4-Amido-2-carboxytetrahydroquinolines. Structure-Activity Relationships for Antagonism at the Glycine Site of the NMDA Receptor

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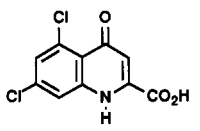
trans-2-Carboxy-5,7-dichloro-4-amidotetrahydroquinolines, evolved from the lead 5,7-dichlorokynurenic acid, have been synthesized and tested for in vitro antagonist activity at the glycine site on the *N*-methyl-D-aspartate (NMDA) receptor. Optimization of the 4-substituent has provided antagonists having nanomolar affinity, including the urea *trans*-2-carboxy-5,7-dichloro-4-[[(phenylamino)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (**35**; IC_{50} = 7.4 nM vs [^{3}H]glycine binding; K_b = 130 nM for block of NMDA responses in the rat cortical slice), which is one of the most potent NMDA antagonists yet found. The absolute stereochemical requirements for binding were found to be 2*S*,4*R*, showing that, in common with other glycine-site NMDA receptor ligands, the unnatural configuration at the α-amino acid center is required. The preferred conformation of the *trans*-2,4-disubstituted tetrahydroquinoline system, as shown by X-ray crystallography and ^{1}H NMR studies, places the 2-carboxyl pseudoequatorial and the 4-substituent pseudoaxial. Modifications of the 4-amide show that bulky substituents are tolerated and reveal the critical importance for activity of correct positioning of the carbonyl group. The high affinity of *trans*-2-carboxy-5,7-dichloro-4-[1-(3-phenyl-2-oxoimidazolidinyl)]-1,2,3,4-tetrahydroquinoline (**55**; IC_{50} = 6 nM) suggests that the *Z*,*Z* conformer of the phenyl urea moiety in **35** is recognized by the receptor. Molecular modeling studies show that the 4-carbonyl groups of the kynurenic acids, the tetrahydroquinolines, and related antagonists based on *N*-(chlorophenyl)glycine, can interact with a single putative H-bond donor on the receptor. The results allow the establishment of a three-dimensional pharmacophore of the glycine receptor antagonist site, incorporating a newly defined bulk tolerance/hydrophobic region.

There is abundant evidence that antagonists acting at the N-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptor can reduce ischaemic brain damage, particularly in experimental models of focal cerebral ischaemia.[1] The search for therapeutically useful antiischaemic agents has been stimulated by the discovery of a site on the NMDA receptor where the amino acid glycine, acting in a strychnine-insensitive manner, dramatically amplifies receptor responses.[2] Several classes of glycine-site directed NMDA receptor antagonists have subsequently been identified.[2-11] In the preceding paper,[11] we described the evolution of our initial glycine antagonist lead, the kynurenic acid derivative **1**,[5] into potent 2-



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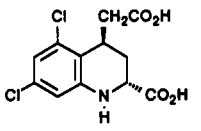

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carboxytetrahydroquinolines, exemplified by *trans*-4-acetic acid derivative **2**. Herein we define the absolute stereochemical requirements for activity and show that the 4-substituent in **2** can be replaced by a substituted amide or urea, resulting in antagonists having low nanomolar affinity for the glycine site.[12] The novel antagonists provide primary details of the stereochemical and bulk tolerance requirements for activity, permitting an extension of our existing receptor model[5] to a three-dimensional pharmacophore of the glycine antagonist recognition site.

Synthesis. Compound **3** has been reported[11]; compounds **4-61** were prepared for this study. The key intermediate *trans*-4-amino methyl ester (**66**) was prepared from ketone **62**.[11] Oxime **63** was reduced with zinc in acetic acid; the resulting mixture of amines separated after *tert*-butoxycarbonyl protection to provide stereoisomers **64** and **65**, and **65** deprotected to yield **66** (Scheme I). Treatment of mixtures of **64** and **65** with catalytic quantities of sodium methoxide in refluxing methanol resulted in epimerization, with the more thermodynamically stable trans isomer **65** predominating by >20:1. Acylation of **66** using acid chlorides in the presence of triethylamine, or carboxylic acids with triethylamine, water-soluble carbo-

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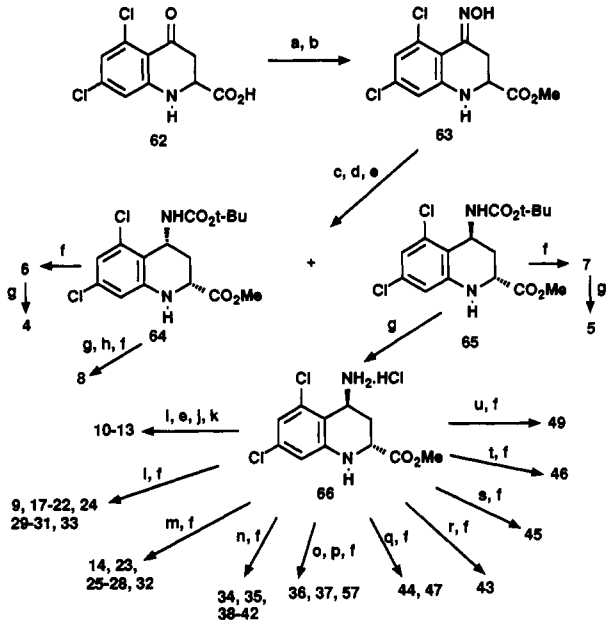
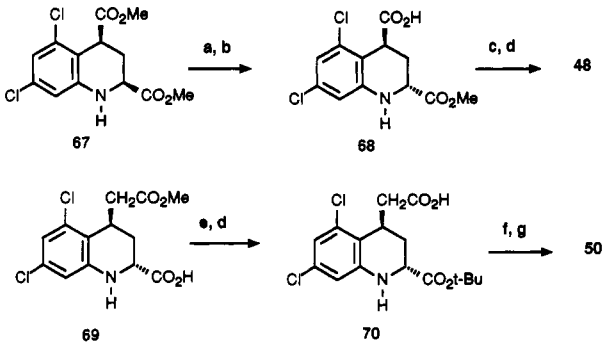
Scheme I[a]



[a] (a) $NH_2OH{\cdot}HCl$, C_5H_5N; (b) MeOH, HCl; (c) Zn, HOAc; (d) $(t\text{-BuOCO})_2O$, $Me_2N(CH_2)_2NH_2$; (e) separate, SiO_2 chromatography; (f) LiOH, H_2O, THF; (g) HCl, EtOAc; (h) PhCOCl, Et_3N; (i) (*R*)- or (*S*)-$PhCH_2CH(NHCO_2t\text{-Bu})CO_2H$, $Me_2N(CH_2)_3N{=}C{=}NEt$, HOBT, Et_3N; (j) CF_3CO_2H; (k) NaOH, MeOH, H_2O; (l) RCOCl, Et_3N; (m) RCO_2H, $Me_2N(CH_2)_3N{=}C{=}NEt$, HOBT, Et_3N; (n) $RN{=}C{=}O$, Et_3N; (o) PhOCOCl, Et_3N; (p) Me_3SiCl, Et_3N, R^1R^2NH; (q) RX, Et_3N, DMF; (r) $PhSO_2Cl$, Et_3N; (s) $PhN{=}C{=}S$, Et_3N; (t) PhNHCSNHCN, $Me_2N(CH_2)_3N{=}C{=}NEt$, DMF; (u) $(PhCH_2O)_2CO$, Et_3N.

diimide reagent and 1-hydroxybenzotriazole (HOBT), followed by hydrolysis of the 2-ester, gave compounds **9–33**. Ureas **34**, **35**, and **38–42** were readily prepared from reactions of **66** with the appropriate isocyanates. The substituted ureas **36**, **37**, and **57** were obtained by conversion of **66** to the corresponding phenyl carbamate derivative, followed by in situ formation of the isocyanate with trimethylsilyl chloride and triethylamine, and reaction with the appropriate anilines. Alkylation of **66** gave **44** and **47**, and cyanoguanidine **46** was obtained using phenylthiourea in the presence of water-soluble carbodiimide.[13]

Scheme II[a]



[a] (a) NaOH, dry MeOH; (b) MeOH, HCl; (c) (i) $(imidazole)_2CO$, DMF, 60 °C, (ii) $PhCH_2NH_2$, DMAP; (d) NaOH, MeOH, H_2O; (e) $Me_2C{=}CH_2$, H_2SO_4; (f) $PhNH_2$, HOBT, Et_3N, $Me_2N(CH_2)_3N{=}C{=}NEt$; (g) 10% aqueous CF_3CO_2H.

4-Benzyl carboxamide **48** was obtained from *cis*-diester **67**[11] (Scheme II). Treatment of **67** with sodium hydroxide in anhydrous methanol caused both ester hydrolysis and epimerization, resulting in a 3:1 mixture of the *cis*- and *trans*-diacids. Esterification proceeded selectively at the less hindered 2-carboxyl to provide **68** (as a 3:1 mixture of stereoisomers), which was coupled with benzylamine; the trans isomer was separated by chromatography and deprotected to give **48**. Protection of the 2-carboxyl of **69**[11] as the *tert*-butyl ester allowed selective hydrolysis of the 4-methyl ester to give **70**, which was converted to 4-benzylacetamide **50**.

An alternative route[14] to the 4-aminotetrahydroquinoline system, involving reactions of enamides with N-arylimino esters,[15] proved to be synthetically useful (Schemes III and IV). Imine **71**, generated in situ, smoothly reacted with *N*-vinylpyrrolidinone to give a 1:1 mixture of isomers. Epimerization with methoxide resulted in enrichment (20:1) of the trans isomer, **72**, which could be isolated in pure form. Using 3-chloro-5-iodoaniline[5] and benzyloxy *N*-vinylcarbamate as the enamide[15] gave **73** as a mixture of stereo- and regioisomers (10:1 trans to cis, and 1:1 5-iodo to 7-iodo). Epimerization provided trans regioisomeric

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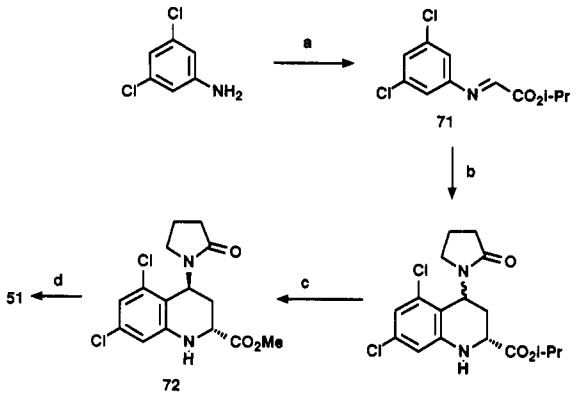
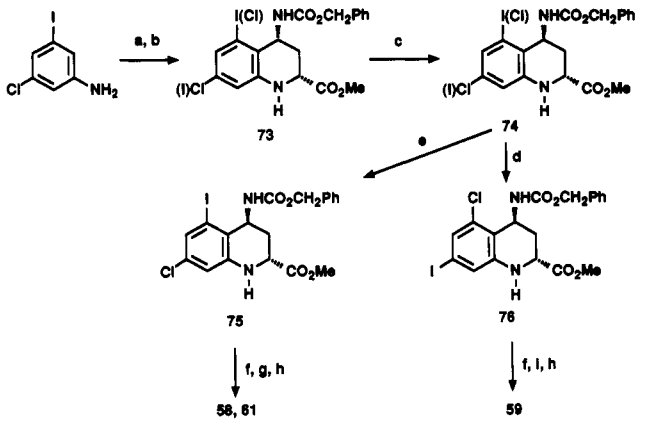
Scheme III[a]



[a] (a) *i*-PrOCOCHO, Na_2SO_4; (b) *N*-vinylpyrrolidin-2-one, $BF_3 \cdot Et_2O$; (c) cat. NaOMe, MeOH; (d) LiOH, H_2O, THF.

Scheme IV[a]



[a] (a) MeOCOCHO, Na_2SO_4; (b) benzyloxy *N*-vinylcarbamate, $BF_3 \cdot Et_2O$; (c) cat. NaOMe, MeOH; (d) recrystallize from EtOAc/hexane; (e) chromatography, SiO_2; (f) HBr, HOAc; (g) $PhCH_2CO_2H$, $Me_2N(CH_2)_3N{=}C{=}CEt$, HOBT, Et_3N or $PhN{=}C{=}O$, Et_3N; (h) LiOH, H_2O, THF; (i) $PhCH_2COCl$, Et_3N.

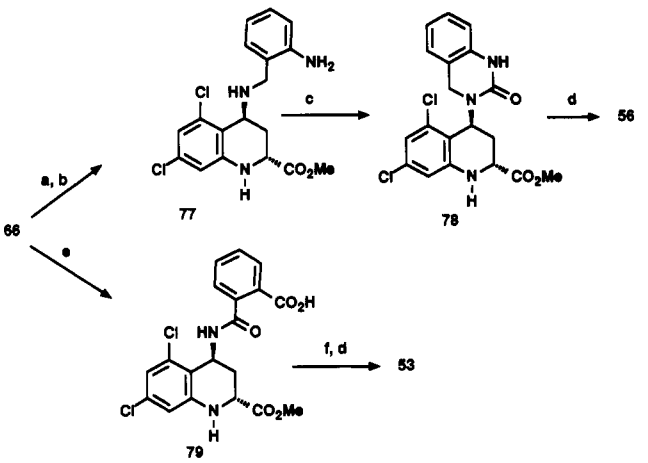
mixture **74** which was separated by exhaustive crystallization and chromatography to yield the 5-iodo (**75**) and 7-iodo (**76**) derivatives. The regiochemistries of **75** and **76** were assigned from catalytic hydrogenolysis of **76** over Pd on carbon, which gave the 5-chloro derivative. 5,7-Dimethyl derivative **60** was prepared from the corresponding dihydrokynurenate.[11]

4-Lactams and cyclic ureas were also prepared from **66** (Schemes V and VI). Thus reactions of **66** with substituted benzyl bromides gave intermediates **77**, **80**, and **81** which were converted to the target molecules **56**, **52**, and **54**, respectively. Acylation of **66** with phthalic anhydride gave **79**, which was cyclized to provide phthalimide **53**. Dihydroimidazolone **55**, required as a constrained mimic of the *Z,Z* conformer of phenyl urea **35**, was prepared via reductive alkylation of **66** with aldehyde **82** to form alkylated intermediate **83** (Scheme VII). Deprotection of **83**, then ring closure with phosgene and hydrolysis, yielded **55**.

Biology. Compounds were evaluated in vitro for their abilities to (1) displace [^{3}H]glycine from rat brain membranes (IC_{50} values) and (2) antagonize NMDA responses in a rat cortical slice preparation (apparent K_b values). Full details of the methods used have been published.[3,9,16]

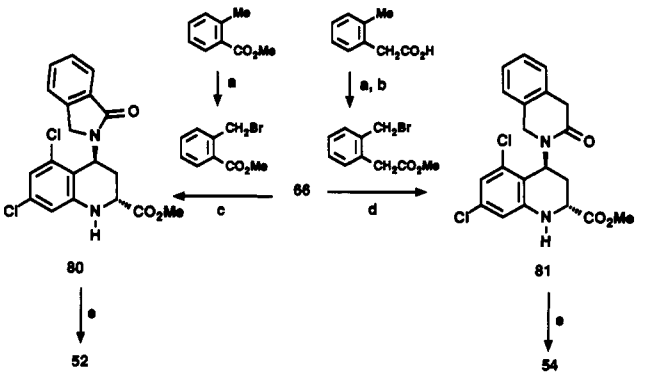
(16) Foster, A. C.; Kemp, J. A. HA-966 Antagonises N-Methyl-D-aspartate Receptors through a Selective Interaction with the Glycine Modulatory Site. *J. Neurosci.* **1989**, *9*, 2191–2196.

Scheme V[a]



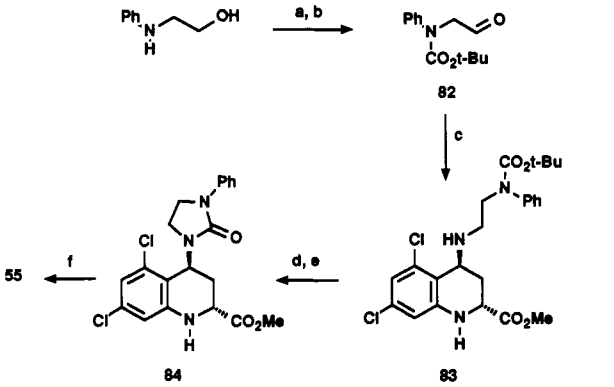
[a] (a) 2-Nitrobenzyl bromide, Et_3N, DMF; (b) H_2, Pd–C; (c) $COCl_2$, Et_3N; (d) LiOH, H_2O, THF; (e) phthalic anhydride, Et_3N, DMAP; (f) $Me_2N(CH_2)_3N{=}C{=}NEt$.

Scheme VI[a]



[a] (a) *N*-bromosuccinimide, CCl_4; (b) HCl, MeOH; (c) Et_3N, DMF, room temperature; (d) Et_3N, DMF, 100 °C; (e) LiOH, H_2O, THF.

Scheme VII[a]



[a] (a) $(t\text{-BuOCO})_2O$; (b) PDC, 4A sieves; (c) **66**, $NaCNBH_3$, 4A sieves, MeOH; (d) HCl, EtOAc; (e) $COCl_2$, Et_3N; (f) LiOH, H_2O, THF.

Identification of 4-Amido Substitution and Stereochemical Requirements for Binding. 4-Amino stereoisomers **4** and **5** (Table I) have similar affinities to the unsubstituted derivative (**3**), but acylation results in a stereoselective enhancement of binding as shown by the *tert*-butoxycarbonyl derivatives (**6** and **7**) and particularly by the benzoyl derivatives, where trans isomer **9** is 80-fold more active than cis isomer **8**. This stereoselectivity is similar to that observed for the isomers of acetic acid **2**[11] and confirms the requirement for the 2,4-trans stereochemistry in this class of glycine antagonists.

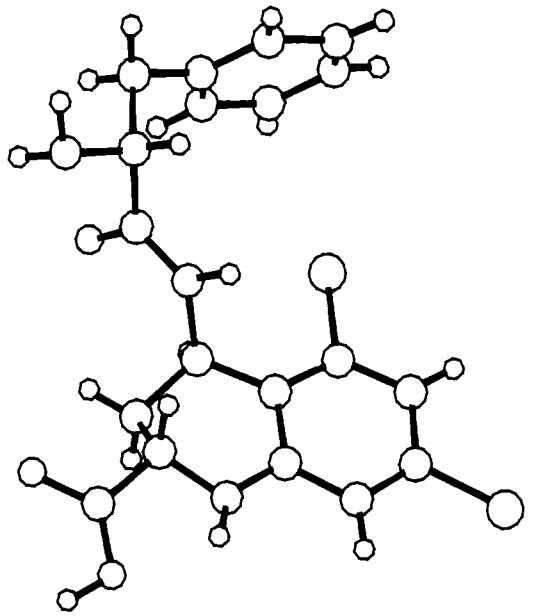
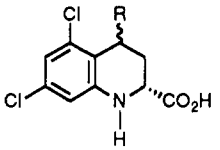


Figure 1. The structure of the (*R*)-phenylalanine derivative **10** as determined by X-ray crystallography.

Table I. 4-Amido-2-carboxytetrahydroquinolines: Stereochemical Requirements

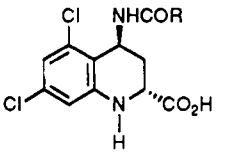


no.	R	IC_{50} (μM) vs [^{3}H]Gly[a]	K_b (μM) vs NMDA[b]
3	H	6.4	84
4	····· NH_2	14.1	51
5	— NH_2	11.3	32
6	····· $NHCO_2t$-Bu	11.4	176
7	— $NHCO_2t$-Bu	0.94	8.2
8	····· NHCOPh	8.3	96
9	— NHCOPh	0.10	1.2
10	— NHCOCH(NH_2)CH_2Ph (*R*,2*S*,4*R*)	>1000	
11	— NHCOCH(NH_2)CH_2Ph (*R*,2*R*,4*S*)	7.0	16.8
12	— NHCOCH(NH_2)CH_2Ph (*S*,2*S*,4*R*)	>100	
13	— NHCOCH(NH_2)CH_2Ph (*S*,2*R*,4*S*)	1.05	>10
14	— $NHCOCH_2Ph$	0.014	0.53
15	— $NHCOCH_2Ph$(−)	0.011	
16	— $NHCOCH_2Ph$(+)	5.9	

[a] Inhibition of [^{3}H]glycine binding to rat cortical membranes. Values given are the means of two to four determinations; the maximum variance (geometric mean) was 60%. [b] Antagonism of depolarizations due to *N*-methyl-D-aspartic acid in a rat cortical slice preparation. Values given are the means from at least three experiments; the maximum variance (geometric mean) was 15%. See refs 3 and 16 for full details of the assay procedures.

In order to determine the absolute stereochemical requirements, the four phenylalanine-derived stereoisomers **10–13** were prepared. The absolute configurations of these compounds followed from the X-ray crystallographic determination of *R*,2*S*,4*R* derivative **10** (Figure 1). Only isomers **11** and **13**, having the 2*R*,4*S* configuration, retain affinity for the glycine site. Thus activity in this series requires the unnatural α-amino acid configuration at the 2-position. The unnatural configuration is also found in glycine-site NMDA agonists (*R*-serine, *R*-alanine)[2] and partial agonists ((+)-HA-966[9] and L-687,414[10]), showing that the glycine site can recognize ligands of differing efficacy with the same stereoselectivity. An exception is the nonenantioselective binding of certain vinyl glycine derivatives which apparently act as agonists.[17]

Table II. *trans*-4-Amido-2-carboxytetrahydroquinolines



no.	R	IC_{50} (μM) vs [^{3}H]Gly[a]	K_b (μM) vs NMDA[b]
17	CH_3	0.90	4.7
18	*n*-Pr	0.37	2.1
19	c-hexyl	0.17	2.1
20	CH_2-c-hexyl	0.11	2.5
9	Ph	0.10	1.2
21	2-furyl	0.15	0.82
22	4-pyridyl	0.63	2.9
14	CH_2Ph	0.017	0.53
23	CH_2(3-thienyl)	0.030	0.71
24	CH_2(2-thienyl)	0.032	0.33
25	$CH_2C_6H_4NH_2$-4	0.018	0.51
26	$CH_2C_6H_4OH$-4	0.030	0.64
27	$CH_2C_6H_4CH_3$-4	0.034	0.72
28	$CH_2C_6H_4OCH_3$-4	0.039	0.83
29	$CH_2C_6H_4Cl$-4	0.052	2.2
30	$(CH_2)_2Ph$	0.076	0.74
31	$(CH_2)_3Ph$	0.17	1.7
32	$CHPh_2$	0.061	2.1
33	9-fluorenyl	0.025	3.2

[a,b] See Table I.

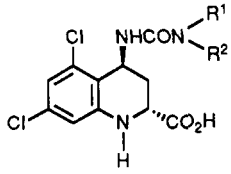
Homologation of benzoyl amide **9** to benzyl derivative **14** results in significantly enhanced activity. Compound **14** was separated into its individual enantiomers by preparative chiral chromatography, and the relative affinities of (−)-**15** and (+)-**16** demonstrate >500-fold enantioselectivity.

The conformation of the active trans-isomers in the solid state, as shown in Figure 1, places the 2-carboxyl pseudoequatorial and the 4-amido group pseudoaxial. The ^{1}H NMR spectra of each of the trans-isomers synthesized consistently support the view that the same conformation predominates in solution. Compound **9** is typical of the series: the α-amino acid proton, NHC*H*CO_2H (assignment based on the chemical shift found for **2**[11]), displays the expected large and small vicinal coupling constants with the adjacent methylene [δ (MeOD) 3.99, J = 2.7 and 12.7 Hz].

Optimization of the 4-Amido Substituent. Having established that the *trans*-4-amides **9** and **14** are high-affinity ligands showing stereoselective and enantioselective binding, a range of derivatives containing the 4-amido group were synthesized to optimize activity. The essential features of the structure–activity relationships are summarized in Table II. Affinity (IC_{50} values) for the glycine site increases with increasing bulk or lipophilicity of alkyl substituents, as shown by the trend methyl (**17**) < propyl (**18**) < c-hexyl (**19**) ~ cyclohexylmethyl (**20**). Interestingly, functional antagonism (K_b) does not significantly differ between these compounds. Aromatic amides however have clearly enhanced activity in both assays, with benzyl or heteroarylmethyl derivatives (**14, 23, 24**) having marginally improved activity in comparison with both lower (**9, 21, 22**) and higher (**30, 31**) homologues. Substitution of the optimal benzyl derivative (**14**) with a range of groups (**25–29**) does not change affinity appreciably, suggesting the benzyl group makes only partial physical contact with

(17) Monahan, J. B.; Hood, W. F.; Compton, R. P.; Cordi, A. A.; Williams, R. M. Identification of a Novel Structural Class of Positive Modulators of the N-Methyl-D-aspartate Receptor, with Actions Mediated through the Glycine Recognition Site. *Eur. J. Pharm—Mol. Pharm. Sect.* **1990**, *189*, 373–379.

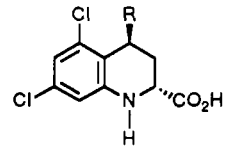
Table III. *trans*-4-Ureido-2-carboxytetrahydroquinolines



no.	R^1	R^2	IC_{50} (μM) vs [^{3}H]Gly[a]	K_b (μM) vs NMDA[b]
34	c-hexyl	H	0.028	0.50
35	Ph	H	0.0074	0.13
36	Ph	CH_3	0.045	0.93
37	Ph	Ph	0.019	0.33
38	CH_2Ph	H	0.030	0.77
39	1-naphthyl	H	0.011	0.35
40	$C_6H_4CH_3$-4	H	0.0050	0.14
41	$C_6H_4CH_3$-3	H	0.018	0.27
42	$C_6H_4CH_3$-2	H	0.0073	0.11

[a,b] See Table I.

Table IV. 4-Amido Modification



no.	R	IC_{50} (μM) vs [^{3}H]Gly[a]	K_b (μM) vs NMDA[b]
9	NHCOPh	0.12	1.2
43	$NHSO_2Ph$	5.2	48
44	$NHCH_2Ph$	10.7	>10
35	NHCONHPh	0.0078	0.13
45	NHCSNHPh	0.090	5.5
46	NHC(NCN)NHPh	0.58	11.2
47	$NHCH_2CONHPh$	0.42	14.7
48	$CONHCH_2Ph$	1.7	14.5
49	$NHCO_2CH_2Ph$	0.079	3.3
50	$CH_2CONHPh$	0.030	1.1

[a,b] See Table I.

the receptor. This conclusion is supported by the affinities of the diphenylmethane (**32**) and fluorenyl (**33**) derivatives, where additional bulk does not significantly affect the IC_{50} values.

Urea derivatives were prepared (Table III) and proved to possess generally enhanced activities relative to the corresponding amides. This is shown by the comparisons between the cyclohexyl derivatives (**34** and **20**), the phenyl derivatives (**35** and **14**), and the diphenyls (**37** and **32**). In common with the amide series, chain extension in the ureas also reduces binding (compare **35** and **38** with the isosteric amides **14** and **30**) and there is tolerance to bulk and substituents (**39–42**). One explanation of the improved activity of the ureas relative to the amides, which is consistent with our receptor model, is the increased ability of the carbonyl group to act as a hydrogen-bond acceptor.[18] Phenyl urea **35** (L-689,560, IC_{50} = 7.4 nM, K_b = 130 nM) is one of the most potent NMDA antagonists yet described and [4′-^{3}H]-**35** has been found to be a highly specific radioligand for the glycine site.[19]

In common with kynurenic acid **1** derivatives,[5] the tetrahydroquinolines also display weaker activity in the functional assay (K_b values) relative to the binding assay (IC_{50} values). This can, in part at least, be explained by the presence of near-saturating concentrations of glycine (or a glycine-like substance) in the cortical slice preparation.[20] However, certain analogues in Table II, notably the highly lipophilic fluorenyl (**33**), diphenylmethyl (**32**), and c-hexylmethyl (**20**) derivatives, possess even weaker functional antagonism than might be expected on the basis of their binding affinities. The reasons for these apparent discrepancies are unclear, but may be related to transport phenomena in the cortical slice preparation limiting access to receptors of bulky or lipophilic analogues.

Modification of the Amide Group. The importance of the amide carbonyl for binding is illustrated by the loss of activity in both sulfonamide (**43**) and benzylamine (**44**) derivatives (Table IV). These results show that the amide carbonyl increases affinity by approximately 100-fold, a free energy change of 2.7 kcal·mol^{-1} which is consistent with H-bond formation at the receptor.[21] The lack of affinity of sulfonamide **43** suggests that there is an important directional component to this interaction. The reduced activities of thiourea **45** and cyanoguanidine **46** relative to urea **35** further underline the importance of the carbonyl oxygen for activity. Moving the carbonyl group by methylene homologation (**47**) or by reversing the amide (**48**) markedly reduces affinity. Correct positioning of the carbonyl oxygen is achieved in urethane **49**, which possesses good affinity in the binding assay. These results led us to predict that amide derivatives of 4-acetic acid **2** would retain activity, and this was demonstrated by phenylamide **50**. These results, together with those previously obtained on other analogues of **2**,[11] strongly suggest that the location of the amide and urea carbonyl groups in the potent analogues is a critical determinant of affinity for the glycine site.

Conformationally Restricted Derivatives. A short series of compounds incorporating rigidifying elements into the 4-substituent was made to probe the conformational characteristics associated with receptor binding (Table V). The comparable activities of pyrrolidone **51** and benzofused derivatives **52** and **54** further demonstrate the freedom for incorporation of bulky substitution at the 4-position, suggesting that the corresponding acyclic amides **9** and **14**, respectively, may have several allowable receptor-active conformations. The reduced activity of phthalimide **53** compared with **52** shows that a second acyl group on the amide nitrogen is disadvantageous. Compounds **55–57**, constrained analogues of the acyclic phenylurea **35**, provide clearer evidence for conformational preferences in this more potent series. Thus dihydroimidazolone **55**, which mimics the extended *Z,Z*-ureide conformer of **35**, retains activity whereas the *Z,E* mimic (quinazolidinone **56**) is 100-fold less active. The reduced activity of indoline **57** in comparison with the corresponding acyclic derivatives **36** and **42** provides evidence that the receptor conformation of the phenyl ring in the potent acyclic compounds is not coplanar with the urea moiety. Cyclic phenylurea analogue **56** has lower affinity

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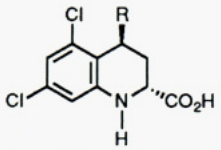
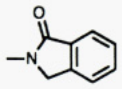
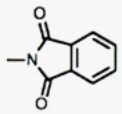
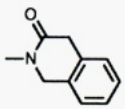
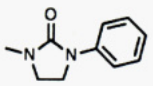
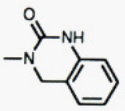
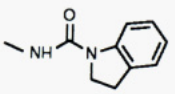
(19) Grimwood, S.; Moseley, A. M.; Carling, R. W.; Leeson, P. D.; Foster, A. C. Characterisation of the Binding of [^{3}H]-L-689,560, an Antagonist for the Glycine Site on the NMDA Receptor, to Rat Brain Membranes. *Mol. Pharmacol.* **1992**, in press.

(20) Fletcher, E. J.; Millar, J. D.; Zeman, S.; Lodge, D. Non-Competitive Antagonism of N-Methyl-D-aspartate by Displacement of an Endogenous Glycine-Like Substance. *Eur. J. Neurosci.* **1989**, *1*, 196–203.

(21) Fersht, A. R.; Shi, J-P.; Knill-Jones, J.; Lowe, D. M.; Wilkinson, A. J.; Blow, D. M.; Brick, P.; Carter, P.; Waye, M. M. Y.; Winter, G. Hydrogen Bonding and Biological Specificity Analysed by Protein Engineering. *Nature* **1985**, *314*, 235–238.

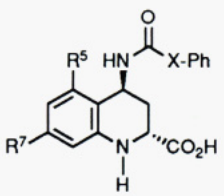
Table V. Conformationally Restricted 4-Substituents



no.	R	IC_{50} (μM) vs [^{3}H]Gly[a]	K_b (μM) vs NMDA[b]
51		0.046	1.1
52		0.027	0.34
53		1.9	4.6
54		0.072	0.83
55		0.006	0.38
56		0.51	>3
57		0.22	2.6

[a,b] See Table I.

Table VI. Modification of the 5,7-Substituents



no.	R^5	R^7	X	IC_{50} (μM) vs [^{3}H]Gly[a]	K_b (μM) vs NMDA[b]
14	Cl	Cl	CH_2	0.014	0.53
58	I	Cl	CH_2	0.010	0.29
59	Cl	I	CH_2	0.042	1.4
60	CH_3	CH_3	CH_2	0.067	0.77
35	Cl	Cl	NH	0.0074	0.13
61	I	Cl	NH	0.0060	0.17

[a,b] See Table I.

than the corresponding lactam **54**, which contrasts with the acyclic analogues, where the urea (**35**) is more potent than the amide (**14**). These results suggest a differing preference for orientation of the pendant phenyl rings in the amide and urea series.

Aromatic Substitution. We have previously shown that optimization of the 5,7-substituents in the kynurenic acid series can enhance affinity.[5] The results suggested the need for size-limited, hydrophobic groups, the optimal 5-iodo-7-chloro derivative being 7-fold more active than **1**. In contrast, 5-iodo-7-chloro derivatives in the tetrahydroquinoline series (**58** and **61**, Table VI) do not improve affinity in the binding assay to the same extent. However, the reduced activity of 7-iodo-5-chloro isomer **59** and the lack of an absolute requirement for halogen substitution (**60**) parallel the results obtained in the kynurenic acid series. The effects of 5-substitution in the kynurenates may reflect an additional role of the substituent in influencing the 4-oxo group interaction, possibly by a peri-effect. In the tetrahydroquinolines, the critical carbonyl group is more remote from the 5-substituent.

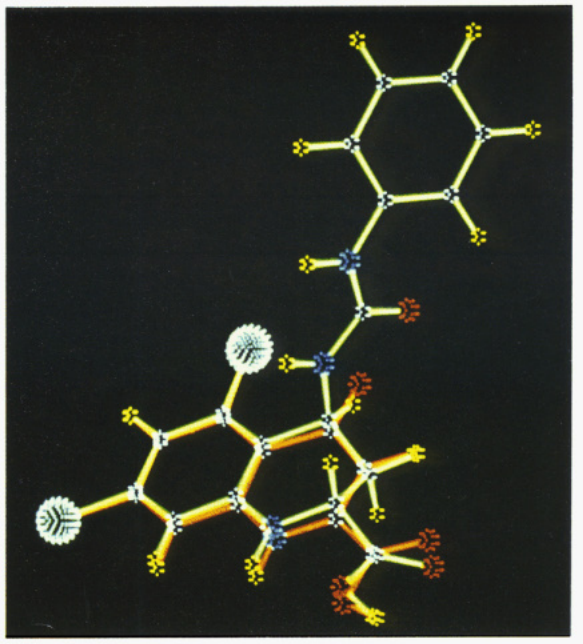


Figure 2. Overlay of kynurenate **2** (red) with tetrahydroquinoline **35** (green). The modeling was done with AMF/Optimol, in-house software written by the Molecular Systems Group, MSDRL, Rahway, NJ.

Development of the Glycine-Site Antagonist Pharmacophore. On the basis of an analysis of achiral, planar antagonists derived from kynurenic acid, quinoxalinedione, quinoxalic acid, and 2-carboxybenzimidazole, we have developed a working pharmacophore model of the glycine site.[5] The model requires H-bonding interactions of the 1-NH and 4-carbonyl groups, size-limited hydrophobic binding of the fused benzene ring, and Coulombic attraction of the in-plane 2-carboxyl. The novel tetrahydroquinolines allow an extension of the model to three dimensions. The X-ray crystallographic analysis (Figure 1) and ^{1}H NMR data show that the preferred conformation of the *trans*-4-substituted 2-carboxy tetrahydroquinoline system, both in the solid state and in solution, places the 2-carboxy pseudoequatorial and the 4-substituent pseudoaxial. An overlay of the structures of kynurenic acid derivative **1** and 4-(phenylureido) derivative **35** is shown in Figure 2. It can be seen that the common *N*-(dichlorophenyl)glycine moieties are well matched, showing that the pseudoequatorial 2-carboxyl group of the tetrahydroquinoline is a good mimic of the in-plane 2-carboxyl of the kynurenic acid. The pseudoaxially positioned carbonyl oxygen atom of **35** does not provide an exact match with the 4-oxo atom of **1**, but the vectors of both carbonyl groups in Figure 1 appear to point to a common region, suggesting that they may bind to a single H-bond acceptor on the receptor. This analysis provides an explanation for the strict requirements found for the positioning of the amide carbonyl in the tetrahydroquinolines. The bulk tolerance and hydrophobic region, as occupied by the phenyl rings of **32**, **35**, and **37**, is located approximately 5 Å above the plane of the tetrahydroquinoline ring system.

The model was refined by including compounds from two recently described series of antagonists based on 4-[(carboxymethyl)amino]-2-carboxyquinoline (**85**)[6] and 3-(2-carboxypropyl)-2-carboxyindole (**86**).[7] These struc-

tures also contain the *N*-(dichlorophenyl)glycine moiety present in **1** and **35**, and this structural element is easily superimposed in all four compounds. The essential car-

85

86

bonyl oxygen atoms at the 4-positions of **1**, **35**, and **85** and at the 3-position of **86** cannot however be easily superimposed. An ammonium group was used as a model for the putative receptor H-bond donor, to which these nonsuperimposing carbonyl oxygens may bind, and was introduced into each molecule at the accepted H-bonding distance (2.8 Å) from the carbonyl oxygens. The rigid structure **1** served as a template for flexible fitting of the other three antagonists. Subsequent energy minimization of each antagonist/ammonium assembly was performed together with superimposition of the 7-chloro, 1-nitrogen, 2-carboxyl carbon, and ammonium nitrogen atoms, resulting in the model shown in Figure 3. The modeling study shows the expected good fit of the 7-, 1-, and 2-substituents, which are essentially linearly disposed in each antagonist, and supports the view that each of the pendant carbonyl groups in the four antagonists can act as an H-bond acceptor, binding to a common site on the receptor.

Halogen substitution of the fused benzene ring considerably enhances affinity in each class of glycine antagonist.[5-7] Inspection of Figure 3 indicates that the two chloro substituents of **35**, **85**, and **86** fit differently to the rigid template **1**. One chloro substituent in each antagonist clearly superimposes with the important 7-chloro of **1**, but the chloros corresponding to the 5-position of **1** are seen to occupy distinct regions. This is consistent with existing structure–activity relationships, which show differing trends in requirements at the 5-position of the kynurenates[5] in comparison with both the tetrahydroquinolines (see Table VI) and the corresponding 4-substituted-2-carboxyindoles.[7c]

Conclusions. We have identified *trans*-2-carboxy-4-amidotetrahydroquinolines as a class of glycine-site NMDA receptor antagonists, with binding affinities in the low nanomolar range. In common with the 5,7-disubstituted kynurenates, the tetrahydroquinolines are selective glycine site NMDA antagonists, compound **35** displaying at least 3 orders of magnitude selectivity versus the glutamate site (labeled by [^{3}H]CPP and [^{3}H]CGS 19755) and non-NMDA amino acid sites (labeled by [^{3}H]AMPA, [^{3}H]kainate, and [^{3}H]strychnine).[22] These and related[11] compounds provide primary details of the stereochemical and conformational requirements for binding, which both support and extend our earlier pharmacophoric model.[5] A pseudoequatorially located 2-carboxyl, together with a pseudoaxial 4-substituent containing a correctly positioned carbonyl oxygen, are both critical for high affinity. The absolute stereochemistry at the α-amino acid center is *R*, in common with glycine site partial agonists. Modeling studies show that antagonists based on *N*-(halophenyl)glycine, including the 2-carboxytetrahydroquinolines as well as kynurenic acid derivatives and 2-carboxy indoles, can interact in a common manner with a putative receptor hydrogen-bond donor. Furthermore, the tetrahydroquinolines define a hitherto unidentified region of bulk tolerance on the receptor, pseudoaxially adjacent to the 4-position. The resulting pharmacophore may be of benefit in the design of further glycine-site directed NMDA receptor antagonists.

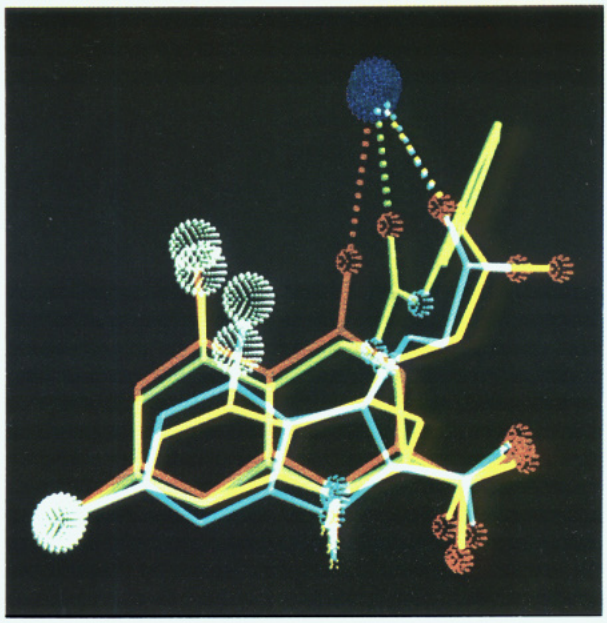


Figure 3. Superimposition of glycine site antagonists [**1** (red), **35** (green), **85** (yellow), and **86** (blue)] containing a common *N*-(chlorophenyl)glycine moiety. Hydrogen bonding of the essential substituent carbonyl groups of **1** and **35**, and the substituent carboxyls of **85** and **86**, is postulated to occur at a common receptor site, modeled here as an ammonium group (see text). The modeling was done with AMF/Optimol, in-house software written by the Molecular Systems Group, MSDRL, Rahway, NJ.

Experimental Section

General directions have appeared previously.[11]

***trans*-4-[[(*tert*-Butyloxy)carbonyl]amino]-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (7).** (a) To a solution of 2-carboxy-5,7-dichloro-4-oxo-1,2,3,4-tetrahydroquinoline[11] (**62**, 14.85 g, 57.1 mmol) in MeOH (300 mL) was added hydroxylamine hydrochloride (4.17 g, 60.0 mmol) followed by dry pyridine (4.85 mL, 60.0 mmol), and the resulting mixture was heated at reflux under N_2 for 2 h. The mixture was then cooled, and a solution of MeOH saturated with HCl (50 mL) was added and the reaction was stirred at room temperature under N_2 for 17 h. The solvent was removed in vacuo and the residue was partitioned between water (300 mL) and Et_2O (300 mL). The aqueous phase was further extracted with Et_2O (2 × 300 mL), the combined organic layers were washed with 0.5 M aqueous citric acid solution (1 × 200 mL), saturated $NaHCO_3$ solution (2 × 200 mL), and brine (1 × 200 mL), and then dried ($MgSO_4$), and the solvent was removed under vacuum to give oxime ester **63** (15.1 g) as a brown solid: mp 216–217 °C; ^{1}H NMR δ (360 MHz, DMSO) 2.79 (1 H, dd, J = 15.4 and 6.1 Hz, $CH_ACH_BH_C$), 3.25 (1 H, dd, J = 15.4 and 5.8 Hz, $CH_ACH_BH_C$), 3.64 (3 H, s, CO_2CH_3), 4.23 (1 H, m, $CH_ACH_BH_C$), 6.70 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 6.82 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 7.01 (1 H, br s, NH), 11.41 (1 H, s, NOH); MS m/e 288 (M^+), 213 (100). Anal. ($C_{11}H_{10}Cl_2N_2O_3$) C, H, N.

(b) To a suspension of the oxime (8.0 g, 27.7 mmol) in glacial acetic acid (240 mL) was added zinc dust (12.0 g, 18 mmol) and the resulting mixture was heated at 60–65 °C, under an atmosphere of nitrogen, with stirring for 4 h. The reaction mixture was allowed to cool and then filtered and the filtrate was evaporated in vacuo. The residue was redissolved in EtOAc (400 mL), washed with saturated $NaHCO_3$ solution (2 × 200 mL) and saturated brine solution (1 × 200 mL), and then dried ($MgSO_4$), filtered, and concentrated under vacuum to give a brown foam (6.60 g). To a solution of this foam in CH_2Cl_2 (350 mL) was added

(22) Foster, A. C.; Kemp, J. A.; Leeson, P. D.; Grimwood, S.; Donald, A. E.; Marshall, G. R.; Priestley, T.; Smith, J. D.; Carling, R. W. Kynurenic Acid Analogues with Improved Affinity and Selectivity for the Glycine Site on the N-Methyl-D-aspartate Receptor from Rat Brain. *Mol. Pharmacol.* **1992**, in press.

di-*tert*-butyl dicarbonate (12.0 g, 55 mmol) and the mixture was stirred at room temperature for 65 h under an atmosphere of nitrogen. To the reaction mixture was added *N,N*-dimethylethylenediamine (6.6 mL, 60 mmol) and stirring was continued for 2 h further. The reaction mixture was washed successively with 0.5 M citric acid solution (2 × 200 mL) and brine (1 × 200 mL), dried ($MgSO_4$), and filtered and the solvent was removed under vacuum to give an oily solid (5.8 g). This was purified by flash chromatography using 20% EtOAc in petroleum ether (bp 60–80 °C) as eluent to give a mixture of **64** and **65**. Crystallization from diethyl ether, then recrystallization from hot EtOAc/petroleum ether (bp 60–80 °C), gave trans-isomer **65** (1.33 g): mp 210–211 °C; ^{1}H NMR δ (360 MHz, $CDCl_3$), 1.48 (9 H, s, $C(CH_3)_3$), 1.66 (1 H, ddd, J = 13.1, 12.7, and 3.6 Hz, $CH_ACH_BH_CCH_D$), 2.61 (1 H, dm, J = 13.1 Hz, $CH_ACH_BH_CCH_D$), 3.82 (3 H, s, CH_3), 4.00 (1 H, dd, J = 12.7 and 3.0 Hz, $CH_ACH_BH_CCH_D$), 4.52 (1 H, m, $CH_ACH_BH_CCH_D$), 4.84 (1 H, br s, NH), 4.98 (1 H, br s, NH), 6.53 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.72 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS m/e (CI^+) 375 ($M + 1^+$). Anal. ($C_{16}H_{20}Cl_2N_2O_4$) C, H, N. Purification of the mother liquors by chromatography on silica gel (Lobar column) using 15% EtOAc/petroleum ether (bp 60–80 °C) as eluent, followed by crystallization from hot EtOAc/petroleum ether (bp 60–80 °C), gave the cis-isomer **64** (0.43 g): mp 172–173 °C; ^{1}H NMR δ (360 MHz, $CDCl_3$), 1.43 (9 H, s, $C(CH_3)_3$), 2.05 (1 H, m, $CH_ACH_BH_CCH_D$), 2.88 (1 H, dm, J = 14.2 Hz, $CH_ACH_BH_CCH_D$), 3.73 (3 H, s, CH_3), 4.08 (1 H, m, $CH_ACH_BH_CCH_D$), 4.34 (1 H, m, $CH_ACH_BH_CCH_D$), 4.58 (1 H, br s, NH), 4.90 (1 H, br s, NH), 6.56 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.75 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS m/e 374 (M^+), 198 (100, M – $NHCO_2$, *t*-Bu, CO_2CH_3, H). Anal. ($C_{16}H_{20}Cl_2N_2O_4$) C, H, N.

(c) To a solution of **65** (0.153 g, 0.408 mmol) in THF (10 mL) was added aqueous LiOH (0.45 mL of a 1.0 M solution, 0.45 mmol) followed by distilled water (3 mL) and the resulting mixture was stirred at room temperature for 4 h. The mixture was then evaporated to dryness under vacuum and the residue was redissolved in water (40 mL). The solution was adjusted to pH 1 with dilute hydrochloric acid and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine and then dried ($MgSO_4$) and concentrated in vacuo to give an oil from which crude product was obtained by crystallization from diethyl ether/petroleum ether (bp 60–80 °C). Recrystallization from diethyl ether gave **7** (0.071 g): mp 193–195 °C; ^{1}H NMR δ (360 MHz, DMSO) 1.40 (9 H, s, $C(CH_3)_3$), 1.61 (1 H, ddd, J = 12.6, 11.9, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.10 (1 H, dm, J = 12.6 Hz, $CH_ACH_BH_CCH_D$), 3.84 (1 H, dm, J = 11.9 Hz, $CH_ACH_BH_CH_D$), 4.75 (1 H, m, $CH_ACH_BH_CCH_D$), 6.63 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.68 (1 H, s, NH), 6.83 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.23 (1 H, d, J = 7.4 Hz, CONH); MS m/e (FAB) 361 ($M + 1^+$). Anal. ($C_{15}H_{18}Cl_2N_2O_4$) C, H, N.

***cis*-4-[[(*tert*-Butyloxy)carbonyl]amino]-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (6).** Compound **64** (220 mg, 0.587 mmol) was hydrolyzed with LiOH as described for **7** to give **6** as a colorless solid (0.161 g): mp 186–188 °C; ^{1}H NMR δ (250 MHz, $CDCl_3$) 1.54 (9 H, s, $C(CH_3)_3$), 1.76 (1 H, m, $CH_ACH_BH_CCH_D$), 2.92 (1 H, dm, J = 14.0 Hz, $CH_ACH_BH_CCH_D$), 3.82 (1 H, m, $CH_ACH_BH_CCH_D$), 4.86 (1 H, m, $CH_ACH_BH_CCH_D$), 6.00 (1 H, br s, NH), 6.56 (1 H, d, J = 3.0 Hz, 6-H or 8-H), 6.63 (1 H, br s, 6-H or 8-H); MS m/e (FAB) 361 (M^+). Anal. ($C_{15}H_{18}Cl_2N_2O_4$) C, H, N.

***trans*-4-Amino-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline Hydrochloride (5).** To a suspension of **7** (80 mg, 0.222 mmol) in EtOAc (3 mL) was added HCl in EtOAc (3 mL of an approximately 5 M solution) and the resulting mixture was stirred at room temperature for 5 h. The solvent was removed under vacuum and the residue was triturated with EtOAc to give **5** (0.054 g): mp 184–188 °C; ^{1}H NMR δ (360 MHz, D_2O) 2.10 (1 H, ddd, J = 14.8, 13.3, and 4.3 Hz, $CH_ACH_BH_CCH_D$), 2.62 (1 H, ddd, J = 14.8, 3.4, and 2.4 Hz, $CH_ACH_BH_CCH_D$), 4.09 (1 H, dd, J = 13.3 and 3.4 Hz, $CH_ACH_BH_CCH_D$), 4.91 (1 H, dd, J = 4.3 and 2.4 Hz, $CH_ACH_BH_CCH_D$), 6.80 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.89 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS m/e (FAB) 261 ($M + 1^+$). Anal. ($C_{10}H_{10}Cl_2N_2O_3$·HCl·0.4H_2O) C, H, N.

***cis*-4-Amino-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline Hydrochloride (4).** Treatment of **6** (100 mg, 0.277 mmol) with HCl in EtOAc, as described above for **7**, gave **4** (0.073 g): mp 176–178 °C; ^{1}H NMR δ (360 MHz, D_2O) 2.42 (1 H, m, $CH_ACH_BH_CCH_D$), 2.67 (1 H, dm, J = 15.6 Hz, $CH_ACH_BH_CCH_D$), 4.27 (1 H, dd, J = 6.6 and 1.7 Hz, $CH_ACH_BH_CCH_D$), 4.90 (1 H, dd, J = 5.6 and 1.4 Hz, $CH_ACH_BH_CCH_D$), 6.77 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.88 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS m/e (FAB) 261 ($M + 1^+$). Anal. ($C_{10}H_{10}Cl_2N_2O_3$·HCl) C, H, N.

***trans*-4-(Benzoylamino)-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (9).** (a) To a suspension of **65** (1.2 g) in EtOAc (25 mL) was added a solution of HCl in EtOAc (25 mL of a 5 M solution), the resulting mixture was stirred at room temperature for 3 h, the solvent was removed in vacuo, and the residue was triturated with EtOAc to give amine ester **66** as a colorless solid (0.96 g): mp 192–194 °C (sublimes); ^{1}H NMR δ (360 MHz, D_2O) 2.13 (1 H, ddd, J = 14.8, 13.2, and 4.4 Hz, $CH_ACH_BH_CCH_D$), 2.65 (1 H, dm, J = 14.8 Hz, $CH_ACH_BH_CCH_D$), 3.85 (3 H, s, CH_3), 4.22 (1 H, dd, J = 13.2 and 3.4 Hz, $CH_ACH_BH_CCH_D$), 4.92 (1 H, dd, J = 4.4 and 2.4 Hz, $CH_ACH_BH_CCH_D$), 6.81 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.92 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS m/e (FAB) 275 ($M + 1^+$). Anal. ($C_{11}H_{12}N_2O_2$·HCl) C, H, N.

(b) To a suspension of **66** (0.2 g, 0.642 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dry Et_3N (220 mL, 1.4 mmol) and the resulting mixture was stirred at room temperature under an atmosphere of nitrogen until dissolution was complete. To this solution was added benzoyl chloride (82 mL, 0.706 mmol) and stirring was continued for 17 h. The solvent was removed and the residue was partitioned between EtOAc (100 mL) and dilute citric acid (150 mL). The organic layer was washed successively with saturated $NaHCO_3$ solution (2 × 50 mL) and brine (50 mL) and then dried ($MgSO_4$) and evaporated to give the crude product (0.26 g), which was recrystallized from EtOAc/petroleum ether (bp 60–80 °C) to give the benzamide derivative as colorless crystals (0.201 g): mp 258–259 °C; ^{1}H NMR δ (360 MHz, DMSO) 1.79 (1 H, dd, J = 13.3, 12.6 and 4.1 Hz, $CH_ACH_BH_CCH_D$), 2.28 (1 H, dm, J = 13.3 Hz, $CH_ACH_BH_CCH_D$), 3.73 (3 H, s, CO_2CH_3), 4.09 (1 H, dm, J = 12.6 Hz, $CH_ACH_BH_CCH_D$), 5.28 (1 H, m, $CH_ACH_BH_CCH_D$), 6.70 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.91 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.93 (1 H, s, NH), 7.42–7.55 (3 H, m, ArH), 7.89 (2 H, d, J = 7.1 Hz, ArH), 8.72 (1 H, d, J = 7.6 Hz, PhCONH); MS m/e (CI^+) 379 ($M + 1^+$), 122 (100). Anal. ($C_{18}H_{16}Cl_2N_2O_3$) C, H, N.

(c) To a solution of the benzamide (0.189 g, 0.499 mmol) in THF (10 mL) was added distilled water (5 mL) followed by aqueous LiOH (1.10 mL of a 0.50 M solution, 0.549 mmol), and the resulting mixture was stirred at room temperature for 3 h. The organic solvent was removed under vacuum and to the aqueous residue was added saturated $NaHCO_3$ solution (20 mL) and deionized water (50 mL). The mixture was washed with EtOAc (2 × 50 mL) and then acidified to pH 1 with dilute hydrochloric acid and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (50 mL) and then dried (Na_2SO_4) and evaporated to give the crude product (0.16 g), which was triturated with diethyl ether to give **9** (0.11 g): mp 233–236 °C; ^{1}H NMR δ (360 MHz, CD_3OD) 1.82 (1 H, ddd, J = 13.4, 12.7, and 4.1 Hz, $CH_ACH_BH_CCH_D$), 2.55 (1 H, dm, J = 13.4 Hz, $CH_ACH_BH_CCH_D$), 3.99 (1 H, dd, J = 12.7 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 5.41 (1 H, m, $CH_ACH_BH_CCH_D$), 6.68 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.74 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.40–7.53 (3 H, m, ArH), 7.80 (2 H, m, ArH), 8.78 (1 H, d, J = 7 Hz, NHCO); MS m/e (FAB^+) 365 ($M + 1^+$). Anal. ($C_{17}H_{14}Cl_2N_2O_3$) C, H, N.

***cis*-4-(Benzoylamino)-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (8).** Compound **64** (0.16 g) was converted to **8** (0.102 g) using the sequence described above for transformation of **65** to **9**: mp 241–245 °C; ^{1}H NMR δ (360 MHz, CD_3OD) 2.12 (1 H, m, $CH_ACH_BH_CCH_D$), 2.90 (1 H, dm, J = 14.2 Hz, $CH_ACH_BH_CCH_D$), 4.12 (1 H, m, $CH_ACH_BH_CCH_D$), 5.34 (1 H, m, $CH_ACH_BH_CCH_D$), 6.65 and 6.67 (1 H each, d, J = 1.9 Hz, 6,8-H), 7.38–7.49 (3 H, m, ArH), 7.72–7.74 (2 H, m, ArH); MS m/e (FAB^+) 365 ($M + 1^+$). Anal. ($C_{17}H_{14}Cl_2N_2O_3$) C, H, N.

Compounds **17–22**, **24**, **29–31**, and **33** were prepared from **66** in the same way as **9**, by using the appropriate acid chlorides.

***trans*-4-(Acetylamino)-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (17)**: mp 223–225 °C; ^{1}H NMR δ (360 MHz, CD_3OD) 1.70 (1 H, ddd, J = 13.3, 12.8, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 1.95 (3 H, s, $COCH_3$), 2.41 (1 H, dm, J = 13.3

Hz, $CH_ACH_BH_CCH_D$), 3.92 (1 H, dd, J = 12.8 and 3.0 Hz, $CH_ACH_BH_CCH_D$), 5.17 (1 H, m, $CH_ACH_BH_CCH_D$), 6.66 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.72 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS m/e 302 (M^+), 198 (100, M - $NHCOCH_3$, CO_2H, H). Anal. ($C_{12}H_{12}Cl_2N_2O_3$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[(*n*-propylcarbonyl)amino]-1,2,3,4-tetrahydroquinoline (18)**: mp 174–176 °C dec; ^1H NMR δ (360 MHz, DMSO) 0.85 (3 H, t, J = 7.4 Hz, $COCH_2CH_2CH_3$), 1.48–1.64 (3 H, m, $CH_ACH_BH_CCH_D$ and $COCH_2CH_2CH_3$), 2.04 (2 H, t, J = 7.2 Hz, $COCH_2CH_2CH_3$), 2.16 (1 H, dm, J = 13.1 Hz, $CH_ACH_BH_CCH_D$), 3.82 (1 H, dd, J = 12.6 and 2.8 Hz, $CH_ACH_BH_CCH_D$), 5.01 (1 H, m, $CH_ACH_BH_CCH_D$), 6.64 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 6.76 (1 H, s, ArNH), 6.87 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 8.10 (1 H, d, J = 7.2 Hz, NHCO); MS m/e 330 (M^+), 198 (100, M - $NHCOCH_2CH_2CH_3$, CO_2H, H). Anal. ($C_{14}H_{16}Cl_2N_2O_3 \cdot 0.2H_2O$) C, H, N.

***trans*-2-Carboxy-4-[(cyclohexylcarbonyl)amino]-5,7-dichloro-1,2,3,4-tetrahydroquinoline (19)**: mp 190–195 °C (Et_2O); ^1H NMR δ (360 MHz, DMSO) 1.05–1.44 (5 H, m, cyclohexyl H), 1.50–1.75 (6 H, m, $CH_ACH_BH_CCH_D$ and cyclohexyl H), 2.02–2.15 (2 H, m, $CH_ACH_BH_CCH_D$ and cyclohexyl H), 3.80 (1 H, dd, J = 12.6 and 2.9 Hz, $CH_ACH_BH_CCH_D$), 4.98 (1 H, m, $CH_ACH_BH_CCH_D$), 6.63 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.73 (1 H, br s, ArNH), 6.86 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.98 (1 H, d, J = 7.2 Hz, CONH); MS m/e (FAB^+) 399 (M + 1^+). Anal. ($C_{17}H_{20}Cl_2N_2O_3 \cdot 0.2H_2O$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[(cyclohexylmethyl)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (20)**: mp 197–200 °C; ^1H NMR δ (360 MHz, DMSO) 0.85–0.92 (2 H, m, cyclohexyl), 1.07–1.23 (3 H, m, cyclohexyl), 1.56–1.65 (7 H, m, cyclohexyl and $CH_ACH_BH_CCH_D$), 1.94 (2 H, d, J = 6.7 Hz, $NHCOCH_2$), 2.16 (1 H, dm, J = 13.3 Hz, $CH_ACH_BH_CCH_D$), 3.81 (1 H, dd, J = 12.6 and 2.6 Hz, $CH_ACH_BH_CCH_D$), 5.01 (1 H, m, $CH_ACH_BH_CCH_D$), 6.65 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.76 (1 H, br s, NH), 6.86 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 8.11 (1 H, d, J = 7.1 Hz, NHCO); MS m/e 384 (M^+), 142 (100). Anal. ($C_{18}H_{22}Cl_2N_2O_3 \cdot 0.35H_2O$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[(2-furylcarbonyl)amino]-1,2,3,4-tetrahydroquinoline (21)**: mp 219–220 °C; ^1H NMR δ (360 MHz, DMSO) 1.72 (1 H, ddd, J = 13.2, 12.7, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.22 (1 H, dm, J = 13.2 Hz, $CH_ACH_BH_CCH_D$), 3.94 (1 H, dd, J = 12.3 and 2.2 Hz, $CH_ACH_BH_CCH_D$), 5.21 (1 H, m, $CH_ACH_BH_CCH_D$), 6.59 (1 H, dd, J = 1.5 Hz, 4-furyl), 6.65 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.79 (1 H, br s, NH), 6.90 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.17 (1 H, d, J = 3.1 Hz, 3-furyl), 7.79 (1 H, d, J = 1.5 Hz, 5-furyl), 8.62 (1 H, br d, J = 7.2 Hz, NHCO); MS m/e 355 (M^+), 198 (100, M - H, CO_2H, $NHCOC_4H_3O$). Anal. ($C_{15}H_{12}Cl_2N_2O_3 \cdot 0.85C_4H_{10}O$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[(4-pyridylcarbonyl)amino]-1,2,3,4-tetrahydroquinoline (22)**: mp 270–275 °C dec; ^1H NMR δ (360 MHz, DMSO) 1.76 (1 H, ddd, J = 13.3, 12.7, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.27 (1 H, dm, J = 13.3 Hz, $CH_ACH_BH_CCH_D$), 3.95 (1 H, dd, J = 12.7 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 5.26 (1 H, m, $CH_ACH_BH_CCH_D$), 6.66 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 6.84 (1 H, s, ArNH), 6.92 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 7.78 (2 H, dd, J = 4.4 and 1.6 Hz, ArH), 8.71 (2 H, dd, J = 4.4 and 1.6 Hz, ArH), 8.99 (1 H, d, J = 7.1 Hz, NHCO); MS m/e (CI^+) 366 (M + 1^+), 123 (100). Anal. ($C_{16}H_{13}Cl_2N_3O_3 \cdot 0.2H_2O$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[(2-thienylmethyl)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (24)**: mp 166–169 °C; ^1H NMR δ (360 MHz, DMSO) 1.61 (1 H, ddd, J = 13.3, 13.0, and 3.7 Hz, $CH_ACH_BH_CCH_D$), 2.17 (1 H, dm, J = 13.3 Hz, $CH_ACH_BH_CCH_D$), 3.63 (2 H, s, $COCH_2$), 3.82 (1 H, dd, J = 12.6 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 5.01 (1 H, m, $CH_ACH_BH_CCH_D$), 6.65 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.79 (1 H, br s, NH), 6.88–6.94 (3 H, m, 3,4-thiophene-H and 6-H or 8-H), 7.34 (1 H, dd, J = 5.0 and 1.2 Hz, 5-thiophene), 8.46 (1 H, d, J = 7.1 Hz, NHCO); MS m/e 384 (M^+), 97 (100, $CH_2C_4H_3S^+$). Anal. ($C_{16}H_{14}Cl_2N_2O_3S \cdot 0.15H_2O$) C, H, N.

***trans*-2-Carboxy-4-[[(4-chlorophenyl)methyl]carbonyl]amino]-5,7-dichloro-1,2,3,4-tetrahydroquinoline (29)**: mp 244–245 °C; ^1H NMR δ (360 MHz, DMSO) 1.61 (1 H, ddd, J = 13.1, 12.6, and 3.7 Hz, $CH_ACH_BH_CCH_D$), 2.14 (1 H, dm, J = 13.1 Hz, $CH_ACH_BH_CCH_D$), 3.41 (2 H, s, $COCH_2$), 3.82 (1 H, dd, J = 12.7 and 2.8 Hz, $CH_ACH_BH_CCH_D$), 5.00 (1 H, m, $CH_ACH_BH_CCH_D$), 6.66 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.79 (1 H, br s, NH), 6.88 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.27 (2 H, d, J = 8.5 Hz, Ar-H), 7.34 (2 H, d, J = 8.5 Hz, ArH), 8.44 (1 H, d, J = 7.1 Hz, NHCO); MS m/e 412 (M^+), 198 (100, M - H, CO_2H, $NHCOCH_2C_6H_4Cl$). Anal. ($C_{18}H_{15}Cl_3N_2O_3$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[(phenethylcarbonyl)amino]-1,2,3,4-tetrahydroquinoline (30)**: mp 188 °C, ^1H NMR δ (360 MHz, DMSO) 1.59 (1 H, ddd, J = 13.2, 13.0, and 3.7 Hz, $CH_ACH_BH_CCH_D$), 2.16 (1 H, dm, J = 13.2 Hz, $CH_ACH_BH_CCH_D$), 2.37 (2 H, t, J = 7.6 Hz, CH_2Ph), 2.83 (2 H, t, J = 7.6 Hz, CH_2CO), 3.79 (1 H, dd, J = 12.6 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 5.02 (1 H, m, $CH_ACH_BH_CCH_D$), 6.63 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.75 (1 H, br s, NH), 6.86 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.13–7.26 (5 H, m, Ar-H), 8.16 (1 H, br d, J = 7.1 Hz, NHCO); MS m/e 392 (M^+), 198 (100, M - H, CO_2H, $NHCOCH_2CH_2C_6H_5$). Anal. ($C_{19}H_{18}Cl_2N_2O_3 \cdot 0.1H_2O$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[(3-phenylpropyl)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (31)**: mp 189–191 °C; ^1H NMR δ (360 MHz, DMSO) 1.61 (1 H, ddd, J = 13.0, 12.8, and 3.7 Hz, $CH_ACH_BH_CCH_D$), 1.80 (2 H, qn, J = 7.5 Hz, $COCH_2CH_2$), 2.09 (2 H, t, J = 7.0 Hz, CH_2Ph), 2.17 (1 H, dm, J = 13.0 Hz, $CH_ACH_BH_CCH_D$), 2.56 (2 H, t, J = 8.0 Hz, $COCH_2$), 3.83 (1 H, dd, J = 12.6 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 5.03 (1 H, m, $CH_ACH_BH_CCH_D$), 6.65 (1 H, d, J = 2.0 Hz 6-H or 8-H), 6.76 (1 H, br s, NH), 6.87 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.14–7.21 (5 H, m, Ar-H), 8.16 (1 H, d, J = 7.2 Hz, NHCO); MS m/e 406 (M^+), 198 (100, M - H, CO_2H, $NHCO(CH_2)_3Ph$). Anal. ($C_{20}H_{20}Cl_2N_2O_3 \cdot 0.45H_2O$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[(9-fluorenylcarbonyl)amino]-1,2,3,4-tetrahydroquinoline (33)**: mp 266–268 °C; ^1H NMR δ (DMSO, 360 MHz) 1.68 (1 H, ddd, J = 13.3, 12.9, and 3.5 Hz, $CH_ACH_BH_CCH_D$), 2.21 (1 H, dm, J = 13.3 Hz, $CH_ACH_BH_CCH_D$), 4.05 (1 H, dd, J = 12.5 and 2.6 Hz, $CH_ACH_BH_CCH_D$), 4.79 (1 H, s, $CHAr_2$) 5.07 (1 H, m, $CH_ACH_BH_CCH_D$), 6.75 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.89 (1 H, br s, NH), 6.94 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.29–7.47 (6 H, m, Ar-H), 7.87 (2 H, d, J = 7.5 Hz, Ar-H), 8.98 (1 H, d, J = 7.1 Hz, NHCO); MS m/e 452 (M^+), 243 (100, M - H, $NHCOC_{13}H_9$). Anal. ($C_{24}H_{18}Cl_2N_2O_3 \cdot 0.4H_2O$) C, H, N.

***trans*-2(*S*)-Carboxy-5,7-dichloro-4(*R*)-[[(2-phenyl-1-(*R*)-aminoethyl)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (10).** To a stirred solution of **66** (0.622 g, 2.0 mmol) and *N*-(*tert*-butoxycarbonyl)-D-phenylalanine (0.284 g, 2.1 mmol) in dry THF (40 mL) containing Et_3N (0.62 mL, 4.4 mmol) was added 1-hydroxybenzotriazole (0.284 g, 2.1 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.384 g, 2.0 mmol). After 14 h, the solvent was evaporated and the residue partitioned between EtOAc (100 mL) and 1 M aqueous citric acid (100 mL). The organic layer was collected, washed with 1 M citric acid (1 × 100 mL), saturated $NaHCO_3$ solution (2 × 100 mL), and brine (100 mL), and then dried (Na_2SO_4) and evaporated to leave a white solid (0.94 g). This was dissolved in 10% aqueous trifluoroacetic acid, left at room temperature for 1 h, and then evaporated, and the residue dissolved in 50% aqueous MeOH (100 mL) containing NaOH (1 g). After 14 h, the mixture was concentrated, the aqueous residue diluted to 150 mL, and the pH adjusted to ~6 with dilute HCl. The solid that precipitated was collected and recrystallized from MeOH/Et_2O to give **10** (0.098 g): mp 170 °C; ^1H NMR δ (360 MHz, NaOD) 1.69 (1 H, ddd, J = 13.7, 13.3, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.28 (1 H, dm, J = 13.7 Hz, $CH_ACH_BH_CCH_D$), 2.91 (1 H, dd, J = 13.5 and 6.6 Hz, $PhCH_EH_FCH_GNH_2$), 2.98 (1 H, dd, J = 13.5 and 7.6 Hz, $PhCH_EH_FCH_GNH_2$), 3.62 (2 H, m, $CH_ACH_BH_CCH_D$ and $PhCH_EH_FCH_GNH_2$), 5.06 (1 H, m, $CH_ACH_BH_CCH_D$), 6.71 and 6.75 (1 H each, d, J = 1.9 Hz, 6,8-H), 7.25–7.36 (5 H, m, ArH); MS m/e (CI^+) 408 (M + 1^+). Anal. ($C_{19}H_{19}Cl_2N_3O_3 \cdot 1.0H_2O$) C, H, N.

Structure Determination of 10 by X-ray Crystallography. Crystals of **10** formed from methanol in space group $P2_1$ with a = 10.222 (1) Å, b = 5.240 (1) Å, c = 19.134 (2) Å, β = 98.36 (1)° for Z = 2, and a calculated density of 1.285 g/cm^3. An automatic four-circle diffractometer equipped with Cu Kα radiation (λ = 1.5418 Å) was used to measure 2154 potential diffraction peaks of which 1250 were observed ($I > 3\sigma I$). Application of a multisolution tangent formula approach to the phase solution gave an

initial model for the structure[23] which was subsequently refined with least squares and Fourier methods. Anisotropic 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 five an unweighted residual of 0.067. The structure is shown in Figure 1.

***trans*-2(*R*)-Carboxy-5,7-dichloro-4(*S*)-[[(2-phenyl-1-(*R*)-aminoethyl)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (11).** The aqueous mother liquors (pH 6, obtained after collection of crude **10**, above) were concentrated to 40 mL and extracted with EtOAc (3 × 200 mL). The organic extracts were dried ($MgSO_4$) and evaporated to dryness to give a white solid (0.17 g). A portion of this material (0.025 g) was purified by reverse-phase HPLC [using a semipreparative ODS-2 column (Spherisorb 250 × 10 mm), eluting with 50 mM NH_4OAc (pH 6.8)/MeCN, 72:28] to give **11** (0.006 g): mp 174–176 °C; ^1H NMR δ (360 MHz, NaOD) 1.59 (1 H, ddd, J = 13.6, 13.0, and 3.4 Hz, $CH_ACH_BH_CCH_D$), 1.97 (1 H, dm, J = 13.6 Hz, $CH_ACH_BH_CCH_D$), 2.86 (1 H, dd, J = 13.1 and 8.9 Hz, $PhCH_EH_FCH_GNH_2$), 2.99 (2 H, m, $CH_ACH_BH_CCH_D$ and $PhCH_EH_FCH_GNH_2$), 3.57 (1 H, dd, J = 8.9 and 5.9 Hz, $PhCH_EH_FCH_GNH_2$), 5.05 (1 H, m, $CH_ACH_BH_CCH_D$), 6.67 and 6.77 (1 H each, d, J = 1.8 Hz, 6,8-H), 7.24–7.36 (5 H, m, ArH); MS m/e (CI^+) 408 ($M + 1^+$). Anal. ($C_{19}H_{19}Cl_2N_3O_3 \cdot 2.0H_2O$) C, N; H: calcd, 5.22; found, 4.69.

***trans*-2(*S*)-Carboxy-5,7-dichloro-4(*R*)-[[(2-phenyl-1(*S*)-aminoethyl)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (12) and *trans*-2(*R*)-carboxy-5,7-dichloro-4(*S*)-(2-phenyl-1(*S*)-aminoethyl)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (13)** were prepared from **66**, as described above for **11** and **12**, using *N*-(*tert*-butoxycarbonyl)-L-phenylalanine. **12**: mp 174–174 °C; spectral data identical to those of **11**. Anal. ($C_{19}H_{19}Cl_2N_3O_3 \cdot 1.0H_2O$) C, H, N. **13** (isolated as its HCl salt): mp 221–223 °C; spectral data identical to those of **10**. Anal. ($C_{19}H_{19}Cl_2N_3O_3 \cdot HCl \cdot 0.7H_2O$) C, H; N: calcd, 9.19; found, 8.65.

***trans*-2-Carboxy-5,7-dichloro-4-[[(phenylmethyl)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (14).** (a) To a suspension of **66** (3.0 g, 9.63 mmol) in anhydrous THF (300 mL) under an atmosphere of nitrogen was added dry Et_3N (2.95 mL, 21.2 mmol) and the resulting mixture was stirred at room temperature for 0.5 h. To this suspension was added phenylacetic acid (1.44 g, 10.6 mmol), 1-hydroxybenzotriazole (1.43 g, 10.6 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.03 g, 10.6 mmol) and stirring was continued for 65 h. The reaction mixture was concentrated in vacuo and the residue obtained was partitioned between EtOAc (1000 mL) and 1 M aqueous citric acid (300 mL). The organic layer was collected, washed successively with 1 M aqueous citric acid (1 × 300 mL), saturated $NaHCO_3$ solution (2 × 300 mL), and brine (200 mL), and then dried ($MgSO_4$) and evaporated. The resulting crude product was recrystallized from MeOH to give the benzylamide ester as colorless needles (3.26 g): mp 226–228 °C; ^1H NMR δ (360 MHz, DMSO) 1.65 (1 H, ddd, J = 12.9, 12.6, and 3.9 Hz, $CH_ACH_BH_CCH_D$), 2.15 (1 H, dm, J = 12.9 Hz, $CH_ACH_BH_CCH_D$), 3.41 (2 H, s, CH_2Ph), 3.72 (3 H, s, CH_3), 3.95 (1 H, dd, J = 12.6 and 2.8 Hz, $CH_ACH_BH_CCH_D$), 5.00 (1 H, m, $CH_ACH_BH_CCH_D$), 6.69 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.87 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.90 (1 H, s, ArNH), 7.18–7.30 (5 H, m, ArH), 8.45 (1 H, d, J = 7.1 Hz, NHCO); MS m/e (CI^+) 393 ($M + 1^+$).

(b) The ester was hydrolyzed with LiOH as described for **7**, to give **14**: mp 186–188 °C dec; ^1H NMR δ (360 MHz, DMSO) 1.60 (1 H, ddd, J = 13.2, 12.5, and 3.8 Hz, $CH_ACH_BH_CCH_D$), 2.16 (1 H, dm, J = 13.2 Hz, $CH_ACH_BH_CCH_D$), 3.41 (2 H, s, CH_2Ph), 3.84 (1 H, dd, J = 12.5 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 5.00 (1 H, m, $CH_ACH_BH_CCH_D$), 6.66 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 6.79 (1 H, s, ArNH), 6.88 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 7.19–7.30 (5 H, m, ArH), 8.43 (1 H, d, J = 7.1 Hz, NHCO); MS m/e 378 (M^+), 91 (100, $PhCH_2^+$). Anal. ($C_{18}H_{16}Cl_2N_2O_3$) C, H, N.

Enantiomers (15 and 16). The benzylamide methyl ester obtained above was separated into its individual enantiomers by chromatography on a π-base type Pirkle column (250 × 10 mm) with D-naphthylalanine as the chiral stationary phase, eluting with 10% 2-propanol in hexane. Chiral stationary phases containing π-acid moieties, including (dinitrobenzoyl)phenylglcyine, (dinitrobenzoyl)phenylalanine, and (dinitrobenzoyl)leucine, did not resolve the enantiomers. These results may be explained by π-interaction of the electron-deficient 5,7-dichlorophenyl ring with the naphthyl residues. The resolved esters were obtained in >99% ee and individual hydrolyses with NaOH in aqueous MeOH gave **15** ($[\alpha]_D$ −130° (c = 0.2, CD_3OD)) and **16** ($[\alpha]_D$ 150° (c = 0.2, CD_3OD)). The spectral properties of **15** and **16** were identical with those of **14**.

Compounds **23**, **25–28**, and **32** were prepared from **66** as described for **14**, using the appropriate carboxylic acid.

***trans*-2-Carboxy-5,7-dichloro-4-[[(3-thienylmethyl)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (23)**: mp 198–200 °C; ^1H NMR δ (360 MHz, DMSO) 1.62 (1 H, ddd, J = 13.0, 12.4, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.17 (1 H, dm, J = 13.0 Hz, $CH_ACH_BH_CCH_D$), 3.42 (2 H, s, CH_2Ar), 3.84 (1 H, dd, J = 12.4 and 2.8 Hz, $CH_ACH_BH_CCH_D$), 5.01 (1 H, m, $CH_ACH_BH_CCH_D$), 6.66 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.79 (1 H, br s, ArNH), 6.88 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.00 (1 H, dd, J = 4.9 and 1.1 Hz, thiophene 5-H), 7.21 (1 H, dd, J = 2.9 and 1.1 Hz, thiophene 2-H), 7.43 (1 H, dd, J = 4.9 and 2.9 Hz, thiophene 4-H), 8.39 (1 H, d, J = 7.0 Hz, NHCO); MS m/e 384 (M^+), 97 (100). Anal. ($C_{16}H_{14}Cl_2N_2O_3S$) C, H, N.

***trans*-4-[[[(4-Aminophenyl)methyl]carbonyl]amino]-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline hydrochloride (25)** was prepared using 4-[(*tert*-butyloxycarbonyl)-amino]phenylacetic acid as the coupling agent, followed by successive treatment of the resulting amide ester with LiOH, and HCl in EtOAc (as described above for **5**): mp 165–167 °C; ^1H NMR δ (360 MHz, DMSO) 1.62 (1 H, ddd, J = 13.2, 12.6, 3.8 Hz, $CH_ACH_BH_CCH_D$), 2.14 (1 H, dm, J = 13.2 Hz, $CH_ACH_BH_CCH_D$), 3.46 (2 H, s, $COCH_2$), 3.86 (1 H, dd, J = 12.6 and 3.8 Hz, $CH_ACH_BH_CCH_D$), 5.00 (1 H, m, $CH_ACH_BH_CCH_D$), 6.66 and 6.89 (1 H each, d, J = 2.1 Hz, 6,8-H), 7.33 (4 H, m, ArH), 8.51 (1 H, d, J = 7.1 Hz, NHCO); MS m/e (FAB^+) 394 (M^+). Anal. ($C_{18}H_{17}Cl_2N_3O_3 \cdot 2HCl$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[[(4-hydroxyphenyl)methyl]carbonyl]amino]-1,2,3,4-tetrahydroquinoline (26)**: mp 259–261 °C dec; ^1H NMR δ (360 MHz, DMSO) 1.59 (1 H, ddd, J = 12.6, 12.4, and 3.8 Hz, $CH_ACH_BH_CCH_D$), 2.14 (1 H, dm, J = 12.6 Hz, $CH_ACH_BH_CCH_D$), 3.22 (2 H, s, $COCH_2$), 3.81 (1 H, dd, J = 12.4 and 2.8 Hz, $CH_ACH_BH_CCH_D$), 4.98 (1 H, m, $CH_ACH_BH_CCH_D$), 6.64 (3 H, m, 6-H or 8-H, ArH), 6.79 (1 H, s, ArNH), 6.67 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.02 (2 H, d, J = 8.5 Hz, ArH), 8.32 (1 H, d, J = 7.1 Hz, NHCO), 9.16 (1 H, br s, ArOH); MS m/e (CI^+) 395 ($M + 1^+$). Anal. ($C_{18}H_{16}Cl_2N_2O_4$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[[(4-methylphenyl)methyl]carbonyl]amino]-1,2,3,4-tetrahydroquinoline (27)**: mp 229–230 °C; ^1H NMR δ (360 MHz, DMSO) 1.60 (1 H, ddd, J = 13.2, 13.0, and 3.6 Hz, $CH_ACH_BH_CCH_D$), 2.14 (1 H, dm, J = 13.2 Hz, $CH_ACH_BH_CCH_D$), 2.26 (3 H, s, $ArCH_3$), 3.35 (2 H, s, $COCH_2$), 3.83 (1 H, dd, J = 12.6 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 5.00 (1 H, m, $CH_ACH_BH_CCH_D$), 6.67 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.83 (1 H, br s, NH), 6.88 (1 H, d, J ≈ 2.0 Hz, 6-H or 8-H), 7.07 (2 H, d, J = 8.0 Hz, ArH), 7.13 (2 H, d, J = 8.0 Hz, ArH), 8.43 (1 H, d, J = 7.1 Hz, NHCO); MS m/e 392 (M^+), 105 (100, $CH_2C_6H_4CH_3^+$). Anal. ($C_{19}H_{18}Cl_2N_2O_3$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[[(4-methoxyphenyl)methyl]carbonyl]amino]-1,2,3,4-tetrahydroquinoline (28)**: mp 245–247 °C; ^1H NMR δ (360 MHz, DMSO) 1.60 (1 H, ddd, J = 13.3, 12.7, and 3.7 Hz, $CH_ACH_BH_CCH_D$), 2.13 (1 H, dm, J = 13.3 Hz, $CH_ACH_BH_CCH_D$), 3.33 (2 H, s, $COCH_2$), 3.72 (3 H, s, OCH_3), 3.82 (1 H, dd, J = 12.6 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 4.98 (1 H, m, $CH_ACH_BH_CCH_D$), 6.67 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.84 (3 H, d, J = 8.6 Hz, NH and ArH), 6.88 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.15 (2 H, d, J = 8.6 Hz, ArH), 8.41 (1 H, d, J = 7.1 Hz, NHCO); MS m/e 408 (M^+), 121 (100, $CH_2C_6H_4OCH_3^+$). Anal. ($C_{19}H_{18}Cl_2N_2O_4$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[(diphenylmethyl)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (32)**: mp 238–239 °C; ^1H NMR δ (360 MHz, DMSO) 1.63 (1 H, ddd, J = 13.2, 12.6, and 3.8 Hz, $CH_ACH_BH_CCH_D$), 2.16 (1 H, dm, J = 13.2

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

Hz, $CH_ACH_BH_CCH_D$), 3.76 (1 H, dd, J = 12.6 and 2.9 Hz, $CH_ACH_BH_CCH_D$), 4.92 (1 H, s, $CHPh_2$), 5.06 (1 H, m, $CH_ACH_BH_CCH_D$), 6.62 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.78 (1 H, s, ArNH), 6.86 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.23 (10 H, m, ArH), 8.62 (1 H, d, J = 7.1 Hz, NHCO); MS m/e (FAB^+) 455 ($M + 1^+$). Anal. ($C_{24}H_{20}Cl_2N_2O_3 \cdot CH_3CO_2C_2H_5$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[(phenylamino)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (35).** (a) To a suspension of **66** (0.200 g, 0.642 mmol) in anhydrous CH_2Cl_2 (20 mL) under an atmosphere of nitrogen was added dry Et_3N (0.098 mL, 0.706 mmol) and the mixture was stirred until dissolution was complete. To this solution was then added phenyl isocyanate (0.077 mL, 0.706 mmol) and the resulting mixture was stirred at room temperature for 2 h. The solvent was removed under vacuum and the residue was partitioned between EtOAc (150 mL) and 1 M aqueous citric acid (75 mL). The organic layer was successively washed with 1 M aqueous citric acid (1 × 75 mL), saturated $NaHCO_3$ solution (2 × 75 mL), and saturated brine (1 × 75 mL) and then dried ($MgSO_4$) and evaporated. The crude product was recrystallized from MeOH to give the phenylurea ester as colorless crystals (0.185 g): mp 228–229 °C dec; ^1H NMR δ (360 MHz, DMSO) 1.67 (1 H, ddd, J = 12.7, 12.4, and 3.5 Hz, $CH_ACH_BH_CCH_D$), 2.34 (1 H, dm, J = 12.7 Hz, $CH_ACH_BH_CCH_D$), 3.73 (3 H, s, CH_3), 4.00 (1 H, dd, J = 12.4 and 2.9 Hz, $CH_ACH_BH_CCH_D$), 4.94 (1 H, m, $CH_ACH_BH_CCH_D$), 6.53 (1 H, d, J = 6.4 Hz, NHCONHPh), 6.72 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.88–6.93 (3 H, m, 6-H or 8-H, ArH and ArNH), 7.20–7.25 (2 H, m, ArH), 7.39 (2 H, d, J = 8.0 Hz, ArH), 8.15 (1 H, s, NHCONHPh); MS m/e 393 (M^+), 198 (100, M – NHCONHPh, CO_2CH_3, H). Anal. ($C_{18}H_{17}Cl_2N_3O_3$) C, H, N.

(b) To this urea ester (0.185 g, 0.47 mmol) in a mixture of THF (10 mL) and water (5 mL) was added aqueous LiOH (1.04 mL of a 0.5 M solution, 0.52 mmol) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated and the aqueous residue was dissolved in dilute $NaHCO_3$ solution (100 mL) and then washed with diethyl ether (100 mL). The aqueous phase was separated, acidified with concentrated hydrochloric acid, and extracted with EtOAc (2 × 100 mL). The combined extracts were washed with brine (100 mL), dried ($MgSO_4$), and evaporated to give the crude product, which was redissolved in MeOH and evaporated to give an oil which was crystallized from diethyl ether to give **35** (0.110 g): mp 148–150 °C dec; ^1H NMR δ (360 MHz, DMSO) 1.63 (1 H, ddd, J = 13.2, 12.6, and 3.7 Hz, $CH_ACH_BH_CCH_D$), 2.33 (1 H, dm, J = 13.2 Hz, $CH_ACH_BH_CCH_D$), 3.89 (1 H, dd, J = 12.6 and 2.8 Hz, $CH_ACH_BH_CCH_D$), 4.94 (1 H, m, $CH_ACH_BH_CCH_D$), 6.51 (1 H, d, J = 6.5 Hz, NHCONHPh), 6.69 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.79 (1 H, s, ArNH), 6.88–6.92 (2 H, m, 6-H or 8-H and ArH), 7.20–7.25 (2 H, m, ArH), 7.37–7.40 (2 H, m, ArH), 8.15 (1 H, s, NHCONHPh); MS m/e (FAB^+) 380 ($M + 1^+$). Anal. ($C_{17}H_{15}Cl_2N_3O_3 \cdot H_2O$) C, H, N.

Compounds **34** and **38–42** were prepared from **66** as described for **35**, using the appropriate isocyanate.

***trans*-2-Carboxy-5,7-dichloro-4-[[(cyclohexylamino)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (34)**: mp 217–219 °C; ^1H NMR δ (360 MHz, DMSO) 1.18 (5 H, m, cyclohexyl H), 1.53 (1 H, ddd, J = 13.0, 12.6, and 3.5 Hz, $CH_ACH_BH_CCH_D$), 1.59 (3 H, m, cyclohexyl H), 1.74 (2 H, m, cyclohexyl H), 2.22 (1 H, dm, J = 13.0 Hz, $CH_ACH_BH_CCH_D$), 3.38 (1 H, m, $CH_DNHCONHCH$), 3.78 (1 H, dd, J = 12.6 and 2.9 Hz, $CH_ACH_BH_CCH_D$), 4.84 (1 H, m, $CH_ACH_BH_CCH_D$), 5.51 (1 H, d, J = 8.11 Hz, $CH_DNHCONH$), 6.00 (1 H, d, J = 6.5 Hz, CH_DNH), 6.64 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 6.72 (1 H, s, ArNH), 6.84 (1 H, d, J = 2.1 Hz, 6-H or 8-H); MS m/e (FAB^+) 386 ($M + 1^+$). Anal. ($C_{17}H_{21}Cl_2N_3O_3$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[[(phenylmethyl)amino]carbonyl]amino]-1,2,3,4-tetrahydroquinoline (38)**: mp 163–164 °C dec; ^1H NMR δ (DMSO, 360 MHz), 1.57 (1 H, ddd, J = 12.9, 12.6, and 3.5 Hz, $CH_ACH_BH_CCH_D$), 2.26 (1 H, dm, J = 12.9 Hz, $CH_ACH_BH_CCH_D$), 3.84 (1 H, dd, J = 12.6 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 4.20 (1 H, dd, J = 15.5 and 5.7 Hz, $PhCH_EH_F$), 4.29 (1 H, dd, J = 15.5 and 6.2 Hz, $PhCH_EH_F$), 4.89 (1 H, m, $CH_ACH_BH_CCH_D$), 6.08 (1 H, m, $NHCONHCH_2$), 6.34 (1 H, d, J = 6.5 Hz, CH_DNH), 6.66 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.73 (1 H, s, ArNH), 6.85 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.19–7.32 (5 H, m, ArH); MS m/e (FAB^-) 392 ($M - 1^-$). Anal. ($C_{18}H_{17}Cl_2N_3O_3$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[(1-naphthylamino)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (39)**: mp 241–242 °C; ^1H NMR δ (360 MHz, DMSO) 1.67 (1 H, ddd, J = 13.0, 12.7, and 3.3 Hz, $CH_ACH_BH_CCH_D$), 2.38 (1 H, dm, J = 13.0 Hz, $CH_ACH_BH_CCH_D$), 3.94 (1 H, dd, J = 12.7 and 2.9 Hz, $CH_ACH_BH_CCH_D$), 5.00 (1 H, m, $CH_ACH_BH_CCH_D$), 6.72 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.85 (1 H, s, ArNH), 6.92 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.96 (1 H, d, J = 6.4 Hz, CH_DNH), 7.50 (4 H, m, ArH), 7.88 (1 H, m, ArH), 8.01 (1 H, m, ArH), 8.12 (1 H, m, ArH), 8.35 (1 H, s, NHCONHAr); MS m/e (FAB^+) 429 (M^+). Anal. ($C_{21}H_{17}Cl_2N_3O_3$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[[(4-methylphenyl)amino]carbonyl]amino]-1,2,3,4-tetrahydroquinoline (40)**: mp 197–198 °C; ^1H NMR δ (360 MHz, DMSO) 1.61 (1 H, ddd, J = 13.1, 13.1, and 3.3 Hz, $CH_ACH_BH_CCH_D$), 2.22 (3 H, s, CH_3), 2.32 (1 H, dm, J = 13.1 Hz, $CH_ACH_BH_CCH_D$), 3.87 (1 H, dd, J = 13.1 and 3 Hz, $CH_ACH_BH_CCH_D$), 4.93 (1 H, m, $CH_ACH_BH_CCH_D$), 6.44 (1 H, d, J = 6.5 Hz, NHCONHAr), 6.68 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.78 (1 H, br s, NH), 6.88 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.03 (2 H, d, J = 8.3 Hz, Ar-H), 7.27 (2 H, d, J = 8.3 Hz, Ar-H), 8.03 (1 H, s, NHCONHAr); MS m/e (FAB^-), 392 ($M - 1^-$), 91 (100, $C_6H_4CH_3$), 183 (100). Anal. ($C_{18}H_{17}Cl_2N_3O_3 \cdot 0.25H_2O$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[[(3-methylphenyl)amino]carbonyl]amino]-1,2,3,4-tetrahydroquinoline (41)**: mp 172–174 °C; ^1H NMR δ (360 MHz, DMSO) 1.61 (1 H, ddd, J = 13.0, 12.5, and 3.9 Hz, $CH_ACH_BH_CCH_D$), 2.24 (3 H, s, CH_3), 2.32 (1 H, dm, J = 13.0 Hz, $CH_ACH_BH_CCH_D$), 3.85 (1 H, dd, J = 12.5 and 2.8 Hz, $CH_ACH_BH_CCH_D$), 4.92 (1 H, m, $CH_ACH_BH_CCH_D$), 6.49 (1 H, d, J = 6.5 Hz, NHCONHAr), 6.68 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 6.72 (1 H, d, J = 7.3 Hz, ArH), 6.77 (1 H, br s, ArNH), 6.89 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 7.07–7.23 (3 H, m, ArH), 8.06 (1 H, s, NHCONHAr); MS m/e (FAB), 392 ($M - 1^-$). Anal. ($C_{18}H_{17}Cl_2N_3O_3 \cdot 0.3H_2O$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[[(2-methylphenyl)amino]carbonyl]amino]-1,2,3,4-tetrahydroquinoline (42)**: mp 196–197 °C dec; ^1H NMR δ (360 MHz, DMSO) 1.63 (1 H, ddd, J = 13.2, 12.6, and 3.5 Hz, $CH_ACH_BH_CCH_D$), 2.14 (3 H, s, CH_3), 2.34 (1 H, dm, J = 13.2 Hz, $CH_ACH_BH_CCH_D$), 3.89 (1 H, dd, J = 12.6 and 2.8 Hz, $CH_ACH_BH_CCH_D$), 4.95 (1 H, m, $CH_ACH_BH_CCH_D$), 6.70 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.82–6.94 (4 H, m, ArNH, ArH, 6-H and 8-H), 7.08 (2 H, m, ArH), 7.46 (1 H, s, NHCONHAr), 7.96 (1 H, d, J = 7.9 Hz, NHCONHAr); MS m/e (FAB^+) 394 ($M + 1^+$). Anal. ($C_{18}H_{17}Cl_2N_3O_3$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[(*N*-methyl-*N*-phenylamino)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (36).** (a) Amine **66** was treated with phenyl chloroformate, under the conditions described for **9**, to give the phenyl carbamate derivative: mp 159–161 °C; ^1H NMR δ (360 MHz, $CDCl_3$) 1.73 (1 H, m, $CH_ACH_BH_CCH_D$), 2.73 (1 H, dm, J = 13.5 Hz, $CH_ACH_BH_CCH_D$), 3.84 (3 H, s, CH_3), 4.07 (1 H, dd, J = 12.6 and 2.6 Hz, $CH_ACH_BH_CCH_D$), 4.82 (1 H, s, ArNH), 5.02–5.16 (2 H, m, $CH_ACH_BH_CCH_D$ and NHCOO), 6.57 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 6.77 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 7.15–7.30 (3 H, m, ArH), 7.35–7.43 (2 H, m, ArH); MS m/e (CI^+), 395 ($M + 1^+$), 258 (100, $M - NHCO_2Ph$).

(b) To a solution of the carbamate (225 mg, 0.587 mmol) in anhydrous toluene (7 mL) was added dry Et_3N (245 μL, 1.76 mmol). The mixture was heated with stirring, in an oil bath to 120 °C, and then allowed to cool to <90 °C before the addition of trimethylsilyl chloride (186 μL, 1.47 mmol). The solution was heated at reflux (120 °C) for 2 h. After cooling to <30 °C, a further 1 equiv of Et_3N was added (81 μL, 0.587 mmol) followed by N-methylaniline (126 mg, 1.174 mmol). The mixture was stirred at room temperature under an atmosphere of nitrogen for 18 h. The organic solvent was removed and the solid residue partitioned between EtOAc (75 mL) and 0.5 M citric acid (100 mL). The organic layer was retained and washed successively with 0.5 M citric acid (100 mL), saturated $NaHCO_3$ solution (2 × 100 mL), and brine (100 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to yield an orange oil. Purification by flash chromatography (solvent; EtOAc/hexane) gave the urea ester as colorless crystals (89 mg): mp 185–189 °C. ^1H NMR δ (250 MHz, $CDCl_3$) 1.64 (1 H, ddd, J = 13.4, 13.1, and 3.6 Hz, $CH_ACH_BH_CCH_D$), 2.73 (1 H, dm, J = 13.4 Hz, $CH_ACH_BH_CCH_D$), 3.30 (3 H, s, NCH_3), 3.80 (1 H, dd, J = 11.7 and 2.8 Hz, $CH_ACH_BH_CCH_D$), 3.81 (3 H, s, OCH_3), 4.23 (1 H, d, J = 5.0 Hz, NHCO), 4.77 (1 H, s, ArNH), 5.11 (1 H, m, $CH_ACH_BH_CCH_D$), 6.47

(1 H, d, J = 1.9 Hz, 6-H or 8-H), 6.68 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 7.22–7.40 (5 H, m, Ar-H).

(c) Hydrolysis of the ester with LiOH, as described above for **7**, gave **36**: mp 204–205 °C; ^{1}H NMR δ (DMSO, 360 MHz) 1.58 (1 H, ddd, J = 13.2, 12.8, and 3.8 Hz, $CH_ACH_BH_CCH_D$), 2.27 (1 H, dm, J = 13.2 Hz, $CH_ACH_BH_CCH_D$), 3.15 (3 H, s, NCH_3), 3.87 (1 H, dd, J = 12.6 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 4.93 (1 H, m, $CH_ACH_BH_CCH_D$), 6.26 (1 H, d, J = 6.9 Hz, NHCO), 6.62 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.67 (1 H, br s, ArNH), 6.82 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.14 (1 H, t, J = 7.3 Hz, Ar-H), 7.25 (2 H, d, J = 8.5 Hz, Ar-H), 7.32 (2 H, t, J = 7.2 Hz, Ar-H); MS m/e 347 (M – CO_2H, H^+), 107 (100, $C_6H_5NHCH_3^+$). Anal. ($C_{18}H_{17}Cl_2N_3O_3 \cdot 0.35H_2O$) C, H, N.

Compounds **37** and **57** were prepared from **66** in a manner similar to that of **36**, using the appropriate aniline.

***trans*-2-Carboxy-5,7-dichloro-4-[[(*N*,*N*-diphenylamino)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (37)** (using *N*,*N*-diphenylamine): mp 214–216 °C; ^{1}H NMR δ (360 MHz, DMSO) 1.63 (1 H, ddd, 13.0, 12.1, and 3.9 Hz, $CH_ACH_BH_CCH_D$), 2.33 (1 H, dm, J = 13.0 Hz, $CH_ACH_BH_CCH_D$), 3.88 (1 H, dd, J = 12.1 and 2.8 Hz, $CH_ACH_BH_CCH_D$), 4.99 (1 H, m, $CH_ACH_BH_CCH_D$), 6.63 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.65 (1 H, d, J = 7.2 Hz, NHCO), 6.80 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.12 (5 H, m, ArH), 7.16 (1 H, s, ArNH), 7.31 (5 H, m, ArH); MS m/e (Cl^+) 456 (M + 1^+). Anal. ($C_{23}H_{19}Cl_2N_3O_3 \cdot 0.5H_2O$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[(2,3-dihydroindolyl-1-carbonyl)amino]-1,2,3,4-tetrahydroquinoline (57)** (using indoline): mp 251–252 °C; ^{1}H NMR δ (360 MHz, DMSO) 1.64 (1 H, ddd, J = 13.2, 13.1, and 3.7 Hz, $CH_ACH_BH_CCH_D$), 2.38 (1 H, dm, J = 13.2 Hz, $CH_ACH_BH_CCH_D$), 3.08 (2 H, t, J = 8.7 Hz, $CH_EH_FCH_2$), 3.76 (1 H, q, J = 9.0 Hz, $CH_EH_FCH_2$), 3.92 (1 H, q, J = 9.0 Hz, $CH_ECH_FCH_2$), 3.98 (1 H, dd, J = 12.9 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 5.04 (1 H, m, $CH_ACH_BH_CCH_D$), 6.65 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.78–6.85 (3 H, m, ArH and ArNH), 6.89 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.06–7.14 (2 H, m, ArH), 8.76 (1 H, d, J = 8.0 Hz, NHCO); MS m/e 405 (M^+), 91 (100). Anal. ($C_{19}H_{17}Cl_2N_3O_3 \cdot 0.2H_2O$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[(phenylsulfonyl)amino]-1,2,3,4-tetrahydroquinoline (43)** was prepared from **66** as described for **9**, by using benzenesulfonyl chloride: mp 190–193 °C dec; ^{1}H NMR δ (360 MHz, DMSO) 1.52 (1 H, ddd, J = 13.4, 12.6, and 3.9 Hz, $CH_ACH_BH_CCH_D$), 2.35 (1 H, dm, J = 13.4 Hz, $CH_ACH_BH_CCH_D$), 3.95 (1 H, dd, J = 12.6 and 3.0 Hz, $CH_ACH_BH_CCH_D$), 4.50 (1 H, m, $CH_ACH_BH_CCH_D$), 6.50 and 6.80 (1 H each, d, J = 1.9 Hz, 6,8-H), 6.73 (1 H, br s, NH), 7.55–7.96 (5 H, m, ArH); MS m/e (Cl^-) 399 (M – 1). Anal. ($C_{16}H_{14}Cl_2N_2O_4S$) C, H, N.

***trans*-4-(Benzylamino)-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (44).** To a solution of **66** (0.300 g, 0.96 mmol) in anhydrous DMF (10 mL) were added Et_3N (0.403 mL, 2.89 mmol), benzyl bromide (0.230 mL, 1.92 mmol), and a catalytic quantity of sodium iodide. This mixture was stirred under an atmosphere of nitrogen at room temperature for 90 h. The solvent was removed in vacuo and the residue obtained was partitioned between distilled water (100 mL) and EtOAc (200 mL). The organic layer was washed with saturated $NaHCO_3$ (2 × 100 mL), brine (2 × 100 mL), and distilled water (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on silica gel (using from 10% EtOAc in hexane to 50% EtOAc in hexane as eluents) to give the *N*-benzyl derivative: mp 112–114 °C; ^{1}H NMR δ (360 MHz, DMSO), 1.41 (1 H, ddd, J = 13.4, 12.3, and 3.1 Hz, $CH_ACH_BH_CCH_D$), 2.33 (1 H, dm, J = 13.4 Hz, $CH_ACH_BH_CCH_D$), 3.73 (3 H, s, CH_3), 3.84 (2 H, d, J = 13.5 Hz, CH_2Ph), 4.13 (1 H, m, $CH_ACH_BH_CCH_D$), 4.27 (1 H, dd, J = 12.3 and 2.8 Hz, $CH_ACH_BH_CCH_D$), 6.60 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 6.73 (1 H, s, ArNH), 6.78 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 7.28 (3 H, m, ArH), 7.37 (2 H, m, ArH), 7.69 (1 H, m, $CHNHCH_2$); MS m/e (CI^+) 365 (M + 1^+). Hydrolysis of this ester with LiOH, as described for **9**, gave **44**: mp 140–143 °C; ^{1}H NMR δ (360 MHz, DMSO) 1.85 (1 H, ddd, J = 13.3, 12.4, and 3.0 Hz, $CH_ACH_BH_CCH_D$), 2.73 (1 H, dm, J = 13.3 Hz, $CH_ACH_BH_CCH_D$), 4.32 (2 H, d, J = 13.4 Hz, CH_2Ph), 4.46 (1 H, m, $CH_ACH_BH_CCH_D$), 4.48 (1 H, m, $CH_ACH_BH_CCH_D$), 6.70 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 6.90 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 7.12 (1 H, s, ArNH), 7.43 (3 H, m, ArH), 7.63 (2 H, m, ArH); MS m/e (FAB^-) 349 (M – 1^-). Anal. ($C_{17}H_{16}Cl_2N_2O_2 \cdot 1.8HCl \cdot 0.2C_6H_{14}$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[(phenylamino)(thiocarbonyl)]amino]-1,2,3,4-tetrahydroquinoline (45).** This compound was prepared from **66** as described for **35**, using phenyl isothiocyanate: mp 186–187 °C; ^{1}H NMR δ (360 MHz, DMSO) 1.64 (1 H, ddd, J = 13.0, 12.5, and 3.9 Hz, $CH_ACH_BH_CCH_D$), 2.63 (1 H, dm, J = 13.0 Hz, $CH_ACH_BH_CCH_D$), 3.86 (1 H, dd, J = 12.5 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 5.51 (1 H, m, $CH_ACH_BH_CCH_D$), 6.69 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 6.80 (1 H, br s, ArNH), 6.90 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 7.04–7.49 (5 H, m, ArH), 8.09 (1 H, d, J = 7.1 Hz, $NHCSNHPh$), 9.31 (1 H, br s, CSNHPh). Anal. ($C_{17}H_{15}Cl_2N_3O_2S$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[*N*-(*N'*-phenyl-*N''*-cyanoguanidinyl)]-1,2,3,4-tetrahydroquinoline (46).** Reaction of **66** (free base, 0.30 g) with the sodium salt of *N*-phenyl-*N'*-cyanothiourea in the presence of water-soluble carbodiimide[13] gave **46** methyl ester (0.31 g): mp 227–228 °C. The ester (0.20 g) was hydrolyzed with LiOH as described for **9**, to give **46** (0.12 g, crystallized from EtOAc/MeOH/petroleum ether): mp 199–201 °C dec; ^{1}H NMR δ (360 MHz, DMSO) 1.69 (1 H, ddd, J = 13.4, 12.7, and 3.9 Hz, $CH_ACH_BH_CCH_D$), 2.37 (1 H, dm, J = 13.4 Hz, $CH_ACH_BH_CCH_D$), 3.95 (1 H, dm, J = 12.7 Hz, $CH_ACH_BH_CCH_D$), 5.10 (1 H, m, $CH_ACH_BH_CCH_D$), 6.70 and 6.86 (1 H each, d, J = 1.9 Hz, 6,8-H), 6.80 (1 H, s, ArNH), 7.06–7.32 (5 H, m, ArH), 7.71 (1 H, d, J = 7.4 Hz, NHC(NCN)NPh); MS m/e (FAB^+) 404 (M + 1^+). Anal. ($C_{18}H_{15}Cl_2N_5O_2 \cdot 0.08EtOAc$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[[(phenylamino)carbonyl]methyl]amino]-1,2,3,4-tetrahydroquinoline Hydrochloride (47).** This compound was prepared from **66** as described for **44**, using *N*-phenyliodoacetamide: mp 163–164 °C dec; ^{1}H NMR δ (360 MHz, DMSO) 1.93 (1 H, ddd, J = 13.3, 12.2, and 3.8 Hz, $CH_ACH_BH_CCH_D$), 2.73 (1 H, dm, J = 13.3 Hz, $CH_ACH_BH_CCH_D$), 4.00 (2 H, d, J = 16.2 Hz, $NHCH_2CONHPh$), 4.32 (1 H, dd, J = 12.2 and 3.8 Hz, $CH_ACH_BH_CCH_D$), 4.78 (1 H, br s, $CH_ACH_BH_CCH_D$), 6.73 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.92 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.10 (1 H, m, ArH), 7.18 (1 H, s, ArNH), 7.35 (2 H, m, ArH), 7.60 (2 H, m, ArH), 9.5 (2 H, br m, NH), 10.72 (1 H, m, $NHCH_2$); MS m/e (FAB^+) 394 (M + 1^+). Anal. ($C_{18}H_{17}Cl_2N_3O_3 \cdot 1.9HCl$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[[(phenylmethyl)amino]carbonyl]-1,2,3,4-tetrahydroquinoline (48).** To a solution of *cis*-dimethyl ester **67**[11] (5.6 g) in MeOH (300 mL) was added NaOH (4 g). The mixture was heated under reflux for 4 h, the solvent evaporated, and then water (300 mL) was added. The mixture was extracted with Et_2O (2 × 100 mL), the organic extracts were discarded, and the aqueous layer was acidified to pH 1 with concentrated HCl, then extracted with Et_2O (2 × 150 mL). The organic extracts were dried ($MgSO_4$) and evaporated to yield a residue which was dissolved in MeOH presaturated with HCl (200 mL). After 40 min, the mixture was evaporated to dryness to give crude *trans*-methyl ester **68** (3.2 g). To a solution of this ester (1.0 g) in dry THF (100 mL) and dry DMF (50 mL) was added carbonyldiimidazole (1.07 g, 2 equiv), the mixture was heated at 60 °C for 5 h and cooled to room temperature, and benzylamine (1.4 mL, 4 equiv) and 4-(diethylamino)pyridine (0.1 g) were added. After 14 h, HOAc (10 mL) was added, the solvents were evaporated, water (80 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The combined organics were dried ($MgSO_4$) and evaporated, and the residue was purified by chromatography on silica gel, eluting with 5–10% EtOAc/hexane to give the amide ester (0.65 g). This material was dissolved in 50% aqueous MeOH containing NaOH (0.133 g, 2 equiv). After 14 h the mixture was evaporated to dryness, water (50 mL) added, and the pH adjusted to 1 with concentrated HCl. The mixture was extracted with EtOAc (2 × 50 mL), the extract dried ($MgSO_4$) and evaporated, and the residue crystallized from Et_2O/hexane to give **48** (0.55 g): mp 196–197 °C: ^{1}H NMR δ (360 MHz, DMSO) 1.83 (1 H, ddd, J = 13.1, 11.7, and 3.5 Hz, $CH_ACH_BH_CCH_D$), 3.87 (1 H, dm, J = 3.5 Hz, $CH_ACH_BH_CCH_D$), 3.91 (1 H, dd, J = 11.7 and 2.9 Hz, $CH_ACH_BH_CCH_D$), 4.24 and 4.32 (1 H each, dd, J = 15.2 and 6.0 Hz, CH_2N), 6.59 (1 H, s, ArNH), 6.61 and 6.81 (1 H each, J = 1.9 Hz, 6,8-H), 7.20–7.32 (5 H, m, ArH), 8.54 (1 H, t, J = 6.0 Hz, NHCO); MS m/e (CI^+) 379 (M + 1^+). Anal. ($C_{18}H_{16}Cl_2N_2O_3$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[(phenylmethoxy)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (49).** A solution of **66** (0.3 g, 0.96 mmol) in CH_2Cl_2 (30 mL) containing Et_3N (0.4 mL, 2.9 mmol) and dibenzyl dicarbonate (0.33 g, 1.15 mmol) was stirred at room temperature for 14 h and then dimethylethylenediamine (0.3 mL) was added. After 2 h the solvents were removed by evaporation, and the residue was redissolved in EtOAc (40 mL) and washed with 1 M citric acid solution (2 × 30 mL), saturated $NaHCO_3$ solution (2 × 30 mL), and brine (1 × 30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to leave a residue which was purified by chromatography on silica gel using 20% EtOAc in hexane as eluent to give a white solid (0.24 g). This was suspended in 50% aqueous MeOH (100 mL) and stirred at room temperature for 60 h in the presence of NaOH (0.2 g). MeOH was removed in vacuo and the aqueous residue acidified to pH 1 with 1 M HCl. The solid which was precipitated was extracted into EtOAc (2 × 50 mL), washed with brine (1 × 40 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was recrystallized from Et_2O/hexane to give **49**: mp 169 °C; ^1H NMR δ (360 MHz, DMSO) 1.65 (1 H, ddd, J = 13.0, 12.4, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.17 (1 H, dm, J = 13.0 Hz, $CH_ACH_BH_CCH_D$), 3.85 (1 H, dm, J = 12.4 Hz, $CH_ACH_BH_CCH_D$), 4.84 (1 H, m, $CH_ACH_BH_CCH_D$), 5.02 (1 H, d, J = 12.6 Hz, $PhCH_EH_F$), 5.11 (1 H, d, J = 12.6 Hz, $PhCH_EH_F$), 6.64 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.74 (1 H, br s, ArNH), 6.85 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.32–7.36 (5 H, m, ArH), 7.70 (1 H, d, J = 7.0 Hz, NHCO); MS m/e (Cl^-), 393 ($M - 1^-$), 243 (100). Anal. ($C_{18}H_{16}Cl_2N_2O_4$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[[(phenylamino)carbonyl]methyl]-1,2,3,4-tetrahydroquinoline (50).** (a) *trans*-2-Carboxy-4-[(methoxycarbonyl)methyl]-5,7-dichloro-1,2,3,4-tetrahydroquinoline[11] (**69**, 4 g, 0.0126 mol) was suspended in CH_2Cl_2 (50 mL) and isobutylene (50 mL) was condensed at −15 °C. Concentrated H_2SO_4 (0.5 mL) was added and the reaction mixture was shaken in a sealed pressure flask for 3 days. The solution was poured into saturated $NaHCO_3$ solution and diluted with CH_2Cl_2 (100 mL). The organic layer was separated and the aqueous solution was washed with Et_2O (100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue obtained was purified by chromatography on silica gel with 20% hexane in CH_2Cl_2 as eluent to give the 2-*tert*-butyl ester as a colorless oil (4.07 g): ^1H NMR δ (250 MHz, DMSO) 1.45 (9 H, s, $(CH_3)_3C$), 1.64 (1 H, ddd, J = 13.0, 12.4, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.10 (1 H, dm, J = 13.0 Hz, $CH_ACH_BH_CCH_D$), 2.49 (2 H, m, $CH_ECH_FCO_2CH_3$), 3.44 (1 H, m, $CH_ACH_BH_CCH_D$), 3.65 (3 H, s, CH_3), 3.97 (1 H, dd, J = 12.4 and 3.4 Hz, $CH_ACH_BH_CCH_D$), 6.63 (2 H, m, 6-H or 8-H and NH), 6.79 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS m/e (FAB) 374 ($M + 1^+$). Anal. ($C_{17}H_{21}Cl_2NO_4$) C, H, N.

(b) This ester (4.0 g, 0.01072 mol) was dissolved in 50% aqueous acetone (300 mL) and cooled to 0 °C, 0.5 M NaOH solution (21.5 mL, 1 molar equiv) was added, and the mixture was stirred at room temperature for 3 h. The acetone was removed under vacuum and the aqueous residue was acidified to pH 1 with 1 N HCl and extracted into EtOAc (2 × 200 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography on silica gel using 4% MeOH, 1% HOAc in CH_2Cl_2 gave recovered starting material (2.5 g) and 4-acetic acid **70** as a colorless solid (0.82 g): mp 160–162 °C; ^1H NMR δ (360 MHz, DMSO) 1.45 (9 H, s, $(CH_3)_3C$), 1.62 (1 H, ddd, J = 13.0, 12.4, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.16 (1 H, dm, J = 13.0 Hz, $CH_ACH_BH_CCH_D$), 2.35 (1 H, dd, J = 16.5 and 10.9 Hz, $CH_EH_FCO_2H$), 2.45 (1 H, dd, J = 16.5 and 2.9 Hz, $CH_EH_FCO_2H$), 3.43 (1 H, m, $CH_ACH_BH_CCH_D$), 3.95 (1 H, dd, J = 12.4 and 3.4 Hz, $CH_ACH_BH_CCH_D$), 6.56 (1 H, br s, NH), 6.62 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.78 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS m/e (CI^+) 360 ($M + 1^+$). Anal. ($C_{16}H_{19}Cl_2NO_4$) C, H, N.

(c) This acid (0.25 g, 0.696 mmol) was dissolved in dry THF with dry Et_3N (0.29 mL, 2.1 mmol), hydroxybenzotriazole (0.141 g, 1.04 mmol), aniline (0.0925 mL, 1.04 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.2 g, 1.04 mmol) and the reaction mixture was stirred at room temperature for 14 h. The solvents were removed in vacuo, and the residue was dissolved in EtOAc (100 mL) and washed successively with 0.5 M citric acid solution (3 × 50 mL), saturated $NaHCO_3$ solution (3 × 50 mL), and brine (1 × 50 mL), dried (Na_2SO_4), filtered, and evaporated under vacuum. The residue obtained was purified by chromatography on silica gel using 10% EtOAc in hexane as eluent to give the amide acid (0.14 g) as a colorless oil: ^1H NMR δ (250 MHz, DMSO) 1.48 (9 H, s, $(CH_3)_3C$), 1.69 (1 H, ddd, J = 13.0, 12.4, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.47 (2 H, m, $CH_ACH_BH_CCH_D$ and $CH_EH_FCONHPh$), 2.73 (1 H, dd, J = 16.5 and 2.5 Hz, $CH_EH_FCONHPh$), 3.73 (1 H, m, $CH_ACH_BH_CCH_D$), 3.98 (1 H, dd, J = 12.4 and 3.3 Hz, $CH_ACH_BH_CCH_D$), 4.72 (1 H, br s, ArNH), 6.50 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.70 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.15 (2 H, m, ArH, PhNH), 7.33 (2 H, t, J = 7.5 Hz, ArH), 7.50 (2 H, d, J = 7.5 Hz, ArH); MS m/e (FAB) 379 ($M + 1^+$).

(d) The amide ester (0.12 g) was dissolved in 10% aqueous trifluoroacetic acid (30 mL) and left at room temperature for 30 min. The solvents were removed under vacuum, and the residue was chromatographed on silica gel using 3% MeOH, 1% HOAc, 96% CH_2Cl_2 to give a solid which was recrystallized from Et_2O/hexane to give **50** (0.035 g): mp 208 °C dec; ^1H NMR δ (360 MHz, DMSO) 1.62 (1 H, ddd, J = 13.0, 12.4, and 3.9 Hz, $CH_ACH_BH_CCH_D$), 2.19 (1 H, d, J = 13.0 Hz, $CH_ACH_BH_CCH_D$), 2.49 (2 H, m, $CH_ECH_FCONHPh$), 3.58 (1 H, m, $CH_ACH_BH_CCH_D$), 4.08 (1 H, dd, J = 12.4 and 3.4 Hz, $CH_ACH_BH_CCH_D$), 6.62 (2 H, m, 6-H or 8-H and NH), 6.80 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.04 (1 H, t, J = 7.4 Hz, Ph-4-H), 7.31 (2 H, t, J = 7.4 Hz, Ph-3,5-H), 7.59 (2 H, d, J = 7.4 Hz, Ph-2,6-H); MS m/e (FAB) 379 ($M + 1^+$). Anal. ($C_{18}H_{16}Cl_2O_3$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[*N*-(2-oxopyrrolidinyl)]-1,2,3,4-tetrahydroquinoline (51).** Isopropyl glyoxalate (3.6-g, 0.0308 mol) was added to a stirred suspension containing 3,5-dichloroaniline (5.0 g, 0.0308 mol) and anhydrous Na_2SO_4 (5.0 g, 0.035 mol) in toluene (100 mL). After 1 h at room temperature the mixture was filtered and the filtrate evaporated to give crude imine **71**. This was dissolved in CH_2Cl_2 (100 mL), the solution was cooled to 0 °C, and 1-vinylpyrrolidin-2-one (3.5 g, 0.0308 mol) and boron trifluoride etherate (0.1 mL, 0.1 mmol) were added. The mixture was allowed to reach room temperature and after 0.5 h saturated $NaHCO_3$ solution (20 mL) was added. The organic layer was removed, dried ($MgSO_4$), and evaporated. The residue crystallized from EtOAc to give a 1:1 mixture of *cis*- and *trans*-5,7-dichloro-2-[(isopropyloxy)carbonyl]-4-[*N*-(2-oxopyrrolidinyl)-1,2,3,4-tetrahydroquinoline: mp 152–154 °C. This mixture (1.0 g, 0.0027 mol) was refluxed for 1 h in MeOH (20 mL) containing NaOMe (20 mg, 0.37 mmol). On cooling, the *trans*-methyl ester **72** crystallized: mp 173–176 °C; ^1H NMR δ (360 MHz, $CDCl_3$) 1.78 (1 H, ddd, J = 11.0, 11.0, and 4.0 Hz, $CH_ACH_BH_CH_D$), 1.97 (1 H, m, $CH_ACH_BH_CH_D$), 2.43 (1 H, t, J = 6.0 Hz, CH_2CHHCH_2CO), 2.62 (1 H, d, J = 1.0 Hz, CH_2CHHCH_2CO), 3.01 (1 H, m, $CHHCH_2CH_2CO$), 3.13 (1 H, m, $CHHCH_2CH_2CO$), 3.81 (3 H, s, OCH_3), 3.96 (1 H, dd, J = 11.0 and 2.0 Hz, $CH_ACH_BH_CH_D$), 4.96 (1 H, br s, NH), 5.26 (1 H, m, $CH_ACH_BH_CH_D$), 6.57 and 6.72 (1 H, d, J = 1.0 Hz, 6,8-H); MS m/e 342 (M^+). Anal. ($C_{15}H_{16}Cl_2N_2O_3$) C, H, N. Hydrolysis of the methyl ester with LiOH, as described for **9**, gave **51**: mp 265–266 °C; ^1H NMR δ (360 MHz, DMSO) 1.80 (1 H, ddd, J = 11.0, 11.0, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 1.95–2.00 (2 H, m, $CH_ACH_BH_CCH_D$ and CH_2CHHCH_2CO), 2.2–2.4 (3 H, m, CH_2CHHCH_2CO), 2.79 (1 H, m, $CHHCH_2CH_2CO$), 3.15 (1 H, m, $CHHCH_2CH_2CO$), 3.89 (1 H, dd, J = 11.0 and 2.0 Hz, $CH_ACH_BH_CCH_D$), 5.01 (1 H, m, $CH_ACH_BH_CCH_D$), 6.66 and 6.74 (1 H each, d, J = 1.0 Hz, 6,8-H); MS m/e (CI^+) 329 (M^+). Anal. ($C_{14}H_{14}Cl_2N_2O_3 \cdot 0.25H_2O$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[*N*-(1-oxoisoindolinyl)]-1,2,3,4-tetrahydroquinoline (52).** To a solution of methyl 2-methylbenzoate (9.6 g, 0.0646 mol) in CCl_4 (100 mL) was added *N*-bromosuccinimide (11.5 g, 0.0646 mol) and the mixture illuminated with a 60-W lamp and heated under reflux. After 2 h the mixture was cooled and filtered and the filtrate evaporated to yield crude methyl 2-(bromomethyl)benzoate. This bromide (0.243 g, 1.06 mmol) was added to a solution of **66** (0.9 g, 0.96 mmol) in dry DMF (30 mL) containing Et_3N (0.294 mL, 2.1 mmol). The mixture was stirred at room temperature for 18 h, heated to 80 °C for 10 h, and then cooled and added to water (200 mL). The mixture was extracted with EtOAc (3 × 50 mL), the combined organic extracts were washed with 1 M citric acid (2 × 50 mL) and saturated Na_2CO_3 solution (2 × 50 mL), and then dried ($MgSO_4$) and evaporated. The residue crystallized from

EtOAc/hexane to yield **80** (0.085 g): mp 235 °C; ^{1}H NMR δ (360 MHz, DMSO) 1.93 (1 H, ddd, J = 13.0, 12.6, and 3.5 Hz, $CH_ACH_BH_CCH_D$), 2.51 (1 H, m, $CH_ACH_BH_CCH_D$), 3.70 (3 H, s, CH_3), 3.84 (1 H, d, J = 17.5 Hz, NCH_EH_F), 4.02 (1 H, dd, J = 12.6 and 2.9 Hz, $CH_ACH_BH_CCH_D$), 4.40 (1 H, d, J = 17.5 Hz, NHC_EH_F), 5.34 (1 H, m, $CH_ACH_BH_CCH_D$), 6.72 and 6.98 (1 H each, d, J = 2.0 Hz, 6,8-H), 7.02 (1 H, s, NH), 7.64–7.72 (4 H, m, ArH). This ester was hydrolyzed as described for **7**, to give **52**: mp 152–156 °C; ^{1}H NMR δ (360 MHz, DMSO) 1.88 (1 H, ddd, J = 13.0, 12.6, and 3.5 Hz, $CH_ACH_BH_CCH_D$), 2.51 (1 H, m, $CH_ACH_BH_CCH_D$), 3.83 (1 H, d, J = 17.5 Hz, NCH_EH_F), 3.99 (1 H, dd, J = 12.6 and 2.9 Hz, $CH_ACH_BH_CCH_D$), 4.40 (1 h, d, J = 17.5 Hz, NCH_EH_F), 5.34 (1 H, m, $CH_ACH_BH_CCH_D$), 6.68 and 6.69 (1 H each, d, J = 2.0 Hz, 6,8-H), 6.91 (1 H, s, NH), 7.46–7.77 (4 H, m, ArH); MS (CI^-) m/e 376 ($M - 1^-$). Anal. ($C_{18}H_{15}Cl_2N_2O_3$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[*N*-(1,3-dioxoisoindolinyl)]-1,2,3,4-tetrahydroquinoline (53).** To a solution of **66** (0.5 g, 1.61 mmol) in dry THF (50 mL) was added Et_3N (0.493 mL, 3.53 mmol), phthalic anhydride (0.285 g, 1.93 mmol), and 4-(dimethylamino)pyridine (5 mg). The mixture was stirred under N_2 for 3 h at room temperature and then added to 1 M aqueous HCl (200 mL) and the mixture extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), and evaporated. The residue crystallized from EtOAc to yield **79**: mp 241–243 °C; ^{1}H NMR δ (360 MHz, DMSO) 1.72 (1 H, ddd, J = 13.0, 12.4, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.46 (1 H, m, $CH_ACH_BH_CCH_D$), 3.73 (3 H, s, CH_3), 4.04 (1 H, dd, J = 12.4 and 2.9 Hz, $CH_ACH_BH_CCH_D$), 5.19 (1 H, m, $CH_ACH_BH_CCH_D$), 6.67 and 6.84 (1 H each, d, J = 2.0 Hz, 6,8-H), 6.82 (1 H, s, ArNH), 7.35–7.57 (4 H, m, ArH), 8.65 (1 H, br d, NHCO), 12.86 (1 H, br s, OH). To a solution of **79** (0.20 g, 0.473 mmol) in dry DMF (10 mL) was added carbonyldiimidazole (0.10 g, 0.63 mmol) and the solution stirred at room temperature under N_2 for 18 h. The mixture was added to saturated $NaHCO_3$ solution (50 mL) and extracted with EtOAc (3 × 50 mL) and the organic extract washed with saturated Na_2CO_3 solution (2 × 50 mL), water (1 × 50 mL), and brine (2 × 50 mL) and then dried ($MgSO_4$) and evaporated. The residue crystallized from EtOAc/hexane to yield **53** methyl ester (0.15 g): mp 254–255 °C. Hydrolysis of the ester with LiOH, as described for **9**, gave **53**: mp 225–227 °C; ^{1}H NMR δ (360 MHz, DMSO) 2.02 (1 H, ddd, J = 13.3, 12.4, and 3.0 Hz, $CH_ACH_BH_CCH_D$), 2.35 (1 H, dm, J = 13.3 Hz, $CH_ACH_BH_CCH_D$), 4.0 (1 H, dd, J = 12.4 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 5.38 (1 H, m, $CH_ACH_BH_CCH_D$), 6.57 and 6.90 (1 H each, d, J = 2.0 Hz, 6,8-H), 7.04 (1 H, s, NH), 7.84 (4 H, br s, ArH), 13.00 (1 H, br s, OH); MS (CI^+) m/e 391 ($M + 1^+$). Anal. ($C_{18}H_{12}Cl_2N_2O_4$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[*N*-(2-oxo-1,2,3,4-tetrahydroisoquinolinyl)]-1,2,3,4-tetrahydroquinoline (54).** A solution of *o*-tolylacetic acid (1.0 g, 6.7 mmol) in CCl_4 containing *N*-bromosuccinimide (1.2 g, 6.7 mmol) was heated under reflux for 2 h, cooled, filtered, and evaporated. The residue was dissolved in 10% HCl in MeOH (100 mL), and after 4 h, the solution was evaporated and the residue purified by flash chromatography, eluting with 20% EtOAc/petroleum ether (bp 60–80 °C) to yield methyl *o*-(bromomethyl)toluate as a pale yellow oil. This ester (0.26 g, 1.06 mmol) was added to a solution of **66** (0.30 g, 0.96 mmol) and Et_3N (0.156 mL, 2.12 mmol) in dry DMF (15 mL) and the reaction mixture heated at 100 °C, under N_2, for 16 h. The cooled mixture was added to 1 M citric acid solution (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organics were successively washed with 1 M citric acid (25 mL), saturated Na_2CO_3 (2 × 25 mL), and brine (2 × 25 mL) and then dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography, eluting with 30% EtOAc/hexane, to yield **81** (75 mg): mp 235 °C; ^{1}H NMR δ (360 MHz, DMSO) 1.86 (1 H, ddd, J = 13.3, 12.7, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.28 (1 H, m, $CH_ACH_BH_CCH_D$), 3.54 (2 H, m, CH_2NCO), 3.60 (3 H, s, CH_3), 3.94 (2 H, m, $CH_ACH_BH_CCH_D$ and $NCOCH_EH_F$), 4.20 (1 H, d, J = 15.2 Hz, $NCOCH_EH_F$), 5.51 (1 H, m, $CH_ACH_BH_CCH_D$), 6.70 and 6.97 (1 H each, d, J = 2.0 Hz, 6,8-H), 6.98 (1 H, s, NH), 7.08–7.23 (4 H, m, ArH); MS m/e 405 ($M + 1^+$). Hydrolysis of **81** with LiOH, as described for **9**, gave **54**: mp 283–284 °C dec; ^{1}H NMR δ (360 MHz, DMSO) 1.81 (1 H, ddd, J = 13.0, 12.5, and 3.9 Hz, $CH_ACH_BH_CCH_D$), 2.25 (1 H, dm, J = 13.0 Hz, $CH_ACH_BH_CCH_D$), 3.54–3.65 (2 H, m, CH_2NCO), 3.82 (1 H, dd, J = 12.5 and 2.7 Hz, $CH_ACH_BH_CCH_D$), 3.93 (1 H, d, J = 15.1 Hz, $NCOCH_EH_F$), 4.20 (1 H, d, J = 15.1 Hz, $NCOCH_EH_F$), 5.52 (1 H, m, $CH_ACH_BH_CCH_D$), 6.68 and 6.97 (1 H each, d, J = 2.0 Hz, 6,8-H), 6.87 (1 H, s, NH), 7.08–7.24 (4 H, m, ArH); MS m/e 391 ($M + 1^+$). Anal. ($C_{19}H_{16}Cl_2N_2O_3 \cdot 0.1H_2O$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[1-(3-phenyl-2-oxoimidazolidinyl)]-1,2,3,4-tetrahydroquinoline (55).** A suspension containing *N*-phenyl-*N*-(*tert*-butoxycarbonyl)-2-aminoethanol (2.0 g), pyridinium dichromate (3.5 g), and crushed 4A molecular sieves in dry CH_2Cl_2 was stirred at room temperature for 14 h and filtered, the filtrate evaporated, and the residue purified by chromatography on silica gel, eluting with 15% EtOAc/petroleum ether, to give aldehyde **82** as an oil (1.28 g): ^{1}H NMR δ (250 MHz, $CDCl_3$) 1.44 (9 H, s, CMe_3), 4.32 (2 H, d, J = 0.8 Hz, CH_2), 7.17–7.37 (5 H, m, ArH), 9.71 (1 H, app s, CHO); MS m/e (CI^+) 236 ($M + 1^+$). To a solution of aldehyde **82** (0.50 g) and **66** (0.60 g) in dry MeOH (30 mL) were added 3A molecular sieves (10 g) and sodium cyanoborohydride (0.081 g). After 3 h the mixture was filtered and evaporated, the residue purified by chromatography on silica gel, eluting with EtOAc/petroleum ether to give **83** as a foam (0.673 g) which was dissolved in EtOAc saturated with HCl (24 mL). After 1 h, the solvent was evaporated and the residue triturated with EtOAc to give the deprotected amine ester (0.57 g). This material (0.30 g) was dissolved in dry THF containing Et_3N (0.19 mL), and phosgene (0.44 mL of a 1.93 M solution in toluene) was added. After 1 h the solvents were removed, the residue was dissolved in EtOAc (100 mL), and the solution was washed with 1 M citric acid, saturated $NaHCO_3$ solution, and brine, and then dried ($MgSO_4$) and evaporated to dryness. Trituration of the residue with MeOH gave **84** (0.215 g): mp 251–253 °C. Compound **84** (0.17 g) was hydrolyzed with LiOH, as described for **7**, to yield **55** (0.137 g): mp 174–178 °C dec; ^{1}H NMR δ (360 MHz, DMSO) 1.77 (1 H, ddd, J = 13.3, 12.7, and 4.0 Hz, $CH_ACH_BH_CCH_D$), 2.38 (1 H, dm, J = 13.3 Hz, $CH_ACH_BH_CCH_D$), 2.89 (1 H, dd, J = 17.8 and 8.9 Hz, $NCH_EH_FCH_GH_H$), 3.29 (1 H, dd, J = 14.8 and 7.0 Hz, $NCH_EH_FCH_GH_H$), 3.75 (2 H, m, $NCH_EH_FCH_GH_H$), 4.04 (1 H, dd, J = 12.7 and 2.9 Hz, $CH_ACH_BH_CCH_D$), 5.04 (1 H, m, $CH_ACH_BH_CCH_D$), 6.69 and 6.94 (1 H each, d, J = 1.9 Hz, 6,8-H), 6.84 (1 H, s, NH), 6.99–7.56 (5 H, m, PhH); MS m/e (FAB) 406 ($M + 1^+$). Anal. ($C_{19}H_{17}Cl_2N_3O_3 \cdot 0.5EtOAc$) C, H, N.

***trans*-2-Carboxy-5,7-dichloro-4-[3-(2-oxo-1,2,3,4-tetrahydroquinazolinyl)]-1,2,3,4-tetrahydroquinoline (56).** A solution of **66** (0.50 g, 1.61 mmol), Et_3N (0.67 mL, 4.82 mmol), and 2-nitrobenzyl bromide (0.69 g, 3.21 mmol) in DMF (15 mL) was stirred at room temperature, under an atmosphere of N_2, for 18 h. The mixture was added to water (200 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water and brine and then dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography to yield the 4-(2-nitrobenzylamine) derivative (0.50 g) which was hydrogenated for 2 h at 50 psi over 10% Pd on carbon (0.15 g) in EtOAc (15 mL). The mixture was filtered, the filtrate evaporated, and the residue purified by flash chromatography, eluting with 50% EtOAc/hexane, to yield **77** (0.21 g). To a solution of **77** (0.20 g, 0.55 mmol) in dry THF were added Et_3N (0.283 mL, 2.03 mmol) and phosgene (0.261 mL of a 20% solution in toluene). The mixture was stirred under N_2 for 2 h and then evaporated to dryness, and the residue partitioned between EtOAc (100 mL) and 1 M citric acid (50 mL). The organic layer was washed with 1 M citric acid (50 mL), water (50 mL), saturated $NaHCO_3$ solution (2 × 50 mL), and brine (2 × 50 mL) and then dried ($MgSO_4$) and evaporated to yield **78**: mp >300 °C. Compound **78** was hydrolyzed with LiOH, as described for **9**, to yield **56**: mp 210–213 °C; ^{1}H NMR δ (360 MHz, DMSO) 1.75 (1 H, ddd, J = 13.0, 12.6, and 3.5 Hz, $CH_ACH_BH_CCH_D$), 2.34 (1 H, dm, J = 13.0 Hz, $CH_ACH_BH_CCH_D$), 3.82 (1 H, d, J = 14.4 Hz, $CONCH_EH_F$), 3.92 (1 H, dd, J = 12.6 and 2.9 Hz, $CH_ACH_BH_CCH_D$), 4.09 (1 H, d, J = 14.4 Hz, $CONCH_EH_F$), 5.43 (1 H, m, $CH_ACH_BH_CCH_D$), 6.68 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.74–7.12 (6 H, m, ArNH, 6-H or 8-H, ArH), 9.28 (1 H, s, NHCON); MS m/e (FAB^+) 392 ($M + 1^+$).

***trans*-2-Carboxy-7-chloro-5-iodo-4-[[(phenylmethyl)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (58).** A suspension containing 3-chloro-5-iodoaniline[5] (17.2 g, 0.0679 mol),

methylglyoxalate (5.98 g, 0.0679 mol) and anhydrous Na_2SO_4 (55 g, 0.39 mol) was stirred at room temperature for 2 h and filtered, the filtrate was cooled to −5 °C, and benzyl *N*-vinylcarbamate (15.6 g, 0.0883 mol) and boron trifluoride etherate (4.5 mL, 0.036 mol) were added. The mixture was stirred under N_2 for 0.5 h and then warmed to room tempeature for 2 h, and saturated $NaHCO_3$ and EtOAc were added. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to leave a residue which solidified with Et_2O to give **73** (15.9 g, 47%), which was shown by ^1H NMR to be a mixture of cis and trans stereoisomers (10:1) each being a 1:1 mixture of 5-iodo and 7-iodo regioisomers. A solution containing **73** (15.3 g, 0.0306 mol) and NaOMe [from 0.175 g of Na (0.0076 g-atom)] in MeOH (70 mL) was heated at reflux for 1.5 h; a white precipitate formed which dissolved on addition of EtOAc (750 mL). The solution was washed with 1 M HCl, saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated and the residue triturated with Et_2O to give crude **74** as a 1:1 mixture of regioisomers. Exhaustive recrystallization from EtOAc/hexane gave **76** (2.3 g, containing ~10% of **75** by ^1H NMR): mp 190–192 °C. The regiochemistry was proven by hydrogenolysis, at 50 psi, of **76** (50 mg, 0.1 mmol) in MeOH (7 mL) in the presence of 10% Pd on carbon (10 mg). The resulting 5-chloro derivative was purified by preparative TLC, eluting with EtOAc/hexane, and identified by ^1H NMR [δ (360 MHz, DMSO) 6.61 (1 H, d, J = 7.8 Hz, 6-H or 8-H), 6.72 (1 H, d, J = 8.1 Hz, 6-H or 8-H), 7.00 (1 H, app t, J = 8.0 Hz, 7-H)]. The Et_2O mother liquors were evaporated and the residue purified by chromatography on silica gel, eluting with EtOAc/hexane and then 1% HOAc/EtOAc/hexane mixtures, to give a material (3.85 g) which was reepimerized with NaOMe. The product was purified by exhaustive chromatography on silica gel, finally using a Waters Prep LC 500A instrument, eluting with 90% CH_2Cl_2 in hexane, and then with CH_2Cl_2, to give **75** (1.9 g, containing ~15% of **76** by ^1H NMR). A solution of **75** (1.87 g, 0.00374 mol) was suspended in dry CH_2Cl_2 and HOAc presaturated with HBr (15 mL) was added. After 2 h, the solvents were removed, and the solid was washed with Et_2O to give the 4-amino derivative (1.56 g, 93%): mp 215–217 °C. Successive treatment of this amine with phenylacetic acid, as described for **14**, and LiOH, as described for **7**, gave **58** (containing 9% of the 7-iodo regioisomer by ^1H NMR): mp 128–130 °C; ^1H NMR δ (360 MHz, DMSO) 1.59 (1 H, ddd, J = 13.1, 12.6, and 3.6 Hz, $CH_ACH_BH_CCH_D$), 2.18 (1 H, dm, J = 13.1 Hz, $CH_ACH_BH_CCH_D$), 3.47 (2 H, s, CH_2), 3.81 (1 H, dd, J = 12.6 and 2.8 Hz, $CH_ACH_BH_CCH_D$), 4.77 (1 H, m, $CH_ACH_BH_CCH_D$), 6.65 (1 H, s, ArNH), 6.93 and 7.03 (1 H each, d, J = 2.0 Hz, 6,8-H), 7.18–7.28 (5 H, m, PhH), 8.34 (1 H, d, J = 6.8 Hz, NHCO): MS m/e 470 (M^+). Anal. ($C_{18}H_{16}ClIN_2O_3 \cdot 0.6Et_2O$) C, H, N.

***trans*-2-Carboxy-5-chloro-7-iodo-4-[[(phenylmethyl)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (59)** was prepared from **76** as described for **58**: mp 216–217 °C; ^1H NMR δ (360 MHz, DMSO) 1.59 (1 H, ddd, J = 13.2, 12.6, and 3.7 Hz, $CH_ACH_BH_CCH_D$), 2.14 (1 H, dm, J = 12.6 and 2.6 Hz, $CH_ACH_BH_CCH_D$), 3.41 (2 H, s, CH_2), 3.81 (1 H, dd, J = 12.6 and 2.6 Hz, $CH_ACH_BH_CCH_D$), 4.98 (1 H, m, $CH_ACH_BH_CCH_D$), 6.67 (1 H, br s, ArNH), 6.91 and 7.19 (1 H each, d, J = 1.5 Hz, 6,8-H), 7.18–7.30 (5 H, m, PhH), 8.42 (1 H, d, J = 7.1 Hz, NHCO); MS m/e 470 (M^+). Anal. ($C_{18}H_{16}ClIN_2O_3 \cdot 0.3H_2O$) C, H, N.

***trans*-2-Carboxy-5,7-dimethyl-4-[[(phenylmethyl)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (60)** was prepared from 5,7-dimethyldihydrokynurenic acid[11] in the same way as described for **14** (with the exception of the oxime reduction, which was performed with $NaCNBH_3/TiCl_3/NH_4Cl$ in MeOH[24]): mp 137–140 °C; ^1H NMR δ (360 MHz, DMSO) 1.59 (1 H, ddd, J = 13.0, 12.6, and 3.5 Hz, $CH_ACH_BH_CCH_D$), 1.96 (3 H, s, 5- or 7-CH_3), 2.16 (4 H, m, $CH_ACH_BH_CCH_D$, 5- or 7-CH_3), 3.41 (2 H, m, $NCOCH_2$), 3.86 (1 H, dd, J = 12.6 and 2.9 Hz, $CH_ACH_BH_CCH_D$), 4.86 (1 H, m, $CH_ACH_BH_CCH_D$), 6.23 and 6.44 (1 H each, d, J = 2.0 Hz, 6,8-H), 7.19–7.31 (5 H, m, ArH), 8.27 (1 H, d, J = 7.4 Hz, NHCO); MS m/e 339 ($M + 1^+$). Anal. ($C_{20}H_{22}N_2O_3$) C, H, N.

***trans*-2-Carboxy-7-chloro-5-iodo-4-[[(phenylamino)carbonyl]amino]-1,2,3,4-tetrahydroquinoline (61)** was prepared from **75** as described above for **58** and **35**: mp 183–184 °C dec; ^1H NMR δ (360 MHz, DMSO) 1.62 (1 H, ddd, J = 13.2, 12.6, and 2.8 Hz, $CH_ACH_BH_CCH_D$), 2.36 (1 H, dm, J = 13.2 Hz, $CH_ACH_BH_CCH_D$), 3.85 (1 H, dd, J = 12.6 and 2.8 Hz, $CH_ACH_BH_CCH_D$), 4.70 (1 H, m, $CH_ACH_BH_CCH_D$), 6.37 (1 H, d, J = 6.0 Hz, $NHCONHPh$), 6.64 (1 H, s, $ArNHCH_A$), 6.90 (1 H, app t, J = 7.3 Hz, Ph-4H), 6.94 and 7.05 (1 H each, d, J = 1.9 Hz, 6,8-H), 7.22 (2 H, app t, J = 7.9 Hz, Ph-3,5H), 7.40 (2 H, app t, J = 7.6 Hz, Ph-2,6H), 8.20 (1 H, s, CONHPh); MS m/e (FAB^+) 472 ($M + 1^+$). Anal. ($C_{17}H_{15}ClIN_3O_3 \cdot 0.8H_2O$) C, H, N.

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Supplementary Material Available: Crystal data, x,y,z coordinates and selected interatomic angles and distances for compound **10** (6 pages). Ordering information is given on any current masthead page.

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