4-Substituted-3-phenylquinolin-2(1*H*)-ones: Acidic and Nonacidic Glycine Site *N*-Methyl-D-aspartate Antagonists with *in Vivo* Activity

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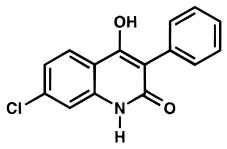
4-Substituted-3-phenylquinolin-2(1*H*)-ones have been synthesized and evaluated *in vitro* for antagonist activity at the glycine site on the NMDA (*N*-methyl-D-aspartate) receptor and *in vivo* for anticonvulsant activity in the DBA/2 strain of mouse in an audiogenic seizure model. 4-Amino-3-phenylquinolin-2(1*H*)-one (**3**) is 40-fold lower in binding affinity but only 4-fold weaker as an anticonvulsant than the acidic 4-hydroxy compound **1**. Methylsulfonylation at the 4-position of **3** gives an acidic compound (**6**, $pK_a = 6.0$) where affinity is fully restored but *in vivo* potency is significantly reduced (Table 1). Methylation at the 4-position of **1** to give **18** results in the abolition of measurable affinity, but the attachment of neutral hydrogen bond-accepting groups to the methyl group of **18** produces compounds with comparable *in vitro* and *in vivo* activity to **1** (e.g., **23** and **28**, Table 2). Replacement of the 4-hydroxy group of **1** with an ethyl group abolishes activity (**42**), but again, incorporation of neutral hydrogen bond acceptors to the terminal carbon atom restores affinity (e.g., **36**, **39**, and **40**, Table 3). Replacement of the 4-hydroxy group of the high-affinity compound **2** with an amino group produces a compound with 200-fold reduced affinity (**43**, $IC_{50} = 0.42$ μM, Table 4) which is nevertheless still 10-fold higher in affinity than **3**. The results in this paper indicate that anionic functionality is not an absolute requirement for good affinity at the glycine/NMDA site and provide compelling evidence for the existence of a ligand/receptor hydrogen bond interaction between an acceptor attached to the 4-position of the ligand and a hydrogen bond donor attached to the receptor.

Introduction

It is accepted that *N*-methyl-D-aspartate (NMDA) receptor antagonists have promise for the treatment of several central nervous system disorders including stroke, epilepsy, and Parkinson's disease.[1] There is evidence that NMDA antagonists that act through blockade of a glycine coagonist site[2] that is linked to the NMDA receptor complex may have a more benign side-effect profile[3] than uncompetitive NMDA antagonists such as MK-801[4] and competitive NMDA antagonists as exemplified by CPP.[5] While the weak affinity, low-efficacy glycine/NMDA partial agonist L-687,414 is active after systemic administration,[6] until recently,[7] full antagonists at the glycine site on the NMDA receptor have shown no significant *in vivo* activity on intraperitoneal or intravenous administration. A recent breakthrough in achieving activity *in vivo* came about through delocalization of anionic functionality, purportedly a prerequisite for *in vitro* affinity,[8,9] through a 3-phenyl-4-hydroxyquinolin-2(1*H*)-one system,[7,10,11] to produce compounds **1** and **2**, both of which show anticonvulsant activity in animal models.[7] The increased *in vivo* activity observed with these compounds relative to carboxylic acid-containing glycine antagonists[12] is probably a consequence of improved penetration of the blood−brain barrier.

In this paper we report the effects of modifying the substituent at the 4-position of 7-chloro-3-phenyl-4-hydroxyquinolin-2(1*H*)-one (**1**). The results obtained indicate that anionic functionality is not an absolute requirement for significant affinity at the glycine site. Some nonacidic derivatives show *in vivo* activity in the DBA/2 mouse audiogenic seizure model, and the strategy of designing higher affinity nonacidic ligands is a possible approach toward further improving blood−brain barrier penetration and overcoming the problem of high plasma protein binding observed in 3-phenyl-4-hydroxyquinolin-2(1*H*)-ones.[13]



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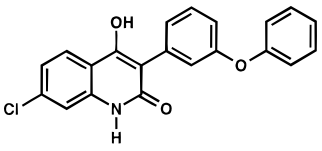

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Chemistry

Compounds **3**−**45** were synthesized for this study. The 4-amino analogue **3** was prepared by cyclization of the 2-cyano phenylacetamide **48** using sodium hydride in dimethylformamide at 100 °C (Scheme 1). The amide **4** was prepared from **3** by deprotonation at the 1- and 4-positions with excess sodium hydride, treatment with excess acetyl chloride at elevated temperature, and then removal of the 1-*N*-acetyl group under basic conditions. Selective sulfonylation of **3** at the 4-position to produce **6** was achieved using a one-pot procedure involving initial deprotonation and *in situ* protection of the 1-position followed by *in situ* deprotonation of the 4-position, reaction with methanesulfonyl chloride, and

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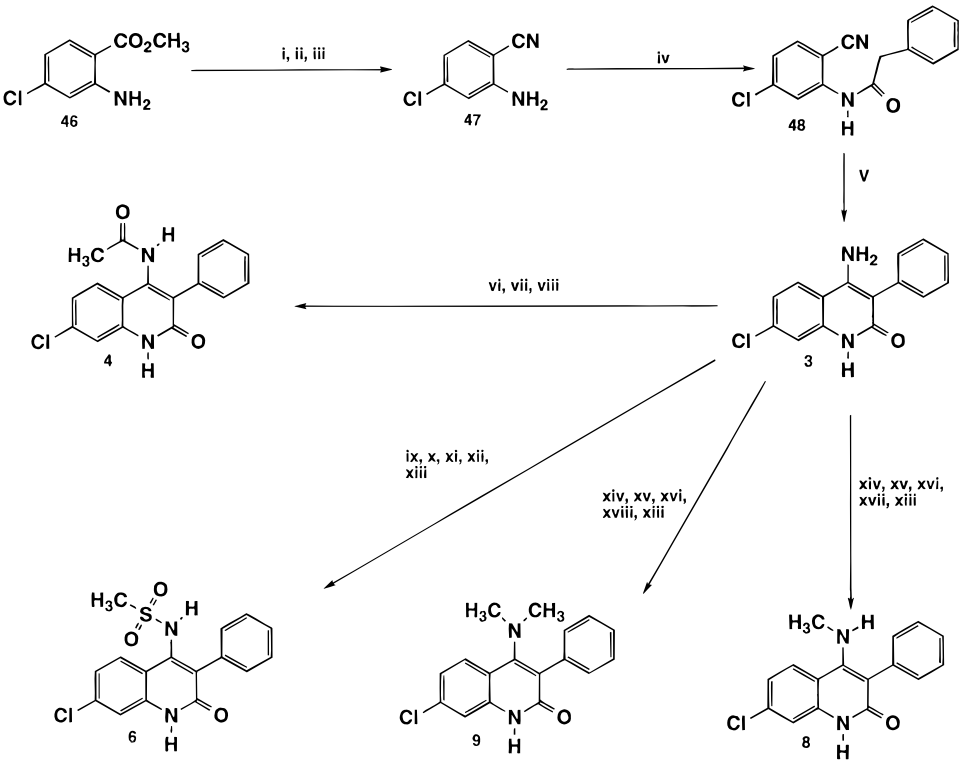
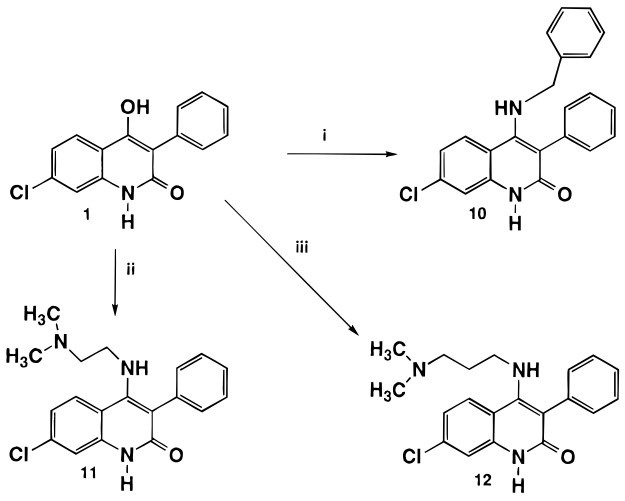
Scheme 1[a]



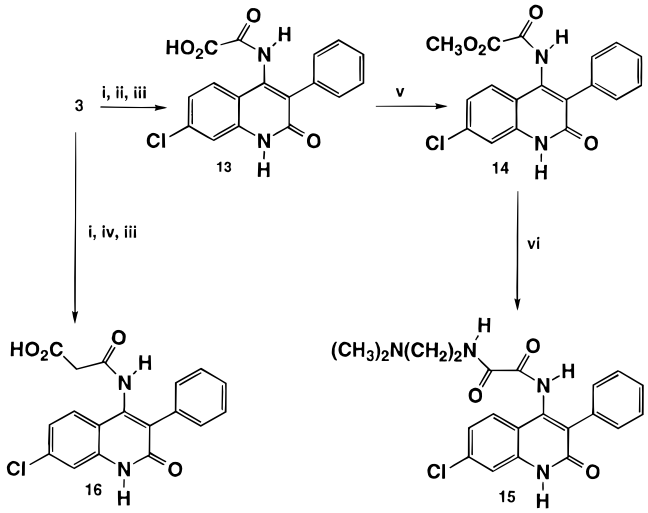
[a] Reagents: (i) NH_3, MeOH, 150 °C, 30 atm; (ii) TFAA, Et_3N, 0 °C; (iii) K_2CO_3, H_2O, MeOH, 65 °C; (iv) $PhCH_2COCl$, DCE, reflux; (v) NaH, DMF, 100 °C; (vi) NaH, THF; (vii) CH_3COCl, 60 °C; (viii) NaOH, ultrasound; (ix) KHMDS, THF; (x) TBDMS-triflate; (xi) KHMDS; (xii) $MeSO_2Cl$; (xiii) HCl, H_2O; (xiv) KHMDS, THF; (xv) TBDMS-triflate; (xvi) KHMDS; (xvii) MeI; (xviii) excess MeI.

Scheme 2[a]



[a] Reagents: (i) $PhCH_2NH_2$, reflux; (ii) $(CH_3)_2N(CH_2)_2NH_2$, 180 °C sealed tube; (iii) $(CH_3)_2N(CH_2)_3NH_2$, reflux.

Scheme 3[a]

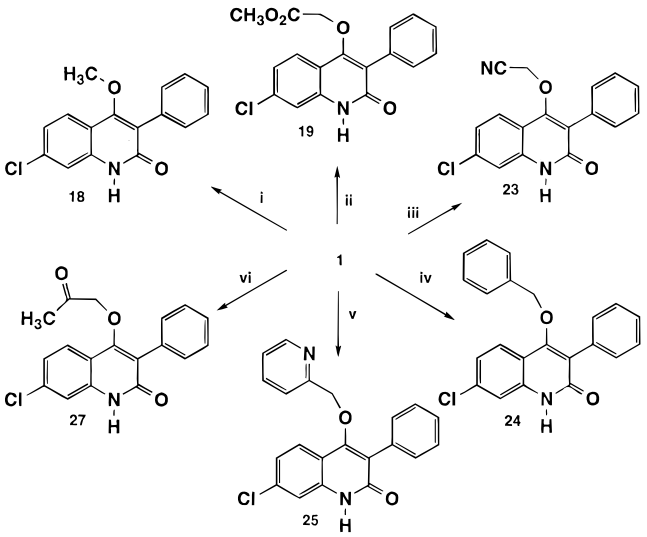


[a] Reagents: (i) NaH, THF; (ii) EtO_2CCOCl; (iii) NaOH; (iv) EtO_2CCH_2COCl; (v) MeOH/HCl; (vi) $(CH_3)_2N(CH_2)_2NH_2$.

removal of the 1-silyl protecting group on acidic workup. The 4-methylamine and 4-dimethylamine derivatives **8** and **9** were prepared using similar methodology to protect the 1-position *in situ*, but methyl iodide, in varying quantities, was employed as the final electrophile. The 4-benzylamino (**10**), the 4-(*N*,*N*-dimethylamino)ethylamino (**11**), and the 4-(*N*,*N*-dimethylamino)-propylamino (**12**) derivatives were all made by reaction of **1** with excess amine at elevated temperature (Scheme 2).[14] The 4-amido acids **13** and **16** were prepared using the procedure described for the synthesis of **4** using the appropriate acid chloride in place of acetyl chloride (Scheme 3). Acid **13** was converted into the methyl ester **14** by treatment with methanolic hydrogen chloride, and **14** was converted to the dimethylamide **15** by reaction with *N*,*N*-dimethylethylenediamine.

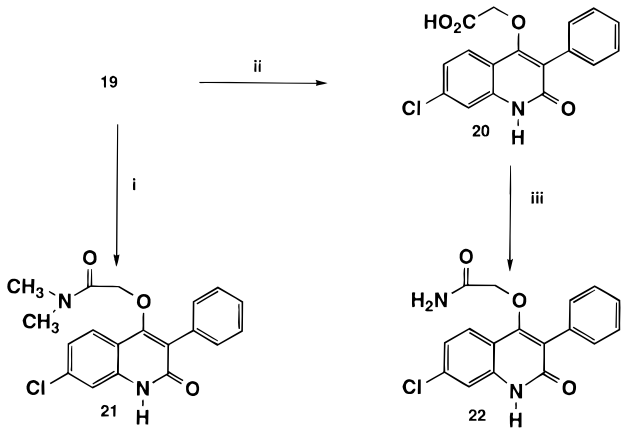
The 4-methoxy analogue **18** was made by reaction of **1** with diazomethane. The ether derivatives **19**, **23**–**25**, and **27** were all made by treatment of **1** with an appropriate alkylating agent in dimethylformamide in the presence of sodium iodide and sodium hydrogen carbonate (Scheme 4). The ester **19** was converted into the dimethylamide **21** by reaction with dimethylamine in methanol (Scheme 5). The acid **20** (made by saponification of **19**) was converted to the carboxamide **22** by reaction with ammonium acetate in the presence of water soluble carbodiimide. The (*N*,*N*-dimethylamino)-

Scheme 4[a]



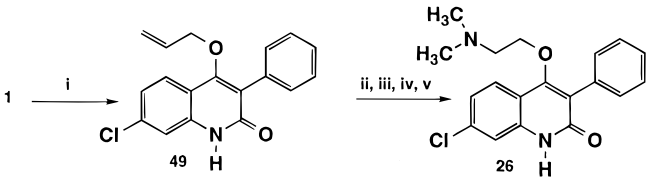
[a] Reagents: (i) CH_2N_2, Et_2O, THF; (ii) $BrCH_2CO_2CH_3$, $NaHCO_3$, NaI, DMF; (iii) $BrCH_2CN$, $NaHCO_3$, NaI, DMF; (iv) $BrCH_2Ph$, $NaHCO_3$, NaI, DMF; (v) $ClCH_2$-2-Pyr·HCl, $NaHCO_3$, NaI, DMF; (vi) $ClCH_2COCH_3$, $NaHCO_3$, NaI, DMF.

Scheme 5[a]



[a] Reagents: (i) $(CH_3)_2NH$, CH_3OH, rt, 5 days; (ii) LiOH, THF, H_2O; (iii) NH_4OAc, $(CH_3)_2N(CH_2)_3N{=}C{=}NCH_2CH_3$, Et_3N, HOBT, THF.

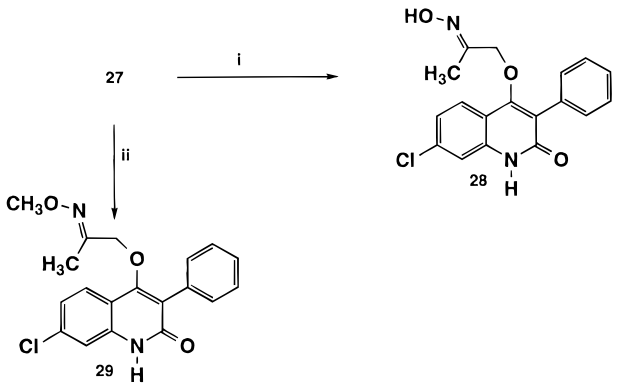
Scheme 6



ethyl ether **26** was prepared *via* a reductive alkylation procedure using dimethylamine hydrochloride and the aldehyde derived from the ozonolysis of the allyl ether **49** (Scheme 6). The ketone **27** was converted to the oxime derivatives **28** and **29** by reaction with the appropriate hydroxylamine salt in pyridine at elevated temperature (Scheme 7).

A mixture of 4-chloro- and 6-chloroisatin,[15] on treatment with phenylacetic acid and sodium acetate at 220 °C, afforded the 7-chloro-4-carboxy analogue **31** in low yield (Scheme 8). Reaction of **31** with diazomethane gave the methyl ester **30**. The homologated methyl ester **33** was synthesized as described in Scheme 9. The aniline **53**[9] was converted into the amide **54** which underwent oxidative cyclization, *via* an *in situ* double

Scheme 7[a]



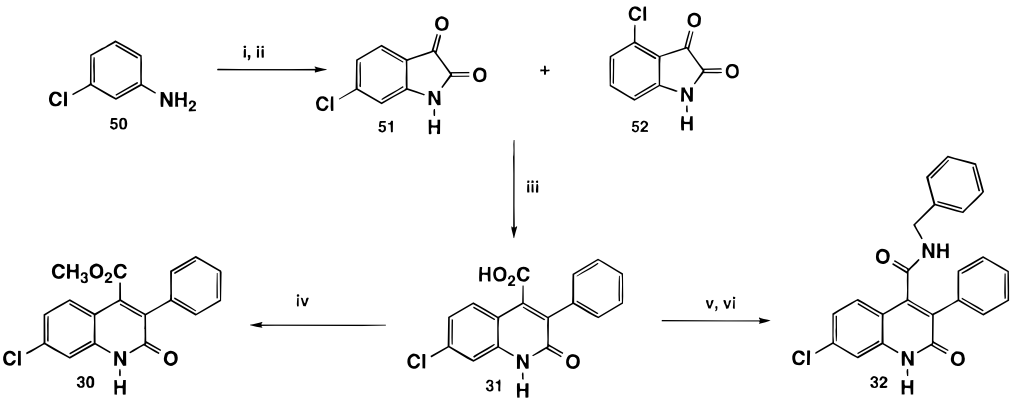
[a] Reagents: (i) NH_2OH·HCl, pyridine, 4 Å sieves, 60 °C; (ii) NH_2OCH_3·HCl, pyridine, 4 Å sieves, 60 °C.

deprotonation/phenylselenoxide elimination procedure, to give the required product. The homologated carboxylic acid **34** was made by saponification of **33**, and the amide **35** was prepared by carbodiimide coupling of **34** with *N,N*-dimethylethylenediamine. 2-(Hydroxymethyl)-5-chloroaniline (**55**) was converted into the aldehyde **56** by bis-phenylacetylation, saponification of the ester intermediate, and oxidation with pyridinium chlorochromate (Scheme 10). The 4-ethyl derivative **42** was prepared from aldehyde **56** by reaction with ethylmagnesium bromide followed by oxidation and base-mediated condensation. The propionate derivative **37** was prepared as described in Scheme 11. Reaction of **56** with [(1-ethoxycyclopropyl)oxy]trimethylsilane[16] at −78 °C in the presence of titanium tetrachloride gave the secondary alcohol **57**. Oxidation of **57** followed by sodium ethoxide-mediated condensation and saponification gave the target compound **37**. Esterification of **37** with methanolic hydrogen chloride gave **36** which underwent reaction with the anion of acetamide oxime to give the methyloxadiazole **38**. The acid **37** was converted into the tetrazole **41** by initial conversion to the carboxamide **39**, subsequent dehydration to the nitrile **40**, and finally reaction with sodium azide. The 4-amino derivative of **2** (compound **43**) was prepared in an analogous manner to that described for the synthesis of compound **3** (Scheme 1) using *m*-phenoxyphenylacetyl chloride instead of phenylacetyl chloride. The 4-alkoxy derivatives of **2** (**44** and **45**) were prepared directly from **2**[7,13] using methodology described in Schemes 4 and 5.

Biology

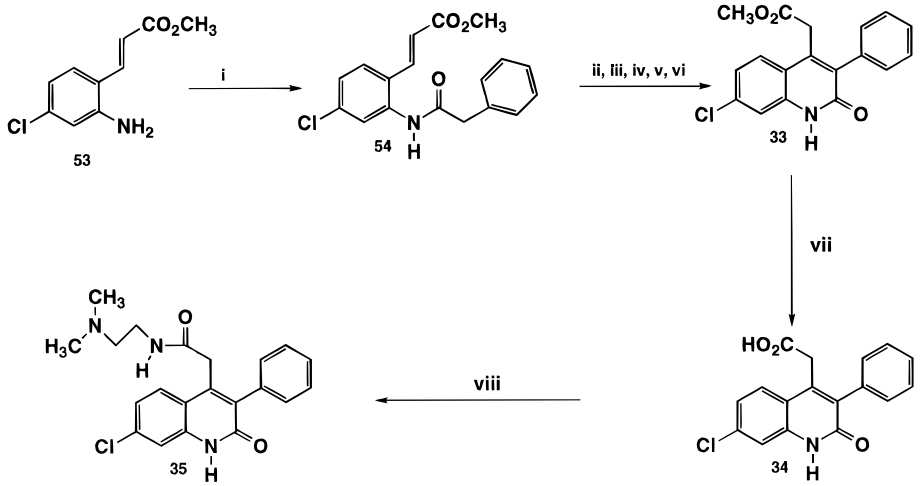
Compounds were routinely evaluated *in vitro* for their ability to displace [^{3}H] L-689,560 from rat cortical membranes (IC_{50} values)[17] and antagonize NMDA responses in a rat cortical slice preparation (apparent K_b values).[18,19] Affinities of test compounds for the glycine site on the NMDA 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 5-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

Scheme 8[a]



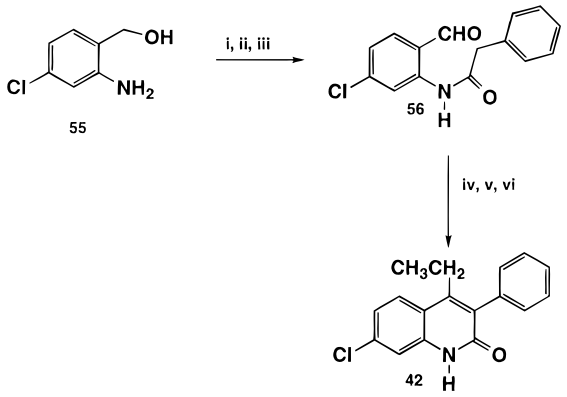
[a] Reagents: (i) $NH_2OH{\cdot}HCl$, $Cl_3CCH(OH)_2$, Na_2SO_4, concd HCl, 1,4-dioxane; (ii) concd H_2SO_4, 80 °C; (iii) $PhCH_2CO_2H$, NaOAc, 220 °C; (iv) CH_2N_2; (v) $SOCl_2$; (vi) $PhCH_2NH_2$, CH_2Cl_2.

Scheme 9[a]



[a] Reagents: (i) $PhCH_2COCl$, $ClCH_2CH_2Cl$, reflux; (ii) KHMDS, THF; (iii) TBDMS-triflate; (iv) KHMDS; (v) PhSeCl; (vi) H_2O_2; (vii) NaOH, MeOH, H_2O; (viii) *N*,*N*-dimethylethylenediamine, $ClCH_2CH_2Cl$, BOP-Cl, Et_3N.

Scheme 10[a]



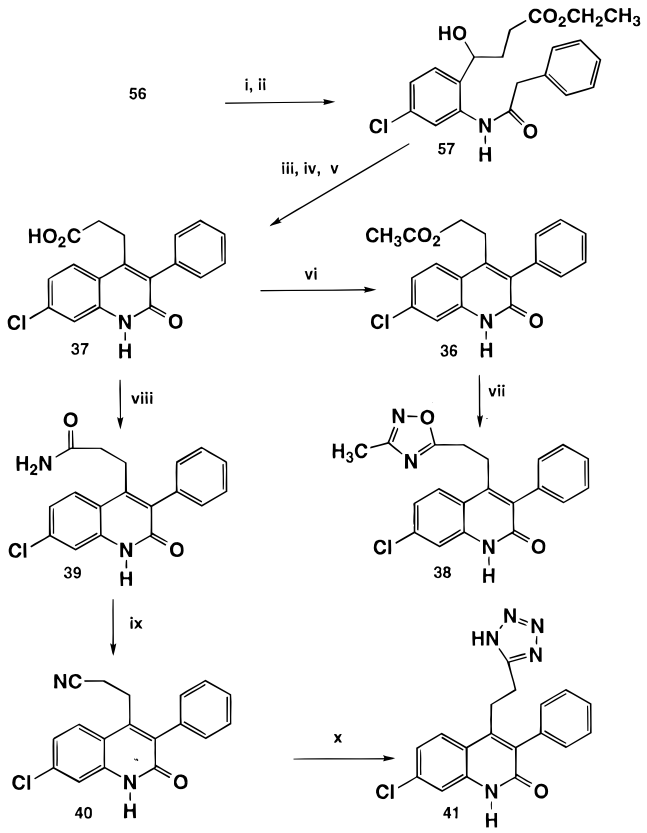
[a] Reagents: (i) $PhCH_2COCl$, Et_3N, $ClCH_2CH_2Cl$; (ii) NaOH, CH_3OH; (iii) PCC, CH_2Cl_2; (iv) EtMgBr, NH_4Cl, THF, 0 °C; (v) PCC, CH_2Cl_2, (vi) NaH, EtOH.

50% at 100 μM (two experiments). Apparent K_b values were calculated from the shift to the right of the NMDA 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).[4] 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

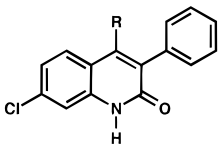
Replacement of the 4-hydroxy group of **1** with amino to give compound **3** results in a 40-fold loss of binding affinity (Table 1). The reduced affinity of **3** is probably a consequence of loss of acidity (pK_a of **1** = 5.4, pK_a of **3** > 11) because the acidic 4-methylsulfonamido derivative **6** (pK_a = 6.0) has comparable affinity to **1**. It is unlikely that the restoration of affinity observed with **6** is a result of a direct interaction of the sulfonyl group with the receptor because the 4-acetylamino compound **4** is less active than the parent 4-amino compound **3**. It is more plausible that the anions generated at the 4-positions of **1** and **6** (Figure 1), at physiological pH, are interacting directly with the receptor as more efficient H-bond acceptors than the 4-amino group of **3**. Introduction of larger acylamino or sulfonylamino groups to the 4-position results in reduced binding activity. Mono- and dimethylation of **3** to give **8** and **9** results in loss of measurable binding affinity, possibly due to conformational constraints making the nitrogen lone pair of each compound less accessible for receptor interaction, thus providing further evidence for a beneficial direct H-bonding interaction between the receptor and groups attached to the 4-position of 3-phenylquinolin-2(1*H*)-

Scheme 11[a]



[a] Reagents: (i) $TiCl_4$, CH_2Cl_2, −78 °C; (ii) 1-ethoxy-1-[(trimethylsilyl)oxy]cyclopropane, −78 °C to rt; (iii) PCC, CH_2Cl_2; (iv) NaOEt, EtOH; (v) NaOH, EtOH·H_2O; (vi) MeOH, HCl; (vii) $CH_3C(NOH)NH_2$, NaH, THF, 60 °C (viii) NH_4OAc, Et_3N, wsCDI, HOBt, THF; (ix) TFAA, Et_3N, THF; (x) NaN_3, Et_3N·HCl, *N*-methylpyrrolidinone.

Table 1



no.	R	IC_{50} (μM) [^{3}H]L-689,560	K_b (μM) vs NMDA	ED_{50} (mg/kg) or prot/tested DBA/2 mouse
1	OH	0.17	0.88	4.5
3	NH_2	6.7	10.5	16.2
4	NHCOMe	14.7		1/8 @ 20 mk/kg
5	$NHCOCH_2Ph$	>100		
6	$NHSO_2Me$	0.27	2.2	0/8 @ 20 mg/kg
7	$NHSO_2Ph$	1.19	2.9	1/8 @ 20 mg/kg
8	NHMe	>100		
9	NMe2	>100		
10	$NHCH_2Ph$	2.0	>3	1/8 @ 20 mg/kg
11	$NH(CH_2)^2$ NMe_2	3.2	12	8/8 @ 100 mg/kg 0/8 @ 20 mg/kg
12	$NH(CH_2)_3NMe_2$	4.2		6/8 @ 100 mg/kg 1/8 @ 50 mg/kg
13	$NHCOCO_2H$	0.58	4.5	0/8 @ 20 mg/kg
14	$NHCOCO_2Me$	2.7		1/8 @ 20 mg/kg
15	NHCOCONH-$(CH_2)_2NMe_2$	25		2/8 @ 20 mg/kg
16	$NHCOCH_2CO_2H$	1.1	11.6	2/8 @ 20 mg/kg
17	H	>100		

ones. Some affinity is regained with the benzylamine analogue **10** and the (*N*,*N*-dimethylamino)ethylamine and (*N*,*N*-dimethylamino)propylamine derivatives **11** and **12** which are all more active than **8**. These results

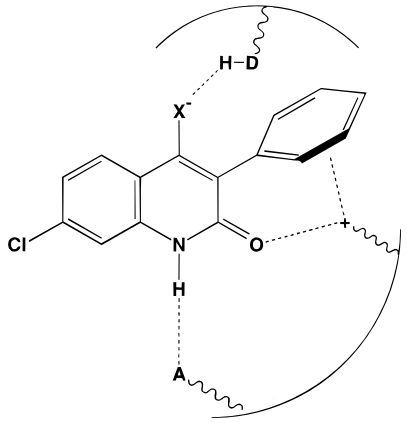
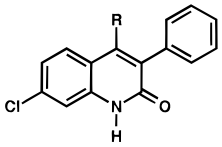


Figure 1. Hypothetical receptor site binding the 3-phenyl-4-substituted-2-quinolone anion. A is a receptor hydrogen bond acceptor, + is a receptor cation, and H−D is a receptor hydrogen bond donor.

Table 2



no.	R	IC_{50} (μM) [^{3}H]-L-689,560	K_b (μM) vs NMDA	ED_{50} (mg/kg) or prot/tested DBA/2 mouse
1	OH	0.17	0.88	4.5
18	OMe	>100		
19	OCH_2CO_2Me	3.2	0.96	1/8 @ 100 mg/kg
20	OCH_2CO_2H	0.11	1.25	3/8 @ 20 mg/kg
21	OCH_2CONMe_2	11.6		
22	OCH_2CONH_2	0.42	3.1	0/8 @ 20 mg/kg
23	OCH_2CN	0.32	4.7	16.3
24	OCH_2Ph	~10		
25	OCH_2-Pyr-2	2.8		1/8 @ 20 mg/kg
26	$O(CH_2)_2NMe_2$	11.0		
27	OCH_2COMe	1.7	11.4	5/8 @ 20 mg/kg
28	$OCH_2C(Me)=NOH$	0.78	2.8	9.4
29	$OCH_2C(Me)=NOMe$	~50		0/8 @ 20 mg/kg

indicate that there is some tolerance for the positioning and type of the purported H-bond-accepting group. Further evidence for this observation is provided by the activity of compounds **13**−**16** where acids, esters, and amides can all act as potential H-bond acceptors. Deletion of the 4-substituent to give **17**[20] produces a completely inactive molecule, thus providing still further evidence for an important ligand/receptor H-bond-accepting interaction adjacent to the 4-position. With the exception of **3**, none of the other compounds in Table 1 show comparable *in vivo* potency to **1** in the DBA/2 mouse audiogenic seizure test. Compound **3** is only 4-fold less active than **1** *in vivo* but has 40-fold lower binding affinity, indicating a 10-fold superior ratio of *in vitro*/*in vivo* activity. This higher than expected *in vivo* activity may well be a consequence of reduced plasma protein binding of **3** in comparison to **1**.[13]

By analogy with N-methylation of **3** to give **8**, O-methylation of **1** to give **18** results in the loss of all measurable affinity (Table 2). Conformational constraints making ligand/receptor hydrogen-bonding interactions less accessible are again a possible explanation. However, the loss of affinity of **18** can also be accounted for by the fact that aryloxy is a relatively poor H-bond acceptor in comparison to arylamine.[21] Also by

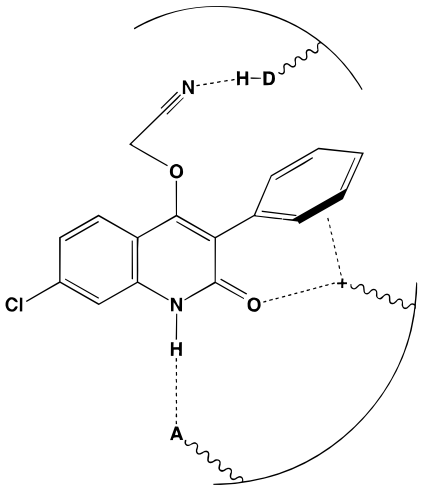
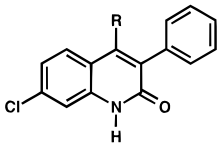


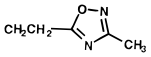
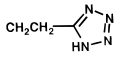
Figure 2. Hypothetical receptor site binding the 3-phenyl-4-[(nitrilomethyl)oxy]-2-quinolone derivative **23**. A is a receptor hydrogen bond acceptor, + is a receptor cation, and H−D is a receptor hydrogen bond donor.

analogy with the results in Table 1, substitution of the methyl group attached to the heteroatom at the 4-position of the quinolone system with potential H-bond-accepting groups results in improved affinity (compounds **19**−**29**). The alkoxy acetic acid **20**, the alkoxy acetamide **22**, and the alkoxy acetonitrile **23** all have comparable binding affinity to **1**. The possibility of conversion of these alkoxy analogues into the active lead compound **1** under the conditions of the binding assay has been discounted by HPLC analysis of the assay solutions. The relatively high affinity of the nitrile (**23**) and amide (**22**) derivatives indicates that when a neutral, efficient hydrogen bond-accepting group is optimally positioned adjacent to the 4-position of 3-phenylquinolin-2(1*H*)-ones, anionic functionality is not a prerequisite for good binding affinity at the glycine site on the NMDA receptor (Figure 2). This result is consistent with the discovery of Nagata et al. [22] who found that high-affinity binding can be obtained in a series of nonacidic tricyclic quinoxalinediones (hybrids of tetrahydroquinolines[23,24] and quinoxalinediones[3,25]). Good affinity in the 3-phenylquinolin-2(1*H*)-one series is also achieved with the ester (**19**), the ketone (**27**), the oxime (**28**), and the 2-pyridine (**25**) derivatives. The benzyl (**24**), the dimethylamide (**21**), the dimethylamine (**26**), and the *O*-methyl oxime (**29**) analogues all have measurable binding affinity but are considerably less active than **1**.

With the exception of the alkoxyacetic acid **20**, all of the new compounds in Table 2 are nonacidic and thus have potential for improved brain penetration in comparison to **1**. All the novel compounds with binding affinity < 10 μM were evaluated in the DBA/2 mouse audiogenic seizure model (Table 2). The alkoxyacetonitrile compound (**23**), the alkoxyacetone derivative (**27**), and the alkoxyacetoxime analogue (**28**) all possess significant anticonvulsant activity, with **28** (ED_{50} = 9.4 mg/kg) having one-half the potency of **1**. The possibility of metabolism of **23**, **27**, or **28** giving rise to **1** *in vivo* cannot be completely discounted as an explanation for the anticonvulsant activity of these compounds, but lower affinity compounds (i.e., **19**, **25**, and **29**), which have the same potential for cleavage to **1**, do not have significant *in vivo* activity.

Table 3

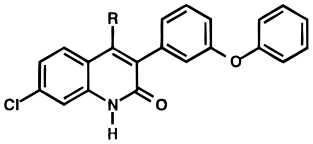


no.	R	IC_{50} (μM) [^{3}H]L-689,560	K_b (μM) vs NMDA	ED_{50} (mg/kg) or prot/tested DBA/2 mouse
1	OH	0.17	0.88	4.5
30	CO_2Me	69% @ 10 μM		
31	CO_2H	0.9	1.3	1/8 @ 20 mg/kg
32	$CONHCH_2Ph$	>100		
33	CH_2CO_2Me	1.1	4.0	1/8 @ 20 mg/kg
34	CH_2CO_2H	0.16	1.4	0.8 @ 20 mg/kg
35	$CH_2CONH(CH_2)_2NMe_2$	29% @ 10 μM		0/8 @ 20 mg/kg
36	$CH_2CH_2CO_2CH_3$	0.5	4.6	0.8 @ 20 mg/kg
37	$CH_2CH_2CO_2H$	0.17	2.2	1/8 @ 20 mg/kg
38		3.5		4/8 @ 20 mg/kg
39	$CH_2CH_2CONH_2$	0.19	2.9	1/8 @ 20 mg/kg
40	CH_2CH_2CN	0.75	>10	0/8 @ 20 mg/kg
41		0.24	1.6	0/8 @ 100 mg/kg
42	Et	>100		

Replacement of the ionizable oxygen at the 4-position of **1** with a carboxylate group, to give **31**, results in only 5-fold loss of affinity (Table 3), again indicating some tolerance for the positioning of the H-bond-accepting group. The corresponding methyl ester **30** is 1 order of magnitude less active, while the benzylamide **32** is essentially inactive. The homologated acid **34** is equiactive with **1** in the binding assay, but the corresponding methyl ester **33** is again 10-fold lower in affinity. The (*N*,*N*-dimethylamino)ethylamide **35**, which was prepared with a view toward improving aqueous solubility, is significantly less active. Further homologation to the propionic acid **37** again results in a compound with identical binding affinity to **1**. In this case the corresponding methyl ester **36** is almost equally active with the acid **37**, providing further evidence that when an efficient H-bond-accepting group is optimally positioned, acidity is not an absolute requirement for binding to the glycine site on the NMDA receptor. The neutral methyloxadiazole **38**[26] is 1 order of magnitude less active than **1**, but the nonacidic carboxamide **39** is equally active. The nonionizable nitrile **40** has marginally reduced affinity, while the acidic tetrazole **41** has similar activity to **1**. Further support for the purported H-bond-accepting interaction between the ligand and the receptor is provided by the lack of affinity of the 4-ethyl analogue **42**. With the exception of the weakly active oxadiazole **38** (ED_{50} ~20 mg/kg), none of the compounds in Table 3 have a significant anticonvulsant effect. The poor anticonvulsant activity of the neutral nitrile **40** is difficult to account for, but the weak *in vivo* activities of the predictably poor brain-penetrating acidic analogues **31**, **34**, **37**, and **41**, the metabolically labile esters **30**, **33**, and **36**, and the high-H-bonding capacity amide[27] **39** are not surprising.

By analogy with the 100-fold improvement of affinity[7] observed on introduction of a *m*-phenoxy substituent to the 3-phenyl group of **1** to give **2**, the corresponding change to the 4-amino compound **3** to give **43** results in only 10-fold improved affinity (Table 4). The same

Table 4



no.	R	IC_{50} (μM) [^{3}H]L-689,560	K_b (μM) vs NMDA	ED_{50} (mg/kg) or prot/tested DBA/2 mouse
2	OH	0.002	0.028	0.9
43	NH_2	0.42	3.4	2/8 @ 20 mg/kg
44	OCH_2CN	1.2	insoluble	8/8 @ 20 mg/kg 1/8 @ 10 mg/kg
45	OCH_2CO_2H	0.024	0.56	0/8 @ 20 mg/kg

change to the 4-oxyacetic acid derivative **20** to give **45** improves activity by 5-fold, but the analogous change to the 4-oxyacetonitrile derivative **23** to give **44** effects a reduction in binding affinity. These results indicate that the ligand-binding interactions of acidic and nonacidic 4-substituted-3-phenylquinolin-2(1*H*)-one glycine antagonists are subtly different. Of the new compounds in Table 4, only the relatively weak binding 4-alkoxyacetonitrile analogue **44** has significant anticonvulsant activity (ED_{50} = 10−20 mg/kg). As in the case of the corresponding 3-phenyl derivative **23**, the possibility of metabolism of **44** to **2** cannot be completely ruled out, but the oxyacetic acid **45**, which also has potential for *in vivo* conversion to **2**, is inactive.

Conclusions

We have demonstrated that anionic functionality, previously believed to be a prerequisite for all glycine/NMDA site antagonists, is not absolutely essential for good affinity binding in 4-substituted-3-phenylquinolin-2(1*H*)-ones. This finding is in accord with the work on tricyclic quinoxalines of Nagata et al.[22] We have also shown that neutral substituents attached to the 4-position of 3-phenylquinolin-2(1*H*)-ones are more sensitive to their relative positioning than carboxylate groups since acids **1**, **13**, **20**, **31**, and **34** are all essentially equipotent. *In vivo* activity comparable with that observed for **1** is achieved with the 4-alkoxyacetonitrile (**23**) and the 4-alkoxyacetoxime (**28**) analogues, but the possibility of these compounds being elaborate prodrugs for **1** cannot be completely discounted. The results described in this present work support our previously proposed pharmacophore models for the binding of 3-phenylquinolin-2(1*H*)-ones to the glycine site on the NMDA receptor.[3,8,10] For the binding of 4-substituted-3-phenylquinolin-2(1*H*)-ones to the glycine site on the NMDA receptor, we can categorically invoke a key ligand/receptor hydrogen bond interaction between an acceptor attached to the 4-position of the ligand and a hydrogen bond donor attached to the receptor. This model accounts for the binding of both anions (Figure 1) and nonacidic compounds (Figure 2), but the results in Table 4 indicate that the binding modes of neutral and acidic ligands are probably subtly different. These results clearly extend current views of structural requirements and tolerance for binding to the glycine site on the NMDA receptor.

Experimental Section

General directions have appeared previously.[28]

4-Amino-7-chloro-3-phenyl-2(1*H*)-quinolone (3). Methyl 2-amino-4-chlorobenzoate (**46**; 20 g, 107 mmol) was heated at 150 °C in methanol (300 mL), which had been presaturated with ammonia, in an autoclave for 3 days. After cooling and evaporation of the solvent a brown solid was obtained. This was triturated with diethyl ether and collected by filtration to give a solid which was suspended in 1 N sodium hydroxide and subjected to ultrasound for 15 min. After collection by filtration, the solid was washed with deionized water and dried in a vacuum oven to give 2-amino-4-chlorobenzamide (11.2 g, 61%). Triethylamine (34 mL, 245 mmol) was added to a solution of the amide (9.5 g, 56 mmol) at 0 °C in THF (200 mL) followed by trifluoroacetic anhydride (20.5 mL, 145 mmol) in THF (50 mL). After 30 min water (200 mL) was added, and the mixture was extracted with Et_2O (2 × 200 mL). The Et_2O layer was dried ($MgSO_4$), filtered, and evaporated to leave a residue which was dissolved in 50% aqueous methanol (200 mL) with potassium carbonate (15 g). The mixture was heated at 70 °C for 24 h, cooled, extracted with EtOAc (2 × 200 mL), washed with water (1 × 100 mL) and brine (1 × 100 mL), dried ($MgSO_4$), filtered, and evaporated to give 2-amino-4-chlorobenzonitrile (**47**; 8.8 g, 88%): NMR ($CDCl_3$) δ 4.47 (2 H, br, s, NH_2), 6.72 (1 H, dd, J = 11.9, 2.6 Hz, H-5), 6.75 (1 H, d, J = 2.6 Hz, H-3), 7.31 (1 H, d, J = 11.9 Hz, H-6); MS (CI^+, NH_3) m/z = 152 ($M^+ + H$).

The nitrile (0.9 g, 5.9 mmol) and phenylacetyl chloride (0.78 mL, 5.9 mmol) were heated together under reflux in dichloromethane (40 mL) for 16 h. The reaction mixture was allowed to cool and then evaporated to leave a residue which was recrystallized from MeOH to give the amide **48** (0.7 g, 44%). Compound **48** (0.7 g, 2.6 mmol) was dissolved in DMF (20 mL) with sodium hydride (0.23 g of an 80% dispersion in oil, 8 mmol) and heated at 100 °C for 3 h. After cooling to room temperature, the reaction mixture was poured into H_2O (150 mL), and the solid that was precipitated was collected by filtration. Recrystallization from DMF/H_2O gave **3** (0.23 g, 33%) as white crystals: mp 337−338 °C; NMR (DMSO) δ 5.96 (2 H, br, s, NH_2), 7.14−8.04 (8 H, m, ArH), 11.1 (1 H, br, s, NH); MS (EI) m/z = 270 (M^+). Anal. ($C_{15}H_{11}ClN_2O$) C, H, N.

4-Acetamido-7-chloro-3-phenyl-2(1*H*)-quinolone (4). A solution of **3** (0.3 g, 1.1 mmol) in THF (30 mL) was treated with sodium hydride (0.2 g of an 80% dispersion in oil, 7 mmol) and stirred at room temperature for 1 h. After this time acetyl chloride (0.7 mL, 9.7 mmol) was added, and after a further 2 h at ambient temperature, the reaction mixture was heated under reflux for 14 h. After cooling, the reaction mixture was partitioned between EtOAc (2 × 100 mL) and H_2O (1 × 50 mL). The combined organic layers were dried ($MgSO_4$) and filtered and the solvents removed under vacuum. The residue was suspended in 1 N NaOH (20 mL) and placed in an ultrasound bath for 5 min. The aqueous phase was washed with Et_2O (2 × 20 mL), and the separated aqueous layer was acidified to pH 1 with concentrated hydrochloric acid to produce a residue which was collected by filtration to give **4** (0.08 g, 23%) as white crystals: mp 275−277 °C; NMR (DMSO) δ 1.88 (3 H, s, CH_3CO), 7.22−7.58 (8 H, m, ArH), 9.69 (1 H, br, s, NH), 12.06 (1 H, br, s, NH); MS (EI) m/z = 312 (M^+). Anal. ($C_{17}H_{13}ClN_2O_2 \cdot 2H_2O$) C, H, N.

4-(Phenylacetamido)-7-chloro-3-phenyl-2(1*H*)-quinolone (5). Treatment of **3** under the same conditions described for the synthesis of **4**, but using phenylacetyl chloride instead of acetyl chloride, gave **5** (0.12 g, 21%) as white crystals: mp 295 °C; NMR (DMSO) δ 3.53 (2 H, s, $PhCH_2$-CO), 7.04 (2 H, d, J = 6.0 Hz, ArH's), 7.20 (6 H, m, H-6, ArH's), 7.33 (3 H, m, ArH's), 7.38 (1 H, d, J = 2Hz, H-8), 7.48 (1 H, d, J = 8.7 Hz, H-5), 9.92 (1 H, br, s, 4-NH), 12.10 (1 H, br, s, 1-NH); MS (EI) m/z = 388 (M^+). Anal. ($C_{23}H_{17}ClN_2O_2 \cdot 0.2H_2O$) C, H, N.

7-Chloro-4-[(methylsulfonyl)amino]-3-phenyl-2(1*H*)-quinolone (6). To a solution of **3** (0.55 g, 2 mmol) in THF (50 mL) at room temperature was added potassium bis-(trimethylsilyl)amide (4 mL of a 0.5 M solution in toluene, 2 mmol). After 10 min, *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.47 mL, 2 mmol) was added, and after a further 10 min, potassium bis(trimethylsilyl)amide (6 mL of a 0.5 M solution in toluene, 3 mmol) was added. After a further 10

min methanesulfonyl chloride (0.48 mL, 6 mmol) was added and the reaction mixture was allowed to stir for 1 h. The solvents were removed under vacuum, and the residue was suspended in 5 M HCl and treated with ultrasound for 10 min before being collected by filtration. The solid was suspended in 1 N NaOH solution (50 mL) and re-exposed to ultrasound for 20 min. The suspension was filtered, and the mother liquors were acidified to pH 1 with 5 N HCl to precipitate a solid which was collected by filtration. Recrystallization from DMF/H_2O gave **6** (0.077 g, 11%) as white crystals: mp 222 °C; NMR (DMSO) δ 2.17 (3 H, s, CH_3), 7.34−7.67 (8 H, m, ArH's), 9.60 (1 H, br, s, 4-NH), 12.16 (1 H, s, br, s, 1-NH); MS (EI) m/z = 348 (M^+). Anal. ($C_{16}H_{13}ClN_2O_3S\cdot0.5H_2O$) C, H, N.

7-Chloro-4-[(phenylsulfonyl)amino]-3-phenyl-2(1*H*)-quinolone (7). Treatment of **3** under the same conditions described for the synthesis of **6**, but using benzenesulfonyl chloride instead of methanesulfonyl chloride, gave **7** (0.05 g, 3%) as white crystals: mp 268 °C; NMR (DMSO) δ 7.14 (6 H, m, ArH's), 7.32 (5 H, m, ArH's), 7.49 (1 H, m, ArH's), 7.67 (1 H, d, J = 8.7 Hz, H-5), 10.02 (1 H, br, s, 4-NH), 12.15 (1 H, br, s, 1-NH); MS (EI) m/z = 410 (M^+). Anal. ($C_{21}H_{15}ClN_2O_3S$) C, H, N.

7-Chloro-4-(methylamino)-3-phenyl-2(1*H*)-quinolone (8). To a solution of **3** (0.5 g, 1.8 mmol) in THF (30 mL) was added potassium bis(trimethylsilyl)amide (4.05 mL of a 0.5 M solution in toluene, 2 mmol), and the reaction mixture was allowed to stir for 10 min before the addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.5 mL, 2.2 mmol). After 30 min a further portion of potassium bis(trimethylsilyl)amide (4.05 mL of a 0.5 M solution in toluene, 2 mmol) was added; then after a further 15 min methyl iodide (0.35 mL, 3.6 mmol) was added, and the reaction mixture was allowed to stir for 14 h. Triethylamine (2 mL) was added, and after 1 h the reaction mixture was poured into 1 N HCl (30 mL) and stirred for 30 min. The solution was extracted with EtOAc (3 × 50 mL), washed with H_2O (1 × 50 mL) and brine (1 × 50 mL), and then dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel using 20−60% ethyl acetate in hexane as eluent and then further purified by preparative HPLC on a Dynamax 300A reverse phase column using 35% acetonitrile/1% trifluoroacetic acid in H_2O to give after freeze-drying compound **8** (0.18 g, 35%) as a white solid: mp 275 °C dec; NMR (DMSO) δ 2.24 (3 H, d, J = 4.9 Hz, CH_3), 6.45 (1 H, m, 4-NH), 7.17 (1 H, dd, J = 8.8, 2.2 Hz, 6-H), 7.21−7.36 (6 H, m, ArH's), 8.00 (1 H, d, J = 2.2 Hz, 8-H), 11.09 (1 H, s, 1-NH); MS (EI) m/z = 285 (M^+). Anal. ($C_{16}H_{13}ClN_2O$) C, H, N.

7-Chloro-4-(dimethylamino)-3-phenyl-2(1*H*)-quinolone (9). Treatment of **3** under the same conditions described for the synthesis of **8**, but using 3 equiv of methyl iodide instead of 2 equiv, gave, after a similar purification procedure, **9** (0.048 g, 9%) as a white solid: mp 270−272 °C dec; NMR (DMSO) δ 2.50 (6 H, s, $(CH_3)_2N$), 7.19−7.42 (7 H, m, ArH's), 7.79 (1 H, d, J = 8.7 Hz, 8-H), 11.64 (1 H, br s, 1-NH); MS (EI) m/z = 299 (M^+). Anal. ($C_{17}H_{15}ClN_2O$) C, H, N.

7-Chloro-4-(benzylamino)-3-phenyl-2(1*H*)-quinolone (10). Compound **1** (0.5 g, 1.8 mmol) was dissolved in benzylamine (20 mL) and heated under reflux for 24 h. Excess benzylamine was removed under high vacuum, and the residue was triturated with diethyl ether to produce a solid which was removed by filtration. The filtrate was evaporated, and the residue obtained was purified by chromatography on silica gel using 25% ethyl acetate in dichloromethane as eluent to give **10** (0.045 g, 7%) as a white solid: mp 179 °C; NMR (DMSO) δ 3.81 (2 H, d, J = 4.8 Hz, $PhCH_2N$), 6.67 (1 H, t, J = 4.8 Hz, 4-NH), 6.85 (2 H, d, J = 6.5 Hz, *ortho* ArH's), 7.10−7.33 (11 H, ArH's), 11.23 (1 H, br, s, 1-NH); MS (EI) m/z = 360 (M^+). Anal. ($C_{22}H_{17}ClN_2O\cdot0.1H_2O$) C, H, N.

4-[[2-(*N*,*N*-Dimethylamino)ethyl]amino]-7-chloro-3-phenyl-2(1*H*)-quinolone (11). Treatment of **1** (1 g, 3.6 mmol) under the same conditions described for the synthesis of **10**, but using (*N*,*N*-dimethylamino)ethylamine instead of benzylamine and carrying out the reaction in a sealed tube at 180 °C for 10 days, gave, after recrystallization from EtOAc, **11** (0.25 g, 20%) as white crystals: mp 230 °C; NMR (DMSO) δ 1.94 (6 H, s, $(CH_3)_2N$), 2.17 (2 H, m, NCH_2CH_2N), 2.69 (2 H, m, NCH_2CH_2N), 5.82 (1 H, br, s, 4-NH), 7.17−7.95 (8 H, m, ArH's), 11.23 (1 H, br, s, 1-NH); MS (EI) m/z = 341 (M^+). Anal. ($C_{19}H_{20}ClN_3O\cdot0.9H_2O$) C, H, N.

4-[[3-(*N*,*N*-Dimethylamino)propyl]amino]-7-chloro-3-phenyl-2(1*H*)-quinolone (12). Treatment of **1** (1 g, 3.6 mmol) under the same conditions described for the synthesis of **10**, but using 3-(*N*,*N*-dimethylamino)propylamine instead of benzylamine and carrying out the reaction in a sealed tube at 180 °C for 10 days, gave, after recrystallization from Et_2O, **12** (0.09 g, 7%) as white crystals: mp 177−179 °C; NMR (DMSO) δ 1.38 (2 H, m, $NCH_2CH_2CH_2N$), 1.98 (2 H, m, $NCH_2CH_2CH_2N$), 2.04 (6 H, s, $(CH_3)_2N$), 2.58 (2 H, m, $NCH_2CH_2CH_2N$), 6.58 (1 H, m, 1-NH), 7.19−7.94 (8 H, m, ArH's), 11.15 (1 H, br, s, 1-NH); MS (EI) m/z = 355 (M^+). Anal. ($C_{20}H_{22}ClN_3O$) C, H, N.

4-[(Carboxycarbonyl)amino]-7-chloro-3-phenyl-2(1*H*)-quinolone (13). Treatment of **3** under the same conditions described for the synthesis of **4**, but using ethyloxalyl chloride instead of acetyl chloride, gave **13** (0.1 g, 26%) as white crystals: mp 240 °C (dec); NMR (DMSO) δ 7.25−7.41 (7 H, m, ArH's), 7.59 (1 H, d, J = 8.7 Hz, 5-H), 10.63 (1 H, s, 4-NH), 12.20 (1 H, s, 1-NH); MS (CI^+) m/z = 343 (M^+). Anal. ($C_{17}H_{11}ClN_2O_4\cdot0.5H_2O$) C, H, N.

7-Chloro-4-[[(methoxycarbonyl)carbonyl]amino]-3-phenyl-2(1*H*)-quinolone (14). Treatment of **13** (0.34 g, 1 mmol) with MeOH (50 mL that had been presaturated with dry hydrogen chloride) for 14 h followed by evaporation and purification of the residue by chromatography on silica gel (using 30−100% ethyl acetate in petroleum ether as eluent) and recrystallization from MeOH/H_2O gave **14** (0.1 g, 29%) as white crystals: mp 254 °C dec; NMR (DMSO) δ 3.77 (3 H, s, CH_3), 7.25−7.42 (7 H, m, ArH's), 7.65 (1 H, d, J = 8.7 Hz, 6-H), 10.71 (1 H, br, s, 4-NH), 12.20 (1 H, s, 1-NH); MS (CI^+) m/z = 357 (M^+). Anal. ($C_{18}H_{13}ClN_2O_4\cdot1.1H_2O$) C, H, N.

7-Chloro-4-[[[[2-(*N*,*N*-dimethylamino)ethyl]amino]carbonyl]carbonyl]amino]-3-phenyl-2(1*H*)-quinolone (15). After treatment of **14** (0.35 g, 1 mmol) with 2-(*N*,*N*-dimethylamino)ethylamine (70 mL) at room temperature for 3 h, the solvent was removed under vacuum. The residue was triturated with ethanol and filtered, and the filtrate was concentrated under vacuum. The residue was dissolved in 1 N HCl (30 mL), and the aqueous solution was washed with EtOAc (2 × 20 mL). The water layer was then basified to pH 14 with 1 N NaOH solution and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum. Recrystallization from EtOAc gave **15** (0.12 g, 29%) as white crystals: mp 217−220 °C; NMR (DMSO) δ 2.15 (6 H, s, $N(CH_3)_2$), 2.34 (2 H, t, J = 6.5 Hz, $CH_2CH_2N(CH_3)_2$), 3.19 (2 H, m, $CH_2CH_2N(CH_3)_2$), 7.25−7.50 (8 H, m, ArH's), 8.55 (1 H, t, m, $NHCH_2CH_2N(CH_3)_2$), 10.65 (1 H, br, s, 4-NH), 12.20 (1 H, br, s, 1-NH); MS (CI^+) m/z = 413 (M^+). Anal. ($C_{21}H_{21}ClN_4O_3\cdot0.3H_2O$) C, H, N.

4-[[(Carboxymethylene)carbonyl]amino]-7-chloro-3-phenyl-2(1*H*)-quinolone (16). Treatment of **3** under the same conditions described for the synthesis of **4**, but using ethylmalonyl chloride instead of acetyl chloride, gave **16** (0.05 g, 7%) as white crystals: mp 260 °C dec; NMR (DMSO) δ 3.33 (2 H, s, CH_2CO_2H), 7.22−7.76 (7 H, m, ArH's), 7.87 (1 H, d, J = 8.4 Hz, 5-H), 9.97 (1 H, br, s, 4-NH), 12.13 (1 H, br, s, 1-NH), 12.62 (1 H, br, s, CO_2H); MS (CI^+) m/z = 357 (M^+). Anal. ($C_{18}H_{13}ClN_2O_4$) C, H, N.

7-Chloro-4-methoxy-3-phenyl-2(1*H*)-quinolone (18). To an ice-cooled solution of diazomethane (16 mmol) in Et_2O (50 mL) was added a suspension of **1** (3 g, 10.8 mmol) in THF (200 mL), and the reaction mixture was stirred at room temperature for 2 h. After this time, dry nitrogen was bubbled through the suspension for 30 min, and a solid was collected by filtration. Recrystallization from DMF/H_2O gave **18** (0.28 g, 9%) as white crystals: mp 270−272 °C; NMR (DMSO) δ 3.45 (3 H, s, CH_3), 7.25 (1 H, dd, J = 8.6, 2.1 Hz, 6-H), 7.35−7.46 (6 H, m, ArH's), 7.82 (1 H, d, J = 2.1 Hz, 8-H), 11.87 (1 H, br, s, NH); MS (CI^+) m/z = 286 (M^+). Anal. ($C_{16}H_{12}ClNO_2$) C, H, N.

7-Chloro-4-[(methoxycarbonyl)methoxy]-3-phenyl-2(1*H*)-quinolone (19). To a solution of **1** (0.5 g, 1.8 mmol) in DMF (30 mL) were added sodium hydrogen carbonate (1.55 g, 10 mmol) and sodium iodide (0.2 g, 1.3 mmol) followed by methyl bromoacetate (0.21 mL, 2.2 mmol), and the reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was poured into H_2O (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with H_2O (1 × 100 mL) and brine (1 × 100 mL) and then dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was recrystallized from EtOAc/hexane to give **19** (0.28 g, 9%) as white crystals: mp 188−191 °C; NMR (DMSO) δ 3.55 (3 H, s, CO_2CH_3), 4.19 (2 H, s, CH_2-CO_2CH_3), 7.28 (1 H, dd, J = 8.7, 2.6 Hz, 6-H), 7.35−7.40 (6 H, m, ArH's), 8.01 (1 H, d, J = 8.7 Hz, 5-H), 11.92 (1 H, s, NH); MS (CI^+) m/z = 344 (M^+). Anal. ($C_{18}H_{14}ClNO_4$) C, H, N.

4-(Carboxymethoxy)-7-chloro-3-phenyl-2(1*H*)-quinolone (20). To a solution of **19** (0.13 g, 0.3 mmol) in THF (50 mL) was added lithium hydroxide (18.2 mL of a 0.5 N solution in H_2O, 0.91 mmol), and the reaction mixture was stirred at room temperature for 30 min. The solvent was removed under vacuum and the residue obtained was dissolved in H_2O (20 mL). Acidification to pH 1 using 1 N hydrochloric acid resulted in a precipitate which was collected by filtration and recrystallized from DMF/H_2O to give **20** (0.023 g, 23%) as white crystals: mp 269−272 °C; NMR (DMSO) δ 4.05 (2 H, s, CH_2), 7.29 (1 H, dd, J = 8.7, 2.7 Hz, 6-H), 7.35−7.47 (6 H, m, ArH's), 8.07 (1 H, d, J = 8.7 Hz, 5-H), 11.68 (1 H, s, NH); MS (CI^+) m/z = 328 (M^+). Anal. ($C_{17}H_{12}ClNO_4$) C, H, N.

7-Chloro-4-[[(*N*,*N*-dimethylamino)carbonyl]methoxy]-3-phenyl-2(1*H*)-quinolone (21). To a saturated solution of dimethylamine in methanol (200 mL) at 0 °C was added **19** (0.3 g, 0.87 mmol). After 5 days in a sealed flask at room temperature, the solvent was removed under vacuum and the residue obtained was recrystallized from MeOH/EtOAc to give **21** (0.21 g, 60%) as white crystals: mp 232−234 °C; NMR (DMSO) δ 2.42 (3 H, s, OCH_2 $N(CH_3)CH_3$), 2.69 (3 H, s, $OCH_2N(CH_3)CH_3$), 4.30 (2 H, s, $OCH_2N(CH_3)CH_3$), 7.24 (1 H, dd, J = 8.6, 2.1 Hz, 6-H), 7.32−7.47 (6 H, m, ArH's), 7.98 (1 H, d, J = 8.6 Hz, 5-H), 11.83 (1 H, s, NH); MS (CI^+) m/z = 403 (M^+). Anal. ($C_{19}H_{17}ClN_2O_3$) C, H, N.

4-[(Aminocarbonyl)methoxy]-7-chloro-3-phenyl-2(1*H*)-quinolone (22). To a solution of **20** (0.93 g, 2.8 mmol) in THF (50 mL) were added triethylamine (1.9 mL, 4.1 mmol), ammonium acetate (0.5 g, 1.8 mmol), 1-hydroxybenzotriazole (0.6 g, 1.3 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (0.9 g, 1.3 mmol). After stirring at room temperature for 3 days, the reaction mixture was poured into H_2O (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with 1 N citric acid solution (1 × 75 mL), H_2O (1 × 75 mL), saturated sodium hydrogen carbonate solution (1 × 75 mL), and brine (1 × 75 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under vacuum. Recrystallization of the residue from MeOH gave **22** (0.29 g, 32%) as white crystals: mp 232−234 °C; NMR (DMSO) δ 3.91 (2 H, s, OCH_2CONH_2), 7.25−7.45 (9 H, m, 7 × ArH's and NH_2), 8.01 (1 H, d, J = 8.7 Hz, 5-H), 11.92 (1 H, br, s, NH); MS (CI^+) m/z = 329 (M^+). Anal. ($C_{17}H_{13}ClN_2O_3$) C, H, N.

7-Chloro-4-(cyanomethoxy)-3-phenyl-2(1*H*)-quinolone (23). Treatment of **1** under the same conditions described for the synthesis of **19**, but using bromoacetonitrile instead of methyl bromoacetate, gave **23** (0.15 g, 26%) as white crystals: mp 209−211 °C; NMR (DMSO) δ 4.59 (2 H, s, OCH_2-CN), 7.31 (1 H, dd, J = 8.6, 2.1 Hz, 6-H), 7.40−7.49 (6 H, m, ArH's), 7.83 (1 H, d, J = 8.6 Hz, 5-H), 12.10 (1 H, br, s, NH); MS (EI) m/z = 311 (M^+). Anal. ($C_{17}H_{11}ClN_2O_2$) C, H, N.

7-Chloro-4-(benzyloxy)-3-phenyl-2(1*H*)-quinolone (24). Treatment of **1** under the same conditions described for the synthesis of **19**, but using benzyl bromide instead of methyl bromoacetate, gave **24** (0.078 g, 12%) as white crystals: mp 167 °C sub, 211 °C; NMR (DMSO) δ 4.56 (2 H, s, OCH_2Ph), 7.10−7.48 (12 H, m, ArH's), 7.76 (1 H, d, J = 8.6 Hz, 8-H), 11.94 (1 H, br, s, NH); MS (CI^-) m/z = 310 (M^+). Anal. ($C_{22}H_{16}ClNO_2$) C, H, N.

7-Chloro-4-(2-pyridyloxy)-3-phenyl-2(1*H*)-quinolone (25). Treatment of **1** under the same conditions described for the synthesis of **19**, but using 2-picolyl chloride hydrochloride instead of methyl bromoacetate, gave **25** (0.33 g, 25%) as white crystals: mp 143 °C sub, 170 °C; NMR (DMSO) δ 4.64 (2 H, s, OCH_2), 7.22−7.47 (9 H, m, ArH's), 7.74−7.83 (2 H, m, ArH's), 8.45 (1 H, d, J = 4.1 Hz, 6-Pyr-H), 11.95 (1 H, s, NH); MS (EI) m/z = 363 (M^+). Anal. ($C_{21}H_{15}ClN_2O_2$) C, H, N.

7-Chloro-4-[[2-(*N*,*N*-dimethylamino)ethyl]oxy]-3-phenyl-2(1*H*)-quinolone (26). Treatment of **1** (5 g, 18 mmol) under the same conditions described for the synthesis of **19**, but using allyl bromide instead of methyl bromoacetate, gave **49** (2.8 g, 50%) as white crystals: NMR (DMSO) δ 4.04 (2 H, dd, J = 6.5, 1.8 Hz, $OCH_2CH{=}CH_2$), 5.08 (2 H, m, OCH_2-$CH{=}CH_2$), 5.88 (1 H, m, $OCH_2CH{=}CH_2$), 7.23 (1 H, dd, J = 8.6, 2.1 Hz, 6-H), 7.36 (6 H, m, ArH's), 7.81 (1 H, d, J = 8.6 Hz, 5-H), 11.94 (1 H, br, s, NH).

Ozone was passed through a solution of **49** (0.3 g, 0.96 mmol) in dichloromethane (50 mL) for 15 min (solution changed to a blue color). The reaction mixture was allowed to warm to room temperature and stirred for 1 h before the addition of dimethyl sulfide (0.5 mL). After a further 30 min the solvent was removed under vacuum to leave a solid which was dissolved in MeOH (50 mL) with dimethylamine hydrochloride (0.4 g, 4.9 mmol) and sodium cyanoborohydride (0.06 g, 1 mmol). The reaction mixture was stirred at room temperature for 16 h; then the mixture was adjusted to pH 5 with 1 N NaOH solution, and the solution was extracted with EtOAc (3 × 50 mL). The combined organic layers were extracted with 1 N HCl (1 × 100 mL), and the aqueous layer was washed with ethyl acetate (2 × 50 mL). The water solution was readjusted to pH 9 with 1 N NaOH solution, and the solution was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solid was removed under vacuum to leave a solid which was recrystallized from EtOAc/hexane to give **26** (0.03 g, 10%) as white crystals: mp 185−187 °C; NMR (DMSO) δ 2.00 (6 H, s, 2 × NCH_3), 2.33 (2 H, t, J = 5.8 Hz, OCH_2CH_2N), 3.55 (2 H, t, J = 5.8 Hz, OCH_2CH_2N), 7.24 (1 H, dd, J = 9.3, 2.1 Hz, 6-H), 7.35−7.46 (6 H, m, ArH's), 7.91 (1 H, d, J = 9.3 Hz, 5-H), 11.67 (1 H, br, s, NH); MS (CI^+) m/z = 343 (M^+). Anal. ($C_{19}H_{19}$-$ClN_2O_2 \cdot 0.1C_6H_{14} \cdot 0.6H_2O$) C, H, N.

7-Chloro-3-phenyl-4-(2-oxopropoxy)-2(1*H*)-quinolone (27). Treatment of **1** under the same conditions described for the synthesis of **19**, but using chloroacetone instead of methyl bromoacetate, gave **27** (0.39 g, 66%) as white crystals: mp 185−186 °C; NMR (DMSO) δ 1.84 (3 H, s, CH_3CO), 4.26 (2 H, s, CH_2), 7.26 (1 H, dd, J = 8.7, 2.1 Hz, 6-H), 7.30−7.46 (6 H, m, ArH's), 8.02 (1 H, d, J = 8.7 Hz, 5-H), 11.90 (1 H, br, s, NH); MS (CI^+) m/z = 328 (M^+). Anal. ($C_{18}H_{14}ClNO_2$) C, H, N.

7-Chloro-3-phenyl-4-(2-oximinopropoxy)-2(1*H*)-quinolone (28). To a solution of **27** (0.5 g, 1.5 mmol) in pyridine (10 mL) were added hydroxylamine hydrochloride (0.63 g, 9.3 mmol) and 4 Å molecular sieves (0.3 g), and the reaction mixture was heated at 60 °C for 24 h. The mixture was diluted with EtOAc (100 mL) and filtered through celite. The solution was washed with 1 N HCl (1 × 100 mL), H_2O (1 × 20 mL), and saturated sodium hydrogen carbonate solution (1 × 20 mL) and then dried ($MgSO_4$), filtered, and concentrated under vacuum to leave a residue which was recrystallized from EtOH/H_2O to give **28** (0.28 g, 54%) as white crystals: mp 196−198 °C; NMR (DMSO) δ 1.60 (3 H, s, CH_3), 4.06 (2 H, s, CH_2), 7.28 (1 H, dd, J = 8.6, 2.1 Hz, 6-H), 7.32−7.48 (6 H, m, ArH's), 7.78 (1 H, d, J = 8.6 Hz, 5-H), 10 88 (1 H, s, NOH), 11.92 (1 H, br, s, NH); MS (CI^+) m/z = 343 (M^+). Anal. ($C_{18}H_{15}ClN_2O_3$) C, H, N.

7-Chloro-3-phenyl-4-[2-(*O*-methyloximino)propoxy]-2(1*H*)-quinolone (29). Treatment of **27** under the same conditions described for the synthesis of **28**, but using *O*-methylhydroxylamine hydrochloride instead of hydroxylamine hydrochloride, gave **29** (0.19 g, 35%) as white crystals: mp 192−195 °C; NMR (DMSO) δ 1.58 (3 H, s, CCH_3), 3.71 (3 H, s, $NOCH_3$), 4.06 (2 H, s, CH_2), 7.28 (1 H, dd, J = 8.7, 2.1 Hz, 6-H), 7.32−7.48 (6 H, m, ArH's), 7.80 (1 H, d, J = 8.7 Hz, 5-H), 11.91 (1 H, br, s, NH); MS (CI^+) m/z = 357 (M^+). Anal. ($C_{19}H_{17}ClN_2O_3 \cdot 0.1\ H_2O$) C, H, N.

4-Carboxy-7-chloro-3-phenyl-2(1*H*)-quinolone (31). A mixture of 4- and 6-chloroisatin (10 g, 55 mmol), phenylacetic acid (13.12 g, 96 mmol), and sodium acetate (1.1 g, 13.3 mmol) was heated at 220 °C for 1 h. Acetic acid (50 mL) was added to the hot reaction mixture, and the cooled solution was partitioned between saturated sodium carbonate solution (300 mL) and EtOAc (300 mL). The aqueous phase was treated with concentrated HCl until pH 1 was obtained, and the resultant precipitate was collected by filtration and recrystallized from ethanol to give **31** (10.8 g, 27%) as white crystals: mp 258 °C; NMR (DMSO) δ 7.30 (1 H, dd, J = 8.7, 2.1 Hz, 6-H), 7.37−7.44 (6 H, m, ArH's), 7.50 (1 H, d, J = 8.7 Hz, 5-H), 12.20 (1 H, br, s, NH); MS (CI^+) m/z = 300 (M^+). Anal. ($C_{16}H_{10}ClNO_3$) C, H, N.

7-Chloro-4-(methoxycarbonyl)-3-phenyl-2(1*H*)-quinolone (30). Compound **31** (1.2 g, 4 mmol) was dissolved in MeOH (100 mL) and treated with diazomethane (16 mmol) in Et_2O. After 1 h, acetic acid (5 mL) was added, and after a further 1 h, the solvents were removed under vacuum. The residue was dissolved in EtOAc (100 mL), washed with saturated sodium hydrogen carbonate solution (1 × 50 mL) and brine (1 × 50 mL), and then dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was recrystallized from DMF/H_2O and collected by filtration to give **30** (0.35 g, 28%) as white crystals: mp 255 °C; NMR (DMSO) δ 3.64 (3 H, s, CH_3), 7.28 (1 H, dd, J = 8.7, 2.1 Hz, 6-H), 7.30−7.45 (6 H, m, ArH's), 7.49 (1 H, d, J = 8.7 Hz, 5-H), 12.31 (1 H, br, s, NH); MS (CI^+) m/z = 314 (M^+). Anal. ($C_{17}H_{12}ClNO_3$) C, H, N.

4-[(Benzylamino)carbonyl]-7-chloro-3-phenyl-2(1*H*)-quinolone (32). A solution of **31** (1 g, 3.3 mmol) in thionyl chloride (10 mL) was heated under reflux for 1 h and then concentrated under vacuum and azeotroped with toluene (2 × 30 mL). The residue was dissolved in dichloromethane (50 mL), benzylamine (0.37 mL, 3.3 mmol) was added, and the reaction mixture was heated under reflux for 1 h. After cooling, dichloromethane (30 mL) was added, and the solution was washed with 1 N NaOH solution (30 mL) and then dried ($MgSO_4$), filtered, and concentrated under vacuum to leave a residue. This was recrystallized from DMF/H_2O and then MeOH to give **32** (0.18 g, 27%) as white crystals: mp 228 °C; NMR (DMSO) δ 4.27 (2 H, d, J = 6.0 Hz, CH_2Ph), 6.72 (2 H, m, ArH's), 7.11−7.48 (11 H, m, ArH's), 8.91 (1 H, t, J = 6.0 Hz, NHCH_2Ph), 12.15 (1 H, br, s, NH); MS (CI^+) m/z = 389 (M^+). Anal. ($C_{23}H_{17}ClN_2O_2$) C, H, N.

7-Chloro-4-[(methoxycarbonyl)methyl]-3-phenyl-2(1*H*)-quinolone (33). To a solution of **53**[9] (4 g, 19 mmol) in 1,2-dichloroethane (100 mL) was added phenylacetyl chloride (5 mL, 38 mmol), and the reaction mixture was heated under reflux for 14 h. After cooling, the solvent was removed under vacuum, and the residue was redissolved in MeOH (100 mL) and concentrated under vacuum again. Trituration with MeOH and filtration gave **54** (5 g, 80%) as white crystals: NMR (DMSO) δ 3.53 (2 H, s, CH_2), 3.73 (3 H, s, CH_3), 6.60 (1 H, d, J = 15.9 Hz, CH_A=C$H_B$$CO_2CH_3$), 7.24−7.38 (6 H, m, ArH's), 7.55 (1 H, d, J = 2.1 Hz, H-6), 7.76 (1 H, d, J = 15.9 Hz, CH_A=$CH_B$$CO_2CH_3$), 7.85 (1 H, d, J = 8.6 Hz, H-3).

To a solution of **54** (0.5 g, 1.5 mmol) in dry THF (100 mL) at −78 °C under nitrogen was added potassium bis(trimethylsilyl)amide (3 mL of a 0.5 M solution in toluene, 1.5 mmol). After 10 min *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.418 mL, 1.8 mmol) was added, and after 45 min a further portion of potassium bis(trimethylsilyl)amide (3.64 mL of a 0.5 M solution in toluene, 1.8 mmol) was added. After 1.5 h at −78 °C, phenylselenyl chloride (0.32 g, 1.65 mmol) in dry THF (10 mL) was added, and the reaction mixture was allowed to stir at −78 °C for 30 min and then at room temperature for 14 h. The reaction mixture was partitioned between EtOAc (200 mL) and saturated ammonium chloride solution (1 × 100 mL). The organic phase was washed with brine (1 × 50 mL) and dried ($MgSO_4$), and the solvent was removed under vacuum. The residue was purified using silica gel chromatography with 15% EtOAc/hexane as eluent. The purified selenide (0.186 g) was dissolved in 12.5% aqueous MeOH (20 mL), and after the addition of sodium periodate (0.25 g, 1.2 mmol) the reaction mixture was allowed to stir at room temperature for 1 h. The precipitate formed was collected by filtration and purified on silica gel using 30−50% EtOAc/hexane as eluent to give **33** (0.021 g, 4%) as white crystals: mp 227 °C; NMR (DMSO) δ 3.58 (3 H, s, CO_2CH_3), 3.75 (2 H, s, C$H_2CO_2CH_3$), 7.18 (2 H, m, ArH's), 7.26 (1 H, dd, J = 8.7, 2.1 Hz, H-6), 7.42 (4 H, m, ArH's), 7.69 (1 H, d, J = 8.7 Hz, H-5), 12.07 (1 H, br, s, NH); MS (EI^+) m/z = 327 (M^+). Anal. ($C_{18}H_{14}ClNO_3$·0.5H_2O) C, H, N.

4-(Carboxymethyl)-7-chloro-3-phenyl-2(1*H*)-quinolone (34). To a suspension of **33** (0.12 g, 0.36 mmol) in 50% MeOH/H_2O (20 mL) was added NaOH (0.2 g, 5 mmol), and the reaction mixture was heated under reflux for 1 h. The MeOH was removed under vacuum, and the residue was extracted with Et_2O (3 × 15 mL). The aqueous layer was acidified to pH 1 with concentrated HCl and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (1 × 30 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to give a residue which was recrystallized from ethanol to give **34** (0.05 g, 44%) as white crystals: mp 175 °C; NMR (DMSO) δ 3.65 (2 H, s, CH_2CO_2H), 7.23 (2 H, m, ArH's), 7.26 (1 H, dd, J = 8.6, 2.1 Hz, H-6), 7.41 (4 H, m, ArH's), 7.69 (1 H, d, J = 8.6 Hz, H-5), 12.03 (1 H, d, J = 8.7 Hz, H-5), 12.07 (1 H, br, s, NH); MS (CI^+) m/z = 313 (M^+). Anal. ($C_{17}H_{12}ClNO_3$) C, H, N.

7-Chloro-4-[[[2-(*N*,*N*-dimethylamino)ethyl]amino]carbonyl]methyl]-3-phenyl-2(1*H*)-quinolone (35). To a solution of **34** (0.66 g, 2 mmol) in 1,2-dichloroethane (50 mL) were added triethylamine (0.56 mL, 4 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.62 g, 2.4 mmol), and *N*,*N*-dimethylethylenediamine (0.22 mL, 2 mmol), and the reaction mixture was heated under reflux for 14 h. After cooling, the solution was extracted with 1 N HCl (3 × 30 mL). The combined acidic layers were treated cautiously with solid sodium hydrogen carbonate solution until a pH of ∼8 was attained and then extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (1 × 50 mL) and then dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was recrystallized from ethanol to give **35** (0.02 g, 3%) as white crystals: mp 280 °C; NMR (DMSO) δ 2.13 (6 H, s, N(CH_3)$_2$), 2.24 (2 H, t, J = 6.5 Hz, NHCH_2CH_2N(CH_3)$_2$), 3.12 (2 H, q, J = 6.5, 5.5 Hz, NHC$H_2$$CH_2$N($CH_3$)$_2$), 3.53 (2 H, s, C$H_2$CONH), 7.22 (1 H, dd, J = 8.7, 2.1 Hz, H-6), 7.29 (2 H, m, ArH's), 7.37−7.42 (4 H, m, ArH's), 7.64 (1 H, d, J = 8.7 Hz, H-5), 7.95 (1 H, t, J = 5.5 Hz, CONH), 11.97 (1 H, s, NH); MS (CI^+) m/z = 384 (M^+). Anal. ($C_{21}H_{22}ClN_2O_3$) C, H, N.

4-(2-Carboxyethyl)-7-chloro-3-phenyl-2(1*H*)-quinolone (37). To a suspension of **55** (16 g, 101.6 mmol) and triethylamine (31.2 mL, 224 mmol) in dichloromethane (400 mL) at 0 °C was added phenylacetyl chloride (29.6 mL, 224 mmol) dropwise over 10 min. When the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solution was washed with 1 N HCl (2 × 250 mL) and brine (1 × 250 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under vacuum to leave an orange solid. This solid was suspended in MeOH (400 mL), sodium hydroxide (4.4 g, 55.9 mmol) in H_2O (100 mL) was added, and the reaction mixture was heated at 50 °C for 45 min. The MeOH was removed under vacuum, and the aqueous residue was extracted with dichloromethane (1 × 400 mL). The organic layer was washed with brine (1 × 150 mL) and saturated sodium hydrogen carbonate solution (1 × 150 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under vacuum to leave a solid (20 g). To a solution of this solid (15.5 g, 56.3 mmol) in dichloromethane (400 mL), at room temperature, were added pyridinium chlorochromate (24.3 g, 112.5 mmol) and crushed 4 A sieves (0.5 g). After stirring at room temperature for 90 min, EtOAc (500 mL) was added and the reaction mixture was filtered through a plug of silica gel. The solvents were removed under vacuum, and the material was dissolved in EtOAc and filtered through silica gel again. The solvent was removed under vacuum, and trituration with Et_2O gave **56** (10.5 g, 48% over two steps): NMR (DMSO) δ 3.82 (2 H, s, CH_2Ph), 7.27−7.39 (6 H, m, ArH's), 7.87 (1 H, d, J = 8.3 Hz, 6-H), 8.36 (1 H, d, J = 1.9 Hz, 3-H), 9.89 (1 H, s, CHO), 10.97 (1 H, br, s, NH).

To a solution of **56** (10.5 g, 38.4 mmol) in dichloromethane (100 mL) under an atmosphere of nitrogen at −78 °C was added titanium tetrachloride (4.3 mL, 42.2 mmol), and [(1-ethoxycyclopropyl)oxy]trimethylsilane (8.8 mL, 46.1 mmol) in dichloromethane (30 mL) was added dropwise over 10 min. The reaction mixture was stirred at −78 °C for 15 min, allowed to warm to 0 °C, and stirred for 45 min and then at room temperature for 3 h. Saturated ammonium chloride solution (100 mL) was added to the reaction mixture, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 75 mL), the combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under vacuum to leave a residue. Purification on silica gel using 20−60% EtOAc/hexane as eluent gave **57** (7.78 g, 54%) as a white solid: NMR (DMSO) δ 1.16 (3 H, t, J = 7.1 Hz, $CH(OH)CH_2CH_2CO_2CH_2CH_3$), 1.60 (2 H, m, $CH(OH)CH_2CH_2CH_2CO_2CH_2CH_3$), 2.15−2.33 (2 H, m, $CH(OH)CH_2CH_2CO_2CH_2CH_3$), 3.70 (2 H, s, $NHCOCH_2Ph$), 4.01 (2 H, q, J = 7.1 Hz, $CH(OH)CH_2CH_2CO_2CH_2CH_3$), 4.68 (1 H, br, s, $CH(OH)CH_2CH_2CH_2CO_2CH_2CH_3$), 5.73 (1 H, br, s, $CH(OH)CH_2CH_2CO_2CH_2CH_3$), 7.16−7.34 (7 H, m, ArH's), 7.79 (1 H, d, 3-H), 9.68 (1 H, br, s, NH).

Subsequent treatment of **57** (8.8 g, 23.4 mmol) under the appropriate conditions described in the conversions of **55** to **56**, **56** to **42**, and **33** to **34** gave **37** (5.5 g, 72%) as white crystals: mp 316−318 °C; NMR (DMSO) δ 2.37 (2 H, t, J = 8.6 Hz, CH_2CH_2), 2.83 (2 H, t, J = 8.6 Hz, CH_2CH_2), 7.22−7.28 (3 H, m, ArH's), 7.36−7.46 (4 H, m, ArH's), 7.82 (1 H, d, J = 8.7 Hz, 5-H), 11.95 (1 H, br, s, NH); MS (CI^+) m/z = 328 (M^+). Anal. ($C_{18}H_{14}ClNO_3$) C, H, N.

7-Chloro-4-[2-(methoxycarbonyl)ethyl]-3-phenyl-2(1*H*)-quinolone (36). Compound **37** (1.17 g, 3.6 mmol) was dissolved in a saturated solution of hydrogen chloride in MeOH (100 mL) and stood at room temperature for 3 h. The solvents were evaporated, and the residue was recrystallized from methanol to give **36** (0.42 g, 34%) as white crystals: mp 193−194 °C; NMR (DMSO) δ 2.47 (2 H, t, J = 8.4 Hz, CH_2CH_2), 2.88 (2 H, t, J = 8.4 Hz, CH_2CH_2), 3.52 (3 H, s, CH_3), 7.21−7.27 (3 H, m, ArH's), 7.36−7.46 (4 H, m, ArH's), 7.82 (1 H, d, J = 8.8 Hz, 5-H), 11.94 (1 H, br, s, NH); MS (CI^+) m/z = 342 (M^+). Anal. ($C_{19}H_{16}ClNO_3$) C, H, N.

7-Chloro-4-[(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-3-phenyl-2(1*H*)-quinolone (38). To a solution of acetamide oxime (0.26 g, 2.93 mmol) in THF (50 mL) under an atmosphere of nitrogen at room temperature was added sodium hydride (0.14 g of an 80% dispersion, 0.46 mmol). The reaction mixture was heated to 60 °C for 90 min; then **36** (0.5 g, 1.46 mmol) was added, and the reaction mixture was heated at 60 °C for 3 h. After allowing to cool, the reaction mixture was poured into H_2O (100 mL) and extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with 1 N citric acid solution (1 × 75 mL), water (1 × 75 mL), saturated sodium hydrogen carbonate solution (1 × 75 mL), and brine (1 × 75 mL). After drying ($MgSO_4$), filtration and evaporation gave a residue which was recrystallized from MeOH/EtOAc to give **38** (0.08 g, 15%) as white crystals: mp 235−238 °C; NMR (DMSO) δ 2.25 (3 H, s, CH_3), 3.04 (4 H, m, CH_2CH_2), 7.16 (1 H, dd, J = 8.8, 1.3 Hz, H-6), 7.18−7.44 (6 H, m, ArH's), 7.87 (1 H, d, J = 8.8 Hz, 5-H), 12.00 (1 H, br, s, NH); MS (CI^-) m/z = 365 (M). Anal. ($C_{20}H_{16}ClN_3O_2$) C, H, N.

4-[2-(Aminocarbonyl)ethyl]-7-chloro-3-phenyl-2(1*H*)-quinolone (39). Treatment of **37** (1.7 g, 5.2 mmol) under the conditions described for the conversion of **20** to **22** gave **39** (0.05 g, 3%) as white crystals: mp 297−299 °C; NMR (DMSO) δ 2.21 (2 H, t, J = 8.3 Hz, $CH_2CH_2CONH_2$), 2.77 (2 H, t, J = 8.3 Hz, $CH_2CH_2CONH_2$), 6.78 (1 H, br, s, 1 × $CONH_2$), 7.21−7.46 (8 H, m, ArH's, 1 × $CONH_2$), 7.81 (1 H, d, J = 8.8 Hz, 5-H), 11.92 (1 H, br, s, NH); MS (CI^+) m/z = 327 (M^+). Anal. ($C_{18}H_{15}ClN_2O_2$) C, H, N.

7-Chloro-4-(2-cyanoethyl)-3-phenyl-2(1*H*)-quinolone (40). To a solution of **39** (0.6 g, 1.84 mmol) in THF (80 mL) under an atmosphere of nitrogen at 0 °C was added triethylamine (1.13 mL, 8.1 mmol) followed by trifluoroacetic anhydride (0.7 mL, 5 mmol). The reaction mixture was stirred at 0 °C for 45 min and then poured into H_2O (100 mL) and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with H_2O (1 × 100 mL) and brine (1 × 100 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to leave a residue which was recrystallized from MeOH/H_2O to give **40** (0.08 g, 14%) as white crystals: mp 252−254 °C; NMR (DMSO) δ 2.66 (2 H, t, J = 7.6 Hz, CH_2CH_2CN), 2.77 (2 H, t, J = 8.3 Hz, CH_2CH_2CN), 7.24−7.48 (7 H, m, ArH's), 7.91 (1 H, d, J = 8.8 Hz, 5-H), 12.03 (1 H, br, s, NH); MS (CI^+) m/z = 309 (M^+). Anal. ($C_{18}H_{13}ClN_2O$) C, H, N.

7-Chloro-3-phenyl-4-(2-tetrazol-5-ylethyl)-2(1*H*)-quinolone (41). To a solution of **38** (0.45 g, 1.5 mmol) in 1-methyl-2-pyrrolidinone (50 mL) under an atmosphere of nitrogen at room temperature were added sodium azide (0.28 g, 4.4 mmol) and triethylamine hydrochloride (0.3 g, 2.2 mmol). The reaction mixture was heated at 150 °C with stirring for 48 h. After allowing to cool, the reaction mixture was poured into H_2O (100 mL), and the pH was adjusted to 1 by the addition of concentrated HCl. The solution was extracted with EtOAc (3 × 75 mL), and the combined organic layers were washed with 1 N NaOH solution (3 × 75 mL). The combined aqueous phases were washed with Et_2O (2 × 75 mL) and acidified to pH 1 with concentrated HCl. The aqueous layer was extracted with EtOAc (3 × 75 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum to leave a residue which was recrystallized from MeOH/H_2O and then EtOAc to give **41** (0.05 g, 10%) as white crystals: mp 231−233 °C; NMR (DMSO) δ 3.05 (4 H, br, s, CH_2CH_2-Tet), 7.10−7.42 (7 H, m, ArH's), 7.86 (1 H, d, J = 8.7 Hz, 5-H), 12.00 (1 H, br, s, NH); MS (CI^+) m/z = 352 (M^+). Anal. ($C_{18}H_{14}ClN_5O \cdot 0.1H_2O$) C, H, N.

7-Chloro-4-ethyl-3-phenyl-2(1*H*)-quinolone (42). To a solution of **56** (0.5 g, 1.83 mmol) in THF (30 mL) under an atmosphere of nitrogen at 0 °C was added ethylmagnesium bromide (2 mL of a 1 M solution in Et_2O). The reaction mixture was allowed to warm to room temperature, stirred for 16 h, and then poured into saturated ammonium chloride solution (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with H_2O (1 × 75 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under vacuum to leave a solid (0.93 g). Treatment of this solid (0.93 g) with pyridinium chlorochromate under the conditions described for the preparation of **56** gave a ketone intermediate (0.28 g), which was dissolved in dry EtOH (30 mL) and treated with sodium hydride (0.06 g of an 80% dispersion, 1.86 mmol) at room temperature under nitrogen. After 30 min, the solvent was removed under vacuum to leave a residue which was partitioned between EtOAc (50 mL) and H_2O (50 mL). The organic phase was washed with brine (1 × 50 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under vacuum to leave a solid. Recrystallization from EtOAc gave **42** (0.28 g, 46% over three steps) as white crystals: mp 244−246 °C; NMR (DMSO) δ 1.04 (3 H, t, J = 7.5 Hz, CH_2CH_3), 2.58 (2 H, t, J = 7.5 Hz, CH_2CH_3), 7.21−7.46 (7 H, m, ArH's), 7.82 (1 H, d, J = 8.8 Hz, H-5), 11.89 (1 H, br, s, NH); MS (CI^-) m/z = 283 (M). Anal. ($C_{17}H_{14}ClNO$) C, H, N.

4-Amino-7-chloro-3-(3-phenoxyphenyl)-2(1*H*)-quinolone (43). Compound **43** was prepared in the same way as **3**, using 3-phenoxyphenylacetyl chloride instead of phenylacetyl chloride, to give **43** (0.31 g, 15%) as white crystals: mp 196−197 °C; NMR (DMSO) δ 6.09 (2 H, br, s, NH_2), 6.70−8.05 (12 H, m, ArH's), 11.06 (1 H, br, s, NH); MS (CI^-) m/z = 362 (M). Anal. ($C_{21}H_{15}ClN_2O_2$) C, H, N.

7-Chloro-4-(cyanomethoxy)-3-(3-phenoxyphenyl)-2(1*H*)-quinolone (44). Treatment of **2** under the same conditions described for the synthesis of **19**, but using bromoacetonitrile instead of methyl bromoacetate, gave **25** (0.13 g, 16%) as white crystals: mp 218−220 °C; NMR (DMSO) δ 4.70 (2 H, s, OCH_2), 7.08−7.51 (11 H, m, ArH's), 7.82 (1 H, d, J = 8.7 Hz, 5-H), 12.10 (1 H, br, s, NH); MS (EI) m/z = 403 (M^+). Anal. ($C_{23}H_{15}ClN_2O_3$) C, H, N.

7-Chloro-4-carboxy-3-(3-phenoxyphenyl)-2(1*H*)-quinolone (45). Treatment of **2** under the same conditions described for the synthesis of **19** and **20** gave **45** (0.05 g, 5% over two steps) as white crystals: mp 246−249 °C; NMR (DMSO) δ 4.18 (2 H, s, OCH_2), 7.04−7.48 (11 H, m, ArH's), 8.02 (1 H, d, J = 8.6 Hz, 5-H), 11.93 (1 H, br, s, NH); MS (EI) m/z = 422 (M^+). Anal. ($C_{23}H_{16}ClNO_5$) C, H, N.

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