

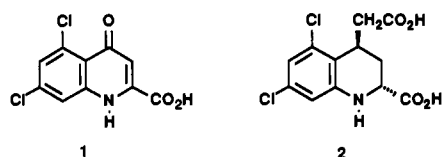
4-Amido-2-carboxytetrahydroquinolines. Structure-Activity Relationships for Antagonism at the Glycine Site of the NMDA Receptor

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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**; IC₅₀ = 7.4 nM vs [³H]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 *2S,4R*, 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 ¹H 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**; IC₅₀ = 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-



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 model⁵ to a three-dimensional pharmacophore of the glycine antagonist recognition site.

Synthesis. Compound **3** has been reported¹¹; 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

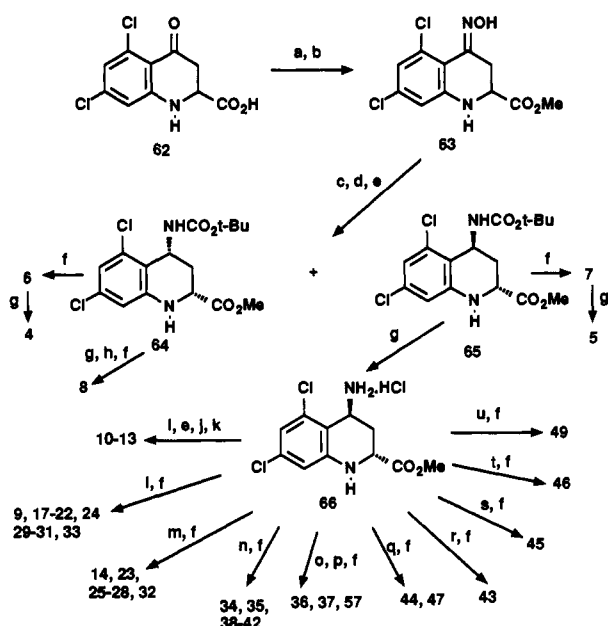
64 and **65**, and **65** deprotected to yield **66** (Scheme I). Treatment of mixtures of **64** and **65** with catalytic quantities of sodium methoxide in refluxing methanol resulted in epimerization, with the more thermodynamically stable *trans* isomer **65** predominating by >20:1. Acylation of **66** using acid chlorides in the presence of triethylamine, or carboxylic acids with triethylamine, water-soluble carbo-

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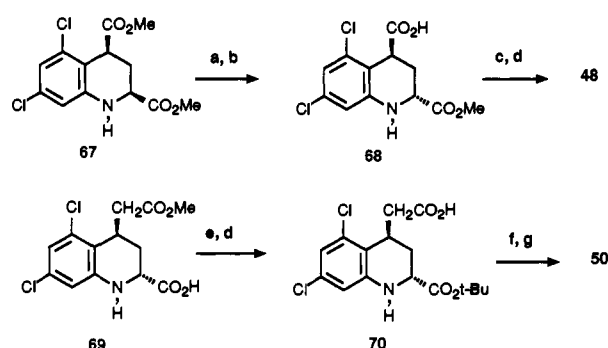
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Scheme I^a

^a (a) $\text{NH}_2\text{OH}\cdot\text{HCl}$, $\text{C}_6\text{H}_5\text{N}$; (b) MeOH , HCl ; (c) Zn , HOAc ; (d) (*t*-BuOCO)₂O, $\text{Me}_2\text{N}(\text{CH}_2)_2\text{NH}_2$; (e) separate, SiO_2 chromatography; (f) LiOH , H_2O , THF ; (g) HCl , EtOAc ; (h) PhCOCl , Et_3N ; (i) (*R*)- or (*S*)- $\text{PhCH}_2\text{CH}(\text{NHCO}_2t\text{-Bu})\text{CO}_2\text{H}$, $\text{Me}_2\text{N}(\text{CH}_2)_3\text{N}=\text{C}=\text{NET}$, HOBT , Et_3N ; (j) $\text{CF}_3\text{CO}_2\text{H}$; (k) NaOH , MeOH , H_2O ; (l) RCOCl , Et_3N ; (m) RCO_2H , $\text{Me}_2\text{N}(\text{CH}_2)_3\text{N}=\text{C}=\text{NET}$, HOBT , Et_3N ; (n) $\text{RN}=\text{C}=\text{O}$, Et_3N ; (o) PhOCOCl , Et_3N ; (p) Me_3SiCl , Et_3N , $\text{R}^1\text{R}^2\text{NH}$; (q) RX , Et_3N , DMF ; (r) PhSO_2Cl , Et_3N ; (s) $\text{PhN}=\text{C}=\text{S}$, Et_3N ; (t) PhNHCNSHCN , $\text{Me}_2\text{N}(\text{CH}_2)_3\text{N}=\text{C}=\text{NET}$, DMF ; (u) $(\text{PhCH}_2\text{O})_2\text{CO}$, 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,

Scheme II^a

^a (a) NaOH , dry MeOH ; (b) MeOH , HCl ; (c) (i) $(\text{imidazole})_2\text{CO}$, DMF , 60°C , (ii) PhCH_2NH_2 , DMAP ; (d) NaOH , MeOH , H_2O ; (e) $\text{Me}_2\text{C}=\text{CH}_2$, H_2SO_4 ; (f) PhNH_2 , HOBT , Et_3N , $\text{Me}_2\text{N}(\text{CH}_2)_3\text{N}=\text{C}=\text{NET}$; (g) 10% aqueous $\text{CF}_3\text{CO}_2\text{H}$.

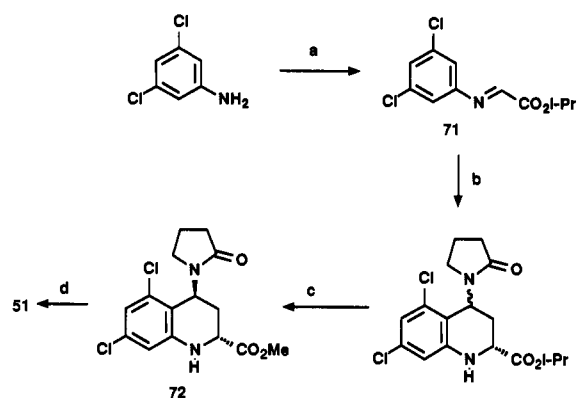
followed by in situ formation of the isocyanate with trimethylsilyl chloride and triethylamine, and reaction with the appropriate anilines. Alkylation of 66 gave 44 and 47, and cyanoguanidine 46 was obtained using phenylthiourea in the presence of water-soluble carbodiimide.¹³

4-Benzyl carboxamide 48 was obtained from *cis*-diester 67¹¹ (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 69¹¹ as the *tert*-butyl ester allowed selective hydrolysis of the 4-methyl ester to give 70, which was converted to 4-benzylacetamide 50.

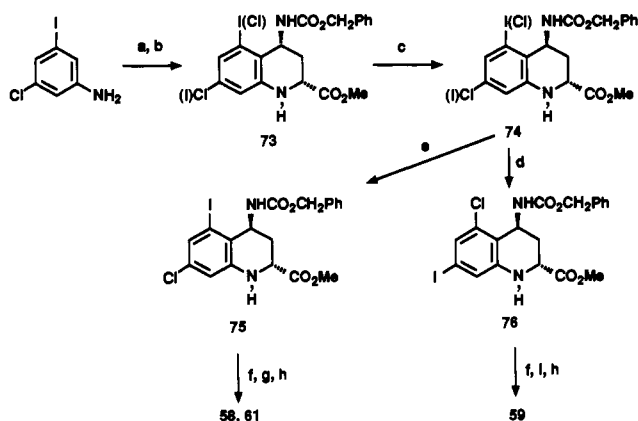
An alternative route¹⁴ to the 4-amino-tetrahydroquinoline system, involving reactions of enamides with *N*-arylimino esters,¹⁵ proved to be synthetically useful (Schemes III and IV). Imine 71, generated in situ, smoothly reacted with *N*-vinylpyrrolidinone to give a 1:1 mixture of isomers. Epimerization with methoxide resulted in enrichment (20:1) of the *trans* isomer, 72, which could be isolated in pure form. Using 3-chloro-5-iodoaniline⁵ and benzyloxy *N*-vinylcarbamate as the enamide¹⁵ 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, Na₂SO₄; (b) *N*-vinylpyrrolidin-2-one, BF₃·Et₂O; (c) cat. NaOMe, MeOH; (d) LiOH, H₂O, THF.

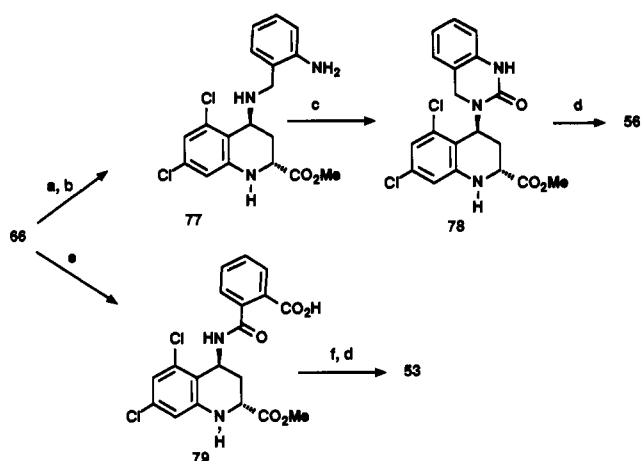
Scheme IV^a

^a (a) MeOCOCHO, Na₂SO₄; (b) benzyloxy *N*-vinylcarbamate, BF₃·Et₂O; (c) cat. NaOMe, MeOH; (d) recrystallize from EtOAc/hexane; (e) chromatography, SiO₂; (f) HBr, HOAc; (g) PhCH₂CO₂H, Me₂N(CH₂)₃N=C=CEt, HOBT, Et₃N or PhN=C=O, Et₃N; (h) LiOH, H₂O, THF; (i) PhCH₂COCl, Et₃N.

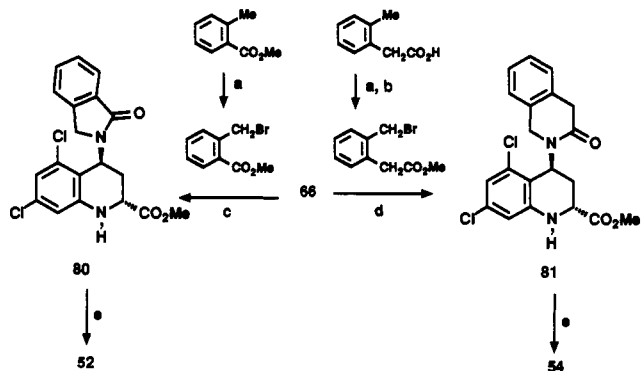
mixture 74 which was separated by exhaustive crystallization and chromatography to yield the 5-iodo (75) and 7-iodo (76) derivatives. The regiochemistries of 75 and 76 were assigned from catalytic hydrogenolysis of 76 over Pd on carbon, which gave the 5-chloro derivative. 5,7-Dimethyl derivative 60 was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

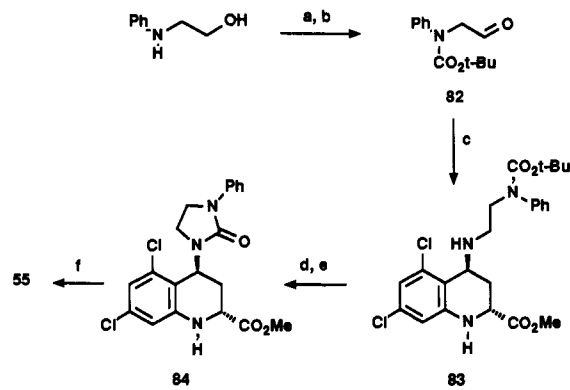
Biology. Compounds were evaluated *in vitro* for their abilities to (1) displace [³H]glycine from rat brain membranes (IC₅₀ values) and (2) antagonize NMDA responses in a rat cortical slice preparation (apparent *K_i* values). Full details of the methods used have been published.^{3,9,16}

Scheme V^a

^a (a) 2-Nitrobenzyl bromide, Et₃N, DMF; (b) H₂, Pd-C; (c) COCl₂, Et₃N; (d) LiOH, H₂O, THF; (e) phthalic anhydride, Et₃N, DMAP; (f) Me₂N(CH₂)₃N=C=NEt.

Scheme VI^a

^a (a) *N*-bromosuccinimide, CCl₄; (b) HCl, MeOH; (c) Et₃N, DMF, room temperature; (d) Et₃N, DMF, 100 °C; (e) LiOH, H₂O, THF.

Scheme VII^a

^a (a) (*t*-BuOCO)₂O; (b) PDC, 4A sieves; (c) 66, NaCNBH₃, 4A sieves, MeOH; (d) HCl, EtOAc; (e) COCl₂, Et₃N; (f) LiOH, H₂O, 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 2¹¹ and confirms the requirement for the 2,4-*trans* stereochemistry in this class of glycine antagonists.

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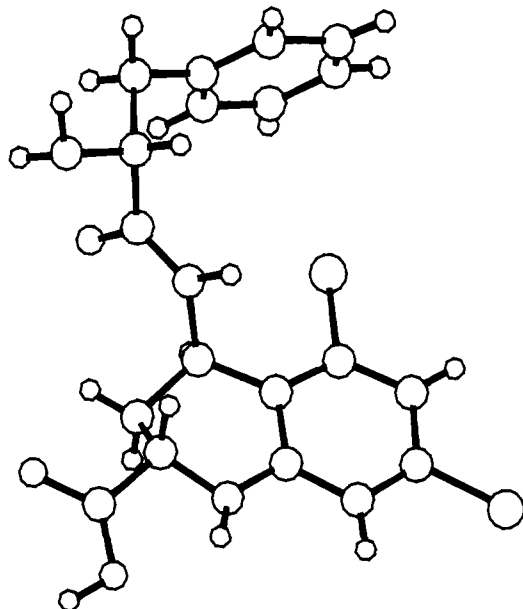
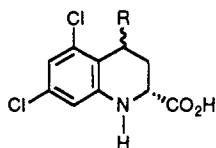


Figure 1. The structure of the (*R*)-phenylalanine derivative 10 as determined by X-ray crystallography.

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

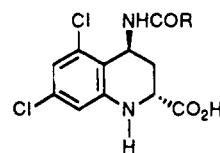


no.	R	IC ₅₀ (μM) vs [³ H]Gly ^a	K _b (μM) vs NMDA ^b
3	H	6.4	84
4 NH ₂	14.1	51
5	— NH ₂	11.3	32
6 NHC(O) <i>t</i> -Bu	11.4	176
7	— NHC(O) <i>t</i> -Bu	0.94	8.2
8 NHCOPh	8.3	96
9	— NHCOPh	0.10	1.2
10	— NHC(O)CH(NH ₂)CH ₂ Ph (<i>R</i> , <i>2S</i> , <i>4R</i>)	>1000	
11	— NHC(O)CH(NH ₂)CH ₂ Ph (<i>R</i> , <i>2R</i> , <i>4S</i>)	7.0	16.8
12	— NHC(O)CH(NH ₂)CH ₂ Ph (<i>S</i> , <i>2S</i> , <i>4R</i>)	>100	
13	— NHC(O)CH(NH ₂)CH ₂ Ph (<i>S</i> , <i>2R</i> , <i>4S</i>)	1.05	>10
14	— NHC(O)CH ₂ Ph	0.014	0.53
15	— NHC(O)CH ₂ Ph(-)	0.011	
16	— NHC(O)CH ₂ Ph(+)	5.9	

^aInhibition of [³H]glycine binding to rat cortical membranes. Values given are the means of two to four determinations; the maximum variance (geometric mean) was 60%. ^bAntagonism 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*,*2S*,*4R* derivative 10 (Figure 1). Only isomers 11 and 13, having the *2R*,*4S* 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-966⁹ and L-687,414¹⁰), 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	<i>n</i> -Pr	0.37	2.1
19	<i>c</i> -hexyl	0.17	2.1
20	CH ₂ - <i>c</i> -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 ₂ Ph	0.017	0.53
23	CH ₂ (3-thienyl)	0.030	0.71
24	CH ₂ (2-thienyl)	0.032	0.33
25	CH ₂ C ₆ H ₄ NH ₂ -4	0.018	0.51
26	CH ₂ C ₆ H ₄ OH-4	0.030	0.64
27	CH ₂ C ₆ H ₄ CH ₃ -4	0.034	0.72
28	CH ₂ C ₆ H ₄ OCH ₃ -4	0.039	0.83
29	CH ₂ C ₆ H ₄ Cl-4	0.052	2.2
30	(CH ₂) ₂ Ph	0.076	0.74
31	(CH ₂) ₃ Ph	0.17	1.7
32	CHPh ₂	0.061	2.1
33	9-fluorenyl	0.025	3.2

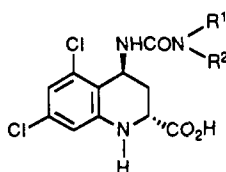
^{a,b}See Table I.

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 ¹H 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, NHCHCO₂H (assignment based on the chemical shift found for 2¹¹), 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 (IC₅₀ 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

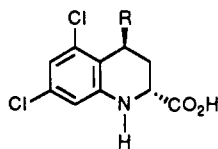
(17) Monahan, J. B.; Hood, W. F.; Compton, R. P.; Cordi, A. A.; Williams, R. M. Identification of a Novel Structural Class of Positive Modulators of the *N*-Methyl-D-aspartate Receptor, with Actions Mediated through the Glycine Recognition Site. *Eur. J. Pharm.—Mol. Pharm. Sect.* 1990, 189, 373–379.

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 ₂ Ph	H	0.030	0.77
39	1-naphthyl	H	0.011	0.35
40	C ₆ H ₄ CH ₃ -4	H	0.0050	0.14
41	C ₆ H ₄ CH ₃ -3	H	0.018	0.27
42	C ₆ H ₄ CH 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 ₂ Ph	5.2	48
44	NHCH ₂ Ph	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 ₂ CONHPh	0.42	14.7
48	CONHCH ₂ Ph	1.7	14.5
49	NHCO ₂ CH ₂ Ph	0.079	3.3
50	CH ₂ CONHPh	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 IC₅₀ 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, IC₅₀ = 7.4 nM, K_b = 130 nM) is one of the most potent NMDA antagonists yet described and [³H]-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 (IC₅₀ 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.

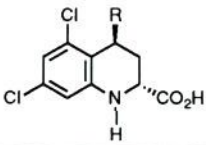
Modification of the Amide Group. The importance of the amide carbonyl for binding is illustrated by the loss of activity in both sulfonamide (43) and benzylamine (44) derivatives (Table IV). These results show that the amide carbonyl increases affinity by approximately 100-fold, a free energy change 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.


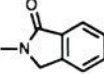
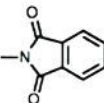
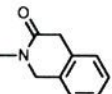
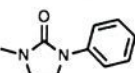
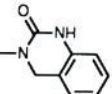
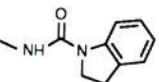
Conformationally Restricted Derivatives. A short series of compounds incorporating rigidifying elements into the 4-substituent was made to probe the conformational characteristics associated with receptor binding (Table V). The comparable activities of pyrrolidone 51 and benzofused derivatives 52 and 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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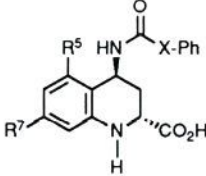
Table V. Conformationally Restricted 4-Substituents



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

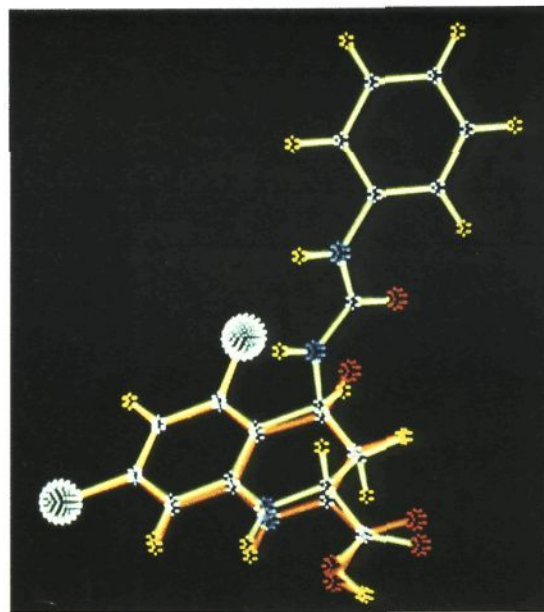


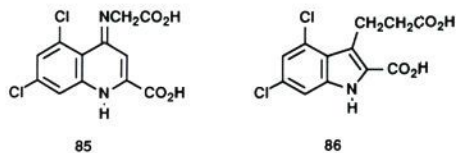
Figure 2. Overlay of kynurenate **2** (red) with tetrahydroquinoline **35** (green). The modeling was done with AMF/Optimol, in-house software written by the Molecular Systems Group, MSDRL, Rahway, NJ.

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.

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 ¹H 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-



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 kynurenates⁵ 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 [³H]CPP and [³H]CGS 19755) and non-NMDA amino acid sites (labeled by [³H]AMPA, [³H]kainate, and [³H]strychnine).²² These and related¹¹ compounds provide primary details of the stereochemical and conformational requirements for binding, which both support and extend our earlier pharmacophoric model.⁵ A pseudo-equatorially 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 do-

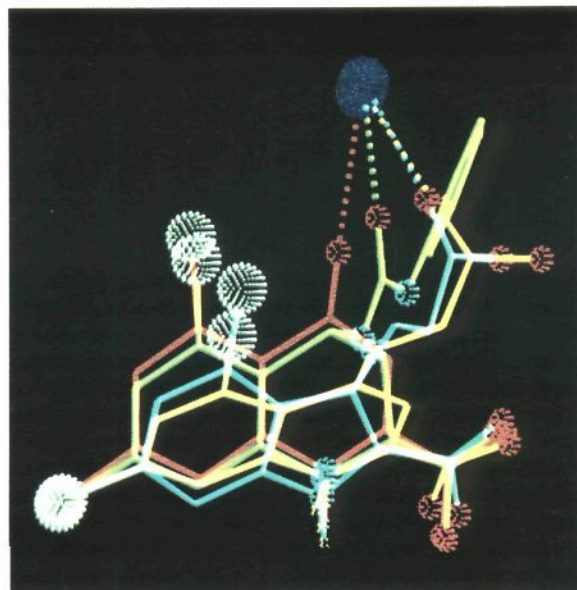


Figure 3. Superimposition of glycine site antagonists [1 (red), 35 (green), 85 (yellow), and 86 (blue)] containing a common *N*-(chlorophenyl)glycine moiety. Hydrogen bonding of the essential substituent carbonyl groups of 1 and 35, and the substituent carboxyls of 85 and 86, is postulated to occur at 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.

nor. 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.

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-tetrahydroquinoline¹¹ (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 N₂ 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 N₂ for 17 h. The solvent was removed in vacuo and the residue was partitioned between water (300 mL) and Et₂O (300 mL). The aqueous phase was further extracted with Et₂O (2 × 300 mL), the combined organic layers were washed with 0.5 M aqueous citric acid solution (1 × 200 mL), saturated NaHCO₃ solution (2 × 200 mL), and brine (1 × 200 mL), and then dried (MgSO₄), and the solvent was removed under vacuum to give oxime ester 63 (15.1 g) as a brown solid: mp 216–217 °C; ¹H 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, CO₂CH₃), 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. (C₁₁H₁₀Cl₂N₂O₃) 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 NaHCO₃ solution (2 × 200 mL) and saturated brine solution (1 × 200 mL), and then dried (MgSO₄), filtered, and concentrated under vacuum to give a brown foam (6.60 g). To a solution of this foam in CH₂Cl₂ (350 mL) was added

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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 (MgSO₄), 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; ¹H NMR δ (360 MHz, CDCl₃), 1.48 (9 H, s, C(CH₃)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, CH₃), 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. (C₁₆H₂₀Cl₂N₂O₄) 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; ¹H NMR δ (360 MHz, CDCl₃), 1.43 (9 H, s, C(CH₃)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, CH₃), 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 – NHCO₂, *t*-Bu, CO₂CH₃, H). Anal. (C₁₆H₂₀Cl₂N₂O₄) 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 (MgSO₄) 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; ¹H NMR δ (360 MHz, DMSO) 1.40 (9 H, s, C(CH₃)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_CCH_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. (C₁₅H₁₆Cl₂N₂O₄) 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; ¹H NMR δ (250 MHz, CDCl₃) 1.54 (9 H, s, C(CH₃)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. (C₁₅H₁₆Cl₂N₂O₄) 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; ¹H NMR δ (360 MHz, D₂O) 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. (C₁₀H₁₀Cl₂N₂O₃·HCl·0.4H₂O) 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; ¹H NMR δ (360 MHz, D₂O) 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. (C₁₀H₁₀Cl₂N₂O₃·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); ¹H NMR δ (360 MHz, D₂O) 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, CH₃), 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. (C₁₁H₁₂N₂O₂·HCl) C, H, N.

(b) To a suspension of 66 (0.2 g, 0.642 mmol) in anhydrous CH₂Cl₂ (15 mL) was added dry Et₃N (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 NaHCO₃ solution (2 × 50 mL) and brine (50 mL) and then dried (MgSO₄) 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; ¹H 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, CO₂CH₃), 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. (C₁₈H₁₆Cl₂N₂O₃) 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 NaHCO₃ 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 (Na₂SO₄) 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; ¹H NMR δ (360 MHz, CD₃OD) 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* = 7.6 Hz, NHCO); MS *m/e* (FAB⁺) 365 (M + 1⁺). Anal. (C₁₇H₁₄Cl₂N₂O₃) 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; ¹H NMR δ (360 MHz, CD₃OD) 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. (C₁₇H₁₄Cl₂N₂O₃) 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; ¹H NMR δ (360 MHz, CD₃OD) 1.70 (1 H, ddd, *J* = 13.3, 12.8, and 4.0 Hz, CH_ACH_BH_CCH_D), 1.95 (3 H, s, COCH₃), 2.41 (1 H, dm, *J* = 13.3

Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.92 (1 H, dd, $J = 12.8$ and 3.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.17 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{12}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_3$) 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, $\text{COCH}_2\text{CH}_2\text{CH}_3$), 1.48–1.64 (3 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$ and $\text{COCH}_2\text{CH}_2\text{CH}_3$), 2.04 (2 H, t, $J = 7.2$ Hz, $\text{COCH}_2\text{CH}_2\text{CH}_3$), 2.16 (1 H, dm, $J = 13.1$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.82 (1 H, dd, $J = 12.6$ and 2.8 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.01 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 - $\text{NHCOCH}_2\text{CH}_2\text{CH}_3$, CO_2H , H). Anal. ($\text{C}_{14}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_3 \cdot 0.2\text{H}_2\text{O}$) C, H, N.

trans-2-Carboxy-4-[(cyclohexylcarbonyl)amino]-5,7-dichloro-1,2,3,4-tetrahydroquinoline (19): mp 190–195 °C (Et₂O); ^1H NMR δ (360 MHz, DMSO) 1.05–1.44 (5 H, m, cyclohexyl H), 1.50–1.75 (6 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$ and cyclohexyl H), 2.02–2.15 (2 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$ and cyclohexyl H), 3.80 (1 H, dd, $J = 12.6$ and 2.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.98 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{17}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_3 \cdot 0.2\text{H}_2\text{O}$) 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 $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 1.94 (2 H, d, $J = 6.7$ Hz, NHCOCH_2), 2.16 (1 H, dm, $J = 13.3$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.81 (1 H, dd, $J = 12.6$ and 2.6 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.01 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{18}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_3 \cdot 0.35\text{H}_2\text{O}$) 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, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.22 (1 H, dm, $J = 13.2$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.94 (1 H, dd, $J = 12.3$ and 2.2 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.21 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 , $\text{NHCOCH}_4\text{H}_3\text{O}$). Anal. ($\text{C}_{15}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_3 \cdot 0.85\text{C}_4\text{H}_{10}\text{O}$) 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, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.27 (1 H, dm, $J = 13.3$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.95 (1 H, dd, $J = 12.7$ and 2.7 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.26 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{16}\text{H}_{13}\text{Cl}_2\text{N}_3\text{O}_3 \cdot 0.2\text{H}_2\text{O}$) 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, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.17 (1 H, dm, $J = 13.3$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.63 (2 H, s, COCH_2), 3.82 (1 H, dd, $J = 12.6$ and 2.7 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.01 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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, $\text{CH}_2\text{C}_4\text{H}_3\text{S}^+$). Anal. ($\text{C}_{15}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_3 \cdot 0.15\text{H}_2\text{O}$) 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, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.14 (1 H, dm, $J = 13.1$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.41 (2 H, s, COCH_2), 3.82 (1 H, dd, $J =$

12.7 and 2.8 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.00 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 , $\text{NHCOCH}_2\text{C}_6\text{H}_4\text{Cl}$). Anal. ($\text{C}_{18}\text{H}_{15}\text{Cl}_3\text{N}_2\text{O}_3$) 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, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.16 (1 H, dm, $J = 13.2$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.02 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 , $\text{NHCOCH}_2\text{CH}_2\text{C}_6\text{H}_5$). Anal. ($\text{C}_{19}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_3 \cdot 0.1\text{H}_2\text{O}$) 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, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.56 (2 H, t, $J = 8.0$ Hz, COCH_2), 3.83 (1 H, dd, $J = 12.6$ and 2.7 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.03 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 , $\text{NHCO}(\text{CH}_2)_3\text{Ph}$). Anal. ($\text{C}_{20}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_3 \cdot 0.45\text{H}_2\text{O}$) 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, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.21 (1 H, dm, $J = 13.3$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.05 (1 H, dd, $J = 12.5$ and 2.6 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.79 (1 H, s, CHAr_2), 5.07 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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, $\text{NHCOCH}_3\text{H}_9$). Anal. ($\text{C}_{24}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_3 \cdot 0.4\text{H}_2\text{O}$) 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 Et₃N (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 NaHCO₃ solution (2 × 100 mL), and brine (100 mL), and then dried (Na₂SO₄) 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/Et₂O 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, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.28 (1 H, dm, $J = 13.7$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.91 (1 H, dd, $J = 13.5$ and 6.6 Hz, $\text{PhCH}_2\text{H}_F\text{CH}_G\text{NH}_2$), 2.98 (1 H, dd, $J = 13.5$ and 7.6 Hz, $\text{PhCH}_2\text{H}_F\text{CH}_G\text{NH}_2$), 3.62 (2 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$ and $\text{PhCH}_2\text{H}_F\text{CH}_G\text{NH}_2$), 5.06 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{19}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_3 \cdot 1.0\text{H}_2\text{O}$) 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, $\beta = 98.36$ (1)° for *Z* = 2, and a calculated density of 1.285 g/cm³. An automatic four-circle diffractometer equipped with Cu K α radiation ($\lambda = 1.5418$ Å) was used to measure 2154 potential diffraction peaks of which 1250 were observed ($I > 3\sigma I$). Application of a multi-solution tangent formula approach to the phase solution gave an

initial model for the structure²³ 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]carbonylamino]-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 (MgSO₄) 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 NH₄OAc (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_GNH₂), 2.99 (2 H, m, CH_ACH_BH_CCH_D and PhCH_EH_FCH_GNH₂), 3.57 (1 H, dd, *J* = 8.9 and 5.9 Hz, PhCH_EH_FCH_GNH₂), 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. (C₁₉H₁₉Cl₂N₃O₃·2.0H₂O) C, H, N: calcd, 5.22; found, 4.69.

trans-2(S)-Carboxy-5,7-dichloro-4(R)-[[2-phenyl-1(S)-aminoethyl]carbonylamino]-1,2,3,4-tetrahydroquinoline (12) and trans-2(R)-carboxy-5,7-dichloro-4(S)-(2-phenyl-1(S)-aminoethyl)carbonylamino]-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. (C₁₉H₁₉Cl₂N₃O₃·1.0H₂O) C, H, N. 13 (isolated as its HCl salt): mp 221–223 °C; spectral data identical to those of 10. Anal. (C₁₉H₁₉Cl₂N₃O₃·HCl·0.7H₂O) C, H, N: calcd, 9.19; found, 8.65.

trans-2-Carboxy-5,7-dichloro-4-[[phenylmethyl]carbonylamino]-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 Et₃N (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 NaHCO₃ solution (2 × 300 mL), and brine (200 mL), and then dried (MgSO₄) 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, CH₂Ph), 3.72 (3 H, s, CH₃), 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, CH₂Ph), 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, PhCH₂⁺). Anal. (C₁₈H₁₈Cl₂N₂O₃) 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)phenylglycine, (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 ([α]_D -130° (c = 0.2, CD₃OD)) and 16 ([α]_D 150° (c = 0.2, CD₃OD)). 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]carbonylamino]-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, CH₂Ar), 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. (C₁₈H₁₄Cl₂N₂O₃S) C, H, N.

trans-4-[[[4-Aminophenyl]methyl]carbonylamino]-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline hydrochloride (25) was prepared using 4-[(*tert*-butoxycarbonyl)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, COCH₂), 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. (C₁₈H₁₇Cl₂N₃O₃·2HCl) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[[[4-hydroxyphenyl]methyl]carbonylamino]-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, COCH₂), 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. (C₁₈H₁₆Cl₂N₂O₄) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[[[4-methylphenyl]methyl]carbonylamino]-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, ArCH₃), 3.35 (2 H, s, COCH₂), 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, CH₂C₆H₄CH₃⁺). Anal. (C₁₉H₁₈Cl₂N₂O₃) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[[[4-methoxyphenyl]methyl]carbonylamino]-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, COCH₂), 3.72 (3 H, s, OCH₃), 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, CH₂C₆H₄OCH₃⁺). Anal. (C₁₉H₁₈Cl₂N₂O₄) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[[[diphenylmethyl]carbonylamino]-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-Nonius, Delft, The Netherlands (1985), locally modified for a Sun Microsystems computer.

H_z, 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, CHPh₂), 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. (C₂₄H₂₀Cl₂N₂O₃·CH₃CO₂C₂H₅) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[[phenylamino]carbonylamino]-1,2,3,4-tetrahydroquinoline (35). (a) To a suspension of 66 (0.200 g, 0.642 mmol) in anhydrous CH₂Cl₂ (20 mL) under an atmosphere of nitrogen was added dry Et₃N (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 NaHCO₃ solution (2 × 75 mL), and saturated brine (1 × 75 mL) and then dried (MgSO₄) 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, CH₃), 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, CO₂CH₃, H). Anal. (C₁₈H₁₇Cl₂N₃O₃) 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 NaHCO₃ 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 (MgSO₄), 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. (C₁₇H₁₅Cl₂N₃O₃·H₂O) 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]carbonylamino]-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, CH₂NHCONHCH), 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, CH₂NHCONH), 6.00 (1 H, d, *J* = 6.5 Hz, CH₂NH), 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. (C₁₇H₂₁Cl₂N₃O₃) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[[phenylmethyl]amino]carbonylamino]-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, PhCH₂H_F), 4.29 (1 H, dd, *J* = 15.5 and 6.2 Hz, PhCH₂H_F), 4.89 (1 H, m, CH_ACH_BH_CCH_D), 6.08 (1 H, m, NHCONHCH₂), 6.34 (1 H, d, *J* = 6.5 Hz, CH₂NH), 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. (C₁₈H₁₇Cl₂N₃O₃) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[[1-naphthylamino]carbonylamino]-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, CH₂NH), 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. (C₂₁H₁₇Cl₂N₃O₃) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[[4-methylphenyl]amino]carbonylamino]-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, CH₃), 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, C₆H₄CH₃), 183 (100). Anal. (C₁₈H₁₇Cl₂N₃O₃·0.25H₂O) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[[3-methylphenyl]amino]carbonylamino]-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, CH₃), 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. (C₁₈H₁₇Cl₂N₃O₃·0.3H₂O) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[[2-methylphenyl]amino]carbonylamino]-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, CH₃), 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. (C₁₈H₁₇Cl₂N₃O₃) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[[N-methyl-N-phenylamino]carbonylamino]-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, CDCl₃) 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, CH₃), 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 – NHCO₂Ph).

(b) To a solution of the carbamate (225 mg, 0.587 mmol) in anhydrous toluene (7 mL) was added dry Et₃N (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 Et₃N 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 NaHCO₃ solution (2 × 100 mL), and brine (100 mL) and dried (Na₂SO₄), 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, CDCl₃) 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, NCH₃), 3.80 (1 H, dd, *J* = 11.7 and 2.8 Hz, CH_ACH_BH_CCH_D), 3.81 (3 H, s, OCH₃), 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; $^1\text{H NMR } \delta$ (DMSO, 360 MHz) 1.58 (1 H, ddd, $J = 13.2, 12.8,$ and 3.8 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.27 (1 H, dm, $J = 13.2$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.15 (3 H, s, NCH_3), 3.87 (1 H, dd, $J = 12.6$ and 2.7 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.93 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 ($\text{M} - \text{CO}_2\text{H}, \text{H}^+$), 107 (100, $\text{C}_6\text{H}_5\text{NHCH}_3^+$). Anal. ($\text{C}_{18}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_3 \cdot 0.35\text{H}_2\text{O}$) 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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.63 (1 H, ddd, 13.0, 12.1, and 3.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.33 (1 H, dm, $J = 13.0$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.88 (1 H, dd, $J = 12.1$ and 2.8 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.99 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 ($\text{M} + 1^+$). Anal. ($\text{C}_{23}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_3 \cdot 0.5\text{H}_2\text{O}$) 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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.64 (1 H, ddd, $J = 13.2, 13.1,$ and 3.7 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.38 (1 H, dm, $J = 13.2$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.08 (2 H, t, $J = 8.7$ Hz, $\text{CH}_2\text{H}_F\text{CH}_G$), 3.76 (1 H, q, $J = 9.0$ Hz, $\text{CH}_2\text{H}_F\text{CH}_G$), 3.92 (1 H, q, $J = 9.0$ Hz, $\text{CH}_2\text{H}_F\text{CH}_G$), 3.98 (1 H, dd, $J = 12.9$ and 2.7 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.04 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{19}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_3 \cdot 0.2\text{H}_2\text{O}$) 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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.52 (1 H, ddd, $J = 13.4, 12.6,$ and 3.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.35 (1 H, dm, $J = 13.4$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.95 (1 H, dd, $J = 12.6$ and 3.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.50 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 ($\text{M} - 1$). Anal. ($\text{C}_{16}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_4\text{S}$) 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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.41 (1 H, ddd, $J = 13.4, 12.3,$ and 3.1 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.33 (1 H, dm, $J = 13.4$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.73 (3 H, s, CH_3), 3.84 (2 H, d, $J = 13.5$ Hz, CH_2Ph), 4.13 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.27 (1 H, dd, $J = 12.3$ and 2.8 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 (Cl^+) 365 ($\text{M} + 1^+$). Hydrolysis of this ester with LiOH, as described for 9, gave 44: mp 140–143 °C; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.85 (1 H, ddd, $J = 13.3, 12.4,$ and 3.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.73 (1 H, dm, $J = 13.3$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.32 (2 H, d, $J = 13.4$ Hz, CH_2Ph), 4.46 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.48 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 ($\text{M} - 1^-$). Anal. ($\text{C}_{17}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_2 \cdot 1.8\text{HCl} \cdot 0.2\text{C}_6\text{H}_{14}$) 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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.64 (1 H, ddd, $J = 13.0, 12.5,$ and 3.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.63 (1 H, dm, $J = 13.0$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.86 (1 H, dd, $J = 12.5$ and 2.7 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.51 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{17}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_2\text{S}$) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[*N*-(*N'*-phenyl-*N''*-cyano-guanidiny)]-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 carbodiimide¹³ 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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.69 (1 H, ddd, $J = 13.4, 12.7,$ and 3.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.37 (1 H, dm, $J = 13.4$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.95 (1 H, dm, $J = 12.7$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.10 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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(NC)NPh); MS m/e (FAB^+) 404 ($\text{M} + 1^+$). Anal. ($\text{C}_{18}\text{H}_{15}\text{Cl}_2\text{N}_5\text{O}_2 \cdot 0.08\text{EtOAc}$) 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*-phenylidooacetamide: mp 163–164 °C dec; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.93 (1 H, ddd, $J = 13.3, 12.2,$ and 3.8 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.73 (1 H, dm, $J = 13.3$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.00 (2 H, d, $J = 16.2$ Hz, $\text{NHCH}_2\text{CONHPh}$), 4.32 (1 H, dd, $J = 12.2$ and 3.8 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.78 (1 H, br s, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 ($\text{M} + 1^+$). Anal. ($\text{C}_{18}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_3 \cdot 1.9\text{HCl}$) 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 67¹¹ (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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.83 (1 H, ddd, $J = 13.1, 11.7,$ and 3.5 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.35 (1 H, dm, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.87 (1 H, dm, $J = 3.5$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.91 (1 H, dd, $J = 11.7$ and 2.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 (Cl^+) 379 ($\text{M} + 1^+$). Anal. ($\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_3$) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[[phenylmethoxy]carbonylamino]-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; $^1\text{H NMR}$ δ (360 MHz, DMSO) 1.65 (1 H, ddd, $J = 13.0, 12.4$, and 4.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.17 (1 H, dm, $J = 13.0$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.85 (1 H, dm, $J = 12.4$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.84 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 (CI $^+$), 393 (M - 1 $^+$), 243 (100). Anal. ($\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_4$) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[[phenylamino]carbonylmethyl]-1,2,3,4-tetrahydroquinoline (50). (a) **trans-2-Carboxy-4-[(methoxycarbonyl)methyl]-5,7-dichloro-1,2,3,4-tetrahydroquinoline¹¹** (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): $^1\text{H NMR}$ δ (250 MHz, DMSO) 1.45 (9 H, s, $(\text{CH}_3)_3\text{C}$), 1.64 (1 H, ddd, $J = 13.0, 12.4$, and 4.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.10 (1 H, dm, $J = 13.0$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.49 (2 H, m, $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 3.44 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.65 (3 H, s, CH_3), 3.97 (1 H, dd, $J = 12.4$ and 3.4 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{17}\text{H}_{21}\text{Cl}_2\text{NO}_4$) 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; $^1\text{H NMR}$ δ (360 MHz, DMSO) 1.45 (9 H, s, $(\text{CH}_3)_3\text{C}$), 1.62 (1 H, ddd, $J = 13.0, 12.4$, and 4.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.16 (1 H, dm, $J = 13.0$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.35 (1 H, dd, $J = 16.5$ and 10.9 Hz, $\text{CH}_E\text{H}_F\text{CO}_2\text{H}$), 2.45 (1 H, dd, $J = 16.5$ and 2.9 Hz, $\text{CH}_E\text{H}_F\text{CO}_2\text{H}$), 3.43 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.95 (1 H, dd, $J = 12.4$ and 3.4 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{16}\text{H}_{19}\text{Cl}_2\text{NO}_4$) 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: $^1\text{H NMR}$ δ (250 MHz, DMSO) 1.48 (9 H, s, $(\text{CH}_3)_3\text{C}$), 1.69 (1 H, ddd, $J = 13.0, 12.4$, and 4.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.47 (2 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$ and $\text{CH}_E\text{H}_F\text{CONHPh}$), 2.73 (1 H, dd, $J = 16.5$ and 2.5 Hz, $\text{CH}_E\text{H}_F\text{CONHPh}$), 3.73 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.98 (1 H, dd, $J = 12.4$ and 3.3 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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; $^1\text{H NMR}$ δ (360 MHz, DMSO) 1.62 (1 H, ddd, $J = 13.0, 12.4$, and 3.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.19 (1 H, d, $J = 13.0$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.49 (2 H, m, $\text{CH}_2\text{CH}_2\text{CONHPh}$), 3.58 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.08 (1 H, dd, $J = 12.4$ and 3.4 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{O}_3$) 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-[(isopropoxy)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; $^1\text{H NMR}$ δ (360 MHz, CDCl_3) 1.78 (1 H, ddd, $J = 11.0, 11.0$, and 4.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{H}_D$), 1.97 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{H}_D$), 2.43 (1 H, t, $J = 6.0$ Hz, $\text{CH}_2\text{CHHCH}_2\text{CO}$), 2.62 (1 H, d, $J = 1.0$ Hz, $\text{CH}_2\text{CHHCH}_2\text{CO}$), 3.01 (1 H, m, CHHCH_2CO), 3.13 (1 H, m, CHHCH_2CO), 3.81 (3 H, s, OCH_3), 3.96 (1 H, dd, $J = 11.0$ and 2.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{H}_D$), 4.96 (1 H, br s, NH), 5.26 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{H}_D$), 6.57 and 6.72 (1 H, d, $J = 1.0$ Hz, 6,8-H); MS m/e 342 (M $^+$). Anal. ($\text{C}_{15}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_3$) C, H, N. Hydrolysis of the methyl ester with LiOH, as described for 9, gave 51: mp 265–266 °C; $^1\text{H NMR}$ δ (360 MHz, DMSO) 1.80 (1 H, ddd, $J = 11.0, 11.0$, and 4.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 1.95–2.00 (2 H, m, $\text{CH}_2\text{CHHCH}_2\text{CO}$ and $\text{CH}_2\text{CHHCH}_2\text{CO}$), 2.2–2.4 (3 H, m, CHHCH_2CO), 2.79 (1 H, m, CHHCH_2CO), 3.15 (1 H, m, CHHCH_2CO), 3.89 (1 H, dd, $J = 11.0$ and 2.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.01 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 6.66 and 6.74 (1 H each, d, $J = 1.0$ Hz, 6,8-H); MS m/e (CI $^+$) 329 (M $^+$). Anal. ($\text{C}_{14}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_3 \cdot 0.25\text{H}_2\text{O}$) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[N-(1-oxoisindolinyl)-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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.93 (1 H, ddd, $J = 13.0, 12.6,$ and 3.5 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.51 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.70 (3 H, s, CH_3), 3.84 (1 H, d, $J = 17.5$ Hz, NCH_2H_F), 4.02 (1 H, dd, $J = 12.6$ and 2.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.40 (1 H, d, $J = 17.5$ Hz, NCH_2H_F), 5.34 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.88 (1 H, ddd, $J = 13.0, 12.6,$ and 3.5 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.51 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.83 (1 H, d, $J = 17.5$ Hz, NCH_2H_F), 3.99 (1 H, dd, $J = 12.6$ and 2.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.40 (1 H, d, $J = 17.5$ Hz, NCH_2H_F), 5.34 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{18}\text{H}_{15}\text{Cl}_2\text{N}_2\text{O}_3$) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[N-(1,3-dioxoisindolinyl)]-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 \times 50 mL). The combined organic extracts were washed with water (2 \times 50 mL) and brine (2 \times 50 mL), dried (MgSO_4), and evaporated. The residue crystallized from EtOAc to yield **79**: mp 241–243 °C; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.72 (1 H, ddd, $J = 13.0, 12.4,$ and 4.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.46 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.73 (3 H, s, CH_3), 4.04 (1 H, dd, $J = 12.4$ and 2.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.19 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 \times 50 mL) and the organic extract washed with saturated Na_2CO_3 solution (2 \times 50 mL), water (1 \times 50 mL), and brine (2 \times 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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 2.02 (1 H, ddd, $J = 13.3, 12.4,$ and 3.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.35 (1 H, dm, $J = 13.3$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.0 (1 H, dd, $J = 12.4$ and 2.7 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.38 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{18}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_4$) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[N-(2-oxo-1,2,3,4-tetrahydroquinolinyl)]-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 \times 25 mL). The combined organics were successively washed with 1 M citric acid (25 mL), saturated Na_2CO_3 (2 \times 25 mL), and brine (2 \times 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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.86 (1 H, ddd, $J = 13.3, 12.7,$ and 4.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.28 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.54 (2 H, m, CH_2NCO), 3.60 (3 H, s, CH_3), 3.94 (2 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$ and NCOCH_2H_F), 4.20 (1 H, d, $J = 15.2$ Hz, NCOCH_2H_F), 5.51 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.81 (1 H, ddd, $J = 13.0, 12.5,$ and 3.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.25 (1 H, dm, $J = 13.0$ Hz,

$\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.54–3.65 (2 H, m, CH_2NCO), 3.82 (1 H, dd, $J = 12.5$ and 2.7 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.93 (1 H, d, $J = 15.1$ Hz, NCOCH_2H_F), 4.20 (1 H, d, $J = 15.1$ Hz, NCOCH_2H_F), 5.52 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_3 \cdot 0.1\text{H}_2\text{O}$) 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): $^1\text{H NMR } \delta$ (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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.77 (1 H, ddd, $J = 13.3, 12.7,$ and 4.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.38 (1 H, dm, $J = 13.3$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.89 (1 H, dd, $J = 17.8$ and 8.9 Hz, $\text{NCH}_2\text{H}_F\text{CH}_G\text{H}_H$), 3.29 (1 H, dd, $J = 14.8$ and 7.0 Hz, $\text{NCH}_2\text{H}_F\text{CH}_G\text{H}_H$), 3.75 (2 H, m, $\text{NCH}_2\text{H}_F\text{CH}_G\text{H}_H$), 4.04 (1 H, dd, $J = 12.7$ and 2.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.04 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{19}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_3 \cdot 0.5\text{EtOAc}$) 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 \times 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 \times 50 mL), and brine (2 \times 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; $^1\text{H NMR } \delta$ (360 MHz, DMSO) 1.75 (1 H, ddd, $J = 13.0, 12.6,$ and 3.5 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.34 (1 H, dm, $J = 13.0$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.82 (1 H, d, $J = 14.4$ Hz, CONCH_2H_F), 3.92 (1 H, dd, $J = 12.6$ and 2.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.09 (1 H, d, $J = 14.4$ Hz, CONCH_2H_F), 5.43 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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)carbonylamino]-1,2,3,4-tetrahydroquinoline (58). A suspension containing 3-chloro-5-iodoaniline⁵ (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 temperature 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 $\sim 10\%$ of **75** by ^1H NMR): mp $190\text{--}192^\circ\text{C}$. 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 $\sim 15\%$ 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 $215\text{--}217^\circ\text{C}$. 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 $128\text{--}130^\circ\text{C}$; ^1H NMR [δ (360 MHz, DMSO) 1.59 (1 H, ddd, $J = 13.1$, 12.6, and 3.6 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.18 (1 H, dm, $J = 13.1$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.47 (2 H, s, CH_2), 3.81 (1 H, dd, $J = 12.6$ and 2.8 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.77 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{18}\text{H}_{16}\text{ClIN}_2\text{O}_3 \cdot 0.6\text{Et}_2\text{O}$) C, H, N.

trans-2-Carboxy-5-chloro-7-iodo-4-[(phenylmethyl)-carbonylamino]-1,2,3,4-tetrahydroquinoline (59) was prepared from **76** as described for **58**: mp $216\text{--}217^\circ\text{C}$; ^1H NMR [δ (360 MHz, DMSO) 1.59 (1 H, ddd, $J = 13.2$, 12.6, and 3.7 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.14 (1 H, dm, $J = 12.6$ and 2.6 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.41 (2 H, s, CH_2), 3.81 (1 H, dd, $J = 12.6$ and 2.6 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.98 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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. ($\text{C}_{18}\text{H}_{16}\text{ClIN}_2\text{O}_3 \cdot 0.3\text{H}_2\text{O}$) C, H, N.

trans-2-Carboxy-5,7-dimethyl-4-[(phenylmethyl)-carbonylamino]-1,2,3,4-tetrahydroquinoline (60) was prepared from 5,7-dimethyldihydrokynurenic acid¹¹ in the same way as described for **14** (with the exception of the oxime reduction, which was performed with $\text{NaCNBH}_3/\text{TiCl}_3/\text{NH}_4\text{Cl}$ in MeOH^{24}): mp $137\text{--}140^\circ\text{C}$; ^1H NMR [δ (360 MHz, DMSO) 1.59 (1 H, ddd, $J = 13.0$, 12.6, and 3.5 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 1.96 (3 H, s, 5- or 7- CH_3), 2.16 (4 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$, 5- or 7- CH_3), 3.41 (2 H, m, NCOCH_2), 3.86 (1 H, dd, $J = 12.6$ and 2.9 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.86 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 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 ($\text{M} + 1^+$). Anal. ($\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3$) C, H, N.

trans-2-Carboxy-5-chloro-7-iodo-4-[(phenylamino)-carbonylamino]-1,2,3,4-tetrahydroquinoline (61) was prepared from **75** as described above for **58** and **35**: mp $183\text{--}184^\circ\text{C}$ dec; ^1H NMR [δ (360 MHz, DMSO) 1.62 (1 H, ddd, $J = 13.2$, 12.6, and 2.8 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.36 (1 H, dm, $J = 13.2$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.85 (1 H, dd, $J = 12.6$ and 2.8 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.70 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 6.37 (1 H, d, $J = 6.0$ Hz, NHCONHPh), 6.64 (1 H, s, ArNH CH_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 ($\text{M} + 1^+$). Anal. ($\text{C}_{17}\text{H}_{15}\text{ClIN}_3\text{O}_3 \cdot 0.8\text{H}_2\text{O}$) 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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