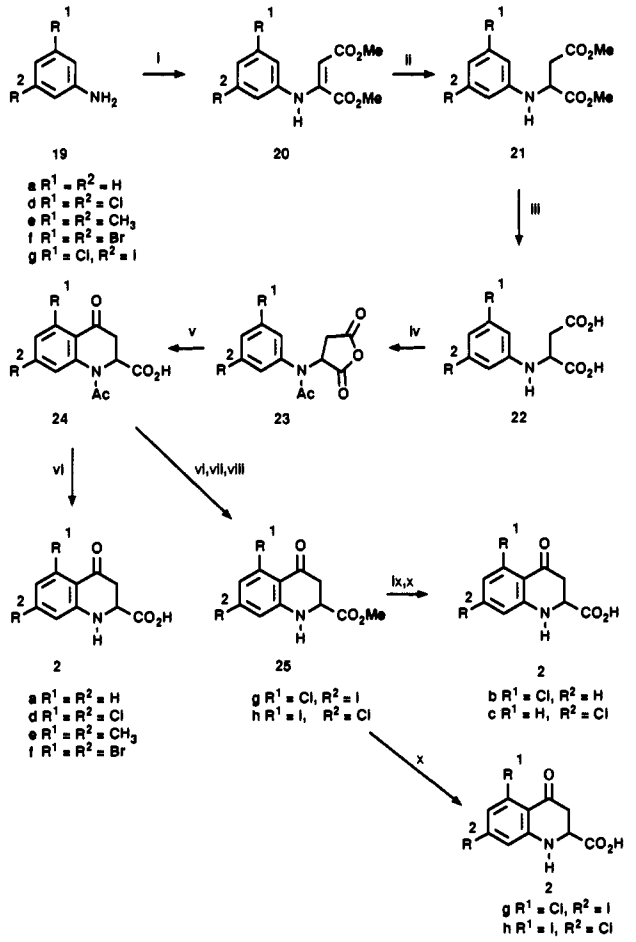
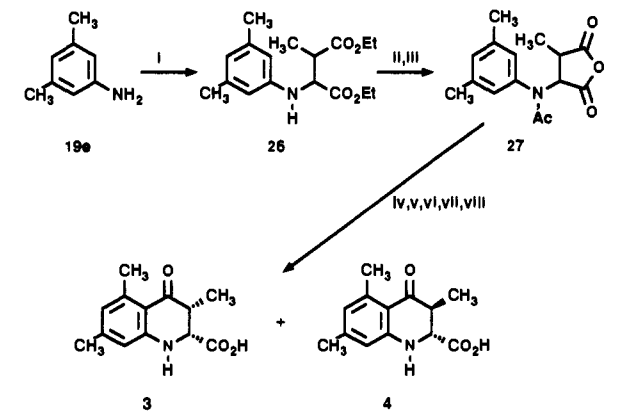
Scheme I[a]



[a] Reagents: (i) $MeO_2CC{\equiv}CCO_2Me$, MeOH, reflux; (ii) H_2–Pd, C, EtOAc or H_2–Pt–S, C, EtOH; (iii) NaOH, aqueous MeOH; (iv) $(CH_3CO)_2O$, 80 °C; (v) $AlCl_3$, 160 °C; (vi) 3 N HCl, 100 °C; (vii) MeOH, HCl; (viii) silica chromatography; (ix) H_2, Pd, C, MeOH; (x) LiOH, THF.

Scheme II[a]



[a] Reagents: (i) $EtO_2CCO{\cdot}CH(CH_3)CO_2Et$, H_2, Pd, C, EtOH; (ii) NaOH, aqueous MeOH; (iii) Ac_2O, 80 °C; (iv) $AlCl_3$, 160 °C; (v) 3 N HCl, 100 °C; (vi) MeOH, HCl; (vii) silica chromatography; (viii) NaOH, aqueous MeOH.

particular are shown to have improved glycine-site antagonist potencies and provide the first details of the stereochemical and conformational requirements for antagonist binding.[11] The overall structure–activity requirements fully support the proposed model for glycine-site antagonist binding and indicate that a variety of 4-substituents can be tolerated.

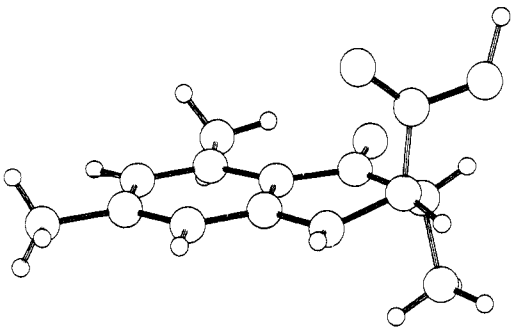


Figure 1. The structure and conformation of 4 as determined by X-ray crystallography.

Synthesis

The 2,3-dihydrokynurenic acid analogues **2a–h** were prepared by the route shown in Scheme I. The appropriate aniline **19a,d–g** and dimethyl acetylenedicarboxylate were heated together in methanol to give the corresponding enamines **20**,[12] which were hydrogenated over palladium on carbon catalyst to produce the reduced amino diesters **21**. In the cases of **20f** and **20g**, sulfided platinum on carbon was used as the hydrogenation catalyst in order to prevent dehalogenation. Saponification of **21** gave the *N*-arylaspartic acid derivatives **22**, which upon treatment with acetic anhydride at 80 °C produced the *N*-acetyl anhydrides **23**. Intramolecular Friedels–Crafts acylation using neat aluminum chloride at 160 °C in the melt according to the conditions of Tokuyama et al.[13] produced the cyclic ketones **24** in yields ranging from 15 to 41%. Removal of the acetyl group to give the required compounds **2** was accomplished by treatment with 3 N HCl at reflux.[13] The iodo and chloro disubstituted compounds **2g** and **2h** were obtained by esterification of the crude mixture produced after deacetylation of **24**, followed by chromatographic separation to give the intermediate esters **25g** and **25h**, which were subsequently saponified. 5-Chloro and 7-chloro derivatives **2b** and **2c** were made by deiodination and hydrolysis of **25g** and **25h**, respectively. The 3-methyl-2,3-dihydrokynurenic acid analogues **3** and **4** were prepared as outlined in Scheme II. 3,5-Dimethylaniline and diethyl oxalpropionate were heated together in ethanol over 4A molecular sieves for several days, and then the reaction mixture was hydrogenated over palladium on carbon catalyst to give diester **26**. Basic hydrolysis followed by treatment with acetic anhydride at 80 °C produced anhydride **27**, which was cyclized under the previously described conditions to give, after deprotection and separation, the *cis*- and *trans*-3-methyl isomers **3** and **4**. The relative stereochemistries of these com-

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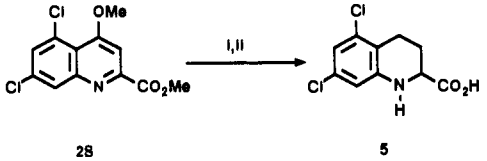
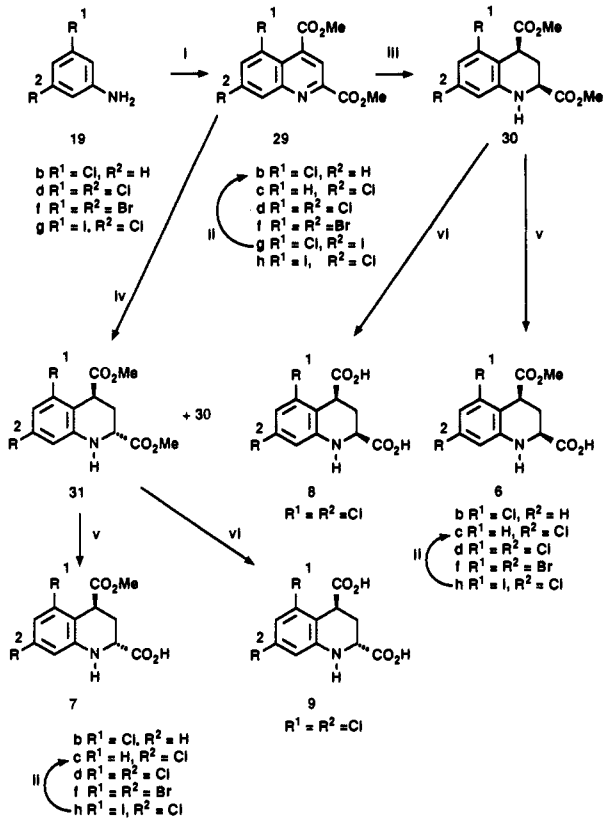
Scheme III[a]



28 5

[a] Reagents: (i) H_2, PtO_2, MeOH; (ii) NaOH, aqueous MeOH.

Scheme IV[a]

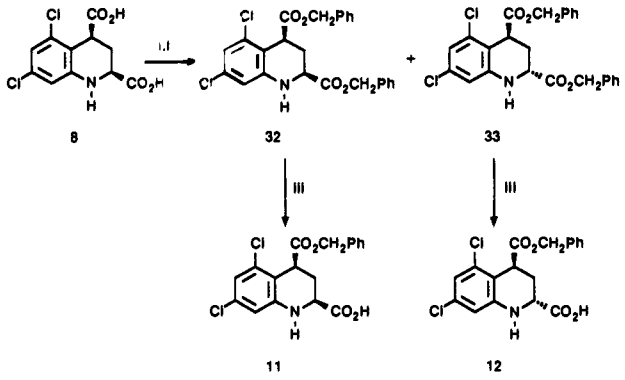


[a] Reagents: (i) $MeO_2CCOCH{=}CHCO_2Me$, HCl, CH_2Cl_2; (ii) H_2, Pd, C, MeOH; (iii) H_2, PtO_2, MeOH; (iv) $NaCNBH_3$, AcOH, 50 °C; (v) 1 equiv NaOH, aqueous $(CH_3)_2CO$; (vi) excess NaOH, aqueous MeOH, reflux, 14 h.

pounds followed from X-ray crystallographic analysis of the 2,3-trans derivative (**4**) (Figure 1). The 4-unsubstituted tetrahydroquinoline **5** was prepared by hydrogenation of 4-methoxyquinoline **28**,[10] followed by saponification (Scheme III).

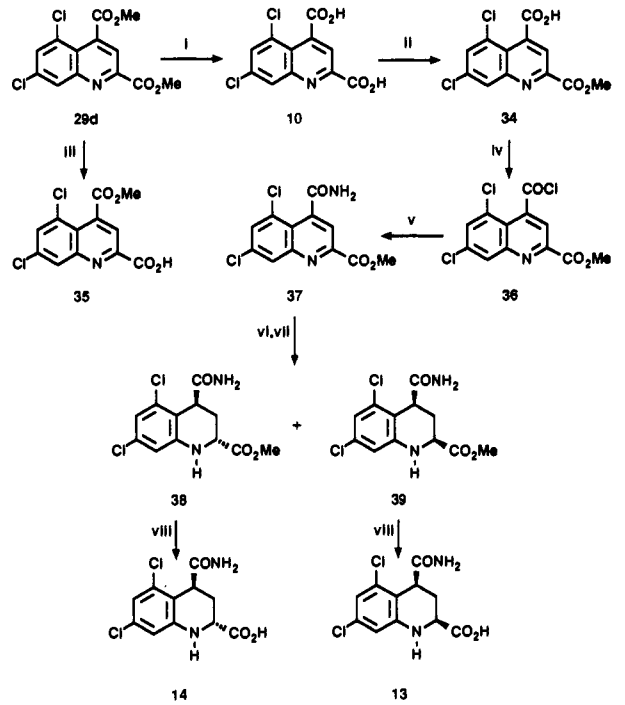
The *cis*- and *trans*-2-carboxy-4-methyl ester tetrahydroquinolines **6b–d,f,h** and **7b–d,f,h**, and the *cis*- and *trans*-2,4-dicarboxytetrahydroquinolines **8** and **9** were prepared as described in Scheme IV. Anilines **19** were stirred with excess dimethyl glutaconate in dichloromethane for several hours and then treated with a catalytic amount of dry hydrogen chloride or boron trifluoride etherate to give quinolines **29**.[14] In the case of 3-chloroaniline (**19b**) the major product was 7-chloroquinoline **29c**, 5-chloro isomer **29b** being formed only in trace amounts. Sufficient quantities of the 5-chloro isomer were obtained by deiodination of the 5-chloro-7-iodo compound **29g** (the major isomer [1.7:1] of cyclizing **19g**) via hydrogenation

Scheme V[a]



[a] Reagents: (i) K_2CO_3, DMF, BnBr; (ii) silica chromatography; (iii) 1 equiv NaOH, aqueous MeOH.

Scheme VI[a]



[a] Reagents: (i) excess NaOH, aqueous MeOH, reflux, 14 h; (ii) MeOH, HCl, 2 h; (iii) 1 equiv NaOH, room temperature; (iv) $SOCl_2$, 60 °C; (v) NH_3, THF; (vi) $NaCNBH_3$, AcOH, 50 °C; (vii) silica chromatography; (viii) NaOH, aqueous MeOH.

over palladium on carbon catalyst. Hydrogenation of **29b–d** and **29f** over platinum oxide produced *cis*-diesters **30b–d** and **30f** exclusively, but deiodination occurred with **29h**. To overcome this problem, and to prepare the corresponding trans isomers **31**, quinolines **29** were reduced by reaction with sodium cyanoborohydride in acetic acid at 50 °C.[15] Typically, formation of the trans isomers was favored by a factor of approximately 2:1. Treatment of compounds **30** and **31** with 1 equiv of sodium hydroxide resulted in selective cleavage of the 2-ester group to give 2-carboxylates **6** and **7**. The origin of this selectivity probably lies with a peri shielding effect of the 4-ester by the 5-chloro substituent. Treatment of compounds **30** and **31** with excess base at room temperature gave incomplete reaction, and more forcing conditions had to be employed to form dicarboxylates **8** and **9**. The regiochemistry of **6h** and **7h** was proven to be 5-iodo-7-chloro by deiodination to produce 7-chloro derivatives **6c** and **7c**, respectively.

The *cis*- and *trans*-4-benzyl ester 2-carboxytetrahydroquinolines **11** and **12** were prepared by reaction of *cis*-

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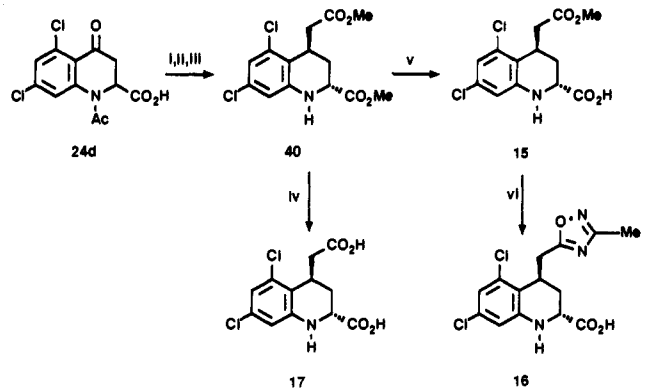
Scheme VII[a]

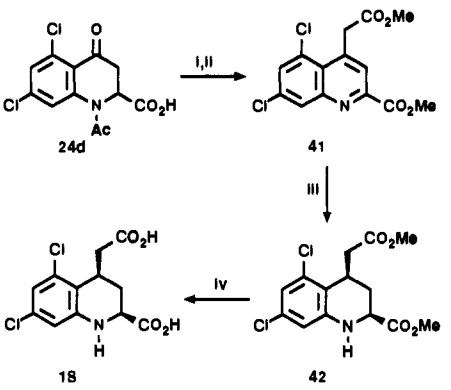


[a] Reagents: (i) $MeO_2CCH_2P(O)(OMe)_2$, $NaNH_2$, THF; (ii) H_2, PtO_2, MeOH, 60 h. (iii) MeOH, HCl; (iv) excess NaOH, aqueous MeOH; (v) 1 equiv NaOH, aqueous MeOH; (vi) $CH_3{=}N(OH){\cdot}NH_2$, NaH, THF.

2,4-dicarboxylate 8 with benzyl bromide in dimethylformamide in the presence of potassium carbonate, followed by chromatographic separation of the isomers **32** and **33** and subsequent treatment with 1 equiv of sodium hydroxide (Scheme V). The *cis*- and *trans*-4-carboxamides (**13** and **14**) were synthesized by the route described in Scheme VI. Quinoline diester **29d** was hydrolyzed under forcing conditions to give quinolinediacid **10**, and treatment of this compound with methanolic hydrogen chloride for 2 h resulted in selective ester formation at the 2-position to give **34**. The regiochemistry of compound **34** was confirmed since treatment of **29d** with 1 equiv of sodium hydroxide cleanly produced the isomeric mono ester **35**, which was significantly different from **34** according to ^1H NMR spectra and reverse-phase HPLC. Reaction of **34** with thionyl chloride at 60 °C produced acid chloride **36**, which underwent reaction with dry ammonia in tetrahydrofuran to give amide **37**. Reduction of the heterocyclic ring was accomplished with sodium cyanoborohydride in acetic acid[15] at 50 °C to give an approximately equal amount of the *cis*- and *trans*-esters **38** and **39**, and the required final compounds **13** and **14** were obtained by simple basic hydrolysis.

trans-4-Acetate derivatives **15–17** were prepared as outlined in Scheme VII. Treatment of **24d** with the anion of trimethyl phosphonoacetate (preformed with sodium amide[16]) gave a crude mixture of olefins which was hydrogenated over platinum then treated with methanolic hydrogen chloride to give *trans*-diester **40**. Basic hydrolysis under forcing conditions gave diacid **17**, and milder conditions mono acid **15**. Methyloxadiazole derivative **16** was prepared by reaction of the anion of acetamide oxime[18] with 4-mono ester **15**. The synthesis of *cis*-4-acetic acid **18** was carried out by the route described in Scheme VIII. Treatment of ketone **24d** with the anion of trimethyl phosphonoacetate gave the same crude mixture of alkenes described previously. This was dissolved in methanol which had been presaturated with dry hydrogen chloride and stood at room temperature for several days. Quinoline **41** was isolated and then hydrogenated over platinum in

Scheme VIII[a]



[a] Reagents: (i) $MeO_2CCH_2P(O)(OMe)_2$, $NaNH_2$, THF; (ii) MeOH, HCl, 42 days; (iii) H_2, PtO_2, MeOH; (iv) excess NaOH, aqueous MeOH.

methanol to produce *cis*-diester **42**, which was hydrolyzed under standard conditions to yield the required compound.

Biology

Compounds were evaluated in in vitro assays predictive for activity at the NMDA receptor, and details of the methodologies used have been published.[10,19,20] Affinities for the glycine binding site were determined by displacement of [^3H]glycine binding to membranes prepared from rat cerebral cortex and hippocampus. The concentrations of test compounds required to inhibit 50% of the specific binding (IC_{50}'s) of [^3H]glycine were indicative of affinities for the glycine/NMDA site. Functional antagonist potency was assessed by determination of the apparent dissociation constants (K_b's) of test compounds for antagonism of the depolarizations induced by NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) in a rat cortical slice preparation.

The IC_{50}'s from the radioligand binding assay are the means of at least three experiments (except where stated) and the maximum variance (geometric mean) was 60%. The K_b values from the cortical slice assay are means from at least three experiments; the maximum variance (geometric mean) was 15%. Generally, IC_{50}'s of compounds in the [^3H]glycine binding assay are around 10-fold lower than apparent K_b's for *N*-methyl-D-aspartate antagonism in the cortical slice. The lower activity in the functional assay is probably a consequence of competition with high levels of endogenous glycine present in the cortical slice preparation. The potencies of selected compounds as antagonists of glycine-induced NMDA currents in isolated cultured neurones, where glycine concentrations can be adjusted, were fully consistent with their affinities for the [^3H]glycine site.[19,21]

Results and Discussion

The effect of reduction at the 2,3-double bond of kynurenic acid and its more potent substituted derivatives is summarized in Table I. The dihydro analogues **2a–h**

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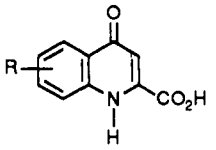
(20) Foster, A. C.; Kemp, J. A. HA-966 antagonizes N-methyl-D-aspartate receptors through a selective interaction with the glycine modulatory site. *J. Neurosci.* **1989**, *9*, 2191.
(21) Kemp, J. A.; Priestley, T. Unpublished results.
(22) MSDRL, molecular modeling program based on MM2, written by the Molecular Systems Group, MSDRL, Rahway, NJ.

Table I. Kynurenic Acids and 2,3-Reduced Kynurenic Acids



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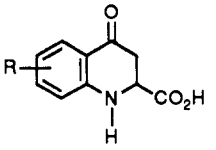


2

R	no.	IC_{50} (μM) vs [^{3}H]Gly[10]	K_b (μM) vs NMDA[10]	no.	IC_{50} (μM) vs [^{3}H]Gly	K_b (μM) vs NMDA
H	**1a**	41	154	**2a**	>100	473
5-Cl	**1b**	5.2	37	**2b**	6.96	
7-Cl	**1c**	0.56	7	**2c**	2.36	39
5,7-Cl_2	**1d**	0.20	3	**2d**	2.31	14
5,7-Me_2	**1e**	0.54	7	**2e**	1.86	57
5,7-Br_2	**1f**	0.086	1.6	**2f**	1.29	12
5-Cl,7-I	**1g**	0.65	10	**2g**	3.84	60
5-I,7-Cl	**1h**	0.032	0.41	**2h**	0.36	2.5

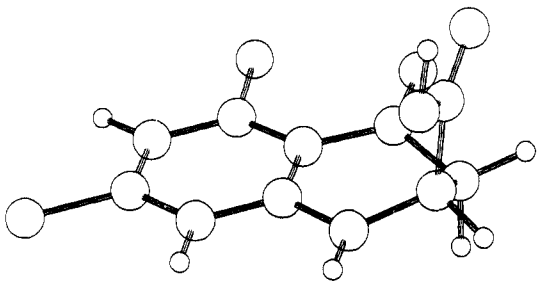


Figure 2. The 2-pseudoaxial conformer of **2d** energy minimized (3.43 kcal) using AMF (Advanced Modeling Facility).[22]

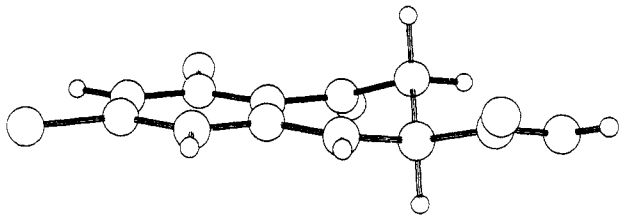


Figure 3. The 2-pseudoequatorial conformer of **2d** energy minimized (2.73 kcal) using AMF.[22]

generally show reduced potency, but the rank order of activity reflects that of the lead compounds, and thus, 5-iodo-7-chloro substitution still optimal. The maintenance of activity in the dihydrokynurenates, which cannot tautomerize, provides further evidence that the 4-oxo tautomer of compounds **1a–h** is required for receptor recognition. The relative reduction in potency observed with the 2,3-reduced kynurenic acids may be attributable to the preferred existence in solution of the pseudoaxial 2-carboxylate conformation (Figure 2). This follows from the absence of a large vicinal coupling in the ^{1}H NMR spectrum for **2d**, where the observed coupling constants for H_A are only 6.8 and 6.2 Hz. The less preferred pseudoequatorial conformer (Figure 3) is clearly a better mimic of the planar kynurenic acid and is almost certainly the conformation needed for binding. Further evidence for this argument is provided by the data summarized in Table II. 2,3-Dihydro-5,7-dimethyl analogue **2e** is approximately 1 order of magnitude less potent than the corresponding kynurenic acid **1e**. *cis*-3-Methyl derivative **3** is equipotent in the functional assay with **2e** while *trans*-3-methyl compound **4** is essentially inactive. In the case of the trans compound **4**, the energy difference between the 2-pseudoaxial and 2-pseudoequatorial conformation is increased by vicinal repulsion between the 2- and 3-substituents (to obtain a dihedral angle of 180°) and so reduced potency is seen. The 2,3-diaxial relationship of compound **4** has been confirmed by X-ray crystallographic analysis (Figure 1). In the case of cis compound **3**, 2,3-substituent gauche interactions are unavoidable in both 2-pseudoaxial and 2-pseudoequatorial conformers, the two conformers are consequently in competition, and so potency is retained.

The reduction in potency seen with the 1,2,3,4-tetrahydroquinoline **5** relative to the corresponding 2,3-dihydrokynurenic acid **2d** (Table III) indicates the importance of the 4-keto group, which is probably acting as a hydrogen-bond acceptor.[10] Further evidence for this hypothesis is the finding that addition of a methoxycarbonyl group to the 4-position of the molecule results in increased potency in both the cis (**6d**) and the trans (**7d**) isomers (Table IV). The effect of aromatic substitution in the trans series (compounds **7b–d,f,h**) is different from that observed in the kynurenic acid and reduced kynurenic acid series since the 5,7-dichloro (**7d**), 5,7-dibromo (**7f**), and 5-iodo-7-chloro (**7h**) derivatives are essentially equipotent. ^{1}H NMR ($J[H_A–H_B]$ = 11.7 Hz) and molecular modeling studies indicate that the preferred conformation of trans compounds **7** is probably 4-pseudoaxial 2-pseudoequatorial (Figure 4). In the *cis* series (compounds **6b–d,f,h**), 5,7-dichloro analogue **6d** is actually the most potent compound and 5-iodo-7-chloro derivative **6h** is markedly less potent. This finding can again be rationalized by consideration of conformational arguments since the size of the 5-substituent is likely to influence conformational preference within the cis series. Steric interaction between 4- and 5-substituents results in the 4-substituent adopting a pseudoaxial arrangement and the degree to which this occurs is likely to depend on the relative sizes of both groups. With the cis isomers (**6b–d,f,h**), ^{1}H NMR studies in DMSO ($J[H_A–H_B]$ = 7.1 Hz) show that the preferred conformation is indeed 2,4-diaxial (Figure 5), and since the pseudoequatorial 2-carboxylate is likely to be preferred for receptor binding, this finding would account for the decrease in potency observed as the size of the 5-substituent increases. 5-Iodo-7-chloro derivative **6h** is less potent than 7-chloro compound **6c** even though the latter compound lacks the usually beneficial effect of a size-limited hydrophobic substituent at the 5-position. This is attributable, again, to an increase in the population of the receptor-active di-pseudoequatorial conformation (Figure 6).

The 5,7-dichloro 2,4-dicarboxylate derivatives (**8** and **9**, Table V) both show a marked reduction in potency relative to the corresponding parent 4-methyl ester derivatives (**6d** and **7d**). 2,4-Dicarboxyquinoline **10** is essentially inactive, providing further evidence of the need for a hydrogen-bond donor at the 1-position.[10,23] The *cis*- and *trans*-4-benzyl esters **11** and **12** are equipotent and both compounds are significantly more active than corresponding acids **8** and

Table II. Reduced and Methylated Derivatives of 5,7-Dimethylkynurenic Acid

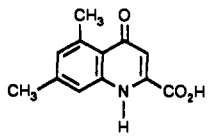
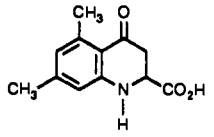
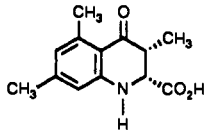
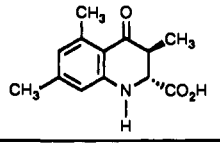
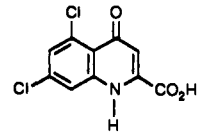
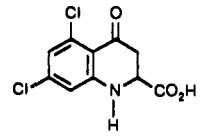
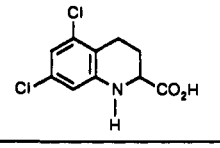
no.	structure	IC_{50} (μM) vs [^{3}H]Gly	K_d (μM) vs NMDA
1e		0.54[10]	7.0[10]
2e		1.86	57
3		13.7	62
4		>100	>100

Table III. Reduced Derivatives of 5,7-Dichlorokynurenic Acid

no.	structure	IC_{50} (μM) vs [^{3}H]Gly	K_d (μM) vs NMDA
1d		0.20[10]	3[10]
2d		2.31	14
5		6.39	84

9, and this result suggests bulk tolerance on the receptor adjacent to the 4-position. The *cis*- and *trans*-4-carboxamides **13** and **14** are also essentially equipotent (in the functional assay), and the general lack of stereoselectivity exhibited throughout Table V indicates that the hydrogen-bonding groups and/or their relative positions are probably not optimal.

Homologation at the 4-position of *trans*-methyl ester **7d** gives methyl acetate derivative **15** (Table VI), which shows a 5-fold improvement in functional potency and is approximately equipotent with the best 4-carboxylic ester analogue **6d**. Methyloxadiazole **16** has only 4-fold reduced potency and is clearly an acceptable replacement for a methyl ester.[24] A marked increase in activity occurs with

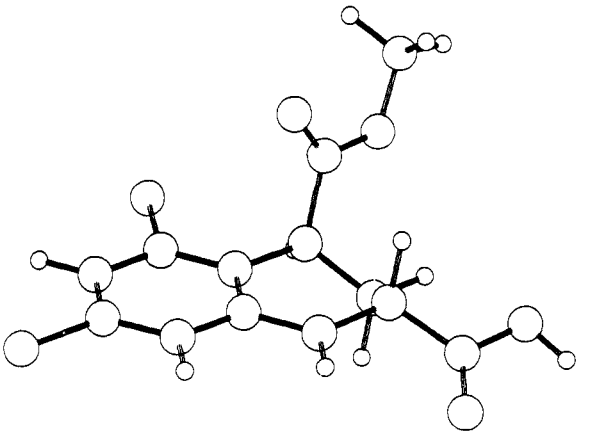


Figure 4. The 4-pseudoaxial-2-pseudoequatorial conformer of **7d** energy minimized (12.812 kcal) using AMF.[22]

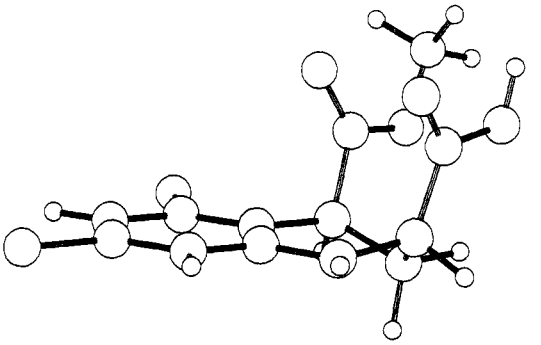


Figure 5. The 2,4-di-pseudoaxial conformer of **6d** energy minimized (14.654 kcal) using AMF.[22]

trans-4-acetic acid derivative **17**, which is more potent than the corresponding lead 5,7-dichlorokynurenic acid (**1d**). Compound **17** is also very selective (K_b vs AMPA > 100 μM; K_b vs NMDA, 1.2 μM) and the high activity of **17** is in agreement with other recent results[23,25] showing that an anionic group is tolerated in the 4-position binding pocket of the glycine receptor. This suggests that the glycine site may have some features in common with the neurotransmitter recognition sites on NMDA and AMPA receptors since the majority of antagonists and agonists (including glutamate itself) that bind to these sites are also α-amino acids which contain remote anionic functionality.[4] The >100-fold binding affinity of **17** relative to cis isomer **18** and the lower acid homologues **8** and **9** may be explained by optimal positioning in **17** of the 4-substituent carboxyl group. The difference in potency between the two isomers **17** and **18** can again be rationalized by conformational analysis. ^{1}H NMR evidence shows cis compound **18** to exist in the 2,4-pseudoaxial (receptor-inactive) conformation ($J[H_A-H_B] < 7.0$ Hz) while the trans compound **17** exists in the 4-pseudoaxial, 2-pseudoequatorial conformation ($J[H_A-H_B] = 12.4$ Hz], which we propose is required for receptor recognition.

Conclusions

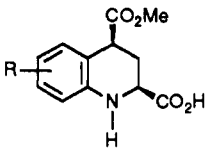
The results of these studies are consistent with the model we proposed previously for high-affinity binding of antagonists to the glycine site of the NMDA receptor.[10] The need for a hydrogen-bond-accepting group at the

(23) Harrison, B. L.; Baron, B. M.; Cousino, D. M.; McDonald, I. A. 4-((Carboxymethyl)oxy)- and 4-((carboxymethyl)amino)-5,7-dichloroquinoline-2-carboxylic acid: New antagonists of the strychnine-insensitive glycine binding site on the N-methyl-D-aspartate receptor complex. *J. Med. Chem.* **1990**, *33*, 3130.

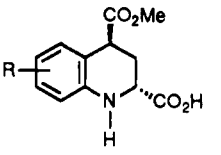
(24) Saunders, J.; Macleod, A. M.; Merchant, K.; Showell, G. A.; Snow, R. J.; Street, L. J.; Baker, R. Ester bioisosteres: Synthesis of oxadiazolyl-1-azabicyclo[2.2.1]heptanes as muscarinic agonists. *J. Chem. Soc. Chem. Commun.* **1988**, *24*, 1618.

(25) Salituro, F. G.; Harrison, B. L.; Baron, B. M.; Nyce, P. L.; Stewart, K. T.; McDonald, I. A. 3-(2-Carboxyindol-3-yl)-propionic acid derivatives: Antagonists of the strychnine-insensitive glycine receptor associated with the N-methyl-D-aspartate receptor complex. *J. Med. Chem.* **1990**, *33*, 2944.

Table IV. 4-(Methoxycarbonyl)-2-carboxytetrahydroquinolines



6



7

R	no.	IC_{50} (μM) vs [^{3}H]Gly	K_b (μM) vs NMDA	no.	IC_{50} (μM) vs [^{3}H]Gly	K_b (μM) vs NMDA
5-Cl	**6b**	26.1	128	**7b**	176	~300
7-Cl	**6c**	5.02	19	**7c**	16.9	75
5,7-Cl_2	**6d**	1.21	5.2	**7d**	2.47	23
5,7-Br_2	**6f**	2.05	10	**7f**	2.89	16
5-I,7-Cl	**6h**	4.18	28	**7h**	3.09	15

Table V. 5,7-Dichloro-4-carboxytetrahydroquinoline Derivatives

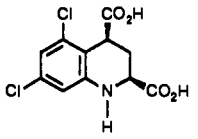
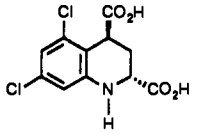
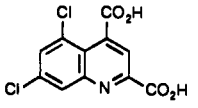
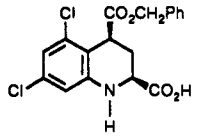
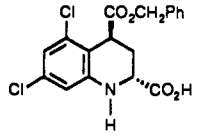
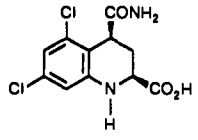
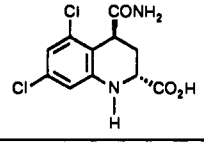
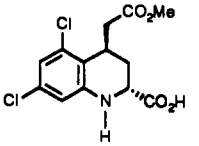
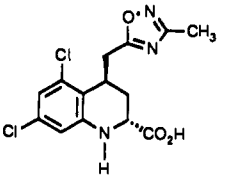
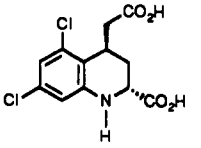
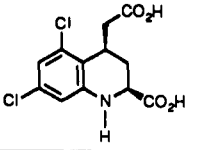
no.	structure	IC_{50} (μM) vs [^{3}H]Gly	K_d (μM) vs NMDA
8		31.4	214
9		20 (n = 1)	>10
10		>100	>100
11		2.33	42
12		1.05	44
13		3.44	27
14		0.72	19

Table VI. 5,7-Dichloro-4-methylenetetrahydroquinoline Derivatives

no.	structure	IC_{50} (μM) vs [^{3}H]Gly	K_b (μM) vs NMDA
15		0.603	5.6
16		2.53	20
17		0.134	1.2
18		15.0	105

4-position of the quinoline ring has been proven by both removal of the 4-oxo group, resulting in reduced potency, and replacement with alternative 4-substituents, realizing increased activity. The requirement of a hydrogen-bond-donating group at the 1-position independently indicated by Leeson et al.[10] and Harrison et al.[23] is supported by the generally high activity seen with the 2-carboxytetrahydroquinolines described in this paper. This finding supports the view that the active tautomer of the kynurenic acid (1) series has the 4-keto-1-amino structure. Conformational arguments, which place the 2-carboxylic acid pseudoaxial as opposed to pseudoequatorial, can account for the differences in biological activity seen with the tetrahydroquinoline stereoisomers. The comparable affinities of benzyl esters **11** and **12** with methyl esters **6d** and **7d** indicate probable bulk tolerance at the receptor adjacent to the 4-substituent. The high potency observed with *trans*-4-acetic acid **17** suggests optimal positioning of the 4-substituent and indicates that the glycine site may have some features in common with the neurotransmitter recognition site on the NMDA receptor. These results clearly extend current views of structural requirements and tolerance for binding to the glycine site on the NMDA receptor.

Experimental Section

General directions have appeared previously.[26]

2-Carboxy-5,7-dichloro-4-oxo-1,2,3,4-tetrahydroquinoline (2d). 3,5-Dichloraniline (**19d**) (104 g, 0.62 mol) and dimethyl acetylenedicarboxylate (79 mL, 0.63 mol) were dissolved in dry methanol (100 mL) and heated under reflux for 14 h. On cooling a yellow solid crystallized out and this was collected by filtration. The mother liquors were concentrated under vacuum to leave a

(26) Leeson, P. D.; Carling, R. W.; James, K.; Smith, J. D.; Moore, K. W.; Wong, E. H. F.; Baker, R. Role of hydrogen bonding in ligand interaction with the N-methyl-D-aspartate receptor ion channel. *J. Med. Chem.* **1990**, *33*, 1296.

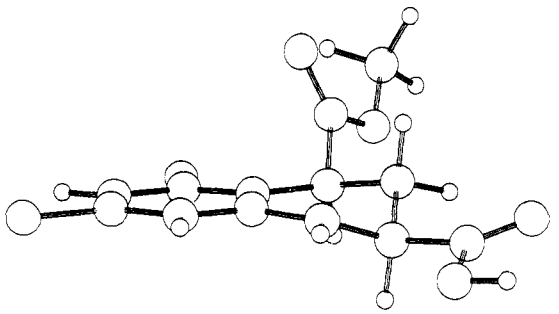


Figure 6. The 2,4-di-pseudoequatorial conformer of **6d** energy minimized (14.371 kcal) using AMF.[22]

residue from which a second crop of product was obtained by recrystallization from diethyl ether/petroleum ether (bp 60–80 °C throughout). From the combined crops (167.5 g, 87%) a portion of this material (105 g) was dissolved in ethyl acetate (100 mL) and hydrogenated over 10% palladium on carbon catalyst (4 g) for 40 h. The catalyst was removed by filtration and the solvent was evaporated under vacuum to leave a residue which was recrystallized from diethyl ether/petroleum ether to give diester **21d** as a white crystalline solid (84.8 g, 80%): mp 66–67 °C; NMR δ ($CDCl_3$) 2.88 (2 H, m, $CH_ACH_BH_CCO$), 3.71 (3 H, s, CH_3), 3.78 (3 H, s, CH_3), 4.36 (1 H, t, J = 5.4 Hz, $CH_ACH_BH_CCO$), 4.71 (1 H, br, s, NH), 6.51 (2 H, d, J = 1.8 Hz, 2-H and 6-H), 6.73 (1 H, t, J = 1.8 Hz, 4-H); MS (EI) m/e 305 [M^+]. Anal. ($C_{12}H_{12}Cl_2NO_4$) C, H, N. Diester **21d** (131.4 g, 0.43 mol) was dissolved in methanol (800 mL) with sodium hydroxide (51.5 g, 1.29 mol, in 600 mL of water) and stirred at room temperature for 5 h. The methanol was removed under vacuum and the residual solution was acidified to pH 1 by the cautious addition of concentrated hydrochloric acid. After extraction with ethyl acetate (2 × 600 mL), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give **22d** as a white solid (116 g, 97%): mp 217 °C dec; NMR δ (NaOD) 2.47 (1 H, dd, J = 15.1 and 10.1 Hz, $CH_ACH_BH_C$), 2.73 (1 H, dd, J = 15.1 and 3.8 Hz, $CH_ACH_BH_C$), 4.06 (1 H, dd, J = 10.1 and 3.8 Hz, $CH_ACH_BH_C$), 6.62 (2 H, d, J = 1.5 Hz, 2-H and 6-H), 6.79 (1 H, t, J = 1.5 Hz, 4-H); MS (EI) m/e 277 [M^+]. Anal. ($C_{10}H_9Cl_2NO_4$) C, H, N. A portion of **22d** (80 g, 0.29 mol) was dissolved in acetic anhydride (600 mL), heated at 80 °C for 2 h, and then allowed to cool to room temperature. A white solid was collected by filtration, and the mother liquors were concentrated under vacuum and triturated with diethyl ether to give a second crop. The combined crops were dried under high vacuum to give **23d** (82.6 g, 92%): NMR δ ($CDCl_3$) 1.97 (3 H, s, $NCOCH_3$), 3.27 (2 H, m, $CH_ACH_BH_C$), 4.44 (1 H, dd, $CH_ACH_BH_C$, J = 9.4 and 7.0 Hz), 7.30 (2 H, d, J = 1.6 Hz, 2-H and 6-H), 7.46 (1 H, t, J = 1.6 Hz, 4-H). A portion of this material (60 g, 0.19 mol) and finely ground aluminum trichloride (168 g, 1.26 mol) was blended together and heated at 160 °C for 30 min. The reaction mixture was poured onto aluminum foil and allowed to cool to room temperature, and the solid mass was ground to a powder and cautiously poured into ice-cold 1 N HCl. After effervescence had ceased, the aqueous layer was decanted and the residual solid was triturated with absolute ethanol to give **24d** as a white solid (10.2 g, 17%): mp 212–213 °C; NMR δ (DMSO) 2.32 (3 H, s, $NCOCH_3$), 3.04 (1 H, dd, J = 17.4 and 1.7 Hz, $CH_ACH_BH_C$), 3.21 (1 H, dd, J = 17.4 and 6.6 Hz, $CH_ACH_BH_C$), 5.59 (1 H, m, $CH_ACH_BH_C$), 7.54 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.81 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS (EI) m/e 301 [M^+]. Anal. ($C_{12}H_9Cl_2NO_4$) C, H, N.

24d (21.17 g, 0.07 mol) was suspended in 3 N HCl (500 mL), heated under reflux for 14 h, and then cooled and extracted with ethyl acetate (3 × 300 mL), washed with brine (1 × 300 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give **2d** as a yellow solid (17.45 g, 96%): mp 218–219 °C; NMR δ (DMSO) 2.73 (1 H, dd, J = 15.7 and 6.8 Hz, $CH_ACH_BH_C$), 2.92 (1 H, dd, J = 15.7 and 6.2 Hz, $CH_ACH_BH_C$), 4.36 (1 H, m, $CH_ACH_BH_C$), 6.67 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.96 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.62 (1 H, br s, NH); MS (FAB) m/e 260 [$MH]^+$. Anal. ($C_{10}H_7Cl_2NO_3$) C, H, N.

Compounds **2e** and **2f** were prepared in the same way as described for **2d** starting with the appropriate anilines.

2-Carboxy-5,7-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline (2e): mp 154–155 °C; NMR δ (DMSO) 2.14 (3 H, s, CH_3), 2.40 (3 H, s, CH_3), 2.65 (1 H, dd, J = 15.9 and 6.7 Hz, $CH_ACH_BH_C$), 2.79 (1 H, dd, J = 15.9 and 6.2 Hz, $CH_ACH_BH_C$), 4.18 (1 H, ddd, J = 6.7, 6.2, and 2.1 Hz, $NHCH_ACH_BH_C$), 6.21 (1 H, s, 6-H or 8-H), 6.54 (1 H, s, 6-H or 8-H), 6.83 (1 H, br s, NH); MS (FAB) m/e 220 [$MH]^+$. Anal. ($C_{12}H_{13}NO_3 \cdot 0.8H_2O$) C, H, N.

2-Carboxy-5,7-dibromo-4-oxo-1,2,3,4-tetrahydroquinoline (2f): mp 213–216 °C; NMR δ (DMSO) 2.74 (1 H, dd, J = 15.7 and 6.4 Hz, $CH_ACH_BH_C$), 2.93 (1 H, dd, J = 15.7 and 6.4 Hz, $CH_ACH_BH_C$), 4.36 (1 H, dt, J = 6.4 and 2.0 Hz, $NHCH_ACH_BH_C$), 6.98 (1 H, d, J = 1.7 Hz, 6-H or 8-H), 7.16 (1 H, d, J = 1.7 Hz, 6-H or 8-H), 7.59 (1 H, d, J = 2.0 Hz, NH), 13.15 (1 H, br s, CO_2H); MS (EI) m/e 349 M [M^+]. Anal. ($C_{10}H_6Br_2O_3$) C, H, N.

2-Carboxy-5-chloro-4-oxo-1,2,3,4-tetrahydroquinoline (2b). A mixture of **24g** and **24h** (4.0 g, 0.012 mol) (which was obtained from 3-chloro-5-iodoaniline (20 g) by the same sequence of reactions described for the preparation of **24d**) was dissolved in 3 N HCl and heated under reflux for 3 h. After cooling, extraction into ethyl acetate, drying (Na_2SO_4), filtration and evaporation, a crude mixture (3.19 g, 89%) of **2g** and **2h** was obtained. Treatment of the mixture with methanolic hydrogen chloride (20 mL) for 3 h, evaporation, and silica gel chromatography using 10% hexane in dichloromethane as eluent gave **25h** (0.3 g, 9%, mp 176–177 °C) as the less polar isomer and **25g** (0.7 g, 21%, mp 208–209 °C) as the more polar isomer. **25g** (0.3 g, 0.82 mmol) was dissolved in methanol (50 mL) and hydrogenated under atmospheric pressure over 10% palladium on carbon catalyst for 8 h. After filtration and evaporation, the residue obtained was purified by silica gel chromatography using 10% hexane in dichloromethane as eluent to give a product (0.069 g) which was dissolved in THF (30 mL) and treated with 0.5 N lithium hydroxide solution (0.58 mL, 0.35 mmol). After 2 h, the solvent was removed under vacuum and the residue was dissolved in water (40 mL) and acidified to pH 1 with 1 N HCl. After extraction into ethyl acetate (2 × 40 mL), washing with brine (1 × 40 mL), drying (Na_2SO_4), filtration, and evaporation, the residue was recrystallized from methanol to give **2b** as a yellow solid (0.042 g, 26% from **25g**): mp 166–167 °C; NMR δ (DMSO) 2.72 (1 H, dd, J = 15.5 and 6.6 Hz, $CH_ACH_BH_C$), 2.91 (1 H, dd, J = 15.5 and 6.2 Hz, $CH_ACH_BH_C$), 4.30 (1 H, dt, J = 6.4 and 3.1 Hz, $CH_ACH_BH_C$), 6.60 (1 H, dd, J = 8.0 and 0.7 Hz, 6-H or 8-H), 6.85 (1 H, dd, J = 8.0 and 0.7 Hz, 6-H or 8-H), 7.18 (1 H, t, J = 8.0 Hz, 7-H), 7.53 (1 H, br s, NH), 13.0 (1 H, br s, CO_2H); MS (CI) m/e 226 [$MH]^+$. Anal. ($C_{10}H_8ClNO_3 \cdot 0.4H_2O$) C, H, N.

2-Carboxy-7-chloro-4-oxo-1,2,3,4-tetrahydroquinoline (2c). Treatment of **25h** under the conditions described for the conversion of **25g** to **2b** gave **2c**, as a yellow solid: mp 232–233 °C dec; NMR δ (DMSO) 2.73 (1 H, dd, J = 16.5 and 7.0 Hz, $CH_ACH_BH_C$), 2.86 (1 H, dd, J = 16.5 and 6.0 Hz, $CH_ACH_BH_C$), 4.34 (1 H, m, $CH_ACH_BH_C$), 6.12 (1 H, dd, J = 8.0 and 1.9 Hz, 6-H), 6.99 (1 H, d, J = 1.9 Hz, 8-H), 7.30 (1 H, s, NH), 7.53 (1 H, d, J = 8.0 Hz, 5-H), 13.0 (1 H, br s, CO_2H); MS (EI) m/e 225 [M^+]. Anal. ($C_{10}H_8ClNO_3 \cdot 0.1H_2O$) C, H, N.

2-Carboxy-5-chloro-7-iodo-4-oxo-1,2,3,4-tetrahydroquinoline (2g). Compound **25g** (0.15 g, 0.41 mmol) was dissolved in THF (30 mL) and 0.5 N lithium hydroxide solution (0.984 mL, 1.2 molar equiv) was added. After stirring at room temperature for 3 h, the solvent was removed under vacuum and the residue produced was dissolved in water (50 mL). The aqueous solution was acidified to pH 1 with 1 N HCl, extracted into ethyl acetate (2 × 40 mL), washed with brine (1 × 40 mL), dried ($NaSO_4$), filtered, and concentrated under vacuum. The product obtained was recrystallized from ethyl acetate/hexane to give **2g** as a yellow solid (0.095 g, 67%): mp 232 °C; NMR δ (DMSO) 2.71 (1 H, dd, J = 15.7 and 6.3 Hz, $CH_ACH_BH_C$), 2.91 (1 H, dd, J = 15.7 and 6.2 Hz, $CH_ACH_BH_C$), 4.33 (1 H, dt, J = 6.3 and 2.8 Hz, $CH_ACH_BH_C$), 6.93 (1 H, d, J = 1.5 Hz, 6-H or 8-H), 7.31 (1 H, d, J = 1.5 Hz, 6-H or 8-H), 7.51 (1 H, d, J = 2.1 Hz, NH), 13.11 (1 H, br s, CO_2H); MS (EI) m/e 351 [M^+]. Anal. ($C_{10}H_7ClINO_3 \cdot 0.1H_2O$) C, H, N.

2-Carboxy-7-chloro-5-iodo-4-oxo-1,2,3,4-tetrahydroquinoline (2h). Treatment of **25h** under the conditions described for the conversion of **25g** to **2g** produced **2h** as a yellow solid: mp 239–240 °C; NMR δ (DMSO) 2.76 (1 H, dd, J = 15.8 and 6.7 Hz, $CH_ACH_BH_C$), 2.93 (1 H, dd, J = 15.8 and 6.2 Hz, $CH_ACH_BH_C$),

4.36 (1 H, dt, J = 6.5 and 2.6 Hz, $CH_ACH_BH_C$), 7.03 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*), 7.19 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*), 7.54 (1 H, d, J = 2.0 Hz, N*H*), 13.1 (1 H, br s, CO_2H); MS (EI) m/e 351 [M^+]. Anal. ($C_{10}H_7ClINO_3$) C, H, N.

***trans*- and *cis*-2-Carboxy-4-oxo-3,5,7-trimethyl-1,2,3,4-tetrahydroquinoline (3 and 4).** 3,5-Dimethylaniline (**19e**) (24.2 g, 0.2 mol) and diethyl oxalpropionate (40.4 g, 0.2 mol) were dissolved in ethanol (800 mL) and crushed 4A sieves (10 g) added. The reaction mixture was heated under reflux for 10 days, cooled, and filtered and the residue obtained was purified by silica gel chromatography (40% CH_2Cl_2 in petroleum ether) to give an oil (32 g). This was dissolved in ethanol (200 mL) and hydrogenated at 50 psi over 10% palladium on carbon catalyst for 14 h to give a crude oil (**26**) as product (24.2 g, 39% from **19e**): NMR δ ($CDCl_3$) 1.24 (9 H, m, 2 × CH_3CH_2O and $CH_ACH_BCH_3$), 2.22 (6 H, s, 2 × CH_3Ar), 2.99 (1 H, m, $CH_ACH_BCH_3$), 4.16 (4 H, m, 2 × CH_3CH_2O), 4.43 (1 H, m, $CH_ACH_BCH_3$), 6.32 (2 H, br, s, 2-H and 6-H), 6.41 (1 H, br s, 4-H). **26** (24.2 g, 0.079 mol) was dissolved in 50% aqueous methanol with sodium hydroxide (20 g, 0.5 mol), stirred at room temperature for 14 h, and then concentrated under vacuum. The residue was dissolved in water (300 mL) and washed with diethyl ether (2 × 200 mL), and then the aqueous layer was acidified to pH 1 with 5 N HCl and the solid produced was collected by filtration, dried under high vacuum, and then heated in acetic anhydride (450 mL) at 80 °C for 2 h. After evaporation of the solvent, the residue was triturated with diethyl ether, and an off white solid (**27**) (21 g, 97%) was collected by filtration: NMR δ ($CDCl_3$) 1.45 (3 H, d, J = 7.5 Hz, CH_3CH), 1.93 (3 H, s, $COCH_3$), 2.36 (6 H, s, 2 × CH_3Ar), 3.59 (1 H, m, CH_3CH), 4.24 (1 H, m, NC*H*), 6.94 (2 H, br s, 2-*H* and 6-*H*), 7.06 (1 H, br s, 4-*H*); MS (EI) m/e 275 [M^+]. **27** (20 g, 0.073 mol) and $AlCl_3$ (58.2 g, 0.44 mol) were blended together and then heated at 160 °C for 20 min. The cooled reaction mixture was poured into ice-cold 1 N HCl, and after effervescence had ceased the solution was decanted off and the residue was triturated with hot diethyl ether to produce a white solid which was collected by filtration (2.82 g, 14%). The white solid (1.5 g, 5.5 mmol) was treated with 3 N HCl (60 mL) at reflux for 2 h, cooled, extracted into EtOAc (2 × 40 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give a mixture of **3** and **4** (1.18 g, 92%). Recrystallization of the residue from diethyl ether gave **4** as yellow needles (0.22 g, 17%): mp 156–157 °C; NMR δ ($CDCl_3$) 1.35 (3 H, d, J = 7.2 Hz, $CH_3CH_BCH_A$), 2.23 (3 H, s, CH_3Ar), 2.54 (3 H, s, CH_3Ar), 2.97 (1 H, m, $CH_3CH_BCH_A$), 3.97 (1 H, d, J = 4.9 Hz, $CH_3CH_BCH_A$), 6.40 (2 H, br s, 6-*H* and 8-*H*); MS (EI) m/e 233 [M^+]. Anal. ($C_{13}H_{15}NO_3$) C, H, N. The mother liquor (a 0.6-g portion, 2.5 mmol) was dissolved in a solution of methanol that had been presaturated with HCl gas and stood at room temperature for 14 h. After removal of the solvent in vacuo, the residue was chromatographed on silica gel with 20% hexane in dichloromethane as eluent. The less polar material (0.13 g) was dissolved in 50% aqueous methanol (60 mL) with 1 N sodium hydroxide solution (1.58 mL, 3 molar equiv) and stirred at room temperature for 2 h. Standard workup gave **3** as a green oil (0.09 g, 30%): NMR δ ($CDCl_3$) 1.17 (3 H, d, J = 7.2 Hz, $CH_3CH_BCH_A$), 2.24 (3 H, s, CH_3Ar), 2.57 (3 H, s, CH_3Ar), 2.95 (1 H, dq, J = 7.2 and 4.0 Hz, $CH_3CH_BCH_A$), 4.43 (1 H, d, J = 4.0 Hz, $CH_3CH_BCH_A$), 4.90 (1 H, br s, N*H*), 6.40 (1 H, s, 6-*H* or 8-*H*), 6.42 (1 H, s, 6-*H* or 8-*H*); MS (EI) m/e 233 [M^+]. Anal. ($C_{13}H_{15}NO_3 \cdot 0.4H_2O$) C, H, N. The relative stereochemistries of **3** and **4** could not be determined by NMR studies, but X-ray crystallography showed **4** to be 2,3-*trans*.

2-Carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (5). Compound **28**[10] (1 g, 3.5 mmol) was dissolved in methanol (200 mL) and hydrogenated at atmospheric pressure over platinum oxide (0.1 g) for 3 h. After filtration and evaporation, the residue was purified by silica gel chromatography using 10% ethyl acetate in hexane as eluent to give a product which was dissolved in 50% aqueous acetone and treated with sodium hydroxide (0.1 g) for 2 h. Standard workup produced a residue which was purified by preparative plate chromatography using 2% methanol/1% acetic acid in dichloromethane as eluent, followed by recrystallization from dichloromethane to give **5** as a white solid (0.039 g, 5% from **28**): mp 143 °C dec; NMR δ (DMSO) 1.99–2.02 (2 H, m, $NCH_ACH_BH_CCH_DH_E$), 2.45–2.53 (1 H, m, $NCH_ACH_BH_CCH_DH_E$), 2.67–2.74 (1 H, m, $NCH_ACH_BH_CCH_DH_E$), 3.95–3.99 (1 H, m, $NCH_ACH_BH_CCH_DH_E$), 6.60 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*), 6.64 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*), 12.74 (1 H, br s, CO_2H); MS (EI) m/e 245 [M^+]. Anal. ($C_{10}H_9Cl_2NO_2$) C, H, N.

***cis*-2-Carboxy-5,7-dichloro-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (6d).** Compound **19d** (75.35 g, 0.465 mol) and dimethyl glutaconate (100 g, 0.058 mol) were dissolved in dichloromethane (800 mL) and stirred at room temperature for 36 h. $BF_3 \cdot OEt_2$ (100 mL) was added and the solution stirred 2 days further. The reaction mixture was quenched with saturated $NaHCO_3$ solution and the organic layer was separated, washed with brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography on silica gel with 15% ethyl acetate in hexane and recrystallization from methanol gave **29d** as a colorless solid (28 g, 19%): mp 116–118 °C; NMR δ ($CDCl_3$) 4.04 (3 H, s, CH_3), 4.10 (3 H, s, CH_3), 7.77 (1 H, d, J = 2.2 Hz, 6-*H* or 8-*H*), 8.19 (1 H, s, 3-*H*), 8.31 (1 H, d, J = 2.2 Hz, 6-*H* or 8-*H*); MS (EI) m/e 313 [M^+]. Anal. ($C_{13}H_9Cl_2NO_4$) C, H, N. **29d** (1 g, 3.2 mmol) was dissolved in methanol (100 mL) and hydrogenated over platinum oxide (0.1 g) at atmospheric pressure for 1 h. Filtration, evaporation, and silica gel chromatography with dichloromethane as eluent gave *cis*-diester **30d** (0.79 g, 78%): mp 152–153 °C; NMR δ (DMSO) 2.28 (1 H, ddd, J = 14.0, 7.1, and 5.4 Hz, $CH_ACH_BH_CCH_D$), 2.80 (1 H, dt, J = 14.0 and 3.5 Hz, $CH_ACH_BH_CCH_D$), 3.64 (3 H, s, CH_3), 3.67 (3 H, s, CH_3), 3.94 (1 H, dd, J = 7.0 and 3.1 Hz, $CH_ACH_BH_CCH_D$), 4.06 (1 H, dd, J = 5.4 and 3.6 Hz, $CH_ACH_BH_CCH_D$), 6.63 (1 H, d, J = 1.8 Hz, 6-*H* or 8-*H*), 6.67 (1 H, d, J = 1.8 Hz, 6-*H* or 8-*H*); MS (EI) m/e 317 [M^+]. Anal. ($C_{13}H_{13}Cl_2NO_4$) C, H, N. **30d** (0.7 g, 2.2 mmol) was dissolved in 50% aqueous methanol (60 mL), and sodium hydroxide (0.097 g, 2.4 mmol) was added. After stirring at room temperature overnight, the solvents were removed under vacuum, and the residue was dissolved in water and washed with diethyl ether. The aqueous layer was acidified to pH 1 with 1 N HCl, extracted into diethyl ether, dried (Na_2SO_4), filtered, and concentrated under vacuum to give an oil which was purified by silica gel chromatography using 2.5% methanol/0.5% acetic acid/97% dichloromethane as eluent. **6d** was obtained as a white solid (0.53 g, 80%): mp 154–156 °C; NMR δ (DMSO) 2.23 (1 H, ddd, J = 13.9, 7.1, and 5.3 Hz, $CH_ACH_BH_CCH_D$), 2.66 (1 H, dt, J = 13.9 and 4.0 Hz, $CH_ACH_BH_CCH_D$), 3.57 (3 H, s, CH_3), 3.86 (1 H, dd, J = 7.1 and 4.0 Hz, $CH_ACH_BH_CCH_D$), 3.91 (1 H, br m, $CH_ACH_BH_CCH_D$), 5.74 (1 H, br, s, N*H*), 6.56 (1 H, d, J = 1.9 Hz, 6-*H* or 8-*H*), 6.58 (1 H, d, J = 1.9 Hz, 6-*H* or 8-*H*); MS (EI) m/e 303 [M^+]. Anal. ($C_{12}H_{11}Cl_2NO_4$) C, H, N.

Compounds **6b**, **6c**, **6f**, and **6h** were prepared in the same way as described for **6d** starting with the appropriate anilines.

***cis*-2-Carboxy-5-chloro-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (6b)**: mp 190–193 °C; NMR δ (DMSO) 2.20 (1 H, m, $CH_ACH_BH_CCH_D$), 2.56 (1 H, dm, J = 13.8 Hz, $CH_ACH_BH_CCH_D$), 3.55 (3 H, s, CH_3), 3.91 (1 H, dd, J = 7.1 and 3.3 Hz, $CH_ACH_BH_CCH_D$), 3.98 (1 H, m, $CH_ACH_BH_CCH_D$), 6.53 (1 H, br s, N*H*), 6.58 (1 H, d, J = 7.8 Hz, 6-H or 8-H), 6.64 (1 H, d, J = 8.3 Hz, 6-H or 8-H), 6.98 (1 H, t, J = 8.0 Hz, 7-*H*). Anal. ($C_{12}H_{12}ClNO_4$) C, H, N.

***cis*-2-Carboxy-7-chloro-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (6c)**: mp 176–178 °C; NMR δ (DMSO) 2.44 (2 H, m, $CH_ACH_BH_CCH_D$), 3.62 (3 H, s, CH_3), 3.87 (1 H, dd, J = 7.0 and 6.8 Hz, $CH_ACH_BH_CCH_D$), 3.97 (1 H, m, $CH_ACH_BH_CCH_D$), 6.34 (1 H, br s, N*H*), 6.48 (1 H, dd, J = 8.2 and 2.2 Hz, 6-H), 6.72 (1 H, d, J = 2.2 Hz, 8-H), 6.85 (1 H, d, J = 8.2 Hz, 5-H); MS (EI) m/e 269 [M^+]. Anal. ($C_{12}H_{12}ClNO_4$) C, H, N.

***cis*-2-Carboxy-5,7-dibromo-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (6f)**: mp 171–173 °C; NMR δ (DMSO) 2.15 (1 H, m, $CH_ACH_BH_CCH_D$), 2.59 (1 H, dm, J = 13.9 Hz, $CH_ACH_BH_CCH_D$), 3.53 (3 H, s, CH_3), 3.82 (1 H, m, $CH_ACH_BH_CCH_D$), 4.00 (1 H, m, $CH_ACH_BH_CCH_D$), 6.89 (3 H, br m, 6-*H*, 8-*H* and N*H*); MS (EI) m/e 393 [M^+]. Anal. ($C_{12}H_{11}Br_2NO_4$) C, H, N.

***cis*-2-Carboxy-7-chloro-5-iodo-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (6h)**: mp 188 °C dec; NMR δ (DMSO) 2.29 (1 H, m, $CH_ACH_BH_CCH_D$), 2.92 (1 H, dm, J = 14.2 Hz, $CH_ACH_BH_CCH_D$), 3.65 (3 H, s, CH_3), 3.91 (1 H, dd, J = 6.4 and 3.4 Hz, $CH_ACH_BH_CCH_D$), 4.10 (1 H, dd, J = 6.1 and 3.3 Hz, $CH_ACH_BH_CCH_D$), 6.66 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.26 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS (EI) m/e 395 [M^+]. Anal. ($C_{12}H_{11}ClINO_4 \cdot 0.4H_2O$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (7d).** Compound **29d** (2 g, 6.4 mmol) was dissolved in glacial acetic acid (15 mL), and sodium cyanoborohydride (2.4 g, 0.0384 mol) was added in portions over a period of 15 min. The reaction mixture was heated at 50 °C for 1 h and then stirred at room temperature overnight. After dilution with dichloromethane (30 mL), ice-cold 50% NaOH solution was added until a pH of 14 was attained, and the two-phase mixture was stirred vigorously for 2 h, after which time more dichloromethane (50 mL) was added. The two layers were separated, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum to give a residue which was purified by silica chromatography using 70% dichloromethane in hexane and then neat dichloromethane as eluents. **31d** was obtained as a white solid (1.3 g, 64%): mp 113–114 °C; NMR δ ($CDCl_3$) 1.88 (1 H, ddd, J = 13.4, 12.2, and 5.9 Hz, $CH_ACH_BH_CCH_D$), 2.67 (1 H, dt, J = 13.4 and 2.6 Hz, $CH_ACH_BH_CCH_D$), 3.74 (3 H, s, CH_3), 3.82 (3 H, s, CH_3), 4.04 (1 H, dd, J = 12.2 and 3.2 Hz, $CH_ACH_BH_CCH_D$), 4.06 (1 H, m, $CH_ACH_BH_CCH_D$), 4.74 (1 H, br s, N*H*), 6.56 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*), 6.73 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*); MS (EI) m/e 317 [M^+]. Anal. ($C_{13}H_{13}Cl_2NO_4$) C, H, N. Treatment of **31d** (1.13 g, 3.6 mmol) with 1.1 equiv of sodium hydroxide under the same conditions as described for the conversion of **30d** to **6d** gave **7d** (0.85 g, 78%): mp 160 °C dec; NMR δ (DMSO) 1.91 (1 H, ddd, J = 13.4, 11.7, and 6.0 Hz, $CH_ACH_BH_CCH_D$), 2.41 (1 H, dm, J = 13.4 Hz, $CH_ACH_BH_CCH_D$), 3.65 (3 H, s, CH_3), 3.79 (1 H, dd, J = 11.7 and 3.2 Hz, $CH_ACH_BH_CCH_D$), 3.96 (1 H, dd, J = 6.0 and 2.5 Hz, $CH_ACH_BH_CCH_D$), 6.66 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*), 6.83 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*); MS (EI) m/e 303 [M^+]. Anal. ($C_{12}H_{11}Cl_2NO_4$) C, H, N.

Compounds **7b**, **7c**, **7f**, and **7h** were prepared in the same way as described for **7d** starting with the appropriate aniline.

***trans*-2-Carboxy-5-chloro-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (7b)**: mp 159–161 °C; NMR δ (DMSO) 1.93 (1 H, m, $CH_ACH_BH_CCH_D$), 2.39 (1 H, dm, J = 13.4 Hz, $CH_ACH_BH_CCH_D$), 3.65 (3 H, s, CH_3), 3.74 (1 H, dd, J = 11.6 and 3.1 Hz, $CH_ACH_BH_CCH_D$), 3.96 (1 H, dd, J = 6.1 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 6.30 (1 H, br s, N*H*), 6.59 (1 H, d, J = 7.7 Hz, 6-*H* or 8-*H*), 6.72 (1 H, d, J = 8.2 Hz, 6-*H* or 8-*H*), 6.99 (1 H, t, J = 8.0 Hz, 7-*H*); MS (EI) m/e 269 [M^+]. Anal. ($C_{12}H_{12}ClNO_4$) C, H, N.

***trans*-2-Carboxy-7-chloro-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (7c)**: mp 122–124 °C; NMR δ (DMSO) 1.88 (1 H, m, $CH_ACH_BH_CCH_D$), 2.33 (1 H, dm, J = 13.5 Hz, $CH_ACH_BH_CCH_D$), 3.65 (3 H, s, CH_3), 3.75 (1 H, t, J = 5.0 Hz, $CH_ACH_BH_CCH_D$), 3.99 (1 H, dd, J = 9.5 and 3.8 Hz, $CH_ACH_BH_CCH_D$), 6.37 (1 H, br s, N*H*), 6.49 (1 H, dd, J = 8.2 and 2.2 Hz, 6-*H*), 6.74 (1 H, d, J = 2.2 Hz, 8-*H*), 6.94 (1 H, d, J = 8.2 Hz, 5-*H*); MS (EI) m/e 269 [M^+]. Anal. ($C_{12}H_{12}ClNO_4$) C, H, N.

***trans*-2-Carboxy-5,7-dibromo-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (7f)**: mp 175–176 °C; NMR δ (DMSO) 1.90 (1 H, dt, J = 13.4 and 5.7 Hz, $CH_ACH_BH_CCH_D$), 2.41 (1 H, dm, J = 13.4 Hz, $CH_ACH_BH_CCH_D$), 3.66 (3 H, s, CH_3), 3.76 (1 H, dd, J = 11.9 and 3.1 Hz, $CH_ACH_BH_CCH_D$), 3.92 (1 H, dd, J = 4.5 and 1.0 Hz, $CH_ACH_BH_CCH_D$), 6.65 (1 H, br s, N*H*), 6.91 (1 H, d, J = 1.8 Hz, 6-H or 8-H), 7.02 (1 H, d, J = 1.8 Hz, 6-H or 8-H); MS (EI) m/e 393 [M^+]. Anal. ($C_{12}H_{11}Br_2NO_4$) C, H, N.

***trans*-2-Carboxy-7-chloro-5-iodo-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (7h)**: oil; NMR δ (DMSO) 1.95 (1 H, ddd, J = 14.2, 12.2, and 5.6 Hz, $CH_ACH_BH_CCH_D$), 2.72 (1 H, dm, J = 14.4 Hz, $CH_ACH_BH_CCH_D$), 3.76 (3 H, s, CH_3), 3.98 (1 H, dd, J = 5.6 and 2.1 Hz, $CH_ACH_BH_CCH_D$), 4.09 (1 H, dd, J = 12.2 and 3.4 Hz, $CH_ACH_BH_CCH_D$), 6.64 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 7.20 (1 H, d, J = 1.9 Hz, 6-H or 8-H); MS (EI) m/e 395 [M^+]. Anal. ($C_{12}H_{11}ClINO_4$) C, H, N.

***cis*-2,4-Dicarboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (8)**. Compound **30d** (0.2 g, 0.66 mmol) was dissolved in 50% aqueous methanol (200 mL) with sodium hydroxide (0.3 g, 0.0075 mol) and heated under reflux for 14 h. After cooling and evaporation of the solvents, the residue was partitioned between water and diethyl ether. The aqueous layer was acidified to pH 1 with 1 N HCl and extracted into ethyl acetate, dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude solid obtained was recrystallized from diethyl ether/hexane to give **8** as a white solid (0.095 g, 53%): mp 225–227 °C; NMR δ (DMSO) 2.19 (1 H, m, $CH_ACH_BH_CCH_D$), 2.53 (1 H, dt, 13.9 and 3.5 Hz, $CH_ACH_BH_CCH_D$), 3.76 (1 H, dd, J = 7.3 and 3.5 Hz, $CH_ACH_BH_CCH_D$), 3.98 (1 H, m, $CH_ACH_BH_CCH_D$), 6.64 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*), 6.70 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*), 6.80 (1 H, br s, N*H*), 12.48 (2 H, br s, 2 × CO_2H); MS (EI) m/e 289 [M^+]. Anal. ($C_{11}H_3Cl_2NO_4$) C, H, N.

***trans*-2,4-Dicarboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (9)**. Treatment of **31d** (0.2 g, 0.66 mmol) under the conditions described for the conversion of **30d** to **8** gave **9** (0.02 g, 11%): mp 135 °C; NMR δ (DMSO) 1.84 (1 H, ddd, J = 13.4, 11.9, and 5.8 Hz, $CH_ACH_BH_CCH_D$), 2.44 (1 H, dm, J = 13.4 Hz, $CH_ACH_BH_CCH_D$), 3.77 (1 H, dd, J = 11.9 and 3.0 Hz, $CH_ACH_BH_CCH_D$), 3.84 (1 H, dd, J = 5.8 and 2.1 Hz, $CH_ACH_BH_CCH_D$), 6.58 (1 H, br s, N*H*), 6.63 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*), 6.81 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*); MS (FAB) m/e 290 [MH]$^+$. Anal. ($C_{11}H_9Cl_2NO_4$) C, H, N.

2,4-Dicarboxy-5,7-dichloroquinoline (10). Treatment of **31d** (0.3 g, 0.96 mmol) under the conditions described for the conversion of **30d** to **8** gave **10** as a white solid (0.098 g, 36%): mp 246 °C; NMR δ (DMSO) 8.09 (1 H, s, 3-*H*), 8.13 (1 H, d, J = 2.2 Hz, 6-*H* or 8-*H*), 8.32 (1 H, d, J = 2.2 Hz, 6-*H* or 8-*H*); MS (EI) m/e 285 [M^+]. Anal. ($C_{11}H_5Cl_2NO_4 \cdot H_2O$) C, H, N.

***cis*-4-(Benzyloxycarbonyl)-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (11)**. Compound **8** (0.47 g, 1.63 mmol) was dissolved in DMF (30 mL) with potassium carbonate (1.12 g, 8.1 mmol) and benzyl bromide (0.43 mL, 3.6 mmol). After stirring for 14 h, the solvent was evaporated under vacuum and the residue was partitioned between water and dichloromethane. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo then purified by silica gel chromatography using 70% dichloromethane in hexane as eluent to give as colorless solids **32** [(0.23 g, 30%) mp 112–114 °C; NMR δ ($CDCl_3$) 2.43 (1 H, dd, J = 13.9, 7.2, and 5.1 Hz, $CH_ACH_BH_CCH_D$), 2.80 (1 H, dt, J = 13.9 and 4.4 Hz, $CH_ACH_BH_CCH_D$), 4.01 (1 H, dd, J = 7.2 and 4.4 Hz, $CH_ACH_BH_CCH_D$), 4.95 (1 H, m, $CH_ACH_BH_CCH_D$), 4.64 (1 H, br s, N*H*), 5.04 (4 H, m, 2 × $PhCH_2$), 6.56 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.77 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.31 (10 H, m, 2 × Ph); MS (EI) m/e 469 [M^+].] and **33** [(0.35 g, 46%) mp 150–152 °C; NMR δ ($CDCl_3$) 1.89 (1 H, ddd, J = 13.5, 11.2, and 5.0 Hz, $CH_ACH_BH_CCH_D$), 2.68 (1 H, dm, J = 13.5 Hz, $CH_ACH_BH_CCH_D$), 4.02 (1 H, dd, J = 12.2 and 3.1 Hz, $CH_ACH_BH_CCH_D$), 4.09 (1 H, dd, J = 5.9 and 2.1 Hz, $CH_ACH_BH_CCH_D$), 4.72 (1 H, br s, N*H*), 5.16 (2 H, s, $PhCH_2$), 5.21 (2 H, s, $PhCH_2$), 6.54 (1 H, d, J = 1.9 Hz, 6-*H* or 8-*H*), 6.72 (1 H, d, J = 1.9 Hz, 6-*H* or 8-*H*), 7.35 (10 H, m, 2 × Ph); MS (EI) m/e 469 [M^+].]. Treatment of **32** (0.23 g, 0.49 mmol) under the conditions described for the conversion of **30d** to **6d** gave **11** as a white solid (0.027 g, 15%): mp 144 °C dec; NMR δ ($CDCl_3$) 2.35 (1 H, m, $CH_ACH_BH_CCH_D$), 2.81 (1 H, dm, J = 13.9 Hz, $CH_ACH_BH_CCH_D$), 4.03 (2 H, m, $CH_ACH_BH_CCH_D$), 5.07 (2 H, s, $PhCH_2$), 6.57 (1 H, d, J = 1.5 Hz, 6-*H* or 8-*H*), 6.77 (1 H, d, J = 1.5 Hz, 6-*H* or 8-*H*), 7.32 (5 H, m, Ph); MS (EI) m/e 379 [M^+]. Anal. ($C_{18}H_{15}Cl_2NO_4$) C, H, N.

***trans*-4-(Benzyloxycarbonyl)-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (12)**. Treatment of **33** (0.35 g, 0.75 mmol) under the conditions described for the conversion of **30d** to **6d** gave **12** as a white solid (0.045 g, 16%): mp 124–126 °C; NMR δ ($CDCl_3$) 1.95 (1 H, m, $CH_ACH_BH_CCH_D$), 2.71 (1 H, dm, J = 12.6 Hz, $CH_ACH_BH_CCH_D$), 4.08 (1 H, dd, J = 12.3 and 3.1 Hz, $CH_ACH_BH_CCH_D$), 4.13 (1 H, dd, J = 5.8 and 2.0 Hz, $CH_ACH_BH_CCH_D$), 5.19 (2 H, s, $PhCH_2$), 6.56 (1 H, d, J = 1.8 Hz, 6-*H* or 8-*H*), 6.75 (1 H, d, J = 1.8 Hz, 6-*H* or 8-*H*), 7.33 (5 H, m, Ph); MS (CI$^+$) m/e 380 [M + H]$^+$. Anal. ($C_{18}H_{15}Cl_2NO_4$) C, H, N.

***cis*-4-(Aminocarbonyl)-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (13)**. Compound **10** (19.5 g, 0.0684 mol) was dissolved in methanol (500 mL) which had been saturated with HCl gas and stood at room temperature for 1 h. The volume was reduced to approximately 100 mL by evaporation under vacuum and the white solid that was produced was collected by filtration to give **34** (18.5 g, 90%): mp 260–262 °C; NMR δ (DMSO) 3.98 (3 H, s, CH_3), 8.11 (1 H, s, 3-*H*), 8.15 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*), 8.36 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*); MS (EI) m e 299 [M^+]. Anal. ($C_{12}H_7Cl_2NO_4 \cdot 0.2H_2O$) C, H, N. **34**

(15.2 g, 0.051 mol) was dissolved in thionyl chloride (300 mL) and the reaction mixture was heated at 60 °C for 3 h. The solvent was removed under vacuum and the residue dried under high vacuum for 14 h to give **36** as a white solid (16.5 g, 102%): NMR δ ($CDCl_3$) 4.12 (3 H, s, CH_3), 7.83 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 8.25 (1 H, s, 3-*H*), 8.35 (1 H, d, J = 1.9 Hz, 6-*H* or 8-*H*); MS (EI) m/e 317 [M^+]. **36** (1.5 g, 0.0047 mol) was dissolved in dry THF (20 mL) at 0 °C and an ice-cold solution of THF (150 mL), which had been presaturated with dry ammonia, was added in one portion. After stirring at room temperature for 30 min, the white solid that precipitated was collected by filtration and dried (1.4 g, **37** contaminated with ammonium chloride). A portion of this solid (1 g) was suspended in glacial acetic acid (20 mL), and sodium cyanoborohydride (1.3 g, 0.02 mol) was added in portions. When the addition was complete, the reaction mixture was heated at 50 °C for 2 h, cooled, and stirred at room temperature for 14 h. The solution was diluted with dichloromethane (80 mL) and ice-cold 50% NaOH was added cautiously until a pH of 14 was attained. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a residue which was purified by silica gel chromatography, using 2% methanol in dichloromethane as eluent to give as white solids **38** [(0.15 g, 11% from **36**) mp 227–229 °C; NMR δ (DMSO) 1.83 (1 H, m, $CH_ACH_BH_CCH_D$), 2.32 (1 H, dm, J = 13.2 Hz, $CH_ACH_BH_CCH_D$), 3.72 (3 H, s, CH_3), 3.78 (1 H, dd, J = 5.8 and 2.0 Hz, $CH_ACH_BH_CCH_D$), 4.01 (1 H, dd, J = 12.2 and 2.1 Hz, $CH_ACH_BH_CCH_D$), 6.63 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*), 6.66 (1 H, br s, N*H*), 6.78 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*), 7.02 (1 H, br s, N*H*), 7.51 (1 H, br s, N*H*); MS (EI) m/e 302 [M^+]. Anal. ($C_{12}H_{12}Cl_2N_2O_3$) C, H, N.] and **39** [(0.14 g, 10% from **37**) mp 203–204 °C; NMR δ (DMSO) 2.05 (1 H, m, $CH_ACH_BH_CCH_D$), 2.52 (1 H, m, $CH_ACH_BH_CCH_D$), 3.54 (3 H, s, CH_3), 3.71 (1 H, dd, J = 7.2 and 3.4 Hz, $CH_ACH_BH_CCH_D$), 4.11 (1 H, dd, J = 5.2 and 3.2 Hz, $CH_ACH_BH_CH_D$), 6.61 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*), 6.70 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*), 6.84 (2 H, br s, $CONH_2$), 7.20 (1 H, br s, N*H*); MS (CI) m/e 303 [MH]$^+$. Anal. ($C_{12}H_{12}Cl_2N_2O_3$) C, H, N. Treatment of **39** (0.12 g, 0.4 mmol) under the conditions described for the conversion of **30d** to **6d** gave **13** (0.082 g, 71%): mp 220–222 °C; NMR δ (DMSO) 2.28 (2 H, m, $CH_ACH_BH_CCH_D$), 3.71 (1 H, m, $CH_ACH_BH_CCH_D$), 3.89 (1 H, m, $CH_ACH_BH_CCH_D$), 6.62 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*), 6.64 (1 H, br s, N*H*), 6.74 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*), 6.81 (1 H, br s, N*H*), 7.26 (1 H, br s, N*H*); MS (FAB) m/e 289 [MH]$^+$. Anal. ($C_{11}H_{10}Cl_2N_2O_3 \cdot 0.4H_2O$). C, H, N.

***trans*-4-(Aminocarbonyl)-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline** (14). Treatment of **38** (0.12 g, 0.4 mmol) under the conditions described for the conversion of **30d** to **6d** gave 14 (0.104 g, 86%): mp 168–170 °C; NMR δ (DMSO) 1.79 (1 H, m, $CH_ACH_BH_CCH_D$), 2.35 (1 H, dm, J = 13.4 Hz, $CH_ACH_BH_CCH_D$), 3.78 (1 H, m, $CH_ACH_BH_CCH_D$), 3.89 (1 H, dm, J = 11.8 Hz, $CH_ACH_BH_CCH_D$), 6.55 (1 H, br s, N*H*), 6.61 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*), 6.81 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*), 7.02 (1 H, s, N*H*), 7.49 (1 H, s, N*H*); MS (FAB) m/e 289 [MH]$^+$. Anal. ($C_{11}H_{10}Cl_2N_2O_3 \cdot 0.4H_2O$) C, H, N: calcd, 9.45; found, 8.95.

***trans*-2-Carboxy-4-[(methoxycarbonyl)methyl]-5,7-dichloro-1,2,3,4-tetrahydroquinoline** (15). Trimethyl phosphonoacetate (32.4 mL, 0.2 mol) was dissolved in dry THF (700 mL) with sodamide (7.8 g, 0.2 mol), heated at 60 °C for 1.5 h, and then cooled to 0 °C. **24d** (16 g, 0.062 mol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 14 h. After quenching with glacial acetic acid (10 mL) and evaporation of the solvents, the residue obtained was dissolved in saturated $NaHCO_3$ solution (800 mL) and washed with ethyl acetate (4 × 500 mL). The aqueous layer was acidified to pH 1 with 1 N HCl and extracted with ethyl acetate (2 × 500 mL). The combined organic layers were washed with water (4 × 300 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue (~16 g) was dissolved in methanol (1400 mL) and hydrogenated under atmospheric pressure over platinum oxide (10 g) for 60 h. After filtration and evaporation, the oily residue was dissolved in methanol (1000 mL) which had been presaturated with dry HCl and stood at room temperature for 8 days. The solvent was removed under vacuum and the oil obtained was purified by silica gel chromatography using 20% hexane in dichloromethane as eluent to give as a white solid **40** (6.53 g, 32%): mp 131 °C; NMR δ (DMSO) 1.69 (1 H, ddd, J = 13.4, 12.3, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.16 (1 H, dm, J = 13.4 Hz, $CH_ACH_BCH_CCH_D$), 2.52 (2 H, m, $CH_2CO_2CH_3$), 3.46 (1 H, m, $CH_ACH_BH_CCH_D$), 3.65 (3 H, s, CH_3), 3.72 (3 H, s, CH_3), 4.11 (1 H, dd, J = 12.3 and 2.9 Hz, $CH_ACH_BH_CCH_D$), 6.64 (1 H, d, J = 1.9 Hz, 6-*H* or 8-*H*), 6.71 (1 H, br s, N*H*), 6.80 (1 H, d, J = 1.9 Hz, 6-*H* or 8-*H*); MS (EI) m/e 331 [M^+]. Anal. ($C_{14}H_{15}Cl_2NO_4$) C, H, N. Treatment of **40** (0.4 g, 1.2 mmol) under the conditions described for the conversion of **30d** to **6d** gave **15** (0.26 g, 63%): mp 181–182 °C; NMR δ ($CDCl_3$) 1.72 (1 H, ddd, J = 13.3, 12.5, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.36 (1 H, dm, J = 13.3 Hz, $CH_ACH_BH_CCH_D$), 2.39 (1 H, dd, J = 16.0 and 11.2 Hz, $CH_ECH_FCO_2CH_3$), 2.72 (1 H, dd, J = 16.0 and 3.5 Hz, $CH_ECH_FCO_2CH_3$), 3.66 (1 H, m, $CH_ACH_BH_CCH_DCH_ECH_FCO_2CH_3$), 3.73 (3 H, s, CO_2CH_3), 3.99 (1 H, dd, J = 12.5 and 5.1 Hz, $CH_ACH_BH_CCH_DCH_ECH_FCO_2CH_3$), 5.15 (1 H, br s, N*H*), 6.56 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*), 6.62 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*); MS (EI) m/e 317 [M^+]. Anal. ($C_{13}H_{13}Cl_2NO_4$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]-1,2,3,4-tetrahydroquinoline** (16). Acetamide oxime (0.22 g, 2.8 mmol) was dissolved in THF (30 mL) with sodium hydride (0.11 g of an 80% dispersion in oil, 2.8 mmol) and heated at 60 °C for 2 h. **15** (0.317 g, 1.0 mmol) was added and the reaction mixture was heated at 60 °C for a further 2 h, then cooled, poured into 1 N HCl (30 mL), and extracted into diethyl ether. After drying (Na_2SO_4), filtration, and evaporation, the residue obtained was purified by silica gel chromatography using 2% methanol and 0.5% acetic acid in dichloromethane as eluent to give **16** as a white solid (0.12 g, 35%): mp 191–192 °C; NMR δ ($CDCl_3$) 1.75 (1 H, ddd, J = 13.5, 12.6, and 4.4 Hz, $CH_ACH_BH_CCH_DCH_ECH_F$), 2.29 (1 H, dm, J = 13.5 Hz, $CH_ACH_BH_CCH_DCH_EH_F$), 2.41 (3 H, CH_3), 2.96 (1 H, dd, J = 15.6 and 11.1 Hz, $CH_ACH_BH_CCH_DCH_ECH_F$), 3.23 (1 H, dd, J = 15.6 and 3.8 Hz, $CH_ACH_BH_CCH_DCH_ECH_F$), 3.75 (1 H, m, $CH_ACH_BH_CCH_DCH_ECH_F$), 4.05 (1 H, dd, J = 12.6 and 3.6 Hz, $CH_ACH_BH_CCH_DCH_EH_F$), 5.25 (1 H, br s, N*H*), 6.60 (1 H, d, J = 1.9 Hz, 6-*H* or 8-*H*), 6.65 (1 H, d, J = 1.9 Hz, 6-*H* or 8-*H*); MS (CI) m/e 343 [MH]$^+$. Anal. ($C_{14}H_{13}Cl_2N_3O_3$) C, H, N.

***trans*-2-Carboxy-4-(carboxymethyl)-5,7-dichloro-1,2,3,4-tetrahydroquinoline** (17). Treatment of **40** (0.4 g, 0.2 mmol) under the conditions described for the conversion of **30d** to **8** gave **17** as a white solid (0.24 g, 66%): mp 229–231 °C; NMR δ (DMSO) 1.63 (1 H, ddd, J = 13.3, 12.4, and 4.0 Hz, $CH_ACH_BH_CCH_DCH_EH_F$), 2.20 (1 H, dm, J = 13.3 Hz, $CH_ACH_BH_CCH_DCH_EH_F$), 2.40 (2 H, m, $CH_ACH_BH_CCH_DCH_EH_F$), 3.39 (1 H, m, $CH_ACH_BH_CCH_DCH_EH_F$), 3.98 (1 H, dd, J = 12.4 and 3.3 Hz, $CH_ACH_BH_CCH_DCH_EH_F$), 6.57 (1 H, br s, N*H*), 6.61 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*), 6.80 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*); MS (FAB) m/e [MH]$^+$. Anal. ($C_{12}H_{11}Cl_2NO_4$) C, H, N.

***cis*-2-Carboxy-4-(carboxymethyl)-5,7-dichloro-1,2,3,4-tetrahydroquinoline** (18). Trimethyl phosphonoacetate (16.2 mL, 0.1 mol) was dissolved in dry THF (350 mL) with sodamide (3.90 g, 0.1 mol), heated at 60 °C for 2 h and then cooled to 0 °C and **24d** (8 g, 0.031 mol) added. The reaction mixture was stirred at room temperature for 14 h and then quenched with glacial acetic acid (10 mL) and concentrated under vacuum. The residue was dissolved in saturated $NaHCO_3$ solution and washed several times with ethyl acetate. The aqueous solution was acidified to pH 1 with 5 N HCl and extracted into ethyl acetate. The organic layer was washed several times with water and then brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was dissolved in methanol (500 mL) which had been saturated with dry HCl and stood at room temperature for 42 days. The solid which slowly precipitated was collected by filtration and recrystallized from methanol/water to give, as an off-white solid, **41** (2.4 g, 24%): mp 140–142 °C; NMR δ ($CDCl_3$) 3.73 (3 H, s, CH_3), 4.08 (3 H, s, CH_3), 4.50 (2 H, s, CH_2), 7.70 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*), 8.01 (1 H, s, 3-*H*), 8.29 (1 H, d, J = 2.1 Hz, 6-*H* or 8-*H*); MS (CI) m/e 328 [MH]$^+$. **41** (2.2 g, 6.7 mmol) was dissolved in methanol (150 mL) and hydrogenated at atmospheric pressure over platinum oxide (0.3 g) for 2.5 h. Filtration and evaporation produced a residue which was purified by silica gel chromatography using 25% ethyl acetate in petroleum ether as eluent to give, as a white solid, **42** (0.61 g, 28%): mp 128–129 °C; NMR δ ($CDCl_3$) 2.16 (2 H, m, $CH_ACH_BCH_CCH_DCH_EH_F$), 2.60 (1 H, dm, J = 14.5 Hz, $CH_ACH_BH_CCH_DCH_EH_F$), 2.72 (1 H, dd, J

= 16.7 and 3.3 Hz, $CH_ACH_BH_CCH_EH_F$), 3.64 (1 H, m, $CH_ACH_BH_CCH_DCH_EH_F$), 4.07 (1 H, dd, J = 6.6 and 2.5 Hz, $CH_ACH_BH_CCH_DCH_EH_F$), 4.59 (1 H, br s, N*H*), 6.51 (1 H, d, J = 1.9 Hz, 6-*H* or 8-*H*), 6.72 (1 H, d, J = 1.9 Hz, 6-*H* or 8-*H*); MS (CI) m/e 331 $[MH]^+$. Treatment of **42** (0.3 g, 0.91 mmol) under the conditions described for the conversion of **30d** to **8** gave **18** as a white solid (0.045 g, 16%): mp 203–204 °C; NMR δ (DMSO) 1.98 (1 H, m, $CH_ACH_BH_CCH_DCH_ECH_F$), 2.19 (1 H, dd, J = 17.2 and 11.7 Hz, $CH_ACH_BH_CCH_DCH_ECH_F$), 2.41 (2 H, m, $CH_ACH_BCH_CCH_DCH_EH_F$), 3.39 (1 H, m, $CH_ACH_BH_CCH_DCH_EH_F$), 4.03 (1 H, br s, $CH_ACH_BH_CCH_DCH_EH_F$), 6.62 (1 H, s, 6-*H* or 8-*H*), 6.64 (1 H, s, 6-*H* or 8-*H*), 6.84 (1 H, br s, N*H*), 12.49 (2 H, br s, 2 × CO_2H); MS (EI) m/e 303 $[M^+]$. Anal. ($C_{12}H_{11}Cl_2NO_4 \cdot 0.25H_2O$) C, H, N.

(27) The following library of crystallographic programs was used: SHELXS-86, G.M. Sheldrick, University of Göttingen, West Germany (1986); PLUTO, W.D.S. Motherwell and W. Clegg, University of Cambridge, England (1978); a version of SDPV.3, Enraf-Nonius, Delft, The Netherlands (1985), locally modified for a Sun Microsystems computer.

Crystallography Data. Crystals of 4 ($C_{13}H_{15}NO_3$) formed in space group $2_1/n$ with a = 10.414 (1) Å, b = 8.392 (1) Å, c = 13.960 (1) Å, β = 103.65 (1)° for Z = 4, and a calculated density of 1.307 g/cm^3. An automatic four-circle diffractometer equipped with Cu Kα radiation (λ = 1.5418 Å) was used to measure 2248 potential diffraction peaks of which 1474 were observed ($I > 3\sigma I$). Application of a multisolution tangent formula approach to phase solution gave an initial model for the structure[27] which was subsequently refined with least squares and Fourier methods. Anisotropic temperature parameters were refined for the nonhydrogen atoms while isotropic temperature factors were applied to the hydrogens but were not refined. The function $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 4F_o^2/\sigma^2(F_o^2)$ was minimized with full matrix least squares to give an unweighted residual of 0.056.

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