3-Nitro-3,4-dihydro-2(1*H*)-quinolones. Excitatory Amino Acid Antagonists Acting at Glycine-Site NMDA and (*RS*)-α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptors

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3,4-Dihydro-2(1*H*)-quinolones, evolved from 2-carboxy-1,2,3,4-tetrahydroquinolines and 3-carboxy-4-hydroxy-2(1*H*)-quinolones, have been synthesized and evaluated *in vitro* for antagonist activity at the glycine site on the NMDA receptor and for AMPA [(*RS*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid] antagonist activity. Generally poor potency at the glycine site is observed when a variety of electron-withdrawing substituents are attached to the 3-position of 3,4-dihydro-2(1*H*)-quinolones. The analogues **5–9** (IC_{50} values > 100 μM, Table I) exist largely in the 3,4-dipseudoaxial conformation (as evidenced by ^1H NMR spectra), whereas the 3-cyano derivative (**10**, IC_{50} = 12.0 μM) has a relatively high population of the 3-pseudoequatorial conformer. The 3-nitro analogue (**4**, IC_{50} = 1.32 μM) has a $pK_a \approx 5$ and thus exists at physiological pH as an anion with the nitro group planar to the quinolone ring. The general requirement of acidity for high affinity binding at the glycine/NMDA site is supported with the good activity of the other 3-nitro derivatives (**13–21**), all of which are deprotonated at physiological pH. The 3-nitro-3,4-dihydro-2(1*H*)-quinolones and 2-carboxy-1,2,3,4-tetrahydroquinolines show quite different structure–activity relationships at the 4-position. The unselective excitatory amino acid activity of **21** is comparable with 6,7-dichloro-quinoxaline-2,3-dione and 6,7-dichloroquinoxalic acid and this suggests similarities in their modes of binding to excitatory amino acid receptors. The broad spectrum excitatory amino acid antagonist activity of the 4-unsubstituted analogue **21** (K_b NMDA = 6.7 μM, K_b AMPA = 9.2 μM) and the glycine/NMDA selectivity of the other 3-nitro derivatives allows the proposal of a model for AMPA receptor binding which differs from the glycine binding pharmacophore in that there is bulk intolerance adjacent to the 4-position. Compound **21** (L-698,544) is active (ED_{50} = 13.2 mg/kg) in the DBA/2 mouse anticonvulsant model and is the most potent combined glycine/NMDA–AMPA antagonist yet reported, *in vivo*, and may prove to be a useful pharmacological tool.

Introduction

It is generally accepted that antagonists which act at the *N*-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptor may be of therapeutic benefit in the treatment of stroke, epilepsy, and Alzheimer's disease.[1] There is increasing evidence that NMDA antagonists which act through blockade of a glycine coagonist site[2] that is linked to the NMDA receptor complex[3] may have a superior side-effect profile[4–6] over uncompetitive antagonists such as Dizocilpine (MK-801).[7] Although 2-carboxy-1,2,3,4-tetrahydroquinolines, exemplified by L-689,560 (**1**),[8,9] have been identified as glycine-site NMDA antagonists possessing low nanomolar binding affinity, these compounds show only weak activity in anticonvulsant tests.[6] The presence of a carboxylic acid group is probably a detrimental feature toward obtaining good *in vivo* activity in the tetrahydroquinoline series, since brain penetration is likely to be adversely affected. In the preceding paper,[10] we described a rational drug design strategy which resulted in a series of derivatives where acidity was delocalized within a quinoline 2,4-dione system, as exemplified by the ester analogue **2**. Herein, we describe our attempts to design glycine-site NMDA antagonists with an electron-withdrawing group at the 3-position of a 3,4-dihydro-2(1*H*)-quinolone (Figure 1). Compounds of this type have the

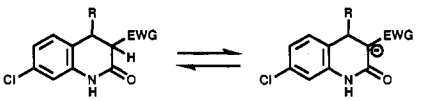
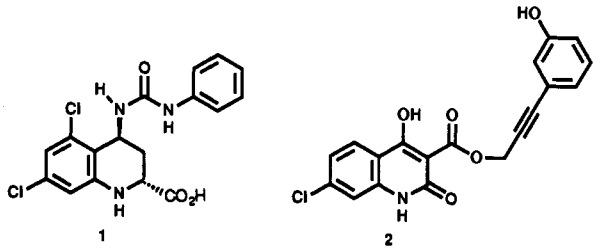


Figure 1. Drug design concept. EWG represents an electron-withdrawing group. R represents a potential hydrogen-bond-accepting group or hydrophobic group or both.



added potential of gaining the beneficial hydrogen-bond-accepting and hydrophobic interactions (through R) that were identified as being pseudoaxially adjacent to the 4-position of the 2-carboxytetrahydroquinoline series.[8,11] The results obtained indicate that overall acidity is probably an important requirement for high affinity binding at the glycine site and show that the 2-carboxy tetrahydroquinolines and the series of delocalized acids described here have different structure–activity requirements at the 4-position. Some insight is gained into the factors which affect glycine-site NMDA and AMPA

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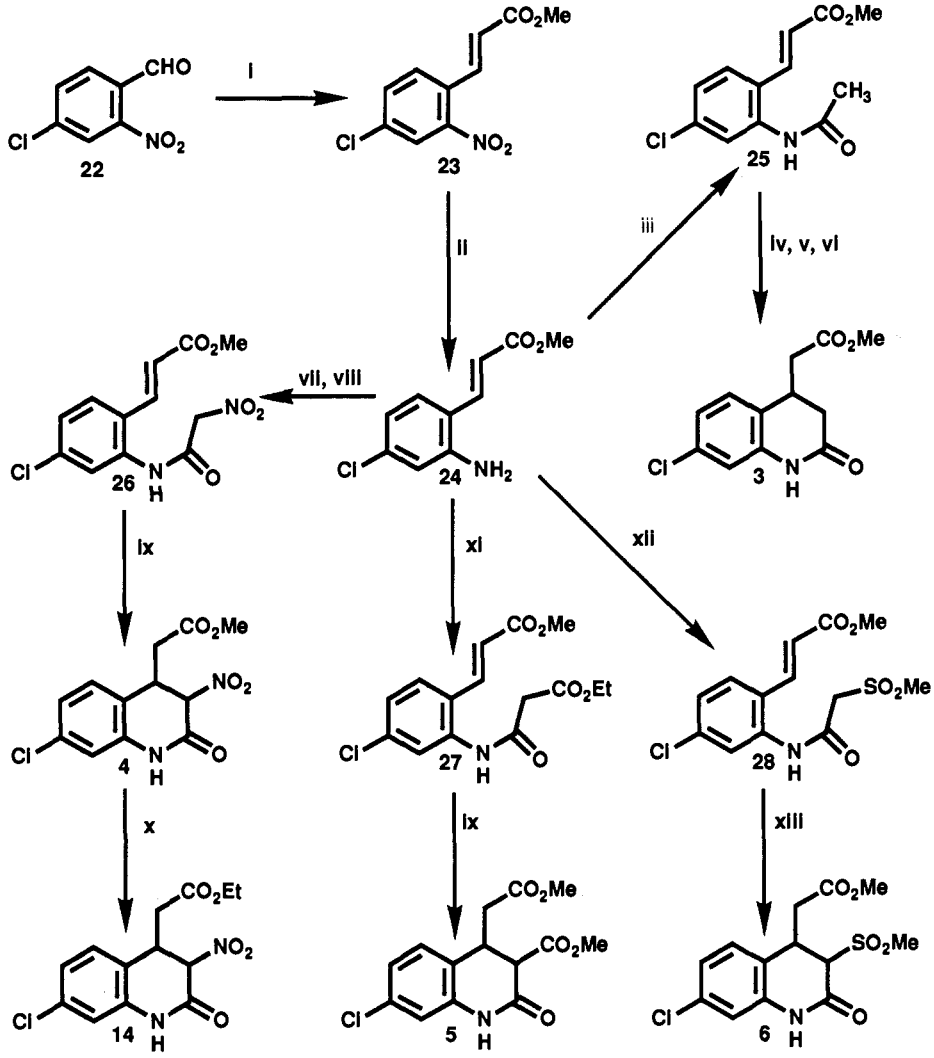
Scheme I[a]



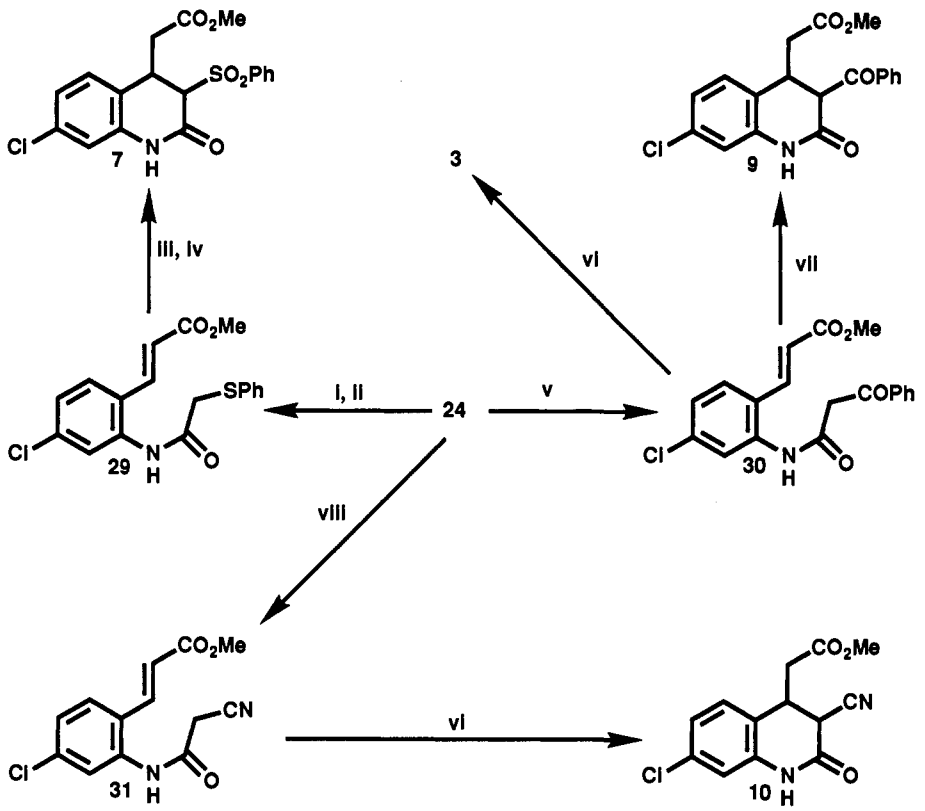
[a] Reagents: (i) $PH_3P{=}CHCO_2Me$, toluene, reflux; (ii) Zn, AcOH, 60 °C; (iii) Ac_2O, CH_2Cl_2, 0 °C to room temperature; (iv) 1 equiv of KHMDS, THF, −78 °C; (v) 1 equiv TBDMS–triflate, −78 °C; (vi) 1.2 equiv of KHMDS; (vii) $COCl_2$, Et_3N, THF, 0 °C; (viii) CH_3NO_2, KOtBu, THF, −78 °C; (ix) NaOMe, MeOH, room temperature; (x) EtOH, HCl; (xi) EtO_2CCH_2COCl, Et_3N, CH_2Cl_2; (xii) $MeSO_2CH_2CO_2H$, BuOCOCl, Et_3N, CH_2Cl_2; (xiii) NaOMe, MeOH, reflux, 5 h.

antagonist selectivity and a potent broad-spectrum excitatory amino acid antagonist with *in vivo* activity has been identified.

Chemistry

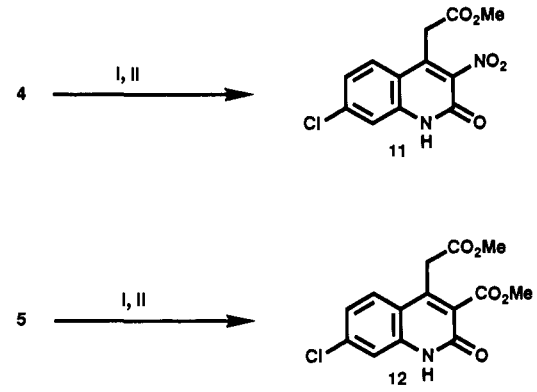
Compounds **3–21** were synthesized for this study. Several 7-chloro-4-[(methoxycarbonyl)methyl]-3,4-dihydro-2(1*H*)-quinolones possessing a variety of electron-withdrawing 3-substituents were prepared by the routes outlined in Schemes I and II. The key intermediate in the synthesis of these derivatives (compounds **3–10** and **14**) was the α,β-unsaturated ester **24**, which was prepared in two steps from 4-chloro-2-nitrobenzaldehyde (**22**), *via* Wittig olefination to give **23** and subsequent nitro group reduction (Scheme I). The analogue with no 3-substituent (**3**) was prepared by acetylation of **24** followed by intramolecular Michael reaction of the intermediate **25**. Cyclization was mediated by *in situ* deprotonation and silylation of the amide nitrogen followed by deprotonation of the methyl group with excess potassium bis(trimethylsilyl)amide. Attempts to prepare **26** (needed for the synthesis of the 3-nitro analogue **4**) by mixed anhydride coupling of **24** with nitroacetic acid[12] were unsuccessful, so an alternative method was developed. Reaction of **24** with phosgene, in the presence of triethylamine, afforded an isocyanate, which on *in situ* reaction with the preformed anion of nitromethane, gave **26**. Since the completion of this work, an alternative procedure for the synthesis of 2-nitroacetanilides has been published.[13] Annulation of **26** was accomplished by reaction with sodium methoxide in methanol at room temperature to give the required compound **4**, as a 9:1 mixture of epimers as estimated by ^1H NMR (a full discussion of epimer/conformer assignments and ratios will appear in the Results and Discussion section). The 7-unsubstituted-3-nitro derivative **13** (epimer ratio 10:1) was synthesized by an analogous route to that described for **4**, but using 2-nitrobenzaldehyde as starting material. Transesterification of **4** to the ethyl ester **14** was effected with ethanol and dry hydrogen chloride (epimer ratio 8:1). Reaction of **24** with ethyl malonyl chloride gave intermediate amide **27**, which on treatment with sodium methoxide in methanol, afforded the 3-methoxycarbonyl derivative **5** (epimer ratio 10:1). Mixed anhydride coupling of **24** with (methylsulfonyl)-acetic acid gave precursor **28** which was cyclized to the 3-methylsulfonyl derivative **6** (epimer ratio >20:1) with sodium methoxide in methanol at reflux, little reaction having occurred at room temperature.

Scheme II[a]



[a] Reagents: (i) BuLi, THF, −78 °C; (ii) $PhSCH_2COCl$, THF, −78 °C; (iii) 2.5 equiv of MCPBA, CH_2Cl_2; (iv) NaOMe, MeOH, reflux; (v) $PhCOCH_2COCl$, Et_3N, CH_2Cl_2; (vi) NaOMe, MeOH, room temperature; (vii) KOtBu, THF, −20 °C; (viii) $NCCH_2CO_2H$; CH_2Cl_2, Et_3N, BuOCOCl, DMAP.

Scheme III[a]

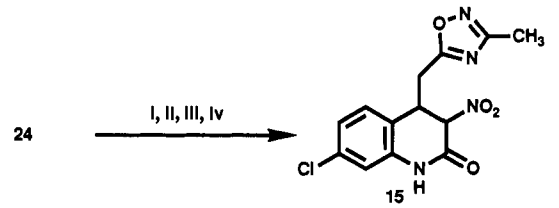


[a] Reagents: (i) Br_2, CH_2Cl_2; (ii) NaOMe, MeOH.

The attempted synthesis of **7** by direct acylation of **24** with (phenylthio)acetic acid under mixed anhydride or acid chloride conditions was unsuccessful. This problem was overcome by deprotonation of aniline **24** at −78 °C, followed by slow addition of (phenylthio)acetyl chloride to give **29** (Scheme II). Subsequent oxidation with *m*-chloroperoxybenzoic acid and cyclization of the crude sulfone with sodium methoxide in methanol at reflux gave **7** (epimer ratio >20:1). The 3-(*p*-nitrophenylsulfonyl) derivative **8** (epimer ratio >20:1) was prepared in a similar manner. Reaction of **24** with benzoylacetyl chloride (prepared from benzoylacetic acid[14] and oxalyl chloride) gave **30**. Treatment of **30** with sodium methoxide in methanol did not give the required product **9** but produced the 3-unsubstituted derivative **3** in high yield. The formation of **3** from **30** is attributable to retro-Claisen condensation followed by ring closure. Derivative **9** was successfully prepared from **30** using potassium *tert*-butoxide in tetrahydrofuran at low temperature. Analysis of the crude product by ^1H NMR showed an epimer ratio of 1:4 but after purification using silica gel chromatography the ratio changed to >20:1, thus indicating that conversion from the kinetic to the thermodynamic product is a facile process. The 3-cyano derivative **10** (epimer ratio 2:1) was prepared by mixed anhydride coupling of **24** with cyanoacetic acid to give **31** which was cyclized with sodium methoxide in methanol. The cyclization of **31** occurs very readily in DMSO solution, even in the absence of base, and it was not possible to obtain a clean ^1H NMR spectrum of **31** due to contamination with **10**. After 10 min in DMSO solution there was ~10% conversion to **10** (as determined by ^1H NMR), after 4 h the cyclized product constituted ~90% of the mixture and after 22 h no starting material was detectable. Compound **10** existed in the same ratio of epimers (2:1) as previously reported for base-induced cyclization.

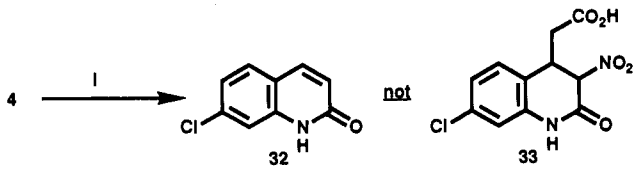
The quinolones **11** and **12** were prepared from their respective 3,4-dihydro precursors **4** and **5** by bromination and elimination of hydrogen bromide (Scheme III). The 3-nitro-4-methyloxadiazole derivative **15** was synthesized by reaction of the preformed anion of acetamide oxime with **24** followed by the standard procedure previously described for the conversion of **24** to **4** (Scheme IV). Ring closure to the final compound was effected with sodium methoxide in methanol. For the preparation of 4-amido derivatives (compounds **16**–**20**) the acid **33** was identified as the ideal advanced intermediate. However attempted saponification of **4** gave the 3,4-unsubstituted quinolone **32** as the only isolable product (52%) with no trace of **33** (Scheme V). The most likely explanation for the formation

Scheme IV[a]



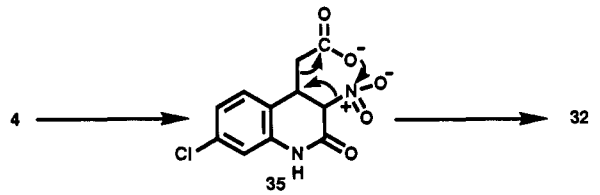
[a] Reagents: (i) $CH_3C(NH_2)$=NOH, NaH, THF, 60 °C; (ii) $COCl_2$, Et_3N, THF, 0 °C; (iii) CH_3NO_2, KOtBu, THF, −78 °C; (iv) NaOMe, MeOH.

Scheme V[a]



[a] Reagents: (i) NaOH, MeOH, H_2O or LiOH, THF, H_2O.

Scheme VI



of **32** is a retro-Claisen-type reaction mediated by intramolecular attack of the carboxylate anion to the 3-nitro group (Scheme VI). The amides **16–20** were eventually prepared by the route outlined in Scheme VII. The nitro ester **23** was hydrolyzed to the acid **35** and then converted to the appropriate amide **36** using conventional coupling procedures. Aromatic nitro group reduction, followed by routine formation of the acyclic precursor **38** and standard cyclization gave the required compounds.

The 4-unsubstituted-3-nitro analogue **21** was synthesized in six steps from 4-chloro-2-nitrobenzyl alcohol **39** (Scheme VIII).[15] Hydrogenation of **39** over sulfided platinum cleanly produced aniline **40** with no trace of dehalogenated side products. Bis-acetylation of **40** followed by saponification gave alcohol **41** which was converted to benzyl chloride **42** by treatment with carbon tetrachloride and triphenylphosphine. Reaction of **42** with ethyl nitroacetate sodium salt[16] in dimethylformamide at 60 °C gave **43** which was converted to the target molecule by treatment with dry hydrogen chloride in methanol under reflux.

Biology

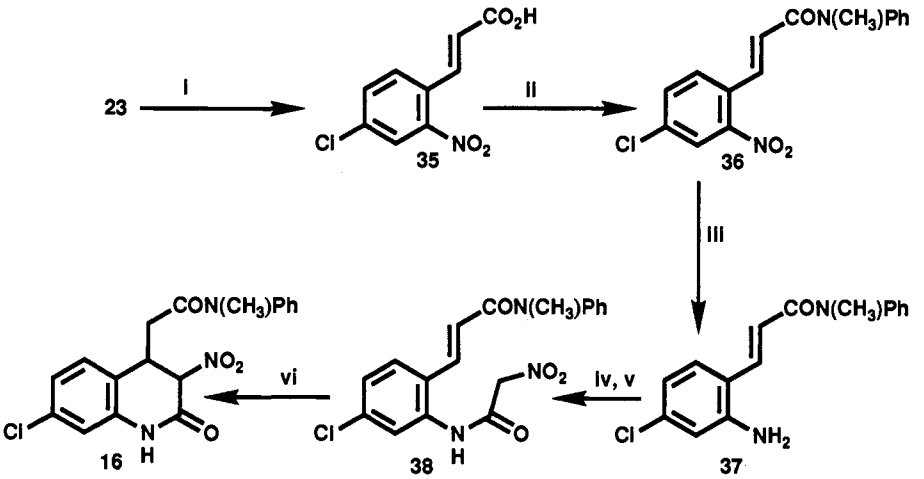
Compounds were routinely evaluated *in vitro* for their ability to (1) displace [^{3}H]-L-689,560 from rat cortical membranes (IC_{50} values)[17], (2) antagonize NMDA responses in a rat cortical slice preparation (apparent K_b values),[4a,18] and (3) antagonize AMPA [(*RS*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid] responses in a rat cortical slice preparation (apparent K_b values)[4a,18]. Affinities of test compounds for the glycine site on the NMDA receptor were determined by displacement of the glycine-site antagonist [^{3}H]-L-689,560 binding to rat cortex/hippocampus membranes.[17] IC_{50} values (concentration of test compound required to inhibit 50% of the specific binding) were evaluated *via* construction of five-point inhibition curves. IC_{50} values given are the geometric means of at least three experiments (except where stated). The maximum standard error calculated from the pIC_{50} values was always less than 5% of the mean. Where IC_{50} > 100 μM, test compound inhibited [^{3}H]-L-689,560 binding by less than 50% at 100 μM (two experiments). Apparent K_b values were calculated from the shift to the right of the NMDA and AMPA concentration–response curves produced by the antagonists and are the means of three determinations. Selected compounds were also evaluated *in vivo* for their ability to protect against audiogenic seizure in DBA/2 mice when dosed ip 30 min prior to noise stimulation (quoted either as ED_{50} values or number protected/number tested at a particular dose).[7] The DBA/2 mouse audiogenic seizure test was chosen for *in vivo* screening because the sensitivity of this model increased the possibility of identifying improved *in vivo* activity.

Results and Discussion

The binding affinities of the various 3-substituted-7-chloro-4-(methoxycarbonyl)-3,4-dihydro-2(1*H*)-quinolones **3–10** are summarized in Table I. Compound **3**, which possesses no 3-substituent, is inactive, but 3-nitro derivative **4** shows good affinity. Compound **4** exists as a 9:1 mixture of epimers, as estimated by ^{1}H NMR, but it is not possible to assign relative stereochemistry or favored conformation on the basis of coupling constant evidence from the ^{1}H NMR spectrum of **4** alone, because the *J* values between the protons at the 3- and 4-positions are not significantly different ($J_{3\text{-H},4\text{-H}}$ = 6.2 Hz major isomer; $J_{3\text{-H},4\text{-H}}$ = 5.0 Hz minor isomer). Some insight is gained from consideration of the ^{1}H NMR spectrum of **3**, where the absence of a large coupling constant for the hydrogen atom at the 4-position (J < 7.5 Hz) indicates the preferred conformation of **3** in DMSO solution is 4-pseudoaxial (Figure 2), as opposed to 4-pseudequatorial (Figure 3). The preference for the 4-pseudoaxial conformer is attributable to steric repulsion between the proton at the 5-position and the large group at the 4-position. From these results it can be assumed that the 4-[(methoxycarbonyl)methyl] moiety will prefer to be pseudoaxial throughout the series of compounds in Table I. In addition, the strongly basic conditions used for the formation of compounds **4–10** and the facile epimerization of **9** in particular, strongly suggests that in each case, the major product observed is the most thermodynamically stable epimer. Thus, from basic conformational analysis, the conclusion is that the major isomer of **4–10** is probably 3,4-*trans* and the major confomation is 3,4-dipseudoaxial (Figure 4). The minor isomer is thus assigned as being 3,4-*cis* and probably exists in the 4-pseudoaxial 3-pseudoequatorial conformation (Figure 5). Because the possibility of a 4-pseudoequatorial group has already been discounted, the *trans*-3,4-dipseudoequatorial (Figure 6) and the *cis*-3-pseudoaxial 4-pseudoequatorial (Figure 7) conformers can probably be ruled out.

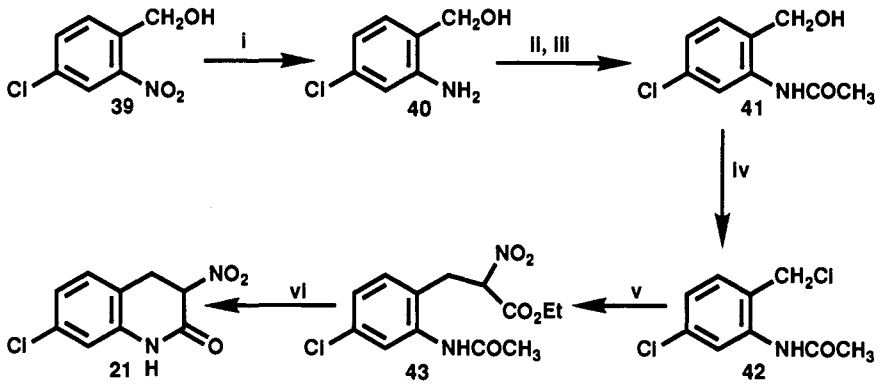
With the exception of 3-nitro derivative **4** and 3-cyano analogue **10**, all of the compounds in Table I are inactive (>100 μM). This can possibly be rationalized by a structure–activity requirement, for activity at the glycine site, of a pseudoequatorial π system at the 3-position. This hypothesis fits in well with results from the preceding paper where when similar-sized π substituents were attached to the 3-position of a quinoline-2,4-dione system good activity was seen and when only hydrogen was attached no significant affinity was observed.[10,15] There

Scheme VII[a]



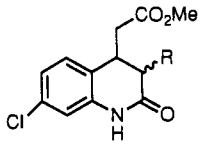
[a] Reagents: (i) NaOH, H_2O, MeOH; (ii) $PhN(CH_3)H$, HOBT, $Me_2N(CH_2)_3N{=}C{=}NEt$, Et_3N; (iii) Zn, AcOH, EtOH, 60 °C; (iv) $COCl_2$, Et_3N, THF; (v) CH_3NO_2, KOtBu, THF; (vi) NaOMe, MeOH.

Scheme VIII[a]



[a] Reagents: (i) 50 psi H_2, PtS-C, MeOH; (ii) CH_3COCl, Et_3N, CH_2Cl_2; (iii) NaOH, H_2O, MeOH; (iv) CCl_4, Ph_3P, THF, reflux; (v) $EtO_2CCH(Na)NO_2$, DMF, 60 °C; (vi) MeOH, HCl, reflux.

Table I. 3-Substituted 7-Chloro-4-[(methoxycarbonyl)methyl]-3,4-dihydro-2(1*H*)-quinolones



no.	R	epimer ratio (^{1}H NMR integral)	IC_{50} (μM) vs [^{3}H]-L-689,560	pK_a (UV 280–300 nm)
3	H		>100	ND
4	NO_2	9:1	1.32	~5–6[a]
5	CO_2Me	10:1	>100	>11
6	SO_2Me	>20:1	>100	>11
7	SO_2Ph	>20:1	>100	10.8
8	$SO_2Ph(NO_2)$-4	>20:1	>100	9.9
9	COPh	>20:1	>100	~9
10	CN	2:1	12.0	10.2

[a] Estimate on the basis of the measured pK_a of 21 (5.8).

is a low population of the *cis*-4-pseudoaxial 3-pseudoequatorial isomer/conformer (Figure 5) in compounds **4–9**; however, for **10** the *cis*-4-pseudoaxial 3-pseudoequatorial isomer/conformer constitutes a significant part of the mixture. This finding is not surprising since the free-energy difference between an equatorial and an axial cyano group in cyclohexane is <0.25 kcal/mol, whereas the value for a methyl ester is >1.25 kcal/mol and the value for a nitro group is ~1.1 kcal/mol.[20] In the case of **4**, the acidity of the molecule (p$K_a \approx 5$) indicates that the compound is

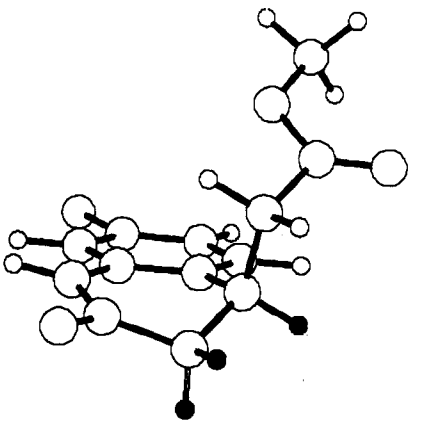


Figure 2. The 4-pseudoaxial conformer of **3** energy minimized (-24.386 kcal) using AMF.[19]

largely deprotonated at physiological pH and thus exists as a nitronate anion with the 3-substituent held in the plane of the ring. Since acidity is generally important for antagonists acting at the glycine/NMDA site,[4a,b,8–11,21,22] the low pK_a value of **4** probably contributes significantly to the relatively high affinity of this compound. This hypothesis is reinforced by the data in Table II. Although the neutral quinolone **11** possesses a 3-nitro group that is held in the plane of the heterocyclic ring, the compound shows only weak activity. Compound **12** is essentially inactive and this indicates that ester functionality is less well tolerated at the 3-position than a nitro group.

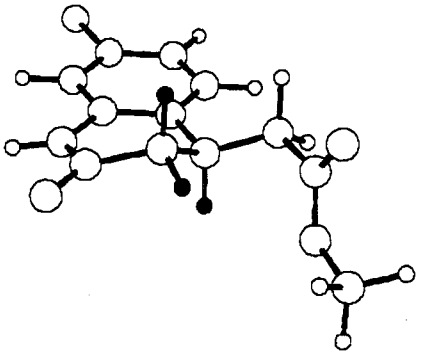


Figure 3. The 4-pseudoequatorial conformer of **3** energy minimized (-21.827 kcal) using AMF.[19]

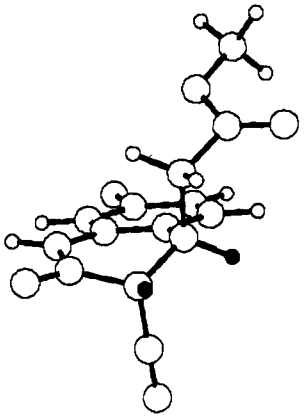


Figure 4. The 3,4-dipseudoaxial conformer of **10** energy minimized (-35.468 kcal) using AMF.[19]

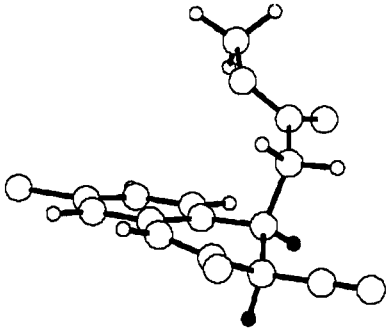


Figure 5. The 4-pseudoaxial 3-pseudoequatorial conformer of **10** energy minimized (-35.368 kcal) using AMF.[19]

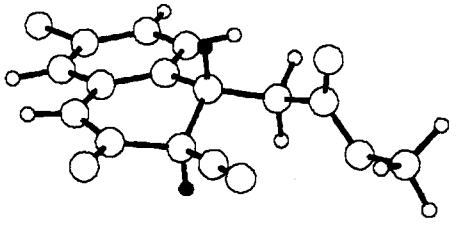


Figure 6. The 3,4-dipseudoequatorial conformer of **10** energy minimized (-31.425 kcal) using AMF.[19]

The 7-chloro-3-nitro-4-methoxycarbonyl derivative **4** is equipotent with 7-chlorokynurenic acid[17] and is more potent than 6-chloroquinoxaline-2,3-dione,[22] indicating it to be a good starting point for further optimization. Removal of the 7-chloro atom to give **13** (Table III) causes a significant reduction in affinity, suggesting similar structure–activity relationships, for aromatic substitution, to the kynurenic acids and the quinoxaline-2,3-diones.[22] Ethyl ester derivative **14** has similar affinity to **4** while methyloxadiazole **15** has only 3-fold reduced activity and

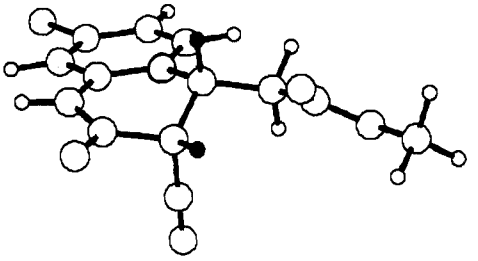
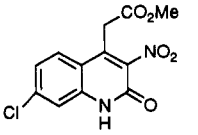
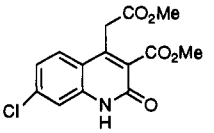


Figure 7. The 3-pseudoaxial–4-pseudoequatorial conformer of **10** energy minimized (-33.235 kcal) using AMF.[19]

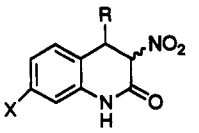
Table II. 3-Substituted 7-Chloro-4-[(methoxycarbonyl)methyl]-2(1*H*)-quinolones

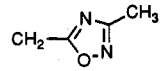
no.	structure	IC_{50} (μM) vs [^{3}H]-L-689,560
11		94.4 (n = 1)
12		>100

is clearly an acceptable replacement for an ethyl ester.[23] Amide derivatives **16–20** show no improvement of *in vitro* activity over the ester **4** and this is contrary to structure–activity relationships at the 4-position within the 2-carboxytetrahydroquinoline series (**1**).[8,11] Complete removal of the 4-substituent to give **21** has no effect on functional NMDA activity, again indicating that the tetrahydroquinolines and kynurenic acids are not congeneric with the series of compounds in Table III. The broad-spectrum excitatory amino acid antagonist profile of **21** in the functional assay (K_b vs NMDA = 6.7 μM; K_b vs AMPA = 9.2 μM) is comparable with 6,7-dichloroquinoxaline-2,3-dione[22] and 6,7-dichloroquinoxalic acid,[22,24,25] and this suggests that all of these compounds may bind in a similar manner to both the glycine site and the AMPA (quisqualate/kainate) site. On this basis, the glycine-site selectivity of compounds **4** and **13–20** is a surprising result. This selectivity may be attributable to bulk intolerance on the AMPA receptor adjacent to the 4-position. On the basis of these results we propose a model for AMPA antagonist binding where hydrogen-bond acceptance adjacent to the 4-position of the quinolone ring is not essential (Figure 8), although size-limited H-bonding groups may be tolerated.[22,26] This model for AMPA binding contrasts the pharmacophore we have previously proposed for glycine–NMDA binding where a hydrogen-bond-accepting group adjacent to the 4-position is obligatory for good potency.[8,11,22] Compound **21** fits the model for both AMPA (Figure 8) and glycine (Figure 9) binding, whereas the other derivatives in Table III only fit the glycine pharmacophore (Figure 10).

Selected compounds from Table III were evaluated in the anticonvulsant assay. Methyl ester **4** is only weakly active *in vivo* and no improvement is obtained with any of the 4-amido derivatives tested. The poor *in vivo* potency of these analogues may be due to rapid metabolism but the potentially more metabolically stable oxadiazole derivative **15** is also inactive. The 4-unsubstituted compound **21**, however, shows good anticonvulsant activity (ED_{50} = 13.2 mg/kg), and this increase in potency over the

Table III. 3-Nitro-3,4-dihydro-2(1*H*)-quinolones



no.	R	X	IC50(μM) (vs[^{3}H]-L-689,560)	K_b (μM) vs NMDA	DBA/2 mouse protected/ tested at dose (mg/kg)
4	CH_2CO_2Me	Cl	1.32	7.0 (139 vs AMPA)	2/8 at 75
13	CH_2CO_2Me	H	28.6		
14	CH_2CO_2Et	Cl	2.23	8.1	
15		Cl	5.59	25.9	0/8 at 100
16	$CH_2CON(CH_3)Ph$	Cl	1.84	>10[a]	0/8 at 50
17	$CH_2CONHPh$	Cl	7.43	>10	
18	$CH_2CONHCH_3$	Cl	12.4	>30	
19	$CH_2CON(CH_3)_2$	Cl	3.72	22.2	0/8 at 100
20	$CH_2CONHCH_2Ph$	Cl	2.53	*b*	0/8 at 100
21	H	Cl	0.414	6.7 (9.2 vs AMPA)	13.2[c]

[a] Not done at higher doses due to poor solubility. [b] Not tested due to poor solubility. [c] ED_{50}.

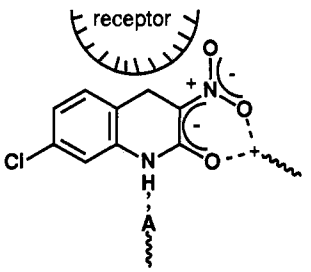


Figure 8. Proposed hydrogen-bonding and Coulombic receptor interactions for AMPA antagonism. "A" represents a receptor hydrogen-bond acceptor, and "+" represents a positively charged receptor group.

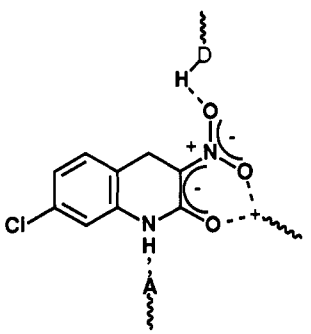


Figure 9. Proposed hydrogen-bonding and Coulombic receptor interactions for glycine-site NMDA antagonism. "D–H" and "A" represent a receptor hydrogen-bond donor or acceptor, and "+" represents a positively charged receptor group.

other 3-nitro analogues is possibly attributable to improved brain penetration due to reduced H-bonding capability, since a minimum of two H-bonding groups have been removed from 4 and **13–20**.[27] 7-Chlorokynurenic acid is equipotent with **21** against NMDA in the functional assay but does not have the same wide-spectrum profile[22] or possess significant anticonvulsant activity on systemic administration.[5,6] The weak *in vivo* activity of 7-chlorokynurenic acid is more likely to be due to low brain penetration rather than selectivity for the glycine/NMDA site because 6,7-dichloroquinoxalic acid,[22,24,25] which possesses a similar broad-spectrum profile to **21**, is also essentially inactive *in vivo*.[28] The almost identical excitatory amino acid profile of 6,7-dichloroquinoxalic acid and **21** is noteworthy because these results support the

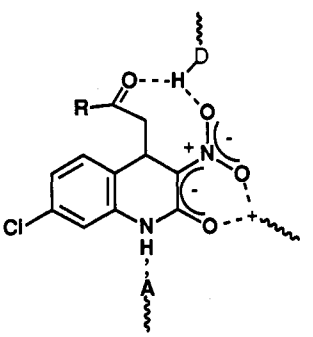


Figure 10. Proposed hydrogen-bonding and Coulombic receptor interactions for glycine-site NMDA antagonism. "D–H" and "A" represent a receptor hydrogen-bond donor or acceptor, and "+" represents a positively charged receptor group.

finding that nitronates can be effective carboxylic acid replacements (pK_a of **21** = 5.8).[29] The poor *in vivo* potency of both 7-chlorokynurenic acid and 6,7-dichloroquinoxalic acid in comparison to **21** is possibly due to the greater H-bonding capacity[27] of the carboxylic acid containing compounds. Compound **21** also exists in the neutral form to a greater extent at physiological pH and has a more favorable log *P* (log D_{oct} = 0.62) than 7-chlorokynurenic acid (log D_{oct} = -1.28) and this too ought to improve relative brain penetrability. 7-Chloro-3-nitro-3,4-dihydro-2(1*H*)-quinolone (**21**, L-698,544), is the most *in vivo* potent broad-spectrum excitatory amino acid antagonist yet described,[30,31] and may prove to be a useful pharmacological tool.

Conclusions

We have identified 3-nitro-3,4-dihydro-2(1*H*)-quinolones as a novel class of potent excitatory amino acid antagonists. The poor activity observed with the alternative 3-substituted 3,4-dihydro-2(1*H*)-quinolones in Table I reinforces the general importance of acidity for good affinity at excitatory amino acid receptors.[4a,b,8–11,21,22] The unexpected affinity of the 3-cyano derivative **10** suggests a possible structure–activity requirement for a π-system, held close to the plane of the heterocyclic ring, for glycine/NMDA antagonism in this series of compounds. Selectivity for the glycine site is obtained in the 3-nitro series when a hydrogen-bond-accepting group is positioned

pseudoaxially at the 4-position but combined AMPA and glycine/NMDA activity is observed when no 4-substituent is present. A binding model that we have previously proposed[22] can account for the glycine-site recognition of compounds 4 and 13–20. We have now proposed a pharmacophore for binding to the AMPA site, where there is both bulk intolerance and no requirement for a hydrogen-bond-donating interaction adjacent to the 4-position of the quinoline ring. This rationalizes the absence of AMPA activity in the 4-substituted derivatives and the broad spectrum activity of 21. The differences observed in structure–activity relationships at the 4-position with the compounds discussed in this paper and the 2-carboxy tetrahydroquinolines[8,11] indicate that these series do not bind to the glycine–NMDA site in an identical manner. The unselective excitatory amino acid activity of 21 is comparable with 6,7-dichloroquinoxaline-2,3-dione and 6,7-dichloroquinoxalic acid and suggests similarities in their modes of binding to excitatory amino acid receptors. These results clearly extend current views of structural requirements and tolerance for binding to the glycine site on the NMDA receptor and the AMPA (kainate/quisqualate) site. 7-Chloro-3-nitro-3,4-dihydro-2(1*H*)-quinolone (21, L-698,544) is the most potent combined glycine/NMDA–AMPA antagonist yet reported, *in vivo*, and may prove to be a useful pharmacological tool.

Experimental Section

General directions have appeared previously.[10]

7-Chloro-4-[(methoxycarbonyl)methyl]-3,4-dihydro-2(1*H*)-quinolone (3). 4-Chloro-2-nitrobenzaldehyde (22) (5 g, 0.027 mol) and methyl (triphenylphosphoranylidene)acetate (9.91 g, 0.03 mol) were dissolved in toluene and heated under reflux for 1 h. The reaction mixture was concentrated under vacuum and the residue obtained was purified by silica gel chromatography using dichloromethane as eluent to give α,β-unsaturated ester 23 as a colorless solid (6.4 g, 98%): mp 83–84 °C; NMR δ ($CDCl_3$) 3.83, (3 H, s, CH_3), 6.36 (1 H, d, J = 15.9 Hz, CH_A=CH_B), 7.58 (1 H, d, J = 8.4 Hz, 6-*H*), 7.63 (1 H, dd, J = 8.4 and 2.0 Hz, 5-*H*), 8.04 (1 H, d, J = 2.0 Hz, 3-*H*), 8.05 (1 H, d, J = 8.4 Hz, CH_A=CH_B); MS (EI) m/e 241 $[MH]^+$. Anal. ($C_{10}H_8ClNO_4$) C, H, N. **23** (2 g, 0.0083 mol) was dissolved in a mixture of glacial acetic acid (20 mL) and ethanol (20 mL) then zinc dust (2 g) was added and the reaction mixture was heated at 60 °C for 4 h under an atmosphere of nitrogen. After cooling, the mixture was filtered and the filtrate was concentrated under vacuum. The residue was dissolved in ethyl acetate (200 mL) and washed with dilute sodium hydroxide solution, and then dried (Na_2SO4), filtered, and concentrated *in vacuo*. Purification of the residue on silica gel, using 20% ethyl acetate in hexane as the eluent, gave 24 as a yellow solid (1.25 g, 71%): mp 124–125 °C; NMR δ ($CDCl_3$) 3.80 (3 H, s, CH_3) 4.02 (2 H, br s, NH_2), 6.32 (1 H, d, J = 15.8 Hz, CH_A=CH_B), 6.70 (1 H, d, J = 1.9 Hz, 3-*H*), 6.73 (1 H, dd, J = 8.3 and 1.9 Hz, 5-*H*), 7.28 (1 H, d, J = 8.3 Hz, 6-*H*), 7.72 (1 H, d, J = 15.8 Hz, CH_A=CH_B); MS (EI) m/e 211 $[MH]^+$. Anal. ($C_{10}H_{10}ClNO_2$) C, H, N. **24** (1.28 g, 0.006 mol) was dissolved in dichloromethane (50 mL) and cooled to 0 °C, and acetic anhydride (2.88 mL, 0.03 mol) was added slowly. After the addition was complete, the reaction mixture was allowed to warm to ambient temperature and stirred for 5 h. The solvents were removed under high vacuum, and the residue was azeotroped with toluene then recrystallized from ethyl acetate to give **25** as a colorless solid (1.26 g, 82%): mp 178–179 °C; NMR δ (DMSO) 2.10 (3 H, s, $NHCOCH_3$), 3.74 (3 H, s, CO_2CH_3), 6.61 (1 H, d, J = 15.9 Hz, CH_A=CH_B), 7.29 (1 H, dd, J = 8.6 and 2.2 Hz, 5-*H*), 7.60 (1 H, d, J = 2.2 Hz, 3-*H*), 7.76 (1 H, d, J = 15.9 Hz, CH_A=CH_B), 7.85 (1 H, d, J = 8.6 Hz, 6-*H*) 9.96 (1 H, br s, $NHCOCH_3$); MS (EI) m/e 253 $[M^+]$. Anal. ($C_{12}H_{12}ClNO_3$) C, H, N. **25** (1.24 g, 0.0049 mol) was dissolved in dry THF (50 mL) and the solution was cooled to −78 °C under an inert atmosphere. Potassium bis(trimethylsilyl)amide (9.86 mL of a 0.5 molar solution in toluene, 0.0049 mol) was added, and after 10 min *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.14 mL, 0.0049 mol) was also added. The reaction mixture was allowed to warm to −40 °C and stirred at this temperature for 1 h. A further quantity of *tert*-butyldimethylsilyl trifluoromethanesulfonate (11.8 mL, 0.0059 mol) was added and stirring was continued at −40 °C for 2 h. The reaction mixture was poured into saturated ammonium chloride solution (200 mL) and extracted with ethyl acetate (3 × 100 mL). The combined layers were washed with water (1 × 80 mL) and saturated brine (1 × 80 mL) then dried ($MgSO_4$) filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (using 0% to 40% ethyl acetate in hexane as eluent) and recrystallization from ethanol to give **3** (0.8g, 65%): mp 147 °C; NMR δ (DMSO) 2.38 (1 H, dd, J = 16.3 and 5.1 Hz, $CH_AH_BCH_CCH_DH_E$), 2.55 (2 H, d, J = 7.4 Hz, $CH_AH_BCH_CCH_DH_E$), 2.68 (1 H, dd, J = 16.3 and 6.0 Hz, $CH_AH_BCH_CCH_DH_E$), 3.37 (1 H, m, $CH_AH_BCH_CCH_DH_E$), 3.59 (3 H, s, CO_2CH_3), 6.90 (1 H, d, J = 2.1 Hz, 8-*H*), 6.97 (1 H, dd, J = 8.1 and 2.1 Hz, 6-*H*), 7.17 (1 H, d, J = 8.1 Hz, 5-*H*), 10.27 (1H, s, N*H*); MS (Cl^-) m/e 252 [M − H]. Anal. ($C_{12}H_{12}ClNO_3$) C, H, N.

7-Chloro-4-[(methoxycarbonyl)methyl]-3-nitro-3,4-dihydro-2(1*H*)-quinolone (4). Compound 24 (1 g, 0.00473 mol) was dissolved in dry THF with triethylamine (1.38 mL, 0.0099 mol) and then cooled to 0 °C, and phosgene (3.1 mL of a 1.93 molar solution in toluene, 0.006 mol) was added. After 20 minute of stirring at 0 °C, a pre-formed solution of the anion of nitromethane (formed from nitromethane (1.3 mL, 0.023 mol) in THF (80 mL) at 0 °C with potassium *tert*-butoxide [26 mL of a 1 molar solution in THF)] was added by cannula and the reaction mixture was stirred at 0 °C for 1 h. The solution was poured into ice-cold 1 N hydrochloric acid and extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuum to give a residue which was purified by trituration with diethyl ether to give **26** as a white solid (0.56 g, 40%): mp 177 °C; NMR δ (DMSO) 3.74 (3 H, s, CO_2CH_3), 5.63 (2 H, s, CH_2NO_2), 6.66 (1 H, d, J = 15.8 Hz, CH_A=CH_B), 7.36 (1 H, dd, J = 8.6 and 1.9 Hz, 5-*H*), 7.65 (1 H, d, J = 1.9Hz, 3-*H*), 7.79 (1 H, d, J = 15.8 Hz, CH_A=CH_B), 7.89 (1 H, d, J = 8.6 Hz, 6-H); MS (EI) m/e 298 $[M^+]$. Anal. ($C_{12}H_{11}ClN_2O_5 \cdot 0.2C_4H_8O$) C, H, N. **26** (0.54 g, 0.00181 mol) was dissolved in dry methanol (100 mL), and a solution of sodium methoxide in methanol [generated from the dissolution of 80% sodium hydride (0.163 g, 0.0054 mol) in methanol (30 mL)] was added. The reaction mixture was stirred at room temperature for 14 h, and then methanol which had been presaturated with dry hydrogen chloride (100 mL) was added, and the solvents were removed under vacuum. The residue was dissolved in ethyl acetate (100 mL) and extracted with saturated potassium carbonate solution (2 × 100 mL). The combined aqueous layers were washed with diethyl ether (2 × 100 mL), acidified to pH 1 with concentrated hydrochloric acid, extracted with ethyl acetate (2 × 100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was triturated with diethyl ether and collected by filtration to give 4 as a colorless solid (0.077 g, 14%): mp 135 °C; NMR δ (DMSO) (9.2:1 mixture of epimers) 2.64 (1 H, dd, J = 16.6 and 7.4 Hz, $CH_AH_BCH_C$), 2.86 (1 H, dd, J = 16.6 and 5.5 Hz, $CH_AH_BCH_C$), 3.60 (3 H, s, CO_2CH_3, major epimer), 3.63 (3 H, s, CO_2CH_3, minor epimer), 4.12 (1 H, m, $CH_AH_BCH_C$), 5.78 (1 H, d, J = 6.2 Hz, $CHNO_2$, major epimer), 5.87 (1 H, d, J = 5.0 Hz, $CHNO_2$), 6.98 (1 H, d, J = 1.9 Hz, 8-*H*), 7.09 (1 H, dd, J = 8.6 and 1.9 Hz, 6-*H*), 7.19 (1 H, d, J = 8.6 Hz, 5-*H* , minor epimer) 7.26 (1 H, d, J = 8.6 Hz, 5-*H*, major epimer); MS (EI) m/e 298 $[M^+]$.

7-Chloro-4-[(methoxycarbonyl)methyl]-3-(methoxycarbonyl)-3,4-dihydro-2(1*H*)-quinolone (5). Compound 24 (0.6 g, 0.002 84 mol) was dissolved in dichloromethane (50 mL) with triethylamine (0.985 mL, 0.007 mol) and 4-(dimethylamino)-pyridine (0.05 g, 0.004 mol) at 0 °C. Ethyl malonyl chloride (0.91 mL, 0.007 mol) was added dropwise, and after 30 min the reaction mixture was allowed to warm to room temperature and stirred for a further 3 h. The solution was diluted with dichloromethane (100 mL), washed with water (2 × 50 mL) and then saturated brine (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography using 20% ethyl acetate in hexane as eluent to give **27** as a colorless solid (0.36 g, 41%): mp 135 °C; NMR δ ($CDCl_3$) 1.34 (1 H, t, J

= 7.1 Hz, $NHCOCH_2CO_2CH_2CH_3$), 3.53 (2 H, s, $NHCOCH_2CO_2CH_2CH_3$), 3.82 (3 H, s, CO_2CH_3), 4.31 (2 H, q, J = 7.1 Hz, $NHCOCH_2CO_2CH_2CH_3$), 6.40 (1 H, d, J = 15.8 Hz, CH_A=CH_B), 7.17 (1 H, dd, J = 8.4 and 2.1 Hz, 5-*H*), 7.48 (1 H, d, J = 8.4 Hz, 6-*H*), 7.84 (1 H, d, J = 15.8 Hz, CH_A=CH_B), 8.02 (1 H, d, J = 2.1 Hz, 3-*H*), 9.55 (1 H, br s, N*H*); MS (EI) *m/e* 325 [M^+]. Anal. ($C_{18}H_{16}ClNO_5$) C, H, N. **27** (0.35 g, 0.001 07 mol) was dissolved in methanol (50 mL), and a solution of sodium methoxide in methanol [generated from the dissolution of 80% sodium hydride (0.09 g, 0.003 mol) in methanol (10 mL)] was added. The reaction mixture was stirred at room temperature for 3 h and then methanol, which had been presaturated with dry hydrogen chloride (50 mL), was added. The solvents were removed under vacuum and the residue was purified by chromatography on silica gel using 30% ethyl acetate in hexane as eluent to give a solid which was recrystallized from diethyl ether to give **5** (0.21 g, 60%): mp 156 °C; NMR δ ($CDCl_3$) (10:1 mixture of epimers) 2.55 (1 H, dd, J = 16.2 and 7.6 Hz, $CH_AH_BCH_C$), 2.63 (1 H, dd, J = 16.2 and 7.4 Hz, $CH_AH_BCH_C$), 3.67 (7 H, m, $CHCO_2CH_3$ and $CH_AH_BCO_2CH_3$), 3.91 (1 H, m, $CH_AH_BCH_C$), 6.85 (1 H, d, J = 2.1 Hz, 8-*H*), 6.99 (1 H, dd, J = 8.1 and 2.1 Hz, 6-*H*), 7.12 (1 H, d, J = 8.1 Hz, 5-*H*, minor epimer), 7.16 (1 H, d, J = 8.1 Hz, 5-*H*, major epimer), 8.57 (1 H, br s, N*H*, minor epimer), 8.72 (1 H, br s, N*H*, major epimer); MS (EI) *m/e* 311 [M^+]. Anal. ($C_{14}H_{14}ClNO_5$) C, H, N.

7-Chloro-4-[(methoxycarbonyl)methyl]-3-(methylsulfonyl)-3,4-dihydro-2(1*H*)-quinolone (6). To a solution of (methylsulfonyl)acetic acid (1.96 g, 0.0142 mol) in dichloromethane (120 mL) at −20 °C was added triethylamine (1.96 mL, 0.0265 mol) and butyl chloroformate (1.8 mL, 0.0142 mol). After 30 min at −20 °C **24** (0.5 g, 0.002 37 mol) was added in dichloromethane (20 mL) and stirring continued for 1 h. After this time the reaction mixture was allowed to warm to room temperature, stirred for 1 h, and then diluted with more dichloromethane (200 mL). The solution was washed successively with 1 N HCl (2 × 50 mL), water (2 × 50 mL), and saturated brine (1 × 80 mL), then dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography using 0–60% ethyl acetate in hexane as eluent to give **28** as a colorless solid (0.575 g, 74%): mp 162–164 °C; NMR δ (DMSO) 3.17 (3 H, s, SO_2CH_3), 3.73 (3 H, s, CO_2CH_3), 4.38 (2 H, s, $NHCOCH_2SO_2CH3$), 6.64 (1 H, d, J = 15.9 Hz, CH_A=CH_B), 7.35 (1 H, dd, J = 8.6 and 2.1 Hz, 5-*H*), 7.61 (1 H, d, J = 2.1 Hz, 3-*H*), 7.79 (1 H, d, J = 15.9 Hz, CH_A=CH_B), 7.89 (1 H, d, J = 8.6 Hz, 6-*H*), 10.40 (1 H, br s, N*H*). Anal. ($C_{13}H_{14}ClNO_5S$) C, H, N. Compound **28** (0.5 g, 0.00153 mol) was dissolved in dry methanol (50 mL) with sodium methoxide (0.494 g, 0.0091 mol), stirred at room temperature for 14 h, and then heated under reflux for 5 h. Saturated methanolic hydrogen chloride (50 mL) was added, and the solvents were removed under vacuum. The residue was purified by silica gel chromatography (using 0–60% ethyl acetate in hexane as eluent) and recrystallization from ethyl acetate/hexane to give **6** (0.149 g, 29%): mp 192–194 °C; NMR δ (DMSO) (>20:1 mixture of epimers) 2.52 (1 H, dd, J = 15.7 and 8.1 Hz, $CH_AH_BCH_C$), 2.75 (1 H, dd, J = 15.7 and 6.1 Hz, $CH_AH_BCH_C$), 3.13 (1 H, s, SO_2CH_3), 3.56 (1 H, s, CO_2CH_3), 4.05 (1 H, dd, J = 8.1 and 6.1 Hz, $CH_AH_BCH_C$), 4.48 (1 H, s, $CHSO_2CH3$), 6.90 (1 H, d, J = 2.0 Hz, 8-*H*), 7.01 (1 H, dd, J = 8.2 and 2.0 Hz, 6-*H*), 7.24 (1 H, d, J = 8.2 Hz, 5-*H*), 10.90 (1 H, br s, N*H*); MS (FAB) *m/e* 332 [M + 1]. Anal. ($C_{18}H_{14}ClNO_5S$) C, H, N.

7-Chloro-4-[(methoxycarbonyl)methyl]-3-(phenylsulfonyl)-3,4-dihydro-2(1*H*)-quinolone (7). To a solution of (phenylthio)acetic acid (1.2 g, 0.009 45 mol) in dichloromethane (10 mL) at 0 °C was added oxalyl chloride (0.929 mL, 0.0106 mol) and DMF (2 drops), and the reaction mixture was stirred for 30 min. The solvents were removed under high vacuum, and the residue was dissolved in THF (10 mL), evaporated under high vacuum again, redissolved in THF (20 mL), and cooled to −78 °C. Meanwhile **24** (0.3 g, 0.001 42 mol) was dissolved in THF (30 mL) and cooled to −78 °C and butyllithium (0.89 mL of a 1.6 molar solution in hexane, 0.001 42 mol) was added by syringe. After 10 min, the aniline solution was transferred by cannula to the acid chloride solution. Stirring was continued at −78 °C for 30 min then the reaction mixture was allowed to warm to room temperature. Saturated methanolic hydrogen chloride (50 mL) was added, and the solvents were removed to leave a residue which was purified by silica gel chromatography using 0–60% ethyl acetate in hexane as eluent to give **29** (0.32 g, 62%): mp 191–193 °C; NMR δ (DMSO) 3.74 (3 H, s, CO_2CH_3), 3.93 (2 H, s, $NHCOCH_2SPh$), 6.61 (1 H, dd, J = 15.8 Hz, CH_A=CH_B), 7.19–7.54 (7 H, m, S*Ph* protons 3-*H* and 5-*H*), 7.76 (1 H, d, J = 15.8 Hz, CH_A=CH_B), 7.84 (1 H, d, J = 8.6 Hz, 6-*H*) 10.19 (1 H, br s, N*H*); MS (EI) *m/e* 362 [M^+]. Anal. ($C_{18}H_{16}ClNO_3S$) C, H, N. To a solution of **29** (0.3 g, 0.000 83 mol) in dichloromethane (100 mL) was added 3-chloroperoxybenzoic acid (0.358 g, 0.002 07 mol). The reaction mixture was stirred at room temperature for 14 h, diluted with dichloromethane (200 mL), washed with saturated sodium hydrogen carbonate solution (5 × 100 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography using 0–80% ethyl acetate in hexane as eluent to give a product. This was dissolved in dry methanol (50 mL) with sodium methoxide (0.194 g, 0.004 85 mol), and the reaction mixture was stirred at room temperature for 1 h and then heated under reflux for 2 h. After the mixture was cooled to ambient temperature, saturated methanolic hydrogen chloride (30 mL) was added and the solvents were removed *in vacuo*. The residue was purified by silica gel chromatography (using 0–100% ethyl acetate in hexane as eluent) followed by recrystallization from ethyl acetate/hexane to give **7** as a colorless solid (0.12 g, 37%): mp 220–222 °C; NMR δ (DMSO) (> 20:1 mixture of epimers) 2.46 (1 H, dd, J = 15.9 and 8.2 Hz, $CH_AH_BCH_C$), 2.79 (1 H, dd, J = 15.9 and 6.3 Hz, $CH_AH_BCH_C$), 3.54 (3 H, s, CO_2CH_3), 4.02 (1 H, m, $CH_AH_BCH_C$), 4.50 (1 H, d, J = 1.0Hz, $CHSO_2Ph$), 6.70 (1 H, d, J = 2.0 Hz, 8-*H*), 6.99 (1 H, dd, J = 8.2 and 2.0 Hz, 6-*H*), 7.21 (1 H, d, J = 8.2 Hz, 5-*H*), 7.54–7.74 (5 H, m, SO_2Ph protons), 10.78 (1 H, br s, N*H*); MS (CI) *m/e* 394 [MH]$^+$. Anal. ($C_{18}H_{16}ClNO_5S$) C, H, N.

7-Chloro-4-(methoxycarbonyl)-3-[(4-nitrophenyl)sulfonyl]-3,4-dihydro-2(1*H*)-quinolone (8). Treatment of **24** under the same sequence of reactions as described for the synthesis of **7**, but using [(4-nitrophenyl)thio]acetic acid[32] instead of (phenylthio)acetic acid in the first step, gave **8**: mp 206–207 °C; NMR δ (DMSO) (>20:1 mixture of epimers) 2.51 (1 H, dd, J = 15.9 and 8.2 Hz, $CH_AH_BCH_C$), 2.81 (1 H, dd, J = 15.9 and 6.1 Hz, $CH_AH_BCH_C$), 3.55 (3 H, s, CO_2CH_3), 4.07 (1 H, m, $CH_AH_BCH_C$), 4.71 (1 H, s, $CHSO_2Ph$), 6.71 (1 H, d, J = 2.0 Hz, 8-*H*), 7.01 (1 H, dd, J = 8.2 and 2.0 Hz, 6-*H*), 7.25 (1 H, d, J = 8.2 Hz, 5-*H*), 7.97 (2 H, d, J = 8.7 Hz, meta nitro protons), 8.37 (2 H, d, J = 8.7 Hz, ortho nitro protons), 10.87 (1 H, br s, N*H*); MS *m/e* [MH]$^+$. Anal. ($C_{18}H_{15}ClN_2O_7S$) C, H, N.

7-Chloro-4-(methoxycarbonyl)-3-(phenylcarbonyl)-3,4-dihydro-2(1*H*)-quinolone (9). To a solution of benzoylacetic acid (0.91 g, 0.005 55 mol) in dichloromethane (50 mL) at 0 °C was added oxalyl chloride (0.53 mL, 0.0061 mol) and DMF (4 drops). The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature. **24** (1.17 g, 0.005 55 mol) and triethylamine (0.78 mL, 0.005 55 mol) were added to the reaction mixture and stirring continued at room temperature for 14 h. Dichloromethane (100 mL) was added, and the solution was washed with 1 N hydrochloric acid (3 × 50 mL) and saturated brine (1 × 50 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was triturated with diethyl ether and then filtered to give **30** as a colorless solid (1.39 g, 70%): mp 163–164 °C NMR δ (DMSO) 3.74 (3 H, s, CO_2CH_3), 4.25 (1 H, s, $NHCOCH_2COPh$), 6.63 (1 H, d, J = 15.9 Hz, CH_A=CH_B), 7.26–8.04 (9 H, m, 3-*H*, 5-*H*, 6-*H*, CH_A=CH_B and $COPh$ protons), 10.21 (1 H, br s, $NHCOPh$); MS (EI) *m/e* 357 [M^+]. Anal. ($C_{18}H_{16}ClNO_4$) C, H, N. To a solution of **30** (0.5 g, 0.0014 mol) in THF (30 mL) at −20 °C was added potassium *tert*-butoxide (1.54 mL of a 1 molar solution in THF, 0.001 54 mol). The resulting yellow solution was allowed to warm to 0 °C and stirred at this temperature for 35 min. The reaction mixture was poured into 1 N hydrochloric acid (100 mL) and then extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were washed with saturated brine (1 × 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography using 0–10% ethyl acetate in hexane as eluent to give **9** as a colorless solid (0.215 g, 43%): mp 180–182 °C; NMR δ (DMSO) (>20:1 mixture of epimers) 2.56 (1 H, dd, J = 16.1 and 7.4 Hz, $CH_AH_BCH_C$), 2.86 (1 H, dd, J = 16.1 and 7.7 Hz, $CH_AH_BCH_C$), 3.60 (3 H, s, CO_2CH_3), 3.65 (1 H, m, $CH_AH_BCH_C$), 4.76 (1 H, d, J = 2.8 Hz, CHCOPh, major epimer), 5.01 (1 H, d,

J = 5.0 Hz, CHCOPh, minor epimer), 6.93 (2 H, m, 6-*H* and 8-*H*), 7.07 (1 H, d, J = 8.7 Hz, 5-*H*), 7.57 (2 H, t, J = 7.8 Hz, meta protons), 7.70 (1 H, t, J = 7.8 Hz, para proton), 8.03 (2 H, J = 7.8 Hz, ortho protons), 10.65 (1 H, br s, N*H*CO); MS (EI) *m/e* 357 [M$^+$]. Anal. ($C_{19}H_{16}ClNO_4$) C, H, N.

7-Chloro-4-(methoxycarbonyl)-3-cyano-3,4-dihydro-2(1*H*)-quinolone (10). To a solution of cyanoacetic acid (1.0 g, 0.0118 mol) and triethylamine (1.64 mL, 0.0118 mol) in dichloromethane (40 mL) at −30 °C was added butyl chloroformate (1.5 mL, 0.0118 mol) dropwise. The reaction mixture was allowed to warm to −10 °C over 50 min and then cooled back down to −20 °C, and **24** (0.5 g, 0.002 36 mol) in dichloromethane (10 mL) was added followed by 4-(dimethylamino)pyridine (0.05 g, 0.000 41 mol) and triethylamine (0.33 mL, 0.0024 mol). After 10 min, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The solution was diluted with dichloromethane (200 mL), washed with 1 N hydrochloric acid (2 × 100 mL) and saturated brine (1 × 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography using 30–50% ethyl acetate in hexane as eluent to give **31** (0.327 g, 50%): mp 182 °C; NMR δ 3.74 (3 H, s, CO_2CH_3), 3.99 (2 H, s, NHCOCH_2CN), 6.63 (1 H, dd, J = 15.8 Hz, CH_A=CH_B), 7.34 (1 H, dd, J = 8.4 and 2.0 Hz, 5-*H*), 7.65 (1 H, d, J = 2.0 Hz, 3-*H*), 7.81 (1 H, d, J = 15.8 Hz, CH$_A$=CH_B), 7.90 (1 H, d, J = 8.4 Hz, 6-*H*), 10.124 (1 H, br s, N*H*); MS (EI) *m/e* 278 [MH$^+$]. Anal. ($C_{13}H_{11}ClN_2O_3$·0.1H_2O) C, H, N. To a solution of **31** (0.30 g, 0.00108 mol) in methanol (50 mL) was added, cautiously, sodium hydride (0.065 g of an 80% dispersion in oil, 0.002 16 mol). After 20 min the reaction was quenched by the addition of saturated methanolic hydrogen chloride (30 mL), and the solvents were removed *in vacuo*. The residue was purified by silica gel chromatography (using 20–40% ethyl acetate in hexane as eluent) and recrystallization from diethyl ether to give **10** (0.25 g, 83%): mp 149–154 °C; NMR δ (DMSO) (2:1 mixture of epimers) major epimer 2.52 (1 H, dd, J = 15.3 and 9.3 Hz, CH_AH$_B$CH$_C$), 2.71 (1 H, dd, J = 15.3 and 4.9 Hz, CH$_A$H$_B$CH$_C$), 3.56 (3 H, s, CO_2CH_3), 3.80 (1 H, m, CH$_A$H$_B$CH_C), 4.75 (1 H, d, J = 6.3 Hz, C*H*CN), 6.94 (1 H, d, J = 2.1 Hz, 8-*H*), 7.06 (1 H, dd, J = 8.2 and 2.1 Hz, 6-*H*), 7.21 (1 H, d, J = 8.2 Hz, 5-*H*), 10.85 (1 H, br s, N*H*CO); minor epimer 2.75 (1 H, dd, obscured by major epimer, CH_AH$_B$CH$_C$), 2.90 (1 H, dd, J = 16.6 and 5.5 Hz, CH$_A$H$_B$CH$_C$), 3.63 (3 H, s, CO_2CH_3), 3.80 (1 H, m, CH$_A$H$_B$CH_C), 4.33 (1 H, d, J = 8.1 Hz, C*H*CN), 6.98 (1 H, d, J = 2.1 Hz, 8-*H*), 7.10 (1 H, dd, J = 8.2 and 2.1 Hz, 6-*H*), 7.26 (1 H, d, J = 8.2 Hz, 5-*H*), 10.93 (1 H, br s, N*H*CO); MS (CI$^+$) *m/e* 279 [M + 1]. Anal. ($C_{13}H_{11}ClN_2O_3$) C, H, N.

7-Chloro-4-[(methoxycarbonyl)methyl]-3-nitro-2(1*H*)-quinolone (11). To a solution of **4** (0.1 g, 0.000 335 mol) in dichloromethane (5 mL) was added bromine (0.057 mL, 0.0011 mol) and stirring was continued for 6 h. After this time the reaction mixture was concentrated *in vacuo* to give a residue which was dissolved in methanol with sodium methoxide (0.027 g, 0.000 675 mol) and left to stand for 14 h. Saturated hydrogen chloride in methanol (5 mL) was added and the solvent was removed by evaporation. The residue was partitioned between ethyl acetate (30 mL) and water (2 × 20 mL), and then the organic layer was washed with brine (1 × 20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. Recrystallization of the crude product from ethyl acetate/hexane gave **11** as a pale yellow solid (0.048 g, 48%): mp 252–254 °C; NMR δ (DMSO) 3.64 (3 H, s, CO_2CH_3), 4.08 (2 H, s, C$H_2CO_2CH_3$), 7.41 (1 H, dd, J = 8.8 and 2.0 Hz, 6-*H*), 7.45 (1 H, d, J = 2.0 Hz, 8-*H*), 7.96 (1 H, d, J = 8.8 Hz, 5-*H*), 12.85 (1 H, br s, N*H*CO); MS (CI$^+$) *m/e* 297 [M + 1]. Anal. ($C_{12}H_9ClN_2O_5$ 0.5 H_2O) C, H, N.

7-Chloro-4-[(methoxycarbonyl)methyl]-3-(methoxycarbonyl)-2(1*H*)-quinolone (12). Treatment of **5** (0.3 g, 0.000965 mol) under the same conditions described for the conversion of **4** to **11** gave **12** as a colorless solid (0.14 g, 47%): mp 271–273 °C NMR δ (DMSO) 3.62 (3 H, s, CO_2CH_3), 3.81 (3 H, s, CO_2CH_3), 3.96 (2 H, s, C$H_2CO_2CH_3$), 7.29 (1 H, dd, J = 8.8 and 2.0 Hz, 6-*H*), 7.37 (1 H, d, J = 2.0 Hz, 8-*H*), 7.81 (1 H, d, J = 8.8 Hz, 5-*H*), 12.23 (1 H, br s, N*H*CO); MS (EI) *m/e* 309 [M$^+$]. Anal. ($C_{14}H_{12}ClNO_5$·0.25H_2O) C, H, N.

4-[(Methoxycarbonyl)methyl]-3-nitro-3,4-dihydro-2(1*H*)-quinolone (13). Treatment of 2-nitrobenzaldehyde under the same series of reactions as described for the conversion of **24** to **4** gave **13** as a colorless solid: mp 118–119 °C; NMR δ ($CDCl_3$) (10:1 mixture of epimers) 2.65 (1 H, dd, J = 16.8 and 6.7 Hz, CH_AH$_B$CH$_C$), 2.76 (1 H, dd, J = 16.8 and 7.1 Hz, CH$_A$H$_B$CH$_C$), 3.71 (3 H, s, CO_2CH_3, major epimer), 3.75 (3 H, s, CO_2CH_3, minor epimer), 4.26 (1 H, m, CH$_A$H$_B$CH_C), 5.42 (1 H, d, J = 6.2 Hz, C*H*NO$_2$, major epimer), 5.54 (1 H, d, J = 6.2 Hz, C*H*NO$_2$, minor epimer), 6.82–7.30 (4 H, m, 5-*H*, 6-*H*, 7-*H*, 8-*H*), 7.79 (1 H, br s, CON*H*); MS (EI) *m/e* 264 [M$^+$]. Anal. ($C_{12}H_{12}N_2O_5$) C, H, N.

7-Chloro-4-[(ethoxycarbonyl)methyl]-3-nitro-3,4-dihydro-2(1*H*)-quinolone (14). Compound **4** (0.3 g. 0.001 05 mol) was dissolved in saturated ethanolic hydrogen chloride at room temperature and left to stand for 7 days. The solvent was removed by evaporation and the residue was recrystallized twice from diethyl ether to give **14** as a pale yellow solid (0.054 g, 17%) mp 159–160 °C; NMR δ (DMSO) (8:1 mixture of epimers) 1.15 (3 H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.61 (1 H, dd, J = 16.4 and 7.5 Hz, CH_AH$_B$CH$_C$), 2.85 (1 H, dd, J = 16.4 and 5.4 Hz, CH$_A$H$_B$CH$_C$), 4.09 (3 H, m, CH$_A$H$_B$CH_C and $CO_2CH_2CH_3$), 5.78 (1 H, d, J = 6.2 Hz, C*H*NO$_2$, major epimer), 5.87 (1 H, d, J = 5.1 Hz, C*H*NO$_2$, minor epimer), 6.99 (1 H, d, J = 2.1 Hz, 8-*H*), 7.10 (1 H, dd, J = 8.2 and 2.1 Hz, 6-*H*), 7.19 (1 H, d, J = 8.2 Hz, 5-*H*, minor isomer), 7.26 (1 H, d, J = 8.2 Hz, 5-*H*, major isomer), 11.10 (1 H, br s, N*H*CO, minor isomer), 11.14 (1 H, br s, N*H*CO, major isomer); MS (EI) *m/e* 312 [M$^+$]. Anal. ($C_{13}H_{13}ClN_2O_5$·0.25H_2O) C, H, N.

7-Chloro-4-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]-3-nitro-3,4-dihydro-2(1*H*)-quinolone (15). To a solution of acetamide oxime (1.75 g, 0.0236 mol) in dry THF (100 mL) was added sodium hydride (0.886 g of an 80% dispersion in oil, 0.0295 mol) in portions at room temperature. When the addition was complete, the solution was stirred at room temperature for 1 h, **24** (2.5 g, 0.0118 mol) was then added, and the reaction mixture was heated at 60 °C for 2 h. After the mixture was cooled to room temperature glacial acetic acid (1.5 mL, 0.026 mol) was added and the reaction mixture was filtered through Celite and concentrated under vacuum. The residue was dissolved in dichloromethane (150 mL), washed with water (1 × 100 mL) and saturated brine (1 × 100 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography to give a yellow solid (0.995). Treatment of this solid under the conditions described for the conversion of **24** to **4** gave **15** as a beige solid: mp 152–154 °C (diethyl ether/hexane); NMR δ (DMSO) (8:1 mixture of epimers) 2.31 (3 H, s, CH_3), 3.24 (1 H, dd, J = 16.2 and 7.2 Hz, CH_AH$_B$CH$_C$), 2.49 (1 H, dd, J = 16.2 and 5.9 Hz, CH$_A$H$_B$CH$_C$), 4.33 (1 H, m, CH$_A$H$_B$CH_C), 5.90 1 H, d, J = 6.1 Hz, C*H*NO$_2$, major epimer), 5.99 (1 H, d, J = 4.8 Hz, C*H*NO$_2$, minor epimer), 6.99 (1 H, d, J = 1.9 Hz, 8-*H*), 7.06 (1 H, dd, J = 8.3 and 1.9 Hz, 6-*H*), 7.23 (1 H, d, J = 8.3 Hz, 5-*H*, major isomer), 11.14 (1H, br s, N*H*CO, minor isomer), 11.17 (1H, br s, N*H*CO, major isomer); MS (CI$^+$) *m/e* 323 [MH$^+$]. Anal. ($C_{13}H_{11}ClN_4O_4$) C, H, N.

7-Chloro-4-[[((*N*-methyl)-*N*-phenylamino)carbonyl]methyl]-3-nitro-3,4-dihydro-2(1*H*)-quinolone (16) Sodium Salt. Compound **23** (6.4 g, 0.0265 mol) was dissolved in 50% aqueous acetone (500 mL) with sodium hydroxide (3.5 g, 0.0875 mol) and stirred at room temperature for 2 h. After this time the acetone was removed under vacuum, the aqueous residue was treated with concentrated hydrochloric acid until a pH of 1 was attained, and the suspension was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum to give **36** as a white solid (5.5 g, 91%): mp 165 °C sublimed; NMR (1:1 mixture of *cis* and *trans* isomers) δ ($CDCl_3$) 6.15 (1 H, d, J = 11.9 Hz, *cis* CH$_A$=CH$_B$), 6.35 (1 H, d, J = 15.7 Hz, *trans* CH$_A$=CH$_B$), 7.45 (1 H, d, J = 11.9 Hz, *cis* CH$_A$=CH$_B$), 7.34–7.64 (4 H, m, *cis* 3-*H* and 4-*H*, *trans* 3-*H* and 4-*H*), 8.06 and 8.17 (2 H, 2 × d, J = 2.0 Hz, 2 × 6-*H*), 8.17 (1 H, d, J = 15.7 Hz, *trans* CH$_A$=CH$_B$); MS (EI) *m/e* 227 [M$^+$]. Anal. ($C_9H_8ClNO_4$) C, H, N. *N*-Methylaniline (3.2 mL, 0.033 mol), 1-hydroxybenzotriazole (4.46 g, 0.033 mol), **36** (5 g, 0.022 mol), triethylamine (9.1 mL, 0.066 mol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (6.5 g, 0.033 mol) were dissolved in THF (200 mL) and stirred at ambient temperature for 14 h. The solvent was removed under vacuum, and the residue was redissolved in ethyl acetate (300 mL) and washed with 0.5 N citric acid solution (3 × 150 mL), saturated sodium hydrogen carbonate solution (3 × 100 mL) and saturated brine (1 × 100 mL). The organic layer was dried (Na_2-

SO_4), filtered, and concentrated under vacuum to give a residue which was purified by silica gel chromatography using 30% ethyl acetate in hexane as eluent to give **37** as a white solid (3.97 g, 57%): mp 99–101 °C; NMR δ (DMSO) (mainly *trans* isomer) 3.32 (3 H, s, NCH_3), 6.39 (1 H, d, J = 15.9 Hz, *trans* CH_A=CH_B), 7.14–7.82 (8 H, m, *trans* CH_A=CH_B, 3-*H*, 4-*H*, and *Ph*), 8.12 (1 H, d, J = 1.9 Hz, 6-*H*); MS (EI) *m/e* 316 [M^+]. Treatment of **37** under the conditions described for the conversion of **23** to **4** gave **16** which was purified as a monosodium salt: mp 240 °C dec; NMR (D_2O) 2.48 (1 H, dd, J = 13.4 and 5.2 Hz, $CH_AH_BCH_C$), 2.52 (1 H, dd, J = 13.4 and 8.6 Hz, $CH_AH_BCH_C$), 3.13 (3 H, s, CO_2CH_3,) 4.66 (1 H, dd, J = 8.6 and 5.2 Hz, $CH_AH_BCH_C$), 6.74 (2 H, m, meta *Ph* protons), 6.88 (1 H, d, J = 1.8 Hz, 8-*H*), 7.02 (1 H, d, J = 8.2 Hz, 5-*H*), 7.06 (1 H, d, J = 8.2 and 1.8 Hz, 6-*H*), 7.36 (3 H, m, ortho and para *Ph* protons); MS (FAB) *m/e* 396 [MH^+]. Anal. ($C_{18}H_{15}ClN_3O_4Na\cdot1.2H_2O$) C, H, N.

Reaction of **36** with the appropriate amine in place of *N*-methylaniline under the conditions described for the formation of **37**, followed by treatment of the product obtained under the conditions described for the conversion of **23** to **4** gave compounds **17–20**.

7-Chloro-4-[[(phenylamino)carbonyl]methyl]-3-nitro-3,4-dihydro-2(1*H*)-quinolone (17): mp 234–235 °C; NMR (DMSO) (8:1 mixture of epimers) 2.63 (1 H, dd, J = 15.4 and 8.2 Hz, $CH_AH_BCH_C$), 2.52 (1 H, dd, J = 15.4 and 5.3 Hz, $CH_AH_BCH_C$), 4.23 (1 H, m, $CH_AH_BCH_C$), 5.83 (1 H, d, J = 5.3 Hz, $CHNO_2$, major epimer), 5.87 (1 H, d, J = 5.0 Hz, $CHNO_2$, minor epimer), 6.99–7.10 (3 H, m, 5-*H*, 6-*H* and 8-*H*), 7.28–7.31 (3 H, m, ortho and para *Ph* protons), 7.52 (2 H, m, meta *Ph* protons), 10.00 (1 H, br s, CONHPh major epimer), 10.07 (1 H, br s, CONHPh minor epimer), 11.12 (1 H, br s, $NHCOCHNO_2$, minor epimer), 11.17 (1 H, br s, $NHCOCHNO_2$, major epimer); MS (EI) *m/e* 359 [M^+]. Anal. ($C_{17}H_{14}ClN_3O_4\cdot0.1H_2O$) C, H, N.

7-Chloro-4-[[(methylamino)carbonyl]methyl]-3-nitro-3,4-dihydro-2(1*H*)-quinolone (18): mp 222 °C; NMR (DMSO) (8:1 mixture of epimers) 2.35 (1 H, dd, J = 15.3 and 8.2 Hz, $CH_AH_BCH_C$), 2.53–2.61 (4 H, m, $CH_AH_BCH_C$ and NCH_3), 4.11 (1 H, m, $CH_AH_BCH_C$), 5.76 (1 H, d, J = 5.3 Hz, $CHNO_2$, major epimer), 5.80 (1 H, d, J = 5.1 Hz, $CHNO_2$, minor epimer), 6.98 (1 H, d, J = 1.9 Hz, 8-*H*), 7.08 (1 H, d, J = 8.4 Hz, 6-*H*), 7.19 (1 H, d, J = 8.4 and 1.9 Hz, 5-*H*), 7.89 (1 H, br s, CH_3NHCO), 11.08 (1 H, br s, $NHCOCHNO_2$, minor epimer), 11.11 (1 H, br s, $NHCOCHNO_2$, major epimer); MS (CI^-) *m/e* 296 [M − H]. Anal. ($C_{12}H_{12}ClN_3O_4$) C, H, N.

7-Chloro-4-[[(*N*,*N*-dimethylamino)carbonyl]methyl]-3-nitro-3,4-dihydro-2(1*H*)-quinolone (19): mp 210–211 °C dec; NMR (DMSO) (11:1 mixture of epimers) 2.69 (1 H, dd, J = 16.6 and 7.4 Hz, $CH_AH_BCH_C$), 2.77–2.85 (7 H, m, $CH_AH_BCH_C$ and $N(CH_3)_2$), 4.14 (1 H, m, $CH_AH_BCH_C$), 5.74 (1 H, d, J = 6.2 Hz, $CHNO_2$, major epimer), 5.80 (1 H, d, J = 5.0 Hz, $CHNO_2$, minor epimer), 6.97 (1 H, d, J = 1.9 Hz, 8-*H*), 7.07 (1 H, dd, J = 8.6 and 1.9 Hz, 6-*H*), 7.20 (1 H, d, J = 8.6 Hz, 5-*H*) 11.08 (1 H, br s, *NH*CO); MS (CI^+) *m/e* 312 [M^+]. Anal. ($C_{13}H_{14}ClN_3O_4$) C, H, N.

7-Chloro-4-[[[(phenylmethyl)amino]carbonyl]methyl]-3-nitro-3,4-dihydro-2(1*H*)-quinolone (20): mp 234–236 °C; NMR (DMSO) (11:1 mixture of epimers) 2.46 (1 H, dd, J = 15.2 and 8.4 Hz, $CH_AH_BCH_C$), 2.85 (1 H, dd, J = 115.2 and 5.8 Hz, $CH_AH_BCH_C$), 4.13–4.30 (3 H, m, $CH_AH_BCH_C$ and CH_2Ph), 5.77 (1 H, d, J = 5.0 Hz, $CHNO_2$, major epimer), 5.84 (1 H, d, J = 5.0 Hz, $CHNO_2$, minor epimer), 6.98 (1 H, d, J = 2.0 Hz, 8-*H*), 7.03 (1 H, dd, J = 8.3 and 2.0 Hz, 6-*H*), 7.10 (1 H, d, J = 8.3 Hz, 5-*H*), 7.15–7.30 (5 H, m, *Ph* protons), 8.47 (1 H, br s, $PhCH_2NHCO$), 11.08 (1 H, br s, $NHCOCHNO_2$, minor epimer), 11.11 (1 H, br s, $NHCOCHNO_2$, major epimer); MS (CI^+) *m/e* 374 [M + H]. Anal. ($C_{18}H_{16}ClN_3O_4$) C, H, N.

7-Chloro-3-nitro-3,4-dihydro-2(1*H*)-quinolone (21). To a solution of 4-chloro-2-nitrobenzyl alcohol (**40**) (25.42 g, 0.136 mol) in methanol (1 L) was added 5% platinum sulfide on carbon (2 g) and the reaction mixture was shaken on a Parr apparatus under 50 psi of hydrogen for 18 h. The mixture was filtered, concentrated under vacuum, and then redissolved in dichloromethane (1 L) with triethylamine (41.8 mL, 0.3 mol), and cooled to 0 °C. Acetyl chloride (21.3 mL, 0.3 mol) was added dropwise, and then the solution was allowed to warm to room temperature and stirred for 14 h. The reaction mixture was washed with 1 N hydrochloric acid (2 × 500 mL) and saturated brine (1 × 500 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was dissolved in methanol (500 mL) and a solution of sodium hydroxide (6 g, 0.15 mol) in water (200 mL) was added. After the mixture stirred at room temperature for 1 h, the methanol was removed in vacuo and the aqueous residue was extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (1 × 200 mL) and then saturated brine (1 × 200 mL), dried ($MgSO_4$), filtered, and evaporated to give **42** as a white solid (24.41 g, 90%): mp 136–139 °C; NMR δ (DMSO) 2.07 (3 H, s, CH_3), 4.48 (2 H, d, J = 5.5 Hz, CH_2OH), 5.36 (1 H, t, J = 5.5 Hz, CH_2OH), 7.18 (1 H, dd, J = 8.5 and 1.9 Hz, 4-*H*), 7.40 (1 H, d, J = 8.5 Hz, 3-*H*), 7.68 (1 H, d, J = 1.9 Hz, 6-*H*), 9.34 (1 H, br s, *NH*CO); MS (EI) *m/e* 199 [M^+]. To a solution of **42** (2 g, 0.01 mol) in THF (50 mL) and carbon tetrachloride (50 mL) was added triphenylphosphine (2.62 g, 0.01 mol), and the reaction mixture was heated under reflux for 2 h. The solvents were removed under vacuum and the residue was purified by silica gel chromatography using 20–40% ethyl acetate in hexane as eluent to give **43** as a white solid (1.16 g, 53%): mp 148–154 °C; δ NMR (DMSO) 2.10 (3 H, s, CH_3), 4.83 (2 H, d, J = 5.5 Hz, CH_2Cl), 7.23 (1 H, dd, J = 8.5 and 2.0 Hz, 4-*H*), 7.48 (1 H, d, J = 8.5 Hz, 3-*H*), 7.68 (1 H, d, J = 2.0 Hz, 6-*H*), 9.56 (1 H, br s, *NH*CO); MS (EI) *m/e* 217 [M^+]. To a solution of **43** (0.55 g, 0.0025 mol) in DMF (20 mL) was added ethyl nitroacetate sodium salt, and the reaction mixture was heated at 60 °C for 1 h. The cooled solution was poured into 1 N hydrochloric acid (200 mL) and extracted with ethyl acetate (2 × 150 mL). The combined organic layers were washed with water (1 × 200 mL) and saturated brine (1 × 200 mL), then dried ($MgSO_4$), filtered, and concentrated in vacuo to give a brown oil. Purification by chromatography on silica gel using 30–50% ethyl acetate in hexane as eluent gave **44** as a white solid (0.296 g, 38%): mp 119–121 °C; δ NMR (DMSO) 1.16 (3 H, t, J = 7.1 Hz, CH_3CH_2O), 2.07 (3 H, s, CH_3), 3.48 (2 H, m, CH_2CHNO_2), 4.19 (2 H, q, J = 7.1 Hz, CH_3CH_2O), 5.83 (1 H, dd, J = 8.8 and 6.6 Hz, CH_2CHNO_2),7.22 (2 H, m, 3-*H* and 4-*H*), 7.53 (1 H, d, J = 1.9 Hz, 6-*H*), 9.54 (1 H, br s, *NH*CO); MS (EI) *m/e* 314 [M^+]. To a solution of methanol (10 mL) that had been presaturated with hydrogen chloride was added **44** (0.25 g, 0.0008 mol), and the resultant solution was heated under reflux for 1 h. The solvents were removed under vacuum, and the residue was recrystallized from ethyl acetate/hexane to give **21** as a white solid (0.083 g, 46%): mp 194–197 °C; δ NMR (DMSO) 3.58 (2 H, m, (2 H, m, CH_2CHNO_2), 5.87 (1 H, dd, J = 10.0 and 6.8 Hz, CH_2CHNO_2), 6.94 (1 H, d, J = 1.9 Hz, 8-*H*), 7.07 (1 H, dd, J = 8.1 and 1.9 Hz, 6-*H*), 7.29 (1 H, d, J = 8.1 Hz, 5-*H*), 10.99 (1 H, br s, *NH*CO); MS (EI) *m/e* 226 [M^+]. Anal. ($C_9H_7ClN_2O_3$) C, H, N.

7-Chloro-2(1*H*)-quinolone (32) [Attempted Formation of 7-Chloro-4-(carboxymethyl)-3-nitro-3,4-dihydro-2(1*H*)-quinolone (33)]. Compound **4** (0.35 g, 0.001 26 mol) was dissolved in 50% aqueous methanol with sodium hydroxide (0.005 mol) and stirred at room temperature for 14 h. The reaction mixture was concentrated under vacuum, and the aqueous residue was treated with 1 N hydrochloric acid (10 mL) and water (30 mL) and then extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum to leave a residue which was purified by recrystallization from ethyl acetate to give **32** as a white solid (0.110 g, 52%): mp 281–282 °C; NMR (DMSO) 6.51 (1 H, d, J = 9.5 Hz, 3-*H*), 7.21 (1 H, dd, J = 8.4 and 2.1 Hz, 6-*H*), 7.32 (1 H, d, J = 2.1 Hz, 8-*H*), 7.69 (1 H, d, J = 8 4 Hz, 5-*H*), 7.91 (1 H, d, J = 9.5 Hz, 4-*H*), 11.79 (1 H, br s, CONH); MS (EI) *m/e* 179 [M^+]. Anal. ($C_9H_6ClNO\cdot0.125H_2O$) C, H, N.

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