3-Quinolinecarboxamides. A Series of Novel Orally-Active Antiherpetic Agents

Mark P. Wentland,*,† Robert B. Perni,*,† Peter H. Dorff,†,⊥ R. Pauline Brundage,† Michael J. Castaldi,†,⊥ Thomas R. Bailey,† Philip M. Carabateas,† Edward R. Bacon,† Dorothy C. Young,‡ Maureen G. Woods,‡ David Rosi,‖ Marion L. Drozd,‖ Rudolph K. Kullnig,§ and Frank J. Dutko‡

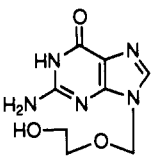
Departments of Medicinal Chemistry, Virology and Oncopharmacology, Drug Metabolism and Pharmacokinetics, and Molecular Characterization, Sterling Winthrop Pharmaceuticals Research Division, Sterling Winthrop Inc., Collegeville, Pennsylvania 19426-0900

Received November 30, 1992

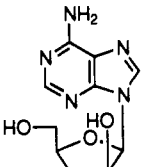
A series of novel 3-quinolinecarboxamides that are structurally similar to the quinolone class of antibacterial agents possess excellent antiherpetic properties. By modifying the quinoline ring at the 1-, 2-, 3-, and 7-positions, analogues were identified that have up to 5-fold increased HSV-2 plaque-reduction potency relative to acyclovir. In a single-dose mouse model of infection, one of the most potent derivatives in vitro, 1-(4-fluorophenyl)-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (**97**), displayed comparable oral antiherpetic efficacy to acyclovir at $^1/_{16}$ the dose; in a multiple-dose regimen, however, **97** was 2-fold less potent. In mice dosed orally with **97**, sustained plasma drug levels were evident that may account for the high efficacy observed. The molecular mechanism of action of these agents is not known; however, based on in vitro studies with acyclovir resistant mutants, it is likely that the mechanism differs from that of acyclovir. In vitro plaque-reduction potency was not generally predictive of oral efficacy in mice. An X-ray crystal structure of **97** corroborated the assignment of structure and provided useful insights as to the effect of conformation on plaque-reduction potency.

Introduction

Acyclovir (**1**) and vidarabine (araA; **2**) are used clinically to treat certain infections caused by herpes simplex virus-1 and -2 (HSV).[1] These compounds are structurally related to natural nucleosides, and their molecular mechanism of antiviral action is well understood.[2] There are also examples of non-nucleoside structures [e.g., foscarnet ($H_2O_3PCO_2H$)][3] that exhibit antiherpetic properties; however, none have achieved widespread clinical use.



1



2

In this paper we report our results showing that a series of novel 3-quinolinecarboxamides, which includes 1-(4-fluorophenyl)-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (**97**), displays HSV-2 plaque reduction that is up to 5-fold more potent than acyclovir. These results were obtained from a screening effort whose goal, in part, was to identify novel biological properties of synthetic intermediates. To study the relationship of structure to the HSV-2 plaque reduction of the carboxamides, we prepared analogues modified at the 1-, 2-, 3-, and 7-positions of the quinoline ring as probes to aid in defining the active pharmacophore. Additionally, **97**, along with several other derivatives, shows significant antiherpetic activity in mouse models of infection when administered by the oral route. It is of interest to note that the corresponding carboxylic acid derivatives of these 3-quinolinecarboxamides are structurally related to the quinolone class of DNA gyrase inhibitors widely used as antibacterial chemotherapeutics.[4]

Chemistry

A series of 1-ethyl-3-quinolinecarboxamides were prepared from rosoxacin (**78**)[5] by conversion to its acylimidazole derivative with 1,1′-carbonyldiimidazole/DMF followed by treatment with the requisite amine (method A, Scheme I). Alternatively, the acylimidazole may be isolated and subsequently treated with an amine or amine hydrochloride in pyridine (method B). Conversion of rosoxacin ethyl ester (**3**)[5] to **75** was carried out directly in neat 1,2-ethylenediamine at elevated temperature. Similarly, **77** was prepared from **3** and 2-aminoethanol.

Unless otherwise specified all other primary amides were prepared via method A or B or by amidation of the quinolone ethyl esters in a stainless steel bomb containing EtOH saturated with ammonia (method C; e.g., **91**). Targets **67–74**, **76**, **83**, **84**, **106–108**, **120–123**, and **125** (Table II) were obtained from known 3-quinolinecarboxylic acids or esters via the methods described above.

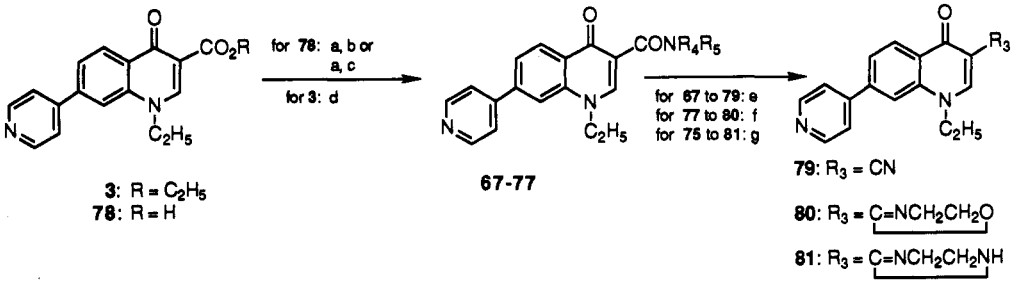
Nitrile derivative **79** was made by dehydration of **67** with $POCl_3$ as shown in Scheme I. Cyclization of the *N*-hydroxyethylamide **77** with $SOCl_2$ in refluxing dioxane gave oxazoline **80**. Similarly, ring closure of **75** with P_2O_5/PPA at 220 °C gave the imidazolinyl derivative **81**.

1-Alkyl variants of **67** were efficiently prepared by treatment of **4** with base (K_2CO_3 or NaH) in DMF followed by addition of an alkyl halide (Scheme II).[5] The resulting 3-quinolinecarboxylic acid esters **5–7** were hydrolyzed to the carboxylic acids with aqueous HCl, KOH, or NaOH and converted to their corresponding 3-carboxamides **85–87** using the methodology previously described (*vide supra*). The 1-H derivative **82** was obtained from **4** via conversion to its hydrazide with neat hydrazine followed by reduction with Raney nickel (Scheme II). Alkylation

† Department of Medicinal Chemistry.
‡ Department of Virology and Oncopharmacology.
‖ Department of Drug Metabolism and Pharmacokinetics.
§ Department of Molecular Characterization.
⊥ Present address: Pfizer Central Research, Groton, CT 06344.

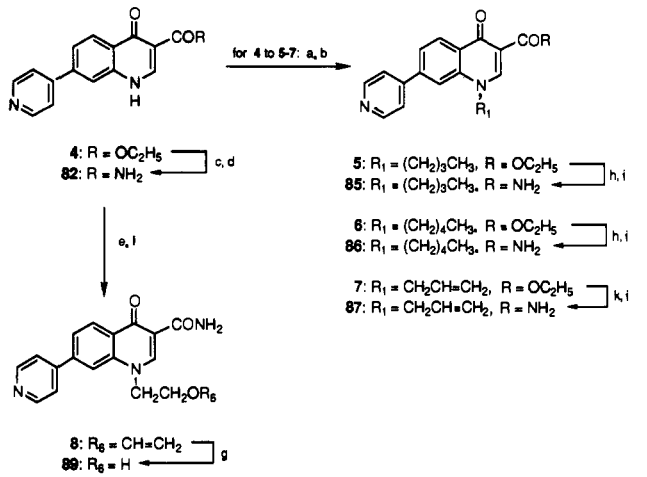
0022-2623/93/1836-1580$04.00/0

Scheme I[a]



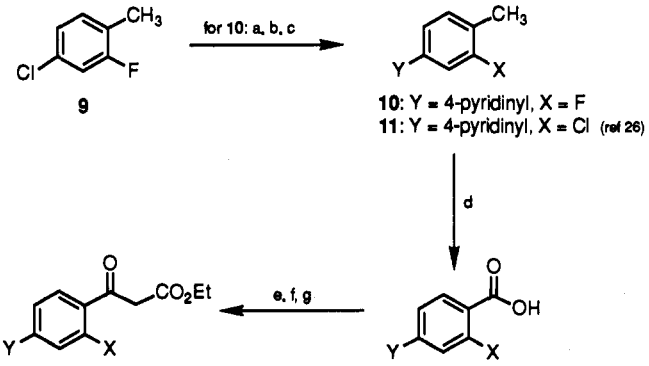
[a] Method A: (a) 1,1'-carbonyldiimidazole, DMF then (b) R_4R_5NH. Method B: (a) then (c) R_4R_5NH, pyridine; (d) R_4R_5NH neat; (e) $POCl_3$, 1-methylpyrrolidone; (f) $SOCl_2$, 1,4-dioxane; (g) PPA, P_2O_5.

Scheme II[a]



[a] (a) K_2CO_3, DMF; (b) R_1X; (c) NH_2NH_2; (d) Raney nickel, DMF; (e) NaH, DMF; (f) NaI, $Cl(CH_2)_2OCH{=}CH_2$; (g) AcOH; (h) HCl, EtOH/water; (i) method A; (k) NaOH, $EtOH/H_2O$.

Scheme III[a]



[a] (a) Mg, Et_2O; (b) *N*-acetylpyridinium chloride; (c) S, xylenes; (d) $KMnO_4$, pyridine–H_2O; (e) $SOCl_2$; (f) $EtO_2CCH(Li)CO_2Li$, THF; (g) aqueous HCl.

of **82** with 2-chloroethyl vinyl ether afforded **8** which upon deprotection with aqueous HOAc gave the 2-hydroxyethyl compound **89**.

For those 1-substituted derivatives (aryl, pyridinyl, or cyclopropyl) that could not be made via S_N2 alkylation, the cycloaracyclation sequence was used.[6] β-Keto esters **15–17** and **41**[7] served as intermediates; compounds **15–17** were prepared by condensing the dilithio anion of monoethyl malonate with the acid chlorides derived from **12–14** (Scheme III).[8] Benzoic acids **12** and **13**, which were not commercially available, were obtained from the corresponding toluene derivatives **10** and **11**, respectively, by oxidation with $KMnO_4$. Compound **10** was made by reacting the Grignard reagent derived from 2-fluoro-4-bromotoluene (**9**) with *N*-acetylpyridinium chloride to give an intermediate 1,4-dihydropyridine species which was oxidized with sulfur.[9]

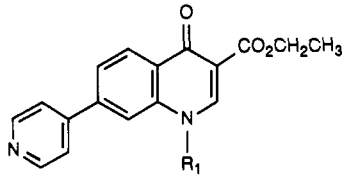
Enamine **18** was obtained from **15** and *N*,*N*-dimethylformamide dimethyl acetal in Et_2O or toluene and converted directly to quinolinecarboxylic acid esters **20–34** (see Table I) by treatment with the requisite amines (methods D and E, Scheme IV). These esters were converted to the corresponding carboxamides via method C or by basic hydrolysis (K_2CO_3/H_2O/THF or NaOH/H_2O/THF) followed by method A. In most quinolone syntheses which utilize this basic methodology, the product from the initial transamination step (e.g., **35**, Scheme IV) is isolated and the ring closure is effected in a separate step.[6] For method D, the refluxing dioxane effects both transamination and ring closure in one step without the benefit of additional base.

The 1-thia analogue **105** was prepared in two steps by first reacting **18** with hydrogen sulfide in EtOH to afford **19** (Scheme IV). Treatment of **19** with ammonia via method C afforded **105**.

Modification of the 7-position was also investigated. The *N*-oxide derivative **109** was made via oxidation of **97** with *m*-CPBA (Scheme IV). The 7-phenyl derivative **110** was obtained by converting **36**[10] to the corresponding hydrazide with neat hydrazine followed by hydrogenolysis with Raney nickel (Scheme V). Nitration of **110** with KNO_3/H_2SO_4 gave the 4-nitrophenyl derivative **112** which was hydrogenolyzed with Raney nickel to afford the 4-aminophenyl analogue **113**.

The aryl- and heteroarylstannanes shown in Scheme VI and the 7-haloquinolone esters **42**[11] and **43–45** shown in Scheme VII served as starting materials for the syntheses of other 7-position variants. The 1-imidazolyl derivative **118** was made from **123** via an Ullmann coupling. The 5-isothiazolyl derivative **117** was obtained from the palladium-mediated coupling of **126** with **39** (Scheme VII).[12] Similarly, **119** was prepared by coupling **42** and **40** to give **47** followed by conversion to the amide by base hydrolysis (NaOH/H_2O/THF) and method A. The 7-phenyl derivative **111** was analogously prepared by coupling **124** with phenyltri-*n*-butylstannane.[13] The preparation of **98** was also carried out in this fashion from 4-pyridinyltrimethylstannane[13] and **46**. The stannane reagent **39** was prepared by quenching the organolithium derivative obtained from 5-bromo-3-methylisothiazole (**37**) with trimethylstannyl chloride (Scheme VI). Deprotonation of 2-methylisothiazole (**38**)[14] with *n*-butyllithium followed by quenching with trimethylstannyl chloride afforded **40**.

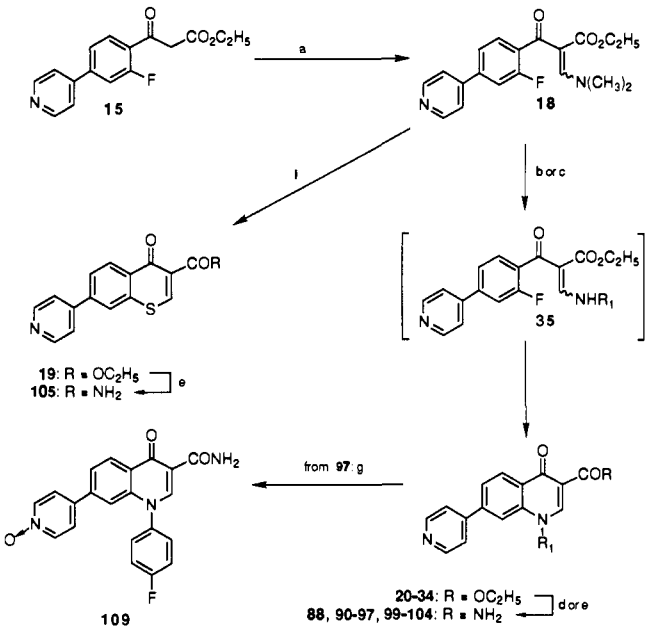
Table I. Physical Properties of Ethyl 1,4-Dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylates



compd	R_1	mp, °C	method	yield, %	formula[b]
20	c-C_3H_5	208–211	E	92	$C_{20}H_{18}N_2O_3$
21	C_6H_5	288–289	E	58	$C_{23}H_{18}N_2O_3 \cdot CH_3SO_3H \cdot H_2O$
22	4-ClC_6H_4	231–233	D	62	$C_{23}H_{17}ClN_2O_3$
23	4-BrC_6H_4	219–222	D	79	$C_{23}H_{17}BrN_2O_3 \cdot 0.5H_2O$
24	4-$CF_3C_6H_4$	192–194	D	55	$C_{24}H_{17}F_3N_2O_3$
25	4-$CH_3C_6H_4$	214–216	D	83	$C_{24}H_{20}N_2O_3$
26	4-$CH_3OC_6H_4$	212–214	D	94	$C_{24}H_{20}N_2O_4 \cdot 0.25H_2O$
27	4-t-BuC_6H_4	161–163	D	98	$C_{27}H_{26}N_2O_3 \cdot H_2O$
28	4-FC_6H_4	252–253	D	92	$C_{23}H_{17}FN_2O_3 \cdot 0.25H_2O$
29	2-FC_6H_4	224–228	D	66	$C_{23}H_{17}FN_2O_3$
30	2,4-$F_2C_6H_3$	216–218	D	42	$C_{23}H_{16}F_2N_2O_3 \cdot 0.25H_2O$
31	3,4-$Cl_2C_6H_3$	238–240	D	66	$C_{23}H_{16}Cl_2N_2O_3$
32	3,4-$(CH_3)_2C_6H_3$	208–210	D	71	$C_{25}H_{22}N_2O_3 \cdot 0.25H_2O$
33	CH_2-2,3-$Cl_2C_6H_3$	193–200	D	52	$C_{24}H_{18}Cl_2N_2O_3 \cdot H_2O$
34	4-pyridinyl	245 dec	E	65	$C_{22}H_{17}N_3O_3 \cdot 0.5H_2O$

[a] See the Experimental Section. [b] C, H, and N elemental analyses were within ±0.4% of theoretical values; the presence of water was confirmed by ^1H NMR.

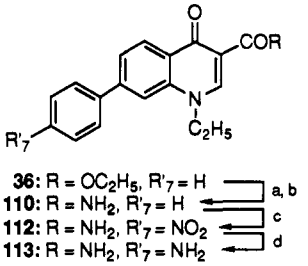
Scheme IV[a]



[a] (a) $(CH_3)_2NCH(OCH_3)_2$, THF; (b) method D: R_1NH_2, dioxane; (c) method E: R_1NH_2, K_2CO_3, DMF; (d) NaOH(aq)/THF or K_2CO_3(aq)/THF then method A; (e) method C: NH_3, EtOH; (f) H_2S, EtOH; (g) *m*-CPBA, AcOH.

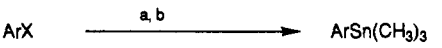
Several 7-(5-isoxazolyl) derivatives (**114–116**) in both the 1-(4-fluorophenyl) and 1-ethyl series were prepared. Compounds **114** and **115** were prepared from the 7-acetylquinolone ester **51**[15] as shown in Scheme VIII. Formation of enamines **52** and **53** from **51** and *N,N*-dimethylformamide dimethyl acetal and *N,N*-dimethylacetamide dimethyl acetal, respectively, followed by cyclization with $NH_2OH \cdot HCl$ gave esters **54** and **55**, respectively; these esters were converted to the corresponding carboxamides and **114** and **115** via acid hydrolysis (6 N HCl, 100 °C) followed by method A. Compound **116** was made by coupling the 7-bromo compound **43** with TMS-acetylene and $PdCl_2(PPh_3)_2$ to give **48** (Scheme IX). Fluoride ion promoted desilylation of **48** gave **49**. A 1,3-dipolar cycloaddition of **49** with the nitrile oxide derived from $EtNO_2$/PhNCO/Et_3N afforded ester **50** which was converted to amide **116** by base hydrolysis (KOH/H_2O/EtOH at reflux) and method A.

Scheme V[a]



[a] (a) NH_2NH_2–H_2O; (b) Raney nickel, EtOH; (c) KNO_3–H_2SO_4; (d) NH_2NH_2–H_2O, Raney nickel, EtOH.

Scheme VI[a]



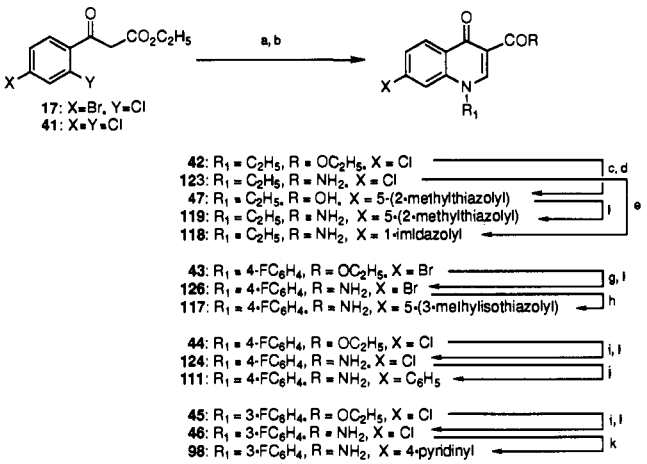
37: Ar = 5-(3-methylisothiazolyl), X = Br
38: Ar = 5-(2-methylthiazolyl), X = H
39: Ar = 5-(3-methylisothiazolyl)
40: Ar = 5-(2-methylthiazolyl)

[a] (a) *n*-BuLi, Et_2O; (b) $(CH_3)_3SnCl$.

Substitution at the 2-position of the quinoline ring was also investigated. Those derivatives possessing a 1-ethyl substituent were made as shown on Scheme X from the known isatoic anhydride **57**.[16] Condensation of **57** with acetoacetamide produced **127**. The 2-hydroxy analogue **128** was derived from **57** and diethyl malonate followed by treatment with ammonia. Condensation of **57** with malononitrile/NaH/DMF followed by hydrolysis of the intermediate nitrile with H_2SO_4 produced **129**.

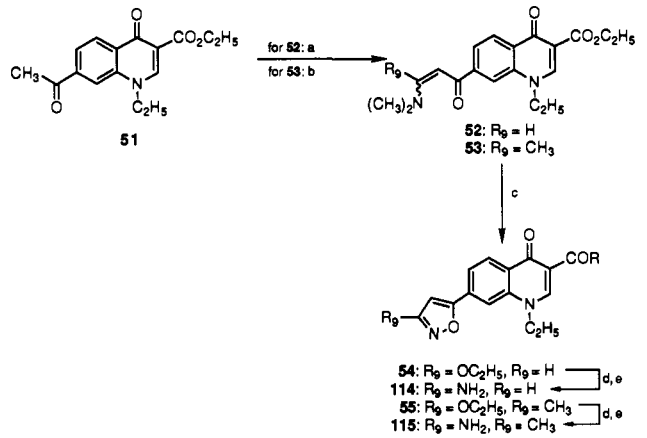
1-(4-Fluorophenyl) 2-substituted analogues were synthesized from β-keto esters **16** or **17** via ketene dithioacetals **58** and **60**, respectively.[17] The 2-hydroxy derivative **130** was prepared from **60** using the four-step sequence shown in Scheme XI. Treatment of **60** with 4-fluoroaniline afforded **61** which was selectively hydrolyzed with aqueous KOH to give **62**. Conversion of **62** to **63** via method C, followed by a palladium-catalyzed coupling with 4-pyridinyltrimethylstannane, gave **130**. The 2-aminoquinoline **131** was made by treating **59** with ethanolic ammonia

Scheme VII[a]



[a] (a) $(CH_3)_2NCH(OCH_3)_2$, Et_2O; (b) R_1NH_2, dioxane; (c) **40**, $PdCl_2(PPh_3)_2$, DMF; (d) 1.5 N HCl; (e) imidazole, NaH, CuBr, DMF; (f) method A; (g) K_2CO_3, EtOH/H_2O; (h) **39**, $PdCl_2(PPh_3)_2$, dioxane DMF; (i) 1 N NaOH, THF; (j) $C_6H_5Sn(Bu)_3$, $PdCl_2(PPh_3)_2$, DMF; (k) 4-pyridinylSn$(CH_3)_3$, $PdCl(PPh_3)_2$, EtOH.

Scheme VIII[a]



[a] (a) $(CH_3)_2NCH(OCH_3)_2$, DMF; (b) $(CH_3)_2NC(OCH_3)_2CH_3$, DMF; (c) NH_2OH·HCl; (d) 6 N HCl, 100 °C; (e) method A.

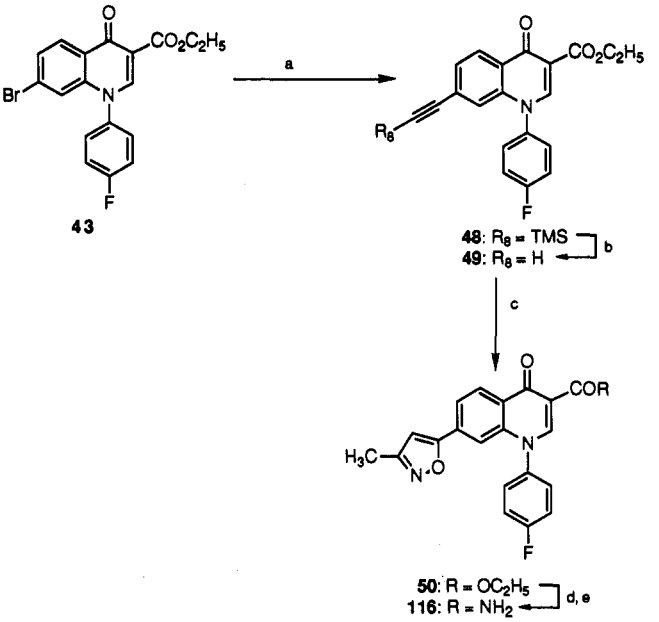
in a sealed tube at 150 °C. Amination of **58** with 4-fluoroaniline gave **59** (Scheme XI) which upon treatment with hydrazine gave the pentacyclic compound **132**.

To study the effect of restricted rotation of the 1-aryl substituent, the pentacyclic derivative **133** was prepared as shown in Scheme XII.[18] Intermediate **66** was obtained by conversion of **15** to ketene dithioacetal derivative **64** followed by condensation with 1,2-phenylenediamine. The resulting intermediate **65** was cyclized to **66** by treatment with methanesulfonic acid. Subjecting **66** to the standard conditions of method C afforded **133**.

Results and Discussion

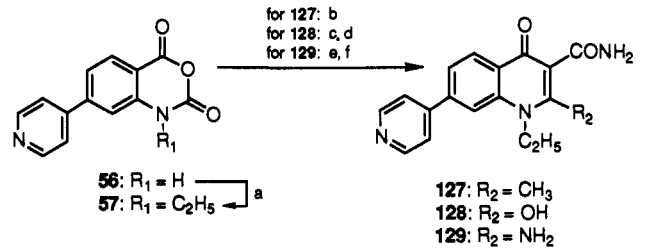
HSV-2 Plaque Reduction Activity. The HSV-2 plaque reduction properties in Vero cells of the target compounds compared to acyclovir are summarized in Table II (see the Experimental Section for definition of terms and variance of testing results). Compound **67** was the first compound in this series observed to exhibit antiherpetic activity and thus served as the initial lead structure/comparitor for the design and synthesis of new analogues. Compared to acyclovir, **67** was 5-fold less potent in vitro. When the primary carboxamide group of **67** was monosubstituted, we found sustained to somewhat diminished plaque reduction potency in derivatives where

Scheme IX[a]



[a] (a) TMS–acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, CH_3CN; (b) KF, EtOH; (c) $EtNO_2$, PhNCO, Et_3N, $CHCl_3$; (d) KOH, EtOH/H_2O, reflux; (e) method A.

Scheme X[a]



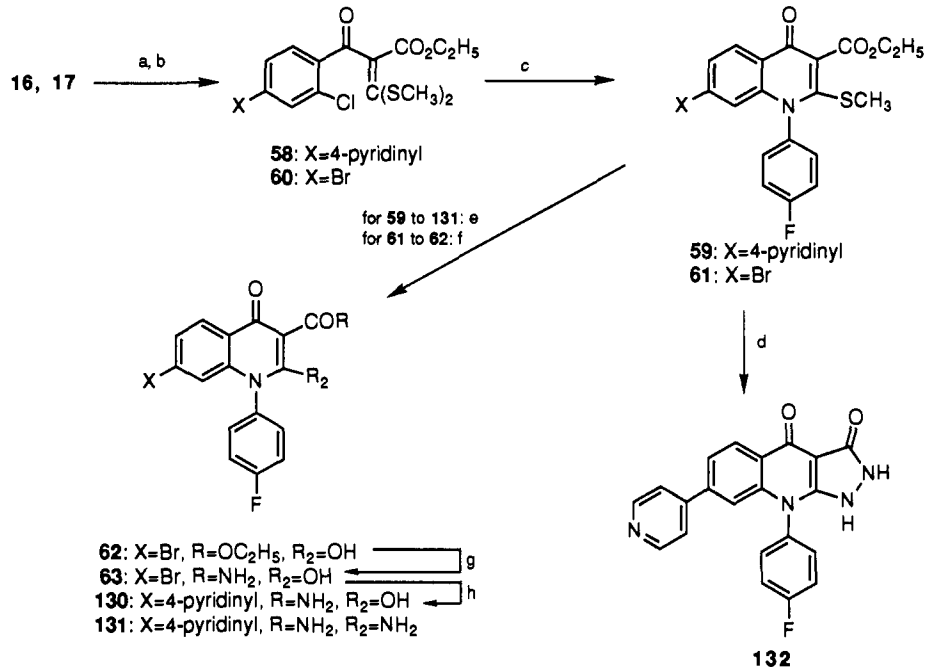
[a] (a) NaH, EtI, DMF; (b) NaH, $CH_3COCH_2CONH_2$, DMF; (c) NaH, $C_2H_5O_2CCH_2CO_2C_2H_5$, DMF; (d) method C; (e) NaH, $NCCH_2CN$, DMF; (f) H_2SO_4.

the substituent was methyl (**68**), hydroxyl (**70**), or amino (**73**). Other N-monosubstituted analogues of **67** that we prepared were **71** (OCH_3), **74** ($NHCH_3$), **75** ($CH_2CH_2NH_2$), **76** ($CH_2CH_2NMe_2$), and **77** (CH_2CH_2OH); these were all devoid of in vitro activity at the MTL. There was also no in vitro activity resident in two tertiary amide derivatives **69** and **72**, the *N,N*-dimethyl and *N*-methyl-*N*-hydroxy analogues, respectively.

The structure of **67** is very similar to the well-known, clinically-used bacterial DNA gyrase inhibitor rosoxacin (**78**);[5] this carboxylic acid analogue had no plaque-reduction activity at 200 μg/mL. This result is similar to findings from a recent study where five fluoroquinolones (ciprofloxacin, lomefloxacin, ofloxacin, pefloxacin, and rufloxacin) were shown to have very poor in vitro activity vs HSV-2.[19] Other 3-position variants having the same oxidation state as amide (or acid) were also devoid of in vitro activity. These compounds were **79** (nitrile), **80** (oxazoline), and **81** (imidazoline). The ethyl ester derivative (**28**) of a closely related 1-FC_6H_4 analogue was also devoid of in vitro activity (MIC > 100 μg/mL).

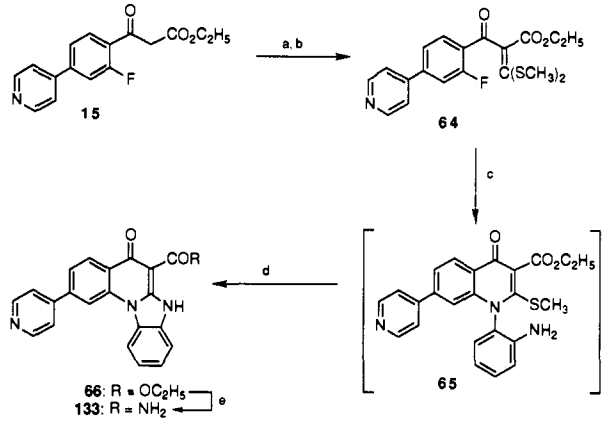
Analogues of **67** where the 1-ethyl appendage was replaced with other alkyl groups (**83**, **85**, and **86**), allyl (**87**), or cyclopropyl (**88**) had similar in vitro potencies to **67**. One exception was **84**, the 1-propyl derivative, which showed no activity at a relatively low MTL. Compound **89**, the 1-CH_2CH_2OH derivative of **67**, was inactive in vitro

Scheme XI[a]



[a] (a) Cs_2CO_3, CS_2, THF; (b) CH_3I; (c) 4-$FC_6H_4NH_2$, K_2CO_3, dioxane; (d) NH_2NH_2, EtOH, H_2O; (e) NH_3, EtOH; (f) KOH, THF-H_2O; (g) method C; (h) 4-$C_5H_4NSn(CH_3)_3$, $PdCl_2(PPh_3)_2$, EtOH.

Scheme XII[a]



[a] (a) Cs_2CO_3, CS_2, THF; (b) CH_3I; (c) 1,2-phenylenediamine, K_2CO_3, dioxane; (d) CH_3SO_3H; (e) method C.

as were the 1-H (**82**) and 1-thia (**105**) analogues. A significant 9-fold increase in plaque reduction potency relative to **67** was observed for the 1-phenyl derivative **90**. When the phenyl ring of **90** was substituted at the 4-position with Cl (**91**), Br (**92**), CF_3 (**93**), CH_3 (**94**), and CH_3O (**95**), in vitro activity was sustained; the *tert*-butyl derivative **96** showed no in vitro activity. The 4-fluorophenyl analogue **97**, however, was 3-fold more potent in vitro than **90**. The fluorine substitution pattern of **97** was varied to include the two other monofluoro analogues, **98** and **99**, as well as the 2,4-difluoro derivative, **100**. Relative to **97**, compounds **98** and **100** had somewhat diminished in vitro activity while the 2-fluorophenyl analogue, **99**, showed no activity at the MTL of 1.6 μg/mL. Two other disubstituted phenyl analogues were prepared; the 3,4-dichloro (**101**) and 3,4-dimethyl (**102**) derivatives were 2- and 4-fold less potent, respectively, than **97**. A 1-benzyl derivative, **103**, was 3-fold less potent in vitro than the corresponding 1-phenyl analogue **101** having the same 3,4-dichloro substitution. Replacing the phenyl group of **90** with 4-pyridinyl gave **104** which resulted in a 10-fold potency decrease.

Also found in Table II are in vitro data for analogues of **67** where the 7-(4-pyridinyl) group was replaced with H, aryl, and other heteroatom-containing groups. Several 7-halo-substituted compounds used as synthetic intermediates were also tested. Relative to **67**, comparable in vitro activity was seen for the 3- and 2-pyridinyl analogues **106** and **107** and the 2,6-dimethyl-4-pyridinyl derivative **108**. Substitution at the 7-position of the quinoline ring with phenyl (**110**), 4-nitrophenyl (**112**), or 4-aminophenyl (**113**) abolished activity.

When the 4-pyridinyl group of **67** was replaced by 5-isoxazolyl groups [either unsubstituted (**114**) or 3-methyl substituted (**115**)], similar plaque reduction potency was seen. In contrast to the isoxazolyl substitutions, other azoles (1-imidazolyl and 2-methyl-5-thiazolyl derivatives, **118** and **119**, respectively) abolished activity. Appending the 4-methyl-1-piperazinyl group (the prototypic 7-substituent of the quinolone class of antibacterial agents) to position 7 (**120**) also abolished activity. Several acyclic 7-position variants were prepared and all showed no plaque reduction activity at the MTL; these were the 7-H (**121**), 7-F (**122**), 7-Cl (**123**), and 7-I (**125**) analogues of **67**.

In a few instances, the 7-substituent modifications just described were also introduced into the structural framework of **97**. Activity differences within two pairs of 1-ethyl and 1-(4-FC_6H_4) analogues varied. In the pair of 7-(3-methyl-5-isoxazolyl) derivatives, the 1-(4-FC_6H_4) partner **116** was 5-fold more potent than **115**. When comparing the pair of 7-phenyl partners, **110** and **111**, there was a >60-fold differential, with the 1-(4-FC_6H_4) companion **111** being more potent. Both 7-Cl derivatives **123** and **124** were inactive. The 7-Br compound **126**, used as a synthetic intermediate, was inactive. A close relative of **116** is the 3-methyl-5-isothiazolyl variant **117**; the potency of both these compounds and **97** is the best within this series and is 5-fold greater than acyclovir. Compound **109**, the

corresponding *N*-oxide of **97**, was found to be devoid of activity at 12.5 μg/mL.

Compounds **67** and **97** were also modified at the 2-position. Compound **127**, the 2-CH_3 analogue of **67**, was devoid of in vitro activity; however, the 2-OH derivative **128** was 3-fold more potent, and the 2-NH_2 analogue **129** had sustained activity relative to **67**. Compound **97** was 5-fold more potent than the 2-OH compound **130**, while the corresponding 2-NH_2 analogue **131** had comparable potency to **97**.

Two variants of **97** were made where the 2-NH_2 group was incorporated into an additional ring. The 2,3-bridged pyrazole **132** and compound **133**, which forms a ring with the 2′-position of the 1-phenyl group, were devoid of activity at the MTL. Of note, the MTL of **133** was only 0.4 μg/mL.

Relationship of Structure to Plaque-Reduction Potency. Without a specific macromolecular target identified and an acellular (enzyme or receptor) assay in place, we relied on the Vero cell-based plaque-reduction assay to study the relationship of structure to activity. It is almost certain that there are differences in the intracellular concentrations of test agents due to permeability differences. While we were unable to measure the intracellular drug concentrations, generalizations concerning SAR could be made only if we assumed that the intracellular concentration of drug was proportional/parallel to the extracellular concentration.

In vitro activity does not appear to be a sensitive function of the size of the 1-substituent. For example, good potency is seen in derivatives with the relatively small group, methyl (**83**), and with the relatively large appendage, 3,4-dichlorobenzyl (**103**). The relatively high bulk of the 4-$tBuC_6H_4$ group of **96**, however, might contribute to that compound being inactive. Size might be a factor in the lack of activity of the 1-H compound **82** or it may be a consequence of an N to O proton tautomerization, a condition that is unique to this analogue. While only one example (**89**; $R_1 = CH_2CH_2OH$) was made, it appears that a hydrophilic 1-substituent is detrimental to activity. As the size of the 1-substituent was judged not to be an important determinant to activity, we made the 1-thia compound **105** in hopes that the electron-releasing properties of sulfur would closely mimic those of NR_1; the compound was inactive.

From the relatively small number of 1-phenyl analogues that were prepared (**90–102**), it appears that activity is not closely related to the pattern or electron-releasing/withdrawing properties of the substituent(s) on the phenyl ring. One possible exception is the 2-F derivative **99** which was inactive; the MTL, however, was only 1.6 μg/mL. Using the modified Topliss Tree approach to identify a QSAR, we found no correlation between in vitro potency and the physicochemical properties of the substituent(s) on the phenyl ring.[20] The 1-(4-pyridinyl) group is not an effective bioisosteric replacement for the phenyl appendage as evidenced by a 9-fold decrease in activity of **104** relative to **90**.

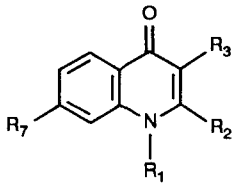
The torsional angle between the 1-(4-FC_6H_4) and quinoline rings of **97** (neutral form) as defined by the X-ray crystal structure shown in Figure 1 is ca. 70°. As a probe to determine if activity is related to that angle, we made **133**, which incorporates a 2-amino group into its cyclic structure. The 2-amino function was previously shown not to be detrimental to activity in the acyclic variant **131**. Compound **133** has a torsional angle near 0° and shows no plaque-reduction activity. This result, however, provided very little insight into this aspect of SAR because testing at concentrations higher than 0.4 μg/mL was precluded due to toxicity to Vero cells.

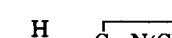
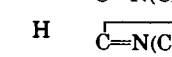
From an analysis of the in vitro data for compounds modified at the 2- and 3-positions, we believe the expected internal, H-bonded conformation of the β-keto amide is also the active conformation. The X-ray crystal structure of **97** shown in Figure 1 shows that the low-energy crystal-state conformation of the β-keto amide is in fact the planar conformation. This is also the case in DMSO-d_6 solution at ambient temperature where the ^1H NMR spectrum of **97** shows the two exchangeable H's (H_a and H_b in Figure 1) are doublets having a very large difference in chemical shifts [δ 9.15 (donor – H_a) and δ 7.62 (H_b)], are coupled to each other (J = 4 Hz), and exchange slowly when D_2O is added. Other primary amides in the series show similar spectral properties. Secondary amides can also adopt this conformation. For example, the chemical shift of the exchangeable H of **68**, the *N*-methyl analogue that shows very good activity, comes far downfield (δ 9.82, q, J = 5 Hz), indicative of the intramolecular H-bonded conformation. However, several secondary amides (**74–77**) are devoid of activity that could be a consequence of the N-substituents being relatively large and/or hydrophilic. For example **76**, an *N*-((dimethylamino)ethyl) carboxamide, still shows the characteristic (of the intramolecular H-bonded conformation) downfield exchangeable H (triplet at δ 9.94) but has an MIC > 100 μg/mL. An intramolecular H-bond with the nitrogen of the side chain in this compound can also account for the observed NMR data and activity.

Carboxamides in the series with optimal or nearly optimal 1-, 2-, and 7-substituents that cannot adopt the intramolecular H-bonded conformation are inactive. For example, two tertiary amides (**69** and **72**) of relatively low bulk are inactive as is **132**, a secondary amide whose cyclic structure precludes the intramolecular H-bonded arrangement. A similar rationalization can be applied to explain the inactivity of the ester, cyano, and oxazoline derivatives **28**, **79**, and **80**, respectively. The inactivity of two compounds [**78** (CO_2H) and **81** (imidazoline)] that can adopt the planar conformation may be due to ionization of these groups at cellular pH.

After analysis of the in vitro and proton NMR data in DMSO-d_6 for 2-substituted analogues of the primary carboxamide **67**, a very interesting relationship between activity, the nature of R_2, and the conformation of the carboxamide group emerged. The 2-H derivative and original lead compound **67** (MIC = 6.5 μg/mL) have the expected spectral properties for the exchangeable H's—δ 9.27 (d, H_a, J = 4 Hz); δ 7.55 (d, H_b, J = 4 Hz). In addition to the downfield chemical shift data for H_a, the stability of the intramolecular H-bonded structure of **67** is also supported by data from NMR coalescence experiments where these two signals broadened but did not coalesce at or below 125 °C and from D_2O exchange experiments where the carboxamide H's of **67** exchanged very slowly at ambient temperature (ca. 85% exchanged after 3 h). The proton NMR spectrum of the inactive (MIC > 100 μg/mL) 2-CH_3 analogue **127** showed splitting of H_a and H_b; however, the two signals were broad singlets at δ 7.91 and 7.37, respectively, with H_a appearing considerably upfield relative to the H_a of **67**. Additionally, H_a and H_b coalesced

Table II. Physical and Antiherpetic Properties of 1,4-Dihydro-4-oxo-3-quinolinecarboxamides



compd	R_1	R_2	R_3	R_7	mp, °C	method[c]	yield, %	formula	antiherpetic activity: in vitro, μg/mL[a] MIC	in vitro, μg/mL[a] MTL	in vivo, mg/kg po[b] MED	in vivo, mg/kg po[b] MTD
1	acyclovir								1.3	>200	12	>200
67	CH_2CH_3	H	$CONH_2$	4-pyridinyl	314–317	A	91	$C_{17}H_{15}N_3O_2$	6.5	12.5	50	50
68	CH_2CH_3	H	$CONHCH_3$	4-pyridinyl	275–278	A	90	$C_{18}H_{17}N_3O_2$	9.0	>25	50	50
69	CH_2CH_3	H	$CON(CH_3)_2$	4-pyridinyl	247–250	A	67	$C_{19}H_{19}N_3O_2$	NA[d]	>100	*e*	
70	CH_2CH_3	H	CONHOH	4-pyridinyl	245 dec	B	72	$C_{17}H_{15}N_3O_3$	6.8	25	NA	100
71	CH_2CH_3	H	$CONHOCH_3$	4-pyridinyl	202–204	B	74	$C_{18}H_{17}N_3O_3$	NA	25	*e*	
72	CH_2CH_3	H	$CON(CH_3)OH$	4-pyridinyl	207 dec	B	84	$C_{18}H_{17}N_3O_3 \cdot CH_3SO_3H$	NA	50	*e*	
73	CH_2CH_3	H	$CONHNH_2$	4-pyridinyl	274–275	A	70	$C_{17}H_{16}N_4O_2$	38	50	NA	100
74	CH_2CH_3	H	$CONHNHCH_3$	4-pyridinyl	241–243	A	47	$C_{18}H_{18}N_4O_2$	NA	25	*e*	
75	CH_2CH_3	H	$CONH(CH_2)_2NH_2$	4-pyridinyl	286–287	*c*		$C_{19}H_{20}N_4O_2 \cdot 2CH_3SO_3H \cdot 0.5H_2O$	NA	>100	*e*	
76	CH_2CH_3	H	$CONH(CH_2)_2N(CH_3)_2$	4-pyridinyl	203–204	B	79	$C_{21}H_{24}N_4O_2$	NA	>100	*e*	
77	CH_2CH_3	H	$CONH(CH_2)_2OH$	4-pyridinyl	>350	*c*		$C_{19}H_{19}N_3O_3 \cdot CH_3SO_3H \cdot 0.25H_2O$	NA	25	*e*	
78[f]	CH_2CH_3	H	CO_2H	4-pyridinyl					NA	>200	*e*	
79	CH_2CH_3	H	CN	4-pyridinyl	326–330	*c*		$C_{17}H_{13}N_3O \cdot HCl$	NA	100	*e*	
80	CH_2CH_3	H		4-pyridinyl	>350	*c*		$C_{19}H_{17}N_3O_2 \cdot 2HCl$	NA	12.5	*e*	
81	CH_2CH_3	H		4-pyridinyl	268–271	*c*		$C_{19}H_{18}N_4O \cdot 2CH_3SO_3H \cdot 0.5H_2O$	NA	>100	*e*	
82	H	H	$CONH_2$	4-pyridinyl	>350	*c*	*c*	$C_{15}H_{11}N_3O_2 \cdot HCl \cdot 0.25H_2O$	NA	12.5	*e*	
83[f]	CH_3	H	$CONH_2$	4-pyridinyl	>350	A	84	$C_{16}H_{13}N_3O_2 \cdot HCl$	4.6	>25	NA	25
84[f]	$(CH_2)_2CH_3$	H	$CONH_2$	4-pyridinyl	303–305	A	49	$C_{18}H_{17}N_3O_2 \cdot CH_3SO_3H$	NA	6.25	*e*	
85	$(CH_2)_3CH_3$	H	$CONH_2$	4-pyridinyl	267–269	A	74	$C_{19}H_{19}N_3O_2 \cdot CH_3SO_3H$	5.2	6.25	NA	50
86	$(CH_2)_4CH_3$	H	$CONH_2$	4-pyridinyl	188–190	A	82	$C_{20}H_{21}N_3O_2$	4.8	6.25	NA	50
87	$CH_2CH{=}CH_2$	H	$CONH_2$	4-pyridinyl	>300	A	91	$C_{18}H_{14}N_3O_2 \cdot CH_3SO_3H$	2.9	6.25	NA	<50
88	c-C_3H_5	H	$CONH_2$	4-pyridinyl	310 dec	A	90	$C_{18}H_{15}N_3O_2 \cdot CH_3SO_3H \cdot 0.25H_2O$	4.0	25	NA	25

89	$(CH_2)_2OH$	H	$CONH_2$	4-pyridinyl	293–295	*c*		$C_{17}H_{15}N_3O_3 \cdot CH_3SO_3H$	NA	50	*e*	
90	C_6H_5	H	$CONH_2$	4-pyridinyl	>310	A	76	$C_{21}H_{15}N_3O_2$	0.78	6.25	25	50
91	4-ClC_6H_4	H	$CONH_2$	4-pyridinyl	280	C	65	$C_{21}H_{14}ClN_3O_2 \cdot CH_3SO_3H \cdot H_2O$	0.40	>25	50	100
92	4-BrC_6H_4	H	$CONH_2$	4-pyridinyl	294–297	C	62	$C_{21}H_{14}BrN_3O_2 \cdot CH_3SO_3H \cdot H_2O$	0.47	>12.5	50	50
93	4-$CF_3C_6H_4$	H	$CONH_2$	4-pyridinyl	270–290	C	39	$C_{22}H_{14}F_3N_3O_2 \cdot CH_3SO_3H \cdot 1.5H_2O$	1.0	>100	NA	50
94	4-$CH_3C_6H_4$	H	$CONH_2$	4-pyridinyl	250 dec	C	69	$C_{22}H_{17}N_3O_2 \cdot CH_3SO_3H \cdot H_2O$	0.63	>25	NA	50
95	4-$CH_3OC_6H_4$	H	$CONH_2$	4-pyridinyl	281–282	A	75	$C_{22}H_{17}N_3O_3 \cdot CH_3SO_3H \cdot 0.5H_2O$	1.3	>25	NA	50
96	4-$tBuC_6H_4$	H	$CONH_2$	4-pyridinyl	225–228	A	83	$C_{25}H_{23}N_3O_2 \cdot CH_3SO_3H \cdot 0.5H_2O$	NA	>25	*e*	
97	4-FC_6H_4	H	$CONH_2$	4-pyridinyl	301–303	A	98	$C_{21}H_{14}FN_3O_2 \cdot CH_3SO_3H \cdot 0.5H_2O$	0.24	6.25	25	50
98	3-FC_6H_4	H	$CONH_2$	4-pyridinyl	>320	*c*		$C_{21}H_{14}FN_3O_2 \cdot CH_3SO_3H$	0.71	>25	50	50
99	2-FC_6H_4	H	$CONH_2$	4-pyridinyl	>300	C	29	$C_{21}H_{14}FN_3O_2 \cdot CH_3SO_3H$	NA	1.6	NA	100
100	2,4-$F_2C_6H_3$	H	$CONH_2$	4-pyridinyl	302–303	A	75	$C_{21}H_{13}F_2N_3O_2 \cdot CH_3SO_3H \cdot H_2O$	2.2	3.1	NA	<25
101	3,4-$Cl_2C_6H_3$	H	$CONH_2$	4-pyridinyl	282 dec	A	40	$C_{21}H_{13}Cl_2N_3O_2 \cdot CH_3SO_3H \cdot H_2O$	0.52	>100	50	100
102	3,4-$(CH_3)_2C_8H_3$	H	$CONH_2$	4-pyridinyl	244 dec	A	84	$C_{23}H_{19}N_3O_2 \cdot CH_3SO_3H \cdot H_2O$	1.0	>100	NA	>200
103	CH_2-3,4-$Cl_2C_6H_3$	H	$CONH_2$	4-pyridinyl	260–276	A	51	$C_{22}H_{15}Cl_2N_3O_2 \cdot CH_3SO_3H$	1.7	>100	NA	>100
104	4-pyridinyl	H	$CONH_2$	4-pyridinyl	>300	A	82	$C_{20}H_{14}N_4O_2 \cdot 2CH_3SO_3H \cdot H_2O$	7.2	>200	75	75
105	$NR_1{=}S$	H	$CONH_2$	4-pyridinyl	>310	C	60	$C_{15}H_{10}N_2O_2S$	NA	>100	*e*	
106[f]	CH_2CH_3	H	$CONH_2$	3-pyridinyl	275–277	A	92	$C_{17}H_{15}N_3O_2$	12	50	NA	100
107[f]	CH_2CH_3	H	$CONH_2$	2-pyridinyl	245–246	A	90	$C_{17}H_{15}N_3O_2$	14	25	NA	100
108[f]	CH_2CH_3	H	$CONH_2$	2,6-$(CH_3)_2$-4-pyridinyl	289–290	A	71	$C_{19}H_{19}N_3O_2$	9.9	12.5	NA	25
109	4-FC_6H_4	H	$CONH_2$	4-pyridinyl 1-oxide	>300	*c*		$C_{21}H_{14}FN_3O_3 \cdot 0.5H_2O$	NA	>12.5	25	100
110[g]	CH_2CH_3	H	$CONH_2$	C_6H_5	235–236	*c*		$C_{18}H_{16}N_2O_2$	NA	50	*e*	
111	4-FC_6H_4	H	$CONH_2$	C_6H_5	289–292	*c*		$C_{22}H_{15}FN_2O_2$	0.82	12.5	NA	>200
112	CH_2CH_3	H	$CONH_2$	4-$NO_2C_6H_4$	>360	*c*		$C_{18}H_{15}N_3O_4$	NA	>100	*e*	
113	CH_2CH_3	H	$CONH_2$	4-$NH_2C_6H_4$	285–287	*c*		$C_{18}H_{17}N_3O_2 \cdot CH_3SO_3H$	NA	6.25	*e*	
114	CH_2CH_3	H	$CONH_2$	5-isoxazolyl	243–245	A	74	$C_{15}H_{13}N_3O_3$	5.0	12.5	NA	>200

Table II (Continued)

compd	R_1	R_2	R_3	R_7	mp, °C	method[c]	yield, %	formula	MIC	MTL	MED	MTD
115	CH_2CH_3	H	$CONH_2$	3-CH_3-5-isoxazolyl	>300	A	94	$C_{16}H_{15}N_3O_3$	12	>100	NA	>200
116	4-FC_6H_4	H	$CONH_2$	3-CH_3-5-isoxazolyl	>300	A	83	$C_{20}H_{14}FN_3O_3$	0.26	>100	NA	>200
117	4-FC_6H_4	H	$CONH_2$	3-CH_3-5-isothiazolyl	221 dec			$C_{20}H_{14}FN_3O_2S$	0.25	>100	NA	>100
118	CH_2CH_3	H	$CONH_2$	1-imidazolyl	294–296	*c*		$C_{15}H_{14}N_4O_2$	NA	50	*e*	
119	CH_2CH_3	H	$CONH_2$	2-CH_3-5-thiazolyl	>320	A	75	$C_{16}H_{15}N_3O_2S$	NA	>100	*e*	
120[h]	CH_2CH_3	H	$CONH_2$	4-CH_3-1-piperazinyl	211–212	A	75	$C_{17}H_{22}N_4O_2$	NA	50	*e*	
121[i]	CH_2CH_3	H	$CONH_2$	H	243–246	A	73	$C_{12}H_{12}N_2O_2$	NA	50	*e*	
122[j]	CH_2CH_3	H	$CONH_2$	F	255–256	A	74	$C_{12}H_{11}FN_2O_2$	NA	50	*e*	
123[k]	CH_2CH_3	H	$CONH_2$	Cl	299–302	A	88	$C_{12}H_{11}ClN_2O_2$	NA	>100	*e*	
124	4-FC_6H_4	H	$CONH_2$	Cl	253–255	A	87	$C_{16}H_{10}ClFN_2O_2$	NA	>12.5	*e*	
125[l]	CH_2CH_3	H	$CONH_2$	I	285–286	A	89	$C_{12}H_{11}IN_2O_2$	NA	>100	*e*	
126	4-FC_6H_4	H	$CONH_2$	Br	250–251	A	45	$C_{16}H_{10}BrFN_2O_2$	NA	6.25	*e*	
127	CH_2CH_3	CH_3	$CONH_2$	4-pyridinyl	>300	*c*		$C_{18}H_{17}N_3O_2$	NA	50	*e*	
128	CH_2CH_3	OH	$CONH_2$	4-pyridinyl	258–260	*c*		$C_{17}H_{15}N_3O_3 \cdot CH_3SO_3H$	2.1	6.25	100	100
129	CH_2CH_3	NH_2	$CONH_2$	4-pyridinyl	>300	*c*		$C_{17}H_{16}N_4O_2$	9.0	>12.5	NA	>100
130	4-FC_6H_4	OH	$CONH_2$	4-pyridinyl	275–278 dec	*c*		$C_{21}H_{14}FN_3O_3 \cdot CH_3SO_3H \cdot 2H_2O$	11	>100	*m*	
131	4-FC_6H_4	NH_2	$CONH_2$	4-pyridinyl	294–296 dec	*c*		$C_{21}H_{15}FN_4O_2 \cdot CH_3SO_3H \cdot 0.5H_2O$	0.33	>100	50	50
132	4-FC_6H_4	R_2, R_3 = NHNHCO		4-pyridinyl	>300	*c*		$C_{21}H_{13}FN_4O_2 \cdot CH_3SO_3H \cdot H_2O$	NA	>100	*e*	
133	R_1, R_2 = 2-C_6H_4NH		$CONH_2$	4-pyridinyl	>300	C	84	$C_{21}H_{14}N_4O_2 \cdot CH_3SO_3H \cdot H_2O$	NA	0.4	e	

[a] Plaque-reduction assay in Vero cells (see the Experimental Section); MIC, minimum inhibitory concentration; MTL, maximum tolerated level. [b] See the Experimental Section; MED, minimum effective dose; MTD, maximum tolerated dose. [c] See the Experimental Section. [d] NA ⇒ no activity at the MTL or MTD. [e] Not determined. [f-l] Prepared from known precursors: [f]*see* ref 5; [g]*see* ref 10; [h]*see* ref 27; [i]*see* ref 28; [j]*see* ref 29; [k]*see* ref 30; [l]*see* ref 31. [m] Insufficient sample size for testing.

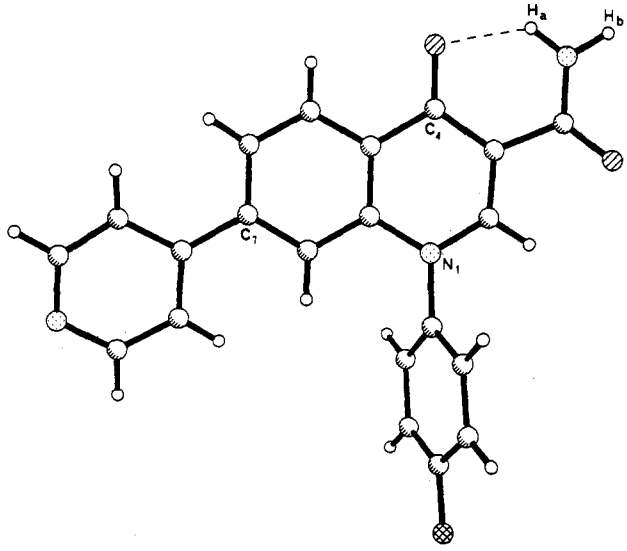


Figure 1. X-ray crystal structure of compound 97.

into a broad singlet at δ 7.40 between 75 and 100 °C and were completely exchanged in 10 min upon addition of D_2O at room temperature. These data indicate the H-bonded conformer of 127 is not as stable as it is in 67, undoubtedly due to $A_{1,3}$ strain between the 2-CH_3 and the C=O of the carboxamide. The relative instability of the intramolecular H-bonded conformer (the active conformation) of 127 may raise the free energy for binding to the molecular target which would result in substantially decreased activity.

Based on bulk parameters alone, one would expect 129 (2-NH_2) to have similar activity to 127 (2-CH_3) since these 2-substituents are of similar size; compound 129, however, has quite good activity (MIC = 9.0 μg/mL). Proton NMR data clearly shows the carboxamide of 129 can adopt the active conformation due to stabilization by an additional intramolecular H-bond between one of the hydrogens of the 2-NH_2 group and the oxygen of the carboxamide. The carboxamide H's are doublets and separated by a large chemical shift [δ 10.65 (d, H_a, J = 4 Hz); δ 7.28 (d, H_b, J = 4 Hz], and while they broaden at high temperatures they do not coalesce at 125 °C. The exchangeable H's of the 2-NH_2 group of 129 are broad singlets at δ 11.73 and 7.88, indicative of an intramolecular H-bond setup, and they coalesce into a broad singlet at δ 9.6 between 50 and 75 °C. The active conformation of the 2-OH analogue 128 may be similarly stabilized. This highly active compound, however, was isolated as the DMSO-insoluble methanesulfonic acid salt which precluded the generation of corroborating NMR data.

The 2-NH_2 (130) and 2-OH (131) analogues were also made in the 1-FC_6H_4 subseries. They also showed good activity, although the rank order of potency (2-H > 2-NH_2 > 2-OH) was different than that observed in the 1-ethyl series (2-OH > 2-H > 2-NH_2).

With regard to the role of the 7-substituent, the best activity was seen when that group was heteroaromatic, specifically, pyridinyl, isoxazolyl, or isothiazolyl. Little information regarding SAR was obtained by introducing a 7-phenyl in that 111 was very potent in vitro while the corresponding 1-ethyl-7-phenyl analogue 110 was inactive as were two substituted-phenyl derivatives, 112 and 113. Compounds with 7-substituents that are ionized or ionizable due to protonation at cellular pH were inactive.

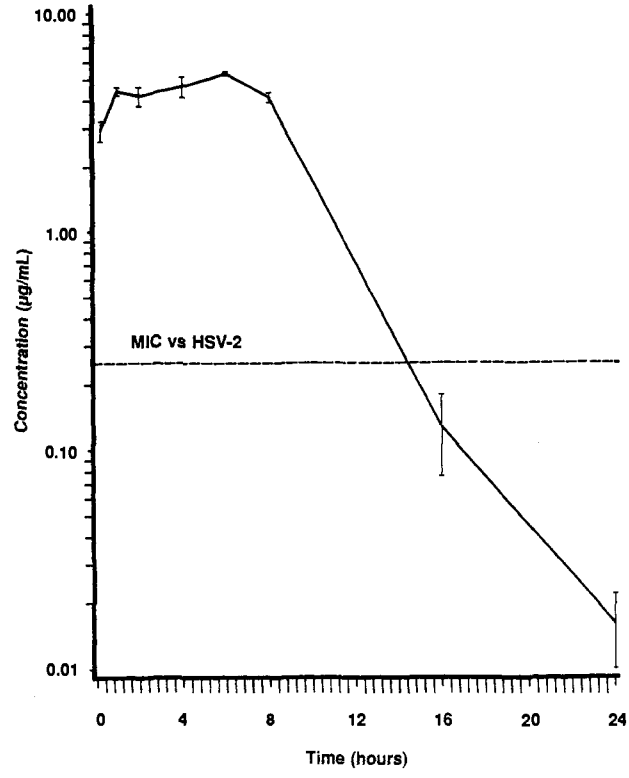


Figure 2. Mean serum concentrations of compound 97 in female Swiss-Webster mice following oral administration at 25 mg/kg.

These are the pyridine *N*-oxide (109) and piperazinyl (120) and imidazolyl (118) analogues.

Biological Properties of Target Compounds in Mice. Derivatives that displayed HSV-2 plaque-reduction activity at or below the MTL were evaluated in the mouse HSV-2 infection model by the oral route of administration (see the Experimental Section for definition of terms). The results of this testing, with acyclovir included for comparison, are shown in Table II. In general, plaque-reduction potency was not predictive of oral efficacy. Among the 34 in vitro active compounds selected for in vivo testing, 12 showed activity in mice. The MIC values of most of these 12 compounds were under 1 μg/mL; all had MIC's 10 μg/mL. There were, however, many compounds with MIC values near or under 1 μg/mL that were devoid of in vivo activity; among them were 116 and 117, two of the most potent analogues in vitro within the series. Compound 97 displayed the best in vivo activity in the series which was 2-fold less potent than acyclovir.

Without knowing the drug metabolism and pharmacokinetic properties (i.e., oral bioavailability, metabolism, clearance rates, volume of distribution) of these compounds it is difficult, at best, to relate in vivo activity to structure and/or in vitro potency. Clearly the 7-(4-pyridinyl) group is beneficial to activity; all analogues in the series with in vivo activity have this appendage.[21] One apparent anomaly is the pyridine *N*-oxide derivative 109 which has considerable in vivo activity despite the lack of in vitro activity. This result is undoubtedly due to a metabolic deoxygenation of 109 in mice to the active drug form, 97.[22]

Serum concentrations of 97 were measured in mice following single oral administration of drug at 25 mg/kg. As shown in Figure 2, absorption was rapid as evidenced by a mean serum concentration of 3.1 μg/mL at 15 min, the first time point examined. Thereafter, serum concentrations remained above the MIC value of 0.24 μg/mL

Table III. In Vitro Activity of 97 against HSV-1 and Acyclovir-Resistant Mutants

virus	MIC, μg/mL[a]	
	97	acyclovir
HSV-2 (Curtis)	0.24	1.3
HSV-1 (F)	0.13	0.29
HSV-1 (KOS)	0.23	0.14
HSV-1 (KOS, ACG^r)	0.32	43
HSV-1 (1142)	0.18	7.8
HSV-1 (2992)	0.24	11
HSV-2 (2011)	0.15	43
HSV-2 (2115)	0.13	77

[a] Plaque-reduction assay in Vero cells; see Table II and the Experimental Section.

for at least 8 h (and up to 14 h assuming the last three serum concentrations represent true first-order elimination). This observation may explain the antiviral efficacy of 97 following oral administration at 25 mg/kg in mice infected with HSV-2.

Based on a comparison of the MED and MTD results for the multiple dose regimen (Table II), it appears that 97 was not as well tolerated in mice as acyclovir and showed a smaller separation between activity and toxicity. This is consistent with the in vitro results in Vero cells. The small separation between toxicity and activity in vivo was modified by using a single therapeutic dose, where compound was administered only once 1.5-h postinfection according to the protocol described in the Experimental Section. The MED for 97 was 25 mg/kg compared to 400 mg/kg for acyclovir. The MTD for both compounds was >400 mg/kg. Thus, in this single-dose regimen, 97 was 16-fold more potent than acyclovir and showed at least a 16-fold separation between activity and toxicity. This result was not unexpected due to the sustained serum concentrations of 97.

In Vitro Activity against HSV-1 and Acyclovir-Resistant Mutants. Compound 97 was tested against two strains of HSV-1 and five acyclovir-resistant mutants of HSV-1 and HSV-2 in Vero cells (Table III). Compound 97 and acyclovir had similar potencies against HSV-1 (KOS) and HSV-1 (F). In contrast, compound 97 was significantly more potent (40–600-fold) than acyclovir against several acyclovir-resistant strains of HSV-1 and HSV-2. These results suggest that 97 has a different mechanism of action than acyclovir. This is supported by studies which indicate that 97 may act at a very early stage in the viral life cycle, since the synthesis of immediate early and early proteins is inhibited by 97, but not by acyclovir.[23] Compound 97 was found to have no topoisomerase II (from HeLa cells) inhibitory or in vitro antibacterial activity.[23] This is consistent with the generally accepted belief that a 3-CO_2H group or isosteric replacement is required for antibacterial activity.[4]

Conclusions

We have identified potent in vitro and in vivo antiherpetic properties in a novel series of quinolinecarboxamides. Among the 68 compounds evaluated in vitro, a common structural feature that appears to be a stringent requirement for in vitro activity is the planar, intramolecular H-bonded conformation of the β-keto amide moiety. Additionally, the 7-(4-pyridinyl) group imparts to these compounds excellent in vivo efficacy. Compound 97, the most potent compound in vitro and in vivo, shows very high and prolonged plasma drug levels in mice and was selected for additional studies. Development of this compound as a human therapeutic, however, was precluded because of an unacceptable toxicity profile in vitro (positive in the CHO/HGPRT mammalian cell forward mutation assay) and in rodents dosed orally.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Proton NMR (IBM AM-200, JOEL GSX-270 FT-NMR, or GE QE-300), chemical ionization mass spectra (Hewlett-Packard 5980A mass spectrometer), and infrared spectra (Nicolet 10DX FT-IR spectrophotometer) were consistent with the assigned structures. Complete ^1H NMR data are reported for all compounds except tin reagents. ^1H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants are in hertz. High-performance liquid chromatography was carried out on a Rainin HPXL system equipped with a Dynamax absorbance detector. Carbon, hydrogen, and nitrogen elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, and were within ±0.4% of theoretical values. Reactions were generally performed under a N_2 atmosphere.

1-Ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (67). Method A. A stirred mixture of 78 (14.7 g, 50 mmol), 1,1′-carbonyldiimidazole (12.2 g, 75 mmol), and DMF (150 mL) was heated to 100 °C for 2 h and chilled in ice. The precipitate was collected, washed with EtOAc and then Et_2O, and dried in vacuo at ambient temperature to afford the acylimidazole (15.2 g, 88%). Anhydrous NH_3 was bubbled through a solution of the acylimidazole (15.2 g) in DMF (200 mL) for 1 h. The resulting mixture was chilled in ice, and the solid was collected and washed with EtOAc followed by Et_2O to give 67 (12.8 g, 99%). Recrystallization from DMF afforded analytically pure material: mp 314–317 °C; ^1H NMR (DMSO-d_6) δ 9.27 (d, J = 4 Hz, 1H), 8.93 (s, 1H), 8.75 (d, J = 4 Hz, 2H), 8.46 (d, J = 6 Hz, 1H), 8.18 (s, 1H), 7.91–7.95 (m, 3H), 7.55 (d, J = 4 Hz, 1H), 4.65 (q, J = 6 Hz, 2H), 1.44 (t, J = 6 Hz, 3H). Anal. ($C_{17}H_{15}N_3O_2$) C, H, N.

1-Ethyl-1,4-dihydro-*N*-hydroxy-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (70). Method B. A slurry of the acylimidazole from method A (15.0 g, 44 mmol), NH_2OH·HCl (6.1 g, 88 mmol), and pyridine (200 mL) was stirred at ambient temperature for 4 h. The pyridine was removed in vacuo and the residue triturated with water and collected. The crude product was washed with water, air-dried, and recrystallized from DMF–Et_2O to afford 70 (10.2 g, 75%): mp 245 °C dec; ^1H NMR (DMSO-d_6) δ 8.92 (s, 1H), 8.75 (d, 2H), 8.45 (d, 1H), 8.17 (s, 1H), 7.85–8.00 (m, 3H), 4.70 (q, 2H), 1.46 (t, 3H). Anal. ($C_{17}H_{15}N_3O_3$) C, H, N.

***N*-(2-Aminoethyl)-1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (75).** A solution of rosoxacin ethyl ester (3)[5] (5.0 g, 155 mmol) and ethylenediamine (50 mL) was heated at reflux for 2 h, cooled, and diluted with Et_2O, and the precipitate was collected. The crude product was washed with Et_2O and dried in vacuo to afford 75 (4.71 g, 90%). The methanesulfonate salt was prepared and recrystallized from MeOH/water to provide analytically pure material: mp 286–287 °C; ^1H NMR (D_2O) δ 8.97 (d, J = 6.0 Hz, 2H), 8.87 (s, 1H), 8.49–8.36 (m, 3H), 8.17 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 4.58 (q, J = 7.7 Hz, 2H), 3.79 (t, J = 6.0 Hz, 2H), 3.56 (t, J = 6.0 Hz, 2H), 2.88 (s, 3H), 1.61 (t, J = 7.7 Hz, 3H). Anal. ($C_{19}H_{20}N_4O_2$·2CH_3SO_3H·0.5H_2O) C, H, N.

1-Ethyl-1,4-dihydro-*N*-(2-hydroxyethyl)-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (77). A mixture of the acylimidazole derived from 78 (method A, 6.89 g, 20 mmol) and 2-aminoethanol (50 mL) was heated at reflux 1.5 h. The reaction mixture was poured into water (100 mL), and the precipitate was collected and washed with additional water. The solid was dried in vacuo to afford 77 (6.67 g, 99%). Recrystallization from a solution of MeOH and methansulfonic acid gave the methansulfonate salt of 77 as pale green crystals: mp >350 °C; ^1H NMR (D_2O) δ 8.93 (d, 2H), 8.52 (s, 1H), 8.31 (d, 2H), 7.98 (d, 1H), 7.89 (s, 1H), 7.70 (dd, 1H), 4.38 (q, 2H), 3.71 (t, 2H), 3.32 (t, 2H), 2.88 (s, 3H), 1.50 (t, 3H). Anal. ($C_{19}H_{19}N_3O_3$·CH_3SO_3H·0.25H_2O) C, H, N.

1-Ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarbonitrile (79). To a stirred mixture of **67** (29.6 g, 0.10 mol) in *N*-methylpyrrolidone (500 mL) was added dropwise $POCl_3$ (50 mL) over 1 h. After the reaction mixture was stirred at ambient temperature overnight, the reaction was quenched by the addition of water (700 mL). The resulting green mixture was made basic with saturated aqueous K_2CO_3 (ca. 150 mL) and further diluted with water (2 L). Filtration afforded a pale yellow solid which was dried in vacuo (50 °C) overnight to give the desired product **79** (25.6 g, 93%). Recrystallization from 1 N HCl gave the hydrochloride salt: mp 326–330 °C dec; ^1H NMR (CF_3COOD) δ 9.18 (d, 2H), 8.98 (s, 1H), 8.93 (d, 1H) 8.56 (d, 2H), 8.48 (s, 1H), 8.23 (d, 1H), 4.86 (q, 2H), 1.79 (t, 3H). Anal. ($C_{17}H_{13}N_3O$·HCl) C, H, N.

1-Ethyl-1,4-dihydro-3-(4,5-dihydro-2-oxazolinyl)-4-oxo-7-(4-pyridinyl)quinoline (80). A mixture of **77** (3.00 g, 8.9 mmol), $SOCl_2$ (33 mL, 45 mmol), and 1,4-dioxane (150 mL) was heated at reflux 1 h. The reaction mixture was cooled and the solid collected. Recrystallization from MeOH gave **80** (1.87 g, 59%) as its dihydrochloride salt: mp >350 °C; ^1H NMR (D_2O) δ 8.96 (d, J = 6.0 Hz, 2H), 8.45 (s, 1H), 8.30 (d, J = 6.0 Hz, 2H), 7.83 (s, 1H), 7.81 (d, J = 9.4 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 4.31 (q, J = 6.8 Hz, 2H), 3.71 (m, 2H), 3.48 (m, 2H), 1.48 (t, J = 7.7 Hz, 3H). Anal. ($C_{19}H_{17}N_3O_2$·2HCl) C, H, N.

1-Ethyl-1,4-dihydro-3-(4,5-dihydro-2-1*H*-imidazolyl)-4-oxo-7-(4-pyridinyl)quinoline (81). A mixture of polyphosphoric acid (30 g) and phosphorous pentoxide (15 g) was heated at 200 °C for 1 h and cooled to 80 °C, and **75** (8.9 g, 26 mmol) was added. The reaction temperature was raised to 200 °C for 2 h and then allowed to cool to room temperature. The glassy mixture was dissolved in water (500 mL) with heating and made basic with NH_4OH, producing off-white needles. The crystals were collected and dried in vacuo to give **81** (5.40 g, 65%). Treatment of **81** with CH_3SO_3H and MeOH afforded the methanesulfonate salt of **81**: mp 268–271 °C; ^1H NMR (D_2O) δ 9.00 (d, 2H), 8.90 (s, 1H), 8.53–8.41 (m, 3H), 8.29 (s, 1H), 8.07 (dd, 1H), 4.66 (q, 2H), 4.05 (s, 6H), 2.87 (s, 4H), 1.67 (t, 3H). Anal. ($C_{19}H_{18}N_4O$·2CH_3SO_3H·0.5H_2O) C, H, N.

1,4-Dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (82). A suspension of **4**[5] (30 g, 0.10 mol) in hydrazine hydrate (300 mL) was maintained at reflux overnight. After being cooled to ambient temperature the reaction mixture was diluted with water (600 mL) and stirred 1 h. The resulting yellow-green solid was collected and recrystallized from DMF to afford the hydrazide (17.5 g, mp >300 °C). A suspension of the hydrazide (13.0 g, 46 mmol) and Raney nickel (5.0 g) in DMF (850 mL) was held at reflux for 36 h. The reaction mixture was filtered hot, and the DMF was removed in vacuo, leaving **82** as an off-white powder (11.6 g, 35%). The hydrochloride was prepared from 6 N HCl: mp >350 °C; ^1H NMR (CF_3COOD) δ 9.72 (s, 1H), 9.10 (d, 2H), 8.95 (d, 1H), 8.79 (s, 1H), 8.59 (d, 2H), 8.38 (d, 1H). Anal. ($C_{15}H_{11}N_3O_2$·HCl·0.25H_2O) C, H, N.

1-[2-(Ethenyloxy)ethyl]-1,4-dihydro-7-(4-pyridinyl)-3-quinolinecarboxamide (8). A mixture of **82** (27.6 g, 0.10 mol), NaH (5.50 g of 50% oil suspension, 0.11 mol), and DMF (400 mL) was stirred at 80 °C for 1.5 h. NaI (1.9 g, 12 mmol) and 2-chloroethyl vinyl ether (12.7 mL, 0.125 mol) were added, and the temperature was raised to 110 °C and maintained for 17.5 h. Additional 2-chloroethyl vinyl ether (5.0 mL) was added, and heating was continued for 4 h. The reaction mixture was concentrated in vacuo to ca. 50 mL total volume, and a small amount of solid was removed by filtration. The filtrate was cooled in ice, and the resulting solid was collected, washed with cold DMF and EtOAc, and dried in vacuo to give a brown crystalline solid. Recrystallization from DMF afforded **8** (17.7 g, 51%) as a light tan solid: mp 238–240 °C; ^1H NMR (DMSO-d_6) δ 9.25 (br d, 1H, CON*H*), 8.87 (s, 1H), 8.75 (dd, 2H), 8.48 (d, 1H), 8.26 (s, 1H), 7.87–8.00 (m, 3H), 7.57 (br s, 1H, CON*H*), 6.48 (dd, 1H), 4.75–5.05 (m, 2H), 4.05–4.30 (m, 3H), 3.97 (dd, 1H). Anal. ($C_{19}H_{17}N_3O_3$) C, H, N.

1,4-Dihydro-1-(2-hydroxyethyl)-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (89). A solution of **8** (13.6 g, 40 mmol) in HOAc (50 mL) and water (5 mL) was heated on a steam bath for 45 min. After 10 min the product began to precipitate. The resulting solid was collected, washed with water, and dried in vacuo to give 9.3 g of tan solid. The mother liquor was concentrated to dryness in vacuo to give a powdery residue which was suspended in water, collected, and washed with water and EtOH to give 3.3 g of a light gray solid. The gray solid was dissolved in dilute HCl (70 mL) on a steam bath, treated with charcoal, and filtered. The filtrated was neutralized with 2 N KOH, and the white precipitate was collected. The combined products were treated with water and methanesulfonic acid to give the methanesulfonate salt of **89** (10.2 g 88%): mp 293–295 °C; ^1H NMR (D_2O) δ 8.38 (d, 2H), 8.45 (s, 1H), 8.28 (d, 2H), 7.86–7.95 (m, 2H), 7.64 (d, 1H), 4.44–4.57 (m, 2H), 3.95–4.08 (m, 2H), 2.87 (s, 3H). Anal. ($C_{17}H_{15}N_3O_3$·CH_3SO_3H) C, H, N.

Ethyl 1-Butyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate (5). A mixture of quinolone **4**[5] (1.00 g, 3.4 mmol), anhydrous K_2CO_3 (1.66 g, 12.0 mmol), and DMF (10 mL) was heated on a steam bath for 30 min, and *N*-butyl iodide was added (0.68 g, 3.7 mmol). The heating was continued for 2 h, and the DMF was removed in vacuo. The residue was partitioned between water and $CHCl_3$. Insoluble material was removed by filtration, and the organic layer was dried over $MgSO_4$. Concentration in vacuo gave a brown oil. Trituration with Et_2O gave a solid which was collected and washed with additional Et_2O, leaving **5** (0.60 g, 50%): mp 102–109 °C; ^1H NMR ($CDCl_3$) δ 8.78 (d, J = 5.4 Hz, 2H), 8.68 (d, J = 8.3 Hz, 4H), 8.54 (s, 1H), 7.60–7.75 (m, 4H) 4.43 (q, J = 7.9 Hz, 2H), 4.29 (t, J = 7.3 Hz, 2H), 1.85–2.00 (m, 2H), 1.30–1.55 (m, 5H), 1.03 (t, J = 7.3 Hz, 3H). Anal. ($C_{21}H_{22}N_2O_3$·0.5H_2O) C, H, N.

Ethyl 1,4-dihydro-4-oxo-1-pentyl-7-(4-pyridinyl)-3-quinolinecarboxylate (6) was prepared according to the same procedure as for **5**: mp 127–129 °C; ^1H NMR ($CDCl_3$) δ 8.76 (d, J = 5.7 Hz, 2H), 8.64 (d, J = 8.3 Hz, 1H), 8.51 (s, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.62 (s, 1H), 7.57 (d, J = 5.9 Hz, 2H), 4.41 (q, J = 7.2 Hz, 2H), 4.26 (t, J = 7.3 Hz, 2H), 1.83–2.03 (m, 2H), 1.25–1.55 (m, 7H), 0.94 (m, 3H). Anal. ($C_{22}H_{24}N_2O_3$·0.25H_2O) C, H, N.

Ethyl 1,4-Dihydro-4-oxo-1-(2-propenyl)-7-(4-pyridinyl)-3-quinolinecarboxylate (7). A mixture of **4** (10.0 g, 34 mmol), K_2CO_3 (9.43 g, 68 mmol), and DMF (20 mL) was heated at 90 °C for 30 min and treated with allyl bromide (2.8 mL, 34 mmol). The resulting mixture was stirred at 90 °C for 4 h and allowed to cool to ambient temperature. The mixture was filtered, and the filtrate was concentrated to dryness in vacuo. The resulting solid was dissolved in $CHCl_3$, treated with decolorizing charcoal, and filtered, and the $CHCl_3$ was removed in vacuo. Recrystallization from CH_2Cl_2 afforded **7** (7.49 g, 66%): mp 155–157 °C; ^1H NMR ($CDCl_3$) δ 8.61–8.79 (m, 2H), 8.44 (t, 2H), 7.41–7.70 (m, 8H), 5.93–6.37 (m, 1H), 5.43 (d, 1H), 5.27–5.54 (m, 2H), 4.89–5.11 (m, 2H), 4.33 (q, 2H), 1.38 (t, 3H). Anal. ($C_{18}H_{18}N_3O_2$) C, H, N.

4-(3-Fluoro-4-methylphenyl)pyridine (10). To a stirred mixture of Mg turnings (35 g, 1.4 mol) in THF (300 mL) was added dropwise a solution of 4-chloro-2-fluorotoluene (**9**, 150 g, 1.0 mol), and the resulting mixture was heated on a steam bath for 3 h. In a separate flask a solution of pyridine (175 mL, 2.2 mol), pivaloyl chloride (176 mL, 1.4 mol), and THF (2 L) was stirred overnight at ambient temperature. To this mixture was added CuI (15.0 g, 0.08 mol). The mixture was cooled to −40 °C, and the Grignard reagent was added dropwise. After the reaction mixture was stirred overnight, the reaction was quenched with saturated NH_4Cl, stirred for 1 h, diluted with water, and extracted with Et_2O (1 L). The Et_2O layer was washed with saturated NH_4Cl and saturated K_2CO_3 and dried (Na_2SO_4). Concentration in vacuo afforded a yellow oil which slowly solidified on standing (210 g). A mixture of a portion of the crude dihydropyridine derivative (119 g), sulfur (30 g), and toluene (1 L) was heated overnight at reflux. The reaction mixture was cooled in ice and filtered. The filtrate was extracted with 6 N HCl (500 mL) and basified with 35% KOH. The resulting mixture was extracted with EtOAc, dried over Na_2SO_4, and concentrated in vacuo to afford **10** (35 g) as a yellow oil. An analytical sample was prepared by flash chromatography (EtOAc): ^1H NMR ($CDCl_3$) δ 8.62 (dd, J = 4.6, J = 1.5 Hz, 2H), 7.44 (dd, J = 4.6, J = 1.5 Hz, 2H), 7.20–7.35 (m, 3H), 2.30 (d, 1.8 Hz, 3H). Anal. ($C_{12}H_{10}FN$) C, H, N.

2-Fluoro-4-(4-pyridinyl)benzoic Acid (12). A mixture of **10** (31 g, 0.17 mol), water (400 mL), and pyridine (200 mL) was treated portionwise with $KMnO_4$ (81 g, 0.51 mol) and was stirred at 60 °C overnight. The reaction mixture was filtered through

Celite and concentrated in vacuo to ca. 250 mL. The yellow solution was washed with EtOAc (150 mL), and the aqueous portion was diluted with water (50 mL). Acidification with HOAc (30 mL) gave a precipitate which was collected and dried to afford 12 (24 g, 57%), which was suitable for use without further purification. An analytical sample of the hydrochloride salt of 12 was prepared by recrystallization from 1 N HCl (mp >300 °C): ^{1}H NMR (CF_3COOD) δ 9.02 (d, 2H), 8.40 (d, 2H), 8.35 (d, 1H), 7.80 (dd, 2H). Anal. ($C_{12}H_8FNO_2$·HCl) C, H, N.

Ethyl 2-Fluoro-4-(4-pyridinyl)-β-oxobenzenepropanoate (15). A solution of 12 (10.7 g, 5 mmol) and $SOCl_2$ (100 mL) was heated at reflux overnight. Removal of solvent in vacuo afforded the acid chloride of 12 as a yellow solid. To a dry solution of monoethyl malonate (15.3 g, 0.12 mol) in THF (150 mL) at −70 °C was added dropwise over 15 min *n*-BuLi (100 mL of 2.5 M solution, 0.25 mol). The reaction mixture was allowed to warm to −10 °C and recooled to −70 °C. To the resulting mixture was added the acid chloride, stirring was continued at −70 °C for 5 min, and the reaction vessel was allowed to warm to 0 °C over 2 h. The reaction mixture was poured into a mixture of 1 N HCl (200 mL) and Et_2O (200 mL). The Et_2O layer was discarded, and the aqueous portion was neutralized with solid $NaHCO_3$ and reextracted with Et_2O (3 × 200 mL). The combined extracts were dried over Na_2SO_4 and concentrated to dryness in vacuo to afford 15 as a yellow oil which slowly crystallized on standing (7.9 g, 59%). An analytical sample was prepared by HPLC chromatography (EtOAc/hexanes): mp 58–60 °C; ^{1}H NMR ($CDCl_3$) indicated a mixture of tautomers δ 8.65–8.80 (m, 2H), 7.98–8.15 (m, 1H), 7.35–7.60 (m, 4H), 5.93 (s, 0.3H), 4.20–4.37 (m, 2H), 4.04 (d, 1.7H), 1.36 (t, 0.8H), 1.29 (t, 2.2H). Anal. ($C_{16}H_{14}FNO_3$) C, H, N.

2-Chloro-4-(4-pyridinyl)benzoic acid (13) was prepared via the same procedure as for 12 in 88% yield from 4-(3-chloro-4-methylphenyl)pyridine (11):[24] mp 290–291 °C; ^{1}H NMR (CF_3COOD) δ 8.95 (d, 2H), 8.41 (d, 2H), 8.31 (d, 1H), 8.05 (s, 1H), 7.90 (dd, 1H). Anal. ($C_{12}H_8NClO_2$·HCl) C, H, N.

Ethyl 2-chloro-4-(4-pyridinyl)-β-oxobenzenepropanoate (16) was prepared from 13 in 50% yield via the same procedure used to synthesize 15. An analytical sample was prepared by recrystallization from hexane: mp 62–63 °C; ^{1}H NMR ($CDCl_3$) indicated a mixture of tautomers δ 8.65–8.76 (m, 2H), 7.68–7.82 (m, 2H), 7.55–7.65 (m, 1H), 7.51 (dd, 2H), 5.66 (s, 0.5H), 4.15–4.38 (q + q, 2H), 4.08 (s, 0.5 H), 1.37 (t, 2H), 1.27 (t, 1H). Anal. ($C_{16}H_{14}ClNO_3$) C, H, N.

Ethyl 2-chloro-4-bromo-β-oxobenzenepropanoate (17) was prepared via the same procedure as for 15 from commercially available 2-chloro-4-bromobenzoic acid (14) in 73% yield, following recrystallization from hexane: mp 43–44 °C; ^{1}H NMR ($CDCl_3$) indicated a mixture of tautomers δ 7.62 (s, 1H), 7.53 (s, 1H), 7.48 (s, 1H), 5.53 (s, 0.5 H), 4.13–4.37 (q + q, 2H), 4.04 (s, 1H), 1.20–1.40 (t + t, 3H). Anal. ($C_{11}H_{10}BrClO_3$) C, H.

Ethyl 1-(4-Fluorophenyl)-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate (28). Method D. A solution of 15 (11.5 g, 40.0 mmol), *N,N*-dimethylformamide dimethyl acetal (10 mL), and THF (100 mL) was stirred overnight at ambient temperature. Decolorizing charcoal was added, and the mixture was boiled and filtered. Concentration in vacuo afforded a yellow solid (8.1 g, 87%). Alternatively, Et_2O or toluene may be used as solvents. A solution of the DMF acetal adduct (3.42 g, 10.0 mmol), 4-fluoroaniline (1.1 g, 10.1 mmol), and dioxane (25 mL) was heated at reflux for 2 days (monitored by TLC/acetone). Solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 followed by treatment with decolorizing charcoal. Concentration afforded 28 (3.5 g, 92%). An analytical sample was prepared by recrystallization from EtOAc: mp 252–253 °C; ^{1}H NMR ($CDCl_3$) δ 9.56–9.73 (m, 3H), 9.51 (s, 1H), 7.68 (d, 1H), 7.47–7.60 (m, 2H), 7.30–7.46 (m, 4H), 7.14 (s, 1H), 4.39 (q, 2H), 1.39 (t, 3H). Anal. ($C_{23}H_{17}FN_2O_3$·0.25H_2O) C, H, N.

Ethyl 1,4-Dihydro-1-phenyl-7-(4-pyridinyl)-4-oxo-3-quinolinecarboxamide (21). Method E. A mixture of 15 (6.0 g, 21 mmol), dimethylformamide dimethyl acetal (2.5 g, 21 mmol), and THF (75 mL) was stirred at ambient temperature overnight. Aniline (2.2 mL, 24 mmol) was added, and the reaction mixture was stirred overnight. The THF was removed in vacuo, the residue was treated with DMF (50 mL) and K_2CO_3 (3.2 g), and the resulting mixture was heated at reflux for 3 h. The solvent was removed in vacuo and the residue partitioned between water and CH_2Cl_2. The organic portion was concentrated in vacuo and the residue triturated with Et_2O to give 21 (4.4 g, 58%). Treatment with methanesulfonic acid and acetone afforded the methanesulfonate salt of 21: mp 288–289 °C; ^{1}H NMR (CF_3COOD) δ 9.38 (s, 1H), 9.10 (d, 1H), 9.06 (d, 2H), 8.43 (d, 1H), 8.35 (d, 2H), 8.01 (s, 1H), 7.63–7.96 (m, 5H), 4.37 (q, 2H), 3.10 (s, 3H), 1.50 (t, 3H). Anal. ($C_{23}H_{18}N_2O_3$·CH_3SO_3H·H_2O) C, H, N.

1-(4-Chlorophenyl)-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (91). Method C. A stainless steel vessel containing 22 (3.40 g, 8.40 mmol) in saturated ethanolic NH_3 (200 mL) was heated at 125 °C for 14 h. The reaction mixture was cooled to 0 °C, and a solid was collected to afford 91 (2.06 g, 65%). Recrystalization from methanesulfonic acid/MeOH gave the methanesulfonate salt: mp 280 °C; ^{1}H NMR (CF_3COOD) 9.55 (s, 1H), 9.02 (d, 3H), 8.34 (d, 3H), 7.95 (s, 1H), 7.75 (q, 4H), 3.10 (s, 3H). Anal. ($C_{21}H_{14}ClN_3O_2$·CH_3SO_3H·H_2O) C, H, N.

1,4-Dihydro-(4-fluorophenyl)-7-[4-(1-oxopyridinyl)]-4-oxo-3-quinolinecarboxamide (109). A mixture of 97 (1.59 g, 4.42 mmol), *m*-CPBA (1.53 g, 8.9 mmol), and glacial HOAc (50 mL) was stirred at ambient temperature overnight. A solution developed after ca. 30 min and a precipitate formed overnight. Additional *m*-CPBA (0.38 g, 2.2 mmol) was added, and the solution was stirred overnight. The reaction mixture was concentrated to dryness in vacuo, and the resulting solid was recrystallized from MeOH to give 109 (1.14 g, 69%): mp >300 °C; ^{1}H NMR (CF_3COOD) δ 9.51 (s, 1H), 9.00 (d, 1H), 8.92 (d, 2H), 8.27 (d, 1H), 8.18 (d, 2H), 7.85 (s, 1H), 7.65–7.80 (m, 2H), 7.40–7.57 (m, 2H). Anal. ($C_{21}H_{14}FN_3O_3$·0.5H_2O) C, H, N.

Ethyl 1,4-Dihydro-4-oxo-7-(4-pyridinyl)benzothiopyran-3-carboxylate (19). Hydrogen sulfide was bubbled through a stirred solution of 18 (5.0 g, 15 mmol) and EtOH (500 mL) for 3 h. The solvent was removed in vacuo, and the gummy residue was partitioned between CH_2Cl_2 and saturated K_2CO_3. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give an oil which was crystallized from Et_2O to give 19 (3.4 g, 75%). Recrystallization from EtOH gave analytically pure material; mp 154–155 °C; ^{1}H NMR ($CDCl_3$) δ 8.75 (dd, 2H), 8.35 (d, 1H), 7.55–7.70 (m, 2H), 7.65 (dd, 2H), 4.42 (q, 2H), 1.40 (t, 3H). Anal. ($C_{17}H_{13}NO_3S$) C, H, N.

1-Ethyl-1,4-dihydro-4-oxo-7-phenyl-3-quinolinecarboxamide (110). A mixture of 36[10] (3.20 g, 10 mmol) and hydrazine hydrate (15 mL) was heated at 100 °C for 10 min. After dilution with water (45 mL) and cooling, a precipitate was collected, washed with additional water, and air-dried. Recrystallization from CH_3CN afforded the hydrazide (2.55 g, 83%); mp 240–241 °C. A mixture of the hydrazide (4.9 g, 16 mmol), Raney nickel (ca. 6 g), DMF (60 mL), water (10 mL), and EtOH (20 mL) was refluxed 1 h. Filtration, concentration in vacuo, and recrystallization from CH_3CN afforded 110 (2.8 g, 60%): mp 235–236 °C; ^{1}H NMR (DMSO-d_6) δ 9.36 (br d, 1H), 8.91 (s, 1H), 8.42, (d, 1H), 7.78–7.97 (m, 3H), 7.40–7.64 (m, 4H), 4.63 (q, 2H), 1.42 (t, 3H). Anal. ($C_{18}H_{16}N_2O_2$) C, H, N.

1-Ethyl-1,4-dihydro-7-(4-nitrophenyl)-4-oxo-3-quinolinecarboxamide (112). A solution of 110 (12.0 g, 41 mmol) and TFA (50 mL) was cooled to 0 °C, added to cold sulfuric acid (75 mL), and stirred at 0 °C. Potassium nitrate (7.0 g) was added portionwise over 10 min and stirred an additional 30 min. The reaction mixture was poured onto ice, and the resulting precipitate was collected, washed with water, and then stirred in a saturated aqueous $NaHCO_3$ solution. Undissolved material was removed by filtration, and the filtrate was concentrated in vacuo. The crude product was recrystallized from HOAc and washed with CH_3CN and Et_2O to give 112 (10.7 g, 78%). An additional recrystallization from DMF afforded analytically pure material: mp >360 °C; ^{1}H NMR (CF_3COOD) δ 9.60 (s, 1H), 8.93 (d, 1H), 8.40–8.60 (m, 3H), 8.32 (d, 1H), 8.06 (d, 2H), 5.05 (q, 2H), 1.85 (t, 3H). Anal. ($C_{18}H_{15}N_3O_4$) C, H, N.

7-(4-Aminophenyl)-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxamide (113). To a mixture of 112 (18.4 g, 55 mmol) and DMF (200 mL) at 100 °C was added portionwise Raney nickel (ca. 5 g). Hydrazine hydrate (20 mL) was then added dropwise over 20 min, during which a solution developed. After an additional 30 min of heating, the hot solution was filtered and concentrated in vacuo to give a brown oil. The crude product was dissolved in EtOAc, and methanesulfonic acid was added.

After the resulting gum crystallized, the EtOAc was decanted, water was added, and the solid was collected. Recrystallization from MeOH afforded 113 as its methanesulfonate salt (3.3 g, 14%): mp 285–287 °C; ^{1}H NMR (DMSO-d_6) δ 9.30 (br s, 1H), 8.90 (s, 1H), 8.41 (d, 1H), 7.99 (d, 2H), 7.93 (s, 1H), 7.84 (d, 1H), 7.52 (br s, 1H), 7.41 (d, 2H), 4.62 (q, 2H), 2.40 (s, 3H), 1.43 (t, 3H). Anal. ($C_{18}H_{17}N_3O_2 \cdot CH_3SO_3H$) C, H, N.

Ethyl 7-bromo-1,4-dihydro-1-(4-fluorophenyl)-4-oxo-3-quinolonecarboxylate (43) was prepared from 17 and 4-fluoroaniline in 74% yield via method E (in DMF): mp 268–270 °C; ^{1}H NMR ($CDCl_3$) δ 8.42 (s, 1H), 8.33 (d, 1H), 7.30–7.55 (m, 5H), 7.70 (d, 1H), 4.38 (q, 2H), 1.38 (t, 3H). Anal. ($C_{18}H_{13}BrFNO_3$) C, H, N.

Ethyl 7-chloro-1,4-dihydro-1-(4-fluorophenyl)-4-oxo-3-quinolinecarboxylate (44) was prepared from 41 and 4-fluoroaniline in 77% yield via method D. An analytical sample was prepared by recrystallization from EtOAc: mp 239–241 °C; ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 8.44 (d, J = 10 Hz, 1H), 7.25–7.55 (m, 5H), 6.90 (d, J = 2 Hz, 1H), 4.48 (q, J = 7 Hz, 2H), 1.40 (t, J = 7 Hz, 3H). Anal. ($C_{18}H_{13}ClFNO_3$) C, H, N.

Ethyl 7-chloro-1,4-dihydro-1-(3-fluorophenyl)-4-oxo-3-quinolinecarboxylate (45) was prepared from 41 and 3-fluoroaniline in 79% yield via method E. An analytical sample was prepared by recrystallization from CH_3CN: mp 268–270 °C; ^{1}H NMR ($CDCl_3$) δ 8.46 (s, 1H), 8.45 (d, J = 9 Hz, 1H), 7.60–7.75 (m, 1H), 7.15–7.45 (m, 4H), 6.95 (d, J = 1.5 Hz, 1H), 4.38 (q, J = 7 Hz, 2H), 1.40 (t, J = 7 Hz, 3H). Anal. ($C_{18}H_{13}ClFNO_3$) C, H, N.

7-Chloro-1,4-dihydro-1-(3-fluorophenyl)-4-oxo-3-quinolinecarboxamide (46) was prepared in 98% yield by the hydrolysis of 45 in 1 N NaOH/THF followed by method A. An analytical sample was prepared by recrystallization from DMF: mp 294–296 °C; ^{1}H NMR (CF_3COOD) δ 9.46 (s, 1H), 8.82 (d, J = 9 Hz, 1H), 7.70–8.00 (m, 2H), 7.30–7.65 (m, 4H). Anal. ($C_{16}H_{10}ClFN_2O_2$) C, H, N.

5-(3-Methylisothiazolyl)trimethylstannane (39). A suspension of 5-bromo-3-methylisothiazole (**37**)[25] (17.5 g, 0.10 mol) and Et_2O (200 mL) was cooled to −78 °C and treated dropwise with n-BuLi (43 mL of 2.5 M solution, 0.11 mol). To this mixture was added dropwise a solution of trimethylstannyl chloride (20.0 g, 0.10 mol) and Et_2O (60 mL). The reaction mixture was allowed to warm to ambient temperature, stirred for 60 h and then poured into water (200 mL). The organic portion was dried (Na_2SO_4) and concentrated in vacuo to afford **39** (24.9 g, 95%). This potentially toxic material was used in the subsequent steps without additional purification.

5-(2-Methylthiazolyl)trimethylstannane (40). A solution of 2-methylthiazole (**38**)[26] (2.60 g, 26 mmol) in dry Et_2O (100 mL) at −78 °C was treated with n-BuLi (3.4 mL of 10 M solution, 34 mmol). The resulting orange suspension was allowed to warm to 5 °C, recooled to −50 °C, and treated with a solution of trimethylstannyl chloride (4.60 g, 0.9 equiv) in Et_2O (30 mL). The reaction was quenched with water and extracted with EtOAc. Flash chromatography (EtOAc/hexanes, 1:1) afforded **40** as an orange liquid which was used without further purification.

1-(3-Fluorophenyl)-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (98). A mixture of **46** (4.14 g, 13.0 mmol), 4-pyridinyltrimethylstannane[13] (3.79 g, 15.6 mmol), $PdCl_2(PPh_3)_2$ (0.46 g), and DMF (200 mL) was heated overnight at 150 °C in a stirred stainless steel pressure reactor. The cooled reaction mixture was filtered and the DMF removed in vacuo to afford a yellow solid (5.45 g). The crude product was treated with MeOH and methanesulfonic acid and concentrated in vacuo, and the residue was triturated with acetone to give the methanesulfonate salt of **98** (4.74 g, 80%). Recrystallization from a dilute solution of methanesulfonic acid in MeOH provided analytically pure material: mp >320 °C; ^{1}H NMR (CF_3COOD) δ 9.59 (s, 1H), 9.05 (br d, 3H), 8.35 (br d, 3H), 7.70–8.00 (m, 2H), 7.45–7.60 (m, 3H), 3.12 (s, 3H). Anal. ($C_{21}H_{14}FN_3O_2 \cdot CH_3SO_3H$) C, H, N.

1-(4-Fluorophenyl)-1,4-dihydro-7-[5-(3-methylisothiazolyl)]-4-oxo-3-quinolinecarboxamide (117) was prepared from **126** and **39** according to the same procedure used for making **98**. Recrystallization from DMF/water gave pure **117** in 72% yield: mp 221 °C dec; ^{1}H NMR (CF_3COOD) δ 9.48 (s, 1H), 8.95 (d, 1H), 8.19 (d, 1H), 7.81 (s, 1H), 7.60–7.80 (m, 3H), 7.52 (t, 2H), 2.90 (s, 3H). Anal. ($C_{20}H_{14}FN_3O_2S$) C, H, N.

1-(4-Fluorophenyl)-1,4-dihydro-4-oxo-7-phenyl-3-quinolinecarboxamide (111) was prepared similarly to **98** using phenyltri-n-butylstannane[13] and **124** except the reaction was carried out in a round-bottom flask and was complete in 1 h. The crude product was boiled in CH_3CN, and insoluble black material was removed by filtration. The product crystallized from the cold CH_3CN in an overall yield of 56%: mp 289–292 °C; ^{1}H NMR ($CDCl_3$) δ 9.7 (br d, 1H), 8.8 (s, 1H), 8.5 (d, 1H), 7.7 (dd, 1H), 7.1–7.6 (m, 11H). Anal. ($C_{22}H_{15}FN_2O_2$) C, H, N.

1-Ethyl-1,4-dihydro-4-oxo-7-[5-(2-methylthiazolyl)]-3-quinolinecarboxylic acid (47) was prepared from **40** and **42** according to the same procedure used for making **98** except HMPA was added to the reaction mixture and the resulting ester was immediately hydrolyzed in 1.5 N HCl. Recrystallization from DMF afforded analytically pure **47** (57%): mp 280 °C dec; ^{1}H NMR (DMSO-d_6) δ 9.04 (s, 1H), 8.41 (s, 1H), 8.39 (d, 1H), 8.09 (s, 1H), 7.85 (d, 1H), 4.65 (q, 2H), 2.73 (s, 3H), 1.43 (t, 3H). Anal. ($C_{16}H_{14}N_2O_3S \cdot 0.25H_2O$) C, H, N.

Ethyl 1-(4-Fluorophenyl)-1,4-dihydro-4-oxo-7-[(trimethylsilyl)ethynyl]-3-quinolinecarboxylate (48). A solution of **43** (25.4 g, 65 mmol) in CH_3CN (975 mL) at 45 °C was treated with CuI (1.4 g, 7 mmol) and Et_3N (325 mL). The resulting blue solution was degassed with argon for 20 min. (Trimethylsilyl)-acetylene (11.0 g, 110 mmol) and $Pd(PPh_3)_2Cl_2$ (1.4 g, 2 mmol) were added, and the resulting solution was heated at reflux for 1 h. The mixture was chilled in ice, and the precipitate was collected, washed with cold CH_3CN, and dried in vacuo (50 °C) to afford **48** as a gray white solid (23.4 g, 88%). Recrystallization from DMF gave analytically pure material: mp 247–249 °C; ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 8.42 (d, 1H), 7.25–7.52 (m, 5H), 6.98 (s, 1H), 4.38 (q, 2H), 1.39 (t, 3H), 0.21 (s, 9H). Anal. ($C_{23}H_{22}FNO_3Si$) C, H, N.

Ethyl 7-Ethynyl-1,4-dihydro-1-(4-fluorophenyl)-4-oxo-3-quinolinecarboxylate (49). A mixture of **48** (23.3 g, 57 mmol), KF (10.5 g, 180 mmol), and EtOH (700 mL) was heated at reflux for 4 h. The solvent was removed in vacuo, and the residue was triturated with $CHCl_3$. The solid was collected and suspended in water and extracted with $CHCl_3$. The organic portion was dried ($MgSO_4$), treated with charcoal, and filtered. Removal of solvent gave a gray white solid which was recrystallized from EtOAc to afford **49** (14.0 g, 73%): mp 227–229 °C; ^{1}H NMR ($CDCl_3$) δ 8.47 (s, 1H), 8.45 (d, 1H), 7.25–7.55 (m, 5H), 7.06 (s, 1H), 4.37 (q, 2H), 3.21 (s, 1H), 1.38 (t, 3H). Anal. ($C_{20}H_{14}FNO_3$) C, H, N.

Ethyl 1-(4-Fluorophenyl)-1,4-dihydro-7-[5-(3-methylisoxazolyl)]-4-oxo-3-quinolinecarboxylate (50). To a stirred solution of **49** (3.2 g, 9.5 mmol), phenyl isocyanate (4.75 g, 40 mmol), and $CHCl_3$ (25 mL) was added dropwise over 4.5 h a solution of nitroethane (3.09 g, 40 mmol), Et_3N (4 mL), and $CHCl_3$ (40 mL). The solid that separated was collected and washed with $CHCl_3$. The filtrate was concentrated in vacuo to give a gummy solid which was triturated with Et_2O, collected, suspended in boiling EtOAc, and collected. The resulting solid was recrystallized from CH_3CN to give analytically pure **50** (2.58 g, 69%): mp 214–216 °C; ^{1}H NMR ($CDCl_3$) δ 8.55 (d, 1H), 8.48 (s, 1H), 7.75 (d, 1H), 7.45–7.58 (m, 2H), 7.30–7.40 (m, 2H), 6.42 (s, 1H), 4.38 (q, 2H), 2.34 (s, 3H), 1.39 (s, 3H). Anal. ($C_{22}H_{17}FN_2O_4$) C, H, N.

1-Ethyl-1,4-dihydro-7-(1-1*H*-imidazolyl)-4-oxo-3-quinolinecarboxamide (118). A mixture of **123** (0.25 g, 1.0 mmol), imidazole (0.14 g, 2.1 mmol), NaH (60% oil suspension, 94 mg, 2.4 mmol), CuBr (30 mg), and DMF (5 mL) was heated at 160 °C for 4 h. The reaction mixture was allowed to cool to ambient temperature, diluted with water (20 mL), and extracted with $CHCl_3$ (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and chromatographed (0–5% isopropylamine/$CHCl_3$) on silica gel to give **118** (0.08 g 29%) as an off-white powder: mp 294–296 °C; ^{1}H NMR ($CDCl_3$) δ 9.62 (br s, 1H, CON*H*), 8.86 (s, 1H), 8.68 (d, J = 8.6 Hz, 1H), 8.01 (s, 1H), 7.54 (dd, J = 9.1, J = 1.7 Hz, 1H), 7.48 (d, J = 1.7 Hz, 1H), 7.41 (s, 1H), 7.32 (s, 1H), 5.77 (br s, CON*H*, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.62 (t, J = 1.7 Hz, 3H). Anal. ($C_{15}H_{14}N_4O_2$) C, H, N.

Ethyl 1-Ethyl-1,4-dihydro-7-(5-isoxazolyl)-4-oxo-3-quinolinecarboxylate (54). A solution of quinolone **51**[15] (30.1 g, 0.105 mol), dimethylformamide dimethyl acetal (21 mL, 0.16 mol), and DMF (100 mL) was heated on a steam bath for 2 h and

cooled. The precipitate was collected, washed with Et_2O, and air-dried to afford **52** (32.1 g, 89%). A solution of **52** (30.8 g, 0.09 mol), NH_2OH·HCl (6.95 g, 0.10 mol), and EtOH (240 mL) was heated at reflux for 6 h. Upon cooling the resulting white solid was collected and washed with EtOH and Et_2O to afford **54** (28.1 g, 100%): ^1H NMR (DMSO-d_6) δ 8.75 (s + d, 2H), 8.36 (d, 1H), 8.17 (s, 1H), 7.95 (d, 1H), 7.35 (s, 1H), 4.51 (q, 2H), 4.24 (q, 2H), 1.41 (t, 3H), 1.30 (t, 3H). Anal. ($C_{17}H_{16}N_2O_4$) C, H, N.

Ethyl 1-Ethyl-1,4-dihydro-7-[5-(3-methylisoxazolyl)]-4-oxo-3-quinolinecarboxylate (55). A solution of **51** (32.6 g, 113 mmol), dimethylacetamide dimethyl acetal (20 mL, 0.135 mol), and DMF (100 mL) was heated on a steam bath for 3 h; additional dimethylacetamide dimethyl acetal (4 mL) was then added, and heating was continued for 1 h. The reaction mixture was concentrated to dryness in vacuo and triturated with EtOAc to afford **53** (27.2 g, 68%). Compound **53** (14.40 g, 40 mmol) was converted to **55** (12.3 g, 94%) according to the same procedure for making **54**. An analytical sample of **55** was prepared by recrystallization from DMF: mp >300 °C; ^1H NMR (CF_3COOD) δ 9.47 (s, 1H), 8.91 (d, 1H), 8.70 (s, 1H), 8.41 (d, 1H), 7.11 (s, 1H), 5.07 (br q, 2H), 4.72 (q, 2H), 2.57 (s, 3H), 1.86 (t, 3H), 1.55 (t, 3H). Anal. ($C_{18}H_{18}N_2O_4$) C, H, N.

1-Ethyl-1,4-dihydro-2-methyl-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (127). A mixture of anhydride **56**[16] (4.8 g, 20 mmol), NaH (2.39 g, 22 mmol), and DMF was stirred for 30 min, and ethyl bromide (2.39 g, 22 mmol) was added to give **57**. Acetoacetamide (4.45 g, 44 mmol) and NaH (2.02 g, 44 mmol) were added, and the reaction mixture was heated to 100 °C for 6 h. The reaction was quenched with water (100 mL) and cooled in ice. The precipitate was collected and recrystallized from DMF to give **127** (1.45 g, 33%): mp >300 °C; ^1H NMR (DMSO-d_6) δ 8.73 (dd, 2H), 8.34 (d, 1H), 8.09 (s, 1H), 7.91 (br s, 1H, CON*H*), 7.89 (d, 2H), 7.80 (d, 1H), 7.37 (br s, 1H, CON*H*), 4.50 (q, 2H), 2.64 (s, 3H), 1.38 (t, 3H). Anal. ($C_{18}H_{17}N_3O_2$) C, H, N.

1-Ethyl-1,4-dihydro-2-hydroxy-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (128). To a stirred mixture of NaH (97%, 0.12 g, 5.0 mmol), diethyl malonate (0.68 g, 2.2 mmol), and DMF (10 mL) was added **57** (0.53 g, 2.0 mmol). After being stirred at ambient temperature for 3 h the reaction mixture was heated on a steam bath for 1 h, cooled, treated with glacial HOAc (1 mL), and concentrated in vacuo. The residue was diluted with water, and undissolved material was removed by filtration. The resulting solution was extracted with $CHCl_3$, and the extracts were dried ($MgSO_4$). The solvent was removed, and the residue was triturated with Et_2O. The brick red powder was collected (0.21 g), and a second crop was obtained from the filtrate (0.11 g), affording an ester (0.33 g, 49%) intermediate which was converted to **128** (94%) via method C. Treatment with methanesulfonic acid and MeOH afforded the salt of **128**: mp 258–260 °C; ^1H NMR (DMSO-d_6) δ 9.65 (br s, 1H, CON*H*), 8.48–8.80 (m, 1H), 8.69 (d, 2H), 8.15 (d, 1H), 7.87 (s, 3H), 7.70 (d, 1H), 4.40 (br q, 2H), 1.22 (t, 3H). Anal. ($C_{17}H_{15}N_3O_3$·CH_3SO_3H) C, H, N.

2-Amino-1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (129). A mixture of NaH (97%, 1.09 g, 44 mmol), malononitrile (1.45 g, 22 mmol), and DMF (40 mL) was stirred at 0 °C for 30 min, and **57** (5.37 g, 20 mmol) was added. After being stirred at ambient temperature overnight the mixture was poured into 1 N HCl (100 mL). After the mixture was stirred for 1 h, the precipitate was collected, washed with water, and dried in vacuo. The resulting orange powder was dissolved in a boiling solution of methanesulfonic acid (5 mL) and water (50 mL), cooled, and diluted with EtOH. The resulting solid was collected, washed with EtOH, and dried. A solution of this material (2.70 g) in concentrated sulfuric acid (25 mL) was heated at 100 °C for 4 h, poured onto ice, and made basic with NH_4OH. A precipitate was collected, washed with water, and dried in vacuo to give **129** (2.35 g 38%). Recrystallization from DMF provided the analytical sample: mp >300 °C; ^1H NMR (DMSO-d_6) δ 11.73 (br s, 1H), 10.65 (d, 1H, CON*H*), 8.72 (dd, 2H), 8.33 (d, 1H), 7.88 (br s, 1H), 7.83–7.90 (m, 3H), 7.70 (d, 1H), 7.28 (br d, 1H, CON*H*), 4.35 (br q, 2H), 1.33 (t, 3H). Anal. ($C_{17}H_{16}N_4O_2$) C, H, N.

Ethyl 1-(4-Fluorophenyl)-1,4-dihydro-2-(methylthio)-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate (59). A mixture of **16** (2.23 g, 7.8 mmol), Cs_2CO_3 (6.32 g, 19.4 mmol), and THF (75 mL) was cooled in an ice bath and treated with CS_2 (2.88 g, 38.8 mmol). After 2 h MeI (2.75 g, 19.4 mmol) was added, the ice bath was removed, and the reaction mixture was stirred at ambient temperature overnight. The reaction was diluted with CH_2Cl_2 (100 mL) and filtered. Concentration in vacuo afforded a brown oil which was chromatographed on alumina (activity IV, 3:1 hexanes–EtOAc) to give **58** (1.16 g, 38%). Compound **58** was dissolved in dioxane (20 mL), treated with 4-fluoroaniline (0.36 g, 3.26 mmol) and K_2CO_3 (0.90 g, 6.51 mmol), and stirred at ambient temperature for 1 h. The reaction mixture was heated at reflux overnight, cooled, diluted with $CHCl_3$, and filtered, and the solvent was removed in vacuo. The residue was triturated with Et_2O and collected to give **59** (0.97 g, 75%): mp 181–183 °C; ^1H NMR ($CDCl_3$) δ 8.64 (dd, 2H), 8.52 (d, 1H), 7.58 (dd, 1H), 7.28–7.40 (m, 6H), 6.85 (s, 1H), 4.47 (q, 2H), 2.32 (s, 3H), 1.42 (t, 3H). Anal. ($C_{24}H_{19}FN_2O_3S$) C, H, N.

Ethyl 7-bromo-1-(4-fluorophenyl)-1,4-dihydro-2-(methylthio)-4-oxo-3-quinolinecarboxylate (61) was prepared from **17** in 15% yield according to same procedure used to synthesize **59**: mp 161–163 °C. ^1H NMR ($CDCl_3$) δ 8.25 (d, 1H), 7.45 (dd, 1H), 7.25–7.38 (m, 4H), 6.80 (d, 1H), 4.43 (q, 2H), 2.28 (s, 3H), 1.38 (t, 3H). Anal. ($C_{19}H_{15}BrFNO_3S$) C, H, N.

Ethyl 7-Bromo-1-(4-fluorophenyl)-1,4-dihydro-2-hydroxy-4-oxo-3-quinolinecarboxylate (62). A mixture of **61** (0.87 g, 2.0 mmol), 1 N KOH (2.2 mL), and THF (10 mL) was heated at reflux overnight. The reaction mixture was concentrated to dryness in vacuo, and the residue was dissolved in water, acidified with 1 N HCl, and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and concentrated in vacuo to give a yellow solid which was triturated with Et_2O to give **62** (0.58 g, 71%): mp 180–182 °C; ^1H NMR ($CDCl_3$) δ 8.06 (d, J = 8.3 Hz, 1H), 7.40–7.15 (m, 5H), 7.73 (d, J = 0.5 Hz, 1H), 4.45 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H). Anal. ($C_{18}H_{13}BrFNO_4$) C, H, N.

7-Bromo-1-(4-fluorophenyl)-1,4-dihydro-2-hydroxy-4-oxo-3-quinolinecarboxamide (63) was prepared in 67% yield from ester **62**, according to general method C: mp >250 °C; ^1H NMR ($CDCl_3$) δ 8.13 (d, 1H), 7.44 (dd, 1H) 7.20–7.40 (m, 4H), 6.81 (s, 1H). Anal. ($C_{16}H_{10}BrFN_2O_3$) C, H, N.

1-(4-Fluorophenyl)-1,4-dihydro-2-hydroxy-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxamide (130). A mixture of **63** (0.28 g, 0.74 mmol), 4-pyridinyltrimethylstannane (0.20 g, 0.82 mmol), $PdCl_2(PPh_3)_2$ (0.026 g), and EtOH (10 mL) was heated in a sealed stainless steel vessel at 150 °C overnight. The reaction vessel was cooled to ambient temperature and the contents rinsed out with DMF (30 mL). The resulting mixture was heated at reflux and filtered while hot. The filtrate was concentrated in vacuo and the residue triturated in Et_2O to give a gummy solid which was triturated in EtOAc. The resulting solid was treated with MeOH, water, and methanesulfonic acid to afford a yellow-green methanesulfonate salt of **130** (0.18 g, 64%): mp 275–278 °C dec; ^1H NMR (CF_3COOD) δ 8.91 (d, J = 6.7 Hz, 2H), 8.67 (d, J = 8.5 Hz, 1H), 8.17 (d, J = 6.9 Hz, 2H), 7.88 (d, J = 8.8 Hz, 1H), 7.20–7.40 (m, 4H), 7.20 (s, 1H), 3.17 (s, 3H). Anal. ($C_{21}H_{14}FN_3O_3$·CH_3SO_3H·$2H_2O$) C, H, N.

2-Amino-1-(4-fluorophenyl)-1,4-dihydro-7-(4-pyridinyl)-3-quinolinecarboxamide (131). A stainless steel vessel containing **59** (0.21 g, 0.50 mmol) and saturated ethanolic NH_3 (10 mL) was heated overnight at 150 °C. The ethanolic solution was concentrated in vacuo and the residue triturated with Et_2O to give **131** (0.14 g, 74%). An analytical sample of the methanesulfonic acid salt was prepared: mp 294–296 °C dec; ^1H NMR (CF_3COOD) δ 8.93 (d, 2H), 8.75 (d, 1H), 8.19 (d, 2H), 8.05 (dd, 1H), 7.50–7.70 (m, 4H), 7.22 (d, 1H), 3.10 (s, 6H). Anal. ($C_{21}H_{15}FN_4O_2$·CH_3SO_3H·$0.5H_2O$) C, H, N.

1-(4-Fluorophenyl)-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-oxopyrazolo[3,4-*b*]quinoline (132). A mixture of **59** (1.00 g, 2.30 mmol), hydrazine hydrate (0.13 g, 2.50 mmol), and absolute EtOH (30 mL) was heated at reflux for 35 h. After 2 h additional hydrazine hydrate (0.50 mL) was added. The reaction mixture was cooled in ice, and the solid was collected. The orange solid (0.88 g) was treated with water and methanesulfonic acid which upon cooling afforded the methanesulfonate salt of **132** (1.01 g, 78%): mp >300 °C; ^1H NMR (CF_3COOD) δ 9.01 (d, 2H), 8.94 (d, 1H), 8.29 (d, 2H), 8.12 (d, 1H), 7.68–7.82 (m, 2H), 7.50–7.65 (m, 3H), 3.11 (s, 6H). Anal. ($C_{21}H_{13}FN_4O_2$·CH_3SO_3H·H_2O) C, H, N.

Ethyl 1,4-Dihydro-4-oxo-7-(4-pyridinyl)-1*H*-benz[*d*]imidazolo[2,3-*a*]quinoline-3-carboxylate (66). A mixture 64 (0.20 g, 0.50 mmol, prepared from 15 in a manner analogous to 58), 1,2-phenylenediamine (0.059 g, 0.55 mmol), K_2CO_3 (0.15 g, 1.1 mmol), and dioxane was stirred overnight at ambient temperature. The resulting mixture was heated at reflux overnight, cooled to room temperature, and concentrated in vacuo. The resulting yellow solid was triturated in water and collected. The crude material was treated with MeOH and methanesulfonic acid to afford the dimethanesulfonate salt of 66 (0.10 g, 34%): mp 200 °C dec; ^{1}H NMR (CF_3COOD) δ 9.36 (s, 1H), 9.20 (d, 2H), 9.08 (d, 1H), 8.64–8.78 (m, 3H), 8.41 (d, 1H), 8.05–8.15 (m, 1H), 7.81–8.10 (m, 2H), 4.93 (q, 2H), 3.12 (s, 6H), 1.69 (t, 3H). Anal. ($C_{23}H_{17}N_3O_3 \cdot 2CH_3SO_3H$) C, H, N.

Plaque-Reduction Assay. Herpes simplex virus type 2 (Curtis) (HSV-2) was obtained from Dr. J. O. Oh, Francis Proctor Foundation, University of California, San Francisco. HSV-1 (F) was obtained from the American Type Culture Collection (ATCC, Rockville, MD). HSV-1 (KOS) and an acyclovir-resistant mutant of HSV-1 (KOS), HSV-1 ACG^{r}4, were obtained from Dr. D. Coen, Harvard Medical School, Boston, MA. Clinical isolates of HSV-1 (1142 and 2992) and HSV-2 (2011 and 2115) resistant to acyclovir were obtained from Burroughs Wellcome Company, Research Triangle Park, NC. Viruses were cultured in Vero (African green monkey kidney) cells obtained from the ATCC. Cell cultures used in plaque-reduction assays were grown in Hank's minimum essential medium containing 5% inactivated fetal calf serum (Gibco Laboratories, Grand Island, NY) in six-well 35-mm^2 tissue culture plates (Costar, Cambridge, MA) at 37 °C and 2% CO_2. Two day old, confluent monolayers were infected with approximately 80 plaque-forming units (PFU) of virus. After a 1-h adsorption period, the inoculum was removed and an overlay containing a 1:150 dilution of human immune serum globulin (Gammar; Armour Pharmaceutical Co., Kankakee, IL) in M199 medium containing 5% inactivated fetal calf serum and a 1:200 dilution of test compounds (serial 2-fold dilutions) in DMSO was added to the cell monolayers. After incubation at 37 °C and 2% CO_2 for 3 d, the cell monolayers were fixed with 5% glutaraldehyde and stained with 0.25% crystal violet in water. The plaques were quantitated using an Artek counter or by visual inspection. The lowest concentration of test compound which inhibited plaque formation by 50% was recorded as the minimum inhibitory concentration (MIC). For active compounds, the MICs shown represent the mean of at least two experiments and had a standard deviation of less than ±50%. The maximum testable level (MTL) was the highest concentration of compound that showed no cellular toxicity by visualization of stained cells.

In Vivo Testing. All animal care and use procedures were conducted in accord with the *Guide for the Care and Use of Laboratory Animals* (NIH Pub. No. 86-23, 1985) and were approved by an Institutional Animal Care and Use Committee. Swiss female albino ICR mice (13–15 g) (Blue Spruce Farms, Altamont, NY) were infected intravaginally with a dose of HSV-2 (Curtis) calculated to cause 80% mortality. Test compounds were suspended in sterile 1% gum tragacanth (Fisher Scientific) containing 2% Tween 80 and were administered intragastrically. Twenty mice per dose level were medicated with compound (serial 2-fold dilutions) 2 h prior to infection and then twice a day for a total of 5 d. Mortality was recorded over a 14-d period. The minimum effective dose (MED) was defined as the lowest dose of compound that resulted in survival times that were statistically different from placebo based on the Mantel-Cox and Breslow statistical methods. For active compounds, the MED is based on at least two experiments. The maximum tolerated dose (MTD) was defined as the highest dose of compound that did not show any overt signs of toxicity.

Serum Concentrations of 97 in Mice. Protocol. Female Swiss-Webster mice weighing 16–18 g were dosed intragastrically with 97 at 25 mg/kg in a vehicle composed of 1% gum tragacanth plus 2% Tween 80. Food and water were available *ad libitum*. At 0 (predose), 0.25, 1, 2, 4, 6, 8, 16, and 24 h after administration, the animals were anesthetized with CO_2, and blood was obtained via cardiac puncture. Blood was pooled from 12 mice at each time point in sets of three, with four mice in each set. The pooled blood was allowed to coagulate, and serum was collected following centrifugation at 2000*g* for 5 min. In a similar manner, control serum was also obtained from nonmediated mice. **Analytical.** Serum samples (200 μL) were diluted with water (100 μL) and basified with 0.005 N NaOH (100 μL). After addition of internal standard, samples were extracted with Et_2O (2 × 5 mL). The extracts were pooled and evaporated to dryness under N_2, and the residues were reconstituted in 1.0 mL of mobile phase for injection into the HPLC chromatographic system. Samples were analyzed using a validated reverse-phase high-performance liquid chromatographic system with UV detection at 272 nm. The detector was interfaced with a Hewlett-Packard Model 3357 laboratory automation system for data acquisition and processing. The mobile phase was CH_3CN/0.3 M ammonium acetate (1:1, v/v). A linear least-squares regression analysis was performed on the peak height ratio (analyte/internal standard) of unknown samples versus calibration curve standards. The latter were prepared in control mouse serum at nine concentrations ranging from 0.025 to 7.5 μg/mL. Quality control samples, prepared in quadruplicate in normal control mouse serum at a nominal concentration of 1 μg/mL, were analyzed with each analytical run. The minimum quantifiable level was determined to be 0.025 μg/mL.

Acknowledgment. We gratefully acknowledge the contributions of following scientists: E. Boll, S. Gangell, A. Hlavac, T. McGuire, and L. McNaughton (generation of spectral data); S. Clemans and C. Rodger (analysis of spectral data); R. Powles (growing crystal of 97 for X-ray); F. Tham (generation of X-ray crystal data); G. Martinson (determination of serum drug concentrations in mice); and S. Kingsley, K. Ryan, A. Erenberg, V. Csontos, and A. Visosky (in vitro and in vivo antiherpetic testing).

Supplementary Material Available: Details of the X-ray crystallographic analysis of 97 and tables giving crystal data (S1), data collection (S2), solution and refinement (S3), atomic coordinates and equivalent isotropic displacement coefficients (S4), bond lengths (S5), bond angles (S6), anisotropic displacement coefficients (S7), and H-atom coordinates and isotropic displacement coefficients (S8) (8 pages). Ordering information is given on any current masthead page.

References

(1) Crowe, S.; Mills, J. The Future of Antiviral Chemotherapy. *Dermatol. Clin.* **1988**, *6*, 521–537.
(2) Oberg, B.; Johansson, N. G. The Relative Merits and Drawbacks of New Nucleoside Analogues with Clinical Potential. *J. Antimicrob. Chemother.* **1984**, *14*, Suppl. A, 5–26.
(3) Diana, G. D.; Pevear, D.; Young, D. C. Antiviral Agents. *Annu. Rep. Med. Chem.* **1989**, *24*, 129–137.
(4) Wentland, M. P. *The New Generation of Quinolones*; Siporin, C., Heifetz, C. L., Domagala, J. M., Eds.; Marcel Dekker: New York, 1990; pp 1–43.
(5) Carabateas, P. M.; Brundage, R. P.; Gellote, K. O.; Gruett, M. D.; Lorenz, R. R.; Opalka, C. J., Jr.; Singh, B.; Thielking, W. H.; Williams, G. L.; Lesher, G. Y. 1-Ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylic acids. II. Synthesis. *J. Heterocycl. Chem.* **1984**, *21*, 1857–63.
(6) Grohe, K.; Heitzer, H. Cycloaracylation of Enamines I. Synthesis of 4-quinolone-3-carboxylic acids. *Liebigs Ann. Chem.* **1987**, 29–37.
(7) Hofer, W.; Mauer, F.; Riebel, H. J.; Schroeder, R.; Uhrhan, P.; Homeyer, B.; Behrenz, W.; Hammann, I. Insecticidal and Acaricidal vinyl(di- or tri-)thiophosphoric(phosphonic)acid esters or ester amides. Ger. Offen. 2536977, 1977; *Chem. Abstr.* **1977**, *87*, 23493y.
(8) Wierenga, W.; Skulnick, H. I. Aliphatic and Aromatic β-Ketoesters from Monoethylmalonate: Ethyl 2-butyryl acetate. *Org. Synth.* **1983**, *61*, 5–8.
(9) Akiba, K.-Y.; Iseki, Y.; Wada, M. Regioselective Syntheses of 4-Alkylpyridines via 1,4-Dihydropyridine Derivatives from Pyridine. *Tetrahedron Lett.* **1982**, *23*, 429–432 and references contained therein.
(10) Lesher, G. Y. Antibacterial 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids and esters. U.S. Patent 3472859, 1969; *Chem. Abstr.* **1970**, *72*, 3393c.
(11) Barton, N.; Crowther, A. F.; Hepworth, W.; Richardson, D. N.; Driver, G. W. Quinolones and therapeutic compositions containing them. Br. Pat. 830832, 1960; *Chem. Abstr.* **1961**, *55*, 7442.
(12) Bailey, T. R. Unsymmetrical Heterobiaryl Synthesis. A Highly Efficient Palladium-Catalyzed Cross-Coupling of Heteroaryl Trialkylstannanes with Aryl Halides. *Tetrahedron Lett.* **1986**, *27*, 4407–4410.

(13) Stille, J. K. The Palladium-Catalyzed Cross-Coupling Reactions of Organotin Reagents with Organic Electrophiles. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.
(14) Suzuki, N.; Tanaka, Y.; Dohmori, R. Synthesis of Antimicrobial Agents. I. Synthesis and Antimicrobial Activities of Thiazoloquinoline Derivatives. *Chem. Pharm. Bull.* **1979**, *27*, 1–11.
(15) Culbertson, T. P.; Domagala, J. M.; Peterson, P.; Bongers, S.; Nichols, J. B. New 7-Substituted Quinoline Antibacterial Agents. The Synthesis of 1-Ethyl-1,4-dihydro-4-oxo-7-(2-thiazolyl and 4-thiazolyl)-3-quinolinecarboxylic Acids. *J. Heterocycl. Chem.* **1987**, *24*, 1509–1519.
(16) Ranken, P. F.; Walter, T. J. 4-(4-Pyridinyl)isatoic anhydride. U.S. Patent 4515945, 7 May, 1985; *Chem. Abstr.* **1985**, *103*, 123492q.
(17) For an alternate method for the synthesis of 2-substituted quinolones, see: Kiely, J. S.; Huang, S.; Lesheski, L. E. A General Method for the Preparation of 2-Substituted-4-oxo-3-quinolinecarboxylic Acids. *J. Heterocycl. Chem.* **1989**, *26*, 1675–1681.
(18) For the synthesis of a similar sulfur-bridged quinolone, see: Chu, D. T. W.; Fernandes, P. B.; Pernet, A. G. Synthesis and Biological Activity of Benzothiazolo[3,2-*a*]quinolone Antibacterial Agents. *J. Med. Chem.* **1986**, *29*, 1531–1534.
(19) Pessina, A.; Mineo, E.; Gribaldo, L.; Neri, M. G. Lack of in vitro antiviral activity of fluoroquinolones against herpes simplex virus type 2. *Arch. Virol.* **1992**, *122*, 263–269.
(20) Topliss, J. G. A Manual Method for Applying the Hansch Approach to Drug Design. *J. Med. Chem.* **1977**, *20*, 463–469.
(21) The 7-(4-pyridinyl) group imparts excellent in vivo properties to rosoxacin (see ref 4). Also 7-(2,6-dimethyl-4-pyridinyl)quinolones have po/iv in vivo antibacterial efficacy ratios near unity: Reuman, M.; Daum, S. J.; Singh, B.; Wentland, M. P.; Carabateas, P. M.; Gruett, M. D.; Coughlin, S. A.; Sedlock, D. M.; Rake, J. B.; Lesher, G. Y. Synthesis and Antibacterial Activity of some Novel 1-Substituted-7-pyridinyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids. Abstracts of the 29th Interscience Conference on Antimicrobial Agents and Chemotherapy, Houston, TX, September 17–20, 1989, Abstr. 1193.
(22) A similar biotransformation has been reported: Chaykin, S.; Bloch, K. The Metabolism of Nicotinamide-N-oxide. *Biochem. Biophys. Acta* **1959**, *31*, 213–216.
(23) Unpublished results. Department of Virology and Oncopharmacology, Sterling Winthrop Inc.
(24) Pesticidal pyridines. Neth. Patent 6414307, 1965; *Chem. Abstr.* **1966**, *64*, 713f.
(25) Adams, A.; Slack, R. Isothiazoles: A New Mononuclear Heterocyclic System. *J. Chem. Soc.* **1959**, 3061–3076.
(26) Erlenmeyer, H.; Weber, O.; Schmidt, P.; Kung, G.; Zinsstag, C.; Prijs, B. The Condensation Ability of the 2-Position Methyl Group in Thiazole Compounds. *Helv. Chim. Acta* **1948**, *31*, 1142–1158.
(27) Minami, S.; Matsumoto, J.; Shimizu, M.; Tekase, Y. Piperazine derivatives. Ger. Offen. 2362553, 1974; *Chem. Abstr.* **81**, 105562.
(28) Agui, H.; Mitani, T.; Nakashita, M.; Nakagome, T. Studies on Quinolone Derivatives and Related Compounds. 1. A New Synthesis of 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids. *J. Heterocycl. Chem.* **1971**, 357–365.
(29) Ridgeway, H. M.; Waters, D. M.; Peel, M. E.; Ellis, G. P. Tetrazolyloxodihydroquinolinecarboxamides. Ger. Offen. 240774429, 1974; *Chem. Abstr.* **1974**, *81*, 169547s.
(30) Raychaudhuri, A.; Basu, U. P. Side products in the preparation of 7-chloro-4-hydroxyquinoline-3-carboxylate, an intermediate for chloroquine. *Curr. Sci.* **1967**, *36*, 459; *Chem. Abstr.* **1968**, *68*, 21811j.
(31) Mahmood, F.; Mahmood, N. H.; Holms, W. H. Antibacterial action of quinolones on Escherichia coli, I. Structure Activity Relationship. *Zbl. Bakt. Hyg., Abt. Orig. A* **1980**, *246*, 329–335.