3-Acyl-4-hydroxyquinolin-2(1*H*)-ones. Systemically Active Anticonvulsants Acting by Antagonism at the Glycine Site of the *N*-Methyl-D-Aspartate Receptor Complex

Michael Rowley,* Paul D. Leeson, Graeme I. Stevenson, Angela M. Moseley, Ian Stansfield, Ian Sanderson, Lesley Robinson, Raymond Baker, John A. Kemp, George R. Marshall, Alan C. Foster, Sarah Grimwood, Mark D. Tricklebank, and Kay L. Saywell

Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, United Kingdom

Received April 16, 1993•

Most full antagonists at the glycine site of the NMDA receptor contain a carboxylic acid, which we believe to be detrimental to penetration of the blood–brain barrier. By consideration of a pharmacophore, novel antagonists at this site have been designed in which the anionic functionality is a vinylogous acid, in the form of a 4-hydroxyquinolin-2(1*H*)-one. In this series, a 3-substituent is necessary for binding, and correct manipulation of this group leads to compounds such as the 3-(3-hydroxyphenyl)propargyl ester **24** (L-701,273), with an IC_{50} for displacement of [^{3}H]-L-689,560 binding of 0.17 μM and K_b against NMDA in the cortical slice of 1.39 μM. Compounds were tested for their ability to prevent audiogenic seizure in DBA/2 mice; the most potent compound in this series is the cyclopropyl ketone **42** (L-701,252), with an ED_{50} of 4.1 mg/kg ip. A model is proposed for binding to the glycine site, in which an important interaction is of a putative receptor cation with the π-system of the 3-substituent.

Over the last few years, a great deal of evidence has been accumulated that over-activation of the *N*-methyl-D-aspartate (NMDA) subtype of central excitatory amino acid receptor plays a role in a number of neurodegenerative disorders. These include the delayed neuronal loss following cerebral ischaemia, epilepsy, Alzheimer's disease, and AIDS-related dementia.[1] NMDA antagonists may therefore be therapeutically useful, as they have been shown to be anticonvulsant and neuroprotective in animal models. There are several sites on the receptor ion channel complex at which antagonists may act:[2] the neurotransmitter (glutamate) recognition site, at which antagonists such as [3-(2-carboxypiperazin-4-yl)propyl]phosphonic acid (CPP)[3] bind; the ion channel, which (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (dizocilpine)[4] blocks; a polyamine binding site, at which a putative antagonist is 1-[2-(4-chlorophenyl)-2-hydroxyethyl]-4-(4-fluorobenzyl)piperidine (SL82.0715);[5] and a site that binds glycine, which has been shown to be necessary for receptor activation.[6] Several types of compound are known to inhibit the binding of glycine to this site, including kynurenic acid derivatives,[7] 2-carboxytetrahydroquinolines,[8] 2-carboxyindoles,[9] some quinoxalinediones,[10] derivatives of the partial agonist 3-amino-1-hydroxy-2-pyrrolidinone (HA-966),[11] and it has recently been disclosed that 3-phenyl-4-hydroxyquinolin-2(1*H*)-ones[12] and imidazoquinoxalinones[13] are glycine antagonists.

However, despite the diversity of potent glycine site ligands available, in most cases *in vivo* activity is poor. One exception to this is (3*R*,4*R*)-3-amino-1-hydroxy-4-methyl-2-pyrrolidinone (L-687,414), which we have shown to be neuroprotective in a rat middle cerebral artery occlusion model of focal ischaemia.[11b] Efforts to improve on this type of partial agonist have proved fruitless,[11c] and we returned our attention to improving *in vivo* properties of full antagonists based on kynurenic acid. As we saw it,

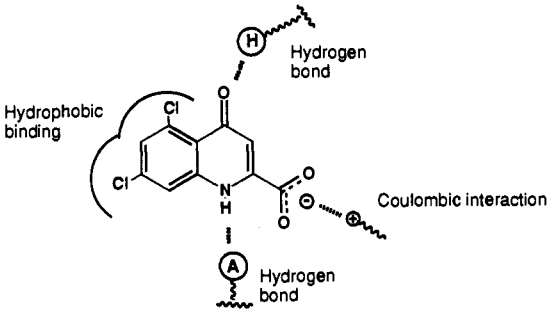


Figure 1. Proposed pharmacophore for the binding of kynurenic acids.

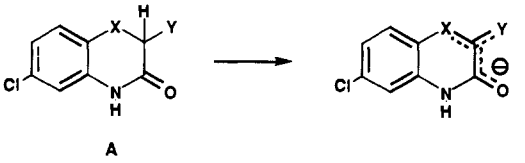


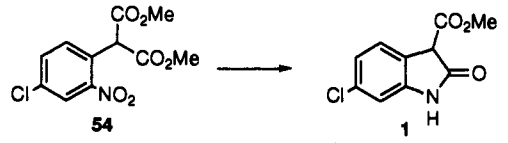
Figure 2. Design for alternatives to carboxylic acids as glycine site ligand.

a major problem with this type of antagonist is the presence of a carboxylic acid, which is likely to be detrimental to penetration of the blood–brain barrier. We have developed[7] a pharmacophore for binding of this type of compound to the glycine site (Figure 1), in which an ionic interaction with a negatively charged group at the 2-position is hypothesized to be important for binding. We therefore sought to keep this interaction, but with an anionic group that is not a carboxylic acid. It was reasoned that a benzolactam of type A (Figure 2), in which X and Y are adjusted so that the 3-proton is acidic, may bind, but greater delocalization of the negative charge over the 2-carbonyl, X, and Y, could lead to improved brain penetration. In this paper we describe the synthesis of several variants of this type of compound, their binding affinity and antagonist potency and show that, indeed, *in vivo* properties can be greatly improved.

• Abstract published in *Advance ACS Abstracts*, September 1, 1993.

0022-2623/93/1836-3386$04.00/0

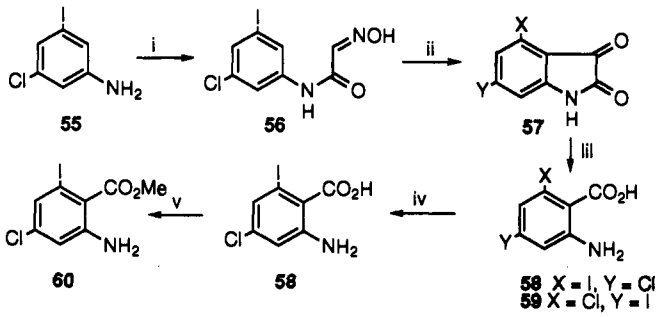
Scheme I[a]



54 1

[a] Reagent: H_2/Pd/C, EtOAc.

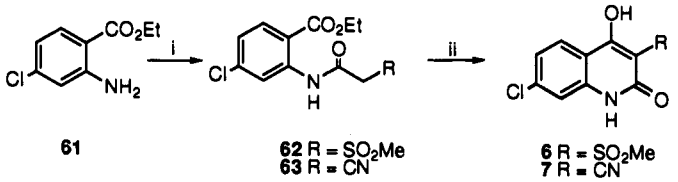
Scheme II[a]



55 56 57 58 59 X = I, Y = Cl 59 X = Cl, Y = I 60

[a] Reagents: (i) $Cl_3CCH(OH)_2$, $H_2NOH{\cdot}HCl$, $NaSO_4$, HCl, dioxane, H_2O; (ii) H_2SO_4; (iii) H_2O_2, NaOH; (iv) Recrystallize from acetone, and then HCl; (v) CH_2N_2.

Scheme III[a]



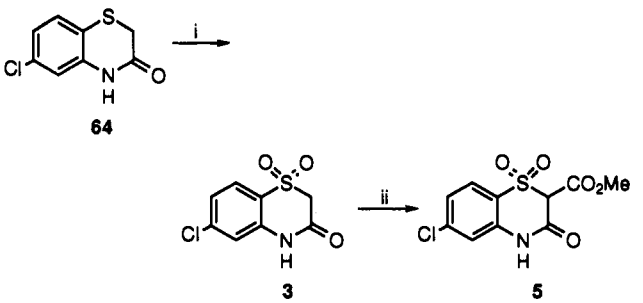
61 62 R = SO_2Me 63 R = CN 6 R = SO_2Me 7 R = CN

[a] Reagents: (i) RCH_2CO_2H, BuOCOCl, Et_3N; (ii) NaOMe.

Synthesis

Compound **4**[14] is known. Oxindole **1** was prepared by hydrogenation of the nitroarylmalonate **54**[15] (Scheme I). The starting material for most of the compounds in this paper is a substituted anthranilic ester. Many anthranilic acids are commercially available and can be esterified by refluxing with an excess of concentrated sulfuric acid in ethanol for several days, or by treatment with ethereal diazomethane. Where the anthranilic acid is not known, it can be prepared from the aniline (Scheme II). For example, 3-chloro-5-iodoaniline (**55**)[7] was treated with chloral hydrate and hydroxylamine hydrochloride to give *N*-(3-chloro-5-iodophenyl)(hydroxyimino)acetamide **56**, which was dehydrated to a mixture of isatins **57** with concentrated sulfuric acid. Oxidation with hydrogen peroxide gave a mixture of 2-amino-4-chloro-6-iodo- and 2-amino-6-chloro-4-iodobenzoic acid (**58** and **59**, respectively), from which the former could be obtained by selective crystallization of its Schiff base, formed from the mixture with acetone, and then hydrolysis to give **58**, which was converted to ester **60** with diazomethane. Sulfone **6** and nitrile **7** were made by coupling of the substituted acetic acids with ethyl 4-chloroanthranilate **61** to give the corresponding amides **62** and **63**, which were cyclized with sodium methoxide (Scheme III). Oxidation of benzothiazine **64**[16] with *m*-chloroperbenzoic acid gave **3** which was carboxylated with sodium hydride and methyl cyanoformate to give **5** (Scheme IV). Treatment of **61** with ethyl malonyl chloride gave the corresponding amide, which was converted to **8** by treatment with 2 equiv of sodium methoxide in ethanol (Scheme V). Ketones in Table IV were made in one of two ways shown in Scheme V. Reaction of **61** with phosgene in toluene gave the isocyanate **65**. Without purification, this was treated with the anion derived from a methyl ketone and lithium hexamethyldisilazide to give the amides, which were then cyclized using sodium methoxide in methanol. Ketones **9** and **34** were made by treatment of isocyanate **65** with the anion derived from the symmetrical diketones to yield derivatives **66** and **67**. Cyclization then proceeded with loss of one of the ketone groups to give the aromatic systems. Esters in Table II and amides, hydroxamic acids and the thioester in Table V were prepared from the ethyl ester **8** (Scheme VI) by reaction with the corresponding neat alcohol, amine or thiol at 130–160 °C, or as a solution in methanol or pyridine. If the boiling point of the alcohol or amine was below 130 °C, sealed apparatus was used. Quinolone **2** was produced by alkaline hydrolysis of ethyl ester **8** (Scheme VII), whereas the acid **46** could be made by treatment of **8** with the sodium anion derived from 4-methoxyphenol in DMF.

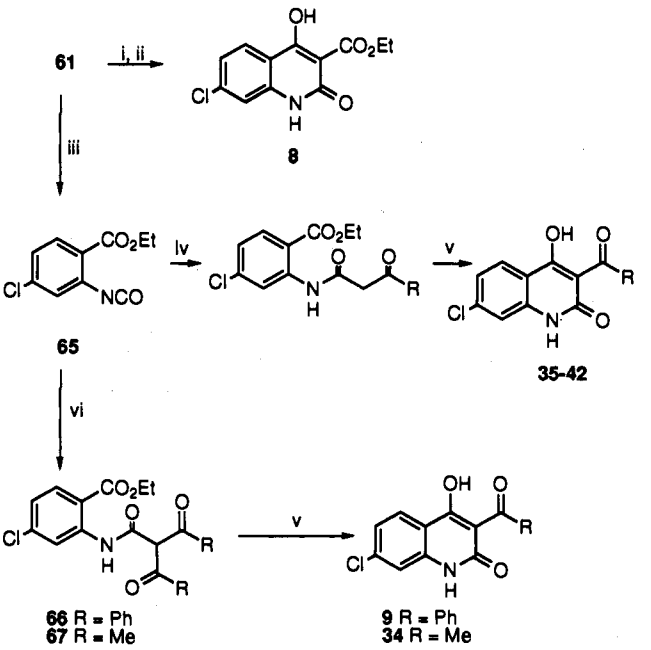
Scheme IV[a]



64 3 5

[a] Reagents: (i) mCPBA; (ii) NaH, MeOCOCN.

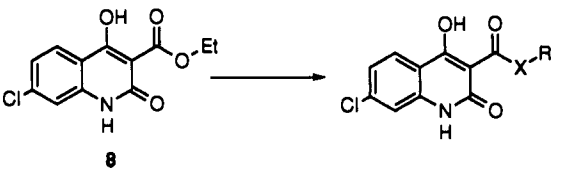
Scheme V[a]



61 8 65 35-42 66 R = Ph 67 R = Me 9 R = Ph 34 R = Me

[a] Reagents: (i) EtO_2CCH_2COCl; (ii) NaOMe, EtOH; (iii) $COCl_2$; (iv) $RCOCH_3$/LiHMDS; (v) NaOMe; (vi) $RCOCH_2COR$/NaH.

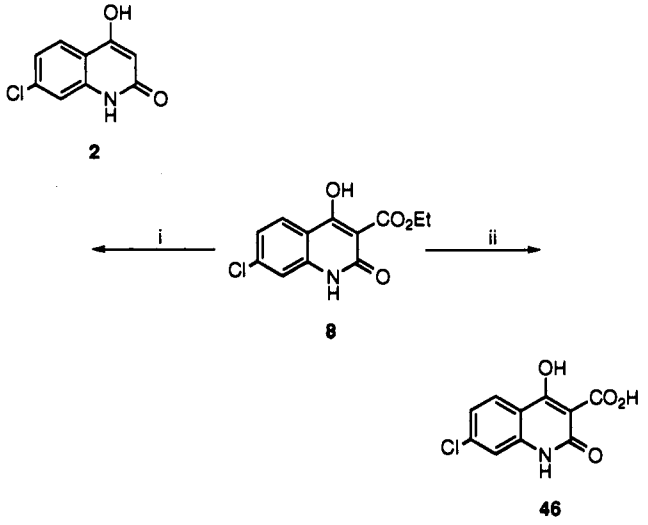
Scheme VI[a]



8

[a] Reagent: RXH, 110–160 °C.

Scheme VII[a]



[a] Reagents: (i) LiOH, THF; (ii) 4-methoxyphenol, NaH, DMF.

Although in Figure 2 compounds of type A are shown as the tautomer having a proton on the 3-carbon, this is not the case in solution for most of the compounds in this paper. The derivatives **3-5** do exist in this 3-protonated tautomer in DMSO at room temperature, whereas **1** is a mixture of keto and enol tautomers in $CDCl_3$ at room temperature, and all the compounds with a carbonyl group at the 4-position in fact exist as the enol (4-hydroxy-2-quinolone) tautomer in the solution in which the NMR spectra were recorded.

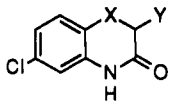
Biology

Compounds were evaluated for their ability to displace [^{3}H]-L-689,560 binding from rat cortical membranes (IC_{50} values), antagonize NMDA-induced responses in rat cortical slice (apparent K_b values), antagonize AMPA-induced responses in rat cortical slice (apparent K_b values), and protect against audiogenic seizure in DBA/2 mice when dosed intraperitoneally 30 min prior to seizure induction (either ED_{50} values, or quoted as number protected/number tested at a particular dose). 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. 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. The maximum standard error calculated from the pIC_{50} values was always less than 5% of the mean. Where $IC_{50} > 100$ μM, the test compound inhibited [^{3}H]-L-689,560 binding by less than 50% at 100 μM (two experiments). The apparent K_b values from the cortical slice assays were calculated from the shift to the right of the NMDA or AMPA concentration–response curves produced by the antagonists, and are means from at least three experiments: the maximum variance (geometric mean) was 15%. Full details of the methods used have been published.[17]

Results and Discussion

A variety of lactams of type A are shown in Table I. Where only one of X and Y is an electron-withdrawing group, **1-3**, affinity for the glycine site is low, as is also the case for **4**, in which an oxygen is in the 4-position. However, where both X and Y are sulfone, carbonyl, or nitrile (**5–9**) the compounds do bind. This may, in part, be attributable to pK_A, as neither **1** nor **4** are acidic. However, the pK_A of the inactive compound **2** is 5.8,[23] and it therefore should be largely deprotonated at physiological pH. The pK_A of **8** is 4.4, similar to that of a carboxylic acid. A model for binding of this type of hydroxyquinolone is suggested at the end of this paper. *In vivo*, it is the last two compounds, ester **8** and ketone **9**, that show anticonvulsant activity in the DBA/2 mouse. We reason that although **8** exists very largely as the anion at pH 7.4, the charge is highly delocalized, and its log *P* of 0.7 at physiological pH allows brain penetration. Given the systemic anticonvulsant activities of **8** and **9**, we decided to optimize them in terms of their binding to the receptor.

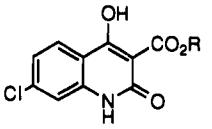
Table I. 3-Substituted Amides

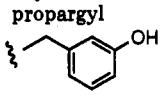
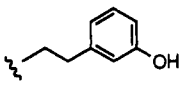
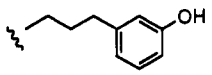
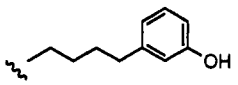
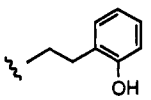
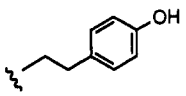
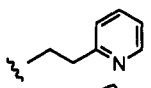
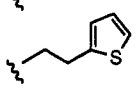
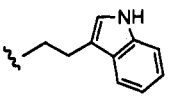
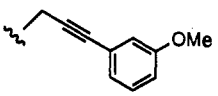
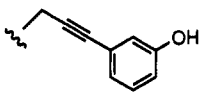


no.	X	Y	IC_{50} (μM) vs [^{3}H]-L-689,560	K_b (μM) vs NMDA	ED_{50} (mg/kg) DBA/2 mouse
1	bond	CO_2Me	>100	441	
2	C=O	H	>100		0/8 at 100
3	SO_2	H	>100		
4	O	CO_2Et	>100		
5	SO_2	CO_2Me	13.6	66.2	0/8 at 50
6	C=O	SO_2Me	15.4	>100	
7	C=O	CN	3.9	20.3	0/8 at 50
8	C=O	CO_2Et	16.7	65.4	41
9	C=O	COPh	3.16	19.3	15.1

In the tetrahydroquinoline series[8] it was found that binding to the glycine site could be very substantially improved by a hydrophobic interaction *via* the 4-position. This type of lipophilic binding is explored here by a number of esters of the 3-carboxylate lead **8** (Table II). In a series of alkyl esters, the affinity drops off with increasing chain length, with the methyl ester **10** (L-695,902) being the most potent *in vitro* and preventing convulsions in DBA/2 mice with an ED_{50} of 12.5 mg/kg. Introduction of unsaturation into the alkyl chain, to give **12** and **13**, improves affinity over the saturated analogue **11**. This prompted us to introduce a range of aromatic substituents onto the alkyl ester. The benzyl and phenethyl esters are too insoluble to test in the binding assay, and for this reason an hydroxyl group was put onto the aromatic ring. These aryl alkyl esters do show improved affinity over the alkyl esters. The effect of chain length was investigated: while keeping the hydroxyl group at the meta position of the benzene ring, a two-carbon chain is optimal for binding affinity and functional potency, as shown by **14-17**. In this two-carbon series, **15**, **18**, and **19**, the optimal position for the hydroxy group is meta. The activities of pyridine **20** and thiophene **21**, together with the above results, suggest that an electron rich aromatic ring is preferred. *In vivo*, none of the hydroxylated compounds have significant activity, a fact that can be explained by the polar nature of the phenol substituent. Thiophene **21** does show anticonvulsant activity but in this case the action is short lasting: when tested 10 min post dosing the ED_{50} is 25.2 mg/kg, but only one animal out of eight is protected by a 50-mg dose when the seizure is induced 30 min post injection. This is possibly due to metabolic instability. Three esters, **22-24**, in which there is a three-carbon chain separating the benzene ring from the ester oxygen, and

Table II. 4-Hydroxyquinolin-2(1*H*)-ones, 3-Esters



no.	R	IC_{50} (μM) vs [^{3}H]-L-689,560	K_b (μM) vs NMDA	ED_{50} (mg/kg) DBA/2 mouse
8	Et	16.7	65.4	41
10	Me	6.4	23	12.5
11	^{n}Pr	>100	95	8/8 at 50 0/8 at 30
12	allyl	6.42	46.6	40.1
13	propargyl	9.0		
14		6.13	35.7	
15		1.82	2.69	0/8 at 50
16		2.64	11.1	
17		2.62	26.5	0/8 at 50
18		7.12	15.6	4/8 at 50
19		2.93	7.29	6/8 at 100
20		27.5	>100	
21		3	8.5	25.2[a]
22		0.43		1/8 at 20
23		0.27	3.96	0/8 at 20
24		0.17	1.39	0/8 at 20

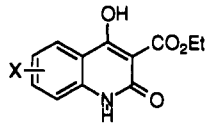
[a] ED_{50} when tested after 10 min. 1/8 animals protected when dosed at 50 mg/kg and tested 30 min later.

with conformational restraints in the chain, were prepared. These all have improved affinity over the conformationally flexible phenylpropyl ester **16**, demonstrating a preference for a particular location of the aromatic ring. The reasons for the lack of anticonvulsant effects of **22** and **23** are not clear.

Keeping the 3-substituent constant as an ethyl ester, aromatic substitution of the benzene ring of the quinolone was investigated (Table III). A substituent is necessary, and the preference is for the 7-position, **8**, **25–28**. A number of small electron withdrawing groups are allowed in the 7-position, **29–31**, with similar affinities. These structure–activity relationships are reminiscent of the kynurenic acids[7] and indeed the best affinity is seen with the 5-iodo-7-chloro compound **32**. Interestingly, the 7-nitro analogue **31** is a more potent AMPA antagonist, with a K_b of 39.3 μM in the cortical slice, than it is against NMDA (K_b 117 μM). The AMPA antagonism is improved by introduction of a second nitro group onto the 6-position, **33** (K_b 12.2 μM), and in this respect the SAR is similar to quinoxalinediones.[10] Compounds with a 7-chloro substituent are selective antagonists at NMDA receptors in the cortical slice preparation: methyl ester **10** has K_b's *vs* NMDA and AMPA of 23 and 323 μM, respectively, and for the most potent NMDA antagonists, **24**, **32**, and **42**, there is little or no shift in the dose–response curve to AMPA at concentrations above the K_b against NMDA.

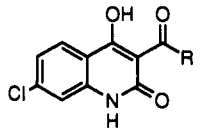
In the ketone series (Table IV) the methyl ketone **34** does not bind to the glycine receptor. In contrast to this, a number of aryl ketones have micromolar affinity, with good *in vivo* activity. Again, the preference is for an electron-rich aromatic ring, with the thiophene **35** and furan **36** having similar profiles, and the pyridine **37** being less potent than phenyl ketone **9**. The interaction of the

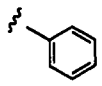
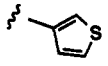
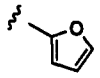
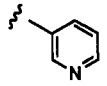
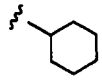
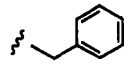
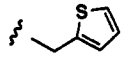
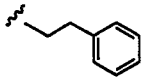
Table III. 3-(Ethoxycarbonyl)-4-hydroxyquinolin-2(1*H*)-ones, Aromatic Substitution



no.	X	IC_{50} (μM) vs [^{3}H]-L-689,560	K_b (μM) vs NMDA	ED_{50} (mg/kg) DBA/2 mouse
25	H	>100		
8	7-Cl	16.7	65.4	41
26	5-Me	>1000		
27	6-Cl	>100		
28	8-Me	>100		
29	7-CN	26.0		
30	7-CF_3	12.3		
31	7-NO_2	25.4	117	47
32	5-I, 7-Cl	1.61	13.3	6/8 at 50 0/8 at 30
33	6,7-$(NO_2)_2$	10.5	30	0/8 at 50

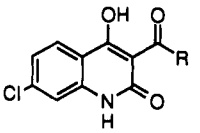
Table IV. 4-Hydroxyquinolin-2(1*H*)-ones, 3-Ketones

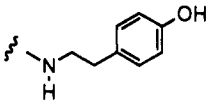
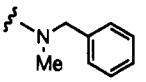
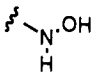
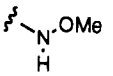
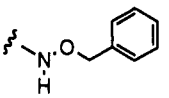
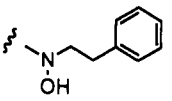
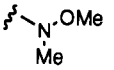
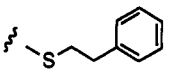


no.	R	IC_{50} (μM) vs [^{3}H]-L-689,560	K_b (μM) vs NMDA	ED_{50} (mg/kg) DBA/2 mouse
34	Me	>100		
9		3.16	19.3	15.1
35		1.97	18.8	12.8
36		2.39	12.9	13.1
37		6.85	41.9	0/8 at 100
38		>100		
39		0.93	3.92	31.6
40		1.07		
41		>100		
42		0.42	3.39	4.1

ketone substituent with the receptor is not due solely to a lipophilic interaction, since the cyclohexyl ketone **38** does not bind. Introduction of a methylene spacer between the ketone and the aromatic ring, as in **39** and **40**, improves affinity and functional antagonism, although when this chain is further extended, to give phenethyl ketone **41**, activity is lost. Interestingly, although other alkyl ketones are not active, the cyclopropyl ketone **42** (L-701,252) is the most potent compound in this series, with submicromolar affinity, and an ED_{50} in the anticonvulsant assay of 4.1 mg/kg. This may be a reflection of the π-character of the bonds in the cyclopropane ring.[18]

Table V. 4-Hydroxyquinolin-2(1*H*)-ones, Other Groups in the 3-Position



no.	R	IC_{50} (μM) vs [^{3}H]-L-689,560
43	NH_2	>100
44		>100
45		>100
46		5.82
47		6.32
48		3.09
49		>100
50		9.3
51		47.1
52		>10

Several other types of carbonyl groups in the 3-position were tested for their affinity at the glycine site (Table V). The carboxamide **43** is inactive, and introduction of the lipophilic group that increased affinity in the esters does not improve matters here. That this is not a function of the amide NH is shown by the *N*-methyl derivative **45**, which is not active. In contrast to this, carboxylic acid acid **46** binds to the glycine receptor, and hydroxamic acid **47** has a very similar profile to methyl ester **34**, both in the binding assay and *in vivo*, with an ED_{50} of 11.6 mg/kg ip in the DBA/2 mouse. With methylation of the hydroxamate oxygen, **48**, activity is retained, but, unlike the ester series, introduction of a large lipophilic substituent onto either oxygen, **49**, or nitrogen, **50**, does not improve affinity and, in fact, is detrimental for **48**. Methylation of both nitrogen and oxygen to give **51** reduces affinity. Thioester **52** could not be tested above 10 μM in the binding assay due to low aqueous solubility, but up to this concentration it did not displace >50% radioligand binding.

Molecular modeling[19] of the anion of methyl ester **10** shows that the plane of the ester group is twisted by 63° relative to the plane of the quinolone in its ground-state conformation (Figure 3). Although this reduces the π–conjugation between the two groups, the ester still serves to lower the pK_A of the system. A model that explains the binding of these compounds to the receptor is shown in Figure 4. As in our previous model (Figure 1), interactions include size-limited hydrophobic binding of the benzene ring of the quinolone, H-bond interactions at the 1- and

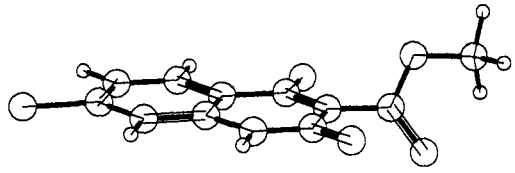


Figure 3. Structure of the anion of **10** (L-695,902) modeled using AMF.[19]

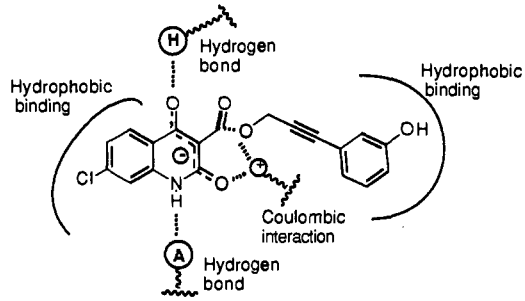


Figure 4. Proposed mode of binding of **24** (L-701,273) to the glycine site.

4-positions, and Coulombic interaction at the 2-position. However, due possibly either to lower charge density on the lactam oxygen as compared to a carboxylic acid or due to its relative position in the quinolones, this Coulombic interaction needs to be reinforced by an interaction with the substituent at the 3-position. It is now well established that π-systems can have energetically favorable interactions with positively charged groups,[20] and we have proposed this type of interaction for binding of 3-aryl-4-hydroxyquinolin-2(1*H*)-ones to the glycine site of the NMDA receptor.[21] We hypothesize similar binding of these 3-acyl-4-hydroxyquinolin-2(1*H*)-ones. In the ester series, it is the 3-atom ester π-system that interacts. In the ketones it is the carbonyl along with the aromatic π-system of the aryl or arylmethyl ketone, but when the carbonyl and the aryl group are separated by more than one methylene unit both cannot interact simultaneously, and affinity is lost. Further binding to the glycine site can be obtained in the ester series by correct positioning of an electron-rich aromatic ring that participates in lipophilic binding to the receptor.

That the carboxylic acid can be replaced in this way has very important implications for systemic *in vivo* activity. In the tetrahydroquinoline series of glycine antagonists which contain a carboxylic acid, compounds can be found with nanomolar affinity for the receptor, but the best anticonvulsant activity in the DBA/2 mouse model is 29 mg/kg ip.[8c] In this novel series a 10-fold improvement in anticonvulsant potency is found in compounds with 100-fold less affinity for the receptor. This cannot be explained on the basis of gross differences in lipophilicity, as methyl ester **10** has a lower log *P* than many of the tetrahydroquinolines. The much improved penetration of the blood–brain barrier by the 4-hydroxy-2-quinolones may be due to the fact that they are vinylogous carboxylic acids, in which the negative charge of the anion is delocalized over a greater number of atoms than in the carboxylic acids.

The situation for the hydroxamic and carboxylic acids in Table V is complicated by there being other acidic protons in the molecules. The measured pK_A's for **47** and **51** are 8.0 and 2.8, respectively. The former is close to that of a normal hydroxamic acid,[22] whereas the latter is more similar to that of **8**. We would speculate that compounds **46–50** adopt a different binding mode (Figure 5) to that proposed above, in which it is the proton on the acidic group of the 3-position that is removed for binding, and, therefore, the increase in affinity afforded by a lipophilic group in the esters is not seen here. This binding mode has been proposed[7] to explain the affinity of quinoxalic acids.

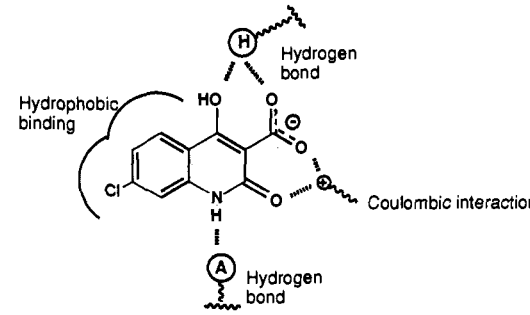


Figure 5. Proposed mode of binding of carboxylic acid **46**.

Conclusions

A novel series of antagonists at the glycine site of the NMDA receptor has been designed on the basis of our published pharmacophore. By the use of an acid bioisostere to replace the carboxylic acid present in many types of antagonist, potent systemic anticonvulsant action has been found, the first time that a series of full antagonists at this receptor has been shown to have consistent *in vivo* activity. *In vitro* potency can be increased by optimization of the aromatic substitution of the quinolone nucleus and by correct positioning of an electron rich aromatic ring, connected *via* the 3-position, to access a lipophilic binding pocket. A model is proposed for binding of these antagonists that includes some of the interactions postulated in a pharmacophore for kynurenic acids, but now the coulombic interaction between the 2-position anion and a positively charged site on the receptor is reinforced by binding to the π-system of the 3-substituent.

Experimental Section

Melting points were taken on a Reichert Thermovar apparatus and are uncorrected. Proton NMR were measured on Bruker AM 360 or AC 250 spectrometers and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. Mass spectra were recorded on a VG 70/250 spectrometer. Merck Kieselgel (230–400) mesh was used for column chromatography. For reactions, dry solvents were used as bought from Aldrich. Organic solutions were dried with anhydrous magnesium sulfate. Elemental analyses were done by C. H. N. Analysis Ltd., South Wigston, Leicester, U.K., and by Elemental Analysis Limited, Okehampton, Devon, U.K.

7-Chloro-3-(methoxycarbonyl)-2(1*H*)-oxindole (1). Ester **54**[15] (3 g, 10.9 mmol) was hydrogenated on Pd/C (10% w/w, 300 mg) in EtOAc (100 mL) at atmospheric pressure for 3 h. The mixture was filtered, evaporated, and recrystallized from EtOAc/hexane, then twice from MeOH to give **1** (0.50 g, 20%): mp 143–144 °C; ^{1}H NMR (360 MHz, $CDCl_3$) shows that **1** exists as a 3:1 mixture of enol/keto tautomers in solution; enol form δ 3.93 (3H, s, CH_3), 7.06 (1H, dd, J = 8.3 and 1.8 Hz, H-5), 7.21 (1H, d, J = 1.8 Hz, H-7), 7.57 (1H, d, J = 8.3 Hz, H-4), 11.4 (1H, br s, NH); keto form δ 3.77 (3H, s, CH_3), 4.37 (1H, s, H-3), 6.90 (1H, d, J = 1.5 Hz, H-7), 6.96 (1H, J = 8.0 and 1.5 Hz, H-5), 7.18 (1H, d, J = 8.0 Hz, H-4), 10.4 (1H, br s, NH); MS (EI) m/z 225 [M$^+$]. Anal. ($C_{10}H_8ClNO_3$) C, H, N.

6-Chloro-1,4-benzothiazin-3(4*H*)-one 1,1-Dioxide (3). 3-Chloroperoxybenzoic acid (1.15 g, 5.01 mmol) was added to a rapidly stirred suspension of 6-chloro-1,4-benzothiazin-3(4*H*)-one (**64**, 1.01 g, 5.01 mmol) in CH_2Cl_2 (50 mL). After 3 h the solvent was removed under reduced pressure and the residue

extracted with EtOAc. The organic extract was washed with $NaHCO_3$, H_2O, and brine, dried, and purified by flash chromatography (30% EtOAc/hexane), to give **3** (215 mg, 18%): mp 199–200°C (from EtOAc/hexane); ^1H NMR (360 MHz, DMSO-d_6) δ 4.77 (2H, s, CH_2), 7.25 (1H, d, J = 1.0 Hz, H-5), 7.37 (1H, dd, J = 7.0 and 1.0 Hz, H-7), 7.84 (1H, d, J = 7.0 Hz, H- 8); MS (EI) m/z = 231 (M^+). Anal. ($C_8H_8ClNO_3S$) C, H, N.

3-(Methoxycarbonyl)-6-chloro-1,4-benzothiazine-3(4*H*)-one 1,1-Dioxide (5). Sodium hydride (13.0 mg, 80% dispersion in oil, 0.4 mmol) was added to a solution of **3** (100 mg, 0.4 mmol) in DMF (5.0 mL) stirring at room temperature. After 15 min methyl cyanoformate (34 mg, 0.4 mmol) was added. After 1 h the reaction was quenched with acetic acid and diluted with H_2O. The aqueous solution was extracted with EtOAc, the organic extracts were washed with H_2O, dried, and evaporated to give 4 (69 mg, 57%): mp 185–187 °C (from EtOH); ^1H NMR (360 MHz, DMSO-d_6) δ 4.99 (1H, s, CH), 7.21 (1H, d, J = 1.0 Hz, H-5), 7.50 (1H, dd, J = 8.5 and 1.0 Hz, H-7), 7.91 (1H, d, J = 8.5 Hz, H-8); MS (EI) m/z = 289 (M^+). Anal. ($C_{10}H_8ClNO_5S$) C, H, N.

7-Chloro-3-(methylsulfonyl)-4-hydroxy-2(1*H*)-quinolone (6). *n*-Butyl chloroformate (1.59 g, 11.7 mmol) was added to a stirred solution of (methylsulfonyl)acetic acid (1.63 g, 11.7 mmol) and Et_3N (1.2 g, 11.8 mmol) in CH_2Cl_2 (20 mL) at −23 °C. After 15 min a solution of ethyl 4-chloroanthranilate (**61**, 2.3 g, 11.7 mmol), Et_3N (1.2 g, 11.8 mmol), and 4-(dimethylamino)pyridine (100 mg, 0.8 mmol) in CH_2Cl_2 (15.0 mL) was added. The reaction mixture was maintained at −23°C for a further 15 min and then at 0°C for 1 h. The solvent was then evaporated and the residue taken up in ethyl acetate (50 mL) and washed with citric acid, $NaHCO_3$, and brine, evaporated, and purified by flash chromatography on silica gel (20% EtOAc/ hexane) to give ethyl 4-chloro-2-[(methylsulfonyl)acetamido]benzoate (**62**, 2.4 g, 63%); mp 190–191°C (from ^{i}PrOH); ^1H NMR (360 MHz, $CDCl_3$) δ 1.42 (3H, t, J = 7.0 Hz CH_2CH_3), 3.18 (3H, s, SO_2CH_3), 4.06 (2H, s, $COCH_2$), 4.41 (2H, q, J = 7.0 Hz, CH_2CH_3), 7.15 (1H, dd, J = 8.5, 2.0 Hz, H-5), 8.01 (1H, d, J = 8.5 Hz, H-3), 8.95 (1H, d, J = 2.0 Hz, H-6); MS (EI) m/z = 319 (M^+ + H). Sodium methoxide (41 mg, 0.76 mmol) was added to a solution of **62** (180 mg, 0.56 mmol) in MeOH (40 mL). The reaction mixture was allowed to stir at room temperature for 18 h and then poured into 1 N HCl, giving a white precipitate which was filtered off to give **6** (85 mg, 60%): mp 238–240 °C sublimes (from DMF); ^1H NMR (360 MHz, DMSO-d_6) δ 3.48 (3H, s, CH_3), 7.32 (1H dd J = 6.5 and 2.0 Hz, H-6),7.35 (1H, d, J = 6.5 Hz, H-5),7.96 (1H, d, J = 2.0 Hz, H-8); MS (EI) m/z = 272 (M^+ + H). Anal. ($C_{10}H_8ClNO_4S$·0.4 H_2O) C, H, N.

7-Chloro-3-cyano-4-hydroxy-2(1*H*)-quinolone (7). *n*-Butyl chloroformate (1.61 g, 11.7 mmol) was added to cyanoacetic acid (1 g, 11.8 mmol) and Et_3N (1.65 mL, 11.9 mmol) in CH_2Cl_2 (20 mL) at −23 °C. After 15 min **61** (901 mg, 4.52 mmol), Et_3N (1.65 mL, 11.9 mmol), and 4-(dimethylamino)pyridine (100 mg, 0.83 mmol) in CH_2Cl_2 (7 mL) were added. After stirring at −23 °C for 15 min the mixture was brought to 0 °C for 1 h, then diluted with EtOAc, washed with 1 M citric acid, saturated $NaHCO_3$, H_2O, and brine, dried, evaporated, and purified by flash chromatography to give ethyl 2-(cyanoacetamido)-4-chlorobenzoate (**63**) as a white solid (214 mg, 18%). **63** (190 mg, 0.71 mmol) was suspended in MeOH (10 mL) and NaOMe (50 mg, 0.92 mmol) added. After stirring at room temperature for 30 min the mixture was acidified with 1 M HCl and extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried, and evaporated to give **7** (81mg, 52%) as long needles: mp 314–316 °C (from DMF/EtOAc/hexanes); ^1H NMR (360 MHz, DMSO-d_6) δ 7.24 (1H, dd, J = 1.8 and 8.6 Hz, H-6), 7.29 (1H, d, J = 1.8 Hz, H-8), 7.97 (1H, d, J = 8.6 Hz, H-5), 11.63 (1H, s, NH); MS (CI^+, NH_3) m/z = 221 (M^+ + H). Anal. ($C_{10}H_5ClN_2O_2$) C, H, N.

Ethyl 7-Chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (8). Ethyl malonyl chloride (26 mL, 30.7 g, 0.204 mol) in CH_2Cl_2 (100 mL) was added dropwise over 1h to a stirred solution of **61** (20.4 g, 0.102 mol), Et_3N (43 mL, 0.31 mol), and 4-(dimethylamino)pyridine (0.5 g, 4.1 mmol) in CH_2Cl_2 (300 mL) at 0 °C. After 1h Et_3N (43 mL, 0.31 mol) was added, and then ethyl malonyl chloride (26 mL, 30.7 g, 0.204 mol) in CH_2Cl_2 (100 mL) was added over 1 h. The suspension was evaporated, diluted with EtOAc, washed twice with 1 M citric acid, then saturated $NaHCO_3$ solution, H_2O, and brine, dried, and evaporated to give an oil (53 g). A 47-g sample of this oil was dissolved in EtOH (500 mL) and then NaOMe (16.2 g, 0.3 mol) was added. After 30 min the mixture was diluted with water and washed with EtOAc, and the aqueous layer acidified with concentrated HCl. The resulting precipitate was collected and dried to give 19g of white solid. A 17-g sample of this solid was recrystallized from DMF (300mL), keeping the temperature below 100 °C, then washed with H_2O, EtOH, and Et_2O, and dried to give **8** (8.81 g, 41% from **61**) as white needles: mp >340 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.1 Hz, CH_3), 4.33 (2H, q, J = 7.1 Hz, CH_2), 7.24 (1H, dd, J = 1.9 and 8.6 Hz, H-6), 7.30 (1H, d, J = 1.9 Hz, H-8), 7.92 (1H, d, J = 8.6 Hz, H-5), 11.58 (1H, s), 13.3 (1H, br s); MS (EI) m/z = 267 (M^+). Anal. ($C_{12}H_{10}ClNO_4$) C, H, N.

7-Chloro-4-hydroxy-2(1*H*)-quinolone (2). Ester **8** (0.5 g, 1.87 mmol) was refluxed in LiOH (0.5 M in H_2O, 15 mL) for 10 h, cooled, and acidified, and **2** (0.32 g, 87%) was collected as white crystals: mp 279 °C dec (from EtOAc); ^1H NMR (360 MHz, DMSO-d_6) δ 5.73 (1H, s, H-3), 7.16 (1H, dd, J = 2.0 and 8.5 Hz, H-6), 7.30 (1H, d, J = 2.0 Hz, H-8), 7.76 (1H, d, J = 8.5 Hz, H-5), 8.26 (1H, s), 11.47 (1H, s); MS (EI) m/z = 195 (M^+). Anal. ($C_9H_8ClNO_2$·0.1 H_2O) C, H, N.

Methyl 7-Chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (10). Ester **8** (0.42 g, 1.57 mmol) and MeOH (25 mL) were heated in a sealed apparatus with an internal temperature of 130 °C for 20 min. The mixture was cooled, and the solid was collected and recrystallized from DMF, keeping the temperature below 110 °C, to give the ester **10** (107 mg, 27%) as white needles: sublimes 240 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 3.85 (3H, s, CH_3), 7.24 (1H, dd, J = 2.0 and 8.6 Hz, H-6), 7.29 (1H, d, J = 2.0 Hz, H-8), 7.93 (1H, d, J = 8.6 Hz, H-5), 11.60 (1H, s); MS (EI) m/z = 253 (M^+). Anal. ($C_{11}H_8ClNO_4$) C, H, N.

The following compounds were made in the same way as **10** using the appropriate alcohol.

Propyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (11): fine white needles; mp >320 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 0.97 (3H, t, J = 7 Hz, CH_3), 1.69 (2H, sextet, J = 7 Hz, OCH_2CH_2), 4.23 (2H, t, J = 7 Hz, OCH_2), 7.23 (1H, dd, J = 0.6 and 8.6 Hz, H-6), 7.29 (1H, d, J = 0.6 Hz, H-8), 7.92 (1H, d, J = 8.6 Hz, H-5), 11.48 (1H, s); MS (CI^+, NH_3) m/z = 282 (M^+ + H). Anal. ($C_{13}H_{12}ClNO_4$) C, H, N.

1-(2-Propenyl) 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (12): white needles mp >320 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 4.81–4.83 (2H, m, OCH_2), 5.27 (1H, d with other fine coupling, J = 9 Hz, C=CH_AH$_B$), 5.57 (1H, d with other fine coupling, J = 17 Hz, C=CH_AH$_B$), 5.96–6.06 (1H, m, CHCH$_2$), 7.25 (1H, dd, J = 1.9 and 8.6 Hz, H-6), 7.30 (1H, d, J =1.9 Hz, H-8), 7.94 (1H, d, J = 8.6 Hz, H-5), 11.58 (1H, s), 13.3 (1H, br s); MS (EI) m/z = 279 (M^+). Anal. ($C_{13}H_{10}ClNO_4$) C, H, N.

1-(3-Propynyl) 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (13): white needles, mp >300 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 3.62 (1H, t, J 2.5 Hz, CH_2CCH), 4.94 (2H, dt J = 2.5 Hz, CH_2), 7.25 (1H, dd, J = 8.6 and 1.8 Hz, H-6), 7.30 (1H, d, J = 1.8 Hz, H-8), 7.94 (1H, d, J = 8.6 Hz, H-5), 11.6 (1H, br s), 13.0 (1H, br s); MS (EI) m/z = 277 (M^+). Anal. ($C_{13}H_8ClNO_4$) C, H, N.

2-(3-Hydroxyphenyl)ethyl 7-Chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (15). Ester **8** (0.43 g, 1.60 mmol) and 2-(3-hydroxyphenyl)ethanol (1 g, 7.2 mmol) were heated together at 140 °C for 20 min and cooled, EtOAc added, and the solid collected, dried, and recrystallized from DMF/acetone/H_2O to give **15** (226 mg, 39%) as white needles: mp 257–259 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 2.92 (2H, t, J = 7.2 Hz, CH_2Ar), 4.44 (2H, t, J = 7.2 Hz, CH_2OCO), 6.62 (1H, dd, J = 1 and 7.8 Hz, CHCHCOH), 6.71 (1H, d, J = 1 Hz, CCHCOH), 6.76 (1H, d, J = 7.8 CHCHCHCOH), 7.08 (1H, t, J = 7.8 Hz, CHCHCOH), 7.24 (1H, dd, J = 1.8 and 8.7 Hz, H-6), 7.29 (1H, d, J = 1.8 Hz, H-8), 7.93 (1H, d, J = 8.7 Hz, H-5), 9.27 (1H, s), 11.58 (1H, s), 13.3 (1H, br s); MS (EI) m/z = 359 (M^+). Anal. ($C_{18}H_{14}ClNO_5$) C, H, N.

The following compounds were made in the same way as **15** with the appropriate alcohol.

3-Hydroxybenzyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (14): white crystals: mp 219–220 °C (from DMF/acetone/H_2O); ^1H NMR (360 MHz, DMSO-d_6) δ 5.28 (2H, s, CH_2), 6.72 (1H, d, J = 8 Hz, ArH, ortho or para to OH), 6.87 (1H, s,

ArH, ortho to OH and CH_2), 6.89 (1H, d, J = 8.0 Hz, ArH, para or ortho to OH), 7.17 (1H, t, J = 8.0 Hz, ArH, meta to OH), 7.25 (1H, dd, J = 1.9 and 9.9 Hz, H-6), 7.31 (1H, d, J = 1.9 Hz, H-8), 7.94 (1H, d, J = 9.9 Hz, H-5), 9.45 (1H, s), 11.56 (1 H, br s), 13.2 (1 H, br s); MS (EI) m/z = 345 (M^+). Anal. ($C_{17}H_{12}ClNO_5$) C, H, N.

3-(3-Hydroxyphenyl)propyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (16): white crystals; mp 224–220 °C (from DMF/acetone/H_2O); ^1H NMR (360 MHz, DMSO-d_6) δ 1.96 (2H, quin, J = 7 Hz, $CH_2CH_2CH_2$), 2.66 (2H, t, J = 7 Hz, CH_2Ar), 4.28 (2H, t, J = 7 Hz, OCH_2), 6.8-6.85 (2H, m, ArH) and 6.57 (1H, dd, J = 1.7 and 8 Hz, ArH), 7.07 (1H, t, J = 8 Hz, HOCCHC*H*), 7.24 (1H, dd, J = 1.9 and 8.6 Hz, H-6), 7.31 (1H, d, J = 1.9 Hz, H-8), 7.93 (1H, d, J = 8.6 Hz, H-5), 9.2 (1H, br s), 11.54 (1H, s), 13.3 (1H, br s); MS (EI) m/z = 373 (M+). Anal. ($C_{19}H_{16}ClNO_5$) C, H, N.

4-(3-Hydroxyphenyl)butyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (17): white lozenges; mp 187–188 °C (from acetone); ^1H NMR (360 MHz, DMSO-d_6) δ 1.69 (4H, br s, $CH_2CH_2CH_2CH_2$), 2.55 (2H, br s, CH_2Ar), 4.30 (2H, br s, OCH_2), 6.56 (1H, dd, J = 7.7 and 2.5 Hz, CHCHC*H*), 6.61 (1H, d, J = 2.5 Hz, HOCC*H*C), 6.62 (1H, d, J = 7.7 Hz, C*H*CHCH), 7.05 (1H, t, J = 7.7 Hz, HOCCHC*H*), 7.24 (1H, dd, J = 1.8 and 8.6 Hz, H-6), 7.30 (1H, d, J = 1.8 Hz, H-8), 7.93 (1H, d, J = 8.6 Hz, H-5), 9.19 (1H, s), 11.54 (1H, s), 13.3 (1H, br s); MS (EI) m/z = 387 (M^+). Anal. ($C_{20}H_{18}ClNO_5$) C, H, N.

2-(2-Hydroxyphenyl)ethyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (18): white needles; mp >320 °C (from DMF/acetone/H_2O); ^1H NMR (360 MHz, DMSO-d_6) δ 2.96 (2H, t, J = 7.4 Hz, CH_2Ar), 4.43 (2H, t, J = 7.4 Hz, OCH_2), 6.71 (1H, t, J = 8Hz, CH_2CCHC*H*), 6.80 (1H, d, J = 8 Hz, HOCC*H*), 7.04 (1H, dt, J = 1.5 and 8 Hz, HOCCHC*H*), 7.18 (1H, dd, J = 1.5 and 8 Hz, CH_2C*H*), 7.24 (1H, dd, J = 1.9 and 8.6 Hz, H-6), 7.29 (1H, d, J = 1.9 Hz, H-8), 7.93 (1H, d, J = 8.6 Hz, H-5), 9.45 (1H, br s), 11.58 (1H, s), 13.3 (1H, br s); MS (EI) m/z = 359 (M^+). Anal. ($C_{18}H_{14}ClNO_5$) C, H, N.

2-(4-Hydroxyphenyl)ethyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (19): white needles; mp 258–260 °C (from DMF/acetone); ^1H NMR (360 MHz, DMSO-d_6) δ 2.89 (1H, t, J = 7.1 Hz, CH_2Ar), 4.39 (2H, t, J = 7.1 Hz, OCH_2), 6.67 (2H, d, J = 8.4 Hz, HOCC*H*), 7.14 (2H, d, J = 8.4 Hz, CH_2CC*H*), 7.24 (1H, dd, J = 1.9 and 8.7 Hz, H-6), 7.29 (1H, d, J = 1.9 Hz, H-8), 7.93 (1H, d, J = 8.7 Hz, H-5), 9.19 (1H, s), 11.59 (1H, s),13.3 (1H, br s); MS (FAB·) m/z = 358 (M^+ - H). Anal. ($C_{18}H_{14}ClNO_5$) C, H, N.

2-(2-Pyridyl)ethyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (20): white needles; mp 319 °C (from MeOH); ^1H NMR (360 MHz, DMSO-d_6) δ 3.19 (2H, t, J = 6.6 Hz, $ArCH_2$), 4.62 (2H, t, J = 6.6 Hz, OCH_2), 7.23 (1H, dd, J = 2.0 and 8.6 Hz, H-6), 7.29–7.31 (2H, m, H-8 and pyridine H-5), 7.46 (1H, d, J = 7.7 Hz, pyridine H-3), 7.77 (1H, dt, J = 1.6 and 7.7 Hz, pyridine H-4), 7.95 (1H, d, J = 8.6 Hz, H-5), 8.52 (H, d, J = 8 Hz, pyridine H-6), 11.5 (1H, br s); MS (EI) m/z = 344 (M^+). Anal. ($C_{17}H_{13}ClN_2O_4$) C, H, N.

2-(2-Thiophenyl)ethyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (21): white needles; mp 293 °C sublimes (from DMF/H_2O); ^1H NMR (360 MHz, DMSO-d_6) δ 3.04 (2H, t, J = 6.7 Hz, CH_2Ar), 4.46 (2H, t, J = 6.7 Hz, OCH_2), 7.19 (1H, dd, J = 4.8 and 1.1 Hz, SCHC*H*), 7.25 (1H, dd, J = 8.7 and 1.9 Hz, H-6), 7.30 (1H, d, J = 1.9 Hz, H-8), 7.41 (1H, d, J = 1.7 Hz, SCHC), 7.45 (1H, dd, J = 4.8 and 3.0 Hz, SC*H*CH), 7.94 (1, d, J = 8.7 Hz, H-5), 11.59 (1H, s), 13.3 (1H, br s); MS (CI^+, NH_3) m/z = 350 (M^+ + H). Anal. ($C_{18}H_{12}ClNO_4S$) C, H, N.

2-(3-Indolyl)ethyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (22): mp 240–244 °C dec; ^1H NMR (360 MHz, DMSO-d_6) δ 3.14 (2H, t, J = 7.2 Hz, CH_2–indole), 4.52 (2H, t, J = 7.2 Hz, CH_2O), 6.98 (1H, t, J = 7.0 Hz, indole H-5 or indole H-6), 7.06 (1H, t, J = 7.1 Hz, indole H-5 or indole H-6), 7.3–7.4 (3H, m, H-6 or H-8, and indole H-2, and indole H-4 or indole H-7), 7.60 (1H, d, J = 7.1 Hz, indole H-4 or indole H-7), 7.87 (1H, d, J = 2.1 Hz, H-6 or H-8), 10.87 (1H, s), 11.67 (1H, s); MS (CI^+) m/z = 365 (M^+ + H - $C_{10}H_{10}N$). Anal. ($C_{20}H_{14}ClN_2O_4$) C, H, N.

3-(3-Methoxyphenyl)prop-2-ynyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (23): white needles; mp >310 °C (from DMF/H_2O); ^1H NMR (360 MHz, DMSO-d_6) δ 3.77 (3H, s, CH_3), 5.20 (2H, s, CH_2), 7.01 (1H, dd, J = 8 and 2.2 Hz, CHCHC*H*), 7.02 (1H, d, J = 2.2 Hz, OCC*H*C), 7.06 (1H, d, J = 7.6 Hz, C*H*CHCH), 7.25 (1H, dd, J = 2.0 and 8.6Hz, H-6), 7.33–7.29 (2H, m, H-8 and OCCHC*H*), 7.95 (1H, d, J = 8.6 Hz, H-5), 11.64 (1H, s), 13.0 (1H, br s); MS (CI^+, NH_3) m/z = 239 (M^+ - $C_{10}H_9O$ + H). Anal. ($C_{20}H_{14}ClNO_5 \cdot 0.1\ H_2O$) C, H, N.

3-(3-Hydroxyphenyl)prop-2-ynyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (24): off-white crystalline solid; mp 234–236 °C (from DMF/acetone/H_2O); ^1H NMR (360 MHz, DMSO-d_6) δ 5.18 (2H, s, CH_2), 6.82 (1H, d, J = 7.8 Hz, CHCHC*H*), 6.83 (1H, s, C(OH) C*H*C), 6.90 (1H, d, J = 7.8 Hz, C*H*CHCH), 7.19 (1H, t, J = 7.8 Hz, CHC*H*CH), 7.26 (1H, dd, J = 8.6 and 1.9 Hz, H-6), 7.3 (1H, d, J = 7.8 Hz, H-8), 7.95 (1H, d, J = 8.6 Hz, H-5), 9.69 (1H, br s), 11.65 (1H, br s), 13.0 (1H, v br s); MS (CI^+, NH_3) m/z = 239 (M - CH_2CCAr). Anal. ($C_{19}H_{15}ClNO_5 \cdot 0.1\ H_2O$) C, H, N.

***S*-2-Phenylethyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-thiocarboxylate (52):** pale yellow needles; mp >320 °C (from DMF/acetone/H_2O), change of crystalline form at 237–241°C; ^1H NMR (360 MHz, DMSO-d_6) δ 2.91 (2H, t, J = 7.6 Hz, CH_2Ph), 3.19 (2H, t, J = 7.6 Hz, SCH_2), 7.34–7.22 (7H, m, H-6, H-8, 5 × Ar), 8.00 (1H, d, J = 8.6 Hz, H-5), 11.82 (1H, br s), 15.0 (1H, br s); MS (EI) m/z = 255 (M^+ + H - $C_8H_5CH_2CH_2$). Anal. ($C_{18}H_{14}ClNO_3S \cdot 0.1H_2O$) C, H, N.

Ethyl 7-chloro-4-hydroxy-5-iodo-2(1*H*)-quinolone-3-carboxylate (32). A mixture of 3-chloro-5-iodoaniline (63.41g, 0.249 mol) in water (150 mL), concentrated HCl (22.1 mL) and 1,4-dioxane (60 mL) was heated to gain solution before being added to a mixture of chloral hydrate (90.24 g, 0.54 mol) and Na_2SO_4 (650 g) in H_2O (600 mL) which had been warmed to 50 °C. $H_2NOH \cdot HCl$ (110.56 g, 1.59 mol) in H_2O (250 mL) was then added and the reaction heated at reflux for 45 min before being allowed to cool to room temperature and the resultant yellow precipitate of *N*-(3-chloro-5-iodophenyl)(hydroxyimino)acetamide was filtered off, washed with H_2O, and dried. The (hydroxyimino)-acetanilide (45 g, 0.138 mol) was added portionwise to prewarmed concentrated H_2SO_4 (175 mL) keeping the internal temperature between 50 and 70 °C using an ice bath. After complete addition, the now dark solution was heated at 80 °C for 10 min before being allowed to cool to room temperature and poured on to 10 times the reaction volume of ice. The resultant slurry was swirled vigorously and left to stand for 1 h before filtering off the resultant rust colored precipitate, washing with water and drying. This yielded a mixture of 6-chloro-4-iodo- and 4-chloro-6-iodoisatins: ^1H NMR (250 MHz, DMSO-d_6) δ 6.98 (1H, d, J = 1.6 Hz, H-5 or H-7), 7.25 (1H, d, J = 1.0 Hz, H-5′ or H-7′), 7.50 (1H, d, J = 1.0 Hz, H-5′ or H-7′), 7.55 (1H, d, J = 1.6 Hz, H-5 or H-7), 11.26 (1H, s, N′H), 11.18 (1H, s, NH). H_2O_2 (30% v/v, 35.7 mL) was added portionwise to a solution of the mixture of the above isatins (53.68 g, 0.174 mol) at room temperature in 1 N NaOH solution (525 mL). Once effervescence had stopped, the reaction was cautiously neutralized with 2 N HCl and filtered to remove insolubles before acidifying to pH 2–3. The resultant sandy yellow precipitate was filtered off and washed with water and dried to yield a mixture of the 2-amino-4-chloro-6-iodo- and 2-amino-6-chloro-4-iodo benzoic acids (10.56 g, 14% from the aniline). Dissolving a mixture of the isomers (8 g) in boiling acetone and reducing the volume until a solid started to crystallize out resulted in the formation of the Schiff's base [enriched (10:1) in the more prevalent 4-chloro-6-iodo isomer]. Hydrolysis of this imine with 2 N hydrochloric acid yielded the aminobenzoic acid. Repetition of this process gave the 2-amino-4-chloro-6-iodobenzoic acid (3.75g) in >95% purity: ^1H NMR (250 MHz, DMSO-d_6) δ 7.05 (1H, d, J = 1.9 Hz, H-3 or H-5), 6.79 (1H, d, J = 1.9 Hz, H-3 or H-5). (At this point the regiochemistry was proven by hydrogenolytic removal of the iodine on Pd/C to give 4-chloroanthranilate.) Treatment of an ethereal solution of the iodo chloro acid (2.68 g) with diazomethane and evaporation yielded **55** (2.81 g, 100%) as a yellow oil which solidified on standing: ^1H NMR (360 MHz, DMSO-d_6) δ 3.61 (3H, s, CH_3), 5.89 (2H, s, NH_2), 6.78 (1H, d, J = 1.9Hz, H-3 or H-5), 7.04 (1H, d, J = 1.9 Hz, H-3 or H-5). This was then treated as for **8** to give **34** as fine needles: mp 212–216 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 7.1 Hz, CH_3), 4.35 (2H, q, J = 7.1 Hz, CH_2), 7.33 (1H, d, J = 2.0 Hz, H-6 or H-8), 7.86 (1H, d, J = 2.0 Hz, H-6 or H-8), 11.65 (1H, s); MS (EI) m/z = 393 (M^+). Anal. ($C_{12}H_9ClINO_4$) C, H, N.

Other compounds in Table III were made in a similar way.

Ethyl 4-hydroxy-2(1*H*)-quinolone-3-carboxylate (25): white needles; mp 194–197 °C (from EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.32 (3 H, t, J = 7.8 Hz, CH_2CH_3), 4.35 (2 H, q, J = 7.8 Hz, CH_2), 7.21 (1 H, t, J = 8 Hz, H-6), 7.28 (1 H, d, J = 8 Hz, H-8), 7.63 (1 H, dt, J = 1.2 and 8 Hz, H-7), 7.94 (1 H, dd, J = 1.2 and 8 Hz, H-5), 11.5 (1 H, br s), 13.4 (1 H, br s); MS (CI$^+$, NH_3) m/z = 234 (M^+ + H). Anal. ($C_{12}H_{11}NO_4$) C, H, N.

Ethyl 4-hydroxy-5-methyl-2(1*H*)-quinolone-3-carboxylate (26): white rhombohedral crystals: mp 198–200 °C (from acetone); ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 7.5 Hz, CH_2CH_3), 2.74 (3H, s, CCH_3), 4.35 (2H, q, J = 7.5 Hz, CH_2), 6.94 (1H, d, J = 9 Hz, H-8), 7.12 (1H, d, J = 9 Hz, H-8), 7.46 (1H, t, J = 9 Hz, H-7), 11.4 (1H, br s); MS (EI) m/z = 247 (M^+). Anal. ($C_{13}H_{13}NO_4$) C, H, N.

Ethyl 6-chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (27): white needles: mp 250 °C dec (from EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.3 (3H, t, J = 7.1 Hz, CH_3), 4.32 (2H, q, J = 7.1 Hz, CH_2), 7.28 (1H, d, J = 8.8 Hz, H-8), 7.64 (1H, dd, J = 2.4 and 8.8 Hz, H-7), 7.88 (1H, d, J = 2.4 Hz, H-5), 11.61 (1H, s); MS (EI) m/z = 267 (M^+). Anal. ($C_{12}H_{10}ClNO_4$) C, H, N.

Ethyl 4-hydroxy-8-methyl-2(1*H*)-quinolone-3-carboxylate (28): white crystals; mp 215 °C sublimes (from EtOH); ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.34 (3H, t, J = 7.5 Hz, CH_2CH_3), 2.41 (3H, s, CCH_3), 4.36 (2H, q, J = 7.5 Hz, CH_2), 7.13 (1H, t, J = 9 Hz, H-6), 7.46 (1H, d, J = 9 Hz, H-7), 7.81 (1H, t, J = 9 Hz, H-5), 10.5 (1H, br s); MS (EI) m/z = 247 (M^+). Anal. ($C_{13}H_{13}NO_4$) C, H, N.

Ethyl 7-cyano-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (29): white crystals; mp 224–228 °C (from DMF); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 7.1 Hz, Me), 4.32 (2H, q, J = 7.1 Hz, CH_2), 7.57 (1H, dd, J = 1.4 and 8.3 Hz, H-6), 7.61 (1H, d, J = 1.4 Hz, H-8), 8.07 (1H, d, J = 8.3 Hz, H-5), 11.77 (1H, s); MS (EI) m/z = 258 (M^+). Anal. ($C_{13}H_{10}N_2O_4$) C, H, N.

Ethyl 4-hydroxy-7-(trifluoromethyl)-2(1*H*)-quinolone-3-carboxylate (30): white crystals; mp >300 °C (from DMF); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 7.1 Hz, Me), 4.33 (2H, q, J = 7.1 Hz, CH_2), 7.51 (1H, d, J = 8.4 Hz, H-6), 7.59 (1H, s, H-8), 8.17 (1H, d, J = 8.4 Hz, H-5), 11.76 (1H, s); MS (EI) m/z = 301 (M^+). Anal. ($C_{13}H_{10}F_3NO_4$) C, H, N.

Ethyl 4-hydroxy-7-nitro-2(1*H*)-quinolone-3-carboxylate (31): white crystals; mp >300 °C (from DMF); ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 7 Hz, Me), 4.32 (2H, q, J = 7 Hz, CH_2), 7.96 (1H, dd, J = 2 and 9 Hz, H-6), 8.06 (1H, d , J = 2 Hz, H-8), 8.16 (1H, d, J = 9 Hz, H-5), 11.9 (1H, br s); MS (EI) m/z = 278 (M^+). Anal. ($C_{12}H_{10}N_2O_8$) C, H, N.

Ethyl 6,7-Dinitro-4-hydroxy-2(1*H*)-quinolone-3-carboxylate (33). Concentrated HNO_3 and concentrated H_2SO_4 (1:1 v/v, 30 mL) was added to a solution of **31** (3.95 g, 14.2 mmol) in concentrated H_2SO_4 (60 mL), and then the solution was heated at 60 °C for 90 min, cooled to room temperature and poured into cold H_2O. **33** (3.82 g, 83%) was collected as crystals: mp 229–231 °C (from DMF); ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7 Hz, CH_3), 4.31 (2H, q, J = 7 Hz, CH_2), 7.81 (1H, s, H-8), 8.68 (1H, s, H-5), 12.4 (1 H, br s); MS (EI) m/z = 322 (M^+). Anal. ($C_{12}H_9N_3O_8$·0.1H_2O) C, H, N.

7-Chloro-4-hydroxy-3-(3-thienoyl)-2(1*H*)-quinolone (35). A solution of $COCl_2$ in toluene (36.3 mL, 20% w/w) was added dropwise over 30 min to a stirred solution of **61** (10.0 g, 50 mmol) and Et_3N (15 mL, 108 mol) in THF at −5 °C. The temperature was maintained at −5 °C for 1 h and then allowed to warm to room temperature. After 1 h Et_2O (200 mL) was added and the solution filtered and evaporated to give 2-(ethoxycarbonyl)-5-chlorophenyl isocyanate (**65**)as a white solid (11.2 g, 99%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.39 (3H, t, J = 7.5 Hz, CH_3), 4.34 (2H, q, J = 7.5 Hz, CH_2), 7.22 (1H, d, J = 1.0 Hz, H-6), 7.28 (1H, dd, J = 6.5 and 1.0 Hz, H-4), 8.31 (1H, d, J = 6.5 Hz, H-3); MS (EI) m/z = 225 (M^+). 3-Acetylthiophene (1.1 g, 8.7 mmol) in THF (10 mL) was added dropwise to a solution of lithium hexamethyldisilazide (9.0 mL, 1 M, 9 mmol) in THF (20 mL) at −78 °C. The resulting solution was allowed to warm to 0 °C over 30 min and then recooled to −78 °C. A solution of **65** (1.0g, 4.4 mmol) in THF (10 mL) was added dropwise over 15 min. The temperature was maintained at −78 °C for 30 min and then allowed to warm to room temperature. After 2 h the reaction mixture was poured into 1 N HCl (50 mL), extracted with Et_2O (4 × 50 mL), washed with H_2O (50 mL) and brine (50 mL), dried, evaporated and recrystallized from MeOH to give ethyl 4-chloro-2-[2-(3-thienoyl)acetamido]benzoate as pale yellow needles (740 mg, 24%): mp 260–263 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.4 (3H, t, J = 7.5 Hz, CH_3), 4.02 (2H, s, CH_2CO), 4.4 (2H, q, J = 7.5 Hz, CH_2CH_3), 7.05 (1H, dd, J = 8.5 and 1.0 Hz, H-6), 7.1–7.2 (1H, m, thiophene-H), 7.4–7.5 (1H, m, thiophene -H), 7.45 (1H, d, J = 8.5 Hz, H-5), 8.0–8.1 (1H, m, thiophene-H), 8.8 (1H, d, J = 1.0 Hz, H-8). NaOMe (61.4 mg, 1.13 mmol) was added to a suspension of this ester (200 mg, 0.57 mmol) in MeOH (20 mL) and refluxed for 18 h. The reaction mixture was cooled to room temperature and poured into 1 N HCl (50 mL). The resulting precipitate was filtered off and recrystallized from DMF to give **35** as pale yellow needles: mp 313–320 °C dec; ^{1}H NMR (360 MHz, DMSO-d_6) δ 7.23 (1H, dd, J = 9.5 and 1.0 Hz, H-6), 7.33 (1H, d, J = 1.0 Hz, H-8), 7.45 (1H, dd, J = 5.5 and 1.0 Hz, thiophene-H), 7.56 (1H, dd, J = 5.5 and 2.0 Hz, thiophene-H), 7.95 (1H, d, J = 9.5 Hz, H-5), 8.26 (1H, dd, J = 2.0 and 1.0 Hz, thiophene-H-2); MS (EI) m/z = 305 [M^+]. Anal. ($C_{14}H_8ClNO_3S$·0.1H_2O) C, H, N.

Other compounds in Table IV were made in a similar way.

7-Chloro-3-(3-phenylpropionyl)-4-hydroxy-2(1*H*)-quinolone (41): mp 244–246 °C (from DMF); ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.92 (2H, t, J = 6.0 Hz, CH_2Ph), 3.50(2H, t, J = 6.0 Hz, $COCH_2$), 7.29 (7H, m, H-6, H-8, and Ph), 7.92 (1H, d, J = 8.0 Hz, H-5), 10.30 (1H, s,); MS (EI) m/z = 327 (M^+). Anal. ($C_{18}H_{14}ClNO_3$) C, H, N.

7-Chloro-4-hydroxy-3-(2-furanoyl)-2(1*H*)-quinolone (36): yellow needles; mp 310 °C (from DMF); ^{1}H NMR (360 MHz, DMSO-d_6) δ 6.69 (1H, dd, J = 3.6 and 1.5 Hz, –OCHC*H*–), 7.24 (1H, dd, J = 8.5 and 2.0 Hz, H-6), 7.3–7.4 (2H, m, –OCHCHC*H*– and H-8), 7.94 (1H, d, J = 8.5 Hz, H-5), 7.99 (1H, d, J = 1.5 Hz, –OC*H*), 11.57 (1H, br s, NH); MS (EI) m/z = 287 (M^+). Anal. ($C_{14}H_8ClNO_4$) C, H, N.

7-Chloro-3-(pyridylcarbonyl)-4-hydroxy-2(1*H*)-quinolone (37): mp 277–280°C (from DMF); ^{1}H NMR (360 MHz, DMSO-d_6) δ 6.90 (1H, dd, J = 8.0 and 1.0 Hz, H-6), 7.10 (1H, d, J = 1.0 Hz, H-8), 7.33 (1H, dd, J = 8.0 and 1.0 Hz, H-5′), 7.77 (1H, d, J = 7.0 Hz, H-5), 7.90 (1H, m, H-4′), 8.50 (1H, dd, J = 8.0 and 1.0 Hz, H-6′), 8.63 (1H, d, J = 1.0 Hz, H-2′), 9.05 (1H, s, O*H*); MS (EI) m/z = 300 (M^+). Anal. ($C_{15}H_8ClN_2O_3$) C, H, N.

3-(Cyclohexylcarbonyl)-7-chloro-4-hydroxy-2(1*H*)-quinolone (38): mp 220–225°C (from DMF); ^{1}H NMR (360 MHz DMSO) δ 1.23–1.36 (5H, m, cyclohexane CH), 1.77–1.84 (5H, m, cyclohexane CH), 3.97 (1H, m, $COCHCH_2$), 7.26 (1H, dd, J = 7.0 and 1.0 Hz, H-5), 7.33 (1H, d, J = 1.0 Hz, H-8), 7.97 (1H, d, J = 7.0 Hz, H-6); MS (EI) m/z = 306 (M^+). Anal. ($C_{18}H_{18}ClNO_3$·0.1H_2O) C, H, N.

7-Chloro-4-hydroxy-3-(2-phenylacetyl)-2(1*H*)-quinolone (39): white needles, mp 174–176 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.80 (2H, s, CH_2), 7.05 (1H, dd, J = 6.0 and 1.0 Hz, H-6), 7.0 (5H, m, Ar-H), 7.99 (1H, d, J = 6.0 Hz, H-5), 8.82 (1H, d, J = 1.0 Hz, H-8), 10.6 (1H, br s); MS (EI) m/z = 327 (M^+). Anal. ($C_{17}H_{17}ClNO_3$·0.75H_2O) C, H, N.

7-Chloro-4-hydroxy-3-(2-thienylacetyl)-2(1*H*)-quinolone (40): mp 305–310 °C (from DMF); ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.49 (1H, s, CH_2) 7.10 (1H, dd, J = 6.0 and 1.0 Hz, H-6), 7.27 (1H, d, J = 6.0 Hz, H-5), 7.36 (1H, d, J = 1.0Hz, H-8), 7.51 (1H, d, J = 3.0 Hz, H-3′), 8.19 (2H, m, H-4′ and H-5′), 11.10 (1H, s); MS (EI) m/z = 320 (M^+). Anal. ($C_{15}H_{10}ClNO_3S$) C, H, N.

7-Chloro-3-(cyclopropylcarbonyl)-4-hydroxy-2(1*H*)-quinolone (42): white needles; mp 227–230 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.2–1.28 (4H, m, CH_2CH_2), 3.96–4.01 (1H, m, $COCHCH_2$), 7.26 (1H, dd, J = 9.0 and 1.5 Hz, H-6), 7.31 (1H, d, J = 1.5 Hz, H-8), 7.97 (1H, d, J = 9.0 Hz, H-5), 11.63 (1H, br s); MS (EI) m/z = 264 (M^+). Anal. ($C_{13}H_{10}ClNO_3$) C, H, N.

3-Benzoyl-7-chloro-4-hydroxy-2(1*H*)-quinolone (9). Sodium hydride (4.5 g, 37.5 mmol) was added to a solution of dibenzoylmethane (5.62 g, 25 mmol) in THF (25 mL), and the resulting mixture was stirred at 0 °C for 1 h and then added to a solution of isocyanate **65** (1.05 g, 5.0 mmol) at 0 °C. The reaction was warmed to room temperature, stirred for 24 h, then quenched with H_2O, and extracted into EtOAc. The organic extract was washed with H_2O and brine, dried, and evaporated to give a yellow oil. This was redissolved in MeOH (25 mL) containing NaOMe

(270 mg, 5.0 mmol) and warmed to 50 °C for 2 h. The reaction was cooled to room temperature and poured into 1 N HCl to give a white precipitate which was filtered off to give **9** (221 mg, 15%): mp 240°C sublimes (from DMF); ^{1}H NMR (360 MHz, DMSO-d_6) δ 7.21 (1H, dd, J = 7.0 and 1.0 Hz, H-6), 7.29 (1H, d, J = 1.0 Hz, H-7), 7.40–7.55 (4H, m, ArH), 7.75–7.8 (1H, m, ArH), 7.89 (1H, d, J = 7.0 Hz, H-5), 11.59 (1H, s); MS (EI$^+$) m/z = 298 (M^+ + H). Anal. ($C_{18}H_{10}ClNO_3$) C, H, N.

3-Acetyl-7-chloro-4-hydroxy-2(1*H*)-quinolone (34): mp 240 °C sublimes (from DMF); ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.70 (3H, s, CH_3), 7.23 (1H, dd, J = 5.0 and 1.0 Hz, H-6), 7.27 (1H, d, J = 1.0 Hz, H-7), 7.94 (1H, d, J = 5.0 Hz, H-5), 11.60 (1H, s); MS (EI$^+$) m/z = 237 (M^+ + H). Anal. ($C_{11}H_8ClNO_3$) C, H, N.

7-Chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxamide (43). A solution of **8** (0.41 g, 1.53 mmol) in EtOH saturated with NH_3 was heated in a sealed apparatus with an internal temperature of 160 °C for 20 min. The mixture was cooled, and the product was collected, washed with HCl solution, H_2O, EtOH, Et_2O, and dried, and recrystallized from DMF to give **43** (219 mg, 60%) as white needles: mp 307–309 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 7.28 (1H, dd, J = 8.6 and 1.9 Hz, H-6), 7.35 (1H, d, J = 1.9 Hz, H-8), 7.94 (1H, d, J = 8.6 Hz, H-5), 8.6 (1H, br s), 9.5 (1H, br s), 11.76 (1H, br s), 17.8 (1H, br s); MS (EI) m/z = 238 (M^+). Anal. ($C_{10}H_7ClN_2O_3$) C, H, N.

3-[[*N*-[2-(4-Hydroxyphenyl)ethyl]amino]carbonyl]-7-chloro-4-hydroxy-2(1*H*)-quinolone (44): white needles; mp 281–283 °C (from acetone); ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.75 (2H, t, J = 7.2 Hz, $ArCH_2$), 3.54 (2H, t, J = 7.2 Hz, NCH_2), 6.68 (2H, d, J = 8.4 Hz, ArH, ortho to OH), 7.06 (2H, d, J = 8.4 Hz, ArH, meta to OH), 7.29 (1H, dd, J = 1.9 and 8.6 Hz, H-6), 7.35 (1H, d, J = 1.9 Hz, H-8), 7.95 (1H, d, J = 8.6 Hz, H-5), 9.20 (1H, br s), 10.19 (1H, s), 11.86 (1H, br s); MS (CI$^+$, NH_3, 550K), 359 (M^+ + H). Anal. ($C_{18}H_{15}ClN_2O_4$) C, H, N.

3-[(*N*-Benzyl-*N*-methylamino)carbonyl]-7-chloro-4-hydroxy-2(1*H*)-quinolone (45): off white needles; mp 295–296 °C (from EtOAc/hexane); ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.83 (3H, s, Me), 4.58 (2H, s, CH_2), 7.20 (1H, dd, J = 2.0 and 8.7 Hz, H-6), 7.2–7.4 (6H, m, Ph and H-8), 7.94 (1H, d, J = 8.7 Hz, H-5), 11.5 (1H, br s); MS (CI$^+$, NH_3) m/z = 343 (M^+ + H). Anal. ($C_{18}H_{15}ClN_2O_3$) C, H, N.

7-Chloro-4-hydroxy-2(1*H*)-quinolone-3-carboxylic Acid (46). Sodium hydride (0.8 g, 80% in oil, 25.6 mmol) was added to a mixture of **8** (0.4 g, 1.5 mmol) and 4-methoxyphenol (0.20 g, 1.6 mmol) in DMF (5 mL) under nitrogen. After heating at 80 °C for 45 min the mixture was cooled, and then water and dilute HCl were added. Acid **46** (0.21 g, 59%) was collected as a light tan solid; mp >310 °C (from acetone); ν_{max} (KBr) 3300–2500 cm^{-1} (OH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 7.45 (1H, dd, J = 1.7 and 8.6 Hz, H-6), 7.48 (1H, d, J = 1.7 Hz, H-8), 8.05 (1H, d, J = 8.6 Hz, H-5); MS (EI) m/z = 239 (M^+). Anal. ($C_{10}H_6ClNO_4$) C, H, N. **46** is unstable with respect to decarboxylation on heating.

7-Chloro-4-hydroxy-2(1*H*)-quinolone-3-hydroxamic Acid (47). Ester **10** (0.44 g, 1.7 mmol) and H_2NOH·HCl (2 g, 28.7 mmol) were refluxed in dry pyridine for 2 h. On cooling and addition of dilute hydrochloric acid the product precipitated and was collected, washed with hydrochloric acid and dried to give **47** (0.14 g, 32%) as fine white needles: mp 280 °C dec; ^{1}H NMR (360 MHz, DMSO-d_6) δ 7.32 (1H, dd, J = 1.8 and 8.6 Hz, H-6), 7.38 (1H, d, J = 1.8 Hz, H-8), 7.96 (1H, d, J = 8.6 Hz, H-5), 9.8 (1H, br s), 11.8 (1H, br s), 11.9 (1H, br s), 18 (1H, br s); MS (CI$^+$, NH_3) m/z = 255 (M^+ + H). Anal. ($C_{10}H_7ClN_2O_4$) C, H, N.

***O*-Methyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-hydroxamate (48):** white needles; mp 307–308 °C (from DMF/acetone); ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.78 (3H, s, Me), 7.32 (1H, dd, J = 1.9 and 8.7 Hz, H-6), 7.37 (1H, d, J = 1.9 Hz, H-8), 7.96 (1H, d, J = 8.6 Hz, H-5), 11.97 (1H, br s), 12.21 (1H, br s); MS (EI) m/z = 268 (M^+). Anal. ($C_{11}H_9ClN_2O_4$) C, H, N.

***O*-Benzyl 7-chloro-4-hydroxy-2(1*H*)-quinolone-3-hydroxamate (49):** white needles; mp 245 °C (from DMF); ^{1}H NMR (360 MHz, DMSO-d_6) δ 5.00 (2H, s, CH_2), 7.33 (1H, dd, J = 1.8 and 8.7 Hz, H-6), 7.3–7.4 (4H, m, 3 of Ph and H-8), 7.48 (2H, dd, J = 7.9 and 1.8 Hz, Ph, ortho to CH_2), 7.97 (1H, d, J = 8.6 Hz, H-5), 11.97 (1H, br s), 12.23 (1H, br s); MS (CI$^+$, NH_3) m/z = 344 (M^+). Anal. ($C_{17}H_{13}ClN_2O_4$) C, H, N.

***N*-(2-Phenylethyl)-7-chloro-4-hydroxy-2(1*H*)-quinolone-3-hydroxamatic acid (50):** yellow cubes; mp 206–207 °C (from MeOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.97 (2H, t, J = 7.5 Hz, $PhCH_2$), 3.9–3.9 (2H, m, NCH_2), 7.2–7.3 (6H, m, Ph and H-6), 7.38 (1H, s, H-8), 7.97 (1H, d, J = 8.7 Hz, H-5), 12.01 (1 H, br s); MS (EI) m/z = 358 (M^+). Anal. ($C_{18}H_{15}ClN_2O_4$·0.1 H_2O) C, H, N.

***O*-Methyl *N*-methyl-7-chloro-4-hydroxy-2(1*H*)-quinolone-3-hydroxamate (51):** buff lozenges, mp 331–333 °C (from DMF/acetone); ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.20 (3H, s, NMe), 3.58 (3H, s, OMe),7.23 (1H, dd, J = 2.0 and 8.7 Hz, H-6), 7.30 (1H, d, J = 2.0 Hz, H-8), 7.90 (1H, d, J = 8.6 Hz, H-5), 11.2–11.7 (1H, br s), 11.56 (1 H, br s); MS (CI$^+$, NH_3) m/z = 268 (M^+ + H). Anal. ($C_{12}H_{11}ClN_2O_4$) C, H, N.

Acknowledgment. We would like to thank Dr. Richard Herbert for NMR experiments and Alan Watt for measurements of pK_A and log P.

References

(1) (a) Meldrum, B.; Garthwaite, J. Excitatory amino acid neurotoxicity and neurodegenerative disease. *Trends Pharmacol. Sci.* **1990**, *11*, 379–387. (b) Rowley, M.; Leeson, P. D. Excitatory amino acid antagonists. *Curr. Opin. Thera. Pat.* **1992**, *2*, 1201–1221. (c) Meldrum, B. Protection against ischaemic neuronal damage by drugs acting on excitatory neurotransmission. *Cerebrovasc. Brain Metab. Rev.* **1990**, *2*, 27–57. (d) Greenamyre, J. T.; Young, A. B. Excitatory amino acids and Alzheimers disease. *Neurobiol. of Aging* **1989**, *10*, 593–603. (e) Lipton, S. A. Models of neuronal injury in AIDS: another role for the NMDA receptor? *Trends Neurosci.* **1992**, *15*, 75–79.

(2) Watkins, J. C.; Collingridge, G. C., Eds. *The NMDA Receptor*; Oxford University Press: London, 1989.

(3) Watkins, J. C.; Krogsgaard-Larsen, P.; Honoré, T. Structure-activity relationships in the development of excitatory amino acid receptor agonists and competitive antagonists. *Trends Pharmacol. Sci.* **1990**, *11*, 25–33.

(4) Wong, E. H. F.; Kemp, J. A.; Priestley, T.; Knight, A. R.; Woodruff, G. N.; Iversen, L. L.; The anticonvulsant MK-801 is a potent N-methyl-D-aspartate antagonist. *Proc. Natl. Acad. Sci.* **1986**, *83*, 7104–7108.

(5) Ransom, R. W.; Stec, N. L. Cooperative modulation of [^{3}H]-MK-801 binding to the N-methyl-D-aspartate receptor-ion channel complex by L-glutamate, glycine, and polyamines. *J. Neurochem.* **1988**, *51*, 830–836. (b) Carter, C.; Rivy, J.-P.; Scatton, B. Ifenprodil and SL 82.0715 are antagonists at the polyamine site of the N-methyl-D-aspartate (NMDA) receptor. *Eur. J. Pharmacol.* **1989**, *164*, 611–612.

(6) (a) Johnson, J. W.; Ascher, P. Glycine potentiates the NMDA response in cultured mouse brain neurons. *Nature* **1987**, *325*, 529–531. (b) Kleckner, D. W.; Dingledine, R. Requirement for glycine in activation of NMDA-receptors expressed in *Xenopus* oocytes. *Science* **1988**, *241*, 835–837. (c) Kemp, J. A.; Leeson P. D. The glycine site on the NMDA receptor - five years on. *Trends Pharmacol. Sci.*, **1993**, *14*, 20–25.

(7) (a) Leeson, P. D.; Baker, R.; Carling, R. W.; Curtis, N. R.; Moore, K. W.; Williams, B. J.; Foster, A. C.; Donald, A. E.; Kemp, J. A.; Marshall, G. R. Kynurenic acid derivatives. Structure-activity relationships for excitatory amino acid antagonism and identification of potent and selective antagonists at the glycine site on the N-methyl-D-aspartate receptor. *J. Med. Chem.* **1991**, *34*, 1243–1252. (b) Moore, K. W.; Leeson, P. D.; Carling, R. W.; Tricklebank, M. D.; Singh, L. Anticonvulsant activity of glycine-site NMDA antagonists—I. 2-Carboxyl prodrugs of 5,7-dichlorokynurenic acid. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 61–64. (c) Harrison, B. L.: Baron, B. M.; Cousino, D. M.; McDonald, I. A. 4-[(Carboxymethyl)oxy]- and 4-[Carboxymethyl)amino]-5,7-dichloroquinoline-2-carboxylic acid: New antagonists of the strychnine-insensitive glycine binding site on the N-methyl-D-aspartate receptor complex. *J. Med. Chem.* **1990**, *33*, 3130–3132.

(8) (a) Carling, R. W.; Leeson, P. D.; Moseley, A. M.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R. 2-Carboxytetrahydroquinolines. Conformational and stereochemical requirements for antagonism on the glycine site of the NMDA receptor. *J. Med. Chem.* **1992**, *35*, 1942–1953. (b) Leeson, P. D.; Carling, R. W.; Moore, K. W.; Moseley, A. M.; Smith, J. D.; Stevenson, G.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Hoogsteen, K. 4-Amido-2-carboxytetrahydroquinolines. Structure-activity relationships for antagonism at the glycine site of the NMDA receptor. *J. Med. Chem.* **1992**, *35*, 1954–1968. (c) Carling, R. W.; Leeson, P. D.; Moseley, A. M.; Smith, J. D.; Saywell, K; Tricklebank, M. D.; Kemp, J. A.; Marshall, G. R.; Foster, A. C.; Grimwood, S. Anticonvulsant activity of glycine-site NMDA antagonists—II. *trans* 2-Carboxy-4-substituted tetrahydroquinolines. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 65–70.

(9) (a) Salituro, F. G.; Harrison, B. L.; Baron, B. M.; Nyce, P. L.; Stewart, K. T.; Kehne, J. H.; White, H. S.; McDonald, I. A. 3-(2-Carboxyindol-3-yl)propionic acid derivatives: antagonists of the strychnine insensitive glycine receptor associated with the N-methyl-D-aspartate receptor complex. *J. Med. Chem.* **1990**, *33*, 2944–2946. (b) Salituro, F. G.; Tomlinson, R. C.; Baron, B. M.; Demeter, D. A.; Weintraub, H. J. R.; McDonald, I. A. Design, synthesis and molecular modelling of 3-acylamino-2-carboxyindole NMDA receptor glycine-site antagonists. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 455–460. (c) Rowley, M.; Leeson, P. D.; Grimwood, S.; Foster, A.; Saywell, K. 2-Carboxy indolines and indoles as potential glycine/NMDA antagonists: effect of five-membered ring conformation on affinity. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1627–1630.

(10) (a) Honoré, T.; Davies, S. N.; Drejer, J.; Fletcher, E. J.; Jacobsen, P.; Lodge, D.; Nielsen, F. E. Quinoxalinediones: potent competitive non-NMDA glutamate receptor antagonists. *Science* **1988**, *241*, 701–703. (b) Randle, J. C. R.; Guet, T.; Bobichon, C.; Moreau, C.; Curutchet, P.; Lambolez, B.; de Carvalho, L. P.; Cordi, A.; Lepagnol, J. M. Quinoxaline derivatives: Structure-activity relationships and physiological implications of inhibition of N-methyl-D-aspartate and non-N-methyl-D-aspartate receptor mediated currents and synaptic potentials. *Mol. Pharmacol.* **1992**, *41*, 337–345. (c) Randle J. C. R.; Guet, T.; Cordi, A.; Lepagnol, J. M. Competitive inhibition by NBQX of kainate/AMPA receptor currents and excitatory synaptic potentials: importance of 6-nitro substitution. *Eur. J. Pharmacol.* **1992**, *215*, 237–244.(d) Grimwood, S; Foster, A. C.; Kemp, J. A.; Marshall, G. R. Unpublished results.

(11) (a) Rowley, M.; Leeson, P. D.; Williams, B. J.; Moore, K. W.; Baker, R. Routes to 4-substituted analogues of the glycine/NMDA antagonist HA-966. Enantioselective synthesis of (3R, 4R) 3-amino-1-hydroxy-4-methyl-2-pyrrolidinone (L-687,414) *Tetrahedron* **1992**, *48*, 3557–3570. (b) Gill, R.; Hargreaves. R.; Kemp, J. A. Neuroprotective effects of the glycine site antagonist (+)cis-4-methyl-HA-966 (L-687,414) in a rat focal ischaemia model. *J. Cereb. Blood Flow Metab.* **1991**, *11* (Suppl. 2), S304. (c) Leeson P. D.; Williams B. J.; Rowley M.; Moore K. W.; Baker R.; Kemp J. A.; Priestley T.; Foster A. C.; Donald A. E. Derivatives of 1-hydroxy-3-aminopyrrolidin-2-one (HA-966). Partial agonists at the glycine site of the NMDA receptor. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 71–76.

(12) McQuaid, L. A.; Smith, E. C. R.; Lodge, D.; Pralong, E.; Wikel, J. H.; Calligaro, D. O.; O'Malley, P. J. 3-Phenyl-4-hydroxyquinolin-2(1*H*)-ones: potent and selective antagonists at the strychnine-insensitive glycine site on the N-methyl-D-aspartate receptor complex. *J. Med. Chem.* **1992**, *35*, 3423–3425.

(13) McQuaid, L. A.; Smith, E. C. R.; South, K. K.; Mitch, C. H.; Schoepp, D. D.; True, R. A.; Calligaro, D. O.; O'Malley, P. J.; Lodge, D.; Ornstein, P. L. Synthesis and excitatory amino acid pharmacology of a series of heterocyclic-fused quinoxalinones and quinazolinones. *J. Med. Chem.* **1992**, *35*, 3319–3324.

(14) Techer, H.; Pesson, M.; Dursin, M. 3(4*H*)-oxo-2*H*-1,4-benzoxazine-2-carboxamides. *C. R. Acad. Sci., Ser. C.* **1969**, *269*, 154–157.

(15) Bourdais, J.; Mahieu, C. *C. R. Acad. Sci., Ser. C.* **1966**, *263*, 84–87.

(16) Huang. X.; Chan, C.-C. Synthesis of 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazines and -1,4-benzothiazines under phase-transfer catalysis. *Synthesis* **1984**, 851–852.

(17) (a) Grimwood, S.; Moseley, A. M.; Carling, R. W.; Leeson, P. D.; Foster, A. C. Characterisation of the binding of [^{3}H]-L-689,560, an antagonist for the glycine site of the N-methyl-D-aspartate receptor, to rat brain membranes. *Mol. Pharmacol.* **1992**, *41*, 923–930. (b) Kemp, J. A.; Marshall. G. R.; Priestley, T. A comparison of the agonist-dependency of the block produced by uncompetitive NMDA antagonists on rat cortical slices. *Mol. Neuropharm.* **1991**, *1*, 65–70. (c) Foster A. C.; Kemp J. A.; Leeson, P. D.; Grimwood, S.; Donald, A. E.; Marshall, G. R.; Priestley, T.; Smith, J. D.; Carling, R. W. Kynurenic acid analogues with improved affinity and selectivity for the glycine site on the N-methyl-D-aspartate receptor from rat brain. *Mol. Pharmacol.* **1992**, *41*, 914–922. (d) Tricklebank, M. D.; Singh, L.; Oles, R. J.; Preston, C.; Iversen S. D. The behavioural effects of MK-801: a comparison with antagonists acting non-competitively and competitively at the NMDA receptor. *Eur. J. Pharmacol.* **1989**, *167*, 127–135.

(18) March, J. *Advanced Organic Chemistry.*, 3rd ed.; John Wiley & Sons: New York, 1985.

(19) Andose, J. D.; Blevins, R. A.; Fluder, E. M.; Halgren, T.; Kearsley, S. K.; Sallamack, S.; Shpungin, J. AMF—The Advanced Modeling Facility, Version 1.12, January, 1991, Merck Research Laboratories, Rahway, NJ 07065.

(20) (a) Suzuki, S.; Green, P. G.; Bumgarner, R. E.; Dasgupta, S.; Goddard, W.A., III; Blake, G. A. Benzene forms hydrogen bonds with water. *Science* **1992**, *257*, 942–945. (b) Sussman, J. L.; Harel, M.; Frolow, F.; Oefner, C.; Goldman, A.; Toker, L.; Silman, I. Atomic structure of acetylcholinesterase from *Torpedo californica*: a prototypic acetylcholine-binding protein. *Science*, **1991**, *253*, 872–879. (c) Deakne, C. A.; Meot-Ner (Mautner), M. Unconventional ionic hydrogen bonds. 2. NH^+ - π complexes of onium ions with olefins and benzene derivatives. *J. Am. Chem. Soc.* **1985**, *107*, 474–479.

(21) Leeson, P. D.; Baker, R.; Carling, R. W.; Kulagowski, J. J.; Mawer, I. M.; Ridgill M. P.; Rowley, M.; Smith, J. D.; Stansfield, I.; Stevenson, G. I.; Foster, A. C.; Kemp, K. A. Amino acid bioisosteres: design of 2-quinolone derivatives as glycine-site N-methyl-D-aspartate receptor antagonists. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 299–304.

(22) Sutherland, I. O. *Comprehensive Organic Chemistry;* Barton, D., Ollis, W. D., Eds; Pergamon Press: Oxford, 1979; Vol. 2, pp 1040–1041.

(23) Schaper, K.-J. Simultaneous determination of electronic and lipophilic properties [pK_a, P(ion), P(neutral)] of acids and bases by nonlinear regression analysis of pH-dependent partition measurements. *J. Chem. Res. (S)* **1979**, 357.